PART 3
PRACTICE OF ONCOLOGY

Chapter 22 Cancer Prevention: Preventing Tobacco-Related Cancers
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Chapter 23 Cancer Prevention: Diet and Chemopreventive Agents

Section 23.1 Fat
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Section 23.2 Dietary Fibers
PETER GREENWALD

Section 23.3 Retinoids, Carotenoids, and Micronutrients
SUSAN TAYLOR MAYNE
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Section 23.4 Naturally Occurring Dietary Anticancerogens
PETER GREENWALD

Section 23.5 Dietary Carcinogens
PETER GREENWALD

Section 23.6 Aspirin and Other Nonsteroidal Antiinflammatory Drugs and the Risk of Cancer Development
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Section 23.7 Physical Activity and Body Weight
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Chapter 24 Cancer Prevention: Role of Surgery in Cancer Prevention
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Chapter 25 Cancer Screening
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JOELLEN SCHILDKRAUT
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Chapter 26 Cancer Diagnosis: Molecular Pathology
JOSE COSTA
CARLOS CORDON-CARDO

Chapter 27 Cancer Diagnosis: Imaging

Section 27.1 Computed Tomography
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Section 27.2 Magnetic Resonance Imaging
ARThUR E. LI
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Section 27.3 Functional and Metabolic Imaging
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Section 27.4 Interventional Radiology
JEAN-FRANCOIS H. DESCHWIND

Section 27.5 Ultrasound
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Section 27.6 Radionuclide Imaging
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Chapter 28 Cancer Diagnosis: Endoscopy
ROBERT C. KURTZ
ROBERT J. GINSBERG

Chapter 29 Specialized Techniques in Cancer Management

Section 29.1 Laparoscopy
ALAN T. LEFOR

Section 29.2 Vascular Access and Specialized Techniques of Drug Delivery
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Section 29.3 Isolation Perfusion
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Section 29.4 Intensity-Modulated Radiation Therapy
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Chapter 52 Treatment of Metastatic Cancer

Section 52.1 Metastatic Brain Cancer
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Section 52.2 Metastatic Cancer to the Lung
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Section 52.5 Malignant Pleural and Pericardial Effusions
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Section 52.6 Malignant Ascites
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Chapter 53 Hematopoietic Therapy

Section 53.1 Transfusion Therapy
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Section 53.2 Autologous Stem Cell Transplantation
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Section 53.3 Allogeneic Stem Cell Transplantation
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Section 53.4 Hematopoietic Growth Factors
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Chapter 54 Infections in the Cancer Patient

Chapter 55 Adverse Effects of Treatment

Section 55.1 Nausea and Vomiting
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Section 55.2 Oral Complications
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Section 55.3 Pulmonary Toxicity
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Section 55.4 Cardiac Toxicity
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Section 55.5 Hair Loss
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Section 55.6 Gonadal Dysfunction
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Section 55.7 Second Cancers
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Section 55.8 Miscellaneous Toxicities
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Stuart Freeman

whose wisdom and extraordinary skills have guided this text from its inception through all six editions.

His vision for the dissemination of information among all treatment modalities and his commitment to excellence have helped improve the lives of cancer patients.
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The rapid pace of change in knowledge of the scientific basis and clinical practice of oncology presents a daunting challenge to the oncologist. The extraordinary increase in understanding of the molecular basis of cellular processes, the rise of biotechnology, and the steady refinement of each of the major treatment approaches have impacted every phase of the care of the cancer patient. In addition, an increased appreciation of the coordinated role of each of the main treatment modalities in the care of an individual cancer patient has emphasized the need for oncologists to be familiar with developments in all treatment modalities. Each edition of this text, first published in 1982, has attempted to help the oncologist keep pace with these changes.

In this sixth edition of CANCER: Principles and Practice of Oncology, we have again attempted to provide a comprehensive resource describing the science underlying recent clinical developments as well as complete information to aid the clinician in the panorama of clinical care ranging from cancer prevention to the care of the terminally ill patient. To accomplish this, the book has been divided into four parts.

PART 1: Essentials of Modern Oncologic Science presents a summary of the major areas of modern bioscience carefully distilled to provide the background necessary for an understanding of recent developments in oncology. Thus chapters on molecular biology, genomics, proteomics, signal transduction, and immunology present a primer for the oncologist in these important areas.

PART 2: Principles of Oncology has been reorganized to present in further detail the specific scientific areas of greatest relevance to the oncologist, including new chapters on cytogenetics, the cell cycle, apoptosis, and angiogenesis, as well as chapters on the etiology of cancer, and a clear description of modern epidemiologic methods and the incidence of and mortality from cancer.

Chapters on the principles underlying the four modalities of cancer treatment—surgery, radiotherapy, chemotherapy, and biologic therapy—present the basis for continuing changes in the development and application of these treatments. The pharmacology of cancer chemotherapy is presented, and a new section is introduced on the rapidly changing area of cancer biotherapeutics as these agents have entered into the practice of oncology.

The final chapter in PART 2 deals with the design and analysis of clinical trials as well as research data and management. As more and more patients are entering clinical trials, knowledge of these areas by the practicing oncologist is of special importance.

PART 3: Practice of Oncology provides the practicing clinician with the specific, practical information needed for the management of each cancer patient. Increased emphasis on cancer prevention relating to diet, tobacco, chemopreventive agents, fat, exercise, retinoids, naturally occurring dietary anticarcinogens, and many other areas are covered in detail. A new chapter on the role of surgery in cancer prevention details the emerging use of surgery in preventing cancer in high-risk individuals. Modern techniques of cancer screening, molecular pathology, imaging, and endoscopy are detailed in this section as well.

The hallmark of this book from its inception to the present and a major reason it has gained worldwide acceptance as a definitive source of cancer information has been the description of the treatment of cancer patients by stage of presentation with a tightly coordinated description of the role of each of the treatment modalities in the care of individual patients. To ensure a balanced multidisciplinary approach, each of the major treatment chapters is co-authored by a surgeon, a medical oncologist, and a radiation oncologist. Each of the major treatment sections is preceded by an updated, brief chapter describing the molecular biology of that cancer and the prospects this new information holds for the improved management of cancer patients.

Increased emphasis on supportive care, palliative care, and the quality of life of the cancer patient has led to an enlargement of sections dealing with these areas, including increased information on pain control and the nutritional, sexual, and psychosocial management of the cancer patient as well as issues related to the specialized care of the terminally ill.

PART 4: Newer Approaches in Cancer Treatment looks to the future of developments in oncology with special sections on gene therapy, molecular therapy, preventive and therapeutic cancer vaccines, image-guided surgery, and proton beam radiation therapy. In this section, we have attempted to identify those areas that we think will be of increasing value in the several years after the appearance of this text.

As we enter the twenty-first century, both the incidence and mortality of many of the major cancers are beginning to decline. We believe that the dissemination of carefully coordinated information of the scientific foundation and practice of oncology has played and will continue to play an important role in decreasing the devastating impact of cancer on modern society. We present the sixth edition of CANCER: Principles and Practice of Oncology to provide the practicing oncologist with the practical as well as cutting-edge information needed to provide the best possible care for each individual patient.

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STORAGE AND TRANSMISSION OF GENETIC INFORMATION

NUCLEIC ACIDS

The genetic material of all known organisms is nucleic acid: deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). Nucleic acids act as an information storehouse. They also actively participate in the reading and transmission of stored information within the cell and from one cell generation to the next. The usual flow of genetic information is from DNA to RNA to protein. The transition from DNA to RNA is called transcription, and the transition from RNA to protein is called translation. The direction of flow from DNA to RNA to protein was considered the “central dogma” in biologic sciences because most organisms exhibit this directionality in the expression of genetic information. However, it was found that some viruses, including retroviruses and the virus that causes autoimmune deficiency syndrome, transmit information from RNA to DNA using an enzyme called reverse transcriptase. Nucleic acids are polymers comprised of nucleotides (generally four different types) chemically linked together in chains that can be many millions of units long. The number of possible nucleic acid combinations \( n \) units long is thus \( 4^n \). A nucleic acid only 10 units in length therefore has \( 4^{10} \) possible sequences.

Each nucleotide in the chain contains a nitrogenous base, a five-carbon sugar, and a phosphate group. The sequence of bases is the form in which the genetic information is coded.

There are two types of bases: pyrimidines and purines. Pyrimidines are six-membered rings and include cytosine (C), thymine (T), and uracil (U). Purines are fused five- and six-membered rings and include adenine (A) and guanine (G). The chemical structures of the bases is shown in Figure 1-1. Bases C, A, and G are found in both DNA and RNA. T is specific to DNA, and U is specific to RNA.

![Figure 1-1. Purines and pyrimidines.](image)

Nucleotides are constituents of a nitrogenous base linked to a five-carbon sugar (pentose). The linkage is from the N1 position of the pyrimidines or from the N9 position of the purines to the carbon at position 1 on the pentose. DNA and RNA use different pentose sugars. The sugar in DNA is deoxyribose, and the pentose in RNA is ribose. The difference in the two sugars is a hydroxyl group at the 2' position on the sugar.

Nucleotides are nucleoside phosphates. A nucleotide is formed when a phosphate group is added to the 5' position of the pentose. The nucleotides that form the nucleic acid chain are connected in a very specific way: The 5' position of one pentose ring is connected to the 3' position of the next pentose ring by a phosphate group. The connection is called a phosphodiester bond.

DNA

The DNA backbone is made up of bonded sugar and phosphate groups in which a phosphate group connects the 5' carbon of one sugar to the 3' carbon of the next sugar in the chain by a phosphodiester bond. As shown in Figure 1-2, the beginning of the DNA chain has a phosphate group attached to the 5' carbon of deoxyribose, whereas the end of the chain has an OH group on the 3' carbon of deoxyribose.
DNA is a double helix. It is a double-stranded polymer. The bases of each chain face inward, with the restriction that a purine is always paired opposite to a pyrimidine; thus, a G on one strand is paired with a C on the other, and an A is paired with a T. The sugar phosphates are on the backbone of the helix. The resulting negative charge on the outside of the helix is neutralized in the chromosome by metal ions or positively charged proteins.

The two polynucleotide chains in the double helix are connected by hydrogen bonds between the bases. As noted earlier, G hydrogen-bonds specifically with a C, whereas an A can only hydrogen-bond with a T. The resulting base pairs are said to be complementary. As shown in Figure 1-3, the GC base pair has three hydrogen bonds, and the AT base pair has only two hydrogen bonds. Each strand can serve as the template for the synthesis of the other, enabling faithful reproduction of the genetic code.

FIGURE 1-3. Base pairs are formed by hydrogen bonds. T=A; G=C.

The two polynucleotide chains of the DNA double helix run in opposite directions (antiparallel). Thus, as one strand runs in the 5' to the 3' direction, the partner strand runs in the 3' to 5' direction, as in the following example:

\[
5' \text{PAGTCGCAOH} 3' \\
3' \text{HOTCAGCCGTTP} 5'
\]

DNA can be methylated in the carbon-5 position of cytosine to form 5-methylcytosine. This occurs in animals in DNA locations where the cytosine is followed on the same strand by guanine. The pattern of methylation is passed on when the DNA replicates.

RNA

In RNA, the pyrimidine uracil replaces the DNA base thymine, and the pentose ribose is used instead of deoxyribose in DNA. During the synthesis of RNA from a DNA template, adenine in DNA is transcribed into uracil in RNA.

Because the pentose ribose is used in RNA instead of deoxyribose, this produces a ribonucleotide having a 2'-OH group on the sugar, whereas the 2'-OH group is not present in DNA. The important consequence is that RNA is much less stable than DNA. RNA is highly base labile. Although RNA can have a complex secondary structure, it is single stranded, not double stranded like DNA.

RNA is transcribed from a DNA template and is the first step by which the genetic information of DNA is converted into the synthesis of specific proteins. A single strand of RNA is generated that is identical in its sequence to one of the strands of the DNA. The DNA strand that has the same sequence (with T instead of U) as the messenger RNA (mRNA) is the coding, or positive, strand; the opposite antiparallel strand is the anticoding, or negative, strand. The RNA itself then becomes the template (mRNA) for translation into the sequence of amino acids that comprise the protein polypeptide.

Three main types of RNA are present in the cell: mRNA, ribosomal RNA (rRNA), and transfer RNA (tRNA). mRNA encodes the sequence for all cellular proteins; however, most initial transcripts of mRNA contain large pieces of intervening sequences, or introns, that must be spliced out to leave the coding sequences, or exons. At the 3' end of most mRNA molecules is a poly(A) tail of 150 to 250 adenine nucleotides. The mRNA also has an untranslated leader and tailer sequence at both ends. rRNA does not code for protein. Instead, it comprises part of the machinery that decodes the information in the mRNA. tRNA also does not code for protein. It reads off the mRNA triplet code and matches it with the correct amino acid. tRNA contains specific bases not found in other RNAs: inosine, pseudouridine, and dihydrouridine. At the end of each tRNA is an acceptor arm whose free end is aminoacylated, or carries the specific amino acid. Another arm on the tRNA contains the anticodon, which recognizes the complementary mRNA codon. Thus, mRNA functions as a transportable copy of the blueprint for the synthesis of protein, and tRNA functions as part of the protein synthetic assembly line.

NUCLEOSIDASES AND POLYMERASES

Endonucleases are enzymes that cleave bonds within a nucleic acid chain. They may be specific for RNA, DNA, or hybrids of RNA-DNA or DNA-DNA. Restriction enzymes are a special class of endonucleases that recognize specific short sequences of DNA and cleave the DNA at or next to the recognition sequence. These enzymes are isolated from bacteria and are named after the genus (first letter) and species (second two letters) of the bacteria they are derived from. Because a bacteria can make more than one restriction enzyme, the specific member is designated by a roman numeral (e.g., EcoRI: Escherichia coli, strain R, first enzyme from that strain). Restriction enzymes cut DNA at palindromes. A palindrome is a sequence of DNA that is the same when one strand is read left to right (5' to 3') or the other is read right to left (still 5' to 3' because of the antiparallel rule). An example for EcoRI is

\[
5' \text{GAATTC} 3' \\
3' \text{CTTAAG} 5'
\]

Restriction endonucleases are now standard tools in molecular biology and permit the cutting of large stretches of DNA at very precise points. They allow fragments of DNA to be “fingerprinted” by the size of the cleaved fragments. Moreover, a restriction enzyme can cleave the DNA so as to leave blunt ends, or staggered “sticky” ends with 5' or 3' overhangs. Because of this property, restriction enzymes are powerful tools to analyze DNA sequences and to create cleaved pieces of DNA that...
can be shuffled, recombined, and reannealed in the process of DNA cloning.

Polymerases are enzymes that synthesize nucleic acid chains. RNA polymerases synthesize RNA, and DNA polymerases synthesize DNA. All polymerases require a template (nucleic acid strand to be synthesized), which is complementary to the strand being synthesized. They also need a primer, which is a short sequence (oligonucleotide) that is complementary to the 3’ end of the template. This provides a free 3’ OH end at which the polymerase starts to build a new chain.

Reverse transcriptase is a special polymerase that has, as its primary function, the ability to use RNA as a template to generate a copy in the form of DNA. It is an important enzyme in the life cycle of the human immunodeficiency viruses that cause autoimmune deficiency syndrome and other disorders, and as such, is a prime target for anti–human immunodeficiency virus therapeutics. Reverse transcriptase is also a unique reagent that can be used to create complementary DNA (copy) from mRNA extracted from cells, and therefore it is used in complementary DNA cloning.

The genetic code is a series of three mRNA nucleotides; each is a codon that encodes one amino acid (Fig. 1-4). Three codons are nonsense or termination codons. The genetic code is degenerate, with more than one codon for most amino acids.

FIGURE 1-4. Genetic code. The first base of each codon is presented vertically outside the left margin. The second base of each codon is presented horizontally above and below the chart. The third (wobble) position of each codon is presented just within the left margin.

GENES AND THEIR EXPRESSION

A gene is a unit of inheritance that carries the information representing a polypeptide or a structural RNA molecule. Genes are stable information packets transmitted from one generation to the next.

A gene includes “control” regions that precede and follow a central coding region and that include the sequences encoding the protein product. The coding region is preceded by a leader sequence and followed by a trailer. The leader and trailer are not translated into protein and represent the 5’ and 3’ untranslated regions of the mRNA that often function in regulating the half-life of the mRNA or in controlling translation.

The coding region is divided into alternating exons and introns. The exons, which are represented in the mature spliced RNA product, are interrupted or intervened by the introns. The introns are spliced out and do not encode amino acids. The reason for the introns is not obvious, but it is a hallmark of all higher order species in evolution. A gene family is a set of genes whose exons are related. A gene cluster is a group of genes related to each other that are adjacent.

Transcription is the process by which a single-stranded RNA is generated that is identical in sequence with the coding strand of the DNA. A transcription unit is a sequence of DNA that can be transcribed by RNA polymerase into a single RNA, beginning at an initiation start point and ending at a terminator.

Three types of genes are found in eukaryotes that are differentiated from each other by the type of RNA polymerase that transcribes the gene: RNA polymerase I, II, and III. RNA polymerase II produces heterogeneous nuclear RNA, which becomes mRNA after processing and splicing.

Proteins are encoded by mRNA. In the vast majority of cases, therefore, it is the protein product of a polymerase II gene that finally determines gene activity. The genetic code that transfers nucleotide sequences into amino acid sequences is organized as triplets of nucleotides forming a codon. Each codon is recognized by the translational machinery as representing an amino acid. Some codons are used as traffic signals that tell the machinery to start and stop translation (therefore their designation as start and stop codons). Mutations in important tumor suppressor genes, such as the breast cancer gene BRCA1 and the colon cancer gene APC, are frequently mutations that convert a codon that normally encodes an amino acid to a stop codon. This results in a prematurely truncated and, therefore, inactive protein.

A series of potential points for control of gene expression and functional protein production exist. These include activation of the gene chromatin complex, initiation of transcription, processing and capping of the RNA transcript, splicing of the RNA, polyadenylation of the RNA transcript, transport of the RNA to the cytoplasm, degradation of the RNA, translation of the mRNA into protein, correct folding and posttranslational modifications of the protein, transport and secretion of the protein, cleavage of the protein, or combination with inhibitors or activators.

In the nucleus, DNA exists in a complex with proteins to form chromatin. Structural changes occur to the chromatin to activate the regions of the DNA and unwind regions of the DNA. The eukaryotic chromosome is made from nucleosomes. A nucleosome contains approximately 200 base pairs (bp) of DNA that is wrapped around an octamer of histone proteins. In between the nucleosomes are linker regions that can be digested by DNAases. Transcribable active DNA is particularly sensitive to DNAases.

Between 2% and 7% of cytosines in animal DNA are modified by methylation, most often in sites where a C is followed by a G (CpG doublets). Methylation most often appears in genes that are not being expressed. DNA that is actively transcribed is often undermethylated. CpG-rich islands are often found upstream of constitutively transcribed genes near or at the promoters. This fact has been used by molecular geneticists to identify potential transcription units in large stretches of sequenced genomic DNA.

TRANSCRIPTION CONTROL: PROMOTORS AND ENHANCERS

A promoter is a region of DNA that is involved in binding of RNA polymerase (and associated factors) to initiate transcription and are therefore cis-acting sites. Promoters for polymerase I and II are usually located upstream of the transcription unit (initiation start point). Promoters for polymerase III are located downstream.

Transcription factors are trans-acting elements that recognize specific cis-acting sites in the promoter. Cis-acting sites can be spread over regions of DNA that are greater than 100 bp. In general, they can be tentatively identified by footprinting experiments that localize sequences covered by transcription factors. In this type of experiment, a putative promoter DNA binding sequence is allowed to bind to the transcription factor. The DNA is radioactively labeled, digested with nucleases, and then electrophoresed on a sequencing gel. In the region of the binding site, access to nuclease digestion is blocked because of the “footprint” of the transcription factor. Once a candidate promoter sequence is mapped, it is possible to directly test its ability to regulate expression of a reporter gene that is positioned downstream.

Promoters are characterized by short consensus sequences called boxes. The TATA box is usually located approximately 25 bp upstream from the start point of transcription. This consensus sequence of AT base pairs (e.g., TATAAAA) is important in the correct positioning of the RNA polymerase II (in concert with a series of transcription factors) at the beginning of the initiation site. The CAAT box (often GGGCAATCT) is located approximately 80 bp upstream of the transcription start point. A large number of different transacting factors recognize the CAAT box. Its role is to determine the strength (frequency or rate of initiation events) of the promoter. The GC box comprises the sequence GGCGGG. It is found in multiple copies in either orientation. The GC box, usually upstream of the TATA box, is the
binding site for the Sp1 transcription factor, which regulates the strength of the promoter. Enhancers are sequences that enhance initiation but may be located at a considerable distance from the start point upstream or downstream. Some enhancers have even been found within introns. Some transcription factors can bind to both promoters and enhancers. In retroviruses, enhancers are located in the viral long terminal repeats and are important for pathogenesis. Papillomaviruses contain enhancer elements that are specific for keratinocytes and thereby contribute to the specific tropism of the virus to these cells. Another example is the immunoglobulin cellular enhancer, which stimulates transcription in specific immune cell types.

Response elements are consensus sequences that allow specific transcription factors to coordinate the transcription of a whole group of genes that all have the consensus sequences. Examples are the heat shock response element, which responds to heat; the glucocorticoid response element, which responds to glucocorticoids; the metal response element; and the tumor promoting element (TRE). The TRE is a response element to TPA the carcinogenic promoting agent. It has the sequence TGACTCA. In response to TPA or phorbol ester, AP-1 transcription factors (a plurifunctional family including Jun and Fos) bind to the TRE.

**PROCESSING OF THE RNA TRANSCRIPT**

A cap is a complex methylated structure at the 5' end of mRNA that is essential for translation. The first base of a gene that is transcribed into an mRNA molecule is usually a purine (A or G). Almost immediately after transcription starts, a nuclear enzyme guanylyl transferase catalyzes the addition of a 5' G to the first transcribed base of the mRNA. This step is followed by a series of methylation events. The final cap structure maintains the stability of the mRNA transcript as it is forming.

Processing of RNA includes termination and polyadenylation. All eukaryotic mRNAs (except histone genes) contain a poly(A) tail at their 3' end, which is added by poly(A) polymerase. A consensus sequence called the polyadenylation signal AUAAA is located 10 to 30 bases upstream of the poly(A) tail. The polymerase transcribes through the polyadenylation signal, and after termination, an endonuclease cleaves the transcribed RNA at a site 10 to 30 bases downstream of the polyadenylation signal. The site of this event involves small nuclear ribonuclear particles. Once the cleavage occurs, the poly(A) polymerase adds A residues one by one to the 3' free end of the RNA. The poly(A) tail added to the end of the cleaved mRNA may assist the mRNA export out of the nucleus and may also be involved in the stability and lifespan of the mRNA molecule.

Processing of the transcribed RNA is required to remove the introns and produce a continuous linear sequence as a template for translation into the protein polypeptide. The coding region of a gene consists of exons and introns. Splicing is the mechanism by which the introns are removed from the precursor RNA to form a mature mRNA.

Splicing mechanisms differ depending on the type of RNA being spliced. Splicing of heterogeneous nuclear RNA requires a cap structure and is not complete until a poly(A) tail is added. The ends of the intron conform to the GT-AG rule, meaning that each intron in the gene begins with GT and ends with AG. The left 5' site is the donor site, and the right 3' site is the acceptor site. Alternative splicing refers to the possibility that there are variations in which exons are spliced together. A large complicated gene with many exons and introns can use alternative splicing to encode different proteins that are generated by different combinations of exons. Cellular genes for structural proteins, such as collagen, fibronectin, and myelin basic proteins, use alternative splicing to produce different proteins with different biologic functions. In this manner, a single gene can produce a number of protein isoforms using sequences within its "start" and "stop" borders.

Translation is the process by which the nucleotide sequence of mRNA is converted into a sequence of amino acids to make a protein. As mentioned, the genetic information of the mRNA is organized into triplets of bases called codons. Translation requires ribosomal RNA that combines with ribosomal protein to form ribosomes. The ribosomes are docking sites for adapter molecules, such as tRNA, that can recognize specific codons and the correct amino acid specified by that codon. Thus, the tRNA translates the base sequence of the mRNA into the different language of the amino acid sequence of the protein.

**REPAIR OF DNA**

Correction of DNA sequence errors is critical to survival. Environmental factors, including radiation, mutagenic chemicals, and thermal energy, can induce errors in the DNA sequence. In addition, errors are occasionally introduced by DNA polymerases during replication. A certain low level of random DNA errors may be required to generate genotype variation to fuel Darwinian evolution. Nevertheless, if most errors were left uncorrected, then both proliferating and nonproliferating cells would accumulate so much genetic damage that they would no longer be viable. Moreover, damage of DNA in germ cells can prevent normal offspring from developing.

Although a significant body of knowledge has been established on DNA polyadenylation proofreading and excision repair in E. coli, many of the enzymes required for repairing DNA damage in eukaryotic cells are now being characterized. DNA repair mechanisms have significant roles in carcinogenesis (see Chapter 2).

**READING THE GENETIC CODE AND PRODUCTION OF ENCODED PROTEINS**

**GENETIC CODE**

The genetic code refers to triplets of DNA or RNA and the amino acids they specify. A triplet code specifies 4 3 words; thus, there are 4 3 codons. The code is redundant because more than one codon can specify the same amino acid.

An open reading frame is a string of codons that are flanked on the 5' side by an initiation codon and on the 3' side by a termination codon. All proteins start with methionine. The codon AUG specifies methionine and is therefore the initiation codon. Termination or nonsense codons are stop signals for the end of a protein chain. They include the codons UAA, UAG, and UGA. Protein synthesis proceeds from the amino-terminus (N-terminus) to the carboxy-terminus (C-terminus).

Because of the triplet codon, each stretch of mRNA contains three potential open reading frames. The reading frame can be shifted by moving the starting point one or two bases to the right or left. Mutations in which a base is deleted or inserted within an exon are called frameshift mutations, because they would alter the reading frame of the sequence.

**RIBOSOMES**

Ribosomes are the protein synthesizing machinery that brings together the mRNA template and the charged tRNAs. The ribosomes contain two subunits. The small subunit is 40S; it contains 18S rRNA and 40 proteins and is responsible for binding the tRNAs and the tRNAs. The large subunit, which catalyzes peptide bonds between amino acids on the growing polypeptide chain, has three rRNAs of 28S, 5.8S, and 18S, as well as 50 proteins.

Every RNA has two properties: It can covalently link to the amino acid it recognizes to form a charged aminoacyl-tRNA, and it contains an anticodon that is complementary to the codon recognizing its amino acid. The anticodon recognizes the codon by complementary base pairing. Some of the base pairs in the third position can be nonstandard or can wobble. This permits one tRNA to recognize more than one codon.

**PROTEIN SYNTHESIS: INITIATION, ELONGATION, AND TERMINATION**

There are three general steps of protein synthesis: initiation, elongation, and termination. Initiation is the recognition by a specific initiating tRNA for the small ribosome subunit, along with guanosine triphosphate (GTP), and the initiating codon of the mRNA. A special tRNA binds to the small ribosome subunit, and a molecule of GTP correctly positions the initiating AUG codon of the mRNA on the ribosomal subunit. In concert with several initiating factors, the large ribosomal subunit now binds to the small subunit, met ferrying tRNA becomes localized to the ribosome at the P site (peptidyl-tRNA).

Elongation is the extension of the amino acid chain by introducing a second aminoacyl-tRNA to the proper site on the ribosome called the A site. With the help of elongation factors, the growing polypeptide chain is attached to the tRNA that brought in the previous amino acid. A peptide bond is formed between the carboxyl group of the methionine and the amino group of the incoming amino acid to make a dipeptide that is attached to the new tRNA. Peptide bond formation requires GTP hydrolysis, which furnishes energy for the reaction. Thus, each elongation step requires two GTPs. Elongation is continued with each new charged tRNA binding to the A site, peptide bond formation, and translocation of the peptidyl-tRNA to the P site (with displacement of the now uncharged tRNA from the P site). In each translocation, the ribosome moves three nucleotides downstream of the mRNA; therefore, more than one polypeptide chain can be produced from one mRNA.
are themselves mutated kinases that are rendered constitutively active [e.g., epidermal growth factor receptor (EGFR), bcr-abl] (Fig. 1-6). Enzymes catalyze these phosphorylations (e.g., src, HER2/neu, RET, and the retinoblastoma gene product). In fact, phosphatase and kinase enzymes themselves can be regulated by phosphate groups for hydroxyl groups on serine, threonine, or tyrosine. The activity of many critical enzymes in cancer biology is regulated by their state of phosphorylation.

Protein functions during cell signaling are also controlled by reversible side-chain modifications. A key modification is phosphorylation, which is the substitution of phosphate groups for hydroxyl groups on serine, threonine, or tyrosine. Special amino acids are cysteine, glycine, and proline. Amino acids with positively charged R groups are lysine, arginine, and histidine. Those with negatively charged R groups are glutamic acid and aspartic acid. Amino acids with hydrophobic R groups include alanine, isoleucine, leucine, methionine, phenylalanine, tryptophan, valine, and tyrosine. Special amino acids are cysteine, glycine, and proline.

PROTEIN STRUCURE AND FUNCTION

The result of the transcription-translation process is the generation of a protein polypeptide. Proteins, the working molecules of the cell, catalyze a diverse range of chemical reactions, act as information sensors, provide structural scaffolding for cells and extracellular tissue components, control membrane permeability, transduce signals, recognize and covalently bind other molecules, and control gene function.

This breadth of tasks are performed by biomolecules constructed from 20 different amino acids. A 100–amino acid protein has 20^100 possible structures. This enormous potential for variation means that cells and organisms can differ greatly in structure and function even though they are built from a limited number of biopolymer subunits using similar biochemical reactions.

Nineteen of the 20 amino acids contain an amino group (-NH2) and an acidic carboxyl group (-COOH). Proline has an imino group (-NH) instead of an amino group. All amino acids contain a carbon atom, called an alpha carbon, which is bonded to an amino (or imino) group, to the carboxyl group, to a hydrogen atom, and to one variable group called a side chain or R group. The side chains give the amino acids their individual characteristics. Amino acids with polar but uncharged R groups are serine, threonine, asparagine, and glutamine. Amino acids with positively charged R groups are lysine, arginine, and histidine. Those with negatively charged R groups are glutamic acid and aspartic acid. Amino acids with hydrophobic R groups include alanine, isoleucine, leucine, methionine, phenylalanine, tryptophan, valine, and tyrosine. Special amino acids are cysteine, glycine, and proline.

PROTEIN FOLDING INTO A COLLECTION OF FUNCTIONAL MOTIFS

Peptides are polymers composed of amino acids connected by peptide bonds. The peptide bond joins the carboxyl group of one amino acid to the amino group of the next amino acid. The nature of the peptide bond limits rotation around the alpha carbon and contributes to the three-dimensional spacing and folding of the protein. The newly synthesized protein adopts a three-dimensional conformation through noncovalent (ionic, hydrogen, van der Waals, and hydrophobic) interactions among the amino acids. The final conformation is stabilized by covalent disulfide bonds between cysteines in different parts of the chain, or between two different chains. Multiple different polypeptide chains can interact with each other by noncovalent forces or by covalent bonds, but polypeptide chains are never branched. Thus, remarkably, the complete three-dimensional shape of a protein is determined by its primary structure, which is the linear sequence of amino acids. The secondary structure of a protein pertains to the folding of parts of the protein into regular structures, such as a helices and b pleated sheets. The tertiary structure describes the interaction of these regular structures into compact domains. The quaternary structure is the final organization of several polypeptide chains (originally encoded by separate genes) into a single protein molecule. The final protein can fold to form a long structural support rod, such as collagen, or a compact ball (globular protein), as in many proteins that catalyze chemical reactions.

Large polypeptides often fold into several globular units rather than one huge unit. Most domains contain between 50 and 300 amino acids. In a water fluid environment, the domains of proteins usually contain a hydrophobic interior and a hydrophilic surface. A regular substructure that occurs in different domains is a motif. Specific motifs are associated with specific functions.

A good example is transcription factor proteins, which have characteristic DNA binding motifs in the protein primary and secondary structure. The helix-turn-helix structure exhibits an a helix, a turn, and a second a helix. An example is the homeodomain in homeobox proteins that regulate development and differentiation. Zinc finger proteins contain tandem repeats of a 30-residue motif that contains cysteine and histidine residues that bind zinc. The zinc finger binds to a consensus sequence GCCTGGGGCG on the DNA. Steroid receptors display a zinc binding domain different from the zinc finger and respond to steroid hormones (e.g., estrogen), retinoids, thyroid hormones, and vitamin D. The leucine zippers protein domain appears in many general transcription factors, including Jun and Fos. The zipper itself is a leucine-rich stretch of amino acids in a 30–to 40–amino acid region. The leucines are separated at regular intervals by six amino acids. A conserved repeat of hydrophobic residues is present; three residues to the N-terminal side of the leucines (valine or isoleucine). In addition, the leucine zipper proteins have a basic region that is rich in arginines and lysines. The basic region binds to the DNA, and the leucine zipper region forms two parallel a helices in a coiled-coil arrangement. In addition to DNA binding, the leucine zipper plays a role in protein dimerization. Molecules that bind with themselves form homodimers, and those that couple with other proteins form heterodimers. Examples are the homodimers Jun-Jun and the heterodimers Jun-Fos, members of the AP-1 binding proteins involved in transcriptional control.

PROTEIN POSTTRANSLATIONAL MODIFICATIONS

Proteins undergo several types of covalent and noncovalent modifications. These include the cleavage of the N-terminal methionine, the formation of disulfide bridges between two cysteine residues, or cleavage of a precursor polypeptide region. A large number of stable protein modifications can be made, including hydroxylation of proline and lysine in collagen, acetylation of lysine, methylation of histidine, attachment of carbohydrate groups to asparagine, presence of serine or threonine side chains, linkage to lipids, and addition of various groups to the N-terminal.

Protein functions during cell signaling are also controlled by reversible side-chain modifications. A key modification is phosphorylation, which is the substitution of phosphate groups for hydroxyl groups on serine, threonine, or tyrosine. The activity of many critical enzymes in cancer biology is regulated by their state of phosphorylation (e.g., src, HER2/neu, RET, and the retinoblastoma gene product). In fact, phosphatase and kinase enzymes themselves can be regulated by phosphorylation. The phosphorylation is mediated by enzymes called kinases and removed by enzymes called phosphatases. Thus, the phosphorylation cascade provides a simultaneous means of information exchange, amplification, pathway channeling, and regulation. Its importance in cancer is the fact that many oncogenes are themselves mutated kinases that are rendered constitutively active [e.g., epidermal growth factor receptor (EGFR), bcr-abl] (Fig. 1-6). Moreover, some tumor
suppressor genes are strong regulators of kinases (e.g., p16, p27).

![Figure 1-6: Oncogenes can arise from protooncogenes that encode cell-surface receptors. On the left, the epidermal growth factor (EGF) receptor becomes oncogenic by loss of the coding region for the extracellular domain. On the right, the neu ERB-2 oncogene encodes a protein with a single amino acid substitution in the transmembrane domain.]

**SUBCELLULAR MOLECULAR STRUCTURE**

**PLASMA MEMBRANE**

Both prokaryotic and eukaryotic cells are enclosed in a plasma membrane. In addition, most eukaryotic cells contain extensive internal membranes interconnected to the plasma membrane. These internal pockets and sacs define a collection of subcellular organelles. The largest organelle is the nucleus. Examples of other organelles are mitochondria (oxidation of small molecules to generate adenosine triphosphate); rough and smooth endoplasmic reticula, a network of membranes in which glycoproteins and lipids are synthesized; Golgi vesicles, which channel membrane constituents to correct locations in the cell; and lysosomes, which degrade proteins. The organelles maintain a specific, demarcated, confined chemical environment (such as an acid pH in the case of lysosomes) and contain a host of bound enzymes that catalyze requisite chemical reactions.

**NUCLEUS**

Chromosomal DNA in eukaryotic cells is wrapped in a set of five different positively charged proteins called histones. Histone-DNA interactions occur at regular intervals. Every sequence of 150 to 180 bp of DNA is bound to one molecule of histone H1 and to two molecules each of histones H2A, H2B, H3, and H4.

The eukaryotic nucleus is surrounded by two membranes containing phospholipids. The outer membrane is continuous with the cytoplasmic membrane system. The space between the inner and outer membrane communicates with the lumenal cavity of the rough endoplasmic reticulum. The inner membrane defines the nucleus proper. Fibrous proteins called lamins form a two-dimensional network on the inner surface of the inner membrane. Ring-like nuclear membrane pores, formed from a special set of membrane proteins, are regulated channels for the movement of material between the nucleus and the cytoplasm.

The nucleolar organizer, a region of one or more chromosomes in the nucleolus, is a focal point for synthesis of ribosomal RNA. Generated ribosomal subunits pass through the nuclear pores into the cytoplasm.

**CYTOPLASM**

The cytoplasm is the region outside the nucleus of eukaryotic cells, and it contains an array of fibrous proteins collectively constituting the cytoskeleton. The most abundant cytoskeleton components are microfilaments, which are built of actin; slightly wider microtubules, made of tubulin; and intermediate filaments, built of a set of rod-shaped protein subunits. The cytoskeleton is not just a structural scaffold, it plays critical roles in cell movement, differentiation, intracellular trafficking, cell division (microtubules mediate chromosome movement), and signal transduction. Some of the most active chemotherapeutic agents, such as the taxanes and the vinca alkaloids, directly affect microtubular assembly as their primary mode of action.

The plasma membrane surface is highly specialized to interact with the environment according to the functional requirements of the individual differentiated cell. Proteins on the surface of the plasma membrane include enzymes and receptor proteins. One type of receptor protein is a transmembrane receptor. The receptor, like a channel protein, has a hydrophobic transmembrane domain. The receptor for the EGF-related ligands (EGFR). Included in the EGFR family is the ERB2/Neu receptor, which plays a major role in the biological function of human breast cancers. When mutated, the RET oncogene encodes a protein with a single amino acid substitution in the transmembrane domain.

**MEMBRANE PROTEINS**

Proteins interact with membranes using a variety of mechanisms. Integral membrane proteins contain amino acid residues with hydrophobic side chains that interact with the fatty acyl groups of the membrane phospholipids. Other integral proteins contain covalently bound fatty acids that function as anchors in the hydrophobic lipid bilayer. An important example is the farnesyl residue of the oncogene p21 ras (the mutant of the normal cellular small g protein) and the myristate residue of the v-src tyrosine kinase oncogene (the mutant of the normal cellular protein c-src). The farnesyl residue is linked by a thioester bond to a cysteine residue four amino acids from the C-terminus of the protein, and then the three C-terminal residues are cleaved off. Myristate is bound by an amide linkage to the glycine residue found at the N-terminus. Cancerous transformation by such oncogenes requires the membrane-attachment function of these covalently attached lipids.

**MOLECULAR ONCOGENESIS: CELLULAR SIGNAL TRANSDUCTION**

Mutations that cause cancer are those that alter the ability of the cell to maintain genetic stability, such as mutations in repair genes, or those that alter the transmission of signals that control the machinery of cell growth and survival (Fig. 1-7). The transmission of signals within the cell and from inside and outside the cell is called signal transduction. Surface receptors are the sensors providing the cell’s window to the outside environment. Most receptors fall into one of three general types depending on the signal transduction mechanism used. Channel-linked receptors are ligand-gated ion channels involved in rapid synaptic signaling. These receptors belong to a family of homologous multipass transmembrane proteins. Catalytic receptors are activated by a ligand to operate directly as enzymes. Most of the known catalytic receptors are transmembrane proteins with a cytoplasmic domain that normally accepts controlled signals from outside the cell and transmits signals to the inside of the cell. Many of these proteins function as a tyrosine-specific protein kinase. An important example is the receptor for the EGF-related ligands (EGFR). Included in the EGFR family is the ERB2/Neu receptor, which plays a major role in the biological function of human breast cancers. When mutated, the RET oncogene is activated and associated with both hereditary and sporadic thyroid cancers, and overexpression of the MET protooncogene leads to increased cell motility and metastatic potential. Conversely, the normal function of the transforming growth factor-beta pathway is to suppress growth and oncogenesis. When mutated, the inactivation of the ligand or receptor renders the cell susceptible to transformation. Intracellular kinases that do not transmit signals across the cell membrane but potentially within the cell are also important in oncogenesis. The ABL kinase is activated when participating in the bcr-abl translocation. The majority of these transmembrane receptors normally transduce signals through the controlled phosphorylation of intracellular substrates, usually on tyrosine, serine, or threonine residues that function as signaling nodes in a complex intracellular communications network. The control of phosphorylation and dephosphorylation events are used by cells to relay signals, amplify signals, and regulate pathways and to act by changing the conformation and, therefore, the function of the phosphorylated protein. Any member of a signaling cascade can be a potential target for oncogenic mutation.
A third class of receptors is the G protein–linked receptors. These sensors indirectly activate or inactivate a separate membrane-bound enzyme or ion channel. The interaction takes place through an intermediary protein, the GTP-binding regulatory protein (G protein). The G protein-linked receptors activate a cascade of downstream intracellular messengers. The messengers in turn activate or regulate other target proteins in the cell. Important intracellular messengers are calcium ions, cyclic adenosine monophosphate, and phospholipids.

The Gs protein functions as a shuttle between two membrane proteins: the receptor for the stimulus and the downstream effort enzyme (adenyl cyclase), which generates the second messenger. Thus, Gs is a signal transducer, relaying to the recipient enzyme the conformational change in the receptor triggered by the ligand binding to the receptor (Fig. 1-8). The Gs protein cycles between active and resting forms, which are determined by the state of its subunits. Gs is composed of three polypeptides: an a chain Gsa, which binds and hydrolyzes GTP and activates adenyly cyclase, and a tight complex of a b chain and a g chain GBg, which anchors Gs to the cytoplasmic face of the plasma membrane. In the resting state, Gsa contains bound guanosine diphosphate (GDP) and is coupled to GBg. When GTP binds to Gsa, it is hydrolyzed to GDP by the reaction: Gsa + GTP \( \rightarrow \) Gsa + GDP + inorganic phosphate. The change in the receptor conformation is passed on through the Gag to the Gsa and causes GDP to be replaced by GTP. When GTP is bound to Gsa, the Gsa dissociates from the GBg subunits. When GTP is bound to Gsa, a conformational change that enables it to bind and activate adenyly cyclase. In a resting cell, most Gs molecules contain GDP. Binding to a hormone or agonist changes the conformation of the receptor protruding on the inner surface of the membrane. The altered receptor can now bind Gs, causing GDP to be displaced and GTP to be bound. The GTP-bound form of Gsa then acts as a shuttle that translocates to bind adenyly cyclase and activate it to hydrolyze adenosine triphosphate to cyclic adenosine monophosphate and inorganic phosphate. Immediately after activation of adenyly cyclase, Gsa hydrolyzes bound GTP to GDP and returns to its coupled state with GBg.

All receptors that interact with a G protein share a common stretch of 22 to 24 hydrophobic amino acids that generate seven back and forth trans membrane a helixes. A large loop between helices 5 and 6 protrudes into the cytosol and interacts with the G protein.

In cancer, the most important G proteins are found in the ras family of oncogenes: N-ras, K-ras, and H-ras. Specific mutations of the normal cellular ras protein causes it to be activated by disarming its GTPase activity. This renders the protein incapable of converting its active GTP-bound form into the inactive GDP-bound form. Thus, mutant ras proteins are constitutively “on” and are oncogenic. The downstream consequences of ras activation are through the induction of cellular proliferation and in enhancing cell motility. Ultimately, these membrane and cytoplasmic signaling molecules all converge to alter cellular transcription through the activation of transcription factors (see Fig. 1-7). Oncogenesis can be initiated by a molecular lesion that disrupts this cascade at any level, from the ligand or receptor all the way to the nuclear transcription factor (Table 1-1). In cancer biology, there is ample evidence of direct mutational activation of transcription factors in the genesis and maintenance of the cancerous state. Myc, AML1, MLL, and the homeobox proteins are all examples of altered transcriptional machinery in the induction of human cancers.
nature, one finds oncogenic mutations in members of signaling pathways. For example, the receptor tyrosine kinase (EGFR; mutated or overexpressed in brain and epithelial cancers; related retroviral oncogene, v-erbB), when stimulated with one of its ligands, transforming growth factor-a (overexpressed in some human cancers), interacts with ras (retroviral homologue, v-H-ras or v-K-ras; mutated in 10% to 20% of human cancers) through bridging proteins. Ras is controlled by GTPase-activating proteins (oncoproteic homologue is NF1, the gene involved in neurofibromatosis) and transmits signals by activating ras (retroviral homologue, v-ras). Signaling through the ras/raf pathway results in increased expression of the nuclear proteins jun, fos, and myc (retroviral homologues, v-jun, v-fos, v-myc). These are also targets of genetic mutations. Mutations in ras alleles result in the constitutive activation of the ras signaling pathway, leading to cell proliferation and transformation.

When the ras/raf pathway is activated, it leads to the phosphorylation and activation of MAP kinases, which regulate the expression of genes involved in cell proliferation and survival. The activation of MAP kinases can lead to the phosphorylation and inactivation of proteins such as p53 and p21, which are important tumor suppressor genes. The inactivation of p53 leads to the accumulation of genetic mutations and the development of cancer.

In summary, the ras/raf pathway is a critical signaling pathway in cancer development. It is involved in the regulation of cell proliferation, survival, and migration. Mutations in the ras/raf pathway can lead to the activation of downstream signaling pathways, which can promote cell proliferation and survival.

**THE WRONG PLACE AT THE WRONG TIME**

In human cancers, mutations in protooncogenes result in altered function. However, inappropriate expression of structurally normal proteins may have no role in the biology of a specific tissue can also lead to cancer. Several transcription factors are involved in this process:

- **MYC**
  - Activates genes involved in cell proliferation and survival
  - Associated with cancer development in many tissues

- **Rb**
  - Inactivates genes involved in cell proliferation and survival
  - Associated with cancer development in many tissues

- **P53**
  - Inactivates genes involved in cell proliferation and survival
  - Associated with cancer development in many tissues

**RELEASE OF SUPPRESSION**

Whereas protooncogenes are identified by a gain of function after mutational damage, another class of cancer genes, tumor suppressor genes, contribute to cancer induction by a loss of function. To this end, tumor suppressor genes, such as the retinoblastoma gene (Rb-1) and p53, block cell proliferation, and each appears to function through distinct pathways. Rb-1 negatively regulates the important transcription factor E2F, and the deletion of the Rb gene (seen in congenital retinoblastoma) releases the suppression of E2F. p53 enhances the expression of p21/CIP1, which is a suppressor of cell-cycle regulatory kinases (cyclin-dependent kinase inhibitors). Activation of these CDKs is necessary for progression through the cell cycle, and CDK inhibitors, such as p21/CIP1, block this process. Thus, the loss of p53 and the attenuation of p21/CIP1 expression result in unmanaged progression through the cell cycle.

Both Rb and p53 are involved in the genesis of cancer is evident by the identification of germline mutations of these genes in individuals with cancer predisposition syndromes, such as congenital retinoblastoma (RB) and the Li-Fraumeni syndromes (p53). As with oncogenes, the presence of a single abnormal tumor suppressor allele alone is insufficient for cancer to develop; lesions at other genetic lesions are necessary. For example, both Rb and p53 may need to be inactivated for some normal cells to be rendered immortal. The DNA tumor virus, the human papillomavirus (HPV) that is the causative agent in cervical, anal, and penile carcinomas, inhibits both these critical proteins through binding with and inactivation by the HPV viral proteins E6 and E7. In this manner, HPV biochemically achieves the same result that carcinogens accomplish through inactivating genetic mutations. In colon cancers, mutations in p53 are frequently associated with other genetic lesions, including those involved in cytoskeletal organization (APC), signal transduction (Cdk), and cell motility (DCC) in the progression toward an invasive cancer.

A tumor suppressor gene can be defined as any gene whose loss of function contributes to cancer progression. One category of suppressor genes are the inhibitors of the CDKs, which are enzymes that control the progression through the cell cycle. They, in turn, are controlled by protein activators (called cyclins) and inhibitors (called CDK inhibitors). The attenuation of expression of CDK inhibitors, such as p16, p27, and p57, has been associated with a diverse range of cancers, from lung to head and neck. Inactivating mutations in the CDKs, such as cdc2, which causes cell cycle withdrawal or DNA damage, can trigger a cascade of events culminating in activation of intracellular proteases. These activated proteases then lead to the regulated cleavage of cellular components, including proteins and DNA, and ultimately to cell death. The cell exerts exquisite control of this process using redundant systems to induce or block apoptosis, and some of these control switches are involved in cancer and cancer treatment.

**CELL DEATH**

Earlier on, the study of molecular oncogenesis concentrated on processes that stimulated growth. However, the accumulation of cancer cells can also be accomplished by a decrease in cell loss as well as by an increase in cell proliferation. Current evidence suggests that the abrogation of programmed cell death (apoptosis) is an important mechanism for neoplastic transformation. Certain cellular processes, such as cytokine signaling (e.g., tumor necrosis factor, interleukin-2), may be among the earliest cellular events that act to accumulate genetic mutations. A cellular event that promotes cell death, such as a decrease in cell loss or DNA damage, can trigger a cascade of events culminating in activation of intracellular proteases. These activated proteases then lead to the regulated cleavage of cellular components, including proteins and DNA, and ultimately to cell death. The cell exerts exquisite control of this process using redundant systems to induce or block apoptosis, and some of these control switches are involved in cancer and cancer treatment.

The clearest example of an oncogene modulating the apoptotic process is in bcl-2, found to be the oncogene involved in the t(14;18) translocation frequently found in follicular lymphomas. bcl-2 blocks apoptosis when overexpressed or inappropriately expressed, and in lymphomas, translation involving bcl-2 may be among the earliest cellular events that act to accumulate genetic mutations. bcl-2-related proteins that promotes cell death. Therefore, augmented Akt function induced by ligand receptor interactions is predicted to have an antiapoptotic effect. It is not clear why certain tumors genetically alter bcl-2 to alter apoptotic pathways. The introduction of molecular tools to manipulate normal cells towards self-sufficing mechanisms that activate suicide programs. When the mitochondrial load of a cell exceeds a critical level, self-destruct processes are activated. Cancer, however, may result when genetically abnormal cells are not cleared but are allowed to proliferate, thus accumulating mutations potentially in important cancer genes.

**GENETIC INSTABILITY**

A characteristic of a cancer cell is its ability to generate and to sustain genetic mutations. Normal cells not only have the ability to identify and repair DNA damage, but also to prevent the expansion of mutation-laden daughter cells by suicide mechanisms such as apoptosis. Defects in DNA repair found in rare disorders such as xeroderma and ataxia-telangiectasia are associated with cancer risk. More recently, however, common human cancers have been linked to abnormalities in repair processes. One example is the hereditary nonpolyposis colon cancer (HNPCC) syndrome. HNPCC is an inherited syndrome characterized by increased risk for colon cancer without the associated polyposis seen in another hereditary cancer syndrome, adenomatous polyposis coli. Affected individuals with HNPCC show signs of a defect in the repair of DNA mismatches. Additions or reductions in the number of two nucleotide repeats found in human DNA (called microsatellite instability) were clonally detected in their tumors. This type of DNA abnormality is a signature for a form of repair defect previously studied in bacteria and yeast. When incorrectly paired nucleotides occur in a DNA duplex, either through misincorporations or nucleotide damage, cells use a mismatch repair system to identify and remove the mismatch. This recognition and cleavage is mediated by the protein products of the MSH2, MSH3, MSH6, MLH1, PMS1, and PMS2 genes. Hereditary patients have primarily mutations in MSH2 and MLH1, although mutations in the other mismatch repair genes are also found. The clinical consequence of this molecular defect in humans is the emergence of colon cancers that differ from the sporadic variety and that are characterized by fewer ras and p53 mutations, as well as fewer allelic losses. Moreover, colon cancer in HNPCC patients appear to have a better prognosis than their sporadic counterparts.

Advances in molecular biology and their application to cancer research have revolutionized our understanding of cancer biology. Genes, proteins, and signaling pathways are now being studied in detail to understand the molecular mechanisms that drive cancer development. This understanding is expected to lead to the development of new therapies that target specific molecular abnormalities in cancer cells.
neoplasms, in different tissues, and even in the same type of pathology. Nevertheless, elucidating each new molecular pathway involved in cancer provides strategies for diagnosis, intervention, and treatment. Thus, a molecular understanding of cancer clarifies why curing this disease is so difficult, while at the same time, this knowledge provides more precise targets for treatments in the future.

SUGGESTED READINGS

CHAPTER 2
Essentials of Molecular Biology: Genomics and Cancer

UNDERSTANDING CANCER AT THE MOLECULAR LEVEL: THE NEW FRONTIER

Genomic and proteome research is a new frontier for the molecular characterization of cancer. The ongoing revolution in molecular medicine can be divided into three phases. The first phase is gene discovery, in which the tools of molecular biology are applied to identify and sequence previously unknown genes. Identification of most of the expressed human genes will be accomplished before 2002. The second phase is molecular fingerprinting, which correlates the genomic state, the cDNA expression pattern, and the protein repertoire with the functional status of the cells or tissue. The promise of this phase is that expression profiles can uncover clues to functionally important molecules and will generate information to tailor a treatment to the individual patient. The third phase is the synthesis of proteomic information into functional pathways and circuits in cells and tissues. This must take into account the dynamic state of protein posttranslational modifications and protein–protein or protein–DNA interactions. Through an integrated genomic and proteomic analysis, the ultimate outcome will be an actual functional understanding of the molecular events underlying normal development and disease pathophysiology. This higher level of functional understanding will be the basis for true rational therapeutic design.

Progress in these three phases of molecular medicine is largely driven by new technologies. The development of polymerase chain reaction (PCR), high throughput sequencing, and bioinformatics has been a driving force in the first phase. In the second phase, microhybridization arrays applied to genetic analysis and gene expression are a powerful new tool that has entered the commercial sector and is becoming widely available to researchers. As more genes are identified, it is likely that specialized arrays will be offered that are specific for a tissue type (e.g., mammary gland chip), physiologic process (e.g., apoptosis chip, angiogenesis chip, invasion chip), or class of genes (e.g., suppressor gene chip, oncogene chip).

GENETIC MECHANISMS OF CANCER PROGRESSION: CANCER IS A GENETIC DISEASE

Cancer is a genetic disease. Progression from normal tissue to invasive cancer takes place over 5 to 20 years and is influenced by hereditary genetic factors as well as somatic genetic changes (Fig. 2-1). Cancer progression is driven by a series of accumulating genetic changes. Some genetic oncogenic changes contribute to uncontrolled growth or loss of senescence. Some oncogenes cause uncontrolled growth by activating persistent growth stimulatory signal transduction pathways. Some oncogenes cause uncontrolled growth by altering critical nodes in the cell cycle. Uncontrolled growth can be caused by deregulation at the level of DNA transcription factors.

Separate genetic changes (beyond those causing uncontrolled growth) are required for tumor invasion and metastasis. Invasion and metastasis form a multistep cascade involving positive and negative regulatory pathways. Cancer invasion and angiogenesis are an uncontrolled version of physiologic invasion.

Genetic instability may predispose the premalignant cell to generate malignant offspring. Instability can take place at the macro level (chromosome karyotype), as well as the micro level (DNA sequence copy fidelity repair). Chromosomal rearrangement can activate silent oncogenes or delete regions containing suppressor genes. Loss of heterozygosity is a hallmark of suppressor gene inactivation in cancer progression. Telomerase defects may affect growth control as well as genetic instability. Mutations in cellular DNA can activate oncogenes or inactivate suppressor genes. Defects in DNA repair mechanisms contribute to the accumulation of genetic defects fueling cancer progression. Genetic defects causing an inhibition of cell death pathways are an important mechanism in tumorigenesis.

CANCER GENES: MODELS OF ACTION

Genetic alterations involved in cancer can activate inductive processes (oncogenes) or block negative pathways (suppressor genes). Early models of cancer genetics categorized cancer genes into oncogenes, which are growth inducing, and tumor suppressor genes, which are growth suppressing. Thus, mutations in oncogenes activate a promoting function, but lesions in tumor suppressors inactivate an inhibitory function. Examples of these models were the ras oncogene and the retinoblastoma (rb) tumor suppressor gene. Mutations in codons 12, 13, and 61 in the ras gene result in biochemical activation of the protein product and an induction of its transforming activity. Deletions or inactivating mutations in the rb gene lead to a compromised suppressor protein that is incapable of inhibiting cell growth. Aberrations in both genes are found as somatic mutations in human cancers and, in the case of rb, also in the germline of individuals at risk for cancer.

Dominant oncogenes play a significant role in human cancers. Ras mutations are found in 10% of cancers and appear frequently in colon and lung adenocarcinomas. Rho is a receptor tyrosine kinase in which activating single nucleotide mutations are associated with hereditary thyroid carcinomas. Myc, encoding a nuclear oncprotein, is involved in the (6;14) translocation, which is etiologic for Burkitt’s lymphoma. Inappropriate overexpression of myc is sufficient for transformation of lymphocytes in transgenic models. Similarly, amplification and overexpression of the HER2/neu receptor tyrosine kinase not only causes mammary malignancies, but is prognostic in human breast cancers. Although originally these oncogene abnormalities were thought to induce cancer primarily through unregulated growth, other cellular phenotypes such as enhanced survival and motility may be equally important contributors to the cancer state.

It was also originally thought that tumor suppressor genes function mainly by inhibiting cell growth. Later, this was expanded to genes that block the emergence of a tumor, but not growth in culture. More recent studies, however, have uncovered other mechanisms unrelated to growth by which tumor suppressor genes act to inhibit cancer formation. In fact, it now seems that the inhibition of growth may not be the most important function of these genetic suppressors. Wild-type (or the normal) p53...
is able to slow the proliferation of cancer cells in culture, and naturally occurring mutants of p53 lose this capability. However, many cell lines grow well with both normal p53 and rb genes, suggesting that they are not necessary for cellular proliferation (reviewed in Chapter 1). In the case of p53, one of its major roles is in DNA repair. As it appears, the regulation of growth is coupled with the regulation of DNA repair. When cells suffer DNA damage, cellular hibernation manifested by an arrest at the G1 or G0 checkpoints permits repair to take place and prevents the accumulation of mutant sequences. Cells harboring mutant p53 genes lose the ability to repair DNA, and every exposure to gamma irradiation or other genotoxins. Mice with p53 gene disruptions are completely viable, but exhibit an enhanced rate of tumor formation. Loss of the p53 homolog G17 at sites of DNA damage and the abrogation of growth arrest and apoptosis. Cells without a functional p53 show an increased ability to amplify their DNA. This measure of genetic plasticity is characteristic of cancer. In addition, a mutant p53 renders cells less likely to undergo apoptosis after cellular stress including gamma irradiation and chemotherapy agents. Normal cells that experience a high level of DNA damage, overwhelming their repair capabilities, trigger cell death. This appears to be a mechanism to prevent the accumulation of cells harboring mutated p53 genes. Taken together, these data suggested that the primary role of p53 is not to regulate growth, but to maintain the genetic integrity of a cell.

We know that other important tumor suppressors have similar policing functions. BRCA1 and BRCA2 are structurally unrelated genes with converging clinical effects: Dysfunctioning mutations in either gene render an individual more susceptible to breast and ovarian cancer. Although both genes carry the hallmarks of a tumor suppressor gene, their main function is not growth regulation. In gene function experiments, BRCA1 is able to inhibit cellular growth only under limited conditions, possibly in cells with an intact retinoblastoma gene product. In other experiments, however, BRCA1 and BRCA2 paradoxically appear to be associated with signs of growth promotion. Both are increased at S phase, and mouse embryos that have either gene disrupted die in utero exhibiting an increase in the cell-cycle inhibitor p21 and a reduction in the cell-cycle inducer Bcl-2. The mutant BRCA1 and BRCA2 gene products disrupt both pathways. More important, however, is the finding that BRCA1 and BRCA2 are both associated with each other and with DNA repair proteins RAD51 and PCNA, especially after DNA damage. The functional conserved nature of this association are exemplified by the experimental data. Cells from a BRCA1 null mouse are defective in transcription-coupled DNA repair. BRCA2 null cells are exclusively sensitive to gamma irradiation and to chemotherapeutic agents. It is remarkable that two structurally dissimilar proteins interact with the same biochemical entities and lead to similar disease phenotypes. Thus, the fundamental lesson learned from BRCA1 and BRCA2 is that the primary causes of breast cancer may be related to DNA damage and repair and not to excessive growth.

The primary repair of overgrowth is reduced in AML, exhibits an increase in the counts of hematopoiesis, and is generally involved in the recognition and repair of mutations between complementary DNA strands. When these mismatch repair (MMR) genes are mutated, the mechanism for the correction of nucleotide mismatches is defective. This defect leads to an increased risk of gastrointestinal (especially colorectal) and endometrial cancers. Oncoproteins such as p53 not only act to induce a cell-cycle arrest in order for DNA repair to complete, but also promotes apoptosis to eliminate damaged cells with a high cancer potential. Therefore, an attenuation of the apoptosis mechanism is therefore likely to support transformation. The cancer susceptibility gene, PTEN/MMAC, is an example of a genetic guardian whose primary function is to regulate cell death and survival. PTEN, localized to 10q23, was identified through positional cloning as the gene responsible for Cowden's syndrome, an autosomal dominant condition characterized by gastrointestinal hamartomas, cutaneous trichilemmomas, and increased rates of breast (25% to 50%) and thyroid cancers (3% to 10%), as well as uterine leiomyomas. Although germline PTEN mutations are distinctive for a relatively rare disorder, somatic mutations leading to the loss of PTEN function are detected in a large number of sporadic cancers including high-grade gliomas, thyroid cancers, and endometrial cancers. Transfection of the wild-type PTEN cDNA inhibits growth in established cell lines, and mice with one disrupted PTEN allele exhibit high rates of tumor formation, especially lymphomas, teratocarcinomas, and liver and prostatic cancer. Thus, PTEN fulfills the classic criteria of a tumor suppressor.

Functionally, PTEN is as a multifunctional phosphatase that removes phospho groups from tyrosine and serine residues as well as from phospholipids such as phosphatidylinositol second messengers. The most important biochemical consequence of PTEN is to desensitize/ALT/PTK pathway in gastrointestinal carcinogenesis. It has been long understood that the peptide factor TGF-b can inhibit tumor formation, and that tumor progression is associated with loss of response to TGF-b. This loss of response now appears to be due to the disruption of the type II TGF-b receptor. TGF-b functions by inducing heterodimers between the C-S domain and II receptor (TGF-bRI and TGF-bRII), resulting in the phosphorylation of the type I receptor and activation of downstream pathways. More recently, it has been found that many of the familial colorectal cancers, essentially colorectal cancers, harbor a short polyadenine tract within the gene that generates a truncated TGF-b protein bearing defective kinase activity. Interestingly, this frameshift mutation occurs most commonly in cancers with concomitant abnormalities in mismatch repair (MMR) as seen in patients with hereditary nonpolyposis colorectal cancer. Moreover, this mutational switch occurs during the conversion from colorectal adenoma to malignant carcinoma. Further downstream, the TGF-b signaling pathway requires engagement by the activated receptors and phosphorylation of the SMAD proteins. Activated SMADs form heterodimers between SMAD1 or SMAD2 with SMAD4 and are transported to the nucleus where they interact with DNA-binding proteins to induce transcription of TGF-b-responsive genes. The importance of this pathway is that SMAD4, which is an essential component in the TGF-b signaling pathway, has been found to be disrupted in 50% of human pancreatic cancers and to a lesser extent in gastric, breast, ovarian, and prostatic cancers. Thus, the TGF-b pathway alone engages three functional nodes with significant roles in human cancers: mismatch repair, TGF-bRI, and SMAD4. The complexity lies in the fact that these elements are connected not only by biochemistry, but genetics and peculiarities in DNA sequence. It is, therefore, with the use of many of the analytical tools described previously that these relationships can be uncovered.

MOLECULAR PROFILING: DIAGNOSIS AND TREATMENT TAILORED TO THE INDIVIDUAL PATIENT

The concept of employing tumor characteristics such as histologic features as a predictor of best treatments has long been part of the practice of oncology. For example, not only are the natural histories of the lymphomas different, but the requirements for optimal therapy are distinct: Burkitt's lymphomas require high-dose alkylator chemotherapy to achieve optimal cure rates, whereas doxorubicin-based therapies are optimal for large cell lymphomas. A dramatic example of the convergence of oncogenic processes is seen in the analysis of the transforming growth factor-b (TGF-b) pathway in gastrointestinal carcinogenesis. It has been long understood that the peptide factor TGF-b can inhibit tumor formation, and that tumor progression is associated with loss of response to TGF-b. This loss of response now appears to be due to the disruption of the type II TGF-b receptor. TGF-b functions by inducing heterodimers between the C-S domain and II receptor (TGF-bRI and TGF-bRII), resulting in the phosphorylation of the type I receptor and activation of downstream pathways. More recently, it has been found that many of the familial colorectal cancers, essentially colorectal cancers, harbor a short polyadenine tract within the gene that generates a truncated TGF-b protein bearing defective kinase activity. Interestingly, this frameshift mutation occurs most commonly in cancers with concomitant abnormalities in mismatch repair (MMR) as seen in patients with hereditary nonpolyposis colorectal cancer. Moreover, this mutational switch occurs during the conversion from colorectal adenoma to malignant carcinoma. Further downstream, the TGF-b signaling pathway requires engagement by the activated receptors and phosphorylation of the SMAD proteins. Activated SMADs form heterodimers between SMAD1 or SMAD2 with SMAD4 and are transported to the nucleus where they interact with DNA-binding proteins to induce transcription of TGF-b-responsive genes. The importance of this pathway is that SMAD4, which is an essential component in the TGF-b signaling pathway, has been found to be disrupted in 50% of human pancreatic cancers and to a lesser extent in gastric, breast, ovarian, and prostatic cancers. Thus, the TGF-b pathway alone engages three functional nodes with significant roles in human cancers: mismatch repair, TGF-bRI, and SMAD4. The complexity lies in the fact that these elements are connected not only by biochemistry, but genetics and peculiarities in DNA sequence. It is, therefore, with the use of many of the analytical tools described previously that these relationships can be uncovered.

The current state of knowledge of tumor suppressors shows a picture of complex interactions between multiple suppressor genes with oncogenes to generate the malignant state. A dramatic example of the convergence of oncogenic processes is seen in the analysis of the transforming growth factor-b (TGF-b) pathway in gastrointestinal carcinogenesis. It has been long understood that the peptide factor TGF-b can inhibit tumor formation, and that tumor progression is associated with loss of response to TGF-b. This loss of response now appears to be due to the disruption of the type II TGF-b receptor. TGF-b functions by inducing heterodimers between the C-S domain and II receptor (TGF-bRI and TGF-bRII), resulting in the phosphorylation of the type I receptor and activation of downstream pathways. More recently, it has been found that many of the familial colorectal cancers, essentially colorectal cancers, harbor a short polyadenine tract within the gene that generates a truncated TGF-b protein bearing defective kinase activity. Interestingly, this frameshift mutation occurs most commonly in cancers with concomitant abnormalities in mismatch repair (MMR) as seen in patients with hereditary nonpolyposis colorectal cancer. Moreover, this mutational switch occurs during the conversion from colorectal adenoma to malignant carcinoma. Further downstream, the TGF-b signaling pathway requires engagement by the activated receptors and phosphorylation of the SMAD proteins. Activated SMADs form heterodimers between SMAD1 or SMAD2 with SMAD4 and are transported to the nucleus where they interact with DNA-binding proteins to induce transcription of TGF-b-responsive genes. The importance of this pathway is that SMAD4, which is an essential component in the TGF-b signaling pathway, has been found to be disrupted in 50% of human pancreatic cancers and to a lesser extent in gastric, breast, ovarian, and prostatic cancers. Thus, the TGF-b pathway alone engages three functional nodes with significant roles in human cancers: mismatch repair, TGF-bRI, and SMAD4. The complexity lies in the fact that these elements are connected not only by biochemistry, but genetics and peculiarities in DNA sequence. It is, therefore, with the use of many of the analytical tools described previously that these relationships can be uncovered.

Many of the genes involved in these leukemia translocations have now been cloned and biochemically characterized. The t(9;22), characterizing common chronic myelogenous leukemia, involves the translocation between bcr on chromosome 22 and the tyrosine kinase abl on chromosome 9. The chimeric bcr-abl oncoprotein activates the abl kinase and the ras pathway and blocks apoptotic processes in hematopoietic precursors. In acute lymphoid leukemias, one of the major discriminating factors also appears to be the presence of the bcr-abl rearrangement as exemplified by the t(9;22) translocation. The Philadelphia chromosome (Ph1) and the resultant bcr-abl fusion gene is the single most common abnormality in adult ALL, accounting for up to 50% of the B-lineage disease. Although bcr-abl–positive ALL cases are more resistant to standard remissions of chemotherapy is low. By contrast, bcr-abl translocations occur only in 5% of pediatric ALL cases, and the low frequency of this adverse prognostic marker may explain some of the differences in survival rates between pediatric and adult ALL.

In AML, the key gene involved in the t(8;21)(q22;q22) translocation found in AML-M2 through positional cloning is AML1, which is related to the runt homology domain. AML1, also known as RAB, is a transcription factor that regulates the expression of specific patterns of the homeobox genes. The human homologues of these homeobox genes have been implicated in hematopoietic differentiation. The normal AML1 binds to a protein partner called CBP to exert its physiologic function as a transcription factor. Coincidentally, translocations of CBP are also involved in leukemias harboring inv(16) that generates the fusion protein CBP-MYH11. This
biochemical interaction between the principal gene products of the E8(21) and the inv(16) rearrangements is even more remarkable in that both translocations are associated with favorable clinical outcomes, although the exact mechanism explaining this association remains unclear. Rearrangements involving chromosome 11q23, however, are uniformly associated with poor outcome and with short durations of remission. Initially described in the uncommon translocation t(4q21;11q23) observed in both AML and ALL, this rearrangement creates a fusion oncogene mutating the ALL1/MLL gene (residing on 11q23). ALL1 is the human homologue of a Drosophila gene, and the translocation appears to result from a breakage at one of the repetitive trithorax elements near the ALL1 gene.

The subsequent phase III study was also significant. The study randomized individuals with metastatic breast cancer to chemotherapy alone or chemotherapy plus weekly Herceptin. The results showed that patients treated with chemotherapy alone had a response rate of 32%, a duration of response at 5.9 months, and time to disease progression of 4.6 months. Those treated with chemotherapy and Herceptin exhibited an improvement in all measures: response rate of 49% (vs. 32% with chemotherapy alone), duration of response of 9.3 months (vs. 5.9 months with chemotherapy alone), and time to progression of 11.3 months (vs. 4.6 months with chemotherapy alone). Thus, as predicted in the in vitro investigations, the combination of chemotherapy and Herceptin led to a more favorable outcome.

Since oncogenes are signaling molecules that rely on protein–protein interactions to conduct their signals, interruption of these interactions was predicted to disrupt critical pathways that maintain the cancerous state. Inactivation of the enzymatic activity of certain oncogenes, such as ras proteins and kinases, with small chemically derived molecules has been both an attractive and ultimately successful approach. Some of the most notable clinical successes have been in the treatment of leukemias. Acute promyelocytic leukemia is characterized by the uniform presence of a cytosolic tyrosine kinase, the reciprocal translocation of chromosomes 15 and 17 (t[15;17]), which results in the production of a chimeric PML-RARA gene. In contrast, the DNA-binding domain of a nuclear PML protein adjacent to a truncated RARA that retains its ligand-binding domain. This observation immediately suggested a molecular explanation for why acute promyelocytic leukemia occasionally responded to available retinoids. This hypothesis was supported by dramatic reports showing clinical responses to treatment with 9-cis retinoic acid, all-trans retinoic acid, or hydroxyurea. This led to the identification of a single-agent response rate of 75%. This response is highly specific: all-trans-retinoic acid is ineffective in the absence of the PML/RARA fusion protein. Another significant development has been the Novartis compound, the 2-phenylaminopyrimidine derivative STI571. Derived to inhibit the activity of the activated BCR-ABL tyrosine kinase, STI571 was found to render remissions in the majority of patients with chronic myelogenous leukemia. In both leukemic cell lines and primary tumors, STI571 uniformly abrogated the BCR-ABL kinase activity. These results suggest that the kinase activity of the drug is sufficient to inhibit the activity of the drug in vivo. The drug was found to be inactive in cell lines and primary tumors that were resistant to 9-cis retinoic acid or all-trans retinoic acid. Thus, as predicted in the in vitro investigations, the combination of chemotherapy and Herceptin led to a more favorable outcome.

There is currently a rich developmental pipeline for these kinase inhibitors with many potential agents that will be ready for or have been in clinical testing. The targets include the ras proteins PDGF and the VEGF receptors. The number and diversity of targets, however, make molecular profiling a necessary adjunct to therapeutic decision making. Thus, a comprehensive approach for target detection will no longer remain solely of academic interest, but is predicted to become a clinical necessity.
up the actual expressed genes and their regulatory elements. The actual number of expressed human genes may be 100,000. However, at any point in time, for any individual cell in any given tissue, the amount of genes in use may be as few as 10,000. Of this 10,000, only a proportion may be susceptible to the influence of carcinogenic events. Thus, an important goal for molecular profiling of cancer is to identify a subset of expressed genes that is correlated with, or causally related to, the development and progression of cancer. Setting aside hereditary susceptibility, it is likely that the majority of cancers may originate in tissue that starts with a completely normal genome. Carcinogenic events produce heritable genetic alterations that expand in microscopic premalignant states such as hyperplasia and dysplasia, before frank malignant cancer ensues. Identification of the important genetic derangements and the causally important genes and proteins will depend on direct analysis of actual human cancer tissues, combined with insights gained using animal and cell culture methods. The massive profiling of genes associated with cancer progression is now possible using new technology for microdissection and array hybridization.

CDNA MICROARRAYS ARE A NEW TOOL TO ANALYZE GENE EXPRESSION PATTERNS IN HUMAN CANCER

Every oncologist is daily faced with the biologic heterogeneity of cancer emergence, aggressiveness, and treatment response in individual patients. Every pathologist is daily faced with the enormous histologic diversity of human neoplasms. We assume that the morphologic microscopic appearance (e.g., staining pattern, nuclear shape and contour, cellular configuration and pleomorphism) of a particular neoplastic lesion that spells cancer is the outward manifestation of molecular changes that are occurring inside the interacting tissue cell populations. Scores of molecules and genes can be involved in the behavior of an individual patient's tumor. The clinical outcome of the tumor reflects the interplay of the various molecular features of the malignant cell. This is evident in the highly variable presence of chromosomal translocations, deletions of suppressor genes, and numbers of chromosomes. Consequently, it is critical for molecular oncology of the future to adopt high-throughput technology to survey panels of genes, ranging from hundreds to even the whole human expressed gene set, and apply this technology to the classification of tumor pathologic entities in individual patients.

In response to this challenge, investigators in both the public and private sectors have been perfecting gene-chip arrays that can be used to survey great patterns of gene expression. Laser capture microdissection (LCM) has been developed to provide scientists with a fast and dependable method of capturing and preserving specific cells from a homogeneous population of cells. The LCM is a manual technique that can be used to isolate a single cell or a small number of cells. The RNA from microdissected cancer lesions has been used as the starting material to produce cDNA libraries, microchip microarrays, differential display, and other techniques to find new genes or mutations. Approaches to molecular analysis of pathologic processes are significantly enhanced. The mRNA from microdissected cancer tissues, combined with insights gained using animal and cell culture methods. The massive profiling of genes associated with cancer progression is now possible using new technology for microdissection and array hybridization.

TECHNOLOGY FOR TISSUE MICRODISSECTION BRINGS MOLECULAR ANALYSIS TO THE TISSUE CELL LEVEL

Molecular analysis of pure cell populations in their native tissue environment will be an important component of the next generation of medical genetics. Accomplishing this goal is much more difficult than just grinding up a piece of tissue and applying the extracted molecules to a panel of assays. This is because tissues are complicated three-dimensional structures composed of large numbers of different types of interacting cell populations. The cell subpopulation of interest may constitute a tiny fraction of the total tissue volume. For example, a biopsy of breast tissue harboring a malignant tumor usually contains the following types of cell populations: (1) fat cells in the abundant adipose tissue surrounding the ducts, (2) normal epithelium and myoepithelium in the branching ducts, (3) fibroblasts and endothelial cells in the stroma and blood vessels, (4) premalignant carcinoma cells in the in situ lesions, and (5) clusters of invasive carcinoma. If the goal is to analyze the genetic changes in the premalignant cells or the malignant cells, these subpopulations are frequently located in microscopic regions occupying less than 5% of the tissue volume. Following the computer adage garbage in, garbage out, if the extract of a complex tissue is analyzed using a sophisticated technology, the output will be severely compromised if the input material is contaminated by the wrong cells. Culturing cell populations from fresh tissue is one approach to reduce contamination. However, cultured cells may not accurately represent the molecular events taking place in the actual tissue they were derived from. Assuming methods are successful, it is important to isolate and grow the tissue cells of interest, the gene expression pattern of the cultured cells are influenced by the culture environment and can be quite different from the genes expressed in the native tissue state. This is because the cultured cells are separated from the tissue elements that regulate gene expression, such as soluble factors, extracellular matrix molecules, and cell-cell communication. Thus, the problem of cellular heterogeneity has been a significant barrier to the molecular analysis of normal and diseased tissue. This problem can now be overcome by new developments in the field of tissue microdissection.

Laser capture microdissection (LCM) has been developed to provide scientists with a fast and dependable method of capturing and preserving specific cells from tissue, under direct microscopic visualization. With the ease of procuring a homogeneous population of cells from a complex tissue using the LCM, the approaches to molecular analysis of pathologic processes are significantly enhanced. The mRNA from microdissected cancer lesions has been used as the starting material to produce cDNA libraries, microchip microarrays, differential display, and other techniques to find new genes or mutations.
FIGURE 2-3. Laser capture microdissection. This new technology enables the investigator or clinician to directly procure pure tissue cell subpopulations under microscopic visualization. A transparent polymer film is placed in contact with the surface of the tissue section. A laser beam activates the film over the selected cells to actively capture the cells of interest and leave all the unwanted cells behind.

FIGURE 2-4. RNA isolated from tissue is reverse transcribed to cDNA. The sample cDNA is used to prepare cDNA libraries of the expressed genes in use by the tissue cells or to probe cDNA arrays of known pathways. EST, expressed sequence tags.

Sgroi et al. have combined LCM of breast cancer tissue with cDNA arrays, as an approach to the identification of genes that change their expression during the progression of breast cancer. The group monitored gene expression in LCM-procured pure normal epithelium, invasive cancer, and metastatic tissue cell populations. Differences in the in vivo gene expression profile were verified and validated by real-time quantitative PCR and immunohistochemistry. The combined use of LCM and cDNA microarray analysis revealed genes specifically associated with the progression from normal to metastatic breast cancer cells (Fig. 2-5). Since normal breast epithelium is a minor component of breast tissue, this analysis could not be done with simple ground-up whole breast tissue samples. This study demonstrated that in vivo gene expression profiling can be done on specific tissue cell populations, and that the results of the cDNA arrays correlated well with the real-time quantitative PCR analysis and immunohistochemistry. Consequently, cDNA arrays can be used to uncover patterns that correlate with the biology and find lead candidate genes that may serve as future markers or drug targets.

FIGURE 2-5. Molecular profiling of cancer premalignant progression. Invasive metastatic cancer emerges after a long premalignant phase that occurs in microscopic regions of the tissue epithelium. Microdissection makes it possible to profile the molecular patterns that track all the way through from normal epithelium to metastatic cancer in the same patient.

The development of the LCM allows investigators to determine specific gene expression patterns from tissues of individual patients. Pure populations of cells can be obtained, RNA extracted, copied to cDNA, and hybridized to thousands of genes on a cDNA microchip microarray. In this manner, an individualized molecular profile can be obtained for each histologically identified pathology. Using such multiplex analysis, investigators will be able to correlate the pattern of expressed genes with the etiology, premalignant progression (see Fig. 2-5), and response to treatment. A patient's risk for disease and appropriate choice of treatment could, in the future, be personalized based on the profile. A growing clinical database of such results could be used to develop a minimal subset of key markers that will lead to a revolutionary approach for early detection and accurate diagnosis of disease.

Efficient coupling of LCM of serial tissue sections with multiplex molecular analysis techniques should lead to sensitive and quantitative methods to visualize three-dimensional interactions between morphologic elements of the tissue. For example, it will be possible to trace the gene expression pattern along the length of a prostate gland or breast duct in order to examine the progression of neoplastic development. The end result will be a new era in the integration of molecular biology with tissue morphogenesis and pathology.

TUMOR TISSUE ARRAYS

Once a putative marker (or set of markers) is identified by cDNA array analysis of cancer tissue samples, the next step is to validate these markers in a large population of human tumors. In the past, immunohistochemistry or in situ hybridization has been the method of choice to evaluate an individual patient's tissue sections one slide at a time. Consequently, in order to screen hundreds of patient specimens, it was necessary to laboriously stain hundreds of microscopic glass slides. This exhaustive process has now been telescoped into a high-throughput miniaturized tissue array. The array consists of 1000 cylindrical tissue biopsies, each from a different patient, all distributed on a single glass slide. Thus, each tumor is represented by a minute disk-shaped tissue section 0.6 mm in diameter and 4 to 8 µm in thickness (Fig. 2-6). Tumor arrays are ideal for comparing large numbers of solid tumor samples. Full automation of tumor array creation and screening is envisioned as a means to expeditiously correlate marker levels over large study sets of tumors.
Furthermore, they reported that different histologic types of cancer and tissue (ovarian, esophageal, prostate, breast, and hepatic) exhibited distinct protein profiles. This pattern of protein information could provide correlates with pathologic state or response to therapy. Using a protein biochip which classified protein expression, the complicated changing pattern of protein expression should contain important information about the pathologic process taking place in the cells of the actual tissue. A pathologic hallmark of early cancer progression from carcinoma in situ to invasive cancer is the loss or redistribution of myoepithelial cells. The conspicuous absence of myoepithelial cells in breast cancer progression could mean that these cells produce suppressor proteins that normally keep the malignant cells in check.

A second major approach to isolate tissue cell subpopulations is affinity cell sorting of disaggregated cells from pieces of fresh tissue. A highly notable application of this technology in the field of breast physiology is the result of a collaboration between Oxford Glycosciences and the Ludwig Institute. In this study the investigators used this technology to procure specific tissue cell subpopulations under direct microscopic visualization of a standard stained frozen or fixed tissue section on a glass microscope slide. Tissue cells procured by LCM have been used for highly sensitive and reproducible proteomic analysis using two-dimensional gels and other analytical methods.

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The term proteome, which denotes all the proteins expressed by a genome, was first coined in late 1994 at the Siena two-dimensional gel electrophoresis meeting. Proteomics is proclaimed as the next step after genomics. A goal of investigators in this exciting field is to assemble a complete library of all the proteins. Only a small percentage of the proteome has been cataloged in 2000. Since PCR for proteins does not exist, sequencing the order of 20 possible amino acids in a given protein requires relatively slow and labor intensive, compared with nucleotide sequencing. Although a number of new technologies are being introduced for high-throughput protein characterization and discovery, the mainstay of protein identification continues to be two-dimensional gel electrophoresis. Two-dimensional electrophoresis can separate proteins by molecular weight in one dimension and charge in second dimension. When a mixture of proteins is applied to the two-dimensional gel, individual proteins in the mixture are separated out into signature locations on the display, depending on their individual size and charge. Each signature is a spot on the gel that can constitute a unique single protein species. The protein spot can be procured from the gel and a partial amino acid sequence can be read. In this manner, known proteins can be monitored for changes in abundance under treatment or new proteins can be identified. An experimental two-dimensional gel image can be captured and overlaid digitally with known archived two-dimensional gels. In this way it is possible to immediately highlight proteins that are differentially abundant in one state versus another (e.g., tumor vs. normal or before and after hormone treatment).

Two-dimensional gels have traditionally required large amounts of protein starting material equivalent to millions of cells. Thus, their application has been limited to cultured cells or ground-up heterogeneous tissue. Not unexpectedly, this approach does not provide an accurate picture of the proteins that are in use by cells in real tissue. Tissues are complicated structures composed of hundreds of interacting cell populations in specialized spatial configurations. The fluctuating proteins expressed by cells in tissues may bear little resemblance to the proteins made by cultured cells, which are torn from their tissue context and are reacting to a new culture environment. Proteins extracted from ground-up tissue represent an averaging of proteins from all the heterogeneous tissue subpopulations. For example, in the case of breast tissue, the glandular epithelium constitutes a small proportion of the tissue: The vast majority is stroma and adipose. Thus, it has previously been impossible to obtain a clear snapshot of gene or protein expression within normal or diseased tissue cell subpopulations.

To address the tissue-context problem, new technology is again coming to the rescue: tissue proteomics is an exciting expanding discipline (see Fig. 2-7). Two major technologic approaches have been successfully used to sample macromolecules directly from subpopulations of human tissue cells. The first technology is LCM, a technology for procuring specific tissue cell subpopulations under direct microscopic visualization of a standard stained frozen or fixed tissue section on a glass microscope slide. Tissue cells procured by LCM have been used for highly sensitive and reproducible proteomic analysis using two-dimensional gels and other analytical methods.

A second major approach to isolate tissue cell subpopulations is affinity cell sorting of disaggregated cells from pieces of fresh tissue. A highly notable application of this technology in the field of breast physiology is the result of a collaboration between Oxford Glycosciences and the Ludwig Institute. In this study the investigators separated and purified normal human breast luminal and myoepithelial from reduction mammoplasty specimens using double-antibody magnetic affinity cell sorting and magnetic bead sedimentation. After using enzymatic treatments and various incubation, separation, and washing steps, the investigators obtained purified luminal and myoepithelial cells in yields of $5 \times 10^4$ to $2 \times 10^5$. Proteins from these cell populations were then analyzed by two-dimensional gels. A master image for each cell type comprising a total of 1738 distinct proteins was derived. The investigators found 170 protein spots that were elevated twofold or more between the two populations. Fifty-one of these were further characterized by tandem mass spectroscopy. The proteins preferential to the myoepithelial cells contained muscle-specific enzymes and structural proteins consistent with the contractile muscle-related derivation of these cell types.

A pathologic hallmark of early cancer progression from carcinoma in situ to invasive cancer is the loss or redistribution of myoepithelial cells. The conspicuous absence of myoepithelial cells in breast cancer progression could mean that these cells produce suppressor proteins that normally keep the malignant cells in check. Thus, one or more of the proteins identified in tissue myoepithelial cells could be candidate cancer prevention molecules.

The complicated changing pattern of protein expression should contain important information about the pathologic process taking place in the cells of the actual tissue. This pattern of protein information could provide correlates with pathologic state or response to therapy. Using a protein biochip which classified protein populations into molecular weight classes, Paweleit et al. showed distinct protein patterns of normal, premalignant, and malignant cancer cells microdissected from human tissue.

Furthermore, they reported that different histologic types of cancer and tissue (ovarian, esophageal, prostate, breast, and hepatic) exhibited distinct protein profiles.
Such a means to display a pattern of expressed proteins from microscopic tissue cellular populations (Fig. 2-8) will potentially be an important enabling technology for pharmaco-proteomics, molecular pathology, and drug intervention. Proteomic array technologies of the future will be used to rapidly generate displays of signal pathway profiles (see Fig. 2-7). Investigators will be able to assess the status of defined pathways that control mitogenesis, apoptosis, survival, and a host of other physiologic states. The information flow through these circuits, separately or through cross-talk, may dictate clinical behavior and susceptibility to therapy.

**FIGURE 2-8.** Surface-enhanced laser desorption and ionization (SELDI) analysis of laser capture microdissection microdissected microscopic stages of human prostate cancer. This technology generates a protein fingerprint consisting of the distribution of molecular weights. In the example study set, the ratios of specific protein peaks change specifically in the invasive carcinoma compared with the normal epithelium.
CHAPTER 3
Essentials of Signal Transduction

INTRODUCTION

Signal transduction is the chemistry that allows communication at the cellular level. Cells sense signals from both the outside environment and other cells and, in response, they regulate protein expression and function. Protein expression is controlled by rates of transcription, translation, and proteolysis, whereas protein activities are affected by location, covalent modifications, and noncovalent interactions. Signal transduction pathways regulate all aspects of cell function, but most pathways target five primary processes: metabolism, cell division, death, differentiation, and movement.

In single-celled organisms, signal transduction pathways determine chemotaxis, mating, and adaptation to varying food sources. In multicellular organisms, signal transduction pathways are necessary for embryonic development, and they regulate differentiation, division, and death in both the mature and developing organism. Signal transduction pathways also control the particular functions of specialized cells (e.g., synthesis and secretion of insulin by the pancreas, migration and phagocytosis by neutrophils) and the abnormal behavior of diseased cells (e.g., invasion and growth of cancer cells).

To emphasize the essentials of signal transduction, we have focused on the variety of solutions to the two common problems faced by cells and organisms in signal transduction: (1) How is a signal sensed and (2) how are the levels and activities of proteins modified in response to the signal? Most signals are transmitted by ligands and are sensed by the receptors to which they bind. Binding of a ligand to a receptor stimulates the activities of proteins necessary to continue the transmission of the signal. Often, this involves the formation of multiprotein complexes and the generation of small-molecule second messengers. Integration of signals from multiple pathways determines the cell's responses to competing and complementary signals.

THE SENSORY MACHINERY: LIGANDS AND RECEPTORS

SIGNS

Signal transduction pathways have evolved to respond to an enormous variety of stimuli and to generate an equally extensive number of signals. Molecules that initiate signaling cascades include proteins, peptides, amino acids, lipids, nucleotides, gases, and light (Table 3-1). Most extracellular signals, such as growth factors, bind to receptors on the plasma membrane, whereas some ligands (e.g., retinoids or nitric oxide) that are membrane-permeable bind to receptors inside the cell. Usually, cells are exquisitely sensitive to ligand-receptor binding. The affinity of receptors for ligands generally is found to be in the pM to nM range, and very few receptors have to be occupied to transmit a signal. Many cytokine-responsive cells express only a few hundred receptors on the cell surface. (Signal amplification, which allows signals to propagate to the entire cell, is discussed later in Multiprotein Signaling Complexes.)

### TABLE 3-1. Ligands That Stimulate Signal Transduction Pathways

<table>
<thead>
<tr>
<th>Type of Ligand</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROTEINS</td>
<td>Insulin, EGF, insulin-like growth factor</td>
</tr>
<tr>
<td>AMINO ACIDS</td>
<td>Glutamate, acetylcholine</td>
</tr>
<tr>
<td>NUCLEOTIDES</td>
<td>ATP, cAMP, cGMP</td>
</tr>
<tr>
<td>LIPIDS</td>
<td>Phosphatidylcholine, phosphatidylserine</td>
</tr>
<tr>
<td>GASES</td>
<td>Nitric oxide</td>
</tr>
<tr>
<td>ELECTROLYTES</td>
<td>NaCl, KCl</td>
</tr>
</tbody>
</table>

### RECEPTORS

Usually, signaling pathways begin with binding of a ligand to a receptor (Table 3-2). Receptors can be located either on the cell surface or intracellularly. Ligands that are on the cell surface or cannot transverse the membrane bind to receptors on the plasma membrane, whereas some ligands (e.g., retinoids or nitric oxide) that are membrane-permeable bind to receptors inside the cell. Usually, cells are exquisitely sensitive to ligand-receptor binding. The affinity of receptors for ligands generally is found to be in the pM to nM range, and very few receptors have to be occupied to transmit a signal. Many cytokine-responsive cells express only a few hundred receptors on the cell surface. (Signal amplification, which allows signals to propagate to the entire cell, is discussed later in Multiprotein Signaling Complexes.)
Both receptors and ligands are multifunctional. Often, ligands can activate more than one receptor, and receptors can bind more than one ligand. The stimulation of most receptors leads to the activation of several downstream pathways that either function cooperatively to activate a common target or stimulate distinct targets. Generally, some of the pathways activated are counter-regulatory and serve to attenuate the signal.

Binding of ligands to receptors leads to a conformational change in the receptor that initiates signaling or oligomerization (or both). As a result of ligand binding, the intrinsic activity of the receptor or of associated proteins is stimulated. Receptors can have intrinsic enzymatic activity or can associate with protein kinases, guanine nucleotide exchange factors, and transcription factors. The receptor families used by eukaryotic cells in signal transduction illustrate both the diversity of receptor type and how signaling is initiated.

**Receptor Tyrosine Kinases**

Receptor tyrosine kinases are transmembrane proteins that have an extracellular ligand-binding domain, a transmembrane domain, and a cytoplasmic tyrosine kinase domain. The ligands for these receptors are proteins or peptides. Most receptor tyrosine kinases are monomeric, but the insulin receptor family are heterotetramers in which the subunits are linked by disulfide bonds. Receptor tyrosine kinases have been divided into six classes, primarily on the basis of the sequence of extracellular domain. Examples of tyrosine kinases include the insulin receptor, platelet-derived growth factor receptor, the epidermal growth factor receptor family, and the fibroblast growth factor receptor family.

Activation of receptor tyrosine kinases requires tyrosine phosphorylation of the receptor. Receptor tyrosine kinases transmit signals both by autophosphorylation of the receptor and by phosphorylation of other substrates. Receptor phosphorylation occurs on multiple sites, some of which stimulate the kinase activity of the receptor and others of which allow binding of downstream-signaling molecules. Ligand-dependent oligomerization of receptors brings the kinase domains into close proximity so that they cross- phosphorylate. Often, this transphosphorylation locks the kinase into a high-activity conformation.

Ligands stimulate receptor oligomerization in a variety of ways (Fig. 3-1). Some ligands, such as platelet-derived growth factor, are dimeric, so that the ligand is able to bind two receptors simultaneously. Other ligands, such as growth hormone, are monomeric but have two receptor-binding sites that allow them to induce receptor dimerization. Fibroblast growth factors (FGF) also are monomeric but have only a single receptor-binding site. FGF molecules bind to heparin sulfate proteoglycans, which promotes dimerization of FGF and the FGF receptor. Epidermal growth factor (EGF) also is monomeric, but it may have a second low-affinity receptor-binding site, or receptor-ligand dimers may bind to a second receptor to allow receptor-receptor interaction and transphosphorylation. Ligands not only stimulate receptor-dependent signaling: some ligand-receptor interactions result in signaling by the ligand. Ephrins are ligands for the protein tyrosine kinase Eph receptors. Ephrins are expressed on the surface of adjacent cells, and interaction of Eph receptors and ephrins both activates the tyrosine kinase activity of the receptor and leads to stimulation of signaling by the ligand in the adjacent cell. Ligands for the insulin receptor are an exception to the idea of dimerization leading to activation. The insulin receptor is a heterotetramer before ligand binding, and likely a conformational change brings the cytoplasmic tails in proximity or stimulates kinase activity (or does both).

**FIGURE 3-1.** Dimerization of tyrosine kinase receptors. Most tyrosine kinase receptors are activated by ligand-induced dimerization. Some ligands, such as platelet-derived growth factor (PDGF), are dimeric and induce dimerization using the two receptor-binding domains. Other ligands, such as growth hormone, contain two receptor-binding domains in the same molecule. The fibroblast growth factors (FGF) rely on proteoglycans to aid the formation of ligand dimers. Some ligands, such as the ephrins (EPH), are present on nearby cells and, when the cells come into contact, bind to the receptors and promote clustering.

Studies of the EGF receptor family illustrate some important concepts in signal transduction. The EGF-signaling pathways involve four known receptors (EGF receptor, erbB2, erbB3, and erbB4) and many ligands. EGF can stimulate homodimerization of the EGF receptor but, under certain conditions, heterodimerization with other family members also occurs. This receptor can activate different signaling pathways, depending on the subgroups of EGF receptor family members expressed in a cell. For example, heparin-binding EGF-like growth factor stimulates mitogenesis but not chemotaxis when it activates the EGF receptor but is both a mitogen and chemotactic factor when it activates ErbB4. Recent work also suggests that different ligands binding to the same receptors can activate distinct downstream-signaling pathways. These findings suggest that different ligands may cause distinct conformational changes that lead to the phosphorylation of different sets of tyrosine residues on the receptor and could lead also to phosphorylation of distinct sets of substrates.

**Receptors that Activate Tyrosine Kinases.** A number of receptors do not have intrinsic enzymatic activity but stimulate associated tyrosine kinases. The cytokine and interferon receptors associate constitutively with members of the Jak family of tyrosine kinases. The kinases appear to be inactive in the absence of ligand but, as happens in receptors with intrinsic tyrosine kinase activity, signaling is initiated by ligand-stimulated heterodimerization of the receptors. Dimerization of the receptors brings the Jak kinases in proximity to each other or to other tyrosine kinases, and transphosphorylation leads to their activation. Downstream signaling is dependent on the active Jak kinases phosphorylating the receptors and other substrates.

**Serine-Threonine Kinase Receptors.** The transforming growth factor-β (TGF-β) family of receptors are serine-threonine kinases. These receptors are transmembrane proteins that have an extracellular ligand-binding domain, a transmembrane domain, and an intracellular serine kinase domain. TGF-β ligands are dimers that lead to oligomerization of type I and type II receptors. The type I and type II receptors are homologous but distinctly regulated. The type II receptors seem to be constitutively active but do not normally phosphorylate substrates, whereas the type I receptors are normally inactive. On ligand-mediated dimerization of the type I and type II receptors, the active type II receptor phosphorylates the type I receptor and converts it to an active kinase. Subsequent signal propagation is dependent on the kinase activity of the type I receptor and the phosphorylation of downstream substrates.
Receptor Phosphotyrosine Phosphatases

Like kinases, receptor protein tyrosine phosphatases (RPTPs) have an extracellular domain, a single transmembrane-spanning domain, and cytoplasmic catalytic domains. The extracellular domains of many receptor tyrosine phosphatases contain fibronectin and immunoglobulin repeats, suggesting that some of these receptors may recognize adhesion molecules as ligands. Several RPTPs are capable of homotypic interaction, but no true ligands are yet known for RPTPs. Most receptor tyrosine phosphatases have two catalytic domains, and both are active in at least some receptors. Both functional and structural evidence suggests that the phosphatase activity of some of these receptors is inhibited by dimerization. Normally, these receptors might be active as tyrosine phosphatases but lose that activity upon dimerization. In this way, constitutive or stimulated tyrosine kinase activity becomes enhanced. Signaling by RPTPs is complicated because they do not always function in opposition to tyrosine kinases. For example, CD45 is necessary for signaling by the B-cell receptor, which also requires tyrosine kinase activity.

G PROTEIN–COUPLED RECEPTORS. G protein–coupled receptors (GPCRs) are by far the most numerous receptors. Of the 19,000 genes in Caenorhabditis elegans, approximately 800 (or nearly 5% of the genome) are GPCRs, and nearly 2000 mammalian GPCRs are known. The number of GPCRs is so high because they encode the light, smell, and taste receptors, all of which require great diversity. These receptors have seven membrane-spanning domains: The N-terminus, and three of the loops are extracellular, whereas the other three loops and the C-terminus are cytoplasmic. A wide variety of ligands bind GPCRs, including proteins and peptides, lipids, amino acids, and nucleotides. No common binding domain exists for all ligands, and interactions of ligands with GPCRs are fairly distinct. In the case of the thrombin receptor, thrombin cleaves the N-terminus of the receptor, freeing a new N-terminus that self-associates with the ligand pocket, leading to activation. Amines and eicosanoids bind to the transmembrane domains of their GPCRs, whereas peptide ligands bind to both the transmembrane domains and the extracellular loops of their GPCRs. Neurotransmitters and some peptide hormones require the N-terminus for binding and activation.

The receptor appears to be in an inactive conformation by intramolecular bonds involving residues in the transmembrane or juxtamembrane regions. In the inactive state, the receptor is bound to a heterotrimeric G protein, which also is inactive. Agonist binding results in a conformational change that activates the guanine nucleotide exchange activity of the receptor. Exchange of guanosine triphosphate (GTP) for guanosine diphosphate (GDP) on the a subunit of heterotrimeric G proteins initiates signaling. Though GPCRs all activate heterotrimeric G proteins, this action ultimately results in the stimulation of other signaling pathways, including protein tyrosine serine kinases, phospholipases (PLCs A, C, and D) and ion channels. Important recent work has shown that certain GPCRs activate receptor tyrosine kinases. Often, stimulation of GPCRs leads to activation of the EGFR receptor, which is necessary for the GPCR to activate the mitogen-activated kinase (MAP kinase) pathway.

NOTCH FAMILY OF RECEPTORS. The Notch receptor has a large extracellular domain, a single transmembrane domain, and a cytoplasmic domain. Ligands for the Notch receptor are proteins expressed on the surface of adjacent cells, and the primary target of notch signaling is activation of the transcription factor SuH in Drosophila species or CBF-1 in mammals. Though the mechanisms by which Notch transmits signals have not been worked out definitively, it appears to be fairly different from other receptors. Current research suggests that the cytoplasmic domain of the Notch is proteolytically cleaved and translocated to the nucleus, where it interacts directly with transcription factors.

GUANYLATE CYCLASES. Cyclic nucleotides are important second messengers and allosteric regulators of enzyme activities. The synthesis of cAMP by adenylyl cyclase is regulated principally by heterotrimeric G proteins, but the synthesis of cGMP is regulated directly by ligands. Plasma membrane guanylate cyclases are receptors for atrial natriuretic hormone, and nitrous oxide binds to soluble guanylate cyclases in the cytoplasm. Both stimuli increase cGMP levels.

TUMOR NECROSIS FACTOR RECEPTOR FAMILY. The tumor necrosis factor family of receptors has a conserved cysteine-rich region in the extracellular domain, a transmembrane domain, and a domain called the death domain in the cytoplasmic tail. The receptors undergo oligomerization after ligand binding, which is necessary for signaling. These receptors are distinct in several respects. Stimulation of the receptor leads to recruitment of cytoplasmic proteins that bind to each other and the receptor through death domains. They activate a protease, caspase 8, that initiates apoptosis, although they also can stimulate antiapoptotic signals. This family of receptors also includes "decays" or receptors that are missing all or part of the cytoplasmic tail and thus cannot transmit a signal. This feature provides a unique mechanism for inhibiting and further regulating signaling.

NUCLEAR RECEPTORS. Some ligands diffuse into the cell and bind to receptors either in the cytoplasm or the nucleus. These ligands include steroids, eicosanoids, retinoids, and thyroid hormone. The receptors for these ligands are transcription factors that have both DNA and ligand-binding domains. The unliganded receptor is bound to heat-shock proteins, from which it is released after ligand binding. Release from the chaperone complex and ligand binding allow the DNA-binding domain to contact DNA and the receptors to regulate transcription directly.

ADHESION RECEPTORS. Cell adherence via integrins either to the extracellular matrix or to other cells is mediated by receptors that function mechanically and stimulate intracellular signaling pathways, primarily through tyrosine kinases. Integrins are composed of heterodimers of a and b subunits and bind to an arginine, glycine, aspartate (RGD) motif found in matrix molecules. Activation of integrin signaling involves both binding to ligand and clustering of integrins. Ligand binding can be stimulated also by intracellular signals, presumably by a change in configuration of the integrin. Integrin signaling is necessary for cell movement but, in contrast to many other pathways, adherence provides a continuous signal to cells. This signal appears to be necessary for survival of many cell types. The ability to circumvent the requirement for adherence-dependent survival plays a major role in the development of human cancers by allowing tumor survival in inappropriate locations.

PROPAGATION OF SIGNALS TO THE CELL INTERIOR

Eukaryotic cells use a varied collection of receptors and ligands to initiate cell signaling. Binding of ligands to receptors may stimulate an intrinsic enzymatic activity of the receptor-like protein tyrosine or serine kinases or the guanine nucleotide exchange activity of GPCR. Other receptors do not have intrinsic enzymatic activity, but binding results in activation of downstream enzymes (e.g., proteases by the tumor necrosis factor receptor family or protein tyrosine kinases by the cytokine receptors). Signals are transmitted by all receptors by affecting the function of downstream proteins (Table 3-3). The function of intracellular signaling proteins is regulated by covalent modifications, by noncovalent binding of other proteins and small molecules, and by the level of protein expression.

<table>
<thead>
<tr>
<th>Enzyme Classes Stimulated by Active Receptors</th>
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<tbody>
<tr>
<td>Enzyme Classes Stimulated by Active Receptors</td>
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<td>Enzyme Classes Stimulated by Active Receptors</td>
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**Table 3-3.** Enzyme Classes Stimulated by Active Receptors

REGULATION OF PROTEIN KINASES

Proteins undergo many covalent modifications, but phosphorylation is the most common covalent modification involved in the regulation of protein function. Both phosphorylation by kinases and addition of a phosphate moiety in the form of GTP exchange for GDP result in conformational changes that regulate protein activity (Fig. 3-2). Phosphorylation is less common in the activation of signaling pathways but is necessary for some pathways (e.g., apoptosis) and also is an important pathway by which signals are attenuated.
The balance between kinase and phosphatase activity controls protein phosphorylation.\cite{22} Protein kinases themselves, transcription factors, and cytoskeletal components are a few examples of proteins regulated by phosphorylation. Most protein kinases in eukaryotic cells are divided into three classes on the basis of residues they phosphorylate: protein tyrosine kinases, protein serine-threonine kinases, and dual-specificity kinases that phosphorylate serine, threonine, and tyrosine residues. Important issues in understanding the role and regulation of protein phosphorylation are how specificities of kinases and phosphatases are determined and how phosphorylation alters the function of proteins. Recent work at both the structural and functional levels provides preliminary answers to these questions.

Most signal transduction pathways activate tyrosine kinases, either directly (as in the case of receptor tyrosine kinases) or indirectly. Phosphorylation of proteins on tyrosine can result in either the stimulation or inhibition of enzymatic activity or can provide sites for protein-protein interaction. An example of how tyrosine phosphorylation regulates enzymatic activity is the Src family of protein tyrosine kinases, which are regulated both positively and negatively by tyrosine phosphorylation.\cite{33} Phosphorylation of a tyrosine residue in the C-terminus leads to an intramolecular bond involving this phosphotyrosine and the Src homology 2 (SH2) domain that blocks access of substrate to the catalytic domain. In contrast, phosphorylation of a tyrosine in the T loop of the catalytic domain stimulates the kinase activity by stabilizing the catalytic pocket in an active conformation.

A common theme in the regulation of the activity of both tyrosine and serine-threonine protein kinases is phosphorylation of the T loop as a mechanism of activation. The T loop forms a lip of the catalytic pocket and may occlude the active site, preventing access of the substrate. In the case of the insulin receptor, the unphosphorylated T loop also appears to interfere with adenosine triphosphate (ATP) binding.\cite{36} Crystallographic studies indicate that the T loop is mobile and thus probably is not always in an inhibitory conformation; hence, a kinase has some constitutive activity. This low level of activity is sufficient to phosphorylate a nearby kinase (e.g., autophosphorylation of a partner in a dimeric receptor). After phosphorylation, the T loop undergoes a conformational change that allows substrate access to the catalytic site.

Once a protein kinase is active, only specific substrates are phosphorylated. This specificity rests on two properties: colocalization of the kinase with the substrate (discussed later in Efficiency and Specificity: Formation of Multiprotein Signaling Complexes) and the presence of sequences in a potential substrate that can be phosphorylated by the kinase. Though protein kinases appear to phosphorylate many substrates in vitro, particular motifs have been identified that in some cases govern absolutely whether a protein will be a substrate, such as a proline following a serine or threonine for substrates of MAP kinases.\cite{36,37} In other cases, particular motifs are favored as phosphorylation sites.\cite{38,39} Likely these motifs fit best into the catalytic cleft of the kinase. In some cases, sequences distant from the site of phosphorylation can mediate low-affinity association of a kinase with a substrate and thus can enhance phosphorylation.

Most signaling pathways also activate serine kinases, but a higher level of constitutive phosphorylation of proteins occurs on serine and threonine. Still unclear is how much of this basal phosphorylation is involved in the regulation of the activity or location of proteins and how much might be irrelevant. Myriad cellular functions are regulated by serine phosphorylation ranging from the activity of transcription factors and enzymes to the polymerization of actin. Serine kinases themselves are regulated in a variety of ways. Mammalian serine-threonine kinases have been subdivided into 11 subfamilies, on the basis of primary sequence homology, which has been predictive also of related function.\cite{30,38} Location, phosphorylation, and ligand binding regulate serine kinases. Activation by ligand binding separates some classes of serine protein kinases. For example, cyclic nucleotides (e.g., cAMP) activate the protein kinase A (PKA) superfamily,\cite{42} Calcium and diacylglycerol activate members of the protein kinase C family.\cite{43} The akt family is activated by phosphorylation in insulin-like growth factor products of phosphoinositide 3-kinases (PI3-kinase), which allows phosphoinositide-dependent kinase 1 (PDK1) to phosphorylate the activation, or T loop.\cite{44} Association with cyclins activates the cyclin-dependent kinase family, and the calcium-calmodulin-dependent kinases are activated by calcium.\cite{45} Kinase cascades also are important in allowing multiple levels of regulation and amplification of serine kinase activity. For example, MAP kinases are activated by phosphorylation of the T loop after activation of upstream kinases: Activation of Raf leads to phosphorylation and activation of MEK1, which phosphorylates and activates the ERKs (Fig. 3-3).\cite{46}

FIGURE 3-2. Regulation of protein activity by phosphate. The activity of many proteins is regulated by phosphate. The exchange of guanosine triphosphate (GTP) for guanosine diphosphate (GDP) bound to G proteins induces an activating conformational change dependent on the additional G phosphate of GTP. This reaction is catalyzed by guanine nucleotide exchange factors. GTPase-activating proteins (GAP) accelerate the hydrolysis of GTP to GDP to remove the g phosphate and attenuate G protein signaling. Protein kinases add phosphate to proteins that can result in conformational changes and changes in enzymatic activity. The phosphate can be removed by protein phosphatases to inhibit the signal. Both G proteins and protein kinase substrates undergo a similar cycle of phosphate addition and removal to regulate their activity. ADP, adenosine diphosphate; ATP, adenosine triphosphate; GEF, guanine nucleotide exchange factor.

REGULATION OF PROTEIN PHOSPHATASES

Protein phosphatases remove the phosphate residues from proteins and can either activate or inactivate signaling pathways, depending on the sites that are dephosphorylated. Protein phosphatases can be divided into the same three groups as are the kinases, on the basis of their substrates: tyrosine phosphatases, serine-threonine phosphatases, and dual-specificity phosphatases. Tyrosine phosphatases and dual-specificity phosphatases use a cysteine/phosphate intermediate, whereas the serine-threonine phosphatases are metal-requiring enzymes that dephosphorylate in a single step.\cite{47,48} Recent structural work has revealed how the activity of some nonreceptor tyrosine phosphatases is regulated. The SHP-2 phosphatase has, in addition to the catalytic domain, two SH2 domains. These domains (discussed in more detail in Domains That Mediate Protein-Protein Binding) mediate binding to other proteins by direct association with phosphorylated tyrosine residues. In the inactive state, the catalytic cleft of SHP-2 is blocked by the N-terminal SH2 domain.\cite{49} Binding of the
N-terminal SH2 domain to a phosphotyrosine residue of a target protein induces a conformational change that allows substrate access to the catalytic domain. Tyrosine phosphatases act both to attenuate signals that require tyrosine phosphorylation and to activate pathways inhibited by tyrosine phosphorylation. An example of the negative regulatory function of tyrosine phosphatases is the role of SHP-1 (a homolog of SHP-2) in inhibiting cytokine and B-cell receptor signaling. In contrast, SHP-2 is necessary for cytokine stimulation of cells. On the basis of the ability of phosphatase inhibitors (e.g., vanadate) to activate tyrosine kinase-dependent signaling in the absence of ligands, acute inactivation of specific tyrosine phosphatases may play a more important role than previously appreciated in regulating the balance of tyrosine phosphorylation and dephosphorylation that controls signaling pathways.

Protein phosphatase 1 (PP1), PP2A, PP2B, and PP2C are the major serine-threonine phosphatase activities in vivo. Both PP1 and PP2A are composed of catalytic and regulatory subunits. PP1 is involved in regulating many pathways, from glycogen metabolism to the cell cycle, whereas PP2A binds to calcineurin and is regulated by calcium. Phosphorylation of either the regulatory or catalytic subunit regulates the activity of many serine phosphatases. More than 100 PP1 regulatory subunit functions target to the catalytic domain to different cellular locations and mediate activation or inhibition. This action provides an example of how a single catalytic activity can perform multiple specific functions as a result of targeting by a regulatory subunit.

GUANOSE TRIPHOSPHATE–BINDING PROTEINS

Just as covalent modification as a mechanism of protein activity regulation is important, so is noncovalent binding to proteins. A number of small molecules regulate protein function, as does protein-protein interaction. G proteins are the best-studied protein mediators that regulate other proteins.

GTP-binding proteins function as digital switches. They are inactive when bound to GDP, but GTP binding results in a conformational change that allows binding to effector molecules and transmission of a signal (see Fig. 5-2). GTP-binding proteins regulate the same molecules activated by receptors: protein and lipid kinases, phosphatases, and phospholipases. GTP-binding proteins are categorized into two large classes: the heterotrimeric GTP-binding proteins and the Ras-like GTP-binding proteins. Activation of GTP-binding proteins is regulated by guanine nucleotide exchange factors that catalyze the release of GDP and allow GTP to bind to and activate the protein. GTP-activating proteins (GAPs) accelerate GTP hydrolysis and regulate inactivation of GTP-binding proteins. All GTP-binding proteins have lipid modifications that promote membrane association.

Heterotrimeric GTP-binding proteins have three subunits and are activated by GPCR. In the inactive state, the α, β, and γ subunits are associated as a heterotrimer. In mammalian cells, 20 α subunits, 6 β subunits, and 12 γ subunits are known. The heterotrimeric forms are divided into four classes on the basis of function. Gα stimulate adenylate cyclase, Gβ inhibits adenylate cyclase, Gγ activates phospholipase C, and Gα and Gβ12 and Gγ13 form a group whose function is not yet known. Activation of GPCR allows them to catalyze GDP/GTP exchange of the a subunit of heterotrimeric G proteins. In response to GTP loading of the a subunit, the α and βγ subunits dissociate. The β and γ subunits do not dissociate in vivo. Both the a and b complex send signals. The a subunit undergoes a conformational change in response to GTP that allows it to bind to effectors. The b complex does not undergo a conformational change, but release from the a subunit exposes surfaces that allows it to bind to effectors. Both the a and b subunits affect the activity of a wide range of downstream effectors, including ion channels, protein kinases, and phospholipases. Domains termed regulators of G protein signaling act as GAPs toward the a subunit and attenuate the signal by catalyzing hydrolysis of GTP to GDP.

Ras-like GTP-binding proteins are monomer and of lower molecular weight than are the heterotrimeric GTP-binding proteins. Ras-like GTP-binding proteins are classified into five families: the Ras, Rho, Rab, Arf, and Ran families. The Ras and Rho families regulate cell growth, transcription, and the actin cytoskeleton; the Arf family regulates phospholipase D and vesicle trafficking; the Rab family regulates vesicle trafficking; and the Ran family regulates nuclear import.

Ras-like GTP-binding proteins are activated in a manner similar to that of the a subunit of heterotrimeric G proteins. Exchange of GTP for GDP results in a conformational change that promotes binding to effector molecules. In contrast to heterotrimeric G proteins, nucleotide exchange for Ras-like GTP-binding proteins is not catalyzed by receptors. Specific exchange factors are activated downstream of receptors or in response to specific cellular events. Signals are attenuated by the action of GAPs, analogous to regulators of the G protein–signaling domain-containing proteins that catalyze GTP hydrolysis.

GTP-binding proteins affect the activity of their targets by causing conformational changes and perhaps by serving to localize the target. Recent crystal structures of the catalytic domain of adenylate cyclase bound to G proteins illustrate the conformational change. Gsa binds to the C2a domain of adenylyl cyclase, causing rotation of the C1a domain, which likely positions the catalytic residues more favorably for conversion of ATP to cAMP. Though crystal structures of small G proteins bound to portions of their targets also have been solved, the effect on the activity of target molecules as a result of binding has not yet been explained. Studies of the role of Ras in the interaction of Raf suggest that an important role of Ras is localization of Raf to the membrane, but Ras also may help to activate Raf directly.

SMALL-MOLECULE SECOND MESSAGERS

Many small molecules transmit signals by binding noncovalently to protein targets and affecting their function. Many of these molecules are called second messengers because they are generated within the cell in response to a first messenger, such as a growth factor, binding to a cell surface receptor. Both the generation and attenuation of small-molecule signals is regulated. Our review of the role of several small molecules in signal transduction pathways is not meant to be comprehensive.

cAMP was the first second messenger discovered. Adenylate cyclase, activated by heterotrimeric G proteins, catalyzes the synthesis of cAMP from ATP. The primary target of cAMP is protein kinase A, and the activation of protein kinase A by cAMP demonstrates how second messengers function. The inactive form of protein kinase A is a tetramer of two catalytic and two regulatory subunits; the regulatory subunit inhibits the activity of the catalytic subunit. The regulatory subunit contains two cAMP-binding sites. Binding of cAMP to the first site causes a conformational change that exposes the second site. Binding of cAMP to the second site causes dissociation of the regulatory and catalytic subunits. The free catalytic subunits are then active.

Many activated receptors stimulate phospholipases C. All three families of phospholipases C (PLC)—b, g, and d—are activated by calcium. PLC b is activated by both the a and the b/g subunits of heterotrimeric G proteins, and PLC g is activated by tyrosine phosphorylation. The regulation of PLC g is not as well understood. Phospholipases C cleave PtdIns-4,5-P2 to produce diacylglycerol and inositol-1,4,5-trisphosphate, resulting in a bipartite signal. Diacylglycerol interacts with the C1 domain of protein kinases C to mediate their membrane localization and activation. Inositol-1,4,5-trisphosphate binds to a calcium channel in the endoplasmic reticulum (ER) and stimulates the release of calcium from intracellular stores. This increase in cytoplasmic calcium is followed by an influx of extracellular calcium via capacitive calcium channels at the plasma membrane. Still unclear is how the capacitive calcium channels are activated. In unstimulated cells, cytosolic calcium is much lower than in the extracellular space or ER (100 nM versus 1 mM), so opening channels in the endoplasmic reticulum or plasma membrane allows calcium to flood into the cytoplasm, temporarily raising the cytoplasmic calcium to micromolar concentrations. Ultimately, calcium returns to basal levels as a result of calcium pumps, which increase the calcium extruded and return it to intracellular sites in the ER and mitochondria. Calcium has a multitudes of cellular effects, including directly regulating enzymatic activities, ion channels, and transcription. Several calcium-binding domains are known, including the C2 domain and EF hands. Calcium binds directly to enzymes and regulates their activity or it can bind to regulatory subunits, such as calmodulin.

Eicosanoids are ubiquitous signaling molecules that bind to both GPCR and transcription factors. Eicosanoid synthesis occurs in response to a number of stimuli and is an example of rapid cell-to-cell signaling. Unlike most second messengers, eicosanoids produced in one cell can escape that cell and diffuse to nearby cells and either bind to receptors or be metabolized further. Eicosanoid synthesis is regulated by the production of arachidonic acid, which can be produced from diacylglycerol (DAG). Phospholipases A2 cleave the sn-2 acyl group of phospholipids to produce free fatty acid and a lysophospholipid. The calcium-regulated form of PL2A shows a preference for substrates containing arachidonic acid. The further metabolism of arachidonic acid results in the synthesis of prostaglandins and leukotrienes.

EFFICIENCY AND SPECIFICITY: FORMATION OF MULTIPROTEIN SIGNALING COMPLEXES

COMPARTMENTATION

The ability of a signal transduction pathway to transmit a signal or to stimulate flux through a pathway is dependent on the probability that a protein finds its target. The likelihood of any two proteins coming into contact is proportional to their concentrations. Recruiting a protein to a specific compartment of a cell allows the local concentration of that protein to be increased markedly, thereby increasing the probability that it will interact with other proteins or small molecules that are recruited to or generated in the same compartment. Colocalization of proteins in a signaling pathway is achieved by recruitment to the same membrane surface or organelle (e.g., plasma membrane versus ER) and ultimately by protein-protein interactions. Conversely, separating proteins or second messengers (or both) into distinct
compartments turns off signaling pathways.

The regulation of transport of signaling proteins into the nucleus is important in a number of signal transduction pathways and illustrates the concept of colocalization in the same organelle. Nuclear transport proceeds through nuclear pores that can be transversed by diffusion of proteins of less than 40 kD. Transport of larger molecules requires a nuclear localization signal to which the importins bind. The importins target the protein to the nuclear pore, and the complex is transported into the nucleus. The Ran G protein dissociates the importins from their cargo once they are in the nucleus. Regulated export of proteins from the nucleus is similar to import. A nuclear export signal (NES) is recognized by the protein exportin which then transports the cargo out of the nucleus.

Regulation of nuclear localization of the transcription factor nuclear factor of activated T cells (NFAT), required for its transcriptional activity, is an example of the importance of nuclear localization in signal transduction. In response to T-cell activation and a rise in intracellular calcium, NFAT is dephosphorylated by the calcium-responsive phosphatase calcineurin. Dephosphorylation allows the nuclear localization signal in NFAT to bind to the importins, and NFAT, along with calcineurin, is imported into the nucleus. NFAT also contains a NES, and phosphorylation appears to allow the NES to bind to exportin, resulting in transport to the cytoplasm.

Protein compartmentation can also occur on a smaller scale. Proteins in a signal transduction cascade can exist in a preformed but inactive complex, such as the yeast MAP kinase module composed of the Ste11, Ste7, and MAP kinases bound to the scaffolding protein Ste5. Pheromone signaling activates a G protein, which in turn activates the Ste20 kinase. Ste20 phosphorylates and activates the Ste11, which activates the kinase cascade on Ste5. Once the first kinase in the cascade is activated, the other kinases are phosphorylated quickly and are activated because of their proximity.

A similar scaffolding probably functions in the activation of the Jnk kinase pathway in mammalian cells. The enzymes in the mammalian MAP kinase cascades are homologues of the yeast proteins. A protein originally thought to inhibit Jnk kinase (JIP-1, jnk inhibitory protein) binds to MLK1, MKK7, and Jnk and facilitates the activation of Jnk, presumably by localizing the components in the cascade. Other examples of scaffolding proteins are the A kinase-anchoring proteins. This family of proteins binds the regulatory subunit of protein kinase A and localizes it to such diverse intracellular locations as ion channels, centrosomes, and mitochondria. This activity results in the preferential activation of PKA at specific intracellular locations where the relevant substrates are.

**DOMAINS THAT MEDIATE PROTEIN-PROTEIN BINDING**

Another way in which signal transduction pathways commonly are stimulated is through regulated assembly of protein-protein complexes. Most often, these interactions are mediated by conserved domains found in many signal transduction proteins that recognize phosphorylated tyrosine or serine residues or proline-rich sequences (Table 3.4).

<table>
<thead>
<tr>
<th>Motif</th>
<th>Domain (Short Name)</th>
<th>Example of Protein (Also Contains the Domain)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SH2</td>
<td>Src, EPDKen, SHPT</td>
<td>Protein kinase C</td>
</tr>
<tr>
<td>SH3</td>
<td>SH3</td>
<td>Src, PDZ domain</td>
</tr>
<tr>
<td>WW</td>
<td>WD</td>
<td>Src, WW domain</td>
</tr>
<tr>
<td>PDZ</td>
<td>PDZ</td>
<td>EBP50, PDZ domain</td>
</tr>
<tr>
<td>PTB</td>
<td>PTB</td>
<td>Src, WW domain, SH2, SH3</td>
</tr>
<tr>
<td>Ena-vasp</td>
<td></td>
<td>Src, WW domain, SH2, SH3</td>
</tr>
<tr>
<td>CUB</td>
<td>CUB</td>
<td>Src, WW domain, SH2, SH3</td>
</tr>
<tr>
<td>Coronin</td>
<td></td>
<td>Src, WW domain, SH2, SH3</td>
</tr>
</tbody>
</table>

**TABLE 3.4. Protein-Protein Interaction Domains and Motifs**

Both SH2 domains and phosphotyrosine-binding (PTB) domains bind to motifs containing phosphorylated tyrosine residues. Tyrosine kinases and phosphatases regulate the formation of complexes involving these domains. Tyrosine kinases themselves can serve as docking sites for other proteins, which is most evident with tyrosine kinase receptors that recruit such proteins as P3-kinase, p120 Ras GAP, PLC γ, and SHP-2 through SH2 domain-dependent interactions. Tyrosine kinases also phosphorylate other proteins. Tyrosine phosphorylation of the insulin receptor substrate 1 protein by the insulin receptor leads to recruitment of SH2 domain-containing proteins to insulin receptor substrate-1. In addition to mediating protein-protein interactions, binding of SH2 domains to phosphotyrosine residues stimulates the enzymatic activities of such proteins as P3-kinase and Src kinases. In some cases, such as Src kinases, the SH2 domain binds to an intramolecular phosphotyrosine to regulate catalytic activity. Usually, this type of regulation is inhibitory. The crystal structures of several SH2 domains have been determined and reveal a pocket that binds the phosphotyrosine and a groove that determines binding specificity based on the fit of the residues C-terminal (or, in a few cases, N-terminal) to the phosphotyrosine.

PTB domains are functionally analogous to SH2 domains in that they bind phosphotyrosine residues to assemble multiprotein complexes, but they have no sequence or structural similarity to SH2 domains. Thus, they represent an independent evolutionary solution to phosphotyrosine-dependent assembly of protein complexes. A few PTB domains bind to a tyrosine-containing motif in the absence of phosphorylation.

In the last few years, it has become evident that recognition of phosphoserine motifs is also an important means of protein-protein interaction. Forkhead-associated domains, 14-3-3 proteins, and some WD40 and WW domains bind to regions of proteins containing phosphoserine. WD40 domains in proteins that are members of the F-box and WD40 repeat family are important in regulating ubiquitination and subsequent proteolysis of proteins, such as the inhibitor of kB (IκB), which regulates the activity of the transcription factor nuclear factor kB (NFκB). 14-3-3 proteins are a family of small proteins whose primary function appears to be binding to phosphoserine motifs. An example of the importance of this interaction is the role of 14-3-3 in regulating the nuclear location of the phosphatase Cdc25 that regulates the cell cycle. Binding of 14-3-3 to phosphorylated Cdc25 leads to its export from the nucleus and a block in the cell cycle.

Src homology 3 (SH3), WW, and ena-vasp homology domains are structurally distinct, but all bind to proline-rich sequences. Still not clear is how the interaction of these domains with proline-rich regions in other proteins is regulated. Many proteins that contain SH3 domains also have proline-rich regions that could be involved in intramolecular binding, suggesting that a conformational change in the protein could disrupt intramolecular binding and allow the SH3 domain to interact with other proteins. Similarly, the accessibility of proline-rich regions to SH3 domains may be regulated by conformational changes that expose the proline-rich region or disrupt an intramolecular interaction.

PDZ domains recognize motifs in the C-termini of proteins. These domains are found in cytosolic proteins, and many contain multiple PDZ domains. PDZ domain-containing proteins often function to aggregate transmembrane proteins, such as the glutamate receptor. Group I PDZ domains bind to a consensus sequence, T/S-K-X-V, where V is the C-terminus of the protein. Phosphorylation of the S or T in this motif can disrupt PDZ binding in some cases. For example, phosphorylation of this serine in the β2-adrenergic receptor was shown to lead to a loss of PDZ domain–mediated binding to EBP50, which regulates endocytic sorting of the receptor.

**DOMAINS THAT MEDIATE PROTEIN BINDING TO MEMBRANE LIPIDS**

Localization of proteins to membranes greatly limits the space in which proteins can diffuse and increases the probability that enzymes and substrates will contact each other. C1 domains present in protein kinases C (PKC) bind to DAG and thereby recruit PKC to the membrane. Membrane recruitment of PKC is aided also by the C2 domain, which binds to anionic phospholipids in the presence of calcium. This pathway is controlled by DAG production, and the primary source is DAG produced by PLC hydrolysis of PtdIns-4,5-P₂.
membrane. Both the accessibility of the PH domain and availability of phosphatidylinositol (PI(4,5)P2) phosphates likely regulate this interaction. Phosphoinositide kinases regulate the production of phosphoinositides. Phosphatidylinositol 4-kinases synthesize PI(4)P from PI. Type 1 phosphatidylinositol 4-phosphate kinases (PIP(K)) phosphatidylinositol 4-kinases at the 5 position to make PI(4,5)P2. PI(3,4,5)P3, PI(3,4)P2, and PI(3,5)P3 receptors are specific for PI(4,5)P2, respectively. PI(4,5)P2 levels also are regulated by phosphatases. The PI-3-K/PDK1/PDK2 pathway is highly sensitive to the affinity of PH domains in a membrane compartment results in the release of phosphatase proteins containing a PH domain that recognizes the phosphoinositide. Co-localization of a subset of these proteins allows them to interact more efficiently. A recent example of the role of PH domains in such a pathway is the activation of Akt by PDK1. PI(3,4,5)P3 recruitment of Akt and PDK1 to the same membrane location. This activity facilitates phosphorylation and activation of Akt by PDK1. Other domains unrelated to PH domains also bind phosphoinositides. For example, FYVE domains are present in several proteins involved in vesicle trafficking, and they bind to PI(3,4,5)P3.

Cellular membranes are not uniform and appear to be highly organized. One of the principal structures in the plasma membrane is lipid rafts. They are composed of regions of the membrane that are rich in sphingolipids and cholesterol on the extracellular side of the plasma membrane. The lipid component of the cytoplasmic face of lipid rafts, but some evidence suggests that lipid rafts are composed of phosphatidylcholine, phosphatidylethanolamine, and sphingomyelin. Phosphatidylserine is enriched. Glycophosphatidylinositol-linked proteins, transmembrane proteins, and src family members have been localized to lipid rafts. Both the Fce receptor and the T-cell receptor cluster in lipid rafts, which is necessary for their signaling. The basis of protein recruitment to rafts is not yet known.

REGULATION OF PROTEIN LEVELS: TRANSCRIPTION, TRANSLATION, AND PROTEOLYSIS

In addition to influencing the activity of proteins in the cell, signal transduction pathways also regulate the type and levels of proteins expressed in cells. This sort of regulation is necessary for differentiation and the specific function of distinct cell types. Whether a protein is expressed at all in a cell is regulated at the transcriptional level, whereas translation, transcription, and proteolysis have a role in determining the amount of an expressed protein present in a cell.

Ultimately, many signal transduction pathways regulate gene transcription and, thus, the level and type of proteins expressed in the cell. The magnitude of the effect of a signaling pathway on the transcriptional output of a cell is illustrated by the effects of serum on levels of particular mRNAs in fibroblasts. Of 860 genes analyzed, mRNA levels of 500 were induced by serum stimulation. In response to serum stimulation, the ability to transcribe a gene is regulated at many levels, including the structure of the gene in the region of the gene, modifications of the promoter regions, and the activity of transcription factors and coactivators. Signal transduction pathways regulate histone acetylases and deacetylases that determine the accessibility of chromatin to the transcriptional apparatus. Recent work has shown that a number of signals lead to histone hyperacetylation that disrupts the nucleosome to allow transcription. For example, the Rho family small protein Cdc42 and one of its effectors, Jnk, lead to histone hyperacetylation. Likely these pathways cooperate with the activation of transcription factor to induce transcription.

Signal transduction pathways activate transcription factors by many different means. The binding of ligands to the nuclear receptor family of transcription factors causes dissociation of the receptor from a complex with heat-shock proteins and allows the receptor to bind to DNA. Tyrosine phosphorylation of the STAT family of transcription factors by Jak kinases in response to stimulation of cytokine receptors allows them to dimerize through their SH2 domains and enter the nucleus to bind DNA.

TGF-beta receptors activate transcription by phosphorylating SMAD proteins on serine residues. Phosphorylation of SMAD proteins modifies homodimerization with SMAD4 and exposes the DNA-binding domain. Activated SMADs translocate to the nucleus, complex with a protein called Fast1, and bind to DNA to regulate transcription.

Activation of transcription factors also can occur much further downstream from the receptor. Stimulation of the transcriptional activity of Elk-1 by EGF requires activation of a Ras exchange factor, which leads to activation of Ras. Active Ras promotes the stimulation of Raf activity. Raf in turn phosphorylates and activates MEK1, which phosphorylates and activates ERK. ERK translocates to the nucleus and phosphorylates and stimulates the activity of the transcription factor Elk-1.

Translation also is controlled at many levels. The sequence of the RNA can result in stable tertiary structures that bind proteins to regulate location or translation. Often, the ability of these types of RNAs to be translated is regulated by protein kinase cascades. A common target of signal transduction pathways is phosphorylation of initiation factor eIF-4E and availability of eIF-4E. p70 56 kinase regulates the translation of specific mRNA's containing a 5' terminal oligopyrimidine tract by phosphorylation of the ribosomal S6 protein. This increases the ability of the ribosome to process such messages.

The levels of proteins also are regulated by proteolysis, which can occur via either the proteosome or the lysosome. Ubiquitination targets proteins to the proteosome. An example of the role of ubiquitination is the regulation of inhibitor of kB (IkB) levels. Phosphorylation of IkB is stimulated by a number of receptor-mediated signaling pathways. This action leads to its dissociation from the transcription factor nuclear factor kB (NFkB) and allows NFkB to enter the nucleus and bind DNA. After phosphorylation, the transcription factor binding contains protein binds to IkB, recruiting ubiquitin ligase that catalyzes the ubiquitination of IkB and leads to its recognition and degradation by the proteosome.

The second major protein degradation pathway is the lysosomal pathway, which is important also in signal transduction. An early response to the stimulation of a Ras exchange factor, which leads to activation of Ras. Active Ras promotes the stimulation of Raf activity. Raf in turn phosphorylates and activates MEK1, which phosphorylates and activates ERK. ERK translocates to the nucleus and phosphorylates and stimulates the activity of the transcription factor Elk-1.

CHAPTER REFERENCES

8. Vanaman TC, Newmark PA. Cdc42 and one of its effectors, Jnk, lead to histone hyperacetylation. Likely these pathways cooperate with the activation of transcription factor to induce transcription.
9. Transduction pathways activate transcription factors by many different means. The binding of ligands to the nuclear receptor family of transcription factors causes dissociation of the receptor from a complex with heat-shock proteins and allows the receptor to bind to DNA. Tyrosine phosphorylation of the STAT family of transcription factors by Jak kinases in response to stimulation of cytokine receptors allows them to dimerize through their SH2 domains and enter the nucleus to bind DNA.
10. TGF-beta receptors activate transcription by phosphorylating SMAD proteins on serine residues. Phosphorylation of SMAD proteins promotes homodimerization with SMAD4 and exposes the DNA-binding domain. Activated SMADs translocate to the nucleus, complex with a protein called Fast1, and bind to DNA to regulate transcription.
11. Activation of transcription factors also can occur much further downstream from the receptor. Stimulation of the transcriptional activity of Elk-1 by EGF requires activation of a Ras exchange factor, which leads to activation of Ras. Active Ras promotes the stimulation of Raf activity. Raf in turn phosphorylates and activates MEK1, which phosphorylates and activates ERK. ERK translocates to the nucleus and phosphorylates and stimulates the activity of the transcription factor Elk-1.
12. Translation also is controlled at many levels. The sequence of the RNA can result in stable tertiary structures that bind proteins to regulate location or translation. Often, the ability of these types of RNAs to be translated is regulated by protein kinase cascades. A common target of signal transduction pathways is phosphorylation of initiation factor eIF-4E and availability of eIF-4E. p70 56 kinase regulates the translation of specific RNA's containing a 5' terminal oligopyrimidine tract by phosphorylation of the ribosomal S6 protein. This increases the ability of the ribosome to process such messages.
13. The levels of proteins also are regulated by proteolysis, which can occur via either the proteosome or the lysosome. Ubiquitination targets proteins to the proteosome. An example of the role of ubiquitination is the regulation of inhibitor of kB (IkB) levels. Phosphorylation of IkB is stimulated by a number of receptor-mediated signaling pathways. This action leads to its dissociation from the transcription factor nuclear factor kB (NFkB) and allows NFkB to enter the nucleus and bind DNA. After phosphorylation, the transcription factor binding contains protein binds to IkB, recruiting ubiquitin ligase that catalyzes the ubiquitination of IkB and leads to its recognition and degradation by the proteosome.
14. The second major protein degradation pathway is the lysosomal pathway, which is important also in signal transduction. An early response to the stimulation of receptors is their internalization into endosomes; some evidence suggests that signaling persists at this location after endocytosis. In the case of receptor tyrosine kinases, ligand-dependent kinase activity is necessary for endocytosis, mediated by clathrin-coated pits. After endocytosis, either receptors may recycle to the plasma membrane or the endosomes may fuse with lysosomes, leading to degradation of the receptor.
INTRODUCTION

Potentially harmful challenges to the body include viruses, bacteria, unicellular and multicellular pathogens, and cancer cells. In response to these challenges, the body has evolved active defenses that compose the immune system. While the immune system is composed of a wide range of distinct cell types, lymphocytes play a central role by providing the specificity of immune recognition. Through its various appendages, the immune system is capable of interacting, directly or indirectly, with nearly every cell in the body.

There is a central division in the immune system between the humoral branch, which is largely composed of B lymphocytes and their products, and the cellular branch, many functions of which are performed by T lymphocytes. The humoral (from the Latin word *umor* meaning “fluid”) branch of the immune system is involved with the production of antibodies that are capable of neutralizing or destroying harmful challenges to the body. Immune functions classically regarded as cellular immune responses include delayed-type hypersensitivity and rejection of foreign grafts or tumors. As techniques for isolating and identifying cells associated with immune responses developed, it became clear that T cells, or thymus-derived lymphocytes, are the cells essential for cellular immune responses. Thus, understanding the principles of cellular immunity has largely come to mean understanding the development, function, and regulation of T cells.

There are fundamental differences in the ways that the cellular and humoral immune systems recognize antigens (Table 4-1). B cells can recognize antigens not presented in the context of other molecules. T cells, on the other hand, generally recognize antigens in the context of a “self” (major) histocompatibility complex (MHC) molecule on the surface of a cell. T cells use structures on their surfaces called T-cell receptors to recognize antigen-MHC molecule complexes. Whereas Ig is secreted, sometimes in extremely large quantities, few, if any, TCRs are shed by T cells. Underlying the difference in the molecules used for recognition is an important difference in the types of antigens recognized: While B cells can recognize antigen in its native conformation, T cells generally recognize antigen that has been “processed” by another cell and then presented on the surface of the cell by MHC molecules. More specifically, antigen is denatured, cleaved within the cell, and transported into specific subcellular compartments where it is bound by MHC molecules. After a complex of antigen and MHC completes its journey to the cell surface, it is potentially recognizable by a T cell.

**TABLE 4-1. Toward a Molecular Understanding of Immune Recognition of Antigen**

<table>
<thead>
<tr>
<th>MHC</th>
<th>Antigen</th>
<th>TCRs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-antigens</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Processing</td>
<td>Protein, nucleic acid, polysaccharide, other</td>
<td>Protein</td>
</tr>
<tr>
<td>Stability</td>
<td>Stable, stable, stable</td>
<td>Stable, stable, stable</td>
</tr>
<tr>
<td>Source</td>
<td>Self, self</td>
<td>Self, self</td>
</tr>
</tbody>
</table>

We use antigen in this chapter for a substance that binds specifically to the combining site of an antibody or a TCR. Some of these substances elicit immune
responses (immunogens), whereas others do not. There are exceptions to this terminology, such as superantigens, which are discussed later in the section Stimulation of T-Cell Receptors by Superantigens. Also, T cells commonly recognize MHC-peptide complexes, but both the peptide and its parent protein often are termed antigens in the literature.

T CELLS AND CELLULAR IMMUNITY

T lymphocytes were first identified as a functional subset of lymphocytes, the development of which depends on the existence of a thymus. In conditions of congenital absence of the thymus or following neonatal thymectomy in animal models, a number of immune responses were found to be impaired, including cell-mediated killing and transplantation reactions such as graft-versus-host disease and allograft rejection. Subsequent to this functional definition of T lymphocytes, differentiation antigens on T cells were identified using antibodies. The ability to identify T cells and thus to isolate T cells and their subsets, and the ability to grow these cells selectively in culture, has resulted in a body of experimental evidence concerning the mechanisms of maturation, activation, and effector function of this population.

Early experiments showed that the growth of a syngeneic tumor in a mouse could be prevented by prior immunization with that same tumor. Since then, the mechanisms involved in the antitumor immune response have been partially elucidated, and T cells have been shown to play a critical role. Guided by results from animal model studies, human T cells have been shown to be capable of specifically lysing autologous tumor cells in vitro. T cells can also specifically secrete cytokines, such as interferon-g (IFN-g), granulocyte-macrophage colony-stimulating factor (GM-CSF), and tumor necrosis factor-a (TNF-a), and proliferate in response to stimulation with autologous tumor cells. Antitumor T cells can be grown to large numbers in vitro and transferred adoptively to treat even substantial tumor burdens in both humans and mice. Finally, tumor antigens recognized by autologous human T cells have been identified by the use of molecular cloning techniques. Taken together, these findings provide nearly incontrovertible evidence that a T-cell immune response can occur against an autologous tumor.

ANTIGEN PRESENTATION TO T CELLS

The relative importance of how antigens are recognized by T cells (i.e., what T cells "see") to the biologic therapy of cancer is linked largely to the establishment of new immunotherapies based on T cells. These new therapies have ushered in an entirely new set of challenges having to do with how T cells recognize, or may fail to recognize, tumor antigens.

T-cell responses were found by early investigators to be controlled by the presence of particular genes encoded in the MHC. Polymorphisms at this genetic region were observed to control the ability of an animal to mount a T-cell response. Early attempts to demonstrate direct binding of antigen to T cells failed, while attempts succeeded in the case of B cells. Although a straightforward and still useful model of the recognition of antigen by humoral factors was promulgated before the 1900s, it took nearly another hundred years for a similar event to occur for T cells.

T cells express on their cell surfaces molecules of exquisite sensitivity, very much like the antibody molecules found on the surfaces of B cells. These molecules, called TCRs, recognize peptide fragments of antigens, called epitopes, that are noncovalently complexed with MHC molecules. The two major types of MHC molecules, class I and class II, are integral membrane glycoproteins that are noncovalently complexed with antigenic peptides. Class I molecules present antigenic peptides to CD8+ lymphocytes; class II molecules perform the same function for CD4+ lymphocytes. CD8+ effector cells sometimes are termed cytotoxic T lymphocytes (CTLs), because they can lyse target cells directly through the release of lytic granules as well as through triggering "death" receptors, such as Fas, on target cells. CD4+ T cells, while also capable of cytotoxic activity in some cases, are called helper T cells, because they enhance antibody responses by activating B cells, promote other T-cell responses, and activate other important cells in the immune system, such as dendritic cells and macrophages.

A model of how the two major types of T lymphocytes may interact with target cells is depicted in Figure 4-1. A CD8+ T cell is shown interacting directly with a tumor cell, while a CD4+ T cell is shown interacting with an antigen-presenting cell (APC) expressing class II molecules. While class I molecules are found on most tumor cells and somatic cells, class II molecules are found in high concentrations only on a subset of tumor cells and on B-cell, bone marrow–derived phagocytic cells (e.g., macrophages), Langerhans’-dendritic cells, follicular dendritic cells and, in lesser quantities, on other cells including subpopulations of thymocytes, activated peripheral T cells, and certain epithelial cells.

FIGURE 4-1. A model for stimulation of CD4+ and CD8+ T-cell antitumor immunity, based on CD8+ T cells interacting with tumor cells and CD4+ T cells interacting with host antigen-presenting cells (APCs). MHC, major histocompatibility complex; TCR, T-cell receptor.

MAJOR HISTOCOMpatibility COMPLEX MOLECULES AS ANTIGEN RECEPTORS

A molecular understanding of the structure of MHC molecules has made clear their function with respect to antigen recognition by T cells: MHC molecules are receptors for peptide antigens. The major locations, or loci, for class I genes are named A, B, and C in the human and K, D, and L in the mouse (Fig. 4-2). Class II molecules originate from three major subregions in the human, designated DF, DQ, and DR, and two in the mouse designated I-A and I-E. MHC molecules from these major subregions are codominantly expressed. The extent of MHC polymorphism present in the gene pool usually results in heterozygosity for most individuals at every major class I and class II locus. Because there are three different major class I loci and three different major class II loci in the human, most individuals express six different class I alleles and six different class II alleles. Codominant expression in a single individual of MHC molecules originating from multiple loci enhances that individual's ability to present a variety of antigens.

FIGURE 4-2. Highly schematic map of the genomic arrangement of the major histocompatibility complex in humans and mice. For simplicity, class Ib genes and the class III regions are not shown.
Sources of Antigens Bound by Major Histocompatibility Complex Class I and Class II Molecules

Although class I and class II molecules are united by their function as receptors for antigenic peptides, the differences in structure and intracellular trafficking are critical. Class I and class II molecules differ structurally, have different genetic organization and tissue distribution, present bound peptides to different T-cell subsets, and elicit different types of immune responses. Class I and class II molecules also differ in their requirements for binding of peptide antigens, and these peptides originate from different sources. Finally, the two types of MHC follow different intracellular routes on their way to the cell surface and noncovalently associate with peptides in different subcellular compartments.

Recognition of Major Histocompatibility Complex–Antigen Complexes by T-Cell Subsets

There are many interactions involved in T-cell activation, but the specificity of T-cell recognition of a cognate partner cell occurs via the interaction of the TCR with an MHC molecule to which is bound a peptide. The TCR, which is a heterodimer associated on the cell surface with the CD3 complex, is discussed in greater detail later, under Antigen-Specific T-cell Receptors. Although no clear structural or sequence differences between TCRs' detecting class I and detecting class II molecules have been found, a clear difference between the two sets of T cells is found in the ligands for the cell surface markers CD4 and CD8, from which the T-cell sets derive their names. CD8 molecules bind to the α domain of the class I molecules on the target cell, and CD4 molecules bind to the β domain of the class II heterodimer on the target cell.

Some peptide-MHC complexes, designated antigenic, trigger a T-cell response that can consist of proliferation, up-regulation of surface molecules, activation of lytic machinery, secretion of cytokines, or even death by apoptosis. The minimum number of MHC molecules that must be occupied by a particular peptide to activate a very responsive T cell is thought to be extremely low: on the order of 0.03% of the total MHC or fewer than several hundred peptide-MHC complexes.

Sources of Antigens Bound by Major Histocompatibility Complex Class I and Class II Molecules

Antigens complexed with MHC class I and class II molecules originate from two different sources. Class I molecules generally present antigens derived from intracellular sources, whereas class II molecules usually present antigens derived from extracellular sources, although clear examples exist that contradict this distinction, especially in “professional” APCs. A more precise understanding of the sources of antigens can result from an understanding of patterns of intracellular trafficking of these two sets of molecules: Class II molecules interact endocyotised antigen, whereas class I molecules efficiently bind to intracellular antigens in the endoplasmic reticulum. Thus, antigens or antigenic fragments intersecting with the endoplasmic reticulum can be presented by class I molecules; those that intersect with the endosomal subcellular compartment can be presented by class II molecules.

As a result of the differences in the cell biology of MHC molecules, peptides binding to class I molecules are derived mainly from intracellular-cytosolic proteins such as histones and stress proteins, whereas class II peptides are derived primarily from membrane glycoproteins or serum proteins known to enter the acidic vacuolar

FIGURE 4-3. Intracellular trafficking pathways in the presentation of endogenous and exogenous antigen (Ag). CPL, compartment for peptide loading; SRP, signal recognition particle; TAP, transporter associated with antigen processing.
compartment in large quantities. Naturally processed peptides bound to class I molecules are of a very specific size (8 to 10 amino acids) and are smaller than those bound to class II molecules (12 to 20 amino acids), which are much more variable and often nested. These peptides bind to MHC molecules with affinities that can range from the picomolar to micromolar range. Despite a restricted length of peptides presented by MHC class II molecules and the even more restricted length of those presented by class I, a tremendous amount of specificity can still occur. (Note that it is possible to make at least 5 × 10^11 different peptides of nine amino acids.)

It is now possible to forecast which epitopes within a protein will bind to particular MHC molecules. Allele-specific epitope forecasting has now been done with a large number of human and murine MHC molecules, which are characterized by strong preferences for particular amino acid side chains at some positions in the bound peptides and a wide tolerance for amino acid side chains at other positions. Although the anchor positions are critically important in the prediction of which peptides will bind to particular MHC molecules, the amino acid side chains at other positions can play a role and cannot be disregarded.

**MAJOR HISTOCOMPATIBILITY COMPLEX CLASS I PATHWAY FOR ANTIGEN PROCESSING**

CD8+ T lymphocytes are able to monitor the contents of cells by interacting with class I molecules, presenting a display of peptides carried from the endoplasmic reticulum (ER) to the cell surface. Antigen processing is generally necessary for the expression of class I molecules at the cell surface, because class I a chains do not efficiently exit the ER in large quantities unless they are fully assembled with peptide and b2-microglobulin. Furthermore, they need to bind a peptide to be thermodynamically stable. “Empty” class I molecules appear to be unstable at 37°C but somewhat more stable at lower temperatures. Such empty class I molecules are short-lived and subject to proteolysis but nevertheless are expressed at relatively low levels by certain cells, especially those deficient in antigen processing. Because most nucleated cells express stable class I molecules on their cell surfaces, antigen processing is probably a universal characteristic of normal cells. Thus, the molecules involved in the processing of antigen are likely to be expressed ubiquitously as well.

**Structure of Major Histocompatibility Complex Class I Molecules**

Class I molecules are heterodimers composed of an extremely polymorphic 45-kD a chain and b2-microglobulin. Class I molecules are considered by some to be true heterotrimers, as a peptide eight to ten amino acids long having a molecular weight of approximately 1 kD is required for stability and proper expression. Highly schematic structures of class I and class II molecules are shown in Figure 4.4. A bound peptide is presented by the class I molecule.

![Figure 4.4](https://example.com/image.png)

**Origin and Generation of Peptides: The Proteasome**

The task of generating peptide fragments from intracellular proteins for presentation by class I molecules is achieved, in part, by a molecular complex known as the proteasome. This bulky complex has a remarkable ring-like appearance when visualized through the electron microscope and is composed of at least 16 subunits. Highly conserved through evolution, the proteasome is thought to be involved in the protein economy of cells. This primitive structure was likely adapted by the primitive eukaryotic immune system to sample the products of cellular proteolysis for display to the immune system by MHC class I.

Two polymeric proteasome component genes (low-molecular-weight proteins) are encoded in the class II region of the MHC and are designated LMP-2 and LMP-7 and appear to affect the peptide sets that are generated by this structure. Like many of the molecules involved in antigen processing and presentation, the expression of LMP-2 and LMP-7 is up-regulated by IFN-g. Interestingly, low or absent expression of these two molecules has been found in some cancer cells. Another molecule, called MECL-1, or LMP-10, is also up-regulated by IFN-g and can replace the proteasome subunit Z.

Other proteasomal subunits that may play a positive role in the processing of some antigens are PA28 and PA700. Although their precise functions are unknown, they need to bind a peptide to be thermodynamically stable. “Empty” class I molecules appear to be unstable at 37°C but somewhat more stable at lower temperatures. Such empty class I molecules are short-lived and subject to proteolysis but nevertheless are expressed at relatively low levels by certain cells, especially those deficient in antigen processing. Because most nucleated cells express stable class I molecules on their cell surfaces, antigen processing is probably a universal characteristic of normal cells. Thus, the molecules involved in the processing of antigen are likely to be expressed ubiquitously as well.

**Translocation of Peptides by TAP and the Role of Tapasin**

Once peptide fragments are generated in the cytosol, they must be transported into the ER, a task largely carried out by another product of the MHC region, the transporter associated with antigen processing, called TAP. The genes encoding TAP are located in the MHC class II region in both the human and mouse genomes and are interdigitated with the genes encoding the two LMP components of the proteasome. The TAP heterodimer is an adenosine triphosphate–dependent peptide pump, is a member of the ABC (ATP-binding cassette) superfamily of transmembrane transporters, and is related to the products of the multidrug resistance gene. TAP transfers peptides from the cytoplasm directly to newly synthesized class I molecules. There is a growing body of evidence for the selectivity...
of peptide transport by TAP, although the specificity of the TAP peptide-binding site is more promiscuous in human cells than in mouse cells.

In addition to their role in antigen processing, TAP molecules are involved in the assembly of the class I a chain/b-microglobulin/antigenic peptide trimolecular complex through a molecule called tapasin. Tapasin, a 48-kD protein, binds to newly born MHC class I heavy-chain b2-microglobulins that have not yet been loaded with peptide, as well as to the TAP heterodimers. Tapasin may facilitate peptide loading of class I molecules in a number of ways. First, it approximates empty class I molecules to the transporters by tethering the two together. Second, tapasin may regulate TAP function by inhibiting TAP's ability to transport peptides in the absence of empty class I molecules in the ER. Third, a part of the tapasin molecule has been hypothesized to bind directly, but with low affinity and with a fast off-rate, to the peptide-binding cleft of the class I heavy chain. This interaction might be similar to the way the peptide-binding grooves of "empty" MHC class II molecules are occupied by a piece of the invariant chain known as CLIP [described later in the section Role of Invariant Chain (i) in the Folding, Trafficking, and Protection of Class II]. ER-60 is part of the late assembly complexes consisting of MHC class I, tapasin, TAP, calreticulin, and calnexin.

Classical class I molecules assemble in the ER with peptides mostly generated from cytosolic proteins by the proteasome. The activity of the proteasome can be modulated by a variety of accessory protein complexes. A subset of the proteasome b subunits (LMP-2, LMP-7, and MECL-1) and one of the accessory complex, PA28, are up-regulated by IFN-g and affect the generation of peptides to promote more efficient antigen recognition. The peptides are translocated into the ER by TAP. A transient complex containing a class I heavy-chain b2-microglobulin dimer is assembled onto the TAP molecule by successive interactions with the ER chaperones calnexin and calreticulin and a specialized molecule, tapasin. Peptide binding releases the class I b2-microglobulin dimer for transport to the cell surface, while lack of binding results in proteasome-mediated degradation. The products of certain nonclassical MHC-linked class I genes bind peptides in a similar way. A homologous set of b2-microglobulin-associated membrane glycoproteins, the CD1 molecules, appears to bind lipid-based ligands within the endocytic pathway.

Chaperones in the Class I Pathway

Although the class I pathway generally presents peptides of cytoplasmic origin, exogenous antigens that are chaperoned by a heat-shock protein (HSP) can gain access to the class I processing pathway of certain cells, such as particular subsets of macrophages. HSPs derived from tumor cells may be useful in stimulating antitumor CTLs in vivo. Furthermore, inoculation of purified HSPs derived from tumor cells can induce protective immune responses against subsequent tumor challenge in experimental animal systems.

Chaperone proteins are involved in the folding of nascent or incompletely folded proteins and are thought to aid proteins in gaining their proper conformation. Two important chaperones that help glycoproteins in the ER to fold are calnexin and calreticulin. Immature class I molecules have been shown to associate transiently with an 88-kD protein called calnexin. Calnexin (also called P88 or IP90) probably is involved in the folding of class I molecules. Association of class I with calnexin is considered a quality-control molecule, because it prevents unfolded, misfolded, or incompletely assembled a chains from exiting the ER. Calnexin plays a similar role for other proteins, among them such immunologically important proteins as MHC class II and the a/b chains of the T-cell receptor, which do not leave the ER until they are fully assembled with the CD3 complex. Calreticulin, another ER-resident molecule, is a lectin-like chaperone that may replace calnexin after the MHC class I heavy chain binds with b2-microglobulin. Calreticulin clearly differs from calnexin in the way that it associates with class I. Another molecule known to associate with immature Ig molecules, called BiP, also may associate with a subset of class I molecules or may associate with class I molecules in some yet-not-understood sequence with calnexin.

Role of Interferon-g

There is genetic evidence for the related functions of many of the various molecules described in the class I pathway: TAP and proteosome component molecules appear to be very closely associated with the MHC region encoding class I a chains and class II on chromosome 17 in the mouse or chromosome 6 in the human. Many of these groups of molecules appear to be regulated in concert, with IFN-g as the conductor. Molecules known to be up-regulated by IFN-g include at least two, but probably three, proteasome component and regulatory molecules, the peptide transporters, class I heavy chain, and b2-microglobulin. Note also that some HSPs also are inducible with IFN-g. Thus, these groups of molecules appear to share regulatory elements that allow them to be regulated in concert.

Nonclassical Major Histocompatibility Complex and Non-Major Histocompatibility Complex—Encoded Class I Molecules

Nonclassical MHC molecules often are labeled as MHC class b2 molecules in the literature. It is now clear that this group of molecules includes members that are not encoded with the MHC region of the genome. As a group, nonclassical MHC molecules generally are expressed at low levels. They are characterized by limited polymorphism, in stark contrast to MHC class I or class II molecules, which are among the most polymorphic genes to be described. Here, we summarize only briefly some examples of nonclassical MHC molecules. A number of excellent reviews of the topic have recently been published.

One important class b2 molecule is designated HLA-E. Its homologue in the mouse is likely to be Ea-a-t. These molecules have limited sequence polymorphism and are expressed on many different tissues. An important function appears to be modulation of NK-cell activity through binding with NK cell surface CD94/NKG2A (inhibition) or CD94/NKG2C (activation).

HLA-G molecules are expressed by the placenta at the maternal-fetal interface. Mice appear to lack any homologue. Although HLA-G is nonpolymorphic, it behaves in many ways like classical class I molecules in that its loading in the ER is TAP-dependent and it binds to b2-microglobulin. HLA-G binds to peripheral blood myelomonocytic cells. Like HLA-E, it may contribute to the inhibition of NK cells.

Two other MHC class b2 molecules are HLA-E and HLA-G. The first is the mouse H2-M3 molecule, which appears to have a specialized capacity to bind to N-formylated peptides. Formylated peptides are characteristic of some peptides derived from microorganisms, as well as from "self" mitochondrial proteins. Finally, CD1 is a molecule encoded outside the MHC that is capable of interacting with both ab and gd T cells. Like HLA-E, it may contribute to the inhibition of NK cells.

MAJOR HISTOCOMPATIBILITY COMPLEX II PATHWAY FOR ANTIGEN PROCESSING

The ability of a cell to process antigens via the class II pathway (see Fig. 4-3) is more specialized than the almost ubiquitous ability of nucleated cells to process antigen via the class I pathway. Class II–producing cells include macrophages, dendritic cells, Langerhans cells, and B lymphocytes. These cells not only bear class II heterodimers but also possess the invariant chain monomer, the requisite enzymatic machinery, an important subcellular compartment, and molecules called HLA-OM, whose essential function in the class II pathway was discovered more recently. In the class I system, the interaction of class II–peptide complexes with T cells can now be studied with class II tetramers.

Structure and Assembly of Major Histocompatibility Complex Class II Molecules

The class II molecule is very similar to the class I molecule in its general shape, but it is composed of an a chain of 34 kD and a b chain of 28 kD, both of which are integral membrane glycoproteins (see Fig. 4-4 for a highly schematic representation). a and b chains have transmembrane regions as well as short intracytoplasmic domains. The a2 and b2 domains of the class II molecule correspond to the a1 and a2 domains of the class I molecule and thus are directly involved in the binding of the presented peptide. The a3 domain of class II corresponds with the b2-microglobulin light chain of class I. Finally, the b4 domain of class II corresponds with the a4 domain of class I and is involved in the binding of CD4.

Newly synthesized MHC class II molecules assemble in the ER. Three a/b dimers assemble together with an invariant chain trimmer to form a nine-chain structure. Such a conglomeration is thought to stabilize these molecules during their transport through the Golgi apparatus and into the endosomal system (sometimes via the cell surface), where they interact with peptides in a specialized subcellular compartment called the compartment for peptide loading (CPL) by some workers.
Compartment for Peptide Loading

The peptides ultimately presented by class II are derived from protein molecules that generally are acquired from outside the cell (i.e., exogenous) by endocytic vesicles. These vesicles change in composition as they move away from the periphery of the cell toward the nucleus, become acidified, and acquire high concentrations of proteolytic enzymes. Pharmacologic agents, such as chloroquine, that disrupt intracellular pH gradients inhibit antigen processing. Furthermore, mutant cell lines, defective in endosomal acidification, diminish antigen-processing abilities. In B cells, surface-bound Ig molecules may be involved in the acquisition of antigens for presentation. Protein molecules to be presented by the class II pathway are processed by denaturation and proteolysis to short linear segments, some of which fit into the antigen-binding groove of class II molecules. These peptides play a role in determining the structure of class II heterodimers.

A unique endosome-related subcellular compartment has been identified in specialized APCs that naturally express class II. Class II molecules are loaded with antigen in this specialized compartment known as the CPL. Morphologically, CPLs are somewhat heterogeneous in structure. They are spherical or tubular and contain internal membrane vesicles or infoldings, covered with class II a/b. These infoldings presumably increase the surface area for class II and help optimize exposure to potentially antigenic peptides. The invariant chain, ii, likely targets the class II a/b complex to the CPL, probably by a dileucine motif in the cytoplasmic tail of the ii. Because the FcRn-B2 receptor also contains a dileucine motif, such a motif could be implicated in the specific delivery of antigen complexed with antibody to the CPL.

Role of Invariant Chain (ii) in the Folding, Trafficking, and Protection of Class II

Class II heterodimers associate with the ii in the ER soon after synthesis. Dissociation occurs before expression on the cell surface (see Fig. 4-3). The invariant chain (ii) has a single transmembrane domain and an amino-terminal cytoplasmic tail. It is coded for on human chromosome 5 and mouse chromosome 18, and it therefore is not genetically linked with the MHC. Human ii has been found in at least four forms: p33, p35, p41, and p43. These variations result from combinations of alternative splicing and alternative points of the initiation of translation; their different functions are incompletely understood.

ii is known to have at least three important functions. First, it facilitates the folding of class II molecules in a chaperone-like fashion. Second, a specialized portion of the ii called CLIP binds to and protects the peptide-binding site from binding by peptides before the designated physiologic site, the CPL. Finally, the cytoplasmic tail of ii contains an endosomal targeting sequence that directs cellular routing of associated class II heterodimers.

Facilitating Peptide Loading with HLA-DM

Efficient processing of extracellularly derived protein antigens for presentation on class II molecules does not occur in the absence of HLA-DM. The human and the murine (designated H-2M) versions of this molecule are heterodimers, the counterparts of which are called DMA and DMB in the human and H-2Ma and H-2Mb in the mouse. These molecules are similar in structure to classical MHC class II molecules, but they are functionally distinct. They do not present peptide antigens to CD4+ lymphocytes but instead reside in the CPL. HLA-DM is likely to induce the dissociation of a nested set of ii-derived peptides (CLIP) from MHC class II a/b dimers and facilitates peptide loading. This is likely to be a direct enzyme-like interaction that is optimized at an acidic pH.

ANTIGEN PROCESSING AND PRESENTATION IN MALIGNANCY

Most cells in the body express class I peptide complexes, which are the ligands for the TCR on CD8+ T cells. Some tumor cells clearly present antigenic peptides in the context of class I, because specific recognition of tumor cells by cytolytic CD8+ T cells results in their destruction in vitro and in vivo. Tumor cells that fail to process or present antigen recognizable by T cells may enjoy a selective advantage, because they are not susceptible to antigen-specific T cells.

Tumor cells escape antigen-specific T-cell recognition by a number of mechanisms. For example, some tumor cells derived from epithelium express either greatly reduced or absent levels of class I molecules on their surfaces. These histologies include embryonal carcinomas, chorionicarcinomas, cervical carcinomas, mammary carcinomas, small cell carcinomas of the lung, neuroblastomas, some colorectal carcinomas, and some melanomas. Other tumors, including melanoma and renal cell carcinoma, have been shown to loose B2-microglobulin. Other tumors can down-regulate the expression of particular class I loci, or loose the genes for particular class I a chains. Still other tumors, including small cell carcinoma of the lung, can down-regulate the proteasome component molecules LMP-2 and LMP-7 and TAP1 and TAP2.

SPECIALIZED ANTIGEN-PRESENTING CELLS

How are antigens, and tumor antigens in particular, presented to the immune system in vivo? Although most tumor cells express class I molecules and some tumor cells express class II molecules, they generally do not express an important set of products called costimulatory molecules (discussed in detail in the next section, Dendritic Cells), which are believed to be critical for the activation of many T cells resting from prior stimulation and for the activation of all naive T cells. Naive T cells are those that have not been stimulated by antigen outside the thymus. Specialized cells designated as accessory cells can help lymphocytes to respond to antigens. These cells include, first and foremost, dendritic cells (DCs), but they also include mononuclear phagocytes (monocytes and macrophages), activated B lymphocytes, and follicular dendritic cells (FDCs). They are distinguished functionally from the vast majority of somatic cells that can present antigens in the context of MHC only for recognition as target cells by effector T cells. Antigen stimulation by “professional” APCs, exemplified by activated DCs, can stimulate responses not only by resting T cells but also by naive T cells.

DENDRITIC CELLS

DCs were so named because of their distinctive cell shapes. They continually extend and retract processes that are reminiscent of dendrites in neural tissue. These processes presumably increase the DCs’ surface area and its ability to sample surrounding tissues. DCs can be differentiated from macrophages by their lack of Fc receptors and their poor endocytic capacity. While macrophages are persistently adherent to plastic in vivo, DCs are transiently adherent. They abundantly express MHC class II molecules as well as a number of costimulatory molecules.

DCs are far more potent initiators of T-cell–dependent immune responses than any other APC that has been tested. They have a remarkably high density of both class II and class I molecules on their surfaces, which are loaded with processed antigen acquired in large part from exogenous sources. DCs are of hematopoietic origin, but they lack B, T, and NK markers, and no specific or unique differentiation antigen has been found on their surfaces. They can be derived from mononuclear phagocytes under the influence of immunomodulatory molecules in vivo. DCs express large quantities of the costimulatory molecules B7-1 (CD80) and B7-2 (CD86) as well as other T-cell–activating ligands, including intracellular adhesion molecule-1/CD54 (ICAM-1/CD54). They are likely to play an important role in the activation of antitumor T cells in vivo.

DCs are mobile, traveling from the epidermis to the afferent lymphatics as part of a process of maturation. They can be found in peripheral blood or in bone marrow, and in extremely low numbers, and generally are isolated from spleen or blood by a combination of their buoyant density and their adhesive properties. Although dendritic cells are a rare fraction of the total leukocyte population, they can present antigens efficiently for several days after activation. They acquire this antigen through a process called cross-presentation or cross-presentation in which T-cell responses are activated, by DCs, to cellular antigens that originate outside of the DCs. The DCs can be activated by a number of stimuli including lipopolysaccharide (LPS), the interaction of CD40 and CD40 ligand, and double-stranded RNA.

FOLLICULAR DENDRITIC CELLS

FDCs differ from the DCs in many ways. FDCs are likely to be stromal or fibroblast in origin and, unlike DCs, are not from bone marrow stem cells. Although their name may be confusing, suggesting some relationship to DCs, FDCs are, in fact, functionally unrelated to DCs. Their role in the activation of antitumor responses is unclear, but they may have an immunologic role in the activation of B lymphocytes.
B LYMPHOCYTES

B cells can concentrate antigen using membrane-bound Ig. Activated B cells can also express large quantities of the costimulatory molecules B7-1 and B7-2. Finally, B cells clearly present exogenous antigens to CD4+ T cells via their class II molecules, and this is a mechanism for B-cell stimulation of antigen-specific T-cell help.

MONOCYTES AND MACROPHAGES

Mononuclear phagocytes consist mainly of macrophages and monocytes. Monocytes are more differentiated and have more endocytic activity than do macrophages. Macrophages are found in virtually all tissues, especially surrounding blood vessels and near epithelial cells. They generally have what is called a "stellar" morphology. Once they are differentiated, monocytes and macrophages do not divide under normal circumstances. Macrophages in different tissues have different morphologies and different functions. For example, liver macrophages (generally designated Kupffer cells) are located in the sinusoids. The Kupffer cells are the major cellular system responsible for the clearance of particulate material or microbes from the circulation. Kupffer cells play a central role in the acute-phase response, releasing IL-1, IL-6, and TNF on phagocytosing bacteria and their products. Macrophages in the peritoneum are a heterogeneous group of cells and can be microbicidal and tumoricidal. Alveolar macrophages efficiently remove particulate materials from the alveolar spaces. They also secrete proteases and bactericidal molecules.

Immunologically, macrophages participate as APCs. They can express high quantities of adhesion molecules and, importantly, they express on their surfaces the costimulatory molecules in the B7 family. As noted later, macrophages can participate as major effector cells in antitumor responses and in resisting infectious agents. Finally, macrophages can serve to dampen the immune response by secreting inhibitory cytokines such as IL-10; transforming growth factor-b1 (TGF-b1), b2, and -3b, and an IL-1 receptor antagonist. They also ameliorate the cellular immune response by promoting connective tissue repair via such factors as fibroblast growth factor.

T-CELL RECOGNITION OF ANTIGENS

Immune activities of T cells commonly are stimulated after they bind to certain types of other cells. The activities are not stimulated simply because of the binding, however. A variety of receptor-ligand interactions occur between the two cell surfaces that initiate T-cell activation. One of these interactions, that between TCRs and MHC-antigen complexes on the opposing cell surface, is critical for normal antigen-specific activation of most T cells.

ANTIGEN-SPECIFIC T-CELL RECEPTOR

Like other T cells, T cells express a wide array of cell surface receptors for different ligands. However, which is which is distinctly designated T-cell receptor reacts with specific antigenics, albeit generally only after proper processing and presentation by MHC on a target cell surface. The TCR consists of two paired proteins that form a transmembrane, nonsecreted heterodimer unique for each clone of T cells and determining the antigen specificity of the TCR. Two types of TCR have been identified, the ab heterodimer and the gd heterodimer. The crystal structures, determined for four TCRs complexed with peptide-MHC class I and for one TCR complexed with peptide-MHC class II, demonstrate the structural basis for a TCR recognizing both peptide and MHC. In addition, recently developed, soluble, fluorescent peptide-MHC complexes permit identification of individual T cells with a particular antigen specificity, including human tumor antigens.

T-Cell Receptor Genetics

TCR genetics provide the primary source of TCR diversity and antigen specificity. The a, b, g, and d genes encode the TCR by rearrangement from their germline configuration, as do Ig heavy- and light-chain antibody genes. Families of TCR variable (V) genes exist for each receptor chain. During T-cell differentiation, one of the V genes rearranges its position among other gene segments by connecting with one of several alternative joining (J) genes, as a result of losing intervening DNA. A diversity (D) gene between the V and J genes is represented in some but not all classes of chains. This rearranged VDJ gene encodes the variable region of each TCR chain. After combination with a constant (C) gene, generation of RNA, and RNA splicing to remove unused intervening sequences between VDJ and C regions, the final protein chain is expressed.

The extracellular, amino-terminal portion of the molecule contains the antigen-binding variable segment, whereas the carboxyl-terminal portion contains the constant region. In contrast to antibodies, the constant region of the T-cell receptor does not contain different subregions that relate to differences in function, such as binding complement or binding to receptors on the surfaces of other cells. The major functions of the constant region appear to be to provide membrane attachment for the TCR and to participate in signal transduction.

The overall diversity in each TCR chain is the result of independent selection of any one of the multiple variable V, D, and J segments and of the combinatorial diversity inherent in the large number of permutations among these choices. Different possible ab or gd pairings also contribute to the TCR diversity. Both molecular and serologic probes allow the determination of specific V-, D-, and J-region usage for the antigen receptor chains of a given TCR. Although somatic mutation does not appear to be a source of diversity in TCRs, non-germline-encoded (N) regions at the junctional sites between V-, D-, and J-encoded segments add to overall receptor diversity.

T-Cell Receptor Structure

Through a process of differentiation, a mature receptor-bearing T cell will express either an ab or a gd heterodimeric TCR. Nearly all T cells that have been characterized as recognizing specific antigens in a MHC-restricted fashion express ab receptors. On the cell surface, a and b chains, each approximately 40 to 45 kD in molecular weight, are disulfide-linked. Each mature T cell expresses only one b chain gene, because productive rearrangement of a TCR b gene prevents subsequent full rearrangements of other b genes (allelic exclusion), with rare exceptions. The TCR a gene is not subject to allelic exclusion, and T cells have the potential to express two different a chains, one from each allele. Most individual T cells, however, appear to be limited to the functional expression of antigen receptors with the same a chains.

A high frequency of T-cell clones react not only with the foreign antigens that stimulated their response but also with allo-MHC determinants. This dual reactivity may represent cross-reactivity of a single TCR with different antigens, which would maintain the rule of one cell, one receptor. Nevertheless, the possibility of significant numbers of T cells expressing two TCR ab receptors has not been excluded.

The second class of T cells are those expressing gd heterodimers in place of ab heterodimers. The g and d chains are also the products of rearranged genes. The family of V-region genes in the germline is smaller than that for a and b chains; however, additional mechanisms of diversification exist that expand the mature TCR gd repertoire. Antigen processing and presentation commonly are not needed, and the antigen specificity mediated by gd receptors is predominantly MHC-unrestricted. Indeed, many TCR gd receptors may recognize intact proteins in their native configuration, as do Ig, rather than as MHC-restricted peptides. TCR gd receptors are not much involved in most of the classical T-cell responses; however, they appear to serve important roles in the immune system. They can react with a variety of different antigens, particularly certain HSPs and phosphate-containing nonpeptic bacterial antigens that have been highly conserved during evolution. TCR gd cells are in the epithelia of the skin, lung, female reproductive tract, and intestine, where they may contribute to an early line of host defense.

T-Cell Receptor CD3 Complex

Expression of TCRs at the cell surface and also triggering of T cells after the cross-linking of TCRs through binding with antigen depend on the close but noncovalent association of TCRs with the CD3 complex, which consists of several invariant proteins. Cytoplasmic portions of this complex are critical to TCR-initiated signal transduction, and particular extracellular portions provide serologic markers commonly used to define mature T cells with anti-CD3 antisera.

Stimulation of T-Cell Receptors by Superantigens

Superantigens involve a very different type of interaction between the TCR, MHC, and antigen that results in linking TCR and MHC. Superantigens (SAgs) bind in varying degrees to many MHC class II molecules on the target cells and to selected TCR b chain variable (Vb) regions on T cells, away from the classic
antigen-binding regions of these molecules. Crystal structures have been determined for the complex of staphylococcal enterotoxin B (SEB), a bacterial superantigen, with TCR and also for SEB with MHC class II. T-cell specificity for SAgs is determined by whether the T cell expresses the relevant TCR Vβ region. SAgs do not require antigen processing and are not MHC-restricted in the classic sense, as they bind to sites on the MHC class II molecule away from the antigen-binding groove. They may be soluble or bound to cells, and they may arise from endogenous cellular genes. SAgs studied thus far are primarily viral and bacterial products, including streptococcal pyrogenic toxins and staphylococcal enterotoxins, notably connected with toxic shock syndrome and selected types of food poisoning. SAgs also appear to be associated with the human immunodeficiency and rabies viruses. Because of SAgs' binding properties, they can interact with a far higher proportion of T cells than do standard T-cell antigens. Both CD4+ and CD8+ T cells, and possibly T cells expressing selected TCR gd receptors, can be stimulated by SAgs. Like T-cell responses to standard antigens, the potential results of SAg stimulation include T-cell proliferation, cytokine production, enhanced expression of particular cell surface molecules, cytotoxic activity, and anergy or cell death.

Major Histocompatibility Complex–Independent Stimulation of T-Cell Receptors

Cross-linking of TCR/CD3 complexes with subsequent cluster formation appears to be a basic requirement for antigen-specific signal transduction in T cells. Antibodies against extracellular domains of the TCR/CD3 complex will substitute for the MHC-antigen complex if the antibodies are anchored to a surface, such as to other cells through the Fc portion of the antibody or to an artificial surface such as plastic. If the antibody specificity is against a nonpolymorphic determinant, T cells are nonspecifically stimulated. On the other hand, if the antibody specificity is against a determinant unique to the TCR, then T-cell stimulation is highly specific.

T-cell mitogens, such as concanavalin A, bind to a variety of cell surface glycoproteins and stimulate T cells in a nonspecific fashion. The stimulation may depend on cross-linking of the TCR/CD3 complex by the mitogens.

Some antigens that are not SAgs may be recognized by T cells in a fashion that is not MHC-restricted and does not require antigen processing. Described as being among these antigens are selected polyvalent haplens, myelin basic protein, the heme component of hemoglobin, and underglycosylated mucins produced by particular adenocarcinomas of the breast, pancreas, colon, and ovary. A common feature of these particular antigens is tandem repeats of an epitope, such as a particular amino acid sequence for tumor mucins. One model envisioned for this reactivity is based on an antigenic molecule with a polyvalent epitope that mediates cross-linking of the TCR. Unlike SAgs, MHC molecules may attach through their epitopes to the classic antigen-binding site of the TCR. However, T-cell activation by the MUC1 mucin tumor antigen requires target cell binding to both the TCR and accessory molecules on the T-cell surface.

In contrast to types of ligands that stimulate T cells independent of MHC, both at least two particular types of antigens can recognize antigen in the absence of classical MHC, namely those expressing TCR gd receptors and also NKT cells, discussed later in the section Natural Killer Cells.

T-CELL MATURATION

During ontogeny and in T-cell development in mature organisms, precursors of T cells migrate from the bone marrow to the thymus, where most T-cell development occurs. A series of important maturation events, which define specific functions of mature T cells, occur in the thymus. Here, among a considerable amount of cell proliferation and cell death, T cells first express antigen specificity, develop MHC restriction for antigen recognition, and express the cell surface CD4 or CD8 molecules that relate closely to whether the T cell will recognize MHC class I- or class II-restricted antigens. It is here that individual T cells are limited to the expression of a single functional TCR specificity. It is also here that the first round of selection occurs against maturing T cells that react against the body’s normal tissue antigens.

Much of the current understanding of T-cell maturation is based on models that involve genetic changes related specifically to T-cell function, such as transgenic or knockout mice with added or deleted germline genes, respectively, and natural mutants that affect the immune system. In addition, mouse models involving T-cell activation by SAgs have served important roles, because they allow one to monitor the maturation of relatively large numbers of T cells with a known antigen specificity.

MARKERS AND PHENOTYPES

Cell surface markers based on antibody reactivity have been identified that permit associating individual T cells with a particular stage of maturation. The markers are cell surface molecules, which present a characteristic identifying phenotype of the cell when expressed individually or in a certain combination. For example, the TCR/CD3 complex now is commonly used as a marker for mature T cells. Thy-1 (mouse) and CD2 are expressed rather ubiquitously but not exclusively on T cells. CD4 and CD8 are expressed differently by distinct T-cell subpopulations, and mature T cells generally express one but not both.

Development of the T-Cell Antigen Repertoire: Role of the Thymus

The antigen repertoire comprises the antigens that a group of T cells can recognize when the T cells are considered as a whole. The limits of the repertoire of all T cells in the body are set by the combined specificities of TCRs that can be generated. The TCRs that are expressed initially by immature T cells in the thymus represent random specificities that include binding affinities not only for determinants foreign to the host but also for determinants produced by the host’s cells, including tumor cells. However, as described later in this section and in T-Cell Death in the Thymus, T cells expressing some specificities are favored, whereas many others are deleted in the thymus.

The TCRs that mediate MHC-restricted recognition of foreign antigens are encoded by germline genes that, with the few exceptions of extrathymic maturation, are first expressed in the thymus. The TCR repertoire that is expressed by mature T cells as a whole in an individual, however, is molded during at least two points in T-cell development. The first point occurs in the thymus. The second occurs with mature T cells that have left the thymus, and it is discussed later in the section T-Cell Tolerance.

In mouse models, cells with the general phenotype of Thy-1+CD4–CD8– contain the precursors of the T-cell lineage and are located primarily under the capsule in the outer cortex of the thymus. Here, they proliferate rapidly. At this stage, rearrangement of the structural gene for the TCR b chain occurs, which suppresses further rearrangements of the gene and allows assembly of a TCR b chain/CD3 complex with a thymus. This primitive TCR/CD3 complex promotes T-cell maturation to the expression of CD4, CD8, a mature TCR a chain, and cell surface expression of a functional TCR/CD3 complex. The CD4+CD8+ cells are in the thymic cortex, are relatively immature with respect to their functional capacity to stimulate, and constitute for the most part the most thymocytes. For the most part, they are destined to die in the thymus.

The CD4+CD8+ double-positive T cells in the thymic cortex undergo selection that results in a variation of their deletion or continued maturation (Fig. 4-5). Positive selection favors the survival of T cells that, outside the thymus (commonly called the periphery), will react with foreign antigens presented by the same MHC determinants that are expressed in the thymic environment. Positive selection and termination of TCR a chain rearrangement follows the interaction of the TCR with MHC-peptide ligands, primarily on the radiation-resistant cortical epithelial cells in the thymus. MHC-bound peptides that promote positive selection are derived primarily from the endogenous pool of normal proteins within the thymus rather than from foreign proteins. Positive selection may depend on an appropriate level of signaling, triggered by the TCR/CD3 complex and determined by the avidity that represents the concentrations of MHC, peptide, TCR, and their affinities. However, the nature of the MHC-peptide ligands driving positive selection in the thymus and their relationship to the MHC-peptide ligands activating T cells in the periphery have not been established; the relationship may include a TCR’s cross-reactivity between one or more MHC-restricted self-peptides in the thymus and an MHC-restricted foreign peptide in the periphery.
Expression of the CD4 and CD8 molecules, as well as CD45, has an important role in positive selection and T-cell conversion to CD4 or CD8 single-positive cells. TCR and CD45, combined with either CD4 or CD8, frequently are considered as a unit with respect to early signals from the TCR/CD3 complex and their regulation. The mechanism by which the irrelevant coreceptor, CD4 or CD8, is lost as selected double-positive cells mature into single-positive CD8+CD4– or CD4–CD8+ T cells and T-cell lineage commitment is not clear.

Self–Maj or Histocompatibility Complex Defined in the Thymus

Under normal development circumstances, the MHC type of the T-cell maturation environment is identical to the genotype of the maturing T cell; that is, the MHC that is functionally recognized as self by the T cell is also genotypically self. However, under certain experimental or clinical circumstances, functional self and genotypic self need not be identical. For example, in bone marrow–transplanted patients or experimental animals, hematopoietic stem cells, including the precursors of T cells, can develop in an MHC environment different from that of the stem cells. In this circumstance, T cells are selected that preferentially recognize foreign antigen in association with MHC determinants of the host type, even when these are different from the genotypically self-MHC determinants of bone marrow–derived cells. This situation may present important constraints on the ability of hematopoietically derived cells to function effectively in an MHC-restricted fashion.

T-Cell Death in the Thymus

There appear to be three paths that end in the disappearance of T cells in the thymus (see Fig. 4-5). First, immature T cells die if they fail to express a functional TCR. Second, they die if the TCR fails to react with MHC-antigen complexes. Third, negative selection deletes many of the T cells in the thymus that would otherwise be reactive against normal tissues. These T cells—primarily CD4+CD8+ but also single positive cells, depending on the experimental system—are deleted or sometimes rendered unresponsive in a clonal fashion, based on the ability of the TCR to react with MHC-antigen complexes expressed by cells in the thymic stroma. In contrast to ambiguity about the nature of the TCR ligands (MHC-antigen complexes) that induce positive selection, investigators have identified a variety of ligands that can cause negative selection. In mouse models involving SAgs or transgenic animals in which many T cells express a selected self-antigen specificity, the antigens that activate mature T cells can also trigger antigen-specific deletion of immature T cells in the thymus. Both bone marrow–derived and thymic epithelial cells are effective as APCs for negative selection, although the former appear to be more involved in vivo. CD4 and CD8 coreceptors appear to contribute to the triggering of negative selection, as does the lymphocyte function-associated antigen-1/intracellular adhesion molecule (LFA-1/ICAM) interaction. Evidence suggests that clonal T-cell deletion in the thymus has a lower activation threshold than that required for the activation of mature peripheral T cells. This balance would reduce the likelihood of mature peripheral T cells that can react against normal tissues.

The fate of T cells maturing in the thymus, based on a model of T-cell receptor (TCR) affinity for the major histocompatibility–antigen complex on antigen-presenting cells. MHC, major histocompatibility complex; NIL, no affinity.

FIGURE 4-5.
CD8 and CD4 Molecules as Coreceptors

CD8 and CD4, which are cell surface glycoproteins expressed by mutually exclusive subsets of mature T cells, serve as coreceptors for delivering the TCR/CD3 signals. Their role as coreceptors is required for most immune responses by naive T cells and by some activated effector T cells. Acting as coreceptors during antigen recognition, CD8 or CD4 binds to nonpolymorphic regions of the same MHC molecule that presents antigen to the TCR, thus joining with a complex of the TCR/CD3. CD8 and CD4 molecules stabilize the TCR/MHC-peptide complex and contribute to both the binding avidity of TCR to the MHC-antigen complex and to the generation of cytoplasmic signals.

CD45 and T-Cell Activation

CD45, a transmembrane protein tyrosine phosphatase on T cells and other hematopoietic cells, also contributes in a critical fashion to TCR signaling. CD45, generally known as the leukocyte common antigen, is expressed as multiple isoforms resulting from alternative splicing of three exons encoded by a single gene. It has an essential role in linking antigen-stimulated TCR/CD3 complexes to their cytoplasmic signaling pathways. Although blocking antibodies have not had a notable effect on T-cell function, T-cell lines lacking CD45 are markedly defective in TCR signaling by MHC-antigen complexes; responsiveness of the cells is restored by introducing normal CD45 genes. In CD45-deficient mice, thymocyte maturation is largely blocked, and responses of the few peripheral T cells to MHC-restricted antigens are defective.

Following activation of normal naive T cells, their expression of CD45 changes to a lower-molecular-weight form. The different isoforms of CD45 that are expressed on naive as compared with activated or memory T cells may contribute to the different triggering responses of these cells.

T-Cell Receptor Signal Transduction

The cascades of biochemical reactions that transmit the TCR/CD3 activation signals from the cell surface to nuclear DNA have been partially established. Phosphorylation of numerous cytoplasmic and membrane proteins is an essential part of the process. Inositol triphosphosphate (IP₃) and diacylglycerol (DG), which are initiated through several biochemical intermediates by triggering the TCR/CD3 complex. Second messenger is a generic term for molecules produced in response to transduction of a signal initiated by an extracellular ligand, which is the first messenger. The signal cascade is commonly referred to as the phosphatidylinositol (PI) second messenger pathway. The second messengers are at the beginning of two major intracellular signaling routes. Inositol triphosphate and diacylglycerol release free calcium from intracellular stores and activate protein kinase C, respectively. The mobilization of calcium and activation of protein kinase C by other means, such as calcium ionophores and phorbol esters, respectively, can also stimulate T-cell division and cytokine production, independent of TCR/CD3 triggering. The two TCR/CD3 signaling routes finally join in a synergistic fashion within the nucleus to initiate gene transcription. TCR/CD3 complexes that have triggered signaling may be internalized, degraded, and replaced. This process permits sequential receptor stimulation by individual MHC-peptide complexes on the target cells, and it improves the opportunity for target cells expressing low densities of antigen to activate T cells.

Some forms of TCR/CD3 triggering may be sufficient to contribute only to partial responses—for example, lymphokine production but not the expression of growth factor receptors or proliferation. Indeed, the type of T-cell response is sensitive even to single amino acid substitutions in the peptide antigen that are sufficiently subtle to preserve TCR/CD3 triggering yet different enough to vary the nature of the TCR/CD3 signal and the T-cell functional response. The ultimate T-cell response depends on the balance of a variety of factors, including the state of differentiation of the responding cell, the nature of the TCR/CD3 signal, and the different modulating signals from its other cell surface receptors, which, in part, reflect the action of cytokines in the environment and the nature of the APC.

Functional Consequences of T-Cell Receptor Triggering

TCR triggering of T cells commonly induces expression of the high-affinity IL-2 receptor, rouses cells to move from the G₀ resting stage of the cell cycle into the G₁ stage, initiates gene transcription for selected cytokines such as IL-2, and activates effector cell functions of cytotoxic T cells. The IL-2 receptor has a major role in the proliferation of T cells after activation by antigen. The high-affinity cell surface receptor for IL-2 consists of three transmembrane chains—a, b, and g—and is expressed only by activated T cells owing to the lack of a chain expression by resting T cells. The high-affinity receptor promotes T-cell proliferation with relatively low concentrations of IL-2. The b chain, which is expressed constitutively by CD8+ but not by CD4+ T cells, combines with the g chain to form an IL-2 receptor with an intermediate affinity that is approximately 1/100 that of the high-affinity receptor and is expressed on naive T cells. Expression of the b chain is also up-regulated following T-cell activation. Thus, signals from triggered TCRs generally leave naive and memory T cells poised to generate the T-cell growth factor, IL-2, among other cytokines. The cells also are poised to proliferate after IL-2 binding to and triggering of IL-2 receptors. The result of TCR signaling, however, is not necessarily the staging of an antigen-specific immune response. As described later in the section, Deletion of Mature T Cells, it may precipitate cell death by apoptosis.

Adhesion and Accessory Molecules

Relatively weak interactions between the TCR and antigen can be reinforced. Binding of accessory molecules to ligands on APCs, such as LFA-1 to ICAMs, CD2 to LFA-3, and CD5 to CD72, enhances conjugation of the two cells and thereby raises the likelihood of interactions between the TCR and the MHC-peptide complexes (Fig. 4-6).

Molecules that facilitate the binding of a lymphocyte to its target cell are referred to as adhesion molecules. However, an increasing number of these molecules also appear to provide signaling activity after engagement with their ligands, either by enhancing the signal generated by the TCR or by contributing independent stimulatory signals. CD28, CD2, CD5, LFA-1, CD44, CD69, CD4, and CD8 are examples of cell surface receptors that contribute to the signaling events. Optimal activation of T cells with weak avidity for an antigen is thus dependent on receptor-ligand interactions that promote the binding of T cells to APCs and that contribute to the T-cell-activating signals.

CD28 SIGNALING IN T-CELL ACTIVATION

Triggering the TCR/CD3 complex is often referred to as the first signal for T-cell activation. With naive CD4+ and CD8+ T cells and many memory cells as well, the first signal alone is commonly insufficient for stimulating IL-2 production, proliferation, and differentiation. CD28 molecules on the T-cell surface can provide a critical second costimulatory signal by engaging the B7 family of ligands on the APCs, particularly in inflamed sites where APCs are optimally activated. Mice that lack CD28 appear unable to generate T-cell responses to certain viruses or to generate T-cell-dependent antibody responses. CD28 is a homodimeric
transmembrane glycoprotein found on the majority of peripheral T-cell populations, and, in the mouse, on almost all T cells in lymphoid organs or the peripheral blood. Activation of T cells enhances the expression of CD28 and also induces the expression of CTLA-4, a structural homologue of CD28 with a lower level of surface expression than CD28 but a far higher avidity for ligands in the B7 family. CD28 and CTLA-4 signals can have opposite effects. Cross-linking CTLA-4 by B7 ligand can inhibit T-cell activation, IL-2 production, and subsequent cell proliferation. Mice lacking CTLA-4 experience severe, generalized T-cell lymphoproliferation and die within several weeks after birth. Consequently, CTLA-4 may provide a mechanism for down-regulating a T-cell response.

### B7 Family of Ligands

The B7 family of ligands for CD28 and CTLA-4 has two key members: B7-1 (CD80), originally called B7 or B61, and B7-2 (CD86), each of which can trigger second signals. They are both expressed by APCs: the DCs, monocyte-macrophages, and activated B cells described earlier in the section [Specialized Antigen-Presenting Cells](#). They have also been detected on activated T and NK cells. Encoded by separate genes, B7-1 and B7-2 each react with CD28 and CTLA-4 with similar binding affinities, and they have, in part, overlapping and redundant functions. However, there are significant differences in their rates of enhanced expression on activated cells and in their contributions to the development of autoimmune disease in several animal models.

### Functional Consequences of the Second Signal

For naive and memory T cells, the signaling pathway associated with triggering CD28 completes the pathway for T-cell activation that was initiated by TCR/CD3. Triggering CD28, among other activities, appears to stimulate prolonged IL-2 production by increasing the half-life of its messenger RNA (mRNA) and by increasing the rate of gene transcription.

IL-2, a single 15-kDa polypeptide, is the major growth factor for T cells. Although not produced by resting T cells, IL-2 is generated after cell activation, particularly by the Th1 subset of CD4+ helper T cells. Extracellular levels of IL-2 are tightly regulated by the requirement for continuous activation signaling for transcription of its gene, by the controlled half-life of its mRNA, by its serum half-life of minutes, and by the short life span of the activated T cells producing IL-2. IL-2 stimulates both cell proliferation and survival. Activated T cells commonly die without IL-2, as described later in the section [Deletion of Mature T Cells](#).

Mice that are unable to produce IL-2 are only modestly immunodeficient, although they are more prone to autoimmune diseases and die at a young age. The explanation may represent imperfect redundancy among subsets of cytokines. For example, partial compensation for IL-2 may be provided by IL-15, which can stimulate proliferation and differentiation of T cells. The second signal also increases the production of other cytokines (e.g., IFN-g and GM-CSF) likely by the same mechanisms as associated with IL-2. In addition, the second signal activates genes whose products, particularly Bcl-xl, protect against apoptosis, as described later in the section [Deletion of Mature T Cells](#).

In some mouse models, CD28/B7 interactions induce sufficiently high IL-2 production by CD8+ cells that CD8+ CTLs can be generated in the absence of CD4+ T-cell help. Indeed, a major function of helper T cells for CD8+ T-cell responses may be to activate major APCs and their expression of costimulatory ligands, such as B7, rather than simply to provide such cytokines as IL-2 directly to the responding CD8+ T cells. Thus, TCR engagement initiates the response in an antigen-specific fashion, while the requirement for a second signal tends to restrict the response of naive T cells to APCs that provide both antigen and second signals.

Normal cells that express a TCR-reactive antigen but lack a second signal ligand will generally not activate naive T cells; indeed, these cells may induce anergy by apoptosis, as described later in the section [T-Cell Clonal Anergy](#). Of note, T cells can respond even if the ligands for first and second signals are on separate cells, as might be the case for activating CD8+ CTL precursors, with a first signal stimulated by tumor cells and a second signal by APCs. Having the two signals initiated by the same cell is far more efficient, however.

The stimulation requirements of one T-cell population can differ substantially from those of another. For example, naive CD4+ and CD4+ T cells require both TCR triggering and second signals to proliferate and generate activated effector cells. Activated effector cells, however, do not require second signals to engage and kill target cells or release cytokines. The effector cells also do not need to produce IL-2 or to proliferate.

Costimulatory molecules on APCs that can provide critical second signals in the absence of the B7 family have been reported, such as ICAM-1 (the ligand for LFA-1), heat-stable antigen, and selected members of the TNF family. They apparently are not, however, the usual primary source of second signals, and the T-cell response is commonly partial and suboptimal. Alternative sources of costimulation are most effective when combined with a strong primary signal from the TCR.

### ENDING THE NORMAL IMMUNE RESPONSE OF ACTIVATED T CELLS

Eliminating most of the activating antigen generally results in death by apoptosis for the responding lymphocytes, except for those remaining as memory cells. Of note, T cells can respond even if the ligands for first and second signals are on separate cells, as might be the case for activating CD8+ CTL precursors, with a first signal stimulated by tumor cells and a second signal by APCs. Having the two signals initiated by the same cell is far more efficient, however.

The stimulation requirements of one T-cell population can differ substantially from those of another. For example, naive CD4+ and CD4+ T cells require both TCR triggering and second signals to proliferate and generate activated effector cells. Activated effector cells, however, do not require second signals to engage and kill target cells or release cytokines. The effector cells also do not need to produce IL-2 or to proliferate.

Costimulatory molecules on APCs that can provide critical second signals in the absence of the B7 family have been reported, such as ICAM-1 (the ligand for LFA-1), heat-stable antigen, and selected members of the TNF family. They apparently are not, however, the usual primary source of second signals, and the T-cell response is commonly partial and suboptimal. Alternative sources of costimulation are most effective when combined with a strong primary signal from the TCR.

### PERIPHERAL T-CELL TOLERANCE

In contrast to immune responses running a normal course, they can be avoided or aborted very early in the face of naive T cells capable of recognizing the antigen of interest. These events contribute to tolerance, which can be considered, in the broad sense, as failure of the host to generate a normal T-cell response against the antigen of interest and, consequently, failure of the host to clear away cells expressing the antigen. From the broad view, immunoregulatory factors that contribute to ending a normal T-cell response, discussed in the previous section, may contribute to tolerance too, if they help to abort the response. Of note, mechanisms not addressed here can account for a host’s failure to reject cells against which a normal, sustained T-cell response has been generated.

The potential for mature T-cell responses to self-antigens is reduced in the thymus in an antigen-specific fashion by negative selection, a condition referred to as central tolerance. However, some T cells leaving the thymus have the potential to react against self-antigens in the periphery. Escape of self-reactive T cells from the thymus is particularly likely for cells that can react in the periphery with tissue-specific antigens unlikely to be presented adequately or imitated in the thymus in a fashion sufficient to induce clonal deletion. The escaped T cells may encounter more potent immunizing conditions in the periphery, which are sufficient to stimulate T-cell activity against MHC/self-peptide complexes on normal host cells that otherwise would be ignored. For example, an inflamed environment occurring naturally or as part of intentional immunization might reach the threshold necessary for triggering otherwise unresponsive, self-reactive T cells by activating APCs and up-regulating cell surface ligands and receptors that promote immune responses. The lack of a reaction between these potential antigen-responsive T cells and relevant antigens that are present in the body has been referred to as a state of immunologic ignorance that, when overcome, may result in autoimmunity.

Tolerance among mature T cells can also be induced in the periphery in an antigen-specific fashion by causing cellular anergy, in which the T cells are unresponsive to the antigen, or by deleting the cells.

### T-CELL CLONAL ANERGY

In a variety of mouse models, primarily in vitro ones, naive T cells and some memory T cells become anergic in an antigen-specific or clonal fashion after TCR triggering (signal 1) in the absence of costimulation (signal 2). The anergic cells are not deleted; they produce cytokines other than IL-2, albeit at subnormal
levels, and they generate increased amounts of high-affinity IL-2 receptor. They do not, however, produce IL-2 or proliferate, even under optimal conditions for normal activation. The antiapoptotic state can develop within a day of antigen exposure and presumably can last as long as the anergic cells are exposed to antigen. The anergy results from a block in IL-2 gene transcription.

CD4+ Th1 and many CD8+ naive T cells are susceptible. Anergy appears to be inducible only in cells that secrete IL-2, and it can be reversed in at least some cases with IL-2 or by removing the source of antigen.

The opportunities for delivery of signal 1 alone for antigens associated with autologous cells are numerous. Most nucleated cells express MHC class I with endogenous antigens, but relatively few can also provide signal 2. Signal 1 for antigens complexed with MHC class II may be provided without signal 2 by resting B cells and by selected cell types in areas of inflammation, such as vascular endothelial cells. DCs that express MHC class I-restricted antigens by cross-presentation, as discussed earlier in the section Dendritic Cells, but are not well activated may be a common source in draining lymph nodes of tolerance-inducing cells for self-antigens. Whether anergy is a prelude to cell death is an unsettled issue.

Other mechanisms or events that have been associated with a reversible, functional inactivation in various models include down-regulation of expression of the TCR/CD3 complex and CD2, CD4, and CD8 and exposure to structurally suboptimal ligands. Future studies will determine the extent to which the existing observations of anergy and ways of reversing it can be generalized to both CD4+ and CD8+ T cells in various states of activation or differentiation and to in vivo situations.

DELETION OF MATURE T CELLS

After activation, mature peripheral T cells can be deleted by repetitive restimulation with high concentrations of antigen. Conventional antigens, SAgs, T-cell epitopes, and antibodies against the TCR/CD3 complex have all been associated with the outcome. The process, referred to as induction of activated cell death (AICD), can affect Th1 and Th2 CD4+, CD8+, and TCR gd+ T cells. In most cases, T-cell deletion is preceded by IL-2 release from the activated cells, rapid proliferation, and enhanced expression of Fas and Fas ligand for several days, followed by an apoptotic death. When activated, proliferating T cells pass through the late G1 or S phase of the cell cycle, where they appear to be far more susceptible to apoptosis than in the resting stage.

The roles of factors contributing to AICD, such as the strength of the TCR stimulation, the presence of various cytokines, and cosignals delivered by accessory cells, are unsettled. However, the deletion appears to be caused by apoptosis triggered primarily by Fas but also by the receptor for TNF, both of which are up-regulated on activated T cells and subject to triggering by their respective ligands, which are also expressed by activated T cells. Studies of Fas-mediated AICD indicate that apoptosis of the activated T cells with TCRs bound to antigen at the time that Fas is triggered. Activated T cells from mice with a defect in the Fas gene are less susceptible to AICD than normal T cells. These mice exhibit lymphoproliferative and autoimmune disorders. AICD may also serve a normal physiologic function by limiting the height and duration of a T-cell response. Products of the Bcl-2–like family of genes appear to protect against peripheral T-cell apoptosis, particularly Bcl-xL, which can be induced by costimulation from CD28 and can resist either death associated with IL-2 withdrawal or, in some cases, death from activation of Fas.

A high and persistent load of antigen can induce clonal deletion of CTLs and result in a state designated as high-zone tolerance. High-zone tolerance may develop through clonal anergy, clonal deletion, or both, and it appears particularly relevant to the tumor-bearing situation where high levels of antigen prevail.

Withdrawal of IL-2 can also result in the death of the activated T cells. The mechanism differs significantly from that associated with the triggering of receptors in the TNF receptor family, such as Fas. IL-2 withdrawal and Fas stimulation probably involve two at least partially different apoptosis pathways. For example, apoptosis associated with IL-2 withdrawal is better inhibited by selected members of the Bcl-2 family than apoptosis associated with Fas. Unlike Fas-mediated apoptosis, IL-2 withdrawal may destabilize mitochondria, resulting in leakage of cytochrome c and subsequent initiation of apoptosis. Moreover, apoptosis from IL-2 withdrawal may be prevented by other T-cell growth cytokines, such as IL-4, IL-7, and IL-15.

STATES OF MATURE T CELLS

NAIVE, EFFECTOR, AND MEMORY T CELLS

Three populations of T cells—naive T cells, effector T cells, and memory T cells—constitute the antigen repertoire of the pool of mature T cells. They differ by their state of activation and by prior exposure to antigen. The T cells commonly referred to as naive or virgin are immunocompetent T cells that have not encountered antigen in the periphery, such as those that have just emerged from the thymus, the primary lymphoid organ for generating mature T cells from nonfunctional precursors. After activation, these cells may develop specific functions associated with cytotoxic activity or the release of particular cytokines. In this activated state, they are referred to as effector cells. After a short period in the activated state, most of the cells die, but some appear to become memory cells. The extent of T-cell death depends, in part, on the dose of antigen, with lower doses resulting in less death. Products of the Bcl-2-like family of genes provide a level of protection against Fas-mediated apoptosis of activated mature T cells, and this may contribute to the survival of memory T cells after a T-cell response.

Naive T cells are long-lived and circulate through the bloodstream and lymphatics between the secondary lymphoid organs, such as lymph nodes, where they may encounter APCs presenting their specific antigens and be activated. The long life span of naive T cells appears to depend on their TCRs interacting with normal cells expressing complexes of MHC/self-peptide; otherwise, the naive cells die by apoptosis. The interaction does not trigger cell activation and the generation of effector functions, perhaps because TCR triggering is relatively weak, as with positive selection in the thymus. Naive T cells are uncommon in nonlymphoid tissues. They are primarily resting cells that do not proliferate rapidly without antigen stimulation, which would change them to the activated or effector category. Consequentially, little of the antigen repertoire represented by naive T cells is against a particular antigen, unless a SA is involved, as discussed earlier in the section Stimulant of T-Cell Receptors by Superantigens.

A whole, naive T cells form the bulk of the body’s antigen repertoire and, in response to general T-cell depletion, the body’s memory T cells expand back to its baseline numbers.

Effector T cells generally are activated, can proliferate rapidly, act immediately after target cell contact (e.g., cytolysis or cytokine release), and are short-lived. Exhibiting homing properties different from those of naive T cells, they are commonly found in nonlymphoid, extravascular tissues.

Memory T cells are characterized by their ability to generate an immune response that is earlier, more intense, and longer-lasting than that of naive cells, after re-exposure or interaction with the same antigen or a cross-reacting antigen. Unlike effector cells, however, they do not carry out effector cell functions immediately after antigen stimulation, in the context of cytolysis or cytokine release. Their presence in both lymphoid and nonlymphoid peripheral tissues, including areas of inflammation, may reflect the homing patterns of different subsets of memory cells. They appear to be descended from naive T cells that have been activated, although the nature of the progenitors has not been settled, such as naive cells versus effector cells. The memory response probably is associated with a higher frequency of precursors to the effector cells and higher levels of cell surface signaling and adhesion molecules on the memory cells. T-cell memory appears to involve a chronic proliferation of T cells responding to persisting antigen, at least for relatively short-term memory. In at least some cases, long-term memory may persist in the absence of the immunizing foreign antigen and even cross-reacting foreign or self-antigen. Some of the memory T cells, probably those not encountering foreign antigen, may be in a resting (nonproliferative) state. As discussed earlier in the section T-Cell Clonal Anergy and Deletion of Mature T Cells, T cells specifically reactive with the antigen may be deleted or functionally inactivated. In response to general T-cell depletion, the body’s memory T cells expand back to their baseline numbers, independent of that for naive T cells and that for B lymphocytes.

PHENOTYPES OF ANTIGEN-STIMULATED T CELLS

Characteristic cell surface markers have greatly facilitated tracking antigen-activated effector T cells and distinguishing them from naive T cells. The activated mature peripheral T cells express CD45RO, a low-molecular-weight isoform of CD45, and relatively little of the higher-molecular-weight form (CD45RA) associated with naive cells. They may also express a variety of cell surface molecules at higher levels than are found on naive T cells, including CD2, LFA-1, LFA-3, CD27, CD29, CD44, CD69, adhesion molecules in the very late activation antigen (VLA) series that react with extracellular matrix proteins, the IL-2Rα chain associated with high-affinity IL-2 receptor activity, and MHC class II molecules. CD44 is commonly used as a marker for memory cells, because of persistent expression by the cells. As the activated cells revert to a resting stage, many of the activation markers are lost. An unsettled issue is how well cell surface markers can distinguish between activated cells and memory cells; consequently, the two types of cells are grouped together here.
T-CELL MIGRATION

The antigen repertoire of peripheral T cells can be partitioned, to an extent, in the body through the selected migration of T cells out of the circulation. Naive T cells exit the circulation directly into lymphoid tissues through a specialized type of venule designated high endothelial venules (HEVs). The movement of the T cells through the endothelium occurs in several sequential steps that involve progressively lighter binding of the lymphocytes to the endothelial wall and, finally, migration through the endothelium into the extravascular space. Specialized adhesion molecules on naive T cells (e.g., L-selectin), binding to particular mucin-like molecules on the high endothelial venule, provide specificity for the exit site. The process of cell migration into particular tissues and microenvironments is also called homing.

Effector and most memory cells do not bear receptors (e.g., L-selectin) associated with migration directly into normal secondary lymphoid tissues. Instead, they migrate to other selected sites, such as the gastrointestinal wall, the skin, and sites of inflammation. Other receptors not expressed by naive cells have been identified (e.g., VLA-4 for inflamed sites and cutaneous lymphocyte antigen for skin) that contribute to the selective exit sites for memory and effector T cells.

Chemotactic cytokines, or chemokines, contribute to the exit sites for cells by binding to specific determinants on the endothelial wall, such as macrophage inflammatory protein-1b (MIP-1b), which binds to selected proteoglycans on the endothelium and promotes T-cell adhesion, particularly of CD4+ T cells. Inflammation and associated cytokines also up-regulate lymphocyte cytotoxic-binding ligands expressed by the endothelial cells.

The tissue migration of lymphocytes, and of leukocytes in general, is largely influenced by chemokines. These small proteins belong to a family of at least 40 members in humans. On the basis of a cysteine motif, most of the chemokines and their receptors are classified as in the CXC (a) or CC (b) subfamilies. At least 15 cell surface, G protein–coupled receptors for chemokines have been identified. Chemokines in the CXC subfamily act primarily on neutrophils and other selected leukocytes, whereas those in the CC subfamily generally act on a different spectrum of leukocytes and not on neutrophils. Within a subfamily, there is redundancy in receptor-ligand pairing in that most receptors bind more than one chemokine and several chemokines can bind to more than one receptor. A single cell can express different chemokine receptors; thus, cell migration may respond to combinatorial patterns and gradients of chemokines. Cells activated by chemokines may change in other ways, too, such as modulating the expression of cell surface adhesion molecules. Although the conditions have not been resolved under which several types of cells do or do not express particular chemokine receptors, a general pattern is emerging in which chemokine receptor expression, and thus responsiveness to chemokines, may vary with the subtype of cell, such as Th1 versus Th2 T cells, with resting or immature versus activated or mature cells, and with the source of activation. For example, immature DCs express receptors for chemokines commonly produced at sites of inflammation by resident cells and infiltrating leukocytes, and, hence, may home to these sites, where they gather antigens, are activated by cytokines associated with inflammation, and appear to alter their expression of receptors to one another with chemokines produced constitutively in normal lymphoid tissues, with subsequent homing to these sites. Consequently, the recruitment of particular combinations of cells to selected sites, such as naive CD8+ T cells, CD4+ Th1 helper cells, and APCs, is strongly influenced by an integrated combination of cytokines and chemokines. By regulating lymphocyte migration to particular anatomic sites, chemokines affect not only the activation of lymphocytes by antigens but the development and maturation of normal lymphoid tissues.

FUNCTIONS OF MATURE T CELLS

T cells carry out direct and final effector functions. They can also regulate the effector functions of distinct cell populations. This multiplicity of functions confers a potentially pivotal role for the T cell in immune responses.

The CD4+ and CD8+ subsets of T cells differ from one another in important functional parameters. CD4+ T cells frequently express a “helper” phenotype, as measured by their ability to help B-cell responses (antibody secretion) or the responses of other T-cell populations. CD8+ T cells frequently are cytotoxic or are capable of suppressing the immune response of other lymphoid populations. However, these correlations of CD4/8 phenotype with function are by no means absolute.

The bias toward helper function in CD4+ T cells appears to be the indirect consequence of the fact that most helper cells are MHC class II–restricted, and the bias toward cytotoxic function in CD8+ T cells results from the fact that these cells are MHC class I–restricted. The restrictions are a consequence of CD4 and CD8 molecules binding to conserved determinants expressed by MHC class II and class I molecules, respectively.

The relationship works out well conceptually in that cells other than APCs, expressing antigenic peptides complexed with MHC class I molecules, generally express endogenously produced antigens, such as virus-infected cells and tumor cells that are targets of the host immune response. In contrast, cells expressing antigenic peptides complexed with MHC class II molecules generally have acquired the antigens from exogenous sources, and these cells stimulate the immune response rather than serve as targets of the response.

HELPER T IMMUNES

In a variety of immune responses, one T-cell population facilitates or helps the development of effector functions of other T or B lymphocytes. The best-studied example is T-cell help for particular antibody responses by B cells. This function may involve specific signals transmitted by direct interaction of helper T cells and B cells as well as signals delivered by T-cell lymphokines.

The generation of CTLs in situ also generally requires help from other T cells. The helper T cells, activated on APCs, may provide IL-2 and other cytokines for nearby CTL precursor cells attached to the same APCs. The predominant activity of helper T cells, however, may be to promote progressive self-activation and APC activation through TCR/MHC-peptide coupling and CD40L/CD40 coupling between conjugated helper T cells and APCs, followed by the activated APCs instigating the critical first (TCR-triggering) and second (e.g., CD28-triggering) signals for activating attached naive CTL precursors. In addition, the activated APCs may provide important cytokines, such as IL-12, for CTL activation. The latter pathway allows for the stimulation of CTL precursors by APCs activated in the absence of helper T cells, which occurs with some types of microbial infections.

CD4+ T-CELL SUBSETS

CD4+ helper T cells have been further subdivided into two groups of cells, Th1 and Th2, on the basis of the patterns of cytokines that they secrete after being stimulated. In contrast to the T-cell receptor, which determines the specificity of the T cell, the secreted cytokines determine the function of the T cell. One group promotes primarily cellular immune responses and the other group humoral immune responses. Thus, in mouse models, Th1 cells secrete primarily IL-2, IFN-γ, and TNF-α (lymphotoxin), but not IL-4, IL-5, IL-6, or IL-10, and they promote delayed-type hypersensitivity responses, cytotoxic cell responses, and macrophage activation. Responses by Th1 cells promote cellular immune inflammatory reactions and appear to provide the primary host immune defenses against intracellular pathogens. By contrast, Th2 cells secrete IL-4, IL-5, IL-6, and IL-10, but not IL-2 or IFN-γ, and they promote B-lymphocyte responses and the synthesis of IgG, IgE, and IgA antibodies. Responses by Th2 cells promote humoral immunity, allergic reactions, and immediate hypersensitivity reactions, which provide defenses against extracellular pathogens. Th1 and Th2 cells appear to represent a later stage of differentiation from Th0 cells, which display an intermediate expression of receptors to ones associated with chemokines produced constitutively in normal lymphoid tissues, with subsequent homing to these sites. Consequently, the recruitment of particular combinations of cells to selected sites, such as naive CD8+ T cells, CD4+ Th1 helper cells, and APCs, is strongly influenced by an integrated combination of cytokines and chemokines. By regulating lymphocyte migration to particular anatomic sites, chemokines affect not only the activation of lymphocytes by antigens but the development and maturation of normal lymphoid tissues.

Patterns of secreted cytokine profiles have been extended to subgroups of CD4+ cytokytic cells and to T gd cells as well, which are referred to as type 1 cells if they secrete Th1-like cytokines (the major subgroup), or as type 2 cells if they secrete Th2-like cytokines. CD4+ T gd cells in these categories are also referred to as Tc1 or Tc2 cells.

Cytokine patterns themselves have been identified as type 1 or type 2, analogous to those typically produced by Th1 or Th2 mouse cells, to refer to their functions.
rather than their cellular source. This frame of reference has been useful when cells other than CD4+ T cells contributed to the cytokine pool, such as NK cells (e.g., IFN-γ) and macrophages or B cells (e.g. IL-10).

### SUPPRESSOR T CELLS

T-cell suppression of other T cells can be mediated by a variety of mechanisms. Suppressor cell activity has been associated with both CD4+ and CD8+ T cells.

In some instances, suppression appears to be antigen-nonspecific. Possible mechanisms include an effect of cytokines that nonspecifically interfere with proliferation of other responsive T-cell targets. For example, CD4+ Th1 and Th2 helper T cells can each release cytokines that nonspecifically suppress the other, promoting an "immune deviation" toward a Th1-polarized cellular response or a Th2-polarized humoral response. Alternatively, bystander T cells, activated against other antigens, may consume the cytokines essential for T-cell responses against the antigen of interest. States of increased nonspecific suppression have been observed in several pathologic conditions, including some tumor-bearing hosts.

In other cases, suppression may be highly antigen-specific. Suppressor T cells may also act directly on the T cells being suppressed, by exerting veto activity. Veto cells destroy T cells that recognize antigens on the surface of the veto cell. In addition, cytotoxic CD4+ Th1 cells may suppress a response by damaging APCs expressing antigens restricted by MHC class II. Cytotoxic CD8+ T cells may act in a similar fashion, as at least some APCs appear able to process exogenous antigens and present them to MHC class I-restricted, as described earlier in the section. Dendritic Cells.

Suppressive influences can exist in any immune response. The absence of a strong immune response does not necessarily reflect the absence of antigen recognition by the immune system but rather may reflect suppression.

### CYTOTOXIC EFFECTOR CELL MECHANISMS

Different host mechanisms for destroying target cells have evolved, resulting in a diverse collection of cytotoxic cells capable of reacting against a wide variety of foreign cells and organisms. A common feature among them, however, is that cytotoxicity is a regulated process. They are generally activated as a result of cell surface ligands on the target cells binding and triggering selected cell surface receptor molecules on the effector cells.

Major sources of cytotoxic effector cells that have been studied extensively are CTLs, NK lymphocytes, and activated macrophages.

### CYTOTOXIC T LYMPHOCYTES

CTLs result from classic T-cell immune responses: (1) The CTL response is initiated by exposure to antigen, (2) generation and regulation of the response depends on a complex MHC-dependent interaction of antigen-processing cells and T cells, (3) the T-cell antigen receptor (TCR) provides MHC-dependent antigen specificity for the interaction between CTLs and target cells, and (4) memory responses commonly follow reexposure to the antigen, resulting in more rapid, longer, and higher-level responses.

CTLs do not have a characteristic morphology. They may appear as small, resting, agranular lymphocytes or as large, blastic, granular cells or as gradations in between.

All CTLs express the TCR/CD3 complex (described earlier in the section T-Cell Receptor CD3 Complex), which triggers antigen-specific responses. Most CTLs do not express cell surface receptors for Ig (FcR). Most CTLs express either CD8 or CD4 molecules (primarily CD8) but rarely both. In mouse models, both CD8+ and CD4+ T cells can mediate tumor rejection. The class of MHC molecule with which the target cell antigen is associated correlates with whether the CTL is CD4+ or CD8+. The recognition of CTLs primarily MHC class I-associated antigens, and CD4+ and CD8+ CTLs recognize primarily MHC class II-associated antigens.

The distinction between T cells with cytotoxic activity and those with helper activity is not absolute. For example, stimulated CD4+ Th1 T cells can be cytotoxic by the Fas ligand pathway described later in this section (probably their most cytotoxic common pathway), by the release of cytotoxic granules, or by the release of a relatively slow-acting cytotoxic product, lymphotixin. Stimulated CD4+ Th1 T cells also may release cytokines, such as IL-2 and IFN-g, that can promote CTL generation. Moreover, these cells may release GM-CSF after stimulation, which can promote tumor rejection, perhaps through enhancing the development of DCs and their role as APCs. Thus, Th1 or inflammatory CD4+ T cells have the potential to be either helper cells or cytotoxic cells; however, antigen-specific triggering of these cells will be primarily from MHC class II-restricted antigens on the target cells.

Although CTLs use different pathways to destroy target cells, common features are found. The cytolytic reactions generally are triggered by cross-linking of the TCRs on CTLs after contact with target cells expressing antigens that are associated with MHC. A variety of costimulatory accessory molecules, mentioned earlier in the section Adhesion and Accessory Molecules, may only facilitate the binding of CTLs to target cells but may contribute to T-cell triggering by the TCRs. Consequently, the activation of only a few TCRs or TCRs with low affinity for MHC-antigen complexes may be capable of triggering T cells with the support of coagonizing molecules. Death of the target cell usually includes apoptosis, with such distinguishing characteristics as membrane blebbing, chromatin condensation, and DNA fragmentation, followed by lysis. In addition, CTLs are not destroyed during the cytolytic reaction; they can recycle to kill more target cells, although their life span is relatively short. CTLs appear to use two significantly different ways of destroying target cells during rapid cytolytic reactions: granule exocytosis and the triggering of target cell receptors by rapid, cytoskeletal reactions. In addition, CTLs are not destroyed during the rapid cytolytic reaction; they can recycle to destroy more target cells, although their life span is relatively short. CTLs appear to use two significantly different ways of destroying target cells during rapid cytolytic reactions: granule exocytosis and the triggering of target cell receptors by rapid, cytoskeletal reactions. In addition, CTLs are not destroyed during the rapid cytolytic reaction; they can recycle to destroy more target cells, although their life span is relatively short. CTLs appear to use two significantly different ways of destroying target cells during rapid cytolytic reactions: granule exocytosis and the triggering of target cell receptors by rapid, cytoskeletal reactions.

Tests of gene-knockout and gene-reconstitution mouse models have clearly established the importance of granule exocytosis and the Fas-mediated cytotoxicity described later in this section (probably their most cytotoxic common pathway), by the release of cytotoxic granules, or by the release of a relatively slow-acting cytotoxic product, lymphotixin. Stimulated CD4+ Th1 T cells also may release cytokines, such as IL-2 and IFN-g, that can promote CTL generation. Moreover, these cells may release GM-CSF after stimulation, which can promote tumor rejection, perhaps through enhancing the development of DCs and their role as APCs. Thus, Th1 or inflammatory CD4+ T cells have the potential to be either helper cells or cytotoxic cells; however, antigen-specific triggering of these cells will be primarily from MHC class II-restricted antigens on the target cells.

With respect to granule exocytosis, specialized granules are secreted into areas of close contact with target cells after triggering of the TCRs on CTLs after contact with target cells expressing antigens that are associated with MHC. A variety of costimulatory accessory molecules, mentioned earlier in the section Adhesion and Accessory Molecules, may only facilitate the binding of CTLs to target cells but may contribute to T-cell triggering by the TCRs. Consequently, the activation of only a few TCRs or TCRs with low affinity for MHC-antigen complexes may be capable of triggering T cells with the support of coagonizing molecules. Death of the target cell usually includes apoptosis, with such distinguishing characteristics as membrane blebbing, chromatin condensation, and DNA fragmentation, followed by lysis. In addition, CTLs are not destroyed during the cytolytic reaction; they can recycle to kill more target cells, although their life span is relatively short. CTLs appear to use two significantly different ways of destroying target cells during rapid cytolytic reactions: granule exocytosis and the triggering of target cell receptors by rapid, cytoskeletal reactions. In addition, CTLs are not destroyed during the rapid cytolytic reaction; they can recycle to destroy more target cells, although their life span is relatively short. CTLs appear to use two significantly different ways of destroying target cells during rapid cytolytic reactions: granule exocytosis and the triggering of target cell receptors by rapid, cytoskeletal reactions.

Other rapid cytolytic reactions of CTLs with target cells, however, lack features of the granule secretion mechanism and appear to depend on the triggering of target cell receptors by the perforin-deficient mice are impaired in their resistance to at least noncytopathic choriomeningitis virus, Listeria monocytogenes, and tumors. Whereas the granule exocytosis pathway may be used more against pathogens, the Fas-mediated pathway may be more involved with down-regulating immune responses. Of note, Fas is markedly up-regulated on activated T cells, B cells, and NK cells. However, not all Fas-expressing lymphocytes are susceptible to apoptosis through this pathway; prolonged stimulation for at least a period of days may be needed. Understanding which cells are susceptible to this mode of down-regulation is at an early stage.

At least some T cells express additional receptors that can down-regulate cytotoxic activity through an interaction with MHC class I determinants on target cells. Initially found on NK cells, the inhibitory receptors are not related to the antigen-specific TCR. They contribute to the balance between activation and inhibition of T-cell cytotoxic function.

The release of cytotoxic mediators by CTLs is generally antigen-specific and MHC-restricted, because of the TCR-mediated triggering. The cytolytic activity of the released mediators, however, is not target-cell-specific. Only to the extent that their activity is limited to the immediate vicinity of the triggered parent CTLs is cytotoxicity specific for target cells bound to the CTLs. Local activity probably is facilitated by focused effector molecules at the site of target cell contact.
concentration gradients, a short burst of cytotoxic molecules from the parent CTLs, and a short half-life of the mediator.

Several exceptions to the antigen specificity of CTL-mediated lysis of target cells have been described. For example, the expression of Fas ligand on the CTL surface at sites other than contact with the TCR-triggering target cell may destroy innocent bystander cells that express Fas and are in contact with the CTL. In addition, nonspecificity may result from lymphotxin/TNF-α-like molecules that are released from CTL on triggering by MHC-restricted antigens but, given an opportunity to accumulate in the intercellular space, are nonspecifically toxic. The TNF-related, apoptosis-inducing ligand, TRAIL, may be an exception, as the soluble form appears to be more toxic for cancer cells than for normal cells; as a result, the soluble form is being evaluated as a possible cancer chemotherapeutic agent.

NONSPECIFIC CYTOTOXIC CELLS

NK cells and activated macrophages are the host's major sources of cell-mediated cytotoxic activity that is not triggered by antigen-specific recognition of foreign cells. They are part of the host's innate or front-line defense mechanisms, because to function they require no antigen-specific adaptation of the host or immunization. Although there is no memory response by these cells, NK cells and macrophages can be activated by T-cell cytokines, such as IFN-γ. After cell contact, both types of effector cells can be triggered to kill sensitive target cells by antibody-independent interactions between surface molecules on effector and target cells. The nature of these molecules is at a relatively early stage of identification. By contrast, Ig receptors on NK cells and activated macrophages can trigger antibody-dependent cellular cytotoxicity, if the bound target cells have reacted with appropriate Ig subclasses. Thus, apart from their independent roles in host defense, these cells are also important sources of nonspecific cytotoxic immunity. In addition, their production of cytokines and chemokines as part of the innate, innate host defense response can strongly influence subsequent adaptive immune responses. For example, activated NK cells may release large amounts of IFN-γ, which can promote inflammatory, Th1-type T-cell responses and also enhance the expression of a wide array of cell surface molecules.

Natural Killer Cells

NK cells are a relatively small population of lymphocytes distinct from T and B lymphocytes. They generally are large, granular lymphocytes that originate in the bone marrow. NK cells share a common progenitor with T cells, and NK cell precursors have been identified in the thymus; however, they do not require the thymus for maturation, and they probably diverge from the T-cell lineage at an early stage of differentiation.

Several markers are particularly helpful in distinguishing between NK cells and CTLs. Human NK cells are primarily TCR/CD3−, CD5−, CD56+, FcR+. These cell surface features have been used both for physically separating the cells and for functionally distinguishing between NK cell and CTL activity.

Although the picture is far from complete, the basic cytotoxic mechanisms of NK cells and CTLs appear to be similar. Granule exocytosis, perforin, and granzymes have well-established roles in cytotoxicity mediated by NK cells. As with CTLs, the bulk of lytic activity from NK cells depends on perforin. Like CTLs, NK cells depend on surface accessory molecules for the initial binding to target cells. Also like CTLs, accessory molecules expressed on NK cells, such as CD2 and CD59, can contribute to effector cell function when bound to ligand. Granule exocytosis is followed by target cell lysis with apoptosis and then detachment of the NK cell.

NK cells, as with CTLs, can also express or secrete molecules related to TNF, such as FasL and TRAIL, and destroy target cells by apoptosis. In T cells, activation of NK cells increases the expression of these molecules.

Although NK cells are not target cell-specific, they exhibit target cell selectivity by mechanisms independent of antibody and antibody-dependent cellular cytotoxicity. For example, they are more toxic for tumor cells and virus-infected cells than for normal cells. Also, different clones of NK cells show different patterns of cytotoxicity with panels of tumor cells from different sources. Different susceptibilities of target cells to NK cells are, in part, due to families of cell surface receptors that can be expressed by NK cells and that recognize polymorphic MHC class I molecules expressed by target cells. One family of inhibitory receptors, the NK cell complex, is controlled by genes clustered on human chromosome 12 that encode glycoproteins of the C-type lectin superfamily. Another family, designated killer inhibitory receptors, is controlled by genes clustered on human chromosome 19 that encode partial glycoproteins in the Ig superfamily. When cross-linked, the receptors can deliver a dominant signal that inhibits triggering of cytotoxic activity and cytokine expression. Function of the different families of inhibitory receptors is related to a component of their intracytoplasmic tails, the immunoreceptor tyrosine-based inhibition motif (ITIM), which on tyrosine phosphorylation can temporarily inhibit the activation of a variety of cellular activities, such as cytotoxicity and cytokine release. This mechanism appears to explain the tolerance of NK cells for normal cells, as a consequence of the inverse relationship between MHC class I expression and susceptibility to NK-mediated cytotoxicity. Thus, there may be two functionally opposed sets of receptors and ligands associated with triggering cytotoxicity. One set, ill-defined, is not MHC-restricted and triggers cytotoxicity. The other set, which recognizes an MHC class I ligand, can inhibit cytotoxicity. If tumor cells lose MHC class I expression, they escape CTLs; however, they become more susceptible to a subclass of NK cells.

The distinction between NK cells and NK-like activity is important. For example, CTLs cultured with IL-2 can exhibit NK-like activity, but they are not NK cells. Also, a subset of T cells, NKT cells, has recently been described, that expresses some of the cell surface markers usually characteristic of NK cells. NKT cells develop outside the thymus, depend on TCR interaction with MHC class I-like CD1 molecules for development, express a very limited TCR repertoire that reacts particularly with galactosylceramide presented by CD1 molecules, and are CD4−/CD8− or CD4+CD8−. The TCRs of NKT cells are composed of an invariant TCR-α chain paired noncovalently with particular Vβ chains (Vβ2/3/Vβ11 in humans), and they commonly are able to recognize glycolipid antigens or hydrophobic peptide antigens presented by cell surface CD1 molecules. NKT cells mediate NK-like cytotoxic activity after triggering of the TCR; however, their role in regulating early responses of NK cells and T cells also appears important because of their ability to release rapidly large amounts of IFN-γ, IL-4, or both after activation.

Lymphokine-Activated Killer Cells

Both CTLs and NK cells cultured with relatively high doses of IL-2 show enhanced nonspecific cytotoxic activity, as revealed by their ability to lyse selectively a broad spectrum of fresh autologous, syngeneic, or allogeneic tumor cells that are relatively insensitive to normal NK-mediated cytotoxicity. As with CTLs, the bulk of lytic activity from NK cells depends on perforin. Like CTLs, NK cells depend on surface accessory molecules for the initial binding to target cells. Also like CTLs, accessory molecules expressed on NK cells, such as CD2 and CD59, can contribute to effector cell function when bound to ligand. Granule exocytosis is followed by target cell lysis with apoptosis and then detachment of the NK cell.

Correlations have been established in several animal models between progressive tumor growth in vivo and resistance of tumor cells to macrophage cytotoxicity in vitro. However, macrophages can also promote growth of some tumors by effects on the tissue stroma, the blood supply, or the tumor cells themselves. The net effect of macrophages on tumors appears to depend on an array of factors that, with naturally occurring host responses, may balance differently for each tumor.
B CELLS AND HUMORAL IMMUNITY

IMMUNOGLOBULIN HETEROGENEITY AND CLASSES

B cells are antibody-producing cells, in addition to serving as APCs. Driven by antigen binding to cell surface, membrane-anchored Ig, mature B cells proliferate and differentiate into end-stage plasma cells, which produce and release soluble antibodies into extracellular fluids. Antibodies are commonly referred to as immunoglobulins, which are highly heterogeneous but have a common basic monomeric structure consisting of four disulfide-linked polypeptide chains (Fig. 4-7). The two smaller polypeptides of an antibody molecule are identical, are either kappa (k) or lambda (l), and are referred to as light chains. The two larger chains of a monomeric Ig, also identical, are referred to as heavy chains. The great structural heterogeneity of antibody molecules that accounts for the body’s ability to react with a vast variety of antigens results from variability in parts of the molecule near the N-terminals of the heavy and light chains, where the binding sites for antigens are located. A four-chain antibody structure has two antigen-binding sites, because each antigen-binding site is formed by the N-terminal regions of a heavy- and light-chain pair.

A second source of structural heterogeneity of antibodies is in the C-terminal portion of the heavy chains. This heterogeneity, which is much less than that associated with antigen-binding activity, accounts for the structural and biologic differences between the five major Ig classes that have been identified in humans: IgG, IgA, IgM, IgD, and IgE. The Ig classes (isotypes) differ from one another with respect to a variety of properties, such as size, carbohydrate content, the concentration in serum, the serum half-life, the portion that is intravascular, and the ability to cross the placenta (Table 4-2). The circulating Ig classes also are associated with particular biologic activities resulting from interactions of the carboxy-terminal region of the heavy chain with Ig receptors on cells or with other soluble molecules. The biologic activities of selected Ig classes bound to antigen include activating the complement cascade (IgG and IgM); triggering cytotoxic activity by macrophages and particular lymphocytes, such as NK cells (IgG); triggering mast and basophil cells to degranulate (IgE); and promoting phagocytosis of antibody-antigen-complement complexes (IgG and IgM). Entering secretions, such as breast milk and on mucosal surfaces, is characteristic of IgA antibodies, and bound antigen is not a prerequisite.

TABLE 4-2. Some Properties of Human Immunoglobulins

MONOCLONAL ANTIBODIES

Normal humoral immune responses by B lymphocytes are polyclonal and, as a result, the antibodies are heterogeneous. By immortalizing and cloning antibody-producing cells, however, large amounts of homogeneous antibody reacting with a single epitope can be generated. Antibody-producing cells, particularly from mice, are commonly immortalized by fusing them with plasma cell tumors that do not produce Ig but nevertheless are capable of supporting antibody synthesis and secretion. The antibody-producing cell contributes the genetic coding for the antibody to the hybridoma brought about by the fusion, and the plasmacytoma provides the ability to replicate indefinitely.

By cloning large numbers of hybridomas and characterizing the antigen specificities of the different monoclonal antibodies, investigators have generated large and renewable quantities of reagents that, as a group, identify an extensive array of biologically important molecules. These include cellular components that stimulate or regulate immune responses, cellular markers that distinguish one class of cell involved with immune responses from another, cellular markers that help to diagnose the nature of a tumor biopsy specimen, and antigens selectively expressed by tumor cells. Monoclonal antibodies are used not only for identifying and purifying molecules or cells but for triggering or blocking activation molecules on cell surfaces and for targeting cytotoxic and diagnostic imaging reagents to tumors in vivo. With access to the mRNA coding, mouse monoclonal antibodies have been restructured genetically by recombinant DNA technology to generate new types that may be useful in diagnosing and treating cancer. Examples include humanizing mouse antibodies by introducing human sequences without altering the antigen specificity and reducing the antibody size by coding for variable regions of heavy and light chains connected by a polypeptide spacer.

B-CELL MATURATION IN THE BONE MARROW

Stem cells develop within the adult bone marrow into B cells expressing surface IgM and IgD lgs in a fashion that does not require interaction with foreign antigens. These naive or virgin B cells then circulate to lymphoid organs where, stimulated by antigen and appropriate cosignals, they mature further into cells expressing the other Ig classes.

Immunoglobulin Gene Rearrangements as Markers of Maturation Stages

The earliest indication of commitment of a bone marrow stem cell to the B-cell lineage appears to be rearrangement of nonadjacent germline variable V, D, and J genes coding for the variable region of the IgM heavy chain, so that they are next to one another. Successful rearrangement of a V(D)J segment is followed by the synthesis of IgM (µ) heavy chains in a fashion similar to that of a T-cell receptor chain, cell surface expression of the µ chain combined with a temporary surrogate light chain, cessation of further rearrangements of H-chain genes, and the start of rearrangements of kappa (κ) light-chain genes. Successful Vk-Jk pairing results in k-chain synthesis, matching of k and µ heavy chains and expression of monomeric surface IgM molecules; and termination of the gene rearrangements. With a few nonproductive Vk-Jk alignments—perhaps only two—rearrangement of k-chain genes stops and that of lambda (λ) light-chain genes starts, with success resulting in µ heavy chains pairing with light chains. The life span appears to be short for cells with nonproductive gene rearrangements. The large diversity among antibody molecules reflects, in part, the different functional gene arrangements and chain pairings that are possible. Developing B cells with light chains and µ heavy chains
express surface IgM alone, followed in time by both IgM and IgD, which mark the completion of antigen-independent maturation in the bone marrow.

B-cell tumors and Ig-deficiency disorders often represent arrested stages of normal B-cell development. Characterizing the Ig gene rearrangements in these situations has provided key information about the sequence of events during normal maturation and has helped to identify and classify B-cell tumors.

Igs anchored by transmembrane domains to the cell surface are specific markers for B cells. CD19 and CD20, which are not Igs, are also used for identifying B cells. These cell surface products are expressed by pre-B cells and by mature B cells but not by plasma cells.

In addition to the conventional B-cell lineage, another lineage has been observed in humans and in animal models. Referred to as B-1 B cells, in contrast to conventional B-2 B cells, they are bone marrow–derived but differ from the conventional lineage, in part by the general location of mature cells (extra lymphoid sites, such as the peritoneal cavity), cell surface markers, and the antigen specificity repertoire, which is more restricted, of lower affinity, and of broader specificity than the conventional repertoire. Although not as common as conventional B cells, like Tgd cells they may contribute to early host reactions against particular pathogens.

**B-Cell Antigen Receptor**

Igs integrated into the cell surface serve as antigen receptors and cell-signaling molecules. These lgs appear to be part of a signaling complex, the B-cell antigen receptor, that includes at least two additional noncovalently bound transmembrane invariant polypeptides, Ig-a and Ig-b, analogous to the TCR/CD3 complex on T cells. Antigen-specific activation of B cells leads to cell proliferation and differentiation through a process of cell signaling that, like T-cell activation, appears to use multiple tyrosine kinases and the phosphatidylinositol second messengers to turn on DNA transcription factors. Analogous to CD4 and CD8 in T-cell activation, the complex of CD19, CD21, and CD81 has been implicated as a coreceptor for B-cell activation by the binding of CD21 (CR2) to fragments of complement CR3 associated with the antigen.

**Regulation of B-Cell Maturation in the Bone Marrow**

The maturation of B cells is sensitive to a variety of factors in the bone marrow environment, including stromal cells that provide supportive cytokines (e.g., IL-7), chemokines (SDF-1), and direct cell interactions. Cell surface IgM on developing B cells may have an important role in signaling, similar to the T-cell receptor on thymocytes. B-cell development is arrested in animals genetically unable to express cell surface IgM, which may serve as a source of positive signals for development as a result of relatively low-affinity interactions with self-antigens. However, activation of immature B cells by cross-linking surface IgM molecules with either antigen or anti-IgM antibodies can result in cell deletion, likely by apoptosis, rather than proliferation and differentiation. Factor-dependent mechanisms appear to be associated with the apoptosis. For antigen-mediated deletion of immature B cells, relatively high-affinity binding to the surface IgM may be needed. A pause in cell maturation appears to precede deletion. During this period, a portion of the autoreactive B cells rearrange their light-chain genes by a process referred to as receptor editing, and cells with successful rearrangements escape negative selection by expressing new antigen specificities that are not autoreactive.

**One Antibody Specificity per Cell**

As a consequence of limiting successful gene rearrangements, each B cell generally expresses the heavy chain of only one chromosome, the light chain of only one chromosome (allelic exclusion) and, moreover, only one class of light chain (k or l, isotype exclusion). Hence, each B cell generally produces only one antibody specificity. For individual B cells expressing both IgM and IgD molecules, the two classes of antibodies have the same heavy-chain variable region and the same light chains, probably as a result of differential splicing of a single primary RNA transcript that includes the rearranged variable region and both µ and d constant region genes. Hence, they have the same basic antibody specificity for antigen and preserve the general observation of one specificity per cell. As with T cells, antigen specificity is established before a mature but naive B cell encounters foreign antigen. These B cells, considered as a whole, comprise a host's primary B-cell repertoire. The primary repertoire represents antibodies of lower affinity and broader specificity than what follows with further antigen-driven maturation.

**B-CELL MATURATION IN LYMPHOID ORGANS**

Mature but naive B cells migrate from the primary lymphoid organ where they are produced—the bone marrow—to secondary lymphoid organs throughout the body, where further maturation is induced by stimulation with antigens and appropriate cosignals. Successfully stimulated B cells differentiate into antibody-secreting plasma cells or into memory cells. Unstimulated cells appear to die by apoptosis after a relatively short life span.

**T-Cell–Dependent Antibody Responses**

B-cell responses to protein antigens commonly depend on helper (CD4+) T cells, and T-cell–dependent activation of naive B cells starts with antigen binding to Ig cell surface receptors. Antigen processing follows with presentation of MHC class II–restricted peptides. In T-cell–rich areas of lymphoid organs, the B cells act as APCs to help T cells, with receptors capable of binding to the MHC-restricted peptide. Successful T-cell/B-cell interactions may require previously activated helper T cells. The cognate T-cell/B-cell interaction results in mutually rising levels of activation, including up-regulation of the cell surface B7 family of costimulatory molecules on the B cells. Engagement of the CD40 receptor on B cells by a CD40 ligand (CD40L) on activated helper T cells leads to B-cell activation, expression of costimulatory molecules on T cells (CD40L), cell-cell cytokines IL-4 and other cytokines, and additional B-cell/T-cell receptor-ligand interactions. Establishing germinal centers that include FDCs and helper T cells, the activated B cells undergo class switching, antibody affinity maturation and, finally, differentiation into antibody-secreting plasma cells or memory B cells. The B-cell response to an antigen not previously encountered is, in the early stage, primarily by activated naive cells producing IgM antibodies of relatively low affinity.

**Class Switching**

Ig class (isotope) switching occurs, in which cells expressing IgM and IgD receptors at the surface differentiate, essentially irreversibly, into cells expressing IgG, IgA, or IgE receptors. Antibody molecules resulting from a class switch express a new isotype and new associated biologic functions; however, the antigen specificity remains intact, because the light chains and the variable region of the heavy chain do not change. The switching is controlled by a combination of factors, including B-cell–activating agents (e.g., antigens), contact with helper T cells, and particular cytokines (e.g., IL-4, IFN-g, and TGF-b). For example, the switch to IgG by B cells previously activated by antigen and T-cell contact is promoted by IL-4 but inhibited by IFN-g. Class switching involves DNA recombination events between switch regions associated with each heavy-chain constant region. As a result, the V(D)J recombination, coding for the variable region of the heavy chain, comes into close approximation to a new constant region gene, probably because of intervening DNA forming a loop and being deleted (e.g., as a circular episome).

**Changes in Antibody Affinity for Antigen**

Somatic hypermutation in the variable region genes for heavy and light chains of dividing B cells in the germinal centers of secondary lymphoid organs increases the antigen repertoire and the range of antibody-binding affinities for each antigen. As a result, B cells expressing high-affinity antibodies preferentially expand in the face of falling levels of antigen associated with the end of the response. If the response is prolonged, such as after immunization with an adjuvant, class switching and affinity maturation may occur later during the initial (primary) response to the antigen.

**Memory**

Most B cells and plasma cells associated with a primary (IgM) antibody response disappear at the end of the response, which is associated with removal of the antigen and Fas-mediated apoptosis. However, some B cells survive responses to T-dependent antigens as memory cells. Memory B cells express surface IgM molecules other than IgM and develop through a T-cell–dependent process. They appear not to be derived from B cells that have generated a primary (IgM) antibody response but rather from a separate differentiation pathway. Expression of Bcl-2 genes in memory cells may protect against apoptosis. Memory cells are not restricted to the site of antigen interaction; they contribute to the pool of recirculating lymphocytes. Long-term memory cells may not need to divide to survive for years. After reexposure to antigen, activated memory cells generate a more rapid response than the primary one. Moreover, the secondary (anamnestic) response is more
The immune system has evolved as a highly complex and adaptive mechanism for distinguishing between self and nonself and for neutralizing or clearing nonself from the host. Extracellular pathogens are attacked primarily by humoral immune responses, which depend on soluble antibodies produced by B lymphocytes for antigen recognition and for recruitment of effector cells, such as phagocytes and the complement system. Foreign cells, including host cells bearing intracellular pathogens, are recognized and destroyed primarily by cellular immune responses, which depend on the TCR for specific recognition of cell surface antigens and for triggering T-cell activities that kill the foreign cells either directly or through recruitment of other host cells, such as macrophages.

**T-cell Antigen Response**

- The thymus and its role in immunity.
- Adoptive T cell therapy of tumors: mechanisms operative in the recognition and elimination of tumor cells.
- Passive transfer of transplantation immunity.
- Crystal structure of an H-2Kb-ovalbumin peptide complex reveals the interplay of primary and secondary anchor positions in the major histocompatibility complex binding groove.
- MHC molecules as peptide receptors.
- Role of different T cell sets in the rejection of syngeneic chemically induced tumors.
- Three-dimensional structure of the human class II histocompatibility antigen HLA-DR1.
- Structure of the human class I histocompatibility antigen, HLA-A2.
- Intradermal immunization of C3H mice against a sarcoma that originated in an animal of the same line.
- Cancer tumors recognized by T lymphocytes.
- From defined human tumor antigens to effective immunization?
- Tumor-specific cytolysis by lymphocytes infiltrating human melanomas.
- Quantitative studies on tissue transplantation immunity: II. The origin, strength, and duration of actively and adoptively acquired immunity.
- H-2 restriction of adoptive immunotherapy of advanced tumors.
- Regulation of immune responses by inhibitory receptors.
- Natural killer cell receptors.
- T lymphocytes and the thymus. In: Paul WE, ed.
- Intracellular antigen processing for T-cell recognition.
- Antigen-specific responses against low doses of haptenated B-cell mitogens (e.g., trinitrophenyl (TNP)-LPS), which can trigger by Fas on susceptible cells may be involved. B cells can also become unresponsive (anergic) to soluble antigens, probably at a lower antigen concentration or after a prolonged incubation period, as a result of a deletion, as evidenced from the thymus (lifESPAN of anergic B cells is relatively short; hence, the anergy blends into cell deletion. The anergic state may be offset by stimulating the cell surface CD40 molecule and adding IL-4 or by transferring the cells to an antigen-free environment. In addition, B-cell responses that depend on T-cell help can fail as a result of T-cell tolerance. Also, autoimmune B cells may be competitively blocked by other antigen-activated B cells from entering the limited space within the lymphoid follicles of secondary lymphoid organs, where conditions favor optimal stimulation, proliferation, and differentiation. Finally, B cells may simply ignore antigens because of insufficient concentrations or avidity.

**Summary**

The immune system has evolved as a highly complex and adaptive mechanism for distinguishing between self and nonself and for neutralizing or clearing nonself from the host. Extracellular pathogens are attacked primarily by humoral immune responses, which depend on soluble antibodies produced by B lymphocytes for antigen recognition and for recruitment of effector cells, such as phagocytes and the complement system. Foreign cells, including host cells bearing intracellular pathogens, are recognized and destroyed primarily by cellular immune responses, which depend on the TCR for specific recognition of cell surface antigens and for triggering T-cell activities that kill the foreign cells either directly or through recruitment of other host cells, such as macrophages.

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Stimulating T lymphocytes in an antigen-specific fashion commonly requires two cell surface signals. The first signal selects the cell to respond and provides specificity as a result of triggering the antigen-specific receptor (TCR) on the cell surface. The second is an essential (but by itself insufficient) costimulatory signal from APCs, which adds stringency and reduces the likelihood of careless responses. A first signal without a second signal commonly results in anergy or death. The immune system is highly selective; many of the millions of T cells made by each host are deleted before or during development by activation of the apoptotic machinery. All TCRs have an exquisite specificity that reactivates specifically with the antigen. After immunization, a select portion of lymphocytes may persist as a pool of antigen-specific memory cells, which generate relatively quickly a more intense and longer immune response after reexposure of the host to the antigen.

Although far from perfect, immune responses avoid activity against self-antigens generally as a result of processes that remove or inactivate self-reactive cells during the early maturation or adult life of T cells and B cells. Because autologous human tumor antigens recognized by the host's T cells commonly involve unaltered self-antigens, the inactive T cells with potential antitumor activity are of particular interest to tumor immunologists.
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CHAPTER 5
Molecular Biology of Cancer: Cytogenetics

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INTRODUCTION

Cytogenetic testing is one of the fastest-growing areas of testing in oncology. In most cytogenetic laboratories, cancer cases have come to constitute more than 50% of cytogenetic testing done. It is difficult to estimate the total testing being done. A recent survey by the Association of Genetic Technologists reported that more than 95,000 cancer studies were performed in the United States in 1998 (reported by 202 responding laboratories from 243 laboratories surveyed). Because large commercial laboratories did not report their numbers, one would estimate that the total number of such tests in the United States is close to 200,000 per year. This number is, however, rapidly rising as clinicians are becoming aware of the prognostic and diagnostic value of chromosome studies. In this chapter, we do not review the molecular cytogenetic knowledge in particular diseases nor discuss the biological effect of cancer chromosomal abnormalities (e.g., oncogene activation or tumor suppressor genes), because these are covered in detail in separate chapters. We do, however, provide an overview of basic cancer cytogenetics covering terminology, chromosome structure, mechanisms of formation of chromosomal abnormalities, and new technical developments in the field, and cover some genetic topics not covered in other chapters. The continuous advances in techniques of molecular cytogenetics in the last decade are emphasized.

HISTORY OF CANCER CYTOGENETICS

Boveri established the modern paradigm that mutations in somatic cells cause the uncontrolled cell proliferation called cancer. The modern era of human cytogenetics confirmed this view. This era was ushered in with the simultaneous publications by Tjio and Levan of good-quality, unbanded human karyotypes showing 46 chromosomes. Technical improvements were the key to the development of clinical cytogenetics. Within a few years (1956 to 1960), researchers identified specific chromosomal abnormalities associated with congenital abnormalities (e.g., Down, Turner's, and Klinefelter's syndromes) and with cancer. The opening salvo in cancer cytogenetics was the demonstration of the Philadelphia chromosome as associated with chronic myelogenous leukemia (CML). The development of banding techniques in 1969 and 1970 allowed further characterization of this aberration as a balanced translocation involving chromosomes 9 and 22. In the last three decades, the knowledge of human cancer cytogenetics has expanded significantly with the addition of new molecular methodologies, such as in situ hybridization (discussed later in in Fluorescence In Situ Hybridization). The field now is best described as molecular cytogenetics.

CHROMOSOME STRUCTURE AND FUNCTION

Each normal human somatic cell nucleus has 46 chromosomes, 23 chromosomes being maternal and the other 23 being paternal in origin. This diploid chromosome number is reduced to 23 (haploid) during meiosis, a specialized nuclear division during gametogenesis in the ovaries and testis. At conception, haploid cells from each parent combine to form a new diploid cell (zygote), which then divides via mitosis (somatic nuclear division), ultimately creating the fetus. Errors in mitosis or meiosis can lead to pathogenetic changes (discussed later in Numeric Abnormalities). Genetic instructions are encoded in DNA. DNA replicates during the S phase of the cell cycle and condenses during the prophase of mitosis (somaticogenesis) and meiosis (gametogenesis). During metaphase, the characteristic chromosome structures can be observed. Each chromosome represents two chromatids joined at an area of constriction known as the centromere.

LOWER-ORDER CHROMATIN STRUCTURE

The human genome consists of approximately $6.8 \times 10^{9}$ base pairs (bp) of DNA in each diploid cell. If stretched end to end, this length of DNA would span 2 meters. In a normal diploid human cell, this DNA is packaged into 44 autosomes and the two sex chromosomes in a compact nucleus. The first level of packaging involves a wrapping of 200 bp in two turns around a histone core, resulting in the complexes called nucleosomes with a diameter of 10 nm. This basic DNA fiber then is further condensed in a 30-nm-diameter spiral called a solenoid fiber. The solenoid in turn forms larger fibers that are visible with the light microscope as chromatin fibers. Chromatin loops of 60 to 90 kb are anchored at scaffold attachment regions. These loops also appear to represent functional replication domains called replicons.

HIGHER-ORDER CHROMATIN STRUCTURE

The development of various banding techniques in the period from 1969 to 1971 revealed that various chromosomal regions respond differently to biochemical and physical treatments. This suggested that there is a higher-order structure for human chromosomes. One of the first recognized divisions of chromatin is into euchromatin and heterochromatin. Heterochromatin was the material that stained dark (heteropyknotic) with various staining techniques, giving rise to chromocenters in interphase. We now know that this dark staining is a result of the more condensed DNA structure in these regions picking up more DNA dyes. There are two types of heterochromatin. Constitutive heterochromatin is chromatin that is constitutionally condensed in all cells and cell types and is composed of highly repeated sequences that can be detected in cytogenetic preparations using the technique of C-banding. In humans, constitutive heterochromatin is found at the centromeric regions of all chromosomes as well as in the pericentromeric areas of chromosomes 1, 9, and 16 and in the distal long arm of the Y chromosome. Facultative heterochromatin can switch from condensed to decondensed and vice versa. An example of the latter type is the inactivation of the X chromosome in female cells for gene dosage compensation. Meiotic pairing has been shown to require heterochromatin homology and to be sensitive to repeat numbers in both male and female Drosophila. Banding is produced along the chromosomal length of euchromatin because of both structural and functional differences in light and dark
A double-strand break in DNA is susceptible to recombination and fusion and also triggers cell-cycle arrest mediated by p53. Further, DNA replication, as it is now understood, would result in shortening of the ends of replicating linear DNA owing to the mechanisms of function of the DNA replication proteins. Thus, there is an obvious need for telomeres to be unique. Examination of human cells as well as cells from other vertebrates showed that the ends of chromosomes are capped by a simple repeat of six nucleotides (TTAGGG). The telomere sequence is synthesized by a specialized DNA polymerase called telomerase (reviewed in ref. 5). The telomerase function includes an enzymic protein component as well as an RNA component acting as a primer. Telomerase is responsible for programmed end healing in vivo after breaks and in maintaining telomere length. The telomeres further bind other specific proteins that appear to function in protecting the ends of the chromosomes from recombination, nuclease attack, activation of cell-cycle checkpoints, and end-to-end fusions.

Hayflick and Moorhead: recognized that fibroblast cells grown in culture have limited replicative potential (50 to 100 cell divisions). This Hayflick phenomenon is now understood as explained by age-related deterioration of telomeres. In the absence of telomerase, the ends of the chromosomes would shorten gradually (by 25 to 200 bp in each replication) owing to the end-replication problem. It is believed that in normal cells, this deterioration of telomeres can eventually lead to cell-cycle arrest and, thus, cellular senescence. The reverse is also true; it was shown that telomerase reactivation is important in immortalization of cell lines and in cancer development and metastasis. The technique developed by Kim et al., called telomeric repeat amplification protocol, is used, with several available commercial and other modifications, to detect telomerase activity in cell extracts.

It is now recognized that telomerase activity is found in the majority of primary human tumors. There is the potential for development of novel cancer therapies by regulating telomerase or proteins that in turn regulate telomerase levels in cancer cells. Prognostic value for examining telomerase activity in certain cancers is being discussed. An example of this is a significantly worse prognosis in meningomas with telomerase activity versus those without it. One complicating factor is that there are other pathways for developing “immortality” besides telomere maintenance or for maintaining telomeres without detectable telomerase activity (e.g., involving recombination). In fact, some human cancer cells even at metastasis have decreased telomeres and are susceptible to end-to-end attachments in metaphase. This phenomenon was recognized very early in human cytogenetics as “sticky” chromosomal ends. This reduction in telomere length is usually attributed to the increased cell division (most cancers start from a single cell with increased proliferative capacity). Further, genetically engineered mice lacking telomerase RNA lose their telomeres but are still capable of developing tumors.

Some human premature aging syndromes result from decreased replicative capacity of the cells. In the example of Hutchison-Gilford progeria, telomeres are markedly reduced, resulting in decreased replicative capacity. Similar findings are reported in Down syndrome, which predisposes to premature senescence of the immune system as well as predisposition to early Alzheimer's disease. Other nuclear and mitochondrial genes seem to influence aging. For example, Werner and Bloom syndromes are characterized by mutations in DNA helicases.

The centromeric DNA is vital to the attachment of specialized proteins to form a functioning structure called the kinetochore. Kinetochore proteins are responsible for the segregation of the chromatids to the opposite poles of the dividing nucleus during anaphase of mitosis and the segregation of the homologous chromosomes during anaphase of the first meiotic division. The centromere provides a useful landmark along the chromosome axis, dividing each chromosome into two segments or arms: a short arm (known as the p arm from the French petit) and a long arm (the q arm, named after the next letter in the alphabet). By convention, chromosomes are identified by their centromeres. Thus, a derivative chromosome, mostly chromosome 3 material but only one centromere of chromosome 21, is a derivative chromosome 21. Human chromosomes are normally monocentric. Cancer cells occasionally have dicentric and even polycentric chromosomes. Chromosomes are classified by their centromere positions and size into seven groups, A through G (Fig. 5–1). Metacentric chromosomes have equal or almost equal arms (centromere at or almost at the middle of the chromosome). Acrocentrics (chromosomes 13, 14, 15, 20, 21) have a very tiny short arm carrying a satellite of repeat sequences and the nucleolar organizer region and the DNA coding for recombinant RNA (rRNA). A submetacentric is a chromosome wherein the short arm is less than one-half the length of the long arm. Centromeres can be detected using antikinetochore antibodies (e.g., from serum of patients with combined calcinosis cutis, Raynaud's phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia) as well as using alpha satellite DNA probes.

![FIGURE 5-1.](image) Chromosome numbering and nomenclature. The figure illustrates a normal male karyotype. Chromosomes are numbered according to size and centromere position (left panel). Chromosomes are classified into groups based on size and centromere position and, within groups, by banding patterns. Groups A (1–3), B (4,5), C (6–12, X), D (13–15), E (16–18), F (19–20), G (21, 22, Y). Examples of a metacentric, a submetacentric, and an acrocentric chromosome (right panel).

### TABLE 5-1. Functional Significance of Chromosomal Banding Patterns

<table>
<thead>
<tr>
<th>Group</th>
<th>Characteristic</th>
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</thead>
<tbody>
<tr>
<td>A</td>
<td>Centromere near the end of the chromosome</td>
</tr>
<tr>
<td>B</td>
<td>Centromere near the middle of the chromosome</td>
</tr>
<tr>
<td>C</td>
<td>Centromere near the short arm</td>
</tr>
<tr>
<td>D</td>
<td>Centromere near the long arm</td>
</tr>
<tr>
<td>E</td>
<td>Centromere near the middle of the chromosome</td>
</tr>
<tr>
<td>F</td>
<td>Centromere near the short arm</td>
</tr>
<tr>
<td>G</td>
<td>Centromere near the long arm</td>
</tr>
</tbody>
</table>

### CENTROMERES

The centromeric DNA is vital to the attachment of specialized proteins to form a functioning structure called the kinetochore. Kinetochore proteins are responsible for the segregation of the chromatids to the opposite poles of the dividing nucleus during anaphase of mitosis and the segregation of the homologous chromosomes during anaphase of the first meiotic division. The centromere provides a useful landmark along the chromosome axis, dividing each chromosome into two segments or arms: a short arm (known as the p arm from the French petit) and a long arm (the q arm, named after the next letter in the alphabet). By convention, chromosomes are identified by their centromeres. Thus, a derivative chromosome, mostly chromosome 3 material but only one centromere of chromosome 21, is a derivative chromosome 21. Human chromosomes are normally monocentric. Cancer cells occasionally have dicentric and even polycentric chromosomes. Chromosomes are classified by their centromere positions and size into seven groups, A through G (Fig. 5–1). Metacentric chromosomes have equal or almost equal arms (centromere at or almost at the middle of the chromosome). Acrocentrics (chromosomes 13, 14, 15, 20, 21) have a very tiny short arm carrying a satellite of repeat sequences and the nucleolar organizer region and the DNA coding for recombinant RNA (rRNA). A submetacentric is a chromosome wherein the short arm is less than one-half the length of the long arm. Centromeres can be detected using antikinetochore antibodies (e.g., from serum of patients with combined calcinosis cutis, Raynaud's phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia) as well as using alpha satellite DNA probes.

### CYTOGENETIC METHODS

#### SPECIMEN REQUIREMENTS

Most cancer cytogenetic testing involves bone marrow for hematologic malignancies. However, solid-tumor cytogenetics is likely to be the next area of increased clinical relevance, especially with the new techniques of molecular cytogenetics. For hematologic malignancies, a bone marrow aspirate is the preferred sample.
although success can also be achieved in some difficult cases using core biopsies. Peripheral blood samples can be submitted if there are circulating blast cells. A lymph node biopsy may also be used in cases with lymph node involvement. Technologies have developed such that even fine-needle aspirates can be tested for cytogenetic abnormalities. Other types of specimens can be studied, including infiltrates, pleural effusion, spinal fluid, and basically any tissue that may contain dividing cancer cells.

It is important to provide clinical information for specimens submitted for testing. This helps to select appropriate culture and analysis procedures and, in some cases, to suggest additional tests. Examples include (1) the need to stimulate cultures with B-cell mitogens (e.g., Epstein-Barr virus, lipopolysaccharide, or 12-O-tetradecanoyl-phorbol-13-acetate) in B-cell malignancies; (2) the importance of longer culture time in some myeloid disorders [e.g., for detection of t(15;17) in acute myelogenous leukemia (AML M3)]; and (3) offering fluorescence in situ hybridization (FISH) tests in cases of certain translocations should the routine cytogenetics prove negative [e.g., inv(16) in M4e or t(9;22) in CML]. It is recommended that cytogenetic studies be performed at diagnosis and for follow-up of cancer progression. Occasionally, failure to obtain results can be due to the fact that a patient is under treatment (treatments are intended to block cell division). Because the study requires viable cells, specimen handling is important in cytogenetics. Drawing of a bone marrow or a blood sample should be performed using heparinized (sodium heparin) and sterile collection tools and containers. For bone marrow aspirates, volumes can be from 0.25 to 1.0 mL; for blood, 3 to 5 mL is adequate. However, small specimens can also be processed; the best approach is to check with the laboratory.

**BANDING TECHNIQUES (CLASSIC CYTOGENETICS)**

Chromosome analysis requires examining cells in the process of mitosis in which the chromosome structure is most clearly defined (most commonly cells in late prophase or early metaphase). Spontaneously dividing tissues, such as occur in hematopoiensis or in cancer, would be expected to provide mitotic cells for analysis even in a direct harvest of the material submitted. In practice, the quality of such preparations is suboptimal, and cell culture may be required in some cases. The time required for culture and analysis varies, depending on the tissue sampled and specific testing requested. Average turnaround time for studies can be as short as 2 to 3 days for bone marrow, 4 to 7 days for blood, and up to 3 weeks for some solid-tissue biopsies. Chromosomes are prepared on glass slides and are treated by digestion (e.g., with trypsin) and then stained to produce a banding pattern. The most commonly used staining techniques are G-banding and R-banding, which produce characteristic staining or banding patterns for each human chromosome. These techniques, in combination with the physical chromosomal structure, allow for the identification of individual chromosomes.

**FLUORESCENCE IN SITU HYBRIDIZATION**

Mammalian DNA is a double-stranded helix with a phosphate and sugar backbone and hydrogen bonds linking the nucleotides cytosine (C) to guanine (G) and adenine (A) to thymine (T). Under appropriate conditions, the double-stranded DNA can be resolved to single strands, and the complementary single-stranded DNA can be rearrested to a double-stranded helix. The property of DNA strand complementarity is used in various molecular methods involving DNA hybridization. By merging the nucleic acid hybridization onto metaphase chromosome spreads, FISH has established a solid technical foundation for the field of molecular cytogenetics. The principle of FISH is the hybridization of a DNA probe with incorporated reporter molecule to its complementary chromosomal locus, followed by detection of the hapten using fluorescent microscopy, usually with computer-assisted imaging analysis. A routine FISH protocol involves multistep procedures. The reporter molecule can be a protein, such as biotin or digoxigenin, or a fluorescent molecule, such as rhodamine or fluorescein isothiocyanate. Incorporation of the reporter molecule in the probe is performed using nick translation or primer extension with labeled nucleotides. The labeled DNA probe and targeted specimen are treated to denature double-stranded DNA to single strands and then are allowed to hybridize for 2 to 4 hours (depending on specimen and probe).

FISH analysis extends routine cytogenetic banding methods by resolving ambiguous diagnosis and providing a new tool to diagnose submicroscopic abnormalities. FISH is a relatively simple, fast, and reliable procedure. Depending on the sequence complexity of labeled DNA probe and the content of tested specimen, FISH has variable signal sensitivity and spatial resolution. Hybridization probes range from very small DNA fragments (500 bp) to large yeast artificial chromosomes or bacterial artificial chromosomes. The spatial resolution measured by the closest separable signals could range from 5 Mbp on metaphase chromosomes to 100 Kbp on interphase chromatids. The most important features of FISH techniques are its applicability to different specimens and its use for simultaneous detection of several targets using multiple probes. Specimens that can be used for FISH include peripheral blood cells, cultured cell lines, bone marrow cells, paraffin-embedded tissue sections, and frozen tissues. Specific applications of FISH include:

1. **Detection of chromosomal numeric abnormalities.** For example, interphase FISH has been used for detection of trisomy 8 in myeloid disorders, trisomy 7 in prostate cancer, and trisomy 12 in chronic lymphocytic leukemia. This is useful for the detection of minimal residual disease.

2. **Gene amplification.** Detection of amplification and overexpression of genes, such as those involving immunoglobulin, T-cell receptor, and farnesyl transferase genes in lymphomas, and other translocation seen in leukemias or solid tumors. (Fig. 5-2C)

3. **Determination of degree of engraftment in sex-mismatched bone marrow and cord blood transplants (see Fig. 5-2D).**

4. **Determining the origin of specific translocations and marker chromosomes using paint probes in cases where G-banding cannot identify the origin (see Fig. 5-2F).**

5. **Revealing cases with gene amplification** (e.g., see Fig. 5-2E).

**FIGURE 5-2.** Examples of application of molecular cytogenetics. **A:** Fluorescence in situ hybridization (FISH) using probes for ETv6 gene at 12p13 (green) and CBFA2 (AML1) gene at 21q22 (red). These are useful probes for the detection of the t(12;21), a very common translocation in childhood acute lymphocytic leukemia. **B:** FISH using probes for BCR at 22q11.2 (green) and ABL at 9q34 in a case of chronic myelogenous leukemia. Arrow shows the Philadelphia chromosome with fused signals. **C:** Using same probes as in B, showing the ability to detect a fusion in the interphase nucleus on the right (arrow). **D:** Use of repetitive probes for X (red) and Y (green) in sex-mismatched bone marrow transplant. **E:** Illustration of FISH use in gene amplification using a probe for c-myc on 8q24. The probe labels the distal 8q in this case (arrow) plus an amplified area on the homologous 8q (between arrows). **F:** Use of FISH to identify two marker chromosomes (arrows) as derived from chromosome 15 (probes for 15p in green and proximal 15q in red). **G:** Comparative genomic hybridization profile of two chromosomes (19 and 20) from a case of melanoma showing amplification of the distal end of 20q. FISH using BTK (11q13), a gene that hybridizes to 20q and is amplified in a number of cancers showing normal signal on metaphases from normal blood cells.

**MULTICOLOR FISH AND SPECTRAL KARYOTYPING**

In the last few years, new development of FISH allowed for detection of different chromosomes using probes combinatorially labeled with several fluorescent dyes. One method of analysis of this is to image each fluorophore separately and then to allow a computer to translate the different color combinations to values or ratios that are then pseudocolored, resulting in a karyotype with 24 colors for each of the human chromosomes (1 through 22, X, and Y). This multicolor FISH technique can be used to identify derivative and marker chromosomes. A similar technique, named spectral karyotyping, also was introduced by using a combination of epifluorescence microscopy, CCD (cooled-coupled device) imaging, and Fourier spectroscopic measurement. Multicolor FISH and spectral karyotyping cannot detect intrachromosomal anomalies, such as inversions, still require metaphases from the test specimen of good quality, and are limited in resolution to abnormalities involving one or more bands at a 450-banding level.

**PRIMED IN SITU LABELING**
NUMERIC ABNORMALITIES

During the anaphase of meiosis I in germ cells, the homologous chromosomes separate (disjoin) after accomplishing recombination (crossover). During the anaphase
of mitosis and the second meiotic division, chromatids separate (disjoin) and migrate to the opposite poles of the cell. A failure of separation in either of these situations is termed nondisjunction. Rather than both daughter cells receiving the expected number of chromosomes, there will be gain of material in one daughter nucleus and loss of genetic material in the other daughter nucleus. For human autosomes, the normal situation is disomy (two copies of each chromosome). Thus, trisomy refers to having an extra chromosome and monosomy to having a missing chromosome.

Another mechanism for producing a chromosome abnormality is anaphase lag, wherein a chromosome lags at anaphase and fails to be included in daughter nuclei and so is lost. This can result only in monosomy. Trisomies and monosomies are common in human cancers. Polyploidy occurs when cells have more than the normal two sets of chromosomes (diploidy). Thus, a triploid cell will have three sets of chromosomes (modal number of chromosomes, 69) and a tetraploid cell four sets (modal number of chromosomes, 92). Polyploidy is noted in both hematologic malignancies and solid tumors and usually is seen duplicating a set of chromosomes that already have abnormal chromosomes (structural or numeric).

Our understanding of the impact of numeric abnormalities on development and progression of cancer has actually lagged behind that of structural abnormalities. For monosomy, speculation about loss of tumor suppressor genes on these chromosomes abound but, for the most common monosomies (e.g., monosomy 7 in myeloid disorders), no confirmed tumor suppressor genes have yet been cloned that are known to be directly related to these monosomies. Trisomies are even more problematic, as it is difficult to show that specific genes on the extra chromosome are responsible for cell proliferation because of a dosage effect (three vs. two copies of the gene). Recently, it was demonstrated that the extra chromosome 7 in papillary renal carcinomas with trisomy 7 includes the mutant MET allele. This indicates that one mechanism for the effect of a trisomy is duplication of mutant oncogenes. Other involved mechanisms include gene interactions, imprinting, or position effects.

**STRUCTURAL ABNORMALITIES**

Numerous chromosomal abnormalities entail loss or gain of whole chromosomes. By contrast, structural abnormalities involve changes in part of one or more chromosomes. By definition, structural chromosomal aberrations require one or more breaks in the DNA sequence. Structural chromosomal rearrangements are expected to be deleterious. Thus, it is not surprising that strong selective forces in evolution resulted in numerous mechanisms to reduce the rate of chromosomal aberrations, including numerous pathways of DNA repair or cell-cycle arrest after DNA breaks (e.g., p53-mediated cell-cycle arrest in response to double-stranded DNA breaks); protective nuclear architecture with chromosome domains; increased nuclear size in the gametocytes; and asynchrony of DNA replication. Despite these mechanisms, a high incidence of chromosomal abnormalities clearly escapes this negative selection, resulting in an estimated 1% of newborns with constitutional chromosomal abnormalities and, of course, the many chromosomal abnormalities seen in cancer.

While DNA breaks can occur in any sequence, there are clear preferential sites for DNA rearrangements. Several studies on recurrent cancer translocations are particularly illustrative of possible mechanisms for the origin of these abnormalities. In lymphoid neoplasms, it is now well established that many translocations in the immunoglobulin family of genes (immunoglobulin heavy-chain and light-chain genes, T-cell receptor genes, etc.) occur during the genomic DNA rearrangements normally seen in those cells. This occurs because of errors involving transposition during attempted normal recombination of these genes. In other structural abnormalities, a role for repeat sequences at the junction points is implicated. There is experimental evidence of the role of interchromosomal recombination using repeat sequences after double-strand break repair.

Studies on the breakpoints involved in simple and complex t(9;22) showed Aleu repeats preferentially localized near the breakpoints. Waterman and Botstein reviewed other examples of involvement of Aleu repeats in both constitutional and somatic genomic rearrangements. This, combined with the observation of proximity of these genes during certain stages of the cell cycle and differentiation of hematopoietic cells, suggests a possible mechanism for their formation by illegitimate pairing and exchange.

The mechanisms by which structural chromosomal rearrangements exert an effect on the phenotype are varied. Clearly, balanced translocations in cancer lead to fusion products or gene regulation changes (e.g., overexpression of certain genes) that have a direct impact on cellular proliferation, escape from cell-cycle arrest, or apoptosis. In the case of deletions, duplications, trisomies, and monosomies, a gene dosage effect can also be involved. However, gene regulation at the translocation breakpoint or dosage effects probably do not explain all cases. Accumulated data suggest that structural chromosomal abnormalities can impact gene expression not only of the affected chromosomes but of nearby chromosomal regions. In cancer, the acquisition of “suites” of particular chromosomal rearrangements in cancers after the presumed initial cancer genetic change may be explained by nuclear position effects. Another example is cited for the repeated establishment of isochromosome 17q in certain cancers. However, gene alterations at or near the breakpoints clearly explain the effects of the majority of translocations in cancer cytogenetics. This still provides a veritable gold mine for positional cloning of new cancer-related genes.

**Reciprocal Translocations**

A common type of structural chromosome change is the reciprocal translocation. This involves breakage of two chromosomes, a reciprocal exchange, and resealing of the broken ends (Fig. 5-4D). Considering the size of the genome and the small percentage of the DNA that is coding, most random breaks resulting in balanced translocations would not produce a phenotypic effect because no genetic material is lost or gained in the process and no genes are disrupted. A clinically significant abnormality may result when a translocation causes disruption or activation of genes or has a long-range effect on other genes. Although phenotypically normal themselves, carriers of constitutional reciprocal translocations are at increased risk of producing chromosomally unbalanced offspring. Somatic (acquired) translocations in cancer usually result in fusion gene products or in activation of an oncogene function or in both (discussed in Chapter 45.1 and Chapter 46.1).

A few examples here are worth commenting on. The t(14;18)(q32;q21) is found in a majority of lymphomas with follicular center cell morphology and in one-third of diffuse large cell lymphomas. The translocation is associated with overexpression of BCL2 gene at 18q21. The BCL-2 protein is localized in mitochondria, the endoplasmic reticulum, and the nuclear envelope and is involved in cell-cycle regulation. Various rearrangements involving 11q23 occur in acute lymphocytic leukemia (ALL) and a subset of cases with AML. The disrupted gene is the MLL gene at 11q23 with more than 30 different partner genes involved (hence, MLL is called a promiscuous oncogene). The t(11;22)(q24;q12) is found in more than 90% of cases of Ewing's sarcoma and can be very diagnostic. FISH can be used to detect all these translocations using dual color probes (see Fig. 5-2).

**Robertsonian Translocations**

Robertsonian translocations specifically involve breakage at or near the centromeres of two acrocentric chromosomes with the long arms joining to form a novel metacentric or submetacentric chromosome. Because the short arms of these acrocentric chromosomes carry only ribosomal genes, these translocations can reduce the chromosome number without causing a phenotypic abnormality. While these are the most common constitutional translocations, they are very rare as somatic mutations in cancer. When they have been noted in cancer, they seem to exert an effect by being unbalanced translocations resulting in trisomies for the long arms of
the acrocentric chromosomes.

Deletions

Deletions are common in cancer cells. At the G-band level, these may appear as terminal deletions (i.e., one breakpoint with loss of material distal to the breakpoint; Fig. 5-4A). However, most, if not all, are likely not true terminal deletions, and there is no proof that terminal deletions exist in cancer, probably because of cell-cycle arrest due to failure to correct breaks. There are very rare examples of telomere regeneration. The single confirmed recappping by telomerases of a terminally deleted chromosome is the reported chromosome 16 deletion noted in rare cases of patients with mental retardation and hemoglobin abnormalities. Deletions designated as terminal are based on G-banding examination and are cryptic deletions or G-ban translocation. For example, a molecular study of melanoma cell lines with identified "terminal deletions" showed that there is subtelomeric material from other chromosomes located at the ends of these shortened chromosomes. A specialized deletion that occurs on both ends of the chromosomes with joining of the two ends results in ring chromosomes.

Duplication

An intrachromosomal duplication requires at least two breakpoints with the segment between them duplicated either head to tail (direct duplication) or head to head (inverted duplication). One of the most common duplications seen in hemotologic malignancies is the duplication of the long arm of chromosome 1 (breakpoints at q12-21 and q31-q44). This duplication is especially noted in lymphoid malignancies (ALL and lymphomas), usually as a secondary abnormality with poor prognosis.

Inversions

An inversion is an alteration in a chromosomal segment involving two breaks, with reintegration of the segment in the chromosome in reverse orientation. When the two breakpoints occur on one side of the centromere, this is termed paracentric inversion. A good example is the paracentric inversion on the long arm of chromosome 3 seen in AML (Fig. 5-4B). If the two breaks surround the centromere (pericentric inversion), a change in arm ratio of the chromosome may occur. The pericentric inversion of chromosome 16 seen in acute myelomonocytic leukemia with abnormal eosinophils (M4eo) is a good example. The result of the inversion is a fusion between the myosin heavy-chain gene (MYH11) on 16p13 and the core-binding factor b, a transcription factor at 16q22. In a subset of patients with inv(16), the breakpoints also appear to cause loss of a gene for a multidrug resistance protein. Because this inversion is rather difficult to see in suboptimal chromosome preparations, FISH is an ideal tool for detecting this inversion. While noted in a number of FAB classes, most cases of inv(16) are classified as M4eo and carry a favorable prognosis. In those patients, trisomy 6, trisomy 22, and deletion of chromosome 7 may also occur.

Isochromosomes and Dicentric Chromosomes

An isochromosome is derived by breaks in one arm of a chromosome followed by rearrangement of the chromatids to produce duplications of the other arm of the chromosome. These are usually dicentric chromosomes, with the net effect being a loss of material from one arm and duplication of the other arm. A classic example is the common observation of isochromosome 17q seen in myeloid and lymphoid malignancies as well as in adenocarcinomas (different organs) and neuroectodermal tumors. In all these cases, the presence of i(17)(q10) carries a poor prognosis. An i(1)(q10) is noted in adenocarcinomas (breast, kidney, intestine, uterus) and less so in hemotologic malignancies. A variation is the break involving two nonhomologous chromosomes forming a dicentric chromosome (Fig. 5-4C).

Gene Amplification

Molecular genetic methods allowed for rigorous study of variations in gene copy number in mammalian cells. This allowed for the understanding of the earlier cytogenetic observation of "double minutes" (DMs) and of homogeneously staining regions (HSRs) in cancer cells and drug-resistant cell lines. HSRs and other forms of chromosomal DNA amplification are notable as unusually banded regions on the chromosomes. DMs are extrachromosomal, acentic (lacking centromeres), circular DNA molecules (lacking telomeres) and can be variable in size. Generally, DMs are less stable than HSRs in culture, which is expected, as DMs lack centromeres and would not segregate properly to daughter nuclei in mitosis. Gene amplification is noted in many biological phenomena, including amplification of insecticide detoxification genes in insects, induced amplification of certain genes in cultured cells (used to produce certain proteins industrially), amplification of developmental genes in Xenopus and other organisms, amplification of drug resistance genes, and amplification of certain oncogenes in cancer. It is the latter topic that is of interest here. A duplication of a chromosome or a chromosome region is not considered here under amplification (e.g., CML patients can have two or three Philadelphia chromosomes harboring the fusion abl-bcr gene). An example of gene amplification in cancer drug resistance is dihydrofolate reductase amplification in methotrexate resistance. Another interesting example is the amplification of the P glycoprotein gene (chromosome 7) in multidrug resistance, causing failure of cancer chemotherapy. Researchers have identified many genes amplified in cancer. Following are a few examples (a complete listing and discussion beyond the scope of this chapter):

- c-myc (8q24) amplification in small cell lung carcinoma (SCLC)
- N-myc (2p23-24) amplification in neuroblastoma (advanced stages), SCLC
- Cholinesterases (3q28) in ovarian carcinoma
- HER-2/neu (C-erbB-2, 17q11.2) in breast carcinoma
- Cellular apoptosis susceptibility at 20q13 in breast cancer
- Epidermal growth factor receptor (7p12.1-12.3) in glioma and non-SCLC
- PRAD1/cyclin D1, bcl-1, HST-1, INT-2 (11q13) in breast, non-SCLC, head and neck, and other cancers
- MDM2 (12q13-14) in neuroblastoma, sarcoma, glioma
- Primase 1 (12q13) in osteosarcoma.

CAUTIONS TO EXERCISE IN INTERPRETING CHROMOSOMAL ABNORMALITIES SEEN IN CANCER STUDIES

FAILURE TO DETECT A CHROMOSOME ABNORMALITY BY ROUTINE G-BANDING

In examining a sample from a presumed malignant tissue, one must always remember that normal cells are found mixed with the malignant cells and, thus, can significantly complicate the analysis. A report of 20 normal metaphases should be read with caution, as these metaphases could be those of a cancer that happens to be diploid and to lack visible structural abnormalities or of normal surrounding cells. In some malignancies, normal cells in the submitted sample can give much better chromosome morphology than abnormal cells. This is especially true in acute lymphoblastic leukemia. Experienced cytogenetic technologists learn to analyze fuzzy, poor metaphases and quickly to identify these abnormalities, even in poor cells. Further, there are expected variations between laboratories owing to different referral bases. Physicians differ in their referral patterns, and individual referral may vary, depending on such factors as the patient-specific situation, stage of the disease, and even financial considerations. As more data accumulate, there are now more clear indications for cytogenetic studies that should decrease (but not eliminate) variation in the rate of detection of chromosomal abnormalities by different laboratories.

Failure to note the aberration in routine analysis may also occur because the abnormality involves a small amount of chromosomal material or produces little change in perceived banding patterns. The t(15;17)(q22;q22) in AML M3 and inv(16)(p13q22) seen in AML M4eo are not easily noted in short or poorly banded lines with identified "terminal deletions." An example of gene amplification in cancer drug resistance is dihydrofolate reductase amplification in methotrexate resistance. Another interesting example is the amplification of the P glycoprotein gene (chromosome 7) in multidrug resistance, causing failure of cancer chemotherapy. Researchers have identified many genes amplified in cancer. Following are a few examples (a complete listing and discussion beyond the scope of this chapter):

CONSTITUTIONAL CHROMOSOMAL ABNORMALITIES

Some chromosomal abnormalities are present at birth and are not related to neoplasia. These include balanced translocations, Robertsonian translocations, inversions, and insertions that are found at some level in normal-appearing individuals (but in most cases affecting their reproductive success or resulting in the birth of children with congenital abnormalities or both). Other constitutional abnormalities can be associated with an abnormal phenotype, and some predispose to cancer development (e.g., Down, Klinefelter's, and chromosome breakage syndromes). Of course, these abnormalities usually are found in all cells in a person and are not limited to a particular tissue type. Thus, when we find such abnormalities in all examined cells, we are suspicious of a potential constitutional translocation. Obvious exceptions to this assumption are translocations classically noted in certain cancers, such as t(9;22) in CML, in which all examined cells may have the translocation,
but it is not a constitutional translocation. To distinguish between a constitutional translocation and a novel translocation found in all sampled cells, a cytogeneticist may request a constitutional chromosome study. The simplest is to get a peripheral blood sample cultured for 48 to 96 hours using B- or T-cell stimulants (mitogens) to ensure adequate numbers of actively dividing cells for analysis. Chromosome studies may also be performed using other cells, such as skin fibroblasts.

**FRAGILE SITES**

Cytogeneticists regularly observe breaks in preparations of human chromosomes. Fragile sites are visible cytogenetically as breaks at consistent sites in the genome. Some of these sites are induced by certain chemicals (e.g., aphidicolin, methotrexate). The sites, which now number more than 100, are heterogeneous in their method of induction (some are constitutively expressed and are not induced) and in their location and the sequences involved. Some are associated with integration sites for oncogenic viruses. Some occur in or near tumor suppressor genes and may be associated with the chromosomal events leading to loss of those genes. The best example of the latter phenomenon is the aphidicolin-induced fragile site at 3p14.2 (FRA3B), which occurs within the tumor suppressor gene FHIT involved in numerous cancers, including the translocation t(3;8)(p14.2;q24) seen in clear cell renal carcinoma. Much more work needs to be done to resolve the relationship between other fragile sites and chromosome translocations and aberrations seen in cancer. When fragile sites are found in one or a few examined metaphases, this is noted in the workup. Such findings may fall into one of three categories: (1) rare events in normal individuals noted as chromatid and chromosome breaks (not clinically significant), (2) breaks at the same site in multiple untreated cells, considered constitutional fragile sites (their relevance to the cancer being unknown now), or (3) multiple breaks in many cells at different sites, possibly suggesting one of the chromosome breakage syndromes (e.g., ataxia-telangiectasia or xeroderma pigmentosum) or other pathologic mechanisms.

**SATELLITE ASSOCIATIONS**

The human karyotype normally includes five pairs of acrocentric chromosomes (chromosomes 13, 14, 15, 21, and 22). On average, seven to eight of the short arms of these chromosomes carry satellites and a satellite stalk with the nucleolar organizer region. Satellite associations can be seen persisting through metaphase as remnants of the nucleolar associations. These are normal findings. Speculations in the literature that this predisposes to Robertsonian translocations have not been confirmed. Robertsonian translocations are common in animals that lack nucleolar organizer regions or satellites on the short arms of involved chromosomes.

**PROBLEMS WITH SOLID TUMORS**

A biopsy of a solid tumor usually contains a number of tissue types (e.g., blood vessels, epithelial cells, fibroblasts) in addition to the tumor cells. Further, tumor cell growth is usually not very good, and normal cells can grow faster than tumor cells in vitro. Various technical tricks can be used to obtain decent results from such specimens, including selecting appropriate media (avoiding media that stimulate growth of normal fibroblasts), treating primary cultures with trypsin to remove fibroblasts, and culturing at lower density. Recent molecular cytogenetic methods can obviate the need for cell culture in assaying for specific chromosomal abnormalities.

**CLONAL EVOLUTION AND CHROMOSOME EVOLUTION**

Early studies using X-inactivation as a marker for clonality in female cells suggested that most, if not all, cancers originate clonally. Later chromosome studies confirmed the clonal origin of cancer cells with specific chromosomal abnormalities. However, there are published cases of apparently independent clones with distinct chromosomal abnormalities (occurring in approximately 1% of cases of leukemias and lymphomas). The generally accepted explanation for most of these cases is that a unifying submicroscopic event occurred, with further genetic alterations appearing as unique events (i.e., they are an evolution of the original clone). True multicolonial cancers are indeed rare. In testing, we usually examine a minimum of 20 metaphases in an attempt to locate a clone with a chromosomal abnormality. According to the ISCN (1995), a clone is recognized if three or more cells have the same missing chromosome or two or more cells exhibit the same additional structural or constitutional abnormality. The reason for the difference in number of cells needed to define a clone with a missing chromosome (monosomy) versus one with trisomy relates to the possibility in cytogenetic preparation of overspreading of chromosomes and, hence, artificial "missing" chromosomes. If one of the first 20 cells showed a particular aberration likely related to the cancer, a count of additional cells can be initiated or molecular cytogenetic methods used to confirm the presence of a clone. In any case, once a clone is identified, this can provide a baseline for diagnosis, prognosis, and follow-up study of relapse.

Many cancers are seen with only simple aberrations, such as the t(9;22) in CML. Early cytogenetic studies, however, still showed significant complex karyotypes in many cancers, suggesting that these early events can progress to more complex karyotypes. The stepwise progression of cancer by acquiring additional abnormalities is now well established for a number of cancers. A good example of this is colorectal carcinoma, which involves a successive series of genetic alterations. One must caution, though, that simplistic multistage scenarios usually are not the common pattern seen. For many solid tumors, chromosome instability results in massive karyotypic changes that appear totally unrelated to selective advantage. One possible explanation is that a genetic event resulting in cancer or predisposition to cancer removes a cell-cycle checkpoint involved in preventing damaged cells from dividing. An example is that cells missing p53 can accumulate chromosomal abnormalities because of the absence of p53-mediated cell-cycle arrest after double-stranded DNA breaks.

**CONSTITUTIONAL CHROMOSOMAL ABNORMALITIES PREDISPOSING TO CANCER DEVELOPMENT**

We do not review here hereditary cancer syndromes due to gene mutation (e.g., hereditary breast cancer and Li-Fraumeni syndrome). We are more interested in syndromes with microscopically visible chromosomal abnormalities that predispose to cancer. A partial listing of the latter conditions is shown in Table 5-3. Many of these syndromes are detailed and continuously updated on the Web via Online Mendelian Inheritance in Man (http://www3.ncbi.nlm.nih.gov/Omim/). Specific information about cancer risks for certain syndromes are available at http://www.infobiogen.fr/services/chronocancer/Kpronos/Kproneliste.html. Both Bloom syndrome and Werner syndrome genes have been cloned and found to code for putative helicases on chromosomes 15 and 6, respectively. Because in both of these conditions, chromosome breakage is increased, it is suspected that the absence of these helices increases the probability of illegitimate recombination.

**TABLE 5-3. Constitutional Chromosomal Abnormalities Predisposing to Cancer Development**

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Description</th>
<th>Chromosome</th>
<th>Gene</th>
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<tbody>
<tr>
<td>Bloom</td>
<td>Microcephaly, immunodeficiency</td>
<td>15</td>
<td>RAD50</td>
</tr>
<tr>
<td>Werner</td>
<td>Growth retardation, diabetes, cataracts</td>
<td>6</td>
<td>WRN</td>
</tr>
</tbody>
</table>

**DATA MINING IN CANCER CYTOGENETICS**

The proliferation of information in the rapidly growing cancer cytogenetics field has been a great asset to both clinicians and researchers. Fortunately, the development of information technology has made it easier to keep abreast of the rapid developments in this field. There are commercial or semicommercial databases for cancer cytogenetics. An example is the software called Cancer Cytogenetics Lookup published by Gilbert B. Coté. Further, the large text by Mitelman, titled Catalogue of Chromosome Aberration in Cancer, is also available as a compact disk (John Wiley & Sons). However, the proliferation of free Internet resources with online direct access to continuously updated data has mushroomed. Table 5-4 lists some specialized Web pages of interest. Of course, there are many other resources to the student of cancer cytogenetics, including subscribing to bibliographic updates (e.g., Current Contents, now available on the Web), running search engines for Web pages (e.g., Yahoo, Infosseek, Excite, etc.), and local and national library search engines (e.g., Medline).
TABLE 5-4. Web Sites of Interest in Cancer Genetics and Cytogenetics

<table>
<thead>
<tr>
<th>Web Site</th>
<th>Description</th>
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<td>Genetics list serve at <a href="http://www.hum-molgen.de">http://www.hum-molgen.de</a></td>
<td>This site is a discussion list for researchers and clinicians interested in genetics.</td>
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<tr>
<td>Web Sites of Interest in Cancer Genetics and Cytogenetics</td>
<td>This site provides a list of web sites that are of interest in cancer genetics and cytogenetics.</td>
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INTRODUCTION

A cell's ability to produce exact replicas of itself is an essential component of life. This process must be performed with great fidelity in order for whole organisms and species to propagate. The molecular machinery used to control the cell division cycle and replicate is highly organized and well conserved through evolution. Although we are only beginning to unravel the mechanisms in this process, it is clear that multiple extracellular and intracellular signals must be integrated in order to accomplish this complex task.

Although evolution and cellular differentiation may rely on some subtle genetic or epigenetic changes in a given cell, these changes must occur in an orderly and controlled fashion to prevent disastrous outcomes. Gross lack of fidelity in the cellular reproduction process leads to genetic instability, which appears to significantly contribute to the development of malignancy. In order to understand how cancers start and to devise optimal strategies to eliminate cancer cells, we must be able to identify the molecular distinctions between normal cells and tumor cells. Aberrations of normal cell-cycle control reflect some of the molecular alterations that are characteristic of cancer cells.

In this chapter, we review (1) the present understanding of mechanisms by which a normal cell controls the ordered progression through its cell cycle, (2) how regulatory mechanisms are integrated with extracellular signals, and (3) how a normal cell monitors its own progress through several checkpoints in the cell division cycle. We emphasize how these normal processes may go awry in cancer cells. Finally, we discuss the potential implications of this knowledge for our understanding of cancer biology and the development of novel therapeutic strategies.

MECHANICS OF THE CELL DIVISION CYCLE

BRIEF OVERVIEW

Cell-Cycle Phases

In any proliferating mammalian cell, the replication of the entire genome and the division of the cell into genetically identical daughter cells can be broken down into four distinct cell-cycle phases (Fig. 6-1). In the first phase, known as G₁ (for gap 1), the cell undergoes biochemical changes to prepare for entry into S phase in which new DNA is synthesized. As discussed later, in section G₁ to S Transition, a number of these biochemical events are now known; however, cellular factors that drive these changes, such as cell size, protein content, or nutrient environment, are still poorly understood for mammalian cells. In S phase, the cell generates a complete copy of its genetic material and then proceeds into a second preparatory phase, known as G₂ (for gap 2), before entry into mitosis (M phase). In M phase, the replicated DNA is carefully condensed into compact chromosomes that are precisely segregated so that two daughter cells each receive a full complement of the genetic material. Following mitosis, a proliferating cell directly reenters G₀ phase as it prepares for further replication.

Because of the complexity and irreversibility of cellular replication, eukaryotic cells have evolved several checkpoints, which are biochemically defined points in the cell cycle that can be activated to prevent the transition across certain cell-cycle phases.

As depicted in Figure 6-1, any proliferating cell has an additional option, which is the entry into a quiescent state known as G₀. Entry into G₀ phase from G₁ is an important decision in cellular development (such as in lymphocyte or skeletal muscle cell maturation). In vitro, it is largely governed by the presence or absence of growth factors or nutrients that allow the procession through G₁ into S phase. If these growth factors are adequate, the cell traverses a point in G₁ phase after which the growth factors are not required. This point or transition is known as the restriction point (see Fig. 6-1). If cellular environmental conditions are not right for a cell to proceed across the restriction point, it enters G₀ phase. Importantly, entry into G₀ may be reversible or it may be irreversible, such as during skeletal muscle or neuronal differentiation. Although the restriction point was described over 20 years ago, the precise biochemical events that define it are still not known.
Regulatory Mechanisms

As described in further detail later in this chapter, research has characterized many of the molecular and biochemical events that control the transition across different cell-cycle phases and into or out of a quiescent phase. Two common regulatory themes have emerged. First, many of the key regulatory proteins are controlled by posttranslational modifications in a cell-cycle-dependent manner. Perhaps the best known example of this is the hyperphosphorylation of the retinoblastoma gene product, RB, which renders it inactive as a cell crosses the restriction point. The hyperphosphorylation of RB and many other components of the cell-cycle machinery is mediated by heterodimeric complexes of regulatory proteins known as cyclins and their catalytically active partners known as cyclin-dependent kinases (cdks). Regulation of cyclin/cdk activity is central to all phases of the mammalian cell cycle.

A second important theme that has emerged is that many of the posttranslational modifications of cell-cycle proteins alter their stability and increase their proteolytic degradation. Because protein degradation is irreversible, it seems to be a natural mechanism to ensure that the cell cycle progresses in only one direction. This regulatory mechanism is important in every cell-cycle phase and has been conserved in many eukaryotic organisms.

As one might expect, because cancer cells have fundamental abnormalities in cell-cycle control, it is not surprising that they have been found to have abnormalities in many of the components that control each of the cell-cycle phases. These abnormalities are described in greater detail as specific phases of the cell cycle are discussed.

G1 TO S TRANSITION

In a proliferating cell, molecular events in G1 phase prepare the cell for the synthesis of new DNA. In different types of mammalian cells grown in culture, there can be great variations in the length of this phase, which may be very short or last for many hours. The length of the G1 phase is somewhat dependent on extracellular signals (such as nutrients or growth factors in the environment) and may be coupled to a cell's growth in size. Although much is known about events that lead up to the exit from G1 into S phase, how the length of G1 is determined for an individual cell is not clear.

Not only is the length of the G1 phase of the cell cycle variable, but whether a cell completely traverses this phase at all seems to be an active decision. As noted previously, when a cell does not traverse G1, it enters a quiescent phase known as G0. In vivo, there are many examples of different types of mammalian cells, such as epithelial cells or lymphocytes, which are normally arrested in a quiescent phase but may be induced to reenter a proliferative phase by certain physiologic stimuli such as mitogenic growth factors (see Fig. 6-1). This arrest and reentry into the cell cycle can be largely recapitulated in cell culture systems for normal cells. However, the ability to arrest in G1 phase of the cell cycle (e.g., because of contact with other cells or lack of external mitogenic growth factors) is fundamentally abnormal in cancer cells.

In addition to entry into a reversible G0 state, under some conditions the entry into such a state can be irreversible (see Fig. 6-1). This occurs during the terminal differentiation of cells such as skeletal muscle or neurons and during cellular senescence, which is largely an in vitro phenomenon that may be analogous to cellular aging. The molecular mechanisms by which this irreversible arrest occurs and is maintained are only now becoming clear in certain settings, such as in skeletal muscle cells, which require the retinoblastoma gene product RB for irreversible cell-cycle arrest.

In vitro, it is clear that the complete transit across G1 phase is governed by the presence of extracellular growth factors that push a cell past the restriction point. This point is functionally defined as a time in late G1 phase beyond which growth factors are not required for initiation and completion of DNA synthesis and mitosis. Without adequate growth factors, the cell enters a reversible G0 arrest described previously. Biochemical events that are concurrent with passage through this restriction point include the hyperphosphorylation of RB, the functional activation of a cellular transcription factor known as E2F-1, the accumulation of a certain threshold level of cyclin/cdk activity, and the loss of key cyclin-dependent kinase inhibitors. However, whether or not this point can actually be attributed to any single event in mammalian cells is formally unknown.

Of these possible biochemical events that may form the restriction point, most work has focused on the role of the retinoblastoma gene product RB. Disruption of the RB gene was first found in retinoblastoma tissue and subsequently in tumors from patients with sporadic forms of cancer. The first clues to RB function came when it was found that its forced expression caused cells to arrest in G1 phase. Naturally occurring mutations in the RB gene rendered the protein unable to stop cell proliferation. Hence, RB was the first tumor suppressor identified that directly functioned to block cell proliferation.

Further insight into how RB itself was regulated came from studying how it was altered during the cell cycle. Numerous studies have now proven that RB becomes progressively hyperphosphorylated as cells pass from G1 into S phase. This correlation suggested that hyperphosphorylation inactivated RB and allowed cell-cycle progression into S phase. Although this inactivation may be important, it is probably not the sole basis for the restriction point because cells that lack the RB gene still retain certain aspects of restriction point control.

One logical extension of these studies was to determine the mechanism by which RB prevented S phase entry and how RB hyperphosphorylation blocked this function. Insight into this has come from a large body of work focused on identifying cellular proteins that interact with RB. There have been over 20 such proteins identified using a variety of assays. One of the proteins identified, the transcription factor E2F-1, is central to how RB prevents cell proliferation.

E2F-1 was the founding member of what is now known to be a family of at least six related transcription factors, which seem to have specific, nonoverlapping functions in vivo. Most is known about E2F-1, which may be particularly important for regulating the G1 to S transition. As a transcription factor E2F-1 activates the expression of a variety of genes, many of which encode either transcription factors that are induced as cells enter S phase or proteins that are involved in DNA synthesis, such as ditydrofolate reductase. In fact, E2F-1–mediated activation of these genes is so critical that the forced expression of E2F-1 alone is sufficient to drive some cells from quiescence into S phase. A number of studies have also shown that when RB physically interacts with E2F-1, it blocks E2F-1–mediated activation of these genes. Hence, it has been proposed that the RB suppresses tumor formation by repressing genes normally induced by E2F-1 and the loss of RB would be expected to disrupt this active repressor complex. How RB and E2F-1 form an active repressor complex is not known, but there are provocative data that this complex may alter chromatin structure by modulating histone deacetylase activity. Despite these studies, the importance of histone deacetylase as a mediator of RB tumor suppression is not yet known.

![FIGURE 6-2. Schematic model for the control of E2F-dependent genes and S-phase entry by RB. A: When active, RB can form a complex with the transcription factor E2F. The localization of RB to this complex by E2F can suppress the transactivation function of E2F as well as other transcription factors that may be colocalized. Other proteins (?) have been suggested to be in such a transcription repressor complex such as histone deacetylase-1. This complex represses the expression of genes required for S-phase entry. B: When RB is inactivated (by phosphorylation of the protein or by mutation of the gene) the repressor complex presumably does not form and genes required for S phase are expressed.](image-url)
Given the proposed model that hypophosphorylated RB and E2F-1 form an active repressor complex that is disrupted by RB hyperphosphorylation, it is important to understand the mechanisms driving RB hyperphosphorylation. The first insight into this came with the discovery of a class of genes known as cyclins in yeast cells. These cyclins are expressed in a cell-cycle–dependent manner and are required for the transition from G₁ to S phase in yeast. It was later discovered that mammalian cells also had cyclins, which were expressed in a cell-cycle–dependent manner and were functionally similar to yeast cyclins. Mammalian cyclins are actually a family of related genes that includes D-type cyclins (D1, D2, and D3) and cyclin E, which are expressed maximally as cells progress from G₁ into S phase, and cyclin A, and B-type cyclins, which are expressed in other phases of the cell cycle (Fig. 6-3). Like the yeast cyclins, mammalian cyclins form complexes with a catalytic partner, known as a cdk. There are at least seven mammalian cdks that function in distinct phases of the cell cycle (see Fig. 6-3) and have different biochemical properties including different cyclin partners, potential substrates, and link to human cancer. Elegant study of the crystal structure of cyclin A and cdk2 demonstrated that the binding of the cyclin to the cdk physically alters the structure of the cdk and activates the enzyme. In addition to this, cyclin binding may provide substrate specificity to the cdk.

With respect to the G₁ to S phase control, the key function of cyclins and cdks is to phosphorylate the RB protein. The phosphorylation of certain serine or threonine residues in RB reverses the cell-cycle arrest by disrupting the RB-E2F-1 complex. In this process, D-type cyclin/cdk complexes are activated earlier than cyclin E/cdk2, and both cyclins are required for the efficient phosphorylation of RB and entry into S phase (see Fig. 6-3). The significance of potential differences in RB phosphorylation mediated by different cyclin/cdk complexes is not known.

It is relevant to emphasize that many aspects of cyclin/cdk biology are unresolved. First, although RB clearly is a target for cyclin/cdk complexes, whether it is the most important substrate for regulating entry into S phase is not known. Other possible substrates include RB-related proteins p107 and p130 (Fig. 6-3) that seem to have partially redundant roles with RB in cell-cycle control, components of the DNA synthesis machinery (discussed later in S Phase), and even E2F-1 itself. Second, it is not obvious why mammalian cells should require so many different cyclins/cdks to phosphorylate RB. This is especially true when one considers, for example, that cyclin E seems to be able to accomplish everything that cyclin D1 can do in an elegant knockout/knockin experiment in mice. It seems likely that as more is understood about possible in vivo targets for different cyclin/cdk complexes, the purpose of such a large family of cyclins will also become clearer.

Because cyclin/cdk activity is so important for regulating the G₁ to S-phase transition, their activity can be regulated at numerous levels. At present, it appears that cyclin/cdk activity can be controlled by at least six different mechanisms (Fig. 6-4). The first level of regulation is that different cyclins are synthesized at different stages of the cell cycle. In this regard, the expression of D-type cyclins is closely coupled to the presence or absence of mitogenic growth factors and may be viewed as growth factor sensors. Second, in addition to the regulation of cyclin synthesis, there is active regulation of cyclin degradation. In yeast cells in G₁, this is mediated by a cellular activity known as the SCF (for Skp-1, cullin, and F-box). A similar complex has been identified in mammalian cells as well. This machine, which is analogous to the anaphase promoting complex (APC), that regulates mitosis, targets certain cell-cycle proteins for degradation by the ubiquitin-proteosome system. Third, in addition to the regulation of cyclin protein levels, cyclin activity is regulated by the requirement for complex formation with a cdk as discussed previously. Fourth, the cyclin/cdk complex must be activated by a cdk-activating kinase, which phosphorylates a conserved threonine residue on the cdk. Fifth, additional amino acid residues in the cdk must be dephosphorylated. This is accomplished by both inhibiting certain kinases (known as Wee1/Myt1) and activating certain phosphatases (known as cdc25 A, B, and C). Finally, cyclin/cdk activity is controlled by further protein-protein interactions between cdks or cyclin/cdk complexes and other proteins known as cyclin/cdk inhibitors (CKIs). Once fully activated, cyclin/cdk complexes phosphorylate a variety of substrates that are involved in both the G₁ to S transition as well as the G₂ to M transition.

FIGURE 6-3. Schematic representation of changes in cyclins and cdks through the cell cycle. Synthesis of D-type cyclins is stimulated by growth factor signals in the G₁ phase of the cycle and associate primarily with cdks 4 and 6. Cyclin E is synthesized later in G₁ and associates with cdk2. Cyclin A is synthesized late in G₂, throughout S phase, and into early G₁ and associates with cdk2 in early S phase and cdk2 in late S phase and early G₂. Cyclin B is synthesized late in G₂ and in M phase and associates with cdk1 (also known as cdc2). The loss of cyclin B/cdc1 activity at the end of M phase is required for reentry into the next G₁ phase.

FIGURE 6-4. Multiple levels of regulation of cyclin/cdk activity. The activity of cdks can be regulated by at least at six different mechanisms: (1) and (2) cyclins are synthesized and degraded at specific stages of the cycle; (3) cdks must associate with cyclins in order to be active; p21-related and p16-related CKIs can positively and negatively influence this step, respectively; (4) cdks complexed with cyclins must be activated by a cdk-activating kinase; (5) cdk activity is further controlled by inhibitory phosphorylation at threonine 14 and tyrosine 15, which can be removed (and thereby activate the cyclin/cdk) by cdk25 phosphatases; and (6) p21-related CKIs can further inhibit cyclin/cdk activity by direct complex formation with the cyclin/cdk. The activated cyclin/cdk complex phosphorylates a variety of substrates to facilitate both the G₁ to S phase and the G₂ to M phase transition.

CKIs have grown in importance and in number since they were first described. Thus far, two groups of CKIs have been identified (Table 6-1). One group includes p21, p27, and p50, which appear to be universal inhibitors of cyclin/cdk activity that function by forming a complex with the cyclin/cdk. A second group includes p16, p15, and p18, and these four specifically inhibit cyclin-D–associated cdk4 and cdk6 (hence, the name inhibitors of cdk4). As was said of cyclins and cdks, why there should be such a large number of CKIs is an interesting question. To be sure, there are clear biochemical differences between these two families. First of all, although p16 clearly functions as a tumor suppressor in humans, the full role of other CKIs in human cancer is not yet clear. There are also biochemical differences among different CKIs. For example, p21-like CKIs bind to the cyclin/cdk complex, whereas p16-like CKIs bind to the cdk4 or cdk6 subunit to prevent cyclin/cdk complex formation (see Fig. 6-4). Intriguingly, p21-related CKIs may function in some capacity as activators of cyclin/cdks. This is based on the observation that p21-like CKIs can bind to cyclin/cdks at greater than 1:1 stoichiometry. The activity of the cyclin/cdk complex is
only inhibited at high ratios of p21-like CKI to cyclin/cdk. Finally, different CKIs can be regulated in distinct ways. For example, p21 \(^{\text{INK4a/b}}\) was identified because the p53 tumor suppressor gene can induce its expression. As such, it was an obvious candidate effector for p53-mediated cell-cycle arrest after genotoxic stress such as gamma irradiation\(^{\text{52}}\) (see Cell-Cycle Checkpoints, later in this chapter). Similarly, both p27\(^{\text{KIP1}}\) and p15\(^{\text{INK4a}}\) can be modulated by transforming growth factor-β, and hence may be functional effectors of the antimitogenic effects of transforming growth factor-β. It is likely that further understanding of the biochemical differences between different CKIs and in vivo studies of their function will help clarify their relevance to human cancer.

**TABLE 6-1. Classes of Cyclin-Dependent Kinase (cdk) Inhibitors**

In summary, mammalian cells have developed an elegant system in which several layers of regulators control the decision to traverse G\(_1\) phase and enter S phase (Fig. 6-5). RB and possibly other RB-related proteins function by actively repressing E2F-1–dependent genes at the working end of this biochemical and genetic pathway. The ability of RB to form a repressor complex with E2F-1 is regulated by multiple members of cyclin/cdk family. Of these, D-type cyclins may be particularly important as an intranuclear sensor of extracellular growth factors. The activity of cyclin/cdk complexes is regulated by multiple mechanisms to coordinate the decision to enter S phase with extracellular cues. These mechanisms include positive and negative influences by members of two families of CKIs that respond to both extracellular and intracellular signals. At some critical point that seems to be defined by the activation of a threshold level of cyclin/cdk activity, the RB-E2F repressor activity is turned off and the cell makes the commitment to enter S phase.

![Fig 6-5](https://example.com/image)

**FIGURE 6-5.** Schematic diagram showing several layers governing the regulation of G\(_1\)-to-S transition. At present, the event most closely correlated with the transition across the restriction point seems to be the phosphorylation of RB, which disrupts the RB/E2F-1 repressor complex. This leads to the induction of E2F-1–dependent genes and commitment to enter and progress through S phase. The function of RB in this complex is controlled by a number of cyclin/cdk (cyclin-dependent kinases) complexes that are active in G\(_1\) phase. These cyclin/cdk complexes are, in turn, largely negatively regulated by a number of cyclin/cdk inhibitors (CKIs). The activity of both cyclin/cdk complexes and CKIs are lastly regulated by a number of extracellular signals (such as mitogenic or antimitogenic factors) and intracellular signals (such as DNA damage or differentiation factors).

Despite this detailed working model, important questions remain. For example, clarifying the molecular basis for the restriction point will be an important advance in the basic understanding of cell-cycle control. Determining the importance of different regulatory proteins in different types of human cancer will also be important. Finally, understanding how RB and E2F actually function as an active repressor may open up new therapeutic avenues based on better understanding of the working end of this pathway.

**S Phase**

The task of generating an exact copy of more than 3 billion base pairs of DNA in the human genome is quite daunting. As is described here, mammalian cells have had to surmount a number of mechanical difficulties to accomplish this. The importance of the machinery that accomplishes this task is clear because many of the components have been highly conserved from bacteria to humans. What is perhaps an even more important task, though, is how to regulate this DNA synthesis machinery. Each of these 3 billion base pairs must be copied one time, and only one time, during each cell division cycle. Except in rare circumstances in certain organisms or certain developmental states, the synthesis of DNA more or less than one time per cell cycle would be devastating. Since the last writing of this chapter, much insight has been gained into how DNA synthesis is regulated.

It is now known that DNA synthesis begins at defined sequences in the genome of most organisms. These origins of replication contain specific DNA sequences, which have been referred to as autonomously replicating sequences or replicator elements. A technique known as DNA footprinting was used to evaluate proteins that were bound to these DNA elements at different phases of the cell cycle. These studies have shown that there are two different footprint patterns on replicator elements at different phases of the cell cycle, and a change in this pattern occurs as DNA synthesis begins. The multiple proteins that form a DNA-binding complex to generate these footprints are known as the origin of replication complex (ORC). Based on the timing of the two observed ORC footprints, it is thought that these represent a prereplication ORC (pre-RC) and a postreplication ORC (post-RC)\(^{\text{64}}\). The pre-RC is assembled and competent to begin replication in G\(_1\) phase, but is held in check by some mechanism to prevent the formal initiation of DNA synthesis (i.e., the conversion of a pre-RC to a post-RC) until S phase. The post-RC represents a complex that is competent to carry out DNA synthesis from the origin of replication to which it is bound.

The molecular components of a pre-RC and post-RC have been studied using biochemical and genetic approaches in different types of eukaryotic cells. There is a large number of proteins of different classes that form these pre-RCs and post-RCs. Some of these proteins, such as ORC proteins 1 through 6 and MCM proteins 2 through 7, have been identified and are beginning to be biochemically characterized. However, mechanistic details for how ORCs function are largely unknown.

In addition to identifying the individual components of the pre-RC and post-RC, work has focused on understanding how a post-RC is converted to a post-RC and how this is directly linked with DNA synthesis. The changes in footprint pattern as a pre-RC becomes a post-RC coincide with the loss or gain of different molecular components of this complex. Because of the importance of cyclin/cdk activation at the G\(_1\) to S transition, it is likely that cyclin/cdk complexes will be shown to phosphorylate particular substrates that directly affect the pre-RC and post-RC complexes. For example, there is some evidence that MCM proteins, which are components of the ORC, are phosphorylated at the transition to S phase. The phosphorylation of at least one of these (MCM4) can be mediated by a cyclin/cdk. Such a posttranslational modification may be involved in changing a pre-RC to a post-RC and actually driving the formal initiation of DNA synthesis.

The regulation of pre-RC and post-RC is also probably coupled to the mechanism by which a cell prevents rereplication of DNA in S phase. The cell cycle can be generally divided into two states: an assembly state and a replication state. The former state allows the assembly of pre-RCs at replicator elements but prevents the formal initiation of DNA synthesis until other critical factors are supplied (such as G\(_S\)/S cyclin/cdk activity) (Fig. 6-6). The latter state allows DNA synthesis from
leading strand

FIGURE 6-7. Schematic model of how the ability to synthesize new DNA may be regulated. After mitosis is complete, a cell becomes competent to initiate new DNA synthesis. This competency correlates with the presence of a prereplication complex (pre-RC) bound to DNA replicator elements. At the formal initiation of DNA synthesis (replication fork initiation), which is driven by certain poorly defined events (activating factors), the pre-RC complex changes to a post-RC complex while DNA is synthesized. This post-RC complex is unable to bind to new DNA replicator elements and, hence, DNA can only be synthesized one time per cell cycle. The transition from a post-RC back to a pre-RC, on completion of the next mitotic phase, is negatively and positively regulated by cyclin B/cdk1 and a poorly defined licensing factor (see text for details).

In addition to the task of allowing DNA synthesis only once during the cell cycle, the cell faces the task of ensuring that newly synthesized DNA is accurately copied. The enzymes that accomplish this are called DNA polymerases, three of which are known to be involved in DNA replication (as opposed to repair) in eukaryotic cells (DNA polymerases a, d, and e). The double-stranded nature of genomic DNA provides a mechanism to ensure accuracy because each existing strand serves as a template for a new strand. Although the DNA polymerases copy it with high fidelity, they are not perfect. Approximately one incorrect nucleotide is incorporated for every $10^5$ to $10^6$ correct nucleotides. At this rate, 1000 to 10,000 mutations would be generated with each cell division. In order to prevent this, the DNA polymerases are endowed with proofreading functions that allow misincorporated nucleotides to be detected and removed by 3' to 5' exonuclease activity of the DNA polymerase. This process reduces the error rate by approximately 1000-fold. In addition to the repair activity that is closely coupled to DNA synthesis, other repair processes detect and replace mismatched DNA bases or other DNA abnormalities to further limit errors associated with DNA replication. Inefficiencies in DNA repair machinery appear to be important in the development of some forms of cancer, such as certain forms of hereditary colon cancer that are linked to abnormalities in DNA mismatch repair enzymes.

In addition to the problem of accuracy, the cell faces a problem due to the sheer magnitude of the task of copying all 3 billion base pairs. A single replication fork traveling at approximately 3000 bases per minute would require approximately 1 month to replicate just one of the 46 human chromosomes. As described previously, the cell addresses this problem by initiating DNA replication at multiple origins of replication. Interestingly, these multiple origins appear to fire in an ordered fashion. The mechanisms by which origins fire early or late in S phase are not understood.

After any individual ORC is activated to begin DNA synthesis, how the polymerase generates an elongating strand of newly synthesized DNA is another mechanistic hurdle. Because DNA is a double-stranded helix, it must be unwound and both strands of the DNA must be copied simultaneously. The synthetic process is started from an RNA primer on each of these strands and makes the new strand in the 5' to 3' direction (Fig. 6-7). Because the double-stranded DNA is arranged in an antiparallel fashion, one new strand is synthesized continuously (leading strand) and the other discontinuously (lagging strand). As described for the ORCs, much work has focused on identifying the proteins that are required for DNA synthesis at the replication forks of eukaryotic cells. These include PCNA, RPA, RFC, DNA polymerases, DNA primase, and RNaseH. Some of the mechanisms of the process are now understood, such as PCNA forming a molecular sliding clamp to hold the polymerase on the DNA. After the DNA polymerase complex has proceeded along the length of a strand of DNA to the next replication, the RNA primer is replaced by DNA and a DNA ligase closes the gap between the two newly synthesized stretches of DNA. With this, DNA synthesis is essentially complete.

One final hurdle, though, for a cell to completely copy the entire genome involves the synthesis of new DNA at the end of each chromosome. Because DNA polymerases require an RNA primer to begin this process and because they only assemble a new strand in the 5' to 3' direction, each linear chromosome would fail to copy DNA at the very 3' end of each chromosome with every round of replication (see Fig. 6-7). This would be deleterious because numerous rounds of DNA replication would result in a large amount of DNA being lost from the chromosome ends.

It appears that eukaryotic cells deal with this end-replication problem by the use of specialized structures called telomeres, which are simple tandemly repeated sequences at the end of each chromosome (see Fig. 6-7). These repeated DNA sequences are recognized by telomerase, a holoenzyme containing a reverse transcriptase (polymerase) and an RNA component that is complementary to the repeated DNA sequences of a telomere. The reverse transcriptase extends the 3' end of the chromosomal DNA by reading the RNA component as a template (see Fig. 6-7). In this way, telomerase prevents the loss of this 3' end of the DNA to defeat the end-replication problem.

In addition to providing a mechanism to complete the DNA synthesis task, telomerase activity is particularly important for cancer biology because it confers unlimited cell proliferation capacity, which is a hallmark of a malignant cancer cell. There is good experimental evidence that most telomerase-deficient cells can only replicate a finite number of times until the telo–meric ends of the chromosomes become shortened to a critical point that arrests further cell proliferation. Because most normal cells in the body do not have telomerase activity, it has been suggested that the loss of telomeric DNA may be the basis for cellular aging. On the other hand, tumor cells appear to be immortalized by virtue of the increased telomerase activity. Because increased telomerase activity is relatively specific to cancer cells in a human body, the pharmacologic inhibition of telomerase may, indeed, be a new therapy for cancer that is directly based on better understanding of the DNA

preassembled ORCs but does not allow assembly of new pre-RCs. The loss of cyclin/cdk5 activity at the end of mitosis is one factor that probably allows the reformation of the pre-RCs. There may also be other factors, such as licensing factor, which seems to be supplied to a cell only after completion of mitosis to prevent rereplication of DNA (see Fig. 6-6). As more is learned about the existence of states that are competent and not competent for new DNA synthesis, many more regulatory details will be elucidated.
M-PHASE ENTRY AND EXIT

Once the cell has copied the entire genome, it enters a second gap phase, known as G<sub>2</sub>, to prepare for entry into mitosis, the phase in which the duplicated genome is segregated to two daughter cells. The successful completion of mitosis may be considered the most crucial phase in the cell cycle because errors in this process are irreversible and lead to dramatic alterations in the genetic material such as the loss or gain of entire chromosomes. Much insight has been gained into the regulation of this process since the last writing of this chapter and can be found in excellent, detailed reviews. Three main features of this regulation are presented here. Because of its complexity, it is helpful to consider mitosis in several distinct phases (Fig. 6-8A). In the first place, the actual entry into mitosis is carefully controlled to prevent the segregation of chromosomes that have not completed DNA synthesis. Second, there are many structural changes that occur in a cell during mitosis such as chromosomal condensation, centrosome migration, microtubule polymerization, spindle assembly, nuclear membrane dissolution, microtubule and kinetochore attachment, alignment of all chromosomes on a plane between the centrosomes, and the separation of sister chromatids (see Fig. 6-8A). The actual separation of sister chromatids, a process that constitutes the metaphase to anaphase transition, represents an important checkpoint for a cell because chromatid separation is not easily reversed. Finally, after anaphase is complete, the chromosomes lose their highly condensed structure, the nuclear envelope reforms, and the cell undergoes cytokplasmic division (cytokinesis) to complete the cell cycle. At this stage, the cell must formally exit mitosis to reset itself for the next cell division cycle. Most of what is known about mitotic control in mammalian cells relates to how the entry into mitosis, the metaphase to anaphase transition, and the exit from mitosis are governed.

The first regulatory mechanism for mitosis involved the maturation- or mitosis promoting factor (MPF), which was identified as a cytoplasmic activity in metaphase-blocked Xenopus oocytes that could drive other cells into mitosis. MPF was characterized as a complex of cyclin B and cdk1 (also known as cdc2) (Fig. 6-8B). Studies have demonstrated that the activation of cyclin B/cdk1 is the most crucial step governing whether a cell enters mitosis. Because of this central role, cyclin B/cdk1 is regulated at many levels, including some that are different from the G<sub>S</sub> to S cyclin/cdk discussed previously. First, the levels of cyclin B protein are increased during late S and G<sub>2</sub>-phase by both increased synthesis and decreased destruction. Second, newly synthesized cyclin B binds to unphosphorylated cdk1, which becomes activated by phosphorylation at threonine 161 by cdk-activating kinase. Approximately concurrent with this, the cytoplasmic cyclin B/cdk1 complexes must be relocated to the nucleus by an as yet unclear mechanism. In addition, the competing kinases (Wee1/Mik1/Myt1) and phosphatases (cdc25 B and C), which govern the phosphorylation of threonine 14 and tyrosine 15 on cdk1, must allow dephosphorylation of these residues to activate the cyclin kinase (see Fig. 6-8B). Once activated, a positive feedback loop between cyclin B/cdk1 and cdc25 exists to allow further activation of B/cdk1, which drives the initiation of mitosis by phosphorylating specific nuclear proteins. The identification of the specific proteins that are phosphorylated by cyclin B/cdk1 to drive the initiation of mitosis will be important for our understanding of this phase of the cell cycle. Because the cdc25 phosphatase plays a key role in the initial activation of cyclin B/cdk1, it is not surprising that it also has an important role in a checkpoint pathway that can be activated to prevent the entry into mitosis in response to genotoxic stress (see section G<sub>2</sub>-to-M-Phase Checkpoint, later in this chapter).

A second important regulatory mechanism may help link biochemical changes such as phosphorylation of specific proteins with structural changes such as spindle body assembly. This mechanism involves a family of kinases known as polo-like kinases (PLKs) after polo kinase, the first of this family identified in Drosohplia. Like cdk1, PLKs represent a family of kinases conserved from yeast to humans. Although they may have functions at several stages of the cell cycle, the best-characterized roles are during the mitosis. In the first place, they indirectly activate cyclin B/cdk1 by phosphorylating and activating cdc25. Whether PLKs are initial activators of cyclin B/cdk1 or play a role in the positive feedback loop for B/cdk1 activation is not known. Second, at different stages of mitosis PLKs are localized to spindle pole bodies, kinetochore, and the spindle midzone, which suggests that they may play a role in spindle apparatus assembly, sister chromatid pairing and separation, and even cytokinesis. Because cyclin B/cdk1 may activate them, PLKs could directly link the biochemical activity of MPF with structural changes that occur during mitosis. However, the mechanistic details of this are far from understood. Finally, PLKs may also activate the APC/cyclosome (APCC), which has roles in both the metaphase to anaphase transition as well as the formal exit from mitosis.

CONTROL OF THE CELL DIVISION CYCLE

Obviously, the cell does not use the complex DNA synthesis and cell division machinery in a vacuum. It must continuously integrate extracellular signals from the environment as well as intracellular signals regarding the status of the genome. These signals contribute to the control of cell division and also constitute formal checkpoints that may be activated in times of cellular stress. How a cell accomplishes the integration of extracellular signals and the mechanisms by which it checks its progress through cell division are reviewed in this section.

EXTRACELLULAR SIGNALS

Nutrient status, cell-cell contact, and extracellular peptides can all influence intracellular events. The significant question that arises is how do these extracellular factors communicate with the intracellular machinery to influence cell-cycle progression? For example, growth factors cause cells in the resting or G<sub>0</sub> phase of the cell cycle to enter and proceed through the cycle. Continued growth factor exposure is required for progression through G<sub>1</sub> until the cell reaches the restriction point (see Fig. 6-3), after which time the cell proceeds through the rest of the cell cycle. How does the presence of an extracellular polypeptide, such as a growth factor,
It must be emphasized that these are only two of a large number of pathways that have been identified. Moreover, these apparently linear pathways are not linear at all, as there is much cross-talk between different components of a pathway, which suggests that the cellular responses to any single factor may depend on the balance of signals from different growth factor pathways.

Despite the complexity of these mitogenic signaling pathways, there is the suggestion that most converge on a common intranuclear event. It has been observed that most, if not all, mitogenic growth factors at some point lead to increased expression of certain D-type cyclins. As noted previously, this is an essential component of the ultimate activation of cyclin D/cdk activity (see Fig. 6-4). However, the induction of cyclin D protein is not sufficient to drive the entire decision for a cell to proliferate. Therefore, it must be integrated with other biochemical events in the nucleus. This observation provides a framework to think about how signaling of cells at the cell membrane by extracellular growth factors can affect the machinery that directly drives cell proliferation across the G to S checkpoint. As more is learned about mitogenic signal transduction pathways, the knowledge of how growth factors influence the cell-cycle machinery should lead to novel therapeutic strategies to treat cancer.

**CELL-CYCLE CHECKPOINTS**

The events of the cell cycle appear to be highly ordered into dependent pathways so that the initiation of any event in the cell cycle is dependent on the completion of earlier events. For example, mitosis is dependent on completion of DNA synthesis, chromatic separation is dependent on kinetochore assembly and chromosome alignment, and DNA replication during S phase is licensed by the cell having completed a prior mitosis. The control mechanisms that enforce this ordered dependency are called cell-cycle checkpoints. It is important to emphasize that a variety of signals, from both extracellular as well as intracellular events, can activate these checkpoints to prevent cell-cycle progression. For example, nutrient deprivation, temperature changes and other forms of environmental stress, nucleotide depletion, or damage to the DNA can all inhibit cell-cycle progression by invoking these cell-cycle checkpoint controls.

It is now clear that cell-cycle checkpoints are actively regulated by components of the cell-cycle machinery. For example, cell-cycle arrest following DNA damage is not simply a by-product of the structural damage to the DNA. Moreover, mutations in the genes that control these checkpoints can disrupt the arrest signals and allow continued cell-cycle progression when it may be inappropriate. Such mutations could result in altered responses to environmental or therapeutic DNA-damaging agents, such as increased or decreased cell death, increased mutation rate, and genetic instability. It is not surprising, then, that mutations in cell-cycle checkpoint genes are now thought to both significantly contribute to cancer development and affect the responses of tumor cells to chemotherapy and radiation therapy.

Damage to the DNA by ionizing radiation is the one stimulus for cell-cycle checkpoint activation that has been the most intensively studied. When nuclear DNA has been damaged by either intrinsic or extrinsic processes, normal cells cease progressing through the cell cycle at one of several points: either before entry into S phase, within S phase, or before entry into mitosis (see Fig. 6-1). Presumably, arrest at these particular points in the cell cycle would limit the propagation of genetic mutations to daughter cells by allowing DNA repair, and it may also prevent cell death. We briefly review what is known about each of these DNA damage checkpoints as well as two additional checkpoints that are not directly activated by DNA damage but may still be relevant to cancer development.

**G1- to S-Phase Checkpoint**

The tumor suppressor gene, p53, appears to be a critical component of the signaling pathway that arrests cells in G1 after DNA damage (Fig. 6-10). It is mutated in a large proportion of human cancers and the Li-Fraumeni familial cancer syndrome is caused by germline mutations in the p53 gene. This supports the importance of p53 function in cancer prevention. There are two potential mechanisms by which the loss of the p53-mediated G1 to S checkpoint could lead to increased cancer susceptibility. First, DNA damage is known to increase p53 protein level and activity, which secondarily increases the level of the p21 

\[\text{WAF1/CIP1}\]

inhibits the activity of cyclin/cdk complexes that drive the G1 to S-phase transition by preventing the hyperphosphorylation of RB (see Fig. 6-10). In cells that lack p21 

\[\text{WAF1/CIP1}\]

the G to S arrest after DNA damage is defective. In addition to being critical for G1 to S arrest, p53 also drives programmed cell death or apoptosis in certain cells in response to DNA damage. What governs whether p53 causes cell-cycle arrest or programmed cell death is not well understood. Nonetheless, it is clear that the loss of p53 can result in inappropriate cellular response to DNA damage by two mechanisms: allowing damaged DNA to be replicated and allowing the survival of cells that normally would undergo programmed cell death (see Fig. 6-10). In this regard, it is easy to understand how p53 mutations would be critical to cancer development. In addition, the loss of p53-mediated apoptosis in response to therapies that cause DNA damage could have a significant effect on tumor response. Two new genes, p73 and p63, have been identified as relatives of p53. The full importance of these p53-related genes in human cancer and the
increase their numbers by acquiring mutations in genes that result in combinations of increased drive through the cell cycle (increased genes) and the gene products that enhance programmed cell death (apoptosis-enhancing genes). Thus, tumors may develop and malignant cells may continue to be considered oncogenes in a simplified model) and the gene products that inhibit cell-cycle progression (considered tumor suppressor genes in a simplified model). In a given tissue. Changes in tissue cell number are dictated by the number of new cells generated by cellular proliferation and the number of cells lost to the cell cycle and cell death machinery and on those gene products involved in directly controlling cell-cycle progression. Loss of either type of function would lead to transformation of a normal cell to a tumor cell appears to be dependent on mutations in gene products important in integrating extracellular and intracellular signals to control cell-cycle progression. Absence of control responses to different types of DNA damage, such as that induced by gamma irradiation versus various genotoxic drugs or ultraviolet irradiation.

S-Phase Checkpoint

The molecular controls of S-phase arrest after DNA damage in mammalian cells are less well understood, but a number of yeast genes, such as MEC1, MEC2, and HUS1, have been identified that control the S-phase checkpoint. Although clear mammalian counterparts to these genes are just now being identified, the ATM gene, which is mutated in ataxia-telangiectasia and is related to MEC1, seems to be particularly important for the S-phase checkpoint. The first insight into this came from the study of a yeast with ataxia-telangiectasia, who are cancer prone, and from study of these patients’ cells, which are defective in all three DNA damage-induced checkpoints, including the S-phase checkpoint. The ATM gene product is a nuclear and cytoplasmic protein kinase that can phosphorylate certain proteins that are known to be involved in DNA damage checkpoint signaling and DNA repair, such as p53. Although studies of ATM-related genes in yeast have suggested potential biochemical and genetic mechanisms, how ATM regulates the S-phase checkpoint is not yet known (see Fig. 6-10).

G₀ to M-Phase Checkpoint

The DNA damage-induced arrest of cells in the G₀ phase of the cell cycle is prominent in most mammalian cell types and has been intensively studied by radiobiologists for years because of an apparent link between G₀ arrest and radiosensitivity. In yeast, the RAD9, RAD17, RAD24, MEC1, MEC2, and MEC3 genes all appear to be involved in signaling the cell to arrest in G₀ after DNA damage; and mutations in these genes lead to increased genetic instability and increased radiosensitivity. Work clarifying many details of this pathway in mammalian cells indicates that it controls the activation of cyclin B/cdk1, which is particularly important for regulating entry into mitosis (see Fig. 6-8). Briefly, in yeast it has been shown that DNA damage activates a kinase known as chk1, which can phosphorylate cdc25, the phosphatase that is critical for activating cyclin B/cdk1 at entry into mitosis. Phosphorylated cdc25 can be bound and, hence, inactivated by interaction with 14-3-3 proteins, which causes either cell-cycle arrest by induction of p21 RAS1CP1 or apoptosis. For cells in S phase, DNA damage arrests further DNA synthesis in an ATM-dependent and an rsn1-dependent manner. In cells in G₂ and M phase, DNA damage leads to the activation of proteins such as chk1 and chk2, which can phosphorylate cdc25 phosphatase. Phosphorylated cdc25 is then bound by, and hence inactivated by, 14-3-3 proteins, which therefore prevents the activation of cyclin B/cdk1 (which controls transition to mitosis). For cells in G₀ and to enter mitosis. Thus, in addition to expressing telomerase activity (see S Phase, earlier in this chapter), the loss of a growth inhibitory checkpoint signal to induce senescence could also contribute to the development of cellular immortality in tumor cells.

Mitotic Spindle Checkpoint

In addition to the DNA-damage-induced checkpoint to prevent entry into mitosis, there is another mitotic checkpoint that involves the mitotic spindle apparatus. This checkpoint functions to prevent the metaphase to anaphase transition until all sister chromatid pairs are aligned and attached to the mitotic spindle apparatus (see M-Phase Entry and Exit, earlier in this chapter) (see Fig. 6-8). Abnormalities in this checkpoint can lead to gross changes in chromosome number, which is a common occurrence in cancer cells. Several yeast genes (MAD1, MAD2, MAD3, BUB1, BUB2, and BUB3) have been found that control mitotic arrests when the microtubule apparatus is poisoned, but mammalian counterparts have not been identified. Interestingly, p53 has been implicated in a spindle checkpoint in mouse cells, which again demonstrates its importance in numerous aspects of cancer cell biology.

Cellular Senescence

Finally, it has been suggested that cellular senescence also represents a type of cell-cycle checkpoint that is activated when chromosomal telomeres become shortened to a critical point. It is thought that critically shortened telomeres may cause DNA strand abnormalities to activate one or more cell-cycle arrest signals and prevent further cell proliferation (hence, senescence). This could be significant for tumorigenesis because tumor cells may have defective checkpoint-signaling pathways. Thus, in addition to expressing telomerase activity (see S Phase, earlier in this chapter), the loss of a growth inhibitory checkpoint signal to induce senescence could also contribute to the development of cellular immortality in tumor cells.

IMPLICATIONS FOR CANCER

CANCER DEVELOPMENT

Cancer exhibits a diverse set of phenotypic abnormalities, including loss of differentiation, increased motility or invasiveness, and decreased drug sensitivity. However, one phenotypic abnormality that is virtually pathognomonic of all cancer cells is dysregulation of cell-cycle control. A common misconception is that cancer cells replicate faster than normal cells. Rather, the growth abnormality in cancer cells appears to result from two factors: (1) lack of appropriate control responses to the signals that normally cause the cell to stop going through the cell cycle, and (2) lack of a cellular death program in response to appropriate stimuli or stresses. The transformation of a normal cell to a tumor appears to be dependent on mutations in gene products important in integrating extracellular and intracellular signals to control cell-cycle progression and cell death machinery and on those gene products involved in directly controlling cell-cycle progression. Loss of either type of function would lead to loss of regulatory cell growth signals.

An evolution has occurred over the past 25 years in our thinking about the nature of the growth abnormalities present in cancer cells. The discovery of oncogenes in the 1970s and their overexpression or increased activity in tumor cells led to the suggestion that the abnormality in tumor cells was the presence of too much of a signal that pushed the cell through the cell cycle. The discovery of tumor suppressor genes in the 1980s added to this model by suggesting that the growth abnormalities of tumor cells resulted from a combination of too few of the cell-cycle brakes (tumor suppressors) and too many of the cell-cycle accelerators (oncogenes).

This model has been even further revised in the past several years with the recognition of the importance of cell death controls in maintaining appropriate numbers of cells in a given tissue. Changes in tissue cell number are dictated by the number of new cells generated by cellular proliferation and the number of cells lost to the signals that normally cause the cell to stop. Changes in tissue cell number are dictated by the number of new cells generated by cellular proliferation and the number of cells lost to the cell cycle and cell death machinery and on those gene products involved in directly controlling cell-cycle progression. Loss of either type of function would lead to loss of regulatory cell growth signals.

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inhibition of cell-cycle progression (loss of tumor suppressor genes), increased ant apoptotic signals (e.g., overexpressed BCL2) and decreased proapoptotic signals (e.g., decreased BAX or mutated p53). Cell differentiation is also probably associated with slowing or stopping cell proliferation, and some abnormal gene products in malignancies that drive proliferation also appear to inhibit differentiation.

FIGURE 6-10. The steady-state number of cells in a tissue is a function of the relative amount of cell proliferation and cell death. Cell proliferation is influenced by the balance of positive effects of oncogenes and negative effects of tumor suppressor genes. Cell death is influenced by the balance of positive and negative effects of proapoptotic and antiapoptotic gene products. Simplistically, cell number may be increased by increased activity of oncogenes or antiapoptotic genes or by decreased activity of tumor suppressor genes or proapoptotic genes.

Oncogenes

One formal definition for an oncogene is that the oncogene product contributes to malignant transformation either in vitro or in vivo. The concept used previously that oncogenes are gene products that enhance cell-cycle progression is not always true, but is useful for the discussion here. Oncogenic mutations in tumor cells will not be discussed in great detail here. However, it is clear that many of the genes that have been classified as oncogenes are positive growth signals. They can fall into categories of abnormally activated growth factors (e.g., c-SIS), growth factor receptors (e.g., HER2/neu and c-FMS), intracellular signaling molecules (e.g., c-SRC, RAS, and c-RAF), and nuclear transcription factors (e.g., c-MYC). Such signaling pathways were discussed previously as influencing the actual cell-cycle machinery, and it is easy to envision how activating mutations in any of these genes could lead to enhanced signals that inappropriately keep the cell going through the cell cycle. Positive signals directly involved in the cell-cycle machinery have been linked to oncogenesis by the observations of abnormally high levels of cyclin expression in certain tumor cells. In addition, the cdk-activating cdc25 phosphatases have been demonstrated to have cooperative onogenic activity in soft agar and nude mouse tumor assays and appear to be overexpressed in a significant percentage of primary human breast carcinomas.

Tumor Suppressor Genes

The existence of tumor suppressor genes, predicted in the 1970s by the elegant epidemiologic studies of Knudson, 122 and by subsequent cell fusion studies, 123 finally became a reality with the discovery of the retinoblastoma (RB) gene and later the role of the p53 gene in the 1980s. 119 Although a number of tumor suppressor genes have been identified to date (including APC, BRCA1, BRCA2, NF1 and NF2, WT1, and VHL), RB and p53 are unusual tumor suppressor genes in that they directly influence the cell-cycle machinery. As discussed previously, RB expression inhibits cell-cycle progression by binding to E2F-1 and blocking transcription of genes necessary for entry into S phase. p53 inhibits cell-cycle progression by inducing the transcriptional activation of the CDK, p21CIP1, which in turn inhibits activation of the cdk such that it cannot phosphorylate substrates such as RB.

As discussed previously, p53 participates in a cell-cycle checkpoint signal transduction pathway that causes either G0 arrest or apoptotic cell death after DNA damage. Loss of p53 function during tumorigenesis thus can result in both inappropriate progression through the cell cycle after DNA damage and survival of a cell that might otherwise have been destined to die. It is easy to conceive how this would cause both increased genetic instability and decreased apoptosis and contribute to malignant transformation. Additionally, roles for p53 in controlling certain aspects of the progression from the G2 phase of the cell through mitosis and chromosome segregation have been suggested. 119,114 Thus, it is not surprising that p53 is the most commonly mutated gene in human cancers identified to date, with at least 50% of tumors having abnormal p53 genes. Some tumors also develop other mechanisms of inactivating p53 function by overexpression of the p53-binding protein, mdm2, 119 or by infection with high-risk human papilloma virus (HPV) and expression of the HPV E6 protein, which binds to p53 and enhances its degradation. 112 Inactivation of p53 by overexpression of mdm2 appears to occur primarily in sarcomas and inactivation by HPV infection in cervical carcinomas. 112,114 Thus, many tumors appear to inactivate p53 function by these mechanisms, rather than by mutation of the p53 gene itself, but the end result is the same since p53 function and certain aspects of cell-cycle control are abrogated.

The RB gene is mutated in a number of different tumor types, but others may have mutations elsewhere in the cell-cycle pathways that use RB. For example, cyclin D/cdk4 complexes phosphorylate RB and it appears that p15INK4a and p16INK4a, which are inhibitors of cyclin D/cdk4, are mutated in a variety of tumor types. In contrast, the p27KIP1 and p21KIP1 cdk inhibitors are rarely mutated. 112 In principle, any cdk inhibitor might act as a tumor suppressor protein. 111 Loss of RB pathway function could certainly lead to loss of normal inhibitory controls of cell-cycle progression. However, some data also suggest that loss of RB function alone enhances apoptosis tendencies of cells, so by itself might not result in tumor development. 113,117,118,119,120 It has been suggested 112 that loss of RB function, leading to enhanced cell proliferation, coupled with genetic changes that cause loss of apoptosis signals, would be an efficient combination for enhancing malignant transformation (see Apoptosis: Another Step in the Cell Cycle That Goes Awry in Tumor Cells?, later in this chapter).

Characterization of the tumor suppressor locus coding for the cyclin kinase inhibitor p16 INK4a revealed a novel tumor suppressor gene and a genomic organization that is unprecedented in mammalian cells and affects both the RB and p53 pathways. 112 The p19ARF gene was found as an alternatively spliced gene encoded within the genetic locus that codes for p16 INK4a. Interestingly, the p19ARF gene product induces a growth arrest that is dependent on the p53 protein. 113,114 Thus, this single genetic locus codes for two proteins, one of which (p16 INK4a) inhibits proliferation via the RB pathway by inhibiting activation of cyclin-dependent kinases and a second protein (p19ARF) that inhibits proliferation via activation of p53 (Fig. 6-12). 112 The mechanism by which p19ARF affects p53 protein levels has been shown to be via binding to the mdm2 protein and sequestering mdm2 in the nucleus. 113,115,116,112,121,122 The sequestration of mdm2 results in increased p53 protein levels because mdm2 normally binds to p53 and enhances its proteolytic degradation. This p19ARF-mediated increased level of p53 protein results in growth arrest of a cell.

FIGURE 6-12. Schematic diagram depicting the cell-cycle checkpoints mediated by the p16 INK4a/p19ARF genetic locus. Mitogenic signals that activate cyclin D/cdk4 to lead to cell proliferation can be blocked by p16 INK4a. In certain cellular contexts, mitogenic signals that would normally drive cell proliferation can instead activate the p19ARF pathway. Activated p19ARF indirectly activates p53 by a mechanism that involves mdm2. Activated p53 may lead to cell-cycle arrest or apoptosis as noted in Figure 6-10. In this way, p19ARF can act as a checkpoint to “sense” what may be inappropriate oncogenic cell proliferation signals. Of note, the DNA damage response
The genetic locus coding for these two genes is on chromosome 9p in human cells and is a common area of mutation in human tumors. Intriguingly, oncogene activation is one cellular stimulus that has been shown to activate p19

\[ p19 \]  

And initiate this p53-mediated growth arrest. If this pathway were not inactivated during tumor formation, activation of an oncogene would simply cause a p53-mediated growth arrest or apoptosis. Thus, tumor cells can bypass this normal cellular response to oncogene activation by mutating either p19

\[ p19 \]  

Or p53 (see Fig. 6-12). Furthermore, since this same locus also codes for a gene product that limits cellular proliferation by inhibiting the RB pathway, deletion of this locus would eliminate two gene products that limit cellular proliferation through two different critical pathways. Thus, it is not at all surprising that this locus is so commonly mutated in human tumors.

### Apoptosis: Another Step in the Cell Cycle That Goes Awry in Tumor Cells?

Apoptosis is a mode of cellular death that is an energy-dependent, programmed event (hence the name programmed cell death) that occurs in response to certain stimuli. There are characteristic morphologic (nuclear condensation and fragmentation, cell shrinkage, and relative sparing of the cellular membrane and internal organelles) and biochemical (DNA fragmentation and selected proteolysis) events that occur during apoptotic cell death. In addition, a variety of stimuli, such as irradiation or chemotherapy, viral infection, growth factor or hormone withdrawal, and cytotxic lymphocyte killing, can initiate this death program. Obviously, some of these stimuli are cell-type specific. Apoptosis is also a critical event in normal development and in normal tissue homeostasis, clearly playing a role, for example, in nervous system development and in lymphocyte selection processes in the immune system.

Some of the gene products that control the cell cycle also appear to influence apoptosis tendencies (e.g., c-myc, p53, RB). It has been suggested that apoptosis occurs when conflicting cell-cycle signals are simultaneously active in the cell or when survival signals coming from extracellular peptides are blocked. Some models also conceive of apoptosis as an integral part of the cell cycle, with apoptotic death being viewed as a type of permanent exit from the cycle, just as the G1 quiescent phase is an exit from the cycle. It has also been suggested that apoptotic death is the natural default outcome for cycling cells unless a survival factor (hormone or growth factor) is present to keep the cell alive as it progresses through the cycle. Since responses to current antineoplastic therapies (chemotherapy and radiation therapy) are also likely to be affected by the apoptosis tendencies of cells, this process has obvious therapeutic implications.

It appears that a decrease in apoptosis tendencies is a key step in tumor development (Fig. 6-13). Experimental tumorigenesis systems using DNA tumor virus models and transgenic animal models led to the suggestion that an initial mutation in a cell may occur in a gene that increases cellular proliferation. Examples of such mutations include loss of function of RB or overexpression of c-MYC. However, these genetic changes, which increase proliferation, also appear to lead to increased apoptotic cell death, thus leading to no net increase in absolute cell number in the tumor. However, if one cell in this proliferating (and apoptotic-prone) population then developed a mutation that abrogated the cell death response, then it is easy to envision how this would lead to a significant increase in cell number in the population. Dysfunction of p53 or overexpression of BCL2 are examples of genetic changes that could inhibit the death response initiated by c-MYC overexpression or RB mutation. Subsequent genetic changes in these cells could then contribute to other phenotypic changes associated with tumors, such as invasiveness and metastasis.

### FIGURE 6-13. Model of multistep tumor progression incorporating current concepts of genetic changes occurring during tumorigenesis. Genetic changes such as loss of RB function or overexpressed c-MYC may lead to increased cell proliferation. However, these changes also lead to increased apoptosis (black oval) and thus there is no significant net increase in cell number. The viral gene products, E1A from adenovirus, T antigen from SV40, and E7 from human papilloma virus, appear to have similar effects on the cell by virtue of binding to RB. Subsequent genetic changes that decrease apoptosis (such as loss of p19

\[ p19 \]  

Or p53 or overexpression of bcl-2) would then lead to increases in total cell number. Viral gene products, such as adenovirus E1b, SV40 large T antigen, and human papilloma virus E6, appear to accomplish this by binding to p53 protein. Additional genetic changes further contribute to the malignant cell phenotype by enhancing local invasiveness and metastasis. Although the order of the genetic events may vary in different settings, the concept that both increased proliferation signals and decreased cell death signals contribute to tumorigenesis probably applies to most tumor types. (Concept adapted from ref. 119, with permission.)

In addition to oncogenic genetic changes providing a selection pressure for loss of apoptotic signals during tumor development, the harsh microenvironment surrounding the tumor mass can similarly favor cellular alterations that oppose death pathways. As the number of cells in a tumor mass grows, significant cellular stresses ensue. For example, the tumor mass is exposed to periods of hypoxia as well as oxidative stress during reperfusion. In addition, suboptimal blood supplies to tumor masses result in periods of time in which the tumor is exposed to acid pH and deprivation of nutrients and glucose. Growth of the tumor mass also results in cellular detachment from normal tissue basement membranes. All of these microenvironmental situations might typically kill the exposed cells. In order for a tumor mass to grow beyond a certain size, it must develop mechanisms to survive in this harsh microenvironment. Similar to the mechanisms a developing tumor uses to survive the oncogenic stresses discussed previously, mutations in death-signaling pathway would allow the developing tumor to survive these microenvironmental stresses. Thus, mutations in survival- signaling molecules or gene products involved the apoptosis machinery, and alterations in growth factor or cytokine exposure favor continued development of a tumor mass (Fig. 6-14).

### FIGURE 6-14. Mutations involved in tumor progression allow tumor cells to survive harsh microenvironmental stresses. Tumor cell stresses (A) would lead to cell death in normal cells. Tumor cells acquire a number of genetic changes (B) that allow the malignant cells to survive these harsh conditions. For any given tumor type, the exact nature of these genetic changes may not be known. Little is known about the sequence of these genetic changes during tumor development in vivo.

Significant insights have been gained into the molecular steps involved in cell death-signaling pathways. These insights began with the molecular characterization of
the (t(14;18)) chromosomal translocation commonly seen in follicular lymphomas resulting in identification of the antiapoptotic gene BCL2. The concept developed in the follicular lymphoma model was that the abnormal lymphoid cells grow initially because of loss of cell death tendencies due to BCL2 overexpression caused by the translocation of the BCL2 gene from chromosome 18 to the actively transcribed immunoglobulin gene on chromosome 14 in B-lymphoid cells. At this point, such lymphomas are rather indolent, but are difficult to cure with chemotherapy. However, at some later stage, they develop other genetic changes and become more aggressive. We now know of a family of related gene products that interact with each other to influence apoptotic tendencies. Korsmeyer and colleagues developed a model in which the bcl-2–like protein, bax, can drive the cell toward apoptosis when it forms complexes with itself (Fig. 6-15). When bcl-2 protein is expressed at high levels in cells, it forms complexes with bax, preventing bax homodimerization and inhibiting cell death. Other antiapoptotic proteins with homologies to bcl-2 and bax, such as bcl-xL and mcl-1, have also been identified. The list of antiapoptotic and proapoptotic gene products continues to grow and it appears that some of this apparent redundancy of proteins results from tissue-specific expression and use of the different proteins in different signaling pathways.

It has been suggested that we could take advantage of altered cell-cycle checkpoints in tumor cells to make chemotherapy and radiotherapy given in a particular time to become resistant. Although it is not clear how one might go about reducing genetic instability, taking advantage of new insights into apoptotic signaling arising from mutations in cell-cycle checkpoint or DNA repair genes, could also give the tumor cell an advantage by creating the capability for it to mutate to find ways specific to irradiation, selective combinations of therapies could theoretically selectively kill the tumor cells that continued to progress through the cell cycle after treatment with the first cytotoxic agent while the normal cells that are arrested are relatively protected. Another scenario arises from the observations that yeast that are defective in the G2 checkpoint are more sensitive to irradiation, and that abrogation of the G2 checkpoint in mammalian cells (e.g., by caffeine) makes the cells more sensitive to radiation. Hence, selective combinations of therapies could theoretically selectively kill the tumor cells that continued to progress through the cell cycle after treatment with the first cytotoxic agent while the normal cells that are arrested are relatively protected. Another scenario arises from the observations that yeast that are defective in the G2 checkpoint are more sensitive to irradiation, and that abrogation of the G2 checkpoint in mammalian cells (e.g., by caffeine) makes the cells more sensitive to irradiation.

Critical details in death-signaling pathways have been elucidated in recent years and incorporate much of what had been known about the bcl-2 family and survival-signaling pathways. One major insight was the identification of a family of specific proteases, now referred to as caspases, which are critical for apoptosis signaling. Current models suggest that apoptosis is dependent on a series of highly regulated proteolytic cleavages that result in selected activation or inactivation of certain molecules and eventually result in the highly ordered internal destruction of the cell (Fig. 6-16). The release of cytochrome C from the mitochondria and association of cytochrome C with the apoptosis inhibitor protein (AIP) and caspase 3, is a critical step in death induced by genotoxic damage, as would be induced by many chemotherapeutic agents. Predictably, growth factors, such as interleukin-3, which provide survival signals to cells, appear to act via modulation of one or more steps in these pathways. One particularly interesting mechanism along these lines is the interleukin-3–induced phosphorylation of the proapoptotic protein, BAX, which causes the release of the antiapoptotic protein, bcl-xL, promoting cell survival. It is now clear that a group of extracellular molecules can also act as death-inducing signals by interaction with selected cell surface receptors (called death receptors) to initiate cellular suicide via activation of a different caspase-dependent pathway, one that may not involve mitochondria (see Fig. 6-16). Fas ligand and Fas receptor are examples of an extracellular molecule and death receptor that initiate programmed cell death in this way, and this pathway appears to be particularly important in the regulation of cell death in lymphoid cells. Tumor necrosis factor and the TRAIL family are additional examples of cytokines that act via this type of pathway. As discussed previously, alterations in these death-signaling pathways can contribute to tumor development by keeping the tumor cells alive in the face of genetic changes or microenvironmental stresses that would normally result in cell death. The potential impact of loss of these death-signaling pathways on tumor responses to therapy is obvious.

It has been suggested that we could take advantage of altered cell-cycle checkpoints in tumor cells to make chemotherapy and radiotherapy given in a particular sequence more specifically toxic for tumor cells. For example, although loss of the G1 checkpoint in tumor cells by itself does not make tumor cells more sensitive to irradiation, selective combinations of therapies could theoretically selectively kill the tumor cells that continued to progress through the cell cycle after treatment with the first cytotoxic agent while the normal cells that are arrested are relatively protected. Another scenario arises from the observations that yeast that are defective in the G2 checkpoint are more sensitive to irradiation, and that abrogation of the G2 checkpoint in mammalian cells (e.g., by caffeine) makes the cells more sensitive to irradiation.
Telomerase provides another potential cell-cycle–related, tumor-specific target. As discussed previously, telomerase activity is expressed in embryonic tissues and is usually turned off in differentiated somatic cells, but appears to be reexpressed in tumor cells, giving them unlimited replication potential. Telomerase provides another potential cell-cycle–related, tumor-specific target. As discussed previously, telomerase activity is expressed in embryonic tissues and is usually turned off in differentiated somatic cells, but appears to be reexpressed in tumor cells, giving them unlimited replication potential. Telomerase provides another potential cell-cycle–related, tumor-specific target. As discussed previously, telomerase activity is expressed in embryonic tissues and is usually turned off in differentiated somatic cells, but appears to be reexpressed in tumor cells, giving them unlimited replication potential.


Molecular Biology of Cancer: Apoptosis

APOTOPSIS

Multicellular organisms have developed a highly organized and carefully regulated mechanism of cell suicide to craft the development of multiple lineages and to maintain cellular homeostasis. Normal development and morphogenesis proceed by the production of excess cells, which are then removed by a genetically programmed, evolutionarily conserved process. This same program of cell death is used by the organism to remove damaged cells, including virally infected cells.

Programmed cell death may have first been recognized in the developing neuronal system of the toad by Vogt. Kerr and colleagues described cell deaths with distinct ultrastructural features, including plasma membrane blebbing, volume contraction, nuclear condensation, and endonucleolytic cleavage of DNA. They noted that these features were consistent with an active, regulated process and coined the term apoptosis from the Greek word used to describe “dropping off” or “falling off” of petals from flowers or leaves from trees.

Studies of chromosomal translocations in human lymphoid malignancies yielded the BCL-2 gene, the first component of the cell death pathway to be identified. The most common chromosomal translocation found in these malignancies is the t(14;18)(q32;q21) harbored by 85% of follicular and 20% of diffuse B-cell lymphomas. The consequence of this rearrangement is to place BCL-2 under the transcriptional control of the immunoglobulin (lg) heavy-chain locus. B cells harboring this translocation express inappropriately elevated levels of BCL-2 protein.

Clues to the biologic consequence of BCL-2 overexpression reside in the natural history of follicular lymphoma. The disease usually follows an indolent course, with symptoms that wax and wane over years. Transformation to a high-grade lymphoma with diffuse mixed or diffuse large cell morphology often occurs within the first decade. When a BCL-2-lg minigene that recapitulated the t(14;18) breakpoint was inserted into the germline of a mouse, follicular hyperplasia resulted (Fig. 7-1). This polyclonal expansion of small resting B cells was principally in G1 of the cell cycle. Over time, these mice progress to diffuse, large cell immunoblastic lymphoma. Long latency followed by progression to high-grade malignancy is essentially diagnostic for the acquisition of second genetic abnormalities. Indeed, approximately one-half of the high-grade tumors have acquired an additional translocation, placing c-myc under the control of the Ig heavy-chain locus, thus combining an inherent survival advantage (Bcl-2) with a gene that promotes proliferation (c-myc). Further evidence for the potent synergy of such a combination emerged when Bcl-2 transgenic mice were mated to myc transgenic mice, resulting in the rapid appearance of an undifferentiated hematolymphoid leukemia. The oncogenic potential of BCL-2 is not restricted to the B-cell lineage; overexpression in T cells results in peripheral T-cell lymphomas.

Tumorigenesis reflects the accumulation of excess cells, which formally results from increased cell proliferation and decreased cell death. The first oncogenes to be discovered were genes involved in signal transduction or regulation of transcription. Gain of function mutations in these genes results in oncogenesis by increased proliferation. A second class of oncogenes was subsequently identified whose normal function is to inhibit growth and proliferation. It is often loss of function mutations in this class of genes that results in tumors. BCL-2 represents the cardinal member of a third class of oncogenes, which regulate cell death, resulting in resistance to apoptosis that enables the accumulation of additional genetic aberrations.

GENETICS OF CELL DEATH

A genetic program of developmental cell death emerged from the study of the nematode Caenorhabditis elegans. These worms are particularly well suited to the study of cell fates because they are transparent, allowing visualization of individual cells. During the development of the C. elegans hermaphrodite, 1090 cells are generated, and 131 of these cells undergo programmed cell death. Genes have been identified that reside in a common, core pathway responsible for the regulation of all 131 cell deaths. Moreover, lineage-specific genes that reside in private pathways more upstream are responsible for initiating the cell deaths. Furthermore, two complementary sets of genes have been identified that control the phagocytosis of cell corpses. Functional mammalian counterparts to many of these genes have been identified (Fig. 7-2), indicating that the basic tenets of apoptosis are conserved from nematodes to humans.
The "ced-9" gene and its mammalian counterparts have been well characterized. The mouse homolog of "ced-9" is known as FLICE-inhibitory protein (FLIP). Caspases are activated by two cleavage events. The first cleavage event results in the formation of the prodomain and the large subunit. The second cleavage event results in the formation of the large and small subunits. The active caspase consists of a complex with two large and one small subunit.

In mammals, the initiation of programmed cell death occurs through interaction of death ligands such as tumor necrosis factor-a (TNF-a), Fas, or TNF-related apoptosis-inducing ligand (TRAIL), with their respective receptors followed by aggregation of these receptors. Recruitment of adaptor proteins, such as Fas-associated death domain (DD) protein (FADD), TNF receptor-associated DD protein (TRADD), and receptor interacting protein (RIP), to a plasma membrane complex ensues through interactions between yet a third domain, the death domain (DD), present on both the receptor and adaptor proteins.

FIGURE 7-2. The genetic pathway regulating cell death in the nematode Caenorhabditis elegans has been well characterized and has been conserved in evolution from worms to mammals. Cell death in the nematode transpires by a mechanism in which death is executed by a single protease (CED-3), whose activity is regulated by a single activator (CED-4) and inhibitor (CED-9). Mammalian counterparts for the C elegans genes are indicated in parentheses.

Three additional genes required for apoptosis have been identified, egl-1 (egg-laying abnormal), ced-3, and ced-4. Loss of function mutations in either ced-3 or ced-4 can rescue cells from death. Egl-1 functions as an upstream, negative regulator of the BCL-2 homologue ced-9. Whereas the killing activity of ced-4 requires functional ced-3, the killing activity of ced-3 is independent of active ced-4. Ced-4 thus appears to function upstream of ced-3 in this genetic pathway. An overall genetic pathway consistent with all the observations would be egl-1>ced-9>ced-4>ced-3.

Ced-3 encodes a cysteine protease homologous to the mammalian interleukin 1 beta-converting enzyme (ICE), or caspase 1, required for the proteolytic activation of pro-interleukin-1b. Transient expression of either CED-3 or ICE induces apoptosis in mammalian cells, suggesting that this family of proteases plays a critical role in programmed cell death. The mechanism by which cell death in the nematode transpires is remarkably simple: Death is executed by a protease (CED-3) whose activity is regulated by an activator (CED-4) and an inhibitor (CED-9). Mammalian counterparts for each of the members of the C elegans apoptotic pathway exist (see Fig. 7-2).

DEATH RECEPTORS

In mammals, the initiation of programmed cell death occurs through interaction of death ligands such as tumor necrosis factor-a (TNF-a), Fas, or TNF-related apoptosis-inducing ligand (TRAIL), with their respective receptors followed by aggregation of these receptors. Recruitment of adaptor proteins, such as Fas-associated death domain (DD) protein (FADD), TNF receptor-associated DD protein (TRADD), and receptor interacting protein (RIP), to a plasma membrane complex ensues through interactions between yet a third domain, the death domain (DD), present on both the receptor and adaptor proteins. Recruitment of the initiator caspase 8 (also called Fas-associated death domain–like interleukin 1 beta-converting enzyme [FLICE]) through interaction of its death effector domain (DED), results in its subsequent activation, evidently by self-proteolytic cleavage (Fig. 7-3). Caspase recruitment can be inhibited by proteins such as FLICE-inhibitory protein (FLIP) whose DED interacts with and ties up adaptor proteins.

FIGURE 7-3. Cell fate after activation of tumor necrosis factor (TNF) family receptors (TNFR) is determined by the balance between cell survival and cell death signals. Signals through Fas-associated death domain (DD) protein (FADD), TNF receptor-associated DD protein (TRADD), and receptor interacting protein (RIP), to a plasma membrane complex ensues through interactions between yet a third domain, the death domain (DD), present on both the receptor and adaptor proteins. Recruitment of the initiator caspase 8 (also called Fas-associated death domain–like interleukin 1 beta-converting enzyme [FLICE]) through interaction of its death effector domain (DED), results in its subsequent activation, evidently by self-proteolytic cleavage (Fig. 7-3). Caspase recruitment can be inhibited by proteins such as FLICE-inhibitory protein (FLIP) whose DED interacts with and ties up adaptor proteins.

In addition to transducing a death signal through caspase activation, engagement of the TNF-a receptor results in a survival signal through nuclear factor kB (NFkB) activation and transcription of genes involved in cell survival. The balance between these two opposing pathways determines the ultimate fate of the cell.

FIGURE 7-4. Model of the mammalian cell death pathway. Left: A major checkpoint in this pathway is the ratio of proapoptotic (BAX) to antiapoptotic (BCL-2) members. Downstream of this checkpoint are two major execution programs: mitochondrial dysfunction and caspase activation. Mitochondrial dysfunction is manifested as altered mitochondrial transmembrane potential (Dym); disturbed mitochondrial physiology, including ROS production; and, at times, mitochondrial swelling. Cytochrome c is released from the mitochondrial membrane space to complex with Apaf-1 and activate caspase 9. Caspase activation may occur following a mitochondrial loop with Apaf-1/cytochrome c or directly in cells in which caspase 8 activates effector caspase 3. Caspases are activated by two cleavage events between the prodomain and the large subunit, and subsequently between the large and small subunits. The active caspase consists of a complex with two large and two small subunits. These activated caspases cleave death substrates, such as poly (ADP-ribose) polymerase (PARP) and laminin, culminating in cell death. Right:
CASPASES

Caspase 1 is the prototype of a large family of proteases whose members function in inflammation or apoptosis. 2 Caspases are expressed as inactive proenzymes and are activated by proteolytic cleavage after a death stimulus. Members of the caspase family possess a common structural motif consisting of three domains: an amino-terminal domain, a large subunit, and a small subunit. Caspase cleavage consensus sites separate each domain. After cleavage, the large and small subunits associate to form a heterodimer. Crystallographic analyses of both caspase 1 and caspase 3 show association of two heterodimers to form a tetramer. Both the large and small subunits contribute residues important for substrate binding and specificity. The two catalytic sites of the tetramer appear to function independently. 3,6,7

Caspases are cysteine proteases that cleave substrates after an aspartate residue. Substrate specificity of individual caspases is determined by the size of the substrate binding pocket, which dictates the preferred amino acids immediately amino-terminal to this aspartate residue. 5,6 Activation of upstream caspases initiates a proteolytic cascade that allows rapid transmission and exponential amplification of a death stimulus. Effector caspases such as caspase 3 are activated, culminating in the destruction of the cell by apoptosis. Depending on the death signal and the cell type involved, this process appears to proceed through a pathway of mitochondrial dysfunction and the release of cytochrome c or, alternatively, a mitochondrial-independent pathway. 8

THE Bcl-2 FAMILY

The Bcl-2 family of proteins is situated upstream of irreversible cell damage in the apoptotic pathway (see Fig. 7-4), 9 providing a pivotal decisional checkpoint in the fate of a cell after a death stimulus. At least two effector pathways exist downstream for the execution of apoptosis, the caspase pathway and mitochondrial dysfunction. Mitochondrial dysfunction manifests as altered mitochondrial transmembrane potential (Dym); release of proteins from the mitochondrial intermembrane space, including cytochrome c, that triggers the activation of Apaf-1 and caspases; and the production of reactive oxygen species. Thus, the effector caspases may be activated directly following engagement of a surface death receptor or downstream of a mitochondrial amplification loop.

Both pro- and antiapoptotic family members have been identified (Fig. 7-5). Members of the family possess up to four conserved a helical domains, designated BH1, BH2, BH3, and BH4. 10 Mutagenesis studies of Bcl-2 indicate that the conserved domains are necessary for the interaction with proapoptotic proteins such as BAX and for the inhibition of cell death. 11 The proapoptotic and apoptotic family members may also have independent activities. 12 An intact amphipathic a helical BH3 domain is required for the proapoptotic proteins BAX or BAK to initiate apoptosis. 13,14 BAX and BAK are more highly conserved prodeath members of the Bcl-2 family bearing BH1, BH2, and BH3 domains. A subset of proapoptotic Bcl-2 family members possess sequence homology only within the BH3 domain, further emphasizing the concept that this region forms a critical DD. The recognition that the upstream proapoptotic molecule in C elegans, EGL-1, was also a "BH3-only" protein supports the role of these proteins at the intersection with the core apoptotic pathway. 12

The three-dimensional structures for both an antiapoptotic molecule, BCL-X L, and the proapoptotic molecule BID have been determined. 37,56 The Bcl-X L a helical structure includes two central hydrophobic cores sandwiched by two amphipathic a helices similar to the membrane translocation domain of the bacterial toxin diphteria toxin fragment B and the colicin. In fact, electrophysiologic studies have shown that BAX and BCL-2 are capable of forming ion channels in artificial membranes. In their closed, monomeric forms, the a helices comprising domains BH1 to BH3 of the full family members are juxtaposed to form a hydrophobic pocket; this pocket receives the hydrophobic face of a BH3 amphipathic a helix to form hetero- or homodimers. 51

As predicted from their structure, antiapoptotic molecules are principally integral membrane proteins found in the outer mitochondrial membrane, endoplasmic reticulum, or outer nuclear membrane. 34,43 In contrast, many of the proapoptotic molecules, especially the "BH3 domain only" subset are localized to the cytosol or cytoskeleton and undergo posttranslational modification after a death signal, which allows them to target and integrate into the mitochondrial membrane. 34,43 These modifications in response to death stimuli suggest that these BH3-only molecules are candidates for an upstream link between the BCL-2 checkpoint and proximal signal transduction (Fig. 7-6).

FIGURE 7-5. Summary of antiapoptotic and proapoptotic BCL-2 members. BCL-2 homology regions (BH1 to BH4) are denoted, as is the carboxy-terminal hydrophobic (TM) domain. (From ref. 66, with permission.)
In support of this thesis, the BH3-only protein BAD is modified by phosphorylation on two serine residues in the presence of the survival factor interleukin-3 (IL-3). Distinct kinases appear to be responsible for the phosphorylation of the two serine sites in BAD. The phosphoinositide 3 kinase pathway regulates the phosphorylation of serine 136 in BAD. Akt, a serine/threonine survival signaling kinase in that pathway, can phosphorylate BAD serine 136. Akt can also phosphorylate and inactivate the proapoptotic transcription factor FKHR1 and caspase 9. The phosphorylation and inactivation of serine 112 is mediated at the mitochondrial membrane by cyclic adenosine monophosphate–dependent protein kinase (PKA). Thus, a single proapoptotic molecule BAD has multiple signal transduction pathways that converge to inactivate it. This example indicates how complex the regulation of this pathway is and offers additional steps for therapeutic intervention.

Another BH3-only protein, BID, connects the death signal through TNF-a or Fas to the downstream death effectors. BID exists in the cytoplasm as an inactive 22-kD protein. After TNF-a or Fas signals, BID is cleaved in an unstructured loop by caspases to generate an active 15-kD fragment, truncated BID (tBID) which translocates and inserts into the mitochondrial membrane. Cleavage eliminates the amino-terminal inhibitory a helix, exposing the hydrophobic face of the BH3 domain as well as two central hydrophobic cores. Once integrated into the mitochondrial membrane, p15 BID results in the release of cytochrome c. The presence of BCL-2 or BCL-X-L is able to prevent the release of cytochrome c.

The proapoptotic full family members BAX and BAK also demonstrate inactive and active conformations. Inactive BAX exists as a monomer in the cytosol, which translocates to the mitochondrial membrane where it resides as an active homo-oligomeric integral membrane protein. The translocation and oligomerization steps that activate BAX are, Interestingly, blocked in cells protected by BCL-2.

**BCL-2 FAMILY MEMBERS PLAY CRITICAL ROLES IN TISSUE HOMEOSTASIS**

The most stringent test for the role of a gene in normal development and homeostasis is an animal in which the gene of interest has been disrupted. Newborn Bcl-2 knockout mice are viable, but the majority die within a few weeks of birth. The surviving mice develop renal failure due to severe polyctic kidney disease. BCL-2 functions in the normal fetal kidney to maintain cell survival during inductive epithelial-mesenchymal interactions. At 5 to 6 weeks, the animals turn gray because of apoptosis of melanocytes. The hematopoietic system is initially normal, but thymus and spleen subsequently undergo massive involution due to apoptosis, reflecting a failure to maintain homeostasis in both B and T cells. Mice lacking Bcl-X-L are unable to complete normal development, with embryos dying of erythroid and neuronal apoptosis. In this way the mitochondria is involved in the oligomerization of the survival molecules BCL-2 and BCL-X-L, as well as the localization of the antiapoptotic molecules BH3-only proteins, which are involved in the activation of the death signal.

Loss of the proapoptotic gene Bax results in hyperplasia of thymocytes and B cells and accumulation of atrophic granulosa cells and excess primordial follicles that fail to undergo apoptosis. The male mice are infertile because of failure of normal postnatal death of spermatogonia. This leads to a markedly disorganized seminiferous tubule and failure to successfully complete meiosis. Increased cell numbers are present in Bax-deficient neurons, indicating that cells that normally would have died during embryonic development because of inadequate innervation are saved in the absence of Bax.

Mice without BID successfully complete embryonic development and appear grossly normal. However, the mice are resistant to Fas-induced hepatocellular apoptosis, indicating a critical role for a BID-dependent mitochondrial amplification loop in this Fas-signaled death.

**ROLE OF MITOCHONDRIA**

The mitochondrial dysfunction that occurs in cell death manifests as an initial hyperpolarization, followed by a loss of Dym; the release of proteins from the mitochondrial intermembrane space, such as cytochrome c; and altered mitochondrial physiology, including the production of reactive oxygen species. Prior studies of necrotic death and late stages of apoptotic cell death have noted mitochondrial swelling attributed to the opening of a mitochondrial permeability transition pore that allows the passage of solutes and dissipation of the transmembrane gradient. The localization of antiapoptotic molecules, such as BCL-2 and BCL-X-L, as well as the translocation of proapoptotic BAX and BID to the mitochondrial membrane, emphasizes the importance of mitochondrial dysfunction in the action of these molecules. The specific mechanisms by which these proteins elicit their mitochondrial effects is an area of intense interest.

The importance of the mitochondria in the execution of apoptosis varies depending on both cell type and death stimulus. In certain cell types, activation of the TNF/Fas death receptor activates robust quantities of caspase 8 and subsequent effector caspase 3 with no requisite role for mitochondria, whereas other cells such as liver require the mitochondrial amplification loop to die. Other death stimuli, such as growth factor deprivation, may proceed in the absence of caspases and depend heavily on mitochondrial effects.

**CELL PROLIFERATION AND APOPTOSIS**

Apoptosis represents a brake on cellular expansion, counteracting abnormal cell proliferation. Substantial evidence exists for cross-talk between proliferation and apoptosis pathways. The oncoproteins c-Myc and adenovirus E1A, both potent inducers of proliferation, have also been shown to possess proapoptotic properties. The mitogenic and apoptotic properties of both c-Myc and adenovirus E1A are genetically inseparable. E1A induces proliferation and apoptosis by interacting with either the retinoblastoma protein (Rb), a regulator of cell-cycle progression, or the transcriptional corepressor p300. c-Myc appears to promote apoptosis by multiple pathways.

Rb itself also provides a link between cell proliferation and apoptosis. Rb functions as a cell-cycle checkpoint between G1 and S phase and mediates its effect through interaction with a family of transcription factors that control the expression of genes required for cell-cycle progression, the E2F proteins. Complexes containing both E2Fs and Rb have been shown to bind to target DNA sequences in a number of promoters and actively repress transcription. Entry into S phase induced by ectopic expression of E2F or mutagenesis, which abolishes interaction with Rb, results in increased apoptosis. Mice in which the Rb gene has been knocked out by homologous recombination die at embryonic day 12 to 13 and exhibit both proliferation and apoptosis of liver, central nervous system,
Oncogenes have been shown to sensitize cells to a wide variety of stimuli, including DNA damage, hypoxia, death receptors such as TNF-a and Fas, and growth factor withdrawal. It appears that the cellular machinery directing cell proliferation and apoptosis is coupled, suggesting that the decision of a cell to undergo apoptosis or proliferation may be determined by the balance between growth and survival signals. A single potential link between these two processes is the p53 tumor suppressor. Loss of p53 has been observed in numerous tumor types, and p53 function is abrogated in a large percentage of tumors. p53 expression is induced in response to a variety of cellular stresses, including DNA damage, hypoxia, and oncogene activation, resulting in cell-cycle arrest or apoptosis. Mice deficient for p53 are developmentally normal, but 75% develop spontaneous tumors by 6 months of age. Germline mutation of p53 in humans results in Li-Fraumeni syndrome, and more than 50% of these individuals develop tumors by 30 years of age.

The majority of p53 mutations in human tumors cluster within the DNA-binding domain, suggesting that p53 exerts its tumor suppressor effects through translational regulation of target genes. The mechanism by which p53 exerts its apoptotic effect appears to be multifactorial. p53 is able to induce the expression of BAX and FAS, as well as another member of the TNF family of death receptors, DR5. In addition, p53 inhibits the expression of BCL-2, and BCL-2 can inhibit p53-induced apoptosis in select settings. p53 also appears to induce apoptosis by post-translational mechanisms.

POSSIBILITIES FOR THERAPEUTIC INTERVENTION

Given the ability to induce apoptosis in lymphoid cells and many types of tumor cells, the death receptors are attractive targets for therapeutic intervention in cancer. However, inhibition of TNF-a causes a lethal inflammatory response resembling septic shock, which results from proinflammatory activation of macrophages and endothelial cells. Apoptosis and inhibition of anti-Fas antibody causes lethal hepatic apoptosis. The related death ligand TRAIL (APO2L) appears to possess the ability to induce apoptosis in a wide variety of tumor cell lines. In vivo administration of a leucine zipper form of TRAIL in which the molecule is stabilized as a trimers suppresses the growth of a mammary adenocarcinoma cell line in SCID (severe combined immunodeficiency) mice. Normal cells treated in vitro with TRAIL showed no decreased viability. Similarly, recombinant TRAIL administered shortly after tumor xenograft injection markedly reduces tumor incidence. In addition, treatment of mice bearing solid tumors results in tumor cell apoptosis as well as improved survival. A synergistic effect was obtained with TRAIL and 5-fluorouracil or irinotecan (CPT-11). Encouragingly, intravenous injections of TRAIL into nonhuman primates did not result in toxicity to tissues or organs.

The BCL-2 gene provides another promising target for therapeutic intervention, particularly in the therapy of low-grade lymphoma in which BCL-2 overexpression plays an important role. The strategy of antisense oligonucleotide therapy has been used to “silence” BCL-2 expression. Antisense oligonucleotides are short single-stranded nucleic acid molecules capable of binding to their target sequences, usually 16 to 20 bases in length. The oligonucleotides are internalized by cells through a saturable endocytosis pathway. On injection into a host, expression of a specific gene can be blocked by hybridization with the target messenger RNA through Watson-Crick base pairing. The result is either degradation of the RNA-DNA complex by Rnase H or block in translation of the RNA.

A 18-base-pair antisense oligonucleotide, G3133 (Genta, San Diego, CA), was designed against Bcl-2 for the treatment of follicular lymphoma. Initial studies in a t(14;18) murine xenograft lymphoma model were encouraging, with absence of disease by polymerase chain reaction in 10 of 12 animals tested. A phase I clinical trial of G3133 has been completed on patients with relapsed B-cell non-Hodgkin’s lymphoma with evidence of BCL-2 overexpression by immunohistochemistry of lymph node biopsy. The main toxicity was reversible thrombocytopenia. Of the 20 evaluable patients (N = 21), one complete response was achieved in a patient with stage IV follicular lymphoma. Two patients had partial responses, eight patients had stable disease, and nine patients progressed. Current phase II studies are under way to investigate the role of G3133 in combination with conventional chemotherapy.

BCL-2 also has been shown to play a role in prostate cancer. In prostate cancer, Bcl-2 overexpression confers both chemoresistance and resistance to apoptotic cell death following oxygen withdrawal. In vitro treatment of prostate tumor cells with antisense BCL-2 enhances cytotoxicity of paclitaxel. In vivo administration of antisense BCL-2 oligonucleotides in combination with paclitaxel to animals with established tumors results in inhibition of tumor growth. In addition, treatment in combination with paclitaxel after castration results in a significant delay in tumor recurrence. BCL-2 is also highly expressed in malignant melanoma. BCL-2 antisense oligonucleotides significantly sensitized the tumor cell response to subsequent dacarbazine. It thus appears that BCL-2 antisense therapy may have a potential role in combination with other chemotherapeutic drugs as a chemoresensitizing agent.

CONCLUSIONS

Apoptosis is an evolutionarily conserved, highly regulated mechanism for maintaining homeostasis in multicellular organisms. Numerous signals are capable of modulating cell death. After a death stimulus, the signal is propagated and amplified through the activation by proteolytic cleavage of caspases, culminating in the ordered disassembly of the cell. The process may transpire through a mitochondrial-dependent or independent pathway, depending on the death signal and cell type involved. Caspase-8 protein is an indispensable cell death in the apoptotic pathway by providing a pivotal checkpoint in the fate of a cell after a death stimulus. The proapoptotic molecules BID, BAD, and BAX undergo modification and intracellular translocation on receipt of a death stimulus, connecting distinct upstream signal transduction pathways with the common, core apoptotic pathway. The distribution of inactive conformers of the BH3-only members suggests that they may function as sentinels for recognizing cellular damage. BIM would monitor microtubule function, BID would amplify minimal caspase activation, and BAD would protect for metabolic stress after loss of critical survival factors. This model would explain how seemingly diverse cellular injuries converge on a final common pathway of cell death.

Finally, the cellular pathway to apoptosis appears to communicate with the pathway for cell proliferation. As a result, activation of cell proliferation by oncogenes also results in sensitization to apoptosis. Reciprocally, the expression of antiapoptotic molecules often retards cell-cycle progression. This interconnection provides a means for limiting the threatening expansion of cells with a lesion in either pathway. These observations fit the evidence that defects are required in both proliferation and cell death pathways, as single defects tend to be self-correcting in their net effect on cell number. The molecules mediating apoptotic pathways provide an exciting opportunity for rational design of new therapeutic agents to specifically promote apoptosis of cancer cells.

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CHAPTER 8
Molecular Biology of Cancer: Invasion and Metastases

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INTRODUCTION

Metastasis is the spread of cancer cells from a primary tumor to vital organs and distant sites in the cancer patient's body. Metastatic disease is the hallmark of malignant cancer. The formation of tumor metastasis is the major cause of treatment failure in cancer patients and is a principal contributing factor to cancer morbidity and mortality. Metastatic disease has significant biologic and prognostic impact on cancer diagnosis and treatment.

The formation of metastatic foci is a continuous process that can begin early in the growth of the primary tumor and increases in frequency with tumor duration and tumor burden. Metastases may also disseminate to form new metastatic lesions in other organs (metastases will metastasize). The variation in size, age, dispersed anatomic location, and heterogeneous composition of metastases makes complete eradication of metastatic disease by currently available therapeutic strategies extremely difficult. The patient with metastatic disease succumbs to organ failure secondary to anatomic compromise caused by multiple metastases or to complications associated with systemic therapy directed against the metastatic disease. The design of more effective therapies to treat metastatic cancer requires better understanding of the molecular events and cellular processes that are involved in the process of metastasis formation.

THE METASTATIC CASCADE

It is well established, from both clinical observations and mechanistic studies, that metastasis formation is an inefficient process. Studies have demonstrated that late events in metastasis formation are largely responsible for the inefficiency of this process. Large numbers of tumor cells and tumor cell clumps are shed into the vascular drainage system of a primary tumor. It has been demonstrated experimentally that, after intravenous injection of highly metastatic tumor cells, only approximately 0.01% of these cells form tumor foci. The number of circulating tumor cells and tumor emboli correlate with the size and age of the primary tumor (i.e., larger tumors shed more tumor cells and emboli). However, the number of circulating tumor cells does not correlate with the clinical outcome of metastases.

The inefficiency of tumor cells in completing the metastatic cascade is the result of the fact that successful formation of metastatic foci consists of several highly complex and interdependent steps. Each step is rate limiting in that failure to complete any of these events completely disrupts metastasis formation. The steps involved in metastasis formation are thought to be similar in all tumors and are characterized as follows (Fig. 8-1).

FIGURE 8-1. The pathogenesis of cancer metastasis. To produce metastases, tumor cells must detach from the primary tumor, invade the extracellular membrane and enter the circulation, survive in the circulation to arrest in the capillary bed, adhere to subendothelial basement membrane, gain entrance into the organ parenchyma, respond to paracrine growth factors, proliferate and induce angiogenesis, and evade host defenses. The pathogenesis of metastasis is therefore complex and consists of multiple sequential, selective, and interdependent steps whose outcome depends on the interaction of tumor cells with homeostatic factors.

1. Oncogenicity (tumorigenesis). After the initial neoplastic transformation, the tumor cells undergo progressive proliferation that is accompanied by further genetic changes and development of a heterogeneous tumor cell population with varying degrees of metastatic potential. The initial growth of the primary tumor is supported by the surrounding tissue microenvironment, which eventually becomes rate limiting for further growth.
2. Angiogenic switch. As the tumor grows and central tumor cells become hypoxic, the tumor initiates recruitment of its own blood supply. This process is called the angiogenic switch and involves the secretion of various angiogenic factors and the removal or suppression of angiogenesis inhibitors. Vascularization of the tumor is also associated with a dramatic increase in the metastatic potential of these tumors. Studies demonstrate that some tumors and metastases arising in vascularized tissues may first co-opt existing vasculature before initiating recruitment of new vessels.
3. Clonal dominance and invasive phenotype. Continued genetic alterations in the tumor cell population results in selection of tumor cell clones with distinct growth advantage and acquisition of an invasive phenotype. Invasive tumor cells down-regulate cell-cell adhesion, alter their attachment to the extracellular matrix (ECM) by changing integrin expression profiles, and proteolytically alter the matrix. Collectively, these changes result in enhanced cell motility and the ability of these invasive cells to separate from the primary tumor mass. These cells can detach from the primary tumor and create defects in the ECM that define tissue boundaries, such as basement membranes, thus accomplishing stromal invasion. Furthermore, the poorly formed tumor vasculature that forms in response to the angiogenic switch in phenotype of the primary tumor, as well as thin walled lymphatic channels in the surrounding stroma, are readily penetrated by these invasive tumor cells and offer ready conduits to the systemic circulation. Endothelial cells responding to the angiogenic stimulus produced by the primary tumor also express an invasive phenotype.
4. Survival in the circulation. Once the tumor cells and tumor cell clumps (emboli) have reached the vascular or lymphatic compartments, they must survive a variety of hemodynamic and immunologic challenges. Little is known about how these factors may impact on the inefficiency of the metastatic process in human cancers.
5. Tumor cell arrest. After survival in the circulation, tumor cells must arrest in distant organs or lymph nodes. This arrest may occur by size trapping on the inflow side of the microcirculation, or by adherence of tumor cells through specific interactions with capillary or lymphatic endothelial cells, or by binding to exposed basement membrane.
6. Extravasation and growth at the secondary site. In most cases, arrested tumor cells extravasate before proliferating. Studies suggest that extravasation of tumor cells is not dependent on protease activity and is independent of metastatic potential. After exiting the vascular or lymphatic compartments, metastatic tumor cells may proliferate in response to paracrine growth factors or become dormant. After extravasation, tumor cells migrate to a local environment more favorable...
for their continued growth. Findings using in vivo videomicroscopy demonstrate that the poor growth of tumor cells after extravasation from the circulation is a major factor contributing to the inefficiency of the metastatic process.

7. Angiogenesis in metastatic foci. Finally, continued growth of the metastatic foci is also dependent on angiogenesis. The development of this neovascular network at the metastatic site enhances the metastatic potential of these cells just as it does for the primary tumor.

8. Evasion of immune response. Metastatic foci of tumor cells must evade eradication by immune responses that may be either nonspecific or targeted directly against the tumor cells.

As might be expected from the highly complex nature of metastasis formation, no single gene product is responsible for metastasis formation. Successful completion of many of the steps of the metastatic cascade is the result of both the acquisition of positive effectors as well as the loss of negative regulators. Unrestrained growth is not sufficient to result in tumor invasion and metastasis. Tumor invasion is not a passive process secondary to tumor growth, and it may require additional genetic changes other than those associated with the tumorigenic phenotype. Tumorigenicity and metastatic competence have some overlapping features but are clearly under separate genetic control. Research indicates that genetic products that can facilitate completion of each of the steps outlined above. These are the molecular effectors of tumor invasion and metastasis. In many cases, research also has identified gene products that function to block successful completion of each of the steps in the metastatic cascade. The idea that there is loss of negative effectors, as well as positive phenotypic changes, associated with malignant progression and metastasis formation is now well established. In this chapter, some of the steps in the metastatic cascade are examined with the aim of identifying both the molecular effectors and the effector and suppressor genes that may become a target for new and effective cancer therapies. Immune modulation of cancer is discussed elsewhere (see Chapter 4), as is the process of tumor-associated angiogenesis (see Chapter 9). In addition, the angiogenic response at the metastatic foci is conceptually the same as in the primary tumor; therefore, the discussion of these points is limited here.

**ONCOGENESIS: METASTASIS AND TUMORIGENESIS ARE UNDER SEPARATE GENETIC CONTROL**

Many tumors progress through distinct stages that can be identified by histopathologic examination. Pathologists use the identification of these distinct phases to diagnose and classify tumors into different prognostic categories (e.g., normal tissue, hyperplasia, dysplasia, carcinoma in situ, and frankly invasive carcinoma). Genetic analysis of these different stages of tumor progression resulted in the multistep theory of tumorigenesis, which involves activation of oncoviruses, inactivation of tumor suppressor genes, and identification of a host of tumor-associated molecules (cancer markers). The progressive alteration in cellular oncogenes and inactivation of tumor suppressor genes that results in uncontrolled growth and loss of contact-dependent cell growth has been well documented in many tumor types, and it is the subject of separate chapters in this text (see Chapter 1 and Chapter 2). It also has been demonstrated that transfection of certain of these oncogenes into the correct recipient cell can result in acquisition of invasive and metastatic phenotype. Thorgeirsson et al. 1 were first to demonstrate that transfection of activated Ras oncogene sequences into fetal mouse fibroblasts results in acquisition of a metastatic phenotype when these cells are implanted in the nude mouse. This finding has been confirmed in fibroblast and epithelial cells of human and rodent origin when transfected with Ras. Similar findings, but with lower efficiency, have been observed with several other oncogenes (Myc, Raf, Src, Fes, and Fms) when transfected into an appropriate recipient cell.

At first, these results might suggest that genetic alterations might arise from genetic alterations associated with the acquisition of tumorigenicity. However, cells can be transformed by oncogene transfection, but not all cells acquire a metastatic phenotype after oncogene transfection. 1 In addition, the adenovirus E2A gene was shown to suppress Ras induction of the metastatic phenotype without alteration in tumorigenicity or inhibition of soft agar colony formation. 1 These findings demonstrate that a clear separation exists between the genetic changes that drive tumorigenicity and the metastatic phenotype. These findings can be explained by the fact that invasion and metastasis require activation of additional effector genes or suppression of local inhibitors over and above those required for uncontrolled growth alone. The failure to induce metastatic competence by Ras in some cell systems is explained by a deficiency or suppression of these effector molecules in these cell types. These metastasis effector genes or gene products may be downstream of Ras or totally independent pathways that are involved in cell attachment or regulation of protease activity. In studies in which Ras effectively confers a metastatic phenotype, the metastasis effector genes are activated and suppressor genes are inactivated before Ras transfection, and the addition of Ras oncogene stimulates completion of the metastatic cascade. This finding is demonstrated by the observation that Ras plus E1A reverses the metastatic potential and metalloproteinase expression observed in rat embryo cells. 2 Candidate effector genes include those associated with cellular adhesion to ECM components, as well as proteases, motility factors, angiogenic factors, and growth regulation. Candidate suppressor genes would include genes associated with enhanced cell-cell attachment; phosphatase activities that regulate focal adhesion assembly; angiogenesis inhibitors; protease inhibitors; and factors that suppress cell migration, invasion, and growth.

**ANGIOGENESIS: BALANCE OF POSITIVE AND NEGATIVE EFFECTORS**

Classic studies by Folkman and colleagues in the 1970s demonstrated that continued growth of tumors requires persistent new blood vessel growth and that inhibition of this process results in tumor growth arrest. The endothelial cell growth, cell attachment, or migration.

The newest member of this group is the cleaved conformation of the serpin antithrombin. It also has been demonstrated that transfection of certain of these oncogenes into fetal mouse fibroblasts result in acquisition of a metastatic phenotype when these cells are implanted in the nude mouse. This finding has been confirmed in fibroblast and epithelial cells of human and rodent origin when transfected with Ras. Similar findings, but with lower efficiency, have been observed with several other oncogenes (Myc, Raf, Src, Fes, and Fms) when transfected into an appropriate recipient cell. Inhibitors of angiogenesis can work at many levels by blocking endothelial cell growth, cell attachment, or migration.

A novel direction in angiogenesis inhibitors is the identification of cryptic inhibitors that are revealed by proteolytic modification of ECM components. This finding suggests a class of angiogenesis inhibitors that are contained within other proteins that are not antiangiogenic and must undergo proteolytic processing to uncover the angiogenic activity. Examples of these types of inhibitors include a 29-kD fragment of fibronectin; the 16-kD fragment of proalpha; and endostatin, a C-terminal fragment of collagen XVIII. The newest member of this class is the cleaved conformation of the serpin antithrombin. Thus, local regulation of angiogenesis can be achieved by proteolytic release of cryptic angiogenesis inhibitors.

In a study by Bergers et al. 13 the RIP1-Taq2 model of pancreatic islet b-cell tumors has been useful in examining the effects of angiogenesis inhibitors on multicystic carcinogenesis in mice. The findings of this study demonstrate that angiogenic drugs can be targeted to selective stages of cancer progression and that combination of agents with different mechanisms of action should be used at different stages of tumor development.

Tumor angiogenesis is the result of a tightly regulated process and a delicate balance of both pro- and antiangiogenic factors. The process of endothelial cell invasion and formation of new blood vessels has many functional similarities to the process of tumor cell invasion. Understanding the mechanisms of cell invasion may allow investigators to design strategies to disrupt this process. In addition, the use of agents that inhibit angiogenic activity, it should be possible to target those molecules that are involved in the process of cellular invasion that is required for tumor invasion and metastasis.

**TUMOR HETEROGENEITY AND CLONAL DOMINANCE**

It is now well recognized that most neoplasms consist of several tumor cell populations that vary widely in several important biologic characteristics. These characteristics include growth rate, karyotype, production of growth factors and stimulators of angiogenesis, hormone production, receptor content, and sensitivity to death by cytotoxic agents, immune response, and hypoxia. Fidler et al. 14 demonstrated the concept of heterogeneity of primary neoplasms in 1977. This concept is important because it suggested that not all tumor cells in the primary tumor population share the same propensity to form metastases and that formation of metastatic foci is a process that requires the presence of the highly aggressive subpopulation. However, evidence of a significant difference between the...
average metastatic propensity of cells comprising a primary tumor compared with those from an established metastasis was not forthcoming. This discrepancy was examined experimentally by Kerbel et al.\textsuperscript{25–28} by using genetic markers to tag different subpopulations in the primary tumor. This work demonstrated that the metastatic subpopulation dominates the primary tumor mass early in its development. This dominance arises secondary to a selective growth advantage in the metastatic cells responding to local growth factors. Thus, the measurement of the average level of a molecular marker associated with metastatic propensity in the primary tumor reflects the likelihood of that tumor to form metastases. This finding has subsequently been confirmed in clinical studies by demonstration that the average level of a specific marker or oncogene measured within the primary tumor can be correlated with clinical evidence of metastasis or recurrence.

**DEFINING THE INVASIVE PHENOTYPE**

During the transition from benign to invasive carcinoma, extensive changes occur in the quantity, organization, and distribution of subepithelial basement membrane. The hallmark of invasive carcinoma is disruption of the epithelial basement membrane and the presence of cancer cells in the stromal compartment. Benign proliferative disorders, such as fibrocystic disease, sclerosing adenosis, intraaductal hyperplasia, intraductal papilloma, and fibroadenoma, are all characterized by disorganization of the normal epithelial architecture. But no matter how extensive this disorganization may become, these benign lesions are always characterized by a continuous basement membrane that separates the neoplastic epithelium from the stroma.\textsuperscript{29}

In contrast, invasive carcinoma is characterized by a loss of basement membrane around the invasive tumor cells in the stroma. Once the basement membrane barrier is compromised, it is impossible to determine the quantity or location of tumor cells that may have escaped from the primary tumor. Thus, local invasion is paramount to malignant conversion.

The ability to cross basement membrane barriers is not unique to malignant carcinoma cells. During an inflammatory response, nonneoplastic immune cells regularly cross the subendothelial basement membranes, as do endothelial cells during the angiogenic response. Trophoblasts invade the endometrial stroma and blood vessels to establish contact with the maternal circulation during development of the hemochorial placenta. However, these normal cell types respond to additional signals that result in differentiation and subsequent loss of their invasive phenotype. Indeed, both normal and tumor cell invasion share functional similarities. In tumor cell invasion, however, it is the lack of response to negative signals or regulators and the continued invasion with ongoing tumor cell growth that is unique to cancer metastasis.\textsuperscript{30}

Tumor cell interaction with the basement membrane is defined as the critical event of tumor invasion that signals the initiation of the metastatic cascade.\textsuperscript{30} Basement membranes are composed of a dense meshwork of type IV collagen, laminin, and heparin sulfate proteoglycans that is interspersed with entactin and other minor components. Basement membranes do not contain pores that would allow passive tumor cell migration. Early studies on defining the invasive phenotype on malignant tumors focused on the interaction of tumor cells with the epithelial basement membrane. These studies defined the three-step hypothesis of tumor cell invasion: tumor cell attachment to the basement membrane, creation of proteolytic defects in the basement membrane, and migration of tumor cells through these defects.\textsuperscript{30} It is now recognized that these three steps describe tumor cell interaction with all types of ECM and not just basement membrane. Furthermore, nonneoplastic invasive cells, such as trophoblasts, endothelial cells, and inflammatory cells, all use mechanisms for invasion that are functionally similar to tumor cells. The difference between these normal invasive processes and the pathologic nature of tumor cell invasion is therefore one of regulation. An understanding of the factors that control cellular processes essential to the invasive phenotype should allow identification of novel targets for therapeutic intervention to prevent and treat both angiogenesis and metastasis formation.

**CELL-CELL ADHESION SUPPRESSES OR FACILITATES METASTASIS FORMATION**

The initial events in cellular invasion are changes in cell adhesion. These changes consist of alteration in both cell-cell adhesion and interactions with the ECM. A variety of cell surface receptors that mediate these interactions have been characterized, including the cadherins, integrins, immunoglobulin superfamily, and CD44. Tumor cells must decrease cell and matrix adhesive interactions to escape from the primary tumor. At later stages in the metastatic cascade, however, tumor cells may need to increase adhesive interactions with cells and ECM, such as during arrest and extravasation at a distant site. The apparent contribution of each class of cell adhesion molecules to invasive behavior will in some way be dependent on the tumor cell population and model system used to study these interactions. We review the contribution of changes in cell-cell adhesion to tumor progression before considering alterations in association with the ECM.

The majority of human cancers arise in epithelial cells. Several types of junctional structures, such as desmosomes, tight junctions, and adherens-type junctions tightly interconnect normal epithelial cells. The formation and maintenance of these contacts require Ca\textsuperscript{2+}-dependent homophilic interactions mediated by the cell-adhesion molecules known as cadherins (Fig. 8-2). Cadherins are a superfamily of single-pass transmembrane glycoproteins that mediate Ca\textsuperscript{2+}-dependent cell-cell adhesion. The cadherin superfamily now consists of five subfamilies: the classic type I and type II cadherins, desmosomal cadherins, proteocadherins, and cadherin-related proteins.\textsuperscript{32} The classic cadherin, epithelial cadherin (or E-cadherin), mediates homotypic cell adhesion in epithelial cells. E-cadherin is a transmembrane glycoprotein that has five extracellular homologous domains (ectodomains), a single membrane-spanning region, and a cytoplasmic domain. E-cadherin is physically anchored to the actin cytoskeleton by cytoplasmic proteins termed catenins. b-Catenin is also a major component of the WNT signaling pathway.

**FIGURE 8-2.** Disruption of cell-cell adhesion concomitant with tumor progression. E-cadherin is a homotypic cell adhesion molecule containing five homologous, extracellular domains (ectodomains) that bind divalent calcium ions. Calcium binding promotes homophilic cell-cell E-cadherin complexes found in such structures as desmosomes, tight junctions, and adherens-type junctions. The cytoplasmic tail of E-cadherin involved in cell-cell adhesion interacts with b-catenin, a-catenin, and p120\textsuperscript{Catenin} (p120). Loss of E-cadherin function, by germline mutation, promoter hypermethylation, or destruction of the ectodomains by matrix metalloproteinase (MMP) activity, results in increased free cytosolic b-catenin levels. Increased cytoplasmic b-catenin can be directed to the proteosome complex by glycogen-synthetase kinase 3b (GSK3b) phosphorylation and subsequent interaction with the adenosomatic polyposis coli (APC) gene product. The frizzled (FRZ)-disheveled (DSH) pathway for WNT signaling can down-regulate the activity of GSK3b. Activation of the WNT signaling pathway or loss of APC function facilitate the increase in cytoplasmic b-catenin levels, which are associated with loss of E-cadherin function, or mutations of the b-catenin gene, which result in reduced association with E-cadherin cytoplasmic domain. Translocation of b-catenin to the nucleus results in gene expression associated with cell transformation and tumor growth (i.e., c-Myc, cyclin D1). It is noteworthy that this cascade of cellular transformation can be initiated by expression of an extracellular protease that culminates in enhanced cell-cell adhesion and cell proliferation.

Any disruption of the intracellular E-cadherin–b-catenin complex results in loss of cell adhesion. This would include changes in E-cadherin expression or function, as well as genes other than E-cadherin that are required for complex formation and function. Abundant evidence indicates that E-cadherin function is frequently lost during progression of many human cancers, including those arising in the breast, prostate, esophagus, stomach, colon, skin, kidney, lung, and liver.\textsuperscript{31} This loss of E-cadherin function arises via several different mechanisms. In familial gastric carcinomas, germline mutations in the E-cadherin gene predispose individuals to develop malignant cancer. Mutations in b-catenin are found in many primary tumors, including prostatic cancer, melanoma, and gastric and colon cancer. Another mechanism disrupting E-cadherin function during tumor progression is hypermethylation of the E-cadherin promoter, resulting in decreased gene expression. This has been found to be a major mechanism in papillary thyroid cancer in that 83% of cases of this disease demonstrated hypermethylation of the E-cadherin promoter. Yet another mechanism to alter E-cadherin function is proteolytic modification. Lochter et al.\textsuperscript{32} have reported that E-cadherin function can be disrupted by degradation of E-cadherin's extracellular domains by stromelysin-1, a member of the matrix metalloproteinase (MMP) family that has been closely linked with tumor progression.
Constitutive expression of active stromelysin in mammary epithelial cells results in cleavage of E-cadherin and progressive phenotypic changes in vitro, including loss of catenins from cell-cell contacts, down-regulation of cytokeratins, and up-regulation of vimentin and MMP-9. These changes result in a stable epithelial to mesenchymal transition of cellular phenotype. In vivo, stromelysin expression promotes mammary carcinogenesis that includes stereotyped genomic changes distinct from those seen in other mouse breast cancer models. It has been reported that loss of H-cadherin expression occurs during the progression of breast cancer, but little is known about the function of other cadherin family members during tumor progression. In summary, a decrease in cell-cell adhesion is associated with malignant conversion. Forced expression of E-cadherin in tumor cell lines results in reversion from an invasive to a benign tumor cell phenotype.

In normal cells, b-catenin is sequestered in the intracellular adhesion complex with the cytoplasmic domain of E-cadherin, a-catenin, g-catenin, and p120 (Crk-associated substrate). Loss of cell-cell adhesion results in disruption of the adhesion complex and free b-catenin. Free b-catenin is bound by the adenosomatous polyposis coli (APC) gene product and is rapidly phosphorylated by glycogen-synthetase kinase 3b (GSK3b). Phosphorylated b-catenin is subsequently degraded in the ubiquitin proteosome pathway. In many colon cancer cells, the tumor suppressor gene APC is nonfunctional. This lack of function can lead to accumulation of high levels of cytosolic b-catenin that can subsequently be translocated to the nucleus. The WNT-1 protooncogene--initiated signaling pathway, which includes the frizzled (FRZ) and disheveled (DSH) gene products, can block activity of GSK3b, which can also result in accumulation of b-catenin. In the nucleus, free nonphosphorylated b-catenin can bind to members of the TCF (transcription factor) Lef-1 (lymphoid enhancer-binding factor 1) family of transcription factors. It has been demonstrated that, after inactivation of APC function, the increase in available b-catenin enters the nucleus, complexes with transcription factor Tcf-4, and up-regulates c-Myc expression. It has also been shown that b-catenin activates transcription from the cyclin D1 promoter and contributes to neoplastic transformation by causing accumulation of cyclin D1. These findings link changes in cell-cell adhesion with intracellular signaling, oncogene expression, and tumor cell growth. Thus, loss of cadherin-mediated cell-cell adhesion is an important event that has many far-reaching consequences for acquisition of the invasive phenotype and tumor progression.

Other types of cell-cell adhesion interactions can actually facilitate metastasis formation. These may be particularly important during tumor cell arrest and extravasation. These molecules include members of the immunoglobulin superfamily, such as nerve cell adhesion molecule and vascular cell adhesion molecule-1. The immunoglobulin superfamily has a wide variety of members involved in cellular immunity and signal transduction, as well as cell adhesion. Members of the superfamily share the immunoglobulin homology unit that consists of 70 to 110 amino acid residues organized into seven to nine b-sheet structures. The diversity of superfamily members precludes generalization about their role in tumor cell invasion and metastasis. However, the role of one family member seems straightforward. Vascular cell adhesion molecule-1 is an endothelial cell, cytokine-inducible, counter-receptor for VLA-4 (very late antigen-4) integrin, also known as αβ, integrin receptor. The role of integrin receptors is discussed separately (see Role of Integrins in Tumor Invasion, later in this chapter). Normally, VLA-4 is expressed on leukocytes and functions in mediating leukocyte attachment to endothelial cells. VLA-4 is also found on tumor cells in malignant melanoma and metastatic sarcoma but not in adenocarcinomas. It is thought that expression of VLA-4 may facilitate interaction of circulating tumor cells with endothelium before tumor cell extravasation. This was demonstrated by intravenous injection of human melanoma cells into nude mice pretreated with VLA-4--inducing cytokines, which resulted in an enhanced number of lung metastases formed compared with no cytokine pretreatment of the mice. Cell-cell adhesive interactions can either suppress or facilitate metastasis formation. Either role is dependent on the specific context and molecular mechanisms of cell-cell interaction.

CELL-EXTRACELLULAR MATRIX INTERACTIONS IN TUMOR PROGRESSION

As already discussed, the interaction of the tumor cell with the ECM, in particular the basement membrane, defines the invasive phenotype, and tumor invasion is paramount to metastasis. It is now recognized that the ECM exerts a profound influence on cell behavior and that cells direct the assembly and disassembly of the matrix. This concept is known as dynamic reciprocity and also applies to the interaction of malignant tumor cells with the ECM. During the process of metastasis formation, malignant tumor cells must interact with a variety of different types of ECM. These types include the subepithelial basement membrane of the tissue of origin, stromal elements of the tissue of origin, subendothelial basement membranes during extravasation, and the stromal and basement membranes of the organ(s) at the site of metastasis growth. Attachment of nonneoplastic cells to the ECM is prerequisite for cell survival. A fundamental difference for neoplastic cells is the loss of anchorage requirement for cell survival and growth. The anchorage-independent growth of tumor cells may result from an uncoupling of cell survival signals transduced from the ECM by attachment, coupled with activation of cell-cycle progression that is associated with neoplastic transformation. Tumor cell interactions with the ECM have profound implications for both metastasis regulation and migration.

ROLE OF CD44 IN TUMOR INVASION

CD44 is a transmembrane glycoprotein with a large ectodomain and single cytoplasmic domain. CD44 is involved in cell adhesion to hyaluronan (HA). The gene encoding CD44 is on the short arm of human chromosome 11 and contains both constant and variable exons. As a result of this gene structure, a number of differentially spliced isoforms of CD44 can be generated. The isoform containing no variant exon sequences is referred to as standard CD44. A total of nine variant regions (v2 to v10) can encode protein sequences. Alternatively spliced messenger RNA variants of CD44 (CD44v) can contain one or more variant coding regions. More than 30 different splice variants have been detected by polymerase chain reaction analysis. In addition to these variants, cell type-specific differences in glycosylation of the core protein also exist. The pattern of glycosylation and presence of variant exons influence the ability of CD44 to function in HA binding.

Several lines of evidence suggest that CD44 expression plays a role in metastasis formation. Clinical correlation studies demonstrate that a variety of different types of cancer that express high cell surface levels of CD44 have a poorer clinical outcome when compared with tumors that have low CD44 surface expression. Forced expression of CD44v to v7 confers metastatic ability to nonmetastasizing rat pancreatic carcinoma cell line. Metastasis formation could be blocked using antivariant antibodies. However, the exact role of CD44v in metastasis formation remains elusive.

In some tumors, CD44-associated increases in tumor growth and metastatic potential correlate with CD44-mediated cell attachment to HA. Forced expression of CD44v to v7 confers metastatic ability to nonmetastasizing rat pancreatic carcinoma cell line. Metastasis formation could be blocked using antivariant antibodies. However, the exact role of CD44v in metastasis formation remains elusive.

ROLE OF INTEGRINS IN TUMOR INVASION

Integrins are heterodimeric transmembrane proteins that are formed by the noncovalent association of a and b subunits. Considerable redundancy within cell-ECM interaction mediated by integrins exist, because most integrins bind to several individual matrix proteins, and ECM components, such as laminin, fibronectin, vitronectin, and collagens, bind to several different integrin receptors. This fact suggests that integrins are capable of providing the cell with detailed information about the surrounding ECM environment, which is then integrated at the cellular level to generate a cellular response (Fig. 8-3). It is now well established that integrins can signal across the cell membrane in both directions. Binding of ECM ligands to integrins is known to initiate signal transduction pathways that can result in cell proliferation, differentiation, migration, or cell death (apoptosis, anoikis). This is referred to as inside-out signaling. Both integrin clustering and ligand occupancy are crucial for the initiation of intracellular integrin-mediated signal pathways.

![FIGURE 8-3. Role of integrins in tumor cell invasion and metastasis: integration of kinase and phosphatase activities. Binding of extracellular matrix components to](image-url)
Integrin receptor initiates an intracellular signaling cascade that results in formation of a focal adhesion complex consisting of cytoskeletal and signal transduction molecules. Ligand binding to the integrin receptor results in integrin clustering and association of signal transduction molecules. Integrin receptor clustering induces autophosphorylation of focal adhesion kinase (FAK) on tyrosine 397. Subsequently, a Src homology 2 (SH2)-containing (Shc) adapter protein of the Src kinase family binds to specific phosphoryosine residues (Y397) on FAK is recruited to the integrin-FAK complex. Recruitment of additional proteins, such as a-actinin, talin, and paxillin, to this complex connects the focal adhesion complex to the filamentous actin cytoskeleton. Interaction of Shc with FAK results in additional sites of phosphorylation on the FAK molecule and subsequent recruitment of additional SH2 adapter proteins, such as Grb2 and the nucleotide exchange factor Sos. These interactions lead to activation of the mitogen activated protein (MAP) pathway, which stimulates tumor cell growth, adhesion, and migration. Similarly, receptors for growth factors can transiently associate with the focal adhesion complex to synergistically activate the MAP kinase pathway. FAK activation also acts upstream of the Akt/protein kinase B (PKB) signaling pathway, which promotes cell survival. Association of the p85 subunit of phosphatidylinositol-3 kinase (PI3K) with tyrosine 397 in FAK mediates this effect. The rapid activation of the phosphatidylinositol(3,4,5)triphosphate (PIP3) lipid product of PI3K activity stimulates the Akt/PKB pathway, leading to enhanced cell survival. Crk-associated substrate (p130CAS) is another SH2- and SH3-containing signal transduction that associates with FAK on integrin binding to the extracellular matrix. Interaction of p130CAS with FAK is mediated by a proline-rich region on FAK (residues 712–178) that interacts with the SH3 domain of p130CAS. Activation of p130CAS promotes cell migration and invasion that is associated with enhanced metastatic behavior. The tumor suppressor gene PTEN inhibits cell adhesion, migration, and invasion. This inhibition is mediated by direct FAK phosphorylation of PTEN, and Shc, leading to negative regulation of the p130CAS pathway, which affects cell attachment, migration, and invasion. Down-regulation of the MAP kinase pathway by PTEN dephosphorylation of FAK and Shc negatively affects cell growth in addition to attachment and migration. PTEN is also known to directly dephosphorylate PIP2, and negatively regulate the downstream Akt/PKB cell survival pathway. PTEN may also disrupt this pathway indirectly by dephosphorylation of FAK, which alters P13K activation. Thus, integrin-mediated regulation of cell growth, adhesion, migration, and invasion is a complex network of signal transduction cascades that have both positive (kinase) and negative (phosphatase) regulatory elements. EGFR, epidermal growth factor; Erk, extracellular signal–regulated kinase; MEK, MAP kinase or ERK kinase; P, phosphorylated amino acid residue(s).

The knowledge that FAK is tyrosine phosphorylated on integrin activation suggests that focal adhesion–associated protein tyrosine phosphatases (PTP) could modulate Fak function. Several PTPs that interact with components of the focal adhesion complex have been identified. These are PTP-α and PTP-PEST (protein tyrosine phosphatase rich in proline (P), glutamic acid (E), serine (S), and threonine (T)), which negatively regulate Src and paxillin, respectively. It has been shown that, in PTP–PEST–deficient cells, a defect in cell motility correlates with an increase in the size and number of focal adhesions. This defect appears to be due in part to the constitutive increase in tyrosine phosphorylation of paxillin, as well as p130CAS and FAK.

A PTP that interacts directly with FAK is referred to as PTEN. PTEN was identified as a tumor suppressor gene on human chromosome 10q23, which is frequently mutated or deleted in a wide variety of human cancers, including gliomas and prostate, breast, lung, bladder, endometrial, kidney, and oropharyngeal cancers. The gene encodes both a phosphatase domain and also has extensive sequence homology to the cytoskeletal protein tensin. PTEN functions as a dual-specificity phosphatase in that not only is it a PTP but it also dephosphorylates the lipid phosphoinosit(3,4,5)triphosphate (PIP3) that leads to binding of link proteins, such as Nck. In addition, phosphorylation of FAK at tyrosine 397 creates a binding site for the regulatory subunit of phosphoinositol-3 kinase and triggers activation of this signal pathway.

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The roles of specific integrins in tumor progression and metastasis formation are dichotomous. The decreased expression of some integrins is associated with cellular invasion, whereas overexpression of others is associated with reduced invasive ability. For example, the αvβ3 integrin is expressed in metastatic melanoma but not in benign melanocytic lesions. Antibodies against α, integrins blocked growth of human melanoma xenografts in nude mice. Integrin αv expression is increased in oropharyngeal and bladder cancers and in lung tumors. Tumor progression is associated with expression of αvβ3 in 82% of tumors. The molecular events associated with enhanced integrin expression and tumor progression are not well defined. Clearly, in nontransformed cells, integrins are implicated in growth regulation. But tumor cell growth and migration–independent. This observation suggests that the role of integrins in tumor invasion and metastasis may only be secondarily related to growth control. Integrins are also directly involved in cell migration.

CELLULAR MIGRATION: NEW INSIGHTS

Cell migration requires transmission of motile force from the ECM to the cytoskeleton of the migrating tumor or endothelial cell (Fig. 8-4). Repetitive assembly of cytoskeletal elements to form membrane ruffles, lamellipodia, filopodia, and pseudopodia accomplishes cell movement. Lamellipodia are broad, flat, sheet-like structures in comparison to filopodia, which are thin, cylindrical projections. Cell movement begins with protrusion of a filopod or lamellipodium. These are formed by polymerization of actin to form elongated central filaments in the filopod and a broader cross-weave mesh in the lamellipodium. At the leading edge of the protruding structures, integrins concentrate in specific regions, and after ligation with ECM, ligands form focal adhesions. These focal adhesions are anchored to the actin filaments.
involves organization of the focal adhesion complex and connection with the actin cytoskeleton. This is accomplished via mechanisms described in Figure 9-3. Evidence suggests that if the integrin component of these complexes is not activated, these complexes are continually recycled across the cell surface without cell movement. Step 3 entails engagement of the integrin with the extracellular matrix, which is mediated by a change in integrin affinity. Traction force is generated and transmitted by the contraction and relocation of the actin cytoskeleton. The final step in cell locomotion is the release or disruption of the focal adhesion complex at the migrating cell. This is accomplished by release of components of the integrin complex or via proteolytic disruption of focal adhesion kinase connections with the filamentous actin cytoskeleton.

Microinjection studies have shown that integrin association with the Rho family of guanosine triphosphate (GTP)ases is critical for organization and assembly of the actin cytoskeleton. It has been demonstrated that a hierarchical cascade exists among these GTPases that controls formation of specific cytoskeletal structures. Cdc42 and Rac control formation of filopodia and lamellipodia, respectively, whereas Rho controls stress fiber formation and focal adhesions. 5

The integrin connection to the ECM provides adhesive traction, and contraction of the actin filaments results in forward propulsion of the cell body. As the cell moves, new cytoplasmic extensions occur at the leading edge and are anchored with newly formed focal adhesions. As the cell moves forward, the focal adhesions appear to move in a retrograde fashion on the cell surface. This apparent movement of the focal adhesions has been observed using fluorescent-tagged beads coated with integrin substrates or antireceptor antibodies. 220-224 These coated beads can also be used to actually measure the integrin-cytoskeletal traction forces generated, which has led to the demonstration that the strength of the integrin-cytoskeletal interaction can be modulated by the rigidity of the extracellular substrate. When cells are on a rigid substrate, the force-restraining force is exerted to prevent movement of the focal adhesion. Cells can detect this change in the substrate, and they respond by increasing the force generated by cytoskeletal linkage to the focal adhesion so that the cell pulls harder. This is referred to as reinforcement of the integrin-cytoskeletal attachments. Data suggest that Src kinases may be selectively involved in regulating this reinforcement. 5 Researchers have shown that beads binding to the fibronectin receptor in fibroblast containing either wild-type or Src-deficient cells show similar reinforcement of the fibronectin-receptor–actin cytoskeletal linkage. In contrast, when they use vitronectin, there is little reinforcement of the vitronectin receptor in wild-type Src-expressing cells, but a strong reinforcement in the Src-deficient fibroblasts. These authors also show selective association of kinase-defective Src–green fluorescent protein fusion with the α1 integrin subunit of the vitronectin receptor, but not with the fibronectin receptor. Possible interpretations of these results are that either Src is normally a selective inhibitor of reinforcement of force generation through the vitronectrin receptor or that Src promotes the turnover of links between cytoskeletal and integrin components of the focal adhesion complex.

Investigators have used a b, integrin–green fluorescent protein chimera to follow focal adhesion cycling over the cell surface. 5 These experiments demonstrate that, in stationary cells, focal adhesions were highly motile and moved in a linear fashion to the cell center. In motile cells, the focal adhesions remained stationary and only moved at the trailing edge of the cell. These authors postulate a cellular “clutch-like mechanism” in which alteration in integrin affinity is seen in response to migratory stimulus. Regulation of integrin-ligand interactions by inside-out signaling helps determine the nature of cellular responses to the ECM, such as whether a cell becomes migratory or remains stationary. 57

The last step in integrin-mediated cell migration is the release of the ECM integrin-cytoskeletal attachments at the trailing edge of the cell. 5 Two mechanisms have been identified in this last step. The first involves the release of the integrins from the cell surface such that it is left on the substratum. Integrin release from the cell membrane has been observed in fibroblast migration and by tumor cell lines in vitro. 5 A second mechanism that mediates release of the trailing edge of the cell is destabilization of cytoskeletal linkages intracellularly by either proteolytic activity or phosphatase activity. Calpain is a Ca2+-dependent protease that localizes to focal adhesions and regulates retraction in Chinese hamster ovary cells migrating on fibronectin by destabilizing cytoskeletal linkages.

Cell motility is a critical component of the invasive phenotype. Understanding the molecular mechanisms that confer tumor cell motility should allow identification of novel targets for disrupting this process and preventing tumor dissemination. Tumor cell motility can be correlated with metastatic behavior. When parameters such as pseudopodia extension, membrane ruffling, or vectorial translation are measured, a quantitative increase in highly invasive and metastatic tumor cells is seen when compared with nonmetastatic counterparts. 15 A variety of stimuli have been shown to stimulate tumor cell motility in vitro, including host-derived factors, growth factors, and tumor-secreted factors that function in an autocrine fashion to stimulate tumor cell motility. Autocrine motility factor is a 60-kD glycoprotein produced by human melanoma cells that stimulates tumor cell migration. Autocrine motility factor has been identified as neuronuclin/phosphohexose isomerase. 58,59 Autotaxin (ATX) is a 125-kD glycoprotein that elicits chemotactic and chemokinetic responses at picomolar to nanomolar concentrations in human melanoma cells. ATX contains a peptide sequence identified as the catalytic site in type I alkaline phosphodiesterases (PDEs), and it possesses 5-nucleotide PDE [EC 3.1.4.1 (Enzyme Commission designation for this enzymatic activity)] activity. 100 102 103 104 ATX binds adenosine triphosphate (ATP) and is phosphorylated only on threonine. Thr210 at the PDE active site of ATX is required for phosphorylation, 5-nucleotide PDE, and motility-stimulating activities. ATX also has adenosine-5-triphosphatase (ATPase) and ATP pyrophosphatase activities. ATX catalyzes the hydrolysis of GTP to guanosine diphosphate and guanosine monophosphate, of either adenosine monophosphate or inorganic pyrophosphate to inorganic phosphate, and the hydrolysis of nicotinamide adenine dinucleotide to adenosine monophosphate, and each of these substrates can serve as a phosphate donor in the phosphorylation of ATX. ATP possesses no detectable protein kinase activity toward histone, myelin basic protein, or casein. These results have led to the proposal that ATX is capable of at least two alternative reaction mechanisms—threonine (T-type) ATPase and 5-nucleotide PDE/ATP pyrophosphatase—with a common site (Thr210) for the formation of covalently bound reaction intermediates, threonine phosphate and threonine adenylate, respectively. 102

PROTEASES IN TUMOR CELL INVASION

As has been noted, matrix proteolysis has been recognized as a key part of the mechanism of tumor cell invasion. Tumor cells must be able to move through connective tissue barriers, such as the basement membrane, to spread from their site of origin. Although a variety of proteases have been implicated in this process, the family of proteases that has received the most attention has been the matrixins or MMPs. Matrixins and their specific inhibitors, the TIMPs, play important roles in normal physiology, because the ECM is a dynamic matrix of structural proteins, growth factors, and latent enzymes that is constantly being remodeled. Approximately 20 matrixins and four TIMPs have been characterized in humans and other animals. 15 16 The matrixins share a common domain structure (Fig. 8-5), although not all domains are represented in all family members. All of the enzymes have a signal peptide sequence, a propeptide domain (prodomain); a catalytic domain, which includes a highly conserved binding site for the catalytic zinc ion; and a hemopexin-like domain. Two family members, MMP-2 and MMP-9, have a gelatin binding domain. The matrixins share a common domain structure (Fig. 8-5), although not all domains are represented in all family members. All of the enzymes have a signal peptide sequence, a propeptide domain (prodomain), a catalytic domain, which includes a highly conserved binding site for the catalytic zinc ion; and a hemopexin-like domain. Two family members, MMP-2 and MMP-9, have a gelatin binding domain. The matrixins share a common domain structure (Fig. 8-5), although not all domains are represented in all family members. All of the enzymes have a signal peptide sequence, a propeptide domain (prodomain); a catalytic domain, which includes a highly conserved binding site for the catalytic zinc ion; and a hemopexin-like domain.
An early indication of the importance of matrixes in tumor biology was the characterization in 1980 of a MMP secreted from a melanoma cell line that was able to degrade basement membrane collagen.\(^{1}\) This finding was followed by numerous studies showing that secretion of matrixes enhanced tumor cell invasion in experimental model systems and that inhibition of protease activity by TIMPs or by synthetic metalloproteinase inhibitors impeded invasion. For example, the invasion of HT-1080 fibrosarcoma cells through Matrigel (a reconstituted basement membrane) is enhanced by addition of activated MMP-2 and inhibited by the addition of TIMP-2 or by zinc chelators.\(^{2}\) In vitro evidence has been supported by the results of in vivo experiments using transfected cell lines. For example, when MYUL bladder carcinoma cells are transfected with \(\text{MMP}-2\), they have enhanced metastatic potential, whereas transfecting the highly metastatic LMC19 cell line with \(\text{TIMP}-2\) reduces its metastatic potential.\(^{3,4}\) Mice genetically engineered to overexpress \(\text{MMP}-3\) in breast epithelial cells develop spontaneous breast carcinomas, possibly through the effects of \(\text{MMP}-3\) on the E-cadherin/b-catenin system.\(^{5}\)

Although these experiments and many others have demonstrated the key role of matrix-initiated degradation in tumor invasion and metastasis, the role of these enzymes in this process is more complicated than an “degradation equals invasion” paradigm would suggest. Uninhibited matrix degradation would lead to complete destabilization of the extracellular matrix, allowing tumor cell invasion and growth attachments to each other or to matrix proteins, which is a necessary part of the tumor invasion mechanism. Thus, there is an implied balance between active proteases and inhibitors that results in an optimal invasive phenotype. As a demonstration of this principle, when A2058 melanoma cells are transfected with either sense or antisense \(\text{TIMP}-2\), the invasive potential is decreased. Increasing \(\text{TIMP}-2\) expression in this cell line enhances cell attachment and decreases mobility, whereas decreasing expression decreases both cell attachment and mobility. Thus, although protease action in tumor cell invasion is abnormal, it cannot be totally unregulated.

Matrixes have been shown to effect other effects of structural barriers to invasion. As noted above, many of these matrixes act on other proteins to reveal hidden activity. \(\text{MMP}-2\) specifically degrades the \(\gamma_2\) chain of laminin-5, a structural protein in basement membrane, to reveal a site on the \(\alpha_3\) chain that has chemotactic properties.\(^{6}\) The physiologic role of this fragment may be to act as a wound-related chemoattractant; in tumors, however, this peptide may attract tumor cells to breaks in the basement membrane. In an analogous situation, MMPs have been shown to degrade plasminogen into angiostatin, the angiogenesis inhibitor.\(^{7,8}\)

Research has focused on the interaction between cell surface adhesion molecules and the matrix family. One obvious interaction is the simple degradation of cell surface adhesion molecules. For example, \(\text{MMP}-3\) degrades E-cadherin on mammary epithelial cells, inducing an increased expression of vimentin and decreased expression of keratin.\(^{9}\) The cell-matrix adhesion molecule \(\text{CD44}\) is also cleaved by matrixins, permitting detachment from the matrix.\(^{10}\) Decreased cell-cell or cell-matrix adhesion can be a proliferative phenotype. However, beyond mere degradation of adhesion molecules, cells may control the scope of degradative activity by binding the available matrixins with cell surface adhesion molecules, thus limiting degradation to a zone in the immediate vicinity of the cell. On endothelial cells, the integrin \(\alpha_v\beta_3\) binds \(\text{MMP}-2\) to the matrixin’s hemopexin domain in response to angiogenic stimuli.\(^{11,12}\) Similarly, \(\text{CD44}\) has been shown to bind \(\text{MMP}-9\) to the surface of breast carcinoma and melanoma cells.\(^{13}\) Interestingly, stimulation of melanoma cells by antibodies to \(\text{CD44}\) increased expression of \(\text{MMP}-2\), suggesting that binding of matrixins to cell surface receptors might not only provide a mechanism for localizing protease activity but also may serve as an autocrine-stimulating loop mechanism for increased expression of matrixins.

### INTRAVASATION, EXTRAVASATION, AND ORTHOTOPIC EFFECT

The mechanisms of tumor cell intravasation have not been investigated as intensively as the other events in the metastatic cascade. This is due in part to the lack of suitable experimental models. A clear role for proteolytic activity in tumor cell invasion has been demonstrated using the chick chorioallantoic membrane (CAM) system. In this model, human tumor cells are placed directly onto the chorioallantoic membrane in which the epithelium and basement membrane have been disrupted, allowing tumor cells direct access to the underlying connective tissue that is highly vascularized. Tumor cell intravasation is then quantitated by using polymerase chain reaction amplification of human-specific Alu genomic DNA sequences of tumor cells present in the chorioallantoic membrane on the other side of the chick embryo from the initial tumor cell inoculation. These experiments demonstrate that MMPs, as well as urokinase-type plasminogen activator and the urokinase-type plasminogen activator receptor, are involved in tumor cell intravasation.

Researchers\(^{14-18}\) have used intravital videomicroscopy to study the events and mechanisms involved in tumor cell extravasation from the circulation. The results of these studies have profoundly changed our thinking about the metastatic process. It appears that a large number (80%) of circulating tumor cells remain viable in the circulation and extravasate up to 3 days after their introduction into the circulation. Surprisingly, both metastatic and nonmetastatic cells extravasate, and this process varies according to the host’s immune status. It appears that a large number of circulating tumor cells remain viable in the circulation and extravasate up to 3 days after their introduction into the circulation. Surprisingly, both metastatic and nonmetastatic cells extravasate, and this process appears to be independent of metastatic potential.

Experiments using transfected cell lines, for example, when \(\text{MYUL}3\) melanoma cells are transfected with \(\text{TIMP}-2\), they increase metastatic potential, whereas transfecting the highly metastatic LMC19 cell line with \(\text{TIMP}-2\) reduces its metastatic potential.\(^{3,4}\) Mice genetically engineered to overexpress \(\text{MMP}-3\) in breast epithelial cells develop spontaneous breast carcinomas, possibly through the effects of \(\text{MMP}-3\) on the E-cadherin/b-catenin system.\(^{5}\)

During the 1990s, tremendous progress has been made in understanding the process of tumor cell invasion and metastasis formation, which is being revealed as a complex cascade of both promoting and suppressive factors. Loss of function (suppressor inactivation) may occur not only in the tumor cell but also in the host. Such tumor-host interactions are complex and difficult to examine in a controlled fashion. However, understanding these complexities is the future of research on cancer metastasis and tumor dissemination; the goal of the research will be the development of new strategies for eradication of established metastases and prevention of new metastatic growth.

### CHAPTER REFERENCES

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CHAPTER 9
Biology of Cancer: Angiogenesis

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INTRODUCTION

One crucial step for the continuous growth of tumors and the development of metastasis is the induction of vasculature (i.e., angiogenesis). A tumor mass that is less than 0.5 mm in diameter can receive oxygen and nutrients by diffusion, but any increase in tumor mass beyond 0.5 mm requires the proliferation and morphogenesis of vascular endothelial cells. The process of angiogenesis consists of multiple, sequential, and interdependent steps. It begins with local degradation of the basement membrane surrounding capillaries, which is followed by invasion of the surrounding stroma by the underlying endothelial cells in the direction of the angiogenic stimulus. Endothelial cell migration is accompanied by the proliferation of endothelial cells and their organization into three-dimensional structures that join with other similar structures to form a network of new blood vessels (Fig. 9-1).

FIGURE 9-1. The angiogenic process. The process of angiogenesis is a series of linked and sequential steps that ultimately lead to the development of a neovascular blood supply to the tumor mass. Different steps in the angiogenic process may be occurring in different parts of the tumor at the same time. Tumor cells or host cells (infiltrating immune cells or adjacent normal tissue) secrete angiogenic growth factors, which then bind to specific receptors on endothelial cells. This ligand-receptor interaction leads to endothelial cell proliferation, migration, invasion and, eventually, capillary tube formation. Factors also affect endothelial cell survival under adverse conditions that occur in tumors. The proangiogenic process is balanced by the activity of antiangiogenic molecules that are necessary for homeostatic processes. When the activity of the proangiogenic molecules exceeds the activity of the antiangiogenic molecules, new blood vessel formation occurs. Proangiogenic factors may be constitutively expressed, but their expression may be increased by certain stimuli, such as hypoxia, low pH, cytokines, growth factors, tumor size, activated oncogenes, signal transduction pathways, or loss of tumor suppressor gene function.

NEOPLASTIC ANGIOGENESIS: THE BALANCE OF PROANGIOGENIC AND ANTIANGIOGENIC MOLECULES

The onset of angiogenesis involves an alteration in the balance between proangiogenic and antiangiogenic molecules. These molecules may mediate multiple steps in the process of angiogenesis and also may affect the function of diverse cell types not involved in angiogenesis. A more refined definition of an angiogenic factor is a factor that selectively alters the characteristics of endothelial cells and associated perivascular structures (i.e., pericytes, vascular smooth muscle cells) but does not affect the function of other cell types. Table 9-1 lists most of the proangiogenic and antiangiogenic factors that have been well characterized to date.

TABLE 9-1. Proangiogenic Growth Factors

Vascular endothelial growth factor–vascular permeability factor (VEGF/VPF) was initially detected as a factor secreted by tumor cells into tissue culture medium or ascites fluid in vivo. The factor was identified as a heparin-binding protein of molecular weight 34 to 42 kD and was termed VPF. It was later demonstrated that VPF also stimulated endothelial cell division. Independently, several groups isolated a secreted protein that had selective mitogenic activity for cultured endothelial cells, which they called VEGF. On the basis of amino acid and complementary DNA sequence analysis, it is now known that VEGF and VPF are the same protein, and VEGF is the term more commonly used to describe this angiogenic factor.

VEGF is a homodimeric heparin-binding glycoprotein that exists in at least four isoforms due to alternative splicing of the primary messenger RNA (mRNA) transcript. The isoforms are designated VEGF121, VEGF165, VEGF189, and VEGF205, according to the number of amino acids that each protein contains. The vascular permeability induced by VEGF is 50,000 times that induced by histamine, the standard for induction of permeability. Induction of permeability by VEGF allows for the
The receptors for VEGF are expressed almost exclusively on endothelial cells. Rarely, expression of the various VEGF receptors has been demonstrated on cells of neural origin, Kaposi's sarcoma cells, hematopoietic precursor cells, and other rare tumor cell types. Three VEGF/VPF receptors have been identified. The fms-like tyrosine kinase (Flk-1) and fms-like tyrosine kinase insert domain-containing receptor (Flt-1) are high-affinity VEGF/VPF receptors with an extracellular domain containing seven immunoglobulin-like domains and a split tyrosine kinase intracellular seven. Flk-1 has 85% homology with the human homologue, KDR. Both Flt-1 and Flk-1/KDR have been shown to be important regulatory systems for vasculogenesis and physiologic angiogenesis. However, the interaction of VEGF/VPF with Flk-1/KDR is believed to be the more important interaction for tumor angiogenesis, as it is essential for induction of the full spectrum of VEGF/VPF functions. In fact, many compounds and molecules developed to block VEGF/VPF activities mediated by Flk-1/KDR have been shown to have antiangiogenic activity in animals. Most recently, VEGFR-3 (Flt-4) has been shown to be the receptor for VEGF-C, which is most likely involved with lymphangiogenesis.

There are at least four other members of the VEGF family. The above-referenced VEGF is referred to as VEGF-A, VEGF-B most likely plays an important role in vasculogenesis but may have other functions such as activation of invasive enzymes on endothelial cells. VEGF-C is most commonly associated with lymphangiogenesis but, more recently, its expression has been associated with tumor angiogenesis in several systems. VEGF-C also binds preferentially to the VEGFR-3. The role of VEGF-D is less well defined, but this protein may bind to VEGFR-2 and VEGFR-3 and may induce in vivo angiogenesis. Little is known about VEGF-E, except that it binds to VEGFR-2 and can induce endothelial cell mitosis and angiogenesis.

Another family of endothelial cell–specific molecules is the angiopoietin (Ang) family. At present, its members are designated angiopoietins 1 through 4. The best characterized of these factors are Ang-1 and Ang-2. Ang-1 and -2 bind to the specific tyrosine kinase receptor Tie-2 on endothelial cells. Ang-1 acts as an agonist and is involved in endothelial cell differentiation and stabilization. In contrast, Ang-2 binds to Tie-2 and blocks the binding of Ang-1 to this receptor. This blockade leads to endothelial cell destabilization and vascular regression. Although the receptor Tie-1 has been identified on endothelial cells, its ligands remain to be identified.

An insightful method for studying the function of various angiogenesis-related molecules is to develop knockout mice for the gene under question. Homozygous knockout of the genes for VEGF or any of the VEGF receptors lead to embryonic death in mice (reviewed in Gale and Yancopoulos 12). Study of these embryos at the time of death reveals defective vascular development. Similarly, knockout of the genes for Ang-1, Ang-2, Tie-1, and Tie-2 also lead to embryonic lethality and defective vascular development in mice. Thus, these factors that are being controlled in such mice are critical for vasculogenesis and likely play an essential role in tumor angiogenesis as well.

Numerous nonspecific angiogenic molecules affect not only the growth of endothelial cells but also the growth of other cell types. These factors include the fibroblast growth factors (FGF), acidic and basic; transforming growth factor-a (TGF-a); and epidermal growth factor (EGF); platelet-derived growth factor (PDGF); platelet-endothelial cell growth factor (PD-ECGF); angiogenin; and the CXC chemokines interleukin-8 (IL-8), macrophage inflammatory protein-1(MIP), platelet factor-4(PF-4), and growth-related oucogene-a(GRO-a).

The process of angiogenesis is dynamic and complex. In fact, the development of a neovascular blood supply is a series of interlinked processes that eventually leads to new blood vessel formation. Studies have demonstrated that different operations in the overall process of angiogenesis may be regulated by different angiogenic factors. For example, basic FGF (bFGF) is the most potent mitogen for endothelial cells, followed by VEGF and PD-ECGF. VEGF and bFGF are also the most potent survival factors for endothelial cells. However, bFGF is the angiogenic factor most associated with increasing activity of degradative enzymes. Hepatocyte growth factor enhances endothelial cell motility more than any other angiogenic factor studied. The more recent recognition of Ang-1 and -2 and their role in endothelial cell stabilization suggests that these molecules are also important in endothelial cell survival.

LYMPHOID CELL–MEDIATED ANGIOGENESIS

Angiogenesis is essential to homeostasis, and its regulation by lymphoid cells, such as T lymphocytes, macrophages, and mast cells, is well recognized. A local inflammatory reaction consisting of T lymphocytes and macrophages often is associated with invasive cutaneous melanoma, and an intense inflammatory reaction often is associated with an increased risk of metastasis, suggesting that angiogenesis induced by inflammation may contribute to melanoma progression and metastasis.

Immunologic mechanisms involved in physiologic angiogenesis are activated subsequent to wound healing. Systemic chemotherapy has been shown to retard the process of wound healing, possibly by decreasing the immune response; whether this is mediated by inhibition of angiogenesis is unclear. We have investigated the role of tumor vascularization and its effect on tumor growth in immunosuppressed mice. The growth of weakly immunogenic B16 melanoma was retarded in myelosuppressed mice as compared with control mice. Similar results were obtained in athymic mice, suggesting that the tumor vascularization observed in doxorubicin-treated mice reconstituted with normal splenocytes was not mediated solely by T lymphocytes. Because reconstitution with spleen cells enhanced vascularization of the B16 tumors, the results suggest that myelosuppressive chemotherapeutic drugs (e.g., doxorubicin) can inhibit host-mediated vascularization and support the concept that developing tumors can usurp homeostatic mechanisms to their advantage.

The role of infiltrating cells in the angiogenesis of human colon cancer has been reported. High expression of PD-ECGF was found in infiltrating cells, mostly macrophages and lymphocytes, though very little PD-ECGF was expressed in the cancer epithelium. The intensity of staining for PD-ECGF in infiltrating cells correlated with vessel counts, suggesting the involvement of these cells in the angiogenesis of human colon cancer.

Macrophages have been recognized for a number of years as important angiogenesis effector cells. They may influence new capillary growth by different mechanisms. First, macrophages produce factors that act directly to influence angiogenesis-linked endothelial cell functions. In vitro studies have shown that macrophages produce in excess of 20 molecules that reportedly influence endothelial cell proliferation, migration, and differentiation in vitro and that are potentially angiogenic in vivo. A second mechanism by which macrophages might modulate angiogenesis is by modifying the extracellular matrix (ECM). The composition of the ECM has been shown to influence endothelial cell shape and morphology dramatically and may profoundly influence new capillary growth. Macrophages can influence the composition of the ECM either through the direct production of ECM components or through the production of proteases, which effectively alter the structure and composition of the ECM. A third mechanism is by producing substances that suppress angiogenesis. Macrophages have been shown to express the angiogenesis inhibitor thrombospondin-1 (TSP-1) when treated with the chemopreventive agent retinoic acid.

The generation of angiotatin by subcutaneous Lewis lung carcinoma requires the presence of macrophages and is directly correlated with their metalloelastase activity. For example, the addition of plasminogen to Lewis lung carcinoma (3LL) cells cultured in vitro did not result in generation of angiostatin, whereas the addition of plasminogen to cocultures of macrophages and 3LL cells did. Elastase activity in macrophages was up-regulated by the cytokine granulocyte-macrophage colony-stimulating factor (GM-CSF). GM-CSF secreted by Lewis lung carcinoma cells significantly enhanced the production of elastase by macrophages and, hence, the generation of angiotatin from plasminogen. These data suggest that elastase released from tumor-infiltrating macrophages is responsible for the angiostatin production in this tumor model and for the angiogenesis-inhibiting role of macrophages.

REGULATION OF ANGIogenic FACTOR EXPRESSION IN TumORS

Tumor cells may constitutively overexpress angiogenic factors, or they may respond to external stimuli. The most potent external stimulus of angiogenic factor expression is hypoxia. Hypoxia is a consequence of tissue that is poorly perfused, and teleologically represents the appropriate response of a cell trying to survive. Hypoxia typically increases angiogenic factor expression by inducing signal cascade pathways that eventually lead to an increase in transcription of VEGF as well as stabilization of the mRNA transcript. The expression of other angiogenic factors such as angiogenin, PD-ECGF, and IL-8 may also be induced by hypoxia. Other microenvironmental factors that increase the angiogenic response include various cytokines and growth factors. The cytokines, insulin growth factor-1, insulin growth factor-2, EGF, hepatocyte growth factor, IL-1, and PDGF have all been shown to up-regulate VEGF. Thus, antiangiogenic therapy may involve down-regulation of upstream targets of the angiogenic factors rather than targeting of angiogenic factors themselves. Furthermore, protein products of tumor
ENDOGENOUS INHIBITORS OF ANGIOGENESIS

A large, growing, and structurally diverse family of endogenous protein inhibitors of angiogenesis has been discovered (e.g., TSP-1; the interferons IFN-α, -β, and -γ; the 16-kD fragment of proclacin; angiostatin; endostatin; VEGF or vascular endothelial cell growth inhibitor; vasoostatin; METH-1 and METH-2); and cleavage products of platelet factor 4 or antithrombin III, among many others (Table 9-2). Some of these are internal fragments of various proteins that normally lack any angiostatic activity; for example, the active component of angiostatin comprises one or more fragments of plasminogen, and endostatin is a fragment of type XVIII collagen.

TABLE 9-2. Some Endogenous Inhibitors of Angiogenesis

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<thead>
<tr>
<th>Inhibitor</th>
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<td>Angiostatin</td>
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<td>Endostatin</td>
<td>Endothelial cell</td>
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<td>Vascular endothelial cell growth inhibitor</td>
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<td>Vasoostatin</td>
<td>Endothelial cell</td>
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<td>METH-1 and METH-2</td>
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<td>Proclacin</td>
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<td>IFN-α, -β, -γ</td>
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<td>Protease</td>
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<td>Antithrombin III</td>
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THE PROGNOSTIC SIGNIFICANCE OF TUMOR ANGIOGENESIS

With few exceptions, benign neoplasms are sparsely vascularized and tend to grow slowly, whereas malignant neoplasms are highly vascular and fast-growing. The increase in vasculature also increases the probability that tumor cells will enter the circulation and possibly give rise to metastases. Immunohistochemical staining of breast cancer sections with antibodies against factor VIII, a protein expressed predominantly on the surface of endothelial cells, allowed Weidner et al. to determine the density of the microvasculature. The number of microvessels in microscopic fields selected from the most vascular areas (“hot spots”) of the sections correlated directly with metastasis and inversely with survival.

Most recent studies have concluded that increased microvessel density in the areas of most intense neovascularization is a significant and independent prognostic indicator in early-stage breast cancer. Studies of other neoplasms such as prostate cancer, melanoma, ovarian carcinoma, gastric carcinoma, and colon carcinoma also support the conclusion that the angiogenesis index is a useful prognostic factor. However, the expectation that an angiogenesis index can identify all patients with occult metastatic disease or those with probable distant metastases may be unrealistic for several reasons. First, human tumors are heterogeneous and consist of subpopulations of cells having different biologic properties. Second, the process of cancer metastasis is sequential and selective, consisting of a series of interlinked but independent steps. To produce clinically relevant metastases, tumor cells must complete all the steps in this process. Tumor cells that can induce intense angiogenesis but cannot survive in the circulation or proliferate in distant organs will not produce metastases. Like all other steps in the metastatic cascade, angiogenesis is necessary but not sufficient for the pathogenesis of a metastasis. Third, although not all large angiogenic tumors metastasize, inhibition of angiogenesis prevents the growth of tumor cells at both the primary and secondary sites and thus can prevent the development of clinically relevant metastases.

To study angiogenesis in tumor specimens using current technology, it is necessary to obtain tissue for histologic evaluation. The criterion standard for evaluation of human tumor specimens is to highlight the tumor endothelium with antibodies that differentiate endothelial cells from other cells within the tumor. The first such antibody used was factor VIII-RA (FVIII-RA), and this is still the antibody used in many studies reported in the literature. Other endothelial cell–specific antibodies that are used in the study of angiogenesis include CD31/PECAM, CD34, CD36, TEC-11, and ulex europaeus (UEA). Currently, the antibodies most commonly used in the study of angiogenesis are FVIII-RA, CD31, and CD34 antibodies. Once histologic preparation of a slide is complete, it is necessary to quantify the level of angiogenesis within the tumor. It is essential that an investigator examine angiogenesis systematically. For example, investigators may choose the five most vascularized areas in a tumor by scanning at low power and then count vessels in these areas under higher magnification. In certain tumors, such as colon cancer and gastric cancer, it is necessary to define the location at which tumor counts are obtained, as counts made close to the invading edge of the tumor may be significantly different from counts made further away from the invading edge. The number of blood vessels in individual tumor specimens can be quantified either as the number in a single high-power field or as the average number in several high-power fields.

In addition to counting blood vessels in a high-power field, it also is possible to grade the degree of vasculature on a scale of 0 to 3+, with 3+ being the most vascular. Obviously, this approach is subjective and prone to problems of reproducibility. Another method of analyzing tumor angiogenesis involves highlighting the vessels with an endothelial cell–specific antibody and, with the aid of computer imaging analysis, determining the area within a high-power field that is occupied by positively stained cells. Access to imaging systems and computer software is necessary for this technique. A third method for quantifying the degree of angiogenesis is to count the number of branch points in vessels within a tumor. Finally, a very common method employed in Europe is the Chalkley Grid method. In this methodology, an eyepiece marked with overlapping crosses is used to visualize the high-power field of a tumor stained with an endothelial cell–specific antibody. The areas where an endothelial cell intersects a crossbar are counted, and the total sum in a high-power field of these counts is equal to the Chalkley score.

The recognition that tumors with a high angiogenic index may be associated with subsequent metastasis suggests that these patients may be the ones most likely to benefit from adjuvant therapy. In a study evaluating the prognostic role of angiogenesis in late-stage lung carcinoma, adjuvant therapy improved survival in patients with a high vessel count but not in patients with a low vessel count. However, the observation that patients with highly angiogenic tumors benefit from adjuvant therapy is not universal. In several studies of node-positive breast cancer patients treated with adjuvant chemotherapy or hormonal therapy, those whose tumors had a high microvessel density were found to have a worse prognosis than those whose tumors had a low microvessel density, despite adjuvant chemotherapy. In fact, one recent study suggested that patients with a low VEGF expression have a more favorable outcome secondary to adjuvant therapy. At the time of this writing, patients with a high angiogenic index may represent a biologically more aggressive variant of the disease, against which conventional adjuvant therapies are ineffective. Perhaps antiangiogenic therapy is indicated in these patients. Obviously, well-controlled clinical trials should be designed to determine the efficacy of antiangiogenic therapy as an adjunct in the treatment of patients with highly vascularized solid malignancies.

OVERVIEW OF ANTIANGIOGENIC STRATEGIES
Antiangiogenic agents currently used in the clinic can be categorized into several broad classes based on the biologic activity of the compounds used. The first class of compounds, metalloproteinase inhibitors, blocks degradation of the basement membrane. Most of the studies on these agents reported to date have been phase I studies in which major toxicity was associated with musculoskeletal and joint pain owing to defects in collagen remodeling.

A second class of angiogenic inhibitors includes those designed to inhibit endothelial cell function. These include TNP-470, thalidomide, squalamine, combretastatin A-4 prodrug, and endostatin. Less is known about the biologic effects of these drugs as compared to the first class, and most of these drugs are currently in phase I or phase II trials. How these drugs exert their antiangiogenic activities in vivo is not fully elucidated at this time; perhaps well-designed clinical trials will shed some light on their mechanisms of action.

A third class of angiogenic agents specifically targets an angiogenic factor or factors. These agents include tyrosine kinase inhibitors of the receptors of such factors as VEGF, bFGF, and PDGF. In addition, antibodies directed against these receptors or the factors themselves are either in clinical trials or in the process of being developed for clinical trials. In preclinical trials in animal models, most of these agents inhibited tumor growth, but very few have had tumor regression.

This suggests that tumor regression, which is the typical end point for successful cytotoxic chemotherapy, may not be appropriate for antiangiogenic therapies. Thus, it is necessary to redefine the end points for biologic therapy.

Because endothelial cell survival has recently been recognized as an important characteristic of the development of a neovascular blood supply, drugs that target survival factors are beginning to be introduced into clinical trials. These drugs include antagonists to integrins that are present on the endothelial cell surface. In addition, as VEGF currently is thought of as both a survival factor for endothelial cells and an angiogenic factor, anti-VEGF therapy may affect the survival of tumor endothelial cells.

**TUMOR ENDOTHELIUM (**"ACTIVATED ENDOTHELIUM") AS DISTINCT FROM NORMAL ENDOTHELIUM**

The discovery of VEGF receptors and their up-regulation in newly formed blood vessels highlights the fact that there can indeed be major phenotypic differences between mature, quiescent vessels and their newly formed counterparts. Such differences are essential to avoid unwanted toxicity to normal vessels when using antiangiogenic drugs while still achieving a sufficient therapeutic index. A number of such differences in the phenotypes of endothelial cells in normal versus malignant tissues are now known and include a significant elevation of expression of the integrins αvβ3 and αvβ5.

In breast cancer, it has been demonstrated that antibodies to αvβ3 preferentially stain the tumor vasculature but not the normal vasculature, suggesting that αvβ3 is a marker for activated endothelium.

An important issue in angiogenic strategies is the fact that tumor endothelium at different sites and within different tumors may be phenotypically distinct. Tumor endothelium is heterogeneous in terms of the ability to bind specific peptide sequences. Other markers that are up-regulated in activated endothelial cells include adhesion molecules such as E-selectin, endoglin, glycoproteins such as prostate-specific membrane antigen, the ED-B domain of fibronectin, and various proteases. Many of these unique characteristics of the tumor endothelium can be exploited not only as potential therapeutic targets but also for detection of cancer by various clinical imaging techniques.

**ANTIANGIOGENIC ACTIVITY OF INTERFERON**

The IFN family consists of three major glycoproteins that exhibit species specificity: leukocyte-derived IFN-α, fibroblast-derived IFN-β, and immune cell–produced IFN-γ. Although IFN-α and IFN-β share a common receptor (the type I IFN receptor) and induce a similar pattern of cellular responses, certain cellular reactions can be stimulated only by IFN-β, probably by the phosphorylation of a receptor-associated protein that is uniquely responsive to IFN-β. In addition to their well-recognized activity as antiviral agents, IFNs regulate multiple biologic activities such as cell growth, differentiation, oncogene expression, host immunity, and tumorigenicity.

IFNs can also inhibit a number of steps in the angiogenic process. IFN has antiproliferative properties, especially on tumor cells, and an effect that has been demonstrated also on endothelial cells in vitro. IFN can inhibit FGF-induced endothelial proliferation, and IFN-γ can also inhibit endothelial proliferation.

IFN-α and IFN-γ are known to be cytostatic to human dermal microvascular endothelial cells and human capillary endothelial cells.

Systemic therapy using recombinant IFNs produces antiangiogenic effects in vascular tumors, including life-threatening infantile hemangioma, Kaposi’s sarcoma, giant cell tumor of the mandible, and bladder carcinoma. These tumors have also been documented as producing the high levels of bFGF often detectable in the urine or serum of these patients. IFN-α and IFN-β, but not IFN-γ, down-regulate the expression of bFGF mRNA and protein in human carcinoma cells. Indeed, systemic administration of human IFN-α decreased the in vivo expression of bFGF, decreased blood vessel density, and inhibited tumor growth of a human bladder carcinoma implanted orthotopically in nude mice.

**ANTIANGIOGENIC THERAPY: ISSUES AND EXPECTATIONS**

The understanding that angiogenesis is essential for tumor growth and metastasis formation has led to a large effort to discover effective antiangiogenic compounds. It must be understood that angiogenesis occurs not only in pathologic processes but also in homeostasis. Physiologic angiogenesis is important in reproduction, wound healing, menses, and vascular diseases such as coronary artery and peripheral vascular diseases. Thus, as always, a balance must be maintained between limiting angiogenesis to the tumor and causing significant toxicity to the host.

In addition to the potential toxicity, another issue in antiangiogenic therapy is the chronic nature of this therapy. Because antiangiogenic therapy is designed to inhibit the development of new blood vessels, the end points for success or failure must be redefined. For example, a desired response to standard chemotherapy is one that decreases the cross-sectional area of a tumor by 50% within a few months. However, antiangiogenic therapy is likely to produce stable disease, which early on may be considered a failure. Thus, in evaluating antiangiogenic therapy in the clinic or the laboratory, different criteria for effectiveness must be outlined.

Because antiangiogenic therapy may not decrease tumor growth, it is likely that this therapy will need to be delivered on a chronic basis. Hence, the agent must be easily delivered (i.e., oral) and have few long-term side effects. One must also consider that the effect of antiangiogenic therapy may require a longer interval between evaluations than chemotherapy, as the stability of disease may be difficult to determine at short intervals.

There have, of course, been reports of complete regression of tumors in experimental models of angiogenesis. However, these reports are few, and the vast majority of studies in this field have demonstrated that antiangiogenic therapy leads to an inhibition of tumor growth.

Thus, it is critical that the reader be able to interpret experimental studies appropriately and avoid creating unrealistic expectations. For example, the sites of tumor injection must be considered when experimental antiangiogenic studies are being conducted. It is clear that endothelia from different organs are phenotypically distinct. Tumor endothelium at different sites and within different tumors may be phenotypically distinct. Tumor endothelium is heterogeneous in terms of the ability to bind specific peptide sequences. Other markers that are up-regulated in activated endothelial cells include adhesion molecules such as E-selectin, endoglin, glycoproteins such as prostate-specific membrane antigen, the ED-B domain of fibronectin, and various proteases. Many of these unique characteristics of the tumor endothelium can be exploited not only as potential therapeutic targets but also for detection of cancer by various clinical imaging techniques.

**ENDOTHELIUM IS HETEROGENEOUS**

Endothelial cell function is highly dependent on the extracellular matrix and the surrounding interstitial connective tissue. Endothelial cells are highly motile and can adapt to changes in their microenvironment. This adaptability is particularly evident in the process of angiogenesis, where endothelial cells proliferate and migrate to form new blood vessels.

Endothelial cells are also subject to various stimuli that can alter their phenotype, including cytokines, growth factors, and hypoxia. These stimuli can induce changes in endothelial cell proliferation, migration, and survival.

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Another possible approach to effect tumor vascular growth could be the increased use of improved antivascular targeting strategies that can cause acute tumor regression, as shown in various preclinical models. For example, certain tubulin-binding agents, \(^{24}\) such as combretastatin A-4, can cause such an effect, \(^{25}\) as can antibodies that target tissue factor to newly formed blood vessels, thus causing an intravascular thrombogenic response in such vessels. \(^{18}\) These drugs kill endothelial cells by forming blood vessels that eventually develop into thrombi, resulting in acute tumor regression and the subsequent destruction of much larger numbers of tumor cells. Clearly, the problem here will be to develop drugs that have this ability to cause such a dramatic tumor necrosis, \(^{25}\) without major, perhaps even life-threatening, toxic side effects. In this regard, a potentially significant development in the near future could be the use of genomics-based technologies to uncover a large number of highly (or even totally) specific molecular markers for the activated endothelial cells of newly formed blood vessels. This could make antibody-based therapies safer and more effective.

Cytostatic antiangiogenic agents have the desired biologic (i.e., antiangiogenic) effect in vivo. In experimental animal models, tumors can be resected and analyzed for changes in the extent of vascularization, vascular structure, and endothelial cell viability or apoptosis as well as for markers of angiogenic activity (e.g., expression of VEGF, bFGF, IL-6). Performing serial biopsies of metastatic tumors will not be practical; thus, reliable surrogate markers of tumor angiogenesis found in serum or urine may be necessary. At present, few, if any such markers (at least of a reliable nature) exist. The use of noninvasive medical imaging strategies (e.g., magnetic resonance imaging, Doppler ultrasound) to monitor changes in tumor blood flow, vascular structure, and permeability may be helpful, and considerable research efforts to determine their efficacy are under way. \(^{16}\) \(^{21}\) \(^{22}\) \(^{23}\)

Toxic effects associated with chronic antiangiogenic therapy may not show up in short-term, early-phase clinical trials or in animal models but, rather, only after very protracted courses of therapy. The development of spastic diplegia in some infants or children who had been treated previously and successfully over 1 year with antivascular agents (e.g., TNP-470) is an example of such delayed toxic side effects. This undoubtedly will increase the need for targeting tumor blood vessels. The growing interrelationship between the clotting and fibrinolytic pathways and angiogenesis \(^{25}\) raises the possibility of inclining bleeding and coagulation disorders in patients who receive certain antiangiogenic drugs, as well as the possibility of causing or exacerbating existing cardiovascular defects in older patients. In addition, there is the obvious concern about affecting physiologic forms of angiogenesis in various situations. Thus, wound healing may be adversely affected in a cancer patient who is receiving antitumor drugs, as reproductive angiogenesis would be (e.g., corpus luteum development in adult women and development of the vasculature in embryos). Growth in neonates may also be compromised by angiogenesis inhibitor therapies. \(^{17}\) However, given the unique structural features of the tumor vasculature, some angiogenesis inhibitors may selectively block tumor angiogenesis without actually affecting other physiologic forms of angiogenesis. This possibility could turn out to be an important factor in selecting the optimal angiogenesis inhibitors for clinical development and their use in cancer patients.

ANTIANGIOGENIC THERAPY AS A COMPONENT OF OTHER ANTIANEoplastIC REGIMENS

The combination of an antitumor drug (or drugs), such as TNP-470, with a conventional cytotoxic agent, such as cisplatin, paclitaxel, or cyclophosphamide, can significantly improve the antitumor efficacy of the cytotoxic drug. \(^{24}\) These effects of combination therapy, which have also been observed for the combination of radiation therapy and angiogenesis inhibitors, \(^{25}\) could play a significant role in the clinical evaluation and effects of angiogenesis inhibitors.

A more rational, yet futuristic, approach to the treatment of patients with malignancies is to determine the molecular alterations that lead to the various processes involved in tumor growth. Angiogenesis is but one component of the process of tumor growth and metastasis, and overexpression of other genes involved in protection from apoptosis, cell proliferation, and cell invasion (i.e., an individual tumor’s malignant fingerprint) must be examined. With the rapid development of gene chip technology, it may become possible in the future to determine the malignant fingerprint of individual tumors and to develop therapies that specifically target the molecular phenotype of an individual tumor. Antiangiogenic therapy may therefore be one component of diverse biologic delivery combined in combination with anti-growth factor therapy or with agents that induce apoptosis in tumor cells and tumor vessel endothelial cells.

CONCLUSIONS

Angiogenesis is a dynamic process essential for the growth of primary and metastatic malignancies as well as hematopoietic cancers. Understanding of the basic principles of the biology of angiogenesis has led to the development of new prognostic factors, tumor markers, imaging techniques, and therapeutic modalities. The challenge lies in integrating this knowledge into the care of patients with malignant diseases of all types and stages. An understanding of the basic biology of angiogenesis and tumor biology ultimately will lead to the rational development of new paradigms for the treatment of patients with cancer.

A comprehensive review of current antiangiogenic clinical trials is not feasible, as this area of clinical research is in constant evolution. However, the U.S. National Cancer Institute maintains an up-to-date Web site at which information on clinical trials can be accessed: http://iccancersinfo.ncc.nih.gov/news/angiogenix.html. In addition, an overview of angiogenesis can be found at http://ccancersinfo.ncc.nih.gov/news/angiogenix.html.

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RETROVIRAL GENETICS: SELECTIVE ACCESS TO THE GROWTH CONTROL GENES OF THE CELL

Special features of their replication cycle have made retroviruses useful for investigating the molecular basis of neoplasia. Retroviruses are unique among animal viruses in having an RNA genome that replicates through a DNA intermediate. The virally encoded reverse transcriptase converts the single-stranded RNA genome into a double-stranded DNA copy; a subsequent reaction catalyzed by the retroviral integrase covalently and irreversibly integrates this DNA molecule into a host chromosome where it resides as a provirus. This process can result in mutagenesis, translocation, or altered regulation of any locus in the genome.

An integrated provirus resembles other multiexon cellular genes in that it is duplicated along with the cell’s genome, passed on to daughter cells during mitosis, and subsequently transcribed into full-length and spliced RNAs [messenger RNAs (mRNAs)]. The ends of the provirus are made up of identical genetic control regions called long terminal repeats (LTRs), which are composed of U3 (unique 3' region), R (repeat), and U5 (unique 5' region). The promoter and enhancer functions necessary for RNA polymerase II to initiate viral mRNA transcription reside within the LTR, primarily in U3. Transcription initiates just downstream of the TATA box at the 5' U3/R junction and proceeds through to the polyadenylation (polyA) signal usually located in the R region of the 3' LTR (Fig. 10.1.1).

The locations of transcription initiation and termination result in virion (genomic) RNA that carries the viral promoter (U3 element) downstream of the genes to be transcribed (in contrast to the structure of the provirus). Because a genomic transcript possesses neither an upstream U3 nor a downstream US, the essential rearrangements that occur during the RNA template strand switching of reverse transcription are establishment of a 5' promoter and of integration-competent termini. The retention of a duplicate U3 promoter element in the 3' LTR of the provirus, though generally not active, has implications for retroviral oncogenesis.

Retrovirus virions normally encapsidate a dimer of identical plus-sense RNA genomes, both of which are used as templates during reverse transcription. However, it is possible for nonidentical transcripts (heterodimers) to be packaged together. Studies with dual selectable markers show that each infectious virion contains both types of RNA. The packaging process produces an active provirus. Heterodimer packaging plays an important role in the creation of oncogenic retroviruses because, after recombination and reverse transcription, it can result in the creation of novel proviruses. Even when identical RNAs are packaged, aberrant strand transfers during reverse transcription result in high rates of genetic recombination and rearrangement, including sequence deletions, duplications, and inversions. Recombination can occur between two viruses infecting the same cell or, less commonly, between viral and cellular sequences.

MECHANISMS OF RETROVIRAL ONCOGENESIS

In the case of acutely transforming retroviruses such as Rous sarcoma virus (RSV), virtually all infected cells are swiftly transformed, whereas for other retroviruses, transformation is an unusual and much delayed outcome that often depends on the cell’s accrual of additional alteration of its DNA. The latter group includes agents such as HTLV-I and avian leukemia virus (ALV). Most transforming retroviruses are not cytopathic. Reverse transcription and integration of the viral genome into that
of the cell favor the three major mechanisms by which retroviruses may participate in the malignant transformation process (Fig. 10.1-2):

1. Acutely transforming retroviruses (e.g., RSV) incorporate and exert control over cellular growth–related genes (protooncogene capture) and subsequently transfer these deregulated genes into new cells.
2. Slowly transforming viruses (e.g., ALV) alter cellular gene expression by chance insertion of cis-acting viral regulatory sequences adjacent to these genes (insertional mutagenesis).
3. Trans-acting retroviruses (e.g., HTLV-I) alter cellular gene expression and function through viral regulatory protein(s) that act in trans.

ACUTELY TRANSFORMING (TRANSUDING) RETROVIRUSES AND GENE CAPTURE

Acutely transforming retroviruses provided evidence for viral oncogenesis even before the existence of viruses was recognized. A porcine filtrate of tumor lysates prepared from chicken sarcomas was shown to cause sarcomas when injected into animals. The causative agent, RSV, is a prototype of the acutely transforming (transducing) retroviruses. It is the only replication-competent oncogene-carrying retrovirus; since oncogene insertions usually supplant essential viral sequences, all other known acutely transforming retroviruses are defective for replication and require a helper virus to supply one or more viral proteins in trans. RSV contains the full complement of replicative genes in addition to a transforming gene.

It was not until the 1940s that the first mammalian retrovirus, mouse mammary tumor virus, was isolated; later, a murine leukemia virus was isolated from neonatal mice. Investigation of the actual physical nature of these agents awaited the advent of cell culture, elucidation of the genetic code, and the framework of the “central dogma” of molecular biology. In the latter part of the 20th century, reverse transcriptase was used to test the hypothesis that retroviral proteins encoded cellular sequences 5′ to, and in the opposite orientation of, the site of provirus integration. In the lower example, insertional mutagenesis is illustrated. This may lead to inactivation of a tumor suppressor or to production of a mutant cellular protein that could lead to oncogenesis. In both cases, aberrant splicing could lead to production of chimeric viral–cellular proteins. Arrows indicate points of initiation and direction of transcription. C: Trans-acting retroviruses. In addition to gag, pol, and env, human T-cell leukemia virus type I (HTLV-I) encodes viral regulatory proteins. Tax is implicated in the genesis of adult T-cell leukemia through its interactions with cellular transcription factors, resulting in alteration of expression of many growth-related genes.

Slowly transforming retroviruses. In the upper example, a provirus has integrated upstream of a cellular protooncogene. The viral promoters may alter protooncogene expression directly [via read-through transcription originating from the 5′ long terminal repeat (LTR) or from transcripts aberrantly originating from the 3′ LTR] or indirectly via the effect of viral enhancers increasing transcription from cellular promoters (the viral enhancer can also affect expression of cellular genes 5′ to, and in the opposite orientation of, the site of provirus integration). In the lower example, insertional mutagenesis is illustrated. This may lead to inactivation of a tumor suppressor or to production of a mutant cellular protein that could lead to oncogenesis. In both cases, aberrant splicing could lead to production of chimeric viral–cellular proteins. Arrows indicate points of initiation and direction of transcription. C: Trans-acting retroviruses. In addition to gag, pol, and env, human T-cell leukemia virus type I (HTLV-I) encodes viral regulatory proteins. Tax is implicated in the genesis of adult T-cell leukemia through its interactions with cellular transcription factors, resulting in alteration of expression of many growth-related genes.

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Slowly transforming (cis-activating) retroviruses: insertional mutagenesis

Genomic insertion of a provirus can itself be tumorigenic by leading to aberrant activity of adjacent cellular genes (see Fig. 10.2). This mechanism by which retroviruses activate the latent oncogenic potential of protooncogenes is the more common transforming process in nature. Retroviruses that act in this manner, such as avian leukemia virus (ALV), have been termed chronic, or slow-acting tumor viruses. They do not transform cells in tissue culture. In vivo, long latency periods between infection and tumorigenesis are typical, whereas acutely transforming retroviruses reliably transform cultured cells and cause tumors with high probability shortly after infection. Also in contrast to acutely transforming retroviruses, the tumors are monoclonal for the site of insertion. In general, slowly transforming viruses require a second mutagenic event for their transforming properties to become apparent.

In B-cell lymphomas associated with ALV, tumors arising from independent transformation events invariably have ALV proviruses clonally integrated in the vicinity of the c-myc gene.11 These tumors illustrate two general ways in which insertional mutagenesis may operate: promoter insertion and enhancer insertion. In the former, the ALV provirus integrates upstream of, and in the same orientation as, c-myc. 3′ LTR-promoted c-myc transcripts are produced at up to 100-fold higher than normal levels (the transcripts, however, encode a normal c-myc protein). Enhancer insertion, however, can occur if the provirus inserts downstream of c-myc or upstream but in opposite orientation to the gene. In this scenario, enhancer elements within the LTR may abnormally increase gene expression. These two roles of retroviruses in studies of myc–gene capture and insertional mutagenesis—elegantly confirm the protooncogene hypothesis: The gene was first identified as a protooncogene not...
from insertional mutagenesis studies, but from its mutant v-onc homologue in a transforming retrovirus. 24

A related transforming mechanism occurs when insertion of a retrovirus occurs within the c-onc site or if the 5′ LTR-promoted read-through RNAs result in downstream protooncogene transcription. 25 In either case, viral-protooncogene hybrid spliced transcripts encoding novel proteins with transforming potential can then be produced.

TRANS-ACTIVATING RETROVIRUSES

A third mechanism of transformation involves a trans-acting viral protein that regulates the expression or function of cellular growth and differentiation genes. This mechanism is exemplified by HTLV-I, the first and only human retrovirus known to directly cause human cancer.

HUMAN T-CELL LEUKEMIA VIRUS TYPE I

HISTORY AND EPIDEMIOLOGY

Today, the concept of a pathogenic human retrovirus has become familiar. However, even in the mid-1970s, although retroviruses had been readily isolated from many species, no human counterparts had been found despite intensive attempts. Soon, however, several technologic advances, combined with epidemiologic insights, began to change the picture. 26

In 1978, a type C–like retrovirus now called HTLV-I was isolated from a CD4+ T-lymphoblastoid cell line established from a patient with a cutaneous T-cell lymphoma, 27 most probably adult T-cell leukemia (ATL). An aggressive malignancy of T cells bearing the CD4 marker, ATL had been characterized as a clinicopathologic entity only in the preceding three years. 28 The disease was then believed confined to the southern islands of Japan, where, in contrast to most of the world, it predominates over mature B-cell leukemia/lymphoma. The geographic clustering suggested an infectious etiology, and serologic testing of Japanese ATL patients with antigens prepared from the newly discovered HTLV-I revealed nearly 100% seropositivity. 29 Other epidemiologic clusters consistent with an etologic role for endemic HTLV-I infection have since been documented, most notably in the Caribbean basin, the southeastern United States, northeastern South America, Central Africa, and Papua New Guinea. Moreover, transmission of HTLV-I by blood transfusion (but, unlike HIV, not cell-free blood products), needle sharing, breast feeding, and from male to female (rarely the reverse) by sexual intercourse has been well documented.

In addition to seroepidemiologic studies of patients and their close contacts, several lines of evidence support a direct causal role for HTLV-I in ATL. The virus can be isolated reproducibly from ATL patients. Leukemic cells invariably contain an HTLV-I provirus, whereas other cells from these patients do not. Infected individuals born in an endemic region carry their risk of developing ATL with them if they move elsewhere, suggesting that risk is not dependent on environmental cofactors peculiar to endemic areas. Infec-
tion clearly precedes transformation, because the tumor cells carry monoclonal or oligoclonal insertions of HTLV-I DNA and have a single T-cell antigen receptor gene rearrangement. 30 This monoclonality also provides additional evidence that transformation is a rare sequel to infection.

Primary T cells infected with HTLV-I do not senesce after a month in culture, as normal T cells do, but become immortalized, acquiring the ability to divide continually in the presence of interleukin-2 (IL-2). Continued culture of immortalized cells eventually can result in selection of a transformed, IL-2–independent clone of cells. There is evidence that, in addition to CD4+ T cells (the phenotype of the majority of ATLS), HTLV-I can also infect and transform CD8+ T cells, as well as immature CD4−CD8− T-cell precursors in bone marrow. 31

THE VIRAL REPLICATION CYCLE AND ITS IMPLICATIONS FOR VIRAL SPREAD AND EVOLUTION

Although HTLV-I shares many features with the type C viruses, it is considerably more complex genetically and biologically. In addition to gag, pol, and env, the virus genome contains several additional open reading frames (see Fig. 10.1-1). Of these, the two best characterized genes code the trans-regulating proteins Tax and Rex. Both proteins are expressed early in the viral replication cycle and are important for expression of viral genes; as such, they are analogous to the HIV proteins Tat and Rev. 32-34 Rex and Rev, through a interaction with a human nuclear export receptor, CRM-1, 35 act as adaptors for the nuclear export of unspliced retroviral mRNA. Additional cellular proteins interacting with the splicing/export pathways are also involved in mediating Rev/Rex function. 36 Tax is a nuclear protein that activates transcription from the HTLV-I LTR in trans by associating with a number of cellular transcription factors. 37 A 21-base-pair repeat sequence within the HTLV-I U3 is necessary for Tax activity and confers Tax inducibility to heterologous genes placed downstream. 38

Little, if any, HTLV-I replication or gene expression is detectable in vivo by analyzing primary leukemic cells from humans. 39-41 Significant viremia is not detected. The molecular mechanisms that maintain viral latency in vivo are unclear. The in vivo latency and low levels of viremia in HTLV patients has important implications both for virus spread and evolution. Unlike HIV, there is remarkably little genetic variability among HTLV-I isolates. 42 With 97% to 99% sequence identity among strains derived from Japanese patients and generally 96% to 99% identity across widely diverse geographic regions. 43 Again, unlike HIV, cell-free transmission rarely occurs, either in cell culture or in vivo. This property is one factor in the less efficient, endemic transmission of HTLV-I compared to the epidemic spread of HIV-1, even though the same routes of infection appear to be operative.

When a cytopathic virus such as HIV rapidly destroys its host cell, continuous viral spread is imperative. The alternative adopted by HTLV-I is to keep virion burden the same routes of infection appear to be operative.

MODELS FOR HTLV-I LEUKEMOGENESIS

The most common outcome of HTLV-I infection is an asymptomatic carrier state; HTLV-I carriers have an estimated lifetime risk of developing ATL of approximately 5%. 44 Therefore, factors other than simple viral infection must be necessary for leukemogenesis. Despite the mono- or oligoclonality of HTLV-I proviral insertions in ATL tumors, the sites of proviral insertion are random from patient to patient, indicating that cis-acting insertional mutagenesis does not play a role in tumorigenesis. Nor does the virus appear to encode a host-derived oncone. No homologues between human cellular genes and nonstructural HTLV-I genes have been observed. A third genetic mechanism for tumorigenesis, which appears to be a multistep process, is thus implicated, with the Tax protein being central to transformation.

Tax promotes viral gene expression by indirectly activating the viral promoter in the LTR via interaction with cellular transcription proteins. However, the interaction of Tax with various transcription factors also transactivates numerous cellular gene promoters. A molecular basis for the pleiotropism of Tax was shown to reside in its interaction with the conserved basic regions of varied basic region–leucine zipper DNA-binding domains within such factors, thus altering both affinity and selectivity of the factors for variant cellular promoters. 45-47 The numerous cellular transcription pathways activated by Tax in this way include activating transcription factor/cyclophilin A–responsive element binding protein (ATF/CREB), nuclear factor (NF)-κB/c-Rel, and serum response factor. 48 Tax is able to bind directly to the TATA-binding protein, a component of the transcriptional complex, and to p300 and CREB-binding protein, both of which are transcriptional coactivators. 49

Among the cellular genes transactivated by Tax, the most relevant are the IL-2 and IL-2 receptor (IL-2R) genes. 50-52 and 53 Unlike normal resting T cells, ATL cells and T cells transformed in vitro by HTLV-I constitutively express the a chain of the IL-2 receptor at high levels that cannot be down-regulated. In this way, an autocrine loop might arise, stimulating continuous proliferation of infected cells. The autocrine mechanism is not sufficient to explain leukemogenesis, however. For example, in contrast to the invariable expression of IL-2R, not all HTLV-I immortalized cells express IL-2. Possible interactions between another HTLV-I protein (p19) and the gamma subunit of IL-2R may contribute to the ligand-independent activation of this receptor, 54 resulting in stimulation and expansion of the pool of infected cells at risk for further genetic alteration.

In regard to the latter process, Tax also has been shown to down-regulate expression of a cellular DNA repair enzyme, beta-DNA polymerase, 55 a potentially straight forward link to accelerated accumulation of mutation. In addition, expression of a large number of genes involved in cell proliferation is transactivated by Tax. These include granulocyte-macrophage colony-stimulating factor (GM-CSF), the protooncogenes c-fos and c-sis, HLA class I molecules, 56 vimentin, and tumor necrosis factor. 57 58 59

The IL-2 independence of HTLV-I–infected T cells involves a cell signaling pathway in which receptor-associated protein kinases in the Janus kinase (Jak) family
phosphorylate cytoplasmic transcription factors called STATS (for signal transducers and activators of transcription). After phosphorylation, STATS translocate to the cell nucleus and bind to specific DNA elements to modulate transcription. The Jak-STAT pathway is triggered by IL-2 in normal T cells, however, transition to IL-2 independence after HTLV-I infection was associated with constitutive activation of the pathway.

Tax also has been shown to interact with and presumably inactivate a number of cell-cycle-related proteins, including the cyclin-dependent kinase (cdk) inhibitor p16^INK4A^ and the cell-cycle checkpoint protein MAD1. Tax activates the promoter of p21^waf1/cip1^, also a cdk inhibitor, and through the activation of the ATF/CREB pathway, suppresses the activity of p53, which can prevent p53-induced apoptosis. It also has been suggested that constitutive action of the IL-2 receptor pathway allows cells, through an unknown mechanism, to avoid apoptosis.

In summary, although the exact steps in HTLV-I–induced leukemogenesis are unclear, Tax seems to play a critical role by direct interaction with cellular proteins involved in transcription, cell-cycle regulation, cell proliferation, and apoptosis. Whatever the role of the virus, however, it seems that a second mutational event is necessary for the transition from cell immortalization to monoclonality and acute ATL. Immortalization and propagation of cells probably allows alterations in the cell cycle and apoptosis pathways to accumulate, allowing a transformed clone to emerge.

**CLINICAL FEATURES OF HTLV-I DISEASE**

The clinical presentation, differential diagnosis, and treatment of ATL are discussed elsewhere in this volume, but are described briefly here. In acute ATL, the tumor aggressively infiltrates multiple organs, commonly involving lymph nodes, liver, spleen, skin, and lung. Median survival is measured in months. The age of onset averages 58 years (range, 24 to 85 years), with a male to female ratio of 1.4:1. Either a leukemic or a non–Hodgkin's T-cell lymphoma presentation may predominate. ATL has been classified into four stages: acute, chronic, smoldering, and lymphomatous. Hypercalcemia is commonly seen in the acute and lymphomatous stages; death is often the result of opportunistic infection.

The differential diagnosis includes mycosis fungoides, Sézary syndrome, Hodgkin's disease, and T-cell chronic lymphocytic leukemia. HTLV-I seropositivity, negative terminal deoxynucleotidyl transferase(TdT) staining, and CD4 positivity are characteristic of ATL. Detection of a monono- or oligoclonally integrated HTLV-I provirus makes the diagnosis definitive.

In addition to ATL, HTLV-I is also associated with tropical spastic paraparesis/HTLV-associated myelopathy (TSP/HAM), a chronic progressive neurologic disorder.

**HUMAN T-CELL LEUKEMIA VIRUS TYPE II**

HTLV-II is closely related to HTLV-I, sharing the same overall genetic organization and 70% homology at the amino acid level. Although it also infects and transforms T cells in vivo, HTLV-II is preferentially tropic for the CD8+ subset. The virus was isolated in 1982 from a patient with atypical T-cell variant hairy cell leukemia and subsequently from two other individuals. Other disease associations have been reported; however, convincing epidemiologic data for an etiologic role for HTLV-II in human disease are lacking. Most patients with either T- or B-cell hairy cell leukemia are not HTLV-II infected, and so far no disease has a demonstrated increased incidence in HTLV-II–infected populations. In contrast to HTLV-I, HTLV-II is able to transform T cells in a manner not dependent on activation of the Jak/STAT pathway, although the exact mechanism of cell transformation by HTLV-II remains unknown.

HTLV-II is transmitted by the same routes as HTLV-I. Like HTLV-I, and unlike HIV, the genome of HTLV-II is quite stable. Again, this is postulated to be due largely to noncompliance or drug resistance are common, the drugs themselves have a number of potentially serious side effects, and the cost of lifelong therapy can be prohibitive, particularly in underdeveloped countries.

**HUMAN IMMUNODEFICIENCY VIRUS**

Although the annual incidence of HIV infection in the United States declined in the late 1990s, HIV disease remains a formidable global health problem. New infections continue at a significant rate, particularly in parts of the world such as Southeast Asia. In addition, a large number of asymptomatic HIV-infected persons are expected to develop AIDS. Newer pharmacologic therapies have slowed the rate of progression to AIDS, but do not eradicate infection. Treatment failures due to noncompliance or drug resistance are common, the drugs themselves have a number of potentially serious side effects, and the cost of lifelong therapy can be prohibitive, particularly in underdeveloped countries.

HIV-1 and HIV-2 are members of the lentivirus subfamily of retroviruses. It is now known that both viruses became human pathogens after zoonotic (cross-species) transmission to humans from primate reservoirs. Sooty mangabeys (Cercocebus atys) are the reservoir of simian immunoodeficiency virus strain sm (SIVsm) and the probable ancestor of HIV-2. A subspecies of common chimpanzee (Pan troglodytes troglodytes) inhabiting west equatorial Africa is the reservoir of SIVcpz and the source of at least three independent transmissions of this virus to humans, resulting in the evolution of HIV-1 groups M, N, and O. The hunting and preparation of chimpanzees for food, a common practice in equatorial Africa, provides the most likely mechanism by which primate zoonotic infections occurred. Although HIV-2 can also cause AIDS in humans and monkeys, the majority of AIDS cases worldwide are the result of HIV-1 infection. Therefore, this discussion focuses on HIV-1 disease.

As with HTLV-I, the HIV genome and replication cycle are complex (Fig. 10.1-3). In sharp contrast to HTLV-I, however, HIV replicates actively after initial infection, which results in high levels of viremia. This high rate of replication, in concert with a high mutation rate, results in the extreme genetic variability that has been documented for HIV-1. This variability occurs both within individual patients, among patients, and between definable geographic subtypes. HIV, unlike HTLV-I, is highly cytopathic for CD4+ T cells.

**FIGURE 10.1-3.** Human immunodeficiency virus (HIV) genome. Overall, the genomic organization of HIV is the same as for the simpler retroviruses, with gag, pol, and env genes flanked on each end by long terminal repeats (LTR). HIV also encodes other proteins involved in the viral replication cycle.
The immunodeficiency resulting from HIV infection can contribute to tumor development and patient prognosis. There is, however, little evidence that HIV is directly oncogenic. Although HIV infection may contribute to the pathogenesis or complicate the treatment of neoplastic diseases, no viral protein has been shown to be directly transforming. Transduction of cellular oncogenes has not been observed. Despite rare reports of insertional mutagenesis resulting in T-cell lymphoma, this disease does not occur disproportionately in HIV infection.

In HIV infected persons, non-Hodgkin's lymphoma, Kaposi's sarcoma (KS), Hodgkin's disease, and cervical cancer are all AIDS-defining illnesses. Many of the neoplasms common to AIDS patients are associated with infection by DNA viruses. These include human herpes virus-8 (HHV-8), Epstein-Barr virus (EBV), and human papillomavirus. These viruses and their associations with oncogenesis are discussed in detail elsewhere in this volume, but are mentioned brieﬂy here.

The tumor biology of KS is not well understood. Unlike most tumors that have readily identifiable neoplastic cells, KS tumors are histologically complex. The predominant cell and the most likely candidate tumor cell of the spindle cell, but other cells, including inﬁltrating leukocytes, are present in the tumor. It is unclear how much of the tumor is made up of spindle cells, or angiogenic cells. Instead of monoclonality, a polyclonal, multicentric proliferative process seems to occur, which is reﬂected in the frequently observed waxing and waning clinical course of KS. For example, lesions may disappear in one region, only to be supplanted by new lesions elsewhere. Although evidence supports HHV-8 as the etiologic agent of KS, HIV is clearly an important cofactor in KS development.

In addition to immunodeficiency induced by HIV-1 infection, the viral Tat protein also may be involved in the pathogenesis of KS. Tat increases the level of a variety of cytokines, including interferon-γ, tumor necrosis factor-α, IL-1, and IL-6. These factors may promote growth of endothelial cells and production of angiogenic stimuli that may contribute to the KS ﬁbroblast growth factor and vascular endothelial growth factor. Additionally, Tat protein that is released from HIV-infected cells can be taken up by other cells, thereby modulating its potential effects. Thus, a complex interplay between HIV, the cytokines induced by HIV infection, and HHV-8 may provide the microenvironment and stimulus for KS development.

AIDS patients are also at increased risk for the development of non-Hodgkin's lymphomas. The majority of these lymphomas are of B-cell origin, and many are associated with EBV infection or with rearrangements of c-myc. In general, these malignancies carry a poor prognosis. An aggressive form of non-Hodgkin's lymphoma seen in AIDS patients is primary central nervous system lymphoma, a malignancy that is rare in the general population. Unlike the systemic lymphomas, primary central nervous system non-Hodgkin's lymphoma is nearly universally associated with EBV infection. In this respect it is similar to the posttransplant lymphoproliferative disorder (PTLD). EBV is not found in organ transplant non-Hodgkin's patients. Among AIDS patients, primary effusion lymphoma, has been associated with infection by HHV-8; co-infection of cells with EBV also has been observed. Multicentric Castleman's disease also is associated with HHV-8 infection. The role that HIV itself might play in the genesis of the AIDS-associated lymphoproliferative disorders is not clear. In addition to the immunosuppression caused by T-cell depletion, it has been theorized that HIV may contribute to lymphomagenesis by affecting cytokine production and by altering B-cell regulation.

Cervical carcinoma and anal squamous cell carcinoma are two other malignancies seen in AIDS patients; both are associated with human papillomavirus infection. These malignancies may present in a more advanced or invasive form than in non-HIV-infected patients. Immune suppression may support development of and complicate treatment of these tumors, but at this time there is no evidence that HIV plays a more direct role in their genesis.

HEPATITIS C VIRUS

HCV infection is a well-established risk factor for the development of hepatocellular carcinoma (HCC), although its role in oncogenesis may not be direct. HCV belongs to the Flaviviridae family of viruses. Virions consist of a single-stranded plus sense RNA molecule surrounded by a nucleocapsid and envelope. The viral genome is approximately 9500 nucleotides long and has a single, large open reading frame encoding viral proteins. The 5' leader sequence of the viral genome contains stem-loop structures, one of which acts as an internal ribosome entry site (IRES). The 5' end of the large open reading frame encodes the capsid (C) protein and envelope (E1,E2) glycoproteins, whereas the enzymatic proteins are encoded by the 3' end. These enzymatic proteins include a metalloprotease, a serine protease and helicase, and the RNA-dependent RNA polymerase responsible for viral nucleic acid replication. The extreme 3' end of the RNA genome contains a short untranslated region.

After entry into cells, the viral genome is replicated via the viral-encoded RNA-dependent RNA polymerase via a minus-strand RNA intermediate; no DNA copy is made. Plus strand viral RNA molecules lack the usual CAP modification at the 5' end of mRNAs and are translated into a single polyprotein, making use of the IRES to initiate translation. The polyprotein produced is processed to yield all HCV enzymatic and structural proteins, including the core and envelope proteins. Genomic RNA and structural proteins associate to form progeny virus particles, which are released from cells, most likely through the endoplasmic reticulum and host cell secretory pathways.

HCV is transmitted by contaminated blood products, by shared needles of intravenous drug users, perinatally, and via sexual routes, but in approximately 10% of cases known risk factors for transmission are not identiﬁed. It is estimated that approximately 3 million people in the United States are chronically infected with HCV. HCV infection is strongly associated with the development of cirrhosis and HCC, although the regional prevalence of HCV infection in HCC varies. HCV infection is found in 30% to 40% of cases, with a subset of people developing chronic hepatitis and cirrhosis. The rate of HCC development in those with cirrhosis is estimated to be 1% to 4% per year. However, an individual patient’s risk for progression to HCC development is difﬁcult to assess because many additional factors affect the likelihood of HCC development. For example, alcohol consumption or co-infection with hepatitis B virus greatly increases the relative risk for developing HCC.

The role of HCV in HCC pathogenesis is not entirely clear. There is a 20- to 30-year period after initial HCV infection before development of HCC. It has been postulated that HCC largely develops indirectly as a result of the inﬂammatory responses that lead to hepatitis destruction, regeneration, and ﬁbrosis. Nevertheless, the virus may play a more direct role in neoplastic transformation of hepatocytes. For example, growing evidence suggests that the HCV core protein may contribute to tumor development. Infection by different strains of HCV may also pose different levels of risk for HCC development. Many groups have reported that HCV genotype 1b confers an elevated risk for developing HCC. However, the observed effects were variable and not seen in all studies.

For those infected with HCV, interferon-α therapy is effective in a minority of cases in stabilizing viral load and improving histologic hepatic changes. In this subgroup of patients, the risk of HCC development appears to be decreased but not eliminated. It is still not certain if this treatment can decrease permanently the risk of developing HCV-associated HCC. Treatment with both interferon and ribavirin, a synthetic guanosine analogue, can increase the number of sustained responders to treatment to 30% to 40%. Unfortunately, attempts at early detection of HCV-associated HCC by ultrasound or α-fetoprotein levels have not proven effective in reducing HCC-related mortality.

In addition to infecting hepatocytes, HCV can infect hematopoietic cells, including lymphocytes and CD34+ precursor cells. Patients infected with HCV are suggested to be at increased risk for the development of B-cell non-Hodgkin's lymphoma. This association, however, has not been observed in all studies. Further studies are needed to resolve fully the potential contribution of HCV infection to the development of some subtypes of B-cell lymphoproliferative disorders.

CHAPTER REFERENCES


SECTION 10.2
DNA Viruses

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INTRODUCTION

Viral oncology has its foundations in scientific observations made at the turn of the twentieth century and defining the transmissibility of avian leukemia (in Denmark in 1908) and an avian sarcoma in chickens (in 1911). These important discoveries were not appreciated at the time, and their impact on virology and medicine was not recognized for decades. The importance of the work of Peyton Rous demonstrating that cell-free extracts from a sarcoma in chickens could, within a few weeks, induce tumors in injected chickens, even when the extracts were passed through filters that retained bacteria, finally was recognized by a Nobel prize in 1968. Rous's original work pointed out that this infectious agent not only was capable of inducing tumors but also imprinted the phenotypic characteristics of the original tumor on the recipient cell. At the time, this early work was relegated to the rank of avian curiosities, and its importance remained unrecognized for several decades.

In the 1930s, Richard Shope published a series of articles demonstrating cell-free transmission of tumors in rabbits. The first studies involved fibromatous tumors found in the footpads of wild cottontail rabbits that could be transmitted by injecting cell-free extracts in either wild or domestic rabbits. Subsequent studies have shown that this virus, now referred to as the Shope fibroma virus, is a pox virus. Additional studies carried out by Shope demonstrated that cutaneous papillomatisis in wild cottontail rabbits could also be transmitted by cell-free extracts. In a number of cases, these benign papillomas would progress spontaneously into squamous cell carcinomas in infected domestic rabbits or in the infected cottontail rabbits. In general, however, the field of viral oncology lay dormant until the early 1950s, with the discovery of the murine leukemia viruses by Ludwig Gross and of the mouse polyomavirus by Gross et al. Such findings of tumor viruses in mice led many cancer researchers and virologists to the field of viral oncology. These researchers hoped that these initial observations in mammals could be extended to humans and that a fair proportion of human tumors might also be found to have a viral etiology. The Special Viral Cancer Program at the National Cancer Institute grew from this intense interest in viral oncology and the hope that human tumor viruses would be identified.

Many of the most important developments in modern molecular biology derive from studies in viral oncology from the 1960s and 1970s. The discovery of reverse transcriptase, the development of recombinant DNA technology, the discovery of messenger RNA (mRNA) splicing, and the discovery of oncogenes and, more recently, tumor suppressor genes all are developments that derive directly from studies in viral oncology. Oncogenes were first recognized as cellular genes that had been acquired by retroviruses through recombinational processes to convert them into acute transforming RNA tumor viruses. It is now recognized that oncogenes participate in many different types of tumors and can be involved at different stages of tumorigenesis and viral oncology. This has contributed significantly to the concepts of nonviral carcinogenesis. It is likely that the direct, transforming, oncogene-transducing retroviruses do not play a major causative role in naturally occurring cancers in animals or in humans but rather represent laboratory-generated recombinants. A list of human viruses with oncogenic properties is presented in Table 10.2-1. This list includes such viruses as the transforming adenoviruses, which are capable of transforming normal cells into malignant cells in the laboratory but which have not been associated with any known human tumors. The list also includes viruses such as the papillomaviruses, which have been etiologically associated with specific human cancers and which have been shown to encode transforming viral oncogenes. Finally, it includes such viruses as the hepatitis B and C viruses, which have been closely linked with a specific human tumor, hepatocellular carcinoma (HCC), for which the evidence of a bona fide viral oncogene remains unclear.

This chapter focuses primarily on the DNA viruses that have been associated with specific human cancers and discusses the biology and pertinent molecular biology of these viruses. Chapter 10.1 deals with the RNA viruses, particularly the human retroviruses. The evidence pertaining to the association of each of these viruses with specific types of human neoplasia is presented, and the mechanisms by which these viruses may contribute to malignant transformation are discussed.

HEPADNAVIRUSES AND HEPATOCELLULAR CARCINOMA

HCC is one of the world's most common malignancies. Though rare in the West, the disease is highly prevalent in Southeast Asia and sub-Saharan Africa. In the 1970s, this distribution was recognized to mirror the distribution of chronic hepatitis B virus (HBV) infection. This fact, and the long-recognized histopathologic association between HCC and chronic hepatitis in the surrounding nontumorous liver, led to the strong presumption that chronic HBV infection predisposes to hepatic cancer. This presumption has been strikingly validated in large prospective epidemiologic studies in Taiwan, in which chronically infected individuals were followed for deaths due to this tumor. These studies showed that chronic HBV infection is associated with a 100-fold increase in HCC risk over that of controls who are not chronically infected.

HBV is a small DNA virus classified as a member of the hepadnavirus family (for hepatotropic DNA viruses); for review, see Ganem and Schneider. HBV is the only human virus in this family, which also includes related viruses of woodchucks [woodchuck hepatitis virus (WHV)], ground squirrels [ground squirrel hepatitis virus, (GSHV)], and ducks [duck hepatitis B virus (DHBV)] (Table 10.2-2). Primary infection of susceptible hosts with HBV produces either a subclinical infection or acute hepatitis B, depending on the age of the host and many other poorly understood factors. In adult hosts, 95% of such infections resolve, with clearance of virus from liver and blood and the induction of lasting immunity to reinfection. However, 5% of these infections do not resolve but result in persistent hepatic infection and viremia; most of the demonstrated HCC risk falls within this subgroup of infections. Persistent HBV infections usually last for the life of the host and can have a variety of pathologic consequences. In many hosts thus affected, such infections are subclinical and accompanied by little hepatocellular injury. This asymptomatic carrier state provides evidence that the HBV replication cycle is not directly cytopathic for host cells, an inference that has been strongly sustained by studies of viral replication in cultured cells. Nonetheless, 20% to 25% of persistently infected hosts display hepatocellular injury, in the form of either chronic persistent hepatitis

TABLE 10.2-1. Human Viruses with Oncogenic Properties

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patients harbor multiple integrated HBV genomes, and in general, active viral replication has been extinguished. Coding region, integration of HBV DNA generally disrupts essential genes and is incompatible with replication. Yet most hepatoma cells arising in HBV-infected replication actually proceeds from episomal DNA via reverse transcription of an RNA intermediate.) In fact, because every nucleotide of the viral genome is in a retroviruses, hepadnaviruses do not specify genetic functions directing genomic integration, and such integration is not essential for HBV replication. Another class of more direct genetic contributions that HBV might make to HCC derives from the existence of integrated copies of viral DNA in the tumor cells. Unlike such reports require confirmation. The relationship of all of these activities to the putative oncogenic function of ORF X is unproven. However, the fact that major liver cell proliferation is operative throughout the prolonged preneoplastic period is undisputed and is believed to be an important precondition for carcinogenesis. This proliferation increases opportunities for replicative errors (mutations) that, over time, can contribute to the loss of normal cellular growth control; cells harboring such mutations will have a selective advantage that further perpetuates this cycle. Attesting to the importance of cellular injury and turnover in HCC development is the fact that HCC usually is accompanied by pathologic signs of severe liver injury (chronic active hepatitis and cirrhosis) in the nontumorous liver; it is distinctly uncommon to see hepatoma in hosts whose livers contain minimal evidence of injury. In the preceding formulation, HBV serves as an agent of oncogenesis chiefly by (indirectly) provoking cellular proliferation in response to immune-mediated injury. In this view, no direct genetic contribution is made by viral sequences acting in cis or viral gene products acting in trans. If this view is correct, then other agents, which similarly provoke chronic liver cell injury and regeneration, should likewise be associated with hepatic cancer. In this connection, it is of interest that chronic infection with hepatitis C virus, a genetically unrelated hepatotropic RNA virus that similarly produces chronic hepatitis, also confers an increased risk for HCC development. Despite strong experimental support for the pathogenetic scheme just presented, there is reason to believe that hepadnaviruses may also make a more direct genetic contribution to HCC. Phylogenetic analyses of hepadnaviral genome organization reveal that the structure of the oncogenic mammalian viruses differs from that of the nononcogenic avian viruses in an important way. The mammalian viruses all harbor an additional coding region, termed ORF X (for open reading frame X; Fig. 10.2-1), that encodes a small regulatory protein. This open reading frame is absent in the avian viruses, which fail to induce HCC in their native hosts despite the regular induction of persistent infection. Interestingly, in several lines of transgenic mice displaying constitutive hepatic expression of ORF X, HCC arises with increased frequency. Tumors in such mice do not begin until midlife, suggesting that additional genetic changes are necessary for loss of normal growth control. The sequence of ORF X reveals no homology to known oncoproteins or growth regulatory loci, and little is known of its biochemical function. In transient cotransfection assays, X expression up-regulates a wide variety of viral and cellular promoters, but the mechanism by which this activation is achieved has remained obscure. In some situations, X appears to stimulate cytoplasmic signal transduction pathways (e.g., the ras-raf MAP kinase pathway), whereas in other settings, it may function as a nuclear transcriptional activator. It has also been suggested that X protein might bind to and inactivate the tumor suppressor gene product p53, but such reports require confirmation. The relationship of all of these activities to the putative oncogenic function of ORF X is unproven. Another class of more direct genetic contributions that HBV might make to HCC derives from the existence of integrated copies of viral DNA in the tumor cells. Unlike retroviruses, hepadnaviruses do not specify genetic functions directing genomic integration, and such integration is not essential for HBV replication. HBV replication actually proceeds from episomal DNA via reverse transcription of an RNA intermediate.) In fact, because every nucleotide of the viral genome is in a coding region, integration of HBV DNA generally disrupts essential genes and is incompatible with replication. Yet most hepatoma cells arising in HBV-infected patients harbor multiple integrated HBV genomes, and in general, active viral replication has been extinguished. The tumors are clonal with respect to these viral insertions: All cells of the tumor bear the same pattern of integrated sequences, indicating that integration preceded or accompanied the final transforming event. However, close inspection of these integrated sequences indicates that they usually are highly rearranged, with multiple deletions, inversions, reduplications, or other mutations typically present. Although individual integrated sequences may retain certain coding functions, no one viral coding region is invariably preserved, as are

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**TABLE 10.2-2. The Hepadnavirus Family**

It is thought that in such hosts, the hepatocyte injury is due to host immune responses triggered by recognition of viral antigens presented on the surface of infected cells. Much has been learned recently about the mechanisms of such injury. Cytotoxic T lymphocytes (CTLs) appear to play a key role in this process. In experiments with transgenic mice expressing viral antigens, transfer of CTLs specific for those antigens leads to a hepatitis, the severity of which depends on the dose of transferred T cells. Importantly, however, direct killing of the cells is only a part of the story. Much of the injury produced in such experiments is due to secondary, antigen-non-specific responses triggered by the initial CTL activation and cytokine release: release of inflammatory molecules that recruit other inflammatory cell types, production of toxic reactive oxygen radicals, and the like. In addition, infected cells displaying deregulated viral gene expression may display enhanced sensitivity to tumor necrosis factor (TNF) and other inflammatory cytokines.

The induction of hepatocellular injury is believed to be important in HCC pathogenesis because it triggers in the liver a stereotypical proliferative response. Two types of regenerative response are known in the liver, which depend to some extent on the nature of the hepatic insult. (The mechanisms by which these responses occur remain obscure.) In classical liver regeneration (as observed, for example, after a partial liver resection), all mature hepatocytes in the liver—which, under normal circumstances, are nondividing—synchronously reenter the cell cycle, resulting in the prompt restoration of normal hepatic mass. A somewhat different proliferative response is observed after treatment with certain toxic or carcinoogenic chemicals. In this response, poorly characterized cells in the periductal areas (termed oval cells, largely on the basis of their morphology) undergo expansion. These cells are thought to be precursor cells to both bile duct epithelium and hepatocytes. They also share many of the biochemical properties of cells seen in hepatic cancers (e.g., a-fetoprotein production) and, for this reason, are thought by some to be the target cell for transformation in hepatic carcinogenesis by a variety of agents. Although it is likely that both forms of proliferative response are operative in chronic hepatitis, considerable debate continues to surround this issue.

In contrast, in the infected liver cells harboring active viral replication, no such regenerative or proliferative response occurs, and the liver responds in a manner that is distinct from normal liver injury. This response involves the activation of the immune system, which results in the production of inflammatory cytokines, chemokines, and other mediators that recruit and activate immune cells, leading to the destruction of infected cells and the subsequent elimination of the virus. However, the process is not always efficient, and in some cases, the virus can persist, leading to the development of chronic hepatitis. Over time, this chronic infection can lead to the formation of cirrhosis, which is characterized by the development of nodules of regenerating hepatocytes, and an increased risk of liver cancer.

In summary, the pathogenesis of HCC involves a complex interplay between viral and host factors. The virus induces a chronic inflammatory response in the liver, which can lead to cellular injury and regeneration. In some cases, this process can be amplified by immune-mediated mechanisms, leading to the development of HCC. However, the precise role of viral and host factors in the development of HCC remains to be fully elucidated.
E6 and E7 of the human papillomaviruses (HPVs; see the section Papillomaviruses and Human Cancer).

These facts have led to interest in the model that the viral sequences might be contributing cis-acting regulatory signals rather than trans-acting proteins to the host cell. Ample precedent for such a model exists in retroviral oncogenesis in animals, wherein insertion of powerful retroviral enhancer sequences into the chromosome can activate the expression of growth-regulatory genes flanking the insert. Strong evidence that hepadnaviruses can mediate such activation events in cis has been proffered for WHV. WHV is strikingly oncogenic in its native host; virtually 100% of animals chronically infected from birth will develop HCC. The oncogenic drive in an infected animal is remarkably strong; many adult animals can be shown to harbor multiple independent HCCs. As in HBV-induced cancer, the tumors display multiple viral insertions, often highly rearranged, and in a clonal pattern. However, here, remarkably, the vast majority of tumors can be shown to harbor at least one viral insertion in cis to the protooncogene N-myc. This gene, normally silent in adult liver, is strongly up-regulated by this insertion, and such activation can be seen early in the oncogenic sequence, even in premalignant lesions. Many insertions are within a few kilobases of the N-myc locus, but insertions as far away as 250 kb appear to be activating. Clearly, insertional activation of N-myc plays a major role in WHV oncogenesis.

Similar efforts to identify common integration sites for integrated HBV genomes in human HCC have not met with comparable success. Human hepatomas do not harbor N-myc rearrangements and, although isolated examples of dramatic insertion events have been described (e.g., insertions near loci for retinoid receptors or cyclin A homologues), none of these has been identified in more than one tumor, despite extensive searches. The practitioner does well to remember that, despite its many similarities to HBV, WHV differs strikingly in its oncogenic potency; it is possible that insertional activation of N-myc loci is responsible for this difference.

PAPILLOMAVIRUSES AND HUMAN CANCER

The viral nature of human warts was first demonstrated at the turn of the century by transmission using a cell-free filtrate. This important group of viruses has remained refractory to standard virologic studies, however, because propagating the papillomaviruses in the laboratory in tissue culture under standard conditions is difficult. Although some advances have been made in propagating the virus using organotypic raft cultures of epithelial cells, most knowledge about the molecular biology and genetics of the papillomaviruses has resulted from advances in basic research and the application of reverse genetics using cloned viral DNAs.

The papillomaviruses are found in many higher vertebrate species ranging from birds to humans. Although originally classified as papovaviruses because of their icosahedral shape and circular, double-stranded DNA genome, the papillomaviruses now are recognized to be separate from the other papovaviruses such as polyoma and simian virus 40 (SV40), on the basis of different biologic and genetic characteristics. The papillomaviruses contain a double-stranded circular DNA genome of 8000 base pairs, which is larger than the polyomaviruses (5000 base pairs), and the virion particles have a correspondingly larger capsid diameter (55 nm vs. 40 nm). The papillomaviruses have not yet been propagated in tissue culture under standard conditions.

More than 80 different HPV types have been described in detail to date, and evidence exists that there may be as many as 30 to 40 additional viruses that have not yet been as well characterized. Unlike some human viruses such as adenoviruses, it has not been possible to type the papillomaviruses by serologic methods, as antisera that can distinguish between the different HPV types are currently not available. Through the 1970s and 1980s, the HPVs were typed by DNA hybridization under stringent annealing conditions, but currently the DNA sequence of a portion of the L1 ORF (in the so-called late region of the HPV genome) is used to define new HPV types. A list of many of the HPV types that have now been categorized, and the clinical syndromes with which they are associated or from which they have been isolated, is presented in Table 10.2-3.

The papillomaviruses are highly species-specific and induce squamous epithelial and fibroepithelial tumors in their natural hosts. These viruses have a specific tropism for squamous epithelial cells, and their full productive cycle is supported only in squamous epithelial cells. The productive infection of cells by papillomaviruses is divided into stages, and these stages are linked to the differentiation state of the epithelial cell. The specific tropism of the papillomaviruses for squamous epithelial cells is evidenced by the restriction of the viral replication functions (vegetative viral DNA synthesis, the production of viral capsid proteins, and the assembly of virions) to the most terminally differentiated keratinocytes.

In a normal squamous epithelium, the basal cell is the only cell normally capable of supporting cellular DNA synthesis and undergoing cellular division. The virus, therefore, must infect the basal cell to establish a persistent lesion. In situ hybridization experiments have demonstrated that the papillomavirus DNA is indeed present within the basal cell of a papilloma. In a squamous epithelium, as the cells migrate upward through the stratum spinosum and into the granular layer, they undergo a program of differentiation. The control of papillomavirus late gene expression is tightly linked to the differentiation state of the squamous epithelial cells. Vegetative viral DNA synthesis and expression of the capsid proteins occurs only in the more differentiated squamous epithelial cells.

All HPV types examined to date have a similar genomic organization. The DNA genomes of each of the HPVs sequenced, as well as of the other animal papillomaviruses, are approximately 8000 base pairs in size. All of the ORFs that could serve to encode proteins are located on only one of the two viral DNA strands. RNA studies have indicated that only one strand is transcribed. A more detailed description of the molecular biology of the papillomaviruses can be found in the current edition of Field's Virology.

The HPV genome can be divided into two distinct regions: an “early” region, which encodes the viral proteins involved in viral DNA replication, transcriptional regulation, and cellular transformation, and a “late” region, which encodes the viral capsid proteins. This functional division is based largely on genetic studies that were carried out with the bovine papillomavirus. A diagram of the organization of a typical HPV-16 is shown in Figure 10.2-2. The genes located in the early region of the genomes are designated as E1, E2, and so on, and the genes located in the late region are designated as L1 and L2. Studies with the HPVs indicate that it is likely that E4 encodes a “late” gene, which is expressed only in productively infected keratinocytes. Thus, although this ORF is located with the early ORFs, its function may be important only in the vegetative replication of the virus. A listing of the functions assigned to the HPV-16 ORFs is provided in Table 10.2-4.

![Figure 10.2-2](https://example.com/fig1022.png)

**Table 10.2-3. The Human Papillomaviruses**

<table>
<thead>
<tr>
<th>ORF</th>
<th>Function</th>
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<tbody>
<tr>
<td>E1</td>
<td>early</td>
</tr>
<tr>
<td>E2</td>
<td>early</td>
</tr>
<tr>
<td>L1</td>
<td>late</td>
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<td>L2</td>
<td>late</td>
</tr>
<tr>
<td>E4</td>
<td>late</td>
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These facts have led to interest in the model that the viral sequences might be contributing cis-acting regulatory signals rather than trans-acting proteins to the host cell. Ample precedent for such a model exists in retroviral oncogenesis in animals, wherein insertion of powerful retroviral enhancer sequences into the chromosome can activate the expression of growth-regulatory genes flanking the insert. Strong evidence that hepadnaviruses can mediate such activation events in cis has been proffered for WHV. WHV is strikingly oncogenic in its native host; virtually 100% of animals chronically infected from birth will develop HCC. The oncogenic drive in an infected animal is remarkably strong; many adult animals can be shown to harbor multiple independent HCCs. As in HBV-induced cancer, the tumors display multiple viral insertions, often highly rearranged, and in a clonal pattern. However, here, remarkably, the vast majority of tumors can be shown to harbor at least one viral insertion in cis to the protooncogene N-myc. This gene, normally silent in adult liver, is strongly up-regulated by this insertion, and such activation can be seen early in the oncogenic sequence, even in premalignant lesions. Many insertions are within a few kilobases of the N-myc locus, but insertions as far away as 250 kb appear to be activating. Clearly, insertional activation of N-myc plays a major role in WHV oncogenesis.

Similar efforts to identify common integration sites for integrated HBV genomes in human HCC have not met with comparable success. Human hepatomas do not harbor N-myc rearrangements and, although isolated examples of dramatic insertion events have been described (e.g., insertions near loci for retinoid receptors or cyclin A homologues), none of these has been identified in more than one tumor, despite extensive searches. The practitioner does well to remember that, despite its many similarities to HBV, WHV differs strikingly in its oncogenic potency; it is possible that insertional activation of N-myc loci is responsible for this difference.
The molecular biology of the papillomaviruses has been most extensively studied for the bovine papillomavirus (BPV-1), which is capable of transforming a variety of rodent fibroblast cell lines in tissue culture. In these transformed cells, the DNA remains as a stable extrachromosomal plasmid, and this system has served as an excellent model for studying latent infection by papillomavirus (reviewed in Spahlholz and Howley). This virus has served as the prototype for unraveling many aspects of the molecular biology of the papillomaviruses over the last 20 years. Two independent transforming activities have been mapped in BPV-1: one to the E5 gene and the other to the E6 and E7 genes. Transformation by the BPV-1 E5 oncoprotein appears to be mediated through activation by binding of the platelet-derived growth factor-b (PDGF-b) receptor. The mechanisms by which the E6 and E7 genes of BPV-1 transform have not yet been fully elucidated. BPV-1 E6 has been shown to bind the focal adhesion protein paxillin, and the binding of E6 to paxillin has been implicated in the cellular transformation phenotype through the disruption of the actin cytoskeleton.

The papillomavirus E2 proteins are regulatory proteins that have roles in viral DNA replication and in viral transcription. E2 is a DNA-binding protein that was first described as a transcriptional activator; however, subsequent studies have shown that it can also function as a transcriptional repressor depending on the context of the E2 binding sites within the promoter. E2 has several roles in viral DNA replication and plasmid maintenance in infected cells. E2 ensures viral DNA partitioning in persistently infected cells by tethering the viral DNA to the mitotic chromosomes during mitosis. E2 also binds to the viral E1 protein and cooperatively promotes origin-dependent viral DNA replication. The E7 gene encodes a protein necessary for extrachromosomal replication and has been shown to have DNA-binding, DNA helicase, and adenosine triphosphatase activities. No function has yet been found for the E3 or E8 ORFs of BPV-1. The L1 ORF of the papillomaviruses encodes the major capsid protein, and the L2 ORF encodes a minor capsid protein. The L1 and L2 ORFs are expressed only in the terminally differentiated keratinocytes.

Although initial papillomavirus transformation studies focused on BPV-1 because it could effectively transform rodent cells in tissue culture, recent studies have focused more on the high-risk HPV, in particular HPV-16 and HPV-18, which are associated with human cervical cancer. Although the genomic organization of the HPV is quite similar to that of BPV-1, there appear to be important differences in the mechanisms by which they transform cells. The principal transforming genes for the cancer-associated HPVs have been mapped to E6 and E7, as will be discussed later in this section. E7 alone is sufficient for the transformation of primary rodent cells. E7 also is capable of cooperating with an activated ras oncogene to transform primary rodent cells. Expression of E6 and E7 together is sufficient for the efficient immortalization of primary human cells, most notably primary human keratinocytes, which are the normal host cell for the HPVs. Cellular targets for the HPV E6 and E7 proteins have been identified, as discussed later in this section. HPV E5 may also have transforming activities, but it has not been studied as well as has HPV E6 and does not appear to function through interaction with the PDGF-b receptor.

Only a subgroup of the papillomaviruses is associated with lesions that are at risk for progression to cancer. These viruses and their associated malignancies are listed in Table 10.2-5. The papillomavirus that infects cottontail rabbits in nature (CRPV) was first identified by Shope as the etiologic agent of cutaneous papillomatosis in rabbits. CRPV has been extensively studied as a model for papillomavirus-induced carcinogenesis. One of the features of carcinogenic progression with the papillomaviruses is the synergy between the virus and carcinogenic external factors (see Table 10.2-3). In the case of CRPV, carcinomas develop at an increased frequency in virus-induced papillomas that are painted with cool tar or methylcholanthrene. These CRPV-associated carcinomas contain copies of the viral DNA that are transcriptionally active, an observation which supports the hypothesis that these viruses play an active role in the cancers that develop. There has been limited study of the molecular mechanisms involved in CRPV-associated carcinogenesis.

In cattle, BPV-4 has been associated with esophageal papillomatosis and also is associated with squamous cell carcinomas of the upper alimentary tract. Interestingly, however, only those cattle from the highlands of Scotland that are infected with BPV-4 and that also feed on bracken fern (known to contain a radiomimetic substance) have a high incidence of squamous cell carcinomas of the esophagus and of the foregut. In contrast to the CRPV-associated carcinomas in which the viral DNA can invariably be found, extensive analysis of the squamous cell carcinomas of the upper alimentary tract in these cattle infected with BPV-4 has failed to reveal a consistent pattern of viral DNA sequences within the malignant tumors. In the case of these alimentary tract tumors, possibly the continued presence of BPV-4 DNA sequences is not required for maintenance of the cancer.
The first evidence that HPVs were associated with human cancer came from studies in patients with epidermodysplasia verruciformis (EV), a rare, lifelong disease in humans that usually begins in infancy or childhood (reviewed in Jablonska and Majewski). The disease is characterized by disseminated, polymorphic cutaneous lesions that resemble flat warts and by reddish macules sometimes referred to as pityriasis-like lesions. Approximately one-half of the patients with EV develop multiple skin cancers, usually during the third or fourth decade of life. Papillomavirus particles have been detected within the benign lesions and not in the carcinomas. EV is considered an autosomal recessive disorder, and genetic studies of affected families have led to the mapping of a susceptibility gene to 17q, the same region that has been found to contain a dominant locus for the susceptibility to familial psoriasis. It is thus tempting to speculate that distinct defects affecting the same gene may be involved somehow in the pathogenesis of these two hyperproliferative skin conditions. Interest of is that the carcinomas that develop in these patients arise in sun-exposed areas, and it is suspected that ultraviolet radiation plays a co-carcinogenic role with the papillomaviruses in the etiology of these cancers. Although EV is a very rare disease, it has been under intense study by dermatologists and virologists. More than 20 different HPV types have now been demonstrated in individual lesions in patients with this rare disease (see Table 10.2-3). Furthermore, recent studies have shown that these EV HPVs are widespread and point to psoriasis as a potential reservoir for HPV-5, one of the HPVs commonly found in EV. Whether the EV-associated HPVs also are involved in the pathogenesis of psoriasis remains to be determined.

The cutaneous carcinomas in patients with EV can be Bowenoid carcinomas, in situ carcinomas, or invasive squamous cell carcinomas. Of the HPV types found in patients with EV, only a subset of them is associated with a risk of malignant progression, notably HPV-5 and HPV-8, although other types occasionally are found in EV carcinomas. The role of the HPVs in EV cancers is suggested by the presence of viral DNA of specific HPV types in the EV cancers. Although metastasis is uncommon in the cancers in these patients, the presence of HPV-5 in the two metastatic lymph node lesions examined strengthens the agreement for an etiologic role for HPV in these carcinomas.

Further studies have established that the viral genomes are transcriptionally active within these carcinomas and that HPV-5 and HPV-6 encode cellular transformation functions. Little work has been done yet to establish the mechanisms by which the EV HPVs contribute to cancer.

The role of HPVs in cutaneous cancers in humans extends beyond EV patients to other patients, both immunosuppressed and immunocompetent. New HPV types have been found in squamous and basal cell carcinomas of immunosuppressed patients and in some of the same tumors in immunocompetent patients. The cutaneous HPVs are very prevalent in the population, and it has not yet been determined whether the virus has a role in promoting these cancers in immunosuppressed patients or whether it merely persists as a passenger.

The epidemiology of genital warts follows a pattern characteristic of a sexually transmitted disease (STD) with a high prevalence in populations of highly promiscuous women. Two general types of genital wart viral infections—condylomata acuminata and squamous intraepithelial lesions (SILs)—are now recognized and can be distinguished by clinical appearance. The anogenital wart is found on the penis, the vulva, the anal region, the cervix, the anus, and the lips, and is caused by papillomaviruses. Papillomavirus particles have been demonstrated by the electron microscope. HPV-6 and HPV-11 DNAs were directly cloned from condylomata acuminata lesions, and the genomes of these HPV types can be demonstrated in more than 90% of the lesions of condylomata acuminata examined. Less frequently, other HPV types can be found in condylomata acuminata. Malignant conversion of condylomata acuminata into squamous cell carcinoma has been described. A lesion described by Buschke and Löwenstein and designated as a giant condyloma has characteristics similar to a locally invasive squamous cell carcinoma. These tumors are also associated with HPV-6 and HPV-11. The majority of cervical carcinomas and other genital tract carcinomas, however, are negative for HPV-6 and HPV-11.

In the mid-1970s, zur Hausen suggested an association between papillomaviruses and genital cancers. Compelling evidence linking an HPV infection with cervical carcinoma came from the recognition that the morphologic changes previously interpreted on Papanicolaou smears and tissue sections of the cervix as cervical dysplasia were due to a papillomavirus infection. The characteristic cells that are diagnostic for a cervical papillomavirus infection is the koilocyte. Electron microscope demonstrated papillomavirus particles in the koliocytic cells supporting the papillomavirus etiology. Subsequent studies found papillomavirus-specific capsid antigens and HPV DNA within cervical dysplastic lesions, providing confirmation of the viral etiology of cervical dysplasia.

Epidemiologic studies had long implicated an infectious agent in the etiology of human cervical carcinoma. Venerally transmission of a carcinogenic factor with a latent long history was suggested by early epidemiologic studies. Sexual promiscuity, an early age of onset of sexual activity, and poor sexual hygiene are known risk factors for cervical carcinoma. There is a correlation between the incidence rates of cervical cancer and penile carcinoma in various geographic areas, although the incidence rates for penile carcinoma are 20-fold lower when compared to those of cervical carcinoma. The similarity in incidence rates suggests that specific viruses are involved in both cancers. The HPV DNA pattern of positivity emerged. Using radioactively labeled HPV-11 DNA under conditions of hybridization of low stringency, Durst et al.

The association of an HPV with cervical dysplasia [also referred to as cervical intraepithelial neoplasia (CIN) and SIL] sparked an examination of cervical cancers for HPV sequences. The natural history linking CIN to carcinoma in situ and to invasive squamous cell carcinoma of the cervix had already been well established. Initial experiments from a number of laboratories revealed HPV sequences in occasional cases of cervical carcinoma and anogenital carcinoma, but no consistent pattern of positivity emerged. Using radioactively labeled HPV-11 DNA under conditions of hybridization of low stringency, Durst et al.

Examination of human cervical carcinoma DNAs for related HPV DNAs and, in the early 1980s, identified two new papillomavirus DNAs, HPV-16 and HPV-18. Using these HPV DNAs as probes, HPV types 16 and 18 could be demonstrated in approximately 70% of cervical carcinomas. The low-stringency hybridization and the polymerase chain reaction with degenerative primers has led to the identification of approximately 20 different HPVs now associated with genital tract lesions (see Table 10.2-3). HPV-31, -33, -39, -42, and other HPVs are each associated with a small percentage of cervical carcinomas. Specific HPVs can be found regularly in 85% to 90% of human cervical carcinoma cases and in a lower percentage of other human genital carcinomas such as penile carcinomas, vulvar carcinomas, and penile intraepithelial neoplasias. The ability of HPV DNA probes of specific clinical types to distinguish HPV types of high-risk from those of low-risk and to detect HPV type-specific cervical lesions was demonstrated. Subsequent studies suggested that high-risk HPVs were associated with high-risk cervical diseases.

The association of HPV with cervical dysplasia was due to a papillomavirus infection. The characteristic cell that is diagnostic for a cervical papillomavirus infection is the koilocyte. Electron microscope demonstrated papillomavirus particles in the koliocytic cells supporting the papillomavirus etiology. Subsequent studies found papillomavirus-specific capsid antigens and HPV DNA within cervical dysplastic lesions, providing confirmation of the viral etiology of cervical dysplasia.
The high-risk HPV E6 proteins also have other activities that are not linked to their ability to target p53. For instance, it has been shown that expression of the HPV E6 oncoprotein results in the activation of telomerase activity in infected cells. Furthermore, E6 can interact with several additional cellular proteins, including a putative calcium-binding protein referred to as the E6-binding protein (E6BP) and a novel GAP protein, E6TP1. The high-risk HPV E6 proteins as well as the oncogenic HPV E6 protein can complex with paxillin, a cellular focal adhesion protein that may serve as an adapter in transmitting signals from integrin molecules to the actin cytoskeleton. The high-risk HPV E6 protein has also been reported to bind p300. HPV-16 E6 can also bind and inhibit the transcription activation function of interferon regulatory factor-3, an interaction that may have role in protecting the virus-evasion host cell defenses from cellular transformation. It should be noted, however, that the significance of the interaction of E6 with these cellular targets and others described in the literature, other than p53 through E6BP, has yet to be fully established.

It is clear that infection by a specific HPV alone is not sufficient for the development of cervical cancer. Only a small fraction of those individuals who are infected by a specific HPV will eventually develop cancer, and the time interval between infection and invasive cancer can be several decades. Thus, the genetic information carried by the virus per se is not sufficient for malignant progression. Other factors must be involved in the progression of virus-associated lesions to these genital tract cancers, and clearly additional genetic mutations in the infected cell are required for a cancer to arise. Epidemiologic studies have suggested that smoking is a risk factor for developing cervical carcinoma. The recognition that other factors are involved in the progression to cervical carcinomas suggests that papillomavirus infections may work synergistically with these other factors. It has been suggested that tobacco condensate in women who smoke could accumulate in the vaginal fluids, bathing the cervix and acting as a cofactor with the papillomavirus infection. Likewise, it has been postulated that herpesvirus infection might act synergistically with specific papillomaviruses to induce human cervical carcinoma.

The use of restriction fragment–length polymorphisms has revealed that a loss of heterozygosity on the short arm of chromosome 3p implicates a potential tumor suppressor gene seen in cervical cancer, which may be the recently described FHIT gene. The somatic cell hybrid work of Stanbridge implicates a potential tumor suppressor gene on human chromosome 11. A gene on human chromosome 11 can suppress the tumorigenicity of HPV-positive cervical carcinoma cells. It has been proposed that the loss of this gene on chromosome 11 in HeLa cells results in loss of expression of the cellular interfering factor, which negatively regulates HPV expression in these cells. Further evidence that a negative regulator of HPV transcription is included on chromosome 11 is that fibroblasts with a deletion in the short arm of chromosome 11 can more efficiently immortalize by HPV-18 than can normal fibroblasts. The identification of genes on human chromosome 11 involved in tumor suppression in cervical cancer cell lines will obviously be a very important advance. Tumor progression, however, is complex and may involve additional loci. It should be noted that late stages of cervical carcinomas are associated with amplification and overexpression of the cellular oncogene myc.

The availability of specific HPV DNA probes has provided investigators the opportunity to carry out extensive screenings of a variety of human cancers for HPV sequences. Based on the animal models, it seemed likely that any carcinomas of any squamous epithelium or an epithelium that can undergo squamous metaplasia would be a potential candidate for association with an HPV. Studies examining oral, upper airway, and tonsillar carcinomas have revealed some HPV-positive carcinomas. HPV DNA has been found in benign oral papillomas, and oral focal epithelial hyperplasia has been firmly established as having a papillomavirus etiology. In addition, papillomavirus DNA sequences have been found associated with some cases of oral leukoplakia. Esophageal carcinomas in humans have not yet been convincingly shown to be associated with an HPV. The esophagus is lined by a squamous epithelium, and squamous cell papillomas of the esophagus have been described in humans. Additional studies would seem warranted to investigate a possible role of HPV in human esophageal cancers. In addition, sporadic reports in the literature of occasional human tumors, including colon cancer, ovarian cancer, prostate cancer, and even melanomas, with the presence of HPV DNA. In general, it seems prudent to be skeptical of such reports until systematic and well-performed studies are confirmed in multiple laboratories.

Significant advances have been made recently in the development of vaccines against papillomavirus infections. The expression in yeast and in insect cells of the major capsid protein L1, either alone or together with L2, leads to the assembly of virus-like particles (VLPs) that are morphologically identical to native virions. These VLPs present the conformational epitopes necessary for the development of a high-titer neutralizing antiserum. Such VLPs now are being used in clinical trials in humans. In addition, there is interest in the development of therapeutic vaccines directed against the E6 and E7 proteins expressed in cancers and preneoplastic lesions. A variety of approaches have already been described in the literature, including the use of vaccinia virus vectors, DNA vaccines, and...
FIGURE 10.2-4. Schematic diagram of the events in Epstein-Barr virus (EBV) infection. Primary EBV infection begins at the oropharyngeal epithelium, where it can produce symptomatic pharyngitis. B lymphocytes are infected as they traffic in close proximity to the oropharyngeal epithelium. EBV BCRF1 is a close homologue of human interleukin-10 and blunts the initial natural killer (NK) CD9 T lymphocyte and gamma interferon responses, enabling EBV better to infect B lymphocytes. In acutely infected B lymphocytes, EBV expresses all early-encoded nuclear antigens (EBNAs), latent infection–associated membrane proteins (LMPs), and EBV encoded small RNA (EBERs), causing cell proliferation. In immunosuppressed patients, an acute lymphoproliferative disease may emerge, and the EBNAs, LMPs, and EBERs are expressed in the tumor cells. An EBV-specific CD8 T-lymphocyte response is demonstrable in normal people shortly after EBV infection and is presumed to account for the fall in peripheral blood EBV-infected B-lymphocyte number from as much as 1 in 10 in acute infection to 1 in 10^3 to 10^4 with convalescence from acute EBV infection. CD9 T lymphocytes recognize determinants from EBN2A, -3A, -3B, -3C or -LP or from LMP1 or LMP2 in the context of specific class I major histocompatibility complex (MHC) molecules. B lymphocytes expressing these proteins must continue to be present, as a high level of EBV-immune CD9 T lymphocytes persists for life. EBV persists in some lymphocytes that express only EBN2A. Because CD8 responses to EBN2A are rare, EBN1-expressing lymphocytes can escape immune surveillance. LMP2 keeps the virus from reactivating as latently infected B lymphocytes circulate in the peripheral blood and tissues, where they encounter ligands for surface immune globulin or for CD19 or class II MHC. Persistent replication of the oropharynx depends on activation of lytic infection in lymphocytes when they traffic close to oropharyngeal epithelial cells. Years after primary EBV infection, Burkitt’s lymphoma, Hodgkin’s disease, and nasopharyngeal carcinoma (NPC) tumors occur. These tumors can originate from a clone of EBV-infected cells. Most African Burkitt’s lymphoma, 50% of Hodgkin’s disease, and all anaplastic nasopharyngeal carcinomas are composed of EBV-infected cells.

The host range of EBV, in vitro, is limited to primate B lymphocytes. B lymphocytes express large amounts of CD21, a surface glycoprotein for which the major EBV envelope glycoprotein has high affinity. Consistent with the notion that EBV is a human tumor virus, infection of normal B lymphocytes confers an ability to proliferate continuously, in vitro, in nude mouse brain after intracerebral inoculation or in the mesenteroy of severely combined immunodeficiency mice after intravenous inoculation. Infection of some new world primates with EBV reproducibly induces an acutely fatal lymphoproliferative disease. A similar lymphoproliferative disease can occur with primary EBV infection in male children with X-linked lymphoproliferative disease or in profoundly immunosuppressed patients with human immunodeficiency virus (HIV) infection or liver, heart, lung, or bone marrow transplantation. Although EBV-transformed B lymphocytes have substantial capacity for proliferative proliferation, they remain fully differentiated and exhibit phenotypic markers similar to antigen-activated normal B lymphocytes.

In latently transformed B lymphocytes growing in vitro, in the peripheral blood of patients with primary EBV infection, or in polyclonal lymphoproliferative disease, EBV encodes latent proteins, two latent infection–associated membrane proteins (LMPs), and two small nonpolyadenylated RNAs (EBV encoded small RNA [EBERs]). Molecular genetic analyses using specifically mutated EBV recombinants indicate that EBN3B, LMP2, the small RNAs, and most of the viral genome that is expressed in lytic infection can be mutated without a significant effect on the ability of the virus to transform primary B lymphocytes. The other EBNAs and LMP1 are important for lymphocyte transformation. Although not a mediator of cell transformation, LMP2 is important in maintaining latency by preventing lytic infection in response to lymphocyte activation signals.

EBN2A is an EBV DNA replication origin-binding protein, which is important in latent infection for origin function in episome maintenance and transcriptional activation. The other EBNAs, the functions of which are established, are regulators of transcription of viral or cellular genes. EBN2A is the best characterized of these virally encoded transactivators and is an acidic type transactivator. EBN2A lacks DNA sequence–specific binding activity and is dependent on interactions with sequence-specific cellular proteins for recognition of enhancer elements. All known EBN2A response elements have a sequence, which binds the cell protein Jk that, in turn, recruits EBN2A. This interaction is not entirely sufficient for EBN2A responsiveness; for example, PU.1 is essential for EBN2A responsiveness of the LMP1 promoter. EBN3A and EBN3C also regulate transcription in lymphocyte transformation. Like EBN2A, EBN3A and EBN3C achieve specificity in their interaction with viral and cellular promoters by interacting with the cell protein Jk. The interaction of three different EBV proteins with Jk may indicate an importance for Jk-mediated cell gene regulation in B-lymphocyte growth. This is reinforced by the recent findings that Notch, a T-cell leukemia gene, activates transcription through Jk. From a different perspective, EBN2A and EBN3As can be viewed as userrpers of the Notch signaling pathway.

LMP1 is a key gene in EBV-mediated cell growth transformation. LMP1 can transform immortalized rodent fibroblasts to loss of contact inhibition, anchorage independence, or nude mouse tumorigenicity. When expressed in normal resting B lymphocytes or in non–EBV-infected Burkitt’s lymphoma cells that have a nonactivated phenotype with regard to markers of normal B-lymphocyte activation, LMP1 induces most B-lymphocyte activation and adhesion markers, activates NFkB, and induces Bcl2 and A20, proteins important in preventing apoptosis. In epithelial cells, LMP1 induces epidermal growth factor receptor expression and inhibits differentiation. Specific mutations in the LMP1 gene in EBV recombinants have provided direct evidence that LMP1 is essential for primary B-lymphocyte growth transformation. Specific mutations in the LMP1 gene in EBV recombinants have provided direct evidence that LMP1 is essential for primary B-lymphocyte growth transformation. The first 45 amino acids of the LMP1 C-terminal cytoplasmic domain are essential for B-lymphocyte growth transformation, whereas the N-terminal cytoplasmic domain and the more distant 155 amino acids of the LMP1 C-terminal cytoplasmic domain are not necessary. The essential C-terminal 45–amino acid domain of LMP1 interferes in the cytoplasm with cellular proteins that ordinarily transduce signals from the TNF receptor (TNFR) family.
Primary EBV infection in most normal people causes clinically apparent or milder forms of acute infectious mononucleosis. Infection initiates in the oropharyngeal epithelium, and then spreads to B lymphocytes. As many as 10% of the circulating B lymphocytes may be EBV-infected and express EBNA and LMPs. These infected cells engender a massive natural killer response, followed by a human leukocyte antigen class I and EBV antigen-specific, cytotoxic CD8+ T-cell response. The number of responding cells substantially exceeds the number of infected B lymphocytes. As a consequence of the cellular response, the number of infected B lymphocytes falls to 1 in 106 and remains at that level. Somewhat higher levels persist in tonsils. The persisting cells may express only EBNA1, EBNA1 and LMP1, or EBNA1, EBNA2a, EBNA3a, and LMP1. The EBNA1-only type appears to be a target for the T-cell response. The EBNA1- and EBNA2a-only type appears to be resistant to the T-cell response but may be eliminated by other mechanisms. In normal people, high-level CD8+ T-cell recognition persists for life, restricting the growth of EBV-infected lymphocytes that progress to expression of all EBNAs and LMPs. The continuous presence of specific CD8+ T cells is unusual and indicates ongoing stimulation of the immune response with EBNA- and LMP-expressing cells. Virus replication also persists in the oropharyngeal epithelium, although this requires reintroduction of virus from the lymphocyte pool. With immunosuppression, latently infected cells in the peripheral blood and persistently infected cells in the oropharynx increase in number.

Long after primary infection, EBV is associated with endemic and nonendemic Burkitt’s lymphoma, Hodgkin’s disease, 127 neural and peripheral B lymphomas and leiomymas in immunocompromised patients, 128–130,152–154 T-cell malignancies, 155 nasopharyngeal carcinoma, 156–158 squamous tumors of the oropharynx, and gastric epithelio malignomas. 159–162 In most instances, the association is based on unusually high serologic reactivity to EBV proteins in a substantial number of patients with the malignancy, on the finding that the tumor cells are infected with EBV, and on the finding that the resident EBV genome in tumors is unincolal with regard to EBV infection events. 163 The finding of markers of the same infection event in all the EBV DNA molecules in tumor tissue and in metastases is evidence that the tumor cells are progeny of a single infected cell and that EBV was present in the cell before the cell became malignant. 164 The EBERs are transcribed in high abundance in latent EBV infection of nonepithelial cells, and in situ hybridization to EBERs has been useful in demonstrating the specific association of EBV with Hodgkin’s disease tumor cells. Hodgkin’s cells express EBNA1 and high levels of LMP1; other EBNAs are not expressed. EBNA1, LMP1, and LMP2 are the only EBV proteins expressed in nasopharyngeal carcinoma and in neoplastic lesions of the nasopharynx, consistent with a role for these proteins in the latent infection and associated cell growth alteration. 165

The role of EBV in Burkitt’s lymphoma and in other late-onset malignancies is complicated. The presence of EBV in all the tumor cells and the unicitylarity of the tumor cells with regard to EBV infection indicate that the tumors arise in an EBV-infected cell. Thus, EBV infection clearly sets the stage at the cellular level for progression to malignancy. At the cellular level, EBV infection may enable further evolution of the malignancy by increasing NFkB, c-myc, immune globulin, and RAG gene expression and by preventing apoptosis. Increased c-myc, Ig, and RAG gene expression may increase the frequency of c-myc/cIg translocation, which can result in constitutive c-myc activation. 166–168 On the basis of transgenic models, constitutive c-myc activation can further expand the B-cell pool and predispose to subsequent genetic changes that lead to more malignant phenotypes. EBV may initially complement c-myc in promoting cell growth but eventually become redundant. In Africa and New Guinea, the very high-level predisposition of EBV to Burkitt’s lymphoma appears to be due to holoendemic malaria; malaria infection stimulates B-cell proliferation and depresses cytotoxic T-cell function. 169,170 In this regard, malarial infection has effects in endemic Burkitt’s lymphoma that overlap with the effects of HIV infection on high-level immunosuppressive therapy. 171–173 The presence of EBV-infected cells in tissue can be detected via in situ hybridization to EBV early region 1 (EBER) transcripts. 174 The significance of the failure of T-cell immune surveillance in the evolution of lymphoproliferative disease in immunosuppressed patients 175,176 has been experimentally confirmed by the beneficial effects of EBV-specific or -nonspecific reconstitutive therapy or prophylaxis. 177,178 Cytotoxic T-cell failure rarely is complete, and Burkitt’s lymphoma or similar uniclonal B lymphomas involving EBV-infected cells that emerge in normal or immunocompromised patients frequently are characterized by the absence of cells that express EBV proteins other than EBNA1. Thus, the current model for EBV-associated B-cell malignancy is that EBV causes B-lymphocyte proliferation. The number of EBV-infected cells can increase as a result of CD8+ T-cell disorders. Given sufficient immunosuppression, several clones of EBV-infected B cells or the best-growing clone may emerge as a lymphoproliferative disease. EBV infection also predisposes to c-myc translocation, and a more malignant cell clone can eventually emerge as a tumor cell in a host with normal immune function.

EBV also causes oral hairy leukoplaikia, a benign proliferation of epithelial cells that occurs in acquired immunodeficiency syndrome (AIDS) patients. The lesions are sites of persistent EBV replication and disappear in response to suppression of EBV replication with acyclovir. 179 As no evidence exists for EBV latency in these lesions, the pathogenesis of oral hairy leukoplaikia may involve secretion of a cytokine from lymphatically infected cells. 180

KAPOSI’S SARCOMA—ASSOCIATED HERPESVIRUS (HUMAN HERPESVIRUS-8)

Kaposi’s sarcoma (KS) is the most common neoplasm associated with AIDS. 181–183 Initially described as a rare and indolent tumor of elderly Mediterranean men, it was later recognized to occur at a higher frequency in Africa. 184–186 KS was documented among immunosuppressed organ transplant recipients. 187 In all cases, the histologic picture of the disease is strikingly similar and highly distinctive. Unlike most tumors, which arise from the clonal outgrowth of a single cell, KS lesions contain many cell types. 188 Advanced lesions contain a predominance of spindle-shaped cells (spindle cells), the histogenesis of which remains uncertain but which are believed to arise from endothelial cells (or a more primitive mesenchymal precursor of such cells). In addition, there are infiltrating mononuclear cells (including plasma cells and monocytomacrophages) and a highly characteristic profusion of slit-like neovascular spaces. The vascularity of the lesion gives KS its distinctive reddish or violaceous appearance.

This complex histology sets KS apart from most other tumors and raises important questions about its pathogenesis. Based on the properties of spindle cells, and KS tissue from AIDS-related KS specimens, many studies have pointed to a key role for growth factors and cytokines in the evolution of a KS lesion. 189–192 In general, such cells are not fully tumorigenic. Most do not produce stable, transplantable tumors in nude mice or grow in soft agar. In fact, they are dependent on exogenous growth factors for their proliferation 193–196 and, in turn, they produce an array of growth factors and angiogenic factors. 197 When transplanted into nude mice, 198,199 they survive only transiently, then involute. However, during their period of viability, they recruit host inflammatory cells and neovascular structures very reminiscent of KS. When the human spindle cells involute, the entire lesion disappears. This suggests a model for KS in which the proliferating spindle cells drive the rest of the lesion via the elaboration of growth and angiogenic factors. The central question then is: What drives the proliferation of the spindle cells?

One early model attempted to relate spindle cell growth to HIV infection. 200–202 Certainly, HIV infection is an enormous risk factor for KS development: The prevalence of KS in AIDS patients is 20,000 times that in the general population and 300 times that observed in other immunosuppressed populations. 203 However, both in vitro and in cell culture, spindle cells do not appear to carry the HIV genome, ruling out direct infection by HIV as the growth-promoting event. Rather, HIV infection is limited to the smaller lymphoid and monocytic cell components of KS. Such HIV-infected cells can be shown in vitro to release factors that promote cultured spindle cell growth, including both cellular cytokines and the HIV tat gene product. 204–206 These observations suggest a plausible mechanism by which HIV infection could drive KS lesion formation without directly infecting the spindle cell.

However, doubts soon arose concerning the ability of HIV infection alone to account for the etiology of KS. First, of course, KS can certainly arise in HIV-negative hosts. More important, even within the HIV-infected population, large differences in KS risk are not accounted for by the preceding formulation. 207–209 KS risk is
highest in homosexual men with AIDS: A full 20% to 30% of such individuals will develop KS in the course of their HIV disease. By contrast, fewer than 1% to 2% of
AIDS cases related to hemophilia (i.e., blood product administration) will be complicated by KS, and KS is rarer still among pediatric AIDS cases in which HIV
infection is acquired vertically from infected mothers. These and other data 231 suggest the possibility of a sexually transmitted cofactor in KS etiology or pathogenesis.
In 1994, Chang et al. 232 used a polymerase chain reaction–based method to identify DNA sequences that were present in DNA extracted from an AIDS-KS specimen
but absent from normal genomic DNA from the same patient. Two small DNA fragments emerged that were shown to be highly correlated with KS: Virtually all
AIDS-KS tumors were positive for these sequences, whereas available tissue specimens from a large number of HIV-negative hosts were negative, as were most
non-KS tissues from patients with KS. Interestingly, approximately 10% to 15% of lymphoid tissues from AIDS patients who did not have KS were also positive,
indicating that the sequences track with both KS and the risk for KS development. Sequence analysis of these two small DNA fragments reveals homology to two
known lymphotropic herpesviruses, human EBV and the simian herpesvirus saimiri (HVS). These seminal findings point to the existence of a novel herpesvirus,
termed KS-associated herpesvirus (KSHV) or human herpes virus-8 (HHV-8), and suggest it as a candidate for the exogenous cofactor earlier predicted by
epidemiologists.
Subsequent work has confirmed these findings and extended them in important ways, all of which are consistent with a role for this virus in KS development. First,
KSHV/HHV-8 sequences are present in virtually all KS specimens from HIV-negative patients with the disease, as well as their HIV-positive counterparts. 233,234,235,236
and 237 Because most HIV-negative KS patients are not grossly immunodeficient, it is unlikely that KSHV/HHV-8 is simply an opportunistic saprophyte that overruns the
profoundly immunodeficient host. In KS tumors, KSHV DNA is found primarily in the spindle cells 238— the key cell type in KS pathogenesis—and active but restricted
viral gene expression consistent with latent infection is demonstrable in the vast majority of these cells. 239,240 In addition, a small subset of the spindle cells appears to
harbor viral genomes undergoing lytic replication. Second, KSHV/HHV-8 sequences have been identified in the peripheral blood mononuclear cells (PBMCs) of 30%
to 50% of KS patients and a much smaller proportion (10% to 15%) of AIDS patients lacking clinical KS. 241 Importantly, in KS-negative AIDS patients, the risk of
subsequent KS development is much greater among patients whose initial PBMC sample harbored KSHV than among those whose PBMCs did not. 241 Thus, viral
infection precedes the development of KS, and prior infection appears to be predictive of increased KS risk.
These early inferences have been sustained by more recent seroepidemiologic studies, which have yielded the following important conclusions. First, KSHV infection
is not ubiquitous; among screened (low-risk) U.S. and European blood donors, only approximately 5% to 7% are seropositive. (This number probably slightly
underestimates the true prevalence of infection in the general population.) However, in HIV-positive populations, seroprevalence tracks very strikingly with KS risk:
While 30% to 60% of HIV-infected homosexual men are KSHV-seropositive, fewer than 5% of HIV-positive hemophiliacs or women show serologic evidence of KSHV
infection, and KSHV seroreactivity is surprisingly rare among U.S. children with AIDS. 242,243,244 and 245 In large prospective studies, KSHV seroreactivity was shown to
antedate the onset of the tumor (often by up to 10 years) and strongly predicted an increased risk of KS development. 246,247 and 248 Studies in male homosexuals in the
United States produced strong evidence for sexual transmission in this group: KSHV seroprevalence rises sharply with increasing numbers of sexual partners and
with histories of other STDs, for example. In a key study, Martin et al. 246 showed that the risk of subsequent KS among KSHV-seropositive individuals was the same
even after normalizing for the prevalence of other STDs. 246 This result indicates that it is KSHV infection itself, not some cotransmitted STD, that is responsible for KS
risk.
These data clearly indicate that KSHV is the agent predicted by KS epidemiology and strongly implicate KSHV in KS pathogenesis. The epidemiologic case for
involvement of KSHV in KS biogenesis now is as compelling as the cases for HBV and hepatoma or HPV and cervical cancer. Given the large number of subjects
studied to date, the evidence supports the assertion that KS is virtually never observed in the absence of documented KSHV infection. Accordingly, most experts in
the field now accept that KSHV is necessary for KS development. However, there is also strong consensus that it is not sufficient for this process. For example, 5% to
7% of the general population in the United States is infected by KSHV, yet this population has no significant KS risk. Clearly, therefore, one or more cofactors, in
addition to KSHV, are required to promote tumorigenesis. In the case of AIDS-KS, of course, that cofactor is HIV, although exactly what HIV contributes to
pathogenesis is much debated. Some argue that HIV's link to KS generation is simply the production of an immunodeficient state; others hypothesize that individual
HIV proteins released from infected cells (specifically tat or HIV-induced host cytokines) participate directly in spindle cell growth deregulation in a paracrine
fashion.226,249,250 Such notions need not, of course, be mutually exclusive. The nature of the cofactors in the HIV-negative forms of KS remains unknown.
Studies of KSHV seroepidemiology conducted in the developing world have yielded additional new insights. First, the prevalence of KSHV in the general population is
remarkably elevated in countries in which classic KS is common. For example, in southern Italy, Sicily, and Sardinia, KSHV antibodies are found in more than 20% of
the general population 251,252; in many populations in sub-Saharan Africa, where classic KS was common even in the pre-AIDS era, 60% to 80% of the population is
seropositive. 253,254,255 and 256 Thus, KS seroprevalence tracks with KS risk even outside of HIV-positive cohorts. However, these numbers also reflect major
epidemiologic differences between KSHV infection in Africa and the Mediterranean, on the one hand, and KS risk in Western Europe and America, on the other. In the
latter countries, homosexual men represent a major reservoir of infection, with much lower rates in women and very little infection in prepubertal children. 257,258 By
contrast, in Africa and the Mediterranean, seroconversions begin in childhood, and the seroprevalence rises nearly continuously throughout the first four to five
decades of life. Moreover, seroprevalence is equal in both genders, in sharp contrast to the developed world. The basis for this strikingly different epidemiology is not
yet understood. The frequent occurrence of infection in young children in the Mediterranean and Africa suggests the existence of nonsexual routes of spread, and the
equal infection rates in adult men and women also suggests different routes of spread from those observed in the West.
How does KSHV infection predispose to KS? Understanding of this association at the molecular level is still fragmentary. Because most KS tumor cells are latently
infected, efforts to identify and characterize KSHV latency genes have been made, presuming, as in EBV, that these genes will play strong roles in spindle cell growth
deregulation. To date, several interesting genes have been identified in this fashion. An important group of latency genes is clustered in one region of the viral
genome, where two transcription units have been mapped. 259,260 One expresses a set of three genes, including (1) LANA, an antigen that appears to function in KSHV
genomic maintenance in latency,261 (2) a viral homologue of cellular cyclin D1, and (3) a homologue of cellular inhibitors of caspase activation (Flice-inhibitory
protein). The viral cyclin can bind and activate cdk6, indicating that it is a functional cyclin. 262,263 It appears to display reduced sensitivity to the inhibitory effects of
certain cdk inhibitors. 264,265 and 266 It is easy to imagine how such a gene might figure in growth deregulation, especially given the known links between deregulation of
cellular cyclin D1 and several forms of human cancer. 267 The viral Flice-inhibitory protein presumably functions to block apoptosis—a potentially important activity, as
overexpression of viral cyclin sensitizes cells to apoptosis. 268 A second transcription unit encodes a family of related proteins, the kaposins, which are generated by a
complex translational strategy. 269 Their transcripts are used widely to identify latently infected cells, 270,271 but the functions of their gene products remain unknown.
Remote from these genes, at the right-hand terminus of the genome, is a coding region for a multiply spliced transcript encoding a series of transmembrane proteins
called latency-associated membrane proteins (LAMPs).272,273 These proteins contain a variety of motifs suggestive of roles in cellular signal transduction and can bind
tumor necrosis factor receptor–associated factors (TRAFs) 1, 2, and 3 in vitro, but their in vivo roles remain to be defined. 272
As noted, KS tumors also harbor smaller numbers of lytically infected cells. 270,274 The significance of lytic infection in KS tumorigenesis is unknown, but there are
reasons to believe that the lytic cycle may play a more profound role in KS than in other herpesvirus-induced malignancies. First, a recent clinical trial has shown that
even in patients with advanced AIDS, treatment with ganciclovir, which is active only against lytic herpesvirus infection, profoundly reduced the subsequent
development of KS over the ensuing 6 to 12 months. 275 Although this result might mean simply that lytic reactivation from the lymphoid reservoir is necessary for
spread to the endothelium to initiate latent infection there, it is also compatible with a requirement for ongoing KSHV replication in KS pathogenesis. The latter is an
attractive notion, because the virus contains numerous genes that are potent signaling molecules expressed principally during lytic growth. 276,277 and 278 Some of these
are secreted factors (e.g., homologues of interleukin-6, chemokines, and other factors), whereas others (e.g., the K1 protein and a virus-specific G protein–coupled
receptor) are transmembrane proteins that trigger deregulated signal transduction in the host, often leading to secretory products that can influence surrounding
cells. 279,280 and 281 For example, virus-specific G protein–coupled receptor expression induces the release of vascular endothelial growth factor, 282 a protein long
speculated to play a role in the angiogenic phenotype of KS. Some of the viral chemokines can trigger angiogenesis as well 283; moreover, these molecules would be
expected to contribute to the influx of inflammatory cells in the lesion, another hallmark of KS. Defining the relative contributions of latency and lytic growth to KS
pathogenesis will be a major focus of KSHV research in the coming decade.
The homologies to EBV and the simian herpesvirus saimiri place KSHV/HHV-8 within the lymphotropic herpesvirus subfamily, an assignment supported by the finding
of viral DNA in the B-cell compartment of the PBMC population. 237 This raises the possibility that the virus might participate in lymphoid neoplasia as well and, in
recent years, viral infection has in fact been associated with at least two lymphoproliferative conditions. The first is a rare B-cell lymphoma, termed body cavity–based
lymphoma, that has thus far been limited to HIV-positive hosts. 284 It presents as ascitic tumors in the pleural and peritoneal cavities, often without clinically evident
lymphadenopathy or bone marrow involvement. Body cavity–based lymphoma cells are uniformly latently infected with HHV-8; many (but not all) also bear latent EBV
genomes. Cultured B-cells derived from such tumors are latently infected and, in some of these cells, lytic viral replication can be induced in vitro with phorbol
esters.285 The other lesion associated with HHV-8 is multicentric Castleman's disease (MCD), a complex and poorly understood lymphoproliferative syndrome that can
occur in both HIV-positive and HIV-negative individuals. The HIV-positive form appears to be uniformly associated with KSHV/HHV-8, whereas only approximately half




CHAPTER 11
Etiology of Cancer: Chemical Factors

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INTRODUCTION

The chemical origin of human malignancies was recognized by observations of unusual cancer incidences in persons in certain occupational groups. The capacity for chemicals to cause cancer was subsequently confirmed in numerous experimental animal studies. The extent to which chemical exposures contribute to cancer incidence was not appreciated fully until population-based studies documented differing organ-specific cancer rates among geographically distinct populations. Changes in cancer frequency among migrating ethnic groups, high cancer rates associated with specific occupations, and the high risk of smoking-associated cancers confirmed that environmental and lifestyle exposures were major determinants of human cancer risk. Current data indicate that changing lifestyles and exposures can modify cancer risk. Individual genetic factors also can influence cancer risk in several ways. In hereditary cancer syndromes, genetic factors dictate a very high cancer risk for a small group of individuals. However, the general population carries hereditary susceptibility genes that increase cancer risk for particular exposures. Thus, most human cancer is not simply a genetically determined sequela of aging but rather the manifestation of personal and cultural behavior superimposed on individually determined hereditary susceptibility.

The experimental induction of tumors in animals, neoplastic transformation of cultured cells by chemicals, and analysis of environmentally induced human tumors have revealed important concepts regarding the pathogenesis of cancer. Often, chemical carcinogens are organ-specific, target epithelial cells, and cause genetic damage (i.e., are genotoxic). Chemically related DNA damage can occur either directly from environmental exposures or indirectly by activation of endogenous mutagenic pathways (e.g., nitric oxide and oxy radicals). Most chemically induced tumors are clonal in origin and require an accumulation of genetic changes in a multistage progression from normal to premalignant to carcinoma. The risk of developing a chemically induced tumor may be modified by nongenotoxic exogenous and endogenous exposures and factors and by accumulated exposure to the same or different genotoxic carcinogens. Somatic mutations relevant to cancer pathogenesis have been documented after carcinogen exposures in experimental animals and humans, and pathways for carcinogen metabolism have defined a set of genetic variables that contribute to human cancer risk. Studies with cultured rodent and human cells confirm the remarkable qualitative similarities among mammalian species for responses to carcinogens but also have revealed some important quantitative differences that have enhanced our understanding of chemical carcinogenesis in human populations.

Analysis of the chemical induction of cancer in animal models and human populations has had a major impact on human health. Experimental studies have been instrumental in validating hypotheses generated from human studies. Animal experiments confirmed the carcinogenic and tumor-promoting properties of cigarette smoke and identified the active chemical and gaseous components. The transplacental carcinogenicity of diethylstilbestrol and the hazards of specific occupational carcinogens [e.g., vinyl chloride, benzene, aromatic amines, and bis (chloromethyl) ether] led to the removal of the suspected human carcinogens from the environment and reduction of the cancer rate. Dietary factors that enhance or inhibit cancer development have been identified in models of chemical carcinogenesis, resulting in a reduction of cancer incidence through nutritional alterations. The application of cancer chemoprevention strategies, particularly retinoids, antiestrogens, and inhibitors of the arachidonic acid cascade, are the direct result of studies conducted in models of chemical carcinogenesis and are reducing the tumor incidence in high-risk chemical populations.

THE NATURE OF CHEMICAL CARCINOGENS: CHEMISTRY AND METABOLISM

A wide variety of chemicals and chemical classes can cause cancer in animals and humans, yet the process is very specific. Most chemicals are not known to be carcinogenic. Within chemical classes, stereoisomers may vary widely in carcinogenicity. Carcinogens can be genotoxic, nongenotoxic, or both. Sometimes, the distinction is arbitrary. Genotoxic carcinogens have high chemical reactivity (such as alkylating agents) or can be metabolized to reactive intermediates by the host. They form covalent adducts with macromolecules and target DNA in the nucleus and mitochondria. Because a good correlation exists between the ability to form DNA adducts and the potency to induce tumors in laboratory animals, DNA is considered the ultimate target for most carcinogens. Genotoxic carcinogens may transfer simple alkyl or complexed (aryl) alkyl groups to specific sites on DNA bases (Fig. 11-1) as exemplified by aryl aromatic amines, aminoazodyes, and heterocyclic aromatic amines; the latter are produced by cooking meat, poultry, or fish at high temperatures. For genotoxic carcinogens, the interaction with DNA is not random, and each class of agents reacts selectively with purine and pyrimidine targets (Fig. 11-1). Furthermore, targeting of carcinogens to particular sites in DNA is determined by nucleotide sequence, by host cell, and by selective DNA repair processes, rendering some genetic material at risk over others. As expected from this chemistry, genotoxic carcinogens are potent mutagens, particularly adept at causing base mispairing or large deletions and leading to missense or nonsense mutations. Others may cause macrogenetic damage, such as chromosome breaks and large deletions. In all cases, mutations detected in tumors represent a combination of the effect of the mutagenic change on the function of the protein product and the effect of the functional alteration on the behavior of the specific host cell type.

FIGURE 11-1: A: Metabolic activation to yield DNA-reactive alkylating, arylaminating, and aralkylating agents. Ar is an aromatic residue, X is a leaving group, and SG represents a glutathione residue. B: Sites of substitution of DNA bases by genotoxic carcinogens. Sites modified by alkylating agents are marked by the numeral i, those modified by arylaminating agents are marked by a II, and those modified by polycyclic aralkylating agents are marked by a III. Because C8-substituted arylamine adducts have been suggested to have arisen from N7-substituted precursors, the arylaminating agents are listed parenthetically at the 7-position of the purines. (Reproduced by permission of the author, Dr. Anthony Dipple, and the publisher, Oxford University Press, from Carcinogenesis 1995;16:437.)
A number of chemicals that cause cancers in laboratory rodents are not demonstrably genotoxic. Synthetic pesticides and herbicides fall within this group, as do a number of natural products that are ingested. In general, these agents are carcinogenic at high doses in laboratory animals and require prolonged exposure. The mechanism of action by nongenotoxic carcinogens is controversial and may be related in some cases to toxic cell death and regenerative hyperplasia. Induction of endogenous mutagenic mechanisms, such as DNA oxy radical damage, depurination, and deamination of 5-methylcytosine by exposure to nongenotoxic carcinogens, may contribute to carcinogenicity of these agents. In other cases, nongenotoxic carcinogens may have hormonal effects, influencing hormone-dependent tissues directly. Though the contribution of nongenotoxic carcinogens to human cancer causation is not certain, they may serve also as modifiers in concert with genotoxic agents.

A number of metabolic pathways activate or detoxify carcinogens and procarcinogens (chemicals that can be transformed into active carcinogens). These pathways are complex and interactive (Table 11-1), and genetic polymorphisms in animal models and humans are thought to be major determinants of cancer susceptibility. In general, metabolic activation of carcinogens involves oxidation at carbon-carbon double bonds or saturated carbon atoms, in the latter case often requiring a further esterification (see Fig. 11-1). Oxidation at nitrogen on aromatic amines or reduction at nitrogen of aromatic nitro compounds yields reactive intermediates that transfer an aryamine residue to DNA. An esterified intermediate may be required, as in the case of heterocyclic amine carcinogens. Conjugations are also frequent intermediates of metabolism of many carcinogens and can be both activating and detoxifying pathways (see Fig. 11-1). The importance of metabolic activation to carcinogenesis and the polymorphic nature of metabolic activity among individuals provides an approach to estimate individual risk profiles for particular exposures. Furthermore, a number of metabolic pathways are inducible (see Table 11-1) and modified by diet, hormones, and additional exposures, adding further complexity to the process of carcinogenesis.

### TABLE 11-1. Enzymatic Pathways of Carcinogen Metabolism in Experimental Animals and Humans

#### ANIMAL MODEL SYSTEMS AND MULTISTAGE CARCINOGENESIS

Virtually every major form of human cancer can be reproduced in experimental animals by exposure to specific chemical carcinogens. In many cases, the cell of origin, morphogenesis, phenotypic markers, and genetic alterations are qualitatively identical to corresponding human cancers (Table 11-2). Animal models have demonstrated the modifying effect of tumor promoters and hormones or cofactors, such as asbestos or viral infections. Furthermore, animal models have revealed the constancy of carcinogen-host interaction among mammalian species by reproducing organ-specific cancers in animals with chemicals identified as human carcinogens, such as coal tar and squamous cell carcinomas, vinyl chloride and hepatic angiosarcomas; aflatoxin and hepatocarcinoma; and aromatic amines and bladder cancer. These results validate the qualitative value of animal models in carcinogenesis research and support the extrapolation of data from experimental studies to human applications with specific limitations. The introduction of genetically modified mice designed to reproduce specific human cancer syndromes has accelerated both the understanding of the contributions of chemicals to cancer causation and the identification of potential exogenous carcinogens.

### TABLE 11-2. Animal Models for Chemical Carcinogenesis

From analyses of both human cancer pathogenesis and experimental animal tumor induction by chemical carcinogens, specific stages that have been identified have typical phenotypic, genetic, and biochemical characteristics (Fig. 11-2). However, in reality, these stages are not distinct, and steps to cancer do not follow a straight line. Mutations in single cells frequently “initiate” carcinogenesis. On clonal expansion, initiated cells form a premalignant lesion, often a benign tumor (e.g., an adenoma) but also recognized as hyperplastic or dysplastic foci in some tissue sites. Agents that cause clonal expansion of initiated cells are called tumor promoters. Tumor promotion may occur as a consequence of exogenous exposures, such as cigarette smoke or viral infections. Promotion may be an endogenous process, such as hormonal stimulation in breast and prostate cancer or bile salts in colon cancer. Premalignant lesions undergo further phenotypic changes, often in a predictable sequence and commonly multifocal within a single lesion. Some foci progress at a faster rate than others, and these are at highest risk for malignant conversion. Premalignant progression encompasses the majority of the tumor latency period prior to malignant conversion, when the lesion shows invasive properties.
usually initiation involves an alteration in signal transduction pathways that regulate cellular responses to extracellular signals, and these are internally regulated by protooncogenes and tumor suppressor genes. Mutational activation of protooncogenes to oncogenes and inactivation of tumor suppressor genes contribute to initiation in most tumor systems.

Usually, experimental tumor promoters are nongenotoxic and frequently are tissue-specific and have multiple mechanisms of action, generally resulting in a disturbance of tissue homeostasis. The mechanisms of tumor promotion include activation of cell-surface receptors; activation or inhibition of cytosolic enzymes and proteins in the susceptibility to spontaneous and chemically induced carcinogenesis at specific tissue sites. Furthermore, carcinogenesis experiments in spontaneous mutant strains or genetically modified mice created by transgenic or knock-out technology have identified specific loci that modify cancer risk. For a variety of tissue sites, including lung, liver, breast, and skin, pairs of inbred mice that differ by 100-fold in risk for tumor development have been characterized. Detailed analyses of these differences using backcross, recombinant inbred, and recombinant congenic breeding protocols have shown specific determinants for initiation, promotion, premalignant progression, and metastatic stages. In most cases, susceptibility or resistance is a property of the target tissue, not the host. Genetically determined differences in the affinity for the aryl hydrocarbon hydroxylase (Ah) receptor or other differences in metabolic processing of carcinogens is one modifier that has a major impact on experimental cancer risk. Other loci regulate the growth of premalignant foci, the response to tumor promoters, the immune response to metastatic cells, and the basal proliferation rate of target cells. In mice susceptible to colon cancer due to a constitutive mutation in the K-ras gene, a locus on mouse chromosome 18 confers resistance to colon cancer. Similarly, an autosomal dominant locus in the rat genome protects susceptible rats from chemically induced mammary gland neoplasia. Recent advances in mapping of the mouse and rat genome promise to provide precise localization and identification of the loci involved in experimental carcinogenic sensitivity, and translation of this information to syntenic loci of the human genome should provide important insights into human susceptibility traits.

**PROTECTION AGAINST CHEMICAL CARCINOGENS: DNA REPAIR, TUMOR SUPPRESSOR GENES, AND TRANSFORMING GROWTH FACTOR-b**

DNA repair defects have been identified in a number of cancer-prone individuals, and repair-deficient mammalian cells are susceptible to transformation by chemical and physical carcinogens. Commonly, nucleotide excision repair removes carcinogen-DNA adducts or ultraviolet photoproducts by a complex process that involves at least 10 gene products, each potentially associated with mutations leading to human DNA repair defect syndromes and increased cancer rates. Nucleotide excision repair commonly favors adduct removal on the transcribed strand to protect protein synthesis, but damage from some mutagens does not exhibit strand bias. Genetically engineered mice deficient in genes involved in nucleotide excision repair are particularly sensitive to chemical and ultraviolet carcinogenesis at particular organ sites. The highly mutagenic O6-methylguanine, a consequence of exposure to certain methylating agents (see Fig. 11-1), is repaired by O6-alkyldeoxyguanosine-DNA alkyltransferase. Overexpression of this enzyme in transgenic mice protects the host from thymic lymphomas, colon neoplasia, and mouse K-ras mutations after exposure to methylating agents. O6-alkyldeoxyguanosine-DNA alkyltransferase activity varies in different tissues and cell types, and the enzyme can be inhibited by exogenous exposures that may act as cofactors in carcinogenesis. Recently, interest has focused on a multicistronic nucleic mismatch repair system designed to repair mismatched bases after replication. Mutations in components of this pathway increase risk for colon cancer in humans, and engineered mice that are null for a gene in this pathway are predisposed to develop tumors.

Tumor suppressor genes represent a growing family of regulators of the cell cycle, genomic stability, cell senescence, cell death, or cell-cell communication that are inactivated during carcinogenesis. Some may be direct targets of carcinogens, such as the PS3 gene in liver and the K-ras gene in lung cancer, whereas others may become spontaneously altered during premalignant progression or may be suppressed by promoter methylation. Suppressor genes can be inactivated by structural gene changes, but genomic imprinting, reduction in stability of the protein product, or mutations with a dominant-negative effect that suppresses the function of the normal allele is more likely to result from a genetic event (in which case inactivating mutations at multiple sites may cause inactivation) occurs commonly, because it is a high probability event than is activation of an oncogene (in which specific changes at a few selected sites are required). However, a dominant effect of a tumor suppressor gene loss requires inactivation of both alleles (e.g., the combination of a point mutation in one allele and chromosome loss of the second allele). Certain carcinogenic hazards, such as ionizing radiation, metals, carcinogenic hormones, and fibers, frequently cause chromosomal abnormalities and may contribute to carcinogenesis through inactivation of suppressor genes.

A unique role in tumor suppression is developing for the growth inhibitory peptide, transforming growth factor-b (TGF-b). Frequently, the regulation of this family of homodimeric growth inhibitors is altered in tumors as they undergo premalignant progression. Dysregulation takes the form of loss of expression, inactivation of the type II receptor and the type I receptor, or reduction in responsiveness of tumor cells. Inactivating mutations in the TGF-b type II receptor or the type I receptor are associated with constitutively active TGF-b receptors in many tumors. The mechanisms of tumor promotion include activation of cell-surface receptors; activation or inhibition of cytosolic enzymes and proteins in the susceptibility to spontaneous and chemically induced carcinogenesis at specific tissue sites. Furthermore, carcinogenesis experiments in spontaneous mutant strains or genetically modified mice created by transgenic or knock-out technology have identified specific loci that modify cancer risk. For a variety of tissue sites, including lung, liver, breast, and skin, pairs of inbred mice that differ by 100-fold in risk for tumor development have been characterized. Detailed analyses of these differences using backcross, recombinant inbred, and recombinant congenic breeding protocols have shown specific determinants for initiation, promotion, premalignant progression, and metastatic stages. In most cases, susceptibility or resistance is a property of the target tissue, not the host. Genetically determined differences in the affinity for the aryl hydrocarbon hydroxylase (Ah) receptor or other differences in metabolic processing of carcinogens is one modifier that has a major impact on experimental cancer risk. Other loci regulate the growth of premalignant foci, the response to tumor promoters, the immune response to metastatic cells, and the basal proliferation rate of target cells. In mice susceptible to colon cancer due to a constitutive mutation in the APC gene, a locus on mouse chromosome 18 confers resistance to colon cancer. Similarly, an autosomal dominant locus in the rat genome protects susceptible rats from chemically induced mammary gland neoplasia. Recent advances in mapping of the mouse and rat genome promise to provide precise localization and identification of the loci involved in experimental carcinogenic sensitivity, and translation of this information to syntenic loci of the human genome should provide important insights into human susceptibility traits.

**GENETIC SENSITIVITY TO CHEMICAL CARCINOGENESIS IN EXPERIMENTAL MODELS**

The identification and characterization of genes that modify risks for cancer development have been facilitated by substantial variation among inbred strains of mice, in their susceptibility to spontaneous and chemically induced carcinogenesis at specific tissue sites. Furthermore, carcinogenesis experiments in spontaneous mutant strains or genetically modified mice created by transgenic or knock-out technology have identified specific loci that modify cancer risk. For a variety of tissue sites, including lung, liver, breast, and skin, pairs of inbred mice that differ by 100-fold in risk for tumor development have been characterized. Detailed analyses of these differences using backcross, recombinant inbred, and recombinant congenic breeding protocols have shown specific determinants for initiation, promotion, premalignant progression, and metastatic stages. In most cases, susceptibility or resistance is a property of the target tissue, not the host. Genetically determined differences in the affinity for the aryl hydrocarbon hydroxylase (Ah) receptor or other differences in metabolic processing of carcinogens is one modifier that has a major impact on experimental cancer risk. Other loci regulate the growth of premalignant foci, the response to tumor promoters, the immune response to metastatic cells, and the basal proliferation rate of target cells. In mice susceptible to colon cancer due to a constitutive mutation in the APC gene, a locus on mouse chromosome 18 confers resistance to colon cancer. Similarly, an autosomal dominant locus in the rat genome protects susceptible rats from chemically induced mammary gland neoplasia. Recent advances in mapping of the mouse and rat genome promise to provide precise localization and identification of the loci involved in experimental carcinogenic sensitivity, and translation of this information to syntenic loci of the human genome should provide important insights into human susceptibility traits.

**DETERMINATION OF CHEMICAL CARCINOGENS FOR HUMANS AND POPULATION-BASED RISK ASSESSMENT**

Current understanding of carcinogenesis and risk to human health comes from a variety of models and methods, including mutagenesis assays, mammalian cell culture experiments, animal studies, and both classic and molecular epidemiology. The goal of these studies is to elucidate cancer etiologies, to define cancer risk factors, and to identify chemopreventive agents that can reduce the risk of cancer.
risks in humans (population and individual), and to identify more rational cancer prevention methods. Physicians are challenged when they attempt to determine what causes a cancer in a particular individual. The determination process requires an accurate history and physical examination and interpretation of research data. Often, the latter are beyond the scope of the practitioner and, in many cases, beyond the current state of knowledge. Nevertheless, methods for cancer risk assessment have been proposed and resources are available. Several types of study models are used to assist in elucidating carcinogenic mechanisms and identifying potential human carcinogens. The usefulness of each method for identifying carcinogenic mechanisms and for identifying cancer risk can be contrasted with its limitations (Table 11-3). A direct relationship of in vitro experimental studies (i.e., metabolic activation of chemicals by cytochrome P-450s), in vitro mutagenicity tests, experimental animal studies, and human epidemiology has not been proved, but most chemicals that are positive in one method generally are positive with other methods. Nevertheless, 100% concordance does not exist; though sensitivity is high, specificity is low. It may be that consideration of multiple assays yields greater productivity, but this is not yet proved, and the concordance from animal to human experience is variable, although carcinogens that are more potent in one species tend to be more potent in others, including humans.

TABLE 11-3. Testing for Carcinogenicity

Human investigations provide the most relevant data regarding human risk. Classic epidemiology measures the incidence or prevalence of disease in human populations. Epidemiologic studies have identified such previously unknown risks as asbestos-related pleural mesothelioma, benzene-induced leukemia, and bladder cancer in dye workers. Study design and controlling for confounding variables are important to the evaluation of a true association. It must be realized that epidemiologic methods, by themselves, do not demonstrate causation, and specific guidelines for assessing causation are available (Table 11-4). The concordance between different scientific methods for inferring human cancer risk is variable.

TABLE 11-4. Evaluating Cancer Etiology: Bradford-Hill Criteria

Physicians can look to various regulatory, governmental, or review organizations for extensive evaluation of the scientific literature. Some organizations generate documents that report findings of experts who critically review the scientific literature, whereas others simply summarize data from other organizations. Several lists of carcinogens also have been published, but the evaluations of the literature and the definitions can vary greatly among organizations. Physicians should be aware of the purposes and goals of an organization when requesting its information. For example, the National Institute for Occupational Safety and Health and the American Council of Governmental Industrial Hygienists are concerned primarily with occupational exposures. The Environmental Protection Agency is concerned primarily with environmental exposures, quantitative risk assessments, and regulations relating to health hazard prevention for the entire population. The International Agency for Research on Cancer and the National Toxicology Program do not limit themselves to occupational or environmental exposures. The Agency for Toxic Substances and Disease Registry was created to study persons exposed to environmental toxins and to evaluate the adequacy of scientific literature. The known and potential human carcinogens, as reported by various regulatory and research organizations, are listed in Table 11-5.

TABLE 11-5. Known or Suspected Chemical Carcinogens in Humans

A formal quantitative risk assessment is used by regulatory agencies to estimate the risk to a population exposed to a particular carcinogen at a specific dose. Risk assessments serve public health interests as they attempt to predict the frequency of cancer in a population before epidemiologic investigations can be performed (i.e., before significant exposure and adverse outcomes occur). Risk estimates are formulated for potential dietary, airborne, and workplace carcinogens. Several mathematical models are used by various regulatory bodies to predict risks and to regulate allowable exposures. Risk assessments include four general steps: (1) hazard assessment, which qualitatively reviews scientific literature to decide whether a hazard might exist; (2) dose-response assessment, which evaluates the doses used in scientific studies and relates them to human exposures; (3) exposure assessment, which examines a population thought to be at risk regarding the quantity, duration, and routes of exposure; and (4) risk characterization, which incorporates the foregoing information and evaluates the assumptions used and the uncertainties to estimate risk. The modeling process requires many assumptions that are open to debate, and safety factors are incorporated to compensate for the uncertainties. At the conclusion, an incidence of cancer will be predicted, such as one additional case in 1 million persons. Owing to methodological limitations and uncertainties, wide confidence limits often prevail for the prediction.

MOLECULAR EPIDEMIOLOGY OF CANCER RISK FROM CHEMICALS
The field of molecular epidemiology seeks to identify cancer risk on the basis of individual exposures and genetically determined susceptibilities to cancer. Cancer epidemiology differs from traditional epidemiology because of its complexity. Traditional epidemiology paradigms implicate single causative agents that cause specific diseases (i.e., demonstrated through Koch’s postulates). However, cancer is caused by multiple agents, and different combinations of agents can cause the same cancer. Conversely, the same agents might contribute to the development of different cancers. Molecular approaches to epidemiology use a priori hypotheses and biomarkers, rather than simply seeking associations between an exposure and disease (Fig. 11-3). Two fundamental principles underlie current studies of molecular epidemiology. First, carcinogenesis is a multistage process, and behind each stage are genetic events and complex pathways that may be responsible for these events. Thus, characterizing a specific risk factor against a background of many risk factors is difficult for scientists and can limit statistical power. Second, wide interindividual variation in response to carcinogen exposure and carcinogenic processes indicate that the human response to carcinogens is not homogeneous; hence, other studies (e.g., the use of a single-cell clone to study a gene’s effect experimentally or the assumption that the population responds similarly to the mean in epidemiology studies) might not be representative of susceptible and resistant groups within a population.

**Fig. 11-3.** Schematic model depicting the range (from exposure to effect) and types of biomarkers that might be used for cancer risk assessments. Aflatoxin-B₁ is shown as a paradigm for the range of biomarkers. CAT, computer-assisted tomography.

The carcinogenic process is driven by genetic events (mutations or epigenetic changes), and in most people they are triggered by environmental exposures modified by host susceptibility. These are so-called gene-environment interactions. Cancer-causing genes can be categorized into caretaker and gatekeeper genes. Caretaker genes are involved in maintaining genomic integrity, such as those of DNA repair and carcinogen detoxification. Gatekeeper genes are involved in normal cellular function, such as those that are involved in cell-cycle control or apoptosis. Also, given that cancers are caused by multiple exposures causing damage in different genes, now the carcinogenic process is being considered as gene-environment interactions. This new paradigm will lead to different perspectives of cancer genetics and cancer risk factors, wherein some genetic effects will be modeled differently (see Fig. 11-2).

**EXPOSURE ASSESSMENT AND INTERNAL DOSIMETRY**

Chemicals cause genetic damage in different ways: formation of carcinogen-DNA adducts leading to base mutations or bringing about gross chromosomal changes. Carcinogen-macromolecular adducts are formed when a mutagen, or part of it, irreversibly binds to DNA so that it can cause a base substitution, deletion, or translocation during DNA replication. Gross chromosomal mutations are chromosome breaks, gaps, or translocations. The level of DNA damage is the biologically effective dose in a target organ, and reflects the net result of carcinogen exposure, activation, lack of detoxification, lack of DNA repair, and loss of programmed cell death or necrosis.

A variety of assays are available to identify carcinogen-macromolecular adducts in human tissues. These assays include the 32P-postlabeling assay-nucleotide chromatography, immunohistochemistry, fluorescence spectroscopy, gas chromatography–mass spectrometry, and electrical chemical detection. Each has its usefulness and limitations, and all are challenged by sensitivity or specificity (or both). The effect of an individual’s metabolism on carcinogen-DNA adduct formation might be different at different levels of exposure—where adduct levels formed from lower exposures are relatively higher—and to similar person with decreased metabolic capacity but higher exposures. The relationship of such surrogate markers as carcinogen-DNA adducts in blood to the target organ has been studied partially but is not yet well established, and the use of target organs can provide specific information about potentially carcinogenic effects.

The detection of gross chromosomal changes in normal-appearing cells is technically difficult. Presumed surrogate measures of chromosomal damage include the estimate of sister chromatid exchanges or baseline gross chromosomal changes. The latter has been associated with increased cancer risk, but these studies have significant limitations.

The effect of some potential carcinogens has been studied extensively using molecular epidemiological tools. These carcinogens tend to be present in tobacco smoke and, in some cases, diet and workplace.

Commonly, people are exposed to N-nitrosamine and other N-nitroso compounds from diet and tobacco exposures, which are associated with DNA adduct formation and cancer in laboratory animals. Exposure can occur through endogenous formation of N-nitrosamines from nitrates in food or directly from dietary sources, cosmetics, drugs, household commodities, and tobacco smoke. The greatest source of exposure in the United States is from processed meats and (until recently) beer. Endogenous formation occurs in the stomach from the reaction of nitrosatable amines and nitrate, used as a preservative, which is converted to nitrates by bacteria. Host capacity to form N-nitrosamines is associated with risk of stomach and esophageal cancer. It has been shown also that coadministration of vitamin C can reduce the rate of endogenous nitrosation. N-nitrosamines undergo metabolic activation by cytochrome P-450 (CYP2E1, CYP2D6, and CYP2D6) and form DNA-adducts that have been identified in target tissues or have been associated with specific cancers.

Exposures to polycyclic aromatic hydrocarbon (PAH) compounds are associated with an increased risk of lung and skin cancer. Industrial pollution, fossil fuels, and tobacco smoke account for the major environmental sources, although diet is considered the major source. PAH-adducts can be formed from the consumption of charcoal-broiled foods, where adduct levels exceed those from smoking.

Substantial data implicate aromatic amines and amides in human carcinogenesis. Aromatic amines have been implicated in bladder carcinogenesis, especially in occupationally exposed cohorts (e.g., dye workers) and tobacco smokers. Some of the largest carcinogenic occupational exposures occur in the dye industry. Initially, aromatic amines are activated by CYP1A2, which ultimately leads to the formation of nitrenium ion that then forms a DNA adduct. N-acetyltransferase-1 and N-acetyltransferase-2 (NAT-2) play an activating or detoxifying role, depending on the alyl amine. Generally, internal dosimetry for the chemicals has focused on hemoglobin rather than on DNA adducts. Levels are higher in smokers than in nonsmokers, and different types of tobacco can lead to higher adduct levels.

Other mutagenic aromatic amines are heterocyclic amines. They are formed from the cooking of meat, poultry, and fish as a result of the condensation of amino acids and creatine during pyrolysis. Some are present also in cigarette smoke. Levels of exposure typical for humans produce DNA adducts at the C8 position of guanine and are associated with cancers in experimental animals. Heterocyclic amines, estimated as consumption of well-done meat, have been associated with breast and colon cancer.

Aflatoxins are suspected human liver carcinogens and are considered to be a major contributor to liver cancer in China and parts of Africa. Aflatoxin remains one of the best examples of the range and use of biomarkers for cancer risk (see Fig. 11-3). The primary adduct formed from aflatoxin exposure is to the N7 position of guanine. The metabolic activation in humans is similar to that of sensitive laboratory animals. Urinary aflatoxin adduct levels vary among regions of the world, depending on dietary exposures. Serum albumin adducts correlate with dietary intake and urinary excretion of the M1 metabolite. Important is that urinary aflatoxin adduct levels correlate with the incidence of hepatocellular carcinomas, and an interaction is seen with hepatitis B infection.
GENETIC SUSCEPTIBILITY

The cancer risk from genetic variation can range from small to large, depending on its penetrance. Highly penetrant cancer susceptibility genes cause familial cancers and account for fewer than 1% of all cancers. Low-penetrant genes cause common sporadic cancers, which have large public health consequences. Table 11-6 lists several investigated genetic polymorphisms and their association with cancer risk. A genetic polymorphism is defined as a genetic variant present in at least 1% of the population.

<table>
<thead>
<tr>
<th>Genes</th>
<th>Description</th>
<th>References</th>
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<tbody>
<tr>
<td>GSTM1</td>
<td>Detoxifying enzyme</td>
<td>118, 119</td>
</tr>
<tr>
<td>CYP1A1</td>
<td>Metabolism of polycyclic aromatic hydrocarbons</td>
<td>120, 121</td>
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Lung cancer has been studied as the most extensively for gene-environment interactions. Among the low-penetrant genes studied most commonly are cytochrome P-450 (CYP1A1) and glutathione S-transferase M1 (GSTM1). The CYP1A1 enzyme is the first step in the metabolic activation of polycyclic aromatic hydrocarbons, which are known human lung and skin carcinogens. Studies of Japanese subjects indicated an interaction between a CYP1A1 polymorphism and smoking for lung cancer risk, wherein the combination of the homozygous minor allele and smoking yielded odds ratios similar to having one of the other genotypes and a greater smoking history. Western studies, however, do not show the same association. Western GSTM1 is a detoxifying enzyme that catalyzes the conjugation of PAHs to glutathione. Expression of GSTM1 is inherited as an autosomal dominant trait, and the cause of low GSTM1 activity is an entire gene deletion of GSTM1. Phenotypically and genetically, this polymorphism has been related to lung cancer risk. Gene-gene interactions for CYP1A1 and GSTM1 have been found in ongoing Japanese studies of lung cancer. Also, the “at-risk” genotype conferred a higher probability for presenting with more extensive cancer, and the combined genotypes yielded a shorter survival time. The lack of GSTM1 activity has been associated also with increased PAH-DNA adducts in human lung tissue, increased sister chromatid exchange, and production of mutagenic intermediates by lung microsomes.

Breast cancer clearly is related to endogenous and exogenous estrogens, but these factors explain less than one-half of the excess risk, and certain reasons implicate nonhormonal chemical etiologies. Thus, the role of exogenous chemicals is being studied actively. For hormonal etiologies, variation in estrogen metabolism by cytochrome P-450 (CYP1A1, CYP1B1, CYP1A2, CYP17) and other genes can be hypothesized to affect hormonal levels, resulting in altered cell proliferation or DNA damage and subsequent cancer risk. One study has implicated cytochrome 17, whereas others have provided conflicting evidence for catechol-O-methyltransferase that detoxifies estradiol. For chemical etiologies, aromatic amines have been implicated as potential human breast carcinogens. These chemicals are detoxified by NAT-2, in which a genetic polymorphism governs the metabolism of isoniazid for tuberculosis treatments. One study indicated that tobacco smoking is associated with breast cancer in white postmenopausal women who have a decreased capacity to detoxify aromatic amines, because they are NAT-2 slow acetylators. Although a prospective study of nurses seemingly provided conflicting data, differences were found in data analysis and study size. A specific role for polycyclic aromatic hydrocarbons in breast cancer, some suggestions posit that one polymorphic variant of CYP1A1 might be a risk factor for breast cancer in subsets of smokers, whereas another polymorphism might be a risk factor in African Americans. A nested case-control study from a prospective cohort of women in Maryland found a 2.1-fold increased risk for women who lacked GSTM1, although two studies have not found similar results. The role for genetic determinants of carcinogenic metabolism in cancer risk is established for other cancers, although this area of study is newer. Several studies have implicated deficient GSTM1 and NAT-2 detoxification of smoke-related or occupational carcinogens in bladder cancer. For colon cancer, studies have demonstrated that risk increases for NAT-2 rapid acetylators, wherein, in contrast to its detoxification role in bladder and breast cancer, evidence suggests that NAT-2 works to activate heterocyclic amines formed from the overcooking of meats.

Genetic polymorphisms for housekeeping genes controlling such cellular functions as cell-cycle control and DNA repair logically may affect cancer risk. In the general population, DNA repair capacity in humans decreases with aging, which would make this decrease an acquired risk factor for cancer and might explain a portion of the increased cancer risk in the elderly. However, inherited susceptibilities via specific genetic polymorphisms that affect the efficiency of DNA repair, such as for nucleotide excision repair, are largely unknown. A nonspecific DNA repair assay that measures chromosomal aberrations in human cultured lymphocytes after an in vitro challenge with a mutagen has shown initial promise. An increased mutagen-related aberration rate has been observed in persons with primary and secondary upper aerodigestive tract cancers, multiple primary cancers, and lung cancer.

MUTATIONAL SPECTRUM OF HUMAN CANCERS

The study of mutations in human tumors and experimental models is elucidating important carcinogenic mechanisms. In vitro studies using prokaryotic and simple eukaryotic assays, including human cells (e.g., site-specific mutagenesis assays), indicate that human exposure to mutagens might result in a narrow spectrum of mutations that are nonrandom. Some carcinogenic agents produce a “fingerprint” of mutations. In eukaryotic studies, for example, examining the mutational spectra in endogenous genes or exogenous genes transfected into cell systems have identified different phenotypes, depending on the exposures. These assays, however, may underestimate the induced mutational frequency due to deletions, chromosomal nondysjunction, and frameshift mutations that cause loss of other genes essential for cell survival and result in cytotoxicity or apoptosis. The data also show that the fingerprint hypothesis is likely the exception rather than the rule, because most mutagens actually can form several types of mutations, depending on the conformation of DNA and the type and the location of the adduct. Nonetheless, a comparison of the mutational spectrum at the aprt locus in Chinese hamster ovary cells induced by ionizing radiation, ultraviolet radiation, or benzo[a]pyrene-diol-epoxide is consistent with the mutagenesis models for these exposures. Promutagenic cytobutane and pyrimidine-pyrimidone mutations are induced by ultraviolet light, whereas ionizing radiation frequently causes deletions, and benzo[a]pyrene-diol-epoxide causes the predicted G:C→A mutation.

The study of mutations in the P53 tumor suppressor gene is suited uniquely for the study of cancer etiology, exposure, and susceptibility, because P53 is involved in many cellular processes, including maintenance of genomic stability, programmed cell death, DNA repair, and others. The P53 mutation frequency varies by organ site and histological subtype, indicating that cancers occur through different pathways and different exposures at the cellular level. Several examples of particular carcinogenic exposures are linked to cancers via a P53 mutational mechanism, especially the demonstration that ultraviolet light exposure and skin cancer are associated with cytosine-to-thymine transversions. Another example is dietary aflatoxin B1 exposure and a consistent finding of mutations in the third nucleotide pair of codon 249 of liver cancers in regions with endemic exposure to aflatoxin B1. Combinations of exposures can lead also to different outcomes in the same organ site. An interactive effect of alcohol drinking and cigarette use in oral cavity cancers yields different types of P53 mutations.

Showing that the P53 mutation frequency is modulated by gene-environment interactions has been difficult because of the technical difficulties in determining the mutational spectra in large numbers of cancer patients, but preliminary evidence exists. The mutational spectra of lung and breast cancers are different among whites, African Americans, and Japanese, consistent with the hypothesis that differences exist in both exposure and the frequency of genetically determined carcinogen metabolism and DNA repair. More specific evidence for a relationship of gene-environment interactions and mutations in the P53 gene can be found from Japanese studies of CYP1A1, GSTM1, and lung cancer.
TOBACCO SMOKING AND CANCER RISK

Tobacco smoking is the major cause of cancer and accounts for almost 96% of all male lung cancers in whites. Though the risk of lung cancer decreases after smoking cessation, the risk never returns to that for nonsmokers. According to 1990 estimates, persons who died of smoking-related diseases would have lived an additional 15 years if they had never smoked. Tobacco smoke contains more than 3500 chemicals, of which more than 20 are carcinogenic. Specific chemicals in tobacco smoke include PAHs and N-nitrosamines, aromatic amines, ethylene oxide, 1,3-butadiene, and agents that cause oxygen radical damage. For example, tobacco-specific nitrosamines (TSN)—that is, 4-(methyl-nitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and N′-nitrosonornicotine (NNN), which are potent carcinogens in laboratory animals result in the formation of hemoglobin adducts. PAHs and TSNs are considered to be the most potent carcinogens in tobacco smoke. During the last 40 years, the approximate threefold decrease in tar (containing PAHs) and nicotine content has been accompanied by an increase of other carcinogens, including TSNS.

Convincing laboratory animal and human studies demonstrate a relationship between tobacco constituents, carcinogen-DNA adduction, and cancer. In humans, case-control studies find a positive relationship for lung and bladder cancer. Also, studies of tobacco smoke exposure have shown increased formation of adduct-related DNA damage in the lung. However, wide interindividual variation for adduct levels is common, so several studies have failed to show a direct relationship between smoking and adducts.

The P53 gene, in particular, has a unique spectrum of mutations in tobacco-associated lung cancers. Also, an increased frequency of P53 tumor suppressor gene mutations has been reported at non-CpG sites in smokers with head and neck cancers, especially in conjunction with alcohol consumption. The decrease in nicotine content in cigarettes has led to a paradoxical increase in smoking, owing to the drive for maintaining higher blood nicotine levels.

Several determinants of tobacco carcinogen exposure and cancer risk exist, including the number of cigarettes smoked per day, years smoked, cigarette type (e.g., tar content, which is the total dry particulate component of smoke), and smoking topography (e.g., how much smoke entering the lung is measured by puff volume, number of puffs per cigarette, puff duration, and interpuff interval).

Also important is that not all smokers experience the same carcinogenic risks; only in 10 heavy smokers develop lung cancer, and some heavy smokers live to their 90s. Thus, interindividual variation in host susceptibility likely is important for cancer risk (e.g., those related to carcinogen metabolism, DNA repair, or behavior). Overall risk is related to dose, which is directly affected by nicotine addiction; more cigarettes are consumed to maintain nicotine blood levels, and cigarettes with lower nicotine levels result in the need to smoke more, thereby increasing the exposure to tobacco carcinogens.

CHAPTER REFERENCES

CHAPTER 12  
Etiology of Cancer: Physical Factors

ROBERT L. ULLRICH

INTRODUCTION

This chapter discusses the induction of cancer by three physical agents that are known to cause cancer in humans: radiation, UV light, and asbestos. Exposures to ionizing radiation can come from both natural and man-made sources. We are continually exposed to naturally occurring radioisotopes contained in soil and rocks, and, as a result, in building materials and even in our own bodies. In addition, we are exposed to cosmic rays from the sun and radon. The levels of this naturally occurring environmental radiation, often referred to as background radiation, vary with altitude, geology, and types of building materials used to construct homes and other buildings. One of the most important man-made sources of exposure is from imaging and therapy procedures in medicine. It is also one of the largest sources of exposure. On average, the dose to the general population from medical exposures is similar to that received from background radiation.

UV light from the sun is responsible for an increasing number of skin cancers throughout the world. Risks for skin cancer vary with altitude, latitude, and pigmentation, all of which modify exposure to UV light. UV light and certain types of ionizing radiation, such as x-rays and gamma rays, are all part of the electromagnetic spectrum, which also includes static magnetic fields, fields generated by 50 or 60 cycle alternating current, radio waves, microwaves, infrared light, and visible light. UV light and electromagnetic forms of ionizing radiation have the highest frequencies and energies.

Asbestos is a third physical agent that is a well-known human carcinogen. Asbestos is a naturally occurring mineral silicone that results from fibrous crystallization. Health effects, including lung cancer, arise from its commercial uses that lead to high occupational exposures. Health effects from low-level exposures, such as those to the general population, are more controversial. The concern over the effects from occupational exposures and potential health risks in the general population has markedly reduced the mining and use of asbestos worldwide.

Because their carcinogenic potential is well known, questions about these physical agents focus on the degree of risk to humans as a function of level of exposure and on mechanisms of cancer development. These mechanistic studies can provide insight into potential risks at very low levels of exposure, for which effects cannot be directly measured by epidemiologic studies. These studies also provide information about potential sensitive subpopulations, suggest ways to reduce risks, and provide insight into fundamental mechanisms of cancer development.

INTERACTIONS OF RADIATION WITH CELLS AND TISSUES

Gamma rays, x-rays, and UV light are all part of the electromagnetic spectrum, which is shown in Figure 12-1. Their interactions with biologic material depend on the frequency or wavelength of the radiation. At the short wavelengths of x-rays, electromagnetic radiation has sufficient energy to produce ionizations as a result of the removal of electrons from atoms. At the longer wavelengths of the other forms of electromagnetic radiation, from UV light to low-level electric and magnetic fields, the energy deposition is insufficient to produce ionizations, and these forms are often generally referred to as nonionizing radiations.

FIGURE 12-1. Electromagnetic spectrum.

IONIZING RADIATION

In addition to the electromagnetic forms of ionizing radiation (such as x-rays and gamma rays), electrons, protons, alpha particles, and neutrons are particulate forms of ionizing radiation. The spatial distribution of the ionizations produced by these different forms of ionizing radiation provide a means of classification based on their interactions in matter, including their interaction with biologic material. This spatial distribution of ionization is measured as the energy transferred per unit track length [linear energy transfer (LET)] in units of keV/μm. On this basis, x-rays, gamma rays, and electrons are classified as sparsely ionizing, whereas alpha particles (such as those associated with radon) and neutrons are densely ionizing. The density of the ionization tracks can have a substantial impact on the biologic effects of the radiation. These influences can be qualitative as well as quantitative. The quantitative differences in the effectiveness of different ionizing radiations are measured by comparing the dose of the test radiation (e.g., neutrons) to produce a specific level of effect against the dose of x-rays (or sometimes gamma rays) to produce that same level of effect. That ratio is the relative biologic effectiveness (RBE). For cell killing effects, RBEs for neutrons and alpha particles are often approximately 3 to 5; for cancer induction in animals, the RBE values can be 20 or higher (RBEs of 50 or more have been reported). The RBE increases with increasing LET to a maximum at approximately 100 keV/μm. At this LET, the average separation of ionizing events is approximately the diameter of the double helix. This results in a high probability that a single track of radiation of this LET can produce a double-strand break. Qualitative differences between high and low LET radiation are suggested by the fact that, for all effects observed, including cell killing, chromosome aberrations, mutations, and cancer induction, the radiation damage that induces these...
effects appears to be less easily repaired by the cell or organism after exposure to high LET radiation. 2

Energy deposited in biologic material can produce ionizations in target molecules, such as DNA, directly or indirectly by interactions with water molecules that result in the formation of free radicals. These free radicals can then produce damage to DNA. Because ionizing events from low LET radiation exposures are sparsely distributed, damage to DNA and other targets from such radiation is principally a result of indirect mechanisms mediated by free radicals. High LET effects are more generally mediated via direct effects on the target molecules. 2

Whether the effects are directly or indirectly produced, ionizing radiation results predominantly in base damage, and single- and double-strand breaks in DNA. As already mentioned, for low LET radiations, these effects are mediated via reactive oxygen species much like those produced by normal cellular processes. The reason that ionizing radiations are able to cause the degree of damage that they do is because of the different spatial distribution of energy that results in a markedly different distribution of these reactive oxygen species than occurs during normal cellular processes. Ionizations from the deposition of ionizing radiation are highly clustered, which results in localized areas of sites in DNA molecules with multiple and complex lesions consisting of a combination of base damage and single- and double-strand breaks. These more complex lesions are less easily repaired with fidelity than are the more simple forms of DNA damage. 2 For high LET radiations, because of the density of the ionization clusters, the molecular damage can be particularly complex and difficult to repair.

ULTRAVIOLET LIGHT

UV radiation does not have sufficient energy to produce ionizations. Rather, its effects are the result of molecular excitation after absorption of energy by the molecule. UV light can be categorized into three types, based on wavelength: UVC with wavelengths ranging from 240 to 290 nm, UVB ranging from 290 to 320 nm, and UVA ranging from 320 to 400 nm. UVC is not in sunlight that reaches earth because it is readily absorbed by the atmosphere. It has proven to be useful, however, for other reasons. It is produced by low-pressure mercury lamps commonly used for sterilization. In addition, because the peak wavelength of these lamps (254 nm) is very close to the peak for absorption in DNA molecules (260 nm), it has been an important experimental tool for studies of UV light effects on DNA. UVB appears to be primarily responsible for skin cancer induction after sunlight exposure via direct damage to DNA. The amount to which the population is exposed depends on many factors, including the ozone layer. Effects of UVB and UVC appear to be mediated via effects on DNA. Interactions of UVB and UVC with DNA result in a number of molecular changes, the most prevalent of which are dimers between adjacent pyrimidines. 5 The most biologically important of these are the cyclobutane dimer and the 6-4 photoproduct. Other products are less frequent, but these two, especially the cyclobutane dimers, appear to play a major role in the mutagenic and carcinogenic effects of UBV. UVA is not absorbed by the atmosphere and penetrates deeper into the skin than UVB. Because of its wavelength, DNA and proteins only weakly absorb UVA, but it has been shown to be carcinogenic. This carcinogenic effect appears to be due to the production of reactive oxygen species and free radicals through its interactions with target chromophores. As a result, such products induce indirect damage to DNA. 7

For UVC and UVB, the distribution of specific changes in the genome depends on base sequence and secondary and tertiary genomic structure. For example, cytosine absorbs higher wavelengths of UV radiation than thymine, resulting in dimers containing cytosine being more readily formed after UVB radiation. Data have shown that methylation at specific sequences in the p53 molecule enhance formation of dimers in specific regions, resulting in mutations that are relatively specific for UV damage. 8 These specific mutations have been found quite early in skin tumors. 9

IONIZING RADIATION AND CANCER

HISTORY AND SOURCES OF INFORMATION

The benefits of ionizing radiation in the diagnosis and treatment of disease were recognized by the medical community very soon after the discovery of x-rays and radioactivity. 10 Almost as quickly, the risks of exposure began to be recognized as well. The first cancers, detected a few years after the discovery of x-rays, were skin cancers that developed after high skin doses received by early workers who often used their hands to test the output of x-ray tubes. These cases were followed by cases of radiation-induced leukemias among radiologists and radioisotope workers. These early studies established that radiation could cause cancer in humans, but the extent of the risk as a function of dose was not known. This began to change in the 1950s and 1960s with the study of the Japanese survivors of the atomic bombs, the study of patient populations exposed to radiation for therapeutic and diagnostic procedures, and occupationally exposed populations, such as radiologists, uranium miners, and nuclear industry workers. A partial list of the principal sources of information is shown in Table 12-1. These studies, which began in the 1950s and continue today, have provided and continue to provide extensive quantitative information about radiation dose and cancer risk. In addition, such studies provide information on tissue and organ sensitivity and risk-modifying factors, such as age and genetic background.

TABLE 12-1. Studies of Radiation-Exposed Populations

The largest population studied and the one that has served as the primary source for risk estimates are the populations in Hiroshima and Nagasaki, Japan, who survived the atomic bombings of these two cities. 11,12,13,14 The doses received were single acute exposures of a mixture of gamma rays and neutrons to the entire body. The doses ranged from lethal to very small, depending on the location of the individuals at the time. The average dose received by the survivors was less than 0.3 Sv. The study of this group, which began a few years after the exposures, has provided extensive information on risk as a function of dose and provided insights into variations in tissue and organ sensitivity. Because the age distribution of the population was wide, including the old and the very young (as well as children exposed in utero), this study is also an important source of information about the effects of age on risk and on the time between radiation exposure and the appearance of leukemias and solid cancers (latent period). This study is still ongoing, and a large fraction of the population exposed as children, adolescents, and young adults are still living. Because of this fact, we are continuing to learn about the risks from radiation exposure, and this population will continue to provide new information for many years to come.

Another major source of information is patient populations exposed to ionizing radiation as a result of therapeutic or diagnostic procedures. The numbers of patients in each individual study are smaller than in the atomic bomb survivors, but the number of such studies is relatively large. 2 In spite of the large numbers of studies, only a few have been useful for the quantification of risk as a function of dose. Because such populations generally receive localized exposures, these groups generally provide information on cancer risks in specific organs and tissues. Such populations also have provided insight into modifying factors, such as age and genetic background. Such an important source has been the Japanese atomic bomb survivors. This group is discussed in more detail later in the section Second Cancer. In the past, radiation was used to treat a number of benign disorders, including enlarged thymus glands and tonsils, linea capitis, ankylosing spondylitis, and peptic ulcers. 15 Epidemiologic studies of such treated populations have provided information on radiation-induced leukemia, as well as thyroid, breast, and stomach cancers. In general, diagnostic procedures result in very low radiation exposures; however, a few studies have provided evidence for increased cancer risks. One of the most intensively studied of these is a group of tuberculosis patients who were subjected to multiple diagnostic fluoroscopies during their treatment. 16,17 In these studies, female patients have been shown to be at an increased risk for breast cancer. Although individual doses were low, the number of exposures resulted in the accumulation of relatively large doses.

As is the case for other carcinogenic agents, occupational exposures also have been a valuable source of information. Studies of uranium miners and other
underground miners have been a particularly valuable source of information on risks of lung cancer after exposure to radon.

**RADIATION AND CANCER RISKS**

**Tissue Sensitivity and Latent Period**

Although radiation can induce many different types of cancer, certain organs, tissues, and cell types are more sensitive than others. Chronic myelocytic leukemia and acute leukemia are very sensitive to induction, whereas no evidence indicates that chronic lymphocytic leukemia, Hodgkin's disease, or non-Hodgkin's lymphoma can be induced by radiation exposure. Among solid cancers, cancers of the thyroid gland, female breast, and lung appear to be the most sensitive. Evidence also suggests increased risk for salivary gland tumors; colon cancer; stomach cancer; and cancers of the liver, ovary, bladder, esophagus, skin, and central nervous system; however, these sites are not as sensitive. Most skin cancers are basal cell and squamous cell carcinomas, whereas there is little evidence for the induction of melanomas. In general, bone sarcoma and cancer of connective tissues require relatively high doses before a significant increased risk can be detected. No clear evidence exists for the induction of cancers of the pancreas, prostate, uterine cervix, small intestine, or most childhood cancers (except for acute leukemia).

Radiation-induced leukemias are the first to appear after radiation exposure. Depending on dose, these leukemias can begin to appear as early as 2 years after exposure, with peak incidence occurring between 4 and 8 years after exposure. After this peak, the incidence begins to drop toward baseline levels. In general, solid cancers, such as breast cancer, appear 10 or more years after the radiation exposure, and it is not unusual for the latent period to exceed 20 years. The time between irradiation can depend on the age at exposure, the dose, and a variety of host factors. For example, the appearance of breast cancer is greatly influenced by age at the time of irradiation. The time between radiation exposure and the appearance of breast cancer is quite long for a prepubertal or adolescent girl, whereas for a woman in her late twenties or early thirties, the latent period is generally shorter. A close look at the relationship between age at exposure and time of appearance for breast cancer indicates that these radiation-induced cancers appear at a time when the natural incidence of these cancers is also rising. This is likely a result of host factors that play an important role in breast cancer development and that also appear to strongly influence the expression of radiation-initiated cells. These data have important implications for potential mechanisms of radiation carcinogenesis. These very long latent periods, particularly for younger individuals, are also important to remember when assessing risks associated with specific treatment protocols.

**Dose-Response Relationships**

Understanding the relationship between cancer frequency, or risk, and radiation dose is important for providing insight into mechanisms underlying radiation carcinogenesis. It is also important for estimating risks at low doses for which effects cannot be directly determined from experimental or epidemiologic studies. Accurate risk estimates at low doses are essential in regulating environmental and occupational exposures. It is also essential in decisions about medical uses of radiation when weighing the benefits of the procedure versus its risks. One of the most prominent examples of this issue has been the debate over mammography, both with respect to its general use to screen women for breast cancer and with respect to the age at which such screening should be initiated and practiced routinely. The question of whether the benefits of this screening outweigh the risks for inducing new breast cancers depends on many complex issues, but central to these issues is the risk of breast cancer from the doses received. It is virtually impossible to observe an increase in risk in an epidemiologic study at the low doses received as a result of a single mammographic procedure (or for that matter any diagnostic procedure) (Table 12-2), so estimates must be based on models of dose-response relationships that allow estimates to be derived. Mainly because of these low-dose risk issues, a substantial amount of effort in epidemiologic studies and in experimental studies of radiation carcinogenesis has been to define dose-response relationships and test predictions of dose-response models.

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Dose (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest x-ray (frontal)</td>
<td>0.16</td>
</tr>
<tr>
<td>Dental x-ray (upper jaws)</td>
<td>1.0</td>
</tr>
<tr>
<td>Mammography (postmenopausal)</td>
<td>1.5</td>
</tr>
<tr>
<td>Radiative therapy (boost)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

**TABLE 12-2.** Approximate Doses from Common Diagnostic Procedures

From theoretical models of radiation interactions at the cellular and molecular level, and from experimental and epidemiologic studies, two dose-response models are most prominent: the linear model and the linear-quadratic model. As suggested by its name, with the linear model cancer risk (or, incidence) is linearly related to dose (d). With the linear-quadratic model, risk (incidence) is related to dose (d) and the square of the dose (d^2). The linear model is based on biophysical theories of radiation interactions. The linear-quadratic model is based on biophysical theories of radiation interactions. The relationship between dose and risk is given by the equation

\[
R = \alpha d + \beta d^2
\]

where \( R \) is the risk, \( d \) is the dose, and \( \alpha \) and \( \beta \) are coefficients that depend on the specific type of radiation and the specific cancer type.

Irrespective of the model, the prediction at low doses is that the dose response is linear. This prediction implies that any dose of radiation received has a probability of inducing damage and, therefore, results in some increased risk for cancer development. Although there is some argument about this assumption at very low doses because of the repair and damage response capabilities of cells, current information about underlying mechanisms of cancer induction by ionizing radiation would tend to support the view that any dose of radiation confers some degree of risk.

At high dose, the linear quadratic and linear models differ not only in form but also in predictions about risks at low dose rates and fractionated exposures. Doses at lower dose rates or for extended periods of time can have a smaller risk compared to the same dose delivered at a higher rate. This is known as the dose-rate effect. The linear-quadratic model predicts that at high total doses, the rate at which the total dose is received or given in multiple small fractions reduces the risk. This makes sense when considering acute effects of radiation. A dose of 4 Gy delivered instantaneously would have the chance of being lethal in a short time, whereas the same dose accumulated over a lifetime would not produce such acutely lethal effects. But whether this same concept holds for the damage that results in increased cancer risk is not certain. Theoretically, because effects are likely to be a result of the interaction of damages produced by independent tracks, lowering the dose rate or fractionating the exposure reduces the probability of the interaction of damage because of cellular repair processes that rapidly respond to such damage. If this theory applies to the damage responsible for radiation-induced cancers, the cancer risk at low dose rates and after low dose fractions would be lower than that predicted from high dose, high-dose-rate exposures. At very low doses and very low doses per fraction, this results in a predicted dose response that simply is a continuation of the slope of the dose-response curve at low doses (i.e., the dose response would be linear (d)). Because most epidemiologic studies involve populations irradiated at high dose rates, the applicability of this model potentially impacts the accuracy of estimates of risk for low dose, low dose-rate, and fractionated exposures derived from such studies. Whether this model is appropriate and the degree of the so-called dose-rate effect is a matter of debate and study. Epidemiologic and experimental data are not adequate to resolve the issue at the present time.

Analyses of results from epidemiologic studies of the atomic bomb survivors suggest a linear quadratic dose response for the induction of all leukemia, although a
simple linear model also fits the data. For all solid cancers combined, a linear dose response is suggested based on the data at hand. Except for a few tumor types, such as breast cancer, data for individual cancers are insufficient to address the issue of dose response. It must be remembered that the solid tumor data are incomplete at present because of the late onset of these cancers and because a significant fraction of the population who were children and young adults at the time of the bombing are still alive. Studies of radiation-induced breast cancer in the atomic bomb survivors support a linear dose response over a wide range of doses.

This linear response is supported by studies of other populations as well.

For breast cancer, limited data on fractionation effects are available from studies of tuberculosis patients who received multiple diagnostic fluoroscopies during their course of treatment. Although the doses from the individual fluoroscopies were small, relatively large total doses were accumulated. Analysis of these data suggest similar risks for radiation-induced breast cancer in this group compared with those derived from the atomic bomb survivors and other groups who received radiation at a high dose rate. The lack of an apparent fractionation effect is in contrast to results of analyses of the same tuberculosis patients for lung cancer. Comparing the risk for lung cancer in the groups receiving fractionated exposures from fluoroscopy to the risk in the atomic bomb survivors indicates that fractionation resulted in a markedly decreased risk for radiation-induced lung cancer.

Information on dose-response relationships for high LET radiation-induced cancer in human populations is relatively limited but suggest linear dose-response relationships. Some of the most extensive dose-response data are for lung cancer in underground miners exposed to radon (see Radiation later in this chapter).

Experimental studies examining dose-response relationships for leukemia and a variety of solid cancers generally support the linear-quadratic model. In addition, most of these studies have found that reducing the dose rate or fractionating the dose into small fractions reduces the risk for development of radiation-induced tumors, as in the manner predicted by the linear-quadratic model. The degree of the dose-rate effect appears to vary with tumor type. Interestingly, in mice the dose-rate effect for the induction of lung cancer is greater than that for breast cancer. Dose-response relationships for cancer induction after exposure to high LET radiation are limited mainly to studies of neutrons and only a few tumor types, but the data available clearly demonstrate linear dose-response relationships. Fractionating the exposure or delivering the exposure at low dose rates has little effect on the dose response in most instances. However, data for mammary tumors in mice, and for transformation in vitro, have shown a so-called inverse dose-rate effect in which doses delivered at low dose rates were seen to be more effective with respect to cancer induction than single acute exposures.

MODIFIERS OF RISK

Age

Age has a significant impact on susceptibility to radiation-induced cancer. Increased risks for thyroid cancer are primarily found after exposure of children to radiation, whereas the risk in adults after exposure to radiation is small. For breast cancer, young children and adolescents are at the highest risk. Risks, although lower for younger women as compared with older women, are lower for young. For women older than 45 to 50 years of age, radiation appears to have little influence on breast cancer risk. Although not as dramatic, risks for acute leukemia, colon cancer, cancer of the central nervous system, and skin cancer are all greater if the exposure occurs early in life.

Reports in the mid-1950s suggested for the first time an increased risk of childhood leukemia and all childhood solid cancers as a result of in utero radiation exposure from diagnostic procedures. Initial concerns of a selection bias that might have resulted in more in utero exposures because of an underlying medical problem that was the actual risk factor were essentially dispelled by confirmation of these results in a study of twins in which such a selection bias could be minimized. Similar studies of effects from in utero exposure in atomic bomb survivors have not observed such an increased risk. However, it is generally accepted that an increased risk exists for childhood cancers, including leukemia, from in utero exposure, which should be avoided.

Studies to date on risks of adult cancers after in utero exposure are inconclusive.

Genetic Susceptibility

It has been recognized for many years that there are individuals within the population who have a higher risk for spontaneous cancer. Studies of these individuals and their families have led to the discovery of several genes involved in heritable susceptibility to specific cancer. A number of these genes have now been cloned. In individuals with such susceptibility, the probability of developing a tumor during their lifetime can exceed 50%, and in some instances the probability is higher.

However, such mutations are relatively rare in the population. The prevalence of currently known, high penetrance genes account for approximately 5% of the total cancers in the population, and the prevalence of such genes in the total population is less than 1%. Because of this incidence, it is difficult to obtain adequate data to assess the impact of such genes on susceptibility to radiation-induced cancer.

Most information has come from studies of second cancers after radiation therapy. Studies to date have demonstrated increased risks for radiation-induced osteosarcoma and soft tissue sarcoma in patients with the hereditary form of retinoblastoma. Studies of patients with basal cell nevus carcinoma syndrome have been found to be at an increased risk for basal cell carcinoma and ovarian tumors in the irradiated field. In addition, patients with Li-Fraumeni syndrome appear to be at an increased risk for radiation-induced cancer. In each instance, these patients have defects in genes that are known to act as tumor suppressor genes, the retinoblastoma gene (RB), the human homologue of the patched gene PTCH, and the p53 gene, respectively. It has also been proposed that the gene involved in ataxia-telangiectasia (AT) may also influence susceptibility to radiation-induced cancer. AT is a recessive inherited syndrome that results in hypersensitivity to acute radiation effects, such as cell killing, because of mutations in the ATM gene, which is involved in DNA damage signaling and response pathways.

Patients homozygous for mutated ATM are extremely sensitive to acute radiation effects and are at a high risk for the development of certain forms of cancer. It has been suggested that individuals heterozygous for mutated ATM are also at an increased risk for radiation-induced cancer, in particular breast cancer. The sensitivity of these individuals to acute effects of radiation is generally within the normal range. This hypothesis has been difficult to definitively test, and the question of enhanced susceptibility remains unresolved. Although unknown at the present time is the impact of the breast cancer genes BRCA1 and BRCA2 on susceptibility to radiation-induced cancer.

A major area of uncertainty and increasing interest is the potential impact of low-penetration mutations that are likely to be relatively common in the population. Such genes are difficult to identify in epidemiologic studies. Experimental studies in animal models and in human cells have provided evidence for such mutations and provided data implicating such mutations in susceptibility to radiation-induced cancer. It is also likely that such low-penetration mutations could be involved in other delayed effects, such as radiation-induced fibrosis. The identification of such susceptible subpopulations is now a major research activity in radiation oncology.

SECOND CANCERS

As the treatment of cancer has improved, long-term survivors have begun to develop second cancers as a result of treatment. Studies of such populations can provide information on the nature of potential risks and suggest new approaches to treatment that may reduce risks. Several studies have now been reported on risks of second cancers from radiation therapy. The most extensive data are available from studies of second cancers arising after treatment for childhood cancer, cervical cancer, Hodgkin's disease, and breast cancer. Data also are becoming available regarding risks of second cancers after whole body irradiation for bone marrow transplantations.

Relatively little information has been reported on radiation-induced second cancers in long-term survivors of childhood cancer. Interpretation of results are complicated by the fact that many of these cancers are associated with germinal mutations that can influence susceptibility to the development of second cancers independent of the radiation or perhaps enhance susceptibility to radiation exposure. Another complicating factor is that many of these patients received chemotherapeutic agents as well. Furthermore, in many cases insufficient time has passed for risks for adult solid tumors to be properly assessed. The most common second cancers appear after treatment of childhood cancers appear to be bone and soft tissue sarcomas. For the farthest source of information on these sarcomas come from study of retinoblastoma patients, many of whom have an elevated risk for such cancers independent of the radiation exposure because of heritable mutations in the RB gene. In these children, risk after radiation therapy can be as high as 50%. Although genetic susceptibility of these children to the familial form of these cancers can complicate interpretation, studies of retinoblastoma patients who do not have the familial form and studies of patients with other forms of childhood cancer also show increased risks for these sarcomas. Not unexpectedly, based on the earlier discussion about age susceptibility (see Age, earlier in this chapter), the risk for thyroid, breast, and skin cancers also are elevated after radiation therapy for a variety of childhood cancers, as are tumors of the central nervous system and leukemias. It appears, however, that the effects of radiation are primarily on the induction of solid cancers. The relative increase in risk for leukemia
development after radiation therapy is lower than that for the development of a subsequent solid cancer.

A series of large studies have examined the development of second cancers in cervical cancer patients treated with high doses of ionizing radiation. Increased risks for second cancers have been difficult to detect, although a small (twofold) increased risk of leukemia was detected when the sample size was increased to include several hundred thousand women. The reason for such a small increase in leukemia risk is likely a result of a number of factors. First, the high doses delivered to a small volume likely resulted in cell killing in nearby target cells, and the dose outside the field was relatively low so that the fraction of target cell irradiated may have been small. Second, the doses were protracted (brachytherapy), fractionated, or both. In spite of the small number of leukemias, a dose-response curve was constructed that showed a rise in leukemia risk up to approximately 4 Gy, followed by a decline from the peak at higher doses. This decline at high doses was suggested to be a result of cell killing rather than to time of onset of disease. However, the latency period of approximately 2 years was seen, and the risk remained elevated for approximately 15 years before declining to normal levels. Within the field of irradiation, cancers of the bladder and bone, as well as soft tissue sarcomas, were observed. Outside of this field, cancers of the stomach were seen, probably as a result of scatter radiation of approximately 1 Gy.

Long-term survivors of Hodgkin's disease, the risk of leukemia appears to be mainly associated with the use of alkylating agents. Radiation in combination with chemotherapeutic agents does not seem to markedly enhance the risk of leukemia over that associated with chemotherapy alone. Although these data would suggest that radiation is not a particularly effective leukemogenic agent, studies of second solid cancers indicate radiation is capable of increasing the risks of a number of solid cancers, including cancers of the breast and thyroid. These cancers are not believed to be directly induced by radiation, but are electrically charged. These charged particles can attach to dust particles and, when inhaled, can deposit in the lung, where distant cells are particularly pronounced in women treated at young ages. It has been reported that the relative risk for women treated when they were younger than 15 years is 136. For those treated between the ages of 15 and 24, the relative risk was 19; for ages 25 to 29 years, a relative risk of 7.3 was reported. Women treated at older ages did not appear to be an increased risk. It is also important to note that the time between radiation exposure and the onset of breast cancer was long. The risk was higher at times beyond 15 years after treatment before than after 15 years. Clearly, such patients should be identified as high risk and monitored carefully on a long-term basis.

In addition to breast cancer, an excess of lung cancer has been reported. Unlike breast cancer, lung cancer has been reported to appear as early as 5 years after treatment. As might be expected, a strong interaction between smoking and radiation with respect to lung cancer risk has been reported. An increased risk for thyroid cancer has been found in patients treated at very young ages but in adults, and an increased risk for bone cancer has been reported mainly in patients treated as adolescents. Concerns over these second cancer risks, particularly breast cancer, has led to treatment modifications but not to elimination of radiation as an important tool in the treatment of Hodgkin's disease. In spite of the risk, radiation is very effective, and the potential benefits of its continued use (a high probability of long-term survival) is thought to outweigh the risks of a second cancer many years later.

On the basis of epidemiologic studies of breast cancer risks in other populations, the dose to the contralateral breast during radiation therapy for breast cancer is sufficient to result in an increased risk for a second breast cancer. This potential risk has been shown to be the case in several studies. An increase in risk has been found in women irradiated before age 45 who survive longer than 10 years. For women older than 45 at the time of treatment, the risk does not appear to be increased. In addition to breast cancer in the contralateral breast, an increased risk of lung cancer also has been reported. Studies have been reported on patients receiving whole body irradiation for bone marrow transplantation who received radiation doses in the range of 10 to 15 Gy. It was found that, in those patients who survived 10 or more years, the risk was 8.3 times higher than expected. Risks were elevated for cancer of the buccal cavity, liver, brain and central nervous system, thyroid, bone, and connective tissue, as well as for malignant melanoma. Those treated at younger ages were at higher risk than those treated at older ages.

MECHANISMS

It is clear from the discussion in the previous section that a single dose of ionizing radiation can result in an increased risk of cancer from years to decades later. Although it is generally assumed that these carcinogenic effects are somehow related to its mutagenic and clastogenic potential, the precise mechanisms through which radiation results in this increased frequency of cancer is unknown. The long period between radiation exposure and cancer development and the multistage nature of carcinogenesis make it particularly difficult to sort out radiation-induced changes from other alterations that occur once the process has been initiated. Radiation-induced cancers do not appear to be unique or specifically identifiable. The mutations and the growth characteristics of tumors likely caused by radiation are the same as those spontaneously occurring tumors of the same site. Attempts to identify radiation-specific changes have not been successful, despite fairly extensive investigation. However, there are clues to possible underlying mechanisms that emerge from epidemiologic and experimental investigations.

Based on experimental studies, it is generally thought that the induction of complex forms of double-strand breaks is the most biologically important type of lesion induced by ionizing radiation. That is, this type of double-strand break is likely to be responsible for subsequent molecular and cellular effects. Attempts to repair these complex lesions are likely to be error-prone, and it is thought that this error-prone repair process can lead to gross chromosomal effects and mutagenesis. Molecular analyses of radiation-induced mutations have found a full range of mutations, including base pair substitutions, frameshift mutations, and deletions. Important radiation-induced alterations other than point mutations. Common alterations other than point mutations, theories of radiation-induced cancer have focused mainly on effects on oncogenes and tumor suppressor genes that would be expected to occur through this mode of action rather than through the induction of point mutations. Thus, mechanisms involving gene and chromosome rearrangements, loss of heterozygosity, and gene deletion are considered the most likely mechanisms for radiation-induced events to initiate the process of cancer development. Some support for this view comes from the molecular analysis of radiation-induced cancers. In the papillary form of thyroid cancer, rearrangements in the RET protooncogene are a common feature, and it has been demonstrated that such rearrangements can occur in thyroid cells after irradiation. Radiation-induced myeloid leukemia in mice appears to be associated with specific deletions in chromosome 2 that occur very early after irradiation. In a murine model of p53 deficiency containing mice with one normal and one mutant allele of the p53 gene, it has been shown that these mice are highly sensitive to radiation tumorigenesis. Analysis of these tumors has demonstrated loss of the wild-type allele and duplication of the mutant p53 allele. In patients with familial forms of RB, basal cell nevus carcinoma syndrome, and Li-Fraumeni syndrome, the pathogenesis of second cancers after radiation therapy appears to involve a similar mechanism. In each case, the patient has a germline mutation in one allele at birth, and radiation appears to facilitate the loss of the normal allele.

More recently, experimental studies have questioned whether the initiating events produced by radiation are direct effects on specific genes or whether the mutations and chromosomal rearrangements result indirectly as a consequence of genomic instability induced by the radiation exposure. The observation of genomic instability is relatively recent. It has been generally believed that all the mutagenic and cytogenetic effects of radiation occurred in the first, or at least the first few, cell divisions that occurred soon after exposure and that no important radiation-induced changes could occur in a later generation of progeny. However, some studies found that many generations later, this hypothesis that this radiation-induced instability, which appears to be broadly based, is the initiating event responsible for subsequent mutations and chromosomal rearrangements that ultimately lead to cancer. Interestingly, analyses of mutations arising in genetically unstable cells indicate that they are more frequently point mutations rather than deletions. According to this hypothesis, this instability puts all genes at an increased
risk for mutations, and it is this increased mutation rate that ultimately results in cancer development (Fig. 12-3).

![Figure 12-3](image)

**FIGURE 12-3.** Proposed role of radiation-induced cytogenetic instability in radiation-induced cancer. Radiation exposure induces instability in a high percentage of the progeny of the irradiated cells (striped cells represent unstable progeny). As a result of this instability, the rate of chromosome aberrations and mutations is increased. Some mutations result in cell death (black) or slow-growing cells (gray), whereas some occur in critical genes involved in the regulation of cell growth and differentiation, or in the maintenance of the stability of the genome. These mutations result in the persistence and amplification of genomic instability or in cells with a growth advantage. As these cells continue to develop into a clonal outgrowth, further mutations result in additional cellular changes, which lead to death or progression toward neoplasia. Cells with other patterns represent cells with specific mutations or sets of mutations that arose subsequent to radiation exposure.

The mechanism for induction of radiation-induced instability is not known, but it does not appear to be a result of the induction of a mutation in a specific gene or set of genes. The argument against a specific gene mutation is based on the high frequency of radiation-induced instability after relatively small doses. The probability of a specific gene mutation after 1 Gy of ionizing radiation ranges from 1 in 10,000 to 1 in 100,000, whereas approximately one in five cells or more will express radiation-induced instability. The strongest evidence to date in support of this hypothesis comes from mouse studies that have found a genetic association between susceptibility to radiation-induced chromosomal instability and susceptibility to breast cancer.

**ULTRAVIOLET LIGHT**

Skin cancer is one of the most common forms of cancer, and its incidence is rising. Although it is difficult to estimate overall incidence rates for nonmelanoma skin cancer, it is estimated that the annual incidence in 1996 was on the order of 800,000 new cases. Approximately 80% of all nonmelanoma skin cancers are basal cell carcinomas. Squamous cell carcinoma comprises the other 20%. Mortality rates for these nonmelanoma cancers are low. However, this is not the case for melanoma, which has been increasing at a rate of approximately 3% per year in the United States. In 1998, an estimated 41,600 new cases of melanoma were diagnosed, an estimated 7300 of which ultimately will be fatal. A major cause of all forms of skin cancer is UV light from the sun.

**SUNLIGHT AND SKIN CANCER**

The evidence that UV light is responsible for a large proportion of skin cancer is considerable. Skin cancer is more frequent in populations in regions with high ambient solar radiation and in individuals exposed to sunlight as a result of their occupations (e.g., farmers). Nonmelanoma skin cancer is most frequent in sites that are the most exposed to sunlight, such as the head, neck, and arms. Pigmented skin is less susceptible to nonmelanoma skin cancer, and lack of pigmentation increases the risk. A high incidence of skin tumors is seen in young individuals associated with sunlight exposure who have xeroderma pigmentosum, a disease that is caused by a deficiency in the ability to repair UV light-induced DNA damage. In the United States, the incidence of basal cell carcinoma and squamous cell carcinoma increase by approximately 2% to 3% for every 1% increase in ambient UV light, and melanoma incidence increases by approximately 0.5% to 1.0%.

On a worldwide level, the incidence of skin cancer is extremely dependent on latitude, which equates with level of exposure to UV light; the closer to the equator, the greater the risk. This is particularly true for countries in which a large proportion of the population is lightly pigmented, such as Australia.

Melanoma is also associated with sunlight exposure but is less dependent on total exposure, and it is not correlated with chronically exposed anatomic sites. Rather, increased risk for melanoma appears to be related more to acute burns rather than accumulated dose. Additional evidence for a role for sunlight in melanoma development comes from the observation that children who move to countries with high ambient sunlight are at an increased risk of melanoma. The same does not appear to be true when individuals move at older ages. These finding suggest that both exposure factors and factors involved in age-dependent susceptibility are involved. A greater risk for nonmelanoma skin cancer is seen in children and adolescents as well.

**GENETICS AND RISK**

One of the major discoveries that established a direct link between UV light to DNA damage and skin cancer was that patients with xeroderma pigmentosum are defective in nucleotide excision repair. Nucleotide excision repair is the repair pathway that removes the cyclobutane pyrimidine dimers produced in DNA by UV light, as well as other large adducts, and replaces the damaged site. This pathway is complex and involves a number of sequential steps, including recognition of the lesion; assembly of the enzymes that make up the excision complex, which excises a 27- to 29-nucleotide region containing the photoproduct; removal of this oligonucleotide containing the damage; and, finally, replacement and filling of the resulting gap by polymerization and ligation. Another pathway, base excision repair, removes less complex base damage. Both pathways are complex processes that are influenced by many factors, including transcriptional activity, the sequence of nucleotides surrounding the damaged site, and DNA conformation.

In addition to xeroderma pigmentosum, a number of other disorders result in increased acute sensitivity to UVC or UVB. These include Cockayne's syndrome and trichothiodystrophy. Both are related to disorders in genes involved in DNA damage repair, but neither has an increased sensitivity to UV-induced skin cancer. Studies of these disorders are providing additional insights into details of underlying mechanisms of UV-induced skin cancer. For example, it has been found that cells from Cockayne's syndrome patients are able to repair only transcriptionally inactive genes. Perhaps repair of transcriptionally active genes is more important for the
MECHANISMS

Squamous Cell Carcinoma and Basal Cell Carcinoma

The development of squamous cell carcinoma and basal cell carcinoma is associated with chronic exposure to sunlight. In other words, multiple exposures of UV light from the sun are necessary for the induction of these cancers. This finding is consistent with experimental evidence indicating that UV radiation (UVB and UVC) acts both as an initiator and a promoter for squamous cell cancers. Moreover, UV-induced mutations in p53 appear to be an early event in this process. Further exposures may lead to additional mutations in oncogenes and tumor suppressor genes, but, in addition, these further exposures facilitate clonal expansion of initiated cells through killing effects on normal but not p53 mutant cells. Exposure to UV light also has been shown to suppress the immune system’s ability to suppress tumor growth. High doses of UV radiation apparently affect the ability of Langerhans’ cells to efficiently transfer antigenic signals to T cells in local lymph nodes.

Studies of patients with basal cell nevus syndrome have provided insight into mechanisms of development of basal cell carcinomas. These patients are highly susceptible to basal cell carcinoma as a result of exposure to both ionizing and UV radiation, but keratinocytes from these patients show no difference in sensitivity to cell killing effects. It has been shown that the gene associated with this syndrome is PTC, which is the human homologue of the Drosophila patched gene (ptc). In Drosophila, this gene plays a role in cell-cell communication and transforming growth factor-b signaling. The most common genetic alteration in nonfamilial basal cell carcinoma is loss of heterozygosity at chromosome 9p22, which contains the PTC locus. This loss of heterozygosity has been observed even in very small tumors, suggesting that alteration of PTC is an early event.

Melanoma

Epidemiologic evidence has established a causal relationship between sunlight exposure and melanoma that appears to be primarily a function of acute sunburn rather than chronic exposure, as is the case for squamous cell and basal cell carcinoma. A history of five or more sunburns as an adolescent has been found to double the risk for melanoma. Experimental studies with a fish model suggest that the majority of melanomas are induced by UVA. If this is the case, DNA damage would be predicted to be a result of damage mediated through reactive oxygen species rather than the cyclobutane dimers and 6-4 photoproducts that are associated with exposure to UVB and UVC. In human melanoma, susceptibility is associated with chromosome 9p21, which contains CDKN2A, the gene encoding p16 and p19. This gene is involved in cell-cycle regulation. In both sporadic and familial forms of melanoma, loss of heterozygosity is found in several chromosomal loci, including 9p, 6, 8, and 10. As yet, no evidence indicates that these changes are a direct result of damage produced by UV light.

ASBESTOS

Asbestos use has spanned many centuries. Major industrial use began in the late 1800s and became widespread during World War II. Use peaked in the 1970s, and recognition of its health effects has led to major reductions in mining and use of asbestos, as well as programs aimed at removal of asbestos from existing structures. The carcinogenic effects of asbestos have been clearly demonstrated in studies of individuals exposed in the mining and industrial use of asbestos.

Fiber Quality and Disease

Asbestos is actually a group of fibers, with each type having a unique structure and chemical composition (Table 12-3). Each type also appears to differ in its chemical reactivity. Not unexpectedly, each type also appears to have differing biologic properties as well. There are two main subgroups. Chrysotile fibers are long, curly snake-like fibers. Amphibole fibers are shorter and rod-like in structure. The most common amphibole types include crocidolite, amosite, and tremolite. Few malignant mesotheliomas are associated with occupational exposure to chrysotile fibers, probably because they do not tend to persist in lung. The persistence of amphibole fibers, which are more commonly linked with mesothelioma, is significantly greater.

Table: Characteristics of Asbestos Fibers

<table>
<thead>
<tr>
<th>Fiber Type</th>
<th>Chemical Composition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chrysotile</td>
<td>Mg₆₃(OH)₂[(Si₆O₁₈)]</td>
</tr>
<tr>
<td>Asbestos</td>
<td>Mg₃[(As₄O₁₃)(Si₄O₁₀)·H₂O]</td>
</tr>
<tr>
<td>Tremolite</td>
<td>Mg₃[(As₆O₂₄)·H₂O]</td>
</tr>
<tr>
<td>Actinolite</td>
<td>Mg₃[(As₄O₁₃)(Si₄O₁₀)·H₂O]</td>
</tr>
</tbody>
</table>

Cancer Risk and Asbestos Exposure

The most common form of cancer associated with asbestos exposure is malignant mesothelioma, but the risk of bronchogenic cancer is also significantly elevated. Although lung cancer generally is associated with asbestos exposure, other cancers that have been reported to occur at an increased frequency include cancers of the larynx, oropharynx, kidney, esophagus, and gallbladder/bile duct.

Because it is so rare, it has been relatively easy to link the risk of mesothelioma to asbestos exposure. Occupational exposure can be linked to 50% to 80% of all patients with malignant mesotheliomas. In a study of 6,500 workers exposed to asbestos over a 50-year period, it was found that the incidence of mesothelioma was as high as 2%. A study of a large group of asbestos insulation workers found that mesothelioma was responsible for approximately 8% of all deaths. The latent period between exposure and development of malignant mesothelioma is usually long, typically 30 to 40 years. Approximately one-half of malignant mesotheliomas are epithelioid, and the other half are sarcomatoid or mesenchymal, or mixed.

A link between asbestos and bronchogenic carcinomas was first reported in the 1930s and has been subsequently confirmed in several investigations. Although the vast majority of bronchogenic carcinomas are related to smoking, it has been estimated that from 3% to 17% of such cancers are from occupational exposures, including asbestos. Asbestos and smoking appear to interact in a multiplicative manner, and risk is decreased when exposure to either agent is stopped. Whereas the majority of smoking-related tumors are squamous cell carcinomas originating in the upper lobes of the lung, those associated with asbestos are more often adenocarcinomas located in the lower lobes.

Mechanisms

Asbestos fibers are cytotoxic and genotoxic. They have been shown to induce DNA damage, including double-strand breaks, mutations, and chromosomal damage. Evidence also indicates that asbestos fibers can impair mitosis and chromosomal segregation, which can result in aneuploidy. The majority of these effects are believed to be due to oxidative processes that result in the formation of reactive oxygen species. Support for this view comes from studies showing that the amount of damage induced is increased if iron is present in the chemical structure of the fibers. Besides the direct induction of reactive oxygen species, these effects may also be induced indirectly as a result of phagocytosis of the asbestos fibers. Fibers also tend to induce inflammatory responses, resulting in the release of cytokines. Such cytokines may facilitate the growth, selection, and expansion of initiated cells.
Loss of one copy of chromosome 22 is one of the most common chromosomal alteration in malignant melanoma. A wide range of other changes are also seen, including deletions in chromosomes 1p, 3p, 6q, 9p, 13q, 15q, and 22q. Analysis of tumors with these chromosomal alterations have found deletions of CDKN2A, located on chromosome 9p, and mutations in NF2 (the neurofibromatosis type 2 gene that is located on chromosome 22q), with the loss of the normal NF2 allele associated with loss of one entire chromosome 22, as common features.

CHAPTER REFERENCES

CHAPTER 13
Etiology of Cancer: Cancer Genetics

INTRODUCTION

Hundreds of genetic traits are associated with an increased risk of neoplasia. The extent to which cancer risk is attributable to genetic factors varies among tumor types. For rare childhood cancers up to 30% occur in genetically predisposed individuals, whereas not more than 5% to 10% of common adult cancers arise in a hereditary setting. For those malignant tumors most closely associated with environmental carcinogens, the risk attributable to genetic factors is low; but genetic variation may still influence the effect of environmental agents on the host (e.g., sun exposure is a major risk factor for skin cancer, but dark-skinned individuals are virtually immune).

Many of the genes underlying hereditary cancer predisposition are fundamentally involved in the control of cell growth and differentiation or in DNA repair and maintenance of genomic integrity. Analysis of the molecular basis for cancer predisposition has contributed a great deal to our understanding of the biology of tumor cells.

CANCER AS A GENETIC DISEASE

Cancer is a clonal disorder. All cells in a tumor arise from a single cell in which regulatory mechanisms for proliferation have been disrupted. Malignant cells have several qualities that distinguish them from their normal counterparts. They are immortal, often grow more rapidly than normal cells of the same origin, and fail to exhibit normal cell-cell interactions. This latter quality results in their ability to invade and to metastasize and grow in an abnormal cellular environment. The transition from completely normal to frankly malignant occurs through a series of steps or hits (e.g., a cell may first acquire one abnormal property, such as immortality, and then become truly malignant when additional abnormal qualities develop) (Fig. 13-1).

FIGURE 13-1. Carcinogenesis is a multistep process. The transition from completely normal to frankly malignant occurs through a series of mutations in genes that control cell growth and differentiation. Epigenetic phenomena, such as methylation, also play a role. Early hits may have little apparent phenotypic effect, but ultimately growth patterns and cellular morphology are altered.

Hits are mutations or other alterations of genes involved in regulation of cell growth and cell interactions. They may occur by random chance during DNA synthesis and cell replication, as the result of exposure to environmental carcinogens (chemical mutagens, ultraviolet or ionizing radiation, oncogenic viruses), or they may be inherited as germline mutations. Regardless of the source of the genetic alterations, a cell must acquire two or more hits before becoming malignant, a process that usually takes years to decades in humans.

Several types of genes are involved in carcinogenesis. Normal cell regulation results from a balance between the function of growth-promoting genes and growth-suppressing genes. When the former type of gene is activated through amplification or mutation to a hyperfunctioning form, it exerts a positive effect of cell growth. Such genes are known as oncogenes. The latter type of gene is known as a tumor suppressor. Loss of function of both homologous copies of a tumor suppressor gene has a powerful growth-promoting effect. Loss of just one copy typically has little effect. DNA repair genes are another class that may be mutated in cancer cells and do not clearly fit into the categories of oncogene or tumor suppressor gene.

MECHANISMS OF CANCER PREDISPOSITION

Molecular analysis of inherited cancer susceptibility has elucidated a number of mechanisms by which germline mutations can lead to cancer predisposition. Several categories can be distinguished based on the functional characteristics of the genes involved, and additional mechanisms may yet be discovered. The examples that follow use rare genetics defects with a very high risk for cancer to illustrate mechanisms of cancer predisposition. Milder and more common defects in genes belonging to any of these categories may account for a significant portion of cancer risk attributable to hereditary factors.

GERMLINE TUMOR SUPPRESSOR GENE INACTIVATION

Tumor suppressor genes were identified through their role in familial predisposition to cancer. However, these genes are now known to be critically important in growth control of both sporadic and hereditary tumors. It appears that the majority of hereditary cancer predisposition is attributable to germline mutations in tumor suppressor genes. Tumor suppressor genes were identified through their role in familial predisposition to cancer. However, these genes are now known to be critically important in growth control of both sporadic and hereditary tumors. It appears that the majority of hereditary cancer predisposition is attributable to germline mutations in tumor suppressor genes.

...
Suppressor genes. The retinoblastoma gene (RB1) was the first of this class to be isolated.

Retinoblastomas are eye tumors occurring in young children. Most are sporadic, occurring in one eye of children between the ages of 2 and 4 years. In 30% of patients, multiple retinoblastomas arise in one or both eyes and occur before the age of 2 years. Such children often come from families in which retinoblastoma is segregating as an autosomal dominant trait. Based on these observations Knudson proposed that children with hereditary retinoblastoma have inherited a first genetic hit that affects every cell in their bodies. Tumors arise from retinoblasts in which a somatic second hit has occurred. Given the large number of retinoblasts in a child’s eye, it is not surprising that retinoblastomas would arise from multiple cells of predisposed children at an early age. In sporadic retinoblastoma, both hits must occur in a single somatic cell. Because of the much lower probability of two somatic hits, sporadic retinoblastomas are uncommon, occur later in childhood, and are solitary. Knudson did not know the nature of the first and second hits. Mapping and cloning of the retinoblastoma gene proved the two-hit hypothesis and elucidated the nature of tumor suppressor genes.

Clues to the location of the retinoblastoma gene came from studies of the constitutional karyotype of a group of patients with multifocal retinoblastoma plus other physical abnormalities. It was hypothesized that such patients might have an abnormality of one copy of the retinoblastoma gene, but had other genetic defects as well. The simplest explanation for this complex phenotype was an underlying deletion involving the retinoblastoma gene and surrounding genes. A variety of deletions of chromosome 13 were found in such patients, the smallest region of overlap being 13q14 (the cytogenetic study of retinoblastoma tumors might have yielded the same information, but as with many types of cancer, retinoblastoma cells show a great variety of chromosomal defects including but not limited to chromosome 13).

This putative location for the retinoblastoma gene was confirmed by linkage studies in hereditary retinoblastoma families. A polymorphic marker, esterase D (ESD), on chromosome 13q14 was shown to map very close to the retinoblastoma locus. In a related study, a patient with bilateral retinoblastoma was described who had half the normal levels of ESD in constitutional tissues but no visible deletion. Presumably, a submicroscopic deletion in one copy of chromosome 13 had eliminated the retinoblastoma gene and the ESD gene. Cytogenetic studies of tumor cells from this patient showed that one copy of chromosome 13 was consistently absent. Biochemical studies of tumors found no ESD activity. Therefore, the first hit in this patient was a constitution deletion involving the retinoblastoma as well as ESD genes. The second hit in tumor cells was loss of the copy of chromosome 13 containing the normal retinoblastoma and ESD homologue. This study indicated that retinoblastomas arise only when both copies of the gene are defective or absent. Several mechanisms for first and second hits have been described. Often the first hit is a point mutation or tiny deletion. The second hit may be loss of the entire homologous chromosome by nondisjunction in mitosis, loss of a portion of the homologous chromosome by deletion, point mutation of the second copy of the gene, or gene conversion through mitotic recombination. An epigenetic mechanism involving methylation of one copy has been shown to play a role in inactivation of other tumor suppressor genes.

The retinoblastoma gene (RB1) was one of the first to be positionally cloned (i.e., the gene was isolated based on its location with no prior knowledge of its sequence). RB1 extends over more than 100 kb of genomic DNA and encodes a nuclear phosphoprotein (pRb), which is constitutively expressed in a large variety of cell types during all phases of the cell cycle. However, its growth-suppressing activity seems to be modulated through varying levels of phosphorylation. It is relatively dephosphorylated during the G1 phase and phosphorylated during the remainder of the cell cycle. It appears that pRb normally maintains cells in a resting state but can be overcame by signals from the cell-cycle machinery, particularly phosphorylation by cyclin-dependent kinases. The effect of pRb is probably mediated through its ability to bind and sequester several transcription factors. The oncogene products of several DNA tumor viruses function by binding and inactivating the pRb protein. Notably, reintroduction of wild-type RB1 into tumors lacking a functional copy of the gene results in reversion of the tumor cells to a less malignant phenotype.

Homozygous inactivation of RB1 may be sufficient to transform a cell from completely normal to frankly malignant. However, additional genetic changes may enhance the growth and invasiveness of retinoblastoma cells. There is compelling evidence that homozygous inactivation of other tumor suppressors is not sufficient for tumorigenesis (e.g., germline homozygous mutation of the CDKN2 gene does not produce a more severe phenotype than heterozygous germline mutation). Other alterations must be required for development of tumors or else tumors would be present in every cell of the relevant organs almost from the time of birth.

The RB1 gene is often inactivated in tumors other than retinoblastoma, such as breast cancer, lung cancer, and germiniocarcinoma, but it may not play an essential role in regulation of cell growth in many tissue types. Patients with germline mutation of RB1 are prone to osteosarcoma, soft tissue sarcoma, and perhaps melanoma and brain tumors, but not breast, lung, and genitourinary cancers. In the latter group of neoplasms, loss of RB1 may contribute to malignant characteristics, but apparently is not essential to growth control in these tissues.

There is increasing evidence that inactivation of just one homologue of a tumor suppressor gene may have an effect on cell growth and differentiation. In the heterogeneous state, mutations in the FAP gene (familial adenomatous polyposis) may promote excessive proliferation of the colon epithelium. A more dramatic effect is seen with heterozygous mutations in the WT1 (Wilms’ tumor gene), which lead to congenital anomalies of the genitourinary system.

GERMINE ONCOGENE ACTIVATION

Expression of protooncogenes in normal cells appears to be carefully regulated. Different oncogenes are turned on and off at different steps of the cell cycle, at different stages of embryologic development, and in different cell types. The biochemistry and molecular biology of oncogene function is a rapidly evolving field. In general, protooncogenes function as messengers in the pathway by which external stimuli received at the cell surface lead to DNA synthesis, cell growth, and division. It follows that activating mutations of such genes could lead to abnormal, unregulated stimulation of cell proliferation in the absence of appropriate signals.

Although activating mutations of oncogenes have for many years been considered as a possible cause of hereditary cancer predisposition, extensive investigations of a wide variety of disorders have until recently yielded no positive results.

The first evidence for constitutional (but not germline) activation of an oncogene came from studies of McCune-Albright syndrome, a sporadic disorder characterized by precocious puberty, adenomas of several endocrine tissues, areas of bone dysplasia, and café au lait spots. Many of the endocrine tumors that can be seen in this syndrome were known to arise with activating mutations of the gene encoding a G protein. G proteins resemble ras very closely and are known to function as oncogenes. Analysis of a variety of normal and neoplastic tissues from patients with the syndrome showed that they are all mosaic for activating mutations in the a subunit of the G(s) gene. These mutations are not inherited, but arise somatically at an early stage in embryogenesis.

The first disorders shown to be caused by true germline activation of an oncogene were multiple endocrine neoplasia (MEN) type 2a and MEN 2b. These autosomal dominant syndromes are characterized by medullary thyroid carcinoma and pheochromocytoma. MEN 2b has additional features including mucosal neuromas, blubberies, and marfanoid habitus; and MEN 2a can be complicated by hyperparathyroidism. The genes for both syndromes were mapped to the centromeric region of chromosome 10, but the related tumors did not show allelic loss at this site, suggesting that a tumor suppressor mechanism did not underlie the
cancer predisposition. The ret protooncogene had previously been mapped to the same region as the MEN 2 genes, and analysis of RET revealed mutations in both MEN 2a and MEN 2b kindreds. Ret encodes a transmembrane receptor tyrosine kinase. All MEN 2b cases have the same single base alteration in exon 16, a region responsible for the tyrosine kinase activity of the protein product. Most MEN 2a patients have a mutation in codon 634 in exon 11, but mutations in exon 10 have been identified as well. All of the exon 10 and 11 alterations lead to substitution of another amino acid for the normal cysteine residue in an extracellular region immediately adjacent to the transmembrane domain. There is a strong correlation between hyperparathyroidism and a cysteine to arginine change in codon 634.

That the spectrum of ret mutations is extremely limited and none is a stop signal suggests that they have a specific and probably activating effect on the gene product. Transfection studies show that MEN 2a and MEN 2b mutations can indeed induce transformation of NIH3T3 cells. Curiously, inactivating mutations of ret have been shown to cause a completely different disorder, Hirschsprung disease. The main clinical feature is pseudo-obstruction of the colon caused by lack of intestinal parasympathetic ganglia. Apparently ret is required for the proper migration of ganglion precursors during embryogenesis.

Other disorders caused by germline activation of growth-promoting genes include hereditary papillary renal carcinoma (met oncogene) and rare cases of familial melanoma (CDK4).

**DNA REPAIR DEFECTS**

In the context of cancer as a genetic disease, it is easy to see how disorders involving DNA repair defects would lead to malignancy because failure to repair DNA damage would increase the risk of mutations in cancer-related genes.

A typical disorder of this type is xeroderma pigmentosum, an autosomal recessive disease characterized by extreme photosensitivity, premature aging of skin, and neoplasia of skin and, to a lesser extent, other organs (Fig. 13-3). The molecular basis for this disease is inability to repair the types of DNA damage caused by ultraviolet light. Complementation studies performed by fusing cells from different individuals with xeroderma pigmentosum suggest that there are at least eight different genes for this phenotype (genetic heterogeneity). The genes for several types of xeroderma pigmentosum have been cloned, and their activities include photoprotect binding, helicase, and endonuclease.

**FIGURE 13-3.** DNA repair defects accelerate the process of multistep carcinogenesis because alterations in tumor suppressors and oncogenes are not corrected. This 13-year-old girl with xeroderma pigmentosum and severe actinic changes (entropigines, atrophy, and ectropion) has had more than 10 epidermal malignancies. Patients with xeroderma pigmentosum are prone to internal malignancies as well as skin cancer. (Courtesy of Drs. J. DiGiovanna and G. Peck.)

Other disorders with faulty DNA repair or replication include ataxia-telangiectasia (x-ray hypersensitivity; defect in a signal transduction protein that mediates multiple responses to DNA damage such as cell-cycle checkpoint control, activation of DNA repair enzymes, and control of programmed cell death). Fanconi pancytopenia (sensitivity to DNA cross-linking agents, several genes of unknown function), Bloom’s syndrome (high frequency of spontaneous chromosome breaks, helicase defect). All of these syndromes are rare autosomal recessive disorders associated with an increased risk of cancer.

BRCA1 and BRCA2, which are responsible for approximately 5% of all breast cancers, are important members of this class. Germline mutations in these genes lead to an autosomal dominant syndrome of breast and other cancers. The genes are homozygously inactivated in tumor tissue from patients with germline mutations, but in contrast to typical tumor suppressors they are rarely mutated in sporadic tumors. There is little evidence that introduction of these genes into breast tumor cells causes reversion of the malignant phenotype toward something more benign. Animal models with hypofunctioning versions of these genes exhibit a phenotype reminiscent of ataxia-telangiectasia, and both in vitro and in vivo studies indicate interactions with the DNA repair genes ATM and RAD51. BRCA genes have often been referred to as tumor suppressors in the scientific literature, but based on their role in coordinating recombination-based DNA repair, these genes might more properly be called mutation suppressors rather than tumor suppressors.

**ECOGENETIC TRAITS**

Although DNA repair disorders predispose to malignancies at some rate with or without exposure to aggravating environmental factors, they can be thought of as extreme examples of ecogenetic traits (i.e., hereditary disorders predisposing to cancer through unusual sensitivity to common carcinogens). A more typical example is epidermodysplasia verruciformis, in which papilloma virus and ultraviolet radiation act as cocarcinogens to produce squamous cell carcinoma of the skin in genetically susceptible individuals. This autosomal recessive disorder is characterized by widespread, scaly, red or brown macules that progress over many years to in situ and invasive squamous cell carcinomas (Fig. 13-4). The macules are benign lesions containing papilloma virus particles. Decreased cellular immunity has been demonstrated in a high percentage of patients. Malignant lesions occur in sun-exposed areas and are much more frequent in light-skinned individuals with epidermodysplasia verruciformis than in black patients.

**FIGURE 13-4.** Benign skin lesions of epidermodysplasia verruciformis. Papilloma virus and ultraviolet light act as cocarcinogens in producing skin cancer in patients with this ecogenetic trait. In the absence of these environmental agents, affected individuals are not predisposed to cancer. (Courtesy of Dr. D. Lowy.)

Genetic factors influencing host responses to environmental carcinogens may contribute to susceptibility to several common cancer types. Lung cancer has a strong association with cigarette smoking, and the risk attributable to hereditary factors is small. Nevertheless, metabolism of the carcinogens in tobacco smoke may be influenced by genetic variation in detoxifying enzymes. Numerous studies have related polymorphisms in CYP1A1, CYP2D6, and CYP2E1 to lung cancer susceptibility. Likewise aflatoxin B1 exposure contributes to the risk of hepatocellular carcinoma, and genetic variation in epoxide hydrolase (EPHX) may have an...
Many disorders involving cancer predisposition are characterized by a distinctive pattern of neoplasia involving several different organs or neoplasia plus unusual twice as likely to get ovarian cancer as those without the variant. Susceptibility to breast cancer is not affected by the presence of these unfavorable variants. Common variants in the HRAS gene appear to influence susceptibility to this malignancy. Women with both a BRCA1 mutation and an unfavorable HRAS variant are.

In addition to the effects of random chance, perhaps coupled with environmental exposures, penetrance may be influenced by modifying genes. For example, women who carry a mutation in the BRCA1 gene have a risk of ovarian cancer in the range of 30%. Why do some BRCA1 carriers get ovarian cancer whereas others do not? Common variants in the HRAS gene appear to influence susceptibility to this malignancy. Women with both a BRCA1 mutation and an unfavorable HRAS variant are twice as likely to get ovarian cancer as those without the variant. Susceptibility to breast cancer is not affected by the presence of these unfavorable variants.

**ABNORMAL TISSUE ARCHITECTURE**

Juvenile polyposis (JPS) is an autosomal dominant disease characterized by hamartomatous polyps and predisposition to colorectal malignancy. JPS can be caused by germline mutations in the PTEN gene on chromosome 10 or the SMAD4 gene on chromosome 18. The polyps in JPS are composed primarily of stromal cells among which nests of epithelial cells become trapped. The growth of these epithelial cells in an abnormal environment is probably responsible for dysplasia and eventual neoplasia. Presumably, the genetic alterations that contribute to malignant transformation of epithelial cells are similar to those that occur in any colon tumor. Allelic loss of PTEN has been seen in the nonmalignant, stromal component of juvenile polyps but not in the epithelial component of malignancies that arise in JPS patients. The best interpretation of these data is that the JPS gene sets the stage for accumulation of other genetic alterations. Another disorder that may follow this model is epidermolysis bullosa dystrophica, a genetically heterogeneous disease characterized by subdermal blistering that results in chronic inflammation and scarring. Aggressive squamous cell carcinoma of the skin is a well-known complication of this disease and probably arises through increased turnover of epidermal cells leading to a risk of genetic alterations during DNA replication. This mechanism is reminiscent of the carcinogenesis that occurs in chronic, nonhealing burn wounds.

**HUMORAL TUMOR PROMOTERS AND REPRESSORS**

Circulating factors, such as hormones and components of the immune system, may play a role in tumor promotion or progression. Genetic disorders causing immune deficiency or an abnormal hormonal milieu can lead to an increased risk of cancer. Polycystic ovary syndrome, for example, is a common disorder characterized by hyperandrogenism and chronic anovulation. Associated malignancies, related to an abnormal balance between estrogen and androgen and possibly excess luteinizing hormone, include endometrial and ovarian cancer. The etiology of polycystic ovary syndrome is heterogeneous, but several studies support a strong hereditary component. Genetic alterations in three genes have been implicated in this disorder including luteinizing hormone, CYP11a (involved in the synthesis of androgens), and the 21-hydroxylase gene (involved in synthesis of many steroids).

**GATEKEEPERS, CARETAKERS, AND LANDSCAPERS**

The term gatekeepers has been proposed to describe genes whose function is essential in control of growth and differentiation. Gatekeepers directly prevent the development of tumors by inhibiting growth or promoting terminal differentiation and cell death. In the original gatekeeper concept, it was proposed that each tissue type had one key gene of this type, and mutation of the gatekeeper gene was necessary for the development of tumors. Hence, both sporadic and hereditary tumors would be expected to bear mutations in gatekeepers. RB1 is a gatekeeper gene with tissue specificity primarily for the developing retina, and this gene is mutated in all or nearly all retinoblastomas. Other genes serve this gatekeeper function in other tissue types. For some tissues, either inactivation of a gatekeeper or activation of another member of the same biochemical pathway can lead to malignant transformation. Melanomas, for example, often arise with inactivating mutations in CDKN2A, a negative regulator of cyclin-dependent kinases. An alternate route to melanoma is mutation of cyclin-dependent kinase 4 to an activated form that is resistant to negative regulation by CDKN2A. Both inactivating mutations in CDKN2A and activating mutations in CDK4 can cause hereditary melanoma. Other examples of tissues that may arise with mutation in a gatekeeper or another member of the same pathway include colon carcinoma and basal cell carcinoma of the skin. Germline mutation of a gatekeeper leads to a risk of cancer at least 100 times greater than that in the general population.

Caretaker genes are involved in DNA repair and maintenance of genomic integrity. Inactivation of a caretaker does not directly promote tumor formation, but facilitates the development of mutations in gatekeeper genes and other cancer-related genes. Caretakers, like gatekeepers, may be tissue specific, but mutation in a caretaker is neither necessary nor sufficient for the development of cancer. The risk of cancer is modestly elevated in syndromes caused by germline caretaker mutations, and sporadic tumors rarely have mutations in these genes. BRCA1 is an example of a gene in this class.

Landscaper genes, such as the genes for JPS, also act indirectly to cause cancer. Mutations in these genes lead to tissue dysplasia, but are not necessary for the development of cancer and are rarely seen in sporadic tumors.

**CLINICAL CHARACTERISTICS OF CANCER FAMILIES**

The hallmarks of hereditary cancer are relatively early age of onset compared with similar sporadic tumors, multiple and bilateral tumors, and a family history of cancer. Some cancer predisposition syndromes also include birth defects or other distinctive physical features. An underlying hereditary disorder should be considered when rare tumor types are encountered because a significant percentage of certain rare cancers are attributable to genetic factors (e.g., retinoblastoma). The same applies to cancers that are common in one gender occurring in the other gender (e.g., male breast cancer).

Because the genes that underlie hereditary cancer predisposition may be important in a variety of tissues, germline mutation may lead to multisystem disease. The production of multiple phenotypic effects by a single mutant gene is called pleiotropy. Often different members of a single kindred have different manifestations of the same genetic defect, a phenomenon known as variable expressivity. Development of cancer is a multistep process involving two or more independent events. There is always some probability that no cell in a genetically cancer-prone individual will suffer sufficient somatic hits to become neoplastic. In this event a gene carrier could escape the development of any manifestations of hereditary disease and be a nonpenetrant carrier. Virtually all adult-onset cancer predisposition syndromes have age-dependent penetrance because the probability of accumulating sufficient hits to develop cancer increases with age. Presumably nonpenetrant carriers would develop cancer if they lived long enough.
physical features. These genetic syndromes often are definitively diagnosed on the basis of medical and family history plus astute physical examination. Hereditary retinoblastoma/osteosarcoma, MEN 2, and xeroderma pigmentosum fall into this group. Several other syndromes are worth mentioning because they are fairly frequent or are responsible for a significant proportion of certain rare tumors.

NEUROFIBROMATOSIS TYPE 1

Neurofibromatosis type 1 (NF1) is an autosomal dominant disorder affecting approximately 1 in 3000 individuals. The defining clinical features are café au lait spots of the skin, benign Schwann cell tumors known as neurofibromas, and hamartomas of the iris known as Lisch nodules. Other manifestations include macrocephaly, segmental hypertrophy, bone dysplasia leading to pseudoarthrosis, learning disability, and seizures. A variety of CNS tumors occur to excess including optic gliomas, astrocytomas, and meningiomas. Malignant tumors such as neurofibrosarcomas, pheochromocytomas, and leukemia are also part of this syndrome. The gene for this disease was mapped to chromosome 17 in 1987 and was cloned in 1990. Its function involves interaction with the ras oncogene product. Ras proteins have a role in growth regulation through adenylate cyclase activation. They are homologous to G proteins and like G proteins they bind guanosine triphosphate (GTP) in response to signals from cell surface. The GTP-bound form is active in promoting cell growth and slowly inactivates itself by hydrolyzing the bound GTP to guanosine diphosphate. The latter function is influenced by another protein known as the GTPase-activating protein. It follows that homozygous inactivation of the GTPase-activating protein would result in unregulated stimulation of adenylate cyclase by the activated ras protein. Portions of the NF gene are highly homologous to GTPase-activating protein. Presumably the normal function of this gene is to negatively regulate cell stimulation by the ras gene product or similar growth-promoting proteins. In both benign and malignant tumors related to neurofibromatosis, the NF1 gene is homozygously inactivated. Other features of the syndrome could be due to haploinsufficiency (i.e., loss of just one copy of the gene may produce abnormalities in some tissues).

No single clinical feature is sufficient for diagnosis of NF1; in particular, many individuals without NF1 have one or more café au lait spots. Until a valid, gene-based test becomes available, the clinical criteria proposed by the 1988 National Institutes of Health Consensus Development Conference should be used. The life expectancy of patients with NF1 is reduced due to malignant complications, and suggested clinical management includes annual evaluation of blood pressure, skin examination, neurologic evaluation, and ophthalmologic examination. In addition, children should be checked for growth and development, with particular attention to learning disability, sexual maturation, skeletal abnormalities, and speech.

NEUROFIBROMATOSIS TYPE 2

Neurofibromatosis type 2 (NF2) shares with NF1 several characteristics including café au lait spots, skin neurofibromas, and an autosomal dominant mode of inheritance. The defining feature of this syndrome, however, is bilateral vestibular schwannomas (previously called acoustic neuromas). Schwannomas of other cranial nerves and spinal nerve roots, meningiomas, and retinal hamartomas are also seen. Cataracts, particularly the posterior capsular type, are common. NF2 is far less common than NF1, with a prevalence of approximately 1 in 35,000. The gene for NF2 is related to the ehrin family of proteins that link the cell cytoskeleton to cell membrane proteins, and its mode of action is not fully understood.

The diagnosis of NF2 should be considered in patients with bilateral vestibular schwannomas, unilateral schwannoma before the age of 40, or meningioma and any other feature of the syndrome. In the setting of a family history of NF2, DNA-based testing of at-risk individuals is recommended. Recommended follow-up studies in gene carriers include gadolinium-enhanced magnetic resonance imaging to detect early spine and CNS tumors. In the case of vestibular schwannomas, surgical removal of small tumors can preserve some useful hearing.

HEREDITARY WILMS' TUMORS AND RELATED SYNDROMES

On the order of 1% of Wilms' tumor cases occur in a familial setting, following an autosomal dominant inheritance pattern with incomplete penetrance. Twenty percent of familial cases and 3% of sporadic cases are bilateral, consistent with a two-hit model for development of this neoplasm. Rare cases have, in addition to Wilms' tumor, aniridia, hemihypertrophy, genitourinary anomalies, and mental retardation (WAGR syndrome). and cyogenetic analysis has revealed deletions of chromosome 11p13 in such patients. The WAGR complex qualifies as a contiguous gene syndrome (i.e., the multiple features are caused by loss of more than one gene). Denys-Drash syndrome involves Wilms' tumor, genitourinary abnormalities similar to those in WAGR, pseudohemorrhaphidrosis, and nephropathy without aniridia or mental retardation; and no chromosome abnormality has been identified.

The Wilms' tumor gene on chromosome 11p13 was isolated by positional cloning, and encodes a zinc finger protein possibly involved in transcriptional regulation of insulin-like growth factor-2 (IGF-2) and a variety of other growth factors. Additional motifs in the gene may have a role in RNA processing. During development WT1 is expressed specifically in the developing kidney and the genital ridge and fetal gonad, and point mutations in WT1 can result in causing the genitourinary abnormalities seen in the WAGR syndrome and Denys-Drash syndrome. It seems clear that there is not a separate gene for the P part of the WAGR syndrome, although there is a separate gene for aniridia and almost certainly for mental retardation.

WT1 mutations are not the only cause of genetic predisposition to Wilms' tumor. Beckwith-Wiedemann syndrome, which maps to chromosome 11p15, is characterized by a high frequency of Wilms' tumor. Other features of this disorder are large size at birth, disproportionately large tongue, omphalocoele, and linear creases in the earlobe. Several families have been described in which the gene causing predisposition to Wilms' tumor maps to neither chromosome 11p13 nor 11p15.

There is no clear consensus on appropriate screening studies in children at risk for Wilms' tumor. Computed tomographic scanning is superior to ultrasound in detecting early tumors. However, the low cost and lack of radiation exposure make ultrasound an attractive option for serial studies. Magnetic resonance imaging may prove useful as a high-quality imaging tool that does not involve radiation exposure. In practice, abdominal ultrasound at 3- to 6-month intervals is the most common screening method. The exact duration of screening is variable, but most tumors in genetically predisposed individuals occur between birth and the age of 5.

LI-FLAURENFI SYNDROME

In 1968, Miller analyzed 21,659 death certificates of U.S. children who died of cancer and found an excess mortality from sarcomas and brain tumors in siblings. To pursue the observation, Li and Fraumeni reviewed several hundred hospital charts of children with rhabdomyosarcoma. There were four families with multiple childhood sarcomas occurring in association with other childhood cancers and early-onset breast cancer. Subsequent studies established an autosomal dominant pattern of occurrence of at least six tumors: premenopausal breast cancer and childhood soft tissue sarcomas, osteosarcoma, brain tumors, adrenal cortical carcinomas, and acute leukemia. Similar familial aggregates were identified by Strong and Birch and colleagues through studies of hospital-based and population-based series of childhood sarcomas, respectively. Segregation analyses suggested that 50% of carriers in affected families would develop cancer by 35 years of age and 90% by age 70. Penetration appears to be higher in female subjects, who are at risk of breast cancer in adulthood. Patients who survive cancer are prone to develop second primary neoplasms, often within the field of prior radiotherapy.

In 1990, germline mutations in the p53 tumor suppressor gene were identified in five families with Li-Fraumeni syndrome, and the observation was soon confirmed by several groups. In addition, germline p53 mutations have been identified in a small fraction of unselected patients with early-onset multiple primary cancers, multifocal brain tumors, childhood sarcoma, and childhood adrenal cortical carcinoma. However, less than 1% of breast cancer patients have germline p53 mutations. The germline p53 mutational spectrum is similar to that for somatic p53 mutations in sporadic cancers and tends to occur in exons 5 through 8. Germline p53 mutations have not been detected in a substantial minority of Li-Fraumeni families, suggesting that other genes might produce the syndrome. Genetic heterogeneity is also indicated by exclusion of linkage to p53 for at least one affected family.

When germline p53 mutations were identified, the possibility of predictive testing to identify unaffected carriers became feasible. However, the risks and benefits of predictive testing for a syndrome of multiple cancers are unknown. In particular, early detection at a curable stage is problematic for the component cancers of this syndrome. Several small research programs of predictive genetic testing for p53 mutations have been offered to adults in families with a known alteration. Lessons from p53 testing may be useful in developing testing programs for more common inherited susceptibility genes for breast and colon cancer.
NEVOID BASAL CELL CARCINOMA SYNDROME

The nevoid basal cell carcinoma syndrome (NBCC), also known as Gorlin syndrome and the basal cell nevus syndrome, is an autosomal dominant disorder that predisposes to basal cell carcinomas of the skin, medulloblastomas, and ovarian fibromas. Its prevalence has been estimated at 1 per 56,000, and 1% to 2% of meningiomas have a familial component attributable to the syndrome. Other neoplasms that probably occur to excess include fibrosarcomas, meningiomas, rhabdomyosarcomas, and cardiac fibromas.

In addition to benign and malignant tumors, malformations are a striking component. The syndrome is associated with pits of the palms and soles, keratocysts of the jaw and other dental malformations, cleft palate, characteristic coarse facies, strabismus, dysgenesis of the corpus callosum, calcification of the falx cerebri, spinal bifida occulta and other spine anomalies, bifid ribs and other rib anomalies, ectopic calcification, mesenteric cysts, macrocephaly, and generalized overgrowth.

The NBCC gene was mapped to chromosome 9q22.3 and the demonstration that the exact same region is deleted in a high percentage of sporadic basal cell carcinomas and other tumors related to the disorder provided strong evidence that the gene functions as a tumor suppressor. Positional cloning identified a human homologue of Drosophila patched as the gene for this syndrome, and subsequent studies showed that patched is mutated in a high percentage of sporadic basal cell carcinomas. Patched is a negative regulator of the hedgehog pathway, several members of which are known to function as oncogenes in skin and brain tumors. Mice lacking patched may be a necessary if not cell carcinoma development. Minute basal cell carcinomas are as likely as large tumors to have patched mutations, and all histologic subtypes, whether primary or recurrent, have a high frequency of loss of patched. Tumors with allelic loss on chromosome 9 sometimes show additional areas of loss on other chromosomes, but no tumors have loss on other chromosomes without involvement of chromosome 9. Patched appears to function as a gatekeeper gene in the epidermal cell type from which basal cell carcinomas arise.

In contrast to many other disorders caused by tumor suppressor congenital anomalies are a prominent feature of NBCC. One hypothesis to explain at least some of these anomalies is a two-hit mechanism in which a single fetal or embryonic cell that has lost the normal copy of the gene gives rise to a developmentally abnormal clone. However, other symmetric generalized features of the syndrome (e.g., overgrowth, corpus callosum defects) suggest that loss of just one copy of the NBCC gene exerts an effect on growth and differentiation.

The diagnosis of NBCC should be considered in anyone below the age of 30 with a single basal cell carcinoma and in older individuals with multiple basal cell carcinomas. Medulloloblastomas, keratocysts of the jaw, and, to a lesser extent, such problems as skeletal defects and cataracts should raise the suspicion of NBCC regardless of the presence or absence of basal cell carcinomas. Palmar and plantar pits are pathognomonic. DNA-based testing is available for individuals with NBCC and for sporadic patients as well. The most important follow-up study in affected individuals is dermato logic examination for basal cell carcinomas at intervals of 6 months to 1 year. Yearly dental examinations, with particular attention to the possibility of jaw cysts, are also recommended. Because the frequency of medulloloblastoma in this syndrome probably does not exceed 5% and may be as low as 1%, screening studies for this tumor type in children are controversial.

TWO MECHANISMS LEADING TO FAMILIAL COLON CANCER

Familial aggregation of carcinomas of the colon and rectum have been reported in multiple studies in the literature. Close relatives of an affected individual have approximately twofold increased risk of the disease. Risk increases with the number of affected members in the kindred. Some families develop colorectal carcinoma in an autosomal dominant pattern, strongly suggesting the influence of highly penetrant gene(s).

Familial adenomatous polyposis (FAP) is the first recognized familial colorectal cancer syndrome to be clinically recognized. The inheritance pattern is autosomal dominant, and the disorder accounts for approximately 1% of colorectal cancer. Affected individuals develop hundreds to thousands of colonic adenomas by the second decade, and almost all develop colorectal carcinomas by age 45. FAP carries a substantial risk for small intestine and gastric adenomas with a 5% lifetime risk of small bowel or gastric carcinoma. Although most families develop only polyposis and cancer of the colon and rectum, others have associated osteomas of the jaw and skull, fibromas of the skin, and benign and malignant tumors of the ampulla of Vater and stomach (Gardner’s syndrome). In addition, polyposis coli has been reported in association with brain tumors, a condition called Turcot’s syndrome. The association of brain tumors and colon cancer without polyposis has also been termed Turcot’s syndrome but is genetically distinct.

Early efforts to identify the gene for adenomatous polyposis coli (APC) were unrevealing. Eventually, a case report of a patient with mental retardation, multiple congenital anomalies, adenomatous polyposis of the colon, and a chromosome 5 deletion localized the APC gene to the long arm of chromosome 5q. In 1991, the APC gene was cloned and shown to have the characteristics of a tumor suppressor gene. APC promotes the degradation of the b-catenin, which can function as an oncoprotein in colon carcinoma. Most APC germline mutations yield a truncated protein product, and correlations have been found between size of the APC protein and phenotype. Mutations in the 5’proximal end of the gene result in small protein products and attenuated manifestations of polyposis coli. Pigmented lesions in patients with polyposis colorectal cancer, including hypertrichosis and hyperpigmentation in skin anogenital regions, are associated with mutations of the APC gene in exons 9 to 15 through 14. An APC mutational hot spot is at codon 1309 (exon 15), and mutations in this region are associated with larger numbers of polyps of early onset. These patients have poor prognoses for survival when compared with those with mutations at other APC sites. I1307K, a common variant among Ashkenazi Jews, causes genetic instability in the APC gene and a tendency toward somatic mutations. This variant is associated with a small increase in the risk of colorectal cancer and possibly an increased risk of other types of cancer as well, but not with large numbers of colon polyps. A role for clinical testing for this mutation is not established.

The other major form of hereditary colorectal cancer is hereditary nonpolyposis colorectal cancer (HNPCC). In this autosomal dominant disorder, the colon is not carpeted with polyps, but the lifetime risk of colon cancer is still very high. Other tumor types that occur in this syndrome include carcinomas of the endometrium, stomach, ovary, small bowel, pancreas, hepatobiliary tract, ureter, and renal pelvis. Muir-Torre syndrome is a variant of HNPCC with sebaceous adenomas, carcinomas, and keratoacanthomas. Because colorectal cancer is common in the general population, familial aggregates of two or three cases might be caused by chance association or shared environmental influences. The International Collaborative Group on HNPCC has proposed that the diagnosis be based on the following findings (called the Amsterdam criteria): three or more relatives with histologically diagnosed colorectal cancer, of whom one is a first-degree relative to the other; two cancers involve at least two generations; at least one case diagnosed before age 50; and exclusion of FAP.

In 1993, an HNPCC gene was mapped to the short arm of chromosome 2 (2p16). Simultaneously, two studies described widespread genetic instability in short repeated DNA markers (microsatellites) in cancers of the proximal colon, particularly within tumors of familial cases. The widespread genetic instability raised the possibility that the inherited defect in HNPCC might involve mutations in mismatch repair genes that had been well characterized in yeast and Escherichia coli. Fishel and associates cloned several human homologues of yeast mismatch repair genes, and found that MSH2 is mapped to human chromosome 2p. They then demonstrated inherited MSH2 mutations in several families with HNPCC. Using a second approach, positional cloning, Leach and colleagues independently demonstrated MSH2 as the colon cancer gene on chromosome 2. Within months, a second HNPCC gene, MLH1, was mapped to the short arm of chromosome 3 and cloned. MSH2 and MLH1 account for the large percentage of HNPCC families including cases of Muir-Torre syndrome. Other genes that can cause HNPCC include MSH6 and PMS1 and PMS2, which are homologous to E coli MUTL and yeast PMS1. Mutations in mismatch repair genes are found in a high percentage of families that conform to the Amsterdam criteria, particularly if endometrial cancer is present in the family as well as colon cancer.

Management of hereditary colon cancer involves surveillance and preventive treatment of affected patients for colon and extracolonic cancers, counseling of patients and their families, and presymptomatic diagnostic testing of at-risk family members. In FAP, prophylactic colectomy is recommended in all affected patients during the second or third decade. Regular endoscopic checkup of the upper gastrointestinal tract is necessary to detect malignant transformation of duodenal and gastric polyps. For HNPCC patients, only preventive measures such as regular colonoscopic and gynecologic examinations are recommended. Prophylactic colectomy or hysterectomy are not considered to be routine procedures at present. On a research basis, trials of chemopreventive agents are under way. Substances being explored in colorectal cancer prevention include (1) the nonsteroidal antiinflammatory drugs, which inhibit the formation and evolution of adenomas in animal models presumably by their inhibition of cyclooxygenase and prostaglandin synthesis; and (2) antioxidants, such as vitamin E or C, which may modulate carcinogenic substances and correlate with lower colon cancer risk in epidemiologic studies. Dietary intervention with decreased fat intake and increased fiber consumption has also been linked to a lower incidence of colon cancer in epidemiologic studies.
INTRODUCTION

Cancer epidemiology is the study of cancer patterns in populations and cancer causation. Through epidemiologic studies, we have learned about changing patterns of cancer incidence and mortality worldwide, risk factors for specific cancers, potential prevention strategies, and the role of genetic variation in cancer etiology. Leads from these studies have formed the basis of many laboratory investigations that have revealed biologic mechanisms for the associations first described in epidemiologic studies. It is beyond the scope of this chapter to detail the complex methodology of epidemiologic studies. A number of excellent texts elucidate the nuances of study design and conduct. The object of this chapter is to provide clinicians with information about epidemiologic approaches and the strengths and shortcomings of various study designs so that they may evaluate the literature more critically.

Similar to clinical trials, epidemiologic studies are of human populations and, therefore, are frequently multiple years in duration and subject to certain limitations. Epidemiologic studies are usually observational and sometimes opportunistic, to learn as much as possible when humans are unexpectedly exposed to potentially harmful substances. An example is the long-term study of the population of Seveso, Italy, after the 1976 explosion that exposed the local population to high levels of 2,3,7,8-tetrachlorodibenzo-p-dioxin. Another example involves the study of long-term toxicities of therapeutic irradiation and chemotherapy for cancer treatment (one of the few instances in which humans are deliberately exposed to well-documented doses of carcinogens; see Chapter 55.7). These studies have greatly enhanced our understanding of cancer biology and have affected treatment (e.g., less radiation therapy for heritable retinoblastoma). The central distinction in epidemiologic studies is between the observational and experimental approaches (Fig. 14.1-1). The experimental approach controls exposures to some extent and, therefore, presents different issues in design, conduct, and analyses of studies. This chapter focuses predominantly on observational studies, since the experimental approach is covered in other chapters on prevention and clinical trials.


OBSERVATIONAL STUDIES

Observational epidemiologic studies can be divided into two broad categories: descriptive studies and analytic studies. Descriptive studies are usually large, population-level studies of patterns of disease based on demographic data, such as age, gender, race, geographic residence, calendar year, type of cancer, and possibly other attributes. Descriptive studies provide important information for public health decisions and are often hypothesis-generating. Examples of these studies are the comparison of cancer rates among migrants to a different country, such as the evaluation of breast and colon cancer in Asians after migration to Western countries and the evaluation of melanoma among individuals of British origin in Australia. Analytic studies are designed to test hypotheses by obtaining individual information about potential risk factors for specific types of cancer. Examples would be the resultant investigation of the role of Western diet and lifestyle among Asian migrants to the United States and the role of sun exposure in the development of melanoma among migrants to Australia.

Certain general concepts are important to the evaluation and interpretation of all epidemiologic studies. The inference of causation from epidemiologic studies is quite complex; there are no fixed and agreed-on criteria to establish causation. Most formulations, however, derive from the criteria originally proposed at the time of the controversy about cigarette smoking and lung cancer. Descriptive studies in general will not lead to causal inferences. No one analytic study, however large and methodologically robust, is likely to “prove” a causal association. Because epidemiologic studies are largely observational, it is important to replicate findings from one study in other groups or populations to evaluate the consistency of the results. The consistency of results should be interpreted taking into account the relative rigor of both the study designs and the conduct of the investigations and the size and statistical power of the studies. Within appropriately designed and conducted studies, the magnitude of the risks demonstrated and the statistical significance of the risks are important. The greater the magnitude of the risk, the stronger the evidence for causation. Evidence of increasing risk of cancer with increasing exposure to a risk factor strengthens a postulated association. Data from studies must be interpreted within the current body of knowledge of that exposure and that cancer. There needs to be sufficient time between the exposure and the development of cancer as well as biologic plausibility of the exposure. Animal studies demonstrating carcinogenicity of an exposure lend credence to the hypothesis.

In trying to determine whether an association found in an investigation is plausible and valid, it is important to consider the possibility of bias in the data, confounding factors, and chance associations. Bias can result from a flaw in the design of the study or in the collection of the data. For instance, the study could be designed such that individuals with cancer are identified several months after the cancer is diagnosed. For individuals with a cancer for which there is high survival, this may not be a problem. For individuals with a cancer for which the survival is poor and mortality is rapid, only a subset of better-prognosis individuals would be alive to participate. This subset of individuals may fundamentally differ from those with more aggressive disease in host susceptibility or in risk factor exposures, if either is related to more aggressive disease. Another type of problem could be in long-term follow-up of groups under study. If there is differential effort in locating individuals with specific exposures or differential effort in locating individuals who may have become ill, there could be profound effects on the data. If interviewers know who has cancer and who does not, they may be (even unconsciously) more persistent in prompting individuals with cancer for answers to specific questions. This could lead to a systematic bias in data collection. These types of difficulties cannot be accommodated well in the data analyses and affect how one can interpret the results.

Confounders are variables associated with disease risk and with an exposure under investigation. If confounder variables are not appropriately recognized and dealt with in analyses, the risks associated with the exposure of interest may be altered, either increased or decreased. Confounder variables must demonstrate three characteristics: (1) The confounder must be related to disease risk in individuals with and without the exposure of interest; (2) the confounder variable must be
associated with the exposure of interest in the group from which the study participants come; and (3) a confounding variable cannot be an intermediate end point in the development of disease. These relationships can be complex to disentangle but can frequently be handled by specific analytic techniques. An example of a confounder would be cigarette smoking in participants in a case-control study that is investigating the role of alcohol consumption in the etiology of oral cancer. Cigarette smoking is related to alcohol consumption and is a risk factor for oral cancer. If the level of cigarette smoking is not accounted for in the analysis, the risk shown for alcohol consumption would be altered.

In interpreting results of epidemiologic studies, one must always also consider that a finding occurs by chance alone. These spurious associations are more likely in large, complex analyses with multiple comparisons. Chance associations usually do not show evidence of a dose response and may or may not have biologic plausibility. In evaluating the level of statistical significance of a finding is usually helpful also. Most risk estimates are accompanied either by a test of statistical significance or by confidence intervals. Ninety-five percent confidence intervals that do not include 1.0 indicate significance of at least the 0.05 level. This can be interpreted as a 1 in 20 likelihood of the observation occurring by chance alone. The more comparisons that are done, the more likely it is that a chance association will occur.

In descriptive studies, many demographic data are collected from institutions, not individuals. In those data, the completeness of ascertainment of data and quality of data from the relevant sources is important to evaluate. In analytic studies, response rates indicate the percentage of people approached who actually complete components of an investigation. Especially in analytic studies, epidemiologists are dependent on the generosity of study participants to spend time, provide sensitive or confidential information (or both), and donate biologic specimens. This is becoming an increasing problem. In the late 1970s and early 1980s, response rates in excess of 90% were not uncommon. As individuals have become more concerned about privacy issues and as studies have become more demanding of time, biologic specimens, and other impositions, response rates have dropped substantially. It is now common to have response rates of 50% or lower if biologic specimens are requested. Lower response rates are of concern because it often is not clear that respondents are identical to nonrespondents in terms of risk factor exposures or genetic susceptibility factors. Inferences about the entire group are quite limited if only a minority of individuals provide information. In addition, low response rates affect the statistical power of the study to detect associations.

DESCRIPTIVE STUDIES

Descriptive studies are important for noting differences in patterns of cancer among different populations or over time. Evaluating changes in cancer incidence has been essential in determining public health priorities. To have equivalent data to compare across populations or time, crude data are adjusted to standard age distributions. Crude incidence is the number of new cancer cases in a selected group that occur over a specified time period, divided by the total number of people in that selected group (usually the number at the midpoint of the specified time period). Similarly, crude mortality is the total number of deaths from cancer in a selected group that occur over a specified time period, divided by the total number of people in that selected group. For international comparisons, these crude rates usually are adjusted to an age-standardized population, as the age structure of populations varies widely and cancer rates are age-dependent. In an equivalent manner, to compare rates in the same population over different calendar periods, the crude rates need to be adjusted to a similar population structure.

Descriptive studies are highly dependent on the quality of data collected. The quality of incidence data varies substantially, depending on the medical care systems, the thoroughness with which a diagnosis of a specific type of cancer is pursued, the completeness of reporting a new diagnosis of cancer to whatever institution is collecting the data, and the accuracy of the population numbers. The percentage of histologic confirmation of new cancer diagnoses also varies widely among health care systems and among tumor registries. In some areas, there may be better reporting of causes of death than of new cases of cancer, mortality may be a more reliable estimate of rates, particularly if the type of cancer is associated with poor survival. The ideal population for evaluating cancer rates would be a large, diverse one in which there is little in or out migration, one health care system provides high-quality care from birth to death, and each individual has a unique identifier for life.

Maintaining the infrastructure for these descriptive studies is essential for monitoring trends in cancer incidence and mortality over time, which is necessary for monitoring the health of the population. For instance, through evaluating data from the Surveillance, Epidemiology, and End Results (SEER) program, it is clear that lung cancer incidence has leveled overall for men. For women, however, the rates are still increasing, and lung cancer now is the leading cause of cancer-related deaths in women. The SEER data are now available on the National Cancer Institute (NCI) Web site http://www.seer.cancer.gov. These data provide population-based incidence rates, survival, and mortality for the United States, based on information from 11 population-based registries and three supplemental registries. These registries cover approximately 14% of the U.S. population, with measures of poverty and education similar to the U.S. population. The SEER population tends to be more urban, with a higher percentage of foreign-born persons than the general U.S. population. For international comparisons, the World Health Organization’s International Agency for Research on Cancer and the International Association of Cancer Registries publishes Cancer Incidence in Five Continents. This volume is extremely useful in comparing the wide variation in cancer incidence. The Scandinavian countries have long-standing active cancer registries. Several years ago, the NCI and the Danish Tumor Registry collaborated on analyzing data regarding multiple primary tumors occurring in Connecticut and Denmark over approximately a 50-year period.

The NCI has also published Atlas of Cancer Mortality in the United States 1950–94, which is available at Web site http://www.cancer.gov/atlas. Two components comprise this atlas: a static version and a dynamic version. These maps were used to show a substantial change in geographic patterns of lung cancer mortality over time that correlates with changes in smoking patterns. The mortality is higher for white male individuals in the Southeast (Fig. 14.1-2), for white female subjects in the West, and for African Americans in the urban North. This is also an example of another variant in descriptive studies, a correlational or ecologic study, in which statistics gathered for another purpose are correlated with cancer incidence. An earlier version of the mortality maps showed an excess of lung cancer in white men along the southern seaboard. A number of analytic studies were undertaken to evaluate potential risk factors that revealed that the excess was largely due to asbestos exposure during World War II. In the recent maps, this coastal excess has essentially disappeared for white men (see Fig. 14.1-2). These mortality maps can be used to generate many new hypotheses related to the geographic clustering. Newer technologies, such as satellite mapping that provides data for geographic information systems, will likely become increasingly important in the future for ecologic or correlational studies.

ANALYTIC STUDIES

In contrast to descriptive studies, in which only demographic information is available, analytic studies obtain information on specific risk factors from individuals. Each of the two broad categories of analytic studies—cohort studies and case-control studies—has specific advantages and limitations.

COHORT STUDIES

Cohort studies are frequently prospective and longitudinal. A group is identified and defined and then followed prospectively for outcomes of interest. There are multiple advantages of this type of design. Information on specific risk factors can be obtained before onset of disease. This is particularly important for risk factors
that may be altered in individuals who have become symptomatic from their disease. For example, the diet of a patient who has just had a colectomy for colon cancer
or a gastrectomy for stomach cancer will be quite different from that patient's diet before diagnosis. There may be recall bias in remembering previous dietary intakes.
Usually, updated information is collected at regular intervals, so that longitudinal patterns of exposure can be obtained (variations in smoking patterns, alcohol
consumption, etc.). Because information is collected on a large number of people at regular intervals, information is best collected on relatively common exposures. It
is impractical to expect participants to complete extensive questionnaires every year or two. Biologic samples can also be obtained, so that sequential patterns of
exposure (micronutrients, viral titers, nicotine metabolites) can be quantified and obtained, again, before alteration by disease status. Usually, as information is
collected from participants routinely before being affected with a specific type of cancer, there is much less problem with differential information from affected and
unaffected participants. Another advantage of cohort studies is that multiple outcomes (several different types of cancer, mortality from other causes, morbidity if data
are collected, etc.) can be evaluated.
In a prospective cohort, when part of the cohort has a specific exposure (e.g., cigarette smoking) and part does not, the relative risk of developing disease is
calculated by the ratio of the proportion of exposed individuals who develop cancer to the proportion of unexposed individuals who develop cancer. 2 This is a direct
comparison of the rate of cancers (or for mortality rate of death) in the exposed and unexposed groups. A relative risk of 2 means that the exposed group is twice as
likely to develop the cancer as the unexposed group; a relative risk of 0.5 means that the exposed group is half as likely to develop the cancer. The terms in these
calculations usually include the time interval over which the event occurred, usually person-years of observation. Relative risks are usually reported with 95%
confidence intervals. If the 95% confidence intervals do not include 1.0, the relative risk is considered statistically significant. One can also calculate other measures
of risk that reflect the percentage of disease attributable to the specific exposure, if it is causal.
Cohorts are sometimes defined by a previous “exposure,” which could be an occupational exposure, an occupational group, a specific disease, a type of vaccination,
a certain medication, and the like. In these retrospective studies, individuals are followed up from a specific time of exposure in the past to onset of disease, death, or
time of study. The rates of cancers (or death, if evaluating mortality) over the time period frequently are compared to the general population rates rather than to an
unexposed group (which may not be available). This comparison assumes that the group under study would have the same baseline rate of cancer as the general
population, absent the exposure under study.
In both the prospective and retrospective cohort designs, careful definition of study participants and exposition of follow-up procedures are crucial for interpreting
data. This includes how potential participants are identified (and contacted), initial and continuing participation rate, loss to follow-up, and refusal rate (which may
change over time). In evaluating the relationship of exposure to disease, methods and precision of quantification of exposure are important. Exposure measures can
range from industrial hygiene estimations of occupational exposures, to dietary histories (or diaries), smoking history, medication records, and biologic measures,
such as DNA adducts or metabolites of specific substances in specimens. The potential error in these measures must be considered in interpreting the data. An
advantage of cohort investigations is that when onset of exposures is well documented, one can evaluate latency of the exposure to disease diagnosis and the
duration of an effect after exposure. For instance, 20 years after the explosion in Seveso, detectable levels of dioxin persisted in the blood of heavily exposed
individuals. 32 As with all epidemiologic studies, confounding variables should be identified when possible.
A relative disadvantage of cohort studies is that they are usually large, long-term, complex, and very expensive endeavors. Outcomes in prospective cohorts may not
be apparent for decades, and it is extremely difficult to motivate study participants to continue. With increasing concerns about privacy and confidentiality of data,
fewer participants are willing to undertake the commitment. If a substantial part of the proposed cohort does not participate or if there is continuous loss of participants
due to refusal or withdrawal from the study, the results may become difficult to interpret. The participant group may no longer reflect the entire group from which they
were derived. Even with very large cohorts, it is difficult to study relatively rare diseases or uncommon exposures (unless the cohort was chosen because of the
exposure). Because of the limitations of imposition on cohort participants, detailed information on other exposures of interest may be lacking. This lack of focused
exposure information can be a problem when specific cancers are evaluated. To overcome these constraints, within larger cohort investigations, additional information
on other exposures of interest (including confounders) may be collected from smaller substudies of identified individuals with a specific cancer and a subgroup of the
cohort (either matched controls or a selected sample of the cohort). 2 These are called either nested case-control or case-cohortanalyses. These approaches may be
cost-effective mechanisms for evaluating specific cancers of interest free of selection bias if the participants with the cancer are still alive to provide the information.
Another approach within the cohort design for evaluating rare cancers is to combine data from several cohorts.
CASE-CONTROL STUDIES
Case-control studies, also called case-referentstudies, usually obtain data within a limited time frame on previous exposures of interest. They are, therefore,
considered retrospective. Cases (individuals with the cancer of interest) and controls (individuals similar to the cases but who do not have the cancer) are identified in
a systematic manner, and data are collected. These data are frequently collected using questionnaires, abstracting occupational or medical records, or examining
participants. Usually, there is not longitudinal follow-up. Several advantages accompany this design. The studies are much shorter in duration than cohort studies
and, therefore, are less costly. The amount of data collected at one time can be greater than in a cohort study because the investigators will not be imposing on the
participants repeatedly over many years. Questionnaires can be longer, with detailed information about more risk factors specific to the type of cancer being studied.
This may allow evaluation of interaction of risk factors. Because the cancers have already occurred, it is more feasible to identify a larger number of individuals with
relatively rarer tumors to include in the study than to wait to accrue a sufficient number in a large cohort. It is, therefore, more efficient and cost-effective to try to study
a rare tumor in a case-control study than in a cohort study.
Biologic specimens can also be collected relatively efficiently, often in close temporal proximity to extensive information about recent exposures. In contrast to cohort
studies, however, for the cases, this will be after the onset of disease. If the disease process directly or indirectly affects the exposure measure, there will be difficulty
in interpreting the results. (Biospecimen collection as part of case-control studies is discussed later in Molecular Epidemiologic Studies .) Other limitations in
case-control studies include recall bias, as individuals with cancer may have spent time already pondering the causes of their illness. In contrast to cohort studies, in
which multiple types of cancers can be evaluated as outcomes, in case-control studies, usually only one cancer type or a small number of closely related cancer types
is evaluated in one study.
The identification of cases and the selection of controls are crucial to the validity of the investigation. Two general approaches are used to identify cases. The first is
through population-based registries. Theoretically, this should lead to the least biased ascertainment of cases and should identify cases representative of the group
from which they are identified. For cancers associated with high survival, this technique can be highly successful. There is frequently a several-month delay between
the time the cancer is diagnosed and the time that the case is identified from the registry, however, which can cause a selection bias for cancers with high mortality.
This delay can also cause problems if biologic specimens to measure exposure or host characteristics are to be collected. Many of the bioassays would be profoundly
altered by interval treatment with radiation therapy or chemotherapy. In some instances, special efforts are made to identify cases rapidly. Although this is necessary
for some types of cancer, it is frequently very costly.
The second general approach is to identify the cases from a hospital or clinic setting. If essentially all cases from a defined area are treated in the hospital from which
the cases are identified, the cases may be essentially as representative of the population as the true population-based ascertainment. An advantage of hospital
ascertainment is that the cases may be more cooperative, and it is logistically easier to enroll them and to collect the data, including biospecimens. Again, if biologic
samples are collected, which could be affected by being in the hospital (dietary factors, smoking, occupational exposures, etc.), the results may be difficult to interpret.
For both of these methods of identification, it is important to evaluate closely how scrupulously the cases were identified.
Equally important to the validity of the study is the selection of the controls. The controls should be from the same population group as the cases. Controls are
frequently matched to the cases on characteristics that are important in determining risk of disease, such as gender, age, and ethnicity, or on potential confounder
variables (e.g., socioeconomic status or, possibly, smoking status). Controls may be population-based (i.e., identified from the same population by use of population
registries or lists, random-digit dialing if telephones are common in the population, neighborhood canvassing, or other methods). Although theoretically these methods
should yield controls that are most representative of the population from which the cases come, if only a small proportion of individuals approached agree to
participate in the study, this may not happen. The participants may differ from the nonparticipants in manners that are difficult to quantify and may not be
representative. True population-based controls are becoming increasingly difficult to enroll in studies, at least partially because of privacy concerns.
If the cases are identified from hospitals or clinics, an alternative control selection could be patients from the same hospital or clinic. Care must be taken to select
individuals who have the same likelihood of coming to that hospital or clinic if they developed the same disease as the cases (a surrogate may be the same catchment
area for the control disease as for the type of cancer the case has). Selecting individuals as possible controls who have a variety of diagnoses that do not include
conditions related to the development of the type of cancer of interest is also important to minimize bias. For instance, considering individuals being evaluated for skin
conditions in a dermatology clinic as controls for a melanoma case-control study would often be inappropriate, because the reason they were being seen may be
related to melanoma risk factors. 33 If there is a clinical component to the study, such as a structured physical examination, this is often best performed in a clinical


setting. Obtaining biologic specimens can also be facilitated in a clinical facility, but similar difficulties in interpreting results can occur as with cases. Cooperation and participation are frequently higher among hospital- or clinic-based controls.

The measure of association in case-control studies is the odds ratio, which is an estimate of the relative risk. Unlike cohort studies, case-control studies cannot directly evaluate the actual rate or risk associated with a specific exposure, because the rates in the unexposed and exposed populations are not known. This estimate is the ratio of the odds of exposure among cases (number of exposed cases divided by number of unexposed cases) to the odds of exposure among controls. The odds ratio is a good approximation of the relative risk when cancer is uncommon in the population. Estimates can also be made for the attributable risk, which also cannot be directly measured as in cohort studies. Similar to cohort studies, the odds ratio shows a positive association between exposure and disease with a probability of less than 1.0. Odds ratios greater than unity are associated with exposure and disease, which are considered statistically significant when they do not include 1.0. In case-control studies, detailed exposure information may have been collected on several exposures and potential confounders identified. The other risk factors and confounders should be considered in the analyses and dealt with appropriately. In large studies, with sufficient numbers of participants exposed to two risk factors, interactions between two exposures, such as asbestos and smoking in lung cancer, can be examined.

In limited situations, a variant of a case-control design or analysis, a case-only or case-case design, may be appropriate. This type of analysis can be useful when attributes or risk factors are not available or present in controls or when controls are not available. This design cannot evaluate main effects of specific genes or exposures but can evaluate the interaction between a genotype and an environmental exposure. Case-only or case-case studies are more efficient than case-control studies for detecting interaction. These analyses require that the genotype and the exposure be independent. The inferences from this type of analysis are often difficult to interpret and somewhat limited, because the risk percentages do not reflect comparisons between affected and unaffected individuals but between affected individuals. An example could be a case-control study with a specific genotype to compare the affected and unaffected individuals. Another example could be a study comparing somatic mutations in tumors to risk factors.

Molecular epidemiologic studies have all of the logistic and methodologic characteristics of conventional epidemiologic studies. They also have the added constraints of laboratory components. Molecular epidemiologic studies are, by definition, interdisciplinary and require investigators from highly divergent fields to collaborate closely from study design to completion. The complexity of these investigations manifests in both the epidemiologic and the laboratory components.

Many of the molecular epidemiologic investigations were relatively small, exploratory studies to determine the feasibility of this approach, to validate biologic markers, and to estimate level of risk. Even when assessing polymorphisms present in one-half of the population, these relatively small studies do not have power to evaluate modest risks, especially in subgroup analyses. The type of specimen collected is determined by the exposure of interest and the methods available to quantify that exposure. Some investigations focus on directly measuring exposure, such as blood levels of substances (e.g., toxins, carcinogens, nutrients, micronutrients, viral titers), DNA adducts, lesion patterns, and the like. These data are then correlated with measures of exposure from occupational records, questionnaire responses, medical records, and other sources of data. If the metabolic pathways of the exposure of interest are known, often genes with variations (polymorphisms) are evaluated and correlated with either biologic measurements of dose or historic measures or both. Other host susceptibility factors (e.g., immune response determinants) may be related to time to progression, disease severity, or other parameters.

Molecular epidemiologic studies have all of the logistic and methodologic characteristics of conventional epidemiologic studies. They also have the added constraints of laboratory components. Molecular epidemiologic studies are, by definition, interdisciplinary and require investigators from highly divergent fields to collaborate closely from study design to completion. The complexity of these investigations manifests in both the epidemiologic and the laboratory components.

The additional complexity of the laboratory components begins with establishing appropriate collection, processing, and transportation of biologic specimens with necessary quality control measures. Because many of the specimens must be stored for various lengths of time before being assayed, some type of repository system is needed to locate and track specimens. As laboratory assays are completed for the samples, each sample becomes more valuable because of the laboratory information in combination with the epidemiologic information connected to each sample. Repository functions, including proper identification and tracking of each sample, remain essential. All the routine difficulties of validity and reproducibility of the laboratory techniques being used on the specimens must be resolved before analysis of the samples. Many of the assays of particular interest may be technically challenging or quite complex. The laboratory collaborators often have to develop the assays for the cohort or case-control studies and do not have the time or resources to perform the complex and expensive assays. In large studies, the laboratory collaborator may develop the specimen collection, storage, and extraction protocols in consultation with the principal investigator to determine the best methods for the study. Because the specimens are stored for a long time, sometimes indefinitely, the laboratory protocols have to be designed to hold the promise of more reliably recovering the information and preparing the samples and assays for laboratory assays.

Many investigators conducting cohort studies try to collect biologic specimens for future use. One major advantage of these collections is that specimen collection occurs before the onset of disease. Because, in large cohorts, a majority of individuals will not develop the diseases of interest, many specimens will not be informative about the diseases the study was designed to investigate. With the sequential information gathered over time, new hypotheses and different outcomes may be evaluated in these cohorts, however. Collection and storage of large numbers of specimens for decades is costly, especially because relatively few of the samples will actually be assayed (in nested case-control or case-cohort analyses). Storage costs are proportional to volume of material and number of specimens collected. For large cohort studies with large numbers and continuing contact with the study participants, the type of specimen collected is connected to the trade-off between collection costs for the participants, the storage needs and costs of the specimen, and the potential number of usable specimens. For low-cost blood storage for DNA, limited quantities of blood (100 to 150 µL) can be stored on collection cards. For noninvasive collection of genetic materials, buccal cell collection is a reasonable option with limitations. Blood spots, spots on filter papers, tissue specimens, extremely low volumes of substances such as plasma, and specimens from biopsies or biopsies for genetic assays is essential. As new laboratory techniques develop that consume less of the total sample, these valuable resources can be increasingly informative.

Case-control studies may offer more efficient collection and storage of specimens but, as noted earlier under Case-Control Studies, these samples may be altered by storage conditions.

Adequate consent procedures are complex and essential. Because many of the exact laboratory assays may not have been selected (or developed) at the time the participant is enrolled in the study, specifying exactly what will be done with the specimen may be somewhat problematic. Many investigators are now using a consent that allows for different levels of use of the specimen (e.g., for only the specified assays or for other assays related to the disease of interest) or for any future use. Analytic methods to incorporate laboratory information as well as more standard epidemiologic information must be carefully developed.

GEnetic Epidemiologic Studies

Genetic epidemiologic studies overlap substantially with molecular epidemiologic studies, particularly when the “molecular” component is evaluating variations in genetic material that are, by definition, increased with the odds of gene mutation (polymorphism or mutation of a gene and its effects. In this context, however, includes families studies, molecular epidemiologic studies with genetic components, and more traditional cohort and case-control studies with family history components. Similar to the molecular epidemiologic studies, genetic epidemiologic studies are multidisciplinary from the outset and involve clinicians, geneticists, epidemiologists, and laboratory investigators. These studies include all the complications of molecular epidemiologic studies, often with the additional
complexity of having to deal with family dynamics.48

Family studies have been essential for mapping and identifying the more than 20 major cancer susceptibility genes found in the late 1990s.32 (The methods for identifying and evaluating these genes are discussed in Chapter 13.) Once the contribution of genetic variation to disease within the families has been established, however, these variations should be evaluated in relation to known exposure factors for the specific cancers of interest (parity, reproductive factors for breast cancer; sun for melanoma, etc.) Complex analytic techniques that incorporate both genotype information and environmental risk factors into a regressive model have been developed.49 Again, large numbers of families are necessary for these gene-environmental and, potentially, gene-gene interactions. Care must be taken in these analyses to account for familial relationships, as the observations within families are not necessarily independent. Families share not only genes but environmental exposures and lifestyles. Within high-risk families, selected because there are many living members, penetrance (risk of developing disease associated with carrying an altered gene) estimates will be high but useful for determining an upper limit on the risk associated with alteration of a specific gene. Larger population studies are important for estimating the effect of an altered gene outside of high-risk families selected for linkage analyses. Because most cancers are not inherited as simple, Mendelian disorders, even when a major susceptibility gene is mutated, other factors may be important. Large epidemiologic studies are needed to identify these additional risk factors so that the complex chain of events that results in a cancer development can be interrupted. One approach is to conduct a large case-control study in which usual risk factors are obtained and large numbers, such as BRCA1 or BRCA2 (each having hundreds of mutations throughout the gene), are analyzed.2 This is logically challenging, laboratory time-intensive, and costly. Even though mutations in such genes as BRCA1 and BRCA2 account for a percentage of familial breast cancer and are important for understanding the biology of breast cancer development, they account for only a small fraction of breast cancer in the general population.2 Sample sizes for these studies must, therefore, be large and, even then, the limitation is the number of mutation carriers in the referent (control) population.

Another approach to understanding the role of mutations in the development of cancers is to take advantage of the opportunity afforded by relatively isolated populations with so-called founder mutations, recurrent mutations prevalent in a specific group. Unlike other populations in which an entire gene needs to be sequenced, these founder mutations can be more easily genotyped because the laboratory searches for one or a limited number of specific mutations.2 It is thus feasible to screen thousands of samples for the specific mutation. Founder mutations have been identified in a number of populations worldwide. For example, breast, ovarian, and prostate cancer risk associated with prevalent mutations in BRCA1 and BRCA2 were estimated in volunteers from the Jewish community of Washington, DC.2 To estimate risk of cancer among mutation carriers, a novel analytic technique was devised, called the kin-cohort method.2 The risk of breast and ovarian cancers could not be directly estimated among the genotyped participants because of the potential survival bias. Information on cancer history of first-degree relatives of genotyped individuals was used to estimate penetrance of breast, ovarian, and prostate cancers. The cumulative risk of each type of cancer in relatives of carriers was compared to that of noncarriers and found to be much lower than that in high-risk families.4 Other novel analytic techniques will be needed for other types of data sets to maximize the information gleaned from both genetic and environmental risk factors.

Family history data from case-control or cohort studies can be used to evaluate clustering of cancers in families. Information on first-degree relatives is usually accurate among well-educated Americans,46 but this type of information is culture-specific. In cultures where notification of cancer diagnoses is not routine, obviously information on cancer diagnoses in relatives will not be accurate. One approach to identifying families with known ascertainment for clustering studies or linkage analyses is to identify individuals from case-control or cohort studies with a family history of interest, contact the individual to ask for permission to contact other family members, and then evaluate the family members who are willing to participate. Another approach to systematically identifying families at increased risk of specific cancers is through population registries, where genetic findings can be extrapolated to the population from which the cases are derived.2 Individuals with a disease of interest are identified at the time of registration, and family history is obtained. If the family meets the criteria, family members are invited to participate in a family registry study. This approach is being developed to provide resources for the research community.2 Genetic epidemiologic studies that investigate other genes not considered among the major susceptibility genes are similar to those described in molecular epidemiology. There are some special issues for genetic epidemiologic studies, however.45 Informed consent is complex. (The issues of consent in families are discussed in Chapter 58.4) A growing concern among potential participants in any type of genetic epidemiologic study is the implementation of confidentiality protection for the privacy of genetic information. Another concern is notifying participants of results and the approach of this notification. If all identifiers are removed, individual notification becomes impossible. In most large studies, it is not feasible to counsel participants individually about their genotype status, even if it were possible to interpret the meaning of such variation. One approach is to notify participants about aggregate results, so that they can then pursue clinical, rather than genetic testing with their physicians.

INTERVENTION STUDIES

In some senses, intervention studies represent the culmination of descriptive studies that reveal patterns of cancer and analytic studies that discover risk factors for developing the cancers. The ultimate goal of both approaches is to identify individuals at high risk of developing cancer, to establish risk factors for the cancer, and to develop rational approaches to interrupting the causal pathway in cancer development. Intervention studies are designed to test ways of disrupting the chain of events that may lead to cancer causation. As such, some investigations are designed to evaluate intermediates in tumor development. The hypotheses in general are derived from both case-control and cohort control and cohort studies. Randomization to control some type of prevention intervention and those not receiving the intervention. The risk of cancer is compared in the two groups using similar analytic techniques as in the cohort studies. These intervention trials may be dietary (e.g., giving supplementary micronutrients to individuals at risk of esophageal or stomach cancer); chemopreventive (e.g., the tamoxifen trial for women at increased risk of breast cancer); vaccine trials (e.g., hepatitis B or the papilloma virus vaccination trials); medical screening (e.g., the NCI’s Prostate, Lung, Colorectal, and Ovarian Cancer Screening trial); or lifestyle-altering (e.g., sun exposure) programs.49 When individuals are randomized, confounding factors should be equally distributed between the groups. The baseline characteristics should also be equivalent among the randomized groups. Most of these trials are conducted with individuals who are considered to be at high risk for disease. An important consideration is that because participants are healthy individuals, prevention strategies should not have substantial side effects: That is, toxicity should not outweigh potential benefit.

In the design of these trials, sample size estimates are crucial. Even among selected high-risk participants, cancer outcomes may be relatively rare, and a large number of participants may have to be enrolled and followed up for decades. Oversight committees are not uncommon; they are quite useful in monitoring data and helping with the ethical decision to stop a trial if a substantial benefit is shown in one group.

FUTURE DIRECTIONS

Epidemiologic studies have pointed to the direction of many fruitful avenues of cancer research in the basic sciences and have established the causes and major risk factors for many cancers. Much needs to be done, however. The major progress in the next few years will likely emerge from large, interdisciplinary, highly collaborative research programs with improved measures of host susceptibility and environmental exposure. A new era of chemopreventive programs, based on identifying high-risk individuals and the biologic mechanisms of tumor progression, hold great promise for altering the natural history of disease. The identification of genetic factors that may influence addiction to tobacco (e.g., nicotine) could, in turn, reduce the number of individuals who smoke.

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REFERENCE TABLES

SECTION 14.2
Descriptive Epidemiology: Cancer Statistics

INTRODUCTION

The malignant diseases have both a descriptive and an analytic epidemiology. Descriptive epidemiology consists primarily of vital statistics, particularly incidence and mortality rates. These usually relate to large populations divided according to age, gender and race. Differences in these statistics from one place or time to another are part of descriptive epidemiology. Survivorship also is descriptive. The descriptive epidemiology of the malignancies is described in this Section.

Analytic epidemiology consists of the knowledge of suspect and known causes of disease. It is developed from disease-specific or cause-specific investigations. The analytic epidemiology of the malignancies is described in Section 3 of this chapter.

DESCRIPTIVE EPIDEMIOLOGY

USA

Most data presented here pertain to the United States of America (USA). This is not limiting in that cancer patterns vary relatively little over the developed world. Further, differences that occur reflect geographic and cultural variations in the distribution of the causes of cancer, not differences in the causes themselves. However, in the developing world cancer patterns vary from that of the developed world and differ from one region to another. In many developing countries there are high frequencies of cancers of the liver, stomach, cervix and, in parts of Asia, cancer of the nasopharynx. Cancer patterns in many newly industrialized societies are changing rapidly towards those of the West. This reflects their recent large-scale adoption of cigarette smoking. § Global variations in the descriptive epidemiology of cancer are reviewed in "Global cancer statistics" by Parkin, Pisani and Ferlay. 2

CANCER ENTITIES

Depending on the cancers of interest and on their grouping, there could be several dozen groups of malignancies for which statistics are available. This Section describes "all cancer" and 20 specific cancers and groups of cancer that cause the largest numbers of deaths in the USA. These entities accounted for 88% of cancer deaths in 1996. Table 14.2-1 ranks them by number of deaths. The names in the table were chosen for brevity. The cancers included in each group will be specified.

| TABLE 14.2-1. Incidence and Mortality Data for Major Forms of Cancer. USA, Total Population 1996 |

INCIDENCE

The incidence (sometimes called the incident number) of a cancer is the number of cases of the disease diagnosed in a specified population, or group of people, over
a specified time, usually one year. The more commonly used measure, the incidence rate (I), relates the incident number to the size of the population and to the interval in which the cases were diagnosed. I is expressed as cases per 100,000 persons per year or, usually, as cases per 100,000 person-years (py). An I may relate to an entire population (the I of lung cancer in the USA is 54 cases per 100,000 py), may be specific, e.g., as to gender (the I of lung cancer among males in the USA is 70 per 100,000 py) or may be ever more specific, e.g., as to males of one race and of a narrow age range. Whether or not they are specific, I's that span a broad age range usually are age-adjusted to facilitate comparison with one another. Age-adjustment nearly eliminates age as the explanation for any differences seen among a group of I's. All I's and mortality rates in the remainder of this chapter are adjusted to the age distribution of the total USA population in 1970. Cancer I data in the USA are provided mainly by population-based cancer registries. These vary in size and somewhat in the quality and completeness of their data. Most of the incidence data come from a national system of cancer registries that has existed since 1973. This Surveillance, Epidemiology and End Results (SEER) Program now includes 11 registries. The incidence data reported for 1973 and later are from SEER's nine original registries which include about 10.5% of the USA population.

Data from a cancer registry less than 20 years old are viewed cautiously. As a registry matures its coverage will improve, possibly giving the false impression of a rise in I's. There are other potential sources of distortion in I's, even those from established registries. These include a population's increased use of cancer screening services and improvements in access to medical care. Improvements in diagnostic capabilities and, rarely, changes in diagnostic categories also affect I's. All of these advances may convey the false impression of a rise in cancer I's.

MORTALITY

Cancer mortality or the number of deaths, and the cancer mortality rate (M) are analogous to the corresponding measures of incidence. Of course these measures relate to deaths certified as due to cancer not to diagnosed cases of cancer. M usually is expressed as deaths per 100,000 py and may be made specific for population subgroups just as is I.

M's are of very high quality in the USA, especially for cancer. Nearly 90% of persons considered to have died from cancer, on the basis of autopsy, will have the disease correctly listed on their death certificate. Numbers of deaths and M's are available annually in great detail for the entire country. In this Section we usually present mortality data for 1996. This is the latest year for which detailed information is available and it is the same as the year for incidence data presented. Preliminary mortality data are available for 1997 and 1998. This recent information extends all of the trends described in this Section. All of the mortality data come from publications of the National Center for Health Statistics.

SEX RATIO

Males and females differ in their rates of most cancers. These male:female differences are expressed as the age-adjusted sex ratio, the ratio of the age-adjusted male I or M to the corresponding female rate. Since this ratio is based on age-adjusted rates it accommodates the fact that the female population is larger and older than the male.

RACE RATIO

For brevity I's and M's are presented for all races combined. However, we also present the ratio of age-adjusted I's and M's of Blacks to those of Whites. The ratio of Black to White M's is typically higher than the I ratios and this discrepancy, for each cancer, may be an index, albeit a crude index, of the access to and use of cancer-related services by the two races.

SURVIVORSHIP

Survivorship is described by the five-year relative survival rate (RSR-5). The RSR-5 is the proportion of persons with a particular form (and usually, stage) of cancer who survive to the fifth anniversary of their diagnosis, divided by the proportion of the general population expected to live that long. The expectation is based on mortality rates from all causes among persons with the same age, gender and race composition as the cancer patients. An RSR-5 of 0.75, indicates that five years after diagnosis the cancer group has 25% fewer survivors than does the comparable population. The RSR-5 is based on all deaths in the cancer group, so it does not describe mortality from the specific cancer in question. Instead, it indicates the incremental mortality imposed by that cancer. Because RSR-5's are available for specific stages of a cancer, they permit evaluation of long-term gains in patient survival.

AGE PATTERNS, TIME TRENDS

Patterns of I's and M's are described by age for men and women for each of the cancers addressed. For cancers of greatest public health importance and for several others of special interest, the age-patterns are also presented graphically. Time trends are presented graphically for I's and M's for cancers of the greatest public health significance and for those of interest for some other reason. Finally, RSR's are presented for 1950-1959, 1974-1976, 1979-1981 and 1989-1991, for all cancer and the 20 cancers of major interest. The data come from the SEER program and its predecessor, the End Results Group.

ALL CANCER

(This category includes all malignant neoplasms except non-melanoma cancers of the skin. It is not limited to the 20 cancer groups that follow.) Variation in the causes and the descriptive patterns of malignancies make statistics for "all cancer" difficult to interpret. Moreover, lung cancer accounts for about 15% of all cancer cases and 30% of deaths. As a result descriptive patterns for "all cancer" reflect those of lung cancer. Yet, an overview of the malignancies as a whole gives perspective to national issues such as time trends, improvements in survivorship, the value of cancer screening, etc. Further, the public has an abiding interest in "cancer" as a group.

Table 14.2-1 shows that the I of all cancers combined in the USA population in 1996 was 389 cases per 100,000 py. Table 14.2-2 shows that the rate was 455 for males and 342 for females, an age-adjusted incidence sex ratio of 1.3. The Black:White (B/W) incidence ratio of 1.1 indicates that for all cancer combined, Blacks have a slightly higher incidence rate than do Whites. Useful explanations of B/W ratios different from 1.0 are specific to each form of cancer and are beyond our scope.
this is best inferred from a comparison of the sex-specific RSR-5's of each form of cancer.

The B/W mortality ratio for all cancer is 1.3, larger than the 1.1 incidence ratio. The discrepancy between the incidence and the mortality ratio may reflect the fact that Blacks have less access to, and use, medical care less than do Whites.

Figure 14.2-1 shows age patterns of I's and M's for all cancer for males and females, respectively, averaged for 1992-1996. These five years were combined because age-specific I's are not available for any individual recent year. The pattern of I's shows an upward inflection during the late 40's for men. The rates start to rise earlier and increase more gradually for women. The earlier rise of I's among women reflects the early onset of breast cancer and cervix cancer. For both genders, I's then increase nearly linearly to about age 75 and peak in the early 80's. The "late-age decline" appearing in these data is common and is usually an artifact due to underdiagnosis of cancer among the elderly and to overestimation of the size of the elderly population. For both genders the pattern of mortality lags that of incidence by about 10 years and there is no late age decline seen for either gender.

Figure 14.2-1. Incidence rates and mortality rates for all cancer and for seven selected cancers. According to age.

Age-specific cancer I's were used to estimate the risk of developing cancer over a lifetime and over several age spans of interest. For a newborn in 1996, the overall cancer I of 389 equates to a 45% risk of developing cancer through age 85. For persons aged 45 in 1996 the risk of developing cancer in the remaining lifetime is 44% while for persons aged 65 it is 35%. These risk projections pertain only to persons who develop cancer or live to age 85. More realistic, actuarial, estimates of these risks are corrected for mortality from all causes and are about 15% lower, that is the 45% figure becomes 38%, etc. More important, cancer I's are declining over time and the risks to be experienced in the future are likely to be lower, perhaps much lower, than even the actuarial projections.

Figure 14.2-2 shows time trends, from 1973 through 1996, of age-adjusted I's and M's for all cancer for males, females and for the genders combined. For men I's rose gradually until 1987 and then sharply for several years before declining. The sharp rise reflects increases in prostate cancer. I's for women increased to 1991 and now are declining. For both genders, M's rose very gradually to 1990 or 1991 and now are declining. Reports in the literature suggest that the overall cancer M peaked in the USA in 1990 or in 1991. The distinction reflects different standard populations used for age-adjustment and is of no practical significance.

Figure 14.2-2. Incidence rates and mortality rates for all cancer and for ten selected cancers. According to time. See Figure 14.2-1 for key.

Finally, discussions of All Cancer often reinforce a view that, "cancer is a disease of old people". In two important ways, it is not. First, the leukemias and tumors of the central nervous system (CNS) remain major threats to children. Young adults experience considerable illness due to Hodgkin's disease and testis cancer as well as death from leukemia, non-Hodgkin's lymphoma and CNS tumors. Second, the frequency of each major cause of death rises sharply with age. Among persons who die from the major diseases, cancer decedents have a below average age at death. In 1996 the average age of all decedents in the USA was 72.0 years, but it was 70.7 years for those who died of cancer. Among deaths occurring after age 45, the average age of all decedents is 78.1 years but it is 72.5 for cancer decedents. Table 14.2-3 shows for each age group the percentage of deaths within it that are certified as due to cancer. In 1996 the proportional mortality for cancer peaked at 37% for ages 55-64. Further, the average cancer decedent lived with his or her disease for more than eight years. Thus, while cancer's highest proportional mortality is at about age 60 it afflicts many persons during their mid-50's. The below average age at death of cancer decedents and the peak of cancer's proportional mortality in middle age are readily explained. The other major chronic diseases, especially cardiovascular diseases, also exact a considerable mortality in middle age but, thereafter, their mortality rates rise more sharply than do those of cancer.

Table 14.2-3. The Proportion of All Deaths Within Each Age Group Attributed To Cancer. USA Total Population, 1996.

<table>
<thead>
<tr>
<th>Age</th>
<th>Cancer Proportional Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4</td>
<td>2</td>
</tr>
<tr>
<td>5-14</td>
<td>10</td>
</tr>
<tr>
<td>15-24</td>
<td>5</td>
</tr>
<tr>
<td>25-44</td>
<td>10</td>
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<tr>
<td>45-64</td>
<td>15</td>
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<tr>
<td>65-74</td>
<td>25</td>
</tr>
<tr>
<td>75-84</td>
<td>10</td>
</tr>
<tr>
<td>All Ages</td>
<td>12</td>
</tr>
</tbody>
</table>

Although cancer decedents die relatively young, that age at death will increase gradually because the population's average age is increasing. Also, many recent advances in cancer treatment, while effective are not necessarily curative. Such treatments postpone death and thereby raise the age of cancer decedents.

CANCER OF THE LUNG AND BRONCHUS

(This category includes cancers of the trachea, lung and bronchus. Less than one percent of cases or deaths in this category are cancers of the
Lung cancer had an overall I of 54 cases per 100,000 py in 1996. 70 for males and 42 for females. The corresponding M's were 49, 68 and 34. Whether based on I's or M's the condition is predominantly male disease with sex ratios of 1.7 and 2.0, respectively. However, the sex ratios are declining. For incidence this is occurring because the male rate is declining while that for females is stable. The declining mortality sex ratio reflects the ongoing steep drop in male M's.

The age pattern of I's and M's for lung cancer for males and for females is shown in Figure 14.2-1. For both genders, I's and M's start to rise at about age 40 and then increase to a peak at about age 75. All four curves then show the late age decline which, for this disease occurs because persons, especially women, born before 1930, did not smoke in large numbers.

Figure 14.2-2 describes lung cancer I's and M's for 1973-1996. Both measures increased until 1991-1992 (incidence) or 1990-1994 (mortality). Both rates were level briefly and now are declining. The incidence rate curve declines more steeply than the mortality curve. I's usually change earlier and more abruptly than do M's, as the M in any year reflects I's of many prior years. The overall I curve for lung cancer should continue to decline even more steeply when I's among women begin to decline. In fact, a leveling began in 1991 and a slight decline occurred in lung cancer I's for women in 1995 and 1996.

Cancer of the lung was for decades the most commonly diagnosed form of cancer in the USA. However, in 1984 the I of prostate cancer began to surge and by 1989 or 1990 more prostate cancers were diagnosed than lung cancers in men and women combined. Yet, lung cancer remains the principle cause of cancer deaths. In fact, lung cancer is the major cause of death as many deaths as do the next four cancers (colon, breast, prostate and pancreas) combined. The singular importance of lung cancer as a cause of death, combined with its strong association with smoking, continue to offer the greatest opportunity for cancer prevention.

The descriptive epidemiology of this disease presents a uniformly unfavorable, seemingly unchanging pattern. Pancreas cancer has an overall M of 136 per 100,000 man-years (my) this cancer is by far the most frequently diagnosed malignancy among men in the USA. With an M of 24 deaths per 100,000 wy, breast cancer kills about 30% fewer women than does lung cancer.

Cancer of the lung is 15.5 per 100,000 py, 19.2 in men and 12.2 in women, an incidence sex ratio of 1.6. The overall I of 14.4 deaths per 100,000 py is similar for men and women. The mortality sex ratio of 1.0 is lowest among the major malignancies.

Age patterns for colon cancer are shown in Figure 14.2-1. Both for males and for females I's start to increase at about age 40 and rise sharply to peaks at the oldest ages. M's lag I's by about 10 years and at first rise more gradually than do I's but then accelerate upward. Colon cancer's time trends appear in Figure 14.2-2. I's peaked at about 38 cases per 100,000 py in 1987 and then began declining. Mortality has declined since at least 1979, the first year for which data specific to the colon are available.

CANCER OF THE BREAST

The incidence of breast cancer in women was 111 cases per 100,000 woman-years (wy) in 1996 making it by far the most frequently diagnosed cancer in women. However, with an M of 24 deaths per 100,000 wy, breast cancer kills about 30% fewer women than does lung cancer.

Both for males and for females I's start to increase at about age 40 and then rise sharply to peaks at the oldest ages. M's lag I's by about 10 years and at first rise more gradually than do I's but then accelerate upward. Colon cancer's time trends appear in Figure 14.2-2. I's peaked at about 38 cases per 100,000 py in 1987 and then began declining. Mortality has declined since at least 1979, the first year for which data specific to the colon are available.

CANCER OF THE PROSTATE GLAND

With an I of 136 per 100,000 man-years (my) this cancer is by far the most frequently diagnosed malignancy among men in the USA. With an M of 24, it ranks second among men in mortality. Figure 14.2-1 shows the I's and M's of prostate cancer by age. The curves are remarkable for their steepness, with rates increasing almost three-fold with every 10-year age increase.

The age pattern of I's and M's for breast cancer for the 1992-1996 interval are given in Figure 14.2-1. I's start to rise in the late 20's and increase more-or-less steadily to about 500 cases per 100,000 wy at age 70. M's rise more gradually with a peak at ages over 85. In data from many Western countries the age pattern shows a notch, with I's declining at ages 45 to 54 before resuming their increase. That pattern does not occur in these data for unknown reasons. The typical bimodal age-incidence pattern of breast cancer, with a trough at age 50, has been offered as evidence that breast cancer is two etiologic entities. In this view, the premenopausal disease is related primarily to reproductive factors and the postmenopausal to body form and menopausal changes.

Figure 14.2-2 shows breast cancer's time trends. The I of breast cancer long was stable but began to rise in the early 1980's. The I peaked in 1987 at 113 and was stable through 1996 at about that level. It is unclear whether the 1980's rise in breast cancer was due to the ever-greater use of breast cancer screening or to an actual increase in the causes of the disease. An increase in I due to screening should be transitory, eventually declining to pre-screening levels even if screening continues. In such a situation the stage distribution of cases detected in the screening era should be favorable relative to that of cases diagnosed in the previous era. It remains to be seen whether the I of breast cancer will decline but earlier diagnosis is occurring; in 1965-1969 47% of cases were "local" when diagnosed but in 1989-1995 the figure was 62%.

Breast cancer's M shows a time trend different from that of its I. M was stable from the 1930's, or even earlier, through about 1990. It is now declining at about 3% per year. This steep decline probably is due both to earlier diagnosis and to improved treatment.

CANCER OF THE PANCREAS

The descriptive epidemiology of this disease presents a uniformly unfavorable, seemingly unchanging pattern. Pancreas cancer has an I of 8.6 per 100,000 py, 10.0 for males and 7.4 for females, an incidence sex ratio of 1.4. The overall I is 8.3 deaths per 100,000 py, 9.6 for men and 7.2 for women, a mortality sex ratio of 1.3, similar to that of incidence. Pancreas cancer is the most highly fatal of all the malignancies.

Both among men and women, I's and M's of pancreas cancer begin to rise in the late 40's and reach a peak of about 110 cases or deaths per 100,000 py among men and of about 90 among women in the oldest age group. For both genders, the two curves, I's and M's, are virtually identical, so highly fatal a disease is this.

The I's and M's of pancreas cancer have varied little over time. Perhaps this is changing, however. From 1973 to 1992 the I of pancreas cancer declined in no consistent pattern by about seven percent from 10 cases per 100,000 py to 9.3. Over the next four years it dropped another eight percent. Mortality data are less encouraging. Despite the declining I's, M's were essentially unchanged from 1973 to 1996.

NON-HODGKIN'S LYMPHOMA

The I and M of this condition, or group of conditions, are higher than is generally recognized even by physicians. This disease is the sixth-ranked cause of death among the malignancies. The overall I is 15.3 per 100,000 py; 19.2 in men and 12.2 in women, an incidence sex ratio of 1.6. The overall M is 6.9 per 100,000 py, 8.6 in men and 5.6 in women, a similar mortality sex ratio of 1.5.
NHL shows increased I's as early as the mid-20's. I's increase sharply after about age 50 and M's after about age 60 in men. For women the upward inflections occur at ages 60 and 70. Figure 14.2-2 shows the time trends in I's and M's. I's now are rising sharply, increasing by 80%, from 8.6 cases per 100,000 py to 15.5 from 1973 to 1996. It has been suggested that some of this increase is an artifact due to changes in diagnostic classifications, which are bringing new entities into the lymphoma family. However, such changes are unlikely to explain more than one-fourth of the increase seen. M's also are increasing but more slowly and may now be stabilizing. The increase from 1973 (4.7 deaths per 100,000 py) to 1994 (6.9 deaths) was 47%. However, there was no further increase in 1995 or 1996.

LEUKEMIA

(Leukemia here refers collectively to the four major forms of the disease, acute lymphocytic leukemia (ALL), acute myelogenous leukemia (AML), chronic lymphocytic leukemia (CLL) and chronic myelogenous leukemia (CML).) This discussion does not specifically address leukemia in children. Ninety percent of all leukemia cases occur after age 20. The statistics presented are inclusive of all ages but the observations pertain to leukemia in adults.

The leukemias are a category of diseases combined under one label both by historical precedent and by practical considerations of contemporary diagnosis and treatment. Nonetheless, while the leukemias eventually may be found to share some etiologic factors, this has been shown only for ionizing radiation and CLL is exempt even from that.

The I of leukemia was 9.7 cases per 100,000 py, 12.3 in males and 7.7 in females, an incidence sex ratio of 1.6. M's were 6.3 deaths per 100,000 py overall and 8.2 and 4.8 for males and females, giving a nearly identical mortality sex ratio of 1.7.

The I of leukemia is relatively high at 6.8 cases per 100,000 under age 5. It is then steady at about 2 to 5 until about age 40 when it begins to rise at a constant rate. The I of leukemia peaks a reach of 120 cases per 100,000 in men and 71 in women at ages 85 and over.

Leukemia M's are no longer particularly high in childhood; they remain under 1.3 deaths per 100,000 py through age 20 and then begin a steady increase to ages 85 and over.

Age-adjusted I's of leukemia were essentially unchanged at about 10.5 cases per 100,000 py from 1973 to 1995. In 1996 the I was 9.7, perhaps signaling the start of a decline. M's have declined from 6.7 deaths per 100,000 in 1973 to 6.3 at present. This 6% decline is identical for males and females and largely reflects treatment advances for the leukemias of childhood.

CANCER OF THE STOMACH

Although cancer of the stomach long has been declining, it remains the eighth-ranked cause of cancer death. The overall I is 6.6 per 100,000 py, 9.8 in men and 4.2 in women, a rather high incidence sex ratio of 2.3. The overall M is 4.0, with rates of 5.7 in men and 2.7 in women giving a sex ratio of 2.1.

I's of stomach cancer start to rise at about age 40. They rise progressively to age 85 and over, reaching a maximum of 119 cases per 100,000 py in men and 58 in women. The age pattern of M's closely follows that of I's but is one-third lower.

The I of stomach cancer has declined one to two percent per year for as long as data have been available, that is, since the mid-1930's. Mortality data suggest that the disease has been declining, at the same rate, since 1900. Stomach cancer was by far the most common cause of cancer death in men until surpassed by colorectal cancer in the late-1940's. It was also the most common cause of cancer death in women until about 1937 when it declined to fourth place. The "intestinal" type of stomach cancer declined two to three times faster than did the "diffuse" type of disease. During the last 25 years or so, the long-term declines in stomach cancer have continued unchanged (Figure 14.2-2). I was 10.2 cases per 100,000 py in 1973 and declined about 1.5% per year to the 1996 level of 6.6, an overall reduction of 35%. The decline was identical in both sexes. M's have declined more, the reduction being 43% from 7.0 deaths per 100,000 py in 1973 to 4.9 in 1996. It was the same in both sexes.

The reason for the declining I of the intestinal type of stomach cancer is unknown. However, the decline extends over 90 years indicating that one or more causes of the disease started downward before 1900. The similarity of the decline in both sexes is remarkable and suggests that the declining cause is closely tied to domestic life or to residential, not occupational, settings. The favored hypothesis relates to the introduction of refrigeration and chemical food additives, several of which have anti-oxidant properties. These twentieth-century methods of food preservation gradually displaced older methods such as the smoking, salting and pickling of foods. This hypothesis is supported by the fact that stomach cancer is strongly, and inversely, associated with economic status as the well-to-do adopted the newer methods first. Some other unidentified aspect of improving living standards also may have played a role in the decline of this disease. For example, Helicobacter pylori, a bacterium that colonizes the stomach of about 45% of Americans, was recognized as a cause of stomach cancer in 1994. The prevalence of H.pylori infection also is strongly and inversely related to economic well being.

CANCER OF THE OVARY

The I of cancer of the ovary is 14.1 cases per 100,000 wy while the M is 7.4. The I has been stable for 40 years. An apparent rise in I from 1945 to 1960 probably resulted from improved ability to diagnose the condition. Despite the constancy of the I's, M's have declined recently from 8.4 in 1973 to 7.4 in 1996, about 0.3% per year.

The age pattern of cancer of the ovary is exceptional in that I's start to increase in the late teens. Both I and M increase slowly until about age 40 or 45 and then rise sharply to peaks at about age 80.

CANCER OF THE NERVOUS SYSTEM

(This entity includes cancers of the brain, spinal cord, other central nervous system and the peripheral nervous system. However, 97% of deaths due to malignancies in this group are from tumors of the brain. We refer to this group as "CNS" cancer.) In 1996 CNS cancer had an overall I of 5.8 per 100,000 py in the USA, 7.2 in males and 4.5 in females. The corresponding M's are 4.2 and 5.0 and 3.4 for men and women respectively. With age-adjusted sex ratios of 1.6 for incidence and 1.5 for mortality this disease has a typical male predilection.

The age patterns for CNS cancer are shown in Figure 14.2-1. They are unusual in the long, gradual rise that extends from about age 20 to age 60 followed by a leveling, and then sharp declines. The leveling and decline in the statistics may result from a progressively greater underdiagnosis of cases and undercertification of deaths due to CNS cancer with increasing age. This would occur because of confusion of the cancer's symptoms with those of the much more common condition, stroke.

The I's of CNS cancer long have been increasing. The rise during the middle of the century was probably due to improving diagnosis. More recently, I's rose from 5.0 cases per 100,000 py in 1973 to a peak of about 6.4 in 1987-1989. There has since been a gradual reduction to the current I of 5.8. The pattern of M's closely follows that of I's with a short lag. M's rose from 3.7 deaths per 100,000 py in 1973 to a peak of 4.3 in 1990. M is now stable at about 4.1 deaths per 100,000 py.

LIVER AND BILIARY TRACT

(This entity includes all primary cancers of the liver, bile ducts and gall bladder. We refer to it as liver cancer.) Liver cancer had an I of 4.2 cases per 100,000 py in 1996. 6.4 for men and 2.4 for women, a high incidence sex ratio of 2.7. For mortality the corresponding figures are 3.6 deaths per 100,000 py overall, 5.3 and 2.3 for men and women, a mortality sex ratio of 2.3.

Age patterns of liver cancer both among men and women are unremarkable. I's start to rise by the mid-30's among men and by the mid-40's among women and peak at about age 80. M's are virtually identical to I's in every respect.

Since 1973 I's for liver cancer have been increasing steadily from 2.3 cases per 100,000 py to the 1996 figure of 4.2. This 80% increase in just 23 years is worrisome
but has attracted little attention. This is strange, since M's show a similar pattern, a 50% increase from 2.4 deaths per 100,000 py in 1973 to 3.6 in 1996. Moreover, the increases are occurring both among men and women.

Liver cancer is caused by the carrier state of the hepatitis-B and -C virus and these agents are the overwhelming cause of the disease in much of the developing world. Together, they probably account for about 50% of the disease in the USA. In the USA there is also a clear association between abuse of alcoholic beverages and liver cancer.

**URINARY BLADDER**

(This entity includes cancer of the urinary bladder and “other urinary organs”, essentially the ureter and urethra. Cancers of the kidney and renal pelvis are in a separate category. Ninety-seven percent of cancers in this group are bladder cancers and we refer to the disease that way.) Bladder cancer is the number 12-ranked cancer killer, responsible for 11,452 deaths in the USA in 1996. The overall I's 16.2 cases per 100,000 py. With F's of 27.7 for men and 7.4 for women, the incidence sex ratio is a striking 3.7. This reflects men's higher prevalence of smoking and greater exposure to occupational carcinogens. The overall M is 3.2 deaths per 100,000 py. With M's of 5.5 and 1.7 for men and women, respectively, the sex ratio is also a remarkably high 3.2.

Bladder cancer I's begin rising at about age 40 in men and 45 in women. A peak of 297 cases per 100,000 py is reached in men at ages 65 and over. A much lower peak of 75 appears at the same age in women. M's lag I's by about 10 years and peak at 139 and 42 deaths per 100,000 py for men and women, respectively.

I's for bladder cancer rose from 14.8 cases per 100,000 py in 1973 to a peak of 17.5 in 1987. A slow decline is now occurring with a rate of 16.2 in 1996. M's for bladder cancer declined 25%, about 1% per year, from 4.2 deaths per 100,000 py in 1973 to 3.2 in 1996. The decline has been slightly greater for men than for women.

**CANCER OF THE ESOPHAGUS**

This disease has an overall I of 4.0 per 100,000 py but for men the I is 6.8 while for women it is 1.7. The corresponding M's are 3.6 overall and 6.3 and 1.5 for men and women respectively. With age-adjusted sex ratios of 4.0 for incidence and 4.2 for mortality, this disease is the most strongly male-associated malignancy.

I's start to rise at about age 35 in men and 45 in women. There is then a sharp rise to an I of 41 cases per 100,000 py in men, 15 in women, at ages over 80. M's are virtually identical to I's. The I of esophageal cancer increased gradually from 3.4 cases per 100,000 py in 1973 to 4.0 in 1996. However, there was almost no change in I's among women while rates among men increased about one percent per year from 5.5 in 1973 to 6.8 in 1996. The patterns of M's are virtually the same.

Cancer of the esophagus results from smoking, alcoholic beverage abuse and the combination of the two. Poor nutrition, particularly micronutrient deficiency may also be involved in causing this disease, especially in regions of the world where rates are very high. If there is some good news in this is that the now ongoing long term decline in smoking should bring reductions in I's of esophageal cancer in developed countries both directly and also by reducing the impact of alcohol abuse. In developing countries the correction of micronutrient deficiencies, which is relatively practical, may produce reductions in the disease.

**CANCER OF THE KIDNEY AND RENAL PELVIS**

(This group includes cancers of the kidney and of the renal pelvis, an unfortunate combination with a historical basis. Kidney cancer nearly always is a renal cell adenocarcinoma while renal pelvis cancer is a tumor of transitional or squamous cells. The renal pelvis is better seen as an extension of the bladder than of the kidney and both the histology and epidemiology of its cancer reflect that. Ninety-eight percent of tumors in this group are kidney cancers and we will refer to it as such.) The I of kidney cancer is 9.4 cases per 100,000 py, 12.9 among men and 6.5 among women. The corresponding M's are 3.5, 5.1 and 2.3. The respective sex ratios remain at 2.0 and 2.2.

Both for men and women the age patterns of cancer of the kidney are unremarkable. I's start to increase in the 30's and peak at about age 80. M's show a similar pattern but lag I's by 5 to 10 years. The I of kidney cancer has undergone a 40% increase from 6.7 cases per 100,000 py in 1973 to 9.4 in 1996, nearly 1.7% per year. The increase is somewhat higher for women (48%) than for men (38%). The time trend in M's is similar but less striking. For both genders there was about a 20% increase from 2.9 deaths per 100,000 py in 1973 to 3.5 in 1996.

Kidney cancer and renal pelvis cancer are clearly though not strongly associated with smoking. This may explain why I's have been rising more sharply among women than among men. The fact that I's of kidney cancer reached a peak among men of 13.3 cases per 100,000 py in 1994 and may now be declining also supports the idea that long-term smoking patterns influence the disease's descriptive statistics. That is, the gender-specific time trends of I's for kidney cancer may duplicate, later in time and at a lower level, those of lung cancer.

**MULTIPLE MYELOMA**

The I of multiple myeloma was 4.2 cases per 100,000 py in 1996. 5.3 in men and 3.4 in women, an incidence sex ratio of 1.6. The corresponding M's were 3.1 deaths per 100,000 py, 3.8 for men and 2.6 for women, a mortality sex ratio of 1.5.

The age patterns, both of I's and M's for multiple myeloma are unexceptional. I's begin to rise in the early 40's and increase to a peak in the late 70's. M's lag I's by about 5 years and both I's and M's rise more sharply among men than among women.

I's of multiple myeloma have changed on a long term basis moving from 3.8 cases per 100,000 py in 1973 to a peak of 4.8 in 1987. There has been some decline since 1987 but the current I remains at 4.2. In contrast, M's have been increasing steadily. Both for men and for women the increase was about 35% from 1973 to 1996.

**CANCER OF THE RECTUM**

(This condition includes cancers of the rectum, rectosigmoid junction and anal canal). Cancer of the rectum had an I of 12.5 cases per 100,000 py in 1996, 16.1 for men and 9.6 for women, an incidence sex ratio of 1.7. In the same year, M's were 2.4 deaths per 100,000 py overall, 2.6 for men and 2.2 for women, a lower mortality sex ratio of 1.2. These statistics are quite different from those of colon cancer which has lower sex ratios of 1.3 and 1.0.

Both for men and women I's rise in the 30's and rise sharply after age 45 to peaks at ages 70-79. For both genders, M's lag I's considerably and peak at 44 deaths per 100,000 py among men and at 34 among women. The time trend for rectum cancer is shown in Figure 14.2-2. The I of cancer of the rectum peaked at 15.2 cases per 100,000 py in 1981 and then declined slowly to 12.5 in 1996, a reduction of 18% in 15 years. This pattern was similar for males and females. M's have shown a similar pattern.

**CANCER OF THE ORAL CAVITY AND PHARYNX**

(This entity includes cancers of the entire oral cavity and of the pharynx. We refer to it as OCC, oral cavity cancer.) In 1996 the I of OCC was 10.0 cases per 100,000 py, 14.8 for males and 5.9 for females. The corresponding M's were 2.6, 3.9 and 1.4. The respective sex ratios were 2.5 and 2.8.

I's of OCC rise sharply among men from about 2 cases per 100,000 py at age 30 to a near peak of 65 at ages 60-64 and then rise slowly to a peak of 77 at ages 80-84. The pattern for women is similar although more gradual with a peak I of 34 at ages 65 and over. For each gender the age pattern of mortality closely follows that of incidence but M's typically are only about one-fourth of the corresponding I's. I's of OCC declined over the period 1973-1996, about 15% for men and 10% for women. M's declined much more, about 30% both for men and women.

OCC shares much of its etiology with cancer of the esophagus, the lower sex ratio notwithstanding. It is not known whether the considerable decline in M's of OCC is due to increased screening for the disease, especially by dentists, or to treatment advances. However, stage-specific increases in survival have been relatively small,
MALIGNANT MELANOMA OF THE SKIN

In 1996 melanoma had an I of 13.8 cases per 100,000 py, 17.8 for men and 11.4 for women, an incidence sex ratio of 1.5. For mortality, the corresponding rates were 2.3 deaths per 100,000 py, 3.2 and 1.5 for men and women, a mortality sex ratio of 2.1, much higher than that of incidence. The relatively poor survival of males occurs because a high proportion of their lesions are on the trunk and carry a poorer prognosis than do those on the extremities. 

I's of malignant melanoma begin to rise early in life, at about age 15 in both genders. There is a steep increase among men to a plateau of about 45 cases per 100,000 py at ages 70 and over. Among women the increase is more gradual to a lower plateau of about 30 cases per 100,000 py at ages 70 and over. For both genders, M's lag I's considerably in age and reach peaks of 27 and 12 deaths per 100,000 py among men and women, respectively, at ages 85 and over. The I's of melanoma have increased greatly, particularly over the last 25 years. This is shown in Figure 14.2-2. The increase from 1973 to 1996 was 140% overall, 178% and 110% for men and women respectively. However, M's have increased much less, 44% among men and only 15% among women. The increase in I's is due in part to an increased awareness of the disease and efforts to find it by physical examination of the skin. Part of the increase is also real and possibly due to increases in leisure time and sun exposure.

CANCER OF THE ENDOMETRIUM

(Continued)

This disease has an I of 7.7 cases per 100,000 py and an M of 2.7 deaths per 100,000 py. The exceptional age pattern of I's for cervix cancer is shown in Figure 14.2-1. The disease occurs among the young and I's rise sharply to about age 35 and are then more-or-less steady for the remainder of the life span. This pattern strongly suggests that the rate of exposure to the causal agent is constant after about age 30 or that the agent's carcinogenic potency is reduced after that age. The age pattern of M's is unexceptional. The continued rise, long after I's have stabilized does, however, indicate that death can occur long after diagnosis.

CANCER OF THE UTERINE CERVIX

Screening cervical cancer with the pap smear probably is responsible for some of the decline in I's and M's. However, the relationship is not straightforward. The use of the pap smear increased greatly during the 1960's, 1970's and 1980's and, while this test is intended to detect dysplasia and in situ carcinoma, it also detects invasive disease. Thus, the early effect of the gradually increasing use of the pap smear should have been to increase the apparent I. Eventually, the identification of large numbers of in situ cases presumably would lower the I of invasive cases and M. Nonetheless, I's and M's of cervical cancer were declining long before pap smear programs could have had any major effect. This is not to deny the value of these programs, especially among high-risk women. Whatever may be the full explanation for the long-term declines of cervical cancer it seems likely that causes of the disease have been diminishing since at least the 1930's.

RELATIVE SURVIVAL RATES

Table 14.2-4 shows RSR-5's for all cancer and for the 20 major forms of cancer. The diagnosis intervals presented are 1950-1959, 1974-1976, 1979-1981 and 1986-1991; hereafter, 1955, 1975, 1980 and 1990. For most of these cancers, information is available for three stages of the disease: local, regional and all. These categories allow reasonably valid comparisons of survival statistics from as long ago as 1975. The 1955 data are of good quality but are not fully comparable with the subsequent data. They are provided for interest but are not discussed.

For all cancer, no improvement is seen in survival for any stage from 1975 to 1980, possibly because of the short interval between the two periods. Substantial gains occurred in each of the three stage groups from 1980 to 1990, a 15% increase (from 78% to 90%) for local disease and 25% for regional. The 16% improvement, from 1975 to 1980. Of these 104 comparisons, 82 (79%) show an increase in the proportion of cancers that are inherently more benign.

In 1986 Bailar and Smith indicated that cancer M's were still increasing and that gains in RSR-5's probably reflected earlier diagnosis or a "lead time" bias, not a true increase in cures or delay of death. The statement regarding mortality rates was accurate but, if lung cancer had been excluded, M's for all other cancers combined would have been seen to be declining as early as the mid 1950's. It is more difficult to exclude lead time as the explanation of the small gains in RSR-5's through 1980 or even of the larger gains thereafter. However, data for breast cancer and prostate cancer may be useful for addressing this. From 1975 to 1990 these cancers became special targets for earlier diagnosis by screening and public education. Most of the lead time bias from screening, in terms of a seeming lengthening of survival, results from advancing the time of diagnosis of local disease and little results from earlier diagnosis of regional disease. Therefore, we may infer that survival gains for regional disease largely reflect actual treatment effects. Both for breast cancer and, especially for prostate cancer, for 1975 to 1990, large gains are
seen in the RSR-5's for regional disease in \textit{Table 14.7.4}. These gains suggest that there has been real improvement from medical care advances above and beyond any lead time effect. In another approach to this question, Cole and Rodu evaluated survival data for patients diagnosed from 1950-1991 and focussed on particular stages of specific cancers for which lead time gains presumably would be minimal or absent. Even for these conditions they found gains of about 0.5% per year in survival. They suggested that about one-half of the ongoing 1.5% per year decline in the overall cancer \textbf{M} that they reported for 1990-1995 was due to real advances in medical care.\footnote{A gain of 0.0% per year due to improvements in all aspects of medical care may seem disappointing. But we should bear in mind that for gains to occur each advance must favorably alter the course of ever more difficult cases, those that were resistant to prevailing diagnosis and treatment.} In fact, the \textbf{M}'s of many forms of cancer, including cancers of the stomach, cervix, endometrium, rectum and oral cavity, were declining during the 1980's or before.

Second, RSR-5 is increasing for most stages of many forms of cancer. It is unlikely that lead-time bias explains this because the improvements are occurring even for conditions for which diagnostic advances probably have been minimal. Further, practicing oncologists now report seeing survival gains on a regular basis among patients with all stages of disease. These clinical observations can not be dismissed as anecdotal because they are nearly universal and because they are supported by improved survival figures and by declining cancer \textbf{M}'s.

Third, \textbf{M}'s are declining for all cancer combined and for most forms of cancer and this has been true since 1991.\footnote{We must conclude that by 1996, there had been a decline in mortality for many forms of cancer extending over a period of at least 35 years that was due at least in part to advances in medical care.} In 1997, Bailar and Gornick\footnote{Bailar J, Gornick H. Cancer undefeated. \textit{N Engl J Med} 1997;336:1569.} repeated the suggestion that declining \textbf{M}'s were unlikely to be due to advances in diagnosis and treatment. This was based primarily on the view that the declines were minimal and that \textbf{M}'s for most cancers were continuing upward. However, the decline in cancer mortality is accelerating downward (from 1996 to 1998 alone, the decline amounted to four percent)\footnote{Rodu B, Cole P. Nicotine maintenance for inveterate smokers. New York: Norton, 1977.} and most forms of cancer are, in fact, declining. Fourth, a national pattern of the breadth and depth of the ongoing cancer mortality reductions can neither start nor stop abruptly. The length of cancer induction periods and the likely reduced exposure to carcinogens over the last 25 years make it reasonable to expect \textbf{M}'s to continue down until at least 2010.

Fifth, we are winning but have not won the war on cancer. Bailar and Gornick\footnote{Munoz N, Connelly R. Time trends of intestinal and diffuse types of gastric cancer in the United States. \textit{Int J Cancer} 1989;44:158.} are correct in their view that more emphasis should be placed on prevention and prevention-related research. Several of the malignancies, notably non-Hodgkin's lymphoma and malignant melanoma, continue to increase in incidence and others, notably cancer of the esophagus and pancreas, remain resistant to diagnostic and treatment advances. Yet, to achieve the greatest overall reduction in cancer deaths, the target remains clear and unchanging; anti-smoking efforts must be reinvigorated and, most especially, heavy smokers must be provided with alternative ways to quit.\footnote{Kisch H, Finkle W. Increased risk of endometrial carcinoma among users of conjugated estrogens. \textit{Int J Epidemiol} 1989;18:342.}

Finally, the largest perspective. During the twentieth century cancer emerged from a minor position and became a major public health problem in the developed world. Over the next 30 to 50 years it will resume a minor position.\footnote{The waxing and waning occurred for virtually all the great scourges of mankind and it will occur for cancer. The descriptive epidemiology tells us that cancer's decline is now well established.} This waxing and waning occurred for most of the great scourges of mankind and it will occur for cancer. The descriptive epidemiology tells us that cancer's decline is now well established.

\section*{CHAPTER REFERENCES}

Most known causes of cancer of human beings became suspect because of observations made by physicians and surgeons treating cancer patients. These “alert practitioners” noted unusual characteristics among several patients with the same disease. Investigations by themselves or others then identified a cause of the cancer. An early example is the observation in 1895 by the German urologist, Rehn, that three men with bladder cancer had worked at a particular chemical facility, a dyestuffs manufacturer.

Cancer causation also is studied in experimental settings. Such studies can be complex and difficult to perform but may permit a straightforward judgement of causation to be made. When several investigators reproduce an experimental finding it is usually accepted as demonstrating causation.

Evaluating causality with epidemiologic research is more problematic. Epidemiology is not an experimental science. The epidemiologist observes heterogeneous, free-living human beings and has no control over their exposures or any other aspect of their lives. Further, the observations may be distorted by the retrospective nature of most epidemiologic research. That is, studies are made of exposures and of illnesses or deaths that occurred in the past, often in the distant past. For these reasons and others epidemiologic studies of cancer causation may produce highly variable results. History shows that studies of true and moderately strong causal associations will be reasonably consistently positive. However, a series of studies of a non-existent association will produce positive findings as well as the correct negative ones.

In 1965 Hill advanced guidelines for evaluating causality in epidemiologic studies of diseases with a long induction period. The “Hill criteria”, especially the major ones, the strength, consistency and plausibility/coherence of associations remain useful. A recently-developed set of guidelines are more detailed than Hill's and are specific to the different circumstances in which causality is assessed. Several of these guidelines apply to the results of an individual study while others apply to a general causal hypothesis. Yet others address causality in the exposure-illness experience of a specific person.

EVALUATING CARCINOGENICITY

Many considerations underlie the judgement that a suspect agent is or is not a carcinogen for human beings. An important factor is whether the determination is to serve scientific or public health and regulatory purposes. The scientific focus addresses the question, “Is this agent, virtually certainly, a cause of cancer in man?” An affirmative response could be based on strong, consistent evidence from epidemiologic studies or on overwhelming evidence of carcinogenicity in animals and the absence of meaningful negative findings in human beings. In practice, a positive judgement usually rests on both consistent human and animal evidence.

When public health and regulatory purposes are the focus the question will be, “Is the probability that this agent is a human carcinogen sufficiently high that exposure to it should be eliminated or restricted?” The evidence needed for a positive response is less than that needed for the scientific question. The use of a lower standard means that a positive judgement does not imply that the agent is considered a carcinogen but only that society should act as if it is.

These different purposes partly explain why available lists of carcinogens are rather different. For example, the National Toxicology Program (NTP) of the USA lists 33 agents as “known to be human carcinogens” and an additional 274 as “reasonably anticipated to be” human carcinogens, the NTP-B list includes 395 entries the International Agency for Research on Cancer (IARC) has a “Group 1” list of 75 items for which there is “sufficient evidence” of human carcinogenicity. This discrepancy seems surprising, since both agencies have a scientific mission. However, the IARC uses three categories: “agents”, “mixtures” and “exposure circumstances”. The category “agents” includes 25 items and, considering variations in the way agents are grouped, is virtually identical to the NTP-A list. The NTP recently has begun to evaluate “mixtures” and “exposure circumstances”. The category “agents” includes 25 items and, considering variations in the way agents are grouped, is virtually identical to the NTP-A list. The NTP recently has begun to evaluate “mixtures” and “exposure circumstances”. When we turn from “known” to “suspect” carcinogens, we find that the NTP-B list includes 274 agents while the IARC has a Group 2A (“probably carcinogenic to humans”) and a Group 2B (“possibly carcinogenic”) which include 59 and 227 listings respectively. It is clear that the NTP, in compiling both lists, is addressing the scientific question. At the other extreme, the EPA of California attempts to serve a regulatory purpose. It lists 456 “known” carcinogens, but there is no representation that the agents are known to cause cancer in human beings.

Agencies also produce differing lists of carcinogens because they evaluate different agents or group them differently. For example, while the NTP-A list includes 33 entries the International Agency for Research on Cancer (IARC) has a “Group 1” list of 75 items for which there is “sufficient evidence” of human carcinogenicity. This discrepancy seems surprising, since both agencies have a scientific mission. However, the IARC uses three categories: “agents”, “mixtures” and “exposure circumstances”. The category “agents” includes 25 items and, considering variations in the way agents are grouped, is virtually identical to the NTP-A list. The NTP recently has begun to evaluate “mixtures” and “exposure circumstances”. When we turn from “known” to “suspect” carcinogens, we find that the NTP-B list includes 274 agents while the IARC has a Group 2A (“probably carcinogenic to humans”) and a Group 2B (“possibly carcinogenic”) which include 59 and 227 listings respectively, a total of 286. While the two lists are not directly comparable their similar lengths suggest correctly that their contents are very much alike.

There are important lessons in the 25-year experience of various agencies in classifying carcinogens. First, once suspicion falls on a true human carcinogen it usually soon is recognized as such. In contrast, despite decades of research on them, hundreds of items languish on lists of suspect carcinogens, especially on those of regulatory agencies. For example, the NTP-B list has included at least 274 agents since 1980. Only two of these ever were “promoted” to the NTP-A list, both in 1998. During the same 18-year interval 12 compounds were added directly to the NTP-A list without appearing on the “B” list. Evidently, the probability that a suspect item will come to be recognized as a human carcinogen is small. Second, the identification of “known” causes of human cancer has slowed. During the 1990’s, the NTP added only four agents to its “A” list of known carcinogens, including the two from the “B” list. Ten had been added during the 1980’s. This slowdown occurred despite ever more intensive searches for causes of cancer. The public health implication of this slowdown is that the extension of declines in cancer rates will require more effort against the known causes of cancer. The clinical implication is that improved access to medical care and improved methods for the detection, diagnosis and treatment of cancer will be needed to extend the ongoing increases in patient survival.

CAUSES OF CANCER

The causes of the malignancies are as diverse as the causes of disease in general. They include genetic defects, environmental and lifestyle factors, and chemical, physical and biologic agents. We address primarily the known human carcinogens but will mention a few suspect agents in context. Our list of 72 causes, or groups of causes Table 14-3-1, is adapted from the IARC’s Group 1 list of 75 agents, mixtures and exposure circumstances for which there was judged to be sufficient evidence of carcinogenicity for human beings. We organized related agents into groups and combined them into five major categories. We added a few lifestyle factors of the type that the IARC does not consider. IARC does not list genetic causes of cancer and this Section does not address them. Finally, we indicate the NTP classification for each agent.
Many items in the table could be listed in more than one of the five categories. For example, solar radiation is an environmental factor but excessive sun exposure could be a lifestyle choice. It also poses an occupational hazard for outdoor workers, especially farmers. We placed each agent in the category where it seemed that most adverse exposure occurs. For each of the five categories, we estimated the attributable risk percent (AR%) for the general population. This is the proportion of cancer cases that would be prevented if the agents in the category were virtually entirely controlled. AR% were determined from estimates of the proportion of the USA population exposed to each agent in a category and the relative risks of cancer for such persons. We also considered the related efforts of Doll and Peto, Trichopoulos et al., and of others. Collectively, a series of AR% provides an overview of the profile of cancer causation in a large population. But AR% are highly variable from one population or time period to another.

Table 14.3-1 includes the major malignancies resulting from each of the causes listed. For cancers for which reasonably reliable data are available, we provide an estimate of the relative risk (RR). This is the I of the cancer among persons with a typical exposure to the listed cause divided by the I among non-exposed.

We do not review the evidence relating to these established causal relationships but provide one or two references in support of each. In some instances we referenced the IARC discussion itself. We describe some of the causal relationships that are of greatest public health significance and a few others because of some biologic or epidemiologic feature that they exhibit. Reviews of known and suspected cause-effect relationships are available in two widely-used textbooks of cancer epidemiology.

ENVIRONMENTAL FACTORS

For decades the mass media represented to the American public that the general environment was becoming polluted and that as a result cancer was increasing. Little attention was given to the underlying issue: Are the carcinogens in the environment or our exposure to them increasing?

From an epidemiologist's view the "environment" includes both the general or shared environment and individual behaviors and lifestyles. Only in this inclusive sense of the word is it correct that more than 80% of cancer is due to environmental, that is to all non-genetic, factors. On the other hand, in lay usage, the word "environment" designates only the shared environment, i.e., the air, water, ground and food supplies. We have adopted this usual meaning of the word, but point out that insofar as is known, individual behaviors are much more important causes of cancer than is the general environment.

All aspects of the long-term environmental deterioration in this country differ from place to place. There is no accurate way to summarize what the major contaminants were, when their inappropriate discharge occurred or when there was human exposure to them. Nevertheless, in much of the country the accumulated contamination had become consequential by about 1940. Most solid tumors of adults have an average induction period of about 20 years so it would be expected that cancers caused by environmental contaminants would have started to occur in about the mid-1950's.

Public awareness of the large scale of America's environmental problems began in 1962 with the publication of Silent Spring. When Lake Erie and the Cuyahoga River caught fire in 1969 there was a public outrage that led to the environmental regulations and the broad-based cleanup that continue to this day. But, despite the cleanup the exposure of human beings to environmental contaminants probably continued to increase in much of the country until at least the mid-1970's and more likely until about 1980. Thus, environmental cancers would have increased in frequency until about 2000 or later.

In reality, AR% from all cancer were increasing in this country by the early 1900's. AR% would have begun to increase even earlier. That is, the overall cancer AR% probably had been increasing for fifty years before environmental pollution could have had any discernible effect. The overall I of cancer began declining in 1991 and many forms of cancer began declining in the 1970's. This implies that many causes of cancer had begun to decline by 1970, that is, 30 or more years before an environmental cleanup could have had a beneficial effect.

While our concern with environmental causes of cancer is focused on AR%, there is reason to review AR% as well. The principle reason is the superior quality and representativeness of AR% over AR% when evaluating long-term, large-scale patterns of a relatively fatal disease. Excluding lung cancer, AR% for "all other cancer" have been declining continuously since 1950. Mortality from all cancer, including lung cancer, has been declining since 1991 and is now accelerating downward. This overall decline reflects reductions in the AR% of many specific forms of cancer, including the four major cancers. In fact, the American cancer experience, never static, is now changing favorably and profoundly; there was no meaningful increase in the number of cancer deaths from 1986 through 1998. This is impressive because the USA's population is increasing in size and age—two demographic changes that would increase the annual number of cancer deaths substantially even if age-specific AR% were constant.

We can not exclude agents in the environment as causes of some cancer. However, the study of general environments has led to the identification of only one cause of cancer in human beings. In that instance, endemic pleural mesothelioma in three villages in Turkey was found to be due to erionite, a naturally-occurring mineral which shares physical properties, including fiber size and shape, with asbestos. Moreover, if an environmental agent were to cause cancer, cases probably would first appear as a "cancer cluster" in a residential or social (e.g., school or house-of-worship) setting. Erionite came to attention in this way. However, none of the other investigations of hundreds of cancer clusters by the Centers for Disease Control and Prevention or by a state health department identified a culpable agent, old or new. There is no way to know how many such investigations have gone unpublished because they provided no useful clue to the identity of a carcinogen. These considerations do not rule out the need to seek environmental carcinogens when their presence is suspected. And, they do not justify the environmental contamination that occurred. But they do indicate that there are more fruitful arenas in which to seek human carcinogens.

Table 14.3-1 lists the four natural environmental agents that are on IARC's list of known carcinogens. Arsenic also could be listed here. Except for the inclusion of radon gas, and occupations involving exposure to radon, IARC makes no mention of ionizing radiation and its sources, natural or man-made. Aflatoxins and erionite are listed in the table.

TABLE 14.3-1. Known Causes of Cancer of Human Beings and the Major Cancers that They Cause

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Environmental Factor</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung cancer</td>
<td>Indoor air pollution</td>
<td></td>
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<tr>
<td>Breast cancer</td>
<td>Indoor air pollution</td>
<td></td>
</tr>
<tr>
<td>Colon cancer</td>
<td>Indoor air pollution</td>
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</table>

Aflatoxins

Aflatoxins are a group of toxins formed by the fungus Aspergillus sps. which lives on peanuts, maize and animal fodder. The aflatoxins kill bacteria which compete with the fungus for the vegetable material as food. Aflatoxin B1, produced by Aspergillus flavus, is a potent cause of several forms of cancer in many species. It is considered a cause of hepatocellular carcinoma (HCC) in man on the basis of animal and epidemiologic studies. HCC caused by aflatoxin is a major public health problem in Africa, in China and elsewhere in Asia. In these regions it also may interact with hepatitis viruses to cause a large amount of HCC, probably the most common cancer in the world, among men. The frequency of HCC caused by aflatoxin in developed countries probably is very low.

Concern over environmental carcinogens usually is focussed on agents discharged in large amounts into the air or water supplies or dumped inappropriately. Rarely is there concern about naturally occurring geophysical factors or agents, even though the cancer burden imposed by natural agents is likely to exceed greatly that imposed by artificial ones. Only three agents on IARC's Group 1 list of known carcinogens were widely distributed in the environment by man. These are arsenic,
asbestos and benzene. These agents were distributed primarily through the application of pesticides (arsenic), use of insulation and automotive brake materials (asbestos) and motor vehicle exhausts (benzene). Other Group 1 agents (e.g., the metals) also were dumped in large amounts but in limited areas.

How much cancer is caused by the three man-made, or man-distributed, agents in IARC's Group 1? That question can not be answered with precision. However, several groups have suggested that less than four percent of cancer deaths in America are caused by known carcinogens that pollute the environment. Perhaps the issue of greatest interest is that of general air pollution and lung cancer. Although this is not an established causal relationship, estimates of the AR% abound. For example, in 1990 the EPA estimated that less than one percent of lung cancer in the USA was caused by all of the "toxic pollutants" in air. However, the estimate related to known, or suspect, carcinogens. Thus, the actual amount of lung cancer caused may be somewhat higher because of the possible additional effects of unidentified agents. On the other hand, the actual percentage may be or soon may become lower if the environmental cleanup of the last 25 years produces benefits.

Benzene can be used to illustrate the effort to estimate the AR% of a widely-dispersed environmental carcinogen. In this example, we focus on benzene as a cause only of leukemia and not of lymphomas as has been suggested by some persons. Several benzene-leukemia risk assessments suggest that a benzene exposure on the order of 100 000 ppm-years is needed to double a person's risk of leukemia. The higher estimate, implying that benzene is weaker, is probably superior but we will use 50 ppm-years as the "first doubling dose" for leukemia. The "years" in the assessments refer to a year's work, that is 240 days at eight hours per day or about 22% of a full year. In highly contaminated public areas, e.g., a congested intersection in a major city, benzene levels in air rarely exceed 0.005 ppm. A person who spent a 75 year lifespan (about 350 work years) in this highly contaminated environment would accumulate a benzene exposure of 1.8 ppm-years (350 years × 0.005 ppm). This is about four percent of the first doubling dose of leukemia. Members of a population currently living under these conditions would have a lifetime probability of death from leukemia of 1.04% instead of the usual 1.0%. This estimate may be too high as there is evidence that the benzene-leukemia relationship is a threshold phenomenon in animals and that benzene does not produce leukemia in human beings at cumulative doses below 50 ppm-ys.

Benzene was used to illustrate the basis for the existing low estimates of the carcinogenic effects of environmental pollutants. Estimates for arsenic and asbestos are even lower because of their limited dispersal. Thus, the suggestion that environmental pollutants cause an appreciable amount of cancer in the USA usually rests upon conjectures: Unrecognized environmental pollutants are the culprits. Risk assessments such as that described are too general; concern should focus on local areas where exposures are uniquely high. However, the risk assessments do not consider possible synergistic effects of combinations of carcinogens. Or, finally, the population includes highly susceptible persons who will develop cancer at doses much lower than those experienced by the workers whose experience provides the basis for most risk assessments. It is correct that IARC's Group 2A and 2B together include about two dozen agents and mixtures that are suspected to cause cancer in human beings and are widespread. Trichloroethylene, polychlorinated biphenyls and diesel exhausts are relevant examples. But, whether these agents, alone or combined, do cause cancer is unknown.

LIFESTYLE FACTORS

There are five "mixtures" on IARC's Group 1 list that are included as lifestyle factors in Table 14.3.1. Except each the third, betel quid with tobacco, is discussed. We added reproductive factors. The NTP includes no lifestyle factor on its lists. We consider that about 45% of cancer in the USA is attributable to lifestyle factors but two-thirds of this 45% results from smoking.

Smoking

Smoking was the first cause of cancer identified in human beings but it is a precursor in almost every other way. It was the first lifestyle factor shown to cause cancer and probably the first established by epidemiologic means. Most important, smoking causes more cancer in the USA than do all other known causes combined. A typical 50 year old smoker has a risk of dying from cancer that is three times as great as that of a nonsmoker. Smoking leads to at least 25% and perhaps 35% of cancer deaths. Finally, smoking is preventable and its elimination would lower cancer mortality more than would the optimization of all other known preventive and treatment strategies combined.

CANCER OF THE LUNG. Cigarette smoking began in about 1900 and increased among men during World War I and the "roaring" twenties. It continued upward through the 1950's. Large numbers of women began to smoke during World War II and their smoking increased until the mid-1960's. By the 1930's many physicians suspected that the increase in lung cancer seen in their practices resulted from cigarette smoking. But this was contentious because many persons thought that the increase was due to previously known causes. Trichloroethylene, polychlorinated biphenyls and diesel exhausts are relevant examples. But, whether these agents, alone or combined, do cause cancer is unknown.

CANCER OF THE LARYNX. Smoking's association with larynx cancer is as strong as that with lung cancer. However, the risk of the disease among nonsmokers is so low that even the high RR among smokers produces rather few cases among them. The increased risk of larynx cancer from smoking is magnified by abuse of alcoholic beverages. A similar interaction or synergy is seen for cancer of the oral cavity and of the esophagus.

CANCER OF THE ORAL CAVITY (OCC). This condition, including cancer of the pharynx, is caused by smoking with a RR of about 5.

CANCER OF THE ESOPHAGUS. The risk of this disease is increased in smokers with a RR of about 4. It is a strikingly male disease, uncommon even among women who smoke.

URINARY TRACT CANCER. Renal cell cancer has a weak association with cigarette smoking with RRs rarely exceeding 2. However, the association is consistent and widely accepted as causal. The disease presumably is caused by a urogenous agent(s), possibly the same as that, or those, which cause squamous and transitional cell carcinomas of the lower urinary tract.

Smoking was causally linked to cancer of the bladder by the mid-1950's. Smoking also is a likely cause of carcinomas of the other urinary passages, the renal pelvis, ureter and urethra. These associations are moderate, with RRs of 2-4 and are consistent. There is some evidence that aromatic amines, especially 4-aminobiphenyl, created from tobacco proteins by the pyrolysis of smoking, explain these causal relationships. One of the largest studies found that persons who quit smoking lowered their RR of bladder cancer by 20 to 30% within about four years. This suggests that the urogenous carcinogen in cigarette smoke acts as a late-stage carcinogen in producing bladder cancer, whether or not it also acts as an early-stage carcinogen.

OTHER CANCERS. IARC considers smoking a cause of pancreas cancer. Smoking is moderately to strongly suspect as a cause of cancer of the cervix and liver and of leukemia.
Smokeless Tobacco

Use of smokeless tobacco imposes a moderate RR of 2 for OCC. However, this risk may be declining because the suspect carcinogens in smokeless tobacco, naturally-occurring tobacco-specific nitrosamines (TSNAs), have been reduced over the past two decades. In Sweden, where per capita consumption of smokeless tobacco is very high, TSNAs levels are undetectable and recent studies report no OCC attributable to the use of Swedish products.

Alcoholic Beverages

Four forms of cancer are caused by abuse of alcoholic beverages (AB), OCC and cancers of the larynx, esophagus and liver. RR's averaged over different levels of AB abuse and from different studies are about 4 for these cancers. Thus, 75% of these cancers that occur among AB abusers is attributable to their drinking. In a general population with six percent prevalence of AB abusers, a typical figure for men and women combined, about 20% of these cancers, and about 3% of all cancers, is attributable to AB abuse. Similar estimates have been made by others. However, none of these estimates includes the synergistic effects of smoking with AB in causing OCC and larynx and esophagus cancer.

Smoking and alcohol show a strong synergy in causing OCC and cancers of the larynx and esophagus. For example, among men, the RR of OCC is 5 for smokers and 5 for AB abusers. However, it is about 25 for men who have both exposures. Each of these three cancers has a distinctly high incidence sex ratio: 4.1, 4.0 and 2.5 for cancers of the larynx, esophagus and OCC, respectively. These high sex ratios probably occur because the combination of heavy smoking and AB abuse is four times as common among men as among women. A practical reality is that all three of the cancers would decline by 40% or so if AB abuse were to cease.

Despite its acceptance as a cause of four forms of cancer, the carcinogenic effect of AB abuse is unexplained. Ethanol is not carcinogenic in animals or in vitro. It has been suggested that AB abuse is associated with cancer because of the poor diet, including micronutrient and vegetable deficiencies, that characterize AB abusers. Another suggestion is that alcohol acts as a topical solvent on epithelial tissues and increases the amounts of carcinogens in food or cigarette smoke or in the AB themselves that penetrate cells. Both suggestions have existed for decades without becoming established or disproven.

Dietary Factors

Diet is widely seen as a cause of a high proportion of cancer in human beings. This perception has three major bases, the 1981 report by Doll and Peto, a wealth of seemingly incriminating research and an intuitive appeal. Doll and Peto estimated that 35% of cancer deaths in the USA might be attributable to diet (with a range of 10-70%). They wrote, "It must be emphasized that the figure chosen is highly speculative and chiefly refers to dietary factors which are not yet reliably identified." This qualification of the 35% estimate is as valid today as it was 20 years ago.

The estimated is restricted to known and strongly suspect dietary causes of cancer it is much lower than 35%. IARC includes only one dietary item, Chinese style salted fish, on its list of known carcinogens. It causes nasopharynx cancer where heavily salted fish is eaten in large amounts by persons of all ages, including children. This item presumably causes almost no cancer in America.

Although not a dietary factor in the usual sense, caloric excess and the resultant obesity may be seen as a cause of cancer. This is virtually certain for cancer of the endometrium and likely for breast cancer.

The items in the American diet often linked to cancer are red meat especially when charred, animal fats and “pesticide residues” ingested on over-treated and under-washed fruits and vegetables. The cancers related to these items are those of the stomach, colon, breast and prostate. None of these associations is established as causal. Similarly, many dietary agents have been suggested as protective against one or another form of cancer. These include, as examples, zinc and cancer of the larynx and esophagus, fruits and vegetables and cancers of the gastrointestinal tract, lung and endometrium. None of these associations is established.

Reproductive Factors

Virtually every aspect of a woman’s reproductive life is associated with alterations in her breast cancer risk. These include age at menarche (earlier, increased risk), age at first delivery (later, including nulliparity, increased risk), parity (more children, lowered risk), lactation (longer, lowered risk), age at menopause (earlier, lowered risk) and the use of exogenous estrogens (increased risk). Prolonged use of oral contraceptives (OCs) by younger women may increase breast cancer risk but this relationship remains poorly understood. The observations seem consistent in suggesting that the duration of a woman's reproductive life is the primary risk determinant. But, there also is evidence that much of a woman's breast cancer risk is determined in her youth and young adulthood. And yet, there is no accepted mechanism that links these reproductive features to a causal agent or to a means of preventing breast cancer.

Cancer of the endometrium and ovary share descriptive epidemiologic features with breast cancer and their risk is increased by nulliparity. But they share few of the other reproductive correlates of risk. Endometrial cancer is caused by use of sequential but not of combined OCs. This is presumably due to the regimen of sequential administration of the estrogens unmodified by a progestogen. Endometrial cancer also is caused by exogenous estrogens, primarily estrone, that until 1975 were prescribed frequently and in relatively high doses for the control of menopausal symptoms. These observations suggest that endogenous estrone is also a cause of the disease. In any event, some aberration of endogenous hormone production or metabolism is likely to cause endometrial cancer. This is consistent with the correlation of endometrial cancer risk with male pattern (upper body) obesity in which hormonal aberrations commonly are seen.

Finally, endometrial cancer is caused by tamoxifen, anti-estrogenic for the breast but estrogenic for the endometrium.

There is no established cause of ovarian cancer except ionizing radiation, although several agents are suspect. These include asbestos, talc and hair dyes. Parity is moderately protective with RR's declining gradually from 1.0 for nulliparas to about 0.4 for women with four or more children. Lactation may be moderately protective with perhaps a 30% risk reduction from prolonged lactation. Five or more years of use of combined OCs may lower risk by 40%. Weiss et al indicated that major progress will require a massive study which evaluates demographic features and possible causes separately for each of the major types of ovarian tumor (germ cell, sex cord and stromal and epithelial).

OCCUPATIONAL FACTORS

No area of epidemiologic research has identified as many human carcinogens as has occupational epidemiology. One-half of the 75 agents on the IARC Group 1 list of known carcinogens were identified, or confirmed, by occupational investigations. Yet, only about four percent of cancer in the USA is due to occupational factors.

The discovery of new carcinogens in occupational settings has slowed but this research setting remains important for four reasons: 1) There are several strong suspect occupational carcinogens. 2) For many agents thousands of workers are exposed in the USA and several hundred thousand worldwide. Thus, the hazard to workers alone from an occupational carcinogen could pose a major public health problem. 3) Workers typically are exposed to high concentrations of the agents with which they work and so serve as sentinels for the general population. 4) Almost all occupational studies are of the retrospective follow-up (also termed retrospective cohort) type. This design permits all causes of death, or all major illnesses, to be identified. Thus, these studies may identify not only carcinogens but causes of other diseases as well.

Only one occupational carcinogen, creosote, has been added to the NTP “A” list since 1981. More generally, the health of employed groups now is remarkably high. And yet, there is no accepted mechanism that links these reproductive features to a causal agent or to a means of preventing breast cancer.

PHARMACOLOGIC/IATROGENIC FACTORS

The use of a carcinogen as a therapeutic agent is justified for treating a life-threatening condition and even for treating severe non-fatal conditions. At least one known carcinogen, tamoxifen, is also a cancer preventative in women at high risk of breast cancer. The need to evaluate carefully the risks from the therapeutic use of a carcinogen in each patient is obvious. This is especially so for children since a child cured of a malignancy has a life expectancy much longer than the induction period of any cancer. It is not so well recognized that the same issue applies to adults. Even a 60 year old person in the USA has a life expectancy of 20 years or
more, an adequate induction period for many forms of cancer and especially for the leukemias induced by oncolytic therapy.

IARC’s Group 1 list of known carcinogens includes 18 agents and mixtures that are, or were, used in medical practice. There are nine alkylating agents (including as one, MOPP and other combinations that include an alkylating agent), four hormone groups, 1 hormone antagonist, two immunosuppressants, and two additional mixtures. They are listed in Table 14.3-1. Most of the agents are used to treat cancer and a few are used to treat other life-threatening conditions, e.g., transplanted organ rejection. Several, such as the estrogen mixtures are, or were, used to treat relatively benign conditions and OCS are used without a therapeutic indication.

The carcinogenic effects of therapeutic agents can be difficult to recognize and to quantify. The reasons are best described if we consider first the agents used for non-malignant conditions. The carcinogenic effect of these agents is difficult to evaluate because, although they are available only on prescription, the actual amounts prescribed and consumed are uncertain as in any patient (or member of the general public) may obtain the drugs. A patient, or another physician may change the drug prescribed to another which has a similar biologic effect but which has a different carcinogenic potential, e.g., substitution of non-steroidal for steroidal estrogens. Finally, if the patient is not under long-term observation at a single medical center a cancer that occurs will not be noted, much less be related to drug use.

Perhaps because of the difficulties just mentioned, as well as the low risk of cancer posed by agents that are not anti-neoplastic, Table 14.3-1 lists few such agents. This deadh does not reflect a lack of suspicion or of searches for carcinogenic effects of pharmacologic agents. Many agents have been evaluated and not found to be carcinogenic. For example, the IARC’s Group 3 (“Unclassifiable as to carcinogenicity to humans”) includes, among other medications, chloral, acetaminophen (the major metabolite of phenacetin), reserpine and spironolactone.

The causal relationship between DES exposure in utero and clear cell adenocarcinoma (CCA) of the vagina in young women warrants mention. DES is the only non-anti-neoplastic agent that increases the risk of certain types of cancers. Although the association is strong with an RR >100 the disease is nonetheless rare among exposed women; their lifetime risk of developing CCA is only 1 in 1000.

When we turn to the anti-neoplastic agents, most of the investigative problems mentioned above are reduced. The identity and dosage of the agents prescribed are documented. Outpatient compliance with treatment is presumed to be good. The agents are not used by the general public and so the baseline number of cancers of a particular type to be expected among treated patients can be estimated. However, there are three problems that complicate the study of the carcinogenicity of anti-neoplastic agents: 1) The agents often are used in combinations both simultaneous and sequential or with radiation therapy. This makes it difficult to identify the effect of any one agent and also introduces the possibility of synergistic effects. There is particular concern about synergy between pharmacologic agents and radiation therapy. However, there is as yet no evidence of this synergy. 2) Many cancer patients survive relatively few years after receiving chemotherapy. This makes it difficult to accumulate a substantial number of person-years at risk after the passage of a reasonable minimum induction period for a second cancer. 3) Cancer patients are at increased risk of developing a second primary cancer for reasons unrelated to their treatment. These include the high risk of a second primary once the first is detected. The causes of one cancer also cause others, e.g., patients with lung cancer also have an increased risk of bladder cancer, and vice versa, because smoking causes both. Also, causes of cancer often cluster in an individual, e.g., smoking, AB abuse and poor diet. Finally, there is the possibility of a “cancer diathesis”, the prospect that, for some constitutional reason, e.g., genetic makeup, a person who developed one cancer has an inherently increased risk of developing another.

The many reasons why a cancer patient might develop a second primary tumor cause us to be skeptical of reports of an excess of second primaries following anti-neoplastic treatment. This is especially so if the excess is minimal or is restricted to cancers of the same type or etiology as the first. However, as Table 14.3-1 indicates, 10% of cancer deaths in the USA might prove to be due to infectious agents.

Now, the discovery of causes of cancer has slowed in virtually every area except that of biologic agents. Almost certainly as a direct result of advances in molecular biology, there are nine biologic agents known to cause cancer in human beings (Table 14.3-1). All nine agents are of considerable scientific and clinical interest but only three of the human retroviruses, the human papilloma viruses (HPV) and H. pylori cause cancer to be considered public health problems in the USA. The hepatitis-B and -C viruses together cause about 50% of the cases of HCC that occur and so cause about 6000 deaths per year. HPV causes about 90% of cervical cancer or 4000 deaths per year. Both categories of agents produce much more disease in the developing world, as does EBV. H. pylori is estimated to cause 60% of stomach cancer or about 7000 deaths per year in the USA. The other known infectious agents combined probably cause less than 500 cancer deaths per year. The total for infectious agents is about 18,000 deaths per year or about four percent of cancer deaths. Doll and Petö’s “best estimate” of 10% still seems reasonable as a virus etiology may yet be found for several forms of cancer, especially in the leukemia-lymphoma group.

Cervical cancer is the most common cancer in the world, among women. It has a long and rich epidemiologic history. Its long-term declining etiology may yet be found for several forms of cancer, especially in the leukemia-lymphoma group.

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PERSPECTIVES

The year 2001 is the thirteenth anniversary of the National Cancer Act and of the USA’s “War on Cancer”. These three decades brought major achievements. Since at least 1972 M’s of most forms of cancer have been declining; in 1991 the overall cancer M started to decline and is now accelerating downward. This favorable trend probably will continue for many years. Thus, progress may now be described as, at the very least, substantial.

Cancer M’s started to decline earlier and still decline more sharply than do F’s. This is prima facie evidence of major improvements in medical care. And yet F’s is finally are also declining indicating that efforts are bringing results. This is what we address here. Do we now know, and protect against, the causes of more cancers than we did 20 or 30 years ago?

ARE MORE CANCERS NOW OF KNOWN ETIOLOGY?

At the beginning of this Section we compared the 1998 NTP-A list of known carcinogens with its 1980 counterpart. The list increased from about 20 agents to about 33. However, the added items are almost all pharmacologic agents that, combined, cause less than three percent of cancer deaths.

In 1981 Doll and Petö estimated the percentage of cancer deaths in the USA attributable to each of 11 major causes or groups of causes of cancer. The left column of Table 14.3-2 is an adaptation of their summary estimates of AR’s. (We made minor alterations in their format, described below.) The 97% figure of Doll and Petö does not imply that they thought they were explaining nearly all cancer. The AR’s are not mutually exclusive and the totals presented are only general indicators of how much disease might be prevented if the causes listed were controlled. The right column in Table 14.3-2 shows our present estimates of the
all-cancer AR%’s for the same categories of agents. A comparison of the two sets of estimates seems to imply that there has been little progress. The total in the second column is actually moderately lower than that in the first! Do we know the causes of fewer cancers than we did 20 years ago? No. The explanation of the decline in the AR%’s lies in the different bases of the two sets of estimates. Doll and Peto addressed what reasonably might be true; we describe what is known or highly probable. To clarify this we address several categories in the table.

<table>
<thead>
<tr>
<th>Category</th>
<th>2017-2016</th>
<th>1998-1996</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Tobacco</td>
<td>29%</td>
<td>30%</td>
</tr>
<tr>
<td>2. Non-tobacco smoking</td>
<td>10%</td>
<td>11%</td>
</tr>
<tr>
<td>3. Alcohol</td>
<td>7%</td>
<td>6%</td>
</tr>
<tr>
<td>4. Diet</td>
<td>5%</td>
<td>4%</td>
</tr>
<tr>
<td>5. Physical activity</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>6. Occupation</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>7. Social factors</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>8. Pharmacologic and iatrogenic agents</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>9. Environmental factors</td>
<td>1%</td>
<td>1%</td>
</tr>
</tbody>
</table>

Whether we refer to “tobacco” or “smoking”, the situation has not changed in 20 years: smoking causes about 30% of cancer deaths. It will now change. Lung cancer and other smoking-related cancers will decline sharply over the next decade. The impending decline in lung cancer deaths will occur because the number occurring among invertebrate, that is, heavy, smokers at last has started down. These persons are literally a dying breed whose numbers, finally, are not being replaced fully by equally heavy smokers. The misfortune is that the decline in smoking-related morbidity and mortality that is now beginning might have occurred 20 or more years ago if our initial efforts against smoking had focused on the heavy smokers.

Doll and Peto thought that dietary factors might cause about 35% of cancer. Yet, the evidence that dietary factors are carcinogens is as elusive today as it was 20 years ago. Our present estimate even of just five percent is defensible only as “strongly suspect”. Despite limitations and controversy the information on diet and cancer is useful. Virtually all of the dietary alterations recommended today to reduce cancer risk are, at the least, prudent. The specific reason why people choose a healthful diet and whether it is the “prudent” diet, the Asian diet, or the Mediterranean diet may matter little. Each of the diets, adopted not as a temporary regimen, but as a part of one’s lifestyle will contribute, if reasonable, to control, reduce intake of animal fats and increase the intake of fruits and vegetables. This should lower the risks of cardiovascular diseases and, perhaps, of cancer.

Doll and Peto considered only two of the virus-cancer relationships in Table 14.3-1 as “likely”. Today, none of the relationships in the table is controversial. However, there is uncertainty over the RR’s and AR%’s of cancer associated with infectious agents. Our summary estimate of four percent, developed above, is a reasonably firm estimate of the minimum amount of cancer caused by infectious agents.

We consider Doll and Peto’s estimate of one percent of cancer due to “medicines, procedures” and our analogous estimate of two percent as identical if only because both are imprecise. The amount of cancer caused by these agents is unlikely to be increasing. In fact, in a carefully developed opinion in 1977 Jick and Smith suggested two percent. Cancer due to pharmacologic and iatrogenic agents probably is declining because of their more guarded use.

No, we do not know the causes of fewer cancers today than we did 20 years ago. But, if we focus on what we know, as distinct from what may be true, we do not know the causes of many more, either.

**H ave W e R e d u c e d E x p o s u r e t o R e c o g n i z e d C a u s e s o f C a n c e r ?**

Yes. The population’s smoking, both active and passive, is diminishing, albeit slowly. Exposure to workplace carcinogens probably is declining and occupational cancers are in decline. H. pylori is treated widely, sunblockers are in common use and carcinogenic agents in medical practice are used carefully. Although obesity unfortunately is increasing, animal fat in the American diet is declining while the amount of fruit and vegetables is increasing. Also, contaminants in the general environment, possibly including carcinogens, are declining. It is impractical to estimate the cancer reductions that these changes will bring. But, the reductions already are evident and appear certain to increase.

**C H A P T E R R E F E R E N C E S**


CHAPTER 15
Principles of Cancer Management: Surgical Oncology

STEVEN A. ROSENBERG

INTRODUCTION

Surgery is the oldest treatment for cancer and, until recently, was the only treatment that could cure patients with cancer. The surgical treatment of cancer has changed dramatically over the last several decades. Advances in surgical techniques and a better understanding of the patterns of spread of individual cancers have allowed surgeons to perform successful resections for an increased number of patients. The development of alternate treatment strategies that can control microscopic disease has prompted surgeons to reassess the magnitude of surgery necessary.

The surgeon who treats cancer must be familiar with the natural history of individual cancers and with the principles and potentialities of surgery, radiation therapy, chemotherapy, immunotherapy, and other new treatment modalities. The surgeon has a central role in the prevention, diagnosis, and definitive treatment of the disease and in palliation and rehabilitation of the cancer patient. The principles underlying each of these roles of the surgical oncologist are discussed in this chapter.

HISTORICAL PERSPECTIVE

Although the earliest discussions of the surgical treatment of tumors are found in the Edwin Smith papyrus from the Egyptian Middle Kingdom (circa 1600 BC), the modern era of elective surgery for visceral tumors began in frontier America in 1809. Ephraim MacDowell removed a 22-pound ovarian tumor from a patient, Mrs. Jane Todd Crawford, who survived for 30 years after the operation. This procedure, the first of 13 ovarian resections performed by MacDowell, was the first elective abdominal operation and provided a great stimulus to the development of elective surgery.

The treatment of most tumors depended on two subsequent developments in surgery. The first of these was the introduction of general anesthesia by two dentists, Dr. William Morton and Dr. Crawford Long. The first major operation using general ether anesthesia was an excision of the submaxillary gland and part of the tongue, performed by Dr. John Collins Warren on October 16, 1846, at the Massachusetts General Hospital. The second major development stimulating the widespread application of surgery resulted from the introduction of the principles of antisepsis by Joseph Lister in 1867. Based on the concepts of Pasteur, Lister introduced carbolic acid in 1867 and described the principles of antisepsis in an article in the Lancet in that same year.

These developments freed surgery from pain and sepsis and greatly increased its use for the treatment of tumors. In the decade before the introduction of ether, only 385 operations were performed at the Massachusetts General Hospital. By the last decade of the nineteenth century, more than 20,000 operations per year were performed at that same hospital.

Table 15-1 lists selected milestones in the history of surgical oncology. Although this list does not include all the important developments, it does provide the tempo of the application of surgery to cancer treatment. Major figures in the evolution of surgical oncology included Albert Theodore Billroth who, in addition to developing meticulous surgical techniques, performed the first gastrectomy, laryngectomy, and esophagectomy. In the 1890s, William Stewart Halsted elucidated the principles of en bloc resections for cancer, as exemplified by the radical mastectomy. Examples of radical resections for cancers of individual organs include the radical prostatectomy by Hugh Young in 1904, the radical hysterectomy by Ernst Wertheim in 1906, the abdominoperineal resection for cancer of the rectum by W. Ernest Miles in 1908, and the first successful pneumonectomy performed for cancer by Evarts Graham in 1933. Modern technical innovations continue to extend the surgeon's capabilities. Recent examples include the development of microsurgical techniques that enable the performance of free grafts for reconstruction, automatic stapling devices, sophisticated endoscopic equipment that allows for a wide variety of “incisionless” surgery, and major improvements in postoperative management and critical care of patients that have extended the safety of major surgical therapy.

Table 15-1. Selected Historical Milestones in Surgical Oncology

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1809</td>
<td>First elective abdominal operation performed by E. MacDowell.</td>
</tr>
<tr>
<td>1838</td>
<td>First successful pneumonectomy for cancer performed by E. Graham.</td>
</tr>
<tr>
<td>1846</td>
<td>First major operation using general ether anesthesia.</td>
</tr>
<tr>
<td>1867</td>
<td>Lister introduced carbolic acid and described the principles of antisepsis.</td>
</tr>
<tr>
<td>1890s</td>
<td>William Stewart Halsted elucidated the principles of en bloc resections for cancer.</td>
</tr>
<tr>
<td>1904</td>
<td>First radical prostatectomy performed by Hugh Young.</td>
</tr>
<tr>
<td>1906</td>
<td>First radical hysterectomy performed by Ernst Wertheim.</td>
</tr>
<tr>
<td>1908</td>
<td>First successful pneumonectomy performed by W. Ernest Miles.</td>
</tr>
<tr>
<td>1933</td>
<td>First successful pneumonectomy performed for cancer.</td>
</tr>
</tbody>
</table>

Critics who believe that the application of surgery has reached a plateau beyond which it will not progress should remember the words of a famous British surgeon, Sir John Erichsen, who, in his introductory address to the medical institutions at University College, said,

There must be a final limit to the development of manipulative surgery, the knife cannot always have fresh fields for conquest and although methods of practice may be modified and varied and even improved to some extent, it must be within a certain limit. That this limit has nearly, if not quite, been reached will appear evident if we reflect on the great achievements of modern operative surgery. Very little remains for the boldest to devise or the most dextrous to perform.

These comments, published in the Lancet in 1873, preceded most important developments in modern surgical oncology.

ANESTHESIA FOR ONCOLOGIC SURGERY

Modern anesthetic techniques have greatly increased the safety of major oncologic surgery. Regional and general anesthesia play important roles in a wide variety of diagnostic techniques, in local therapeutic maneuvers, and in major surgery. These techniques should be understood by all oncologists.

Anesthetic techniques may be divided into those for regional and general anesthesia. Regional anesthesia involves a reversible blockade of pain perception by the application of local anesthetic drugs. These agents generally work by preventing the activation of pain receptors or by blocking nerve conduction. Agents commonly
used for local and topical anesthesia for biopsies in cancer patients are shown in Table 15-2 and Table 15-3. Topical anesthesia refers to the application of local anesthetics to the skin or mucous membranes. Good surface anesthesia of the conjunctiva and cornea, oropharynx and nasopharynx, esophagus, larynx, trachea, urethra, and anus can result from the application of these agents.

**TABLE 15-2. Infiltration Anesthesia**

<table>
<thead>
<tr>
<th>Local Anesthesia</th>
<th>Regional Anesthesia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lidocaine (Xylocaine)</td>
<td>Bupivacaine</td>
</tr>
<tr>
<td>Procaine (Novocaine)</td>
<td>Mepivacaine</td>
</tr>
<tr>
<td>Prilocaine (Citanest)</td>
<td>Etidocaine</td>
</tr>
</tbody>
</table>

**TABLE 15-3. Various Preparations Intended for Topical Anesthesia**

Local anesthesia involves injecting anesthetic agents directly into the operative field. Field block refers to injection of local anesthetic by circumscribing the operative field with a continuous wall of anesthetic agent. Lidocaine (Xylocaine) in concentrations from 0.5% to 1% is the most common anesthetic agent used for this purpose. Peripheral nerve block results from the deposition of a local anesthetic surrounding major nerve trunks. It can provide local anesthesia to entire anatomic areas.

Major surgical procedures in the lower portion of the body can be performed using epidural or spinal anesthesia. Epidural anesthesia results from the deposition of a local anesthetic agent into the extradural space within the vertebrae canal. Catheters can be left in place in the epidural space, allowing the intermittent injection of local anesthetics for prolonged operations. The major advantage of epidural over spinal anesthesia is that it does not involve puncturing the dura, and the injection of foreign substances directly into the cerebrospinal fluid is avoided.

Spinal anesthesia involves the direct injection of a local anesthetic into the cerebrospinal fluid. Puncture of the dural sac generally is performed between the L-2 and L-4 vertebrae. Spinal anesthesia provides excellent anesthesia for intraabdominal operations, operations on the pelvis, or procedures involving the lower extremities. Because the patient is awake during spinal anesthesia and is breathing spontaneously, it often has been thought that spinal anesthesia is safer than general anesthesia. There is no difference in the incidence of intraoperative hypotension with spinal anesthesia compared with general anesthesia, and there is no clear benefit in using spinal anesthesia for patients with ischemic heart disease. Because patients are awake during spinal anesthesia and can become agitated during the surgical procedure, spinal anesthesia actually can cause more myocardial stress than general anesthesia. The health status of patients with preoperative evidence of congestive heart failure is more likely to be worsened by general anesthesia than by spinal anesthesia. In one series, heart failure developed de novo in 4% of adults older than age 40 who were undergoing major surgery and worsened in 22% of patients who had a history of heart failure. Spinal anesthesia was not associated with any new or worsened heart failure. Because of local irritating effects of general anesthesia on the lung, it has been suggested that spinal anesthesia may be safer for patients with severe pulmonary disease.

**General anesthesia** refers to the reversible state of loss of consciousness produced by chemical agents that act directly on the brain. Most major oncologic procedures are performed using general anesthesia, which can be induced using intravenous or inhalational agents. The advantages of intravenous anesthesia are the extremely rapid onset of unconsciousness and improved patient comfort and acceptance. Ultra-short-acting barbiturates, such as sodium thiopental, or tranquilizers, such as the benzodiazepines or droperidol, are the most frequently used intravenous agents for general anesthesia or for sedation during regional anesthesia.

A variety of inhalational anesthetic agents are in clinical use. Nitrous oxide is popular, usually in combination with narcotics and muscle relaxants. This technique provides a safe form of general anesthesia with the use of nonexplosive agents. Two other agents in widespread use are the fluorinated hydrocarbons, halothane (Fluothane) and enflurane (Ethrane). Although they are used frequently, the fluorinated hydrocarbons have a variety of side effects. Halothane depresses myocardial function, reduces cardiac output, causes significant vasodilation, and sensitizes the myocardium to endogenous and administered catecholamines that can lead to life-threatening cardiac arrhythmias. In rare instances, halothane can cause severe hepatotoxicity, which begins 2 to 5 days after surgery. Enflurane also depresses myocardial function but does not appear to sensitize the myocardium to catecholamines and has not been associated with hepatic toxicity. The newest of the halogenated hydrocarbons is isoflurane, which was introduced in 1980. Isoflurane depresses the myocardium less than halothane or enflurane, but it has more potent vasodilatory properties.

Virtually all general anesthetics affect biochemical mechanisms, including depression of bone marrow, alteration of the phagocytic activity of macrophages, and exhibition of immunosuppressive properties. General anesthetic agents, such as cyclopropane and diethyl ether, rarely are used because of their explosive potential.

Intravenous neuromuscular blocking agents, called muscle relaxants, are commonly used during general anesthesia. These agents are nondepolarizing (e.g., curare), preventing access of acetylcholine to the receptor site of the myoneural junction, or are depolarizing (e.g., succinylcholine), acting in a manner similar to that of acetylcholine by depolarizing the motor end plate. These agents induce profound muscle relaxation during surgical procedures but have the disadvantage of inhibiting spontaneous respiration because of paralysis of respiratory muscles. Succinylcholine is short-acting (3 to 5 minutes), with a rapid recovery phase. Curare-induced paralysis lasts for 30 to 40 minutes after usual clinical doses of 0.3 to 0.5 mg/kg. Pancuronium has fewer side effects than curare but can induce tachycardia by means of sympathetic stimulation.

**DETERMINATION OF OPERATIVE RISK**

As with any treatment, the potential benefits of surgical intervention in cancer patients must be weighed against the risks of surgery. The incidence of operative mortality is of major importance in formulating therapeutic decisions and varies greatly in different patient situations (Table 15-4). The incidence of operative mortality is a complex function of the basic disease process that involves surgery, anesthetic technique, operative complications and, most important, the general health status of patients and their ability to withstand operative trauma.
In an attempt to classify the physical status of patients and their surgical risks, the American Society of Anesthesiologists (ASA) has formulated a general classification of physical status that appears to correlate well with operative mortality. Patients are classified into five groups depending on their general health status (as shown in Table 15-5).

Operative mortality usually is defined as mortality that occurs within 30 days of a major operative procedure. In oncologic patients, the basic disease process is a major determinant of operative mortality. Patients undergoing palliative surgery for widely metastatic disease have a high operative mortality rate even if the surgical procedure can alleviate the symptomatic problem. Examples of these situations include surgery for intestinal obstruction in patients with widespread ovarian cancer and surgery for gastric outlet obstruction in patients with cancer of the head of the pancreas. These simple palliative procedures are associated with mortality rates of approximately 20% in most series because of the debilitated state of the patient and the rapid progression of the basic disease.

Mortality caused by anesthetic administration alone is related directly to the physical status of the patient. In a review of 32,223 operations, Dripps et al. determined the mortality thought to be related to anesthetic administration alone (Table 15-6). It is extremely difficult to differentiate the mortality caused by anesthesia from that resulting from other contributors to operative mortality. However, this analysis indicates that operative mortality due to anesthesia in physical status class 1 patients is extremely low, fewer than 1 in every 16,000 operations. The anesthetic mortality increased with worsened physical status.

There is considerable evidence that anesthesia-related mortality has decreased in the last two decades, largely because of the development of rigid practice standards and improved intraoperative monitoring techniques. A summary of the specific intraoperative monitoring methods used to achieve improved anesthetic safety is presented in Table 15-7. A study of 485,850 anesthetics administered in 1986 in the United Kingdom revealed the risk of death from anesthesia alone in patients from all ASA classes to be approximately 1 in 185,000. In a retrospective review encompassing cases from 1976 through 1988, Eichorn estimated anesthetic mortality in ASA class I and II patients to be 1 in 200,200. These are probably underestimates, since underreporting of anesthetic-related deaths is a problem in all studies. Most cancer patients undergoing elective surgery fall between physical status I and II; thus, an anesthetic mortality rate of 0.01% to 0.001% is a realistic estimate for this group.

TABLE 15-4. Determinants of Operative Risk

TABLE 15-5. American Society of Anesthesiologists Classification of Physical Status

TABLE 15-6. Mortality Related to Physical Status

TABLE 15-7. Summary of Specific Intraoperative Monitoring Methods
Anesthesia-related mortality is rare, and factors related to the patient's preexisting general health status and disease are far more important indicators of surgical outcome. A study of the factors contributing to the risk of 7-day operative mortality after 100,000 surgical procedures is shown in Table 15-8. The 7-day perioperative mortality in this study was 71.4 deaths per 10,000 cases, and the major determinants of death were the physical status of the patient, the emergent nature of the procedure, and the magnitude of the operation.

### Table 15-8. Risk Factors Associated with 7-Day Operative Mortality

Several specific health factors can increase the risks of the operative procedure. Using discriminant analysis, Goldman et al. identified nine independent variables that correlated with life-threatening and fatal cardiac complications in patients undergoing noncardiac surgical procedures. By assigning a point value to each variable, a cardiac risk index could be computed (Table 15-9) that separated patients into four categories of risk (Table 15-10). The two risk factors most predictive of life-threatening complications were the presence of a third heart sound (S₃) or jugular vein distention (11 points) or a myocardial infarction in the previous 6 months (10 points).

### Table 15-9. Computation of the Cardiac Risk Index

A recent myocardial infarction significantly increases the incidence of reinfarction and cardiac death associated with surgery (Table 15-11). Significant improvements have occurred as new techniques of anesthetic monitoring and hemodynamic support have been developed.

### Table 15-10. Cardiac Risk Index

The impact of general health status on operative mortality is seen when operative mortality as a function of age is analyzed. Palmberg Hirsjarvi studied the postoperative mortality of 17,199 patients undergoing general surgical procedures. The overall mortality rate of patients younger than age 70 was 0.25%, as compared with 9.2% for patients older than 70. In these elderly patients, the operative mortality rate for emergency operations was 36.8%, as compared with 7.8% for elective surgical procedures. The four leading causes of operative mortality that accounted for approximately 75% of all postoperative deaths in this age group were pulmonary embolism, pneumonia, cardiovascular collapse, and the primary illness itself.

More recently, Hoskings et al. reviewed the outcome of surgery performed on 795 patients aged 90 or older. Surgery was generally well tolerated. As with younger
In excisional biopsy, an excision of the entire suspected tumor tissue with little or no margin of surrounding normal tissue is done. Excisional biopsies are performed excisional biopsy can compromise subsequent surgical excision. When this is a possibility, incisional biopsies should be performed.

Underlying conditions or congenital or genetic traits are associated with an extremely high incidence of subsequent cancer. When these cancers are likely to occur in nonvital organs, it is necessary to remove the offending organ to prevent subsequent malignancy. Examples of diseases associated with a high incidence of cancer that can be prevented by prophylactic surgery are presented in Table 15-12. An excellent example is presented by patients with the genetic trait for multiple polyposis of the colon. If colectomy is not performed in these patients, approximately one-half will develop colon cancer by the age of 40. By age 70, virtually all patients with multiple polyposis will develop colon cancer. It is, therefore, advisable for all patients containing the mutant gene for multiple polyposis to undergo prophylactic colectomy before age 20 to prevent these cancers.

**ROLES FOR SURGERY**

**PREVENTION OF CANCER**

Because surgeons are often the primary providers of medical care, they are responsible for educating patients about carcinogenic hazards and about direct surgical intervention for the prevention of cancer. All surgical oncologists should be aware of the high-risk situations that require surgery to prevent subsequent malignant disease.

Other disorders that require early treatment to prevent subsequent cancers include cryptorchidism and multiple endocrine neoplasia. Cryptorchidism is associated with a high incidence of testicular cancer that probably can be prevented by early prophylactic surgery.

In the past, patients with multiple endocrine neoplasia type 2a (MEN 2a) were screened for the presence of C-cell hyperplasia and calcitonin secretion using pentagastrin stimulation tests to determine the possible need for prophylactic surgery to prevent the occurrence of medullary thyroid cancer. Recent studies using polymerase chain reaction–based direct DNA testing for mutations in the RET protooncogene have shown it to be the preferred method for screening MEN 2a kindreds to identify individuals in whom total thyroidectomy is indicated, regardless of the plasma calcitonin levels.

A more complex example of the role of surgery in cancer prevention involves women at high risk for breast cancer. Because the risk of cancer in some women is increased substantially over the normal risk (but does not approach 100%), counseling is required. Women in this situation must carefully balance the benefits and risks of prophylactic mastectomy. A careful understanding of the factors involved in increased breast cancer incidence is essential for the surgical oncologist to provide sound advice in this area. Statistical techniques can provide approximations of the risk for patients, depending on the frequency of disease in the family history, the age at the first pregnancy, and the presence of fibrocystic disease. For example, a woman who has a family history of breast cancer in a sister or mother, has fibrocystic disease, and is nulliparous or had a first pregnancy at a late age has an 18% probability of developing breast cancer over a 5-year period. These estimates can be of value in advising women about prophylactic mastectomy.

**DIAGNOSIS OF CANCER**

The major role of surgery in the diagnosis of cancer lies in the acquisition of tissue for exact histologic diagnosis. The principles underlying the biopsy of malignant lesions vary, depending on the natural history of the tumor under consideration. Various techniques exist for obtaining tissues suspected of malignancy, including aspiration biopsy, needle biopsy, incisonal biopsy, and excisional biopsy.

Aspiration biopsy involves the aspiration of cells and tissue fragments through a needle that has been guided into the suspect tissue. Cytologic analysis of this material can provide a tentative diagnosis of the presence of malignant tissue. However, major surgical resections should not be undertaken solely on the basis of the evidence of aspiration biopsy. Even the most experienced cytologist can mistake inflammatory or benign reparative changes for malignant cells. This error is inherent in the uncertainties of an individual cell analysis and, even in the best of hands, provides an error rate substantially higher than that of standard histologic diagnosis.

Integration biopsy refers to obtaining a core of tissue through a specially designed needle introduced into the suspect tissue. The core of tissue provided by needle biopsies is sufficient for the diagnosis of most tumor types. Soft tissue and bony sarcomas often present major difficulties in differentiating benign and reparative lesions from malignancies and often cannot be diagnosed accurately. If these latter lesions are considered in the diagnosis, attempts should be made to obtain larger amounts of tissue than are possible from a needle biopsy.

In excisional biopsy, an excision of the entire suspected tumor tissue with little or no margin of surrounding normal tissue is done. Excisional biopsies are the procedure of choice for most tumors if they can be performed without contaminating new tissue planes or further compromising the ultimate surgical procedure.

**TABLE 15-12. Conditions in Which Prophylactic Surgery Can Prevent Cancer**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Associated Cancer</th>
<th>Prophylactic Surgery</th>
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In this situation, as for many of the other familial conditions associated with a high incidence of cancer, the surgeon has a responsibility for alerting the family to the hereditary nature of the disorder and its possible occurrence in other family members. Another high incidence of cancer of the colon is ulcerative colitis. Approximately 40% of patients with total colonic involvement ultimately die of colon cancer if they survive the ulcerative colitis.

Three percent of children with ulcerative colitis develop cancer of the colon by the age of 10, and 20% develop cancer during each ensuing decade. Colectomy is indicated for patients with ulcerative colitis if the chronicity of this disease is well established.

**ROLES FOR SURGERY**

**PREVENTION OF CANCER**

Because surgeons are often the primary providers of medical care, they are responsible for educating patients about carcinogenic hazards and about direct surgical intervention for the prevention of cancer. All surgical oncologists should be aware of the high-risk situations that require surgery to prevent subsequent malignant disease.

Underlying conditions or congenital or genetic traits are associated with an extremely high incidence of subsequent cancer. When these cancers are likely to occur in nonvital organs, it is necessary to remove the offending organ to prevent subsequent malignancy. Examples of diseases associated with a high incidence of cancer that can be prevented by prophylactic surgery are presented in Table 15-12. An excellent example is presented by patients with the genetic trait for multiple polyposis of the colon. If colectomy is not performed in these patients, approximately one-half will develop colon cancer by the age of 40. By age 70, virtually all patients with multiple polyposis will develop colon cancer. It is, therefore, advisable for all patients containing the mutant gene for multiple polyposis to undergo prophylactic colectomy before age 20 to prevent these cancers.

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The following principles guide the performance of all surgical biopsies:

1. Needle tracks or scars should be placed carefully so that they can be conveniently removed as part of the subsequent definitive surgical procedure. Placement of biopsy incisions is extremely important, and misplacement often can compromise subsequent care. Incisions on the extremity generally should be placed longitudinally so as to make the removal of underlying tissue and subsequent closure easier.

2. Care should be taken not to contaminate new tissue planes during the biopsy. Large hematomas after biopsy can lead to tumor spread and must be scrupulously avoided by securing excellent hemostasis during the biopsy. For biopsies on extremities, the use of a tourniquet may help in controlling bleeding. Instruments used in a biopsy procedure are another potential source of contamination of new tissue planes. It is not uncommon to take biopsy samples from several suspected lesions at one time. Care should be taken not to use instruments that may have come in contact with tumor when obtaining tissue from a potentially uncontaminated area.

3. Choice of biopsy technique should be made carefully to obtain an adequate tissue sample for the needs of the pathologist. For the diagnosis of selected tumors, electron microscopy, tissue culture, or other techniques may be necessary. Sufficient tissue must be obtained for these purposes if diagnostic difficulties are anticipated.

4. Handling of the biopsy tissue by the pathologist is also important. When the orientation of the biopsy specimen is important for subsequent treatment, the surgeon should mark in distinctive areas of the tumor carefully to facilitate subsequent orientation of the specimen by the pathologist. Certain fixatives are best suited to specific types or sizes of tissue. If all biopsy specimens are placed in formalin immediately, the opportunity to perform valuable diagnostic tests may be lost. The handling of excised tissue is the surgeon’s responsibility. Biopsy tissue obtained from breast cancer lesions, for example, should be saved for estrogen receptor studies and placed in cold storage until ready for processing.

Surgery also has a role in diagnosing pathologic states in cancer patients that do not directly involve the diagnosis of cancer. Cancer patients often are immunosuppressed by their disease or their treatment and are subject to opportunistic infections not commonly seen in most general surgical patients. Open lung or liver biopsies are often important in diagnosing these lesions adequately and in planning suitable therapy.

Oncologists are becoming increasingly aware of the need for precise staging of patients when planning treatment. Lack of proper staging information can lead to poor treatment planning and compromise the ability to cure patients. Staging laparotomy can be important in determining the exact extent of spread of lymphomas.

In performing accurate surgical staging, the surgeon must be familiar with the natural history of the disease under consideration. The development of ovarian cancer treatment is an excellent example. The tendency of ovarian cancer to metastasize to the undersurface of the diaphragm is a good example of the need to obtain a biopsy of an anatomic site that would not normally be subjected to biopsy by most surgeons. Extensive surgical staging may be required before undertaking other major surgical procedures with curative intent. For example, biopsy of the celiac and paraaortic lymph nodes in patients with cancer of the esophagus is often important so that unnecessary esophageal resections can be avoided.

Placement of radioopaque clips during biopsy and staging procedures is important to delineate areas of known tumor and as a guide to the subsequent delivery of radiation therapy to these areas.

### TREATMENT OF CANCER

Surgery can be a simple, safe method to cure patients with solid tumors when the tumor is confined to the anatomic site of origin. When patients with solid tumors present to the physician for the first time, approximately 70% already have micrometastases beyond the primary site. The extension of the surgical resection to include areas of regional spread can cure some of these patients, although regional spread often is an indication of undetectable distant micrometastases.

The emergence of effective nonsurgical therapies has had a profound impact on the treatment of cancer patients and on the role and responsibilities of the surgeon treating the cancer patient. John Hunter, a brilliant eighteenth-century surgeon, characterized surgery as being “like an armed savage who attempts to get that by force which a civilized man would get by stratagem.”

Although surgery continues to be the most important aspect of the treatment of most patients presenting with solid tumors, modern clinical research in oncology has been devoted to applying other adjuvant “strategies” to improve the cure rates of those 70% in whom surgical therapy alone ultimately fails. The role of surgery in the treatment of cancer patients can be divided into six separate areas: (1) definitive surgical treatment for primary cancer, selection of appropriate local therapy, and integration of surgery with other adjuvant modalities; (2) surgery to reduce the bulk of residual disease (e.g., Burkitt’s lymphoma, ovarian cancer); (3) surgical resection of metastatic disease with curative intent (e.g., pulmonary metastases in sarcoma patients, hepatic metastases from colorectal cancer); (4) surgery for the treatment of oncologic emergencies; (5) surgery for palliation; and (6) surgery for reconstruction and rehabilitation. In each area, interactions with other treatment modalities can be essential for a successful outcome.

#### Primary Cancer

There are three major challenges confronting the surgical oncologist in the definitive treatment of solid tumors: accurate identification of patients who can be cured by local treatment alone; development and selection of local treatments that provide the best balance between local cure and the impact of treatment morbidity on the quality of life; and development and application of adjuvant treatments that can improve the control of local and distant invasive and metastatic disease. The selection of the appropriate local therapy to be used in cancer treatment varies with the individual cancer type and the site of involvement. In many instances, definitive surgical therapy that encompasses a sufficient margin of normal tissue is sufficient local therapy. The treatment of many solid tumors falls into this category, including the wide excision of primary melanomas in the skin that can be cured locally by surgery alone in approximately 90% of cases. The resection of colon cancers with a 5-cm margin from the tumor results in anastomotic recurrences in fewer than 5% of cases.

In other instances, surgery is used to obtain histologic confirmation of diagnosis, but primary local therapy is achieved through the use of a nonsurgical modality, such as radiation therapy. Examples include the treatment of Ewing’s sarcoma in long bones and the treatment of selected primary malignancies in the head and neck. In each instance, selection of the definitive local treatment involves careful consideration of the likelihood of cure balanced against the morbidity of the treatment modality.

The magnitude of surgical resection is modified in the treatment of many cancers by the use of adjuvant treatment modalities. Rationally integrating surgery with other treatments requires a careful consideration of all effective treatment options. The surgical oncologist must be thoroughly familiar with adjuncts and alternatives to surgical treatment. It is a knowledge of this rapidly changing field that separates the surgical oncologist from the general surgeon most distinctly.

In some instances, effective adjuvant modalities have led to a decrease in the magnitude of surgery. The evolution of childhood rhabdomyosarcoma treatment is a striking example of the successful integration of adjuvant therapies with surgery in the treatment of cancer. Childhood rhabdomyosarcoma is the most common soft tissue tumor seen in children. Before 1970, surgery alone was used almost exclusively, and 5-year survival rates of 10% to 20% were commonly reported. Local surgery alone failed in patients with rhabdomyosarcomas of the prostate and extremities because of extensive invasion of surrounding tissues and the early development of metastatic disease. The failure of surgery alone to control local disease in patients with childhood rhabdomyosarcoma led to the introduction of adjuvant radiation therapy. This resulted in a marked improvement in local control rates that was further improved dramatically by the introduction of combination chemotherapy with vincristine, dacarbazine, and cyclophosphamide. Long-term cure rates are in the range of 80%. Many other examples of the integration of surgery with other treatment modalities appear throughout this book.

#### Residual Disease

The concept of cyoreductive surgery has received much attention in recent years. In some instances, the extensive local spread of cancer precludes the removal of all gross disease by surgery. The surgical resection of bulk disease in the treatment of selected cancers may well lead to improvements in the ability to control residual gross disease that has not been resected. Studies that suggest the merit of this approach are discussed in Chapter 45 and Chapter 36 (Burkitt's lymphoma and ovarian cancer, respectively).

Enthusiasm for cyoreductive surgery has led to the inappropriate use of surgery for reducing the bulk of tumor in some cases. Clearly, cyoreductive surgery is of benefit only when other effective treatments are available to control the residual disease that is unresectable. Except in rare palliative settings, there is no role for
The surgical oncologist can also be involved in administering and defining the need for adjuvant treatments. Adjuvant chemotherapy commonly is administered by medical and radiation oncologists. Successful coordination with these nonsurgical specialists requires expertise in medical oncology and radiation therapy that is not surgical oncology patients treated by all surgeons at that institution. A large surgical group should have a surgical specialist capable of coordinating efforts with the divisions of medical oncology present in 95%, radiation oncology in 94%, pediatric oncology in 76%, and gynecologic oncology in 79%.

In most hospital settings, general surgeons operate on cancer patients. It is often essential, however, that patients receiving care for various cancers enter clinical teaching programs for general surgical staff, residents, and students.

Several factors have led to a recent increase in the development of surgical oncology and to the organization of separate sections of surgical oncology in large hospitals and departments of surgery within universities. This enthusiasm derives from the recognition that modern oncologic management requires levels of expertise in cancer surgery, chemotherapy, and radiation therapy that are not common to most general surgeons and from a desire to use effectively the resources being committed to cancer care and research by hospitals, private foundations, and the federal government. A sense of urgency has existed because some surgical leaders believe that the surgeon is experiencing a declining intellectual role in modern cancer treatment and research and that steps must be taken to reassert the surgeon's role in modern oncology.

Many surgeons have resisted the development of surgical oncology as a specialty area because of the fear of fragmenting the field of general surgery. A survey of 124 university surgery departments in the United States between January and July of 1985 revealed that 38% had formal divisions of surgical oncology, compared with the divisions of medical oncology present in 95%, radiation oncology in 94%, pediatric oncology in 76%, and gynecologic oncology in 79%. Of the 47 divisions of surgical oncology that did exist, only 13 (28%) had formal clinical training programs in surgical oncology. This lack of emphasis on surgical oncology at universities may be a factor in the decreasing success of surgeons in obtaining grant support from the National Cancer Institute. From 1965 to 1985, an analysis of 6407 applications submitted from clinical departments of medical schools for peer-reviewed grants revealed that 44% were submitted from departments of medicine and only 16% from departments of surgery. Thirty-four percent of applications submitted from departments of medicine were awarded, compared with 25% from departments of surgery. The publication of research in major surgical journals appears to be decreasing.

The development of research in surgical oncology is of interest not only to surgeons but to all health professionals involved with cancer care. The development of new treatments and innovations in surgical techniques is of equal importance to those involved with the care of patients with cancer. The surgical oncologist has a unique role in the management of cancer patients, and the development of new surgical techniques is a key component of the treatment of cancer.

The surgical oncologist can play a valuable role in the care of cancer patients at major tumor centers. The surgical oncologist can perform a wide variety of surgical procedures, including resection of primary tumors, biopsy of metastatic disease, and palliative procedures. The surgical oncologist can also be involved in the evaluation of new surgical techniques and in the development of clinical trials. The surgical oncologist can also be involved in the administration and coordination of multidisciplinary care for cancer patients. The surgical oncologist can also be involved in the education of medical students, residents, and fellows. The surgical oncologist can also be involved in the development of new surgical techniques and in the evaluation of new surgical devices. The surgical oncologist can also be involved in the development of new surgical treatments and in the evaluation of new surgical devices. 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treatments can be logically administered by surgical oncologists to their patients after recovery from the surgical procedure.

The surgical oncologist, when the situation allows, is in a position to perform experimental research in oncology that can lead to the introduction of new diagnostic and treatment regimens in clinical care. Laboratory research programs that contribute to basic knowledge of cancer biology also provide an important source of stimulation to residents and students.

The emergence of a subspecialty of surgical oncology within general surgery requires that special attention be given to the training of surgeons interested in pursuing this area of clinical care. Although it is generally agreed that all surgical oncologists should be well-trained general surgeons, attempts have been made to define additional areas of expertise that must be studied. In 1975, a group of surgical oncologists met under the sponsorship of the Society of Surgical Oncology and the Division of Cancer Research, Resources, and Centers of the National Cancer Institute to develop guidelines for the training of surgical oncologists. The guidelines adopted by this meeting include suggestions for such training:

- Two-year training program on a surgical oncology service after completion of eligibility for general surgical certification by the American Board of Surgery or other surgical specialty board
- Training at an institution with a cancer program approved by the Commission on Cancer of the American College of Surgeons and whose clinical resources provide a sufficient variety and volume of clinical material to ensure exposure to a broad variety of clinical cancer problems
- Training at a center with sufficient basic science resources to provide education in these areas, with exposure to basic and clinical research
- Training at an institution that provides adequate operative experience, including standard curative and palliative procedures, with broad exposure to surgical procedures unique to the oncologic patient
- A full-time assignment during the training period to radiation oncology and chemotherapy services to allow the trainee to gain confidence and knowledge in these nonsurgical disciplines

These training recommendations are designed to provide general surgeons with the expertise in oncology and nonsurgical disciplines necessary to bring the best aspects of all disciplines of modern oncology to the care of the cancer patient.

**CHAPTER REFERENCES**

CHAPTER 16
Principles of Cancer Management: Radiation Therapy

SAMUEL HELLMAN

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Electromagnetic Radiation
Radiation Techniques
Beam-Modifying Devices
Radiation Treatment
Electrotherapy
Biologic Considerations
Radiation Interaction with Biological Materials
Cell Survival Considerations
Transcriptional Activation, Gene Induction, and Regulation after Ionizing Radiation
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INTRODUCTION

To understand the practice of radiation therapy, one must seek its roots in principles derived from three separate areas. The first is practical radiation physics, which must be understood much as the surgeon understands the use of the equipment available in the operating room and as the internist understands the pharmacologic basis of therapeutics. The basic concepts of physics necessary to consider radiation therapy in the disease-related chapters of this textbook are introduced in this chapter.

The second important discipline to be understood is cell, tissue, and tumor biology. This chapter describes the fundamental principles of radiation biology and cell kinetics. These two discussions provide the rudiments of cell biology necessary to understand the uses of radiation.

A large clinical experience in radiation use has resulted in certain principles of treatment. These are discussed separately and are related to the physical and biologic concepts that may underlie their success.

PHYSICAL CONSIDERATIONS

Only the most important concepts of the physics of ionizing radiation can be discussed in this chapter. If more detailed information is needed, a standard textbook of radiation physics is a more appropriate source of information. 1

Ionizing radiation is energy that, during absorption, causes the ejection of an orbital electron. A large amount of energy is associated with ionization. Ionizing radiation can be considered as a wave and as a packet of energy (a photon). The packet of energy is large enough to cause ionizations, and these are distributed unevenly through tissue. Examples of particulate radiation are the subatomic particles: electrons, protons, a particles, neutrons, negative pi mesons, and atomic nuclei. All of these have been experimentally considered or are being used in radiation therapy.

ELECTROMAGNETIC RADIATION

Electromagnetic radiation consists of roentgen and gamma radiation. They differ only in the way in which they are produced: Gamma rays are produced intranuclearly, and roentgen rays are produced extranuclearly. In practice, this means that gamma rays used in radiation therapy are produced by the decay of radioactive isotopes and that almost all of the roentgen rays used in radiation therapy are made by electrical machines. Exceptions are roentgen rays produced by orbital electron rearrangements, as in the decay of iodine 125 ( 125I), which is a radioactive isotope but produces photons by extranuclear processes. 125I also emits a small number of gamma rays from the nucleus.

The intensity of electromagnetic radiation dissipates as the inverse square of the distance from the source. The dose of radiation 2 cm from a point source is 25% of the dose at 1 cm.

The relative prevalence of the three dominant absorption mechanisms of electromagnetic radiation depends on the energy of the radiation. The first is photoelectric absorption, which predominates at lower energies. In this circumstance, the photon interaction results in the ejection of a tightly bound orbital electron. The vacancy left in the atomic shell is then filled by another electron falling from an outer shell of the same atom or from outside the atom. All or most of the photon energy of the transition is lost in this process. Photoelectric absorption varies with the cube of the atomic number ( Z3). This fact has significant practical implications because it explains why materials with high atomic numbers, such as lead, are such effective shielding materials. It also means that bones absorb significantly more radiation than soft tissues at lower photon energies, the basis for conventional diagnostic radiology.

The second type of absorption is the Compton type. In this process, the photon interaction is with a distant orbital electron that has a low binding energy. In this absorptive process, the photon does not give up all its energy to a single electron; an appreciable portion reappears as a secondary photon, which is created in the interaction. In contrast to the photoelectric effect, the probability of Compton absorption does not depend much on atomic number, but rather on electron density. This explains why films made at supervoltage energy do not show much difference between bone and soft tissue, but air cavities are clearly distinguished.

The third type of absorption is the pair production process. This type of absorption requires an incident photon energy greater than 1.02 MeV. In this process, positive and negative electrons are produced at the same time.

The fundamental quantity necessary to describe the interaction of radiation with matter is the amount of energy absorbed per unit mass. This quantity is called absorbed dose, which was the most commonly used unit. Absorbed dose is measured in joules per kilogram; another name for 1 J/kg is the gray (1 Gy = 100 rad), which is now the recommended unit. The roentgen (R) is a unit of roentgen rays, or gamma rays, based on the ability of radiation to ionize air. At the energies used in radiation therapy, 1 R of roentgen rays, or gamma rays, results in a dose of somewhat less than 1 rad (0.01 Gy) in soft tissue.

The different ranges of electromagnetic radiations used in clinical practice are superficial radiation, or roentgen rays from approximately 10 to 125 keV; orthovoltage
radiation, or electromagnetic radiation between 125 and 400 keV; and supervoltage, or megavoltage, radiation for energies of more than 400 keV. There are important
differences between these classes. As energy increases, the penetration of the roentgen rays increases (Fig. 16-1), and at supervoltage energies, absorption in bone
is not higher than that in surrounding soft tissues, as is the case with lower energies. This is because at supervoltage energies, Compton absorption predominates.
Compared with orthovoltage, supervoltage radiation is skin sparing, meaning that the maximum dose is not reached in the skin, but instead occurs below the surface.
The electrons created in the interaction travel some distance and do not attain full intensity until they reach some depth, resulting in a reduced dose to the skin. With
orthovoltage radiation, the skin frequently is the dose-limiting normal tissue.

**FIGURE 16-1.** Relative dose at different depths for various types of ionizing radiation.

**RADIATION TECHNIQUES**

Two general types of radiation techniques are used clinically: brachytherapy and teletherapy. In brachytherapy, the radiation device is placed within or close to the
target volume. Examples of this are interstitial and intracavitary radiation used in the treatment of many gynecologic and oral tumors. Teletherapy uses a device
located at a distance from the patient, as is the case with supervoltage machines.

Because the radiation source is close to or within the target volume with brachytherapy, the dose is determined largely by inverse-square considerations. This means
that the geometry of the implant is important. Spatial arrangements have been determined for different types of applications based on the particular anatomic
considerations of the tumor and important normal tissues. An example of isodose distribution around an intracavitary application for carcinoma of the cervix is shown
in Figure 16-2. The dose decreases rapidly as the distance from the applicator increases. This emphasizes the importance of proper placement. The applicator
pictured is used to treat the cervix, uterus, and important paracervical tissues while limiting excessive irradiation of the bladder and rectum in front of and behind the
tumor.

**FIGURE 16-2.** Isodose distribution around an intrauterine radium (Ra) applicator. A: Anteroposterior view. B: Lateral view.

Historically, the removable interstitial and intracavitary sources used were radium and radon, the latter primarily for permanent implants. Marie Curie, the discoverer of
radium, recognized its importance early and championed the medical use of these isotopes. They were important tools in early cancer therapy but now have been
largely replaced by man-made isotopes, which overcome most of the disadvantages of the naturally occurring ones.

Initially, even removable isotopes were used by directly applying the isotope, thereby exposing the operator to significant radiation doses. This problem has largely
been circumvented through the use of cesium 137, iridium 192, and cobalt 60. The iridium and cesium have a lower energy and are much easier to shield.
Afterloading techniques are used for removable implants as often as possible. Receptacles for the radioactive material are placed in the patient in the form of needles,
tubes, or intracavitary applicators. When they have been satisfactorily placed, they are afterloaded with the radiation sources. Remote afterloading using
high-intensity sources whose dwell time is determined for a particular dose distribution is now a common treatment method. Permanent implants are primarily done
today with gold 198 and 125I and palladium 109.

Typical teletherapy isodose distributions are shown in Figure 16-3. The dose depends on inverse-square considerations and tissue absorption. The distribution of
radiation depends on characteristics of the machine and the patient. The isodose curve depends on the energy of radiation, the distance from the source of radiation,
and the density and atomic number of the absorbing material. The beam of radiation produced in typical radiation treatment may be modified to make isodose
distributions conform to the specific target volume, and individually designed shields are used to protect vital normal tissues.

**FIGURE 16-3.** Isodose distributions for 4 MeV without (A) and with (B) a wedge filter.

**Figure 16-4** shows some radiation treatment plans in which the target volumes are depicted. This volume contains the tumor and the normal tissues intimately
involved with the tumor. The diagram also contains the transited normal tissues, or transit volume. The purpose of the treatment plan is to maximize the dose to the
target volume and minimize the dose to the transit volume. It is important that the tumor dose is relatively homogenous, because the maximum dose in the target
volume is often the cause of complications, and the minimum dose in the target volume determines the likelihood of tumor recurrence. The volumes of interest in the
patient have been specified as the: gross tumor volume (GTV), clinical tumor volume, and planning target volume. The GTV is the clinically evidenced tumor volume, taking into account all diagnostic procedures. The clinical tumor volume is the GTV plus the volume considered at risk for microscopic extensions. The planning target volume includes the GTV and a margin for physiologic organ motion.

FIGURE 16-4. Typical supervoltage treatment plans for opposing fields (A), rotation (B), three fields (C), and wedge rotation (D).

BEAM-MODIFYING DEVICES

In modern radiation therapy, teletherapy is given almost exclusively with supervoltage equipment. These radiations are produced by the decay of radioactive cobalt or with the production of roentgen rays in the range of 2 to 35 MeV (the most common are 4 to 8 MeV). High-energy photons and electrons are made by linear accelerators.

Regardless of the radiation source, the beam must be modified for clinical use. With electrical machines, the beam tends to have a much greater intensity in the center than on the sides. Modification to give a uniform dose of radiation across the beam is done with a flattening filter (unnecessary in cobalt units). For the beam to be limited to the designated size, collimators are placed in the head of the machine. These usually are made of materials that have a high $Z$ value and can be varied to conform to the exact rectangular beam dimensions desired.

It is sometimes desirable for the beam to be more intense on one side than the other. This is especially important when fields at angles to each other are to be used. To modify the beam in this fashion, wedge filters are used (see Fig. 16-3B). These wedge-shaped pieces of metal absorb the beam differentially, depending on the thickness that produces the desired angled isodose curves.

The primary radiation beam is rectangular. This rectangle may be varied for individual patients using the secondary collimators in the head of the machine. These can then be further modified by individually constructed blocks shaped to the contour of the normal tissue (Fig. 16-5). The newest equipment has multileaf collimators, which permit the collimator to follow closely the desired portal contour, rather than being restricted to a rectangular shape. This type of collimator can be moved while the radiation beam is on, allowing the physicist to shape the dose distribution within each radiation field in a desired fashion. The result of multiple fields treated in such a fashion can greatly improve the dose distribution so that the transited normal tissue dose is greatly reduced. This is described in Chapter 29.4.

FIGURE 16-5. A: A film made on a therapy simulator on which outlines for shielding blocks are drawn. B: Supervoltage portal film with blocks in place. C: Technique for checking accuracy of the blocks with simulator films.

RADIATION TREATMENT

Once the decision has been made to treat a patient with radiation, pretreatment procedures must be performed. First, the target volume must be accurately localized and the dose-limiting, transited normal tissues must be determined. This localization requires physical examination, radiography, ultrasonography, computed tomography (CT), and other diagnostic procedures. Before this step, the clinician must understand the natural history of the disease and its patterns of spread.

Once localization has been completed, the treatment planning process begins, in which alternative techniques of treatment are considered. The selection of the appropriate treatment plan is made by the clinician in consultation with the radiologic physicist and dosimetrist. This team effort must consider the best beam distribution, homogeneity within the target volume, and appropriate minimizing of dose in the transit volume.

Once the appropriate treatment plan has been accepted, the technique is tested using a radiation simulator. This device mimics the treatment machine but produces superficial radiation that can be used for direct imaging with an image intensifier and for producing radiographs that delineate exactly the beam location. Treatment simulation often causes modifications to be made in the treatment plan, allowing further sparing of normal tissues. Simulator films must be compared with the check, or portal, films made with the supervoltage machine, which confirm the treatment plan (see Fig. 16-5). Image quality is poor because these films do not distinguish bone from soft tissue. This is because supervoltage radiation is absorbed primarily by the Compton process, which does not depend on $Z$. In contrast, the simulator films are made with radiations of 80 to 110 keV, which are in the photoelectric range and therefore dependent on $Z^2$. Treatment planning and simulation are now greatly facilitated using a CT simulator. This single device combines CT image acquisition with treatment planning in the treatment position.
**FIGURE 16-6.** Electron and superficial roentgen ray depth–dose curves.

For the treatment to be applied as designed on the radiation simulator, proper immobilization and marking techniques must be used. These also ensure that daily treatments are given to the same volume. Markings on the patient's skin may be temporary or permanent. Usually, temporary marks are used to supplement the permanent small dots, or "tattoos," ensuring that the treatment is given to the same volume each day. Should the patient require further therapy at a later date, these markings accurately indicate the location of previous treatment portals. Within the treatment room, light localizers describe the outline of the field, and small laser dots are used to check whether the patient is in the correct position. Immobilization of the patient usually is achieved by devices made of foam, plastic, plaster, and other materials that can be made to conform to each patient's anatomy. It is most important that the patient be put in a position that is comfortable and easily reproduced from day to day.

**ELECTRON THERAPY**

Electrons differ greatly in their characteristic depth-dose distributions (Fig. 16-6). The maximum dose is reached and followed by a prompt fall. Little skin sparing is possible with electron beam therapy. It is the most useful radiation in the treatment of superficial tumors because the deeper tissue is spared by the prompt fall in the radiation dose. With higher electron energy, the penetration is greater and the fall in depth dose not as steep. A major problem with electrons is that absorption can be modified greatly by bone or air-containing tissues. Bone greatly reduces the depth dose because it absorbs much more of the radiation; the contrary is true for air-containing spaces.

Currently there is a great deal of interest in proton therapy, which is discussed in more detail in Chapter 65.

**BIOLOGIC CONSIDERATIONS**

**RADIATION INTERACTION WITH BIOLOGIC MATERIALS**

Because mammalian cells may be considered dilute aqueous solutions, there are two possible mechanisms of interaction with biologically important molecules—the direct effect of radiation on the important target molecule, and the indirect effect produced by intermediary radiation products. For most events, the important target molecule is thought to be the DNA, and when considering the maintenance of reproductive integrity, it is useful to assume that DNA is the target. Whatever the critical target, it can be affected directly by ionizing radiation that causes a change in the molecular structure of the biologically important molecule. This direct effect is most common for high linear energy transfer (LET) radiation. Alternatively, the photon may interact with water, the predominant molecule in these dilute solutions, to produce free radicals. All of these forms of radiation are short-lived; they can interact with biologically important material, causing a detrimental effect, or they can react innocently and revert to their former state. The likelihood of interaction or reversion can be modified by reaction with molecular oxygen, which favors prolonging the life of a reactive species, or by reaction with sulfhydryl compounds, which reduces the lifespan of the free radicals by combining with them to return to innocuous substances.

**CELL SURVIVAL CONSIDERATIONS**

Radiation effects, whether direct or indirect, are random, an important principle in the general nature of cell killing. The biologically important effects of radiation therapy are those concerned with reproductive integrity. It usually is assumed that DNA is the critical target for this radiation effect, although it has not been proved with certainty. Other biologically important effects of radiation (e.g., edema) are far more likely to be caused by its action on membranes.

At least four possible consequences of radiation interaction with cells can affect long-term reproductive viability of the cell or its progeny: necrosis, apoptosis, accelerated senescence, and terminal differentiation. Current research is focused on these different effects of radiation on cells.

A cell that is damaged by radiation and loses its reproductive integrity may divide once or more often before all the progeny are rendered reproductively sterile. Possible consequences to the cell include the following:

1. Rapid death by apoptosis
2. It may die while trying to divide.
3. It may produce unusual forms as a result of aberrant attempts at division.
4. It may stay as it is, unable to divide, but physiologically functional for a long period. Such functional but sterile cells do not appear different from fertile cells.
5. Some of these may be terminally differentiated cells.
6. The cell may undergo no alterations in the divisional process or only minor ones.

Except for those cells undergoing apoptosis, some delay in division is usually produced, even in cells that are not damaged lethally.

**Survival Curves**

Survival curves plot the fraction of cells surviving radiation against the dose given. Survival is determined by the ability to form a macroscopic colony. The simplest relation can be seen for bacteria in which survival is a constant exponential function of dose. The importance of this exponential relation is that, for a given dose increment, a constant proportion (rather than a constant number) of cells is killed. Because of the randomness of radiation damage, if there is, on average, one lethal lesion per cell, some cells have one lesion, some more than one, and some fewer than one. Under such circumstances, the proportion of cells that have fewer than one (i.e., no lethal events) is $e^{-1}$, or a survival fraction of 0.37. The dose required to reduce the survival fraction to 37% on the exponential curve is known as the $D_{0}$.

This term is related to the slope of the exponential survival curve. If a smaller dose is required to reduce the survival fraction to 37%, the cells are more sensitive to radiation.

Survival curves of most mammalian cells differ from those of bacterial cells by having a "shoulder" in the low-dose region and the exponential relation at higher doses. This shoulder indicates a reduced efficiency of cell killing. Such an idealized curve is shown in Figure 16-7, with the shorthand terminology used to describe survival curves. The terminal exponential portion is described by the $D_{0}$, whereas the initial shoulder region can be described by the extrapolation number n or the $D_{q}$ the quasi-threshold dose. The former is the number on the ordinate found when the exponential portion is extrapolated to O dose, whereas $D_{q}$ is the dose at which the straight portion of the survival curve extrapolated backward intersects the line where the survival fraction is unity. If any two of these are known, the third can be calculated. The survival curve is described as follows: $log e = D/D_{0}$. This curve is best described by a linear quadratic model with the following formula $S = e^{-(nD + \beta D^{2})}$.
The a and b terms in this equation and their ratio are used to describe survival curve characteristics and to classify cellular response to radiation. Survival curves have been determined for benign or neoplastic mammalian cells in culture. No general characteristics of tumor cells make them different from normal cells in culture. The survival curves for various human tumors thought to be sensitive and resistant to radiation were studied by Weichselbaum and colleagues, who did not show any survival-curve characteristics that allow these two to be separated. Therefore, the differences in clinical response cannot be explained by simple acute differences in survival curves, although recurrent tumors have the radiobiologic characteristics of the more resistant subclones of the primary tumor.

Normal tissues also have been studied using clonogenic survival as an end point, with survival curves determined analogously to those for cells in tissue culture. The simplest clonal system, as originally described by Till and McCulloch, is that used for murine bone marrow stem cells. When bone marrow cells are injected into lethally irradiated recipient animals, colonies are formed in the animals’ spleens. These can be used to assess the reproductive integrity of the injected cells. The viability of the small intestinal clonogenic mucosal cells can be assessed by looking at sections of the small intestine at various times after irradiation and determining the appearance of colonies derived from cells surviving this radiation. Using these and other techniques, the general properties of survival curves of normal and tumor cells are shown in Table 16-1. There are no characteristic differences in survival curves between normal tissues and tumors. Tumors generally resemble their normal tissue of origin in this respect.

FIGURE 16-7. Idealized radiation survival curve. $D_0$, dose required to reduce the survival fraction to 37% on the exponential curve, $D_{eq}$, the quasi-threshold dose, i.e., dose energy divided by dose loss.

TABLE 16-1. Survival Curve Parameters for Some Mammalian Cells

### Repair of Radiation Damage

When cells are irradiated, lethal damage can occur, or the damage may be modified and not lead irrevocably to cell death. Such amelioration of radiation damage is called repair. Repair can be divided into potentially lethal damage repair and sublethal damage repair.

Potentially lethal damage, under certain circumstances, leads to cell death. If postirradiation conditions are modified to allow repair, cells that would have died can be salvaged. In general, postirradiation conditions that suppress cell division are the ones most favorable to repair of potentially lethal damage. The simplest example of this was shown first in bacteria for UV and x-radiation. A similar effect was seen in mammalian cells and persists into the first few postirradiation generations. Potentially lethal damage repair may be most important in relating the cell culture studies of human tumors to their clinical response. Weichselbaum and colleagues have shown that osteogenic sarcoma, a tumor characteristically thought to be resistant to radiation, has a great capacity for potentially lethal damage repair compared with tumors that may be much more responsive to radiation. After irradiation in the clinical circumstance, the tumor cell may not be faced with the necessity of rapid cell division, and it may have the opportunity for potentially lethal damage repair.

One explanation for the shoulder of the radiation survival curve is that the cell can repair some of the radiation damage, including a great proportion of the damage incurred with low doses of radiation. This is called sublethal damage. Elkind and Sutton have studied the shoulder and its return by using divided doses of radiation. They have shown that if the dose of radiation is divided into two fractions and a few hours elapse between radiation doses, the shoulder will return. Therefore, two doses of radiation separated in time are less effective than the same total dose given as a single dose. Both $D_{eq}$ and the a/b ratio measure similar characteristics of the survival curve. With the exception of the bone marrow stem cells, acutely responding normal tissues have a large $D_{eq}$ and a large a/b ratio. This suggests that multiple small fractions of radiation can preserve these tissues, but not bone marrow.

Varying the dose rate of radiation may be considered a form of radiation fractionation. When the dose rate is low, such as during interstitial or intracavitary irradiation, it can be considered as a large number of small doses on the shoulder of the survival curve. Therefore, differences between the dose-limiting normal tissues and the tumor in their shoulder characteristics and differences in the break point between shoulder and steep exponential have great clinical implications for such continuous radiation.

Apoptosis is an important response to radiation in many cells. The relative proportion of cells undergoing apoptosis rather than pausing in the cell cycle to repair radiation damage may be a very important determinant of the likelihood of the radiation curability of a tumor. Certain normal cells, such as lymphocytes and germ cells, show apoptosis with very small doses of radiation. The reciprocal nature of radiation repair and apoptosis may explain the correlation between potentially lethal damage repair and radiosensitivity; cells with a great capacity for potentially lethal damage repair have little apoptotic response to radiation. It may be the latter that is the determining characteristic. The loss of the apoptotic response seems to be correlated to tumor progression. A number of genes associated with oncogenesis affect the likelihood of a cell demonstrating programmed cell death after DNA damage, including Bcl-2, Bcl-x, and P53. A variety of factors can induce or stimulate apoptosis, including those stimulated by radiation.

### Importance of Oxygen

The most important modifier of the biologic effect of ionizing irradiation is molecular oxygen. First noted in the 1920s, its importance was not realized until Mottram studied it systematically. The general scientific community became aware of this phenomenon with the publications by Read and Gray et al. in the early 1950s. Figure 16-8 shows a survival curve for cells under aerobic and hypoxic conditions. For equivalent cell killing at every level of survival, greater doses are required under hypoxic conditions compared with aerobic conditions. There is some disagreement in the literature as to whether the dose ratio is the same throughout the survival curve. Most data suggest a smaller difference when low doses are used. A shorthand term, the oxygen enhancement ratio (OER), often is used. OER is the ratio of dose required for equivalent cell killing in the absence of oxygen compared with the dose required in the presence of oxygen. This term has most relevance on the exponential portion of the curve, because there appears to be a reduced shoulder on the survival curve of cells under hypoxic conditions. Tumor cells allowed to
grow into physiologic hypoxia have reduced capacity to repair sublethal damage (Fig. 16-9).

**FIGURE 16-8.** In vivo survival curves for oxic and hypoxic tumor cells. (From ref. 21, with permission.)

**FIGURE 16-9.** In vivo curves comparing two-dose survival to single-dose survival for oxic and hypoxic tumor cells. (From ref. 21, with permission.)

The OER range for different cells that have been studied varies from approximately 2.5 to 3.5. This means that, for reduction to a given survival level, three times as much radiation is required under hypoxic conditions as under oxic conditions. Because the curves are exponential, the ratio of survival fractions increases with dose. For example, in Figure 16-8, at 1000 rad the ratio of survival is 30.

Study of the phenomenon reveals that oxygen must be present during irradiation. Figure 16-10 shows the relative radiosensitivity of cells as a function of the oxygen tension at the time of irradiation. A low oxygen tension must be reached before there is a protective effect of hypoxia. The exact mechanism of the oxygen effect has not been determined definitively. It is believed that oxygen affects the initial chemical products of the interaction of radiation with biologic material. The important free radicals have short half-lives. A useful way to think about them is that they may return to an innocuous state or remain highly reactive molecules. Oxygen appears to favor the latter, whereas the presence of high levels of sulfhydryl compounds favors the former.

**FIGURE 16-10.** Radiation sensitivity as a function of ambient oxygen pressure. (Modified from Deschner EE, Gray LH. Influence of oxygen tension of x-ray induced chromosomal damage in Ehrlich ascites tumor cells irradiated in vitro and in vivo. Radiat Res 1959;11:115, with permission.)

Thomlinson and Gray recognized the importance of the oxygen effect in a classic paper in which they showed that tumors from humans frequently had anoxic regions. Calculations of oxygen diffusion from capillaries and metabolism predicted that the oxygen tension would decrease to zero at approximately 150 µm. They measured the width of tumor cords and showed that tumors can be modeled as shown in Figure 16-11. Those cells within approximately 100 µm of the capillary are well oxygenated, those beyond 150 µm are anoxic and necrotic, and those between 100 and 150 µm are hypoxic at an oxygen tension that might protect cells from radiation. This model has had a profound influence on radiobiologic and radiotherapeutic thinking. If all tumors look this way and such hypoxic regions contain cells that ultimately could cause tumor regrowth, then no clinically apparent tumor would be cured by radiation therapy. Because this is not the case, this paradox must be explained.

**FIGURE 16-11.** Diagrammatic representation of a tumor.

Laboratory experiments have indicated that immediately after a single dose of radiation, the surviving tumor cells are mainly the original hypoxic cells. After a period, the proportion of hypoxic cells returns to the preradiation level. This process has been called reoxygenation. The term can be confusing because these are indirect experiments and do not record the fate of individual cells. The results of these experiments can be explained by suggesting that tumor cells do reoxygenate for
several reasons: (1) reduced total tumor cell population relative to the surface area of tumor blood vessels; (2) reduced separation of hypoxic cells from the blood vessels, resulting from preferential cell kill of oxygenated cells; (3) increased oxygen diffusion; and (4) decreased intratumoral pressure, which opens blood vessels. Alternatively, a large number of these hypoxic cells might in fact be doomed because, with proliferation in the oxic regions, they are pushed outward, ultimately forced to reside in the anoxic regions, and therefore die. Hypoxic cells, rather then being determinant in tumors surviving irradiation, may be on the way to anoxia and death, thus having limited clinical importance. It is likely that different mechanisms pertain under different circumstances in the laboratory and in the clinic.

The clinical importance of the oxygen effect has led to clinical and laboratory experiments, including the use of high-pressure oxygen with radiation therapy to improve results. These studies have indicated that, with a small number of radiation fractions, hyperbaric oxygen increases curability. If normal fractionation schemes are used, hyperbaric oxygen often does not show an advantage. However, some reports of tumors of the head, neck, and uterine cervix indicate that hyperbaric oxygen with 10 fractions of radiation results in greater cure than conventional daily fractionation. Table 16-2 depicts the results with head and neck cancers. Despite these promising studies, the hyperbaric oxygen technique is cumbersome, difficult for the patient, and prohibits the use of the careful beam definition and beam modification so important in radiation therapy. The technique has been abandoned in most radiotherapy centers.

<table>
<thead>
<tr>
<th>Hyperbaric oxygen</th>
<th>Conventional treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>60</td>
<td>60</td>
</tr>
</tbody>
</table>

**TABLE 16-2. Results of a Randomized Prospective Trial of Hyperbaric Oxygen in the Radiation Treatment of Head and Neck Cancer**

A more attractive alternative has been the development of hypoxic cell sensitizers. In the 1960s, Adams and colleagues began searching for compounds that would mimic oxygen in its effect. They sought agents that would be metabolized slowly and reach all portions of the tumor. This is an important distinction, because high-pressure oxygen increases diffusion only slightly, whereas slowly metabolized sensitizers can reach all areas of the tumor. Although newer methods were based on replacing molecular oxygen, other effects of the nitroimidazoles, the most well-studied class of these agents, have been described. They appear to be cytotoxic to hypoxic cells and may sensitize cells to chemotherapeutic agents. How important these last two points are in their use remains to be seen. However, this general class of agents offers a whole new approach to the chemical treatment of tumors based on a known tumor-normal tissue difference (i.e., the presence of hypoxic cells in tumors).

A practical clinical concern is whether the presence of anemia affects tumor response to radiation. Historic review and a prospective study from the Princess Margaret Hospital (Table 16-3) appear to indicate that anemia results in an adverse effect on tumor curability by radiation, presumably because it increases the hypoxic component of tumor cells.

<table>
<thead>
<tr>
<th>Hemoglobin</th>
<th>Proliferation</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;12 g/dl</td>
<td>&gt;25%</td>
</tr>
<tr>
<td>10-12 g/dl</td>
<td>11-16%</td>
</tr>
<tr>
<td>13-14 g/dl</td>
<td>11-16%</td>
</tr>
</tbody>
</table>

**TABLE 16-3. Effects of Anemia on Pelvic Recurrence in Stage IIB or III Cervical Cancer**

A review of intercapillary distance and tissue oxygen tension correlates local recurrence with evidence of hypoxia using these parameters in studying carcinoma of the cervix. These studies emphasize the promise of techniques that improve tissue oxygenation in the treatment of epithelial cancers. In vitro measurement of hypoxia using radioactively labeled hypoxic sensitizers may alter selection of appropriate tumors for such therapeutic manipulation.

**Variable Radiation Response during the Division Cycle**

The cell cycle can be divided into four phases: G₁, S, G₂, and M. Terasima and Tolmach and Sinclair and Morton studied synchronized populations to determine whether there is a difference in response to radiation as a function of the cell’s position in the division cycle. They found that, generally, the mitotic phase (M) is most sensitive and G₂ almost as sensitive. G₁ is relatively sensitive in cells with a short G₁ phase. Cells gradually increase in resistance as they proceed through the late G₁ and S phases, reaching a maximum of resistance in the late S phase. In cells with a long G₁ phase, a peak of resistance is seen early in G₁. These findings in vitro also seem to be true in vivo for normal and tumor cells.

The changes in radiation response are reflected in changes in the shoulder of the survival curve and in the terminal slope. These differences can be large. The difference between the most resistant and the most sensitive can show slope ratios equal to that of the oxygen effect.

The clinical consequences of different fractional survival after 2 Gy can be seen in Table 16-4. Small differences in fractional survival when repeated have profound consequences in the level of cell killing.

<table>
<thead>
<tr>
<th>Survival Fraction</th>
<th>α/β</th>
<th>α/β</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1</td>
<td>6.28</td>
<td>4.12</td>
</tr>
<tr>
<td>0.2</td>
<td>6.30</td>
<td>4.13</td>
</tr>
<tr>
<td>0.3</td>
<td>6.35</td>
<td>4.16</td>
</tr>
<tr>
<td>0.4</td>
<td>6.40</td>
<td>4.19</td>
</tr>
<tr>
<td>0.5</td>
<td>6.45</td>
<td>4.22</td>
</tr>
<tr>
<td>0.6</td>
<td>6.49</td>
<td>4.25</td>
</tr>
</tbody>
</table>

*Values based on cumulative survival fraction from either 50 or 70% regressed time after treatment for the same number of normal and tumor cells.
TABLE 16-4. Calculated Cumulative Survival Fraction

A second consequence of differential cell killing and the mitotic delay induced by radiation is a tendency to partially synchronize the cells. The timing of the second dose of a fractionated scheme may be critical. This synchronization is short-lived because cells desynchronize rapidly and redistribute themselves according to the original cell age distribution. This phenomenon, which could pose a clinical problem or a clinical advantage, does not seem to be important unless an incomplete redistribution between fractions exists.

**Cell Proliferation**

During a course of fractionated radiation, the ultimate response of the tumor and normal tissue depends on whether cell proliferation has taken place between the fractions, thereby increasing the number of cells exposed to radiation. This cell increase may be caused by cell proliferation within the irradiated volume (i.e., within the tumor or normal cell renewal tissue) or by cells that immigrate from unirradiated adjacent areas. The latter situation is seen in the skin, oral gastrointestinal mucosa, or from great distances, as found with bone marrow and lymph node repopulation. The balance between radiation-induced cell killing and repopulation is responsible for most of the clinical findings seen during fractionated radiotherapy treatment.

In addition to spontaneous repopulation, an induced cell proliferation, or recruitment of cells, may take place. Physiologically, many tissues of the body respond to trauma by being recruited into rapid proliferation (e.g., after a wound in the skin, a break in bone, or a partial hepatectomy). The reparative process requires proliferation of the undamaged cells. Similarly, when the oral mucosa is irradiated, strong evidence indicates that the cell-cycle time is decreased and that net cell proliferation increases. This may also occur in some tumors but appears to be of less magnitude than that in normal tissues. If cell proliferation is greater in the tumor, then fewer fractions will be desired. Part of the differential effect of fractionated radiation may lie in differential recruitment of normal versus tumor cells.

**TRANSCRIPTIONAL ACTIVATION, GENE INDUCTION, AND REGULATION AFTER IONIZING RADIATION**

A new class of actions of ionizing radiation may explain a number of perplexing effects. Immediately after exposure to ionizing radiation, expression of genes such as FOS, JUN, and EGR1 appear to take place. This seems to occur in the presence of protein synthesis and is thought to be due to transcriptional activation and inhibition of protein degradation. Radiation also induces tumor necrosis factor-α, which may produce additive, synergistic, and distant cytotoxic effects of radiation. Platelet-derived growth factor-α and fibroblast growth factor are induced and released from vascular endothelium. It is suggested that this release stimulates proliferation of smooth muscle cells in the smaller arterioles and contributes to the undesirable long-term vascular events associated with radiation exposure.

**PHARMACOLOGIC MODIFICATION OF RADIATION EFFECTS**

Pharmacologic agents can modify the basic parameters of radiation response. Figure 16-12 shows a radiation survival curve for cells that have semiconservatively incorporated the halogenated pyrimidine bromodeoxyuridine into their DNA. Under such circumstances, these cells are more sensitive to radiation, their survival curve having the slope and the shoulder modified. This occurs only when the halogenated pyrimidines bromodeoxyuridine or iododeoxyuridine are incorporated into the DNA; their presence at the time of radiation is not sufficient. Sublethal damage repair also is markedly inhibited under these circumstances.

![Figure 16-12. Radiation survival curve for cells incorporating halogenated pyrimidines. (From ref. 50, with permission.)](image)

A second class of agents includes those that primarily affect the shoulder and only slightly affect the slope. The two most important of these agents are dactinomycin and doxorubicin. Sublethal damage apparently is inhibited by dactinomycin but not by doxorubicin. Strong evidence suggests that these drugs can and do modify radiation effects when given simultaneously. Furthermore, when given after radiation therapy, they can recall the irradiated volumes by erythema on the skin or by producing pulmonary reactions. Chemicals may also interact with radiation by preferentially killing cells that are more resistant to radiation. For example, agents that, along with radiation, preferentially destroy cells in the most resistant phase of the cell cycle (S) increase the cell kill; an example of this is hydroxyurea. Radioprotective agents, such as sulfhydryl-containing compounds, act in the reverse fashion and tend to make cells more resistant. They also reduce the chromosome abnormalities associated with radiation.

Agents with dose-limiting normal tissue toxicities different from radiation may be used effectively with radiation. This is one of the basic principles of multiple-drug chemotherapy—add agents with nonoverlapping toxicities. This strategy also works well with radiation.

The combined effects of drugs and radiation, or of two drugs, can be divided into the following types:

1. **Independent.** The agents act independently, their mechanisms of action are independent, and their damage is independent.
2. **Additivity.** The agents act on the same loci, and therefore their sublethal damage and their lethal damage are additive. Because of additive sublethal damage, the lethality of the two together may be greater than the lethality of each alone added together.
3. **Synergism.** The two agents have a result that is more effective than pure additivity.
4. **Antagonism.** The cell killing is less than independent action.

The most important parameter for the clinician is the therapeutic index. The sigmoid curve of tumor cure and that of dose-limiting toxicity are portrayed in Figure 16-13. If both curves are moved but their relative place (one to the other) is not changed, then the proportion cured for a given level of toxicity is unchanged. Drug-roentgen ray interaction is useful only when the curves are separated and not merely displaced.
Fig. 16-14

Fig. 16-15

Fig. 16-16

HIGH LINEAR ENERGY TRANSFER RADIATION

Most of the discussion so far has been concerned with sparsely ionizing radiation, such as that produced by photons or high-energy electrons. More densely ionizing radiation is produced by larger atomic particles. The biologic actions of these two types of radiation are different and relate to the density of ionization. LET is the rate of energy loss along the path of the particle (\(\frac{dE}{dl}\)). High LET radiations are densely ionizing, with \(\frac{dE}{dl}\) being high. In general, the density of ionization depends on \(Z^2v^2\), where \(Z\) is the atomic number and \(v\) is the particle velocity. Photons and electrons are characterized by high energy and low mass. Therefore, the density of ionization is low until the secondary electrons come to rest at the end of their path. Particulate radiation ionizes directly. Gamma particles and stripped nuclei have a high LET; neutrons have an intermediate LET because of recoil protons. The \(Z^2\) is large for large particles, intermediate for protons, and low for photons. High LET radiations have little or no shoulder on the survival curve (Fig. 16-14).

Fig. 16-17

Fig. 16-18

RELATIVE BIOLOGIC EFFECTIVENESS

Relative biologic effectiveness (RBE) is a commonly used parameter in radiation biology. It is the dose ratio of different average LET beams required to produce the same biologic effect. If the biologic end point of interest is associated with a high survival fraction, then the RBE is large because it considers shoulder differences and those of the terminal slope. If the biologic end point involves a low survival fraction, the RBE is less because it primarily considers slope differences. In general, RBE increases as the dose decreases. Not only is the shoulder reduced, but other measures of sublethal damage repair or potentially lethal damage repair are markedly reduced with high LET radiation.

A general explanation is that the ionization is so dense that, when a cell is hit, the damage is so great it cannot be repaired. It is also true that the oxygen effect decreases as the LET increases. With very high LET radiation, no oxygen effect is seen.

Although this advantage in RBE and OER suggests the possible therapeutic use of these radiations, a cautionary note must be made. Increasing RBE in itself does not afford a therapeutic advantage. It is the therapeutic gain factor that is important—the RBE of the tumor compared with the RBE of the normal tissue. This factor is complicated and greatly depends on the specific tumor and the dose-limiting normal tissue being considered.

TUMOR RADIOBIOLOGY

Many experiments have been done using animal tumors. In general, these tumors are spontaneous tumors occurring with reasonably high frequency in certain strains of mice (e.g., mammary carcinoma in C3H mice) or tumors induced by carcinogens. Such primary tumors of animals are difficult to use experimentally because their production is time consuming, and numbers of tumors of the same size and location are limited, restricting some experimental designs. A much more common technique is the use of transplanted tumors. These are tumors that may have occurred spontaneously or from the application of a carcinogen but have now been transplanted from animal to animal. They grow with predictable and known kinetics. Although this is a great advantage in experimental work, it does increase the likelihood that the application of the results may be somewhat limited. Because these tumors are selected for rapid growth and for the ability to transplant serially, they may not represent tumors that occur spontaneously in the host animal. Currently, many laboratories study human tumors transplanted into “nude” mice. These genetically immunosuppressed mice permit the growth of these xenographs, but interpretation of these experiments is limited by the artificiality of the experimental circumstance.

Tumors can be used in radiobiologic experiments and assayed in a number of ways. The simplest is to study the likelihood for cure. A researcher implants a tumor into animals, allows it to grow to palpable size, treats it with a specific regimen, and then determines how many tumors of this type in various host animals are cured. If the dose of radiation is plotted against the likelihood for cure, a sigmoid curve is generated (Fig. 16-15). There is insufficient cell kill to cause tumor cure at very low doses. As the dose is raised (to approximately one lethal event per cell), the statistics of random cell kill become important. Occasionally, tumors have zero viable cells and are cured. The likelihood of cure rises rapidly with dose at this portion of the curve, it starts to plateau when the maximum effect of the particular technique is reached. The dose required to increase a 10% likelihood of tumor control to 90% is approximately three times the \(D_{90}\) dose. This sigmoid relation is important, because it is true not only for tumors in experimental animals but also for clinical situations. The steepness of the curve in the effective range emphasizes the importance of small increases in dose.
The shape and steepness of the sigmoid dose-response relation for tumors can be affected by many factors. If the $D_2$ is large, then the dose-response curve is also shallow. It also is affected by host defense mechanisms. This curve is steep with nonimmunogenic tumors or in hosts with an abrogated immune response, but it is significantly shallower in immunogenic tumors. The shallowness means that occasional cures are found at low doses and occasional failures are noted at very high doses.

A similar sigmoid relation is seen when plotting the likelihood for complications against tumor control. Figure 16-13 shows the two sigmoid curves, one for cure and one for complications. This is presented optimistically—the important complication curve is placed to the right of the sigmoid curve. The difference between these curves is a measure of therapeutic gain. Much of clinical medicine and research in cancer treatment is concerned with separating these curves. After the curves are separated, for a given level of complications, the likelihood of cure can be increased. Or, for a high likelihood of cure, the likelihood of complications can be decreased. Some methods for separating these curves include better restriction of the radiation dose by using techniques such as intensity-modulated radiation therapy (see Chapter 29.4). Combining agents with nonoverlapping toxicity, such as certain chemotherapeutic agents, angiogenic agents, or even gene therapy, offer the promise of improved cure without increasing the radiation toxicity. It may also be possible to modify radiation toxicity without decreasing effectiveness.

Tumors, like normal tissues, have certain physiologic characteristics. We associate some of these with the definition of malignancy: continued growth and extension into surrounding tissues, and the ability to metastasize. In addition, growing tumors must induce a blood supply to meet their increasing metabolic needs. The production of these blood vessels appears to result from the release of substances described by Folkman and colleagues as "tumor angiogenesis factors" and may have important clinical implications. If tumors can be prevented from producing such substances, they cannot grow beyond a size supported by diffusion alone. From the radiobiologic point of view, it means that, when irradiating a tumor, the radiobiology of the tumor and the vascular endothelial cells are important. Complete destruction of the ability of tumor blood vessels to proliferate effectively limits tumor growth.

As tumors grow, they often exceed their blood supply and develop areas of necrosis and hypoxia (see Fig. 16-11). The proportion of hypoxic cells in a tumor can be determined by studying the radiation survival curves. In Figure 16-16, curve A represents a well-oxygenated cell population, curve B describes hypoxic cells, and curve C represents a mixture of oxic and hypoxic cells (as in a tumor). Extrapolation of the curves to the ordinate gives the proportion of hypoxic cells within a tumor, first described by Powers and Tolmach. In most experimental tumors studied, the percentage of hypoxic cells is 10% to 20%.

There has been great interest in trying to determine whether appropriate laboratory correlates exist for clinical radiation treatment. Table 16-5 shows important parameters found by in vitro survival determinations for six histologic groups of human tumor cells. The first four parameters have already been described. $S_2$ and $S_8$ are the survival fractions found with 2 Gy and 8 Gy, respectively. $T$ is the mean inactivation dose, a mathematically determined characteristic of the initial portion of the survival curve. It appears that $S_2$ and $S_8$ correlate directly with clinical radiocurability, whereas $T$ is inversely related. All of these are measures of the initial portion of the radiation survival curve; $S_2$ is the most closely correlated with clinical practice, because doses between 1.5 and 2.5 Gy are used most often in patient care.

Because in radiation therapy the dose is divided into many fractions, small differences in $S_2$ can have significant consequences. Table 16-4 shows that, in a typical 32-fraction radiation treatment, the difference between survival fractions of 0.45 and 0.60 results in an ultimate survival fraction of $10^{-11}$ compared with $10^{-7}$, respectively. Also, certain tumors that are known to be difficult to cure by radiation have been shown to have great capacity to repair radiation damage, as measured by allowing the cells time for repair before plating them for in vitro growth. These two simple laboratory determinations correlate with clinical results gives hope that in vitro techniques can be used to determine mechanisms of modifying clinical parameters. This does not mean that the other biologic parameters, such as oxygenation, position in the cell cycle, and cell proliferation, are not important; no doubt, all of these factors add to the complexity of correlating the clinical response with in vitro determinations.

NORMAL TISSUE RADIATION BIOLOGY

To understand normal tissue radiation biology, an appreciation of the cell kinetics of cell renewal tissues is vital. The effects on organ function depend on the reproductive requirements of the irradiated cells. Tissues whose functional activity does not require cell renewal (e.g., muscle and neurologic tissue) are considered resistant to radiation. Both muscle and neurologic tissue also have important vasculoconnective tissue stroma that support them. These stromal cells may be required to divide and, therefore, determine the organ's response to radiation. The radiation response of endothelial cells demonstrates a $D_{0.5} = 340$ rad, $n = 7$, and a $D_{10} = 170$ rad, values similar to those of epithelial cells.
Many tissues of the body require continued cellular proliferation for their function, and they promptly demonstrate the effects of radiation. These cell renewal tissues include the skin and its appendages, the gastrointestinal mucosa, bone marrow, reproductive tissues, and many exocrine glands. Clonogenic survival curves for bone marrow stem cells, gastrointestinal epithelial cells, and skin are all available.

Tissues such as the liver and bone require little or no proliferation during the steady state, and normal function can be maintained despite large doses of radiation. However, both of these respond to injury with rapid cell renewal. If trauma (fracture or partial hepatectomy) occurs, then the cells die when they attempt repair.

Irradiation of the liver has few consequences in moderate doses, but if this is followed by a partial hepatectomy, hepatic failure can occur. This finding has been of clinical importance in the preoperative irradiation of right-sided Wilms’ tumors attached to the liver, in which a significant amount of liver must be removed. Under such circumstances, it is far better to operate, allow the liver to regenerate, and then irradiate.

Patients who have received large amounts of radiation to the bone do perfectly well unless the bone is fractured. The damaged bones fail to be reconstituted or heal slowly, causing a significant deformity and disability to the patient. These examples are included to stress that it is not the different cells that have such great differences in radiation response, but rather that the proliferative requirements of different tissues largely determine the radiation effects. If the proliferative requirements are low, the organ is considered resistant to radiation. If the proliferative requirements are high, it is considered radiosensitive. Some common limitations on all systems may apply, based on the radiosensitivity of the stromal support cells, such as connective tissue and endothelial cells. Stem cells of the cell renewal tissues may have a limited proliferative capacity, and stem cell exhaustion appears to be a cause of late organ failure after irradiation.

Many other effects of radiation that do not depend on reproductive viability may have clear clinical relevance. For example, radiation is damaging to the cell membrane and changes membrane transport. Subsequent radiation-induced edema is seen with moderate doses of radiation. Damage to certain membrane lipids can cause apoptosis without nuclear damage. These nonreproductive effects of radiation are far less well understood but may be important in understanding the effects of radiation on nondividing tissue, especially on the central nervous system.

Large doses of whole body irradiation have obvious clinical consequences, which generally are not relevant to conventional radiation therapy. However, because whole body irradiation has been used in low doses in treating the lymphomas and in high doses in treating metastatic carcinoma, this topic is discussed briefly.

After large doses of radiation, the prodromal syndrome of nausea, vomiting, diarrhea, cramps, fatigue, sweating, fever, and headache occurs. Three distinct modes of death may occur. The first, with very high doses of radiation (more than 10,000 rad), is seen within hours and appears to result from neurologic and cardiovascular damage. Because this occurs so quickly, it probably is not caused by failure of cell proliferation but rather by extraneural events within these organs. At intermediate doses of radiation (500 to 1000 rad), death occurs within days. It is associated with extensive gastrointestinal mucosal damage, resulting in prolonged, severe, bloody diarrhea; dehydration; and secondary infection occurring as the gastrointestinal mucosa is denuded. At lower doses of radiation (near the LD₅₀), death is caused by hematopoietic failure. This complication has a latent period because the damaged bone elements are nondividing, and bone marrow failure does not occur until the progeny of the proliferating cells are required to maintain the patient. The lymphocyte level falls promptly as some of these cells die by apoptosis. The granulocyte level falls on approximately day 5 or 6, and thrombocytopenia occurs later. Anemia does not occur as a direct result of a failure of red blood cell production, because of the long life of the red blood cell, but it may be caused by hemorrhage.

Whole body irradiation appears to have significant antitumor activity exceeding that seen when the same dose is given to the tumor alone. Very low doses of whole body radiation in humans (10 to 15 rad, two to three times per week for 6 to 10 fractions) may be effective for lymphomas and may cause marked depression of the formed blood elements. The mechanism of action of this type of treatment is not understood. The effects on tumor and normal tissue are greater than can be explained by the typical survival curve. One possible explanation is the release of TNF-α after irradiation. Perhaps the release of this and other factors may contribute to the general effects of low-dose whole body radiation and the abscopal (distant) effects of regional irradiation. Many of the effects of radiation on both tumors and normal tissues may be mediated or modified by the release of cytokines. Their effect may be tissue specific; for example, basic fibroblast growth factor protects against the apoptotic microvascular component of radiation pneumonitis but has no effect on other mediastinal organs.

ADVERSE EFFECTS OF RADIATION

Some biologic considerations of localized radiation may decrease the likelihood for tumor control. The first and most commonly discussed is the effect of radiation on the immune response. High-dose, whole body irradiation has a well-known and profound effect on the immune response. This generalized treatment rarely is used in clinical therapy, however, except as preparation for bone marrow transplantation.

Shortly after the discovery of roentgen rays, whole body irradiation before the administration of antigens was found to suppress the production of antibodies. After whole body irradiation, a prompt fall in the lymphocyte count is seen. The lymphocytes appear to have two types of radiation response: Approximately 80% apoptosis, but some lymphocytes survive the radiation. When assayed on the basis of reproductive capacity by exposure to mitogens after irradiation or other functional end points, their radiation survival curves looked similar to that of hematopoietic cells with a D₅₀ of approximately 70 to 80 rad and an n of approximately 1. Response depends on the classes of lymphocytes involved, the extent of cell proliferation required, cell traffic, and the balance between suppressor and helper systems. The following conclusions concerning the effect of radiation on the immune response can be made:

1. B lymphocytes are radiosensitive and undergo interphase (apoptosis) and mitotic death after irradiation.
2. All functional T-cell subpopulations have sensitive precursor cells. Suppressor T-cell precursors may undergo interphase death.
3. The homing potential of cells is affected by radiation.
4. Remaining cells are more sensitive to interphase death than are the same cells when stimulated to divide before irradiation. (In the latter case, they have an n and D₅₀ similar to those of hematopoietic stem cells.)
5. The effects of whole body irradiation are qualitatively and quantitatively different from those caused by local or regional irradiation.

Whole body irradiation is more effective in preventing response to new antigens than in modifying response to a previously encountered antigen. Survival of second-set skin grafts are affected much less than are initial grafts. Localized radiation, as used in radiation therapy, affects the immune response by decreasing the number of circulating lymphocytes, presumably by irradiating and destroying them as they pass through the irradiated volume and by the release of certain cytokines.

Other adverse effects of radiation on the patient may be seen in addition to those affecting host-defense mechanisms. Radiation-induced mutagenesis is of concern for germline and somatic cells. If the gonads are irradiated, there is an increased likelihood of mutation with increasing doses, without any evidence of a threshold dose or of an ameliorating effect of fractionation. At higher doses, significant cell killing takes place, and the dose-response curve is no longer linear, presumably because the cells that mutated received sufficient radiation to become sterile. Abnormal live births are uncommon after gonadal irradiation because most radiation-induced mutations are recessive. Furthermore, dominant mutations, when they occur, usually are lethal. In the mouse, some evidence indicates that the risk of mutation decreases with time after ovarian irradiation. Whether this is true in humans and how the mechanism occurs in animals are not known. It does not appear to be true for irradiation of the testes.

The mutagenic effects of radiation depend on the type of irradiation. The RBE for high LET radiation can be extremely high for mutations. It is difficult to quantify the risk because experiments with mice indicate a large difference in the mutation rate for different loci, with as much as a 1000-fold variation in the mutation rate. In general, the prudent figure used is that the mutation rate doubles with approximately every 50 rad.

Perhaps of even greater concern are somatic mutations, especially those that may lead to tumors. A great deal of evidence indicates that low doses of radiation increase the incidence of leukemia in mice after a long latency of years. The risk increases largely from periods of whole body exposures to the atomic bomb and experience with patients irradiated for benign diseases. In general, there appears to be a linear increase in tumor incidence with dose until high doses are reached, at which point the incidence reaches a plateau or even falls. Presumably, this is true, again, because of cell killing. Figure 16-17 is an example of this biphasic dose-response curve. Such tumor induction is associated with a latent period of 3 to 5 years for leukemia but is much longer for solid tumors. There are different ages at which tumor induction is most likely. For example, the induction of breast cancer by radiation appears primarily with exposure in the first and second decades of life and decreases with radiation later in life.
FIGURE 16-17. Biphase curve of tumor incidence. (Adapted from refs. 85 and 86.)

CLINICAL CONSIDERATIONS

It is often suggested that the goal of treatment is the greatest probability of uncomplicated cure. Although this goal is desirable, circumstances actually may dictate a different policy. Consider Figure 16-13, in which the curve for complications is to the right of the sigmoid curve for tumor control. If tumor failure can be salvaged by subsequent surgery but complications are severe, long-lived, and difficult to manage, then line A is the optimal line. An example of this would be the treatment of T2 and T3 glottic cancer. On the other hand, if complications are not severe or are remediable but cancer failure is fatal, then line B would be appropriate. This is the case in stage II and III carcinoma of the uterine cervix. There is no simple answer. Often, the worst complication of treatment is tumor recurrence.

Many clinical examples of sigmoid dose-response curves have been reported. An example for tumors of the head and neck is shown in Figure 16-18 and for Hodgkin’s disease in Figure 16-19, in which a consistent ~10% change in dose was used. Figure 16-20 shows the results in tumor control and complications. The small increase in dose markedly improved the curability of the larger tumors, presumably because this dose is on the steep portion of the sigmoid dose-response curve. It did not change the cure rate for small tumors very much because, presumably, the dose already was large enough to be on the plateau of the dose-response curve, where changes in dose do not affect the cure appreciably. Similarly, complications were not increased significantly. The point indicating complications is to the right, still on the shallow portion of the curve. This is a good example of separation of response between tumor and normal tissues. It also shows displacement of the curve for cure as a function of tumor size.

FIGURE 16-18. Tumor control versus dose for supraglottic carcinoma. (From ref. 87, with permission.)

FIGURE 16-19. Tumor control versus dose for Hodgkin’s disease. (From ref. 88, with permission.)

FIGURE 16-20. Tumor control versus dose for cancer of the larynx (4 MeV given over 3 weeks for a treatment period of 5 years). (From ref. 89, with permission.)

Even though tumors have a very steep dose-response relationship, significant intertumor heterogeneity may cause great flattening in the radiation dose-control curves. Considerable heterogeneity exists between tumors of the same histologic type and location, and this consideration explains the shallower nature of the clinical dose-response curves compared with those for experimental animals. These analyses further indicate that, when the tumor control probability is low, the major reason is a high $S_2$. This fact emphasizes the importance of identifying prospectively tumors that have a high $S_2$. Changes in the likelihood of apoptosis after radiation may have an important effect on $S_2$.

FRACTIONATION
Early in the twentieth century, as the practice of radiation therapy evolved, the virtues of dividing the radiation into small fractions were noticed. The reasons given were often incorrect, but the clear observation was that fractionation of the dose allowed more effective tumor cure without excessive complications.

Fractionation considers the size and number of radiation increments. Protraction considers the overall time during which the course of radiation therapy is given. Both factors affect all radiation therapy plans. The fashioning of a plan for fractionated radiation therapy for carcinoma of the larynx by Coutant, whose work was based on the principles of Regaud, laid the foundation for the development of radiation therapy. The principles of such treatment were as follows:

1. Fractionation is important.
2. A relation exists between the acute reaction of the skin and oropharyngeal mucosa to cure and to late effects.

The association between acute and late effects has sometimes led radiotherapists astray. This relation depends on the fractionation scheme, the energy of radiation used, and other factors. In general, acute effects are much more dependent on time than late effects. Late effects are influenced primarily by the total dose and fraction size.

CONTINUOUS RADIATION

Another important technique of radiation therapy that evolved in the early part of the twentieth century was the application of continuous radiation by interstitial or intracavitary application. If the dose rate was too high or the volume too large, unacceptable complications occurred. Rules for treatment were developed that resulted in the cure of certain tumors without unacceptable complications. These rules required that the dose rate be kept moderate (less than 100 rad/hour) and an attempt at a good implant geometry be made to avoid unnecessary hot and cold spots.

The whole question of homogeneity of dose is much more difficult with intracavitary and interstitial irradiation than with external-beam techniques. To a great extent, the clinical use of radioactive isotopes, especially by implantation techniques, developed separately from external-beam radiation therapy. Some physicians only practiced one or the other of these techniques. More recently, external-beam and interstitial treatment have been used together to take advantage of the virtues of both modalities. Good examples of this combined treatment are described in the chapters dealing with tumors of the head and neck and uterine cervix (see Chapter 36.2). The increase in the use of high-dose-rate afterloading techniques, although having the practical and logistical advantages, eliminate the dose-rate advantage of brachytherapy. It remains to be determined whether this will have significant clinical consequences (see Chapter 36.3).

ACUTE AND LATE NORMAL TISSUE EFFECTS

Acute radiation effects occur largely in renewing tissues, such as skin, oropharyngeal mucosa, small intestine, rectum, bladder mucosa, and vaginal mucosa. These cell-renewing tissues are rapidly proliferating, and as they are confronted with fractionated radiation, the processes of repair, repopulation, and recruitment all obtain. Because the response of rapidly renewing tissues depends on the balance between cell birth and cell death, acute tissue reaction is crucially affected by the time allowed for repopulation and, therefore, is dependent on protraction. It also depends on the cell kill per fraction, so fraction size is important. The radiotherapist observing an excessive reaction by the oral mucosa knows that a small decrease in fraction size or a small treatment break allows rapid resolution of the problem, because these changes permit reconstitution of the normal tissue.

Late effects are really the dose-limiting factor in radiation therapy. These include necrosis, fibrosis, fistula formation, nonhealing ulceration, and damage to specific organs, such as spinal cord transection and blindness. Although the mechanisms of these phenomena are not clear, they do not appear to depend primarily on the rapid proliferation of cells. Clinically late effects appear to depend much more on the total dose of radiation and the size of the fractionation scheme than on protraction. Only if the same fractionation scheme is used with the same normal tissue end point, the same irradiated volume, and the same treatment technique, can acute and late effects be correlated. If any of these parameters are varied, the acute reactions to radiation may be dissociated from eventual late effects and are misleading.

Two hypotheses for late effects are worth discussion. One theory holds that all late effects result from damage to vasculoconnective stroma. Because this tissue is common throughout the body, it would suggest a common mechanism for the late effects in any organ. A variation on this hypothesis is that it is damage to the endothelial cells, ubiquitous throughout the body, that determines late effects. An alternative hypothesis suggests that the acute and the late effects of radiation and cytotoxic chemotherapy are caused by cell depletion of the targeted cell-renewal tissues. Acute effects depend on the balance between cell killing and compensatory replication of the stem and proliferative cells. The development of late effects requires that stem cells have only a limited proliferative capacity. Compensation for extensive or repeated cell killing may exhaust this capacity, resulting in eventual tissue failure.

ALTERING THE THERAPEUTIC INDEX

Goodman and Gilman define the therapeutic index as the relation between desired and undesired effects of therapy. For the oncologist, separation of the sigmoid curve of complications from that of local control (see Fig. 16-13) is the graphic representation of manipulation of the therapeutic index. Some techniques of time-dose relationships use normal-tissue damage to advantage in the form of fractionation, protraction, split-course technique, interstitial technique, interstitial treatment, and manipulation of the target volume. Although fractionation has been discussed, the use of multiple small fractions two, three, or more times a day (hyperfractionation), is being explored, with some good results.

Another technique to reduce complications is the use of normal-size fractions given more than once a day. This is referred to as multifraction, multiple daily fractions, or accelerated fractionation.

When tumor cells are proliferating rapidly, accelerated fractionation makes sense. Waiting 24 hours between each fraction may allow significant proliferation. Perhaps the best example of the changing therapeutic index obtained with accelerated fractionation is the enhanced success in treating Burkitt’s lymphoma.

In general, most radiotherapists administer conventional radiation in fractions between 180 and 250 rad each day. This allows tumor control without excessive acute or late effects. The fraction size that is tolerated in terms of acute effects depends on the volume irradiated (the larger the volume, the smaller the fraction size), the amount and type of dose-limiting normal tissue, the age of the patient, and other clinical factors.

Small changes in fraction size make a big difference in tolerance. Patients often are given small breaks during the treatment. These rest periods usually are caused by weekend interruptions of daily fractionation. This protraction of the treatment allows for repopulation and recruitment. The days of rest also allow amelioration of many acute effects, and they may allow time for tumor regression, resulting in reoxygenation.

An attempt to formalize and extend treatent breaks is the so-called split course technique. Two to three weeks are allowed in the middle of treatment for recovery from the acute effects and to permit tumor regression. When the dose of radiation is not increased, accumulating evidence indicates that this treatment (although better tolerated) may be associated with less tumor control. When the split course is administered with an increase in total dose, the results seem to be comparable to conventional fractionation but perhaps with greater late effects.

Interstitial irradiation is administered by permanently or temporarily placing radioactive material into tissues. It requires biologic and physical considerations. Great inhomogeneity is found, even in the most geometrically perfect implant. There is large inhomogeneity of dose and a similar variation in dose rate; the dose rate of radiation is greater in areas of high dose. The half-life of is long (60 days), resulting in a significant amount of the dose being given so slowly that significant cell division may occur in the tumor and some normal cells. Therefore, the important dose may not be the total dose, but rather the dose per cell cycle, which is different for each cell type and different as the isotope decays. Also, iridates primarily by the emission of very low-energy photons, some of which are absorbed by the seeds themselves, leading to further inhomogeneity.

When implants can be used alone or in combination with external irradiation, the results are often better in terms of the therapeutic index than with external-beam techniques alone. The high local dose, continuous radiation, and even inhomogeneity allowing normal tissue regrowth all contribute to better cosmetic and functional results and cure of the tumor. Examples are breast cancer and tumors of the tongue and other head and neck sites. Tumor volume also is important in clinical radiotherapy. Although the gross tumor extent can be determined, most clinicians recognize that a characteristic of tumors is to extend beyond those macroscopically
identifiable borders. Determination of the target volume must include this consideration, but if a larger volume must be irradiated, then a smaller dose is tolerated. Conversely, if the volume of the tumor is larger, then a larger dose is required. This dilemma limited the success of early radiotherapy of certain tumors by reducing the target volume, resulting in recurrences at the treatment margins, or by causing significant complications in the treatment of large target volumes. Today, distinctions are made between gross tumor and the subclinical extensions into apparently normal tissues. Subclinical disease means small numbers of cells, perhaps favorable to irradiation (well oxygenated), which can be controlled with modest doses of radiation (Table 16-6). The large number of cells present in the clinically evidenced tumor requires higher doses (see curves in Fig. 16-20 and Fig. 16-21). This difference has led to the development of techniques for administering different doses to microscopic tumor extensions and to the gross tumor. These include shrinking-field techniques, boost treatments, and certain strategies of combined surgery and radiotherapy.

### Table 16-6: Control of Subclinical Disease

<table>
<thead>
<tr>
<th>Technique</th>
<th>Dosage (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative</td>
<td>40-50</td>
</tr>
<tr>
<td>Postoperative</td>
<td>40-50</td>
</tr>
<tr>
<td>Boost</td>
<td>40-50</td>
</tr>
</tbody>
</table>

Shrinking-field technique means giving the largest potential tumor bed a moderate dose of radiation, then reducing the target volume to the tumor and its immediate confines and raising the dose. This can be done by reducing the fields, changing the treatment technique and target volume; or using a treatment technique such as intensity-modulated radiation therapy, which gives the desired moderate dose to the larger volume and a higher dose to the smaller volume. Attempts have been made to consider fractionation, protraction, and even implantation used with external beam in some form of mathematical formulae, all of which tend to oversimplify complex clinical circumstances and can be misleading.

The dose-limiting normal tissues are of two kinds: those fixed by the radiation as a consequence of irradiating the target volume, and those normal tissues within the target volume (e.g., the urethra in a prostatic target volume). Radiotherapy with detailed treatment planning, CT scanning, and computer-controlled radiation therapy may reduce the dose to the transferred volume, possibly changing the therapeutic index. However, it is unlikely that significant physical techniques will be available for reducing the dose to normal tissues in the target volume. This can be done only by some biologic mechanism that distinguishes tumor from normal tissues.

### Radiosensitivity

The term radiosensitivity is used in different ways in the literature and can mean what is defined as radiosensitivity, radioresponsiveness, or radiocurability. Each is a somewhat different concept. To the radiation biologist, radiosensitivity means the innate sensitivity of the cells to radiation. For cells that die a reproductive death, this is related to the slope of the survival curve, or the $D_{50}$.

Radiosponsiveness means the clinical appearance of tumor regression promptly after moderate doses of radiation. This may be a function of the cell's radiosensitivity, but it also may be a function of the active cell kinetics of a tumor. Bergonie and Tribondeau first established an association between the rate of proliferation and the response of normal tissues, although they considered this to be radioresponsiveness. A similar relation was presumed to apply to tumors. Because cells do not undergo a reproductive death until they face mitosis, some tumors that proliferate rapidly regress rapidly, but they also may regrow rapidly. This is often confused with radiosensitivity.

Radiocurability means that the tumor-normal tissue relationship is such that curative doses of radiation can be applied regularly without excessive damage to normal tissues. Examples of such radiocurable tumors are carcinomas of the cervix, larynx, breast, and prostate, in addition to Hodgkin's disease and seminomas. Some of these are radioresponsive, some are radiosensitive, and some are neither.

### Radiation and Surgery

Radiation and surgery can be combined in many different ways. The general rationale for combining surgery and radiation is that the mechanism of failure for the two techniques is different. Radiation rarely fails at the periphery of tumors, where cells are small and well vascularized. When radiation fails, it usually occurs in the center of the tumor where there are large volumes of tumor cells, often under hypoxic conditions. Surgery, in contrast, is limited by the required preservation of vital normal tissues adjacent to the tumor. In resectable cancers, the gross tumor can be removed, but it is these vital normal tissues that limit the anatomic extent of the dissection. When surgery fails under these circumstances, it is usually because of microscopic tumor cells left behind. It seems logical, therefore, to consider combining the two techniques.

Radiation can be given before or after surgery. Preoperative radiation has the advantages of sterilizing cells at the edges of the resection, sterilizing cells that perhaps would be dislodged and seeded at the time of surgery and, in the special circumstance of unresectable tumors, reducing the tumor volume sufficiently to allow resection. It is not clear how often this results in a cure, because it may only change gross tumor to microscopic tumor and still result in tumor recurrence. It does seem to benefit selected cases of large unresectable cancers.

There are disadvantages in the use of preoperative irradiation. The pathology reports are not valuable because, if sufficient time is allowed between the radiation and the surgery, the destruction of tumor caused by preoperative radiation prevents ascertainment of the tumor's initial anatomic extent. In contrast, if the tumor is slow-growing or if the surgery is done shortly after the radiation, the consequences of the radiation will not be represented in the pathologic evaluation of the material because sufficient time was not allowed for tumor destruction and regression.

Another disadvantage is that the patient is irradiated before the careful staging available at surgical exploration, and some patients who would not benefit from preoperative radiation are given this treatment (e.g., preoperative radiation to a colorectal carcinoma in a patient with occult liver metastases). Metastases may be found only at the time of surgery.

A disadvantage often mentioned is the delay before surgical resection. This may not be a disadvantage, because as long as the patient's tumor is being treated, the order of treatments should make no difference. The radiation dose usually is moderate (40 to 50 Gy) and given in conventional 2-Gy fractions 5 days a week or in smaller total doses given more quickly in larger fractions. If the total dose of radiation is kept small (less than or equal to 20 Gy), then the delay between radiation and surgery is small. When the dose reaches approximately 40 Gy, it is valuable to delay the surgery (usually 4 to 6 weeks) to allow the tissues to recover from the treatment. If the total dose is greater than 50 Gy, then the surgery often will be more difficult. However, with moderate doses of radiation and some time allowed between radiation and surgery, the resection can proceed without difficulty.

Postoperative radiation has a number of advantages as well. The subgroup of patients who may be helped by radiation can be defined accurately as a consequence of the surgical exploration and pathologic review. Unnecessary irradiation to patients who are not likely to benefit can be avoided, and the target volumes are tailored to meet what is found at surgery. Time can be allowed for wound healing so that the radiation does not interfere with this process. A disadvantage of such treatment is that it has no effect on seeding at the time of surgery. Surgery also may alter the physiology of the tumor left behind because of reduction of the vascular supply. Cells that were well oxygenated may be rendered physiologically hypoxic and more resistant to radiation. Another disadvantage in the peritoneal cavity is that the surgery causes loops of bowel to be fixed in specific positions and increases the likelihood of small intestinal damage by radiation.
Some uncertainty exists as to which technique is better for particular clinical circumstances. Both preoperative and postoperative radiation appear to be valuable, and the choice of the method, the dose of radiation, and time between radiation and surgery should be considered in terms of the goals planned.

An additional technique for combining surgery with radiation is limited surgical removal of the gross tumor. Because the gross tumor limits the radiotherapeutic treatment, new interest has been raised in using surgery as the boost technique. Full courses of radiation combined with tumor cytoreduction are given. This surgery can be done before or after the irradiation. An example of this strategy is the "lumentropy" used in the treatment of breast masses before definitive radiation (see Chapter 37.2). In the latter there appears to be evidence to suggest that the removal of gross tumor displaces the sigmoid curve of cure to lower radiation doses and makes it change more steeply with dose (see Fig. 16-21).

**FIGURE 16-21.** Tumor control versus dose for stage II and III breast cancer. (From Hellman S. Improving the therapeutic index in breast cancer treatment. Cancer Res 1980;40:4335, with permission.)

## RADIATION AND CHEMOTHERAPY

The purpose of combined radiation and chemotherapy treatment is not to decrease the dose of radiation to gain the same effect, but rather to increase the therapeutic index. This may be achieved using systemic techniques that take advantage of the different mechanisms of action of radiation and chemotherapy, and by simultaneous chemotherapy agents that directly modify the radiation survival curve may be used. A good example of this is the use of dacarbazine in the treatment of childhood rhabdomyosarcoma or Wilms' tumor. A second way to increase the therapeutic index is to use drugs that specifically affect tumor response to radiation; the most exciting of these are the hypoxic sensitizers, because they affect hypoxic cells that usually are restricted to tumors.

A third mechanism is the combination of drugs and roentgen rays with independent action or additivity. This strategy is just beginning to be explored but appears to be of value in increased local control achieved in head and neck cancer. Because the major advantage of chemotherapy is its wide distribution throughout the body, the combination of radiation and chemotherapy may improve the therapeutic index because, like the combination of surgery and irradiation, the target volumes are different. Adjunct chemotherapy with radiation for breast cancer treatment, or with surgery and radiation for colon cancer, may improve survival because the chemotherapy is effective against occult micrometastases outside the radiation field. Similarly, radiation may be of value in the treatment of leukemia by chemotherapy because the radiation can be applied to specific sanctuary sites, such as the central nervous system.

**CHAPTER REFERENCES**


The work with the L1210 model also was the basis for the long-held dogma that rapidity of growth and frequency of cycling in responsive tumors determined sensitivity properly account for the ability to cure some human cancers with a relatively small fraction of cycling cells.

...defect in the ability to control its own growth. cycle more frequently was referred to as the quick... proper therapy. This new level of understanding of the molecular pathways through which chemotherapy works and by which genetic change can result in resistance to drug therapy has opened the door for novel therapeutic strategies in which molecular, genetic, and biologic therapies can be used in combination to attack directly new and specific targets to increase the chemosensitivity of malignant cells to treatment and to protect the normal tissues of the body from therapy-induced side effects. The implementation of such novel therapeutic approaches may provide an important paradigm shift in the manner in which therapy is delivered as we move into the next millennium. Clearly, the long-term goal is to improve the outcome of cancer patients undergoing treatment, especially in those with neoplasms that currently are resistant to conventional-dose therapy.

Alkylating agents represent the first class of chemotherapeutic drugs to be used in the clinical setting. Of note, they were a product of the secret gas program of the United States in both world wars. The exposure of military seamen to mustard gas in World War II led to the observation that alkylating agents caused marrow and lymphoid hypoplasia. This observation then led to the direct application of such agents in humans with hematologic neoplasms, including Hodgkin's disease and lymphocytic lymphomas, at the Yale Cancer Center in 1943. However, given the secret nature of the gas warfare program, this work was not published until 1946. The demonstration of dramatic regressions in advanced lymphomas with chemotherapy generated much excitement. At approximately this same time, Sidney Farber reported that folic acid had a significant proliferative effect on leukemic cell growth in children with lymphoblastic leukemia. These observations led to the development of folic acid analogs as cancer drugs to inhibit folate metabolism; thus, the era of cancer chemotherapy began in earnest.

The systemic treatment of cancer has its roots in the work of Paul Ehrlich, who coined the word chemotherapy. Ehrlich's use of in vivo rodent model systems to develop antibiotics for treatment of infectious diseases led George Clowes, at Roswell Park Memorial Institute in Buffalo, New York, in the early 1900s, to develop inbred rodent lines bearing transplanted tumors that could be used to screen potential anticancer drugs. This in vivo system provided the foundation for mass screening of novel compounds. Alkylating agents represent the first class of chemotherapeutic drugs to be used in the clinical setting. Of note, they were a product of the secret gas program of the United States in both world wars. The exposure of military seamen to mustard gas in World War II led to the observation that alkylating agents caused marrow and lymphoid hypoplasia. This observation then led to the direct application of such agents in humans with hematologic neoplasms, including Hodgkin's disease and lymphocytic lymphomas, at the Yale Cancer Center in 1943. However, given the secret nature of the gas warfare program, this work was not published until 1946. The demonstration of dramatic regressions in advanced lymphomas with chemotherapy generated much excitement. At approximately this same time, Sidney Farber reported that folic acid had a significant proliferative effect on leukemic cell growth in children with lymphoblastic leukemia. These observations led to the development of folic acid analogs as cancer drugs to inhibit folate metabolism; thus, the era of cancer chemotherapy began in earnest.

The development of novel therapeutic strategies provides an opportunity to improve the efficacy of chemotherapy in the treatment of cancer. One such strategy is the use of antiangiogenic agents, which work by interfering with the formation and function of blood vessels that are essential for tumor growth and survival. Another strategy is the use of immune checkpoint inhibitors, which work by blocking proteins that can prevent the immune system from attacking cancer cells. These strategies have shown promise in the treatment of certain types of cancer, and ongoing research is focused on identifying new targets and combinations of drugs to further improve treatment outcomes.

The era of cancer chemotherapy began in earnest with the development of in vivo rodent model systems to evaluate the potential of novel anticancer drugs. These model systems allowed researchers to test drugs in the context of human cancer, providing important insights into the mechanisms of drug resistance and the potential for repurposing existing drugs. The use of in vivo rodent models has since been replaced by more sophisticated in vitro and in vivo assays, which allow for more precise evaluation of drug efficacy and resistance. However, the lessons learned from early studies continue to inform our understanding of the complex biology of cancer and the development of new therapeutic strategies.
tumor transforms, however, to a highly aggressive phenotype, paradoxically it often becomes almost totally incurable.

Non-Hodgkin's lymphoma is an ideal example of this treatment paradox. Diffuse large cell lymphoma (DHL) is a more rapidly growing form of non-Hodgkin's lymphoma that is curable by combination chemotherapy in its advanced stages. Indolent, low-grade lymphomas are more slowly growing tumors than DHL and, while they are highly responsive to treatment, they are generally incurable in their advanced form with conventional-dose chemotherapy. Thus, despite a similar cell of origin, the more rapidly proliferating cells are subject to complete eradication by chemotherapy. However, further increases in growth rates within populations of patients with diffuse aggressive lymphomas, as predicted by the degree of expression of the KI-67 antigen, a nuclear antigen that closely parallels the labeling index, negatively predict for both response to treatment and curability. This finding suggests that, beyond a certain point, the emergence of drug resistance in some way accompanies an increase in the growth rate of the tumor.

Another important and curious clinical observation not easily explained by the dogma on acquired drug resistance was that normal renewing tissue, such as the bone marrow and gastrointestinal (GI) mucosa, never develop resistance to these drugs. These are the two host tissues that are most commonly affected by most anticancer agents used in the clinic. It is a consistent and disconcerting clinical experience to have a patient's tumor respond to treatment with associated marrow suppression, only to have the tumor grow back in the face of continued treatment while the sensitivity of the marrow to chemotherapy-induced toxicity remains invariant. The same can be said for toxicity to GI mucosa. It is now well-appreciated that the genetic machinery involved in the cell-cycle checkpoint and apoptosis is preserved in normal host tissues. This fact most likely explains why normal host cells are constantly sensitized to the toxic effect of cytotoxic agents.

CHEMOTHERAPY AS PART OF THE INITIAL TREATMENT OF CANCER

Currently, chemotherapy has a role in four different clinical settings: (1) as induction treatment for advanced disease, (2) as an adjunct to local methods of treatment, (3) as the primary treatment for some patients who present with localized disease, in whom local forms of therapy by themselves are inadequate, and (4) by direct instillation into sanctuary sites or by site-directed perfusion of specific regions of the body directly affected by the cancer.

The term induction chemotherapy has been used to describe drug therapy given as the primary treatment for patients who present with advanced cancer for which no alternative treatment exists. Adjunctive chemotherapy denotes the use of systemic therapy after the primary tumor has been controlled by an alternative modality, such as surgery and radiation therapy. The selection of an adjuvant treatment program for a particular patient usually is based on response rates in separate groups of patients with advanced cancers of the same histologic type. The determination of a population of patients as suitable for adjuvant treatment is based on available data about their average risk of recurrence after local treatment alone. Currently, adjuvant chemotherapy is considered standard treatment for early-stage breast and colorectal cancer. There is also evidence to support the use of chemotherapy after surgical resection of anaplastic astrocytomas.

Primary (neoadjuvant) chemotherapy denotes the use of chemotherapy as the initial treatment for patients who present with localized cancer for which there is an alternative but less than completely effective local treatment. For chemotherapy to be used as the initial (primary) treatment of a cancer partially curable by either surgery or radiation, there must be considerable evidence for the effectiveness of the drug program in the treatment of the specific disease being considered. At this time, neoadjuvant chemotherapy has been effectively used in the treatment of anal cancer, bladder cancer, breast cancer, esophageal cancer, laryngeal cancer, locally advanced non–small cell lung cancer, and osteogenic sarcoma. For some of these tumors, it has now been determined that chemotherapy, when given concurrently with radiation therapy, is superior to sequencing chemotherapy before radiation therapy.

CLINICAL END POINTS IN EVALUATING RESPONSE TO CHEMOTHERAPY

INDUCTION CHEMOTHERAPY

In induction chemotherapy for patients with advanced cancer and measurable disease, it is possible to assess response to drugs on a case-by-case basis. Partial response is usually defined as the fraction of patients who demonstrate at least a 50% reduction in measurable tumor mass. There is growing evidence to suggest that quality-of-life indices are better in patients who show either a response to therapy or a minimal response as compared to supportive care, even if overall survival is not improved. However, partial responses are also useful in the evaluation of new drugs or new drug regimens, to determine whether the particular experimental approach is worthy of further clinical development.

It is clear, however, that the most important indicator of the effectiveness of chemotherapy is the complete response rate. No patient with advanced cancer has ever been cured without first achieving a complete remission. When new programs consistently produce more than an occasional complete remission, they have invariably been proven to be of significant practical value in medical practice. Thus, in clinical trials, complete and partial responses should always be reported separately. The most important indicator of the quality of a complete remission is the relapse-free survival from the time treatment is discontinued. This criterion is the only clinical counterpart of the quantifiable cytoreductive effect of drugs in the in vivo rodent system. The use of freedom from progression in patients who have attained a mixture of complete and partial responses can be misleading when evaluating a new treatment. This method of analyzing clinical outcomes is a relatively simple indicator of the practical potential of a new treatment, but, for experimental treatments, it obscures the value of a relapse-free survival of complete responders as the major determinant of the quality of remission and the potential for cure. Other endpoints, such as median response duration and median survival, are also of little practical value until treatment results have been refined so that the complete response rate is higher than 50%.

ADJUVANT CHEMOTHERAPY

There was initially great excitement with the concept of using chemotherapy as an adjunct to local treatment. The rationale for adjuvant chemotherapy was to treat micrometastatic disease at a time when tumor bulk would be at a minimum, thereby enhancing the potential efficacy of drug treatment. It was assumed that drug therapy, at this stage, would result in a much higher cure rate.

The major indicator of effectiveness of a chemotherapy program—the complete remission rate—is lost in the adjuvant setting because the primary tumor has already been removed. In the clinic, treatment is selected for individual patients based on response rates in an entirely different population of patients with advanced disease of the same histologic type. In adjuvant programs, relapse-free survival remains the major end point but, in each patient, micrometastases consist of a mixture of tumor cells, some of which could have been expected to be sensitive to chemotherapy and others of which could have been expected to be resistant to chemotherapy. The relapse-free survival in the adjuvant setting, therefore, measures time to regrowth to clinically detectable levels of cells unresponsive, partially responsive, or very sensitive to chemotherapy and is the equivalent of the duration of remission of a combined group of complete responders, partial responders, and nonresponders. In this sense, it is similar to the use of freedom from progression in patients with advanced disease.

PRIMARY (NEOADJUVANT) CHEMOTHERAPY

The unique feature of using chemotherapy in patients with localized tumor before or in place of purely local treatments, such as surgical excision or radiation therapy (or both), is the preservation of the presenting tumor mass as a biologic marker of responsiveness to the drugs. Moreover, this approach has allowed the sparing of vital normal organs, such as the larynx, the anal sphincter, and the bladder, as the primary tumor is reduced in size and rendered easier to deal with by traditional alternative treatment modalities. When chemotherapy is administered concurrently with radiation therapy, the determinants of sensitivity to drugs are obviated unless compared to radiation alone in a control arm.

The use of chemotherapy as primary treatment is reviewed in each of the appropriate disease-oriented chapters. Table 17-1 lists the specific malignancies in which primary chemotherapy for localized forms of the cancer in question already have been incorporated into clinical usage (first and second categories) and in which current clinical trials show considerable promise (third category).
The Goldie-Coldman hypothesis, therefore, predicts that cellular drug resistance should be present even with small tumors and that the maximal chance for cure drug-resistant clone; however, the absolute number of resistant cells in a tumor composed of 10⁶ cells). The probability that a given tumor will contain resistant clones when a patient's disease is newly diagnosed would be a function of both tumor size and the at population sizes between 10⁶ and 10⁷ that tumor cells mutate to drug resistance at a rate intrinsic to the genetic instability of a particular tumor. Their model predicted that such events would begin to occur without prior exposure to these drugs. They proposed that the nonrandom cytogenetic changes now known to be associated with most human cancers probably were resistance to phage infection. This was a seminal principle in bacterial genetics that laid the framework for the understanding of the development of spontaneous resistance to bacterial viruses (bacteriophage) not by surviving exposure but by expanding clones of bacteria that had spontaneously mutated to a type inherently resistant to phage infection. In 1979, Goldie and Coldman[], a tumor composed of 10⁶ cells would be relatively small. Therefore, in the clinic, such tumors should initially respond to treatment with a partial or complete remission but would recurr as the resistance clone expands to repopulate the tumor mass. Such a pattern is commonly seen in the clinical setting with the use of chemotherapy in many drug-responsive tumors.

With rare exceptions (e.g., choriocarcinoma and Burkitt's lymphoma), standard single drugs at clinically tolerable doses have been unable to cure cancer. In the early years of cancer chemotherapy, drug combinations were developed based on known biochemical actions of available anticancer drugs rather than on their clinical efficacy. These regimens were largely ineffective. The era of effective combination chemotherapy began when an array of active drugs from different classes became available for use in combination in the treatment of leukemias and lymphomas. Combination chemotherapy has now been extended to the treatment of most solid tumors, as described throughout this book.

Combination chemotherapy using conventional cytotoxic agents accomplishes several important objectives not possible with single-agent treatment. First, it provides maximal cell kill within the range of toxicity tolerated by the host for each drug as long as dosing is not compromised. Second, it provides a broader range of interaction between drugs and tumor cells with different genetic abnormalities in a heterogeneous tumor population. Finally, it may prevent or slow the subsequent development of drug resistance.

Certain principles have been useful in the selection of drugs in the most effective drug combinations, and they guide the development of new drug therapeutic programs. First, only drugs known to be partially effective against the same tumor when used alone should be selected for use in combination. If available, drugs that produce some fraction of complete remission are preferred to those that produce only partial responses. Second, when several drugs of a class are available and are equally effective, a drug should be selected on the basis of toxicity that does not overlap with the toxicity of other drugs to be used in the combination. Although such selection leads to a wider range of side effects, it minimizes the risk of a lethal effect caused by multiple insults to the same organ system by different drugs and allows dose intensity to be maximized.

Additionally, drugs should be used in their optimal dose and schedule, and drug combinations should be given at consistent intervals. Because long intervals between cycles negatively affect dose intensity (discussed in further detail later in Concept of Dose Intensity), the treatment-free interval between cycles should be the shortest possible time necessary for recovery of the most sensitive normal target tissue, which is usually the bone marrow. Finally, there should be a clear understanding of the biochemical, molecular, and pharmacokinetic mechanisms of interaction between the individual drugs in a given combination, to allow for maximal effect.

Omission of a drug from a combination may allow overgrowth by a cell line sensitive to that drug alone and resistant to other drugs in the combination. In addition, arbitrary reduction in the dose of an effective drug to add other less effective drugs may dramatically reduce the dose of the most effective agent below the threshold of effectiveness and destroy the capacity of the combination to cure disease in a given patient.

Most standard treatment programs were designed around the kinetics of recovery of the bone marrow in response to exposure to a cytotoxic agent. The introduction of the colony-stimulating factors (CSFs) has been a significant advance for cancer therapy, as they help to accelerate bone marrow recovery and prevent the occurrence of severe myelosuppression. They play an instrumental role in decreasing the incidence of infections and the need for hospitalizations and allow for maintenance of optimal dose intensity of chemotherapy. Clearly, these cytokine growth factors have revolutionized the next generation of chemotherapy treatment.

Bone marrow has a storage compartment that supplies mature cells to the peripheral blood for 8 to 10 days after the stem cell pool has been damaged by cytotoxic drugs. Events in the peripheral blood are usually a week behind events occurring in the bone marrow. In previously untreated patients not primed by CSFs, leukopenia and thrombocytopenia are observed on the ninth or tenth day after initial dosing. Nadir blood counts are noted between days 14 and 18, with the onset of recovery beginning by day 21 and usually completed by day 28 in patients who have not had prior treatment with drugs or x-irradiation. This sequence may be altered in patients with previous therapy by depletion of the stem cell pool, shortening the time to the appearance of leukopenia and thrombocytopenia and prolonging the recovery time. The interval of greatest importance in the clinic is the duration of the nadir level of leukocytopenia and plateletopenia. The highest risk of infection or bleeding occurs with granulocyte counts lower than 500/dL and platelet counts lower than 10,000/dL. If this nadir lasts only 4 to 7 days, it is tolerated by most patients without the need for supplemental support. Increasing doses of most anticancer drugs within the range of the maximally tolerated standard dose does not usually ablate the marrow or even prolong the time to recovery; however, it does usually influence the nadir count levels. Repeated dosing during the phase of early recovery of the marrow (days 16 to 21) may result in more severe toxicity in the second treatment cycle in patients whose marrow is not the source of, or involved with, the tumor.

These clinical observations, coupled with the kinetic studies of bone marrow recovery in mice and humans, led to the now-familiar 2-week interval between cycles of the most effective drug combinations, using standard doses without CSFs (new cycles begin on days 21 or 28 after the first dose) to accommodate the recovery time of human bone marrow. Although this treatment schedule is suitable for some tumors, the rapid regrowth of others, such as DHLs, Burkitt's lymphoma, and leukemia, often permit the tumor volume to return to pretreatment levels in the interval required for bone marrow recovery, and other approaches to cycling drug combinations are being explored.

For many years, clinical trial design was dominated by the use of alternating cycles of combination chemotherapy. The basis for this study design came from the translation of preclinical experimental data into a model for clinical treatment. In 1943, Lukis and Debruck observed that the bacterium Escherichia coli developed resistance to bacterial viruses (bacteriophage) not by surviving exposure but by expanding clones of bacteria that had spontaneously mutated to a type inherently resistant to phage infection. This was a seminal principle in bacterial genetics that laid the framework for the understanding of the development of spontaneous resistance to cancer chemotherapy. In 1979, Goldie and Coldman applied this principle to the development of resistance to anticancer drugs by cancer cells without prior exposure to these drugs. They proposed that the nonrandom cytogenetic changes now known to be associated with most human cancers probably were tightly associated with the development of the capacity to resist the action of certain types of anticancer drugs. They developed a mathematical model that predicted that tumor cells mutate to drug resistance at a rate intrinsic to the genetic instability of a particular tumor. Their model predicted that such events would begin to occur at population sizes between 10⁶ and 10⁷ tumor cells (1000 to 1 million cells), much lower than the mass of cells considered to be clinically detectable (10⁶, or 1 billion cells). The probability that a given tumor will contain resistant clones when a patient's disease is newly diagnosed would be a function of both tumor size and the inherent mutation rate. If the mutation rate is as inertious as 10⁻⁶, a tumor composed of 10⁶ cells (a 1-cm mass) would be predicted to have at least one drug-resistant clone; however, the absolute number of resistant cells in a tumor composed of 10⁶ cells would be relatively small. Therefore, in the clinic, such tumors should initially respond to treatment with a partial or complete remission but would recur as the resistance clone expands to repopulate the tumor mass. Such a pattern is commonly seen in the clinical setting with the use of chemotherapy in many drug-responsive tumors.

The Goldie-Coldman hypothesis, therefore, predicts that cellular drug resistance should be present even with small tumors and that the maximal chance for cure
occurs when all available effective drugs are given simultaneously. Because this would involve using eight to 12 drugs simultaneously, this approach has not generally been tested in the clinic for fear that the use of more than five cytotoxic drugs, at full doses, would not be possible. An alternative approach, using two programs of equally effective, non-cross-resistant drug combinations in alternating cycles, has been under evaluation since the mid-1980s. However, many studies purporting to test the Goldie-Coldman hypothesis have not been properly designed. First, in many instances, inadequate testing has been carried out to determine whether the alternate combination is truly non-cross-resistant. In most instances, these requirements are not met. Second, except in rare instances, dosing is usually not controlled properly. Doses of essential drugs are modified downward, a priori, without testing the potential impact of such dose reductions on outcome. Finally, the requirement for symmetry in biologic characteristics of tumors in different patients is unrealistic. The use of alternating cycles of combination chemotherapy has not yet proven to be more effective than full doses of a single effective combination program.

In 1986, Day and Norton and Day reanalyzed the Goldie-Coldman hypothesis and relaxed the requirement for symmetry in the model. Although it verified the basic tenets of the Goldie-Coldman hypothesis, their model suggested a different approach to sequencing combinations: In many instances, the sequential use of combinations should outperform alternating cycles, because no two combinations are likely to be strictly non-cross-resistant or have equal cell-killing capacity, the symmetry assumed by Goldie and Coldman. Day formed the "worst-drug rule," which refers to using more or earlier doses of a treatment that is the least effective of two or more available options. The worst-drug rule has interesting implications. First, it is a nonintuitive approach. If two treatments—treatments A and B—are available and B is known to be better, a physician is more likely to use B first. Cells that are resistant to the best treatment, B, must be eliminated by the weaker program, A; however, because it is the weak drug that is used first, it cannot wait too long to do so. The physician and patient in a situation that is difficult to overcome. The model predicts that if six cycles of A and B are planned, use of the weaker program, A, first offers a better outcome. There have been clinical examples in which sequential therapies have outperformed alternating cyclic use of the same programs if the dose intensity of the two regimens is carefully controlled.

**EFFECT OF THE BIOLOGY OF TUMOR GROWTH ON RESPONSE TO CHEMOTHERAPY**

Applying the principles of chemotherapy developed by Skipper et al. in leukemia L1210 to the drug treatment of human cancers requires a clear understanding of the differences between the growth characteristics of this rodent leukemia and of human cancers as well as an understanding of the differences in growth rates of normal target tissues between mice and humans. For example, L1210 leukemia has a rapidly growing phenotype with a high percentage of cells synthesizing DNA, as measured by the uptake of tritiated thymidine (the labeling index). Because L1210 leukemia has a growth fraction of 100% (i.e., all its cells are actively progressing through the cell cycle), its life cycle is consistent and predictable.

The time to death of animals bearing L1210 leukemia is the interval required to achieve a population size of approximately 10^9 (1 billion) cells. With a growth fraction of 100% and a doubling time of 12 hours, 10^10 cells accumulate by 19 days after the injection of a single cell, by 10 days after the injection of 10^5 cells, and by 5 days after the administration of 10^6 cells. Skipper et al. postulated that the increase in host life span after cytotoxic chemotherapy of L1210 leukemia was largely due to the cytoidal effect of treatment on the tumor cell population. In these early elegant mouse experiments, they calculated the residual number of cells after treatment by extrapolation of the 10^6 cells to 10^4 and 10^3, which is equivalent to the initial number of tumor cells (a 1-log kill), or a reduction in the cell number from 10^6 to 10^3. A 99.999% destruction of tumor cells, a number that seems enormous to most clinicians, represents only a 5-log kill and does not cure animals unless the initial inoculum is small, perhaps 10^3 cells or fewer. If multiple treatments are given, the net tumor cell kill per treatment is the sum of the surviving cells plus the regrowth of the tumor cell population before the next treatment.

The cytotoxic effects of cancer drugs in this tumor model follow log cell-kill kinetics. Thus, if a particular dose of an individual drug kills 3 logs of tumor cells and reduces tumor burden from 10^10 to 10^7 cells, the same dose used at a tumor burden of 10^10 cells reduces the tumor mass to 10^7. Cell kill, therefore, is proportional, regardless of tumor burden. This model fits the response of L1210 murine leukemia to chemotherapy. When treatment failed in sensitive cell lines, it was because the initial tumor burden was too high to allow the delivery of curative doses of chemotherapy to eradicate the last tumor cell. The cardinal rule of chemotherapy—the invariant inverse relation between cell number and curability—was established in this model and applies to other tumor systems. Skipper et al. showed that this rodent leukemia could be cured by specifically designed doses and schedules of administration that were based on tumor volume and growth characteristics.

Although growth of murine leukemia closely follows exponential cell kinetics, available data suggest that most human solid tumors do not grow in an exponential fashion. For example, the concept of log kill would have predicted that some large tumors in the clinic should have been more sensitive to treatment than has been experienced. In toto, the experimental data in human solid cancers support a Gompertzian model of tumor growth and regression. The critical distinction between Gompertzian and exponential growth is that in Gompertzian kinetics, the growth fraction of the tumor is not constant but decreases exponentially with time (exponential growth is matched by exponential retardation of growth). The growth fraction peaks when the tumor is approximately 37% of its maximum size. In a Gompertzian model, when a patient with advanced cancer is treated, the tumor mass is larger, its growth fraction is low, and the fraction of cells killed is, therefore, small. An important feature of Gompertzian growth is that response to chemotherapy in drug-sensitive tumors depends, in large measure, on where the tumor is in its particular growth curve. Sensitive Gompertzian-growing tumors respond to cytotoxic drugs in a Gompertzian fashion.

Because this would involve using eight to 12 drugs simultaneously, this approach has not been properly designed. In many instances, inadequate testing has been carried out to determine whether the alternate combination is truly non-cross-resistant. In most instances, these requirements are not met. Second, except in rare instances, dosing is usually not controlled properly. Doses of essential drugs are modified downward, a priori, without testing the potential impact of such dose reductions on outcome. Finally, the requirement for symmetry in biologic characteristics of tumors in different patients is unrealistic. The use of alternating cycles of combination chemotherapy has not yet proven to be more effective than full doses of a single effective combination program.

In 1986, Day and Norton and Day reanalyzed the Goldie-Coldman hypothesis and relaxed the requirement for symmetry in the model. Although it verified the basic tenets of the Goldie-Coldman hypothesis, their model suggested a different approach to sequencing combinations: In many instances, the sequential use of combinations should outperform alternating cycles, because no two combinations are likely to be strictly non-cross-resistant or have equal cell-killing capacity, the symmetry assumed by Goldie and Coldman. Day formed the "worst-drug rule," which refers to using more or earlier doses of a treatment that is the least effective of two or more available options. The worst-drug rule has interesting implications. First, it is a nonintuitive approach. If two treatments—treatments A and B—are available and B is known to be better, a physician is more likely to use B first. Cells that are resistant to the best treatment, B, must be eliminated by the weaker program, A; however, because it is the weak drug that is used first, it cannot wait too long to do so. The physician and patient in a situation that is difficult to overcome. The model predicts that if six cycles of A and B are planned, use of the weaker program, A, first offers a better outcome. There have been clinical examples in which sequential therapies have outperformed alternating cyclic use of the same programs if the dose intensity of the two regimens is carefully controlled.

**APPOINTOSIS, CELL-CYCLE CONTROL, AND RESISTANCE TO CHEMOTHERAPY**

The kinetic models described are realistic only in the context of a tumor that is sensitive to chemotherapy. Recently, there have arrived at a new understanding of the critical determinants of drug sensitivity and resistance. For more than 30 years, the classic view of anticancer drug action has involved the specific interaction between drug and target; resistance has arisen as a direct consequence of this drug-receptor interaction. However, the critical molecular mechanisms involved in facilitating the initial coupling of the stimulus to the final response of the cell were never clearly elucidated. With an enhanced understanding of the molecular mechanisms underlying the control of the cell cycle and the process of programmed cell death (apoptosis), it is now clear that this very simplistic model is an oversimplification. In contrast to the notion that cell death as viewed to date is a result of the genetic and critical pathways of cell-cycle checkpoint genes, oncogenic viruses, transcription factors, apoptosis, and chemotherapy as they relate to drug resistance, more detailed discussion of these topics are reviewed elsewhere.

As noted earlier in the "History" section of this chapter, normal tissues never develop resistance to chemotherapy. However, one of the most remarkable features of both radiation therapy and chemotherapy, when used to treat sensitive tumors, is that their cytotoxic effects may be initially greater in neoplastic cells than in normal host tissues, including the bone marrow and the GI tract. Doses that eradicate some sensitive tumors will not ablate the bone marrow or destroy the capacity of the GI mucosa to regenerate. No molecular basis for this therapeutic selectivity was available until just recently. However, this difference in cytotoxic action between normal
and malignant cells appears to relate to mechanisms that allow normal renewing cell populations, such as bone marrow and GI precursor cells, to monitor and repair damaged DNA or destroy cells with irreparable DNA, rather than allowing damaged cells to proceed through the cell cycle and potentially replicate their damaged DNA. Because they express an intact genetic machinery, normal cells can almost always recover from exposure to DNA-damaging anticancer agents, except in the case of high-dose chemotherapy, as used in transplantation programs. In this particular setting, the high doses of chemotherapy are able to overwhelm these protective mechanisms or to destroy the DNA of exposed cells by direct necrosis (or both). Initially, sensitive cancer cells can be destroyed by ineffective chemotherapy but, if not, they develop resistance to further treatment, perhaps in part because of drug-induced mutations in their DNA. This resistance may be linked to the dysregulation of the same genetic and signaling pathways that control entry into the cell cycle and the process of programmed cell death.

p53

p53 (Fig. 17-1) is a tumor suppressor protein and critical transcriptional activator that causes both G1 and G2 arrest of the cell cycle when cells are exposed to DNA-damaging agents. This function is thought to be critical in preserving the integrity of the cellular genome in response to treatment with a cytotoxic agent. In addition to its role in the cell-cycle checkpoint, p53 is a potent inducer of programmed cell death (apoptosis) within a cell in which DNA damage has occurred. The basis for the cell's decision either to undergo growth arrest and repair DNA damage or to induce apoptosis remains unknown. Significant research efforts are focused on elucidating the critical factors that determine the eventual cellular function of p53. This is undoubtedly a complex issue, however, that must take into account the extent of DNA damage, the stage of the cell cycle at which the DNA damage occurs, the presence of other genetic abnormalities in either the cell-cycle regulatory apparatus or the signaling machinery, or the specific cellular context. It is now clear that some cell types, such as lymphocytes and the tumors derived from them, have a more rapid access to apoptotic mechanisms than the large majority of epithelial cancers.

FIGURE 17-1. Role of p53 in chemotherapy sensitivity in normal and neoplastic cells. Exposure of normal cells (A) to DNA-damaging agents results in increased levels of p53, which induces an arrest of progression from the G0 or quiescent phase to the S or DNA synthetic phase of the cell cycle. Exposure of cancer cells (B) to DNA-damaging agents increases p53 but does not stop cell-cycle progression to S phase, owing to mutant Ras. This results in apoptosis. (From AB Deisseroth, VT DeVita. The cell cycle: probing new molecular determinants of resistance and sensitivity to cytotoxic agents. Cancer J Sci Am 1995;1:118, with permission.)

Mutations in the p53 gene are among the most common genetic alterations observed in human tumor samples and have been estimated to occur in at least 50% of all human tumors. The initial studies showing that loss of p53 function was associated with resistance to radiation therapy as well as chemotherapy came from in vivo model systems using p53 knockout mice. Subsequent studies have confirmed that various malignant cell lines and tumors expressing mutant or deleted p53 are chemoresistant to a wide range of anticancer agents. However, loss of p53 function is not always associated with chemoresistance. Some studies suggest that cells with impaired p53 function can become sensitized to various anticancer agents. Thus, the relationship between p53 status and chemosensitivity is complex and is presumably dependent on a number of factors, including the specific cytotoxic stimuli, tissue-specific differences, and the specific cellular context that incorporates the overall genetic machinery and the various intracellular signaling pathways.

The specific cytotoxic treatment, the conditions of treatment, p53 status, and other cell-cycle regulatory elements may all contribute to the outcome of an exposure of a cell to DNA-damaging agents. If the dose of the treatment is very high, nonapoptotic cell death (e.g., necrotic cell death due to DNA or other damage) may occur. At an intermediate level of dose intensity, p53-dependent or p53-independent apoptotic cell death can occur. When p53 function is intact, the level of inhibitors of p53 is not high, and the regulatory environment of the cell is such that the cell circumvents the interruption of the cell-cycle progression that occurs after DNA damage, the cell will undergo p53-dependent apoptosis. However, in the setting of abnormal p53 function, whether through the acquisition of point mutations in the p53 gene, posttranslational inactivation of p53 through binding to other protein partners (e.g., MDM2) or enhancement of the degradation (e.g., the E6 protein of the human papilloma virus), or decreased translation of wild-type p53 messenger RNA by the folate-dependent enzyme thymidylate synthase, the cell is unable to undergo cell-cycle arrest or apoptosis in response to DNA damage. In a tumor population, the functional inactivation of p53 through any of these regulatory mechanisms facilitates genomic instability and contributes to the development of cellular resistance. Normal hematopoietic cells tend to be more genetically stable during chemotherapy as a result of an intact p53 mechanism that provides an opportunity to repair DNA damage. In contrast, the malignant cell with functional p53 may be more sensitive to chemotherapy than normal cells because of the fact that common transforming mutations in other proteins, such as ras, which tend to drive cells into S phase, overcome the p53-dependent mechanisms that allow for repair. Because the p53-dependent apoptotic mechanisms, triggered by DNA damage, may remain intact, the tumor cell dies after chemotherapy, whereas the normal cell survives. When the function of p53 is finally lost, the stability of the genome of the tumor cells decreases, and the disease progresses rapidly to higher and higher levels of resistance to therapy and to a more advanced pattern of dysregulated growth and metastasis.

Although it was initially thought that drug-curable tumors, in general, were less often found to have p53 mutations, this is not always the case. In addition to p53-dependent mechanisms, it is well appreciated that p53-independent mechanisms also exist. In general, the presence of p53 mutations has been correlated with a poor prognosis, even in such treatable tumors as lymphomas. However, the issue of whether mutations determine cure or no cure will be addressed only by reexamination of the tissue specimens of patients cured many years ago, to separate easily the impact of a damaged cell-cycle checkpoint control system on early response to treatment rather than cure.

This is an important question. If drugs can kill only cells with an intact apoptotic mechanism, as expressed by a functioning p53 gene, the chemotherapy of cancer may have gone as far as it can go in its present form, except for the increment of additional cures that may be attained by using high-dose regimens that overwhelm these mechanisms. If cures are possible in tumors with mutant p53, responsiveness to treatment may relate more to the degree of dysregulation of the checkpoint control system, which is downstream from p53 in the growth regulatory pathway, something that possibly can be manipulated as an approach to treatment.

How might dysregulation of this pathway increase drug resistance beyond the failure to induce apoptosis? p53 affects events within the cell by binding to p53-dependent mechanisms, it is well appreciated that p53-independent mechanisms also exist. In general, the presence of p53 mutations has been correlated with a poor prognosis, even in such treatable tumors as lymphomas. However, the issue of whether mutations determine cure or no cure will be addressed only by reexamination of the tissue specimens of patients cured many years ago, to separate easily the impact of a damaged cell-cycle checkpoint control system on early response to treatment rather than cure.

Some of the genes that are transcriptionally activated by p53 belong to a class of proteins known to inhibit the cyclin-dependent kinases (Fig. 17-2). One of these proteins, known as p21 (Waf-1, Cip-1), can form a complex with proliferating cell nuclear antigen or inhibit the full activation of the cyclin-dependent kinase. When the cyclin kinase is fully active, it acts on another tumor suppressor, the retinoblastoma (RB) gene, to phosphorylate it. This causes the release of the E2F family of transcription factors, which then bind to the regulatory regions of a number of genes that participate in the synthesis of DNA. These genes are shown in Figure 17-2 and include ribonucleotide reductase, dthrydofolate reductase, DNA-dependent RNA polymerase, thymidylate synthase, c-myc, c-fos, and c-myb.
Activation of this family of proteins promotes and supports the entry of the cell into S phase. The activation of cyclin-dependent kinases and the consequent turning on of the DNA synthetic machinery by release of E2F from RB occur in normal cells after growth factor stimulation, which probably provides the signal for the initiation of the cyclin clock. When normal p53 is activated after DNA damage, the levels of the p21, p27, and other gene products, such as MDM-2, an apparent feedback regulator of p53, and GADD 45, a gene involved in DNA repair, may become very high. When the expression of p21 is induced to high levels, it exerts an inhibitory effect on the formation of the active cyclin kinase complex. This critical checkpoint function of p53, which restricts the procession of the cell into the DNA synthetic phase of the cell cycle, also prevents the E2F-dependent expression of gene products related to rapid cell growth.

The mdr-1 gene has been added to the list of those potentially influenced by p53 because it has been shown that wild-type p53 suppresses the promoter of the mdr-1 gene, whereas the mutant protein can actually stimulate the promoter. The biologic basis for this action is not readily apparent but, when the foregoing effects are considered in toto, dysregulation of the p53 pathway, which would be expected to be associated with more rapid growth, might well be a prominent mechanism of drug resistance due to the overproduction of gene products responsible for entry into S phase and rapid cell growth. The activation of these genes could theoretically increase the resistance of cells to the following chemotherapeutic agents: methotrexate, 2-chlorodeoxyadenosine, hydroxyurea, fludarabine, cytosine arabinoside, and 5-fluorouracil. Furthermore, the action of an entire array of the most effective natural product antitumor agents could be suppressed through stimulation of the mdr-1 promoter directly by a mutant form of p53.

Thus, an active p53 in the setting of such DNA-damaging agents as chemotherapy or irradiation increases the levels of key gene products to levels that are sufficient to inhibit the phosphorylation of the RB gene by cyclin-dependent kinase (Fig. 17-3). This, in turn, prevents the expression of the gene products necessary for DNA synthesis to occur.

It is conceivable that increasing growth rates may be associated with increasing levels of drug resistance through the increased transcription of genes involved in rapid cell growth and entry into the cell cycle. The high degree of resistance in more advanced tumors, including the spontaneous development of resistance, which was the basis of the Goldie-Coldman hypothesis, and the development of multidrug resistance, appear more likely to be related to mutations in key genes in the cell-cycle regulatory system than to drug-specific spontaneous mutations, as has been proposed in the past. Cell death in response to exposure to DNA-damaging agents may require an intact p53-dependent apoptotic mechanism under some experimental circumstances. On the other hand, it also may depend on the activation of alternative pathways of apoptosis or some degree of reregulation of the system which would ultimately lead to the reduced release of transcription factors from the DNA synthetic machinery by release of E2F from RB occur in normal cells after growth factor stimulation, which probably provides the signal for the initiation of the cyclin clock. When normal p53 is activated after DNA damage, the levels of the p21, p27, and other gene products, such as MDM-2, an apparent feedback regulator of p53, and GADD 45, a gene involved in DNA repair, may become very high. When the expression of p21 is induced to high levels, it exerts an inhibitory effect on the formation of the active cyclin kinase complex. This critical checkpoint function of p53, which restricts the procession of the cell into the DNA synthetic phase of the cell cycle, also prevents the E2F-dependent expression of gene products related to rapid cell growth.

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FIGURE 17-3. DNA damage induced by anticancer drugs and irradiation and oncogene expression initiate pathways involved in apoptosis or cell-cycle arrest (or both). CDKs, cyclin-dependent kinases; UV, ultraviolet. (From ref. 56, with permission.)
exposure to certain forms of cell stress and that defects in SAPK signaling promote cell survival. With regard to chemotherapy, SAPK functions are an important mediator of apoptosis. Inhibition of SAPK activation has a protective effect against cancer cells treated with various anticancer agents, including the anthracyclines and etoposide. In addition, SAPK is required for ceramide-induced apoptosis, a key mediator of cytotoxicity induced by various cancer drugs. Thus, the SAPK-signaling pathway plays an essential role in facilitating chemotherapy-induced apoptosis. The precise mechanism by which the SAPK pathway is actually activated remains a matter of much research. However, one potential clue rests with the observation that DNA damage induced by genotoxic stress is sensed by kinases, including the DNA-dependent protein kinase or the ataxia-telangiectasia-mutated gene product (or both). These proteins can then phosphorylate p53, resulting in its activation. In addition, DNA-dependent protein kinase can stimulate c-Ab1 tyrosine kinase, which in turn leads to direct activation of SEK-1, an upstream signal in the SAPK cascade.

DEATH EXECUTIONER PATHWAY

The molecular mechanisms and signal transduction pathways initiated by a given cellular stress may differ significantly. However, the final stage of these various death pathways occurs through the activation and function of the caspases (see Fig. 17.3). The caspases represent a conserved family of cysteine proteases with specificity for aspartic acid residues in their substrates. Exogenous vectors that express p53 have been injected into human tumors, resulting in suppression of tumor growth.

DEVELOPMENT OF NOVEL THERAPEUTIC STRATEGIES

Significant efforts continue to be placed on elucidating the critical intracellular signal transduction pathways required for cell-cycle control and the induction of apoptosis and cell death. However, based on current knowledge, attempts are already being made to manipulate these intracellular programs so as to design and develop novel therapeutic approaches to improve the efficacy of chemotherapy. Tumor suppression genes were originally identified because of the ability of transforming viruses to bind to the protein product of the tumor suppressor gene and induce the growth required for the virus lytic cycle. It has been shown that the adenovirus E1A protein, which by itself is nontransforming, can actually sensitize cells to agents that induce apoptosis. E1A is involved in the release of E2F from the RB protein, which could be expected to facilitate entry of cells into S phase. It has been hypothesized that the transmission of conflicting signals, we act both to slow growth and to stimulate growth simultaneously, may lead to E1A-induced apoptosis.

CELL SURVIVAL PATHWAYS

It has been shown that a number of external stimuli, including various cytokines, tumor necrosis factor-a (TNF-a), chemotherapy, and radiation, lead to activation of the transcription factor NF-kB. This transcription factor is a potent regulator of the expression of various genes whose products are involved in the control of cell growth, survival, and death. The effects of TNF-a and the related cytokine to chemotherapy,

Thus, in vivo mouse models bearing human tumor xenografts suggest that this may be so. An antiedimeral growth factor receptor, monoclonal antibody C225 targeted to the epidermal growth factor receptor, was used in combination with the anticancer agent doxorubicin against human A375 squamous carcinomas and human MDA468 breast carcinomas. The effects of either the antibody alone or the drug are alone moderate, with no long-term survivors. However, when the antibody is administered before doxorubicin, the effects of the combination are dramatic, often leading to complete tumor regression and long-term survival. Similar results were observed in mice bearing human GEO colon cancer xenografts. Doxorubicin treatment was noted only in mice treated with the C225 monoclonal antibody to induce apoptosis in response to chemotherapy.

CONCEPT OF DOSE INTENSITY

Irrespective of the molecular mechanisms underlying the development of human cancers, a principal factor limiting the capacity to cure is proper dosing. The dose–response curve in biologic systems is usually sigmoidal in shape, with a threshold, a lag phase, a linear phase, and a plateau phase. For radiation therapy and chemotherapy, therapeutic selectivity is dependent on the difference between the dose–response curves of normal and tumor tissue that must be exploited during treatment. In experimental models, the dose–response curve is usually steep in the linear phase. Almost without exception in rodents bearing transplantable tumors, a reduction in dose in the linear phase of the dose–response curve usually results in a loss of the capacity to cure the tumor effectively before a diminution in the response rate. Although some compromise of tumor response can be achieved by reducing the dose, a reduction in tumor size of 50% is a minimal response. Studies are ongoing to determine whether TRAIL-based therapy may be used either alone or in combination with other cytotoxic agents and whether these promising results can be effectively translated into the clinic.

It has been suggested that initiation of the cyclic production of cyclins in the cell is due, in part, to the effect of growth factors. Some cyclin classes, such as the D cyclins, may indeed be the essential sensors for multiple growth factor signals. In some experimental systems, a determining factor in the decision of a cell either to undergo cell-cycle arrest and repair damaged DNA or to undergo apoptosis may be the presence of key growth factors within the cellular environment. Thus, in the absence of a growth signal, with growth factors serving as a survival factor, the cell becomes committed to the apoptotic pathway. It is presumed that apoptosis is taking place within the context of an intact p53 mechanism. However, one question is whether, even in the presence of mutations of p53 or other checkpoint genes (or both), deprivation of critical growth factor signals would still result in enhanced sensitivity to chemotherapy.

Experiments using in vivo mouse models bearing human tumor xenografts suggest that this may be so. An antiedimeral growth factor receptor, monoclonal antibody C225 targeted to the epidermal growth factor receptor, was used in combination with the anticancer agent doxorubicin against human A375 squamous carcinomas and human MDA468 breast carcinomas. The effects of either the antibody alone or the drug are alone moderate, with no long-term survivors. However, when the antibody is administered before doxorubicin, the effects of the combination are dramatic, often leading to complete tumor regression and long-term survival. Similar results were observed in mice bearing human GEO colon cancer xenografts. Doxorubicin treatment was noted only in mice treated with the C225 monoclonal antibody to induce apoptosis in response to chemotherapy.

Based on the promising clinical results, these combination regimens have been approved by the U.S. Food and Drug Administration for women with advanced breast cancer.
data indicates that the general principle may be applied to the clinic. Because anticancer drugs are toxic, it is often appealing to avoid acute but not life-threatening toxicity by either reducing the dose or increasing the time interval between each cycle of treatment. This kind of empiric dose adjustment is a major reason for treatment failure in patients with drug-sensitive tumors who are undergoing induction chemotherapy.

### Table 17-2. Risky Osteogenic Sarcoma: Response to Different Dose Intensity of Two-Drug Combination of Cyclophosphamide and L-PAM

One problem facing clinicians is the difficulty in adequately comparing the impact of different dosing practices on the clinical efficacy of chemotherapy. To approach this issue, Hryniuk et al. analyzed treatment outcomes in various tumor types as a function of dose intensity. Dose intensity is defined as the amount of drug delivered per unit of time, expressed as milligrams per square meter per week, regardless of the schedule or route of administration. Relative dose intensity (RDI) is the amount of drug delivered per unit of time relative to an arbitrarily chosen standard single drug or, for a combination regimen, the fractional decrease of the ratio of the average dose intensity of all drugs of the test regimen compared with the standard regimen. A sample calculation of the RDI for a commonly used regimen, the cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) combination for breast cancer, is provided in Table 17-3. To calculate the average RDI for a regimen containing fewer drugs than the standard regimen, a dose intensity of zero is assigned to the missing drug, and the average RDI of the test regimen is divided by the total number of drugs in the standard regimen.

### Table 17-3. Sample Calculations: Dose Intensity, Relative Dose Intensity, and Average Relative Dose Intensity

Because dose intensity is determined based on the amount of drug given per week, regardless of schedule, treatment delays are given equal weight with dose reductions. Calculations of the dose intensity, therefore, assume that differences in scheduling do not influence treatment outcome. Although this concept may at first appear contradictory, close scrutiny of all available data in humans and rodents reveals that the schedule of administration influences outcome mainly by affecting toxicity. In this way, higher doses of drug can be administered over the same time frame. As one example, daily administration of low doses of methotrexate is extremely toxic and severely limits the dose and duration of therapy with this drug. However, a twice-weekly schedule, which is much more effective in rodents and humans, allows much higher doses to be delivered over a longer period. Of note, this particular schedule is associated with significantly less host toxicity. As calculated, the dose intensity of the twice-weekly schedule is much greater than that of the daily oral schedule. In practice, the impact of scheduling on the calculation of dose intensity can be neutralized by comparing programs in which drugs with toxicities affected by scheduling, such as the antimetabolites, are given on similar schedules.

One of the potential limitations of the dose-intensity concept is that calculations of an average RDI of a drug combination assume that each drug has equal efficacy and anticancer activity. Therefore, for proper assessment of the impact of dose delays in clinical trials, it is critical that such data be provided.

The steep dose-response curve for anticancer drugs indicates that dose reductions in adjuvant drug treatment programs are likely to be associated with significantly less therapeutic effect. Dose reduction, however, has been the norm in the design of adjuvant trials. One example is the standard CMF regimen for breast cancer referred to in Table 17-3. The initial reports of this regimen revealed an impressive complete remission rate of approximately 30%, albeit at the expense of considerable host toxicity. When this regimen was advanced for use in the cooperative group setting, initially for advanced disease and later for adjuvant trials by Bonadonna et al., its doses were arbitrarily reduced without pretesting the potential impact of such reductions on clinical outcome. In addition, further reduction was empirically made for patients older than 60 years, with the assumption that such a dose reduction would be required for age. When the effect of these reductions is correlated with outcome, there is a strong suggestion of a negative impact. In premenopausal women, the differences in relapse-free survival at both low and high doses of CMF are statistically significant. The importance of dose effect was further confirmed by a large study in which a survival benefit was observed as a result of increasing dose intensity in the adjuvant chemotherapy for women with stage II, node-positive breast cancer.

An increase in the dose intensity represents one approach to improve on the effect of specific drugs or drug combination, but it may not be useful in all clinical circumstances. In the setting of large tumor burdens, the dose-response curve tends to shift to the right. At the low end of the curability curve (i.e., in the presence of the highest tumor burdens), an increase in dose intensity may not improve treatment outcome, as the dose-response curve is flat, but most often leads to unacceptable host toxicity. In addition, increasing the dose intensity of drug regimens that are already associated with curing nearly 100% of a subset of patients would not be expected to be of clinical benefit. Such a scenario would hold for the treatment of germ cell cancer using the cisplatin, etoposide, bleomycin combination and for Hodgkin’s disease, using either the methotrexate, vincristine (Oncovin), procarbazine, and prednisone regimen; the doxorubicin, bleomycin, vinblastine, and dacarbazine regimen; or regimens derived from them, such as BEACOPP (see Chapter 45.3). However, for most drugs, there appears to be a threshold dose that...
produces clinical response. The success of high-dose chemotherapy programs with stem cell support in refractory lymphomas, breast cancer, childhood sarcomas, and neuroblastomas suggests that maximizing dose intensity can improve response rates or cure in drug-responsive tumors.

Frei et al. and Hryniuk et al. have proposed the term summation dose intensity to reflect the relationship between dose and combination chemotherapy. As part of this concept, they suggested that the final outcome of either a high-dose or combination treatment must be related in some manner to the sum of the dose intensities of all the agents used in that treatment. The intrinsic chemosensitivity of a given tumor is critical for treatment success. An active agent is defined as one that, when used alone, is associated with at least a 30% response rate for a given tumor. It is now well appreciated that for almost all malignancies, a combination regimen incorporating at least three active drugs is necessary for cure. In the case of childhood leukemia, the cure rate increases linearly when the number of active drugs increases from three to seven. The critical issue for this concept is that all active agents must be used at their full therapeutic doses. However, until the advent of the various cytokine growth factors and autologous or peripheral stem cell transplantation (or both), the effective administration of maximal doses of chemotherapy has not been possible. Although the concept of summation dose intensity is not new, it does offer a unified approach for the careful design and interpretation of clinical trials.

**IN VITRO DRUG-RESPONSE ASSAYS**

Several methods have been developed since the 1950s to determine the in vitro drug sensitivities of human tumor cells to various anticancer agents. In the mid-1950s, Black and Spear were the first to report the use of an in vitro assay to predict patient response. Their studies compared the in vitro activity of aminopterin with its clinical response. The assay technology was based on the colorimetric detection of viable cells using a substrate for mitochondrial succinate dehydrogenase. Although the predictive accuracy of their results was not particularly strong, the development of the clonogenic stem cell assay in the 1970s brought in vitro testing of solid tumors into the mainstream. However, the results of these studies indicated that there were significant technical issues to overcome. As illustrated in Table 17-4, further work to improve on the technology led to a variety of techniques and approaches with a pronounced ability to identify drug resistance accurately. The major distinction among the differing assay methods is the end point used to measure cell viability. Assay end points include colony growth from single cell suspensions, incorporation of tritiated thymidine, microscopic examination of cells with vital dyes, mitochondrial enzyme activity, cytosolic esterase activity, and adenosine triphosphate content. Given the variety of assay types, it is remarkable that the predictive accuracy for the identification of chemosensitivity for most of these approaches appears to be at least 90%. Several issues should be considered when evaluating an assay technology (Table 17-5).

**TABLE 17-4. Correlations of In Vitro Test Results with Patient Response**

<table>
<thead>
<tr>
<th>Assay Type</th>
<th>Correlation with Patient Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thymidine Incorporation</td>
<td>High correlation</td>
</tr>
<tr>
<td>MTT Assay</td>
<td>Moderate correlation</td>
</tr>
<tr>
<td>Colcemid Assay</td>
<td>Low correlation</td>
</tr>
</tbody>
</table>

**TABLE 17-5. Factors Influencing the Utility of the In Vitro Assay**

The clonogenic assay evaluates the ability of chemotherapeutic agents to inhibit tumor stem cell proliferation in agarose, a medium that precludes proliferation of nontransformed cells. Most of the in vitro drug-response techniques use similar methods for tumor preparation. Solid tumors are disaggregated into suspensions of multicellular clumps with scissors and by passing the fragments through mesh or by stirring tissue fragments with collagenase. Single-cell suspensions then are generated by passing the cellular aggregates through high-gauge needles. Cell suspensions are incubated with drug for 1 hour, rinsed, and plated on an agar base with growth media. After a period of 14 to 28 days, the number of colonies that have grown from the treated cells is compared with the number of colonies from untreated control cells. The fraction of control growth provides an index of drug activity. Studies by the National Cancer Institute and the Southwest Oncology Group indicate that the assay is reproducible among multiple laboratories. Problems with assay interpretation arising from the initial plating of small cell clumps were overcome with the use of chromomycin A3.

The conventional clonogenic stem cell assay has suffered from a relatively low success rate (<50%) of specimens yielding results, rendering it difficult to accrue adequate numbers of patients into clinical trials. Although this factor initially dampened enthusiasm for this approach, a significant number of clonogenic assays (>2500 cases) have now been performed by various groups, with an overall positive predictive value of 69% and a negative predictive value of 91% (see Table 17-4).

Tritiated thymidine incorporation, as an assay end point, was introduced in part to eliminate the problem of discriminating between true colony growth from a single cell and from a clump of cells plated at the outset. This technique also decreased the assay time from more than 14 days to less than 1 week and was associated with an improved success rate of diagnostic yield to 85%. Processing and plating of the tumor for the thymidine assay is similar to that for the clonogenic assay. However, in the thymidine assay, small clumps rather than single cells are preferred to maintain cell-cell interactions. In addition, cells are grown in an agar suspension, which allows tumor growth in vitro to recapitulate the three-dimensional in vivo morphology. Cell-cell interactions resulting from three-dimensional growth may be critical for the detection of acquired drug resistance, which can be missed in monolayer cultures.
In contrast to the clonal agonist to cancer, prolonged drug exposure is utilized in the thymidine-based assay. Tumor suspensions are continuously exposed to drug for 5 days. Cell Tissue Kinet 1962;28:1015. The prolonged drug exposure in the thymidine assay results in a five- to 20-fold higher concentration × time factor than that used in the clonogenic assay, biasing assay accuracy toward detection of drug resistance. Tumor growth after drug exposure in the thymidine assay is associated with multidrug resistance, which led the authors of one article to describe it as the “extreme drug resistance assay.” Some paclitaxel-resistant tumors identified with this technique have been found to overexpress P170 glycoprotein, suggesting that this assay can be used to identify the activity of specific mechanisms of drug resistance in different tumor histologies.

Another promising assay is the differential staining cytotoxicity (DISC) assay. The DISC assay relies on the structural integrity of cells. In the DISC assay, cells are incubated with drugs for 4 days. Dead cells are stained in suspension with fast green dye in the absence or presence of nigrin, and duck red blood cells are added to the suspension. The standard for counting the surviving standard is cytocentrifuged to deliver discs of cells onto microscope slides. Live cells then are stained with either hematoxylin-eosin or Romanowsky stain. The end point of this test is the morphologic identification of tumor cell cytotoxicity as compared with the internal control of fixed duck erythrocytes. The DISC assay requires more than 10% tumor cells and measures cell kill in both dividing and nondividing tumor cell populations. 215,214 Microscopic identification of the cell population renders it possible to determine the differential kill of normal and tumor cells, and this is the therapeutic index for new agents undergoing in vitro screening for activity. The DISC assay (see Table 17.4) offers an overall predictive accuracy of 83%, with a sensitivity of 94% and a specificity of 71%. 215,214

The potential efficacy of individualized chemotherapy selected by in vitro drug sensitivity testing for patients with cancer has been reviewed. 216,215 A number of issues seriously limit the widespread use of this approach in the clinic. First, in vitro drug sensitivity testing is relatively expensive and time-consuming. Second, the efficient procurement of tumor tissue remains a serious problem. In fact, only two studies, both from the National Cancer Institute, have evaluated the ability to obtain tumor tissue from patients with limited- and extensive-stage small cell lung cancer. 217,216 Tumor tissue was obtained from 30% of patients with limited-stage disease, in contrast to nearly 70% of patients with extensive-stage disease. Third, even with successful procurement of tumor tissue, a host of technical issues limits the ability for efficient and successful drug testing. In fact, of 12 different trials reviewed, only slightly more than one-half of all tumor samples had sufficient cell numbers for drug testing. Finally, only one-third of all patients entered in prospective trials of in vitro drug testing were actually treated with an in vitro best regimen. In those patients, the response rates appear to be as good as, and perhaps even slightly better than, those achieved with empiric therapy. It is not surprising, then, that when all the clinical studies are taken together, no potential benefit in survival is observed for this approach. Of note, however, is a survival advantage that has been reported, in a small select series of studies, in patients treated with an individualized in vitro best regimen.

The reliability of newer in vitro assay technologies to identify drug sensitivity suggests that such assays can help the clinician to avoid exposure of patients to the toxicological and immunological chemical. Although the combination of in vitro sensitivity assay has not yet been met, there remains value in identifying inactive agents before their administration and eliminating them from drug combinations. These tests render it possible to tailor drug combinations for the individual cancer patient. They also offer a rational stopping point for both the patient and clinician in situations in which the patient's tumor demonstrates extreme resistance to all conventional anticancer agents. An understanding of when to terminate therapy in hopeless situations is as important as any management issue facing the clinician. Although overexpression of p53 has been extensively evaluated for survival, it is intuitively obvious that there should be a therapeutic advantage in the activity of agents to which a tumor is highly responsive in vitro as compared with agents that demonstrate significant in vitro drug resistance. Further prospective, randomized studies are needed to define more properly the true role of in vitro drug testing in the selection of chemotherapy for cancer patients in the adjuvant, induction, or salvage setting.

Although in vitro tissue culture studies serve as an important guide for selecting chemotherapy, they are inadequate at addressing the issues of tumor cell heterogeneity, drug distribution, drug bioactivation, and host toxicity. In vivo model systems overcome some of these obstacles, and several have been developed, including the subrenal capsule assay, a semipermeable membrane in the Millipore diffusion chamber as vessels for tumor implantation into mice, and the tumor xenograft model, which is perhaps the most widely used method for drug testing. 155,154 However, each of these experimental systems has its unique drawbacks. Recently, a novel system was developed using a semipermeable polysulfone fiber with a molecular weight cutoff of 30 kDa. Human cancer cells derived from tissue culture or from patient tumor specimens are injected directly into semipermeable fibers that are then implanted into immunocompetent rats. Animals are treated with the given drug and, after a defined period, they are sacrificed, the fibers are recovered, and the remaining viable cells are counted using the trypsin dye exclusion method. There are several advantages to this polysulfone fiber model. First, the entire process of tumor recovery, injection, and implantation of fibers, drug treatment, fiber recovery, and cell analysis can be completed in less than 1 week. This short period minimizes the potential waiting time for selection of the optimal drug, thereby rendering this model feasible for application in the clinical setting in treating a patient. Second, the results from this model system are consistent, reliable, and highly reproducible. As many as six to seven fibers can be implanted into an individual rat; thus, each fiber can be injected with the same cell type and the individual rat treated with the same drug. In addition, this reduces the unnecessary expense of using multiple animals for drug in vivo testing. Third, because up to six to seven fibers can be implanted into an individual rat, cancer cells derived from different primary tumors can be tested simultaneously for drug sensitivity, a process that can result in greater cost and time efficiency. Further testing and validation are required to determine whether such a novel in vivo system can help to individualize and optimize the clinical therapy of cancer patients.

Finally, studies by Waldman et al. have raised concerns regarding the validity of the in vitro colony formation assay as a measure of the cytotoxicity of DNA-damaging agents in tumor cells with altered checkpoint response. Using the human colon cancer HCT116 cell line that expresses wild-type p53 and p21 (p21+/+), inactivation of p21 was achieved by chemical introduction in an in vitro sensitivity assay and an in vivo xenograft model. Of note, they observed no differences in sensitivity to ionizing radiation, as determined by the clonogenic assay. In contrast, a significant fraction of the tumors deficient in p21 underwent apoptosis and were thus completely cured. Clearly, the formation of clones is not a consistent predictor of sensitivity, a process that can result in greater cost and time efficiency. Further testing and validation are required to determine whether such a novel in vivo system can help to individualize and optimize the clinical therapy of cancer patients.

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INTRODUCTION

Biologic therapy is cancer treatment that produces antitumor effects primarily through the action of natural host defense mechanisms or the administration of natural mammalian substances. Biologic therapy has emerged as an important fourth modality for the treatment of cancer. Its increased application is the result of a better understanding of the basic aspects of host defense mechanisms against cancer and rapid biotechnologic developments that made molecules available in quantities large enough for use in manipulating biologic processes in vivo. Although this field is still in its infancy, there are many examples of the successful application of biologic therapy to the treatment of human cancers.

BASIC PRINCIPLES OF TUMOR IMMUNOLOGY

Most applications of biologic therapy for cancer have attempted to stimulate immune defense mechanisms. The immune system evolved as a means to detect and eliminate molecules or pathogens that are recognized as “nonself” but not to react to host (self) tissues. Many immunotherapies attempted to cause the tumor to appear more “foreign” compared with normal tissues or to magnify relatively weak host immune reactions to growing tumors.

The immune system differs from most other organ systems because its cells are not in constant contact with each other. They circulate freely throughout the body in and out of the circulatory and lymphatic systems. Immune reactivity involves the integrated action of lymphocytes, monocytes, macrophages, basophils, eosinophils, dendritic cells, endothelial cells, and many other cells throughout the body. Although separate functions have been assigned to these cell types, it is now clear that they interact in many ways and can regulate one another’s activities.

Immune cells secrete two major classes of soluble protein. The first of these lymphocyte products to be recognized was the antibody. Antibodies are a group of proteins composed of one or several units, each of which is composed of two pairs of different polypeptide chains (i.e., heavy and light chains). Each unit possesses two recognition sites, which are capable of combining with the immunizing antigen. The unique bond between antigen and antibody is part of the basis for the exquisite specificity that is the hallmark of immunologic reactivity. The existence of circulating antibodies was first demonstrated in 1890, and until recently, scientific studies of antibodies monopolized the study of immune reactions.

Since the 1970s, it has become clear that selected subpopulations of lymphoid cells can secrete a second (nonantibody) class of protein molecules. These molecules are not biochemically similar to antibodies, are produced in tiny amounts, and are not normally detectable in the circulation. Collectively called cytokines, they represent a new class of hormones with actions on many different target cells within and outside the immune system. Increasing knowledge of a wide variety of cytokines has dramatically altered the understanding of the functions of the immune system and created new possibilities for cancer immunotherapy.

CELLS OF THE IMMUNE SYSTEM

The central cell in immune function is the lymphocyte. Lymphocytes constitute approximately 20% of blood leukocytes and fall into three major classes—B cells, T cells, and null cells—on the basis of ontogeny and function. Basic aspects of modern cellular immunology are presented in Chapter 4. Analysis of cell surface molecules, usually using monoclonal antibodies, revealed substantial heterogeneity in human leukocytes and lymphocytes. In 1982, the First International Workshop on Human Leukocyte Differentiation Antigens was held in Paris to attempt to codify the proliferating number of cell surface determinants detected on leukocytes and the antibodies used to detect them. As a result of the testing of large numbers of antibodies on target cells of many different leukocyte types, cluster analysis permitted the definition of groups of antigens that are similar and those that are clearly different on each type of target cell. This workshop defined the clusters of differentiation (CD), now used to describe cell surface components on leukocytes. A summary of selected CD classifications, the cells on which they are found, and the principal antibodies that are used to detect them as assigned by the Fourth International Workshop in 1989 are shown in Table 18-1.
rapidly expanding as new hormones produced by cells of the immune system are described. A term
thymocyte mitogenic factor, killer cell helper factor costimulator, in Ermatingen, Switzerland, reached a consensus that a variety of lymphokines that had been referred to as
leukocytes”) has been introduced that supplants the acronyms based on functional properties. In 1979, a meeting of the Second International Lymphokine Workshop
homogeneity, and produce large amounts of homogeneous cytokines for detailed study. A new nomenclature referring to cytokines as
cytokines are produced by mononuclear cells of the immune system (usually lymphocytes or monocytes) that have regulatory actions on other cells
Cytokines are soluble proteins produced by mononuclear cells of the immune system (usually lymphocytes or monocytes) that have regulatory actions on other cells
of the immune system or target cells involved in immune reactions. Cytokines produced by lymphocytes are referred to as
lymphokines. Cytokines are true hormones, acting on other cells at a distance from the secreting cells.
substances produced by immune cells are involved in immune function and regulation. These cytokines
lymphocytes produce lymphokine-activating factor and killer cell mitogenic factor. These factors play a role in sensitizing NK cells to the target cell. NK cells must
be sensitized to lyse tumor cells. The most common target for NK cells is the K562 leukemia cell line. NK lymphocytes have little or no ability to kill fresh tumor cells, and their physiologic role as an antitumor effector mechanism is unclear.
Natural killer (NK) cells can lyse selected cultured target cells without a prior sensitizing stimulus. The most common target for NK cells is the K562 leukemia cell line. NK lymphocytes have little or no ability to kill fresh tumor cells, and their physiologic role as an antitumor effector mechanism is unclear.
Lympokinone-activated killer (LAK) cells are lymphocytes that acquire the ability to lyse a broad array of tumor cells after incubation in interleukin (IL)-2. The precursor
of LAK cells is a null lymphocyte, and most mature LAK cells do not bear T- or B-cell markers. However, one subpopulation of LAK cells has been shown to be CD3+, and precursor and effector LAK cells appear to bear the Leu-19 cell surface marker. LAK cells also can lyse normal and malignant cultured lines. LAK cells are capable of lysing most cells that have their membranes perturbed by malignant transformation, culture, or other activation processes.
Activated macrophages also recognize and lyse tumor cells. Although most lymphocyte-mediated lysis can easily be detected in 4 hours, the measurement of
significant macrophage-mediated lysis often requires 48 to 72 hours.
Many of the cytokines secreted by immune cells can mediate toxicity of tissue directly or by the recruitment of other inflammatory processes. For example, tumor
necrosis factor (TNF) can interfere with the blood supply of tumors. Interferon (IFN)-g has an antiproliferative effect on some tumor cells. Many chemotactic and
vascular permeability factors that are involved in inflammatory responses also can indirectly mediate tumor destruction and may play a role in tumor immune
phenomena.
CYTOKINES
Cytokines are soluble proteins produced by mononuclear cells of the immune system (usually lymphocytes or monocytes) that have regulatory actions on other cells
of the immune system or target cells involved in immune reactions. Cytokines produced by lymphocytes are referred to as lymphokines, and cytokines produced by
monocytes are referred to as monokines. Cytokines are true hormones, acting on other cells at a distance from the secreting cells.
It has been known for more than two decades that the soluble substances produced by immune cells are involved in immune function and regulation. These cytokines
were first identified by the function they exhibit in in vitro assays. Lymphokines that inhibited the migration of macrophages were known as migration-inhibition factors, and other factors that activated macrophages were known as macrophage-activation factors. This identification of cytokines on the basis of function led to a confusing situation in which the same molecules were often described by various investigators using different assays for their detection.
Substantial progress in this field resulted from the use of molecular biologic techniques to clone the genes for these cytokines, express them in bacteria, purify them to
homogeneity, and produce large amounts of homogeneous cytokines for detailed study. A new nomenclature referring to cytokines as ILs (meaning “between
leukocytes”) has been introduced that supplants the acronyms based on functional properties. In 1979, a meeting of the Second International Lymphokine Workshop
in Ermatingen, Switzerland, reached a consensus that a variety of lymphokines that had been referred to as T-cell growth factor, thymocyte-stimulating factor,
thymocyte mitogenic factor, killer cell helper factor costimulator, and secondary CTL-inducing factor were all the same molecule and should be referred to as IL-2. The
term IL-2 was adopted to refer to a monocyte product previously called lymphocyte-activating factor. Since that time, many cytokines have been described. This list is
rapidly expanding as new hormones produced by cells of the immune system are described.
Cytokines are proteins or glycoproteins, mostly with molecular weights in the range of 15,000 to 40,000, and many are glycosylated, although it appears that the glycosylation is often not essential for function. In many cases, the cytokines described in mouse and human are structurally related. For example, IL-1α shows a 61% to 65% amino acid homology among human, rabbit, and mouse. Some lymphokines exhibit species specificity; for example, IL-1, IL-2, IL-5, and IL-6 derived from human are active on cells from mouse and human, but IL-3, IL-4, and IFN-γ derived from humans are active only on human cells and not on mouse cells.

Most research on cytokines has involved in vitro studies or animal studies. Many cytokines, such as IFN-α, IFN-β, IFN-γ, IL-2, TNF, and the colony-stimulating factors, have reached clinical application in patients with cancer.

A summary of the major characteristics of IL-1 through IL-18 follows and is taken from S. K. Durum in Principles and Practice of Biologic Therapy of Cancer, S. A. Rosenberg, ed. The characteristics of the IFN and colony-stimulating factors are shown in Table 18-3 and are further discussed in Chapter 20.1 and Chapter 53.4.

### Table 18-3. Interferons, Colony-Stimulating Factors, and Tumor Necrosis Factor, with Their Biologic Activities

#### INTERLEUKIN-1

IL-1 was among the earliest cytokines identified because it has so many potent activities. Many features of the IL-1 system, however, are not particularly representative of cytokines. IL-1 has an unusual mechanism of release from the cells that produce it. The two family members, α and β, are only distantly related but act on the same receptor. It has two dedicated inhibitors that block ligand-receptor interaction. IL-1 is a powerful inducer of inflammatory processes, both local and global, although knockout of the IL-1 system only modestly reduces these processes. Clinically, the main goals have been to block the IL-1 system in inflammatory states, such as rheumatoid arthritis (RA) and septic shock.

#### Proteins

Three members of the IL-1 family exist: α, β, and the receptor antagonist, encoded by a cluster of genes. IL-1α and -β have little homology to one another, but it is accurate to term them both IL-1 because they act on the same receptor. Neither α nor β has a typical signal sequence, and both are released from the producing cell by an unusual mechanism. Mature 17-kD IL-1α is produced from a biologically inactive 31-kD precursor by cleavage with caspase 1. Mature 17-kD IL-1α is also produced by cleavage from a different 31-kD precursor, which is biologically active. The receptor antagonist is produced in two forms by alternative message splicing: one secreted form with a signal peptide and a second intracellular form lacking a signal peptide.

#### Producers

The most prolific IL-1-producing cells are macrophages following stimulation with a variety of microbial products or other agents, including cytokines. Many other cell types, such as keratinocytes, also produce IL-1. The IL-1 promoters are complex, perhaps accounting for the ability of these genes to respond to so many different stimuli in different cell types. In macrophages, the mechanism of IL-1 induction is partly based on the PU-1 transcription factor in cooperation with other nuclear factors. IL-1 production is also regulated by message stability, message translation, and the release mechanism. The receptor antagonist is produced concurrently with IL-1α and -β in many cell types, acting as a natural buffer to the action of IL-1.

#### Receptors and Cellular Response

Two IL-1 binding proteins exist: IL-1RI, which serves all known receptor function, and IL-1RII, which serves as a “decoy” receptor. These genes are also linked to the IL-1 gene cluster in humans, but not in mice. IL-1RI is a member of the “toll” family of receptors. After IL-1 binding, IL-1 receptor accessory proteins, a kinase [IL-1 receptor–associated kinase (IRAK)], and TRAF6, are recruited to the complex. IL-18 receptor forms a similar complex (see Interleukin-18, later in this chapter). MyD88 serves as an adaptor protein, linking IRAK to the receptor complex. Intracellular cascades lead to activation of several types of transcription factors, including nuclear factor κB and AP-1. This results in the induction of many genes, including a number of other inflammatory cytokines, such as IL-6. A wide variety of cell types respond to IL-1. IL-18 signaling has many parallels with that of IL-1.

#### Activities

IL-1 is considered a key mediator of inflammation. It has a broad spectrum of inflammatory activities, including local effects, such as induction of prostaglandins, chemokines, and adhesion molecules. IL-1 also has global effects, such as fever, the acute-phase response, and hypotension. Knockout mice show deficiency in local inflammation and delayed-type hypersensitivity and are resistant to collagen-induced arthritis. The fact that IL-1 deficiency does not eliminate inflammation has been interpreted to mean that other cytokines with overlapping activities, such as TNF and IL-6, are equally important.

#### Clinical Use

Trials were performed in cancer patients with some benefit in preventing thrombocytopenia induced by chemotherapy, but significant toxic side effects, such as hypotension, arrhythmia, and pulmonary-capillary leakage, occurred. Intratymoral injection in mouse cancers has shown promising responses. Blocking IL-1 activity via receptor antagonist, soluble receptors, or newly tailored drugs shows promise in controlling inflammatory diseases, such as RA and septic shock, probably most effectively if combined with blockade of other inflammatory cytokines, such as TNF and IL-6.

#### INTERLEUKIN-2

IL-2 was originally discovered as a growth factor for T cells in vitro and is one of the most extensively studied cytokines. Knockout of IL-2 in mice suggests complex regulatory roles, perhaps in programming T cells for death. The IL-2 receptor complex shares components with receptors for IL-4, -7, -9, and -15. IL-2 has been used clinically for acquired immunodeficiency syndrome, cancer, and for ex vivo expansion of T cells directed against tumors and viruses.

#### Protein

IL-2 is a 15-kD protein, contains one internal disulfide bond, and is a member of a family of cytokines (IL-4, -7, -9, and -15) containing a helices.

#### Producers

IL-2 is produced by T lymphocytes after activation by antigen-MHCs and costimulators on the surface of antigen-presenting cells. The T helper 1 (Th1) subset of
memory T cells retains the capacity to produce IL-2, whereas the Th2 subset loses this capacity, producing IL-4 instead. 21

Receptor and Cellular Response

The IL-2 receptor comprises three chains: a, 22 b,23 and g.24 The b and g chains are members of a cytokine receptor superfamily, whereas the a chain is related to IL-15Ra. The b and g chains are essential for signaling, whereas the a chain increases affinity of the complex for IL-2 but is not required. After binding of IL-2, the Janus kinase Jak3,25,26 associated with the g, chain, phosphorylates tyrosines on the b chain, which serve as docking sites for signal transducers and activators of transcription protein (STAT)3 and -5. The STATs 27,28 are then phosphorylated and translocate to the nucleus, where they serve as transcription factors. Many other intracellular second messenger pathways are also triggered by IL-2 29 and involve ick, syk, ras, phosphoinositide 3 kinase (PI3-kinase), protein kinase C, and Akt. The g chain of the IL-2 receptor is shared by the receptors for IL-4, -7, -9, and -15. Jak3 is also a component of the signaling complex in these receptors.

Activities

The property that led to the discovery of IL-2 was its induction of activated T-cell proliferation. 22 Thus, IL-2 is widely used for propagating T-cell lines. Knockout of IL-2 in mice,30 however, resulted in excessive, uncontrolled T-cell proliferation, leading to the concept that IL-2 is not essential for growth in vivo, but is essential for programming T cells to die. Other activities of IL-2 include stimulation of cytotoxicity in NK and T cells and acting as a cofactor in activating macrophages and B cells.

Clinical Use

IL-2 has been used clinically in several ways (see Chapter 20.2). Treatment of malignant melanoma renal cell carcinoma has shown efficacy. 31 A significant side effect of IL-2 is the vascular leak syndrome. 22 IL-2 has been used for ex vivo expansion of LAK cells, tumor-infiltrating T cells, 32 and antiviral T cells, 33,34,35 and 36 which are then returned to the patient. Anti–IL-2 receptor shows promise in blocking rejection of organ transplants. 37

INTERLEUKIN-3

IL-3 is produced by activated T cells and induces hematopoiesis. Its receptor shares components with IL-5 and granulocyte-macrophage colony-stimulating factor (GM-CSF). It is used clinically to sustain explanted hematopoietic stem cells before reinfusion.

Proteins

IL-3 38,39 is linked to IL-4, -5, -9, and -13 in humans.

Producers

Activated T cells are the major producers of IL-3. 39 Activated mast cells are also producers.

Receptors

Two chains that compose the IL-3 receptor exist in humans: IL-3Ra 40 and IL-3Rbc. 41 which are shared by the receptors for GM-CSF and IL-5. In the mouse, two different b chains exist. Both a and b are members of the cytokine receptor superfamily. Cross-linking of the a to the b chain triggers receptor activation. 22 The nature of this cross-linking process is thought to resemble that of the IL-2 and IL-4 receptors, in that the ligand directly binds one chain with intermediate affinity. The second receptor chain, which cannot bind ligand on its own, then recognizes some features of the complex formed by the ligand and the other receptor component. Jak2 is associated with the b chain42 and activates STATS. 43 A number of other second messenger pathways are also activated. 44 The cellular response includes survival, such as the pathway leading to disposal of BAD, the proapoptotic protein. 45,46

Activities

IL-3 stimulates production of macrophages, granulocytes, erythrocytes, and megakaryocytes from primitive pluripotent stem cells. Knockouts indicate that IL-3 is not required during normal hematopoiesis, indicating its importance probably lies in the hematopoietic stimulation during immune responses. Mature myelomonocytic-lineage cells also react to IL-3.

Clinical Use

IL-3 has been tested extensively for a variety of potential clinical uses. 47 In individuals with normal hematopoiesis, IL-3 treatment increased platelets, reticulocytes, and leukocytes and showed only mild side effects. 47 To increase hematopoiesis, IL-3 has been tested in myelodysplastic syndrome, aplastic anemia, Diamond-Blackfan anemia, chemotherapy, bone marrow transplantation, and stem cell mobilization. Although responses were observed, it has not been adopted as a therapeutic agent. IL-3 is widely used, however, as part of a cytokine cocktail to sustain hematopoietic stem cells ex vivo for treatment after radiation or chemotherapy (i.e., promoting introduction of recombinant constructs for gene therapy). 47,48

INTERLEUKIN-4

IL-4 is an important cofactor in B-lymphocyte activation, particularly for production of immunoglobulin E (IgE). One type of IL-4 receptor incorporates g chain, as do IL-2, -7, -9, and -15. IL-4 is closely related to IL-13 and can share some receptor components and signaling pathways. IL-4 is critical in directing activated T cells into the Th2 pathway. Overproduction is implicated in atopy.

Proteins

IL-4 36,38,49 and 50 is 20 kD, with six cysteines involved in intrachain disulfide bonds, and forms four a helices. The human IL-4 gene is found in a cluster together with genes for IL-3, -5, -9, and -13.

Producers

Several types of T cells produce IL-4 after activation by antigen-MHC complexes and costimulators on the surface of antigen-presenting cells. 22 IL-4 is a key member of the spectrum of cytokines produced by Th2 T cells. In mice, CD4 T cells that express NK1 are also producers, as are a subset of CD8 T cells. Mast cells and basophils also produce IL-4. 51 The induction of Th2 cell development is dependent on IL-4 produced by T cells themselves. 52 Production of IL-4 requires the transcription factor GATA3 53 and, possibly, c-maf. 54

Receptors

The primary binding chain, IL-4Ra, 55 forms two types of receptor complexes: IL-4Ra + g and IL-4Ra + IL-13Ra. 56 These receptor chains are members of the cytokine receptor superfamily. IL-4 first binds to IL-4Ra; g is then recruited to the complex. The Janus kinase Jak3, bound to the intracellular domain of g chain, is required for many, but not all, IL-4 effects. 57 STAT6 is required for IL-4 signaling. 58 IRS-1 is an important adaptor molecule, coupling the receptor to second messenger pathways other than the Jak-STAT pathway. 59,60

Activities
IL-4 was discovered as a growth factor for preactivated B cells and induces class II MHC expression on B cells. In macrophages, it suppresses production of inflammatory cytokines and it has effects on endothelial cells and fibroblasts. Knockout mice show major defects in Th2 cell generation and in IgE production, suggesting that the selective value of IL-4 may be immunity against parasitic infections.

Clinical Use

An overactive IL-4 pathway appears to be one component of atopy. Therefore, IL-4 presents a therapeutic target for allergy. IL-4 itself could be used to divert immunity away from autoimmune or inflammatory directions.

INTERLEUKIN-5

IL-5 induces production of eosinophils during immune responses, which probably contributes to protection against some kinds of parasites. It shares a receptor component with IL-3 and GM-CSF.

Proteins

IL-5 consists of two bundles, each with four a helices.  It is genetically linked to IL-3, -4, -9, and -13 in humans.

Producers

IL-5 is produced by activated Th2 cells, as well as mast cells and eosinophils.

Receptors

The receptors for IL-5 consist of two chains: IL-5Ra and IL-5Rb, which is shared by the receptors for GM-CSF and IL-3. Both chains are members of the cytokine receptor superfamily. Cross-linking principles are similar to IL-3, as are the ensuing Jak2-STAT5 pathways and other second-messenger pathways.

Activities

IL-5 was initially identified as a T-cell factor that induced production of eosinophils. Knockout of IL-5 eliminated the eosinophilia induced by helminth infection, whereas baseline production of eosinophils was normal. IL-5 also promotes local accumulation and sustains the life span and function of eosinophils in tissues, such as the lung and bowel. Evidence exists that IL-5, presumably via its eosinophil activities, contributes to protection from helminth infections.

Clinical Use

IL-5 has long been implicated in allergic asthma. Efforts are therefore being made to develop IL-5 antagonists.

INTERLEUKIN-6

IL-6 is a key inflammatory mediator produced by many cell types. It is the major inducer of the acute-phase response and fever. IL-6 receptor shares the gp130 chain with several other cytokine receptors.

Proteins

IL-6 is a glycoprotein of 21 to 28 kD.

Producers

IL-6 is produced after stimulation by many cell types, including T and B lymphocytes, macrophages, fibroblasts, and endothelial cells.

Receptors

Two components of the IL-6 receptor exist: a ligand-specific a chain and a signal-transducing gp130 chain, which is shared by receptors for GM-CSF and IL-3. Both chains are members of the cytokine receptor superfamily. Cross-linking principles are similar to IL-3, as are the ensuing Jak2-STAT5 pathways and other second-messenger pathways.

Activities

IL-6 was originally characterized based on its activity in inducing Ig synthesis by activating B cells. Knockout of IL-6 showed defects in a number of inflammatory processes, including production of acute-phase reactants and bone loss after estrogen depletion. Fever responses depend on IL-6. Hematopoietic defects were also found in IL-6 knockout mice.

Clinical Use

Blocking IL-6 may alleviate RA and may also be effective in other autoimmune, inflammatory, and bone-erotic diseases. In mice, IL-6 is required for development of oil-induced plasmacytomas and is involved in tumor cachexia. In humans, IL-6 is a growth factor for myelomas, suggesting further applications of IL-6 blockers.

INTERLEUKIN-7

IL-7 is produced by stromal cells and is essential for T lymphopoiesis, partly because of a survival or “trophic” effect, a partial role in VDJ recombination. This is the pathway deficient in X-linked, severe combined immunodeficiency in humans. IL-7 also has trophic effects on mature T and B lymphocytes and is therefore potentially useful in the clinic as an adjuvant.

Proteins

IL-7 is a 25-kD protein predicted to contain four a helices and an internal disulfide bond. After secretion, it binds to extracellular matrix via a glycosaminoglycan-binding site, which could be the form encountered by developing thymocytes.

Producers

Unlike most ILs, IL-7 is produced constitutively by nonhematopoietic cells. In the thymus, the IL-7 producer resembles the cortical epithelial cell. In bone marrow, the producer is a reticular stromal cell. Other sources include the intestine, skin, and follicular dendritic cells.
Receptors

The primary binding chain for IL-7 is IL-7RA. The IL-7–IL-7RA complex then recruits g-c chain bearing Jak3 to the complex. TSLP, a homologue of IL-7, also binds the IL-7RA chain but does not recruit g-c and Jak3. Jak1 and a number of other kinases are induced, including PI3-kinase. STAT3 and -5 partly mediate the nuclear effects. Because g-c is also a component of the receptors for IL-2, -4, -9, and -15, some similarities appear to exist in the signal transduction pathways.

Activities

IL-7 was discovered based on its activity in inducing proliferation of murine pro-B cells. B-cell development depends on IL-7 in mice, but not in humans. Normal T-cell development requires IL-7 based on the knockout phenotypes for IL-7 and its receptor, which show a severe block at an early stage in T-cell development. A related block is seen in X-linked, severe combined immunodeficiency in humans, which is in g-c, a component of the IL-7 receptor. This requirement for IL-7 is partly attributed to its trophic activity on lymphoid progenitors and its promotion of VDJ recombination. In mice, the g-s lineage is particularly dependent on IL-7, perhaps not only during thymic generation, but also for survival in the intestine and skin. Pharmacologic activity of IL-7 has been observed in mice, inducing increases in B and T cells. Overexpression of IL-7 in mice can induce lymphomagenesis. In human skin, IL-7 may provide trophic support for the survival of lymphoma cells.

Clinical Use

IL-7 is a potential cytokine in the treatment of T-cell deficiencies, infectious diseases, and some neoplasms. Normal T-cell growth role should be ascribed to IL-9, because normal T cells have not been found to proliferate in response to it until after 10 days or so of prior in vitro stimulation. Some transformed T cells, however, can respond to IL-9.

INTERLEUKIN-8

IL-8 induces chemotaxis and activation of neutrophils. It is one of the chemokines, a large group of chemotactic cytokines. IL-8 signals through seven transmembrane G protein–coupled receptors that are related to other chemokine receptors.

Proteins

IL-8 is a 6- to 8-kD glycoprotein containing two intrachain disulfide bonds. At high concentrations, IL-8 homodimerizes via hydrogen bonding. It is presented to neutrophils on endothelial cell surfaces. IL-8 was the first to be discovered of the family of cytokines known as chemokines. More than 50 members have been identified; only IL-8 has the IL-8 terminology. IL-8 is one of a subgroup termed CXC chemokines and is linked to a group of these genes. Mouse lacks a close homologue to human IL-8. It is thought that IL-8's inflammatory roles are fulfilled in mice by other chemokines using the same receptor.

Producers

Many cell types produce IL-8 after stimulation with lipopolysaccharide, IL-1, or TNF, including macrophages, endothelial cells, and keratinocytes.

Receptors

Two functional IL-8 receptors exist: CXCR1 and CXCR2. They are both members of the seven-transmembrane family of receptors that includes rhodopsin. These receptors also respond to other chemokines. The two receptors induce some overlapping and distinct responses. Receptors are coupled to G proteins, including Gq2a, which trigger downstream events involving phospholipase C, diacylglycerol, inositol triphosphate, release of calcium from intracellular stores, RhoA, and the ras pathway.

Activities

IL-8 induces neutrophil chemotaxis, respiratory burst, and degranulation. In rabbits, blocking IL-8 with antibodies has potent inhibitory effects on some inflammatory processes, particularly in the lung. Knockouts in mice cannot directly address IL-8 function because no close IL-8 homologue exists in mice. Mice lack CXCR1. Knockout of the receptor CXCR2, however, greatly affects neutrophil attraction to inflamed peritoneum, which establishes that chemokines are involved in neutrophil accumulation in vivo. IL-8 also induces angiogenesis.

Clinical Use

Increased IL-8 is detected in a variety of human clinical conditions, ranging from myocardial infarction to RA, and suggests potential applications for IL-8 blockers. In rabbits, a number of studies have shown that anti–IL-8 inhibits inflammation of various tissues. Despite the numerous chemokines that exist, blocking IL-8 alone can be sufficient.

INTERLEUKIN-9

IL-9 is related to IL-2, -4, -7, and -15 and has some overlapping activities based most likely on sharing some receptor components. It is produced by T cells and acts on lymphocytes and mast cells. It may be involved in Hodgkin's disease and lymphoma.

Proteins

IL-9 is predicted to have an a-helical topology like IL-2, -4, -7, and -15. The human IL-9 gene is found in a cluster together with genes for IL-3, -4, -5, -9, and -13. This does not apply to mice. Ten cysteines exist, implying extensive intrachain disulfide bonding, heavy N-linked glycosylation, and a high isoelectric point (approximately ten).

Producers

Memory helper T cells produce IL-9 after activation. This induction involves a cascade of cytokines, including IL-2, -4, and -10, eventually leading to IL-9 production. Murine Th2 clones are producers.

Receptors

The IL-9 receptor a chain is a member of the hematopoietin superfam. In humans, the IL-9 receptor a chain is unusual because it is encoded on chromosomes X and Y. Four IL-9Ra pseudogenes also exist. The receptor complex shares the g-c chain with receptors for IL-2, -4, -7, and -15. After receptor ligation, Jak3 (g-c-associated) and Jak1 (IL-9Ra–associated) increase their tyrosine kinase activity, phosphorylating the IL-9Ra chain, adaptor protein IRS-1, and transcription factors STAT1, -3, and -5.

Activities

IL-9 was discovered as a growth factor for T-cell clones and independently as a growth factor for mast cell lines. It is not clear, however, whether a normal T-cell growth role should be ascribed to IL-9, because normal T cells have not been found to proliferate in response to it until after 10 days or so of prior in vitro stimulation. Some transformed T cells, however, can respond to IL-9, and human T-cell leukemia–transformed T cells produce it, overexpression of IL-9 as a transgene induced T-cell transformation, suggesting possible autocrine function. This was also suggested for Hodgkin's disease. Mast cells and eosinophils, B...
lymphocytes, and hematopoietic stem cells also respond to IL-9. Because its receptor is a member of the g family, overlapping activities are expected to be present with other cytokines in this group.

Clinical Use
No extensive preclinical data on IL-9 are available. The possibility that it has autocrine activity in Hodgkin's disease and T lymphomas suggests potential uses for IL-9 antagonists.

INTERLEUKIN-10
IL-10 is a powerful inhibitor of inflammatory and immune responses, partly via its inhibition of some macrophage functions. It is produced by Th2 cells. Its receptor is related to IFN receptors.

Proteins
Human IL-10 is an 18-kD monomer with little glycosylation and two presumed intrachain disulfide bonds.

Producers
Activated Th2 cells were the originally described IL-10 producers. Other cell types, including macrophages and keratinocytes, however, also produce IL-10. Epstein-Barr virus encodes an active IL-10 homologue.

Receptors and Cellular Response
The first identified component of IL-10 receptor is related to the IFN receptors. It is expressed by many types of hematopoietic cells. In mice, a second receptor component, CRF2-4, has been identified, which is related and linked to the IFN receptors. Jak1 and Tyk2 are activated by IL-10. STAT3 mediates some downstream effects in macrophages.

Activities
IL-10 was originally discovered and cloned as an inhibitor of the ability of Th1 cells to synthesize IFN. This inhibition occurs largely via effects on antigen-presenting cells, such as macrophages, especially by inhibiting their IL-12 production. Other macrophage functions also are inhibited, such as synthesis of inflammatory cytokines (i.e., IL-1, IL-6, IL-8, and TNF) and phagocytosis. IL-10 knockout mice show extensive pathology, particularly in the gut, which is thought to arise from unattended immune responses to gut flora. Receptor knockout mice have similar pathology.

Clinical Use
IL-10 has been shown to inhibit some lipopolysaccharide-induced inflammatory responses in humans. Clinical trials are under way in inflammatory bowel disease, RA, thoracic-abdominal aortic surgery, acute lung injury, multiple sclerosis, psoriasis, and human immunodeficiency virus infection. Evidence exists that the Epstein-Barr virus IL-10 homologue acts as an autocrine in B lymphomas, suggesting benefit in blocking IL-10.

INTERLEUKIN-11
IL-11 is a mesenchymal cell product with activity on hematopoietic cells. IL-11 has been used to promote hematopoiesis in patients. IL-11 receptor shares the gp130 component with IL-6, LIF, OSM, CNTF, and CT-1. IL-11 is required for embryonic implantation in the uterus.

Proteins
IL-11 is a 19-kD protein with no intrachain disulfide bonds. IL-11 is slightly homologous to IL-6, OSM, and LIF.

Producers
IL-11 is produced by a variety of mesenchymal cells, including keratinocytes, chondrocytes, osteoblasts, fibroblasts, and bone marrow stromal cells.

Receptors and Cellular Response
The IL-11 receptor includes a ligand-specific a chain and gp130, which is common to IL-6, LIF, OSM, CNTF, and CT-1. Two alternative a chains exist in the mouse. The ligand-binding chains of this family do not contribute to signaling, which is wholly performed by gp130. Thus, the intracellular cascades should be the same for all members (gp130 signaling is discussed in Interleukin-6, earlier in this chapter). As in the IL-6 system, soluble IL-11 receptor can capture its ligand and then associate with cell-bound gp130 and signal.

Activities
IL-11 was originally discovered and cloned as a growth factor for a plasmacytoma line. It stimulates multilineage hematopoiesis when administered to mice and humans and is particularly effective in stimulating thrombopoiesis by inducing production of megakaryocytes. Knockout of the major receptor did not show a requirement in hematopoiesis but revealed an IL-11 requirement in the uterine response to implantation.

Clinical Use
Trials performed in breast cancer patients show that IL-11 can significantly restore suppressed hematopoiesis and alleviate thrombocytopenia induced by chemotherapy. In mice, IL-11 also protects intestinal cells from damage induced by chemotherapy and radiotherapy.

INTERLEUKIN-12
IL-12 is produced by antigen-presenting cells. IL-12 promotes Th1 cell development and IFN production. It is required for development of some types of autoimmunity in mice.

Proteins
IL-12 is a heterodimer consisting of disulfide-linked 35-kD and 40-kD subunits encoded by distinct genes. Both subunits are glycosylated and have intrachain disulfide bonds. Homodimers of p40 also are observed and, in mice, have receptor-antagonist activity. This does not apply to humans.

Producers
Macrophages, B lymphocytes, and dendritic cells are major producers of IL-12. In macrophages, this synthesis is stimulated by microbial products and during contact with T cells via CD40L-CD40 interaction. The two IL-12 chains associate intracellularly before secretion. The p35 subunit is expressed by a much wider range of
cell types than the p40 subunit. 105, 176

Receptors and Cellular Response

Two components comprise the IL-12 receptor, the b1 and b2 chains. 171, 177 Th2 cells fail to respond to IL-12 because they lack the b2 chain. 179 Many protein kinases are triggered by the IL-12 receptor, including the Janus kinases tyk2 and Jak2, 170 which are associated with the b1 and b2 chains, respectively. 171 STAT3, STAT4, and IRF-1 are implicated in gene induction by IL-12. 173, 177

Activities

IL-12 was discovered as one factor promoting CTLs and as an independent factor for promoting NK cells. These activities include proliferation, differentiation, and cytokine secretion, especially of IFN. The IFN-g–inducing activity of IL-12 is cofactor, such as with IL-18 (see Interleukin-18, later in this chapter). IL-12 knockout mice showed greatly suppressed IFN production and revealed a requirement for IL-12 in development of Th1 cells in some settings but not in others. 179

Clinical Use

IL-12 has been tested in cancer patients in phase 1 trials with no major toxicity other than a decrease in circulating lymphocytes, which, nevertheless, showed increased activity. 180 In preclinical studies, antitumor activity of IL-12 was detected, 181 and increased effects were seen in combination with a pulse of IL-2. 182 In mice, IL-12 is a required component of some types of autoimmunity in tissues, including the bowel, joint, eye, pancreas, and central nervous system. 182

INTERLEUKIN-13

IL-13 is a T-cell product closely related to IL-4 and shares a receptor component. It elicits a subset of IL-4 responses and is implicated in Th2 cell generation and IgE synthesis. IL-13 is antiinflammatory. 185

Proteins

IL-13 is a 12-kD protein, and it is structurally related to IL-4, although the homology is low. 183 The gene is clustered together with IL-3, -4, -5, and -9.

Producers

IL-13 is expressed in Th2 cells after activation by antigen-MHC complexes and costimulators on the surface of antigen-presenting cells. Unlike IL-4, IL-13 expression is not strictly repressed in Th1 cells. IL-13 also is produced by dendritic cells.

Receptors and Cellular Response

The IL-13 receptor is comprised of IL-13Ra together with IL-4Ra. The same receptor complex also responds to IL-4. Two homologous IL-13Ra chains exist with different affinities for IL-13 in the absence of IL-4Ra: a high-affinity a2 chain 187 and a low-affinity a1 chain. 186 Receptors are expressed on monocytes, macrophages, eosinophils, basophils, mast cells, keratinocytes, and endothelial cells. Human B cells express the receptor, whereas mouse B cells do not. T cells have not been found to express receptors or respond to IL-13. Jak1 and Tyk2 are activated by receptor ligation. Unlike IL-4, Jak3 is not activated, 188 because it is associated with g0, which is not part of this receptor complex. STAT6 is phosphorylated and accounts for one set of responses, whereas IRS-2 is phosphorylated and initiates other second-messenger pathways.

Activities

Knockout of IL-13 revealed a requirement in Th2 development, which is perhaps indirect given the lack of receptors on T cells. IL-13 induces a subset of IL-4 effects, including effects on human B cells and macrophages, but not T cells. No apparently unique IL-13 effects have been noted. IL-13 activities include inducing IgE synthesis in human B cells. Whereas an IL-4 requirement for B cells to produce IgE was verified by IL-4 knockout, the same logic cannot be applied to IL-13. IL-13 is expressed in T cells after activation by antigen-MHC complexes and costimulators on the surface of antigen-presenting cells. Unlike IL-4, IL-13 expression is not strictly repressed in Th1 cells. IL-13 also is produced by dendritic cells.

Clinical Use

The induction of IgE synthesis implicates blocking the IL-13 pathway as a potential target in atopy. Other applications are suggested by IL-13 inhibiting inflammatory processes in mice. 188

INTERLEUKIN-14

Difficulties have occurred in reproducing the original observations regarding IL-14 and are therefore not discussed.

INTERLEUKIN-15

IL-15 resembles IL-2 in its activities on T cells and shares some receptor components with IL-2. It is essential for NK cell development. Unlike IL-2, the IL-15 gene is expressed by many cell types, but little protein is produced.

Proteins

IL-15 is a 15-kD glycoprotein with two internal disulfide bonds. IL-15 is predicted to fold into a four-part a helix structure like IL-2 and IL-4. It is genetically linked to IL-4, -5, and -9.

Producers

Unlike most of the ILs, many cell types constitutively transcribe the IL-15 gene. However, considerable constraints on translation imposed by the 5' and signal peptide region of the message exist. 189

Receptors and Cellular Response

The IL-15 receptor shares the b and g0 chains with the IL-2 receptor 185 but uses its own unique a chain that is expressed on more cell types than the IL-2Ra chain. 185 Mast cells appear to have a different receptor. 189 Jak1 and -3, and STAT3 and -5 are activated by the receptor in T cells, whereas Jak2 and STAT5 are activated in mast cells.

Activities

IL-15 was discovered as a T-lymphocyte growth factor activity. NK cell development can be induced by IL-15. 189 The knockout of IL-15Ra verified its requirement for NK development. 189 Mast cells also respond to IL-15, as do mature T and B lymphocytes, which are also deficient in knockouts.
Clinical Use

IL-15 has not been tested clinically. It may find use in boosting innate or T-cell immunity, or in ex vivo expansion of NK and T cells before reinfusion. Antagonists could be immunosuppressive.

INTERLEUKIN-16

IL-16 is a product of CD8 T cells that has activities on CD4 cells, including chemotaxis. It is implicated in airway inflammation in asthma.

Proteins

IL-16 is the C-terminal 17-kD peptide cleaved from a larger nonglycosylated precursor by caspase. IL-16 lacks a typical signal peptide and is therefore released from cells by an atypical process. It is not homologous or linked to other cytokines, has an unusual protein structure with a PDZ domain otherwise found in intracellular proteins, and aggregates in solution.

Producers

IL-16 is constitutively transcribed and translated by CD8 T cells. Release of the active form is then induced by stimuli, such as T-cell antigen cross-linking, histamine, and serotonin. Other producers include eosinophils and airway epithelial cells.

Receptors and Cellular Response

IL-16 binds to CD4, which it appears to cross-link, inducing signaling. The second messenger pathway does not require Ick, which is associated with CD4. Implications of PI3-kinase and protein kinase C involvement exist.

Activities

IL-16 was discovered based on chemotactic activity for CD4 T cells. It is also chemotactic for monocytes and eosinophils. IL-16 induces G_s to G_t transition in CD4 T cells, but not entry into S phase, which can be induced by IL-2. IL-16 inhibits the activation of T cells induced by the T-cell receptor, perhaps by sterically inhibiting CD4 interaction with class II MHC. It inhibits human immunodeficiency virus replication, not through competing with entry via CD4, but through the human immunodeficiency virus promoter.

Clinical Use

IL-16 has been implicated as the attractant for CD4 T cells in asthmatic inflammation of airways in humans, suggesting uses for antagonists. It could possibly be used to induce T-cell blast transformation.

INTERLEUKIN-17

IL-17 is a product of memory T cells, with inflammatory, immunologic, and hematopoietic activities. IL-17 and its receptor bear little resemblance to other genes, although they do bear resemblance to the IL-17 homologue in a herpesvirus.

Proteins

IL-17 is a 17-kD peptide that can dimerize via disulfide bridges.

Producers

IL-17 is produced by activated T cells, particularly the memory CD4 subset. The gene was captured by Herpesvirus saimiri, whose product is biologically active.

Receptors and Cellular Response

One IL-17 receptor chain has been identified that bears remarkably little resemblance to other receptor types and results in nuclear factor kB activation. This receptor chain is expressed on many different cell types.

Activities

IL-17 was discovered as a complementary DNA (cDNA) of unknown function, homologous to a sequence in a herpesvirus also of unknown function. It has been shown to trigger several types of responses in cells, including IL-6 and IL-8 induction in fibroblasts. It also has induced production of hemopoietic cytokines and neutrophils in bone marrow cultures and in vivo. Blocking IL-17 suppresses T-cell proliferative responses. This result may partly be because IL-17 promotes dendritic cell differentiation. This, in turn, may explain how blocking IL-17 prolonged allografts in mice. Preliminary IL-17 receptor knockout data have not shown gross abnormalities.

Clinical Use

IL-17 appears to promote immune and inflammatory responses. Thus, blocking its activity in humans could be immunosuppressive, as it is in mice.

INTERLEUKIN-18

IL-18 was discovered based on its induction of IFN-g synthesis. Its own structure and that of its receptor system resemble IL-1. It promotes Th1 activities, inhibits Th2 activities, and induces macrophages to produce inflammatory cytokines.

Protein

IL-18 is a member of the IL-1 family. Like IL-1b, IL-18 is synthesized as a biologically inactive proform, which is cleaved by caspase 1, generating the active mature form.

Producers

Kupffer cells were the source that led to the cloning of murine IL-18. Blood and tissue macrophages are avid producers, but unlike most cytokines, IL-18 production and release do not require stimulation of the macrophage. Keratinocytes also produce IL-18 constitutively.

Receptors and Cellular Response

The organization of the cellular receptors for IL-18 is remarkably similar to that of IL-1. IL-18 initially associates with a binding chain, which is encoded near IL-1.
Several techniques for cloning tumor antigens recognized by CD8+ cells and presented on MHC class I have been developed and are presented in lymphocytes, respectively, appear to be important in mediating immune destruction.

Attempts to apply the insights gained from increasing knowledge of cellular immunology to the development of effective immunotherapies for patients with cancer fall effectively demonstrated tumor antigens on animal tumors. Attempts to detect human tumor antigens have relied almost exclusively on the availability of the nucleus and is necessary to maintain the malignant phenotype of these tumor cells.

In most animal studies of tumor immunity, tumor antigens are detected in experiments in which animals are immunized and then challenged with the same tumor.

Clinical Use

Possible clinical uses based on animal studies include giving IL-18 to promote IFN-γ production during viral or mycobacterial infections. IL-18 may combat allergy or asthma. Antagonizing IL-18 (i.e., by using the decoy receptor) could have antinflammatory uses.

**TUMOR ANTIGENS**

**IMMUNE RESPONSE TO TUMORS IN RODENTS**

Early attempts to identify tumor antigens in mouse models by immunizing mice with spontaneous or carcinogen-induced tumors were confused by the immune reactions that arose to normal transplantation antigens present on tumors. The development of inbred mouse strains made it possible to differentiate tumor antigens from normal histocompatibility antigens and led to the first demonstrations that tumors did contain unique tumor-associated antigens on their surface.

In 1943, Gross demonstrated that the intradermal immunization of inbred mice against a methylcholanthrene-induced sarcoma could result in immunization of that mouse against subsequent tumor challenge. These findings encouraged studies of the nature of the immune response to transplantable tumors in inbred mice, which demonstrated that tumor-specific antigens did exist in a variety of murine tumors. These tumor antigens could not be detected in the normal tissues of mice, as demonstrated by studies showing that immunization with tumor cells did not immunize mice against normal tissue grafts from the mouse donating the tumor.

In no inbred strain of mice does the spontaneous incidence of tumors bear any relation to the incidence of tumors in the same mouse do not cross-react. The sharing of antigens on tumors induced by RNA and DNA viruses has facilitated the study of the biologic and molecular nature of these antigens. For example, studies performed with simian virus 40–induced tumors identified the large T antigen, which is expressed primarily in the nucleus and is necessary to maintain the malignant phenotype of these tumor cells. Similarly, the polyomavirus has a middle T antigen and small T antigen localized in the nucleus that can be detected by serologic tests. These tumor-associated antigens were found on a variety of tumors induced with chemical or physical carcinogens and on spontaneous tumors.

Tumors induced by chemical carcinogens appear to have limited cross-reactivity, as evidenced by immunization-challenge experiments: Even two sarcomas induced in the same mouse do not cross-react. The sharing of antigens on tumors induced by RNA and DNA viruses has facilitated the study of the biologic and molecular nature of these antigens. For example, studies performed with simian virus 40–induced tumors identified the large T antigen, which is expressed primarily in the nucleus and is necessary to maintain the malignant phenotype of these tumor cells. Similarly, the polyomavirus has a middle T antigen and small T antigen localized in the nucleus that can be detected by serologic tests. These tumor antigens could not be detected in the normal tissues of mice.

In animal studies of tumor immunity, tumor antigens are detected in experiments in which animals are immunized and then challenged with the same transplantable tumor. Lack of growth of a tumor challenge after immunization is taken as evidence for the existence of tumor antigens. In vitro assays involving reactivity of the tumor cell with antibodies or immune cells can also provide evidence for the existence of tumor antigens. Although tumors induced by high doses of chemical carcinogens or by viruses often exhibit high levels of immunogenicity in mice, it has been thought that spontaneous murine cancers are far less immunogenic. The ability to detect tumor-associated antigens depends on the method used, and as more sensitive methods for detecting tumor antigens are developed, unsuspected antigens are likely to be observed.

A significant difference exists in the nature of the antigens recognized by humoral and cellular detection systems. Humoral antibodies detect specific epitopes on antigenic molecules, and it is the interaction of these molecules with the variable region of the antibody that produces recognition. In contrast, antigens recognized by T-cell receptors recognize processed peptides on the surface of the tumor cell or on an antigen-presenting cell in conjunction with MHC molecules. CD4+ lymphocytes recognize small peptides bound to MHC class II molecules, and CD8+ cells recognize peptides attached to class I molecules. Monoclonal antibodies are not capable of detecting the small processed peptides on MHC molecules on the cell surface, and the nature of the antigens recognized by humoral and cellular immune responses are therefore very different.

Tumor-infiltrating lymphocytes (TILs) provide a valuable reagent for detecting cellular immune responses to tumor antigens, revealing unique tumor antigens on a variety of methylcholanthrene-induced sarcomas in inbred mice. TILs can recognize tumor antigens based on direct lysis of tumor cells or by the specific release of cytokines such as IFN-γ, GM-CSF, or TNF-α when the TILs are cocultured with the specific tumor. These TILs are derived from animals bearing established tumors and may differ from the cellular immune responses that are detected in animals that are highly immunized against the tumor as a result of artificial manipulations.

The detection of tumor antigens on human cancers presents unique problems because of the inability to use the immunization-challenge experiments, which have so effectively demonstrated tumor antigens on animal tumors. Attempts to detect human tumor antigens have relied almost exclusively on the availability of in vitro assays that could detect humoral or cellular immune responses.

**IDENTIFICATION OF HUMAN CANCER ANTIGENS RESTRICTED BY CLASS I MAJOR HISTOCOMPATIBILITY COMPLEX AND RECOGNIZED BY CD8+ T CELLS**

Attempts to apply the insights gained from increasing knowledge of cellular immunology to the development of effective immunotherapies for patients with cancer fall into three main areas: (1) The identification of antigens on human cancers that are capable of mediating immune responses, (2) the development of techniques for effective immunization of humans using tumor antigens, and (3) overcoming obstacles that enable the tumor to escape antitumor immune responses. Significant progress has been made in the identification of human tumor antigens, and extensive efforts to develop effective means of immunizing patients have begun. Although substantial progress has been made, the clinical impact of these advances is still limited.

Much experimental evidence points to the importance of cellular immune reactions in mediating the regression of established tumors. Thus, considerable effort has been devoted to identifying human cancer antigens that elicit cellular immune responses. Both class I and class II restricted antigens, mediated by CD8+ and CD4+ lymphocytes, respectively, appear to be important in mediating immune destruction.

Several techniques for cloning tumor antigens recognized by CD8+ cells and presented on MHC class I have been developed and are presented in Table 18-4. Most class I-restricted antigens have been identified by screening cDNA libraries from tumor using MHC class I–restricted T cells to identify the relevant transfectants. Alternatively, peptides have been eluted from tumor cells, pulsed onto target cells bearing the appropriate MHC class I antigen, and then tested by using the MHC class I–restricted T cells to identify the appropriate peptide fractions. By obtaining partial sequences from cDNA libraries or from eluted peptides, it has been possible to identify a variety of class I–restricted tumor antigens.
Both of these approaches, however, depend on the ability to generate T cells capable of recognizing antigens presented on the surface of tumor cells. It is often difficult to generate these T cells in vitro, and thus a third approach, commonly referred to as reverse immunology, has been used. This approach attempts to determine whether candidate antigens, presumed to have a high likelihood of being tumor antigens based on their biologic characteristics, are actually presented on tumor cells. Class I–restricted T cells that work against these candidate antigens are raised by in vitro sensitization techniques. A variety of techniques have been developed, including the use of protein-pulsed or transfected antigen-presenting cells, or in vitro sensitization against synthetic peptides from the candidate antigen. If MHC class I–restricted T cells can be raised by these in vitro sensitization techniques, then the T cells are tested for the ability to recognize tumor cells and thus confirm the ability of these putative antigens to act as immunotherapeutic targets.

By making use of these approaches, a variety of cancer antigens restricted by MHC class I and recognized by CD8+ T cells have been derived (Table 18-5). The first cancer antigens to be described were shared cancer-testes antigens. These antigens are present on a subset of patients with a variety of tumor types and appear to be expressed on cells in the testis but not on other normal cells. Several families of these cancer-testes antigens have been described and are presented in Table 18-6.

Another major class of tumor antigens are the shared melanocyte-differentiation antigens (see Table 18-5). These antigens are present on melanomas as well as on normal melanocytes, the cells of origin of melanomas. At least six different shared melanocyte differentiation antigens have been described, including MART-1, gp100, tyrosinase, TRP1, TRP2, and MC1R. The identification of these differentiation antigens on melanomas has led to the conjecture that differentiation antigens unique to other tissues might also be expressed on tumors arising from those tissues and thus serve as immunotherapeutic targets. Thus, differentiation antigens present on the epithelial cells of a variety of organs not essential for life, such as testis, ovary, prostate, breast, and thyroid, might also serve as tumor antigens.

Several tumor antigens such as beta-catenin, CDK4, MUM1, caspase 8, and KIA have been described and result from individual base mutations that give rise to amino acid differences. These mutated proteins thus represent antigens expressed only on cancer cells and not normal cells. Because each of these antigens is unique to the individual patient bearing the mutation, its use in the development of generally applicable cancer vaccines is limited.

Several unusual antigens with selective expression on cancer cells have been identified. Messenger RNA–encoding antigens, such as p15, PRAME, gp100, MART-1, and gp100 have been described and appear to be present on cells other than cancers.

Several viral epitopes are known to be expressed on tumors caused by these viruses. Examples in this category include antigens from the Epstein-Barr virus, human T-cell leukemia virus type 1, the hepatitis B virus, and the E6 and E7 proteins from human papillomavirus-16. Several other normal or mutant proteins that are overexpressed in epithelial cells or represent mutated oncogenes or fusion proteins have been hypothesized to be capable of acting as tumor antigens, although convincing evidence to support this hypothesis is lacking.

CANCER ANTIGENS RESTRICTED BY CLASS II MAJOR HISTOCOMPATIBILITY COMPLEX AND RECOGNIZED BY CD4+ T CELLS

Three general techniques for identifying MHC class II–restricted antigens recognized by CD4+ T cells are presented in Table 18-7. The testing of known class I–restricted antigens for the presence of class II–presented epitopes resulted in the identification of class II–restricted epitopes on tyrosinase and gp100 (Touloukian et al., unpublished data). CD4+ T cells can recognize antigen-presenting cells pulsed with tumor lysates or proteins. It has thus been possible to purify proteins from tumor cell lysates that can elicit CD4 reactivity; the triosephosphate isomerase antigen was identified using this technique. A general technique for the identification of class II antigens present on cancers as well as on cells from a variety of other diseases has been described. This technique involves the screening of cDNA libraries transfected into antigen-presenting cells engineered to express the appropriate class II a and b molecules, the DNA and DMB molecules required for antigen processing as well as invariant chain. This technique was based on the unique aspects of the presentation of class II antigens and the inability of normal
cytoplasmic proteins to be presented in the class II pathway. Using this genetic approach, several antigens, such as the CDC27 protein and a mutated fusion protein, were identified (Table 18-6).

<table>
<thead>
<tr>
<th>Antigen</th>
<th>mRNA Source</th>
<th>Peptide</th>
<th>References</th>
</tr>
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<td>Tyrosinase</td>
<td>TREM</td>
<td>Tyrosinase</td>
<td>273, 292, 296, 297</td>
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TABLE 18-7. Techniques for Cloning Tumor Antigens Recognized by CD4+ Cells and Presented on Major Histocompatibility Complex Class II

HUMAN CANCER ANTIGENS: GENERAL PRINCIPLES

Tumor antigens can be derived from a variety of sources, including normal differentiation antigens, normal nonmutated antigens expressed on tumors and germ cells, intronic sequences, single base mutations, chromosomal rearrangements, aberrant processing, or alternative open reading frames of normal genes (Table 18-9). Because of the large number of mutations and chromosomal abnormalities present in cancer cells, it appears likely that many, if not all, cancers contain unique sequences capable of being recognized by human immune reactions. In support of this hypothesis are the examples that exist of individual patients who develop immune reactions against multiple different antigens present on their tumor. Two examples of this are shown in Table 18-10. TIL 586 from patient B.C. developed HLA-A31–restricted reactivity against four different epitopes, including one from an alternative open reading frame of TRP1, from the normal open reading frame of TRP2, and from both the normal and alternative open reading frames of the NY-ESO-1 antigen. Similarly, patient M.G., whose tumors gave rise to TIL 888 and 1290, developed HLA-A24–restricted epitopes from four completely different proteins, including tyrosinase, p15, b-catenin, and gp100.

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<thead>
<tr>
<th>T Cell Antigen</th>
<th>HLA Class II</th>
<th>Peptide</th>
<th>References</th>
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TABLE 18-8. Cancer Antigens Restricted by Class II Major Histocompatibility Complex and Recognized by CD4+ Tumor-Infiltrating Lymphocytes

<table>
<thead>
<tr>
<th>T Cell Antigen</th>
<th>HLA Class II</th>
<th>Peptide</th>
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<td>HLA-A3</td>
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TABLE 18-9. Sources of Human Tumor Antigens

<table>
<thead>
<tr>
<th>T Cell Antigen</th>
<th>HLA Class II</th>
<th>Peptide</th>
<th>References</th>
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<td>HLA-A3</td>
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TABLE 18-10. A Single Patient Can Develop Reactivity against Multiple Epitopes on Different Antigens

Of importance for the general application of tumor antigens in human immunization is the ability of individual tumor antigens to present immune epitopes on a variety of HLA antigens (Table 18-11). Thus, the gp100 molecule has peptide epitopes that are presented on HLA A2, A3, A24, CDW8, and DR4. Similarly, tyrosinase has known epitopes presented on HLA A1, A2, A24, and DRB1*0401, DRB1*1501, and B*4402. Thus, individual antigens can potentially be applicable to the immunization of a majority of patients with different HLA types.
TABLE 18-11. A Single Cancer Antigen Can Present Peptides on Multiple Class I and Class II Major Histocompatibility Complex Types

ANTIBODIES FOR DETECTING TUMOR ANTIGENS

Igs in all species have the same basic structure and consist of two polypeptide chains: the light chain, with a molecular weight of approximately 23,000, and the heavy chain, with a molecular weight of 55,000 to 70,000 (reviewed in Chapter 4).

Five different classes of Igs have been identified based on structural differences within the heavy-chain constant regions: IgM, IgG, IgA, IgD, and IgE. IgG constitutes the predominant Ig fraction in sera, and most antibody activity is associated with IgG antibodies. IgM constitutes approximately 5% to 10% of serum Igs and is the largest of the Ig molecules. IgA is the predominant Ig in exocrine secretions, and IgE Igs are involved in allergic reactions. The exact function of IgD Igs is unknown.

Kohler and Milstein were the first to demonstrate that somatic cells could be fused with murine myelomas and that monoclonal antibodies with unique specificities could be produced. A vast array of monoclonal antibodies have now been produced against a wide variety of human tumor-associated antigens (reviewed in Chapter 20.5). Most hybridoma cell lines can produce between 1 and 10 µg of Ig per 1 mL in culture, and ascites fluids can produce between 1 and 10 mg of Ig per 1 mL. In the generation of most monoclonal antibodies, mice are immunized against a specific antigen, and their cells are fused with the mouse myeloma cell. It is possible, however, to use human lymph node or peripheral blood cells for fusion with human myelomas. These human monoclonal antibodies may be able to identify antigens that are not immunogenic in the mouse and are less immunogenic in humans than murine monoclonal antibodies. It is possible to make recombinant chimeric monoclonal antibodies that contain the variable region of murine origin and the constant region of human origin.

Virtually all monoclonal antibodies have at least some reactivity with normal tissues, although the degree of cross-reactivity can be minimal. The potential clinical applications of monoclonal antibodies are summarized in Table 18-12 and Chapter 20.5.

TABLE 18-12. Clinical Applications of Monoclonal Antibodies (MoAbs)

IMMUNOTHERAPY

Strategies for the immunotherapy of cancer can be divided into active and passive approaches (Table 18-13). Active immunotherapy refers to the immunization of the tumor-bearing host with materials designed to elicit an immune reaction capable of eliminating or retarding tumor growth. Active immunotherapy can be subdivided into nonspecific or specific immunization. Most early attempts at the immunotherapy of cancer used nonspecific active approaches to immune stimulation with adjuvants such as bacillus Calmette-Guérin, Corynebacterium parvum, and levamisole. These early approaches were almost uniformly unsuccessful in humans and have largely been abandoned.

TABLE 18-13. Classification of Cancer Immunotherapies

The advent of recombinant cytokines provided a more selective means for stimulating the immune system. Treatment with the IFNs or with IL-2 is a form of nonspecific active immunotherapy, although the selective action of these purified lymphokines provides a greater ability to manipulate immune responses than was previously possible.

INTERLEUKIN-2

Major progress in immunotherapy has resulted from the identification of the cytokine IL-2 that enabled the ex vivo growth of human T lymphocytes. The identification of the gene encoding IL-2, the biologic characterization of recombinant IL-2, increasing information about the dominant role of IL-2 in regulating immune reactions, and extensive studies of IL-2 administration to tumor-bearing mice led to studies of the clinical use of this molecule in patients with advanced cancer (see Chapter 20.2). IL-2 is now in common use for the treatment of patients with metastatic melanoma and renal cancer and has been instrumental for the conduct of in vitro studies identifying human cancer antigens. IL-2 also has been used as an adjuvant for in vivo immunization protocols.
The best evidence that manipulation of the human immune system can result in the regression of advanced cancer in patients resulted from clinical studies in which high-dose bolus IL-2 was administered to patients with metastatic melanoma and metastatic renal cancer. IL-2 has no direct impact on cancer cells, and all of its effects result from its ability to stimulate in vivo immune reactions. In the National Cancer Institute’s Surgery Branch, 409 consecutive patients with either advanced melanoma (n = 182) or renal cancer (n = 227) were treated with high-dose bolus IL-2 alone at a dose of 720,000 IU/kg every 8 hours. The results of the treatment are shown in Table 18-14 and Table 18-15. Seven percent of patients with melanoma underwent a complete response, and 9% underwent a partial response. In patients with renal cancer the complete and partial response rates were 9% and 10%, respectively. Complete responses were most often durable. Of 12 patients with metastatic melanoma who achieved a complete response, only two have recurred, with the remainder having ongoing complete responses of between 95 and 173 months. Of 21 patients with metastatic renal cell cancer who achieved a complete regression, four have recurred and 17 have ongoing responses between 46 and 159 months. The lack of recurrences after 5 years and the follow-up of several patients beyond 10 years indicate that these patients have probably been cured by the administration of high-dose IL-2 (Fig. 18-1).

<table>
<thead>
<tr>
<th>TABLE 18-14. Response of Patients with Metastatic Cancer Treated with High-Dose Bolus Interleukin-2</th>
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<tbody>
<tr>
<td><strong>Diagnosis</strong></td>
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</tr>
<tr>
<td>Melanoma</td>
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<tr>
<td>Renal cancer</td>
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<table>
<thead>
<tr>
<th>TABLE 18-15. Duration of Response in Patients with Metastatic Cancer Treated with High-Dose Bolus Interleukin-2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diagnosis</strong></td>
</tr>
<tr>
<td>------------</td>
</tr>
<tr>
<td>Melanoma</td>
</tr>
<tr>
<td>Renal cancer</td>
</tr>
</tbody>
</table>

FIGURE 18-1. Complete response to treatment with high-dose interleukin-2, with deaths due to other causes censored.

As experience with the use of IL-2 increased, improved methods for managing the side effects of its administration were developed, and the safety of IL-2 administration has improved dramatically. A consecutive series of 1241 metastatic cancer patients who received 720,000 IU/kg IL-2 every 8 hours by intravenous bolus infusion, either alone or in conjunction with other treatments, were evaluated for the incidence of treatment-related toxicities. Significant decreases in the incidence of grade III and IV toxicities were found as experience with the use of IL-2 increased over the 12 years of this study. Although a 1% to 3% treatment-related mortality was seen in the first 4 years of the administration of IL-2, no treatment-related deaths were reported in this series between May 1989 and January 1997, including the treatment of 809 consecutive patients. These trends suggested that high-dose IL-2 could be safely administered to metastatic cancer patients when appropriate treatment guidelines were used and that the administration of IL-2 could result in durable responses in a small subset of patients with metastatic melanoma and metastatic kidney cancer.

**INTERFERONS**

The IFNs are a family of proteins that are produced by cells in response to viral infection or stimulation with double-stranded RNA, antigens, or mitogens. The IFNs can interfere with subsequent viral challenge, and they have many immunomodulatory and antiproliferative effects (see Chapter 20.1).

More than 20 closely related genes coding for IFN-a exist, and they have approximately 80% to 85% amino acid homology with one another. IFN-b is quite similar in many of its properties to IFN-a. The gene for IFN-g has three introns, and there are no introns in the genes that code for IFN-a and IFN-b. IFN-a and IFN-b are stable to pH 2, although IFN-g is labile at this pH. IFN-b and IFN-g are glycosylated, but most IFN-a species are not.

IFN-a can be produced by a variety of cells, including macrophages and lymphocytes. IFN-b is produced mainly by fibroblasts and epithelial cells. IFN-g can be produced by a variety of lymphocyte subtypes, such as CD4+ or CD8+ cells, NK cells, and LAK cells. Secretion of IFN-g occurs after stimulation by mitogens or antigens. IFNs have a variety of biologic properties, including immunomodulatory activities, antiviral activities, the ability to enhance cell proliferation, inhibition of angiogenesis, regulation of differentiation, and enhancement of the expression of a variety of cell surface antigens. Although the direct antiproliferative activity of the IFNs is thought to play a major role in the antitumor effects of these compounds, other actions of the IFNs may also be important.

The IFNs have antitumor activity against a variety of tumor types, including hairy cell leukemia, chronic myelogenous leukemia, cutaneous T-cell lymphoma, and Kaposi’s sarcoma.

The response rates of various solid tumors and hematologic malignancies to treatment with IFN-a are summarized in Table 18-16. IFN-a and IFN-b, but not IFN-g, demonstrate direct antitumor activity. The side effects associated with IFN therapy include flu-like symptoms, rashes, gastrointestinal complaints, hepatic dysfunction,
neurologic complaints, and chronic fatigue, and they are highly dose and schedule dependent.

TABLE 18-16. Response of Various Cancers to Interferon-a

DEVELOPMENT OF APPROACHES TO THE IMMUNIZATION OF HUMANS AGAINST CANCER ANTIGENS

Although many human cancer antigens have now been identified, relatively little is known about the best methods for successful immunization of patients against these antigens. The number of variables involved in determining optimal methods of immunization of humans presents a daunting challenge and are shown in Table 18-17.

TABLE 18-17. Variables Involved in the Immunization of Humans against Cancer Antigens

A variety of cancer antigens are available. Multiple vectors can be used to provide immunization, including peptides, proteins, DNA, and a variety of recombinant viruses such as adenovirus, fowlpox virus, and vaccinia virus. When using these immunizing vectors, the vehicle can be important as well. It is possible to inject these vectors in saline and in a variety of adjuvants, such as incomplete Freund's adjuvant, QS21, or others. Similarly, these antigens can be presented on professional antigen-presenting cells, such as mature dendritic cells. The route of immunization is also a variable that must be considered (e.g., intradermal, subcutaneous, intramuscular, or intravenous injection). Immune adjuvants may increase the immune response to these immunogens, and studies exploring the use of IL-2, IL-7, IL-10, and IL-12 have been performed. Because of the myriad of possibilities for immunization of humans, substantial effort has been placed on elucidation in animal models of the general principles for vaccination against cancer antigens. Four general principles resulting from these murine studies are presented in Table 18-18 and have guided the work in humans. A detailed discussion of cancer vaccines is presented in Chapter 63.1 and Chapter 63.2.

TABLE 18-18. General Principles for Human Vaccination against Cancer Antigens Based on Animal Models

It is possible to immunize cancer patients against antigens present on their autologous cancers and raise high levels of circulating immune lymphocytes. An example of one such series of experiments in which 11 patients with metastatic melanoma were immunized with a modification of the gp100:209–217 epitope, from the gp100 melanoma antigens, which was modified with a methionine substitution in the 210 position, is shown in Table 18-19. The introduction of this amino acid modification greatly increased the binding of this peptide to the HLA-A2 molecule and thus appeared to increase both its in vitro and in vivo immunogenicity. Despite the ability to reproducibly generate immune reactions against this tumor epitope, little antitumor effect was seen unless IL-2 was simultaneously injected. In pilot human trials, it appeared that the response rate to immunization with the gp100 209–217 (210M) epitope plus the administration of IL-2 resulted in response rates almost three times greater than that due to IL-2 alone. However, the confirmation of this result will require evaluation in prospective randomized trials in which patients are treated with either IL-2 alone or IL-2 plus the peptide immunogen.

TABLE 18-19. Reactivity of Peripheral Blood Mononuclear Cells from Patients Immunized with 209-2M Peptide in IFA
ADOPTIVE IMMUNOTHERAPY

Adaptive immunotherapy—the transfer to the tumor-bearing host of cells with antitumor activity—has substantial therapeutic attractiveness as an approach to treating human cancer. Early cell-transfer experiments in animals demonstrated that the cellular arm of the immune response is crucial in mediating the rejection of allogeneic grafts and syngeneic tumors. In most experimental systems, the transfer of immune cells, but not of antibody directed against cellular antigens, produces immunity to tissue transplantations.

The major obstacle to the development of successful adoptive immunotherapies for the treatment of cancer in humans has been the inability to develop immune cells with specific reactivity for human tumors that could be obtained in large enough numbers for transfer to tumor-bearing patients. However, several new approaches have been developed for generating human cells with reactivity to tumor.

Beginning in 1980, Rosenberg and colleagues described a technique for generating lymphoid cells from mice and humans that were capable of lysing fresh tumor cells but not normal cells. The incubation of resting murine splenocytes or human peripheral blood lymphocytes with IL-2 for 3 to 4 days generates LAK cells that can lyse fresh tumor cells.

The characteristics of LAK cells have been extensively studied. These cells represent a lytic population distinct from NK cells or CTLs, and their phenotypic surface markers are characteristic of non–MHC-restricted killer cells. LAK cells can be CD3+ or CD3−, are nonadherent, and bear NK-like markers such as CD16 and CD56. The nature of the determinants recognized on fresh tumor targets by LAK cells is unknown, although the determinants appear to be broadly expressed on fresh and cultured tumor cells and in cultured normal cells. Fresh normal cells do not appear to bear cell surface determinants recognized by LAK cells.

After the description of the LAK cell phenomenon, animal studies evaluated the use of LAK cells in the adoptive immunotherapy of established tumors. These studies demonstrated that the adoptive transfer of LAK cells in conjunction with IL-2 could mediate the regression of established pulmonary, hepatic, and subdermal metastases in a variety of animal models. IL-2 stimulated in vivo expansion of LAK cells with maintenance of cellular function.

Based on these in vitro studies and animal models, clinical protocols were developed for the systemic administration of LAK cells plus IL-2 to patients with advanced cancer. Results from a prospective randomized trial in the National Cancer Institute’s Surgery Branch comparing treatment of patients with metastatic melanoma or renal cancer using either IL-2 or LAK cells plus IL-2 revealed no difference in survival.

TUMOR-INfiltrATING LYMPHocytes AND INTERLEUKIN-2

TILs are lymphocytes that infiltrate growing tumors and can be isolated by growing single-cell suspensions from the tumor in IL-2. In animals, the adoptive transfer of TILs can be from 50 to 100 times as potent as LAK cells in mediating the regression of established micrometastases. TILs have been isolated from virtually all types of human tumors and can recognize tumor-associated antigens. This study and additional efforts to develop gene therapies for patients with cancer are considered in Chapter 62.1. Improved methods for developing lymphocytes with antitumor activity by in vitro sensitization with tumor-specific peptides, as well as the use of cloned cells, are under development and may provide valuable reagents for use in future adoptive immunotherapy studies.

TABLE 18-20. Treatment of Patients with Melanoma with Tumor-Infiltrating Lymphocytes

<table>
<thead>
<tr>
<th>Patient Name</th>
<th>Objective</th>
<th>Response</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gordon</td>
<td>Complete</td>
<td>In vivo</td>
<td>Waterman MW, et al.</td>
</tr>
<tr>
<td>Waterman</td>
<td>Complete</td>
<td>In vivo</td>
<td>Waterman MW, et al.</td>
</tr>
</tbody>
</table>

*Tumor-infiltrating lymphocytes (TILs) traffic to and accumulate in tumor deposits. This finding led to attempts to genetically alter TILs to increase their antitumor activity at the tumor site. In an initial phase of this effort, TILs transduced with the gene for neomycin phosphotransferase were infused into patients with advanced melanoma, as were TILs transduced with the gene for TNF. This study and additional efforts to develop gene therapies for patients with cancer are considered in Chapter 62.1. Improved methods for developing lymphocytes with antitumor activity by in vitro sensitization with tumor-specific peptides, as well as the use of cloned cells, are under development and may provide valuable reagents for use in future adoptive immunotherapy studies.

CHAPTeR REFERENCES


Tavernier J, Devos R, Cornelis S, et al. A human high affinity interleukin-5 receptor (IL5R) is composed of an IL5-specific alpha chain and a beta chain shared with the receptor for GM-CSF. Proc Natl Acad Sci U S A 1996;93:16293.


INTRODUCTION

Medical oncologists prescribe and administer those drugs with the narrowest therapeutic index in all of medicine. Thus, understanding variability in toxicity and response is of utmost importance. Such variability can be divided into two components, pharmacokinetics and pharmacodynamics. Pharmacokinetics, the relationship between time and plasma concentration (Fig. 19.1-1), is concerned with understanding issues such as metabolism and excretion. It can be simply described as “what the body does to the drug.”

The clinical interpretation of pharmacokinetic results requires another set of information, the relationship between plasma concentrations (or dose as a surrogate) and effect, or pharmacodynamics (Fig. 19.1-2). This can be described as “what the drug does to the body.” The understanding of anticancer pharmacodynamics has increased dramatically, although most studies that have successfully correlated concentration with effect have focused on toxicity end points. 

It has become fashionable to conduct clinical pharmacology studies in conjunction with early clinical trials of new anticancer agents, even in multiinstitution (i.e., Cooperative Group) studies. Such studies may have as their objectives pharmacokinetic or pharmacodynamic end points, or both. In phase I trials, the primary pharmacologic objective is to define the pharmacokinetics to optimize scheduling and dosing for subsequent studies. Pharmacodynamic end points are generally secondary, unless an adequate number of patients are studied at or near the recommended phase II dose. Phase II trials offer a different opportunity, because generally all patients are treated at the same dose. Thus, variability in toxicity or response may potentially be related to variability in pharmacokinetics. In addition, population pharmacokinetic studies can be conducted at this phase, with a relatively large patient base, sparse sampling (one to four samples per patient), and the implementation of sophisticated modeling programs.

PHARMACOKINETICS: FUNDAMENTAL PRINCIPLES

The study of pharmacokinetics is classically considered to consist of four aspects: absorption, distribution, metabolism, and excretion. Each of these issues is
ABSORPTION

Because most anticancer drugs are administered intravenously, most oncologists have only infrequently dealt with those issues specific to the clinical pharmacology of orally administered agents. The term absorption has historically implied transport across the intestinal mucosa, although it has been recognized that the intestinal mucosa is important in xenobiotic metabolism.

The degree of absorption can be expressed as the bioavailability, which in practice is determined by comparing the area under the concentration-time curve (AUC) for oral administration to the AUC after intravenous administration. A low bioavailability can be due to either poor absorption per se, or high first-pass metabolism. In addition, the presence of transport proteins in the gut, such as P-glycoprotein, also impact on the oral bioavailability of anticancer agents.

Alteration in gastrointestinal absorptive capacity can be due to a variety of factors common in patients with cancer. Recent surgery may influence absorption, as demonstrated in regard to UFT (tegafur, uracil, and 5-fluorouracil) administration in the early postoperative period after partial gastrectomy. Prior chemotherapy can be a major issue, and diminished absorption may be present in the absence of clinical gastrointestinal toxicity. Concomitant medications affecting gastrointestinal motility, such as opiates or metoclopramide, may also be a factor.

Absorption also must be considered in regard to subcutaneous or intramuscular dosing. Although bioavailability via these routes is usually close to 100%, there may be decreased bioavailability due to local drug degradation or other factors.

DISTRIBUTION

Drugs usually distribute after administration from the plasma into extracellular and intracellular fluids. If a hypothetical drug were given as a 100-mg instantaneous bolus, the initial concentration would be 100 mg divided by the volume of distribution (the higher the volume, the lower the initial concentration). Subsequent concentrations would then be determined by the drug’s rate of elimination. In the simplest pharmacokinetic model, the clearance is equal to the product of the volume of distribution and the elimination rate constant.

In actuality, distribution is much more complex. A drug's pharmacokinetics can be described by one or more interconnected compartments, and distribution is then represented by drug moving from the “central” compartment to a “peripheral” compartment (Fig. 19.1-3). This description is important for several reasons.


Because the central compartment is usually plasma, the site of action is probably more closely related to a peripheral compartment (i.e., intracellular fluid). Thus, plasma concentrations may be falling as the pharmacologic effect increases (Fig. 19.1-4). This inverse relationship may be compounded further for anticancer drugs by the known delay between the cytotoxic event and its clinical manifestations.

FIGURE 19.1-4. A reverse hysteresis loop representing the relationship between concentration, time, and pharmacologic effect (e.g., DNA damage). The plasma concentration rises during the period of drug administration (i.e., 24-hour infusion). The plasma concentration falls immediately after the infusion ends, but the tumor concentration continues to rise (due to distribution). Thus, the maximal effect occurs later than the end of the infusion (maximal plasma concentrations). Although the same plasma concentration occurs both during infusion and after infusion, the effect is greater when the concentration is falling.

In general, drug that distributes to the peripheral compartments eventually redistributes back to the plasma or central compartment. Drugs that are extensively distributed usually have a long terminal half-life, which can be highly dependent on the rate of redistribution. Such drugs are often highly protein-bound. This can have important clinical ramifications for highly schedule-dependent agents such as methotrexate, which distributes to “third spaces” such as pleural effusions or ascites.

METABOLISM

Metabolism is the most critical and complex aspect of pharmacokinetics for most agents. The great majority of xenobiotic metabolism takes place in the liver, although cytochrome P-450 enzymes and uridine diphosphate–glucuronosyltransferases are present in the small bowel, and both carboxylesterases and deaminases are present in plasma and other tissues.

Xenobiotic metabolism can be divided into phase I and phase II reactions (Table 19.1-1). Phase I reactions are oxidative, or reductive, reactions and include the P-450 system. Phase II reactions are conjugative reactions, such as acetylation and glucuronidation. Phase I reactions usually make a drug more susceptible to phase II reactions, which generally produce molecules amenable to biliary or renal excretion. These metabolic reactions evolved for the purpose of xenobiotic detoxification, but can also result in drug activation.
Table 19.1-1. Selected Drug-Metabolizing Enzymes of Importance in Oncology

An area of rapidly increasing importance is genetically determined variability in drug-metabolizing enzymes. Such genetic variability can result in enhanced toxicity because of impaired detoxification. or lack of desired effect due to impaired activation. Furthermore, genetically determined variability may also be a risk factor for carcinogenesis. A number of distinct drug-metabolizing enzymes have been conclusively demonstrated to be polymorphic (see Table 19.1-1).

An individual's metabolic capacity can also be affected by a variety of other factors, such as hepatic dysfunction, nutrition, and other medications. These are all factors that are highly variable in patients receiving chemotherapy.

Phase I metabolism (i.e., the P-450 system) appears to be more sensitive to hepatic dysfunction than phase II enzymes (i.e., glucuronidation). Although oncologists generally monitor liver function tests during chemotherapy, the serum bilirubin (the most commonly used measure) is a very insensitive measure of changes in plasma drug clearance. Malnutrition, like hepatic dysfunction, may result in decreased synthesis of drug-metabolizing enzymes, decreased clearance, and enhanced toxicity.

One of the most important considerations with regard to the elimination of anticancer drugs is the effect of other medications. Cancer patients receive a large number of medications that can affect metabolism (and excretion) of concomitant chemotherapy (Table 19.1-2). Given the complexity of most treatment regimens (multiple cytotoxic agents, antiemetics, analgesics, anticonvulsants, corticosteroids), relatively few specific data are available in this regard.

Table 19.1-2. Potential Drug Interactions with Chemotherapy

EXCRETION

There are two major routes of excretion, renal and biliary. Both are complex processes involving a chain of events, any of which can be modulated by disease processes or other medications.

Xenobiotics may undergo filtration, secretion, and reabsorption on their journey from the glomeruli to the ureter. The creatinine clearance, either measured from a timed urine specimen or calculated based on a variety of formulas, is often used as a surrogate for the glomerular filtration rate (GFR), although these formulas have limited accuracy. Furthermore, this surrogate may be used to describe an individual’s overall renal function. Patients with reduced renal function should be considered for dose reduction if renal excretion is a major component of the agent's clearance.

A great effort has been expended in trying to predict carboplatin pharmacokinetics. The most accurate approach uses chromium-labeled EDTA (ethyleneediamine-tetraacetic acid). Simpler techniques, such as using a measured or calculated creatinine clearance, have inconsistently been predictive, because of the poor correlation between creatinine clearance and GFR.

Physicians also commonly use a measured or estimated creatinine clearance to guide cisplatin dosing, primarily as a determinant of dose modifications from a standard body surface area (BSA)-adjusted dose. It is important to recognize that GFR is normally correlated with BSA, so that smaller patients appear to have poorer renal function, unless the GFR is also adjusted for the BSA (mL/min/m² or mL/min/1.73 m²).

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Tubular secretion and reabsorption may also be important in drug excretion. As an example, it has been suggested that cisplatin’s reabsorption is saturable, resulting in enhanced proportional reabsorption when administered by infusion, potentially resulting in enhanced toxicity. Methotrexate and topotecan also undergo secretion and reabsorption in the renal tubules. Methotrexate's renal handling is highly influenced by the urinary pH, and because it is a weak acid, alkalinization results in enhanced excretion.

Biliary excretion involves a number of transport systems, including P-glycoprotein, a known cause of multidrug resistance. Another important system appears to be the more recently described multifunctional organic anion transporter, cMOAT (canalicular multispecific organic anion transporter). cMOAT is the primary transporter of SN-38, the active metabolite of irinotecan. These systems can be inhibited by a variety of disease processes, as well as by other drugs (cyclosporine A, PSC-833) or formulants (Cremophor).

After biliary excretion, reabsorption may take place in the small intestine, leading to an enterohepatic circulation. This is particularly relevant for those drugs whose primary metabolite is a glucuronide, because of the presence of bacterial β-glucuronidases in the gut, which cleave off the glucuronide.

The serum bilirubin is often used to determine dose modifications for hepatically cleared drugs. However, this is only a marker of impaired excretion, and it is poorly correlated with impaired metabolism. (Metabolism may be better represented by measures of synthetic function, such as serum albumin.)

PHARMACOKINETICS: WHAT’S IMPORTANT TO THE CLINICIAN?
CLEARANCE

The generation of pharmacokinetic data is easy, but its interpretation can be quite overwhelming, especially to a clinician attempting to apply such data to a particular patient or study. A good starting point is the assessment of total plasma clearance. Clearance can be calculated in one of two ways: either by measurement (or estimation) of the AUC after a single dose (see Fig. 19.1-1), or by determination of the steady-state concentration (C_{ss}) during continuous infusion.

\[
\text{Clearance} = \frac{\text{dose}}{\text{AUC}}
\]

or

\[
\text{Clearance} = \frac{\text{dose rate}}{C_{ss}}
\]

Although the absolute value of the clearance may be of some interest to the pharmacologist, the clinician should be primarily concerned with variability in clearance, best represented as the coefficient of variation (CV), the ratio of the standard deviation (not standard error) to the mean. The CV may be as low as 10% to 20% for drugs with low variability, or as high as 75% to 100% for drugs with high variability. Most drugs have a CV in the 20% to 40% range.

After understanding the extent of variability, the next question is to explain it, particularly if the CV is quite large. This becomes even more relevant if patients with a low clearance have an increased risk of toxicity. Drugs with a very high CV should be closely studied for genetically determined polymorphisms of the primary metabolizing system.\(^{56,65}\)

Another important source of variability is saturation of the major metabolic or excretory site. If saturation occurs at clinically relevant concentrations, the clearance generally decreases dramatically at higher doses, and the drug is considered to have nonlinear pharmaco kinetics. Optimal administration of such drugs requires a full understanding of the complexities involved, as well as the potential effects of disease and other medications.

In assessing variability in AUC or clearance, variability in protein binding may be an important issue. The degree of protein binding may range from negligible to more than 99%. Only the free (unbound) drug is active, whereas conventional assays quantitate the total (free plus bound) drug. If significant variability in protein binding is found for a highly bound drug, it may be difficult to interpret plasma concentrations without directly measuring the free drug or extent of protein binding. For some agents, however, such as etoposide, it may be possible to estimate protein binding from simple parameters, such as serum albumin, bilirubin, and age.\(^{54,55,65}\)

A potential source of variability that has been greatly exaggerated in oncology practice is variability in body size. Minimal data support the dosing of chemotherapy on the basis of BSA in adults. Because size may have no significant correlation with clearance, this practice may even increase the extent of variability in AUC.\(^{55,58,66,77}\)

Further studies of this important issue are needed, if only to decrease the complexity of oncology practice.

HALF-LIFE

For highly schedule-dependent drugs, variability in half-life may be more important than variability in clearance. Although half-life and clearance are generally inversely correlated, an increased half-life may also be a consequence of an increased volume of distribution. This may have significant consequences, as has been well established for methotrexate's distribution into ascites or pleural effusions.\(^{62}\)

Variability in half-life influences variability in time above any specific plasma concentration. This finding is becoming increasingly well recognized as an important factor in both toxicity and response.\(^{62,67}\)

Knowledge of the half-life may also be important for protocol designs, because schedule-dependent drugs with short half-lives (e.g., cytarabine, 5-fluorouracil) might be best administered by continuous infusions or frequent dosing. It may also be critical to know the half-life for estimating when plasma cytotoxic activity is negligible in the context of peripheral stem cell reinfusion or colony-stimulating factor administration.\(^{62,74}\)

ACTIVE METABOLITES

Although metabolism generally results in detoxification, some drugs may have active circulating metabolites (Table 19.1-3). These include drugs that are true prodrugs, having no intrinsic cytotoxic activity, and drugs that have metabolites with comparable or greater cytotoxicity to the parent. It is also important to understand the pathways through which activation occurs. There may be theoretical advantages to enhancing or inhibiting formation of the active metabolites, which may have a different “therapeutic index” (ratio of beneficial to harmful effects) than the parent drug. This alteration of active metabolite formation can potentially be accomplished by the use of inhibitors (e.g., ketoconazole) or inducers (i.e., phenobarbital) of specific drug-metabolizing enzyme systems.\(^{62,67}\)

Finally, an identifiable genetic basis for differences in activation may exist, which leads to different effects in specific patient populations.\(^{62}\)

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**TABLE 19.1-3. Oncology Drugs with Active Circulating Metabolites**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Metabolite</th>
<th>Activity</th>
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**ROUTES OF ELIMINATION**

Oncologists are generally well aware of the potential for drug elimination to be impaired in patients with end-organ dysfunction. However, relatively little information is available to guide dose modifications. Even if a physician knew an individual's clearance before dosing, it would be difficult to predict the extent of toxicity because of the risk of prolonged low concentrations (for schedule-dependent drugs) or concomitant pharmacodynamic factors (resulting in enhanced sensitivity, such as malnutrition).

The only generalization that can be made is that variability increases as end-organ dysfunction develops. Formal phase I studies are warranted in patients with end-organ dysfunction.\(^{62,72}\)

**BASIC METHODOLOGY OF PHARMACOKINETIC STUDIES**
The first pharmacokinetic studies of a new agent are almost always conducted in conjunction with phase I studies. Proper conduct of such studies requires a great deal of planning, as well as technical and logistical expertise. Data from preclinical studies are critical in the design. These generally include evaluations of in vitro cytotoxicity, preclinical pharmacokinetics, in vitro metabolism, in vitro toxicology (myelosuppression), and whole-animal toxicology.

Pharmacokinetic data can be collected using either intensive or sparse sampling strategies. In the first pharmacokinetic studies, intensive sampling is used to try to model each individual's pharmacokinetics. Data from all patients can be combined in two basic ways: either with a simple descriptive summary (mean ± standard deviation) of the fundamental parameters, or by pooling all data into a single analysis. The latter approach requires a high level of statistical and computational sophistication, but may generate insights not available by other means.

It is also useful to begin to plan subsequent pharmacologic studies in the context of the initial pharmacokinetic analysis. These subsequent studies are often primarily concerned with pharmacodynamic issues, relating toxicity or response to pharmacokinetic variables. Such studies benefit greatly from the use of optimal sampling strategies, in which only a few samples are collected on each patient.

### PHARMACODYNAMICS

#### FUNDAMENTAL PRINCIPLES

The fundamental objective of pharmacodynamic studies is understanding variability in effect. In phase I trials, the primary objective is to understand variability in effect (toxicity) as a function of dose. The investigator can also begin to understand the relationship between pharmacokinetic end points (i.e., AUC) and effect.

However, because phase I trials encompass multiple doses, dose is correlated with AUC (and other end points), and relationships between AUC and effect are confounded if the dose range is wide. Thus, phase II trials in which all patients receive a single drug at a fixed dose offer an important opportunity to correlate pharmacokinetic end points (due solely to pharmacokinetic variability) and effect (both toxicity and response).

Since the 1980s, a progressively increasing number of studies have been published that have included pharmacodynamic end points. Such studies primarily have used AUC or C₀ as the pharmacokinetic parameter, and blood count nadirs as the pharmacodynamic end point. More recently, several studies have demonstrated that time above a threshold concentration is an important pharmacokinetic parameter, which is consistent with the understanding that schedule is an important determinant of antineoplastic drug action.

#### METHODOLOGIC ISSUES

The methodology for pharmacodynamic studies should use generally recognized outcomes. Historically, blood count nadirs have been used, although this approach has several limitations. Nadir blood counts, by definition, measure the lowest observed blood count, which is highly dependent on the number of observations. In addition, nadir blood counts are not useful in the context of high-dose chemotherapy. Thus, it is potentially desirable to incorporate all blood counts and to use a methodology robust enough to properly analyze missing data.

Nonhematologic toxicity is an even more difficult problem, as it is often graded rather than continuous, and subjective rather than objective. Statistical methodologies appropriate for such end points are necessary, such as logistic regression and its variants.

The “holy grail” of antineoplastic clinical pharmacologists is to correlate pharmacologic end points with response. Although examples of plasma clearance being correlated with response are available, it is likely that variability in response is primarily due to tumor factors (i.e., intrinsic drug resistance) rather than patient factors (i.e., altered clearance).

Another major challenge is to expand the knowledge of anticancer pharmacodynamics from single agents to combinations. Such studies are logistically difficult, because plasma samples must be collected at times appropriate for each of the drugs in the regimen. Some work in this area has been done with regard to the effect of a second drug on carboplatin-induced thrombocytopenia.

#### RATIONAL USE OF PHARMACOKINETIC AND PHARMACODYNAMIC DATA IN CLINICAL ONCOLOGY

Although oncologists may have difficulty exactly defining pharmacokinetics and pharmacodynamics, many of the important principles are incorporated into oncology clinical practice. By understanding that the principles are not foreign, the oncologist can better use principles of clinical pharmacology to optimize dosing of these highly toxic agents.

#### DOSE MODIFICATION FOR TOXICITY

It is common practice to reduce drug dosages for excessive toxicity. But a variety of reasons may be responsible for excessive toxicity, which can generally be categorized as either pharmacokinetic or pharmacodynamic. It is important to understand this distinction. If one assumes that decreasing drug exposure (AUC) reduces the likelihood of response, then dose reduction may be inappropriate for patients with increased toxicity on a pharmacodynamic basis, whereas patients with altered clearance can be dose-reduced yet maintain an acceptable AUC.

### Table 19.1-4: Pharmacokinetic and Pharmacodynamic Determinants of Chemotherapy Toxicity
DOSE MODIFICATION FOR IMPAIRED CLEARANCE

It is common practice to assess hepatic and renal function (as appropriate for specific drugs) before initial (and subsequent) treatment. Such dose modifications are encouraged but are generally empiric with a few exceptions (e.g., carboplatin, topotecan, paclitaxel). For other drugs, it may be obvious that a dose reduction is necessary, but the appropriate degree of reduction may be unclear. It is also important to understand that the serum bilirubin, which is commonly used to screen for hepatic dysfunction, is insensitive, and it should be complemented by measures of synthetic function, such as albumin.

DOSE MODIFICATION FOR ALTERED PHARMACODYNAMICS

It is well accepted that heavily pretreated patients have a lower chance of response. For the most part, this is due to altered pharmacodynamics (increased sensitivity to myelosuppressive chemotherapy coupled with tumor resistance). If one proceeds with myelosuppressive therapy in this situation, a high degree of toxicity should be expected. Thus, it is common to prospectively reduce doses to prevent such toxicity. It is also not surprising that achieving responses is very difficult in this setting, because the patient's tolerance is less while the tumor's "tolerance" has increased.

Other situations may be much less clear. In such cases, determination of the patient's pharmacokinetics may be useful (in theory) in deciding whether dose adjustment is appropriate, while aiming to avoid undertreatment (based on AUC) of the patient. Some evidence indicates that there are pharmacogenetic determinants of cellular susceptibility to cytotoxic agents. Thus, one consideration in the management of patients with unexplained toxicity is to change the treatment (hypothesizing that the patient has unique cellular susceptibility), rather than reducing the dosages.

ADAPTIVE CONTROL OF CHEMOTHERAPY

In most fields of medicine, the dosing of drugs with a relatively narrow therapeutic index is carefully monitored and controlled. Examples include antibiotics (e.g., aminoglycosides, vancomycin), psychotropic medications (e.g., lithium carbonate), anticonvulsants (e.g., phenytoin, carbamazepine, phenobarbital), cyclosporine A, and antiarrhythmics (e.g., digoxin, quinidine). Why has this approach not been widely implemented for cytotoxic chemotherapy, which inarguably has a narrow therapeutic index?

The major difference is that cytotoxic drugs are administered infrequently and usually in combination (with overlapping side effects). It is generally believed that higher doses are more effective; thus, any attempt to individualize dosing would attempt to deliver the maximal dose tolerated by each individual patient. This approach has been applied in research settings, with varying degrees of success (Table 19.1-5).

![Figure 19.1-5](https://example.com/figure1915.png) Comparison of effect of altered pharmacokinetics and pharmacodynamics on toxicity and tumor concentrations. alteration of pharmacokinetics (B) compared to an average patient (A) results in enhanced toxicity due to an increased area under the concentration-time curve (AUC), whereas altered pharmacodynamics (C) may result in enhanced toxicity at an average AUC. Dose reduction in the former case (B) results in an average tumor AUC, whereas in the latter case (C), the tumor AUC may be subtherapeutic.

**TABLE 19.1-5.** Studies of Therapeutic Drug Monitoring (Adaptive Control) in Oncology

Investigators have used a variety of approaches to individualize dosing of cytotoxic drugs. These include using a target concentration or AUC, a target percentile, individualization based on both concentration and pharmacodynamic factors, and individualization based on metabolism of a probe drug. These studies have yielded important insights into the understanding of the potential importance of pharmacokinetic and pharmacodynamic variability. However, adaptive control remains a research tool. Analysis of methotrexate levels after high-dose methotrexate is still the only generally accepted use of plasma level monitoring in clinical oncology.

**MODULATING DRUGS**

The use of biochemical modulators of chemotherapy has a long history. Such an approach has been used to enhance the cytotoxicity of a specific agent (e.g., leucovorin with 5-flourouracil) or to overcome drug resistance. Such modulators have generally been used to affect the pharmacodynamics of one or more agents.

Modulators can also be administered because of pharmacokinetic issues. Leucovorin is commonly dosed on the basis of methotrexate levels, but drugs have not yet been routinely used in oncology to specifically affect the pharmacokinetics of another agent.

The first decade of the twenty-first century will probably bring such approaches into mainstream oncology, driven both by technological and cost issues. For example, ketoconazole is now widely used with cyclosporine to improve its bioavailability, thus reducing the overall cost of cyclosporine therapy. A similar approach has been applied to oral anticancer agents, using cyclosporine (an inhibitor of CYP3A4 and P-glycoprotein) to increase the oral bioavailability of paclitaxel. The ongoing development of inhibitors of dihydropyrimidine dehydrogenase may allow 5-fluorouracil to be effectively administered orally.

Pharmacokinetic modulators may also be beneficial to reduce toxicity, if there is more than one route of elimination. As an example, it has been suggested that cyclosporine A may ameliorate irinotecan-induced diarrhea by inhibiting biliary excretion of the toxic metabolite SN-38.

**ORAL ADMINISTRATION**
A resurgence of interest has been seen in oral administration of cytotoxic chemotherapy. If successful, this route of administration may be more acceptable to patients caused by diet, drug interactions, and compliance. Oncologists should become familiar with these issues and master a general understanding of interpatient and intrapatient variability in bioavailability.

**CHAPTER REFERENCES**

INTRODUCTION

More than five decades of research effort in cancer drug discovery and development have provided approximately six dozen approved products for the treatment of malignancy. Although major advances have been made in the chemotherapeutic management of some patients, particularly in hematologic malignancies, one-half of all cancer patients either do not respond to therapy or relapse from the initial response and ultimately die from their metastatic disease. Thus, the continued commitment to the arduous task of discovering new cancer therapeutic agents remains critically important. Many of the existing antineoplastic agents share a common mechanism of action. Current research efforts are more diverse than ever, being driven by explosive discoveries in molecular biology and related areas to fully elucidate the development of the malignant process (e.g., factors controlling tumor angiogenesis and metastatic potential). The hope for improvement in treatment outcome for most patients with metastatic disease resides in continued research designed to discover novel therapeutic products that exploit differences in molecular targets between normal and tumor cells and to use them in combination with biologic agents and immune therapies to eradicate systemic disease not curable by surgery or irradiation.

Beyond the intellectual challenge of drug discovery, formidable effort, time, and expense are required for the complex development processes that move a new agent from discovery to its ultimate approval for use in the treatment of malignancy. Numerous pitfalls may threaten the progress of a promising agent (e.g., excessive early toxicity, ineffective route or schedule of administration, inappropriate formulation, long-term unpredicted toxicities, and delays in the execution of clinical trials). Although the time to drug approval for the treatment of cancer has varied considerably, depending on the specific agent (e.g., 6 to 12 years from the time of initiation of clinical trials), efforts are being made to expedite both the preclinical and clinical components of investigation. In other areas of medicine, the time to develop specific drugs may be equally long and difficult. However, the potentially fatal consequences of unsuccessful treatment of this disease continue to impart urgency in the discovery and development of novel anticancer agents.

DRUG DISCOVERY

HOW DRUGS ARE DISCOVERED

This section considers strategies for identifying new chemical entities, whether they be synthesized chemicals or compounds extracted or derived from plant, microbial, and marine animal sources. The parallel process for discovery and development of biologic agents is discussed elsewhere in this text. (See Chapter 18.)

In establishing a program for drug discovery, cancer researchers must address two fundamental questions: What screening system should be used to detect a compound of interest? What compounds should be tested in this system? The answers to these questions determine whether the research effort is empiric, with few preconceived notions about where to search for compounds and what to use as the screen, or whether it focuses on a specific biologic target, such as an oncogene, and tests a specific set of materials, such as natural products and rationally synthesized inhibitors of a target enzyme. The history of cancer drug discovery reflects an evolution from highly empiric approaches, based on testing of randomly selected compounds against rapidly proliferating murine leukemia, to the current, more focused testing of natural products, rationally synthesized agents, and biologic products against well-characterized tumor cell lines or molecular targets. Even in its earliest days, however, cancer drug discovery attracted scientists who had a theoretical basis for testing certain types of compounds. Perhaps the two best examples are the antifolates, initially tested by Farber et al., and the fluoropyrimidines synthesized by Heidelberger and colleagues (see Chapter 19.5).

The story of the discovery of antifolates is particularly instructive because it illustrates the important interplay between cancer biology and drug discovery. The earliest uses of an antifolate as a chemotherapeutic agent resulted from the astute observations of Farber and associates, who observed an acceleration of the leukemic process in patients being treated with folic acid. A series of folic acid antagonists were provided to Farber and colleagues by the medicinal chemists at Lederle Laboratories. Although structure-activity relations of antifolates and the intracellular target of these compounds were unknown at that time, it was clear from laboratory studies that modified folates could inhibit tumor cell growth. The initial clinical trial involved the administration of pteroylglutamic acid (an analogue of folic acid, or pteroylglutamate) to a moribund patient with progressive acute myelogenous leukemia, which resulted in a markedly hypocellular bone marrow without actually producing clinical benefit. The investigators were sufficiently encouraged, however, to administer a more powerful folic acid antagonist, aminopterin (2,4-diaminopteroylglutamate), to children with advanced stages of acute leukemia. Substitution of an amino group at the 4 position of the folate pteridine ring created a tight-binding inhibitor of dihydrofolate reductase and yielded drugs with the potential to induce remissions. Approximately 10 of the first 16 patients treated with aminopterin demonstrated evidence of hematologic and clinical improvement. These early clinical experiences provided the foundation for medicinal chemists to synthesize a number of agents with structural similarities to naturally occurring folates. Moreover, these studies revealed that various substitutions resulted in different sites of action, in addition to inhibition of dihydrofolate reductase (Fig. 19.2-1).


From these relatively primitive beginnings, rational design efforts have progressed to the use of computer modeling of drug-enzyme interactions as the basis for
cancer drug discovery. Advances in x-ray crystallographic and nuclear magnetic resonance structural characterization of ligands and their target molecules have significantly enhanced the potential for rational design and, as is described later (see the section Molecular-Targeted Screening), such research efforts are now beginning to identify effective small molecules with efficacy against various human malignancies. Symmetric inhibitors of the protease of human immunodeficiency virus type 1 that were designed on the basis of the three-dimensional symmetry of the active enzyme site are currently in clinical use, thus demonstrating the feasibility and merit of such an approach. 1 

In most current drug discovery efforts, the rational and empiric approaches are being combined. Lead compounds are identified as inhibitors for molecular targets through molecular screening. 2 The lead compound can then be modified or enhanced by chemical analogue synthesis based on a variety of considerations, including a detailed study of target–inhibitor interaction. The complete characterization of the target and its interaction with the lead agent provides the basis for enhancing drug-target interaction. A key decision in this approach is the selection of a suitable target that is likely to have an impact on clinical outcome (enzyme, growth factor receptor, or oncogene product). The next challenge is the development of an appropriate and practical assay to identify the actual lead agents.

Although early efforts in cancer drug discovery tested agents either from the broad universe of synthetic chemicals or from a more targeted rational effort, attention increasingly has focused on natural products as an important, untapped source of promising lead compounds with unique sites of action as antineoplastic drugs. 3 The enormous diversity and complexity of chemical entities that have evolved as part of nature's chemical warfare cannot be readily duplicated by compounds synthesized in the laboratory and be made available for screening. However, the technological advances in combinatorial approaches for synthesizing large numbers of complex substances have provided an entire new source for novel antineoplastic agents. 4–6 Combinatorial chemistry can provide two different kinds of libraries that can then be used for further drug development. 7–9 The first is a generic library, which is used to discover a novel structural motif or feature that possesses a certain biologic activity. The goal of such an unbiased library is to identify a completely novel lead compound. The second type is a focused, biased library that serves to fine-tune the properties and biologic activity of an existing lead compound. In this case, the objective is to identify new lead compounds based on known structures that have already proven to be biologically active.

Approximately 30% of the currently effective antineoplastic agents are from natural sources or are derivatives of a natural product lead. 10 Certain themes run through the efforts to discover and develop natural products. Active compounds often have exceedingly complex structures that complicate efforts at total synthesis. Problems of supply and dependence on a natural resource, therefore, must be anticipated. Structure-activity relations are difficult to elucidate because of the basic problems presented by the unusual chemistry of these compounds and by the multiple chiral centers in these molecules (Fig. 19.2-2). However, the overall contribution of these complex chemical entities to the management of patients has been extremely rewarding.

Among the natural products, microbial antibiotics have been the most important source of cytotoxic agents. As a result of the great advances in the field of microbiology during the 1940s and the dawn of effective antibiotic therapy, potent anticancer drugs were sought in fermentation broths obtained from soil microbes, including bacteria, fungi, and related organisms. The discoveries of the actinomycins, anthracyclines, bleomycin, doxorubicin, and other agents have contributed valuable new entities to the repository of effective antineoplastic agents. Natural product drug discovery, however, must be complemented by efforts to improve leads through chemical modification and analogue synthesis. The discovery and subsequent clinical development of anthracyclines highlights the need for the close interplay of chemistry, biology, and clinical pharmacology in producing improved anticancer agents.

Daunorubicin, isolated from a colony of Streptomyces in 1957, eventually was demonstrated to have significant antileukemic activity in patients. 11 Additional research to induce mutant strains of the fungus Streptomyces resulted in the isolation of doxorubicin. Although the difference between these two anthracyclines is limited chemically to a single hydroxyl group, a marked difference exists in their spectrum of antitumor activity. Doxorubicin has been more effective than daunorubicin in the treatment of metastatic solid tumors and sarcomas. The cardiac toxicity associated with the chronic administration of both these agents, however, has provided impetus to devise a new generation of anthracycline analogues. The long-term assessment of clinical outcome for children successfully treated for malignancy further substantiates the concerns regarding anthracycline-induced cardiotoxicity. 12 None of these anthracycline analogues is devoid of cardiac toxicity, but closely related molecules may have significant advantages. For example, the anthraquinones (e.g., mitoxantrone) demonstrate less cardiotoxicity and have remission-inducing activity in acute nonlymphocytic leukemia. 13 Thus, in modifying the chemical structure of a natural product in an attempt to enhance its therapeutic selectivity, the synthetic organic chemist plays a critical role in this process of drug development.

Natural product research has yielded other effective antineoplastic drugs. Although most of these agents have been identified in fermentation broths of microbial organisms, plants also have provided a number of active antineoplastic agents. One of the earliest plant-derived drugs resulted from a chance observation. In the 1950s, Noble and colleagues 14 were investigating interesting plant extracts used by primitive peoples. This attempt to take advantage of tribal medications, primarily natural products, represented an early entree into the discipline known as ethnopharmacology.

The leaves of the Jamaican periwinkle plant, Vinca rosea, were used to make a tea that was reported to be of benefit in diabetes. 15 During the initial animal investigations, the extract of these leaves was administered orally to both rats and rabbits without any observed effect on blood sugar levels. Subsequent administration of the aqueous extract of the periwinkle plant by injection to rats had a dramatic lethal effect within a week. Postmortem examination of the animals demonstrated that the rats had died of sepsis related to bone marrow suppression. Isolation and chemical characterization of the responsible chemical factors were accomplished using a bioassay-guided approach (i.e., granulocytopenia in the treated animals) for identifying the effective component of this aqueous extract of the plant. The compound was determined to be an organic base and subsequently was called vincaleukoblastine. This agent demonstrated carcinostatic activity against both a transplanted murine mammary adenocarcinoma and a rat-transplanted sarcoma. 16 The mechanism of action (i.e., inhibition of microtubule formation) proved to be unique and provided the basis for an entirely new area of research for cancer drug development.

In contrast to using the complicated biologic end point of the peripheral blood granulocyte count from an intact animal, simple and more rapid screens (e.g., molecular target–based or in vitro cell cytotoxicity assays) currently are used to guide fractionation of extracts for isolation and characterization of active components. After final chemical identification of the plant-derived chemical antineoplastic entity, validation of antitumor activity in an in vivo tumor model is still required. Sufficient supplies of the active agents isolated from natural product sources are needed to conduct adequate in vivo confirmatory studies. Adequate supply was a problem with the periwinkle extract in its early development, and it remains problematic for many natural product agents now being isolated.

Several new plant-derived natural products have proven to be of extreme interest in the treatment of cancer. Taxol was isolated from the bark of the Pacific yew tree in 1971, 17 and it has a unique mechanism of antitumor activity that involves stabilization of microtubule assembly with resultant inhibition of the normal dynamics of microtubule formation. 18 This agent has a broad spectrum of antitumor activity, and it is active against a number of human tumor xenografts, including breast cancer, ovarian cancer, and other malignancies. Subsequent clinical studies have confirmed the high degree of activity in patients with a wide range of solid tumors, including breast, ovary, head and neck, esophageus, testes, and lung malignancies. 19 Initially, a major obstacle to defining the role of Taxol in cancer therapy related to the difficulties encountered with drug supply. 20 Semisynthesis from 10-acetyl baccatin III, was eventually accomplished, and new sources of Taxol from nursery species have been identified. The supply issue has now been fully resolved with the successful total synthesis of this complex molecule. 21 Moreover, advances in the
chemistry of isosorbenes and taxoid anticancer agents have facilitated the synthesis of second-generation taxoid compounds with activity against drug-resistant cancer cells. The history of the development of Taxol is important because it highlights the complexities involved with development of any cancer drug—namely challenges in supply of drug, difficulties with synthesis of drug, issues of drug formulation, and obstacles associated with the implementation of successful clinical studies.

Another natural product that has been under investigation for many years, but only now found to have broad activity against various human malignancies, is derived from the bark of Camsiptoma acuminate, a tree prized for its medicinal properties in traditional Chinese medicine. The camptothecin derivatives are unique because they inhibit topoisomerase I, a key enzyme that maintains DNA in a torsionally relaxed state. Both topotecan and CPT-11, which are derivatives of camptothecin, have significant activity in patients with advanced malignancies, including colorectal cancer, esophageal cancer, non–small cell and small cell lung cancer, and cervical cancer. Significant efforts continue to focus on developing novel analogues of camptothecin with enhanced biophysical and biologic activity. 9-Nitrocamptothecin and 9-amino camptothecin are currently in advanced stages of clinical testing.

Marine organisms represent a largely unexplored and untapped source of unique toxic chemicals. These toxins are elaborated by sponges and other sessile saltwater organisms as defenses against their predators. Several highly potent agents demonstrate interesting antitumor activity against unique molecular targets in preclinical models, and some examples include the bromostatins (which inhibit protein kinase C), the dolastatins and halichondrins (which bind to microtubules), and the tunicate-derived ecteinascidins (which bind in the minor groove of DNA). Although the marine environment represents a untapped potential source for interesting new chemical entities, certain unique problems affect this biosphere. Scale-up procurement of bulk material from marine sources presents a special challenge in biochemical mass collection. The potency of many of these agents may ameliorate this supply problem, but selectivity against the tumor (and not the normal host) must first be demonstrated. In addition, the highly potent natural products present additional challenges for clinical investigators conducting phase I studies. For example, clinical pharmacologic studies may be impossible if the active species is present in such low levels that detection by even very sensitive analytic methods is not feasible at clinically tolerated doses. The rich diversity of chemical structures found in nature provides the impetus for continued research in this area. Moreover, the use of combinatorial chemistry technology may be incorporated into the process once novel therapeutic leads are identified from these natural products.

Cancer drug discovery may also result from a totally fortuitous experimental observation. The discovery of platinum complexes as antiproliferative agents with remarkable clinical activity demonstrates the importance of enlightened empiricism combined with dogged persistence in clinical testing and development. In 1965, Rosenberg observed that an electric current passing through platinum electrodes could inhibit Escherichia coli bacterial cell division. This discovery was confirmed by the subsequent testing of platinum complexes in murine tumor model systems. Cisplatin inhibited the development of sarcomas, and other platinum complexes also were found to be effective in the preclinical models. The early clinical trials demonstrated antitumor activity in patients with advanced malignancies, but the excessive initial toxicity (nephrotoxicity) raised serious concern among the clinical investigators. The demonstration that adequate hydration and slow infusion reduce the degree of renal toxicity permitted further evaluation of the agent. The responses observed in testicular cancer and ovarian cancer led to approval of the drug approximately 6 years after the initial clinical trial. This excellent anticancer drug might have been discarded in error without the foresight of both preclinical and clinical investigators who were convinced of the drug's potential, were committed to the systematic testing of the drug, and were clever enough to find ways to deal with its toxicity. Most of the anticancer agents that have been discovered though empiric screening efforts or represent chemical modifications of lead compounds discovered in cancer screenings.

Screening methods can either be simple, such as a well-characterized cell line or a defined enzymatic target, or complex, such as an in vivo animal tumor. In general, current efforts favor simple systems that accommodate high volumes of unknown compounds. The end point of the cancer screen may be a biologic target (e.g., tumor cell cytotoxicity, growth inhibition, differentiation) or a biochemical-molecular target that is known to be important for the survival of cancer cells. The advantages and disadvantages of each of these approaches is presented in Table 19.2-1. Both the cell line and molecular approach may be combined through the use of genetically engineered cell lines that express a specific molecular target.

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<th>TABLE 19.2-1. Comparison of Cancer Screening Devices</th>
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The evolution of strategies at the National Cancer Institute (NCI) illustrates the changes in screening that have resulted from the advances in cancer biology and cancer genetics. The early NCI cancer screening efforts used murine leukemias (L1210 and P388) as the index tumors in an in vivo screening effort. The screen identified agents that had efficacy in humans in the treatment of leukemias and lymphoproliferative malignancies, such as hydroxyurea and the nitrosoureas. However, the failure of this screen to identify active drugs for the major solid tumors resulted in a significant change in 1975 in the approach of the NCI when animal solid tumor and human tumor xenographs were added as a secondary in vivo tumor panel. In 1985, a second major change was made. The increasing availability of a growing number of cell lines derived from human solid tumors and well characterized with respect to drug response patterns, growth factor dependence, oncogene expression, and other biochemical and molecular features presented an opportunity to focus screening efforts on the unique biology of human solid tumors. A total of 60 human solid tumor cell lines were selected to provide a disease-oriented approach to drug discovery in contrast with the previous compound-oriented drug discovery methods. A total of 60 human solid tumor cell lines derived from seven cancer types (e.g., lung, colon, melanoma, kidney, ovary, brain, leukemia) formed the original cell line panel. Breast cancer cell lines were subsequently added. The initial concept proposed that leads demonstrating disease specificity would be identified, and activity could be further examined by in vivo testing in nude mice, using the most sensitive in vitro index tumor cell lines.

In the current NCI anticancer screen, each candidate agent is tested over a broad concentration range against every cell line in the panel. Active compounds are selected for further testing based on several different criteria: disease-type specificity in the in vitro assay, unique structure, potency, and demonstration of a unique pattern of cellular cytotoxicity or cytostasis, indicating a unique mechanism of action or intracellular target. The agents selected for further investigation are then subjected to additional testing to assess their in vivo therapeutic index. The current version of the cancer drug screening program of the NCI has been in operation since 1990, and a number of novel chemical entities have been identified for further evaluation. This high-capacity screen was designed to accommodate approximately 10,000 individual chemicals tested annually, with additional capacity for screening natural product extracts. Approximately 5% of the compounds tested in the initial screen show sufficient activity to warrant further evaluation in in vivo screens or biochemical-molecular assays. More than 60,000 agents have been screened against a panel of 60 human cancer cell lines. The tumors that are represented in this cell line panel include melanomas; leukemias; and cancers of the breast, prostate, colon, ovary, kidney, and central nervous system. To date, this approach has identified five novel agents (e.g., a tyrosine kinase inhibitor, a protein kinase C inhibitor, and several disease-specific agents) for further testing in clinical trials. It is hoped that an overall assessment of the clinical usefulness of this novel cell line screening approach will be feasible in the near future.

The concept of cancer drug discovery that is based on high-volume screens, whether oriented toward a cell line–based or molecular target, relies on the acquisition of a large source of diverse materials for examination. In the case of the NCI, an extensive program for acquiring both defined chemical entities and diverse natural products has been pursued. Enormous effort was initially invested to standardize the in vitro assay, and sufficient time should be provided to fully evaluate the clinical utility of its early findings.

The pharmaceutical industry is also actively engaged in the procurement of large numbers of interesting chemical structures and natural products for testing in their respective cancer screens, many of which focus on specific molecular targets. Difficult decisions must be made to choose among the large number of unknown entities for initial testing and to aid in the prioritization of known active compounds for further development. Computer programs have been developed to assist in this
molecular targeting. Advocates for the use of mechanistic-based approaches to novel drug discovery have emphasized the potential for selectivity that may result from the use of agents that produce the same level of response for all the cell lines in the screen forms an anchor point for this graphic presentation. The individual response of each cell line to the agent is then depicted by a bar graph extending to the right or left of the mean, depending on whether the cell line was more or less sensitive than the average response, respectively. The length of each bar is proportional to the relative sensitivity of the cell lines. Thus, each agent can be represented by a characteristic fingerprint of cell line responsiveness.

After an agent has been tested in the cancer screen, its unique response pattern can be compared with the results from all other agents within the database. A computer program called COMPARE uses a simple algorithm for aligning and contrasting the patterns for each compound with the patterns of other compounds in the database. A compound is entered into the program as a seed, and the computer database elicits a list of those agents that have similar patterns of tumor cellular responsiveness. In Table 19.2-2, an example is presented for the introduction of a seed compound and the resulting list of agents that had similar patterns of cellular cytotoxicity. A correlation coefficient is also expressed, relating the closeness of the seed to those agents listed by the computer program. Close correlations between agents appear to have biologic and pharmacologic importance, implying a common intracellular target despite a dissimilarity in structure (e.g., tubulin-binding agents, topoisomerase-interactive agents). The COMPARE program has several important features. It can identify the intracellular target or mechanism of action of a new compound through a comparison of its fingerprint with known agents. It can search for compounds previously tested in the cancer screen that have a fingerprint similar to that of a lead compound known to inhibit a unique target. It also has the power to detect inhibition of integrated biochemical and molecular pathways that are not adequately represented by a single molecule or molecular interaction. The comparison also allows recognition of a new agent that does not match with compounds of known mechanisms of action. Given the critical roles of an intact cell-cycle checkpoint and apoptotic pathways in determining chemosensitivity, it is clear that such an algorithmic approach may help identify candidate anticancer drugs that are not dependent on an intact checkpoint and apoptosis function. Finally, this strategy provides the rational basis for future pharmacophore development.

Computer approaches to data analysis similar to that described by the NCI are being developed by industry to search for agents interacting with specific molecular targets. In addition, the NCI has conducted an elaborate characterization of specific molecular targets expressed by the existing tumor cell lines within its screen. For example, because certain cell lines are known to contain a mutated or overexpressed oncogene, such as k-ras or HER-2/neu, it is possible to search the existing database for agents active against only those particular cell lines. This process may ultimately combine the advantages of both cell line–based and molecular screens, but will require separate validation to confirm that identified leads do indeed interact with the purported molecular target in specific assays directed at that entity. Although the NCI cell line screen represents a carefully constructed system for obtaining and analyzing voluminous data on diverse compounds, alternative screening systems in academic centers and industry increasingly rely on high throughput assays based on specific molecular targets, against which combinatorial chemistry inventories are tested. A good example of this approach is the potent antimitotic agent monastrol, isolated by Mayer et al. This agent targets kinesin Eg5, a mitotic protein required for spindle bipolarity and, thus, acts to inhibit the process of mitosis.

MOLECULAR-TARGETED SCREENING

From a scientific perspective, a compelling argument can be made for focusing on a well-defined molecular target and for using computer-based approaches to design small molecules that would specifically interact with this target.

With the rapid advances being made in defining the molecular pathology of neoplastic cells, specific oncogenes have been identified that are expressed uniquely in malignant tissue. The discovery of inappropriately expressed or mutated genes has provided an impetus for the establishment of numerous screens designed to detect specific inhibitors or modulators of the products of these abnormal genes. Intracellular signaling pathways that mediate the actions of growth factors and oncogenes on cell proliferation, such as protein kinases, G proteins, and transcription activators, provide additional novel targets for anticancer drugs. However, given the considerable overlap of access to various growth-factor signaling pathways (many signals use the same distal steps), signal transduction inhibitors may lack specificity for the neoplastic cells.

As an alternative to targeting these intracellular pathways, significant attention has focused on strategies to inhibit the process of angiogenesis. This concept stems from the seminal work of Folkman and colleagues who proposed that the growth of a tumor mass is dependent on the formation of a vascular network that supplies the tumor with essential nutrients. The targeting of the tumor vasculature has two potential advantages over conventional biochemical and molecular targets. The first is that this approach does not require tailoring of therapy to the unique genetic makeup of the tumor, because it appears that all solid tumors are dependent, to some extent, on angiogenesis for growth. In addition, the target of this approach is the normal vascular endothelial cells that are genetically stable and, thus, less likely to become drug-resistant.

Advocates for the use of mechanistic-based approaches to novel drug discovery have emphasized the potential for selectivity that may result from the use of molecular targeting. The expression of identical or closely related molecular or biochemical targets in normal tissue must always be considered. Mutant
oncogenes and their corresponding protein products appear to be the most attractive targets for drug design. Two examples include the fusion protein that results from the BCR-ABL translocation in chronic myelogenous leukemia (CML) and the interference with tumor suppression resulting from the binding of papillomavirus proteins to the RB (retinoblastoma) gene in cervical carcinoma.

In CML and in approximately 20% of adult patients with acute lymphocytic leukemia (ALL), a characteristic reciprocal translocation between chromosomes 9 and 22 is observed. The protooncogene (ABL) from chromosome 9 is translocated at the breakpoint cluster region (BCR) on chromosome 22. This translocation encodes the Bcr-Abl protein, which expresses constitutively activated tyrosine kinase function. It is a 210-kD oncoprotein, and expression of p210 Bcr-Abl induces a disease in mice resembling CML, confirming the critical role of this oncoprotein in the development of CML. The p210 Bcr-Abl protein is present in 95% of patients with CML and in 5% to 10% of adults with ALL for whom there is no evidence of CML. A second fusion protein of 185 kD is found in 10% of adult cases and 5% to 10% of pediatric cases of ALL, but not in CML.

It is clear that expression of this genetic rearrangement is essential for maintaining the malignant phenotype. In addition, transfection of the specific DNA for the BCR-ABL-encoded protein kinase into the hematopoietic stem cells of mice results in the induction of a malignant disorder in vivo with similarities to the clinical illness in humans. Modification of these murine models could provide a potential opportunity to test promising new therapeutic products in vivo. Moreover, the aberrant tyrosine kinase resulting from these abnormal genetic rearrangements (BCR-ABL) within the hematopoietic stem cells does not exist in normal host cells. This abnormal gene provides an ideal molecular target for therapeutic intervention. The crystal structure of several protein kinases has been solved, and a number of compounds have been designed based on the structure of the adenosine triphosphate (ATP) binding site or the active site of the enzyme. In screening against the recombinant BCR-ABL kinase protein, the 2-phenylaminopyrimidine derivative known as CGP 57148 (ST1 STI) proved to be a potent and selective inhibitor, targeting the ATP binding pocket. This compound inhibits all ABL tyrosine kinases at submicromolar concentrations in vitro, and it has minimal to no inhibitory effect on the colony-forming potential of normal bone marrow cells. CGP 57148 appears to be selectively toxic to cells expressing the BCR-ABL tyrosine kinase.

A phase I clinical trial has been completed in CML patients who were unsuccessful with interferon therapy. CGP 57148 was given orally on a daily basis, and treatment was well tolerated, with the most common toxicities being only mild nausea (grade 1), muscle cramps, and arthralgias. With regard to its clinical activity, significant hematologic responses have been observed, with 100% clinical complete response at daily doses greater than 300 mg and a 40% to 50% cytogenetic response. Clinical investigations are in progress to validate the clinical efficacy of this novel agent. Studies have shown that the drug also has potent activity against the platelet-derived growth factor receptor, and in experimental studies, it inhibits tumors that overexpress this receptor. Thus, this compound may have broader application than just for CML.

Another potential target for therapeutic intervention has evolved from an enhanced understanding of the role of aberrant tumor suppressor protein function in the malignant process. It is appreciated that more than 80% of cervical carcinomas have evidence of integrated DNA sequences from papillomaviruses. Human papillomavirus-16 has been implicated frequently as a causal role of this malignancy. Extensive molecular investigation of the association of human papillomavirus with cervical carcinoma has identified specific nuclear proteins that interact with the tumor suppressor gene RB. In fact, the complex protein-protein interaction between the E7 protein from human papillomavirus-16 and the retinoblastoma suppressor protein (pRB) is believed to be important in the cellular transformation that leads to cervical carcinoma. Expression of the E7 protein apparently occurs both within cells from patients with cervical carcinoma and from cell lines derived from this malignancy. The inactivation of the RB tumor suppressor gene by this protein appears to be reversible. There is significant interest in identifying agents that could selectively interfere with this deleterious E7-RB interaction.

**DRUG DEVELOPMENT**

There is an urgent need to move promising new therapies into clinical trials. However, important and clinically relevant information may be lost by proceeding immediately from a primary in vivo screen to a clinical trial without defining the in vivo activity of an agent, its pharmacokinetics and schedule dependency in animals, and its profile of toxicity for normal and malignant cells and tissues. Each of these issues is important and must be addressed in a timely manner to provide safe and reasonable starting doses for implementing phase I trials in patients. The steps required in the development of a cancer agent for clinical practice are complex, and as outlined in Figure 19.2.4, they are both time- and resource-intensive.

![Figure 19.2.4: Steps in cancer drug development. FDA, U.S. Food and Drug Administration.](image)

Secondary in vitro studies to optimize the exposure time to an agent and to define mechanisms of resistance are useful for the investigators planning in vivo studies. Examination of the dose-response data for several tumor cell lines should permit a selection of the optimal tumor system for subsequently evaluating in vivo efficacy. Furthermore, preliminary pharmacologic studies in non–tumor-bearing animals provide useful information about the plasma concentrations achievable and an estimate of the acute toxicity after systemic administration of a new agent. Success in identifying new therapies relies on the expeditious, yet careful, conduct of those studies pertinent to developing a promising in vitro observation (derived from either the cell line screen or the molecular models) into an actual drug candidate.

**IN VIVO ANTITUMOR ASSAYS CURRENTLY IN USE**

In the current NCI development schema, the human tumor cell line most sensitive to an active candidate in vitro is selected for testing as a xenograft in a subcutaneous implant site in a nude mouse. Compounds identified in molecular screens are usually tested against human or murine tumors engineered to overexpress the specific drug target.

Failure to demonstrate in vivo efficacy for agents that display strong in vitro evidence of antitumor activity should prompt additional studies to determine whether a pharmacokinetic or metabolic explanation exists for the loss of activity. The initial lead, either discovered by an empirical screen or as a result of rational chemical design, is usually not the optimal chemical entity for clinical investigation. Lead optimization is an iterative process between chemists and tumor biologists may be required to enhance the in vivo therapeutic index. Factors such as poor solubility and rapid in vivo metabolism may be corrected by analogue development. More potent and less toxic derivatives can often be subsequently developed (i.e., provided the molecule is amenable to modification).

**PRECLINICAL PHARMACOLOGY**

Preclinical studies in mice, rats, and dogs provide essential information about pharmacokinetics and provide a basis for rational schedule development for the new drugs in humans. Factors such as bioavailability (for agents administered by the oral route), metabolism, renal excretion, and penetration into the central nervous system contribute to the understanding of how best to test a new drug in humans. Although there is no guarantee that human subjects will handle a new drug in the same way as the animal species, in most instances the major pathways for drug metabolism and excretion are qualitatively, if not quantitatively, the same across species.

Pharmacokinetic information in animals can also provide a rational basis for dose escalation in humans. Collins and associates have hypothesized that dose-limiting toxicity in mice and humans is a function of drug exposure, as measured by the area under the drug concentration in plasma × time curve (C × T). They predict that
animals and humans encounter dose-limiting toxicity at the same C × T for any given drug and that the experimentally determined dose-limiting C × T can be used as a target for dose escalation in humans. An analysis of experience with phase I drug trials suggested that for most, but not all, drugs, the relationship of C × T to toxicity holds across species. This work potentially allows the clinical investigator to base initial dose escalation steps on measurements of C × T. Dose escalation can proceed in a more rapid fashion than formerly possible using empiric schemes, and wasteful multiple steps in dose escalation can be avoided. This approach, although apparently valid in retrospective studies, still requires broader validation in a prospective manner.

Drugs that demonstrate substantial interspecies variation in patterns of target tissue activation are not good candidates for this approach. For example, drugs activated by deoxycytidine kinase, such as fludarabine phosphate, are much more toxic to human marrow cells than to mouse bone marrow, presumably as a result of the higher levels of this activating enzyme in human cells. In this instance, toxicity in humans would not be accurately predicted by the C × T approach. Furthermore, drug candidates that are excessively potent (e.g., several of the marine natural products) may have biologic effects at plasma concentrations lower than the level of reproducible detection. Consequently, such agents are not acceptable candidates for pharmacologically guided dose escalation.

**FORMULATION STUDIES**

Although the preliminary pharmacologic and toxicologic studies may begin before a decision on the formulation of a product, the Investigational New Drug (IND)--directed toxicology should be performed with the final formulation. In addition, other critical studies may be influenced by the formulation (e.g., bioavailability of an oral formulation, insolubility of an agent demonstrating interesting antitumor activity in the cancer screen). Three important factors that have an impact on formulation studies include solubility, stability, and dosage requirements.

Because the route of drug administration for antineoplastic agents has primarily been through the intravenous approach, the issue of solubility has provided a substantial challenge for a number of agents with limited aqueous solubility. Efforts to improve the solubility of an agent have primarily involved physical measures, including the use of various mixed solvent systems. Novel approaches, including the use of micronization, liposomal encapsulation, and other unique delivery systems (e.g., cyclodextrins and coacervate systems), have been investigated in an effort to improve methods of drug delivery to tissues. Major efforts are needed to expand the vehicles that are available for intravenous drug delivery of agents with limited aqueous solubility and stability.

The prodrug approach uses chemical modification to solve the difficulty associated with drug insolubility. The most recent example of a simple prodrug approach is the synthesis of the monophosphate of 2-fluoro-adenine arabinoside (fludarabine). In essence, the halogenated nucleoside was poorly soluble in aqueous solution. In contrast, the monophosphate (fludarabine) was more soluble and readily cleaved enzymatically in vivo to the 2-fluoro-adenine arabinoside. The nucleoside is rapidly phosphorylated after transport to the intracellular compartment and, thus, can be effective as an anticancer agent.

Unique opportunities exist to use monoclonal antibodies to selectively deliver antineoplastic agents to targeted tumor cells. New methods of prodrug administration (e.g., ADEPT) are being evaluated that couple the administration of an anthracycline glucuronide and the use of a human b-glucuronidase conjugated to a monoclonal antibody for selected delivery to a tumor-bearing animal. It is hoped that this novel approach will enhance the selectivity of anticancer agents, and it may have particular utility in the case of highly potent compounds.

**TOXICOLOGIC INVESTIGATION**

Preclinical toxicology is frequently the final step in the progression of a new chemotherapeutic drug from discovery to initial phase I testing in humans (see Table 19.2–4). The major objectives of the preclinical toxicologic studies include (1) the definition of the qualitative and quantitative organ toxicities (including dose and schedule dependencies), (2) the reversibility of these effects, and (3) the initial safe starting dose proposed for humans. In general, the ideal approach is to ensure that the preclinical toxicologic studies accurately reflect the intended clinical investigations in humans (i.e., identical formulation, schedules, and routes of drug administration, and dose levels anticipated to reflect the likely experience in patients).

The protocols for performing the preclinical toxicity at the NCI have changed dramatically since the late 1970s. Numerous schedules of drug administration were examined in a variety of animal species in the era before 1980. The emphasis later focused on mouse lethality studies for the initial dose-range--finding studies [i.e., lethal dose in 10% of mice (LD$_{10}$), LD$_{50}$, and LD$_{90}$]. The subsequent toxicologic studies were performed on fixed schedules to refine the doses associated with lethal and nonlethal toxicities. The preclinical toxicities reported correlated reasonably well with the subsequent clinical observations. However, the extent of useless information relating to highly lethal murine doses (LD$_{10}$ and LD$_{90}$) led to a redesign of the toxicologic studies.

The current toxicologic investigations accepted by the U.S. Food and Drug Administration involve a simplified two-step approach. The initial step focuses on acute toxicity in small animals (e.g., mice), and the major end point is a determination of the LD$_{50}$ level. The second phase of preclinical toxicologic investigation is more extensive. In this case, emphasis is placed on a careful qualitative and quantitative characterization of the organ-specific toxicities in rodents associated with the schedule and route of administration that is to be used in the initial clinical trial. Attention is given to defining accurately those toxicities that are likely to be observed at doses slightly higher than the highest nontoxic dose. Careful investigation of the toxicities in the animals that approximate the highest projected tolerable dose in the model should provide data that are more relevant to the anticipated clinical experience in patients.

In the past, most new antineoplastic agents were tested clinically on two relatively fixed schedules of drug administration—that is, single-bolus intravenous dose once every 3 to 4 weeks, and 5 consecutive days of treatment repeated at 3- to 4-week intervals. The most frequently used toxicologic protocols reflect each of these schedules. Some newer agents entering preclinical evaluation for cancer therapy are being proposed for weekly intravenous administration, continuous intravenous infusion, or oral dosing. It is critically important that the preclinical toxicologic protocol simulates the planned therapeutic approach in patients.

Because substantial variation may exist between species in their tolerance to a given drug, the safety of a projected starting dose in humans is confirmed by examining the preclinical toxicities in at least two species. Both the qualitative and the quantitative toxicities are usually well defined after investigation of a small animal model (e.g., mouse) and a larger animal (e.g., dog). Only occasionally is testing needed in an additional large animal (e.g., monkey), although this species has been shown to be especially useful for defining central nervous system pharmacokinetics.

Certain organ-specific toxicities are reliably detected with the current toxicologic models (e.g., myelosuppression and gastrointestinal toxicity). In contrast, hepatic and renal toxicities are often missed or falsely positive in animal testing. Toxicities involving the heart, lung, nervous system, pancreas, and integument are even less reliably appreciated. At best, the preclinical evaluation can establish a safe starting dose for humans and predict acute organ toxicity. A complete definition of the toxicologic profile of a new agent usually emerges only after extensive clinical experimentation.

**CONCLUSION**

The discovery and development of novel anticancer agents involves substantial time, effort, and resources. The strategies used for drug discovery range from empiric screening (the source of most of the current active drugs) to rational drug design based on an enhanced understanding of the various biochemical and molecular targets. As outlined in this chapter, an extensive series of preclinical investigations are necessary before the decision to enter clinical trials is made. Significant efforts are then required for the successful completion of clinical studies, in which an individual agent is taken from the initial phase I testing through to the randomized phase III and IV settings. The effective development of new cancer agents demands the close cooperation of a multidisciplinary team that includes basic research scientists, clinical pharmacologists, clinical research nurses, data managers, and clinical investigators. The combined resources of government, academic centers, and the pharmaceutical industry are needed for successfully dealing with the formidable task of identifying effective new therapeutic agents for cancer patients.
Principles of Combinatorial Chemistry

Revolution in Synthetic and Medicinal Chemistry

What is Combinatorial Chemistry and How Does it Relate to Chemical Diversity?

The History of Combinatorial Chemistry

Technical Advances That Enabled Combinatorial Synthesis

High-Throughput Screening and Combinatorial Libraries

The Benefit of Solid-Phase Synthesis

Parallel versus Combinatorial Synthesis

The Practice of Combinatorial Chemistry

Identifying an Inhibitor for a Specific Receptor

Natural Peptides as a Starting Point for Chemical Diversity

Natural Products as a Starting Point for Chemical Diversity

The Mathematics of Diversity

Combinatorial Chemistry in Pharmaceutical Drug Development

"Hit" Generation and "Hit to Lead" Development

Combinatorial Chemistry and Lead Development

Cancer-Related Targets

Combinatorial Biology: Nature’s Biologic Diversity

The Future of Chemical Diversity in Drug Development

Chemical Reference

PRINCIPLES OF COMBINATORIAL CHEMISTRY

REVOLUTION IN SYNTHETIC AND MEDICINAL CHEMISTRY

The field of combinatorial chemistry represents a revolution in both the concepts and construction of chemical entities. This revolution has not only changed the fields of chemical catalysis, materials science, and methods development, but also has impacted the field of drug development. The impact of combinatorial chemistry is likely to be as significant to drug development as the polymerase chain reaction was in advancing cloning techniques for molecular biology. The postgenomic era is predicted to present us with between 50,000 and 150,000 unique genes, each encoding a protein product that is potentially a therapeutic target. Between 1000 and 3000 unique members are predicted to exist within the protein kinase family, which is an important class of therapeutic targets. Because the average medicinal chemist can synthesize approximately 100 molecules per year, it is difficult to envision the identification of unique inhibitors for thousands of proteins using traditional techniques.

This chapter introduces the field of combinatorial chemistry and describes how it has impacted drug development and how it will likely impact future drug development. The aim of this introduction is to serve as a primer for researchers wishing to incorporate chemical diversity into their research program.

WHAT IS COMBINATORIAL CHEMISTRY AND HOW DOES IT RELATE TO CHEMICAL DIVERSITY?

To properly understand what combinatorial chemistry is, the concept of chemical diversity must first be addressed. If diversity is defined as that which represents all possible permutations of a given set, then chemical diversity can be described as the atomic representation of all possible permutations of molecular structure or functional space. The concept of chemical diversity has been recognized since the early days of drug development, when natural products (biologically active chemical entities found in nature) were the main focus of the pharmaceutical industry. At that point, the methods of achieving chemical diversity—in other words, the techniques required to synthesize 10^3 to 10^4 molecules—were unknown, and researchers depended on nature for diversity. Combinatorial chemistry is a collective term referring to those techniques that are used to achieve chemical diversity. A collection of diverse molecules is referred to as a chemical library or, often, a combinatorial library.

THE HISTORY OF COMBINATORIAL CHEMISTRY

TECHNICAL ADVANCES THAT ENABLED COMBINATORIAL SYNTHESIS

The chemical techniques for generating diversity have their origin in the solid-phase synthesis of peptides and nucleotides, both of which had a major impact on the growing field of molecular biology and biotechnology. These technical developments in combinatorial chemistry can be grouped into three major categories: the development of solid-phase chemical synthesis techniques, the development of deconvolution and encoding strategies for combinatorial library construction, and the development of arrayed technologies and chemical synthesizers for the rapid synthesis of molecules. A search of literature reference databases for the keywords combinatorial chemistry or solid-phase organic synthesis provides interesting insight into the rapidity of growth in the field of combinatorial chemistry. By plotting the number of literature citations as a function of year, an almost logarithmic growth is seen in the number of references between the years 1993 and 1996. Most of the major technical achievements in combinatorial chemistry were made before 1990 and were largely influenced by the demands of the pharmaceutical industry.

It should also be noted that the decrease in references to combinatorial chemistry that begins in 1997 is most likely not a function of the field slowing down, but rather a function of the acceptance of combinatorial chemistry in science as a whole. This can be thought of as the keyword disappearance. In an analogous fashion, every paper mentioning the polymerase chain reaction technique shortly after its development would contain the phrase in the title or abstract. After its acceptance as a common technique, however, it was relegated to the experimental section of papers. As the technique of combinatorial chemistry becomes more widespread in the literature, it will cease to be the main focus of papers, becoming merely the technique used to solve much greater research problems. This is likely the trend that is taking place now, as illustrated in Figure 19.2-5.

FIGURE 19.2-5. Graphic representation of the number of literature articles containing the keywords combinatorial chemistry or solid-phase organic synthesis, from 1979 to 1999.
HIGH-THROUGHPUT SCREENING AND COMBINATORIAL CHEMISTRY

Since its inception, high-throughput screening has become a major source of novel drug leads in the pharmaceutical industry. After the existing pharmaceutical chemical stocks had been processed, however, a need for more screening materials emerged. This need far outweighed the potential efforts of the medicinal and natural product isolation chemists. The initial technical advances required for combinatorial chemistry were already in place (see Figure 19.2-6) and promised to be a potential source for large quantities of new chemical entities. Initial libraries were composed mainly of natural peptides. Later, as newer and more general coupling techniques became available, libraries of peptides with unnatural amino acids became commonplace. In general, peptides and peptide-like molecules are usually not a direct source of drugs because of their susceptibility to proteases, poor pharmacodynamics, and potential for antigenic response; therefore, they require extensive chemical development. This fact prompted a large effort in the development of novel chemistry that would be compatible with solid-phase resins. The growth of solid-phase organic synthesis began with the development of solid-phase protocols of known solution-phase reactions. As solid-phase synthetic efforts became more sophisticated, the emergence of complex, even pharmacologically proven, molecules (such as the benzodiazepine core) became commonplace.1

THE BENEFIT OF SOLID-PHASE SYNTHESIS

The development of solid-phase techniques for the manipulation of peptides and nucleotides preceded the development of combinatorial library techniques and thus paved the way for automation by allowing the synthesis of biopolymers in a reproducible format.2 As mentioned earlier, solid-phase synthesis was an important factor in the development of consistent, high-yielding syntheses of polynucleotides and polypeptides. The concept of solid-phase synthesis is summarized in Figure 19.2-6. A solid-phase resin is a beaded form of polystyrene, or any polymeric material, that is chemically functionalized to allow the synthesis of molecules while they are attached to the bead. As is shown in Figure 19.2-6A, each new component can be attached to the previous one in a processive manner, allowing both the automation of the synthesis procedure and a reduced need for chemical purification. Because reagents can be used in large excess, then simply washed away, the only purification step that is required is the last one, after resin cleavage. Developments in solid-phase chemistry involve the development of new resins, more advanced chemistry, and improvement in linking strategies. More advanced approaches to solid-phase synthesis involve improvements in the cleavage step (see Figure 19.2-6B), in which the final transformation in a synthesis alters the nature of the connection to the solid support. In this manner, a selective resin cleavage is achieved, thereby removing the need for purification altogether. This has been demonstrated in many cases, including cyclic peptides,16 metabolism reactions,14-16 and cycloaddition-cycloreversion reactions.15,17

**Figure 19.2-6.** Solid-phase synthesis and selective resin cleavage. A: The major benefit of solid-phase synthesis is a reduced need for chromatographic separation, because only the last step requires purification. B: Through synthetic design, some solid-phase synthesis techniques eliminate chromatography altogether.

PARALLEL VERSUS COMBINATORIAL SYNTHESIS

It should be pointed out that the term combinatorial, which is often used as a general term for the entire field, has a specific meaning in terms of library synthesis. The field is collectively known as chemical diversity; however, the term combinatorial chemistry is still largely ingrained in the literature. Two types of synthetic procedures are used in chemical diversity: parallel and combinatorial synthesis. Figure 19.2-7A shows an example of a combinatorial synthesis. In this method, each reaction takes place in a separate reaction vessel. After the first step, the beads are combined and split apart again. Each mixture is then subjected to a second chemical reaction, pooled, and then split apart again. This process is commonly referred to as the split-pool technique. Each bead travels through a different path in the overall scheme, and ultimately, each possible combination is made. In parallel synthesis (Fig. 19.2-7B), the pools are never recombined and the syntheses proceed independently. The benefits, drawbacks, and required technical advances for each of these synthetic protocols are discussed in the next two sections, Combinatorial Chemical Libraries and Parallel Chemical Libraries.

**Figure 19.2-7.** Combinatorial versus parallel library synthesis. A: Combinatorial synthesis involves the combination of library components during the synthetic sequence. Parallel synthesis involves the spatial segregation of library members during each reaction scheme.

Combinatorial Chemical Libraries

The major difficulty with the implementation of a combinatorial synthesis strategy is the identification of active molecules. Because the strategy involves the pooling of beads, all of the molecules are mixed together in solution, and individual library members must somehow be characterized once they are identified as having biologic activity. For this reason, early developments in combinatorial synthesis focused on deconvolution strategies. Later, methods were developed that involved the encoding of individual beads. The combinatorial deconvolution procedure involves a split-pool synthesis, as seen in Figure 19.2-7A. However, the last set of mixtures are not pooled together, but rather are tested as a mixture. The active “pool” is then resynthesized, but during the resynthesis, the final mixtures are not pooled. This method is called serial deconvolution.20 A related method, referred to as recursive deconvolution, has been developed, in which a fraction of each reaction mixture is saved at each stage of synthesis.22 In this manner, resynthesis involves only adding the last monomer at each stage of deconvolution. This method works best when evaluating a combinatorial library in cell-based assays, because the mixtures can be cleaved from the resin and tested as a whole.

Another type of combinatorial synthesis is referred to as the “one bead, one molecule” approach.21 This procedure also uses the split-pool technique; however, instead of relying on a deconvolution strategy, each bead is chemically tagged after it has been chemically modified. These tags are chemically orthogonal to the growing chemistry chain and have proven useful for the on-bead analysis of protein affinity2 and in off-bead strategies using spatial arrays of beads.23 Once a bead has been identified to contain an active component, the tag is removed and “read” to determine the identity of the molecule. Some of the tagging strategies that have been used include nucleotides,18-17 gas-chromatography (GC)–detectable electrophoric molecules,19 and high pressure liquid chromatography (HPLC)–detectable
secondary amines. Modern mass spectrometry methods are becoming powerful enough to allow the direct detection of the molecules attached to the solid-phase resin. The split-mix technology remains the best method for the construction of libraries of more than 10^19 members.

Parallel Chemical Libraries

The need for technical advances in the development of parallel synthetic techniques is much less than for combinatorial approaches, because the major requirement involves the spatial arraying of each molecule. Two early developments in this field involve the pin and teabag methods. In pin-based library synthesis, the molecules are synthesized on the head of functionalized pins, which serve as probes that can be inserted into any number of solvent or reagent wells. The randomization process takes place by the nature of the fact that each pin is exposed to a different set of reagents or monomers. The teabag approach is similar, in that each separate bag is moved from one reagent or reaction mixture to another. In this case, the molecules are spatially arrayed in the individual bags. A popular advance on this technique involves the use of radialetals to tag each bead, thus allowing a rapid handling of each bag. Microarray chip technology also allows the spatial arraying of a combinatorial library and has proven useful in library synthesis. More recent developments involve synthesis in multwell plates on automated synthesizers. In general, the pharmaceutical industry has turned to this technique, using discrete molecules in a high-throughput format. This technique has been facilitated by the development of large-scale machine-based organic synthesizers.

THE PRACTICE OF COMBINATORIAL CHEMISTRY

IDENTIFYING AN INHIBITOR FOR A SPECIFIC RECEPTOR

Once a protein is identified as a potential therapeutic target, the major goal is to evaluate a biologic system in the absence of the protein activity. Genetchnology has been developed to generate knockout mice that lack a specific protein of interest; however, the mouse must reach development without the aid of this protein and often this gene is required for proper development. Furthermore, it is often more desirable to study the biologic effect in a cell line before proceeding to an animal model.

A number of methods have been developed for identifying inhibitors of receptors. The most common, often used in the pharmaceutical industry, is high-throughput screening. This method often involves an automated assay based on affinity or some related in vitro cell-based or cell-free phenotype and a large library of chemical compounds. These chemicals may originate from a natural product isolation, combinatorial synthesis, or an in-house library grown over many years of chemical development. Such a library can be a great place to start to determine whether a molecule or class of molecules with affinity for either the receptor of interest or a closely related receptor from the same family has already been identified.

In the case in which no known inhibitor exists for the class of receptor of study, or for identifying a novel inhibitor for a specific receptor, then access to chemical diversity is essential. There are two ways of obtaining chemical diversity: It can be made or bought. Because this chapter is intended for a nonchemical audience, we discuss methods of buying chemical diversity.

NATURAL PEPTIDES AS A STARTING POINT FOR CHEMICAL DIVERSITY

The presentation of peptides on the surface of bacteriophage particles is known as phage display. Phage display of peptide libraries has become a common method for quickly obtaining large libraries of natural peptides. The benefit of a natural peptide is that it can elucidate the type of functionality that binds to the receptor of interest, and many peptide phage display libraries are commercially available. Once a natural peptide inhibitor is identified, peptidomimetic strategies can be used to identify nonpeptide inhibitors. The development of nonpeptide inhibitors is usually performed by the further analysis of molecules that mimic the functional nature of the peptide, yet eliminate the poor drug-like qualities of the peptides. One popular and potentially very powerful modification of peptides to improve function and biologic activity is the cyclization of the peptide, which results in a cyclic peptide with a limited number of ground-state conformations and a reduced susceptibility to proteases. However, the cyclization may result in locking the peptide in an inactive conformation, limiting the success of the method. For this reason, many individuals begin screening with cyclized libraries rather than cyclizing a linear peptide. This can even be achieved in phage display by using a randomized peptide sequence that is flanked by cysteine residues. Once the phage is secreted from the cell, the flanking cysteine residues form a disulfide bond and create a cyclic structure. Peptidomimetics has become one of the most studied areas of molecular recognition. Indeed, many natural products themselves are mimics of biologically active peptides.

NATURAL PRODUCTS AS A STARTING POINT FOR CHEMICAL DIVERSITY

Natural products have a rich history in the elucidation of biologic processes and in drug development. Even in those cases in which the natural product itself is not a potential drug, it can offer a glimpse as to what kinds of molecules will be effective in drug development. It is often found that the product of nature lacks the specificity that is desired for therapeutic activity. Combinatorial chemistry offers the possibility of developing a more specific inhibitor using the chemical nature of the natural product as a good starting point for diversity. However, the modification of a natural product or the construction of a novel library based on a natural product is chemically intensive and usually requires collaboration with a chemistry laboratory or pharmaceutical company.

THE MATHEMATICS OF DIVERSITY

One issue that must be addressed when designing a chemical library or evaluating a combinatorial phage peptide library is the total number of individual molecules in that library. Table 19.2.4 shows the diversity that one might expect from different chemical and biologic libraries. The formula for diversity, in any library, can be described as the number of monomer units raised to the power of the number of variable positions. For example, if we chemically synthesize a heptapeptide library using all 20 natural amino acids, our library will contain 20^7, or 1.28 billion different molecules. If we use phage display to create the same heptapeptide library, we must account for the redundancy of the genetic code and consider each codon as a monomer unit. In this case, the diversity increases to 64^7, or 4.4 × 10^19, library members, which is an unmanageable number of clones. Proper design of the library and use of the wobble position can reduce the required number of codons to 32, reducing the diversity to 32^7, or 3.4 × 10^15, library members. This is still a very large number but is slightly more realistic.

<table>
<thead>
<tr>
<th>TABLE 19.2-4. The Mathematics of Chemical Diversity</th>
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<tr>
<td>This table shows the diversity that one might expect from different chemical and biologic libraries. The formula for diversity, in any library, can be described as the number of monomer units raised to the power of the number of variable positions.</td>
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SECTION 19.3
Antitumor Alkylating Agents

OLIVER MICHAEL COLVIN

HISTORY OF THE ALKYLATING AGENTS

A nitrogen mustard alkylating agent was the first nonhormonal chemical that demonstrated significant clinical antitumor activity. The clinical evaluation of nitrogen mustards as antitumor agents evolved from the observed clinical effects of sulfur mustard gas used as a weapon in World War I. This gas was used because of its vesicant effect on the skin and mucous membranes, especially the eyes and respiratory tract. However, in addition to this deadly effect, depression of the hematopoietic and lymphoid systems was observed in victims and experimental animals. These observations led to further studies that used the less volatile nitrogen mustards (Fig. 19.3-1). Studies published in 1946 demonstrated regression of tumors, especially lymphomas, and led to the introduction of the compound nitrogen mustard (mechlorethamine, Mustargen) into clinical practice. Subsequently, less toxic and more clinically effective nitrogen mustard derivatives and other types of alkylating agents have been developed.

CHEMISTRY AND CYTOTOXICITY OF ALKYLATING AGENTS

The alkylating agents react with (or “alkylate”) many electron-rich atoms in cells to form covalent bonds. The most important reactions with regard to their antitumor activities are reactions with DNA bases. Some alkylating agents are monofunctional and react with only one strand of DNA. Others are bifunctional and react with an atom on each of the two strands of DNA to produce a “cross-link” that covalently links the two strands of the DNA double helix. Unless repaired, this lesion will prevent the cell from replicating effectively. The lethality of the monofunctional alkylating agents results from the recognition of the DNA lesion by the cell and the response of the cell to that lesion. Analogous cellular reactions may occur to the interstrand cross-links, but such reactions have not been definitively established.

CLASSES OF ALKYLATING AGENTS AND THEIR PROPERTIES

NITROGEN MUSTARDS

Mustargen

Mustargen is currently used in the MOPP [Mustargen, vincristine (Oncovin), procarbazine, prednisone] regimen for the treatment of Hodgkin’s disease but rarely for other purposes. The other nitrogen mustards in significant clinical use are cyclophosphamide, ifosfamide, melphalan, and chlorambucil (Fig. 19.3-2). All these compounds produce cytotoxicity by forming covalent interstrand cross-links in DNA (as shown in Fig. 19.3-3 for Mustargen). The nitrogen mustard cross-link has been demonstrated to occur in the G-X/C-Y-G configuration, as opposed to the G-C/C-G cross-link that had previously been predicted. The formation of the G-X/C-Y-G cross-link has been postulated to occur on the basis of the greater frequency of approximation of the N7 atoms of the two guaninylates in the G-X/C-Y-G configuration, as opposed to the G-C/C-G configuration.
Mustargen is available only as an intravenous preparation that can also be used topically for cutaneous malignancies. In the MOPP regimen, Mustargen is used at a dose of 6 mg/m² on days 1 and 8 of the monthly schedule. Toxicities unique to the agent are topical irritation and pain on injection if given too rapidly. The clearance of the drug is very rapid, but pharmacokinetics have not been performed with modern techniques.

**Cyclophosphamide**

The most frequently used alkylating agent, cyclophosphamide, is used for the treatment of breast cancer in combination with doxorubicin (Adriamycin) or with methotrexate and 5-fluorouracil and for the treatment of lymphomas, childhood tumors, and many solid tumors. High doses of cyclophosphamide are frequently used in conjunction with bone marrow transplantation and for the treatment of autoimmune diseases.

Cyclophosphamide is inactive in vitro and is metabolized by P-450 enzymes in the liver to active species, as shown in Figure 19.3-4. The initial product is 4-hydroxycyclophosphamide (4-HC), which is released from the liver into the circulation. This compound is in equilibrium with an open-ring tautomer, aldophosphamide. Aldophosphamide spontaneously eliminates acrolein to produce phosphoramide mustard, which is an active bifunctional alkylating species. Phosphoramide mustard is zwitterionic at physiologic pH and enters cells poorly. 4-HC-aldophosphamide is not charged and enters cells facilely. While phosphoramide mustard is toxic to cells in vitro at concentrations of 100 µM and higher, 4-HC is cytotoxic in the range of 10 µM. Thus, 4-HC-aldophosphamide serves as an efficient delivery system for phosphoramide mustard, which has been demonstrated to produce an interstrand DNA cross-link analogous to the cross-link produced by mechlorethamine. Recent studies by Shulman-Roskes et al. have demonstrated that phosphoramidé mustard readily eliminates chloroethylaziridine, which probably also plays a role in the cross-linking of DNA in cells exposed to 4-HC.

**FIGURE 19.3-3.** Alkylation of DNA and formation of interstrand cross-link by nitrogen mustard.

As shown in Figure 19.3-4, 4-HC is a substrate for the enzyme aldehyde dehydrogenase. In cells that contain this enzyme, the bulk of the 4-HC is oxidized to carboxyphosphamide, which is not an active alkylating agent. Consequently, cells with high aldehyde dehydrogenase (ALDH) content are resistant to the metabolites of cyclophosphamide. Early hematopoietic stem cells and megakaryocytes contain high levels, as do the epithelial stem cells in the small intestine and mucous membranes. These observations explain why cyclophosphamide administration produces a shorter period of hematopoietic depression, is relatively sparing of platelets, and is associated with less gastrointestinal toxicity and mucositis than other alkylating agents.

4-HC is too unstable to be used as a reagent, but the compound 4-hydroperoxycyclophosphamide (see Fig. 19.3-4) is spontaneously converted in aqueous solution to 4-HC and can be used for invitro studies of cell sensitivity. This compound has also been used for the invitro treatment of autologous bone marrow to reduce the number of tumor cells returned to the patient.

Cyclophosphamide is available as tablets for oral administration or as an intravenous preparation. The drug is used at a variety of doses and schedules. Oral administration is particularly used for autoimmune diseases at a daily dose of approximately 100 mg. Because of its rapid absorption and high bioavailability, even very high doses can be given orally, but high intermittent doses are usually given intravenously. In moderate-dose combination chemotherapy, doses of cyclophosphamide in the range of 750 mg are usually used. For high-dose therapy in conjunction with hematopoietic cell transplantation, doses of up to 50 mg/kg for 2 or 4 days in combination with other agents are used.

The bulk (nearly 70%) of a dose of cyclophosphamide is excreted in the urine as the inactive carboxyphosphamide. At high doses (approximately 50 mg/kg), plasma concentrations of up to 400 µM of cyclophosphamide are achieved, and clearance depends on the renal clearance and the rate of microsomal metabolism in the liver. With improved and more facile techniques to measure 4-HC concentrations accurately, the clinical pharmacology of cyclophosphamide and this critical transport intermediate are being more carefully defined. Studies in patients receiving high-dose therapy have demonstrated considerable variation in the rates of clearance of cyclophosphamide between patients, with consequent differences in the peak concentrations (1 to 15 µM) and total exposure of the patient to 4-HC (60

**FIGURE 19.3-4.** Metabolism of cyclophosphamide.
to 140 µM.hours). The total exposure to 4-HC is probably the major determinant of therapeutic effect. Currently, several programs are evaluating dose adjustment regimens based on the initial pharmacokinetics of cyclophosphamide and 4-HC. While it is known that substantial concentrations of phosphoramidate mustard are present in plasma (up to 10 µM after 60 mg/kg of cyclophosphamide), this concentration is well below the concentrations needed for in situ cytotoxicity of phosphoramidate mustard.

A unique toxicity of cyclophosphamide and other oxazaphosphorines is a characteristic hemorrhagic cystitis due to irritation of the bladder mucosa from urinary metabolites. Acrolein has been identified as the metabolite most responsible for this effect, but phosphoramidate mustard and chloroacetalddehyde may contribute to this toxicity. Careful hydration and emptying of the bladder are crucial to avoiding this toxicity, which has produced massive and even fatal hemorrhage. Another toxicity that has been associated with cyclophosphamide is an antidiuretic effect, especially at high doses. This effect may produce marked fluid retention and electrolyte abnormalities, particularly low sodium, and seizures and fatalities have been seen. It is important to avoid low-sodium-containing fluids after high-dose cyclophosphamide, and the fluid retention syndrome has been treated with furosemide to promote free water clearance. The most severe dose-limiting toxicity of cyclophosphamide is a fulminant cardiac toxicity, which is often fatal when seen clinically. This toxicity is seen only after the high doses used in bone marrow transplantation. It was initially seen in patients receiving 80 mg/kg/d of cyclophosphamide for 4 days, and the incidence has decreased since lower doses have been used. The syndrome usually presents with severe cardiac failure, beginning approximately 10 days after drug administration, with a dilated heart and low electrocardiogram voltage. There is a characteristic pathologic picture of edema, interstitial hemorrhage, and cardiac necrosis.

**Ilofamide**

Ilofamide is a structural isomer of cyclophosphamide that is often used in the treatment of sarcomas and pediatric tumors (see Fig. 19.3-2). There is more chloroethyl side chain oxidation of ilofamide (up to 50%) than of cyclophosphamide (<10%), and the degree of such metabolism is more variable than with cyclophosphamide. Oxidation of the chloroethyl groups produces chloroacetalddehyde, which is probably responsible for the neurotoxicity and renal toxicity that have been seen with ilofamide therapy. Since the oxidation of a chloroethyl side chain produces a much less toxic monofunctional agent, higher doses of ilofamide than cyclophosphamide must be used clinically. The studies of the clinical pharmacology of ilofamide have been more limited than those of cyclophosphamide but have demonstrated large intrapatient variability in the pharmacokinetics and metabolism of the agent during repeated administrations.

**Melphalan**

Melphalan is now used principally for the treatment of multiple myeloma, for high-dose myeloablative therapy in conjunction with bone marrow transplantation, and for the isolated limb perfusion of localized tumors, especially malignant melanoma and sarcomas (see Fig. 19.3-2). Melphalan is an amino acid analogue and is actively transported into cells by amino acid transport systems. It has been demonstrated that cellular uptake and transport into the central nervous system (CNS) of melphalan can be modulated by the amino acid content in the extracellular fluid. Melphalan is available both as tablets and as an intravenous preparation. For the treatment of multiple myeloma, melphalan is usually used orally at a dose of 0.25 mg/kg for 4 days, with prednisone on the same schedule every 4 to 6 weeks. At these doses, peak plasma concentrations of 0.625 µM are found, but absorption is variable. For bone marrow transplantation, doses of melphalan of 100 to 140 mg/m² are used. At these doses, peak concentrations of melphalan of 40 to 50 µM are reached.

**Chlorambucil**

Chlorambucil is used for the treatment of B-cell chronic lymphocytic leukemia and lymphomas and for the immunosuppressive therapy of autoimmune diseases. It is administered orally and is well tolerated when given either by daily administration or intermittent high-pulse doses. Chlorambucil is well tolerated by most patients and can be used successfully for patients who have severe nausea and vomiting with cyclophosphamide or melphalan.

Chlorambucil is available only in an oral formulation. For chronic leukemia and immunosuppression, daily doses of 3 to 6 mg are given for a number of weeks, or 12 mg/m² may be given monthly. Pulsed dose pulse chlorambucil for lymphoma is given orally at a dose of 16 mg/m² daily for 5 consecutive days each month. Chlorambucil is metabolized to a less active derivative—phenylacetic acid mustard—and the clinical pharmacology of chlorambucil is very similar to that of melphalan.

**AZIRIDINES AND EPOXIDES**

The aziridine agents are related to the nitrogen mustards but contain uncharged aziridine rings that are less reactive than the aziridinium rings formed by most of the nitrogen mustards. The two aziridine agents that are frequently used clinically are thiota and mitomycin C (Fig. 19.3-5). The diepoxide dianhydrogalactitol reacts with DNA in a similar fashion to the aziridines but has been succeeded in clinical use by dibromodulcitol, which spontaneously generates dianhydrogalactitol. Structures of dianhydrogalactitol and its prodrug, dibromodulcitol.
Thiotepa

Thiotepa is now used most frequently in combination with other alkylating agents in high-dose therapy with stem cell support. It has been demonstrated to react with the N7 position of guanine in DNA and to cross-link DNA, indicating that it is acting similarly to the nitrogen mustards. Thiotepa is dealkylated by cytochrome P450 enzymes to produce tepa. Tepa is less toxic than thiotepa and has been demonstrated to produce alkali-labile sites in DNA, rather than cross-links. These findings suggest that tepa reacts differently from thiotepa and produces monofunctional alkylation of DNA.

In combination with cyclophosphamide for high-dose therapy, thiotepa has been given as a continuous infusion for 4 days, at a daily dose of 200 mg/m². Under these conditions, steady-state levels of 2 to 6 µM of thiotepa are rapidly achieved. Thiotepa is also used at a dose of 900 mg/m² in combination with high-dose cyclophosphamide and cisplatin.

Mitomycin C

Mitomycin C is an antibiotic extracted from a Streptomyces species and is used for the treatment of breast cancer, esophageal cancer, and gastrointestinal tumors. As seen in Figure 19.3-5, this compound contains an aziridine ring. Particularly under hypoxic conditions, mitomycin C is reduced, with activation of the C1 position of the aziridine ring. This carbon then reacts in the minor groove with the extracyclic N2 amino group of a guanylic acid, positioning the 10 carbon of the carbamate moiety to react with the N2 of a guanylic acid residue in an adjacent base pair in the complementary DNA strand. Mitomycin C and its reduced metabolites can also produce intrastrand guanylic acid–guanylic acid cross-links that produce bending of the DNA.

In combination regimens, mitomycin C is given at doses of 10 to 15 mg/m² every 4 to 6 weeks. After a dose of 15 mg/m², peak plasma concentrations of 3 µM are seen.

Dianhydrogalactitol

Dianhydrogalactitol (see Fig. 19.3-6) is a hexitol derivative that contains two epoxide groups and cross-links DNA through the N7 atoms of guaninc acid, presumably through the nucleophilic attack of the N7 atoms on the strained-ring epoxide groups. This compound was evaluated in clinical trials and demonstrated modest antitumor activity. However, the structurally related dibromodulcitol (see Fig. 19.3-6) has demonstrated more antitumor activity and is still being used in combination chemotherapy of breast cancer, cervical cancer, and brain tumors. Dibromodulcitol is hydrolyzed to dianhydrogalactitol, and its better antitumor activity is presumably due to more effective localization of the reactive agent in tumor cells. Dibromodulcitol is usually administered at a dose of 1 g/m², which produces a maximum plasma concentration of approximately 50 µM.

ALKYL SULFONATES: BUSULFAN

Busulfan (Myleran), other alkyl sulfonates, and the related sulfamates react with DNA by a direct displacement reaction (as shown in Fig. 19.3-7). Busulfan has been demonstrated to cross-link DNA, but the structure of the cross-link has not been established. A chemically related agent, hepsulfam, with seven methylene units between the reactive groups, has been demonstrated to form a DNA G-X-C/C-X-G interstrand cross-link analogous to those formed by the nitrogen mustards. Haddow and Timmis reported in 1953 that busulfan was active against chronic myelogenous leukemia. Busulfan was for many years the principal agent used to treat this disease, before being replaced by the use of hydroxyurea and interferon-α, both of which have proved to be more effective than busulfan. The most frequent use of busulfan in cancer therapy today is in high-dose therapy for many tumors, including chronic myelogenous leukemia, in conjunction with bone marrow or stem cell transplantation. For this application, high doses of busulfan are combined with cyclophosphamide, total body irradiation, or other agents. The effectiveness of busulfan for this purpose is undoubtedly related to its marked myeloablative properties, the mechanistic bases of which are not understood.

**FIGURE 19.3-7.** Alkylation of guanylate in DNA by busulfan through \( S_2 \) alkylation. A second displacement reaction with the N7 of a guanylate in the complementary strand creates a G-X-C/C-X-G interstrand cross-link.

Until recently, busulfan was available only as an oral preparation, but intravenous preparations are now available. For hematopoietic transplantation, busulfan is usually given as 1 mg/kg every 6 hours for 4 days, for a total dose of 16 mg/kg. Peak concentrations of busulfan after each dose are approximately 10 µM. High doses of busulfan have been associated with venoocclusive disease of the liver. This syndrome consists of hepatomegaly, jaundice, ascites, and hepatic failure with a high mortality rate. Grochow et al. have demonstrated that pharmacokinetic monitoring and dose adjustment of the busulfan can markedly reduce the incidence of venoocclusive disease.

**NITROSOURAES**

The members of the nitrosourea group of therapeutic alkylating agents are related to the alkyl nitrosoureas and similar compounds that have long been known to be carcinogenic. Methyl nitrosoguanidine and methyl nitrosourea are monofunctional alkylation agents and were found to have modest antitumor activity. Montgomery and others evaluated a number of analogues of these compounds and demonstrated remarkable antitumor effects of bischloroethyl nitrosourea (BCNU) against mouse tumors, and particularly against intracranial tumors, which had been refractory to most agents because of the blood–brain barrier. BCNU was found to produce interstrand cross-linking of DNA, which has been demonstrated to occur through the spontaneous generation of a chloroethyl diazonium species and the series of reactions illustrated in Figure 19.3-8. As illustrated, this interstrand cross-link occurs between a guanilate in DNA and the base-paired cytidylate in the other strand of the DNA.
FIGURE 19.3-8. Nitrosoureas.

FIGURE 19.3-9. Reaction of BCNU with DNA to produce a G-C interstrand cross-link.

**Bischloroethylnitrosourea**

BCNU (carmustine; see Fig. 19.3-8) demonstrated activity against brain tumors clinically and has continued to be used in the treatment of gliomas and other brain tumors. BCNU has also been used in the treatment of multiple myeloma and in high-dose therapy in conjunction with bone marrow and stem cell transplantation. BCNU can also be administered to brain tumors by direct injection and by the implantation of biodegradable polymers containing BCNU into the brain.

**Cyclohexylchloroethylnitrosourea**

Cyclohexylchloroethylnitrosourea (CCNU, lomustine; see Fig. 19.3-8) is a more lipid-soluble nitrosourea. It is administered orally and is used in the treatment of brain tumors.

**Methylcyclohexylchloroethylnitrosourea**

Methylcyclohexylchloroethylnitrosourea (semustine; see Fig. 19.3-8) is an oral investigational drug that has been used in the treatment of gastrointestinal tumors.

**N’-[(4-amino-2-methyl-5-pyrimidinyl)methyl]-N-(2-chloroethyl)-N-nitrosourea**

N’-[(4-amino-2-methyl-5-pyrimidinyl)methyl]-N-(2-chloroethyl)-N-nitrosourea (nimustine; see Fig. 19.3-8) is more water-soluble than the other chloroethylnitrosoureas and has been used for the treatment of CNS tumors by the intraarterial and intrathecal routes.

**Clinical Pharmacology**

As a single agent, BCNU is usually used in a dose of 125 to 200 mg/m² every 6 to 8 weeks. In combination with doxorubicin for multiple myeloma, a dose of 30 mg/m² every 3 to 4 weeks has been used. After doses in the range of 100 mg/m², peak plasma concentrations are in the range of 5 µM. For high-dose therapy of breast cancer, BCNU is given at a dose of 600 mg/m² in combination with cyclophosphamide and cisplatin. After this dose of BCNU, the peak plasma levels of BCNU have been shown to be approximately 5 µM.

**Specific Toxicities**

Hematopoietic toxicity of the nitrosoureas is severe and is delayed, with the nadir of the granulocytes occurring approximately 5 to 6 weeks after administration. This finding indicates that these agents selectively damage a very primitive hematopoietic precursor.

**HYDRAZINE AND TRIAZINE DERIVATIVES**

The hydrazine and triazene derivative compounds are analogous to the nitrosoureas in that they decompose spontaneously or are metabolized to produce an alkyl carbonium ion, which alkylates DNA. Hydrazine and its substituted analogues are known carcinogens that inhibit gluconeogenesis in cells and have been promoted as antitumor agents. However, objective preclinical and clinical studies have not supported a significant antitumor effect for hydrazine analogues in general.

**Procarbazine**

Procarbazine is a phenylhydrazine derivative that was initially developed as an inhibitor of monoamine oxidase but was found to have significant antitumor activity in preclinical models and clinically. Procarbazine was one of the components of the first effective combination chemotherapy regimen, MOPP, for Hodgkin’s disease. The agent is currently used for the treatment of Hodgkin’s disease and for the treatment of primary brain tumors. Procarbazine has been demonstrated to be metabolized to a DNA-methylating agent, which is most likely methylazoxymethanol. Since procarbazine is a monoamine oxidase inhibitor, patients can experience CNS depression or stimulation and acute hypertension, especially after the ingestion of tyramine-rich foods.
**Dacarbazine**

Dacarbazine, or DTIC [(dimethyltriazeno)imidazole-carboxamide], is a triazene derivative that is metabolized by microsomal N-demethylation, predominantly in the liver, to an intermediate that spontaneously decomposes to release a methylidiazonium that methylates DNA (Fig. 19.3-11). It is used in the regimen of doxorubicin, bleomycin, vinblastine, and dacarbazine for the treatment of Hodgkin's disease and for the treatment of malignant melanoma. Dacarbazine is usually given orally at 150 to 250 mg/m² for 14 days. Reid et al. measured peak concentrations of MTIC of 0.5 to 5 µM after administration of these doses of temozolomide. This agent has been used as a single agent with bone marrow transplantation at a dose of 2000 mg/m². At this dose, the maximum plasma concentration of dacarbazine was 800 µM. Temozolomide is usually given orally at 150 to 250 mg/m² for 5 days. Reid et al. measured peak concentrations of MTIC of 0.5 to 5 µM after administration of these doses of temozolomide. Because of its complex metabolism, pharmacokinetic studies have been limited. Dacarbazine is an intravenous preparation and is used in the regimen of doxorubicin, bleomycin, vinblastine, dacarbazine for Hodgkin's disease at a dose of 375 mg/m² for 15 days. For the treatment of malignant melanoma, a dose of 200 to 250 mg/m² for 5 days is used and, at this dose, peak plasma concentrations of dacarbazine are approximately 30 µM. This agent has been used as a single agent with bone marrow transplantation at a dose of 2000 mg/m². At this dose, the maximum plasma concentration of dacarbazine was 800 µM. Temozolomide is usually given orally at 150 to 250 mg/m² for 5 days. Reid et al. measured peak concentrations of MTIC of 0.5 to 5 µM after administration of these doses of temozolomide. Baker et al. studied the pharmacokinetics of ¹³C-labeled temozolomide and found peak concentrations of temozolomide of approximately 30 µM and peak concentrations of MTIC of approximately 1 µM.

**MECHANISMS OF TOXICITY AND DRUG RESISTANCE**

**REACTION WITH CELLULAR MOLECULES**

The alkylating agents are potent electrophiles and react with many electron-rich molecules within the cell to be inactivated. The principal such molecule is glutathione (GSH), a tripeptide with a free cysteine sulfhydryl that is present at millimolar concentrations in cells (Fig. 19.3-12). This small nucleophile is known to react with and inactivate virtually all the therapeutic alkylating agents, and a correlation between elevated cellular GSH concentrations and resistance to nitrogen mustards has been demonstrated. The GSH S-transferase enzymes catalyze the conjugation of GSH with electrophiles, and increased activity of this class of enzymes enhances GSH-mediated resistance. The GSH conjugates of specific alkylating agents have been characterized, and the specific isoenzymes of GST that catalyze their formation have been characterized.}

**FIGURE 19.3-11.** Generation of methyl diazonium from the triazenes dacarbazine and temozolomide.

**Temozolomide**

Temozolomide is a triazene analogue that spontaneously decomposes to produce a methyl diazonium ion, as illustrated in Figure 19.3-11. This compound may produce a more homogeneous distribution of the short-lived MITC [(dimethyltriazeno)-imidazole-carboxamide], which is spontaneously generated from temozolomide at all sites, than does dacarbazine, which is metabolized to MTIC in the liver. The principal toxicities seen in phase I trials have been neutropenia and thrombocytopenia, and tumor responses were seen in those trials in patients with glioma and melanoma. Phase II trials in patients with gliomas have shown response rates of 20% to 30%, but phase II trials in patients with sarcomas did not demonstrate significant responses.

**FIGURE 19.3-12.** Structure of glutathione.

Buthionine sulfoximine is an inhibitor of gamma-glutamylcysteine synthetase, the rate-limiting enzyme in the GSH synthesis pathway, and decreases the GSH concentration in cells. Exposure to this compound sensitizes both normal and tumor cells to alkylating agents. In a phase I clinical trial, buthionine sulfoximine has been shown to increase the hematologic toxicity of melphalan and is currently in further clinical trials to determine whether this agent can increase the clinical antitumor efficacy of melphalan.

Cells can also be sensitized to alkylating agents by exposure to inhibitors of GSH S-transferases, and a clinical trial of the GSH S-transferase inhibitor sulfasalazine with melphalan demonstrated increased nausea and vomiting but no increase in hematopoietic toxicity. The membrane transporter multidrug resistance protein is known to mediate the efflux of GSH conjugates from the cell, and Barnouin et al. have demonstrated that this system can transport the GSH conjugates of chlorambucil and melphalan from cells. The observations suggest that modulation of these systems could enhance the efficacy of alkylating agents.

Kelley et al. demonstrated that transfection of metallothionein into cells produced increased resistance to chlorambucil and melphalan. Subsequently, Yu et al. have demonstrated that the thiol groups of metallothionein will bind melphalan and phosphoramide mustards. It has also been demonstrated that exposure of cells to zinc will increase metallothionein concentration in the cell and increase resistance of the cells to melphalan, doxorubicin, and cisplatin.

**ENHANCED DNA REPAIR: C³ ALKYLLATION**
Another mechanism of cellular resistance to alkylating agents is repair of the DNA damage that the agents produce. The most defined mechanism of cellular repair of alkylating agent damage is that of the enzyme O^6-alkylguanine-DNA alkyltransferase. As illustrated in Figure 19.3-13, this enzyme can remove an alkyl group from the O^6 position of guanine, and the alkylated enzyme is then rapidly degraded. This mechanism has been shown to be effective in protecting normal and tumor cells from the carcinogenic and toxic effects of DNA methylating agents, such as temozolomide and procarbazine. Erickson et al. demonstrated that this enzyme would also remove the 6-chloroethyl lesion produced by the alkylation of guanine by the chloroethylnitrosoureas and produce resistance to these compounds, and this observation has been confirmed and extended.

**Figure 19.3-13.** Interactions of O^6-alkylguanine-DNA alkyltransferase. Pathway A: Repair of O^6 alkylation by O^6AT. Pathway B: Inactivation of O^6AT by benzylguanine.

It has been shown that such compounds as O^4-benzylguanine will be acted on by O^6-alkylguanine-DNA alkyltransferase (see Fig. 19.3-13) to remove the benzyl group and that the enzyme will be rapidly degraded and depleted. Such compounds have been demonstrated to reverse tumor resistance due to O^6AT to the O^6 alkylating agents in vitro and in vivo and clinical trials of the combination of such agents and O^6-methylguanine are currently in progress.

However, inhibitors of O^6AT enhance the hematopoietic toxicity of O^6 alkylating therapeutic agents. Hematopoietic stem cells have been successfully transfected with O^6AT variants that are resistant to O^6-benzylguanine and related compounds. The hematopoietic systems of animals populated with these cells are resistant to the combination of O^6-benzylguanine and BCNU, and clinical trials of this approach to improve the efficacy of chloroethyl nitrosoureas and methylating agents are planned.

**CROSS-LINK REPAIR**

The use of alkaline elution and other techniques (Fig. 19.3-14) has demonstrated that DNA interstrand cross-links produced by nitrogen mustards can be removed in bacteria and mammalian cells. The mechanism of such repair has not been elucidated, but nucleotide excision repair and polyadenosine diphosphate-ribose polymerase appear to play a role.

**Figure 19.3-14.** DNA lesions produced by alkylating agents.

Caffeine and related compounds have been demonstrated to enhance the cytotoxicity of nitrogen mustard. This effect was associated with abrogation of G_2 arrest. O'Connor et al. demonstrated that the G_2 arrest associated with nitrogen mustard resistance was associated with decreased activity of cdc2 kinase in the resistant cells. Caffeine has also been shown to inhibit nucleotide excision repair by binding to the subunit that recognizes the damage and helps to mediate this repair activity. Elevated Bcl-2 has also been associated with nitrogen mustard resistance.

A medulloblastoma cell line has been demonstrated to be resistant to activated cyclophosphamide (4-hydroperoxycyclophosphamide) on the basis of increased removal of DNA interstrand cross-links. This cell does not appear to repair cross-links produced by BCNU and busulfan, indicating that the recognition of the nitrogen mustard cross-link is fairly specific.

**IN VIVO RESISTANCE**

Kobayashi et al. and St. Croix et al. have described resistance to alkylating agents and other antitumor agents that is associated with aggregation of tumor cells. This resistance is present when the tumor cells are growing in vivo or in three-dimensional culture with adherence between the cells but is not present when the cells are dispersed in two-dimensional culture. This type of resistance has also been associated with increased metastatic potential.

**COMMON TOXICITIES**

Toxicsities that are associated with specific alkylating agents are described in the discussions of the individual agents. The toxicities common to the alkylating agents as a class are described here.

**HEMATOPOIETIC TOXICITY**

The usual dose-limiting toxicity for an alkylating agent is hematopoietic toxicity. As described, cyclophosphamide usually produces a relatively rapid nadir of the granulocytes, with recovery within 3 weeks after a single dose or short course. Cyclophosphamide is also relatively platelet-sparing. The reason for the relative hematopoietic sparing properties of cyclophosphamide is the high concentration of the enzyme aldehyde dehydrogenase in hematopoietic stem cells and megakaryocytes. The nitrosoureas produce an unusual delayed hematopoietic toxicity, with nadirs of both granulocytes and platelets at 5 to 6 weeks after administration. Severe granulocytopenia and thrombocytopenia are also characteristic of busulfan. An interesting characteristic of busulfan is its relative sparing of lymphocytes. The different hematopoietic effects of alkylating agents, except for the characteristics of cyclophosphamide, are not explained but suggest significant differences in
selectivity of the agents for hematopoietic precursors.

GASTROINTESTINAL TOXICITY

The alkylating agents frequently produce nausea and vomiting, although this effect is usually not as severe as with the platinum agents. Cyclophosphamide produces severe nausea and vomiting in some patients, but these patients usually tolerate chlorambucil, which is clinically less emetogenic. The nausea and vomiting produced by alkylating agents are known to be mediated significantly through the CNS. With the higher doses of alkylating agents used in bone marrow transplantation, increased nausea and vomiting are seen but can usually be controlled by corticosteroids and the newer antiserotonin antemetics. The alkylating agents can cause significant toxicity to the gastrointestinal mucosa and produce mucositis, stomatitis, and diarrhea, especially with the high doses of methotrexate and thiopeta used in bone marrow transplantation.

GONADAL TOXICITY

The alkylating agents can produce significant gonadal toxicity. The characteristic testicular lesion in men is depletion of germ cells without damage to the Sertoli cells, which was first described with nitrogen mustard in 1948. This lesion is also seen, often in association with oligospermia or aspermia, after treatment with other alkylating agents. Spermatogenic dysfunction is reversible in some patients.

Women treated with alkylating agents may develop amenorrhea associated with a marked decrease in ovarian follicles. This complication and its irreversibility increase with the age of the woman.

PULMONARY TOXICITY

Interstitial pneumonitis and fibrosis were initially reported as a consequence of busulfan therapy but have subsequently been reported to occur after therapy with melphan, but have subsequently been reported to occur after therapy with melphan, chlorambucil, cyclophosphamide, mitomycin C, and BCNU. The clinical manifestations of this toxicity are dyspnea and a nonproductive cough, which can progress to cyanosis, pulmonary insufficiency, and death. The syndrome has particularly been associated in frequency and severity with high doses of BCNU. The greater pulmonary toxicity of BCNU may be due to the spontaneous decomposition of BCNU, which produces chloroethyl isocyanate in addition to the alkylating chloroethyl diazonium moiety described. Chloroethyl isocyanate is an analogue of methyl isocyanate, a known pulmonary toxin that produced many deaths when released in an industrial accident in Bhopal, India.

ALOEPECIA

Alloxan from chemotherapy was first described after administration of dimethylmyleran, an analogue of busulfan. The alkylating agents now most associated with alopecia are cyclophosphamide and ifosfamide. Feil and Lamoureux examined the alopecia-producing effects of metabolites and analogues of cyclophosphamide and proposed that the alopecia effect was due to the facile entry of a lipophilic metabolite (now known to be 4-CH) into the hair follicles. This hypothesis is consistent with the fact that vincristine, doxorubicin, and the taxanes, all associated with alopecia, are fairly lipophilic.

TERATOGENICITY

All the therapeutically used alkylating agents are teratogenic in animal studies. A review of the literature in 1968 found that 4 of 25 children born to mothers who received alkylating agents during the first trimester of pregnancy had fetal malformations. On the basis of the limited information available, women treated with an alkylating agent during the first trimester of pregnancy may have a risk as high as 15% of having a malformed infant. Administration of alkylating agents during the second and third trimesters has not been associated with increased fetal malformations. More recent reviews support the lack of malformations produced by treatment during the second and third trimesters.

IMMUNOSUPPRESSION

In 1921, Hektoen and Corper reported an inhibitory effect of sulfur mustard on antibody production. While all the alkylating agents produce some degree of immunosuppression, cyclophosphamide is the most immunosuppressive. Cyclophosphamide and chlorambucil are the alkylating agents most commonly used for the treatment of autoimmune diseases.

Selective inhibition of immunosuppressor cells with low doses of an activated analogue of cyclophosphamide and with melphan has been demonstrated in vivo and in vitro and enhancement of the immune response has been shown in vivo. For this reason, low doses of cyclophosphamide have been used in conjunction with immunotherapy. Because of its potent immunosuppressive properties, cyclophosphamide has been used in preparative regimens for allogeneic stem cell transplantation for malignancy and more recently for the autologous transplantation of autoimmune disease. The use of high doses of cyclophosphamide without stem cell support has now been reported to produce complete remissions in autoimmune diseases.

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SECTION 19.4
Cisplatin and Its Analogues

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INTRODUCTION

The platinum drugs represent a unique and important class of antitumor compounds. Alone or in combination with other chemotherapeutic drugs, cis-diaminedichloroplatinum (II) (cisplatin) and its analogues have made a significant impact on the treatment of a variety of solid tumors. The realization that platinum complexes exhibit antitumor activity arose somewhat serendipitously in a series of experiments carried out by Rosenberg and colleagues beginning in 1961.1 These studies involved determining the effect of electromagnetic radiation on the growth of bacteria in a chamber equipped with a set of platinum electrodes. Exposure of the bacteria to an electric field resulted in a profound change in their morphology and, in particular, the appearance of long filaments that were several hundred times longer than that of their untreated counterparts. This effect was not due to the electric field directly, but to the electrolysis products produced from the platinum electrodes. An analysis of these products revealed that the predominant species was ammonium chloroplatinate \([\text{NH}_4\text{H}_2\text{PtCl}_6]\). This compound was inactive at reproducing the filamentous growth originally observed; however, Rosenberg and colleagues1 soon discovered that the conversion of this complex to a neutral species by UV light resulted in an active species. Attempts to synthesize the active neutral platinum complex failed. They realized, however, that the neutral compound could exist in two isomeric forms, cis or trans, and that the latter species is the one they had synthesized. Subsequently, the cis isomer was synthesized and shown to be the active compound.

The observation that cis-diaminedichloroplatinum (II) and cis-diaminetetraethylplatinum (IV) inhibited bacterial growth led to the testing of four neutral platinum compounds for antineoplastic activity in mice bearing the Sarcoma-180 solid tumor and L1210 leukemia cells.2 All four compounds showed significant antitumor activity, with cis-diaminedichloroplatinum (II) exhibiting the most efficacy. Further studies in other tumor models confirmed these results and indicated that cisplatin exhibited a broad spectrum of activity. Although early clinical trials demonstrated significant activity against several tumor types, particularly testicular tumors, the severe renal and gastrointestinal toxicity caused by the drug nearly led to its abandonment. Cvitkovic et al.3 showed that these effects could be ameliorated, in part, by aggressive prehydration, which rekindled interest in its clinical use. Currently, cisplatin is curative in testicular cancer and significantly prolongs survival in combination regimens for ovarian cancer. The drug also has therapeutic benefit in head and neck, bladder, and lung cancer.4

The unique activity and toxicity profile observed with cisplatin has fueled the development of platinum analogues that are less toxic and more effective against a variety of tumor types, including those that have developed resistance to cisplatin. Two other platinum drugs are widely used: cis-diamminecycllobutene-carboxylato platinum (II) (carboplatin) and 1,2-diaminocyclohexaneoxalato platinum (II) (oxaliplatin). Several new analogues with unique activities are currently in various stages of clinical development. Continued progress in the development of superior analogues requires a thorough understanding of the chemical, biological, pharmacokinetic, and pharmacodynamic properties of this important class of drugs. A review of these properties is the focus of this chapter.

PLATINUM CHEMISTRY

Platinum exists primarily in either a 2+ or 4+ oxidation state. These oxidation states dictate the stereochemistry of the carrier ligands and leaving groups surrounding the platinum atom. Platinum (II) compounds exhibit a square planar geometry, whereas platinum (IV) compounds exhibit an octahedral geometry. Interconversion of the two oxidation states may readily occur. However, the kinetics of this reaction depend on the nature of the bound ligands. The nature of the ligands also determines the stability of the complex and the rate of substitution. For platinum (II) compounds, the rate of substitution of a ligand is strongly influenced by the type of ligand located opposite to it. For cis-diaminedichloroplatinum (II), the two chloride ligands are prone to substitution, whereas substitution of the amino groups is thermodynamically unfavorable.5 The stereochemistry of platinum complexes is critical to their antitumor activity, as evidenced by the significantly reduced efficacy observed with trans-diaminedichloroplatinum (II).

In aqueous solution, the chloride leaving groups of cisplatin are subject to mono- and diaqua substitution, particularly at chloride concentrations below 100 mmol, which exist intracellularly. The equilibria may be described by the following two equations:

\[
\begin{align*}
\text{cis(NH}_3\text{)}_2\text{PtCl}_4 + \text{H}_2\text{O} &\rightleftharpoons \text{cis(NH}_3\text{)}_2\text{Pt}^{2+} + 2\text{H}_2\text{O} \\
\text{cis(NH}_3\text{)}_2\text{Pt}^{2+} + \text{H}_2\text{O} &\rightleftharpoons \text{cis(NH}_3\text{)}_2\text{Pt}^{2+} + \text{H}_2\text{O} \rightleftharpoons \text{cis(NH}_3\text{)}_2\text{PtCl}_2 \rightleftharpoons \text{cis(NH}_3\text{)}_2\text{Pt}^{2+} + 2\text{H}_2\text{O} + \text{H}_2\text{O} \rightleftharpoons \text{cis(NH}_3\text{)}_2\text{Pt}^{2+} + \text{H}_2\text{O} \rightleftharpoons \text{cis(NH}_3\text{)}_2\text{PtCl}_2
\end{align*}
\]

where equilibria constants for each reaction may be written

\[
K_1 = \frac{[\text{Cl}^\cdot][\text{cis - (NH}_3\text{)}_2\text{Pt}^{2+}]}{[\text{cis - (NH}_3\text{)}_2\text{PtCl}_2]} \quad \text{and} \quad K_2 = \frac{[\text{Cl}^\cdot] + [\text{cis - (NH}_3\text{)}_2\text{PtH}_2\text{O}_2^{2+}]}{[\text{cis - (NH}_3\text{)}_2\text{PtCl}_2]}
\]

These descriptions illustrate the key role of ambient chloride concentrations in determining aquation rates. In weakly acidic solutions, the monochloromonoaqua and
diaqua complexes become deprotonated to form the neutral dihydroxo species. The monohydroxo and dihydroxo complexes are the predominant species present in low chloride-containing environments, such as the nucleus. A detailed analysis of the equations and rate constants that govern these reactions has been published.

Based on studies of the reaction of cisplatin metabolites with inosine, the predominant cisplatin species that react with DNA are likely to be the chloroaqua and hydroxoaqua species.

**EVOLUTION OF NOVEL PLATINUM COMPLEXES**

Cisplatin therapy has two major limitations: an undesirable toxicity profile and the development of resistance by tumor cells. Therefore, substantial effort has gone into developing analogues that are less toxic, with a different spectrum of antitumor activity. Progress in understanding the chemistry and pharmacokinetics of cisplatin has guided the development of new analogues. In general, modification of the chloride leaving groups of cisplatin results in compounds with different pharmacokinetics, whereas modification of the carrier ligands alters the activity of the resulting complex. This section summarizes the features of the more important platinum analogues that have been developed, which are shown in Figure 19.4-1.

**CARBOPlatin**

The search for a less toxic platinum drug, pursued at the Institute for Cancer Research in the United Kingdom, led to the development of carboplatin. It was hypothesized that modification of cisplatin to contain a more stable leaving group could alter toxicity without necessarily influencing the cytotoxicity profile. Using a murine screen for nephrotoxicity, it was discovered that substituting a cyclcobutenedicarboxylate moiety for the two chloride ligands of cisplatin resulted in a complex with reduced renal toxicity. Instead, myelosuppression was dose-limiting, a toxicity that is not associated with cisplatin therapy. At effective doses, carboplatin produces less nausea, vomiting, nephrotoxicity, and neurotoxicity than cisplatin and has demonstrated essentially equivalent survival rates in ovarian cancer patients. Similar findings have been observed in other solid tumors. Therefore, based on its superior therapeutic index, greater ease of administration, and more predictable individualized dosing, carboplatin has replaced cisplatin in many chemotherapeutic regimens.

**1,2-DIAMINOCYCLOHEXANE DERivATIVES**

The example of carboplatin provided a paradigm for the development of other platinum coordination compounds with modified leaving groups. However, the antitumor activity of these drugs generally overlaps, and they are not considered effective for the treatment of cisplatin-resistant disease. Therefore, the development of platinum analogues that produce responses in cisplatin/carboplatin-resistant tumors became necessary, and it was hypothesized that modifying the carrier ligands might achieve this. The antitumor activity of a series of platinum compounds containing the 1,2-diaminocyclohexane (DACH) carrier ligand was initially described by Calvert et al. in 1999. Several of these complexes were active in cisplatin-resistant murine leukemias. Kidani et al. also reported significant antitumor activity of DACH platinum complexes. Burchenal et al. selected several DACH derivatives for preclinical development based on their activity in cisplatin-resistant murine leukemias. Subsequent in vitro studies supported the idea that DACH-based platinum complexes were non-cross-resistant in cisplatin-resistant cell lines. In support of these studies, Rix et al. showed that DACH derivatives exhibited a unique cytotoxicity profile compared with cisplatin and carboplatin using the National Cancer Institute 60 cell line screen. Several DACH-platinum compounds have been tested in clinical trials; however, each has had limitations that prevented their continued use.

Interest in DACH compounds has been rekindled by the clinical development of oxaliplatin. Oxaliplatin has demonstrated activity alone or in combination with 5-fluorouracil/leucovorin in colon cancer, a disease that was previously considered to be unresponsive to platinum drugs. Like cisplatin, oxaliplatin preferentially forms adducts at the N7 position of guanine and, to a lesser extent, adenine. However, evidence suggests that the three-dimensional structure of the DNA adducts and biological response(s) they elicit are different from that of cisplatin.

**PLATINUM (IV) STRUCTURES**

The octahedral stereochemistry adopted by platinum (IV) compounds has led investigators to speculate that they may exhibit a different spectrum of activity than that of platinum (II) drugs. Two compounds that have been tested clinically without much success are ormaplatin and iproplatin. Ormaplatin was neurotoxic in phase I trials, and iproplatin did not demonstrate activity in phase II trials. Two platinum (IV) compounds, JM216 [bis(acetato)amminedichloro(cyclohexylamine) platinum (IV)] and JM335 [trans-ammine(cyclohexylamine)dichloroadduct (IV)], have been developed in the United Kingdom and contain several unique features. These compounds may also be classified as mixed amines or ammine/amine platinum (IV) complexes. JM216 is the first orally active platinum compound and is currently undergoing phase II testing. A response rate of 38% was observed in patients with small cell lung cancer; however, no significant antitumor activity was observed in patients with non–small cell lung cancer. Based on the lack of antitumor activity of transplatin [trans-diaminedichloroplatinum (II)], it has been generally believed that most, if not all, trans platinum compounds were inactive. Renewed interest in trans compounds has occurred, however, with the observation that JM335 and a related group of complexes exhibited significant antitumor activity in murine ADJ/PC6 and human ovarian cancer models. Khokhar and colleagues also have produced trans-platinum (IV) compounds containing the DACH moiety that they demonstrated to be non–cross-resistant to cisplatin.

**MULTINUCLEAR PLATINUM COMPLEXES**

The synthesis and preclinical studies of multinuclear platinum complexes was first reported by Farrell et al. These compounds are unique in that their interaction with DNA is considerably different from that of cisplatin, particularly in the abundance of intrastrand cross-links formed. Also, the observation that multinuclear platinum complexes containing the trans geometry exhibit antitumor activity contradicts the original dogma that platinum drugs containing the trans geometry are inactive. Currently, the lead compound in this class of drugs is BBR3464. Its structure is described as two trans-[PtCl(NH3)2] units linked together by a noncovalent tetraamine [P[NHNH2](2)] units linked together by a noncovalent tetraamine [P[NHNH2](2)] unit. Preliminary testing of BBR3464 shows it to be significantly more potent than cisplatin and to be active in cisplatin-resistant xenografts and p53 mutant tumors. Preliminary data from a phase I clinical trial of BBR3464 have indicated that diarrhea and myelosuppression are dose-limiting (P. Calvert, H. Calvert, C. Sessa, G. Cambozi, personal communication, 1999). In this study, a partial response was observed in a patient with metastatic pancreatic cancer.

**OTHER PLATINUM COMPLEXES**

Another approach for the design of novel platinum analogues is to identify compounds that can circumvent specific cisplatin resistance mechanisms. An example of this is ZD0473 (AM7435) [cis-amminedichloro(2-methylpyridine) platinum (III)], which is a sterically hindered platinum complex that was designed to preferentially react with nucleic acids instead of thiol-containing molecules such as glutathione. ZD0473 exhibits activity against acquired cisplatin-resistant cell lines and is active when administered by oral or intraperitoneal routes in human ovarian cancer xenografts. The results of a phase I clinical trial have indicated that myelosuppression is dose-limiting and that nephrotoxicity, neuropathy, and ototoxicity are not prominent. Antitumor activity was observed in previously platinum-treated head and neck
**DNA ADDUCT FORMATION**

The observation by Rosenberg that cisplatin induces filamentous growth in bacteria without affecting RNA and protein synthesis implicated DNA as the cytotoxic target of the drug. Evidence from several subsequent experiments supported this idea. The differential cytotoxic effects observed with platinum drugs are determined, in part, by the structure and relative amount of DNA adducts formed. Cisplatin and its analogues react preferentially at the N7 position of guanine and adenine residues to form a variety of monofunctional and bifunctional adducts. The first step of the reaction involves the formation of monoadducts. These monoadducts may then react further to form intranstrand or interstrand cross-links. The predominant bidentate lesions that are formed with DNA in vitro or in cultured cells are the d(GpG)Pt, d(ApG)Pt, and d(GpNpG)Pt intranstrand cross-links. In a study of cisplatin-treated Chinese hamster ovary (CHO) cells, these lesions were determined to account for approximately 60, 15%, and 20% of the total platinum DNA adducts, respectively. Cisplatin also forms interstrand cross-links between guanine residues located on opposite strands that account for less than 5% of the total DNA bound platinum. These adducts may contribute to the drug's cytotoxicity, because they impede certain cellular processes that require the separation of both DNA strands, such as replication and transcription.

The adducts that are formed between the reaction of carboplatin with DNA in cultured cells are essentially the same as that of cisplatin. However, higher concentrations of carboplatin are required to obtain equivalent total platinum-DNA adduct levels because of cisplatin's slower rate of aquation. The relative amounts of each lesion are different, with the d(GpG)Pt intranstrand adduct being the most prevalent (approximately 40%) followed by the d(GpNpG)Pt (approximately 30%) and the d(ApG)Pt (approximately 15%) intranstrand adducts, respectively.

**MECHANISM OF ACTION**

ASK1, also influences cellular drug sensitivity. Prolonged activation of JNK by cisplatin that was related to cell death. Modulating the activity of kinases upstream of JNK, including c-Abl, MKK3/MKK6, MEKK1, and p38, may account for differences in the cytotoxic mechanism of the two platinum compounds.

Cisplatin-induced accumulation of human tumor cells in G2 phase is necessary for G2 progression through S phase and accumulated in G2. Scheef et al. used computer modeling to demonstrate that oxaliplatin produces a similar DNA bend, base rotation, and base propeller as cisplatin. The major difference, however, is the protrusion of the DACH moiety of oxaliplatin into the major groove of DNA, thus producing a bulkier adduct than that of cisplatin. This bulkier, more hydrophobic adduct may be recognized differently by a host of cellular proteins involved in sensing DNA damage. The functional consequence of these effects is twofold: Proteins, such as polymerases, that recognize and participate in reactions on DNA under normal circumstances may be perturbed, whereas processes that are controlled by proteins that recognize damaged DNA may become activated. The latter group of proteins may function in the DNA repair process or in the initiation of programmed cell death.

**PLATINUM-DNA DAMAGE–RECOGNITION PROTEINS**

The sequence of events that lead to cell death after the formation of platinum-DNA adducts have not yet been elucidated. However, cells treated with platinum drugs display the biochemical and morphologic features of apoptosis. These features are common to cells treated with other cytotoxic and biological agents. Therefore, understanding the pathway(s) that are involved in the early stages of programmed cell death, including the detection/initiation and decision/commitment phases, are important for understanding the unique activities of platinum drugs. The sensitivity of a cell to a platinum drug depends, in part, on cell cycle. For example, proliferative cells are sensitive, whereas quiescent cells, in G0 or G1, are relatively insensitive. Thus, it is possible that programmed cell death initiated at various cell-cycle checkpoints is governed by different proteins and signal transduction pathways.

A model for cisplatin-induced cell death in CHO cells has been provided by Sommerson and Eastman. In this study, cisplatin-treated CHO/AA8 cells experienced slow progression through S phase and accumulated in G2. At low drug concentrations, the cells recovered and continued to cycle. At high drug concentrations, the cells died after a protracted G2 arrest. An aberrant mitosis was observed before apoptosis. Further studies with G2-synchronized cells revealed that passage through S phase is necessary for G2 arrest and cell death, suggesting that DNA replication on a damaged template may result in the accumulation of further damage, ultimately causing the cells to die. Cisplatin-induced accumulation of human tumor cells in G2 has also been observed in mice. Abrogating the G2 checkpoint with pharmacologic agents, such as caffeine or 7-hydroxystaurosporine, have been shown to enhance the cytotoxicity of cisplatin. It is not yet clear how these events specifically transduce a proapoptotic signal. However, the observations provide a valuable framework to begin to elucidate the initial steps.

The decision/initiation/commitment phase of apoptosis hinges on the balance between survival and death signals. Each cell contains a damage threshold that, once surpassed, results in the onset of apoptosis. It is not clear what signaling pathways influence the response of cells to platinum drugs. However, it has been shown that activation or inhibition of known signal transduction pathways can influence platinum drug sensitivity. For example, treatment of various cell lines with tamoxifen, epidermal growth factor, interleukin-1a, tumor necrosis factor-a, and ropamycin enhance cisplatin cytotoxicity. Also, the expression of certain protooncogenes, including Ha-Ras, v-Abl, and Her2/neu, has been shown in some instances to promote cell survival after cisplatin exposure. This is an area of investigation that requires further study, and the overall balance of cell survival and cell death signals may be critical in determining the response of tumors to chemotherapy.

In addition to the mounting evidence supporting the existence of programmed cell death pathways, substantial evidence indicates that cell death is influenced by cellular signal transduction pathways such as those that control growth, differentiation, and stress responses. These signals are mediated primarily by small guanosine triphosphatases and protein serine-threonine kinases. Members of the extracellular signal-related kinase/mitogen-activated kinase family, as well as their upstream activators, have been implicated in these events. The c-JUN amino-terminal kinase (JNK)/stress-activated protein kinase (SAPK) and p38 kinase pathways have been shown to be activated by a variety of environmental stimuli and inflammatory cytokines. JNK/SAPK and p38 phosphorylate and regulate the activity of the ATF2 (alcohol acetyltransferase II) and Elk-1 transcription factors. JNK/SAPK also phosphorylates c-JUN, a component of the AP-1 (activating protein 1) transcription factor complex, on serine residues 63 and 73. Considerable evidence suggests that these protein kinases are involved in transmitting a drug-induced cell death signal. For example, Zanke et al. demonstrated that, in mouse fibroblasts, the inhibition of JNK phosphorylation by the stable transfection of a dominant-negative complementary DNA encoding SEK1, the protein kinase responsible for activating JNK, resulted in reduced sensitivity to cisplatin. Sanchez-Perez et al. observed a prolonged activation of JNK by cisplatin that was related to cell death. Modulating the activity of kinases upstream of JNK, including c-Abl, MKK4/MKK6, MEKK1, and ASK1, also influences cellular drug sensitivity. For example, Chen et al. demonstrated that overexpression of a dominant-negative ASK1, which inhibits activation of JNK, resulted in an inhibition of cisplatin-induced apoptosis. Clearly, activation of these pathways occurs after drug exposure in some cells, and it is important to understand the contribution of these intracellular signaling events to overall platinum drug sensitivity. Within these pathways may reside the key to understanding the...
molecular basis for platinum drug–induced cell death.

MECHANISMS OF RESISTANCE

The major limitation to the successful treatment of solid tumors with platinum-based chemotherapy is the emergence of drug-resistant tumor cells. Platinum drug resistance may be intrinsic or acquired and may occur through multiple mechanisms. These mechanisms may be classified into two major groups: (1) those that limit the formation of cytotoxic platinum-DNA adducts and (2) those that prevent cell death from occurring after platinum-DNA adduct formation. The first group of mechanisms includes decreased drug accumulation and increased drug inactivation by cellular protein and nonprotein thiols. The second group of mechanisms includes increased platinum-DNA adduct repair and increased platinum-DNA damage tolerance. These mechanisms have been described previously in in vitro resistance models, and their relevance to clinical resistance is unknown (Table 19.4-1).

REDUCED ACCUMULATION

The majority of cell lines that have been selected for cisplatin resistance in vitro exhibit a decreased platinum accumulation phenotype, and it is generally believed that this is due to decreased drug uptake rather than enhanced drug efflux. Cisplatin and its analogues may accumulate within cells by passive diffusion or facilitated transport. Cisplatin uptake has been shown to be nonsaturable, even up to its solubility limit, and not inhibited by structural analogues. Carrier-mediated transport is supported by the observation that uptake is partially energy-dependent, ouabain-inhibitable, sodium-dependent, and influenced by membrane potential and cyclic adenosine monophosphate levels. Although no specific drug transports have been implicated in the reduced platinum accumulation phenotype, some insight into a possible pathway has been provided. Using two different acquired cisplatin resistance model systems, Shen et al. reported that the loss of the folate binding protein (FBP) was associated with decreased cellular accumulation of cisplatin, methotrexate, arsenate, and arsenite. Although the loss of FBP was not shown to be directly responsible for reduced cisplatin accumulation, the regulatory mechanism responsible for the reduction in FBP gene expression may be linked to the expression of a transport protein that may influence cisplatin uptake.

The prospect of an active efflux mechanism for platinum drugs has been rekindled by the discovery of a group of multidrug resistance protein (MRP)-related transport proteins. MRP is a member of the ABC superfamily of transport proteins that participates in the extrusion of glutathione-coupled and unmodified anticancer drugs out of cells. Overexpression of MRP confers resistance to a variety of drugs, but not to cisplatin. For platinum complexes, the formation of a glutathione-platinum drug conjugate may be the rate-limiting step for producing an MRP substrate. The MRP homologue cMOAT (canalicular multispecific organic anion transporter) shares 49% amino acid sequence identity and a similar substrate specificity with that of MRP. Taniguchi et al. has shown that cMOAT (MRP2) overexpression is associated with cisplatin-resistant human cancer cell lines exhibiting a decreased platinum accumulation phenotype. These investigators also demonstrated that transfection of an antisense cMOAT complementary DNA into HepG2 cells results in decreased cMOAT protein levels and a fivefold increase in cisplatin sensitivity.

Kool et al. examined the expression of MRP, cMOAT, and three other MRP homologues (MRP3, MRP4, MRP5) in a set of cell lines selected for cisplatin resistance in vitro. MRP1 and MRP4 messenger RNA levels were not increased in any of the cisplatin-resistant sublines. MRP3 and MRP5 were overexpressed in a few cell lines, but the messenger RNA levels were not associated with cisplatin resistance. In contrast, cMOAT was substantially overexpressed in some of the cisplatin-resistant cell lines. An immunohistochemical analysis of the expression of P glycophorin, MRP1, and MRP2 revealed that none of these transporters was associated with response to platinum-based chemotherapy in ovarian cancer.

INACTIVATION

As mentioned above, the formation of conjugates between glutathione (GSH) and platinum drugs may be an important step for their inactivation and elimination from the cell. For many years, investigators have attempted to make positive correlations between platinum drug sensitivity, GSH levels, and the relative expression of the enzymes involved in GSH metabolism. There have been many reports showing a strong association between platinum drug sensitivity and GSH levels. However, reducing intracellular GSH levels with drugs such as buthionine sulfoximine has resulted in only low to modest potentiation of cisplatin sensitivity. Part of the reason for this may be due to the fact that the formation of GSH-platinum conjugates is a slow process. The formation of a GSH-platinum complex, however, has been reported to occur in cultured cells, and GSH has been shown to quench platinum-DNA monoaducts in vitro, preventing them from being converted to potentially cytotoxic cross-links. These findings raise the question of whether the intracellular reaction is catalyzed by glutathione S-transferases (GSTs). In support of this theory, a threefold increase in cisplatin resistance in CHO transfected with the GSTp isoenzyme. In contrast, transfection of NIH3T3 cells with GSTp resulted in hypersensitivity to cisplatin. Studies attempting to associate GST activity with cisplatin sensitivity in cell lines and tumor biopsies have not consistently shown a positive correlation between GST expression or activity and cisplatin sensitivity.

Inactivation of the platinum drugs may also occur through binding to the metallothionein (MT) proteins. The MTs are a family of sulfhydryl-rich, small-molecular-weight proteins that participate in heavy metal binding and detoxication. In vitro, cisplatin binds stoichiometrically to metallothionein, and up to ten molecules of cisplatin can be bound to one molecule of metallothionein. Kelley et al. demonstrated that overexpression of the full-length MT-Ib in mouse C127 cells conferred a fourfold resistance to cisplatin. Furthermore, this group showed that embryonic fibroblasts isolated from MT-null mice were hypersensitive to cisplatin. These studies clearly show that modulating MT levels can alter cisplatin sensitivity. However, the contribution of MT to clinical platinum drug resistance is unclear. In some cell lines, overexpressed in some cisplatin-resistant human cancer cell lines exhibiting a decreased platinum accumulation phenotype. These investigators also demonstrated that transfection of an antisense cMOAT complementary DNA into HepG2 cells results in decreased cMOAT protein levels and a fivefold increase in cisplatin sensitivity.

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INCREASED DNA REPAIR

Once platinum-DNA adducts are formed, cells must either repair or tolerate the damage to survive. The capacity to rapidly and efficiently repair DNA damage clearly plays a role in determining a tumor cell's sensitivity to platinum drugs and other DNA damaging agents. Evidence suggests that cells lines derived from tumors that are unusually sensitive to cisplatin, such as testicular nonseminomatous germ cell tumors, are deficient in their ability to repair platinum-DNA adducts. Increased repair of platinum-DNA lesions in cisplatin-resistant cell lines as compared with their sensitive counterparts has been shown in several human cancer cell lines, including ovarian, breast, and murine leukemia cell lines. Evidence for increased repair of cisplatin interstrand cross-links in specific gene and nonogene regions in cisplatin-resistant cell lines also has been demonstrated. These studies have been done using a variety of in vivo methods, including unscheduled DNA synthesis, host cell reactivation of cisplatin-damaged plasmid DNA, atomic absorption spectrometry, quantitative polymerase chain reaction, and renaturing agarose gel electrophoresis.

The repair of platinum-DNA adducts occurs predominantly by nucleotide excision repair (NER). However, the molecular basis for the increased repair activity

<p>| TABLE 19.4-1. Correlation Coefficients Derived from the Relationships between Cisplatin-Sensitivity and Cisplatin-Resistance Mechanisms in Two Human Ovarian Cancer Model Systems |
|----------------|----------------|----------------|----------------|</p>
<table>
<thead>
<tr>
<th>Resistance Mechanism</th>
<th>In Vivo-Selected Cisplatin-Resistant</th>
<th>Cisplatin Sensitivity</th>
<th>Cisplatin Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin uptake</td>
<td>0.84</td>
<td>0.74</td>
<td>0.74</td>
</tr>
<tr>
<td>GSTp expression</td>
<td>0.66</td>
<td>0.70</td>
<td>0.70</td>
</tr>
<tr>
<td>MT expression</td>
<td>0.74</td>
<td>0.74</td>
<td>0.74</td>
</tr>
<tr>
<td>MRP expression</td>
<td>0.68</td>
<td>0.70</td>
<td>0.70</td>
</tr>
</tbody>
</table>

Part of the reason for this may be due to the fact that the formation of GSH-platinum conjugates is a slow process. The formation of a GSH-platinum complex, however, has been reported to occur in cultured cells, and GSH has been shown to quench platinum-DNA monoaducts in vitro, preventing them from being converted to potentially cytotoxic cross-links. These findings raise the question of whether the intracellular reaction is catalyzed by glutathione S-transferases (GSTs). In support of this theory, a threefold increase in cisplatin resistance in CHO transfected with the GSTp isoenzyme. In contrast, transfection of NIH3T3 cells with GSTp resulted in hypersensitivity to cisplatin. Studies attempting to associate GST activity with cisplatin sensitivity in cell lines and tumor biopsies have not consistently shown a positive correlation between GST expression or activity and cisplatin sensitivity. Inactivation of the platinum drugs may also occur through binding to the metallothionein (MT) proteins. The MTs are a family of sulfhydryl-rich, small-molecular-weight proteins that participate in heavy metal binding and detoxication. In vitro, cisplatin binds stoichiometrically to metallothionein, and up to ten molecules of cisplatin can be bound to one molecule of metallothionein. Kelley et al. demonstrated that overexpression of the full-length MT-Ib in mouse C127 cells conferred a fourfold resistance to cisplatin. Furthermore, this group showed that embryonic fibroblasts isolated from MT-null mice were hypersensitive to cisplatin. These studies clearly show that modulating MT levels can alter cisplatin sensitivity. However, the contribution of MT to clinical platinum drug resistance is unclear. In some cell lines, elevated MT levels have been shown to be associated with cisplatin resistance, whereas in others, they have not. Studies with human tumors have shown that, in some instances, metallothionein expression level is associated with response to chemotherapy. For example, a significant correlation between MT overexpression and response or survival was reported in uterine transitional cell carcinoma patients. Overexpression of MT also has been observed in bladder tumors from patients that were unsuccessful with cisplatin chemotherapy.
observed in cisplatin-resistant cells is unknown.34 Because the rate-limiting step in this process is platinum-adduct recognition/inclination, increased expression of the proteins that control this step are likely to enhance nucleotide excision repair activity. Using an in vitro assay, Ferry et al. demonstrated that the addition of the ERCC1/XPF (excision repair) protein complex increased the platinum-DNA adduct excision activity of an ovarian cancer cell extract. Circumstantial evidence also implicates ERCC1 expression with increased NER and cisplatin resistance. For example, expression levels of the ERCC7 and XPA genes have been shown to be higher in malignant tissue from ovarian cancer patients resistant to platinum-based therapy compared with those responsive to treatment.35 ERCC7 expression also has been shown to correlate with NER activity and cisplatin resistance in human ovarian cancer cells.36 Increased levels of XPF, a putative DNA repair protein that recognizes many DNA lesions, including platinum-DNA adducts, has been observed in tumor cell lines resistant to cisplatin.37 It should be noted, however, that XPF is not a necessary component for the in vitro reconstitution of NER.38,39 Increased expression of DNA polymerases and b have been observed in cisplatin-resistant cell lines, and increased expression of these polymerases, as well as DNA ligase, has been described in human tumors after cisplatin exposure in vivo.40 The possible significance of these findings is unclear because the primary polymerases involved in NER are thought to be DNA polymerases δ or ε.41 Although it is probably not involved in NER, DNA polymerase b may be involved in translesion DNA synthesis.42

Inhibiting DNA repair activity to enhance platinum drug sensitivity has been an active area of investigation. Agents that have been used include nucleoside analogs, such as gemcitabine, fludarabine, and cytarabine; the ribonucleotide reductase inhibitor hydroxyurea; and the inhibitor of DNA polymerases a and g, aphidicolin. All of these agents interfere with the repair synthesis stage of various repair processes, including nucleotide excision repair, and it should be noted that these compounds are also likely to affect DNA replication and, as such, should not be strictly characterized as repair inhibitors. The potentiation of cisplatin cytotoxicity by treatment with aphidicolin has been studied extensively in human ovarian cancer cell lines. Although some studies have demonstrated a clear synergism with this drug combination,43 others have not.44 In an in vivo mouse model of human ovarian cancer, the combined treatment of cisplatin and aphidicolin glicinate, a water-soluble form of the drug, was found to be significantly more effective than cisplatin alone.45 The combination of cytarabine and hydroxyurea was found to demonstrate cytotoxic synergy with cisplatin in a human colon cancer cell line46 and in rat mammary carcinoma cell lines.47 Moreover, the modulatory effect of cytarabine and hydroxyurea on cisplatin was associated with an increase in DNA interstrand cross-links in both cellular systems. Similarly, the drugs gemcitabine48 and fludarabine49 have both been shown to synergize with cisplatin in causing cell death in in vitro systems, and both of these drugs have been shown to interfere with the removal of cisplatin-DNA adducts. The likelihood of a significant improvement in the therapeutic index of cisplatin in refractory patients by the coadministration of a repair inhibitor, however, is limited by the multifactorial nature typical of resistant tumor cells. The combination of an inhibitor of the repair process with other modulators of resistance may be a more viable avenue in treating patients with recurrent disease. Furthermore, a modest change in drug sensitivity may bring some refractory tumors into a range that is treatable with conventional chemotherapy.

INCREASED DNA DAMAGE TOLERANCE

Platinum-DNA damage tolerance is a phenotype that has been observed in both cisplatin-resistant cells derived from chemotherapy-refractory patients and cells selected for cisplatin resistance in vitro. The contribution of this mechanism to resistance is significant, and it has been shown to correlate strongly with cisplatin resistance as well as to resistance to other drugs in two ovarian cancer model systems (see Table 19.4-1). Like other cisplatin resistance mechanisms, this phenotype may result from alterations in a variety of cellular pathways.

One component of DNA damage tolerance that has been observed in cisplatin-resistant cells involves the loss of function of the DNA MMR system. The main function of the MMR system is to scan newly synthesized DNA and to remove mismatches that result from nucleotide incorporation errors made by the DNA polymerases. In addition to causing genomic instability, it has been reported that loss of MMR is associated with low-level cisplatin resistance and that the selection of cells in culture for resistance to this drug often yields cell lines that have lost a functional MMR system.50 MMR deficiency may create an environment that promotes the accumulation of mutations in drug-sensitive genes. Another hypothesis is that the MMR system serves as a detector of platinum-DNA adducts. MSH2 alone, and in combination with MSH6, has been shown to bind to cisplatin 1,2-d(GpG)Pt intrastrand adducts with high efficiency.50,51 Additionally, MSH2- and MLH1-containing platinum-DNA complex have been observed when nuclear extracts of MMR-proficient cell lines were incubated with DNA preincubated with cisplatin, but not with oxaliplatin. These data suggest that MMR recognition of damage may trigger a programmed cell death pathway, rendering cells with intact MMR more sensitive to DNA damage.52 Another possibility is that the cytotoxicity involves repeated rounds of synthesis past the platinum-DNA lesions followed by recognition and subsequent removal of the newly synthesized strand by the MMR system. This futile cycling may generate DNA strand gaps and breaks that trigger programmed cell death.53 Loss of MMR thus increases the cell's ability to tolerate platinum-DNA lesions.

Another possible tolerance mechanism related to MMR is enhanced replicative bypass, which is defined as the ability of the replication complex to synthesize DNA past a platinum adduct.54,55 Increased replicative bypass has been shown to occur in cisplatin-resistant human ovarian cancer cells.56 These cells are also MMR-deficient, and it has been shown that in steady-state chain elongation assays, a 2.5- to 6.0-fold increase in replicative bypass of cisplatin adducts occurred. Oxaliplatin adducts are not recognized by the MMR complex, and no significant differences in bypass of oxaliplatin adducts in MMR-proficient and -defective cells were observed. DNA polymerase δ, the most inaccurate of the DNA polymerases, may also function in this process.56 The activity of this enzyme was found to be significantly increased in cells derived from a human malignant glioma resistant to cisplatin compared with its drug-sensitive counterpart.55

The tolerance mechanisms just mentioned are related primarily to cisplatin resistance. Because the platinum-DNA damage tolerance phenotype is often associated with cross-resistance to other unrelated chemotherapeutic drugs,57 the existence of a more general resistance mechanism must be considered. One possible explanation is that the platinum-DNA damage tolerance phenotype is the result of decreased expression or inactivation of one or more components of the NER pathway. At multiple stages of NER, a number of pro- and antiapoptotic proteins regulate the NER pathway and its up-regulation may have been implicated in cisplatin sensitivity. The possibility exists that cells containing defective or constitutively down-regulated stress signaling pathways, such as SAPK/JNK, may exhibit resistance to platinum drugs. Many of these proteins are highly expressed in cisplatin-resistant cell lines. The expression of these pathways may also have the capacity to influence drug sensitivity. In addition, cell death may also be influenced by expression of members of the bcl-2 gene family. This group of pro- and antiapoptotic proteins regulates mitochondrial function, and they serve as a cell survival/ cell death rheostat by forming homo- and heterodimers with one another. The antiapoptotic bcl-2 and bcl-XL proteins are localized in the outer mitochondrial membrane and may be involved in the formation of transmembrane channels. Overexpression of bcl-2 or bcl-XL has been shown to prevent disruption of the mitochondrial transmembrane potential and to prolong cell survival in some cells after exposure to cisplatin and other anticancer drugs.58 The activity of these proteins is negated, however, in the presence of high levels of the proapoptotic protein BAX, another bcl-2 family member. Therefore, the relative intracellular levels of these proteins may also confer resistance to platinum drugs. An interesting connection between the bcl-2 gene family and SAPK/JNK has been reported by Kharbanda et al.59 They found that, after genotoxic stress, SAPK/JNK is translocated to the mitochondria, where it phosphorylates bcl-XL, presumably rendering it inactive.

CLINICAL PHARMACOLOGY

PHARMACOKINETICS

The pharmacokinetic differences observed among platinum drugs may be attributed to the structure of their leaving groups, which are summarized in Table 19.4-1. Platinum drug pharmacokinetics also have been reviewed elsewhere.60-62

<table>
<thead>
<tr>
<th>Compound</th>
<th>Caspase</th>
<th>Carboplatin</th>
<th>Oxaliplatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1/2 (h)</td>
<td>16-49</td>
<td>18-64</td>
<td>30-140</td>
</tr>
<tr>
<td>T1/2 (h)</td>
<td>11-15</td>
<td>10-13</td>
<td>9-12</td>
</tr>
<tr>
<td>T1/2 (h)</td>
<td>7.4-8.6</td>
<td>1.2-4.6</td>
<td>1.1-9.5</td>
</tr>
<tr>
<td>Unchanged</td>
<td>7.4-8</td>
<td>1.5-9</td>
<td>1.1-9.5</td>
</tr>
<tr>
<td>Dose (mg)</td>
<td>100-400</td>
<td>100-200</td>
<td>100-200</td>
</tr>
<tr>
<td>Plasma clearance</td>
<td>14-35 mL/min/m²</td>
<td>14-35 mL/min/m²</td>
<td>14-35 mL/min/m²</td>
</tr>
<tr>
<td>Urinary excretion</td>
<td>20-40%</td>
<td>14-45%</td>
<td>10-45%</td>
</tr>
</tbody>
</table>

Table 19.4-1. ErbB family, bcl-2, and bcl-XL. The significance of these findings is unclear because the primary polymerases involved in NER are thought to be DNA polymerases δ or ε.41 Although it is probably not involved in NER, DNA polymerase b may be involved in translesion DNA synthesis.42

Inhibiting DNA repair activity to enhance platinum drug sensitivity has been an active area of investigation. Agents that have been used include nucleoside analogs, such as gemcitabine, fludarabine, and cytarabine; the ribonucleotide reductase inhibitor hydroxyurea; and the inhibitor of DNA polymerases a and g, aphidicolin. All of these agents interfere with the repair synthesis stage of various repair processes, including nucleotide excision repair, and it should be noted that these compounds are also likely to affect DNA replication and, as such, should not be strictly characterized as repair inhibitors. The potentiation of cisplatin cytotoxicity by treatment with aphidicolin has been studied extensively in human ovarian cancer cell lines. Although some studies have demonstrated a clear synergism with this drug combination, other studies have not. In an in vivo mouse model of human ovarian cancer, the combined treatment of cisplatin and aphidicolin glicinate, a water-soluble form of the drug, was found to be significantly more effective than cisplatin alone. The combination of cytarabine and hydroxyurea was found to demonstrate cytotoxic synergy with cisplatin in a human colon cancer cell line and in rat mammary carcinoma cell lines. Moreover, the modulatory effect of cytarabine and hydroxyurea on cisplatin was associated with an increase in DNA interstrand cross-links in both cellular systems. Similarly, the drugs gemcitabine and fludarabine have both been shown to synergize with cisplatin in causing cell death in in vitro systems, and both of these drugs have been shown to interfere with the removal of cisplatin-DNA adducts. The likelihood of a significant improvement in the therapeutic index of cisplatin in refractory patients by the coadministration of a repair inhibitor, however, is limited by the multifactorial nature typical of resistant tumor cells. The combination of an inhibitor of the repair process with other modulators of resistance may be a more viable avenue in treating patients with recurrent disease. Furthermore, a modest change in drug sensitivity may bring some refractory tumors into a range that is treatable with conventional chemotherapy.
TABLE 19.4-2. Comparative Pharmacokinetics of Platinum Analogues after Bolus or Short Intravenous Infusion

Cisplatin
After intravenous infusion, cisplatin rapidly diffuses into tissues and is covalently bound to plasma protein. More than 90% of platinum is bound to plasma protein at 4 hours postinfusion. The disappearance of ultrafilterable platinum is rapid and occurs in a biphasic fashion. Half-lives of 10 to 30 minutes and 0.7 to 0.8 hours have been reported for the initial (T_{1/2a}) and terminal phases (T_{1/2b}). Cisplatin excretion is dependent on renal function, which accounts for the majority of its elimination. The percentage of platinum excreted in the urine has been reported to be between 23% and 40% at 24 hours postinfusion. Only a small percentage of the total platinum is excreted in the bile.

Carboplatin
The differences in pharmacokinetics observed between cisplatin and carboplatin depend primarily on the slower rate of conversion of carboplatin to a reactive species. Thus, the stability of carboplatin results in a low incidence of nephrotoxicity. Carboplatin diffuses rapidly into tissues after infusion, but it is considerably more stable in plasma. Only 24% of a dose was reported to be bound to plasma protein at 4 hours postinfusion.

The disappearance of platinum from plasma after short intravenous infusions of carboplatin has been reported to occur in a biphasic or triphasic manner. The initial half-lives for total platinum, which vary considerably among several studies, are listed in Table 19.4-2. Plasma elimination of total platinum and ultrafiltrates is biphasic. The T_{1/2a} and T_{1/2b} are 26 minutes and 38.7 hours, respectively, for total platinum and 21 minutes and 24.2 hours, respectively, for ultrafilterable platinum (see Table 19.4-2). As with carboplatin, substantial differences between total and free drug kinetics are not observed. Similar to cisplatin, a prolonged retention of carboplatin is observed in red blood cells. Unlike cisplatin, however, oxaliplatin does not accumulate to any significant level after multiple courses of treatment. This may explain why neurotoxicity associated with oxaliplatin is reversible. Oxaliplatin is eliminated predominantly by the kidneys, and cumulative urinary excretion of platinum is 54% to 82%, most as unmodified carboplatin. The renal clearance of carboplatin is closely correlated with the glomerular filtration rate (GFR).

PHARMACODYNAMICS
Pharmacodynamics relates pharmacokinetic indices of drug exposure to biological measures of drug effect, which is usually defined by toxicity to normal tissues or by amount of tumor cell kill. Two issues to be addressed in such efforts are whether the effectiveness of the drug can be enhanced or the toxicity attenuated by knowledge of the platinum pharmacokinetics in an individual. These questions are appropriate to the use of cytotoxic agents with relatively narrow therapeutic indices. Toxicity to normal tissues can be quantitated as a continuous variable when the drug causes myelosuppression. Thus, the early studies of carboplatin demonstrated a close relationship of changes in platelet counts to the area under the concentration-time curve (AUC) in the individual. The AUC was itself closely related to renal function, which was determined as creatinine clearance. Based on these observations, Eggin et al. and Calvert et al. derived formulas based on creatinine clearance to predict either the percent change in platelet count or a target AUC. More recently, Chatelut and colleagues have derived a formula that relies on serum creatinine as well as morphometric determinants of renal function. Application of pharmacodynamically guided dosing algorithms for carboplatin has been widely adopted as a means of avoiding overdosage (by producing acceptable nadir platelet counts) and of maximizing dose intensity in the individual. Good evidence suggests that this approach can decrease the risk of unacceptable toxicity. Accordingly, a dosing strategy based on renal function is recommended for the use of carboplatin.

A key question is whether maximizing carboplatin exposure in an individual can measurably increase the probability of tumor regression or survival. In an analysis by Jodrell et al., carboplatin AUC was a predictor of response, thrombocytopenia, and leukopenia. The likelihood of a tumor response increased with increasing AUC up to a level of 5 to 7 mg × hr/mL, after which a plateau was reached. Similar results were obtained with carboplatin in combination with cyclophosphamide, and neither response nor survival rates were determined by the carboplatin AUC in a cohort of ovarian cancer patients. The differences in pharmacokinetics observed between cisplatin and carboplatin depend primarily on the slower rate of conversion of carboplatin to a reactive species. Thus, the stability of carboplatin results in a low incidence of nephrotoxicity. Carboplatin diffuses rapidly into tissues after infusion, but it is considerably more stable in plasma. Only 24% of a dose was reported to be bound to plasma protein at 4 hours postinfusion.

Cisplatin
Approximately 85% of the total platinum is bound to plasma protein at 2 to 5 hours postinfusion. Plasma elimination of total platinum and ultrafiltrates is biphasic. The T_{1/2a} and T_{1/2b} are 26 minutes and 38.7 hours, respectively, for total platinum and 21 minutes and 24.2 hours, respectively, for ultrafilterable platinum (see Table 19.4-2). As with carboplatin, substantial differences between total and free drug kinetics are not observed. Similar to cisplatin, a prolonged retention of carboplatin is observed in red blood cells. Unlike cisplatin, however, oxaliplatin does not accumulate to any significant level after multiple courses of treatment. This may explain why neurotoxicity associated with oxaliplatin is reversible. Oxaliplatin is eliminated predominantly by the kidneys, and cumulative urinary excretion of platinum is 54% to 82%, most as unmodified carboplatin. The renal clearance of carboplatin is closely correlated with the glomerular filtration rate (GFR). This observation enabled Calvert et al. to design a carboplatin dosing formula based on an individual patient's GFR.

Oxaliplatin
After oxaliplatin infusion, platinum accumulates into three compartments: plasma-bound platinum, ultrafilterable platinum, and platinum associated with erythrocytes. Approximately 85% of the total platinum is bound to plasma protein at 2 to 5 hours postinfusion. Plasma elimination of total platinum and ultrafiltrates is biphasic. The T_{1/2a} and T_{1/2b} are 26 minutes and 38.7 hours, respectively, for total platinum and 21 minutes and 24.2 hours, respectively, for ultrafilterable platinum (see Table 19.4-2). As with carboplatin, substantial differences between total and free drug kinetics are not observed. Similar to cisplatin, a prolonged retention of oxaliplatin is observed in red blood cells. Unlike cisplatin, however, oxaliplatin does not accumulate to any significant level after multiple courses of treatment. This may explain why neurotoxicity associated with oxaliplatin is reversible. Oxaliplatin is eliminated predominantly by the kidneys, and cumulative urinary excretion of platinum is 54% to 82%, most as unmodified carboplatin. The renal clearance of carboplatin is closely correlated with the glomerular filtration rate (GFR). This observation enabled Calvert et al. to design a carboplatin dosing formula based on an individual patient's GFR.
Oxaliplatin is more frequently given as a single dose every 2 weeks (85 mg/m²) or every 3 weeks (130 mg/m²), although with other active agents. It is common to pretreat patients with active antiemetics, such as a 5-HT₃ antagonist, but the nausea is not as severe as with cisplatin. No prehydration is required. The predominant toxicity of oxaliplatin is neurotoxicity. The development of an oropharyngeal dysphasia, often precipitated by exposure to cold, requires prolongation of the duration of administration to 6 hours.

**Carboplatin**

Carboplatin treatment over 3 to 6 hours is burdensome for clinical resources and tiring for cancer patients. Previously given as in-hospital treatment, it is now usually administered in the outpatient setting. The exigencies of the modern health care environment have contributed to the expanding use of carboplatin as an alternative to cisplatin, except in circumstances in which cisplatin is clearly the superior agent. Carboplatin is substantially easier to administer. Extensive hydration is not required because of the lack of nephrotoxicity at standard doses. Carboplatin is reconstituted in chloride-free solutions (unlike cisplatin, because chloride can displace the leaving groups) and administered over 30 minutes as a rapid intravenous infusion. Carboplatin has been incorporated in high-dose chemotherapy regimens at doses more than threefold higher than those of the standard regimens. In some regimens, continuous infusion has been substituted for a rapid intravenous infusion; however, it is doubtful that there is an advantage to this approach. Carboplatin doses up to 20 mg × min/mL may be safely administered in 200 mL of D5W over 2 hours.

**TOXICITY**

A substantial body of literature documents the side effects of platinum compounds. The nephrotoxicity of cisplatin almost led to its abandonment, until Cvitkovic and colleagues introduced aggressive hydration, which prevented the development of acute renal failure. As already noted, the toxicity of cisplatin was a driving force both in the search for less toxic analogues and for more effective treatments for its side effects, especially nausea and vomiting. The toxicities associated with cisplatin, carboplatin, and oxaliplatin are described in detail in the next three sections and are summarized in Table 19.4-3.

### TABLE 19.4-3. Toxicity Profiles of Platinum Analogues in Clinical Use

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Cisplatin</th>
<th>Carboplatin</th>
<th>Oxaliplatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myelosuppression</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Nephrotoxicity</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Neurotoxicity</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Ototoxicity</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

**Cisplatin**

The side effects associated with cisplatin (at single doses of more than 50 mg/m²) include nausea and vomiting, nephrotoxicity, ototoxicity, neuropathy, and myelosuppression. Rare effects include visual impairment, seizures, arrhythmias, acute ischemic vascular events, glucose intolerance, and pancreatitis. The nausea and vomiting stimulated a search for new antiemetics. These symptoms are currently best managed with 5-HT₃ antagonists and usually given with a glucocorticoid, although other combinations of agents are still widely used. In the weeks following treatment, continuous antiemetic therapy may be required. Nephrotoxicity is ameliorated but not completely prevented by hydration. The renal damage to both glomeruli and tubules is cumulative, and after cisplatin treatment, serum creatinine is no longer a reliable guide to the measurement of glomerular filtration rate. An acute elevation of serum creatinine may follow a cisplatin dose, but this index returns to normal with time. Tubule damage may be reflected in a salt-losing syndrome that also resolves with time.

Ototoxicity is a cumulative and irreversible side effect of cisplatin treatment that results from damage to the inner ear. Therefore, audiograms are recommended every 2 to 3 cycles. The initial audiographic manifestation is loss of high-frequency acuity (4000 to 8000 Hz). When acuity is affected in the range of speech, cisplatin should be discontinued under most circumstances and carboplatin substituted where appropriate. Peripheral neuropathy is also cumulative, although less common than with agents such as vinca alkaloids. This neuropathy usually is reversible, although recovery is often slow. A number of agents with the potential for protection from neuropathy have been developed, but none is yet used widely.

**Carboplatin**

Myelosuppression, which is not usually severe with cisplatin, is the dose-limiting toxicity of carboplatin. The drug is most toxic to the platelet precursors, but neutropenia and anemia are frequently observed. The lowest platelet counts after a single dose of carboplatin are observed 17 to 21 days later, and recovery usually occurs by day 28. The effect is dose-dependent, but individuals vary widely in their susceptibility. As shown by Egorin et al. and Calvert et al., the severity of platelet toxicity is best accounted for by a measure of the drug exposure in an individual, the AUC. Both groups derived pharmacologically based formulas to predict toxicity and guide carboplatin dosing. That of Calvert and colleagues targets a particular exposure to carboplatin:

\[
\text{Dose (mg)} = \text{target AUC \times (mg \cdot min) / (ml \cdot (GFR \cdot ml / min + 25))}
\]

This formula has been widely used to individualize carboplatin dosing, and it permits targeting at an acceptable level of toxicity. Patients who are elderly or have a poor performance status or a history of extensive pretreatment have a higher risk of toxicity, even when dose is calculated with these methods, but the safety of drug administration has been enhanced. In the combination of carboplatin and paclitaxel, AUC-based dosing has helped to maximize the dose intensity of carboplatin. Doses some 30% higher than a dosing strategy based solely on body surface area may safely be used. A determination of whether this approach to dosing improves outcome requires a randomized trial, which is in progress.

The other toxicities of carboplatin are generally milder and better tolerated than those of cisplatin. Nausea and vomiting, although frequent, are less severe, shorter in duration, and more easily controlled with standard antiemetics (i.e., Compazine, dexamethasone, lorazepam) than those symptoms typical after cisplatin treatment. Renal impairment is infrequent, although alopecia is common, especially with the paclitaxel-containing combinations. Neurotoxicity is also less common than with cisplatin, although it is observed more frequently with the increasing use of high-dose regimens. Ototoxicity is also less common.

**Oxaliplatin**

The dose-limiting toxicity of oxaliplatin is sensory neuropathy, a characteristic of all DACH-containing platinum derivatives. The severity of the toxicity is dramatically less than that observed with another DACH-containing analogue, ormaplatin. This side effect takes two forms. First, a tingling of the extremities, which may also involve the perioral region, occurs early and usually resolves within a few days. With repeated dosing, symptoms may last longer between cycles but do not appear to be of long duration or cumulative. Laryngopharyngeal spasm and cold dysesthesias also have been reported but are not associated with significant respiratory symptoms; they can be prevented by prolonging the duration of infusion. A second neuropathy, more typical of that seen with cisplatin, affects the extremities and


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METHOTREXATE

Aminopterin was the first antimetabolite to demonstrate clinical activity in the treatment of patients with malignancy. This antifolate analogue was used to induce remissions in children with acute leukemia in the 1940s. ¹ Aminopterin has since been replaced by methotrexate (MTX), the 4-amino, 10-methyl analogue of folic acid.

MTX remains the most widely used antifolate in cancer chemotherapy, with documented activity against a wide range of human malignancies, including leukemia, breast cancer, colorectal cancer, head and neck cancer, lymphoma, osteogenic sarcoma, uterine cancer, and choriocarcinoma. Antifolates have also been used to treat a host of nonmalignant disorders, including psoriasis, rheumatoid arthritis, graft-versus-host disease, bacterial and plasmodial infections, and parasitic infections associated with the acquired immunodeficiency syndrome. ² This class of agents represents the best-characterized and most versatile of all chemotherapeutic drugs in current clinical use.

MECHANISM OF ACTION

MTX is a tight-binding inhibitor of dihydrofolate reductase (DHFR), a critical enzyme in folate metabolism. ³ The importance of DHFR stems from its role in maintaining the intracellular folate pool in its fully reduced form as tetrahydrofolates. These compounds serve as one-carbon carriers required for the synthesis of thymidine-5'-monophosphate (thymidylate), purine nucleotides, and certain amino acids. Thymidylate synthase (TS) catalyzes the formation of thymidine-5'-monophosphate from 2'-deoxyuridine 5'-monophosphate (deoxyuridylate, dUMP) ⁴ This reaction uses 5,10-methylenetetrahydrofolate as a methyl donor and results in the oxidation of the reduced folate to dihydrofolate. The activity of the TS reaction thus creates the requirement for DHFR to maintain the intracellular reduced folate pool needed for one-carbon transfer reactions. The reduced folate, 10-formyltetrahydrofolate (10-CHO-FH₄), serves as a substrate for two folate-dependent enzymes of de novo purine synthesis, glycinamide ribonucleotide (GAR) transformylase and aminoimidazole carboxamide ribonucleotide transformylase. An intact DHFR pathway is therefore necessary for continued de novo thymidylate and purine nucleotide biosynthesis.

FIGURE 19.5-1. Sites of action of methotrexate (MTX), its polyglutamated metabolites [MTX(Glu)n], and folate by-products of the inhibition of dihydrofolate reductase, including dihydrofolate (FH₂) and 10-formyl-dihydrofolate (10-CHO-FH₂). Also shown are 5,10-methylenetetrahydrofolate (CH₂FH₄), the folate cofactor required for thymidylate synthesis, and 10-formyltetrahydrofolate (10-CHO-FH₂), the required cofactor for de novo purine synthesis. AICAR, aminoimidazole carboxamide ribonucleotide transformylase; AMP, adenosine monophosphate; dTMP, thymidylate; dUMP, deoxyuridylate; GAR, glycinamide ribonucleotide transformylase; GMP, guanine monophosphate; IMP, inosine monophosphate.

FIGURE 19.5-2. The thymidylate synthase enzyme pathway. dTDP, thymidine diphosphate; dTMP, thymidylate; dTTP, thymidine triphosphate; dUMP, deoxyuridylate; FdUMP, 5-fluoro-2'-deoxouridine monophosphate.
The precise mechanism by which MTX produces metabolic inhibition remains a subject of ongoing debate. The long-held view has been that inhibition of DHFR results in reduced folate metabolism, leading to the continued synthetic function of TS. Ultimate depletion of the required reduced folates would result in cessation of de novo thymidylate and purine biosynthesis as well as inhibition of protein synthesis. However, several investigators have demonstrated that after exposure of malignant cells to inhibitory concentrations of MTX, intracellular reduced folates are depleted by only 50% to 70%, a level presumably insufficient to account for the observed inhibition of DNA synthesis. 

2 Additional metabolic effects of MTX result from its transformation to polyglutamate forms (see Fig. 19.5-1). MTX and physiologic folate polyglutamates are formed by the enzyme folypolyglutamyl synthetase, which adds up to five to seven glutamyl groups in a p-peptide linkage. Polyglutamation is a time- and concentration-dependent process that occurs in tumor cells and, to a lesser extent, in normal tissues. These polyglutamate metabolites have a prolonged intracellular half-life and allow for prolonged drug action in malignant cells. The relative difference in polyglutamate formation in normal versus malignant cells may account for the selective activity of the drug. As much as 80% of MTX found in malignant tissues is in the polyglutamated forms, and these metabolism-dependent folate-dependent, direct-acting antimetabolites, including DHFR, TS, and aminopterin, inhibit dihydrofolate and GAR transformylases.

2 Thus, metabolic inhibition resulting from MTX exposure is a multifactorial process and may depend on several factors, including partial depletion of reduced folate and direct inhibition of folate-dependent enzymes by the polyglutamates of both MTX and dihydrofolate that accumulate after inhibition of DHFR.

The precise mechanism by which MTX induces cytotoxicity remains an area of continued investigation. MTX-induced depletion of thymidine triphosphate (dTTP) and purine nucleotides interferes with the cellular capacity to repair DNA, resulting in DNA strand breaks. Further, the need for repair is accentuated by an intracellular accumulation of dUMP resulting from the inhibitory effects of MTX on TS. dUMP can be converted to the triphosphate nucleotide form (dUTP), which is then incorporated into DNA, resulting in inhibition of chain elongation and DNA synthesis. Excision repair of the DNA containing these misincorporated dUTP moieties by the enzyme uracil DNA glycosylase results in further DNA fragmentation.

Novel mechanisms by which MTX may exert its cytotoxic action have been described. Treatment with MTX results in a significant dose-dependent reduction in methionine synthase enzyme activity. 

2 This enzyme catalyzes the folate-dependent reaction in which 5-methyltetrahydrofolate serves as a critical one-carbon carrier. Methyl donor and mediates the conversion of homocysteine to methionine. Thus, inhibition of methionine synthase leads to inhibition of a number of key downstream pathways, including transmethylating reactions, polamine biosynthesis, protein synthesis, or all three.

2 Treatment of cultured Ehrlich ascites tumor cells with MTX results in a concentration-dependent inhibition in p53-dependent apoptosis and was associated with a 10-fold decrease in p53 protein expression. In addition, MTX and reduced folates compete with one another for transport. Coadministration of MTX and hypoxanthine completely protected against the growth-inhibitory action of MTX and reversed the effect on PRPP production and on the rate of glucose transport. Thus, MTX may exert its anticancer effect, in part, through inhibition of critical glucose transport mechanisms, thereby starving the cancer cell of essential nutrients required to maintain cellular metabolism and growth.

MTX is most active against rapidly proliferating cells, as its cytotoxic effects occur primarily during the S phase of the cell cycle. During longer periods of drug exposure, a higher fraction of cells can enter the S phase of the cell cycle, resulting in greater cell kill. In addition, MTX polyglutamate formation is substantially enhanced with longer periods of drug exposure, thereby increasing cytotoxicity. The cytotoxic effects of MTX are also greater with increasing drug concentrations. Therefore, MTX cytotoxicity is highly dependent on the absolute drug concentration and the duration of drug exposure.

MTX enters cells by the same active transport mechanisms used by physiologic reduced folates. In general, intracellular drug concentrations reach steady state in less than 30 minutes. Folate transport is a complex process with at least two carrier-mediated, energy-dependent mechanisms existing in mammalian cells. The first is the classic reduced folate carrier (RFC) system that has a relatively low affinity for MTX and reduced folates such as leucovorin (LV), with affinity constants in the micromolar range.

2 These isoforms have unique folate-binding affinities and variable expression in specific tissues. FR-a is highly expressed in human epithelial tissues and in blood and lymphoid tissues as well.

2 It is expressed on the surface of various normal tissues, including human placenta, choroid plexus, renal tubules, and gallbladder lining. Folates. Of note, this receptor is also highly expressed on the surface of a number of epithelial tumors, including ovarian cancer, but not on normal ovarian tissue, making it an attractive target for antigen-directed anticancer therapies. Alterations in the tissue expression of FR can be induced by changes in the exogenous folate concentration or by alteration in normal physiology such as in pregnancy. At least three different isoforms of the human FR have been described to date, and they are classified as FR-a, FR-b, and FR-g. 

2 These isoforms have unique folate-binding affinities and variable expression in specific tissues. FR-a is highly expressed in human epithelial tissues and in some cancers such as ovarian cancer, whereas FR-b is expressed in human placenta and other nonepithelial tissues. Although the FR-a and FR-b isoforms share 70% to 80% amino acid sequence homology, they differ significantly in their respective affinities and stereospecificities for reduced folates. Human FR-g lacks a glycosylphosphatidylinositol tail, and this isoform most likely represents a secretory protein.

An additional MTX transport system has been described in murine L1210 leukemic cells that is completely distinct from either the RFC or the FR systems. Further studies are under way to characterize the role of this transporter as a determinant of MTX cytotoxicity. It is likely that the relative function of each of these distinct transport systems depends on the extracellular folate concentration, and their expression may vary significantly among different cell lines. Their interrelationship and role in MTX transport remains an active area of research. Nonclassic antifolate compounds, such as trimetrexate and trimethoprim, do not rely on specific transport systems for cellular entry. Such analogues are active against various malignant cell lines resistant to MTX on the basis of decreased transport capacity. In addition to these transport systems, two energy-dependent MTX efflux transport systems have been described in murine leukemic L1210 cells using inside out membrane vesicles. These two systems appear to be functionally distinct and sensitive to a different range of chemical inhibitors. The major efflux transporter is identical to a glutathione conjugate membrane pump and accounts for nearly 70% of MTX efflux.

Reduced folates, such as 5-formyltetrahydrofolate (LV), prevent, rescue, or both prevent and rescue cells from the toxic effects of MTX. The predominant species of reduced folate in human plasma, 5-methyltetrahydrofolate, circulates with levels in the range of 5 to 50 nM, a concentration inadequate to rescue cells. Administration of appropriate doses of LV after high-dose MTX therapy can prevent toxicity to the bone marrow and gastrointestinal epithelium, the two most rapidly dividing cells in the body. The dose of LV required to rescue normal tissues is dependent on the antifolate concentration at the time of antidote administration. 

2 The competitive nature of this rescue suggests that LV does more than simply replete intracellular reduced folate pools. LV is converted to intracellular folates that can compete with both MTX and dUMP for polyglutamate synthetase, thereby overcoming the inhibition of TS and further purine synthesis. In addition, MTX and reduced folates compete with one another for transport into cells and for subsequent intracellular polyglutamation. Presumably, rescue from MTX-associated metabolic inhibition occurs only when adequate levels of dihydrofolate are in excess after LV administration. The administration of exogenous thymidine may also be used to decrease MTX toxicity. This approach appears to be less effective than LV, as inhibition of the de novo purine pathway by MTX remains unaffected by its use. Administration of the reduced folate enzyme carboxyptidylase G2, which hydrolyzes MTX to inactive metabolites, is currently undergoing clinical testing as an alternative strategy to rescue from high-dose MTX therapy.

**MECHANISMS OF RESISTANCE**

The development of cellular resistance to MTX remains one of its most striking effects. Many mechanisms, including an alteration in antifolate transport due to either a defect in the RFC or FR systems, 

2 and decreased capacity to polyglutamate MTX through either decreased expression of polyglutamyl synthetase or increased expression of the catalytic enzyme gamma-glutamyl hydrolase, 

2 and alterations in the target enzyme DHFR through either increased expression of the wild-type protein or overexpression of a mutant protein with reduced binding affinity for MTX.

Amplification of the DHFR gene is one of the most common forms of MTX resistance observed in experimental systems. The amplified gene may be stably integrated into chromosomal DNA in the form of a homogeneously staining region, or it may exist in extrachromosomal pieces of DNA known as double-minute chromosomes. The integration of DHFR into the chromosome region is associated with development of stable resistance to MTX. In contrast, double-minute chromosomes are unequally distributed during cell division, and, in the absence of continued selective pressure of MTX, cells eventually revert to a sensitive phenotype with wild-type levels of DHFR expression. It was shown that resistant human leukemic HL-60 cells coamplify both DHFR and hMSH3, the human mutS
homologue 3 gene. Overproduction of HMG3 results in virtually complete sequestration of the nuclear HMG2 mismatch repair (MMR) protein. The net effect of this protein-protein interaction is a marked reduction in the efficiency of base-base MMR. As MMR deficiency has been implicated as a potential mechanism of resistance to the platinum analogues cisplatin and carboplatin, DNA methylating agents, and doxorubicin (Adriamycin), it is conceivable that this same resistance phenotype may contribute to the development of resistance to MTX and other antifolate analogues.

An alternative mechanism of resistance has been ascribed to mutations that result in a DHFR protein product with an altered binding affinity for MTX. There is evidence that naturally occurring DHFR alleles with differing affinities to MTX may exist in cells and provide a mechanism for the rapid emergence of MTX resistance. In several in vitro experimental model systems, the levels of DHFR enzyme activity acutely increase after exposure to MTX, other antifolate analogue compounds, or both. This acute induction of DHFR in response to drug exposure is mediated, in part, by a translational regulatory mechanism. DHFR protein, in its normal cellular environment, is capable of specifically repressing the translation of its own messenger RNA (mRNA). However, when DHFR protein is bound to an antifolate inhibitor, it is unable to repress DHFR mRNA translation, and the rate of new DHFR protein synthesis increases. Thus, induction of DHFR may represent a clinically relevant mechanism for the acute development of cellular drug resistance.

Apoptosis, the process of programmed cell death, is a critical event during normal development and in the pathogenesis of several disease states, including cancer, autoimmune disorders, viral infection, and neurodegenerative diseases. Bcl-2 can repress cell death triggered by a wide array of stimuli, including chemotherapy and gamma-irradiation. Bcl-XL, a structural homologue of Bcl-2, has also been shown to provide protection against a wide range of anticancer agents. These prosurvival proteins presumably act at some common final steps to prevent or overcome the cell death pathway induced by various anticancer agents. It has been shown that murine lymphoid FL5.12 cells transduced with Bcl-XL as compared with another antipapoptotic gene Bcl-2, become resistant to the cytotoxic effects of MTX. Thus, the expression of Bcl-XL may represent an important indicator for predicting chemosensitivity to MTX and other antifolate analogues.

Despite many years of active investigation, the relative contribution of each of these mechanisms as a determinant of MTX resistance remains unclear. However, there is growing evidence to support the concept that the emergence of MTX resistance, in the clinical setting, is a multifactorial process. In fact, DHFR gene amplification, defective transport, and decreased polyglutamate formation have all been observed in clinical specimens taken from MTX-resistant patients.

CLINICAL PHARMACOLOGY AND PHARMACOKINETICS

Accurate monitoring of MTX concentrations in plasma is essential for the safe and optimal use of this agent in cancer chemotherapy, particularly with high-dose regimens. At least four methods are presently available for the clinical monitoring of MTX drug levels, including the DHFR enzyme inhibition assay, a competitive protein-binding assay, a fluorescence-polarization radioimmunoassay technique, and an enzyme-multiplied immunoassay system. 7

The absorption of oral MTX is saturable and erratic at higher doses, such that oral doses should be kept to less than 25 mg/m². The drug is usually administered intravenously. The volume of distribution of MTX approaches that of total body water, and approximately 60% of the drug is bound to serum albumin at pharmacologic drug concentrations. 8 Although the plasma pharmacokinetics are variable, MTX metabolism generally follows a three-phase pattern. The initial distribution phase, which lasts for only a few minutes, is followed by a second phase lasting 12 to 24 hours, during which time the drug is eliminated with a half-life of 2 to 3 hours. The final phase of drug clearance has a half-life of 8 to 10 hours. The last two phases of drug elimination are considerably lengthened in patients with renal dysfunction. There is substantial evidence that a more rapid systemic clearance of drug is associated with a high risk of relapse in children receiving MTX for maintenance therapy of acute lymphocytic leukemia.

The distribution of MTX into third-space fluid collections, such as pleural effusions and ascitic fluid, can substantially alter MTX pharmacokinetics. The slow release of accumulated MTX from these third spaces over time prolongs the terminal half-life of the drug, leading to potentially increased clinical toxicity. Although no strict guidelines exist for the treatment of patients with ascites or pleural effusions, it is advisable to evacuate these fluid collections before treatment and monitor plasma drug concentrations closely. In addition, patients with bladder cancer who have undergone cystectomy and ileal conduit loop diversion may experience a significant increase in toxicity secondary to MTX treatment. Thus, caution should be given when beginning therapy with MTX in this particular subset of patients.

Elimination of MTX occurs primarily through renal excretion. MTX is filtered by the glomerulus and is actively secreted in the proximal tubule. Renal clearance usually equals or exceeds creatinine clearance. However, rates of drug clearance may vary widely, and they do not necessarily parallel renal function. Renal excretion of MTX is inhibited by probenecid, penicillins, cephalosporins, aspirin, and nonsteroidal antiinflammatory drugs. 9 The combination of MTX and nonsteroidal antiinflammatory drugs has been associated with severe toxicity in patients receiving high-dose MTX. Patients with impaired renal function (creatinine clearance less than 60 mL/min) should not be treated with high-dose MTX. Moreover, standard doses of MTX should be reduced in proportion to reductions in creatinine clearance.

The introduction of high-dose MTX regimens led to the identification of at least two MTX metabolites. 7-Hydroxymethotrexate (7-OH-MTX) constitutes 20% to 46% of drug excreted in urine from 12 to 24 hours after the start of a high-dose infusion. It is formed through the action of aldehyde dehydrogenase in the liver and is a weak inhibitor of DHFR. 7-OH-MTX is a substrate for folicpolyglutamyl synthetase, and the resulting polyglutamate metabolites are inhibitors of the folate-dependent enzymes TS and aminomimidazole carbamide ribonucleotide transformylase, with a potency similar to that of MTX polyglutamates. 10 A second metabolite, 2,4 diamino-N10-methyl pteric acid (DAMPA), a product of bacterial degradation of MTX in the gut lumen, is inactive and constitutes approximately 25% of the excreted drug at 24 to 48 hours after drug infusion. The exact role of these metabolites in producing MTX toxicity or enhancing therapeutic activity remains uncertain.

Biliary excretion of MTX represents approximately 10% of overall MTX drug clearance. However, in the presence of renal dysfunction, enterohepatic circulation may represent an important pathway of drug elimination. Most MTX excreted in bile is reabsorbed as intact drug, but an undefined fraction is excreted in bile. It is advisable to evacuate these fluid collections before treatment and monitor plasma drug concentrations closely. The adjustments in MTX dose are necessary for patients with hepatic dysfunction.

SCHEDULES OF ADMINISTRATION

The safe use of high-dose MTX with LV rescue requires a thorough understanding of MTX pharmacokinetics. High-dose MTX therapy is used in the treatment of high-grade lymphomas, osteogenic sarcoma, and acute leukemia. These regimens use otherwise lethal infusions of MTX given over 6 to 42 hours in doses of 500 mg/m² or higher. High-dose MTX can be safely administered to patients provided that careful attention is paid to intravenous fluid hydration, urinary alkalinization, and adequate administration of MTX.

During infusion of high-dose MTX, rapid renal excretion results in high urinary drug concentrations. Urinary MTX concentrations approaching 10 mM exceed solubility, respectively. Drug levels should be measured every 6 hours and acute renal insufficiency with partially diminished consequenses. This complication can be avoided by vigorous hydration (3 L fluid/m²/24 hours, beginning 12 hours before infusion and continuing for 36 hours), and urinary alkalinization to increase drug solubility. Administration of MTX should not begin until urine flow is 100 mL/h and urine pH is 7 or greater, and these parameters should be carefully monitored during the course of therapy. High-dose MTX therapy should not be used in patients with impaired renal function (creatinine clearance less than 60 mL/min).

Close monitoring of MTX plasma levels is essential for guiding the duration and amount of LV required to prevent severe MTX-associated toxicity. Given the competitive interaction between MTX and LV, the dose of the rescue agent must be increased in proportion to the plasma concentration of MTX. If the MTX level exceeds 0.5 µM 48 hours from the start of the infusion, the LV dose may be adjusted to 15, 100, or 200 mg/m² every 6 hours for MTX levels of 0.5, 1.0, and 2.0 µM, respectively. Drug levels should be rechecked every 24 hours and the LV dose adjusted until the drug concentration is less than 50 nM. However, clinicians should be aware that overzealous use of LV may counteract the cytotoxic effects of MTX in tumor cells as well as in host cells. For this reason, it is important to use doses of LV that are adequate but not excessive, so that normal but not tumor cells will be rescued. In patients with delayed MTX excretion, LV is usually given intravenously, because its oral bioavailability is decreased at total doses higher than 40 mg.

Despite careful attention to detail, persistent elevations of plasma MTX levels may sometimes occur. Plasma MTX levels higher than 10 µM at 48 hours are poorly rescued even with high doses of LV. Hemodialysis and peritoneal dialysis are ineffective in removing MTX, with clearance rates of only 35 to 40 mL/min. Experimental approaches to reduce toxic levels of MTX include hemofiltration over a charcoal column, oral administration of activated charcoal or cholestyramine to increase enterohepatic drug loss, and intravenous infusion of the degradative enzyme carboxypeptidase G. 11

MTX penetrates poorly into the cerebrospinal fluid (CSF), and CSF levels are 30-fold lower than plasma levels at equilibrium. However, after high-dose MTX
therapy, peak CSF levels greater than the therapeutic threshold of 1 µM can be achieved. Systemic high-dose MTX therapy has been used to prevent meningeal leukemia and lymphoma. Intrathecal injection of MTX can also be used for prophylaxis. For treatment of meningeal carcinomatosis, injection of MTX through an indwelling Ommaya reservoir is recommended because drug administered into the CSF via the lumbar space circulates poorly into the ventricles, resulting in inadequate CSF drug levels. A total intrathecal dose of 12 mg is advised for all persons older than 3 years of age. In normal patients, the CSF half-life is approximately 2 hours, but it may be prolonged in patients with active meningeal disease. Delayed clearance from the CSF has been associated with an increased risk of MTX neurotoxicity.

TOXICITY

The primary toxic effects of MTX therapy are myelosuppression and gastrointestinal mucositis. The occurrence of these adverse effects and other toxicities depends on the dose, schedule, and route of drug administration. Mucositis usually appears 3 to 7 days after MTX therapy and precedes the decrease in granulocyte and platelet count by several days. Myelosuppression and mucositis are usually completely reversed within 14 days, unless drug elimination mechanisms are impaired. In patients with compromised renal function, even small doses of MTX may result in serious toxicity.

MTX-induced nephrotoxicity is thought to result from the intratubular precipitation of MTX and its metabolites, 7-OH-MTX and DAMPA, in acidic urine. Antifolates may also exert a direct toxic effect on the renal tubules. Vigorous hydration and urinary alkalization have greatly reduced the incidence of renal failure in high-dose regimens.

MTX is associated with both acute and chronic hematotoxicity. Acute elevations in hematologic enzyme levels, as well as hyperbilirubinemia, are often observed during high-dose therapy, but these usually return to normal within 10 days. Chronic administration of daily oral MTX, as has been used in the treatment of psoriasis, is associated with the development of hepatic fibrosis in as many as 25% of patients. Cirrhosis of the liver has also been described in this group. Intermittent, weekly MTX therapy, rather than continuous daily treatment, is associated with a lower incidence of hematotoxicity. Although the precise mechanism of MTX hepatoxicity is not known, liver biopsies of patients with drug-induced liver disease reveal increased lipid deposition in the liver.

MTX causes a poorly defined, self-limited pneumonitis characterized by fever, cough, and interstitial pulmonary infiltrates. Lung biopsies have not revealed consistent pathologic findings. Although a hypersensitivity reaction has been proposed as a possible explanation, rechallenge with MTX does not uniformly result in a return of symptoms. With the increasing use of chronic, low-dose MTX therapy for rheumatoid arthritis, there is now a growing number of cases of MTX-associated lung damage. No specific therapy for MTX pneumonitis is recommended other than withholding MTX therapy during the acute episode.

Three distinct neurotoxic syndromes are associated with intrathecal MTX therapy. The most common syndrome is an acute chemical arachnoiditis that arises immediately after drug administration. This syndrome is characterized by severe headaches, nuchal rigidity, vomiting, fever, and an inflammatory cell infiltrate in the CSF. A subacute form of neurotoxicity is seen in approximately 10% of patients and usually occurs after the third or fourth course of intrathecal therapy. It is most common in adults with active meningeal leukemia and consists of motor paralysis, cranial nerve palsies, and seizures or coma, or both. A change in therapy is absolutely indicated, because continued intrathecal MTX therapy may result in death. The third syndrome is a chronic, demyelinating encephalopathy, typically occurring in children months to years after receiving intrathecal MTX. Patients present with dementia, limb spasticity, and, in advanced cases, coma. Computed tomography scan reveals ventricular enlargement, cortical thinning, and diffuse intracerebral calcifications.

High-dose systemic MTX therapy is occasionally associated with an acute, transient central nervous system syndrome. Although a hypersensitivity reaction has been described in 4% to 15% of patients receiving high-dose MTX, symptoms occur within 6 days of MTX treatment and usually completely resolve within 48 to 72 hours. In addition, a chronic form of neurotoxicity is manifested as an encephalopathy with dementia and motor paraparesis developing in the second or third month after treatment. At present, the underlying mechanism of CNS toxicity from MTX remains unknown. There is no evidence to support the therapeutic use of LV in patients who develop neurotoxic symptoms.

True anaphylactic reactions to MTX are exceedingly rare. There have been a few reported cases of toxic skin erythema and desquamation of the hands after high-dose MTX therapy. In men treated with high-dose MTX, a reversible defect in spermatoogenesis may occur. However, no alterations in reproductive function have been reported in women treated with MTX.

NEW ANTIFOLATES

TRIMETREXATE

In the 1990s, several new antifolates were developed in an attempt to circumvent some of the known mechanisms of resistance to MTX, to target folate-dependent enzymes other than DHFR, or both. The more lipid-soluble quinazoline antifolate trimetrexate (TMTX, Neutrexin) differs from MTX by not requiring the RFC system for cellular transport and by lacking the potential for polyglutamation. Like MTX, it is a potent inhibitor of DHFR and produces metabolic inhibition through mechanisms similar to MTX. It is believed that malignant cells that have become resistant to MTX, by virtue of either reduced membrane transport or deficient polyglutamation, would remain sensitive to this antifolate analogue. Because TMTX is not polyglutamated, its intracellular half-life is shorter than MTX, necessitating frequent or continuous dosing schedules. In contrast to MTX, TMTX can serve as a substrate for the P-glycoprotein-associated efflux pump. As a result, cross-resistance to TMTX and a host of natural products, including anthracyclines, taxanes, and vinca alkaloids, can develop in multidrug resistant cancer cells overexpressing the P170 glycoprotein.

TMTX has been tested using a variety of dose schedules. It is highly protein bound (more than 90%) and cleared principally from the body by hepatic metabolism. The terminal half-life of the half-life of the drug ranges from 12 to 20 hours. TMTX has been tested in the phase II setting for the treatment of a variety of malignancies, principally with a regimen of 8 to 12 mg/m² daily for 5 days every 3 weeks.

The dose-limiting toxicity has been myelosuppression. Other toxicities include rash, mucositis, fever, nausea and vomiting, and reversible transaminasemia. Antitumor responses have ranged from 25% to 30%. As a single agent, the compound has shown little activity against gastrointestinal cancers. However, when used in combination with 5-fluorouracil (5-FU) and LV, response rates on the order of 30% to 35% have been reported in patients with previously untreated cancers. In the 1990s, several new antifolates were developed in an attempt to circumvent some of the known mechanisms of resistance to MTX, to target folate-dependent enzymes other than DHFR, or both. The more lipid-soluble quinazoline antifolate trimetrexate (TMTX, Neutrexin) differs from MTX by not requiring the RFC system for cellular transport and by lacking the potential for polyglutamation. Like MTX, it is a potent inhibitor of DHFR and produces metabolic inhibition through mechanisms similar to MTX. It is believed that malignant cells that have become resistant to MTX, by virtue of either reduced membrane transport or deficient polyglutamation, would remain sensitive to this antifolate analogue. Because TMTX is not polyglutamated, its intracellular half-life is shorter than MTX, necessitating frequent or continuous dosing schedules. In contrast to MTX, TMTX can serve as a substrate for the P-glycoprotein-associated efflux pump. As a result, cross-resistance to TMTX and a host of natural products, including anthracyclines, taxanes, and vinca alkaloids, can develop in multidrug resistant cancer cells overexpressing the P170 glycoprotein.

TOMUDEX

Raltitrexed (ZD1694, Tomudex) is a quinazoline antifolate that is a potent and specific inhibitor of TS. Like MTX, raltitrexed is transported into the cell via the RFC. To exert its cytotoxic activity, this compound needs to be metabolized to its higher polyglutamated forms. The polyglutamates of raltitrexed are approximately 100-fold more potent than the parent compound with regard to their affinity for TS, and they exhibit prolonged intracellular retention. The principal mechanism of action of this compound is induction of TS, resulting in depleting of key nucleotide precursors required for DNA repair and synthesis. Mechanisms of resistance to raltitrexed include reduced transport, decreased polyglutamation, and overexpression of the target enzyme, TS.

Raltitrexed has undergone phase I testing, and the recommended dosing schedule is 3 mg/m² given as a 15-minute intravenous infusion every 3 weeks. The drug is cleared from the body principally by renal excretion, and its clearance follows a three-compartment elimination model with a terminal half-life of 10 to 22 hours. The major toxicities include an anorexia and fatigue syndrome, diarrhea, myelosuppression, and reversible transaminasemia. Several phase II clinical trials have investigated the activity of this drug in patients with a wide spectrum of malignancies, including advanced colorectal, breast, hepatocellular, platinum-resistant ovarian, non–small cell lung, gastric, and pancreas cancers. Response rates have ranged from 14% for patients with pancreas cancer to 25% for those with breast cancer. The largest reported experience has been for first-line treatment of patients with advanced colorectal carcinoma. An overall response rate of 28% was observed in a phase II trial involving 176 patients. Randomized, phase III trials to compare the efficacy of raltitrexed versus LV-modulated 5-FU have been completed. Raltitrexed has comparable response rates and similar palliative and survival benefits when compared with 5-FU/LV. Reduced toxicity was observed with this novel antifolate analogue, however, and it was associated with a more convenient administration schedule. This drug is approved as first-line therapy for patients with advanced colorectal cancer in Australia, Canada, and several European countries. Further studies are ongoing to determine the role of this antifolate TS inhibitor compound, either alone or in combination with other anticancer agents, in the therapy of colorectal cancer in North America.

OTHER ANTIFOLATES
Several pteroyl glutamate analogues have shown superior preclinical activity compared with MTX, and this enhanced effect is thought to be due to enhanced transport, more avid polyglutamation, or a unique site of action. 10-Ethyl-5-deaza-aminopterin (Edatrexate), a potent inhibitor of DHFR with enhanced transport and more efficient polyglutamation relative to MTX, has demonstrated activity against non–small cell lung cancer. 5,10-Dideazatetrahydrofolate (Lometrexol) is a new antifolate that impairs de novo purine synthesis by virtue of its direct inhibitory effects on GAR transformylase. Phase I studies have been performed, and this agent is currently undergoing phase II clinical investigation.

LY231514 was originally developed as a pure antifolate inhibitor of TS. However, preclinical studies suggest that it is not entirely specific for TS and that it inhibits other folate-dependent enzymes, including DHFR and GAR transformylase. Like raltitrexed, this analogue requires polyglutamation for its potent inhibitory effects on TS, and it uses the RFC for entry into cells. This compound has been investigated in several phase I studies, and the major toxicities include neutropenia, anorexia and fatigue syndrome, gastrointestinal toxicity, and reversible transaminasemia. Promising antitumor activity has been noted in a wide variety of tumor types, and phase II studies have confirmed activity against non–small cell lung cancer and mesothelioma.

5-FU has antitumor activity against a wide spectrum of solid tumors, including epithelial malignancies arising in the breast, gastrointestinal tract, head and neck, and ovary, with single-agent response rates of 10% to 30%. Significant efforts have focused on identifying agents that can biochemically modulate the cytotoxic effects of 5-FU. Such modulators of 5-FU include other antineoplastic agents such as MTX, cisplatin, and CPT-11, ionizing radiation, cytokines such as the interferons, and agents that by themselves have little to no activity such as LV and 5-ethyluracil (EU). Thus, in the clinical setting, 5-FU is most often incorporated as part of a combination regimen.

Intracellular Metabolism and Mechanism of Action

Intracellular activation is required for the fluoropyrimidines to exert their cytotoxic effects. 5-FU readily enters cells via the facilitated uracil transport mechanism, whereas FUdR is a substrate for the facilitated nucleoside transport system. These compounds are anabolized to cytotoxic forms by several biochemical pathways. The deoxyribonucleoside derivative, 5-fluoro-2′-deoxyuridine (FUdR) is limited in its clinical use because of its rapid degradation in normal and tumor tissues. It has mainly been used for hepatic arterial infusions. Flurouracil and 5-deoxyfluorouridine represent two fluoropyrimidine analogues that have been incorporated in oral prodrug forms of 5-FU, and they both demonstrate promising clinical activity.

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Inhibition of TS leads not only to depletion of dTPP, but to accumulation of dUMP. Both FdUMP and dUMP may be subsequently metabolized to their respective triphosphate forms. Incorporation of dUTP and FdUTP into cellular DNA, with resultant inhibition of DNA synthesis and function, may represent another mechanism of cytotoxicity. Two enzymatic mechanisms limit the DNA incorporation of (F)dUTP: dUTP deoxycytidylase degrades the triphosphate forms, and uracil-DNA glycosylase removes uracil residues from DNA. The combined effects of dTPP depletion and (F)dUTP-DNA incorporation are associated with inhibition of nascent DNA chain elongation, altered DNA stability, production of DNA single-strand breaks, and interference with DNA repair. The genotoxic stress resulting from TS inhibition may activate programmed cell death pathways in susceptible cells, resulting in induction of parental DNA fragmentation. Both intercellu

The relative contribution of each of these mechanisms of action to the cytotoxicity of 5-FU remains unclear and may depend on the specific patterns of intracellular 5-FU metabolism, which vary among different normal tissues and tumor types. The concentration of drug and the duration of exposure play crucial roles in determining the ultimate mechanism of cytotoxicity. However, there is now increasing support for the critical role of TS as a therapeutic target. The specific lines of evidence for this view include the enhanced activity of LV-modulated 5-FU in the therapy of both early stage and advanced colorectal cancer, the strong correlation between low TS content in tumor tissue and response to 5-FU-based therapy, the correlation between level of TS enzyme inhibition in tumors after 5-FU administration and response to 5-FU therapy, and the clinical activity of selective TS inhibitors such as Tomudex.

Mechanisms of Resistance

Given the multiple sites of cytotoxic action of 5-FU and the various metabolic pathways required for its activation, it is not surprising that several mechanisms of resistance have been identified in experimental and clinical settings. However, the relative contribution of each of these mechanisms in the development of cellular resistance to 5-FU in the actual clinical setting remains unclear.

In human and murine tumor cells selected in vitro for resistance to 5-FU, a variety of mechanisms have been described. Deletion or diminished activity of thymidylate synthetase (TS) and uridine kinase, thymidine or uridine phosphorylase, and orotate phosphoribosyl transferase interferes with metabolic activation. Decreased accumulation of FdUTP, FdUMP, and (F)dUTP may result from increased activity of catabolic enzymes [acid and alkaline phosphatases, dUTP hydrolase, and dihydropyrimidine dehydrogenase] (5-FU metabolism) or from increased transcription of these TS regulatory activities (the TS protein being directly responsible for inhibition of uridine kinase, thus decreasing the metabolism of 5-FU to ribonucleoside forms. Decreased incorporation of 5-FU into both RNA and DNA may result in decreased sensitivity. A relative deficiency of the reduced folate substrate, 5,10-methylenetetrahydrofolate may also compromise the cytotoxic action of FdUMP on TS. This may result from low extracellular levels of reduced folates, decreased membrane transport of reduced folates, or reduced activity of polyglutamate synthase, thereby preventing its polyglutamation.

Alterations in the target enzyme TS represent the most commonly described mechanism of resistance to 5-FU. A decrease in binding affinity of the 5-FU metabolite FdUMP to the TS target has resulted from point mutations in the protein-coding region of the TS gene. In vitro, in vivo, and clinical model systems have shown a strong correlation between the levels of TS enzyme activity and TS protein and chemosensitivity to 5-FU. In this regard, cell lines, tumors with higher levels of TS, or both are relatively more resistant to 5-FU. This increase in TS protein content is usually associated with amplification of the TS gene. In cell lines made resistant to cisplatin or doxorubicin, cross-resistance to 5-FU may develop on the basis of increased TS expression as a consequence of increased transcription of the TS gene. In several in vitro and in vivo model systems, the levels of TS enzyme activity and TS protein have been shown to acutely increase after exposure to 5-FU, other specific TS inhibitor compounds, or both. Moreover, acute increases in the expression of TS protein have been identified in the clinical setting in paired tumor tissue biopsies obtained from patients before and during therapy with 5-FU. This acute induction of TS protein in response to drug exposure is mediated by a translational regulatory mechanism. TS protein, in its unbound or free state, is capable of specifically repressing the translation of its own mRNA. However, when the TS protein is bound to either nucleotide, antifolate inhibitors, or both, it is unable to repress TS mRNA translation, and the rate of new TS protein synthesis increases. Thus, induction of TS may represent an efficient and clinically relevant mechanism for the acute development of drug resistance.

Clinical Pharmacology

An understanding of 5-FU pharmacokinetics is important given the wide choice of routes and schedules of administration available, each of which has advantages in terms of differing spectrum of host toxicity. The most widely used methods for quantitating 5-FU in biologic fluids are high-pressure liquid chromatography (HPLC) and gas chromatography–mass spectrometry. Nuclear magnetic resonance imaging with 19F offers the potential for noninvasive monitoring of intratumoral accumulation of 5-FU; trapping of 5-FU within tumor tissue has been associated with clinical response.

5-FU is administered either by intravenous bolus or continuous infusion. The volume of distribution is slightly higher than the extracellular space, and 5-FU readily penetrates into tissues, CSF, and extracellular third-space accumulations such as ascites or pleural effusions. After intravenous bolus doses of 370 to 720 mg/m², peak plasma concentrations reach 300 µM to 1 mM; thereafter, metabolic elimination is rapid, with a primary half-life of 8 to 14 minutes. Plasma levels of 5-FU fall below 1 µM about 2 hours after the bolus. An approximate third elimination phase, corresponding to terminal elimination half-life, is 5 hours, detected by a sensitive gas chromatography–mass spectrometry method, may reflect release of 5-FU from tissues. Less than 10% of parent drug is excreted in the urine, whereas the balance is cleared through metabolic pathways (catabolism is greater than intracellular anabolism). 5-FU is enzymatically inactivated to dihydrofolate by dihydrofolate reductase. Although the liver expresses the highest levels of 5-FU in the body, this enzyme is widely distributed in other tissues, including gastrointestinal tract, bone, breast, lung, and skin. Dihydropyrimidine dehydrogenase converts dihydrofolate to a-fluoro-a-ureidopropionic acid, then a-fluoro-}

Rare patients with inherited DPD deficiency may have life-threatening or fatal toxicity if treated with fluoropyrimidine-based chemotherapy.

In human and murine tumor cells selected in vitro for resistance to 5-FU, a variety of mechanisms have been described. Deletion or diminished activity of thymidylate synthetase (TS) and uridine kinase, thymidine or uridine phosphorylase, and orotate phosphoribosyl transferase interferes with metabolic activation. Decreased accumulation of FdUTP, FdUMP, and (F)dUTP may result from increased activity of catabolic enzymes [acid and alkaline phosphatases, dUTP hydrolase, and dihydropyrimidine dehydrogenase] (5-FU metabolism) or from increased transcription of these TS regulatory activities (the TS protein being directly responsible for inhibition of uridine kinase, thus decreasing the metabolism of 5-FU to ribonucleoside forms. Decreased incorporation of 5-FU into both RNA and DNA may result in decreased sensitivity. A relative deficiency of the reduced folate substrate, 5,10-methylenetetrahydrofolate may also compromise the cytotoxic action of FdUMP on TS. This may result from low extracellular levels of reduced folates, decreased membrane transport of reduced folates, or reduced activity of polyglutamate synthase, thereby preventing its polyglutamation.

Alterations in the target enzyme TS represent the most commonly described mechanism of resistance to 5-FU. A decrease in binding affinity of the 5-FU metabolite FdUMP to the TS target has resulted from point mutations in the protein-coding region of the TS gene. In vitro, in vivo, and clinical model systems have shown a strong correlation between the levels of TS enzyme activity and TS protein and chemosensitivity to 5-FU. In this regard, cell lines, tumors with higher levels of TS, or both are relatively more resistant to 5-FU. This increase in TS protein content is usually associated with amplification of the TS gene. In cell lines made resistant to cisplatin or doxorubicin, cross-resistance to 5-FU may develop on the basis of increased TS expression as a consequence of increased transcription of the TS gene. In several in vitro and in vivo model systems, the levels of TS enzyme activity and TS protein have been shown to acutely increase after exposure to 5-FU, other specific TS inhibitor compounds, or both. Moreover, acute increases in the expression of TS protein have been identified in the clinical setting in paired tumor tissue biopsies obtained from patients before and during therapy with 5-FU. This acute induction of TS protein in response to drug exposure is mediated by a translational regulatory mechanism. TS protein, in its unbound or free state, is capable of specifically repressing the translation of its own mRNA. However, when the TS protein is bound to either nucleotide, antifolate inhibitors, or both, it is unable to repress TS mRNA translation, and the rate of new TS protein synthesis increases. Thus, induction of TS may represent an efficient and clinically relevant mechanism for the acute development of drug resistance.

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Rare patients with inherited DPD deficiency may have life-threatening or fatal toxicity if treated with fluoropyrimidine-based chemotherapy. Because affected individuals are otherwise in good health, the first indication of the presence of this inborn error of metabolism usually follows an unexpectedly severe reaction to 5-FU chemotherapy. Careful testing of DPD-deficient patients has revealed an autosomal recessive pattern of inheritance. It is now estimated that as many as 3% to 5% of adult cancer patients may have this pharmacogenetic syndrome. Several molecular defects, including point mutations and deletions due to exon skipping, have been identified in DPD-deficient patients who experience severe toxicity to 5-FU. Further studies are in progress to establish the precise relationship between the level of DPD activity and 5-FU toxicity.
systemic 5-FU may respond to hepatic arterial infusion FUdR. Systemic toxicities are usually dose limiting with hepatic arterial infusion of 5-FU, presumably because a higher concentration of drug reaches the systemic circulation. These side effects include oral mucositis and gastrointestinal symptoms such as nausea, vomiting, and diarrhea. Myelosuppression occurs less often. Local and regional toxicities include peptic ulceration and chemical hepatitis (usually mild). In contrast, systemic toxicities are less common with FUdR, whereas local and regional toxicities predominate. Hepatic toxicity is dose limiting, and gastritis, duodenitis, or frank ulcers occur in 20% to 25% of patients.

5-FU and FUdR may also be given by the intraperitoneal route. Both drugs are absorbed primarily through the portal circulation and are subject to first-pass clearance in the liver before reaching the systemic circulation. In early trials, dialysate concentrations of 5 mM or less 5-FU maintained by intermittent exchanges of fluid for up to 24 hours were used. As the dose was increased, and the ratio of intraperitoneal to plasma 5-FU levels was approximately 300, 5-FU clearance is slower from the peritoneal cavity than from plasma (half-life approximately 1.5 hours). Up to 200 mg 5-FU given intraperitoneally for 4 hours with 90 mg/m² cisplatin every 4 weeks is tolerated, except for mild nausea and vomiting and sometimes diarrhea, whereas granulocytopenia occurs with higher dialysate concentrations. FUdR, 3000 mg given in 2 L of dialysate for 4 hours daily for 3 days, is well tolerated. The major systemic toxicity is nausea and vomiting, and this is usually well controlled. The perfusion to plasma FUdR ratio is approximately 2700, suggesting a potential pharmacologic advantage for the use of intraperitoneal FUdR over 5-FU.

**Clinical Toxicity**

The primary effects of 5-FU are exerted on rapidly dividing tissues, specifically gastrointestinal mucosa and bone marrow. The spectrum of toxicities associated with 5-FU varies considerably according to the dose, schedule, and route of administration. The most frequently used dose and schedules of single-agent 5-FU given by bolus injection are 600 mg/m²/week and 425 mg/m²/week for 5 days every 3 to 4 weeks. The dose of 5-FU generally should be reduced when used in combination with LV, the magnitude of which varies according to the schedule and LV dose. Epithelial ulceration may occur during the treatment course and may manifest as mucositis, pharyngitis, dysphagia, esophagitis, gastritis, colitis, or proctitis. Diarrhea may be watery or bloody, and the combination of nausea, vomiting, and proctitis may lead to profound dehydration and hypotension. Disruption of the integrity of the gut lining may permit access of enteric organisms into the blood stream, with the potential for overwhelming sepsis, particularly if the granulocyte nadir coincides with diarrhea. 5-FU should be withheld in the face of ongoing mucositis or diarrhea, even if mild, and subsequent doses should be reduced when the patient has fully recovered. If diarrhea occurs, supportive care and vigorous hydration should be given. Antidiarrheal agents, such as diphenoxylate and loperamide, may help control mild diarrhea, but they are generally ineffective in controlling diarrhea of greater severity. In this setting, the somatostatin analogue octreotide seems to have greater efficacy. Mouth cooling (oral cryotherapy) with oral ice chips for 30 minutes starting immediately before bolus 5-FU substantially reduces the severity of mucositis. Nausea and vomiting may occur but are usually controlled with antiemetics. Myelosuppression may also be observed, with granulocytopenia occurring more than thrombocytopenia. The schedule of a daily dose for 5-FU may be adjusted according to the granulocyte and platelet nadirs to occur during the second or third week of treatment. In contrast, myelosuppression generally occurs after the fourth weekly dose of the weekly bolus 5-FU schedule.

Continuous intravenous infusion of 5-FU at doses of 1000 mg/m²/week for 5 days every 3 weeks results in only minor myelosuppression, whereas stomatitis and diarrhea are the principal dose-limiting toxicities. With protracted venous infusion of 5-FU (300 mg/m²/week), serious myelosuppression is less common. The infusion can be interrupted at the first signs of mouth soreness or diarrhea, thus limiting the severity of toxicity. However, palmar-planar erythrodysesthesia (hand-foot syndrome) is a more-subacute toxicity that may eventually be dose limiting. With a weekly 24-hour infusion of 2600 mg/m² 5-FU, neurotoxicity and gastrointestinal toxicity are dose limiting.

Other dermatologic toxicities associated with 5-FU therapy include alopecia, changes in the fingernails, and dermatitis that varies from a pruritic erythematous rash followed by scaling to more severe cases of alopecia universalis. 5-FU enhances the cutaneous toxicity of radiation, and reactions usually occur within 7 days of radiation. Photosensitivity reactions, increased pigmentation over the veins into which 5-FU has been administered, as well as more generalized hyperpigmentation, and atrophy are possible. Hand-foot syndrome most often occurs with protracted infusion schedules of 5-FU, but may also be seen in patients receiving LV-modulated 5-FU. Occult toxicity includes alopecia, erythema, and xerosis of the skin, children often develop chilnitis with acute anasarca and chronic conjunctivitis. The acute inflammatory response is reversible when the drug is discontinued early in the treatment course, but progression may require surgical correction of ectropion and tear duct stenosis.

Acute neurologic symptoms, including somnolence, cerebellar ataxia, and upper motor signs, are primarily seen in patients receiving intracavitary infusions for head and neck tumors. 5-FU toxicity may result in long-term sequelae, with neurotoxicity seen in children when the drug is given by the intraperitoneal route. The cumulative effect of 5-FU is more than myelosuppression. Neurotoxicity is greater than myelosuppression, and the myelosuppression is more transient. The sequential administration of 5-FU and MTX may play a role in the neurotoxicity is supported by preclinical models of neurotoxicity. However, patients with DPD deficiency may experience severe neurologic toxicity in the absence of myelosuppression and gastrointestinal toxicity after 5-FU therapy. Thus, the exact 5-FU metabolite responsible for 5-FU neurotoxicity remains unclear.

A syndrome of chest pain, cardiac enzyme elevations, and electrocardiographic changes consistent with myocardial ischemia may be seen in temporal association with 5-FU administration. In some patients, coronary angiography revealed no abnormalities, suggesting vasospasm as a possible mechanism. This toxicity has been attributed to parent drug and to the metabolites, fluoro-b-alanine and fluoroacetate. Concentration-dependent vasconstriction occurs when isolated vascular smooth muscle rings are exposed in vitro to 5-FU, and this can be reversed with nitrates.

Intrahepatic administration of FUdR is complicated mainly by cholestasis jaundice and biliary sclerosis. These adverse side effects are thought to result from direct perfusion of the blood supply to the gallbladder and upper bile duct with high local drug concentrations. Of note, this complication occurs much less frequently with hepatic arterial infusion of 5-FU. Biliary sclerosis typically occurs by the third cycle of treatment. Therapy with FUdR may be reinitiated at a lower dose after normalization of serum hepatic enzyme levels, but most patients become progressively less tolerant. Catheter-related complications include thrombosis of the catheterized vessel, hemorrhage or infection at the site of insertion, and slippage of the catheter into the gastro-duodenal artery with resultant necrosis of the intestinal epithelium, hemorrhage, and perforation.

**Drug Interactions**

A host of drug interactions have been investigated in an attempt to enhance the cytotoxicity and therapeutic selectivity of fluoropyrimidine chemotherapy. The interaction of 5-FU with MTX is of particular interest as both drugs are often used in combination chemotherapy for breast and colorectal cancer. When given before 5-FU, MTX-mediated inhibition of DHFR results in accumulation of PRPP. Increased availability of PRPP promotes formation of fluorouridine monophosphate via the reaction catalyzed by orotic acid phosphoribosyltransferase, with enhanced FUTP incorporation into RNA. In contrast, administration of 5-FU after MTX antagonizes the antipurine effects of MTX by preventing the accumulation of dihydrofolate and maintaining the pool of reduced folates needed for the reaction catalyzed by orotic acid phosphoribosyltransferase, with enhanced FUTP incorporation into RNA. The dose of MTX in clinical trials has varied, but doses of 100 mg/m² or more are usually followed by LV rescue. A metaanalysis of randomized trials of MTX and 5-FU revealed a higher response rate compared with single-agent bolus 5-FU. Synergy between 5-FU and cisplatin has been noted in several preclinical models. Possible mechanisms of interaction include cisplatin-mediated increases in the intracellular content of the reduced folate pool, enhanced DNA damage, and interference with repair of cisplatin-DNA adducts. In some preclinical models, concurrent exposure to both drugs produces synergy, whereas others model suggest that preexposure to 5-FU before cisplatin administration is superior to the opposite sequence. In addition, the intraperitoneal 5-FU and cisplatin is evident in tumor types that are sensitive to both drugs, such as squamous cell cancers of the head and neck and esophagus, whereas randomized trials in colorectal cancer show no benefit with the addition of cisplatin. The influence of sequence of cisplatin and 5-FU on therapeutic outcome has not been carefully studied in clinical trials.

The salvage enzyme thymidine kinase converts thymidine to thymidine monophosphate, thereby bypassing the TS-mediated inhibition of de novo thymidylate production. In tissue culture models, thymidine (10 to 20 µM) is frequently used to replete dTTP pools and thus negate its potential contribution to toxicity. In some models, pharmacologic concentrations of thymidine 5-FU RNA incorporation (by feedback inhibition of thymidine kinase and RT). In vivo, thymidine 5-FU (and its carbamate thymine) increased the half-life of 5-FU by interfering with the catabolism of 5-FU to dihydrofurfuryluracil, leading to a marked increase in 5-FU toxicity with no improvement in antitumor activity. Simultaneous exposure to pharmacologic concentrations of uridine may antagonize the RNA-directed cytotoxicity of 5-FU by decreasing its activation to the ribonucleotide level by uridine kinase; furthermore, expanded UTP pools may decrease FUTP incorporation into RNA. Delayed administration of uridine increases the rate of recovery from 5-FU-associated inhibition of both RNA and DNA synthesis in some models. Delayed administration of oral uridine to patients decreases the myelosuppression associated with weekly bolus 5-FU, but the effect on therapeutic activity has yet to be determined.

Interferons (IFNs) increase the in vitro and in vivo activity of 5-FU and FUdR in a cell-line–dependent manner. Heterogeneity exists among cancer cell lines as to the specific type of IFN that enhances fluoropyrimidine toxicity. IFN-A may increase the activity of thymidine and uridine phosphorylases, and increased FdUMP

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formation has been reported in some cell lines. In other models, IFN-α may enhance fluoropyrimidine-mediated DNA damage in the absence of a direct effect on FUUMP pools or the extent of TS inhibition. In a human colon cancer cell line, IFN-γ abrogated the acute increase in TS protein accompanying 5-FU exposure, and in so doing, enhanced the cytotoxic effects of 5-FU. IFN-α may decrease the clearance of 5-FU in some individuals in a dose- and schedule-dependent manner, particularly with consecutive daily administration of IFN-α in combination with bolus 5-FU. Initial clinical trials appeared promising, although the toxicity of IFN-α may prove intolerable. The trial’s design has been re-evaluated in a 2-weekly schedule of IFN-α given 1 day before a 24-hour infusion of 5-FU (2600 mg/m²), a randomized phase II trial conducted by the Southwest Oncology Group failed to demonstrate an improvement in response rate compared with the same schedule of 5-FU alone. Results from other multimodular phase III trials are pending.

Preclinical studies show that 5-FU enhances the covalent binding of ionizing radiation, and both preclinical and clinical studies have revealed that radiosensitization appears to be enhanced with prolonged exposure. The underlying mechanisms for this synergistic interaction may include increased DNA damage, inhibition of DNA repair, and accumulation of cells in S phase. Some work suggests that the G1/S checkpoint may play a critical role in determining the ability of 5-FU to enhance the cytotoxic effects of radiation therapy. Moreover, this effect may not depend on normal p53 function, but instead, may rely on intact cyclin E-dependent kinase activity. One example highlighting the successful clinical application of this approach is the use of protracted infusional 5-FU during pelvic radiation in the adjuvant treatment of rectal cancer.

**STRATEGIES TO PERMIT ORAL ADMINISTRATION OF FLUOROPYRIMIDINES**

**TEGAFUR, URACIL, 5-FUOROURACIL**

Administration of 5-FU by the oral route has generally been avoided because of erratic bioavailability. Several strategies to allow oral dosing by decreasing the catabolism of 5-FU are being explored. One approach involves the drug tegafur, uracil, 5-fluorouracil (UFT), a combination of Flurafur (1:1 molar ratio of tegafur, uracil, 5-fluorouracil), and S1, a 1:4 molar ratio with uracil. Preclinical studies indicated that UFT resulted in significantly higher tumor-to-serum 5-FU ratios than Flurafur alone. UFT is administered orally in divided doses, and it has been given daily for 5 to 28 days. With oral dosages ranging from 50 to 300 mg/m², maximum plasma levels of Flurafur and 5-FU occur between 0.6 and 2.1 hours. Flurafur levels (2.7 to 20.0 μg/mL) exceed 5-FU levels (0.025 to 0.9 μg/mL). UFT contains a 70% 5-FU. In patients treated with UFT, the drug has single-agent activity (19% to 32% response rate) in advanced colorectal tumors. Toxicity of UFT in advanced colorectal cancer is generally mild, with myelosuppression predominating. Phase I and II studies are under way in the United States to confirm its clinical activity.

**5-ETHYNYLURACIL**

Aminopterin (an oral formulation composed of the 5-FU prodrug Ftorafur, the DPD inhibitor 5-chloro-2,4-dihydroxypyridine, and oxonic acid. S1 is an oral formulation of the 5-FU prodrug Flurafur, the DPD inhibitor 5-chloro-2,4-dihydroxyprydine, and oxonic acid. 5-Chloro-2,4-dihydroxyprydine is a competitive, reversible inhibitor of DPD that helps to significantly prolong the half-life of 5-FU and improve oral bioavailability. Oxonic acid is an inhibitor of pyrimidine phosphoribosyltransferase, and it acts to prevent 5-FU phosphoribosylation and subsequent incorporation of 5-FU metabolites into the RNA of normal tissues in the gastrointestinal tract. Given its mechanism of action, the goal of oxonic acid is to protect against 5-FU-mediated gastrointestinal toxicity. Phase I studies revealed the dose-limiting toxicity was myelosuppression mainly in the form of neutropenia. In Japan, where this drug was initially developed, phase II trials have been conducted in several malignancies, including gastric, colorectal, breast, and head and neck cancer. Response rates have ranged between 30% and 50%, and toxicity has been generally mild, with myelosuppression predominating. Phase I and II studies are under way in the United States to confirm its clinical activity.

**CAPECITABINE (XELODA)**

Capcitabine (Xeloda) represents another oral prodrug of 5-FU that was designed with the rationale of generating selective 5-FU activation in tumor tissue. When administered orally, it is absorbed intact through the intestinal mucosa, metabolized by a carboxylesterase enzyme in the liver to 5-deoxy-5-fluorocytidine, and then converted directly to 5'-deoxy-5-fluorouridine by cytidine deaminase, an enzyme principally located in the liver. 5'-Deoxy-5-fluorouridine is then converted directly at the tumor site by the thymidine-metabolizing enzyme, thymidine phosphorylase, a protein that has been shown to function as an angiogenic factor.

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**EU** is a promising biochemical modulator of 5-FU, and clinical studies suggest that it may help to improve the antitumor activity and host toxicity profile of 5-FU chemotherapy. Currently, there are two large randomized, phase III studies comparing 5-FU and EU with either the Mayo Clinic daily for 5 days regimen of 5-FU and LV in advanced colorectal cancer.
Cytarabine (1-b-D-arabinofuranosylcytosine, Ara-C) is one of several arabinose nucleosides isolated from the sponge Cryptotheca crypta differing from its physiologic counterpart by virtue of a stereotypic inversion of the 2'-hydroxyl group of the sugar moiety (Fig. 19.5-5). Ara-C is regarded as one of the most important drugs in the treatment of acute myelogenous leukemia (AML). A regimen of Ara-C combined with an anthracycline, given as a 5- or 7-day continuous infusion is considered the standard induction treatment for AML. Furthermore, Ara-C is used in the treatment of other hematologic malignancies, such as non-Hodgkin's lymphoma, chronic myelogenous leukemia, and acute lymphocytic leukemia.

**Intracellular Metabolism and Mechanism of Action**

As with other nucleoside analogues and their physiologic counterparts, Ara-C enters cells via nucleoside-specific transmembrane transport proteins, the most important one being the es (equilibrative inhibitor-sensitive) receptor. Studies with blasts from patients with acute leukemias have shown a strong correlation between expression of es transporters and in vitro sensitivity to Ara-C.

Once within the cytoplasm, Ara-C requires activation for its cytotoxic effects. The first metabolic step is the conversion of Ara-C to ara-cytidine monophosphate (Ara-CMP) by the enzyme deoxycytidine kinase (dCK) (Fig. 19.5-6). This enzyme is the rate-limiting step in intracellular anabolism of Ara-C. This metabolic step is saturable, and the Kₘ is approximately 20 µM. Ara-CMP is subsequently phosphorylated to ara-cytidine diphosphate (Ara-CDP) and Ara-CTP by the enzymes pyrimidine monophosphate kinase and pyrimidine diphosphate kinase, respectively. Ara-CTP competes with the native substrate deoxycytidine triphosphate (dCTP) for DNA incorporation by DNA-directed DNA polymerase (Kₘ approximately 1 µM). The incorporated Ara-CTP residue is a potent inhibitor of DNA polymerase a (involved in Okazaki fragment synthesis on the lagging strand of the replication fork), DNA polymerase d (the leading strand replicase), and DNA polymerase b (involved in the repair of chemically induced DNA damage). Inhibition of DNA polymerases, in turn, interferes with DNA chain elongation during both semiconservative DNA replication and DNA repair. The incorporated Ara-CTP residue functions as a relative DNA chain terminator, and interference with chain elongation is influenced by sequence specificity of the DNA template. Initiation of new DNA replication intermediates continues, however, with accumulation of nascent DNA fragments. This process may result in abnormal duplication of limited portions of DNA, thus increasing the possibility of recombination, crossover, and gene amplification. Over time, the nascent strand can be extended beyond the arabinosylcytidine residue, and digestion of DNA reveals the presence of Ara-CMP in the internucleotide (internal) position. In some human leukemic cell lines, Ara-C–mediated DNA damage is accompanied by a pattern of internucleosomal DNA fragmentation typical of apoptosis (programmed cell death). There is evidence suggesting that Ara-C metabolism in AML blasts differs from that in normal bone marrow mononuclear cells and CD34+ hematopoietic stem cells. The total levels of phosphorylated Ara-C metabolites, including Ara-CMP, Ara-CDP, Ara-CTP, Ara-CDP-choline, and Ara-UMP, were two- to fourfold higher in leukemic blast cells when compared with normal bone marrow cells, both at standard and high doses of Ara-C. The most striking difference was found with the Ara-CDP-choline metabolite in the setting of Ara-C dose escalation. The level of this metabolite was 4.3-fold higher in leukemic blast cells.

In animal studies, Ara-CMP inhibits transfer of galactose, N-acetylgalactosamine, and sialic acid to cell surface glycoproteins. Ara-CTP (0.1 to 1.0 mM) inhibits synthesis of CMP-acetylneuraminic acid, and Ara-CDP choline can be incorporated into membranes. These effects on phospholipid synthesis and incorporation into membranes may possibly affect membrane structure and function. Catabolism of Ara-C involves two key enzymes, cytidine deaminase and deoxycytidylate deaminase. They convert Ara-C and Ara-CMP into their respective nontoxic analogues deoxyxycytidine, 5'-nucleotidase, and alkaline and acid phosphatases. The balance between intracellular activation and degradation is critical in determining the amount of drug that is ultimately converted to Ara-CTP and, thus, its subsequent cytotoxic and antitumor activity (see Fig. 19.5-6).

**Mechanisms of Resistance**

Ara-C is most active during the S phase of the cell cycle. The rate of DNA synthesis influences Ara-C cytotoxicity, with maximum effects observed when cells are exposed to Ara-C during periods of rapid DNA synthesis. Longer exposures allow a greater proportion of cells to enter S phase and are associated with enhanced incorporation of Ara-CTP into DNA. Therefore, the duration of Ara-C exposure seems to be a critical determinant of its cytotoxicity.

Several mechanisms of resistance to Ara-C have been described. Impaired transmembrane transport, decreased rate of anabolism, increased rate of catabolism, or all three may result in the development of Ara-C resistance. In vitro studies have demonstrated that amplification of the cytidine deaminase gene with resultant overexpression of the corresponding protein product leads to Ara-C resistance. The level of cytidine deaminase enzyme activity has been shown to correlate with...
clinical response in patients with AML undergoing induction chemotherapy with Ara-C-containing regimens. Blasts from patients who attained complete remission and from those with previously untreated leukemia had significantly higher levels of cytidine deaminase than blasts from patients with refractory disease.

Deletion of the gene encoding deoxycytidine kinase, expansion of CTP and dCTP pools, overexpression of bcl-2, and decreased intracellular half-life of Ara-CTP after drug removal are mechanisms that have been implicated in Ara-C resistance. The cytotoxicity of Ara-C in leukemic cells isolated from patients correlates well with both the extent of DNA incorporation and the intracelular retention of Ara-CTP after drug exposure.

Cellular sensitivity to Ara-C can also be influenced by the concomitant use of other drugs. For example, all-trans-retinoic acid was found to enhance Ara-C cytotoxicity, as well as Ara-C–induced apoptosis in HL-60 human leukemia cells. However, the mechanism by which this sensitization is mediated remains unclear. The sensitivity of human leukemic cell lines to Ara-C has also been tested in the presence of stem cell factor. The addition of stem cell factor to a suspension culture system leads to a significant increase in the toxicity of Ara-C to self-renewing blast progenitors, especially when associated with an increase in DNA synthesis.

Hypersensitivity reactions are also possible with high-dose Ara-C. Although limited in its current clinical application, 6-mercaptopurine (6-MP) has shown a positive interaction with Ara-C. By inhibiting cytidine deaminase enzyme activity in L1210 murine leukemia cells, 6-MP is able to maintain high concentrations of Ara-C in the culture medium. This effect results in an enhanced incorporation of Ara-C into cells and subsequent activation to Ara-CTP.

Clinical Pharmacology and Pharmacokinetics

Ara-C has poor oral bioavailability (approximately 20%) due to extensive deamination within the gastrointestinal tract. Consequently, Ara-C is administered via the intravenous route. The drug can also be given subcutaneously. After intravenous bolus administration, Ara-C is rapidly cleared with biphasic elimination: The initial half-life is approximately 12 minutes, whereas the terminal half-life is approximately 2 hours. Within 24 hours, 76% of a bolus dose is excreted in the urine (71% as Ara-U, 7% as Ara-C). During continuous intravenous infusion, steady-state plasma levels of Ara-C increase linearly to 5 to 10 µM, and drug clearance is approximately 1000 mL/min/m². Thereafter, deamination is saturated, and plasma levels can increase unpredictably. With continuous infusion of doses from 100 to 200 mg/m², steady-state plasma levels range from 0.2 to 1.0 µM, and CSF levels are approximately 50% of the plasma levels.

When administered as a high-dose (greater than 2 g/m²) intravenous infusion over 1 to 3 hours, the plasma elimination is triphasic: a, b, and g half-lives are 16 minutes, 1.8 hours, and 6 hours, respectively. The mean plasma concentration at the end of infusion ranges from approximately 60 to 150 µM, but 12 hours later falls to less than 0.5 µM. Ara-C crosses the blood–brain barrier when used at high doses, with CSF levels between 7% to 14% of plasma levels, reaching peak levels of up to 10 µM. Because cytidine deaminase enzyme activity is nearly completely absent in CSF, the drug displays a longer half-life in the CSF (approximately 2 to 4 hours).

Ara-C can also be given intrathecally as prophylaxis against CNS tumor involvement and to treat leptomeningeal disease of both hematologic and solid malignancies. The usual dose is anywhere from 30 to 60 mg in 5 to 10 mL diluent twice weekly until documentation of three consecutively negative CSF cytology results. Intrathecal administration of 50 mg/m² Ara-C yields peak concentrations of 1 mM, and cytotoxic concentrations (0.4 µM or above) are maintained for 24 hours. Of note, the diluent supplied with commercial formulations of Ara-C contains 0.945% benzyl alcohol. Given the potential toxicity of benzyl alcohol, diluents containing this preservative should not be used for intrathecal administration in neonates or with high-dose regimens. In these situations, preservative-free 0.9% sodium chloride injection or other isotonic buffered diluents should be used to reconstitute the drug. Finally, Ara-C can also be used intraperitoneally. This approach is commonly used as second-line treatment for ovarian cancer patients presenting primarily with intraperitoneal disease, and it is usually given in combination with cisplatin.

Toxicity

The toxicity profile of Ara-C is highly dependent on the dose and schedule of administration. Myelosuppression is the dose-limiting toxicity with a standard regimen of 100 to 200 mg/m² for 7 days. Leukopenia and thrombocytopenia are the most severe cytopenias, with the nadir occurring between days 7 and 14 after drug administration. However, the duration of the nadir can be significantly influenced by the concomitant use of other cytotoxic agents and also by previous treatment with chemotherapy.

Gastrointestinal toxicity commonly manifests as a mild to moderate degree of anorexia, nausea, and vomiting. Mucositis, diarrhea, ileus, and abdominal pain can also be observed. Less common, epithelial ulceration can occur, ranging from superficial ulceration to intramural hematoma formation and perforation. Transient hepatic dysfunction, manifested as elevation of liver enzymes, may also occur with Ara-C given at conventional doses. Acute pancreatitis has been associated with Ara-C, mostly when given as a continuous infusion. The Ara-C syndrome has been described in pediatric patients receiving Ara-C for hematologic malignancies and is characterized by fever, myalgia, bone pain, maculopapular rash, conjunctivitis, malaise, and occasional chest pain. These symptoms usually begin within 12 hours after Ara-C infusion. This syndrome most likely represents an allergic reaction to Ara-C, as patients usually develop symptoms months after the first dose, and corticosteroids can prevent its onset.

Administration of Ara-C at high doses (2 to 3 g/m² intravenously over 1 to 3 hours, every 12 hours; 100 mg/m²/h for 24 hours) produces severe myelosuppression, sometimes with prolonged nadirs. Severe gastrointestinal toxicity in the form of mucositis, diarrhea, or both, is also frequently observed. Neurologic toxicity is significantly more common with high-dose Ara-C than with standard doses. The clinical manifestations of neurologic toxicity are diverse and include seizures, cerebral and cerebellar dysfunction, peripheral neuropathy, bilateral rectus muscle palsy, aphasia, and Parkinsonian symptoms. Clinical signs of cerebellar dysfunction occur in up to 15% of patients within 8 days and include dysarthria, dysdiadochokinesia, dysmetria, and ataxia. Change in alertness and cognitive ability, memory loss, and frontal lobe release signs reflect cerebral toxicity. Despite discontinuation of therapy, clinical recovery is incomplete in up to 30% of affected patients. The severity of cerebellar toxicity increases with higher cumulative Ara-C dose. Electroencephalography and nerve conduction test results suggest a demyelinating polyneuropathy with axonal degeneration. Significant neurotoxicity appears uncommon at cumulative doses of 36 g/m² or less. Neurotoxicity may also be reduced by prolonged intravenous administration (over 3 hours or more). Patients older than 50 years and patients with elevated serum creatinine levels are particularly susceptible to neurologic toxicity.

Other side effects are less commonly seen. Pulmonary complications may include noncardiogenic pulmonary edema, acute respiratory distress, and pneumonia, resulting from Streptococcus viridans infection. Other side effects associated with high-dose Ara-C include conjunctivitis (often responsive to topical corticosteroids), a painful hand-foot syndrome, and, rarely, anaphylactic reactions. A fatal case of toxic epidermal necrolysis has been described. Neutrophilic eccrine hidradenitis, an unusual cutaneous reaction manifested as plaques or nodules, can occur during the second week after high-dose Ara-C.

Intrathecal administration of Ara-C is usually uneventful. However, it may produce fever, seizures, and alterations in mental status within the first 24 hours of administration. Ara-C is teratogenic in animals. Although Ara-C produces chromosomal breaks in both cultured cells and bone marrow, it is not an established carcinogen in humans.

Drug Interactions

In vitro studies and animal tumor model systems have provided evidence for synergistic activity between Ara-C and alkylating agents, platinum compounds, purine analogues, antifolates, and fluoropyrimidines. More recently, synergism has also been observed with Ara-C and other agents, such as bryostatin 1, fludarabine, and paclitaxel. The use of IFN-α combined with Ara-C in low doses is useful in the treatment of patients with early chronic phase chronic myelogenous leukemia, despite the inconvenience of high-dose intravenous therapy. Specific biochemical, or both, kinetic mechanisms have been described for each of these interactions, and the sequence of drug administration may be critical in some cases. Ara-C enhances the cytotoxicity of various DNA-damaging agents, including alkylating agents (cyclophosphamide, carmustine), topoisoenzyme II inhibitors (ansamycin, etoposide), cisplatin, and ionizing radiation. The mechanism underlying these positive interactions appears to be interference by Ara-C with the process of DNA repair, resulting in enhanced DNA damage.

The metabolism of Ara-C, the main catalytic by-product of Ara-C, is important for the metabolism and toxicity of Ara-C. Ara-U is mainly excreted in the urine. High concentrations of Ara-U can decrease deamination of Ara-C through feedback inhibition of cytidine deaminase, thus resulting in the increased intracellular levels of Ara-C. Ara-U also increases the fraction of murine leukemia cells entering S phase, thereby enhancing Ara-C cytotoxicity. Accumulation of high levels of Ara-U may occur in both plasma and CSF following administration of high-dose Ara-C, with a possible increase in Ara-CTP formation in brain tissue. These observations may explain the increased risk of neurotoxicity with high-dose Ara-C, especially in those with impaired renal function.
Interruption of the DNA incorporation of Ara-C (e.g., by pretreatment with TS inhibitors) may antagonize its cytotoxicity.\textsuperscript{144} MTX pretreatment, however, may increase Ara-CTP formation. Antimetabolites that decrease the competing pools of dCTP may enhance Ara-C anabolism, DNA incorporation, and its subsequent cytotoxicity. Such agents include inhibitors of RR (fludarabine, hydroxyurea, and high-dose thymidine), and inhibitors of CTP synthase (the investigational drugs acivicin, cyclophosphamide, and 3-deazauridine).

Interactions between cytostatics and Ara-C may have potential clinical implications. A 24-hour exposure of human myeloid leukemic cells to PIVX 321, a fusion protein combining granulocyte-macrophage colony-stimulating factor and interleukin-3, enhances high-dose Ara-C-mediated induction of apoptosis.\textsuperscript{145}

**GEMCITABINE**

Gemcitabine (2',2'-difluorodeoxycytidine, dFdC, Gemzar) is a difluorinated analogue of deoxycytidine (see Fig. 19.5-5). This compound has shown significant preclinical and clinical activity against several human solid tumors, including cancer of the pancreas, small cell and non–small cell lung cancer, and bladder cancer. In contrast to Ara-C, the spectrum of antitumor activity of gemcitabine is much broader, despite the similarities in structure, metabolism, and mechanism of action.\textsuperscript{152} The most commonly used schedule in clinical practice is 1000 mg/m\(^2\) intravenously administered weekly for 3 weeks, followed by a 1-week rest. This schedule seems to provide the most acceptable toxicity profile with the greatest dose intensity. This compound has been moved rapidly from phase I/II studies into phase III studies, mostly in combination with other established anticancer agents.

**Intracellular Metabolism and Mechanism of Action**

Transport of gemcitabine into cells requires the nucleoside transporter system. Nucleoside transport–deficient cells are highly resistant to the drug. Furthermore, the specific type of nucleoside transporter expressed on the cell surface may be an important determinant of drug sensitivity.\textsuperscript{144,146} The intracellular concentration of adenosine triphosphate (ATP) may also be an additional sign of the sensitivity to gemcitabine. In head and neck cancer cell lines, ATP-replete cells accumulated significantly less gemcitabine, when compared with ATP-deplete cells. This finding suggests the existence of an active efflux mechanism for gemcitabine.\textsuperscript{147}

Gemcitabine is fivefold more lipophilic than Ara-C, a feature that is thought to contribute to the 65% greater rate of accumulation of gemcitabine in cells when compared with Ara-C.

Gemcitabine requires intracellular activation for its cytotoxic effects. The steps involved in its metabolic activation of gemcitabine are similar to those observed with Ara-C, with both drugs being activated by the same enzymatic machinery. Deoxycytidine kinase converts dFdC into dFdCMP.\textsuperscript{148,150} The drug is subsequently phosphorylated by nucleoside monophosphate and diphosphate kinases to the respective 5'-diphosphate (dFdCDP) and 5'-triphosphate derivatives (dFdCTP).\textsuperscript{151,152} dFdCTP is the major cellular metabolite of dFdC. The intracellular concentration of dFdCTP determines to a large extent its subsequent metabolism. In cells with lower concentrations of this metabolite (less than 100 µmol/L) the main route of elimination is by deamination, whereas in cells with higher concentrations (greater than 100 µmol/L) dephosphorylation and urinary excretion predominate. Furthermore, dFdCTP, by inhibiting dCMP deaminase, establishes a mechanism of self-potentiating, with a marked prolongation of its terminal half-life from 3.6 hours to 19.0 hours. This phenomenon may explain, at least in part, the differences observed between Ara-C and dFdC in their spectrum of clinical activity.

The intracellular metabolites of gemcitabine have not yet been determined. The accumulation of dFdCTP in plasma samples by HPLC and an enzyme-linked immunosorbent assay. As dFdC is rapidly deaminated, blood collection tubes must contain detraining scavenger to prevent degradation in vivo.\textsuperscript{153}

The potential role of RR as a determinant of drug resistance has been confirmed in the human erythroleukemia K562 cell line, where high RR enzyme activity was directly correlated with resistance.\textsuperscript{171} However, experiments using human epidermoid carcinoma KB cells suggest that the enzyme RR may play an important role as well. RR is an S-phase–specific, rate-limiting enzyme of the DNA synthesis pathway. Cells exhibiting resistance to gemcitabine demonstrated a ninefold overexpression of RR mRNA, a twofold overexpression of RR protein, and a 2.3-fold higher RR enzyme activity when compared with gemcitabine-sensitive cells.\textsuperscript{171} The pattern of cross-resistance between various nucleoside analogues may have potential clinical implications. For example, gemcitabine was found to have higher antitumor activity than Ara-C in both Ara-C–sensitive (L1210 and BCLO) and Ara-C–resistant (LA46 and Bara-C) cell lines.\textsuperscript{171} The potential role of RR as a determinant of drug resistance has been confirmed in the human erythroleukemia K562 cell line, where high RR enzyme activity was directly correlated with resistance.\textsuperscript{172}

**Mechanisms of Resistance**

Several mechanisms of resistance to gemcitabine in cell lines have been described. Nucleoside transport–deficient cells are highly resistant to gemcitabine.\textsuperscript{144} Furthermore, the efficiency of gemcitabine uptake can vary significantly according to the specific nucleoside transporter expressed on the cell surface.\textsuperscript{144}

Clinical Pharmacology and Pharmacokinetics

**dFdC** can be measured in plasma samples by HPLC and an enzyme-linked immunosorbent assay. As dFdC is rapidly deaminated, blood collection tubes must contain detraining scavenger to prevent degradation in vivo.\textsuperscript{153} The concentration versus time curve (area under the concentration time curve) increases in a linear fashion.

A phase I trial of dFdC in cancer patients explored the maximally tolerated duration of dFdC infused at a dose rate of 10 mg/m\(^2\)/min, calculated to produce steady-state levels of 20 µM (Fig. 19.5-5)). The maximum tolerated duration was 2.5 hours and 6.8 hours.

Facultative mononuclear cells, which are insensitive to dFdC, do not incorporate dFdC into any DNA.\textsuperscript{156} However, experiments using human epidermoid carcinoma KB cells suggest that the enzyme RR may play an important role as well. RR is an S-phase–specific, rate-limiting enzyme of the DNA synthesis pathway. Cells exhibiting resistance to gemcitabine demonstrated a ninefold overexpression of RR mRNA, a twofold overexpression of RR protein, and a 2.3-fold higher RR enzyme activity when compared with gemcitabine-sensitive cells.\textsuperscript{171} The potential role of RR as a determinant of drug resistance has been confirmed in the human erythroleukemia K562 cell line, where high RR enzyme activity was directly correlated with resistance.\textsuperscript{172}

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**Clinical Pharmacology and Pharmacokinetics**

**dFdC** can be measured in plasma samples by HPLC and an enzyme-linked immunosorbent assay. As dFdC is rapidly deaminated, blood collection tubes must contain detraining scavenger to prevent degradation in vivo.\textsuperscript{153} The concentration versus time curve (area under the concentration time curve) increases in a linear fashion.\textsuperscript{152} The compound is rapidly eliminated from plasma, mainly by deamination. The median half-life and clearance of dFdC are 8 minutes and 119 L/h/m\(^2\), respectively.\textsuperscript{152} Renal clearance of parent drug is less than 10% of the systemic clearance. dFdU, the main catabolic by-product, is eliminated by biphosphokinetics characterized by a long terminal phase (half-life of 14 hours).\textsuperscript{152} The pharmacokinetics and toxicity of dFdC in patients with impaired hepatic and renal function has not yet been determined. The accumulation of dFdCTP in circulating mononuclear cells appears to be saturated when plasma levels exceeded 15 to 20 µM; the median half-life for intracellular retention was 4.7 hours.\textsuperscript{152}
**Toxicity**

Although gemcitabine is a relatively well-tolerated drug when used as a single agent, its toxicity profile can vary significantly according to the schedule of administration. The most commonly used schedule is a weekly dose of 600 to 1250 mg/m², administered intravenously over 30 minutes, for 3 weeks on an every 4-week cycle. With this schedule, myelosuppression is the dose-limiting toxicity, and all three lineages can be affected. A published series of more than 3000 patients treated with gemcitabine for pancreatic carcinoma revealed that nonhematologic side effects are relatively uncommon. They include fever (7.3%), pain (6.8%), asthenia (6.0%), abdominal pain (5.5%), dyspnea (5.0%), vomiting (3.9%), anorexia (3.6%), and deep venous thrombosis (3.2%). A particularly unusual side effect of dFdC is anal pruritus, which may be prevented with the use of corticosteroids.

Although dyspnea is a relatively uncommon side effect of gemcitabine, its development during the treatment with the drug may require discontinuation of the treatment. Continuation of treatment once dyspnea develops may lead to a fatal outcome. Patients usually present with a clinical picture consistent with acute respiratory distress syndrome, with hypoxemia, pulmonary infiltrates, and no evidence of left ventricular failure. The onset of acute respiratory distress syndrome in these patients can take place anywhere between 2 and 40 days after the first dose of the drug. Thus, close monitoring of patients for any change in baseline respiratory status is crucial.

A rare yet potentially fatal complication of dFdC is hemolytic-uremic syndrome (HUS). The incidence of this complication has been estimated to be less than 1%. Early recognition of HUS is important and should prompt the immediate discontinuation of therapy to prevent death from HUS-related complications.

**Drug Interactions**

Gemcitabine has been combined with various chemotherapeutic agents in the treatment of several solid tumors. Preclinical in vitro studies have provided evidence of synergism between gemcitabine and various anticancer agents to support these associations. Cisplatin is one of the agents most commonly used in combination with gemcitabine. In vitro studies with different human cancer cell lines have shown synergistic interaction between gemcitabine and cisplatin. These ribonucleotide monophosphates inhibit the first step of purine synthesis, such as MTX, interact in a synergistic manner with 6-thiopurines because the MTX-induced block in purine synthesis expands the PRPP pool required for thiopurine activation. Both ribonucleotide and deoxyribonucleotide metabolites of the thiopurines are formed, which can then be incorporated into cellular RNA and DNA. Incorporation of fraudulent nucleotides into DNA interferes with DNA replication and results in the formation of DNA strand breaks. In some model systems, incorporation of thiopurine nucleotides into DNA correlates with cytotoxicity.

In vitro studies have provided evidence of this synergism is maximum when cells are exposed first to etoposide and then to gemcitabine. This may be due to the fact that cells exposed first to etoposide have low levels of dCTP in the cytoplasm, which then allow for enhanced phosphorylation of dFdC and subsequent incorporation of dFdCTP into DNA.

**6-THIOPURINES**

The development of the purine analogues in cancer chemotherapy began in the early 1950s with the synthesis of the thiopurines. For this seminal work, Hitchings and Elion received the Nobel Prize in Medicine in 1988. The purine analogues, 6-MP and 6-thioguanine (6-TG) continue to be used principally in the management of acute leukemia. 6-MP has an important role in the maintenance therapy of acute lymphoblastic leukemia (ALL), whereas 6-TG is active in remission induction and in the maintenance therapy of AML. These analogues have a single substitution of a thiol group in place of the 6-hydroxyl group of the purine base (Fig. 19.5-7). 6-MP is a structural analogue of hypoxanthine, whereas 6-TG is an analogue of guanine. Azathioprine is a derivative of 6-MP and acts as a prodrug to provide sustained release of 6-MP.

**Intracellular Metabolism and Mechanism of Action**

6-MP and 6-TG act similarly with regard to their cellular biochemistry. In their respective monophosphate nucleotide form, they inhibit de novo purine synthesis and purine interconversion reactions, whereas the nucleotide triphosphate metabolites are incorporated directly into nucleic acids. The relative contribution of each of these actions to the mechanism of cytotoxicity of these agents is unclear. Both 6-MP and 6-TG are converted to their respective monophosphate forms by hypoxanthine-guanine phosphoribosyl transferase (HGPRT) (Fig. 19.5-8). These ribonucleotide monophosphates inhibit the first step of de novo purine synthesis catalyzed by glutamine phosphoribosylpyrophosphate aminotransferase and block the conversion of inosinic acid to adenylic acid or to guanylic acid. Inhibition of purine nucleotide synthesis leads to the build-up of PRPP, which facilitates the activation of 6-MP and 6-TG to their active nucleotide forms by HGPRT.

**Inhibitors of de novo purine biosynthesis, such as MTX, interact in a synergistic manner with 6-thiopurines because the MTX-induced block in purine synthesis expands the PRPP pool required for thiopurine activation. Both ribonucleotide and deoxyribonucleotide metabolites of the thiopurines are formed, which can then be incorporated into cellular RNA and DNA. Incorporation of fraudulent nucleotides into DNA interferes with DNA replication and results in the formation of DNA strand breaks. In some model systems, incorporation of thiopurine nucleotides into DNA correlates with cytotoxicity.**

In addition to 6-MP effects on DNA biosynthesis, there is now evidence that the glycolytic pathway may also be affected. 6-Phosphofructo-2-kinase, an essential enzyme for carbohydrate metabolism, is inhibited by 6-MP. Finally, this class of compounds may inhibit the process of angiogenesis, as studies have shown in vivo.
antiangiogenic activity of a thiopurine metabolite, methylmercaptopurine riboside, in a human endometrial adenocarcinoma xenograft model. 185

Mechanisms of Resistance
 Biological resistance to 6-mercaptopurine (6-MP) results from an increased ability to form cytidylic nucleotide metabolites. In experimental systems, resistant cells express either a complete or partial deficiency of HGPRT. 186 An alteration in the affinity of HGPRT for 6-thiopurines has also been described. 187 Studies have shown that decreased transmembrane transport of 6-TG can also result in drug resistance. 188 In the HHUA, DLD-1, and HCT 166 human cancer cell lines, MMR-defective cells exhibited higher levels of drug resistance and increased mutagenic response at the HGPRT locus to 6-TG when compared with their MMR-proficient counterparts. Thus, the inability to properly repair damaged or mutant DNA may provide a selective growth advantage for MMR-defective cells. Moreover, this finding may provide a mechanism by which 6-TG treatment results in the development of secondary malignancies. 189

In clinical samples derived from patients with AML, drug resistance has also been associated with either increased concentrations of a membrane-bound alkaline phosphatase or a conjugating enzyme, 6-thiopurine methyltransferase (TPMT). 190 Patients who express high levels of TPMT activity are unable to form sufficiently high levels of active nucleotide metabolites after treatment with 6-MP. As such, they may be more likely to benefit from treatment with 6-TG. 191

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 HPLC analysis using the phenylcynuronic or sulfonated derivatives of the thiopurines is able to detect plasma drug levels as low as 0.1 mM. An HPLC method was developed to measure thiopurine levels in erythrocytes in the 18 to 20 pmol range. 192 Oral doses of 6-MP of 70 to 100 mg/m^2 are commonly used in the maintenance therapy of ALL. Oral absorption of 6-MP is highly erratic, with only 16% to 50% of the administered dose reaching the systemic circulation. This effect is mainly due to rapid first-pass metabolism in the liver. 193 Food intake and coadministration with the antibiotic cotrimoxazole significantly reduce drug absorption. The variable bioavailability of oral 6-MP is an important determinant of therapeutic outcome, because low plasma drug concentration over time may correlate with an increased risk of relapse in children with ALL. 194 6-MP bioavailability is increased when combined with high-dose (2 to 5 g/m^2 intravenous) MTX. 195 Studies have shown that MTX inhibits xanthine oxidase, an important enzyme in the catabolism of thiopurines. 196

Oral 6-MP is well distributed into most body compartments, with the exception of the CSF. With high-dose intravenous 6-MP (200 mg/m^2 bolus followed by 800 mg/m^2 over 8 hours), a CSF to plasma ratio of 0.15 is achieved. This schedule is currently being used to prevent CNS relapse in ALL. 197 Approximately 30% of the drug binds weakly to plasma proteins. The plasma half-life is approximately 50 minutes after intravenous injection and 90 minutes after oral administration. When studied in children with ALL, plasma concentrations and erythrocyte thioguanine nucleotide levels are highly variable and independent from dose. 198

The major route of drug elimination is via metabolism by several enzymatic pathways. 6-MP is oxidized to the inactive metabolite 6-thiouric acid by xanthine oxidase. Enhanced 6-MP toxicity may result from the concomitant administration of both oral and intravenous 6-MP and the xanthine oxidase inhibitor allopurinol. 199 In patients receiving both 6-MP and allopurinol, the dose of 6-MP should be reduced by at least 50–75%.

6-MP also undergoes S-methylation by the enzyme TPMT to yield 6-methylmercaptopurine. After further phosphorylation, 6-methylmercaptopurine nucleotides are, themselves, capable of inhibiting de novo purine biosynthesis, but to a lesser extent than thioguanine nucleotides (TGNs). TPMT plays a similar role in 6-TG and azathioprine metabolism. 200 It has been shown that TPMT enzyme activity may vary considerably between patients. Moreover, the levels of TPMT enzyme activity correlate inversely with intracellular levels of TGNs and with the duration of 6-MP–induced cytoxicity, suggesting that the level of inherited TPMT activity may affect directly 6-MP cytotoxicity and host toxicity. 201 Due to an autosomal codominant genetic polymorphism, a series of TPMT phenotypes, with alleles of differing enzymatic activity, are present in the general population. Point mutations or loss of alleles of TPMT resulting in altered enzyme activity correlate with a defect in thiopurine metabolism, thus defining a true pharmacogenetic syndrome. 202 A polymerase chain reaction–based method is widely used for the genetic detection of these TPMT mutations. 203 Approximately 0.3% of the white population expresses either a homozygous deletion or mutation of both alleles of the TPMT gene. In these patients, grossly elevated TGN concentrations, profound myelotoxicity with pancytopenia, and extensive gastrointestinal symptoms are seen after only a brief course of thiopurine treatment. 204 An estimated 10% of patients may be at increased risk for toxicity due to heterozygous loss of the gene or a mutant allele coding for a less enzymatically active TPMT. 205 Drug interactions affecting TPMT activity have also been reported with aspirin, sulfasalazine, 5-aminosalicylic acid, furosemide, and disulfiram. 206

Refrain excretion of 6-MP is minimal, but at high doses, as much as 20% to 40% of the drug is removed by the kidneys. 207 Exceedingly high doses of 6-MP (more than 1 g/m^2) in children may cause renal precipitation of drug with hematuria and crystalluria. In patients with renal dysfunction, dose reductions of 6-MP should be considered.

6-THIOGUANINE
 The main intracellular pathway for 6-TG activation is catalyzed by HGPRT, with resultant formation of ribonucleotide monophosphates. Although the main metabolites of 6-TG are TGNs, thionucleosides are formed as well. However, the clinical significance of these respective metabolites as determinants of 6-TG cytoxicity remains unclear. 208 Although higher erythrocyte levels of TGNs are detected after treatment with maximum tolerated dose levels of 6-TG than 6-MP, this pharmacodynamic parameter does not clearly correlate with the myelosuppression associated with 6-TG. 209

6-TG is administered orally in doses of 75 to 200 mg/m^2 for 5 to 7 days in the treatment of AML. Its oral bioavailability is erratic, with peak plasma levels occurring 2 to 4 hours after ingestion. The median plasma half-life of 6-TG is approximately 90 minutes. The catabolism of 6-TG differs from 6-MP in that S-methylation with subsequent removal of the sulfur atom is an important pathway of drug elimination. 210 In a second catalytic pathway, 6-TG undergoes deamination by the enzyme guanylate deaminase (guanase), resulting in 6-thioxanthene, which is then oxidized by xanthine oxidase to 6-thiouric acid. In contrast to 6-MP, 6-TG is not a direct substrate for xanthine oxidase. Because the inhibition of xanthine oxidase results in the accumulation of 6-thioxanthene, an inactive metabolite, adjustments in 6-TG dosage are not required for patients receiving allopurinol.

Toxicity
 The major dose-related toxicities of 6-MP are myelosuppression and gastrointestinal toxicity. Leukopenia and thrombocytopenia are maximal 7 days after treatment. Full hematologic recovery usually occurs after 14 days. In TPMT-deficient patients, dose reduction to 5% to 25% of the standard dose (75 mg/m^2) is necessary to prevent excessive toxicity. Gastrointestinal toxicities include nausea and vomiting, anorexia, diarrhea, and stomatitis. 6-MP hepatotoxicity occurs in up to 30% of adult patients and is manifested as mainly cholestatic jaundice, although elevations of hepatic transaminases may also be seen. Hepatotoxicity is usually mild and reversible after discontinuation of 6-MP, but frank hepatic necrosis can occur after high doses of the drug. Combinations of 6-MP with other known hepatotoxic agents should be avoided, and liver function test results should be closely monitored. The mechanism of liver toxicity is not known, but may relate to the P-450–dependent metabolism of 6-MP to a hepatotoxic metabolite or accumulation of 6-MP metabolites in the liver. 211 6-TG also causes dose-limiting bone marrow suppression but is associated with fewer gastrointestinal side effects and less hepatotoxicity than 6-MP.

As a class of drugs, the thiopurines analogues are potent suppressors of cell-mediated immunity. As such, prolonged therapy results in an increased predisposition to bacterial and parasitic infections. Given their immunosuppressive effects, these agents have been used to prevent rejection of transplanted organs and to treat autoimmune diseases, such as Crohn's disease, ulcerative colitis, and rheumatoid arthritis. Therapeutic immunosuppression occurs at 100 mg/d, a dose associated with only mild leukopenia. Long-term immunosuppressive therapy with azathioprine increases the risk of squamous carcinoma of the skin, non-Hodgkin's lymphoma, and Kaposi's sarcoma. Chronic 6-MP treatment is associated with teratogenic effects during the first trimester of pregnancy, and AML has been reported as a secondary malignancy after 6-MP treatment for Crohn's disease. 212

FLUDARABINE
 Fludarabine (9-B-D-arabinosyl-2-fluoroadeneine, Fludara) was synthesized as part of a rational process to develop more active analogues of cytarabine (Fig. 19.5-9). The first compound in this series was adenine arabinoside (vidarabine; Ara-A). However, this compound was deaminated to its inactive form to a significant extent, thereby negating its clinical application. The 2'-fluoro derivative of Ara-A was subsequently found to be relatively resistant to deamination, but was difficult to formulate and poorly soluble. Addition of a 5'-monophosphate moiety to the sugar group yielded fludarabine, which is relatively resistant to deamination and displays...
Mechanism of Action

After intravenous administration, F-Ara-adenosine monophosphate (F-Ara-AMP) is rapidly dephosphorylated to F-Ara-A, which enters cells by nucleoside-specific membrane transport mechanisms. The es and ei nucleoside transporter systems facilitate the cellular uptake of the hydrophilic nucleoside analogues. F-Ara-A is then phosphorylated by dCK to F-Ara-AMP, which is subsequently metabolized to the triphosphate form. This nucleotide is the active metabolite of the drug. It competes with deoxycytidine triphosphate (dATP) for incorporation into DNA, and serves as a highly effective chain terminator. In addition, F-Ara-ATP directly inhibits DNA polymerases involved in DNA synthesis and repair, such as DNA polymerase a and b, and inhibits other enzymes involved in DNA synthesis, such as DNA primase, DNA ligase I and RII. DNA polymerase ε is unable to remove F-Ara-AMP from the 3'-end of DNA even in the presence of excess enzyme and substrate nucleotides, resulting in the formation of dead-end complexes.

Fludarabine is also incorporated into RNA, causing inhibition of RNA function, processing, and mRNA translation. In contrast to other antimitabotides, fludarabine is also active against nondividing lymphocytes. In fact, the primary effect of fludarabine may result from activation of apoptosis, as evidenced by the presence of typical apoptotic fragmentation of DNA into high-molecular-weight fragments, after drug treatment. The induction of apoptosis may explain the activity of this drug in indolent lymphoproliferative diseases with relatively low S-phase fractions.

Mechanisms of Resistance

Fludarabine-resistant cell lines, such as JOK-1 (human hairy cell leukemia [HCL]), K562 (human erythroleukemia), and L1210 (murine leukemia) have been established. In these resistant lines, nucleoside transport of F-Ara-A is intact, and no alterations in intracellular drug accumulation or multidrug-resistant (mdr 1) expression are observed. However, decreased dCK activity with diminished intracellular formation of F-Ara-ATP is the principal mechanism of resistance in each of these cell lines. Subsequent work has shown that one allele of dCK is sufficient for one allele of dCK's syndrome, and sufficient for decreased expression of dCK. Of note, a high degree of cross-resistance develops to multiple nucleoside analogues requiring activation by dCK, including Ara-C, 2-CDA, and gemicitabine. Fludarabine resistance in WSU-CLL xenografts in SCID mice can be decreased by pretreatment with bryostatin, a macrocyclic lactone. Although the underlying mechanisms for this interaction remain to be defined, preliminary studies suggest that bryostatin may induce differentiation of B-CLL cells into HCL-like cells, with expression of CD11c, CD25, and latrache-resistant acid phosphatase (TRAP), markers typically seen in HCL.

Clinical Pharmacology and Pharmacokinetics

Peak concentrations of F-Ara-A are reached 3 to 4 hours after intravenous or oral administration. Mean plasma levels are proportional to dose. After intravenous administration, the decline in plasma levels has been reported to be bi-exponential, with a distribution half-life of 0.6 to 2.0 hours and a terminal half-life of 6.9 to 19.7 hours. However, other reports describe a three-compartment model with a terminal half-life between 10 and 30 hours. The rate-limiting step in elimination is release from tissues and renal function affecting clearance. Dose adjustment in the setting of renal impairment is recommended, and a 30% dose reduction in patients with a serum creatinine above 1.5 mg/dL or creatinine clearance below 70 mL/min should be considered.

The median peak concentration of F-Ara-ATP in lymphocytes of leukemic patients occurs approximately 4 hours after the start of a 30-minute intravenous infusion of 25 mg/m². Intracellular F-Ara-ATP elimination exhibits a single phase with a dose-dependent terminal phase. The oral bioavailability of liquid fludarabine is 60% to 80%, leading to approximately two-thirds of the intracellular F-Ara-ATP levels in chronic lymphocytic leukemia (CLL) cells achieved with intravenous administration.

Treatment

Fludarabine is the most active single agent in the treatment of CLL. It is also active against indolent non-Hodgkin's lymphoma, prolymphocytic leukemia, cutaneous T-cell lymphoma, and Waldenström's macroglobulinemia. This agent has shown promising activity in approximately one-third of patients with mantle cell lymphoma, albeit with relatively brief response. In contrast to its activity in hematologic malignancies, this compound displays minimal activity against common solid tumors.

Toxicity

In initial trials, fludarabine, when administered as a single 260 mg/m² dose or 112 mg/m² given daily for 5 days, resulted in profound myelosuppression. This effect was not initially predicted from preclinical in vivo studies in mice and beagle dogs, given the extensive tissue binding and relatively low renal excretion in humans. In addition, a dose range of 75 to 150 mg/m² four times a day for 5 to 7 days resulted in severe prohibitive neurotoxicity characterized by delayed onset cortical blindness, seizures, coma, and death. Subsequent trials demonstrated that fludarabine could be safely administered at much lower doses of 25 to 30 mg/m² daily for 5 days every 28 days. At standard doses, neurotoxicity occurs in approximately 15% of patients. This toxicity is rarely severe, generally reversible, and usually presents as headache, somnolence, or peripheral neuropathy.

At currently used doses, myelosuppression and immunosuppression are the major side effects of fludarabine. Dose-limiting and possibly cumulative lymphopenia and thrombocytopenia are well established. Suppression of the immune system affects T-cell more than B-cell function. Fevers, often in the setting of neutropenia, occur in 20% to 30% of patients. Lymphocyte counts, particularly CD4+ cells, decrease rapidly after initiation of therapy, and levels can drop to as low as 150/µL by approximately 6 months. CD4+ cell recovery is slow and may take longer than 1 year to recover to normal levels. Common opportunistic pathogens include herpes zoster, Candidiasis, and Pneumocystis carinii. The addition of prednisone to fludarabine does not improve the response rate or survival, but significantly increases the risk of opportunistic infections, notably listeriosis and Pneumocystis carinii. If concurrent corticosteroids are necessary, such as in patients with autoimmune anemia or thrombocytopenia, long-term prophylaxis against Pneumocystis carinii is mandatory. Hemolytic anemia has been observed, and in some instances, has resulted in death on rechallenge with fludarabine. Prolymphocytic leukemia, and prolymphocytic leukemia have been reported. The prolonged immunosuppression experienced with fludarabine has raised the possibility of an increased incidence of secondary malignancies. However, this increased risk is now thought to be due to the underlying immune defects of the malignancy and not to the carcinogenic effects of the nucleoside analogue.

Tumor lysis syndrome occurs in less than 1% of patients, and in some cases, it can be fatal. However, this event does not usually recur on retreatment with fludarabine. Prophylaxis is not uniformly effective. Other uncommon toxicities include rash, nausea, vomiting, diarrhea, stomatitis, anorexia, increased salivaion, abdominal cramps, a metallic taste, transient elevations in hepatic enzymes, and renal dysfunction. Treatment-associated disseminated skin rash, progressing to pemphigus-like epidermal necrolysis, has been described. Pulmonary toxicity, in the form of interstitial pneumonitis, can develop after multiple courses of treatment. At times, the pulmonary sequelae may be difficult to distinguish from those associated with opportunistic infections. This toxicity usually responds to corticosteroids and enhanced solubility.
Drug Interactions

Purine analogues achieve significant response rates in low-grade lymphomas, presumably due to their ability to induce apoptosis in these otherwise drug-resistant malignancies. The responses seen, however, are mostly partial and of short duration. This has fostered interest in identifying drug regimens incorporating fludarabine with enhanced activity. Fludarabine inhibits the nucleotide excision repair used by cells to remove the DNA cross-links induced by alkylating agents (cyclophosphamide, cisplatin). Complete response rates of nearly 90% have been observed when fludarabine and cyclophosphamide are used in combination for patients with previously untreated low-grade lymphoma. The combination of fludarabine with the anthracycline analogue mitoxantrone in the presence or absence of dexamethasone (FN and FND regimens) has been successfully used to treat indolent non-Hodgkin’s lymphomas. In fact, response rates in excess of 90%, with half of these being complete responses, are seen with the triple combination, FND. This compares favorably with the 60% to 70% response rate observed with single-agent fludarabine.

Fludarabine-induced dCTP depletion increases deoxyctydinyl kinase activity in K562 human leukemia cells. This enzyme, in addition to playing a key role in generating active fludarabine metabolites, is also capable of phosphorylating Ara-C into its active metabolite, Ara-CTP. The resulting synergistic effect of fludarabine on Ara-C is now established both in vitro and in vivo in leukemic blast cells derived from patients with AML. This combination has clinical efficacy in childhood AML in combination with idarubicin, in adult CLL in refractory or relapsed AML and perhaps in patients with myelodysplastic syndromes.

The immunosuppressive effect of fludarabine is being used in a novel, nonmyeloablative bone marrow transplant preparative regimen called transplant lite. The goal of this approach is to achieve allogeneic stem cell engraftment and graft-versus-leukemia/lymphoma effect in patients with CLL and low-grade lymphomas. In a pilot study, engraftment was achieved in 11 of 15 patients, with eight showing complete response.

CLADRIBINE

2-Chlorodeoxyadenosine (Cladrabine, 2-CdA) is a deoxycytidylate, a single substitution of a chlorine atom for a hydrogen atom at the 2-position of the pyrimidine ring of deoxyadenosine renders this compound resistant to adenosine deaminase (ADA) (see Fig. 19 5-9). It was developed initially as an immunosuppressive agent. 2-CdA exhibits a dose-dependent in vitro inhibition of lymphoid neoplasms and human leukemic cell lines, but has no activity against solid tumors. Currently, it is the drug of choice in HCL with activity in low-grade lymphoproliferative disorders as well.

Mechanism of Action

Deoxycytidine is cleaved within cells by the enzyme ADA, to the deoxynucleosine form. A deficiency of this enzyme leads to toxic accumulation of deoxycytidine in lymphocytes, manifesting as the severe combined immunodeficiency clinical syndrome. 2-CdA enters cells via the nucleoside transporter system. Given its resistance to deamination by ADA, an ADA-deficiency-like state develops, in which 2-CdA accumulates within cells, eventually reaching lymphotoxic levels. On entry into the cell, it first undergoes conversion to cladribine-monophosphate (Cd-AMP), which is then eventually metabolized to the active metabolite, cladribine-triphosphate (Cd-ATP). The rate-limiting step is catalyzed by dCK. In contrast, catabolism of 2-CdA is mediated by a 5'-nucleotidase. The greatest accumulation of Cd-AMP is observed in cells with high levels of dCK and low 5'-nucleotidase activity. Cd-ATP competitively inhibits incorporation of the normal nucleotide dATP into DNA, a process that results in termination of chain elongation. Progressive accumulation of Cd-ATP leads to an imbalance in deoxynucleotide pools, thereby inhibiting further DNA synthesis and repair. At concentrations of 0.3 µM, 2-CdA inhibits DNA synthesis by 90% within 30 minutes. The accumulation of unrepaird DNA breaks over time may initiate the apoptosis of quiescent, nondividing lymphocytes. Activation of the caspase-3 proteolytic cascade has been implicated as a potential mechanism for the onset of apoptosis. Finally, 2-CdA is a potent inhibitor of RN, and in so doing, it may further inhibit the synthesis of the key nucleotide substrates required for DNA biosynthesis.

Mechanisms of Resistance

Resistance to 2-CdA has been attributed to altered intracellular metabolism of the drug. A reduction in dCK activity, the enzyme responsible for generating cytotoxic nucleotide metabolites, is a major determinant of acquired resistance. Cd-AMP and Cd-ATP are dephosphorylated by the cytoplasmic enzyme, 5'-nucleotidase. WSU-CLL cells, derived from a patient with CLL, exhibit both low levels of dCK expression, and high levels of 5'-nucleotidase, and accordingly, they are resistant to 2-CdA. Interestingly, restoration of 2-CdA chemosensitivity by pretreatment of WSU-CLL cells in vitro with bryostatin has been reported. Bryostatin may induce differentiation of CLL cells into a hairy cell–like phenotype, evidenced by the induced expression of TRAP, CD11c, and CD25 in WSU-CLL cells.

Clinical Pharmacology and Pharmacokinetics

Pharmacokinetic analysis suggests a two-compartment model, with mean a and b half-lives of 35 ± 12 minutes and 6.5 ± 2.5 hours, respectively. The steady-state concentration after a 2- or 24-hour infusion of 0.14 mg/kg was 22.5 ± 11.1 ng/mL. After a 24-hour infusion of 0.14 mg/kg, the mean maximum plasma concentrations were in the range of 100 to 400 mmol/L. The disposition of 2-CdA in plasma remains linear over a dose range of 0.2 to 2.5 mg/m², with limited interindividual variation. Absorption of 2-CdA is limited to a dose-related extent, and the relationship between dose and plasma steady-state concentrations, the relationship between dose and clinical activity remains to be defined. When mean plasma concentrations were fitted to a three-compartment model, the half-lives of the a, b, and g phases ranged between 3 and 12 minutes, 0.7 to 1.5 hours, and 5.7 to 19.0 hours, respectively.

The dose of 2-CdA used in early clinical trials was 0.09 to 0.10 mg/kg administered as a 7-day continuous infusion. As the long terminal half-life suggested the feasibility of intermittent infusions, 2-CdA has also been tested as a 2-hour infusion of 0.09 to 0.10 mg/kg/d for 5 to 7 days or a 1-hour infusion at 6 mg/m² for 5 days with a 28-day cycle. A dose-escalation study of bolus daily claddribine established no dose-limiting nonhematologic toxicity up to 21.5 mg/m²/day, given on a daily 1-hour intravenous bolus infusion for 5 days to patients with advanced hematologic malignancies. At higher dose levels, prolonged cytopenias and severe infections define the upper dose limit of the drug. In a small series of patients with HCL, no significant difference in response rate or toxicity was observed between a 7-day continuous infusion and a daily 2-hour bolus for 5 days. The daily dose for 5 days appears to be better suited as an outpatient regimen. After a 2-hour or a continuous infusion of 0.12 mg/kg in patients with CLL, mean intracellular concentrations of 2-CdA nucleotides are 12.2 and 10.8 µmol/L, respectively. Intracellular concentrations of phosphorylated CdA derivatives thus exceed plasma concentrations of the metabolites by several hundredfold.

In circulating leukemic cells of CLL patients treated with 2-CdA for 10 mg/m²/day for 3 days, Clad-AMP and Clad-ATP median half-lives of 15 and 10 hours were observed, respectively. While maximum plasma 2-CdA and intracellular Clad-AMP concentrations correlate well, no clear relationship exists between the level of deoxycytidine kinase activity, the levels of the intracellular metabolites (Clad-AMP, Clad-ATP), and response to treatment. These findings indicate that other, as yet, unknown determinants of clinical efficacy may be present.

2-CdA is effectively cleared by the kidneys. Renal clearance is approximately 50%, while 20% to 35% of the drug is excreted unchanged in the urine. 2-CdA is able to cross the blood-brain barrier and penetrates into the CSF. While CSF concentrations in patients, in the absence of meningeal disease, reach only 25% of detected plasma levels, CSF levels exceed plasma levels in patients with meningeal involvement.

The bioavailability of the drug is almost 100% when given at a dose of 0.14 mg/kg via the subcutaneous route. The area under the curve achievable with subcutaneous administration is almost identical to that of the intravenous route. Oral 2-CdA reaches lower, but clinically relevant levels of bioavailability at 37% to 51%. Absorption of the oral form is decreased by gastric pH values below 2, an effect that cannot be prevented or reversed with concomitant proton pump inhibitor use. The bioavailability of oral 2-CdA correlated linearly with dosing in a small study with oral and intravenous cross-over design. Oral dosing showed no cumulative peak concentration or toxicity, and its pharmacokinetics are well-described by a three-compartment model. An oral dose of 0.28 mg/kg achieved similar peak concentrations and area under the concentration time curve as 0.14 mg/kg given either intravenously or subcutaneously. The overall feasibility of intermittent intravenous, subcutaneous, or oral dosing suggests that these different routes of administration may compete with and possibly replace continuous infusional schedules.

Treatment
A single course of CdA achieves durable complete remissions in 65% to 91% of patients with HCL. \[229,230\] Salvage treatment of patients previously treated with IFN-α or splenectomy is as effective as first-line treatment. Maintenance therapy is not required. Although minimal residual disease is often found on reexamination of bone marrow specimens of HCL patients in clinical complete response, relapse rates are low. Treatment with cladribine results in complete response in up to 60% of relapsing patients. \[231\] However, it remains unclear whether cladribine offers any significant long-term survival benefit over another nucleoside analogue, pentostatin. Responses in patients with CLL and non-Hodgkin’s lymphoma tend to be brief, and in those of relapsed or refractory disease is less efficacious than in HCL. \[232,233\] 2-CdA achieves high response rates in pediatric patients with AML, but not in adult patients. 2-CdA has minimal activity against solid tumors.

Toxicity

At conventional doses, myelotoxicity is dose limiting. Decreased counts in all three cell lines are typically observed. Thrombocytopenia usually recovers within 2 to 4 weeks, and neutropenia in 3 to 5 days, after a single course of the drug. Severe, prolonged myelotoxicity is reported, however, after repeated cycles of cladribine used in the treatment of CLL or low-grade lymphomas. \[232\] Severe autoimmune hemolytic anemia with fatal bone marrow aplasia has been described in CLL patients receiving repeated cycles of the drug, as CdA-induced lymphopenia may exacerbate autoimmune hemolysis. Of note, foal of bone marrow hypoplasia are seen in cladribine-treated patients, although the long-term clinical significance of this effect remains unclear.

Immunosuppression accounts for the late morbidity observed in CdA-treated patients. Lymphocyte counts, particularly CD4+ cells, decrease within 1 to 4 weeks of drug administration and may remain depressed for several years. \[232\] After discontinuation of cladribine, a median time of up to 40 months may be required for complete recovery of normal CD4+ counts. \[232\] Fevers occur in 40% to 50% of patients, typically correlating with the duration of granulocytopenia. These episodes may be profound, prolonged, and cumulative. \[232\] Opportunistic infections are common, although usually seen less frequently than with fludarabine. Herpes zoster is most typical, and a variety of other pathogens are also seen, including Candida, Pneumocystis, Pseudomonas aeruginosa, Listeria monocytogenes, Cryptococcus neoformans, Aspergillus, cytomegalovirus, and common bacterial infections. Infectious complications correlate with decreases in CD4+ count, and they are more frequent with repeated courses of therapy. \[232\] Treatment-related deaths have been reported in more than 30% of patients. \[232\]

In patients with HCL and CLL, long-term studies have failed to identify an increase in drug-related mortality. Specifically, initial concerns about an increased risk for secondary malignancies have not been confirmed, as the incidence of second cancers is not higher than what would be expected from the underlying hematologic disorder. \[232\] Severe neurotoxicity was encountered at high doses of 2-CdA in phase I trials, with quadriparesis and paraparesis, proximal neuromyopathy, and rarely, Benign-Barré and Guillain-Barre syndromes. At currently recommended doses, mild to moderate neurotoxicity occurs in 15% of patients and is, at least, partly reversible with discontinuation of the drug. \[232\]

Tumor lysis syndrome is rare, tends to occur after the first course, and is generally mild and reversible. However, in rare instances, this process may be fatal, even in patients with prior therapy. Cardiotoxicity is uncommon, but cardiac deaths have been reported, mainly in patients with a prior cardiac history. Pulmonary complications of 2-CdA therapy are uncommon, but in some cases, they have been fatal. Rashes, although uncommon, may be severe and can present as fatal toxic epidermal necrolysis. Mild to severe gastrointestinal toxicities occur in 15% of patients, with nausea, vomiting, and diarrhea, and there have been rare reports of anorexia, severe mucositis, or both. Transient elevations in hepatic enzymes may occur, with exacerbation of hepatitis B, which may be fatal. Renal failure occurs only at high doses.

Drug Interactions

Inhibition of RR by 2-CdA depletes intracellular dCTP pools. This effect leads to compensatory increases in intracellular dCK activity. dCK activity plays a critical role in the formation of the active intracellular Ara-C metabolite, Ara-CTP. Synergistic interaction between 2-CdA and Ara-C was observed in leukemic blast cells isolated from patients with AML, in which 2-CdA pretreatment led to increases of intracellular Ara-CTP pools by up to 40%, with sustained inhibition of DNA synthesis in the circulating leukemia blasts. \[232\] Studies are ongoing to translate the positive interaction between Ara-C and 2-CdA into the clinical setting.

2'-DEOXYCOFORMICYN

2'-Deoxycoformycin (Pentostatin), a fermentation product of Streptomyces antibioticus, was developed as a potent inhibitor of ADA (see Fig. 19.5-9). \[232\] ADA is present in high concentrations in lymphoid tissues, and this enzyme plays a vital role in the differential of both T and B cells. Genetic absence of ADA leads to severe combined immunodeficiency disorder in children, and this syndrome is characterized by profound T- and B-cell lymphopenia. Inhibition of this enzyme leads to an accumulation of deoxyadenosine as there is no alternate route for its metabolic conversion to deoxyinosine and uric acid. Deoxyadenosine is subsequently phosphorylated by deoxycytidine kinase to deoxyadenosine monophosphate, which is then further metabolized to the triphosphate form. This metabolite accumulates within cells and inhibits RR, a key enzyme in DNA synthesis. \[232\]

Mechanism of Action

Pentostatin enters cells via the nucleoside transport system, and once within the cell, it forms a tight inhibitory complex with ADA. \[232\] Exposure of both murine L1210 leukemic cells and normal resting human lymphocytes results in progressive accumulation of DNA breaks along with a decrease in RNA synthesis. In response to drug treatment, DNA repair is activated, resulting in depletion of critical intracellular nicotinamide-adenine dinucleotide levels. This then leads to exhaustion of ATP pools, resulting in eventual cell death.

Clinical Pharmacology and Pharmacokinetics

After rapid intravenous infusions (1 to 9 minutes), pentostatin shows dose-independent first-order elimination, with a biphasic decay characteristic of a two-compartment open model. The rapid disposition phase is short, with a mean half-life of 8.72 minutes and a mean terminal half-life of 4.93 hours. The mean volume of distribution is 23.1 ± 6.16 L/m². Nearly 100% of an administered dose is excreted in urine within 48 hours. \[232\]

Treatment

Initial clinical trials with high doses of pentostatin in patients with ALL and HCL revealed prohibitive myelosuppression and neurotoxicity, the latter manifesting as somnolence, lethargy, confusion, seizures, and coma. \[232\] Current standard regimens consist of 4 mg/m² doses every 1 or 2 weeks. \[232\] With this schedule, pentostatin exhibits remarkable activity against HCL. In phase II studies, durable response rates over 90% are routinely achieved, and maintenance treatment is not required. On relapse, retreatment with the drug can be effective. \[232\] In a large, prospective phase III trial, pentostatin achieved significantly higher response rates (79% vs. 38%) and relapse-free-survival than IFN-α₂. However, this effect was not translated into overall survival benefit. \[232\] Although a small number of pentostatin-pretreated patients showed good response to cladribine, pentostatin use in patients who have progressed on cladribine has not been investigated in a systematic manner. Minimal residual disease on immunohistochemical examination of bone marrow specimens is detectable in 20% to 40% of HCL patients, who achieve complete response after pentostatin treatment. Although minimal residual disease may be associated with an increased risk of relapse, it remains unclear whether treatment of asymptomatic patients with minimal residual disease provides clinical benefit. \[232\]

Pentostatin is also active in CLL, prolymphocytic leukemia, cutaneous T-cell lymphoma, indolent non-Hodgkin's lymphoma, chronic myelogenous leukemia, and Langerhans' cell histiocytosis. \[232\] Overall response rates in these malignancies are less than that achieved with either fludarabine and cladribine or that observed with pentostatin in HCL. No significant activity is seen in multiple myeloma or in solid tumors.

Toxicity

The profound immunosuppression associated with pentostatin may persist for several years after therapy is discontinued. \[232\] T-cell function is affected more than B-cell or natural killer cell function, perhaps because of higher baseline levels of ADA in T cells. A standard course of pentostatin is associated with more prolonged
immunosuppression than that observed with a single-course of cladribine treatment in patients with HCL. The time mean of recovery of CD4+ cells to normal levels is up to 50 months after completion of treatment. Myelosuppression with neutropenia and thrombocytopenia is commonly described. Thrombotic thrombocytopenic purpura and HUS and persistent bone marrow failure with myelodysplastic features have been reported. Neutropenic fever is seen in up to 30% of cases, and opportunistic infections occur with Candida, herpes zoster, Pneumocystis carinii, and a variety of other pathogens. Although an increased incidence of second cancers has been noted in patients treated with cladribine, the relative risk is similar to that observed with the underlying disease in the absence of nucleoside analogue treatment.

Ovarian complications include conjunctivitis, desquamative keratitis, or periorbital edema. Dermatologic toxicity in the form of skin rash, photosensitivity reactions, and alopecia has been reported. Not all patients will develop side effects: stomatitis, constipation, diarrhea, cardiac toxicity, pulmonary toxicity, renal insufficiency, urate nephropathy, and allergic reactions. Transient and reversible increases in enzymes and fulminant hepatic failure have been described.

CHAPTER REFERENCES

SECTION 19.6
Topoisomerase Interactive Agents

Isolation and characterization of the topoisomerase enzymes have provided a basis for development of anticancer drugs that contribute to the treatment of patients with a wide range of malignancies. Simply stated, the topoisomerase enzymes control and modify the topologic states of DNA. The mechanisms of these enzymes involve DNA cleavage and strand passage through the break, followed by religation of the cleaved DNA. The precise manner by which these complicated events occur in a single cell is the source of intense research, and the results of this research promise to provide additional targets for anticancer drug therapy.

The first DNA topoisomerase was discovered in the early 1970s. Since then, many different DNA topoisomerases have been found in eukaryotic and prokaryotic cells. In mammalian cells, these enzymes have been differentiated into two type I topoisomerases and type II—based on their mechanistic and physical properties. The characteristics of each topoisomerase are summarized and compared in Table 19.6-1.

**Table 19.6-1. Characteristics and Comparison of Mammalian DNA Topoisomerases**

The type I topoisomerase (top I) found in mammals is a monomeric protein encoded by a single-copy gene located on chromosome 20; its activity is adenosine triphosphate (ATP)–dependent. This enzyme binds preferentially to double-stranded DNA and cleaves one of the DNA strands of the duplex, simultaneously forming an enzyme-DNA covalent bond between a tyrosine residue and the 3'-phosphate of the cleaved DNA. Through a swivel mechanism, the unbroken strand can pass through this enzyme-mediated nick and release the torsional stress of the DNA double helix. Top I has been shown to be regulated at the transcriptional, translational, and posttranslational levels. Phosphorylation-dephosphorylation and polyadenosine-diphosphoribosylation are important mechanisms of top I regulation in vitro, but the therapeutic implications of these findings are not known.

Numerous reports have shown malignant tissue to contain higher levels of top I than its normal counterpart. Specifically, this was observed for colon and ovarian carcinoma, chronic lymphocytic leukemia, and diffuse histiocytic lymphoma. This initial observation of increased levels of top I in malignant tissues suggested to investigators that use of top I interactive agents might lead to a selective antitumor effect; however, results from subsequent clinical trials have not supported this hypothesis. In fact, more recent studies in vitro suggest that the apparent high level of top I in malignant tissue might be related to differences in malignant compared to normal tissue. Other factors, such as rate of DNA synthesis, repair of drug-induced double-strand breaks, or presence of drug transporters, are also potential determinants of drug activity in the cell.

Two top II isoenzymes have been identified in humans. The a form, which has an apparent molecular weight of 180 kd and has been mapped to chromosome 3p, is relatively constant over cell and growth cycles. Top IIa and b have different subnuclear distributions and DNA binding patterns, supporting the hypothesis that each isoform has a specific cellular function, but these precise functions are not known. Whereas top IIb is relatively constant over cell and growth cycles, top IIa increases in rapidly proliferating cells.

In contrast to type I topoisomerase, the function of type II topoisomerases is ATP-dependent. Once top II binds to duplex DNA, nucleophilic reactions sequentially cleave the two complementary strands of DNA 4 base pairs apart, and the resulting 5'-phosphoryl groups become covalently linked to a pair of tyrosine groups, one in each half of the dimeric top II enzyme. Once the double-strand break has been made, the cleaved ends must be moved apart by at least 2 nm (the diameter of a double-stranded DNA helix) and a second double-strand segment of DNA passed through the break. DNA strand passage is completely dependent on the binding of magnesium and ATP. Once strand passage is complete, the cleaved DNA is religated. As with top I, top II is a phosphoprotein, and casein kinase II and protein kinase C can phosphorylate it in vitro, resulting in an enhancement of enzyme activity.

**MECHANISM OF ACTION OF TOPOISOMERASE INTERACTIVE AGENTS**

Although much is known about the biochemical effects of the topoisomerase interactive agents, very little is known about the actual mechanism by which cell death mediated by these agents occurs. Presumably, the damage done to DNA ultimately leads to necrosis or apoptosis through a series of cellular processes, such as cell cycle perturbations (possibly involving cyclins or cyclin-dependent kinases) or DNA repair deficiency. Figure 19.6-1 is a diagrammatic depiction of the normal activities of the topoisomerases and the effect of topoisomerase interactive agents.
Top I interactive agents, thus far consisting primarily of camptothecin analogues, interact with the enzyme-DNA complex. This interaction prevents the resealing of the top I-mediated DNA single-strand breaks. However, these breaks result in cell death only if DNA synthesis is ongoing. A collision between the advancing replication fork and the drug-stabilized single-strand break in DNA results in replication fork breakage and double-strand breaks in the DNA. Treatment of mammalian cells with top I inhibitors induces inhibition of DNA synthesis, cell cycle arrest in G1, and cell death by apoptosis. Drug-induced G2 arrest has been associated with a failure to activate cdc2 kinase. Because the cytotoxicity associated with top I interactive agents is highly dependent on DNA synthesis, any deregulation of cyclins, cell cycle–regulated kinases, or phosphatases may influence the cytotoxicity of top I interactive agents (see Fig. 19.6.4). Several other types of chemotherapeutic agents, such as doxorubicin or actinomycin D, inhibit both top I and top II by a similar mechanism, but at different sites in the DNA.

Top II is the molecular target for many anticancer drugs, such as the aminoacridines, anthracyclines, and epipodophyllotoxins. These drugs inhibit religation of DNA cleaved by top II and induce protein-linked breaks in the DNA, as documented by DNA alkaline elution assays. When drug is removed, these breaks are reversible. The first evidence that drug-induced, protein-associated strand breaks were mediated through interaction with top II occurred when Chen and Liu were able to show that the protein covalently bound to DNA fragments induced by these drugs was top II. They used the term cleavable complex to refer to these lesions because the enzyme-DNA complex could be isolated (cleaved) after protein denaturation. The cleavable complex in situ is a covalent topoisomerase-DNA complex.

In addition to the top II interactive agents that stabilize top II–DNA complexes, other inhibitors apparently inhibit the enzyme before covalent binding to DNA occurs. However, these agents have not yet proven useful clinically. Except for the epipodophyllotoxins, all mammalian top II inhibitors are DNA intercalators that insert a planar moiety between two adjacent base pairs in duplex DNA. However, as more is learned about the biochemical mechanisms of the top II interactive agents, it becomes clear that the historical characterization of top II interactive agents based simply on DNA-binding properties is no longer an appropriate means of classifying their mechanism of action. Further study is required to understand the molecular mechanisms by which DNA strand breaks lead to antitumor activity.

**EPIPODOPHYLLOTOXINS**

**ETOPOSIDE AND TENIPOSIDE**

The historical details of the development of the epipodophyllotoxins for clinical use have been reviewed. The path that led to the final development of etoposide and teniposide began in 1820 with the inclusion of podophyllin in the United States Pharmacopeia Drug Information. Although extracts of the Podophyllum peltatum (May apple, mandrake plants) had been used for years by natives of the Himalayas and the Americas as cathartics and anthelmintics, it was not until 1942, when the curative effect of podophyllin in condylomata acuminata was demonstrated, that a number of derivatives were isolated and synthesized. Early clinical trials of constituents of the resinous extract of podophyllin included the derivative podophyllotoxin, but clinical responses were poor, with excessive toxicity. Further chemical modification of podophyllotoxin by addition of the carbohydrate moiety b-D-erythrydine glucoside led to the compound teniposide, which was first introduced into clinical trials in 1970 (Fig. 19.6.2). The second derivative formed by addition of b-D-ethylidene glucoside to the podophyllotoxin molecule led to the compound etoposide, which, because of advantages in formulation, has been studied more thoroughly. The differences in physicochemical properties of these two compounds are presented in Table 19.6.2.

**TABLE 19.6-2. Physicochemical Properties of Etoposide and Teniposide**

Etoposide (VP-16-213), a semisynthetic podophyllotoxin derivative, was introduced into clinical trials in 1973 and within 1 year had a major role in the treatment of small cell lung cancer (SCLC) and lymphoma. Clinical trials of teniposide began in the United States in 1967 and, because antitumor effects were seen in early trials, generated enthusiasm. Since then more aggressive teniposide dosing regimens have been evaluated, and teniposide has shown activity as a single agent in the treatment of SCLC. In 1983 etoposide was approved for the United States treatment of refractory testicular tumors and SCLC; however, it is now used in frontline combination therapy for many malignancies. In 1993, teniposide was approved for use in combination with other approved anticancer drugs for induction therapy in patients with refractory acute lymphoblastic leukemia. The enhanced role of epipodophyllotoxins in anticancer therapy has resulted primarily from an improved understanding of their clinical pharmacology. Through rational application of pharmacologic principles, the role of these agents in cancer therapy can be
further refined. Future clinical studies must include biochemical pharmacology studies to identify and exploit potential pharmacologic differences between teniposide and etoposide. These studies should also focus on schedule dependency, rational drug combinations, new disease targets, central nervous system (CNS) penetration, and toxicity considerations. 13

Therapeutic success with oral epipodophyllotoxin therapy, primarily etoposide, has stimulated an increase in the understanding of etoposide and teniposide oral absorption (Table 19.6-3). Because of solubility concerns, the commercially available form of etoposide has a special formulation; however, in some pediatric studies of oral etoposide and all studies of oral teniposide, the injectable formulation has been used orally. Although delayed absorption of etoposide (e.g., longer than 4 hours) has been observed in patients receiving concurrent narcotics, the basis for this observation is unknown. 14 Marked intrapatient and interpatient variability characterizes both etoposide and teniposide oral bioavailability. 15 Oral absorption of etoposide and teniposide is nonlinear, with less than a proportional increase in etoposide in the area under the plasma concentration-time curve (AUC) with increased oral dose. The cause for these findings is unknown, but they suggest that more frequent oral administration of low doses are preferable to less frequent administration of high doses to increase dose intensity.

### Table 19.6-3. Comparison of Oral Absorption between Etoposide and Teniposide

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<tr>
<th>Parameter</th>
<th>Etoposide</th>
<th>Teniposide</th>
</tr>
</thead>
<tbody>
<tr>
<td>%Absorption</td>
<td>45-60%</td>
<td>60-65%</td>
</tr>
<tr>
<td>Mean Cmax</td>
<td>10-20 mg/L</td>
<td>10-25 mg/L</td>
</tr>
<tr>
<td>Mean Tmax</td>
<td>4-6 hours</td>
<td>4-6 hours</td>
</tr>
<tr>
<td>Steady-state volume of distribution</td>
<td>100-250 L</td>
<td>150-350 L</td>
</tr>
<tr>
<td>Total clearance</td>
<td>80-120 mL/min</td>
<td>90-150 mL/min</td>
</tr>
<tr>
<td>Hepatic clearance</td>
<td>60-100 mL/min</td>
<td>120-160 mL/min</td>
</tr>
<tr>
<td>Renal clearance</td>
<td>20-50 mL/min</td>
<td>30-60 mL/min</td>
</tr>
</tbody>
</table>

The disposition of etoposide in patients with renal and hepatic dysfunction has been extensively studied, whereas little is known about the effect of organ dysfunction on teniposide. Numerous metabolites of etoposide have been identified, although they comprise only a minor percentage of the administered dose and have little, if any, inherent cytotoxic activity. Similarly, only trace quantities of teniposide metabolites have been found in humans. 16 More recent work with in vitro incubation of etoposide or teniposide with human liver microsomes has shown that O-demethylation by cytochrome P-450 enzymes leads to formation of a catechol metabolite. 17 Further studies with a panel of prototypical substrates and inhibitors demonstrated the catechol formation is catalyzed by human CYP3A4. 18 Formation of these reactive metabolates may have important clinical consequences because they covalently bind to DNA and cellular protein and have intrinsic cytotoxic activity. 19,20

Renal clearance of etoposide is greater than teniposide. Approximately 10% or 50% of an administered dose is recovered in the urine as unchanged etoposide or teniposide, respectively. 21

Nonrenal clearance accounts for 70% to 90% of etoposide and teniposide elimination, respectively. The exact extent and clinical relevance of this route of elimination are unknown. Numerous metabolites of etoposide have been identified, although they comprise only a minor percentage of the administered dose and have little, if any, inherent cytotoxic activity. Similarly, only trace quantities of teniposide metabolites have been found in humans. 22 More recent work with in vitro incubation of etoposide or teniposide with human liver microsomes has shown that O-demethylation by cytochrome P-450 enzymes leads to formation of a catechol metabolite. 23 Further studies with a panel of prototypical substrates and inhibitors demonstrated the catechol formation is catalyzed by human CYP3A4. 24 Formation of these reactive metabolates may have important clinical consequences because they covalently bind to DNA and cellular protein and have intrinsic cytotoxic activity. 25,26

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The disposition of etoposide in patients with renal and hepatic dysfunction has been extensively studied, whereas little is known about the effect of organ dysfunction on teniposide. 27,28,29,30,31,32,33,34,35,36,37,38,39 From early reports, etoposide clearance in patients with chronic renal failure was not altered by hemodialysis 40,41; however, this may be attributed to poor dialyzer efficiency, lack of penetration of etoposide into the dialysis membrane, or high protein binding. Etoposide systemic clearance is significantly correlated with creatinine clearance 42; however, few of these studies have reported the clinical relevance of altered renal function on etoposide toxicity. In a study of 1% of patients with normal albumin and hepatic transaminases, an increase in etoposide AUC was seen in patients with serum creatinine greater than 1.4 mg/dL. 43 Based on increased myelosuppression seen in the patients with elevated creatinine, the authors recommend a 30% decrease in etoposide dose for patients with serum creatinine greater than 1.4 mg/dL. Other approaches to adjusting etoposide dosage for altered renal function include use of measured renal function [e.g., 51Cr-EDTA clearance], 25 or adaptive control dosing based on measured plasma concentrations. 26 These approaches provide more accurate methods of determining patient-specific dose reductions for renal dysfunction; furthermore, they allow for dose escalation in patients with unusually rapid renal function. Thus far, all dosage adjustment recommendations for etoposide in patients with renal dysfunction are based on hematopoietic toxicity; whether adjusting etoposide dosage compromises antitumor efficacy is unknown. Although etoposide is renally excreted (approximately 50%), a significant nonrenal or metabolism component exists (primarily etoposide glucuronide formed in the liver and excreted in the urine). 44 However, data from three studies show that total etoposide clearance and half-life are not significantly altered in patients with hepatic dysfunction (i.e., total bilirubin 2 to 32 mg/dL and elevated transaminases) compared with controls. This seeming contradiction of no change in etoposide total systemic clearance in patients with hepatic dysfunction could be explained by concomitant increases in unbound drug (e.g., bilirubin displacement or hypoalbuminemia) countering a reduction of nonrenal clearance (e.g., hepatocellular metabolism of unbound drug). The relationship between reduced unbound clearance and increased fraction unbound, leading to offsetting changes in total drug clearance, is depicted in Figure 19.6-3.

![Figure 19.6-3](image-url)
Etoposide dosage adjustment in patients with organ dysfunction should not be made solely on changes in etoposide pharmacokinetics, although they can aid in the understanding of altered drug toxicity and therapeutic efficacy associated with impairment of renal and hepatic function. Quantitation of the relation between pharmacokinetics and clinical outcome (pharmacodynamics) provides the clinician with a model to optimize etoposide dosage for an individual patient. The three primary determinants of etoposide disposition, and presumably pharmacologic effect, include excretion (renal), metabolism (hepatic), and protein binding. In a clinical situation in which excretion or metabolism is altered, the pharmacologic effect of etoposide could also be affected. In the absence of prospectively validated dosing recommendations, any recommendations for dosage alterations can only be considered as guidelines for initial dosing. Clinical effects and patient tolerance should guide subsequent etoposide dosing. Other clinical considerations include the current condition of the patient (e.g., performance status), previous cytotoxic chemotherapy, and the therapeutic goal (palliation vs. cure). Arbitrary reductions in etoposide dosage based solely on estimates of renal and hepatic function without regard to pharmacologic effect may lead to overdosing and toxicity or to undertreating and inadequate antitumor effects. Table 19.6-5 summarizes what effect different clinical conditions may have on etoposide protein binding and suggested dosage adjustments.

Inclusion of patient-specific variables, such as serum albumin in pharmacodynamic models, provides indirect evidence for the importance of protein binding to etoposide pharmacodynamics. Because only unbound drug is active, systemic exposure to unbound drug should be more informative of response in a patient population in which protein binding might be considered to be variable. In a number of clinical trials, a statistically significant mathematical relation between systemic exposure to unbound etoposide and myelosuppression has been observed. Thus, in patients with anticipated variable etoposide protein binding (e.g., hypoalbuminemia), measured unbound etoposide systemic exposure could be a more informative measure of drug effect than total systemic exposure.

The effect of schedule on etoposide activity has been the subject of intense investigation. Although an early study suggested prolonged schedules of etoposide were more effective in patients with SCLC, convincing evidence for schedule dependency came from two studies of single-agent intravenous etoposide in previously untreated SCLC. In the first study, 500 mg/m² was given either as a 24-hour infusion or in five daily 2-hour infusions. The systemic exposure to total etoposide was identical between the two treatment arms, but the duration of exposure to putatively cytotoxic concentrations (1 μg/mL) was 15 hours in the daily arm compared to 46 hours in the 24-hour infusion arm. Furthermore, the overall response rate in the 5-day arm was 89%, compared with only 10% in the 24-hour arm. Confirmation of this observation was derived from a randomized trial of 500 mg/m² given intravenously over either a 5-day or an 8-day schedule. No difference in antitumor activity was noted between the two schedules, although hematologic toxicity was more severe in the 5-day schedule.

Etoposide total systemic clearance is increased in the presence of the anticonvulsants (e.g., phenytoin or phenobarbital) often administered with high-dose chemotherapy. Because etoposide undergoes hepatic metabolism, induction of hepatic enzymes by anticonvulsants may be of clinical relevance. Median etoposide systemic clearance in adults receiving phenytoin was approximately 40% greater than in patients not receiving anticonvulsants as part of their bone marrow conditioning regimen. In children, median etoposide systemic clearance was 77% higher in those receiving phenobarbital or phenytoin than in those not taking anticonvulsants. The increased systemic clearance associated with anticonvulsant coadministration translates into a lower systemic exposure at the same dose. Thus, patients receiving anticonvulsants or other drugs known to induce hepatic enzymes need a higher dose of etoposide to achieve a similar systemic exposure to that attained in the absence of this interaction. In contrast, etoposide systemic clearance is decreased in patients receiving cyclosporine or its analogue valspodar, suggesting inhibition of P-450 metabolism, disruption of P glycoprotein function, or modulation of other mechanisms of etoposide elimination.

Etoposide and cisplatin are widely used to treat solid tumors. Because cisplatin causes both acute and chronic decreases in renal function, numerous studies have investigated the potential for it to alter etoposide excretion. The concurrent infusion of cisplatin with high-dose etoposide (i.e., 350 mg/m² for 5 consecutive days) did not alter the pharmacokinetics of cisplatin or etoposide. However, etoposide systemic clearance was significantly lower in the first 48 hours after cisplatin, as compared to 21 days later. Early studies suggested cumulative cisplatin exposure was associated with lower etoposide systemic clearance; however, data from more patients have failed to demonstrate a persistent decrease in clearance with up to 360 mg/m² cisplatin. Whether etoposide excretion would be affected by larger cumulative cisplatin doses remains to be determined.

Phenytoin and sodium salicylate (at pharmacologic concentrations) were able to displace etoposide from plasma protein binding sites. Other drugs (e.g., ifosfamide, indomethacin, nafcinil) were able to displace etoposide, but only at suprapharmacologic plasma concentrations. Unpublished data suggest that therapeutically relevant concentrations of tolbutamide, sodium salicylate, and sulfamethizole can displace protein-bound teniposide in fresh human serum. The clinical relevance of this displacement is unknown.
Myelosuppression is the dose-limiting toxicity for etoposide and teniposide, and only at very high doses is mucositis dose-limiting (i.e., >1000 mg/m²). Granulocyte nadir counts occur between 5 and 15 days after intravenous etoposide administration, and recovery is usually complete by day 28. After continuous oral administration, the nadir granulocyte count occurs between day 21 and 28, and in most patients, recovery is sufficient by day 35 for retreatment. 32-34 Thrombocytopenia occurs less often, with nadir counts observed within 9 to 16 days after drug administration. Regardless of route of administration, myelosuppression is reversible and usually not cumulative. To avoid the potential of severe myelosuppression, consideration should be given to reducing the etoposide dosage for patients who have received extensive prior myelosuppressive chemotherapy or radiation to marrow-bearing areas of the skeleton. Mild to moderate nausea and vomiting occur in approximately 30% to 40% of patients and may be more frequent with oral than intravenous administration. Other gastrointestinal toxicities, including constipation, diarrhea, stomatitis, and anorexia, have been reported but are infrequent at standard intravenous doses; however, with divided-dose oral etoposide, diarrhea and mucositis were dose-limiting. At etoposide dosages used in bone marrow transplantation regimens, mucositis occurs more frequently, and as the dosage increases, the severity also increases. Two patients receiving high-dose etoposide (cumulative dose at least 6.8 g/m²) had elevations in bilirubin, alkaline phosphatase, andaminotransferase levels that reversed within 12 weeks. 32

Hypersensitivity reactions (including vasomotor changes), symptoms related to the gastrointestinal tract, and pulmonary symptoms are observed after therapy with etoposide. Although the rate reported in adults is less than 3%, children with acute lymphocytic leukemia have an incidence as high as 51%; 32 however, children appear to develop more frequent reactions to etoposide than adults. Premedication with histamine (H₁ and H₂ blockers and a slower infusion rate may reduce the risk of further hypersensitivity reactions upon rechallenge with etoposide, although patients developing bronchospasm, urticaria, and severe hypotension or in whom symptom resolution was slow probably should not be rechallenged.

Therapy-associated acute nonlymphocytic leukemia (t-ANLL) has been described after epipodophyllotoxin-containing therapy for both solid tumors and acute lymphocytic leukemia. 33-35 The incidence of t-ANLL varies widely from 1.0% to as high as 25%. These leukemias appear relatively early after diagnosis of the primary tumor (<5 years), present in overt leukemia without preceding myelodysplasia, and are usually French-American-British (FAB) subtypes of M4 and M5. Relationships between the cumulative dose and schedule of etoposide therapy and development of t-ANLL have been described. Cumulative etoposide doses greater than 2 g/m² or 3 g/m² have been associated with a greater incidence of t-ANLL, although this association has not been found in all studies. A relationship between schedule of administration and development of t-ANLL also has been suggested, with frequent administration of high-dose intravenous epipodophyllotoxin associated with an increased incidence of t-ANLL. Reports suggest that t-ANLL may also occur with oral etoposide therapy. 32 If the metabolism of the epipodophyllotoxins has prognostic significance to the development of t-ANLL, as suggested by some investigators, 32 then pharmacogenetic differences may be important. 32

A somewhat unexpected adverse event associated with teniposide is characterized by somnolence, hypotension, and metabolic acidosis and has been described in three children receiving more than 500 mg/m² of intravenous teniposide over 4 hours. 32 Due to poor water solubility, teniposide is formulated with polyoxyethylated castor oil (Cremophor EL) and 42.7% (volume to volume ratio) dehydrated ethanol, and in these patients, clinically significant (i.e., >60 mg/dL) ethanol concentrations were detected at the time of the adverse event. To avoid high ethanol and teniposide concentrations, teniposide doses of more than 500 mg/m² should be given over 8 hours. With the exception of this acute, vehicle-related reaction, the pattern of toxicity for teniposide and etoposide are identical.

ETOPOSIDE PHOSPHATE

Because of poor water solubility, etoposide is formulated with modified polysorbit 80 (Tween 80), polyethylene glycol 300, and ethanol. Preparation of an etoposide prodrug by modification of the etoposide molecule to add a phosphate group at the 4 position in the E ring led to a more water-soluble compound. Etoposide phosphate is rapidly and completely converted by endogenous phosphatases to etoposide. Initial studies have evaluated parenteral administration, but etoposide phosphate can also be given orally. 32,33,34

In early phase I studies, etoposide generated from etoposide phosphate showed the same pharmacokinetic and toxicity pattern as etoposide, but with a number of advantages over the parent compound. 32,33,34 Excipients known to be toxic are not found in etoposide phosphate. The drug can be given by intravenous bolus (i.e., 5 minutes vs. 30 to 60 minutes), reducing the cost of drug preparation and increasing patient convenience. Etoposide phosphate is more stable and can be given at higher dosage levels than etoposide. The incidence of hypersensitivity reactions upon rechallenge with etoposide is lower with etoposide phosphate than etoposide, although patients developing bronchospasm, urticaria, and severe hypotension or in whom symptom resolution was slow probably should not be rechallenged.

CAMPTOTHECIN ANALOGUES

The antitumor activity of 20(S)-camptothecin, a plant alkaloid isolated from Camptotheca acuminate, has been recognized for more than 20 years. 32,33 Although 10-hydroxycamptothecin demonstrated active in activity studies conducted primarily in China, its use was associated with severe and unpredictable toxicity. Several camptothecin derivatives have been evaluated in clinical trials, including 9-amino-20(S)-camptothecin (9-AC), 9-nitrocamptothecin (rubitecan), lurtotecan (GI 147211), 10-hydroxycamptothecin demonstrated activity in studies conducted primarily in China, its use was associated with severe and unpredictable toxicity. Several camptothecin analogues have been developed for clinical use (topotecan and irinotecan) contain the camptothecin pentacyclic structure with a lactone (closed ring) moiety in the E ring. This lactone is essential for cytotoxicity because the open ring, or hydroxy acid form, is inactive. Because of logistical difficulties in stabilizing the lactone, before analysis, many investigators have chosen to decarboxylate the lactone form which makes all hydroxy acid isomer of the lactone form. Thus, these investigators measure the sum of lactone and hydroxy acid, or total drug. The clinical pharmacokinetics of the camptothecin analogues are summarized in Table 19.6-6. Many different routes, doses, and schedules of administration have been evaluated for the camptothecin analogues, and controversy exists over which is optimal.

**FIGURE 19.6-4.** Camptothecin analogues.
Topotecan disposition and hematologic toxicity were not significantly altered in patients with hepatic dysfunction (as defined by elevated total bilirubin); therefore, no hepatic dysfunction was defined as a total bilirubin greater than 1.5 mg/dL. A control group of patients with normal renal and hepatic function was also studied.

The primary route of elimination from the body varies between topotecan and irinotecan. For topotecan, 50% to 65% of a dose is recovered in the urine; thus, renal excretion is a major route of elimination. Although topotecan has been measured in human bile, the importance of biliary excretion is unknown. Approximately 30% to 40% of topotecan is eliminated by nonrenal pathways, and the N-desmethyl metabolite of topotecan has been isolated from urine of patients receiving topotecan.

This metabolite has antitumor activity equal to that of the parent compound, and its formation is catalyzed by the cytochrome P-450 system. The maximum plasma concentration of total (sum of lactone and hydroxy acid) N-desmethyl topotecan is only 0.5% of total topotecan, and its inhibitory activity in recovery is less than 5% of the administered dose. Two other metabolites, topotecan O-glucuronide and N-desmethyl topotecan O-glucuronide have been reported; however, they accounted for only 13.5% of the urinary recovery of the administered dose. Thus, other nonrenal routes (e.g., metabolism) of topotecan elimination are yet to be identified.

In contrast, irinotecan itself has little in vitro cytotoxicity and requires conversion, by the carboxylesterase enzyme, to 7-ethyl-10-hydroxy camptothecin (SN-38) for antitumor activity. In vitro studies have shown decreased carboxylesterase activity may be a mechanism of cellular resistance to irinotecan. Furthermore, transfection of carboxylesterases into tumor cells increases the activation and cytotoxicity of irinotecan. SN-38 is conjugated to glucuronic acid at the C2 position by UGT1A1, and this metabolite has no intrinsic antitumor activity. The extent of conversion of SN-38 to its glucuronide has been inversely correlated with the risk of severe diarrhea, because the other major route of SN-38 excretion is biliary excretion by canalicular multispecific organic anion transporter (cMOAT) (presumably leading to mucosal injury). In addition to SN-38 and SN-38 glucuronide, 7-ethyl-10-(4-N-5(aminopentanoic acid)-1-piperidino)carbonyloxy camptothecin (APC) and 7-ethyl-10-(4-amino-1-piperidino)carbonyloxy camptothecin (NPC) are oxidative metabolites of irinotecan formed by CYP3A4. Renal excretion is a minor route of elimination for irinotecan and SN-38.

The disposition of topotecan in patients with renal and hepatic dysfunction has been studied in adults receiving intravenous topotecan daily for 5 consecutive days. Patients with renal dysfunction were placed into three groups according to their creatinine clearance (20 or below, 21 to 40, or 41 to 60 mL/min), and hepatic dysfunction was also studied. Topotecan disposition and hematologic toxicity were not significantly altered in patients with hepatic dysfunction (as defined by elevated total bilirubin); therefore, no dose adjustment is recommended for these patients. Severe neutropenia was observed in patients with moderate to severe renal dysfunction treated at one-third of the adult maximal tolerated dosage (i.e., 0.5 mg/m²/d). Based on the results of this study, the investigators recommended an initial topotecan dosage of 0.75 mg/m² when given daily for 5 consecutive days to patients with moderate renal dysfunction (i.e., creatinine clearance <39 mL/min). In another study of patients with renal dysfunction, no correlation was found between topotecan clearance and a more specific measure of glomerular filtration rate [technetium Tc 99m DPTA clearance]. Furthermore, one patient studied with a technetium clearance of 19 mL/min/m² had a normal topotecan total clearance, suggesting topotecan may undergo renal tubular secretion in addition to glomerular filtration. Results of a study in mice showed that probenecid would inhibit renal tubular secretion of topotecan and decrease topotecan renal and systemic clearance, leading to an increase in topotecan lactone systemic exposure. Irinotecan undergoes significant hepatic metabolism, and preliminary pharmacokinetic and toxicity results of a study of irinotecan administration in adults with liver dysfunction suggest that the irinotecan dosage should be reduced by one-third in patients with total bilirubin more than the upper limit of normal.

As with the epipodophyllotoxins, results of preclinical studies of the camptothecin analogues show a definite relationship between dose and antitumor effect in mice bearing human tumor xenografts. These studies have evaluated a variety of schedules and routes of administration, and the results suggest that the camptothecin analogues are highly schedule-dependent. Early clinical studies of the relationship between systemic exposure and pharmacologic effect reported a statistically significant and clinically relevant relationship between drug exposure and myelosuppression (i.e., percentage change in absolute neutrophil count and platelets).

A significant correlation was reported between systemic exposure to 9-aminocamptothecin lactone and the extent of neutropenia observed after a 72-hour continuous infusion. Few studies have looked at the relationship between drug exposure and antitumor efficacy; however, one study of continuous infusion topotecan in children with relapsed acute leukemia found a correlation between topotecan lactone systemic exposure and toxicity and topotecan lactone systemic exposure and oncologic effect.
The presence of the pH-sensitive lactone ring present in the two commercially available camptothecin analogues, topotecan and irinotecan, raises the question of whether lactone or total systemic exposure is a better representation of pharmacologic effect. The advantage of measuring total drug is the elimination of the more cumbersome determination of the lactone concentrations, which require immediate sample processing. Total concentrations (lactone plus hydroxy acid) may be determined without immediate processing, and assays may be performed several weeks or months later, thus, making it feasible to do large population studies. Use of total drug as a surrogate for systemic exposure to the active lactone has potential drawbacks (e.g., presence of active metabolites, inpatient variability), although the lactone and hydroxy acid exist in a pH-dependent equilibrium that varies little at physiologic pH.

Reversible myelosuppression, with both neutropenia and thrombocytopenia, is the dose-limiting toxicity observed with topotecan. After intravenous dosing of topotecan, the neutrophil nadir occurs between 8 and 10 days, and recovery is usually complete by day 21. On a schedule of extremely high doses given daily for 5 days, hematologic anemia was observed as a dose-limiting toxicity. Reversible moderate to severe anemia also has been reported with topotecan. The use of growth factors to further escalate the topotecan dose has been used with success. With oral topotecan, prolonged oral administration (i.e., twice daily for 21 days every 28 days) resulted in gastrointestinal side effects as the dose-limiting toxicity, whereas, when given in the short term (i.e., once daily for 5 days every 21 days), myelosuppression was the dose-limiting toxicity. For topotecan, the only nonhematologic dose-limiting toxicity reported is mucositis, but only after a 120-hour continuous topotecan infusion.

The major dose-limiting toxicities for irinotecan are myelosuppression and diarrhea. Irinotecan-induced diarrhea is generally of two types. The first type has an early onset, beginning during or immediately after the irinotecan infusion. This is often accompanied by facial flushing and abdominal cramping characteristic of diarrhea associated with vasoactive compounds. Standard-dose anticholinergic drugs, such as scopolamine or atropine, can be used to control this diarrhea, which is caused by the cholinergic effects of irinotecan. The second type of diarrhea, a cholera-like syndrome unresponsive to loperamide or codeine, is often dose-limiting. Many therapeutic approaches have been tried to ameliorate or prevent the diarrhea associated with irinotecan, including the use of the cyclooxygenase inhibitor indomethacin and the enkephalinase inhibitor acetorphelin, but none has been universally successful. Modulation of irinotecan pharmacokinetics by inhibitors of SN-38 biliary excretion or inducers of SN-38 glucuronidation may be another method to reduce the severity of irinotecan-associated diarrhea.

Other nonhematologic toxicities seen with the camptothecin analogues are generally reversible and not dose-limiting. Mild nausea and vomiting have occurred in approximately 20% to 30% of patients. Low-grade fever has been observed in approximately 20% of patients, and alopecia occurs at higher doses. Other mild toxicities observed include fatigue, anorexia, and skin rash. Top I interactive agents have not been in clinical use long enough for therapy-associated malignantities to be reported; however, sister chromatid exchanges and gene deletions or rearrangements have been induced in vitro.

Topotecan systemic clearance and the formation of the N-desmethyl topotecan metabolite are increased in the presence of enzyme-inducing anticonvulsants (e.g., phenytoin). Although hepatic metabolism is a relatively minor component of topotecan disposition, the steep exposure-response relationship observed with topotecan makes this interaction clinically relevant. Patients concomitantly administered enzyme-inducing anticonvulsants may require an increase in topotecan dose to achieve a similar pharmacologic effect as a patient not receiving anticonvulsants. This interaction with anticonvulsants was also observed in a group of patients receiving 9-aminocamptothecin, a camptothecin analogue that has no known hepatic metabolism. In this study, patients receiving 9-aminocamptothecin and anticonvulsants did not have the expected extent of myelosuppression. On further study of 9-aminocamptothecin pharmacokinetics, it was found that the median steady-state 9-aminocamptothecin plasma concentrations in patients on anticonvulsants (25.3 nM) was significantly lower than patients not receiving anticonvulsants (76.5 nM). Anticonvulsants also increased irinotecan clearance in a study of patients with glioma, which led to a decrease in the mean irinotecan and SN-38 AUC. Although the numbers of patients studied were small, it appears that phenobarbital may have a different effect from carbamazepine and phenytoin, in that phenobarbital increased SN-38 glucuronide and APC AUC by 1.6- and 2.6-fold, respectively. In another study of adults with malignant glioma receiving irinotecan and anticonvulsants and dexamethasone, the irinotecan clearance was twofold and the systemic exposure to irinotecan, SN-38, and SN-38 glucuronide was statistically lower compared with a historical control group of patients with non-CNS tumors.

ANTHRACYCLINES AND RELATED COMPOUNDS

Anthracyclines, anticancer agents consisting of a pigmented aglycone, an amino sugar, and a lateral chain ([Fig. 19.6-6]), have been in clinical practice since the 1960s and represent one of the most commonly used classes of anticancer drugs. The first anthracyclines in clinical use, doxorubicin and daunorubicin, were produced by the Streptomyces species, and the anthracyclines have thus been classified as antitumor antibiotics; however, classification by mechanism of action is more rational, especially because the second-generation anthracyclines (e.g., idarubicin, epirubicin) are synthetic. The first anthracycline, doxorubicin, still remains the most widely used and is the benchmark against which new analogues are compared.

The anthracyclines induce formation of covalent topoisomerase-DNA complexes and prevent the enzyme from completing the religation portion of the ligation-religation reaction. These agents are also DNA intercalators that insert part of their planar structures between two adjacent base pairs in DNA, causing single-stranded and double-strand breaks. The anthracyclines can undergo chemical reduction through enzymatically catalyzed or iron-catalyzed pathways to yield reactive free radical intermediates. Through hydrogen peroxide and hydroxyl radicals, these free radical intermediates can cause oxidative damage to cellular proteins. Under hypoxic conditions, these free radicals can rearrange to form metabolites capable of covalently binding to DNA. Although the anthracyclines are associated with all of these reactions, it is their interaction with top II that is the most important mechanism of cytoxicity.

With the exception of idarubicin, none of the anthracyclines are administered orally. Idarubicin, a synthetic analogue of daunorubicin, has increased lipophilicity compared to daunorubicin, which allows it to be readily absorbed from the gastrointestinal tract. Absorption of idarubicin is erratic and incomplete ([Table 19.6-7]); however, higher concentrations of its active metabolite, idarubicinol, are achieved after oral than intravenous administration because of first-pass hepatic metabolism.

![FIGURE 19.6-6. Structures of the four anthracyclines in current clinical use. Epirubicin differs from doxorubicin in the steric position of the 4'-OH group, whereas idarubicin differs from daunorubicin in lacking an A-ring methoxy substitution.](image-url)
Anthracyclines as a class are unable to cross the blood–brain barrier either because of low lipophilicity, the presence of P-glycoprotein in the cells of brain endothelial vessels, or both. After intravenous administration of idarubicin, its metabolite, idarubicinol, can be detected in the CSF (1% to 13% simultaneous plasma concentration) at concentrations associated with in vitro cytotoxicity. The plasma protein binding for the anthracyclines is probably not clinically relevant, with the exception of idarubicin and idarubicinol, as hypoalbuminemia may increase systemic exposure to unbound idarubicin and idarubicinol.

Several metabolic pathways have been reported for the anthracyclines. Reduction of the ketone on carbon 13 yields 13S-dihydro derivatives, which are then named after the parent anthracycline with the suffix -oa (e.g., doxorubicinol). This reaction is catalyzed by the ubiquitous aldo/keto reductases, which in general convert daunorubicin and idarubicin more rapidly than doxorubicin and epirubicin. Thus, plasma concentrations of daunorubicinol and idarubicinol rapidly exceed those of the parent drug (AUC ratio of metabolite to parent drug, 2 to 5), compared with doxorubicinol and epirubicinol (AUC ratio, 0.3 to 0.5). Most 13-dihydro metabolites of the anthracyclines do not have antitumor activity; however, idarubicinol is an exception, primarily due to its lipophilicity, which allows entry into the cell. At one time, deglycosylation was thought to represent a metabolic pathway, but now the clinical significance of the anthracycline aglycones is unknown. Epirubicin, an epimer of doxorubicin, is characterized by a unique metabolic step only present in humans. The equatorial position of the 4′ hydroxyl group allows epirubicin to be conjugated to glucuronic acid. The glucuronide AUC is similar to that of the parent compound, potentially explaining the lower myelotoxic and cardiotoxic properties of epirubicin compared with doxorubicin; however, the exact clinical significance of this metabolic step is unknown.

Elimination of the anthracyclines proceeds primarily through the bile, with urinary excretion accounting for less than 10% of the total dose administered. No evidence for enterohepatic recirculation has been observed. Although epirubicin is excreted in the bile, a larger proportion of an injected dose is recovered in the urine relative to the other anthracyclines, due to formation of soluble glucuronides.

In patients with hyperbilirubinemia or reduced renal function, dose reduction recommendations for daunorubicin and doxorubicin are provided in the package literature. These dose reductions are based on retrospective data and have not been prospectively validated. The results of a study of patients with hyperbilirubinemia receiving doxorubicin raise questions about the validity of adjusting doses in patients with hyperbilirubinemia. The systemic clearance of epirubicin and idarubicin in patients with liver disease is decreased, and although a dosage reduction is recommended based on bilirubin or serum aspartate, as with doxorubicin, it is unclear if a dosage reduction is clinically indicated. Whereas renal impairment reduces the clearance of epirubicin and idarubicin, only idarubicin has been adequately studied to provide dosing guidelines.

As with other anticancer drugs, few clinical studies have related exposure to anthracyclines and antitumor effect. Early studies suggested doxorubicin concentration, peak or 3 hours after end of infusion, was associated with outcome of remission induction or reduction of tumor mass, respectively. These findings have led investigators to speculate that improved tumor response might be linked to high initial plasma doxorubicin concentrations. The contribution of the anthracycline metabolites to overall effect depends on the anthracycline under study. As discussed previously, idarubicin has significant cytotoxic activity; patients with a low rate of epirubicin glucuronidation had a lower percent change in neutrophils and better tumor response. The only pharmacodynamic relation between doxorubicin systemic exposure and toxicity (e.g., decrease in WBC) was noted after continuous doxorubicin infusion. A positive correlation was noted between the AUC for epirubicin, or epirubicin and epirubicinol, and logarithm of the WBC survival fraction.

Although a number of drugs have been reported to interact with doxorubicin, most of these have been in experimental systems, so their clinical significance is unknown. Of the drug interactions reported in patients with cancer, only a few are of clinical consequence. Despite numerous studies showing pharmacologic prevention of anthracycline-induced cardiotoxicity, only dexrazoxane has been able to significantly retard development of cardiotoxicity. The reversal of doxorubicin-induced multidrug resistance has been attempted using a variety of pharmacologic modulators, such as trifluoperazine, verapamil, and cyclosporine, and has met with mixed success.

The dose-limiting acute toxicity of the anthracyclines is myelosuppression, primarily affecting the neutrophils; in the treatment of leukemia, however, this may be considered a desirable side effect. The onset of myelosuppression is usually 7 days after administration, with maximum effect seen at approximately day 10 to 14.

Recovery is usually complete by day 21 to 28. Gastrointestinal toxicities are common, including nausea and vomiting, diarrhea, and mucositis. Although not dose-limiting, alopecia also occurs in almost all patients. Although not always readily apparent when it occurs, extravasation of the anthracyclines can lead to severe local tissue damage and deep ulcerations that progress over weeks. These lesions are slow to heal and often require skin grafting, although the graft is not always successful. Once an extravasation has been discovered, the optimal method of management is unknown, although most agree that local measures such as ice packs and subcutaneous injections of saline, steroids, or bicarbonate may be useful. Topical dimethylsulfoxide has been suggested to be a safe and effective approach to reducing the tissue damage associated with anthracycline-induced extravasation. The best approach to avoiding extravasation is to take all possible precautions when administering an anthracycline, such as ensuring good blood return on the intravenous line, monitoring the intravenous site carefully, and good patient education.

The anthracyclines are associated with both acute and chronic cardiac toxicity. The less common acute cardiac toxicity includes nonspecific electrocardiographic changes that may be observed during or immediately after the infusion. In its extreme form, this acute toxicity can include a pericarditis-myocarditis syndrome with onset of fever, pericarditis, and congestive heart failure. No association between the acute toxicity and later development of chronic toxicity has been shown. Besides symptomatic management, no specific therapy is recommended for this relatively rare syndrome.

Anthracyclines also produce a dose-dependent congestive myopathy that often leads to congestive heart failure. This typically becomes apparent 4 to 8 weeks after the last anthracycline dose, although it may occur during treatment or years later. The clinical significance of this chronic toxicity has been its inability to treat it, leading to a drug-induced mortality ranging in early reports from 33% to 70%, and in more recent reports to less than 30%. If a sufficiently high cumulative dose is administered, all anthracyclines can cause cardiac toxicity; however, idarubicin and epirubicin are associated with a lower incidence than doxorubicin and daunorubicin. The mechanisms of the chronic cardiotoxicity have been reviewed extensively. To summarize, they include enzymatic-mediated formation of oxygen free radicals that initiate lipid peroxidation and a nonenzymatic pathway for free radical formation. Iron is central to both pathways; it is required to begin hydroxyl radical production in the first pathway, and to form an iron–drug complex in the second. The risk of anthracycline-associated congestive heart failure is increased by free radicals that initiate lipid peroxidation and a nonenzymatic pathway for free radical formation.

Patients receiving anthracyclines should be monitored for the onset of cardiomyopathy. The most useful noninvasive test is serial radionuclide angiography, which provides a reproducible measure of LVEF and is sensitive to subclinical cardiac dysfunction. This technique and others have done much to allow earlier detection of subclinical cardiac toxicity and to reduce the mortality associated with it. Management of the cardiomyopathy involves bed rest and afterload reduction.
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SECTION 19.7
Antimicrotubule Agents

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INTRODUCTION

The microtubule is increasingly recognized as a strategic subcellular target against which to direct therapeutic efforts, owing to the widespread use of the vinca alkaloids in both curative and palliative chemotherapeutic regimens and the successful incorporation of the taxanes in cancer chemotherapeutics. This chapter reviews the vinca alkaloids, taxanes, and estramustine and other novel antimicrotubule agents in early development.

MICROTUBULES

Microtubules are integral components of the mitotic spindle, which can be disrupted by the vinca alkaloids, taxanes, and an increasing number of both natural products and synthetic compounds, resulting in metaphase arrest in dividing cells. However, they are also involved in nonmitotic functions, such as chemotaxis, membrane and intracellular scaffolding, transport, secretory processes, anchorage of subcellular organelles and receptors, cell adhesion, and locomotion transmission of receptor signaling. Antimicrotubule agents may disrupt a range of these nonmitotic functions.

Microtubules are polymers of dimeric subunits of α- and β-tubulin (each tubulin subunit consisting of approximately 450 amino acids with a molecular weight of 50,000) that are arranged into 13 protofilaments. The dimers are aligned side by side around an apparently hollow core with the β subunit of one dimer in contact with the α-tubulin subunit of the next. The microtubule polymer is in a dynamic equilibrium with the intracellular pool of tubulin dimers, which results in the simultaneous incorporation of free dimers into the polymerized structures and release of dimers into the soluble tubulin pool. The direction of the equilibrium—toward polymerization or depolymerization—is influenced by several cofactors, including guanosine triphosphate (GTP), the ionic environment, and microtubule-associated proteins (MAPs), which is a family of proteins that regulate tubulin polymerization and microtubule function. Microtubule growth occurs spontaneously at the plus end, resulting in the hydrolysis of GTP, which weakens the binding affinity of tubulin for adjacent molecules. This, in turn, favors the opposing process: depolymerization. Net shortening occurs at the opposite minus end. In essence, microtubules are under the control of two dynamic processes. The first is dynamic instability, which is the process whereby microtubule ends switch spontaneously and stochastically between slowly growing and rapidly shrinking states. The rate of dynamic instability is accelerated during some processes, such as mitosis, so that chromosomes can readily be “captured” by growing microtubules, thereby leading to the formation of mitotic spindles; dynamic instability is suppressed, perhaps by MAPs, during nonproliferative processes (e.g., differentiation). When both these actions occur simultaneously, the microtubule is said to be treadmilling, which plays a role in the polar movement of the chromosomes during anaphase.

There are at least six isotypes of both α- and β-tubulin in humans; they are distinguished by slightly different amino acid sequences and appear to be encoded by different genes. The C-terminal amino acid sequence of β-tubulin is the most variable in terms of amino acid composition, and both posttranslational modifications, including phosphorylation and glutamylation (which may account in part for their structural diversity) have been described. Equivalent isotypes expressed in specific tissues of different species are highly conserved, indicating that expression of tubulin isotypes may be important in specific microtubule functions. Analysis of tubulin isotype expression in various tissues has demonstrated a complex pattern of isotype distribution, suggesting functional specificity. In neurons, for example, isotype segregation within cells, and both differential isotype synthesis and posttranslational modification during neurite outgrowth, suggest functional specialization. A third member of the tubulin superfamily, γ-tubulin, which is less abundant than the α and β forms, completes the microtubule-organizing center (MTOC) or centrosome. Although tubulin can polymerize into microtubules in acellular preparations, they are polymerized from, and nucleated by, the MTOC, with minus ends located at the MTOC. The MTOC in the cytoplasm of mammalian cells duplicates and separates before cell division.
MICROTUBULE-ASSOCIATED PROTEINS AND MICROTUBULE MOTORS

The dynamic behavior of microtubules is regulated by a variety of MAPs. The number of MAPs identified is increasing rapidly, and these proteins appear to be diverse, differing from species to species and cell type to cell type. Among the best-characterized MAPs are those that come from mammalian brain, including the tau proteins, MAP1, MAP1c (an adenosine triphosphatase), MAP2, MAP4, and dynein (a GTPase), which promote tubulin polymerization and microtubule stability. Some MAPs, such as the dynes and kinesins, function as microtubule motors, transmitting chemical energy to mechanical sliding force and moving various solutes and subcellular organelles along the microtubule. Motor proteins function in many types of cellular events, such as mitosis, premiotic events, and organelle transport.

VINCA ALKALOIDS

The vinca alkaloids are naturally occurring or semisynthetic compounds that are found in minute quantities in the periwinkle plant Catharanthus roseus g. Don. The early medicinal uses of this plant led to the screening of these compounds for their hypoglycemic activity, which was of little importance as compared to their cytotoxic effects. Although many vinca alkaloids have been investigated clinically, only vincristine (VCR), vinblastine (VBL), and vinorelbine (VRL) are approved for use in the United States. The vinca alkaloids are dimeric molecules composed of two multiringed units (Fig. 19.7-2), an indole nucleus (catharanthine) and a dihydroindole nucleus (vindoline). VCR and VBL are structurally identical except for a single substitution on the vindoline nucleus, where VCR and VBL possess formyl and methyl groups, respectively. Despite this small difference, these two agents significantly differ in their antimicrotubule properties. VCR is used more commonly in pediatric oncology than in adults with cancer, most likely owing to the higher level of sensitivity of pediatric malignancies to VCR and to the better tolerance of higher VCR doses in children. VCR is an essential part of the combination chemotherapy regimens used for adult non-Hodgkin's lymphomas and Hodgkin's disease, and plays an important role in the treatment of both Hodgkin's and non-Hodgkin's lymphomas. The agent also plays a role in the multimodality therapy of Wilms' tumor, Ewing's sarcoma, neuroblastoma, and rhabdomyosarcoma in children, as well as in the treatment of multiple myeloma and small cell lung cancer in adults. VBL has been an integral component of chemotherapeutic regimens for germ cell malignancies and advanced lymphoma and is used in combination with other agents to treat Kaposi's sarcoma and bladder, brain, and breast cancers.

FIGURE 19.7-2. Structural modifications of the vindoline and catharanthine rings in various vinca alkaloids.

Deacetyl vindesine (vindesine, or VDS), initially identified as a metabolite of VBL, was introduced in the 1970s. VDS is registered in many countries but available only for investigational purposes in the United States. The agent is most commonly used in combination with other agents, particularly the platining agents or mitomycin C (or both), in treating non–small cell lung cancer, but it is also active in several hematologic and solid neoplasms. The semisynthetic VBL derivative VRL (5'-norhydro-VBL), which is structurally modified on its catharanthine nucleus, is approved in the United States for treating non–small cell lung cancer as either a single agent or in combination with cisplatin and has been registered for advanced breast cancer in many other countries. VRL has also demonstrated anticancer activity in advanced ovarian carcinoma and lymphoma, however, a unique role in the therapy of these malignancies has not been defined.

MECHANISM OF ACTION

The principal mechanism of cytotoxicity of the vinca alkaloids is by interacting with tubulin and disrupting microtubule function, particularly of microtubules that compose the mitotic spindle apparatus, leading to metaphase arrest. However, they are also capable of many other biochemical and biologic activities that may or may not be related to their effects on microtubules. In support of antimicrotubule actions or, more specifically, antimitotic actions as the principal cytotoxic effect of the vinca alkaloids is that the dissolution of the mitotic spindle apparatus, appearance of mitotic figures, and cytotoxicity strongly correlate with both the duration and concentration of drug treatment. Nonetheless, the vinca alkaloids and other antimitotic agents also affect both nonmalignant and malignant cells in the nonmitotic cell cycle, which is not surprising, as microtubules are involved in many nonmitotic functions.

The vinca alkaloids bind to sites on tubulin that are distinct from the binding sites of the taxanes, colchicine, podophyllotoxin, and GTP. Binding is rapid and readily reversible. There appear to be two binding sites per mole of tubulin dimer. Vinca alkaloid binding to tubulin induces tubulin to self-associate into nonmicrotubule polymers and ordered aggregates through a self-association pathway, which in turn increases the affinity of one of the binding sites for the drug. The vinca alkaloid self-association of tubulin can lead to the formation of paracrystalline structures in vitro, which generally occurs at high drug concentrations. The vinca alkaloids bind to the ends of microtubules with different affinities, depending on whether the binding sites are located at the microtubule ends or situated along the microtubule surface. There are approximately 16 to 17 high-affinity binding sites per microtubule (K<sub>a</sub> 1 to 2 µmol) located at the ends of each microtubule. Binding of the vinca alkaloids to these sites disrupts microtubule assembly. The main effect of low drug concentrations is to decrease the rates of both growth and shortening at the assembly end of the microtubule, which in effect produces a “kinetic cap” and suppresses function.

Despite the wide range of sensitivities of different tissues to the actions of the vinca alkaloids in vivo, the qualitative effects of these agents on tubulin, as well as both tubulin-binding and inhibitory constants, are similar. The differential sensitivities of various tissues appear to be multifactorial. One of the most likely explanations is that each tissue type has a distinct tubulin isotype composition and that vinca alkaloid sensitivity is, in part, tubulin isotype–dependent. In addition, differences in the tissue content of cofactors, such as MAPs and GTP, which may influence drug interactions with tubulin, and variability in cellular permeation and retention may influence the formation and stability of vinca alkaloid-tubulin complexes. Differences in the pharmacokinetics between the vinca alkaloids may also contribute to differential tissue sensitivity.

The vinca alkaloids are rapidly taken up into cells and then accumulate intracellularly, with intracellular-extracellular concentration ratios as high as 5- to 500-fold, depending on the cell type. In murine leukemia cells, the intracellular concentrations of VCR are 5- to 20-fold higher than the extracellular concentrations, and this ratio has been reported to range from 150- to 500-fold for other vinca alkaloids in human leukemia cell lines. In isolated human hepatocytes, VRL is more rapidly taken up and metabolized than other vinca alkaloids. There are also marked differences in cellular retention between the vinca alkaloids. VBL is retained to a much greater degree than either VCR or VDS. Overall, the most important determinant of the rates of drug accumulation and retention is lipophilicity.

Drug uptake and retention may also be tissue-specific as well as drug-specific, as illustrated by studies indicating that the accumulation and retention of VRL in
neurons are much less than with other vinca alkaloids. 31

It was originally believed that the vinca alkaloids entered cells by both energy-dependent and temperature-dependent transport processes. 32 However, it appears that temperature-independent, nonsaturable mechanisms, analogous to simple diffusion, account for the majority of drug transport, and temperature-dependent, saturable processes are less important. 33-35 Although the drug concentration and duration of treatment are important determinants of both drug accumulation and cytotoxicity, the duration of drug exposure above a critical threshold concentration appears to be the most important determinant. 35-37

MECHANISMS OF RESISTANCE

Two mechanisms of resistance to the vinca alkaloids in vitro have been well characterized. The first is pleiotropic or multidrug resistance (MDR), which can be innate or acquired. MDR-mediating proteins include permeability glycoprotein (P-gp), MDR protein, and lung resistance protein, which are overexpressed in resistant cells and function as drug efflux pumps. 37,38,39-41 The best characterized mechanism is mediated by the 170-kD P-gp drug efflux pump that is encoded by the mdr1 gene and results in decreased drug accumulation. The MDR phenotype confers varying degrees of cross-resistance to other structurally bulky natural products, such as the taxanes, anthracyclines, epipodophyllotoxins, and colchicines. 37,38,39,40,42-44 The amino acid sequence of the specific P-gp associated with resistance to the vinca alkaloids differs slightly from P-gp of cells selected for resistance to other agents. 42,44 These proteins also undergo posttranslational modifications, resulting in further structural diversity, which may explain the greater degree of resistance for the specific agent, in which resistance was selected against, and the variable degrees of resistance to agents aside from that specific agent. The composition of membrane gangliosides in VCR-resistant cells has also been demonstrated to be different from wild-type cells, which may have functional significance. 45 The clinical ramifications of these mechanisms are not entirely known. In one study in childhood acute lymphoblastic leukemia, VCR resistance measured in vitro did not correlate with P-gp overexpression. 42 Although many types of agents reverse resistance conferred by P-gp in vitro and the role of MDR modulators has been a source of great contemporary interest, the interpretation of clinical studies of resistance modulation has been confounded by the fact that MDR modulators also enhance drug uptake in normal cells, decrease biliary elimination and drug clearance, and lead to enhanced toxicity. 42-45 Overall, strategies aimed at reversing resistance to the vinca alkaloids in the clinic with pharmacologic modulators of MDR have been disappointing. 46

Structural and functional alterations in a- and b-tubulins, resulting from either genetic mutations or posttranslational modifications, have also been identified in tumor cells with acquired resistance to the vinca alkaloids. 56,57 Tubulin alterations may result in either decreased drug-binding affinity of the altered tubulin or increased resistance to microtubule disassembly. These “hypersensitive” microtubules are collaterally sensitive to the taxanes, which inhibit microtubule disassembly (discussed later in Taxanes, Mechanisms of Resistance). Although the precise mechanisms that lead to cell death after treatment with the vinca alkaloids are not entirely clear, these mechanisms appear similar to those that have been elucidated for the taxanes and involve the action of such genes as p53, bcl-2, and bcl-x and gene products that trigger programmed cell death or apoptosis after significant microtubule disruption. 42,45

PHARMACOLOGY

General Overview

The vinca alkaloids are usually administered intravenously as a brief infusion, and their pharmacokinetic behavior in plasma is optimally described by three-compartment models. Table 19.7-1 displays several pertinent pharmacokinetic features of these agents. At conventional adult doses, peak plasma concentrations range from 100 to 500 nmol, but levels of this magnitude are sustained in plasma for only short periods (alpha half-lives, <5 minutes). 37,38,41 and 50,51 The vinca alkaloids share many pharmacokinetic characteristics, including large volumes of distribution, high clearance rates, and long terminal half-lives, which reflect the high magnitude and avidity of drug binding in peripheral tissues. There is also great interindividual and intranidividual variability in their pharmacologic behaviors, which has been attributed to many factors, including differences in protein binding and both hepatic and biliary clearance. 42 Although it has been proposed that prolonged infusion schedules may avoid excessive toxic peak concentrations and increase the duration of drug exposure in plasma above biologically relevant threshold concentrations for any given tumor, there is little (if any) evidence to support the notion that prolonged infusion schedules are more effective than bolus schedules. This approach has primarily been directed at achieving plasma concentrations that likely underestimate drug concentrations in peripheral tissues where binding is high and avid, owing to the ubiquitous nature of tubulin.

TABLE 19.7-1. Vinca Alkaloids: Comparative Pharmacokinetic and Toxicologic Characteristics

In comparative studies of the vinca alkaloids, VCR had the longest terminal half-life and the lowest clearance rate. VBL had the shortest terminal half-life and the highest clearance rate, and VDS had intermediate characteristics. 5,17,38 and 60-65 Comparable values for VLR overlap with those of VDS and VBL. The longest half-life and lowest clearance rate of VCR may account for its greater propensity to induce neurotoxicity, 5,19 but there are many other nonpharmacologic determinants of tissue sensitivity (discussed earlier in the section Mechanism of Action under Vinca Alkaloids).

Vincristine

After conventional doses of VCR (1.4 mg/m²) given as brief infusions, peak plasma levels approach 0.4 µmol. 50,51,52,53 VCR binds extensively to both plasma proteins (48%) and formed blood elements, particularly platelets, which contain high concentrations of tubulin and led, in the past, to the use of VCR-loaded platelets for treating disorders of platelet consumption, such as idiopathic thrombocytopenia purpura. 50 The platelet count inversely has been demonstrated to influence drug exposure. 52,53 Penetration of VCR across the blood–brain barrier is poor, probably because of its large size and the fact that it is an avid substrate for the multidrug transporter pumps that maintain the integrity of the blood–brain barrier. 52,53,54,55,56,57 Plasma clearance is slow, and terminal half-lives range from 23 to 85 hours. 52,53,54,55,56,57

VCR is metabolized and excreted primarily by the hepatobiliary system. Seventy-two hours after the administration of radiolabeled VCR, approximately 12% of the radiolabel is excreted in the urine (50% of which consists of metabolites), and approximately 70% is excreted in the feces (40% of which consists of metabolites). 52,53,54,55,56,57,58,59 The nature of the VCR metabolites identified to date, as well as the results of metabolic studies in vitro, indicate that VCR metabolism is mediated by hepatic cytochrome P-450 CYP3A. 52,53,54,55,56,57 There has been conflicting, albeit sparse, evidence indicating that peak VCR plasma concentration or systemic exposure correlates positively with the degree of neurotoxicity. 52

VINBLASTINE

The clinical pharmacology of VBL is similar to that of VCR. Binding of VBL to plasma proteins and formed elements of blood is extensive. 62,63 Peak plasma drug concentrations are approximately 0.4 µmol after rapid intravenous injections of VBL at standard doses. Distribution is rapid, and terminal half-lives range from 20 to 24 hours. 62,63,64,65,66 Tissue sequestration appears to be greater for VBL than VCR, with 73% of radioactivity retained in the body 6 days after treatment with
radicalized drug. Like VCR, VBL disposition is principally through the hepatobiliary system. Fecal excretion of the parent compound is low, indicating that the metabolism is significant. In vitro studies indicate that the cytochrome P-450 CYP3A isofrom is primarily responsible for the drug biotransformation. Although the metabolic fate of VBL has not been fully characterized, 4-deacetyl-VBL, or VDS, which appears to be as active as the parent compound, is the principal metabolite of VBL.

VINDELINE

VDS is rapidly distributed to tissues, and terminal half-lives range from 20 to 24 hours. The large volume of distribution, low renal clearance, and long terminal half-life of VDS suggest that it undergoes extensive tissue binding and delayed elimination and that drug accumulation may occur with repeated administration at short intervals. Although peak VDS concentrations ranging from 0.1 to 1.0 µmol are achieved with rapid injections, levels typically decline to less than 0.1 µmol in 1 to 2 hours after treatment. Plasma levels achieved with rapid injections are approximately 16-fold higher than those achieved with protracted infusions; however, prolonged periods of exposure above plasma concentrations resulting in cytotoxicity in vitro (0.01 to 0.1 µmol) are readily achieved using protracted infusions (1.2 to 2.0 mg/ml for 2 to 5 days). Renal clearance is negligible, accounting for 1% to 12% of drug disposition. Similar to the other vinca alkaloids, VDS disposition is primarily by hepatic metabolism and biliary clearance, and the cytochrome P-450 isoforom CYP3A plays a major role in drug metabolism.

VINORELBRINE

The pharmacologic behavior of VRL is essentially similar to that of the other vinca alkaloids, with plasma concentrations declining in either a biexponential or triexponential manner. After intravenous administration, there is a rapid decay of VRL concentrations followed by a much slower elimination phase (terminal half-life, 18 to 49 hours). Plasma protein binding has been reported to range from 80% to 91%, with binding primarily to a -acid glycoprotein, albumin, and lipoproteins. Drug binding to platelets is also extensive. The unbound fraction has been reported to range from 0.09 to 0.20.

VRL is widely distributed, and high concentrations are found in virtually all tissues, except brain. The wide distribution of VRL reflects the agent's lipophilicity, which is among the highest of the vinca alkaloids. In fact, drug concentrations in human lung have been demonstrated to be 300-fold greater than plasma levels and 3.4- to 13.8-fold higher than lung concentrations achieved with VDS and VCR, respectively. As with other vinca alkaloids, the liver is the principal excretory organ, and 33% to 35% of the drug is excreted in the feces, whereas urinary excretion represents only 16% to 30% of total drug disposition, the bulk of which is unmetabolized VRL. Studies in humans indicate that 4-O-deacetyl-VRL, 3,6-epoxy-VRL, and several hydroxy-VRL isomers are the principal metabolites. Although most metabolites are inactive, deacetyl-VRL may be as active as VRL. The cytochrome P-450 CYP3A isoform appears to be principally involved in biotransformation. Human studies of powder- and liquid-filled gelatin capsules have shown that bioavailability of the parent compound is 43% for the powder-filled and 27% for the liquid-filled capsules. Plasma concentrations peak within 1 to 2 hours after oral treatment, and interindividual variability is moderate.

DRUG INTERACTIONS

Methotuxate accumulation in tumor cells is enhanced in vitro by the presence of VCR or VBL, an effect mediated by a vinca alkaloid–induced blockade of drug efflux; however, the minimal concentrations of VCR required to achieve this effect occur only transiently in vivo. The vinca alkaloids also inhibit the cellular influx of the epipodophyllotoxins in vitro, resulting in less cytotoxicity, but the clinical ramifications of this effect are unknown. Asparaginase may reduce the hepatic clearance of the vinca alkaloids, particularly VCR, which may result in increased toxicity. To minimize the possibility of this interaction, VCR should be given 12 to 24 hours before l-asparaginase.

Treatment with the vinca alkaloids has precipitated seizures associated with subtherapeutic plasma phenytoin concentrations. Reduced plasma phenytoin levels have been noted from 24 hours to 10 days after treatment with both VCR and VBL. Because of the importance of the cytochrome P-450 CYP3A isoenzyme in vinca alkaloid metabolism, administration of the vinca alkaloids with erythromycin and other inhibitors of CYP3A may lead to severe toxicity. Concomitantly administered drugs, such as pentobarbital and other -receptor antagonists, may also influence VCR clearance by modulating hepatic cytochrome P-450 metabolic processes.

Another potential drug interaction may occur in patients who have Kaposi's sarcoma related to acquired immunodeficiency syndrome (AIDS) and are receiving other agents that affect glucuronidation, such as pentobarbital and H-acid glycoprotein, albumin, and lipoproteins. Asparaginase may reduce the hepatic clearance of VCR by modulating hepatic cytochrome P-450 metabolic processes.

Despite close similarities in structure, the vinca alkaloids differ significantly in their toxicologic profiles. VCR principally induces neurotoxicity characterized by a peripheral, symmetric mixed sensory-motor, and autonomic neuropathy, and altered mental status occurs in 15% to 20% of treated patients. The primary pathologic effects are axonal degeneration and decreased axonal transport due to interference with microtubule function. Initially, only symmetric sensory impairment and paresthesias in a length-dependent manner (distal extremities first) usually are encountered. Neuropathy is more severe, with ataxia, muscle weakness, and weakness of the extremities. In infants, VCR doses are calculated now according to body weight. Patients with antecedent neurologic disorders, such as Charcot-Marie-Tooth disease, hereditary and sensory neuropathy type 1, Guillain-Barré syndrome, and childhood polyneuropathy, are highly predisposed to VCR neurotoxicity. VCR treatment in patients with hepatic dysfunction or obstructive liver disease is associated with an increased risk of developing neurotoxicity because of impaired drug metabolism and delayed biliary excretion.

The only known treatment for VCR neurotoxicity is discontinuation of the drug or reduction of the dose or frequency of treatment. Although a number of antidotes, including thiamine, vitamin B6, folinic acid, and pyridoxine, have been used, these treatments have not been clearly shown to be effective. Results, however, vary with several other protective agents appear promising. In one randomized, double-blind trial, coadministration of glutamic acid and VCR has been demonstrated to decrease neurotoxicity. The adrenocorticotropic hormone (4-9) analogue ORG 2766 has also been shown to protect against VCR-induced neurotoxicity in a randomized, double-blind trial. However, the ORG 2766–treated group as compared to the placebo group may have accounted for this result. Experimental results indicate that several other agents, such as nerve growth factor, insulin-like growth factor I, and amifostine, might alter the natural course of drug-induced neurotoxicity.

Severe neuropathy is observed infrequently with both VBL and VDS. VRL has been shown to have a lower affinity for axonal microtubules than either VCR or VBL, which seems to be confirmed by clinical observations. Milder to moderate peripheral neuropathy, primarily characterized by sensory effects, occurs in 7% to 31% of patients, and constipation and other autonomic effects are noted in 30% of subjects, whereas severe toxicity occurs in 2% to 3%. Muscle weakness, jaw pain, and discomfort at the injection site may also occur. In a study in patients with non–small cell lung cancer randomly assigned to treatment with either VRL alone, VRL plus cisplatin, or VDS plus cisplatin, the rate of severe neurotoxicity was lower in both the single-agent VRL and VBL plus cisplatin arms than in the VDS plus cisplatin arm. Furthermore, the addition of cisplatin did not significantly increase the incidence of severe toxicity in excess of that observed with VRL alone.

Neutropenia is the principal dose-limiting toxicity of VBL, VDS, and VRL. Thrombocytopenia and anemia are usually less common and less severe. The onset of
neutropenia is usually 7 to 11 days after treatment, and recovery is generally by days 14 to 21. Myelosuppression is not typically cumulative. Gastrointestinal toxicities, aside from those caused by autonomic dysfunction, may be caused by all the vinca alkaloids. Gastrointestinal autonomic dysfunction, as manifested by bloating, constipation, ileus, and abdominal pain, occur most commonly with VCR or high doses of the other vinca alkaloids. Mucositis occurs more frequently with VBL than with VRL or VDS and is least common with VCR. Nausea, vomiting, and diarrhea may also occur to a lesser extent. Pancreatitis has also been reported with VRL. 

All vinca alkaloids are potent vesicants and may cause significant tissue damage if extravasation occurs. If extravasation occurs or is suspected, treatment should be discontinued, and aspiration of any residual drug remaining in the tissues should be attempted. The application of local heat and the injection of hyaluronidase, 150 mg subcutaneously, in a circumferential manner around the needle site is thought to minimize both discomfort and latent cellulitis. Phlebitis may also occur along the course of an injected vein, with resultant sclerosis. The risk of phlebitis may increase if veins are not adequately flushed after treatment.

Mild and reversible alopecia occurs in approximately 10% and 20% of patients treated with VRL and VCR, respectively. Acute cardiac ischemia, chest pains without evidence of ischemia, fever without an obvious source, acute pulmonary effects (alone or in combination with mitomycin C), Raynaud's phenomenon, hand-foot syndrome, and both pulmonary and liver toxicity have also been reported with the vinca alkaloids. All the vinca alkaloids have been implicated as a cause of SIADH, and patients who are receiving intensive hydration are particularly prone to severe hyponatremia secondary to SIADH. This entity has been associated with elevated plasma levels of antidiuretic hormone and usual remits in 2 to 3 days. Hyponatremia generally responds to fluid restriction, as with hyponatremia associated with SIADH due to other causes.

The structures of paclitaxel, docetaxel, and their precursor 10-deacetylbaccatin III are shown in Image 72x94 to 272x235. The taxanes are complex esters consisting of a 10-deacetylbaccatin III, an inactive taxane precursor found in the needles and other components of more abundant yew species. The supply of paclitaxel is no longer a limiting issue because the agent is also produced semisynthetically from 10-deacetylbaccatin III and other abundant precursors.

Interest was maintained during this time by the characterization of its novel mechanism of cytotoxic action and the availability of an adequate drug supply for requisite preclinical and limited clinical evaluations. The early search for taxanes of bulk compound for a natural product; and its poor aqueous solubility.

The most common schedule for VBL in combination chemotherapeutic regimens uses a rapid intravenous injection at a dose of 6 mg/m² weekly. Approved dosing recommendations for weekly dosing are 2.5 and 3.7 mg/m² for children and adults, respectively, followed by gradual escalation in increments of 1.8 and 2.5 mg/m² weekly based on hematologic tolerance. It is recommended that weekly VBL doses of 18.5 mg/m² in adults and 12.5 mg/m² in children not be exceeded as a single agent. However, these doses are substantially higher than most patients can tolerate because of myelosuppression, even on less-frequent schedules of administration. Because the severity of leukopenia that may occur with identical VBL doses varies widely, VBL should probably not be given more frequently than once each week.

VDS has been administered intravenously on many schedules, including weekly and biweekly bolus and prolonged infusion schedules. The agent has also been given in fractionated doses as either an intermittent or a continuous infusion over 1 to 5 days. VDS is most commonly administered as a single intravenous dose of 2 to 4 mg/m² every 7 to 14 days. Intermittent or continuous infusion schedules usually employ VDS doses of 1 to 2 mg/m²/d for 1 to 2 days or 1.2 mg/m²/d for 5 days every 3 to 4 weeks.

VRL is usually administered at a dose of 30 mg/m² on a weekly or biweekly schedule as a 6- to 10-minute intravenous injection through a side-arm port into a running infusion (alternatively, a slow bolus injection followed by flushing the vein with 5% dextrose or 0.9% sodium chloride solutions) or as a short infusion over 20 minutes. It appears that the more rapid infusions are associated with less local venous toxicity. Oral doses of 80 to 100 mg/m² given weekly are generally well tolerated, but an acceptable oral formulation has not yet been approved. Other dosing schedules that have been evaluated include chronic oral administration of low doses, intermittent high dose, and prolonged intravenous infusion schedules.

The vinca alkaloids are potent vesicants and should not be administered intramuscularly, subcutaneously, intravesically, or intraperitoneally. Direct intrathecal injection of VCR and other vinca alkaloids, which has occurred as an inadvertent clinical mishap, induces a severe myeloencephalopathy characterized by ascending motor and cranial nerve deficits, and ileus, until toxicity resolves. In clearly palliative situations, dose reductions, lengthened dosing intervals, or selection of an alternative agent may be justified in the event of moderate neurotoxicity. A routine prophylactic regimen to prevent severe autonomic toxicity, particularly severe constipation, is also recommended.

THE TAXANES

The unique chemical structure and mechanism of action of the taxanes, coupled with their antitumor activities against a broad range of cancers, has rendered the taxanes one of the most important new classes of anticancer agents. Interest in the taxanes began in 1963, when a crude extract of the bark of the Pacific yew tree, Taxus brevifolia, was shown to have broad activity in preclinical tumor models. In 1971, paclitaxel was identified as the active constituent of the bark extract. The initial development of paclitaxel was hampered by the limited supply of its primary source; the difficulties inherent in large-scale isolation, extraction, and preparation of bulk compound for a natural product; and its poor aqueous solubility. Interest was maintained during this time by the characterization of its novel mechanism of cytotoxic action and the availability of an adequate drug supply for requisite preclinical and limited clinical evaluations. The early search for taxanes derived from more abundant and renewable resources led to the development of docetaxel, which is synthesized by the addition of a side chain to 10-deacetylbaccatin III, an inactive taxane precursor found in the needles and other components of more abundant yew species. The supply of paclitaxel is no longer a limiting issue because the agent is also produced semisynthetically from 10-deacetylbaccatin III and other abundant precursors.

The structures of paclitaxel, docetaxel, and their precursor 10-deacetylbaccatin III are shown in Figure 19 7-3. The taxanes are complex esters consisting of a 15-member taxane ring system linked to an unusual 4-member oxetan ring. The taxane rings of both paclitaxel and docetaxel (but not 10-deacetylbaccatin III) are linked to an ester side chain attached to the C13 position of the ring, which is essential for antimicrotubule and antitumor activity. The structures of paclitaxel and docetaxel differ in substitutions at the C10 taxane ring position and on the ester side chain attached at C13.
The most impressive clinical activity of paclitaxel has been in patients with ovarian and breast cancers. Paclitaxel initially received regulatory approval in the United States and many other countries for the treatment of patients with ovarian cancer after failure of first-line or subsequent chemotherapy. It subsequently received regulatory approval for patients with advanced breast cancer after failure of combination chemotherapy or at relapse within 6 months of adjuvant chemotherapy. Its use in combination with a platinum compound as primary induction therapy in suboptimally debulked stage II or IV ovarian cancer and as a component of adjuvant chemotherapy after primary local treatment in high-risk patients with early-stage breast cancer has demonstrated a survival advantage in randomized phase III studies. Paclitaxel has also received regulatory approval in the United States for second-line treatment of Kaposi’s sarcoma associated with AIDS, in combination with cisplatin as primary treatment of non–small cell lung cancer, and as a component of adjuvant chemotherapy in high-risk lymph node–positive breast cancer.

Docetaxel initially received regulatory approval in the United States for patients with metastatic breast cancer that has progressed on or relapsed after anthracycline-based chemotherapy, which was later broadened to a general second-line indication. Its role as a component of adjuvant and neoadjuvant chemotherapy after local treatment of early-stage breast cancer and first-line chemotherapeutic agents for locally advanced and metastatic breast cancer is being evaluated. Furthermore, docetaxel has received regulatory approval in many countries for treatment of locally advanced or metastatic non–small cell lung carcinoma and in the United States for treatment of non–small cell lung cancer after failure of cisplatin-based therapy. The clinical antitumor spectra for paclitaxel and docetaxel are similar, with activity noted in many other diverse tumor types that are generally refractory to conventional therapies, including lymphoma, and small cell lung, head and neck, esophageal, endometrial, bladder, and germ cell carcinomas.

MECHANISMS OF ACTION

Schiff et al., Schiff and Horwitz, and Manfredi et al. initially identified the unique mechanism of action for paclitaxel in 1979. The taxanes bind to tubulin polymers (microtubules) at binding sites that are distinct from exchangeable GTP, colchicine, podophyllotoxin, and the vinca alkaloids. Paclitaxel binds preferentially to the N-terminal 31 amino acids of the b-tubulin subunit, although additional sites of interaction on b-tubulin and a-tubulin may also be involved. The binding of paclitaxel to polymerized tubulin is reversible, with a binding constant of approximately 1 µmol. Docetaxel, which most likely shares the same tubulin-binding site as paclitaxel, appears to have a 1.9-fold higher affinity for the site. Tubulin assembly induced by docetaxel also proceeds with a critical protein concentration that is 2.1-fold lower than that of paclitaxel. However, these differences may not translate into greater therapeutic indices for docetaxel in the clinic, as greater potency may also portend more severe toxicity at identical drug concentrations in vivo. Nevertheless, the results of both preclinical and clinical studies suggest that the taxanes may not be completely cross-resistant.

The taxanes stabilize the microtubule network at both ends of the microtubule, suppressing both tumorigenicity and microtubule dynamics. They profoundly alters the tubulin dissociation rate constants at both ends of the microtubule, suppressing both tumorigenicity and microtubule dynamics. On removal of the drug after treatment, even at substoichiometric concentrations that do not increase microtubule mass, cells exit from mitosis but do not continue to proliferate. Instead, the cells undergo apoptosis, and cell death ensues in 2 to 3 days. Although the precise mechanism by which microtubule disturbances lead to apoptosis has not been determined, the taxanes interact with numerous substances, including regulatory molecules and oncoproteins that bind to the mitotic apparatus. Paclitaxel has been reported to induce transcription factors and enzymes that govern proliferation, apoptosis, and inflammation and, interestingly, some of these effects, such as the induction of tumor necrosis factor-a. The taxanes also inhibit angiogenic activity at concentrations below those that induce cytotoxicity.

Both paclitaxel and docetaxel have been shown to enhance the effects of ionizing radiation in vitro at clinically achievable concentrations (<50 nmol) and in vivo, which may relate to the inhibition of cell-cycle progression in the G_{2} phase, which is the most radiosensitive phase of the cell cycle.

MECHANISMS OF RESISTANCE

The best characterized mechanism of resistance to the taxanes is the MDR phenotype, mediated by the 170-kD P-gp efflux pump, encoded by the mdr1 gene (discussed previously in the section "Mechanisms of Resistance"). The MDR protein has been shown to be an efficient transporters of the vinca alkaloids but not of the taxanes. The results of early studies evaluating the role of MDR in the clinic indicate that cross-resistance to the taxanes and anthracene is incomplete, which has significant clinical ramifications in treating breast cancer. Strategies aimed at reversing drug resistance in the clinic with various types of P-gp substrates and inhibitors are also being evaluated, but the interpretation of the results is confounded by the effects of P-gp modulators on taxane clearance.

Several taxane-resistant mutant cell lines that have structurally altered a- and b-tubulin proteins and an impaired ability to polymerize into microtubules have also been identified (discussed previously in the section "Mechanisms of Resistance"). These mutants lack normal interphase mitotic spindles and have an inherently slow rate of microtubule assembly, which is normalized in the presence of the drug. Mutants with "hyposensitive" microtubules exhibit collateral sensitivity to the vinca alkaloids. A number of cell lines resistant to tubulin-binding agents, including the taxanes, have been shown to have alterations in tubulin content, expression of tubulin isoforms, tubulin polymerization dynamics, or tubulin isoform content. Mutations of tubulin isoform genes have also been reported in taxane-resistant cell lines, and b-tubulin gene mutations have been reported to be a strong determinant of paclitaxel resistance in patients with non–small cell lung cancer.

The regulation and integrity of genes that regulate apoptosis, such as p53, bcl-2, and bcl-x, may be determinants of sensitivity to the taxanes. MAP4 are also likely to be involved in these mechanisms of resistance to drug-induced apoptosis, as illustrated by the fact that MAP4, which is negatively regulated by wild-type p53, has been shown to increase the sensitivity to paclitaxel. It has been proposed that paclitaxel induces apoptosis through two different mechanisms—a p53-independent pathway in cells blocked in prophase and a p53-dependent mechanism in cells that accumulate in the G_{2} cell-cycle phase—and requires functional p53. However, there are conflicting data as to the role of p53 as an exponential of cell sensitivity to paclitaxel and other anticancer agents. Several lines of experimental evidence suggest that the induction of p53 in cells treated with paclitaxel represents a mechanism of drug resistance.

The taxanes have also been shown to modulate the function of genes involved in apoptotic regulation and in the disruption of microtubule dynamics by paclitaxel and other antmitotobiole drugs, and docetaxel results in the phosphorylation of such regulatory proteins as Bcl-x and Bcl-2, thereby annulling the antiapoptotic functions of these regulators.

Interestingly, paclitaxel-resistant cell lines, which have mutations in tubulin and fail to exhibit phosphorylation of Bcl-x, after paclitaxel treatment, have been described. These cells demonstrate Bcl-x phosphorylation in the presence of other antmitotobiole agents, suggesting that apoptosis mediated by paclitaxel is related to the drug’s ability to interact with microtubules.
PAUCITAXEL

Pharmacologic studies of paclitaxel on both long and short administration schedules have been performed (discussed later in the section Administration, Dose, and Schedule). Early studies that principally evaluated prolonged (6- to 24-hour) schedules, substantial interpatient variability was noted, and nonlinear, dose-dependent behavior was not observed. As shown in Table 19.7-2, paclitaxel and docetaxel share the following pharmacokinetic characteristics: large volumes of distribution, rapid and avid binding to all tissues except for the unperturbed central nervous system, long terminal half-lives and substantial hepatic metabolism, biliary excretion, and fecal elimination.

TABLE 19.7-2. Taxanes: Comparative Pharmacokinetic and Toxicologic Characteristics

<table>
<thead>
<tr>
<th>Taxane</th>
<th>Pharmacokinetic Parameters</th>
<th>Toxicologic Characteristics</th>
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| Paclitaxel | Terminal half-lives ranging from 11.1 to 18.5 hours were reported. | Drug exposure and the pretreatment plasma concentration of a1–acid glycoprotein had significant (albeit minor) influences on clearance. As with paclitaxel, renal clearance of paclitaxel and metabolites is minimal, accounting for 26% of the administered dose. In humans, cytochrome P-450 mixed-function oxidases are responsible for the bulk of drug disposition, specifically the isoenzymes CYP2C8, and CYP3A4, which metabolize paclitaxel to hydroxylated a1-hydroxytaxol (major) and another hydroxylated metabolite, both of which are inactive. Pharmacodynamic analyses as part of individual phase I and II trials demonstrated that several pharmacokinetic indices of drug exposure can be related to the various toxicities of paclitaxel, the most important and consistent of which is the relationship between the severity of neutropenia and the duration of drug exposure above biologically relevant plasma concentrations ranging from 0.05 to 0.1 µmol. However, a prospective analysis of pharmacokinetic determinants of outcome in several hundred patients with advanced non–small cell lung cancer treated with the combination of cisplatin and paclitaxel at either 135 or 250 mg/m² over 3 hours demonstrated that the magnitude of the steady-state plasma paclitaxel concentration correlated poorly with antitumor activity, disease-free survival, and overall survival.

| Docetaxel | The main pharmacokinetic and toxicologic interactions between paclitaxel and several other chemotherapy agents have been noted. The sequence of cisplatin followed by paclitaxel (24-hour schedule) induces more profound neutropenia than the reverse sequence, which is explained by a 33% reduction in the clearance of paclitaxel after cisplatin. The least toxic sequence—paclitaxel before cisplatin—was demonstrated to induce more cytotoxicity in vitro; therefore, this drug sequence was selected for further clinical development. However, sequence dependence does not appear to be a clinically relevant |

Pharmacologic studies of paclitaxel on both long and short administration schedules have been performed (discussed later in the section Administration, Dose, and Schedule). The oral bioavailability of both paclitaxel and docetaxel is poor, owing in part to the constitutive overexpression of P-gp by enterocytes or first-pass metabolism in the liver or intestines (or both). However, biologically relevant plasma concentrations are transiently achieved if the taxanes are administered orally after treatment with oral cyclosporin or other modulators of P-gp and cytochrome P-450 mixed-function oxidases. As shown in Table 19.7-2, paclitaxel and docetaxel share the following pharmacokinetic characteristics: large volumes of distribution, rapid and avid binding to all tissues except for the unperturbed central nervous system, long terminal half-lives and substantial hepatic metabolism, biliary excretion, and fecal elimination.

Paclitaxel's volume of distribution is much larger than the volume of total body water, indicating extensive drug binding to plasma proteins or other tissue elements, probably tubulin. Plasma protein binding is high (>95%) and readily reversible. Drug binding to platelets is extensive and saturable, and animal distribution studies with radiolabeled paclitaxel indicate extensive drug uptake and retention by virtually all tissues, except for the normal brain and testes. In humans, peak plasma concentrations achieved with 3- to 96-hour schedules (>0.5 to 10 µmol) and drug concentrations in third-space fluid collections, such as ascites (>1 µmol), are capable of inducing significant biologic effects in vitro, but drug penetration into the normal central nervous system is negligible.

The liver is the principal organ involved with paclitaxel clearance, which metabolizes and excretes both paclitaxel and metabolites into the bile. Ninety-eight percent of radioactivity is recovered from feces collected for 6 days after rats are treated with radiolabeled paclitaxel, and approximately 71% of an administered dose of paclitaxel is excreted in the feces over 5 days as either parent compound or metabolites in humans, with 6a-hydroxytaxol being the largest component and accounting for 26% of the dose. Only 5% is unchanged paclitaxel. Renal clearance of paclitaxel and metabolites is minimal, accounting for 14% of the administered dose. In humans, cytochrome P-450 mixed-function oxidases are responsible for the bulk of drug disposition, specifically the isoenzymes CYP2C8, and CYP3A4, which metabolize paclitaxel to hydroxylated 6a-hydroxytaxol (major) and another hydroxylated metabolite, both of which are inactive. Pharmacodynamic analyses as part of individual phase I and II trials demonstrated that several pharmacokinetic indices of drug exposure can be related to the various toxicities of paclitaxel, the most important and consistent of which is the relationship between the severity of neutropenia and the duration of drug exposure above biologically relevant plasma concentrations ranging from 0.05 to 0.1 µmol. However, a prospective analysis of pharmacokinetic determinants of outcome in several hundred patients with advanced non–small cell lung cancer treated with the combination of cisplatin and paclitaxel at either 135 or 250 mg/m² over 3 hours demonstrated that the magnitude of the steady-state plasma paclitaxel concentration correlated poorly with antitumor activity, disease-free survival, and overall survival.

Docetaxel

The pharmacokinetics of docetaxel on a 1-hour schedule are linear at doses of 115 mg/m² or less and optimally fit a three-compartment model. Terminal half-lives ranging from 11.1 to 18.5 hours have been reported. In one population study, plasma concentration data were optimally fit by a three-compartment model, and the following pharmacokinetic parameters were generated: 1/2 of 12.4 hours, clearance of 1 L/h/m², and steady-state volume of distribution of 74 L/m². The most important determinants of docetaxel clearance were the body surface area, hepatic function, and plasma a1–acid glycoprotein concentration, whereas age and albumin level had significant (albeit minor) influences on clearance. As with paclitaxel, renal clearance of paclitaxel and metabolites is minimal, accounting for 26% of the dose. Only 5% is unchanged paclitaxel. Renal clearance of paclitaxel and metabolites is minimal, accounting for 14% of the administered dose. In humans, cytochrome P-450 mixed-function oxidases are responsible for the bulk of drug disposition, specifically the isoenzymes CYP2C8, and CYP3A4, which metabolize paclitaxel to hydroxylated 6a-hydroxytaxol (major) and another hydroxylated metabolite, both of which are inactive. Pharmacodynamic analyses as part of individual phase I and II trials demonstrated that several pharmacokinetic indices of drug exposure can be related to the various toxicities of paclitaxel, the most important and consistent of which is the relationship between the severity of neutropenia and the duration of drug exposure above biologically relevant plasma concentrations ranging from 0.05 to 0.1 µmol. However, a prospective analysis of pharmacokinetic determinants of outcome in several hundred patients with advanced non–small cell lung cancer treated with the combination of cisplatin and paclitaxel at either 135 or 250 mg/m² over 3 hours demonstrated that the magnitude of the steady-state plasma paclitaxel concentration correlated poorly with antitumor activity, disease-free survival, and overall survival.

The main pharmacokinetic and toxicologic interactions between paclitaxel and several other chemotherapy agents have been noted. The sequence of cisplatin followed by paclitaxel (24-hour schedule) induces more profound neutropenia than the reverse sequence, which is explained by a 33% reduction in the clearance of paclitaxel after cisplatin. The least toxic sequence—paclitaxel before cisplatin—was demonstrated to induce more cytotoxicity in vitro; therefore, this drug sequence was selected for further clinical development. However, sequence dependence does not appear to be a clinically relevant

DRUG INTERACTIONS

Both sequence-dependent pharmacokinetic and toxicologic interactions between paclitaxel and several other chemotherapy agents have been noted. The sequence of cisplatin followed by paclitaxel (24-hour schedule) induces more profound neutropenia than the reverse sequence, which is explained by a 33% reduction in the clearance of paclitaxel after cisplatin. The least toxic sequence—paclitaxel before cisplatin—was demonstrated to induce more cytotoxicity in vitro; therefore, this drug sequence was selected for further clinical development. However, sequence dependence does not appear to be a clinically relevant

The main pharmacokinetic and toxicologic interactions between paclitaxel and several other chemotherapy agents have been noted. The sequence of cisplatin followed by paclitaxel (24-hour schedule) induces more profound neutropenia than the reverse sequence, which is explained by a 33% reduction in the clearance of paclitaxel after cisplatin. The least toxic sequence—paclitaxel before cisplatin—was demonstrated to induce more cytotoxicity in vitro; therefore, this drug sequence was selected for further clinical development. However, sequence dependence does not appear to be a clinically relevant
phenomenon on shorter schedules. Treatment with paclitaxel on either a 3- or 24-hour schedule followed by carboplatin has been demonstrated to produce equivalent neutropenia and less thrombocytopenia as compared to carboplatin as a single agent, which is not explained by pharmacokinetic interactions. 228,229 Although sequence dependence has not been noted with carboplatin and paclitaxel in clinical studies, this phenomenon has been noted with other paclitaxel-based chemotherapy combinations, the most important of which involve the anthracyclines. 20 Both neutropenia and mucositis are more severe when paclitaxel on a 24-hour schedule is administered before doxorubicin, compared to the reverse sequence, which is most likely due to an approximately 32% reduction in the clearance of doxorubicin and doxorubicinol when it is administered after paclitaxel. 228,229 Although neither sequence-dependent pharmacologic interactions nor toxicologic interactions between doxorubicin and paclitaxel on a shorter (3-hour) schedule have been noted, pharmacologic interactions occur with both sequences, and combined treatment with paclitaxel (24-hour schedule) and doxorubicin as a bolus infusion has been associated with a higher frequency of congestive cardiotoxicity than either agent alone. 230,231,232,233,234 Similar decrements in the clearance of epirubicin and its metabolites have also been noted in studies of paclitaxel combined with epirubicin, but a similar enhancement of cardiotoxicity has not been observed. 230 The precise etiology for these interactions is unclear; however, competition for the hepatic or biliary P-Gp transport of the anthracyclines with paclitaxel or its polyoxylated castor oil vehicle (or both) is a logical explanation. 229 The vehicle is suspected because similar effects have not been noted with doxetaxel, which is not formulated in polyoxylated castor oil. Hematologic toxicity has been more profound with the sequence of cyclophosphamide before paclitaxel (24-hour schedule) than the reverse sequence. 234 In human tumor xenografts, both paclitaxel and docetaxel have been demonstrated to induce thymidine phosphorylase activity, which may increase the metabolic activation of the oral fluoropyrimidine prodrug capecitabine. 235

Drug interactions may also result from the effects of other classes of drugs on the cytochrome P-450–dependent metabolism of the taxanes. Various inducers of cytochrome P-450 mixed-function oxidases, such as the anticonvulsants phenytoin and phenobarbital, accelerate in the metabolism of both paclitaxel and docetaxel in human microsomal studies and in both children and adults who are concurrently receiving treatment with these anticonvulsants, as manifested by rapid drug clearance and tolerance of high drug doses. 235,236,237,238,239 Conversely, many types of agents that inhibit cytochrome P-450 mixed-function oxidases, such as oral contraceptives, bupropion, fluoxetine, terfenadine, lamotrigine, trimethoprim, propranolol, polyoxylated castor oil vehicle, and corticosteroids, may decrease the metabolism of paclitaxel and docetaxel in human microsomes in vitro; however, the inhibitory concentrations of these agents exceed those achieved in clinical practice, and the clinical relevance of these findings is not known. 237,238,239,240,241,242 Although there has been concern that the use of corticosteroids and different H2-receptor antagonists with variable cytochrome P-450 inhibitory activities as components of predmedication regimens may differentially affect drug clearance and hence toxicity, neither toxicologic nor pharmacologic differences between the agents were noted in a randomized clinical trial. 243

TOXICITY

Myelosuppression is the principal toxicity of paclitaxel and docetaxel. However, despite similar structures, these agents differ modestly in their toxicity spectra.

Paclitaxel

Neutropenia is the principal toxicity of paclitaxel. The onset is usually on days 8 to 10, and recovery is generally complete by days 15 to 21. The main clinical determinant of neutropenia severity is the prior chemotherapy treatment history. Neutropenia is a dose-limiting toxicity and the duration of neutropenia is longer when premedications are not given. Even in heavily pretreated patients, is usually brief. The most important pharmacodynamic determinant of the severity of neutropenia is the duration that plasma concentrations are maintained above biologically relevant levels (0.05 to 0.10 µmol; discussed earlier in the section Pharmacology), which may explain why neutropenia is more severe with longer infusion schedules. 228 This does not necessarily mean that longer schedules will potenti al antitumor activity in the clinic. Instead, most randomized clinical data do not indicate that there is an optimal schedule for any particular tumor, although treatment with higher doses should be considered if shorter schedules are used. 228 At paclitaxel doses exceeding 175 mg/m2 on a 24-hour schedule and 225 mg/m2 on a 3-hour schedule, nadir neutrophil counts are typically less than 500 µL for fewer than 5 days in most courses, even in untreated patients. Even patients who have received extensive prior therapy can usually tolerate doses of 175 to 250 mg/m2 (or 3 or 4 hours). More frequent administration schedules (e.g., weekly treatment) have been associated with less severe neutropenia as compared to single-dose schedules (discussed later in the section Administration, Dose, and Schedule). Severe thrombocytopenia and anemia are unusual, except in heavily pretreated patients.

Although the incidence of major hypersensitivity reactions in early phase I trials approached 30%, the incidence is 1% to 3% with effective prophylaxis. 243,244,245 Most major reactions, which are characterized by dyspnea with bronchospasm, urticaria, and hypotension, occur within the first 10 minutes after the first (and less frequently after the second) treatment and resolve completely after stopping treatment and occasionally occur after treatment with antihistamines, fluids, and vasopressors. Patients who have major reactions have been rechallenged successfully after receiving high doses of corticosteroids, but this approach has not always been successful. 245 Although minor reactions, such as flushing and rashes, have been noted in as many as 40% of patients, minor hypersensitivity reactions do not portend the development of major reactions. The hypersensitivity reactions most likely caused by a nonimmunologically mediated release of histamine or histamine-like substances, owing to the taxane moiety or, more likely, its polyoxylated castor oil vehicle, possibly through complement activation. 246 Although the incidence of major hypersensitivity reactions is reduced with lower administration rates and longer infusion durations, the rates of major reactions are low on both 3- and 24-hour schedules when patients are premedicated with corticosteroids and both H2-receptor and H2-receptor antagonists (discussed later in the section Administration, Dose, and Schedule). In an assessment of the relative safety of two different paclitaxel schedules (3 vs. 24 hours), the rates of major reactions were low and similar (2.1% vs. 1.0%) in patients receiving paclitaxel for 3 or 24 hours, respectively, with premedication. 247

Paclitaxel induces a peripheral neuropathy characterized by sensory symptoms, such as numbness in a symmetric glove-and-stocking distribution. 248,249,250 Neuropathic episodes reveal sensory loss and loss of deep tendon reflexes. Neuropathological studies support a primary disruption of neuronal microtubules resulting in axonal degeneration and demyelination as the primary pathogenic mechanism; however, manifestations suggestive of microtubule disruption resulting in a neuropathy may be noted, particularly at higher doses or when combined with other neurotoxic agents, such as cisplatin. 251 Severe neurotoxicity is uncommon when paclitaxel is given alone at doses below 200 mg/m2 on a 3- or 24-hour schedule every 3 weeks or below 100 mg/m2 on a continuous weekly schedule, but almost all patients experience mild or moderate effects. Symptoms of neurotoxicity may begin as soon as 24 to 72 hours after treatment and higher doses (200 mg/m2 or greater) but usually occur only after multiple courses at 135 to 250 mg/m2 every 3 weeks. Neurotoxicity is generally more pronounced when paclitaxel is administered on short infusion schedules, indicating that peak plasma concentration is a principal determinant. The combination of paclitaxel on a 3-hour schedule and cisplatin is particularly neurotoxic. Motor and autonomic dysfunction may occur, especially at high doses and in patients with preexisting neuropathies due to diabetes mellitus and alcoholism. Transient myalgia, usually noted 24 to 48 hours after therapy, is also common, and a myopathy has been described in patients receiving high doses with cisplatin. Although several measures, such as the administration of amifostine, glutamate, and pyridoxine, appear to reduce the neurotoxic effects of paclitaxel in animal models and in patients, the precise mechanism of the neurotoxicity remains unknown. 252 Although major peripheral neuropathy is associated with paclitaxel, the exact mechanism is not known. 252,253,254,255 Paclitaxel causes cyclic cardiac disturbances, but the clinical relevance of these effects is not known. 252,256,257,258 The most common rhythm disturbance, a transient bradycardia, was noted in 29% of patients in one trial. 254,257,258 Isolated asymptomatic bradycardia without hemodynamic effects does not appear to be an indication for discontinuing paclitaxel. More important bradycardythmias, including Mobitz I (Wenckebach syndrome), Mobitz type II, and third-degree heart block, have been noted, but the incidence in a large National Cancer Institute database was only 0.1%. 254 Most documented episodes have been asymptomatic. These events primarily occurred in patients enrolled in early trials that required continuous cardiac monitoring, indicating that second- and third-degree heart block are likely underreported because such monitoring is not usually performed. These bradycardythmias are probably caused by paclitaxel, as related taxanes affect cardiac autonomic and different bradycardic disturbances have been noted in animal models in which animals who have ingested various species of young plants. Myocardial infarction, cardiac ischemia, atrial arrhythmias, and ventricular tachycardia have been noted, but there whether there is a causal relationship between paclitaxel and these events is uncertain.

There is no evidence that chronic, long-term treatment with paclitaxel causes progressive cardiac dysfunction. Routine cardiac monitoring during paclitaxel therapy is not necessary but is advisable for patients who may not be able to tolerate bradycardythmias, such as those with atrialventricular conduction disturbances or ventricular dysfunction. Although patients with a wide range of cardiac abnormalities and cardiac histories were broadly and empirically restricted from participating in early clinical trials, paclitaxel treatment has been reported to be well tolerated in a small series of gynecologic-treatment cancer patients with major cardiac risk factors. 259 On the other hand, repetitive treatment of patients with the combined regimen of paclitaxel on a 3-hour schedule and doxorubicin as a brief infusion is associated with a higher frequency of congestive cardiotoxicity than would be expected to occur with the same cumulative doxorubicin dose given without paclitaxel (discussed previously in the section Drug Interactions) in one study of previously untreated women with advanced breast cancer treated with escalating doses of paclitaxel as a 3-hour infusion and doxorubicin, 60 mg/m2 to a cumulative dose of 480 mg/m2, which would be predicted to result in a lower than 5% incidence of congestive
Intriguing results were initially obtained with more protracted schedules, such as a 96-hour infusion schedule in patients with advanced breast cancer. However, the incidence of fluid retention typically occurred during the first two courses and within minutes after the start of treatment. Signs and symptoms generally resolve within 15 minutes after cessation of treatment, and docetaxel is usually able to be reintroduced without sequelae after treatment with an H₂-receptor antagonist. However, most hypersensitivity reactions are minor. Both the incidence and severity of hypersensitivity reactions appear to be reduced by premedication with corticosteroids and H₁ and H₂-receptor antagonists. Recall reactions in previously irradiated sites have also been noted.

**Docetaxel**

Neutropenia is the principal toxicity of docetaxel. At a dose of 100 mg/m², neutrophil counts are below 500/µL in most patients. Similar to paclitaxel, the onset of neutropenia occurs on approximately day 8, and complete resolution typically occurs by days 15 to 21. As with paclitaxel, neutropenia is significantly less when low doses are administered frequently (i.e., on a weekly schedule; discussed later in the section Administration, Dose, and Schedule). The most important determinant of neutropenia is the extent of prior treatment. Significant effects on platelets and red blood cells are uncommon.

Although docetaxel is not formulated in polyoxycarbonylated castor oil, hypersensitivity reactions have been reported in approximately 31% of patients receiving docetaxel without premedications in early phase II studies. As with paclitaxel, major reactions characterized by dyspnea, bronchospasm, and hypotension typically occur during the first two courses and within minutes after the start of treatment. Signs and symptoms generally resolve within 15 minutes after cessation of treatment, and docetaxel is usually able to be reintroduced without sequelae, occasionally after treatment with an H₂-receptor antagonist. However, most hypersensitivity reactions are minor. Both the incidence and severity of hypersensitivity reactions appear to be reduced by premedication with corticosteroids and H₁ and H₂-receptor antagonists. Like paclitaxel, patients who experience major reactions have been retreated successfully after the resolution of symptoms and after treatment with corticosteroids and H₂-receptor antagonists.

**Skin toxicity** may occur in as many as 50% to 75% of patients; however, premedication may reduce the overall incidence of this effect. An erythematous pruritic maculopapular rash that affects the forearms, hands, or feet is typical. Other cutaneous effects include desquamation of the hands and feet, palmar-plantar erythrodysesthesia that may respond to pyridoxine or cooling, pruritic maculopapular rash that affects the forearms, hands, or feet, and diarrhea have also been observed.

**Drug-related gastrointestinal effects**, such as vomiting and diarrhea, are uncommon. Higher paclitaxel doses may cause mucositis, especially in patients with leukemia who may be more prone to mucosal barrier breakdown or in patients receiving 96-hour infusions. Rare cases of neutropenic enterocolitis and gastrointestinal necrosis have been noted, particularly in patients given high doses of paclitaxel in combination with doxorubicin or cyclophosphamide. Severe hepatotoxicity and pancreatitis have also been noted, but these events are rare. Acute bilateral pneumonitis has been reported in fewer than 1% of patients treated on a 3-hour schedule in one series, and both interstitial and parenchymal pulmonary toxicity have been reported, but clinically significant pulmonary effects are uncommon.

Paclitaxel also induces reversible alopecia of the scalp, but all body hair is usually lost with cumulative therapy. Although the agent is often not considered a vesicant, extravasation of large volumes can cause moderate soft tissue injury. Inflammation at the injection site and along the course of an injected vein may occur. Alopecia also occurs in most patients. Nails disorders have been reported, particularly in patients treated on weekly schedules.

**ADMINISTRATION, DOSE, AND SCHEDULE**

**Docetaxel**

Intriguing results were initially obtained with more protracted schedules, such as a 96-hour infusion schedule in patients with advanced breast cancer. Nearly identical results have been obtained in a phase III study in patients with metastatic breast cancer, in which efficacy was not increased in patients treated with paclitaxel doses greater than 175 mg/m² on a 3-hour schedule. The following doses have been recommended on less conventional schedules: 200 mg/m² over 1 hour as either a single dose or 3 divided doses every 3 weeks; 140 mg/m² over 96 hours every 3 weeks; and 80 to 100 mg/m² over 24 hours every 3 weeks.
mg/m² weekly. The most common schedules evaluated in patients with AIDS-associated Kaposi’s sarcoma are paclitaxel, 135 mg/m² over 3 or 24 hours every 3 weeks, and 100 mg/m² every 2 weeks. Paclitaxel has also been administered into the pleural and peritoneal cavities. Biologically relevant plasma concentrations have been achieved with intraperitoneal administration, and concentrations in the peritoneal cavity are several orders of magnitude greater than plasma concentrations.

The following premedication is recommended to prevent major hypersensitivity reactions: dexamethasone, 20 mg orally or intravenously, 12 and 6 hours before treatment; an H₂-receptor antagonist (such as diphenhydramine, 50 mg intravenously) 30 minutes before treatment; and an H₂-receptor antagonist (such as cimetidine, 300 mg; famotidine, 20 mg; or ranitidine, 150 mg intravenously) 30 minutes before treatment. A single dose of a corticosteroid (dexamethasone, 20 mg intravenously) administered 30 minutes before treatment has been reported to confer very effective prophylaxis of major hypersensitivity reactions. Contact of paclitaxel with plasticized polyvinyl chloride equipment or devices must be avoided because of the risk of patient chloride exposures to plasticizers that may be leached from polyvinyl chloride infusion bags or sets. Paclitaxel solutions should be diluted and stored in glass or polypolyethylene bottles or suitable plastic bags (polypropylene or polylef in) and administered through polyethylene-lined administration sets that include an in-line filter with a microporous membrane not greater than 0.22 μm.

The extensive involvement of hepatic metabolism and biliary excretion in the disposition of paclitaxel—similar to that of other anticancer drugs, such as the vinca alkaloids—in which dose modifications are required indicates that doses should be modified in patients with hepatic dysfunction. Official recommendations have not been formulated, but prospective evaluations indicate that patients with moderate to severe elevations in serum concentrations of hepatocellular enzymes or bilirubin (or both) are more likely to develop severe toxicity than patients without hepatic dysfunction. Therefore, it would be prudent to reduce paclitaxel doses by at least 50% in patients with moderate or severe hepatic excretory dysfunction (hyperbilirubinemia) or significant elevations in hepatic transaminases. Renal clearance contributes minimally to overall clearance (5% to 10%), and patients with severe renal dysfunction do not appear to require dose modification. Based on the pharmacologic behavior, particularly the wide distributive properties of the taxanes, dose modifications are not required solely for peripheral edema and third-space fluid collections.

**Docetaxel**

In the United States, docetaxel is indicated at a dose range of 60 to 100 mg/m² and 75 mg/m² over 1 hour in patients with breast and non–small cell lung cancers, respectively, but most early clinical trials in advanced breast, ovarian, and non—small cell lung cancers evaluated doses in the higher end of this range (75 to 100 mg/m²), with scant data available for patients treated at 60 mg/m². Although some untreated or minimally pretreated patients generally tolerate docetaxel at a dose of 100 mg/m² without severe toxicity, emerging data indicate poorer tolerance in more heavily pretreated patients in whom 75 mg/m² appears to be more reasonable from a toxicologic perspective. Like paclitaxel, docetaxel has also been administered as a 1-hour infusion weekly. Although there are no clear benefits of chronic weekly drug administration in terms of antitumor activity, hematologic toxicity is much less than with conventional dose schedules, with a high incidence of cumulative asthenia and neurotoxicity noted with docetaxel doses exceeding 36 mg/m²/wk.

A retrospective review of docetaxel pharmacokinetics in patients without hyperbilirubinemia demonstrated that docetaxel clearance is reduced by approximately 25% in patients with elevations in serum concentrations of both hepatic transaminases (1.5-fold or greater) and alkaline phosphatase (2.5-fold or greater), regardless of whether the elevations are due to hepatic metastases. Therefore, dose reductions by at least 25% are recommended for such individuals. More substantial reductions (50% or greater) may be required in patients who have moderate or severe hepatic excretory dysfunction (hyperbilirubinemia). As with paclitaxel (discussed previously in the section *Administration, Dose, and Schedule, Paclitaxel*), there is no rationale for dose modification solely for renal deficiency or third-space fluid accumulation (or both). Also similar to the case with paclitaxel, glass bottles or polypolyethylene or polylef in plastic products should be used for preparation and storage, and docetaxel should be administered through polyethylene-lined administration sets.

**ESTRAMUSTINE PHOSPHATE**

Estramustine phosphate (Fig. 19.7-4) is a conjugate of the alkalizing agent nonimustine mustard linked to 17b-estradiol by a carbamate ester. This agent was originally designed so that estramustine would accumulate specifically in estrogen receptor–bearing breast cancer cells via the 17b-estradiol component followed by degradation of the carbamate ester and release of the alkylating nor-nitrogen mustard moiety. Estramustine phosphate, however, did not demonstrate useful anticancer activity in clinical trials in breast cancer and, thereafter, it was determined that alkylation of DNA did not occur. Further investigations later established that preferential accumulation of radiolabeled estramustine phosphate in the ventral prostate of rats occurred unrelated to the estrogen receptor. This selective accumulation was mediated by the presence of a specific protein in prostate tissue, subsequently labeled *estramustine-binding protein (EMBP)*. Clinical studies of estramustine phosphate were initiated in advanced prostate cancer based on this unique pattern of drug distribution. Anticancer activity was subsequently demonstrated in prostate cancer patients with disease refractory to diethylstilbestrol.

![Figure 19.7-4](https://example.com/fig19.7-4.png)

**FIGURE 19.7-4.** Structure of estramustine phosphate undergoing dephosphorylation to estramustine.

**MECHANISMS OF ACTION**

Several mechanisms of cytotoxic activity have been attributed to estramustine phosphate. The preponderance of data indicates that cell death is principally mediated through a direct effect on microtubules. Estramustine is known to inhibit mitotic microtubule networks and to depolymerize interphase microtubules. Consonant with other antimicrotubule agents, estramustine-treated cells arrest in the G₂/M phase of the cell cycle and then undergo apoptosis. Estramustine inhibits microtubule function through direct binding to b-tubulin independent of MAPs while also inhibiting microtubule function through an interaction with MAPs. Once bound to tubulin, estramustine inhibits the dynamic growth and shortening of microtubules. Like the taxanes, estramustine can also exert an antiproliferative effect via stabilization of spindle microtubules. The binding of estramustine to b-tubulin, however, occurs at a unique site distinct from those of the taxanes, colchicine, and vinca alkaloids. Finally, the antimicrotubule effects of estramustine are mediated by the intact conjugate and not the individual nor-nitrogen or estradiol components.

The specific binding of estramustine and its metabolite, estromustine, to EMBP permits tissue selectivity for estramustine accumulation and action. After exposure to estramustine, cell lines that contain high levels of EMBP exhibit a greater fraction of cells arresting in the G₂/M phase as compared to those with low levels of EMBP expression. Proteins similar to EMBP have also been found in other tumors, including gliomas and astrocytomas. Because estramustine phosphate induces a G₂/M block, crosses the blood–brain barrier, and accumulates in gliomas and astrocytomas, the potential for estramustine selectively to sensitize central nervous system tumor cells to irradiation is an area of active investigation.
MECHANISMS OF RESISTANCE

Investigations with cell lines made resistant to estramustine have characterized several mechanisms of acquired drug resistance. Consistent with its antimicrotubule mechanism of action, resistance to estramustine can be mediated by alterations at the site of estramustine-tubulin interaction, increased microtubule stability through overexpression of specific tubulin isoforms, or alterations in MAPs. A drug efflux mechanism, distinct from classical MDR, has been described.

The targets of estramustine—β-tubulins—are composed of multiple isoforms encoded by separate cellular genes. An increase in β2- and β3-β-tubulin isoforms relative to other β-tubulin isoforms occurs in human prostate cancer cells rendered eight- to ninefold resistant to estramustine. Although the precise site of estramustine binding is not known, microtubules containing β2- and β3-tubulin isoforms appear to bind estramustine less efficiently as compared to either other β-tubulins or a-β-tubulin. Furthermore, tubulin isoforms differ from one another principally at MAP binding sites. Because the binding of different β-tubulin subtypes to a-β-tubulin alters the dynamic properties of microtubule growth and stability, a change in the relative β-tubulin isoforms may counter the inhibitory and destabilizing effects of estramustine on microtubule assembly.

Some prostate cancer cell lines with acquired resistance to estramustine overexpress the MAP tau. The capacity to maintain microtubule stability and kinetics involves the interaction of tubulin with MAPs. Exposure to estramustine induces both quantitative and qualitative changes in tau, leading to a sevenfold increase in estramustine resistance in some cell lines. To what extent alterations in tau or other altered MAPs contribute to clinical estramustine resistance is not known.

Although estramustine can bind to the classical MDR efflux pump, P-gp-overexpressing cells are not cross-resistant to estramustine. Estramustine may, in fact, act as a competitive inhibitor of P-gp action, reducing the efflux of other cytotoxic agents subject to P-gp-mediated resistance. A drug efflux mechanism distinct from P-gp has been described that is distinct from P-gp and can mediate estramustine resistance. Some cell lines with acquired estramustine resistance exhibit a sixfold resistance to estramustine commensurate with the degree of overexpression of the gene encoding this new efflux pump.

PHARMACOLOGY

After oral administration, estramustine phosphate undergoes rapid dephosphorylation within the gastrointestinal tract, as shown in Figure 19.7-4. The bioavailability of oral estramustine phosphate is 37% to 75%. The majority of absorbed estramustine is rapidly metabolized to an oxidized isomer, estromustine, which is the principal component detected in the plasma. Maximal estramustine plasma concentrations are reached within 2 to 4 hours after oral consumption, and the mean estramustine half-life is 14 hours. Estramustine pharmacokinetics are linear over the usual administered oral doses of estramustine phosphate. Peak plasma concentrations in patients treated chronically with oral estramustine phosphate at 560 mg/d have been 227 ng/mL for estromustine, 23 ng/mL for estramustine, and 95 ng/mL for estrone and 9.3 ng/mL for estradiol.

Further hydrolysis of the estromustine and estramustine carbamate linker in the liver yields estrone and estradiol, respectively, and the nor-nitrogen group. Studies of oral and intravenously administered radiolabeled estramustine phosphate indicate that estromustine and estramustine and their metabolites are largely excreted in the feces, with only small amounts of conjugated estrone and estradiol found in the urine (<1%).

In contrast to oral administration, intravenous estramustine phosphate delivers significantly higher plasma concentrations of estramustine phosphate and metabolites while reducing the marked interpatient variability noted for the oral route. Intravenous estramustine phosphate is currently investigational in the United States.

DRUG INTERACTIONS

Coadministration of food or dairy products significantly impairs the absorption of estramustine phosphate. Calcium-rich foods appear to lead to the formation of a poorly absorbable calcium complex. Current recommendations include fasting before the oral administration of estramustine phosphate and avoidance of calcium-rich foods and calcium antacids.

Preliminary evidence suggests that oral estramustine phosphate, when coadministered with intravenous docetaxel, significantly delays the clearance of docetaxel, with disproportionate increases in docetaxel concentrations. This has led to a reduction in the recommended dose for docetaxel when combined with estramustine phosphate despite the fact that, for the most part, these two agents have nonoverlapping toxicities. The mechanism by which estramustine impairs docetaxel clearance is not known.

TOXICITY

Nausea and vomiting, which are the principal toxicities encountered with oral estramustine phosphate, may infrequently necessitate discontinuation. At conventional dosing schedules, nausea and vomiting can be prevented by antiemetic therapy. Diarrhea has also been observed in some patients with chronic use. Myelosuppression is not associated with estramustine phosphate when administered as a single agent.

Commonly observed estrogenic side effects of estramustine therapy include gynecomastia, nipple tenderness, and fluid retention. Caution should be exercised in prescribing estramustine phosphate to patients with congestive heart failure because of the risk for fluid retention and edema. Thromboembolic complications represent the most hazardous toxicity of estramustine phosphate therapy and may occur in as many as 10% of patients. These include venous thrombosis, pulmonary emboli, and cerebrovascular and coronary thrombotic events. Transient elevations in hepatic transaminases occur in approximately one-third of patients receiving estramustine phosphate therapy. The rate of hepatic toxicity is similar to that described for diethylstilbestrol in a randomized study of estramustine phosphate versus diethylstilbestrol.

ADMINISTRATION, DOSE, AND SCHEDULE

Estramustine phosphate is approved for the treatment of metastatic prostate cancer, particularly hormone-refractory disease. The recommended daily dose of estramustine phosphate (available as a 140-mg capsule) is 14 mg/kg of body weight given in three to four divided doses, though most patients are usually treated in the dosing range of 10 to 16 mg/kg. Patients should be instructed to take estramustine phosphate with water at least 1 hour before or 2 hours after meals. Patients are generally treated for 30 to 90 days before assessment of therapeutic benefit. Chronic oral therapy can be maintained for months or even years as long as the patients exhibit a sixfold resistance to estramustine commensurate with the degree of overexpression of the gene encoding this new efflux pump.

NOVEL COMPOUNDS TARGETING MICROTUBULES

Many other structurally—and functionally—unique antimicrotubule compounds are the focus of discovery efforts, preclinical development, and clinical evaluations. Although the majority of efforts are being directed toward agents that interfere with tubulin, other potential strategic components of the microtubule, including motor proteins, are the focus of discovery and developmental efforts.

The successes with the taxanes have provided the impetus to discover new chemotypes that work by a similar mechanism but yet have higher therapeutic indices. Several natural products that are structurally dissimilar to the taxanes, share their mechanism of action, and show comparable activities have been identified. For example, rhazinilam, like paclitaxel, originates from tree bark but is the first nontaxane identified that induces cold-stable tubulin polymerization in vitro and microtubule bundling in cells. Unlike paclitaxel, rhazinilam is capable of inducing tubulin polymerization at 0°C; however, the resulting polymerized product is unstable. In contrast, discodermolide, which originates from a marine sponge, polymerizes tubulin at 37°C in vitro more potently and rapidly than does paclitaxel,
yielding polymerization products that are cold-stable, and it polymerizes tubulin almost as rapidly at 0°C.


The primary action of HHT appears to be inhibition of protein synthesis, with degradation of polyribosomes, delayed inhibition of initiation of protein synthesis, and inhibition of chain elongation by interference with peptide bond formation. DNA effects may also be important, with a block in progression of cells from G1 into S phase and from G2 phase into M phase. Prolonged drug exposure is necessary for maximal antileukemic effect in vitro. Preclinical toxicity identified toxicities of the bone marrow, gastrointestinal tract, kidneys, and heart. Radiolabeled HHT exhibits a triphasic plasma decay, with a terminal half-life of 65.3 hours and an apparent volume of distribution of 2.4 L/kg. In early phase I studies, HHT was administered as a daily 10- to 360-minute infusion for up to 10 days. Dose-limiting cardiovascular toxicity with hypotension began 4 or more hours after drug administration, which is presumed secondary to vasodilatation with a compensatory increase in cardiac output. Hypotension is ameliorated by interrupting the infusion or by fluid administration, or both, and prolonging the duration of administration. The major dose-limiting toxicity with currently used infusion schedules is myelosuppression.

Initial clinical studies with HHT conducted in China identified activity against acute myeloid leukemia and chronic-phase chronic myelogenous leukemia (CML). Clearing of central nervous system blasts occurred after intrathecal administration. Variable activity was observed in the initial series of phase II trials in U.S. pediatric and adult patients with acute leukemia or myelodysplastic syndrome. In late chronic-phase CML, a continuous intravenous infusion of HHT, 2.5 mg/m²/d, for 10 to 14 days each month induces complete hematologic remission in 72% of cases, with cytogenetic response in 31%. HHT is being combined with interferon or cytarabine in early chronic-phase CML. O'Brien et al. reported that HHT followed by interferon did not achieve a higher cytogenetic response rate than previously observed with HHT alone.

Nonmyelosuppressive toxicities have been minimal, including diarrhea, hyperglycemia, nausea and vomiting, tachycardia, chest pain, headache, and fatigue.

SURAMIN

Suramin is a polysulfonated naphthylurea first used for the treatment of onchocerciasis and trypanosomiasis in the 1920s. Its use against parasites and dicoid lupus erythematosus was abandoned because of the availability of more effective drugs. Its inhibition of reverse transcriptase and other RNA polymerases led to trials in patients with autoimmune deficiency syndrome. However, initial clinical enthusiasm was not substantiated by additional study.

The precise mechanism of suramin's antitumor action is unknown. The drug binds nonspecifically to a wide variety of plasma proteins and enzymes. It inhibits the binding and mitogenic action of many polypeptide autocrine growth factors, including platelet-derived growth factor, fibroblast growth factor, transforming growth factor-a and -b, epidermal growth factor, insulin-like growth factor-1 and -2, interleukin-2, transferrin, and nerve growth factor. It is capable of dissociating growth factors from their receptors, with higher affinity to heparin binding growth factors. It interferes with glycosaminoglycan catabolism, leading to an accumulation in the liver and blood of heparan sulfate and dermatan sulfate, which are thought to be related to cell proliferation. Suppression of bone resorption may contribute to the decreased pain reported in patients with prostate cancer.

Suramin exhibits antitumor activity against a number of cell lines, notably growth factor-responsive tumors, but low doses induce proliferation in some cell lines. It inhibits the growth of malignant, but not normal, prostate cells. Early clinical trials suggested activity against adrenal, renal, and other cancers. Activity in prostate cancer has led to phase III studies.

CLINICAL PHARMACOLOGY

Suramin has limited absorption from the gastrointestinal tract. The intravenous route is recommended because of better bioavailability.

The original dosing schedule of 1 g weekly for 6 weeks resulted in plasma concentrations that fell over the first few hours after administration but gradually increased over time, with increasing trough levels before each injection. The pharmacokinetics were described by a two-compartment model, with an initial (distribution) half life (t1/2a) of 2 days and an elimination half life (t1/2b) of 48 days (range, 44 to 54 days). Suramin is 99.7% protein bound, primarily to albumin, and may persist in the blood for 3 months after administration, with no evidence of metabolism and 80% renal clearance. The total body clearance is only 0.41 mL/min, with little interpatient variability. Suramin does not cross the blood–brain barrier. It may displace other highly protein-bound drugs.

DOSE AND SCHEDULE

The optimal schedule of administration is still being determined. Earlier schedules used adaptive control feedback in which the timing and calculated dose were pharmacologically computed for individual patients to maintain plasma concentrations in the range of 200 to 300 µg/mL. Labor-intensive
pharmacologic monitoring was used because of concern that the severe neurologic toxicity with suramin was directly correlated with high blood levels. More recently, other pharmacokinetic correlations have been postulated, including time above a threshold concentration, total dose, and others. The relative importance of free drug concentration is unknown. However, several phase I studies have determined that concentrations in the 200 to 300 µg/mL range are better tolerated overall. Phase I studies have demonstrated little pharmacokinetic variability, making complex adaptive control algorithms unnecessary. This observation has led to investigation of a wide variety of schedules, including a 14-day continuous infusion, intermittent short infusions, and intermittent bolus administration.

Suramin has modest activity in patients with prostate cancer. Combinations with other agents have been studied in prostate cancer and other solid tumors, but without clear additive benefit. The future of this drug is uncertain.

TOXICITY
The most serious toxic effect of suramin is a polyneuropathy, which may begin within several weeks of therapy and peaks in severity 3 to 6 months after the drug is discontinued. It ranges from mild stocking-glove paresthesia to paralysis requiring mechanical ventilation, and it is an indication to discontinue treatment. At 350 mg/m² by continuous infusion, a Guillain-Barré syndrome occurred in 11% of patients; the incidence increased to 40% with levels of more than 350 µg/mL. Suramin may lead to a progressive, reversible myopathy; hyperesthesia of palms and soles; headache; and altered taste. Adrenal insufficiency is very common and may be irreversible. All patients receive concurrent corticosteroids until normal adrenal function can be documented.

Infections are frequent with suramin therapy because the drug induces lymphocytotoxicity and myelosuppression and inhibits phagocytosis and bacterial killing, which is compounded by the addition of hydrocortisone.

Other common toxicities include renal dysfunction, transaminase elevations, and coagulopathy. Prophylactic vitamin K has been used to minimize the contribution from other causes. Bleeding is managed by replacement of blood and plasma. Heparin can be given safely using careful monitoring. An increase in serum creatinine or the development of a coagulopathy necessitates interruption of therapy. Other serious toxicities include supraventricular arrhythmias, especially atrial fibrillation, pericardial effusions, and deep venous thromboses.

Rash has been reported, occasionally with desquamation or toxic epidermolysis as well as keratoacanthomas and superficial actinic keratoses. Vortex keratopathy, which resolves after therapy, also has been reported. Metabolic consequences include hyponatremia, hypokalemia, hypocalcemia, hypermagnesemia, hypophosphatemia, hypouricemia, and elevations in amylase and lipase. Rash and renal dysfunction may not recur if the drug is resumed.

Bleomycin
The bleomycins are a group of glycopeptides originally extracted from a strain of Streptomyces verticillus from culture broths obtained from the soil of a Japanese coal mine. The most active agent was a mixture of peptides now known as bleomycin, with a molecular weight of 1200.

The primary action of bleomycin is to produce single- and double-strand DNA breaks, which result from the production of free radicals by an Fe(II)-bleomycin complex intercalated between opposing strands of DNA. It is ineffective in producing strand breaks of native RNA or synthetic ribonucleotide polymers. Cells are most sensitive to bleomycin during the G₂ and M phases and least sensitive in the G₁ phase. Noncycling cells may be more sensitive than cycling cells. The observation that cells were killed during G₂ suggested an advantage for a continuous infusion, which was not supported by clinical trials.

CELLULAR PHARMACOLOGY
Bleomycin is taken up by cells slowly and inactivated by an aminohydrolase found in normal and malignant cells. Hydroxide levels are higher in animal species resistant to the pulmonary toxicity of bleomycin and is low in lung and skin, the two organs most susceptible to bleomycin toxicity. Levels in tumor cell lines do not appear to correlate with drug resistance.

CLINICAL PHARMACOLOGY
Using a 4- to 5-day continuous intravenous infusion, the steady-state concentration is approached approximately 12 hours after initiation of infusion and ranged from 0.132 to 0.312 mµg/mL. After an intravenous bolus of 15 U/m², peak plasma concentrations reach 1 to 10 mµg/mL, with a rapid two-phase disappearance from plasma with a half-life of elimination of approximately 3 hours. Approximately two-thirds of excretion is renal, and the half-life increases rapidly in patients with a creatinine clearance of less than 25 to 35 mL/min. There is increased pulmonary toxicity with renal insufficiency, but no formal guidelines for dose reduction have been determined. Bleomycin is absorbed rapidly after intramuscular administration, resulting in peak plasma concentrations approximately one-third to one-half of those obtained after rapid intravenous administration. One hour after intramuscular injection, maximum serum levels range from 0.13 to 0.35 mµg/mL, with no drug detectable in the serum 24 hours after injection. Absorption after subcutaneous injection has not been clearly defined. Intracavitary administration of bleomycin achieves levels 10- to 20-fold higher than simultaneous plasma levels and is effective in the control of malignant effusions. Approximately 46% of the intracavitary dose is absorbed into systemic circulation. Bleomycin also has been applied topically. No pharmacologic advantage to intraperitoneal administration has been reported.

TOXICITY
A test dose of 1 mg of bleomycin is generally administered before a weekly or twice-weekly dose of 5 to 15 U/m² by continuous infusion, a Guillain-Barré syndrome occurred in 11% of patients; the incidence increased to 40% with levels of more than 350 µg/mL.

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TOXICITY
A test dose of 1 mg of bleomycin is generally administered before a weekly or twice-weekly dose of 5 to 15 U/m² because of the risk of hypersensitivity with urticaria, periorbital edema, and bronchospasm. The dose-limiting toxicity of bleomycin is pulmonary fibrosis of uncertain pathogenesis, which occurs in 10% of patients and is more common in patients older than 70 years, with doses of more than 400 U, or in those with a history of chest radiotherapy and in the postoperative period. The onset is usually delayed, and the initial physical examination and chest x-ray may be normal. Eventually, rales, rhonchi, and pleural friction rubs are noted, and abnormal pulmonary function, with decreased lung capacity and increased lung stiffness, is seen. Clinical parameters better predict outcome than pulmonary function studies. Chest x-ray may reveal increased interstitial markings, patchy reticulonodular infiltrates, consolidation, or nodules indistinguishable from metastatic lesions, which may cavitate. Biopsy findings are nonspecific. After the drug is discontinued, reversal may take months, and fibrosis may be only partially reversible and may be fatal. A number of investigational approaches are being evaluated to prevent or reduce the severity of this complication.

Myelosuppression and immunosuppression are not prominent. Fevers occur in 20% to 50% of patients, occasionally with hyperpyrexia. Mucocutaneous toxicities are common, with mucositis, alopecia, and hyperpigmentation, erythema, induration, hyperkeratosis, and peeling that may progress to ulceration. The digits, hands, joints, and areas of prior radiation or surgery are most affected. Acute arthritis may occur.

L-ASPARAGINASE
The growth of malignant and normal cells depends on the availability of specific nutrients and cofactors required for protein synthesis. Some nutrients can be synthesized within the cell, whereas others, such as essential amino acids, require exogenous sources. L-asparagine is a nonessential amino acid synthesized by the transamination of L-aspartic acid by a reaction catalyzed by the enzyme L-asparagine synthetase. The ability to synthesize asparagine is notably lacking in malignancies of lymphoid origin. In 1953, Kidd first reported that the growth of transplantable lymphomas of rat and mouse was inhibited by guinea pig serum, and subsequent experiments demonstrated that the responsible factor was L-asparaginase. Subsequent purification from Escherichia coli and Erwinia carotovora permitted production of large quantities of the enzyme for clinical use. The purified bacterial enzyme has a molecular weight of 133,000 to 141,000 daltons and is composed of four subunits, each with one active site. The enzymes are specific for the L-isomer. Asparaginase catalyzes the conversion of L-asparagine to aspartic acid and ammonia. The enzyme does not enter cells, instead circulating asparagine to aspartic acid, which cannot be converted to asparagine by the cancer cell. In contrast, most normal cells can synthesize asparagine from aspartic acid by induction of asparagine synthetase. This metabolic difference is not absolute, as demonstrated by the toxicity profile of the agent. Resistance occurs through increased expression of the asparagine synthetase gene, which is transcriptionally silent in most tissues and leads to increased enzyme synthesis in response to a decrease in intracellular L-asparagine levels. Resistance may also be mediated by the formation of asparaginase antibodies that alter asparaginase pharmacokinetics.
L-asparaginase is administered either intravenously or intramuscularly. The intramuscular route produces peak blood levels 50% lower than the intravenous route, but the former may be less immunogenic and is more commonly used. Three preparations of L-asparaginase are in clinical use. The most widely used is derived from E. coli, and an Erwinia preparation is available for patients who develop hypersensitivity to the E. coli–derived agent. The usual doses are 6000 IU/m² three times weekly for 3 to 4 weeks, or daily doses of 5000 to 20,000 IU/m² for 10 to 20 days. The optimal dose and schedule are unknown. Intermittent schedules with less frequent administration are associated with reduced efficacy and increased anaphylaxis. An E. coli preparation modified by the covalent attachment of polyethylene glycol (PEG) has a prolonged half-life, thus permitting lower doses and less frequent administration. The approved dose of PEG-asparaginase is 2500 IU/m² every 14 days, either intravenously or intramuscularly.

L-asparaginase concentration in plasma is proportional to a total dose up to 200,000 IU/m² and falls with a primary half-life of 14 to 22 hours after administration. Blood levels of the E. coli enzyme are detectable for 1 to 2 weeks after a single dose, and concentrations of L-asparaginase fall below 1 nmol within minutes of enzyme injection and remain low for 7 to 10 days after completion of therapy. The half-life is independent of the dose administered, disease status, renal or hepatic function, age, or gender. The pharmacokinetics of asparaginase depend on the preparation.55 66 76 With E. coli–derived enzyme, the t½ (1.14 to 1.35 days) administered by the intramuscular route is the same irrespective of dose (2500 or 25,000 IU/mL) or with repeated doses. Peak serum levels are reached in 24 to 48 hours and are no longer detectable in serum by day 10 to 14 days. Extremely low levels are found in the urine at 24 hours, suggesting clearance of L-asparaginase by mechanisms other than urinary excretion. Cerebrospinal fluid levels disappear rapidly. The serum t½ for Erwinia is 0.65 days, and enzyme was no longer detectable by 7 days. This value is shorter than the E. coli preparation, although similar schedules are often used. The serum t½ of PEG-modified L-asparaginase as an initial dose was 5.73 days, which is significantly longer than after subsequent doses.

Patients who experience a hypersensitivity reaction to E. coli asparaginase have a decreased t½. Subsequently with PEG asparaginase,65 88 Serum L-asparaginase activity is undetectable in the week after an anaphylactoid reaction. Even a silent anaphylactoid reaction to E. coli may result in neutralizing antibodies and reduced drug efficacy.63

TOXICITIES

L-asparaginase has no effect on bone marrow function. Hypersensitivity is the most serious toxicity, and it occurs in fewer than 10% of patients. It is manifested by urticaria, nausea, vomiting, and chills, and less often by a serum sickness-like reaction or by anaphylaxis with hypotension, laryngospasm, and cardiac arrest, which is fatal in fewer than 1% of reactions. Reactions generally occur during the second week of treatment or later, and they mandate a change to another preparation. The risk of hypersensitivity is greater when the drug is used as a single agent than with concurrent immunosuppressive agents (steroids, 6-mercapto purine), at doses higher than 6000 IU/m² administered by the intravenous route and with repeated courses of treatment. Neither skin testing nor antibody levels have been sufficiently predictive. The PEG formulation is the least immunogenic52 72 and may be more cost-effective.12 The development of an allergic reaction does not appear to compromise the efficacy of the agent.66

Decreased protein synthesis leads to reduced albumin and serum lipoprotein concentrations. A reduction in vitamin K–dependent clotting factors, a fall in fibrinogen levels, and decreased platelet aggregation to collagen may lead to bleeding. Decreases in antithrombin III, proteins C and S, and increased endogenous thrombin generation are associated with venous thrombosis and embolism.53 54 55 56 73 84 92 Other toxic effects include confusion, aphasia, stupor, or coma in 25% to 33% of patients52 54 55 56 73 84 and abnormal liver enzymes with fatty metamorphosis. L-asparaginase is contraindicated in patients with a history of pancreatitis because of the risk of acute pancreatitis.52

AMIFOSTINE

Amifostine is a phosphorylated amidophosphonic acid that is produced by the Walter Reed Army Medical Institute (the military code name WR-2721) during the cold war as part of a classified research project to identify an agent that would protect military personnel from radiation in the event of nuclear war. Amifostine was found to afford greater protection against radiation than more than 4000 other compounds screened. Nevertheless, the army terminated development of this compound in 1988 because of its poor oral bioavailability and the prohibitive nausea, vomiting, diarrhea, and abdominal cramps noted with the oral formulation.

When administered intravenously, the pharmacokinetics (PK) of amifostine varies somewhat with dose.41 The clearance from plasma is rapid (distribution and elimination phases in humans of t½,a, less than 1 minute, t½,b, 8.6 minutes), with a plasma half-life of 1 minute and almost all drug cleared by the plasma within 10 minutes. Bioavailability from the subcutaneous route is high but variable.41

Amifostine is dephosphorylated at the tissue level to its active metabolite, the free thiol WR-1065, by membrane-bound alkaline phosphatase. WR-1065 is rapidly taken up by cells and is thought to be the major cytoprotective metabolite. WR-1065 protects normal cells by acting as a free radical scavenger and by hydrogen ion buffering. The hypovascular, hypoxic nature of tumors results in anaerobic metabolism and a low interstitial pH, which are associated with a low rate of prodrug activation by alkaline phosphatase.

Separate phase I trials of amifostine were conducted in conjunction with radiotherapy or chemotherapy. A true maximum tolerated dose was not identified in either setting, but the recommended dose ranges from 740 mg/m² to 910 mg/m².67 84 92 93 94 The approved dose of PEG-asparaginase is 2500 IU/m² every 14 days, either intravenously or intramuscularly.

CHEMOTHERAPY-RELATED NEPHROTOXICITY

Amifostine has been evaluated for its ability to prevent chemotherapy-related nephrotoxicity, especially that induced by cisplatin.101 102 103 In the only phase III trial, Kemp et al.105 randomized 242 women with advanced ovarian cancer to six cycles of chemotherapy, with or without amifostine, 910 mg/m², before each cycle. The severity of renal toxicity was reported to be lower in the group receiving amifostine. Fewer patients discontinued therapy on the amifostine arm because of toxicity. The response rates and survival durations were comparable between the two arms. However, the doses of cisplatin used in this study are higher than the dose currently recommended, and this regimen is less commonly used than other less nephrotoxic programs.

NEUROLOGIC TOXICITIES AND OTOTOXICITY

Several small phase II studies and one phase III trial suggest that amifostine may offer modest protection against the neurologic toxicities of cisplatin, but with no effect on ototoxicity.104 105 106

NEUTROPENIA AND THROMBOCYTOPENIA

Various phase I, II, and III trials suggest a myeloprotective effect from amifostine. Glover et al.121 conducted a phase II trial of amifostine in combination with cyclophosphamide with 21 patients used as their own controls; 90% had an improved white blood cell count with the second course of cyclophosphamide compared with the first course. Whether these findings are clinically meaningful is questionable.107 108 109 In a study conducted by the Cancer and Leukemia Group B,110 patients with solid tumors were treated with high-dose cyclophosphamide with amifostine alone or with amifostine and granulocyte-macrophage colony-stimulating factor. No
additional protection was noted with the combination.

Preliminary phase I data suggest less thrombocytopenia in patients treated with carboplatin and amifostine. However, the aggregate data from subsequent studies provide less support for clinically meaningful benefit.

ADDITIONAL OBSERVATIONS

Limited data suggest that amifostine may modulate the cardiotoxicity of doxorubicin and the pulmonary toxicity of bleomycin.

RADIOPROTECTION

Amifostine has been evaluated in combination with radiation therapy or combined modality treatment for patients with head and neck and lung cancers. The suggestion has been made of a reduction in esophagitis in lung cancer patients and less xerostomia and loss of taste with amifostine, but with no clear impact on mucositis or salivary gland function. There is no clear radioprotective effect in patients with rectal cancer.

TOXICITIES

The major toxicities associated with amifostine include nausea and vomiting, hypotension, hypocalcemia, and allergic reactions. The onset of nausea and vomiting is generally within 15 to 30 minutes of the start of the infusion, and they resolve spontaneously. Pretreatment with dexamethasone and a 5-hydroxytryptamine receptor antagonist is recommended.

Hypotension is a potentially serious side effect. It is generally systolic, lasting 5 to 15 minutes, without central nervous system, renal, or cardiovascular consequences. Administration issues that influence the frequency and severity of hypotension include patient hydration, infusion duration, position of patient, and antiemetic pretreatment. Patients should not be receiving agents that potentiates the potential for hypotension, and the drug should not be administered to patients who cannot be without antiemetics for at least 24 hours. Dehydrated patients should not receive the drug until the problem has been corrected. Patients should be hydrated before administration of amifostine. Patients should remain supine or reclining during amifostine therapy.

Hypocalcemia is clinically significant in approximately 1% of patients and can be managed with oral calcium carbonate and vitamin D. The drug has been used successfully to treat hypercalcemia.

Allergic reactions occur in fewer than 1% of patients and are successfully treated with diphenhydramine.

DRUG ADMINISTRATION

Amifostine should be administered over 15 minutes, 5 to 30 minutes before cytotoxic chemotherapy. The patient should be well hydrated in a reclining position, with frequent blood pressure monitoring. The recommended dose with radiation therapy is 200 mg/m²/d, as a slow intravenous push over 3 minutes, 15 to 30 minutes before each radiation fraction. Bolus schedules have been studied as well.

MELODYSPLOID SYNDROMES

Amifostine stimulates hematopoiesis in animal models, and in vitro studies it stimulates the formation of hematopoietic progenitors from myelodysplastic syndrome bone marrow. In a phase I/II study, the drug was administered at doses of 100, 200, or 400 mg/m² three times per week, or 740 mg/m² weekly for 3 weeks. Hematologic improvement was observed in 83% of patients with the thrice-weekly schedule, including either an increase in neutrophils or a reduction in red cell transfusions. More than 40% of patients had a rise in their platelet counts. Acceleration to acute myeloid leukemia was noted in several patients with RAEB-T (refractory anemia with excess of blasts in transformation). In a subsequent multicenter trial, there was single or multilineage improvement in 35%. A poor response rate was reported using a continuous schedule of eight uninterrupted thrice-weekly doses of 300 to 450 mg/m². The role of this agent in myelodysplastic syndrome is being elucidated.

RECOMMENDATIONS FOR THE USE OF AMIFOSTINE

Based on a careful review of the data, the American Society of Clinical Oncology made the following recommendations regarding the use of amifostine.

- It may be considered for the reduction of nephototoxicity in patients receiving cisplatin-based chemotherapy.
- Although it may be considered for the reduction of neutropenia in patients receiving alkylating agents, chemotherapy dose reduction or growth factor use should be considered as an alternative to the use of amifostine.
- Present data are insufficient to recommend the use of amifostine for protection against thombocytopenia or the routine use of amifostine to prevent cisplatin-associated neurotoxicity or ototoxicity. Similarly, the data were felt to be insufficient to support the use of amifostine for the prevention of paclitaxel-associated neurotoxicity.
- The use of amifostine may be considered to decrease the incidence of acute and late xerostomia in certain patients undergoing fractionated radiation therapy in the head and neck region, although the present data are insufficient to recommend the use of amifostine to prevent radiation therapy–associated mucositis.

CHAPTER REFERENCES


RATIONAL FOR INVESTIGATION OF INTERFERONS: DIRECT REGULATION OF CELL GROWTH, DIFFERENTIATION, ANTIGEN EXPRESSION; INDIRECT EFFECTS MEDIATED THROUGH MODULATION OF THE HOST IMMUNE RESPONSE

The interferons (IFNs) are a complex family of inducible natural host proteins that have been traced in phylogeny to prevertebrate species. The physical and chemical immunologic and biologic differences among the IFNs have served as a basis for speciation of these molecules, long before the knowledge of intracellular signaling pathways that have been more recently elucidated was known. These intracellular pathways activated by the IFNs (signal transducers and activators of transcription) are triggered by a large number of signaling polypeptides, but are activated in different patterns by different signaling polypeptides, to induce precise cellular responses in mammalian (as well as insect and slime mold) cells, demonstrating critical roles in different phases of cell biology. Disruption of the STAT genes in the mouse has shown roles in viral/bacterial defense (STAT 1). Early lethality has been reported for STAT 2 and 3 lesions, whereas disruption of TH1 has been identified as a consequence of disruption of STAT 4. The role of IFN-induced gene regulation in many diverse tissues is likely to account for the effects of IFNs on a variety of neoplastic, viral, and angiocentric conditions in which IFN therapeutic activity has been clinically observed since the 1980s.

The IFNs have been empirically tested as therapies for a multitude of hematologic and solid neoplasms, demonstrating therapeutic benefits in more than a dozen cancers, leading to regulatory approval in multiple countries across the world. This chapter reviews the biology and preclinical effects of the IFNs, discussing the multiple mechanisms of potential relevance to cancer and the therapeutic advances that have been made with IFNs as single agents and combined with chemotherapy, radiotherapy, and other biologic agents, including vaccines, particularly as these relate to the solid tumors.

INTERFERONS OF TYPE I: INTERFERON-a, -b, -t, AND -w

Human IFN-a comprises a complex array of subtypes, each of approximately 165 to 166 amino acids encoded by a superfamily of closely related genes located with the IFN-a and -b genes on the short arm of human chromosome 9 that are variably modified by posttranslational glycosylation. In the human, 14 nonallelic IFN-a genes and four pseudogenes are clustered together with genes for IFN-a. A variable mixture of IFN-a species is induced in leukocytes and other host cells by a range of stimuli classically including virus or nucleic acids. The biologic effects of the many subtypes are overlapping in large part, despite differences in relative antiviral, antiproliferative, antigen-modulating, and immunomodulating effects to be discussed later in this chapter.

IFN-a and -b bind with high affinity (dissociation constant of 10^{-10} to 10^{-12} mol/L) to a single receptor of 110 kD specified on chromosome 21, ranging in density from 100 to 10,000 receptors per cell. A range of cellular processes induced by IFNs follow the production of a new set of proteins, after binding and internalization. Knowledge of the events that occur after binding of IFN to its receptor has become of significantly. A multimeric transcription activator ISGF3 is stimulated to translocate to the nucleus, where it binds cis to the IFN response element of DNA and induces genes that make up the array of IFN-stimulated genes. The cytoplasmic and nuclear components of the transcription-activating factor ISGF3 associated with IFN-a are activated, such that ISGF3-g (the complex specifically recognizing the ISRE) and ISGF3-a (which contains three polypeptides activated specifically on phosphorylation) interact and translocate to the nucleus without the requirement of protein synthesis to activate the IFN response element.

INTERFERON-BINDING RECEPTOR OF TYPE II: INTERFERON-g

IFN-g binds a receptor that is discrete from that bound by type I IFNs. Evidence for two classes of receptors, one with low (10^{-12} mol/L) and one with high (10^{-11} mol/L) affinity, has been reported. In vivo and in vitro immunomodulatory activity of IFN-g in experimental animals as well as the human has been one of the most potent of all IFNs, leading to expectations that IFN-g would also be the most therapeutically active of all IFNs against cancer. Trials of IFN-g in patients with advanced metastatic melanoma and renal cell carcinoma, as well as adjuvant trials in patients with a high risk of relapse, have been conducted, but have not shown therapeutic effects equivalent to the IFN-a-b, biologic, molecules. Reasons for this may relate to effect on antigen presentation and the proteosome complex.

The pleiotropism of the IFNs has posed significant challenges in their quantification and the definition of mechanism of action. The specific activity of various IFN preparations may be expressed in terms of differing functions (e.g., antiviral, antiproliferative, differentiating, effector cell activating, antigen augmenting, and enzyme inducing). Antiviral activity has been accepted as the basis of IFN standardization, although it is far from clear that this function is related to the effects of IFN-g in cancer therapy. Units of antiviral activity determined against reference standards of the Center for Biologics (Washington, DC) are commonly used to quantify IFN-a and -b, but recombinant IFN-g and newer polyethylene glycol (PEG) bound forms of IFN-a, are generally reported in terms of mass. The various species, subtypes, and molecular variants (mutants) of IFNs argue for adoption of functional standardization in terms of alternative mechanisms relevant to antitumor activity for clinical trials.

MECHANISMS RELEVANT TO ANTITUMOR ACTION

The pleiotropic actions of IFNs may be separated into several categories that are useful in analyzing preclinical and clinical data, as summarized in Table 20.1-1. Direct effects of the IFNs include antiproliferative and differentiating effects that may be demonstrated against fresh melanoma tissues or cultured cell lines in vitro. Effects have been designated as composite that result in alterations in tumor cell surface antigen expression without direct effect on tumor cell growth, invasion, and metastasis. These effects may permit host recognition and response in vivo. Each of three major categories of IFN effects that are potentially relevant to melanoma has been studied in some detail and may provide a basis for understanding the outcome of therapeutic trials (as discussed). Indirect effects of the IFNs are those that are mediated by the host immune system, including the cellular elements such as the large granular lymphocyte or natural killer (NK) lymphokine-activated killer cell, macrophage/dendritic cell, neutrophil, and T and B cells.
TABLE 20.1-1. Pleiotropy of Interferons: Direct, Composite, and Indirect Effects

DIRECT EFFECTS ON TUMOR CELL PROLIFERATION AND ENZYME AND SIGNALING PATHWAYS

The actual mechanism(s) responsible for the antitumor action of IFNs in human cancer remain uncertain. Nonrecombinant IFN-a and -b and recombinant subtypes of IFN-a, -b, and -g have been evaluated in vitro for their antiproliferative activity against cultured and fresh solid tumor cells. These demonstrate comparable growth-inhibitory activity, and one may draw the general observations that (1) there exists a direct dose-response tumor-inhibiting relationship for each species; (2) there is considerable heterogeneity among different tumors regarding sensitivity to inhibition; and (3) solid tumors are generally sensitive to IFNs in vitro if exposed to high levels (greater than 500 μM) of IFN-a, -b. Molecular pathways of IFN signaling have been defined, allowing analysis of the proximate intracellular pathways of action, which may prove more informative than the measurement of IFN-induced enzymes such as oligoadenylate synthetase, and more distal effects such as induction of major histocompatibility complex (MHC) antigen expression. Studies of cultured in vitro tumor cells have suggested acquired defects in the STAT signaling pathway and the absence of STAT that may be associated with IFN resistance. By contrast, studies of human tumor tissues in vivo have revealed the constitutive activation of STAT pathways and nuclear correlation of STAT, in melanocytic nevi tissues of patients untreated with IFN as well as in solid tumor tissues (squamous carcinoma of the upper aerodigestive tract). The analysis of signal transduction intermediates of the IFNs in tumor cells of patients undergoing therapy with the IFNs is now feasible. The prospective evaluation and correlation of these intermediate end points of IFN action with clinical evidence of response, progression, or both will be of interest in future trials.

Enzyme Induction

A number of enzyme pathways are activated after induction of the IFN response element, including some that have been evaluated in clinical trials. These include 25′oligoadenylate synthetase (25′o-As) and protein kinase (p67). Two molecular forms of 25′o-As of 33 kD and 110 kD have been identified differing in subcellular localization and activation requirements. The role of the different forms of 25′o-As as in relation to antitumor effects of IFNs has yet to be established. Indoleamine 2,3 dioxygenase is induced by IFNs in a dose- and time-dependent fashion; this enzyme alters tryptophan metabolism and with xanthine oxidase generates superoxides that may relate to both therapeutic and toxic effects of IFN, as well as depression of cytochrome P-450 enzymes levels. Neopterin production induced by IFN-γ may provide an additional biochemical tool for the analysis of intermediate effects of IFN-γ in vivo.

Antiproliferative Effects of Interferons in Combination with Chemotherapy and Other Biologic Agents In Vitro

The presence of additive or synergistic effects of chemotherapeutic agents has been examined with IFNs in vitro using isobologram plots to compare various combinations for synergistic, additive, or subadditive effects against tumor cells. Although synergism and additive effects have been identified with some combinations and negative interactions for others, there is no compelling evidence that these in vitro effects have been useful in the development of therapeutic regimens for the clinic.

IFN-γ has been shown to potentiate apoptotic cell death and DNA fragmentation induced by tumor necrosis factor (TNF), whereas IFN-α and -γ potentiate the tumor-cytotoxic activity of TNF in clonogenic stem cell assays.

Differentiation In Vitro and In Vivo

Differentiative and growth regulatory or apoptotic effects of the IFNs have become focal points of interest in multiple solid and hematopoietic neoplasms. A number of adhesion molecules, growth factors, and receptors have been identified in the process of malignant progression that are subject to IFN regulation. The receptor-ligand pairs may serve as paracrine or autocrine growth-stimulating circuits that may be interrupted at various stages. IFN-α and retinoic acid inhibit epidermal growth factor receptor expression, and retinoic acid as well as IFNs are under study as potential inhibitors of progression.

COMPOSITE (ANTIGENIC) ANTITUMOR MECHANISMS: MODULATION OF MELANOMA-ASSOCIATED CELL SURFACE ANTIGENS

The antitumor effects of IFNs have been attributed to their effects on cell surface antigens of several tumors. The histocompatibility complex is among the most consistent and sensitive targets of the IFNs. It is well established that MHC class I antigens are inducibly type I IFNs, whereas MHC class II antigens are the target of type II IFNs (IFN-γ). In vivo studies have suggested an even broader pleiotropic type of the IFNs than in vitro, in which induction of both MHC class I (ABC) and II (DR, DP, DQ) antigens have been reported with IFN-α, -β, and -γ.

IFNs modulate the expression of many cell surface molecules, not all of which have been assigned physiologic functions, and a number of which play roles in the progression from neoplastic to invasive neoplastic disease.

The clinical implications of altered MHC antigen expression relate to their pivotal function in intercellular immunologic recognition and communication at multiple levels. Antigen presentation to T cells by Langerhans'/dendritic cells of the macrophage monocyte lineage and B cells is associated with the expression of MHC class I and II antigens. IFN-γ has been shown to potentiate apoptotic cell death and DNA fragmentation induced by tumor necrosis factor (TNF), whereas IFN-α and -γ potentiate the tumor-cytotoxic activity of TNF in clonogenic stem cell assays.

The induction of MHC class I and II antigens by IFNs may provide an additional biochemical tool for the analysis of intermediate effects of IFN-γ in vivo.

DIRECT IMMUNOMODULATORY EFFECTS

Natural Killer, Macrophage, and Dendritic Cells

The macrophage is a key target of IFN-γ, which was earlier described as macrophage activating factor (see Table 20.1-1). The large granular lymphocyte known as the NK cell is a well-recognized target of the type I and II IFNs. Clinical relevance of the effects of IFNs on NK activity has been sought for many years, both in vitro and in vivo for IFN-α, -β, and -γ. NK activity measurements performed in the context of multiple trials has depended on assay conditions, effector cell manipulation, and the delay from blood-drawing to assay (real period). To date, no convincing evidence of a relationship between NK cell activity and therapeutic activity of IFNs in patients with solid tumors has been documented. Antibody-dependent cellular cytotoxicity of peripheral blood lymphocytes is...
mediated in part by NK cells and augmented in vitro and in vivo by IFN-a, as well as interleukin-2 (IL-2). As trials of antitumor antibodies are further developed, the optimization of NK activity and antibody-dependent cellular cytotoxicity with IFNs, IL-2, as well as IL-12, and other newer biologic agents will continue to be important.

The dendritic cell, a central antigen-presentation cell, is influenced by multiple cytokines, including granulocyte-macrophage colony-stimulating factor, IL-4, IL-12, and IFN-a. The immunomodulatory effects of IFN-a may thus be due to altered numbers or functional capacities of dendritic cells, although studies in vivo during IFN therapy have yet to be performed to evaluate this potential mechanism.

### T Cell

Specific T-cell-mediated immunity has been implicated as the basis of antitumor effects of the IFNs in many solid tumors. Durable complete responses have been reported in multiple clinical trials of IFN-a for chemotherapy-refractory solid tumors, including renal cell carcinoma and melanoma. Shifts in T-cell subsets (CD4 to CD8 ratio increased) have been correlated with clinical antitumor response to IFN-a and -g. IFN-a modulates mixed leukocyte reactions in vitro and the modulation of specific cytotoxic T-cell immune responses to solid tumors by IFN-a remains a leading hypothetical basis for the durable antitumor effects observed clinically with IFN-a, in melanoma, renal cell carcinoma, and other solid tumors. This is prospectively being evaluated in the context of current trials for several solid tumors. The prognostic importance of CD4+ T-cell infiltrates in predicting response of melanoma and other solid tumors has been suggested by Hakansson et al. and is now being tested prospectively as a means to select a more IFN-responsive population. The definition of both MHC class I–restricted and MHC class II (DR)–restricted epitopes recognized by CD4+ T cells in melanoma, renal cell carcinoma/hNF cancer, and other solid tumors adds a new dimension to the expanse of CD8+ T-cell–defined MHC class I–restricted epitopes for analysis of IFN-modulated effector functions.

In preclinical systems, Belardelli and Gresser et al. have shown that IFN prevents the outgrowth of experimental murine tumors that does not correlate with the tumor cell susceptibility to direct tumor growth inhibition by IFN. This effect depends critically on the presence of an intact immune system in the host and particularly the CD4 T cell. Tumor response suggesting that tumor regression induced by IFN in this system is dependent on immunomodulatory effects of IFN on the tumor and host.

### B Cell

IFN-a increases production of IgG2a and decreases that of IgG3, IgG1, IgG2b, and IgE by human B cells. Several tumor vaccines have been evaluated in conjunction with IFN-a2a to evaluate the immunomodulatory role (and possible inhibitory effects) of IFN-a2a administered together with or following GM2 vaccine (Eastern Cooperative Oncology Group trial E2696. GMK, Progenics, Tarrytown, NY). The results of these trials have established the feasibility of this combination and the absence of inhibitory interactions between ganglioside GM2 vaccination and high-dose IFN-a2a in regard to serologic IgM and IgG response and pave the way for IFN combinations in other disease settings.

The specific effects of IFN-a, -b, and -g on specific immune function against autologous solid tumors have not been examined due to the complexity of measuring immune responses to autologous tumor cell surface antigens in clinical trials. Analyses of specific immune responses to tumor-associated antigens will be essential to interpret therapeutic responses to IFN, much as it is critical to the analysis of an array of vaccine trials underway for many solid tumors.

### ROLE OF INTERFERON-\(\gamma\) AS A MEDIATOR OF CLINICAL EFFECTS OF OTHER CYTOKINES

IFN-\(\gamma\) induction by IL-2 and IL-12 has been documented in vivó in humans. Ambient levels of 1 to 7 U/mL have been demonstrated after continuous intravenous infusion of IL-2 and are likely to be a major component of the dose-limiting toxicity of IL-12. The IFN-\(\gamma\) induced during therapy with IL-2, IL-12, and other cytokines may play a role in therapeutic as well as toxic effects of a number of biologic agents.

### DENDRITIC CELL MODULATION

A cell that has taken center stage and is central to antigen presentation is the dendritic cell. In preclinical systems, Belardelli and Gresser et al. have shown that IFN prevents the outgrowth of experimental murine tumors that does not correlate with the tumor cell susceptibility to direct tumor growth inhibition by IFN. This effect depends critically on the presence of an intact immune system in the host and particularly the CD4 T cell. Tumor response suggesting that tumor regression induced by IFN in this system is dependent on immunomodulatory effects of IFN on the tumor and host.

### CLINICAL EVALUATION

#### TOXICITY AND PHARMACOKINETICS OF THE INTERFERONS

**General**

The clinical toxicity of the different species of IFNs involves a similar range of target organs, although the relative components of toxicity differ from species to species and in the human from individual to individual. Acutely, a flu-like constitutional syndrome with fever, chills, headache, malaise, myalgia, arthralgia, and fatigue occurs in the majority of patients and diminishes over time with continued daily or alternate-daily administration. For this reason, therapy is best tolerated in many patients at bedtime. Low back pain and headache with severe rigors have been associated with IFN-a in particular. Metabolic alterations in the blood lipid profile have been noted with hypertriglyceridemia, and elevated low-density lipoprotein is seen due to inhibition of lipoprotein lipase. IFN-a may depress the plasma cholesterol in 15% to 40% of patients, with a parallel decrement in both high- and low-density cholesterol, without alteration of very low-density lipoproteins. Long-term toxicity of IFN consists in constitutional flu-like symptoms compounded by anorexia, weight loss, and fatigue. These late toxicities are the result of dysgeusia, low-grade fever, and nutritional compromise and may be difficult to differentiate from the appearance of thyroid dysfunction or other endocrine pathology on the basis of autoimmune processes associated with IFN-a (as for IL-2). Neuropsychiatric toxicity ranges from mild cognitive deficits to frank depression and psychosis (see Neurologic Effects, later in this chapter).

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**TABLE 20.1-2.** Toxicities of Interferons
Hematologic Effects
Hematologic toxicities of the IFNs include leukopenia and, less frequently, thrombocytopenia and anemia; infections are a recognized complication of the leukopenia, but bleeding complications have been rare. Diminished colony-forming capacity and hypocellularity have been noted in the bone marrow, which are rapidly reversible on withdrawal of IFN.

Hepatic Effects
Hepatotoxicity observed at high doses frequently includes elevated circulating transaminase enzyme levels that are dose related and reversible on withdrawal of the agent, without evidence of cachexia. Rarely, subacute hepatic necrosis and cholestatic liver failure with death have been observed when IFN has been administered in the face of hepatotoxicity with hyperbilirubinemia or a history of antecedent viral or alcoholic liver disease. Careful observation of hepatic function generally permits the avoidance of such problems, with treatment modification according to signs and symptoms of toxicity. Indeed, after the initial report of two cases of fatal hepatotoxicity of high-dose IFN in the pivotal E1664 adjuvant trial for high-risk melanoma, the confirmatory intergroup trial E1690 was completed without any instance of life-threatening hepatotoxicity, and the only two toxic fatalities noted were cardiovascular and cerebrovascular, occurring with low-dose IFN.

Cardiac and Renal Effects
Cardiovascular, renal, and CNS toxicity are less common. Supraventricular tachyarrhythmias noted with the IFNs may be direct effects or the consequence of fever or nutritional and fluid imbalances. Complex conduction disturbances have been observed with IFN-g, including bradycardia with high-grade heart block. Cardioxicity is increased among elderly patients and patients with underlying heart disease or prior exposure to cardiotoxic agents, but the mechanism has not been defined. Hypotension occurs through at least two separate mechanisms: acute hypotension, occurring 1 to 2 hours after administration of IFNs, may be related to peripheral vasodilatation and responds to fluid repletion or rarely may require pressors. Hypotension during chronic administration of IFNs is related to subclinical low-grade fever with insidious fluid losses, anorexia, dysgeusia, and diminished fluid intake. Proteinuria is the most common renal manifestation of the IFNs and is generally reversible on withdrawal of IFN. Rarely, interstitial nephritis and nephrotic syndrome have been reported with IFN-a and -g.

Neurologic Effects
CNS toxicity associated with global changes in mentation is often subtle. The cognitive dysfunction induced by IFN may be documented in formal testing, but is often more apparent to family and friends of patients. Supranuclear and subcortical or diffuse slowing of the electroencephalographic pattern have infrequently been reported and are reversible on discontinuation of IFN. Mild peripheral neuropathy has also been noted, with paraesthesia and slowing of nerve conduction velocity. Most recently, reversible retinal microvascular toxicity has been noted during studies of IFN-a administered for macular degeneration, which may indicate the need for ophthalmologic evaluation of patients with visual changes during IFN-a therapy in other settings.

Musculoskeletal Effects
Rhabdomyolysis has rarely been reported in association with IFN-a at high dosages. However, the significance and even the attribution of such occurrences is difficult to resolve at this time, as this complication has been reported as early as the first week into IFN-a therapy in postoperative patients in whom it is difficult to exclude other contributory factors. Although monitoring for elevations in creatine phosphokinase enzymes has been suggested, this has not been adopted in practice because of the rarity of the event and the early occurrence of the event, which would preclude use of laboratory values to monitor treatment and supportive care.

PHARMACOLOGY AND DOSAGE

Recombinant Interferon of the First Generation
The maximum tolerated dose for IFN-a lies between 10 and 20 µm-1 daily and 50 µm-2 on alternating days for periods of weeks to months, regardless of subspecies. The half-life of IFN-a is 6 hours in the blood and has allowed alternative daily schedules out of patient administration by intramuscular and subcutaneous routes. The maximum tolerated dose for IFN-a varies according to the industrial preparation used, schedule, and route; acceptable absorption and activity have been reported with IFN-g administered intravenously or intramuscularly. Early pharmacokinetic studies of IFN-a have demonstrated that peak levels at 5 µm-2 obtained by the intravenous route do not reach 100 µmL, whereas the intramuscular and subcutaneous routes generally administered for therapy remain under 50 µmL. By contrast, the administration of doses of 20 µm-2 (or 36 µdose in early pharmacodynamic studies) achieves serum levels approaching 10,000 µmL. This difference in the pharmacodynamics and peak levels has been the focus of considerable interest, as the positive results of trials using the intravenous administration of 20 µm-2 have shown the first survival benefits in melanoma, whereas lower dosages administered by alternative routes have yielded antitumor effects in terms of delayed recurrence (during therapy) without significant survival prolongations.

Recombinant Interferons of the Second Generation
A second generation of recombinant IFN-a therapy is currently unfolding, with intense exploration of linear polyethylene glycol–conjugated IFN-a2 (PEG-Intron, Schering-Plough Corporation, Kenilworth, NJ) and larger branched chain formulations of IFN-a1 (Pegasys, Roche Laboratories Inc., Nutley, NJ) entering multicenter trials in the United States, Canada, and Europe. The half-life of these species is substantially prolonged, allowing twice weekly and weekly administration, with concentration time products that are significantly higher than can be achieved with the first-generation recombinant IFN-a species as initially formulated, regardless of route. Clinical studies, accompanied by more sophisticated molecular laboratory corollaries, are under way in the context of these trials in leukemia (chronic myelogenous leukemia), solid tumors (melanoma, renal cell carcinoma), and viral diseases (hepatitis).

ANTIBODIES
The development of anti-IFN neutralizing serum antibodies has been correlated with loss of toxicity and antitumor effects in chronic myelogenous leukemia. The role of anti-IFN antibodies appears to vary with the disease state as well as the species of IFN used. In representative series, antibodies have been detected in from 0% to 5% of patients after 2 to 6 months of therapy, without demonstrable adverse consequences for therapeutic effects in patients with most solid tumors to date. Strategies to reduce the immunogenicity and increase the likelihood of tolerance to recombinant IFN-a have included the initial use of intravenous, as opposed to subcutaneous or intramuscular, routes and continuous as opposed to interrupted schedules. Despite the delayed release and depot-like behavior of polyethylene glycol–bound IFN-a, the immunogenicity of polyethylene glycol–bound IFN formulations appears to be less than that of the parent recombinant IFN-a species.

CLINICAL EFFICACY OF INTERFERONS ADMINISTERED SYSTEMATICALLY
Nonrecombinant IFN-a was initially evaluated in clinical trial against several solid tumors in 1978, when the American Cancer Society began a series of trials of buffy coat leukocyte IFN produced by Cantell with the Finnish Red Cross. These trials were limited by the extremely short supply of the agent (the trials lasted for only 6 weeks) from which no firm conclusions can be drawn. The trials served as an important impetus for the pharmaceutical industry to begin commercial production of IFN-a, as well as IFN-b, -g, and other biologic agents, using recombinant DNA technology. The large-scale production of IFNs by recombinant DNA technology enabled the first systematic evaluation of appropriate dose, route, and schedule of IFN-a, as well as the other major subspecies of IFN-a, -b, and -g.

Phase II trials have documented the antitumor activity of recombinant IFN-a in many solid tumors as documented elsewhere in this volume. Table 20.1-3 lists the applications of IFN-a that have received approval by the U.S. Food and Drug Administration in the United States. General principles that can be drawn from this experience are that the hematologic neoplasms appear to respond to lower dosages than the solid tumors and to respond on the basis of direct effects that are either antiproliferative, prodifferentiative, or proapoptotic. The mechanism for IFN-a activity in solid tumors appears to be indirect, as the result of antigenic modulation (MHC), modulation of host immune responses (CD4/CD8 T cell), or both, or antigen presentation (dendritic cell), although vascular...
effects may also be implicated.

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<th>Table 20.1-3. Efficacy of Interferon-α in Human Cancer</th>
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<td><strong>REGIONAL THERAPY WITH INTERFERON-α</strong></td>
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| Intralesional administration of IFN-α in 6 to 10 Mu twice or three times weekly has been used for refractory solid tumors such as melanoma, but offers little advantage over systemic therapy. Regional in-transit disease of the extremity is an infrequent manifestation of melanoma that continues to be studied with hyperthermic isolated limb perfusion using combinations of chemotherapy (melphalan) and two cytokines (TNF, together with IFN-γ). IFN-γ was given for the original hypothermic isolated limb perfusion with TNF. The role of IFN-γ in this combination is debated, but the reported response rates of 90% with the original combination have been confirmed by investigators in the United States and the Netherlands. TFN given alone at comparable doses has shown only brief and limited antitumor activity, suggesting that melphalan, or melphalan and IFN-γ, may be critical to the therapeutic effects of the triple combination. Fraker and colleagues are undertaking a controlled study of isolated limb perfusion that will allow more definitive conclusions.

**COMBINATIONS**

Phase II Trials of Combinations of Biologic Agents: Types I and II, Interferon-a, Plus Interferon-g

Combinations of IFNs of types I and II (IFN-α, -b, and -g, respectively) have been of theoretical interest, given the potential synergism of IFNs interacting through the two separate classes of IFN receptor. The modulation of receptors for IFN-α by IFN-b and elucidation of signal transduction pathways through which IFN-b and IFN-a act at a molecular level provide a further impetus for exploration of combined IFN therapy. The molecular synergism of IFN-g and IFN-a through signal transducer and transcriptional activators of IFN summarized by Darnell is currently under investigation with IFN-a and IL-12 (an inducer of IFN-g).

Clinical studies of combinations of IFN-α and IFN-g have generally followed two strategies: concurrent and sequenced administration. Increased toxicity without apparent therapeutic benefit was seen with concurrent regimens, whereas sequenced regimens have improved therapeutic and immunomodulatory activity in renal cell carcinoma.

**Modulation of Antitumor and Immunologic Effects of Interferons by Biologic Agents, Cytotoxic Drugs, and Nonsteroidal Antiinflammatory Drugs**

The pleiotropic effects of IFN-α include the induction of a variety of feedback mechanisms of immunosuppression that may be associated with progestagenoids for which nonsteroidal antiinflammatory drugs might be of benefit. In addition, it has been hoped that these agents might alleviate some of the significant constitutional toxicity and flu-like symptoms of IFN therapy.

Miller et al. have conducted a randomized controlled trial of indomethacin with IFN-α demonstrating neither clinical nor immunologic untoward interactions.

Combination of IFN-a and chemotherapy has suggested improved duration of response in myeloma, whereas sequenced regimens have improved therapeutic and immunomodulatory activity in renal cell carcinoma.

**Combinations of Interferon-a and Retinoids**

Broad interest exists in the potential applications of retinoids for therapy and prevention of squamous carcinomas of aerodigestive tract skin, carcinoma of the cervix, and other epithelial neoplasms. There have been unexpected and dramatic clinical responses of acute promyelocytic leukemia with the retinoids, and this disorder is associated with a lesion in the chromosomal region coding for the retinoic acid receptor. The retinoic acid receptors exhibit sequence homology with the corticosteroid hormone receptor superfamily, suggesting that both may function through the regulation of gene transcription, although the mechanism and optimal combination of retinoids and IFN-α have not been established.

**Combined Modality Therapy**

Given the differing presumed mechanisms and nonoverlapping toxicities of cytotoxic chemotherapy and IFN regimens available for hematologic neoplasms and solid tumors as well as the lack of a survival effect of previous combination chemotherapy, the combination of chemotherapy and IFN-α has been an obvious one. The combination has shown mixed results. The Eastern Cooperative Oncology Group has tested combinations of tamoxifen, IFN-α, or both versus dacarbazine in a factorial two-by-two study that demonstrates a lack of any advantage of IFN (high-dose) (or hormonal combination therapy with tamoxifen) over standard chemotherapy in melanoma. Combinations of IFN-a and chemotherapy have suggested improved duration of response in myeloma and non-Hodgkin’s lymphoma.

In melanoma, combination chemotherapy has been found to induce complete responses in a small fraction (less than 5%), and IL-2 has been shown to achieve a durable complete response in 8%. IFN-a, with IL-2 and combination chemotherapy has been associated with complete responses in more than 10%, and overall complete and partial responses in more than 50% of patients in multiple single-institution trials, leading to exploration of the role of IFN-a plus IL-2 with cisplatin, vinblastine, and dacarbazine, as opposed to polychemotherapy alone, in the current intergroup E3695 trial for metastatic melanoma.

A number of regimens have evaluated the role of IFN-a in combination with complex cisplatin-based polychemotherapy regimens, with or without IL-2. These regimens have generally achieved greater toxicity than the binary regimens, requiring hospitalization for administration of IL-2 when administered by continuous intravenous infusion or high-dose bolus schedules.

More complex regimens using multiple cytotoxic agents, IFN-α, and IL-2 have been reported from multiple centers in the United States and Europe. Regimens known collectively as biochemotherapy have consistently achieved response rates greater than 50% with complete response in 10% or greater, at the cost of significant toxicity and hospitalization for metastatic melanoma. Intergroup study E3695 of the Eastern Cooperative Oncology Group and Southwest Oncology Group is evaluating whether IL-2 as a continuous infusion at high dosage for 4 days and IFN-a at a daily dosage of 5 µg/m² subcutaneously prolongs the survival of patients.
with metastatic melanoma over cisplatin, vinblastine, and dacarbazine polychemotherapy.

The application of IFN as systemic adjuvant therapy is currently focused on melanoma, in which the prognostic assessment for regional lymph node disease has advanced substantially. The risk category of patients with nodal metastasis defined using sentinel node mapping has improved substantially. Melanoma risk may be categorized as very high, high, intermediate, and low, according to 5-year relapse and mortality. The prognosis of clinically localized primary melanoma may be estimated rather precisely by the Breslow depth of primary tumor invasion (in millimeters) at the site of origin, the presence or absence of ulceration, and sentinel lymph node status. The poor prognosis for cure for deep or ulcerated primary disease, or node-positive patients has provided the rationale for postoperative adjuvant therapy of these categories of high-risk patients. ADJUVANT TRIALS OF INTERFERON-α IN MELANOMA

On the basis of the antitumor activity of IFN-α in metastatic melanoma and the gradient of response with patients having the smallest size and number of metastases exhibiting the best response, many melanoma relapse were commenced in the United States and international cooperative groups during the 1980s. The three largest and most mature studies of IFN-α conducted to date adopted similar entry criteria, including patients with deep (T4) primary lesions or pathologically proven involvement of regional lymph nodes. The groups that have undertaken these studies were the Eastern Cooperative Oncology Group, North Central Cancer Treatment Group, and the World Health Organization. Eastern Cooperative Oncology Group

E1684 accrued 287 patients between 1984 and 1990, was unblinded and reported to the American Society of Clinical Oncology in 1993 at 5 years of median follow-up, and published in 1996 at 6.9 years median follow-up. This trial used an aggressive therapy of 1 year's duration, 20 μ/m² intravenously daily for 5 days a week for 1 month, then 10 μ/m² subcutaneously t.i.w. for the balance of the year with IFN-α or observed as the reference standard of care. Risk groups were defined by lymph node pathology (reviewed in all cases) and stratified to allow the analysis of therapeutic effect in homogeneous groups of patients whose susceptibility to this therapy was postulated to be potentially related to tumor burden and disease extent. The analysis of treatment effect for high-dose IFN-α on relapse for the overall trial revealed a highly significant reduction of relapse rate (P = .004) and a significant survival benefit in the intention-to-treat analysis (P = .046). A Cox multivariate analysis demonstrated significant improvement in the disease-free and overall survival (P = .001 to .01) and estimated the relative improvement in continuous relapse-free survival to be 50%. The median interval to relapse with IFN-α adjuvant therapy was prolonged from 0.9 to 1.6 years, whereas the median survival of treated patients has been prolonged from 2.6 to 7.8 years. A retrospective-quality-adjusted analysis of time spent without symptoms or toxicity (Q-TWIST) study has been conducted in the context of this trial. After 84 months, the group of patients receiving IFN-α gained a mean of 8.9 months quality-adjusted time without relapse (P = .03) and 7 months of overall survival time (P = .02) compared with the observation group.

E2896 has tested the anti-GM2 antibody IgG and IgM response induced by the vaccine alone, in comparison with the vaccine combined with or followed by IFN-α, at high dosage as in E1684/E1690. This trial has been completed and analyzed, demonstrating no significant inhibition of the immunogenicity of the GMK vaccine in terms of anti-GM2 antibody immunoglobulin G and immunoglobulin M. Thus, it is reasonable to consider the combined use of vaccine, and high-dose IFN-α in future adjuvant trials, as any vaccine has been demonstrated to be of benefit in appropriate randomized controlled trials, alone.

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INTRODUCTION

Interleukin-2 (IL-2) is the first agent available for the treatment of metastatic cancer that functions solely through the activation of the immune system. Originally described as a growth factor for activated T cells, IL-2 was subsequently found to exert multiple effects on cellular immune function and to induce tumor regression in mice. Subsequent clinical trials in patients with renal cell carcinoma and malignant melanoma demonstrated sufficient efficacy to establish IL-2 as a U.S. Food and Drug Administration (FDA)-approved treatment for both of these malignancies.

ISOLATION, CHARACTERIZATION, AND CLONING OF INTERLEUKIN-2

In 1976, Morgan et al. demonstrated the existence of a growth factor present in the conditioned medium of lectin-stimulated human peripheral blood mononuclear cells that could sustain indefinitely the ex vivo proliferation of human T cells. This initial report was followed in short order by the isolation, biochemical characterization, and, ultimately, the cloning of what was then termed T-cell growth factor. Subsequently designated IL-2, this factor was shown to be a 15-kD polypeptide made up of 153 amino acids, the first 20 of which form a signal sequence that is proteolytically cleaved during secretion. Natural IL-2 is glycosylated, although the attachment of sugar moieties is not essential for biologic activity. The molecule has cysteine residues at positions 58, 106, and 125, the first two of which form an intramolecular disulfide bridge. The third cysteine is not essential for biologic activity and can be replaced with alternative amino acids to minimize polymerization and increase shelf life. Crystallographic analysis indicates that IL-2 is a spherical molecule comprised of six a helical regions.

INTERLEUKIN-2 RECEPTOR

The various biologic effects of IL-2 are the result of the binding of the lymphokine to specific surface receptors. As with IL-2 itself, the expression of high-affinity IL-2 receptors is induced as a result of signaling through the T-cell antigen receptor. With the exception of a minor population of memory T cells that presumably were activated in vivo by a prior antigen exposure, freshly isolated peripheral blood T cells do not constitutively express high-affinity IL-2 receptors.

The high-affinity IL-2 receptor consists of three distinct subunits designated the α, β, and γ chains (Fig. 20.2-1). The α chain is a 251 amino acid polypeptide with a large extracellular domain, a transmembrane span, and a short 13-residue cytoplasmic tail. The extracellular domain of this protein binds IL-2 with low affinity. The cytoplasmic domain of this receptor has no known biologic function and is dispensable for IL-2–induced signaling.

FIGURE 20.2-1. The high-affinity interleukin-2 receptor and associated signaling pathways. The cytoplasmic domains of the β and γ chains contain several tyrosines that, when phosphorylated, provide docking and activation sites for numerous downstream kinases that affect cell proliferation, gene expression, and cell motility. GTPases, guanosine triphosphatases; JAK, Janus kinase; PI3K, phosphoinositide 3 kinase; STAT, signal transduction and activators of transcription.

The IL-2 receptor β chain has a 214 amino acid extracellular domain, a transmembrane motif, and a large 286-residue cytoplasmic tail. In contrast to the cytoplasmic domain of the α chain, that of the β chain is essential for IL-2 signaling. The IL-2 receptor β chain has paired cysteines at two sites within the extracellular domain and a perimembrane WSLXWS motif characteristic of the members of an enlarging cytokine receptor superfamily that includes the receptors for IL-3, IL-4, IL-6, IL-7, granulocyte-macrophage colony-stimulating factor, prolactin, erythropoietin, and growth hormone.

The γ chain is a novel 64-kD protein that physiologically associates with the β chain. Like the β chain, the γ chain is a member of the cytokine receptor superfamily. These two together bind IL-2 with intermediate affinity. When cotransfected along with the complementary DNAs of the α and β chains, the complementary DNA encoding the γ chain yields a high-affinity IL-2 receptor that transduces signals and is internalized in response to IL-2 binding. More recent studies have demonstrated that this receptor chain is shared by the receptors for several lymphokines, including IL-4, IL-7, IL-9, and IL-15, as well as IL-2. Mutations in the gene encoding this receptor chain account for most, if not all, cases of X-linked severe combined immunodeficiency. Using antibodies against these receptor chains, resting T cells were found to constitutively express low levels of the IL-2 receptor chain, but not the α or β chains. All three chains are up-regulated as a result of antigenic stimulation. Resting natural killer cells constitutively express the β chain, and both the α and γ chains are induced in these cells by exposure to IL-2 or IL-12.

INTERLEUKIN-2–ACTIVATED SIGNALING PATHWAYS

The binding of IL-2 to its receptor induces the tyrosine phosphorylation of numerous cellular proteins, including the IL-2 receptor β chain itself. Because all three chains of the IL-2 receptor lack intrinsic tyrosine kinase activity, these events must be transduced through kinases that physically associate with the cytoplasmic domains of the receptor subunits (see Fig. 20.2-11). Indeed, the src family member pp60 has been shown to associate with the β chain, and its kinase activity is augmented by IL-2. IL-2 also induces the recruitment and subsequent tyrosine phosphorylation of the adapter protein SHC to the IL-2R β chain. This particular association is thought to be largely responsible for the activation of p21 and the downstream mitogen-activated protein kinases erk-1 and erk-2 in response to
IL-2. IL-2 receptor g chain is also essential for IL-2–induced signaling, because T-cell lines expressing the a and b chains and a mutant version of the g chain lacking the C-terminal 60 residues fail to express the protooncogenes c-fos, c-jun, and c-myc when stimulated with IL-2. 11 In addition to the association with src family tyrosine kinases, both the b and g receptor chains associate with members of the Janus kinase family of tyrosine kinases. 12 Janus kinase family member JAK3 associates with the C-terminus of the IL-2 receptor g chain, and both JAK1 and JAK2 associate with the b chain. JAK1 has no specific sequence with domain present in the membrane-proximal region to a specific chain. Janus kinases activate various members of the signal transduction and activators of transcription (STAT) family of transcription factors. The binding of IL-2 to its receptor results in the activation of STAT1, STAT3, and STAT5 in T cells, and an additional member, STAT4, in natural killer (NK) cells. 13

IN VITRO EFFECTS OF INTERLEUKIN-2

IL-2 was originally isolated based on its ability to induce the growth of previously activated T cells. 14 In addition to its proliferative effects, IL-2 induces the synthesis of an array of secondary cytokines, such as IL-1, tumor necrosis factor (TNF), IL-6, and lymphotixin. 15 Several of these secondary cytokines are detectable in the circulation of cancer patients receiving IL-2 immunotherapy (see later, Toxicity of High-Dose Interleukin-2 Administration) and are thought by many investigators to contribute to the side effects of IL-2. 16 The biologic effect of IL-2 arguably most pertinent to its use as an antitumor agent may be its ability to enhance the cytolytic activity of antigen-specific cytotoxic T lymphocytes and NK cells. 17 The biochemical basis for this enhanced cytolytic function is currently unclear, but it is thought to be due in part to the increased expression of genes encoding the lytic components of cytotoxic granules (e.g., perforin, granzyme) as well as the lytic adhesion molecules (lymphocyte function-associated antigen 1) that facilitate the binding of activated leukocytes to tumor endothelium and the tumor cells themselves. In addition to increasing the HLA-restricted cytolytic activity of cytotoxic T lymphocytes for cells expressing a particular antigen and that of NK cells for susceptible tumor cell targets, IL-2 markedly diversifies the range of target cells susceptible to killing by these effectors. 17,20 Indeed, human peripheral blood lymphocytes exposed only to high concentrations of IL-2 without prior exposure to tumor cells are able to kill virtually all tumor cell lines and most freshly isolated tumor cells in vitro, regardless of the particular HLA class I alleles expressed by the target cell. Some nontransformed cells, in particular cultured endothelial cells, are similarly susceptible to IL-2–primed peripheral blood lymphocytes in isozone release assays. 21 The cells responsible for this HLA-unrestricted killing in response to IL-2 have been termed lymphokine-activated killer (LAK) cells. 22 LAK cells appear to be a mixture of activated NK cells and CD3+CD8+ cytotoxic T cells, the relative contributions of which depend on the duration of culture in IL-2 and whether human peripheral blood lymphocytes or murine spleen suspensions are used as a LAK cell source. As described below, these ex vivo–activated LAK cells featured prominently in the early clinical trials carried out with IL-2 in cancer patients.

PRECLINICAL STUDIES WITH INTERLEUKIN-2 IN TUMOR-BEARING MICE

The results of the in vitro studies demonstrating that IL-2 could enhance the cytolytic activity of NK cells and tumor-specific cytotoxic T cells suggested that systemically administered IL-2 might induce tumor regression in tumor-bearing mice. IL-2 has since undergone extensive evaluation as an antitumor agent in a variety of murine tumor models. IL-2 has been used alone, in combination with other cytokines, and in conjunction with the adoptive transfer of various ex vivo–activated lymphoid preparations to eradicate a wide range of local and metastatic tumors. Early studies demonstrated that IL-2 used alone could reduce or eliminate pulmonary metastases from methylcholanthrene-induced sarcoma and melanoma cell lines and that this antitumor effect was strictly dependent on the dose of IL-2 administered. 23 In another early study, IL-2 was able to cure 50% of mice inoculated with FBL-3 leukemia cells. 24 In this study, mice cured of leukemia by IL-2 were resistant to the subsequent inoculation of the same tumor cell line, suggesting that IL-2 treatment had effectively immunized the tumor-bearing mice against this particular tumor. In more recent studies in which mice were immunized with dendritic cells pulsed with tumor lysates, the concurrent systemic administration of IL-2 was shown to enhance the efficacy of the vaccine. 25

In several studies, the effects of IL-2 could be enhanced by the concurrent administration of LAK cells generated by culturing splenocytes ex vivo in IL-2–containing media. 26 Mice bearing hepatic micrometastases from poorly immunogenic MCA-105 or MCA-102 sarcomas or MCA-38 adenocarcinoma cells, for example, were highly responsive to treatment with the combination of IL-2 and LAK cells but were unresponsive to LAK cells alone and only partially responsive to IL-2 alone. Lymphocytes present within tumor infiltrates are presumably enriched for effector cells capable of killing tumor cells. 27 When isolated and tested in vitro for cytolytic activity against autologous tumor cells, these tumor-infiltrating lymphocytes (TILs) are 50- to 100-fold more potent than IL-2–activated splenocytes (LAK cells). This apparent superiority was also evident in vivo. The infusion of 2 × 107 TILs with IL-2, for example, completely eradicated the pulmonary metastases of mice previously inoculated with MCA-105 sarcoma cells. 28 As many as 2 × 108 LAK cells were required for a comparable effect.

CLINICAL APPLICATIONS OF INTERLEUKIN-2

The potent immunomodulatory and antitumor effects of IL-2 in the in vitro experiments and preclinical animal tumor models described in the previous two sections prompted the rapid movement of IL-2 into the clinical setting. Early clinical trials involving the brief administration of modest doses of purified, cell-derived IL-2 produced only transient fever and lymphopenia, but no sustained IL-2 effects or tumor responses. 29 Because preclinical trials had shown that tumor responses were dose-dependent and maximal when IL-2 was combined with LAK cells, the advent of recombinant IL-2 led quickly to a series of trials using higher doses of IL-2, with and without LAK cells.

CLINICAL INVESTIGATIONS INVOLVING HIGH-DOSE INTERLEUKIN-2

Investigators at the National Cancer Institute (NCI) Surgery Branch developed a regimen that involved the administration of high-dose intravenous bolus IL-2. 30 In this regimen, IL-2 (aldesleukin (Proleukin); Cetus/Chiron, Emeryville, CA) was administered at 600,000 to 720,000 IU/kg intravenously every 8 hours on days 1 to 5 and 15 to 19 of a treatment course. A maximum of 28 to 30 doses per course was administered; however, doses were frequently withheld for excessive toxicity. Treatment courses were repeated at 8- to 12-week intervals in responding patients. During initial studies, patients underwent daily leukaphereses on days 8 to 12, during which large numbers of lymphocytes were obtained to be cultured in IL-2 for 3 to 4 days to generate LAK cells; these LAK cells were then reinfused into the patient during the second 5-day period of IL-2 administration.

This high-dose IL-2 regimen, with or without LAK cells, produced overall tumor responses in 15% to 20% of patients with metastatic melanoma or renal cell cancer in clinical trials conducted at either the NCI Surgery Branch or within the Cytokine Working Group (formerly the Extramural IL-2 and LAK Working Group). 31 Despite noted in 4% to 6% to be frequently durable. Rare responses, usually partial and of shorter duration, were also noted in patients with either Hodgkin's or non-Hodgkin's lymphoma, 32 or non–small-cell lung, colorectal, or ovarian carcinoma. 33 Randomized and sequential clinical trials comparing IL-2 plus LAK cells with high-dose IL-2 alone did not show sufficient benefit for the addition of LAK cells to justify their continued use. 34 The quality and durability of tumor responses to this high-dose IL-2 regimen led to IL-2 receiving FDA approval for the treatment of metastatic renal cell carcinoma in 1992 and metastatic melanoma in 1998. 35

TOXICITY OF HIGH-DOSE INTERLEUKIN-2 ADMINISTRATION

The utility of high-dose IL-2 has been limited by toxicity, many features of which resemble bacterial sepsis. Side effects are dose-dependent and largely predictable and rapidly reversible. Common side effects include fever, chills, lethargy, diaphoresis, nausea, anemia, thrombocytopenia, eosinophilia, diffuse erythroderma, hepatic dysfunction, and confusion. 36 Myocarditis also occurs in approximately 5% of patients. IL-2 therapy also commonly produces a "capillary leak syndrome," leading to fluid retention, hypotension, early adult respiratory distress syndrome, prerenal azotemia, and, occasionally, myocardial infarction. As a consequence of these side effects, few patients are able to receive all of the proposed therapy. IL-2 also has been shown to produce a neutrophil chemotactic defect that predisposes patients to infection with gram-positive and, occasionally, gram-negative bacteria. 37 Early high-dose IL-2 studies were associated with 2% to 4% mortality, largely related to infection or cardiac toxicity. 38 The routine use of antibiotic prophylaxis, more extensive cardiac screening, and more judicious IL-2 administration have greatly enhanced the safety of this therapy; since 1990, the mortality rates at experienced treatment centers have been less than 1% (Table 20-2.1). Nonetheless, the considerable toxicity of the high-dose IL-2 regimen has continued to limit its application to highly selected patients with excellent performance status and adequate organ function treated at medical centers with considerable experience with this approach.
low-dose intravenous regimen. The relationship of these differing pharmacokinetic profiles to the biologic and antitumor effects of IL-2 remains to be determined.

Levels in excess of 18 IU/mL were maintained between injections in patients receiving either the high-dose intravenous or the subcutaneous regimen cited, but not the IL-2 administered subcutaneously at a dose of 250,000 IU/kg had peak serum levels of 61 ± 34 IU/mL 2 to 3 hours after the injection, with a half-life of 5.3 ± 1.9 hours. Patients receiving low-dose 20.2-2 = 6 IU; 1 Hoffman-LaRoche unit = 1 Biologic Response Modifier Program = 2.6 IU. It has become apparent, however, that many other differences may exist between Although only the recombinant IL-2 manufactured by Chiron (Proleukin) is currently FDA approved for clinical use, several different IL-2 preparations have been used COMMONLY USED TREATMENT REGIMENS OF INTERLEUKIN-2 ALONE

The maximum tolerated dose for IL-2 when administered by a 5-day (120-hour) continuous infusion was shown to be 18 MIU/m^2/d or only approximately one-fifth the total amount of IL-2 tolerated by intravenous bolus IL-2 regimens. Although continuous infusion IL-2 regimens were shown to produce response rates similar to the high-dose intravenous bolus IL-2 regimen, the toxicity was also generally comparable. Other regimens, such as those using lower doses of IL-2 administered either by intravenous bolus or subcutaneous injection, are much better tolerated, enabling treatment to be provided in a routine ward or even an outpatient setting. The side effects are generally limited to the flu-like symptoms and constitutional symptoms already described, allowing treatment to be provided safely, even to patients with more limited cardiac, pulmonary, and renal function. These regimens have produced roughly comparable response rates in patients with renal cell carcinoma; however, the quality and durability of these responses have yet to be shown to be comparable to the responses observed with high-dose intravenous regimens. Lower-dose IL-2 regimens have been largely inactive in patients with metastatic melanoma.

BIOLOGY AND PHARMACOKINETICS OF INTERLEUKIN-2

Although only the recombinant IL-2 manufactured by Chiron (Proleukin) is currently FDA approved for clinical use, several different IL-2 preparations have been used in clinical trials. These preparations differ in potency and, in some instances, biologic activity. By convention, the following conversion factors are used: 1 Cetus unit = 6 IU; 1 Hoffman-LaRoche unit = 1 Biologic Response Modifier Program = 2.6 IU. It has become apparent, however, that many other differences may exist between these preparations and, therefore, these simple conversions may not be entirely valid.

Yang et al examined the pharmacokinetics of IL-2 (Proleukin) administered to patients with advanced renal cell carcinoma on three distinct treatment regimens (Fig. 20.2-2). Patients undergoing treatment with high-dose intravenous IL-2 (720,000 IU/kg) achieved peak serum concentrations of 480 ± 1188 IU/mL shortly after the first injection. Subsequent clearance was biphasic, with an initial half-life of 12.6 ± 5.4 minutes and a terminal half-life of 1.6 ± 0.4 hours. Patients receiving low-dose intravenous IL-2 (72,000 IU/kg) exhibited peak levels of 486 ± 198 IU/mL after the first injection, with a similar clearance pattern and rates. Those patients receiving IL-2 administered subcutaneously at a dose of 250,000 IU/kg had peak serum levels of 61 ± 34 IU/mL 2 to 3 hours after the injection, with a half-life of 5.3 ± 1.9 hours. Levels in excess of 18 IU/mL were maintained between injections in patients receiving either the high-dose intravenous or the subcutaneous regimen cited, but not the low-dose intravenous regimen. The relationship of these differing pharmacokinetic profiles to the biologic and antitumor effects of IL-2 remains to be determined.
**FIGURE 20.2-2.** Examples of pharmacokinetic studies on representative patients with metastatic renal cell carcinoma measuring biologically active serum interleukin (IL-2) levels after the first administration of recombinant IL-2 at (A) 72,000 IU/kg by intravenous bolus, (B) 72,000 IU/kg by intravenous bolus, or (C) 250,000 IU/kg by subcutaneous injection. (From ref. 56, with permission.)

### ATTEMPTS TO IMPROVE ACTIVITY OF INTERLEUKIN-2–BASED THERAPY

A number of approaches have been tried in an effort to improve the activity of IL-2–based therapy. These are listed in Table 20.2-3. Although preclinical laboratory and animal studies provided a strong rationale for the clinical investigations involving the combination of IL-2 and interferon-a (IFN-a), early clinical studies appeared promising, but subsequent clinical trials have not shown superiority for this combination relative to high-dose IL-2. Nonetheless, combinations of low-dose IL-2 with IFN have been developed that can be administered safely in an outpatient setting, and they appear to possess sufficient antitumor activity to enable them to be considered by many as an alternative to high-dose IL-2. In addition, low-dose IL-2 and IFN regimens have been better able to accommodate the addition of other potentially active agents, such as chemotherapy or cellular therapy.

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SECTION 20.3
Hormonal Therapies

INTRODUCTION

There are many hormonal agents used in the treatment of patients with cancer. The primary use of these agents is in hormonally responsive cancers such as breast, prostate, or endometrial carcinomas. Other uses for some hormonal therapies include paraneoplastic syndromes, such as carcinoid syndrome, or symptoms caused by cancer, including anorexia. This chapter discusses the major hormonal agents for such therapy, first with a general overview of their use in practice, then with more detailed pharmacologic information regarding them.

SELECTIVE ESTROGEN RECEPTOR MODULATORS

TAMOXIFEN

Tamoxifen is most frequently used in the adjuvant treatment of women with resected breast cancer. There is general consensus, at present, that tamoxifen should be continued for 5 years. Tamoxifen is also used for treating patients with metastatic breast cancer if their disease has characteristics that would suggest hormonal responsiveness. In addition, tamoxifen has undergone prospective evaluation as a potential breast cancer chemoprevention drug. The study reported that tamoxifen decreased the incidence of breast cancer by approximately 50%. Nonetheless, this treatment has not been widely used to date in clinical practice for several reasons, including: (1) the vast majority of treated patients do not get benefit; (2) there is not yet any significant effect on patient survival; (3) the economic cost of the drug is high; (4) toxicities occur from this drug; and (5) the findings of this study have not been confirmed by two ongoing European trials (which underwent interim analyses).

The standard dose of tamoxifen is 20 mg. The long terminal half-life of the drug indicates that this can be given once daily. Tamoxifen is among the least toxic antineoplastic agents. Randomized, placebo-controlled trials have demonstrated that it does not cause any more gastrointestinal symptoms than placebo. The most prominent toxicity from tamoxifen is hot flashes, which affect approximately one-half of women. These hot flashes are of varying intensity and varying duration. Tamoxifen-induced hot flashes appear to increase over the first 3 months of therapy and then plateau. They appear to be more prominent in women with a prior history of hot flashes or a prior history of using estrogen replacement. They can be ameliorated by the concurrent use of low doses of megestrol.

The estrogenic properties of tamoxifen are responsible for both beneficial and deleterious side effects. The most prominent deleterious one, endometrial cancer, is increased approximately threefold in incidence over the general population. It has not yet been determined if progestins can prevent this toxicity of tamoxifen as they do with estrogen treatment. Beneficial estrogenic effects from tamoxifen include a decrease in total cholesterol, a suggestion of decreased cardiovascular disease, and a preservation of bone density in postmenopausal women. In premenopausal women, tamoxifen appears to have a negative effect on bone density. Although most patients do not complain of vaginal symptoms, a few complain of vaginal dryness, whereas others have increased vaginal secretions with a resultant vaginal discharge. An uncommon effect from tamoxifen is retinal toxicity. This has usually been associated with high drug doses or prolonged drug use. Tamoxifen may predispose to thromboembolic phenomena, especially if used with concomitant chemotherapy. Depression has also been described, but this association with tamoxifen is not clear. Although liver cancers have been noted in laboratory animals, there is no clear-cut association between tamoxifen and liver cancers in humans.

Pharmacology

The chemical structure of tamoxifen is shown in Figure 20.3-1. It acts by blocking estrogen stimulation of breast cancer cells, inhibiting both translocation and nuclear binding of the estrogen receptor. This alters transcriptional and posttranscriptional events mediated by this receptor. In vivo, tamoxifen activity is complicated by the potential actions of the metabolite 4-hydroxy-tamoxifen, which is a potent antiestrogen. Tamoxifen has agonistic, partial agonistic, or antagonistic effects depending on the species, target, or end points that have been assessed. Other effects that have been attributed to tamoxifen include inhibition of the conversion of estrone sulfate to estradiol, inhibition of protein kinase C, and reversal of multidrug resistance.

![Figure 20.3-1. Structure of tamoxifen.](image-url)
Resistance to tamoxifen develops with resultant recurrence or progression of metastatic breast cancer. Several mechanisms for this resistance have been proposed. At each step of the signal transduction pathway with which tamoxifen interferes, there is potential for an alteration in response. Tamoxifen binds to the estrogen receptor, and subsequent translocation of this complex to the nucleus and binding to the estrogen response element occurs. This binding prevents transcriptional activation of estrogen-responsive genes. Decreased tamoxifen metabolism to the potent antianti estrogen 4-hydroxy-tamoxifen and increased metabolism to estrogenic compounds such as metabolite E have been proposed as possible mechanisms of resistance. In some cases resistance occurs after loss of estrogen receptor-positive cells. Although estrogen receptor mutation has been suggested as a mechanism of resistance, two groups have found little evidence for such changes in the estrogen receptor. Phosphorylation of the estrogen receptor can mediate the hormone binding, DNA binding, and ultimately transcriptional activation. Alterations in the phosphorylation mediated by changes in protein kinase A and C could lead to resistance. Finally, modifications of the estrogen-receptor element such as sequence alteration or element duplication may lead to binding of the tamoxifen-estrogen receptor complex with increased transcription of the estrogen-response genes. At present, the primary mechanisms of tamoxifen action remain unknown, and further studies are needed.

The carcinogenic potential of tamoxifen has been recognized in rat studies and in humans. Although the mechanism of these carcinogenic effects is not understood, it has been proposed that generation of reactive intermediates that bind covalently to macromolecules underlies the process. Such reactive intermediates have been demonstrated in vitro. In addition, induction of covalent DNA adducts in rat livers treated with tamoxifen has been reported. Both constitutive and inducible cytochrome P-450 enzymes have been implicated in the formation of metabolites with tamoxifen, and the flavine-containing monooxygenase has been implicated in the formation of the N-oxide of tamoxifen. Reactive intermediates from such metabolic steps are being evaluated for their carcinogenic potential in vitro and in vivo.

The pharmacokinetics of tamoxifen have not been fully elucidated despite clinical use of the drug for more than 20 years. The oral bioavailability is not known. Results from animal studies suggest that the drug is well absorbed. Oral administration of [14C]tamoxifen results in only 30% of radioactive material detectable in feces and approximately 11% in urine. Whereas oral absorption may be good, first-pass metabolism may significantly alter exposure in vivo. The metabolic pathway of tamoxifen outlined in Figure 20.3-2 is dependent on the cytochrome P-450 3A subfamily-mediated demethylation and hydroxylation (possibly by an as yet undefined cytochrome P-450 isoenzyme) followed by glucuronidation and biliary excretion. 4-Hydroxy-tamoxifen, which exists as two stereoisomers, is a potent antiestrogen as the trans-isomer, but is much less potent as the cis-isomer. The predominant species in serum are N-desmethyl-tamoxifen and N-desmethyl-4-hydroxy-tamoxifen whereas 4-hydroxy-tamoxifen and 4-hydroxy-N-desmethyl-tamoxifen and metabolite Y, which are more hydrophilic, are found in lower concentrations. Mechanisms affecting the activity of tamoxifen by the hydroxylated metabolites have higher affinity for the estrogen receptor than the parent compound. Tamoxifen is 98% bound to human serum albumin. A -acid glycoprotein binding by tamoxifen may have an impact on its clinical activity because the presence of a -acid glycoprotein in tissue cultures abolishes the inhibitory effect of tamoxifen and toremifene on P glycoprotein.

![FIGURE 20.3-2. Tamoxifen metabolism.](image)

Peak plasma levels of tamoxifen (Cmax) are seen 3 to 7 hours after oral administration. Assuming an oral bioavailability of 30%, the volume of distribution has been calculated to be 20 L/kg, and plasma clearance ranges from 1.2 to 5.1 L/h. The terminal half-life of tamoxifen has been reported to range between 4 and 11 days. The elimination half-life of tamoxifen increases with successive doses. This finding is consistent with tamoxifen inhibition of its own metabolism. The drug's distribution in the tissues and plasma and metabolites have been reported to be higher in tissue than in plasma in animal studies. The metabolism of tamoxifen concentrations 10- to 60-fold higher than plasma concentrations in liver, lung, brain, pancreas, skin, and bone have appeared. Concentrations of tamoxifen in pleural, pericardial, and peritoneal effusions approach those in plasma, with effusion to serum ratios ranging between 0.2 and 1.0. These findings are consistent with the large calculated volume of distribution. Elevated levels of tamoxifen with biliary obstruction have been reported.

Tamoxifen has been reported to interact with coumadin, digitoxin, phenytoin, and medroxyprogesterone. Lien et al have reported that tamoxifen serum concentrations and those of metabolites Y, 4-hydroxy-tamoxifen, 4-hydroxy-N-desmethyl-tamoxifen, N-desmethyl-tamoxifen, and N-desdimethyl-tamoxifen are markedly reduced after aminoglutethimide administration. The mean increase in tamoxifen clearance was 249% when administered with aminoglutethimide. Elevated levels of tamoxifen with biliary obstruction have been reported.

Toremifene , an agent similar to tamoxifen, is thought to be a more pure antiestrogen. It has become available in the United States for the treatment of patients with metastatic breast cancer. A randomized comparison of toremifene and tamoxifen in metastatic breast cancer suggested that these two medications were equivalent. Toremifene, an agent similar to tamoxifen, is thought to be a more pure antiestrogen. It has become available in the United States for the treatment of patients with metastatic breast cancer. A randomized comparison of toremifene and tamoxifen in metastatic breast cancer suggested that these two medications were equivalent. Clinical trials in postmenopausal women with metastatic breast cancer concluded that there is major cross-resistance between tamoxifen and toremifene.

**Pharmacology**

Toremifene is an antiestrogen with a chemical structure that differs from that of tamoxifen by the substitution of a chlorine for a hydrogen atom that is retained when toremifene undergoes metabolism. Like tamoxifen, toremifene is metabolized by cytochrome P-450 3A. Toremifene and its 4-hydroxylated metabolite both bind to the estrogen receptor. Although the oral bioavailability has not been defined, toremifene's oral absorption appears to be good. The time to peak plasma concentrations after oral administration ranges from 1.5 to 6.0 hours, with the terminal half-lives for toremifene and one metabolite, 4-hydroxy toremifene, being 5 to 6 days. The apparent clearance is 5.1 L/h. The terminal half-life for the major metabolite, N-desmethyl-toremifene, is 21 days. Time to reach plasma steady-state concentrations is 1 to 5 weeks. Plasma protein binding is more than 99%. As with tamoxifen, toremifene tissue distribution in rats has been studied and found to be extensive and in high concentrations. Consistent with this is the high apparent volume of distribution, 958 L. Seventy percent of the drug is excreted in feces as metabolites. Studies in patients with impaired liver function secondary to alcoholic cirrhosis and in patients on anticonvulsants known to induce cytochrome P-450 3A have been undertaken. Those patients with hepatic dysfunction had decreased clearance of toremifene and N-desmethyl-toremifene, whereas those patients on anticonvulsants had an increased clearance. Interestingly, toremifene appears to be less carcinogenic than tamoxifen in preclinical models.

**RALOXIFENE**

Raloxifene is an estrogen agonist and antagonist that was initially developed as an anti-breast cancer agent. Initial studies were not promising regarding this approach, but large placebo-controlled randomized studies have reported that this drug does retard osteoporosis in women at risk for such. These studies demonstrated an apparent reduction in breast cancer in treated women, leading to the development of a second-generation breast cancer chemoprevention trial in which it will be compared with tamoxifen in high-risk postmenopausal women. Although this drug is relatively well tolerated, it can produce hot flashes. A potential
advantage for raloxifene over tamoxifen is that it does not appear to induce endometrial cancer.

**Pharmacology**

Raloxifene is partially estrogenic in bone and lowers cholesterol.

It is antiestrogenic in mammary tissue and uterine tissue.

The mechanism whereby raloxifene exerts tissue-selective effects is not clear. Several hypotheses have been proposed. Coactivators and corepressor proteins are involved in the transcription complex when estrogen receptor is bound. There may be differential distribution of these coactivators or corepressors, which are responsible for the changes in estrogenicity seen in tissue. The discovery of a second estrogen, estrogen receptor-β, with 55% homology between it and estrogen receptor-α raises the possibility that there is a differential expression of these two estrogen receptors in different tissue.

This presence of two forms of the receptor also raises the possibility that there are different downstream effectors when one or the other estrogen receptor is activated.

The pharmacokinetics of raloxifene have been studied principally in postmenopausal women. Pharmacokinetic parameters of raloxifene show considerable interindividual variation. Limited information is available on the pharmacokinetics of raloxifene in individuals with hepatic impairment, renal impairment, or both.

Raloxifene is rapidly absorbed from the gastrointestinal tract. Because raloxifene undergoes extensive first-pass glucuronidation, oral bioavailability of unchanged drug is low. While approximately 60% of an oral dose is absorbed, absolute bioavailability as unchanged raloxifene is only 2%. However, systemic availability of raloxifene may be greater than that indicated in bioavailability studies because circulating glucuronide conjugates are converted back to the parent drug in various tissues.

Following oral administration of a single 120- or 150-mg dose of raloxifene hydrochloride, peak plasma concentration of raloxifene and its glucuronide conjugates are achieved at 6 and 1 hours, respectively. Plasma concentrations of raloxifene's glucuronide conjugates exceed those of the parent drug, and the time to achieve maximum concentrations of the drug and glucuronide metabolites depends on the extent and rate of systemic interconversion and enterohepatic circulation. Following oral administration of radiolabeled raloxifene, less than 1% of total circulating radiolabeled material in plasma represents parent drug.

Area under the curve (AUC) for plasma concentration-time of raloxifene following a single dose is the same as the AUC following multiple doses of the drug.

Increasing the dose of raloxifene hydrochloride over a range of 30 to 150 mg results in a slightly less than proportional increase in the AUC of raloxifene.

Administration of raloxifene with a standardized high-fat meal increases the raloxifene peak plasma concentration by 28% and AUC by 16%, when compared with administration on an empty stomach, but does not result in clinically important changes in systemic exposure.

Results of a single-dose study in patients with cirrhosis of the liver (Child-Pugh class A) and total serum bilirubin concentrations of 0.6 to 2.0 mg/dL indicate that plasma raloxifene concentrations correlate with serum bilirubin concentrations and are 2.5 times higher in such individuals compared with normal individuals with normal hepatic function. In postmenopausal women receiving raloxifene in clinical trials, plasma concentrations of raloxifene and the glucuronide conjugates in those with renal impairment (i.e., estimated creatinine clearance values as low as 23 mL/min) were similar to values in women with normal renal function.

Distribution of raloxifene into body tissues and fluids has not been fully characterized. Raloxifene and raloxifene 4'-glucuronide have been detected in saliva following oral administration of radiolabeled drug. In studies in rats given radiolabeled raloxifene 6-glucuronide, the liver contained the highest concentration of radioactivity, followed by serum, lung, and kidney. While bone and the uterus contained relatively low concentrations of radiolabeled metabolite, 24% of the radioactivity in bone, 14% in the uterus, and 23% in the liver represented raloxifene. Results of this study indicate that the conversion of metabolite to parent drug occurs readily in a variety of tissues including the liver, lung, spleen, kidney, bone, and uterus. The apparent volume of distribution following oral administration of single doses of raloxifene hydrochloride, 30 to 150 mg, is 2348 L/kg, suggesting extensive tissue distribution. The volume of distribution is not dose dependent over a dosage range of 30 to 150 mg daily.

Raloxifene and its monoglucuronide conjugate are more than 95% bound to plasma proteins. Raloxifene binds to albumin and a -acid glycoprotein.

Raloxifene undergoes extensive first-pass metabolism to the glucuronide conjugates raloxifene 4'-glucuronide, 6-glucuronide, and 6,4'-diglucuronide. Metabolism of raloxifene does not appear to be mediated by cytochrome P-450 enzymes, since metabolites other than glucuronide conjugates have not been identified.

The plasma elimination half-life of raloxifene at steady state averages 32.5 hours (range, 15.8 to 66.6 hours).

Raloxifene is excreted principally in feces as unabsorbed drug and via biliary elimination as glucuronide conjugates, which subsequently are metabolized by bacteria in the gastrointestinal tract to the parent drug. Following oral administration, less than 0.2% of a raloxifene dose is excreted as parent compound and less than 6% as glucuronide conjugates in urine.

**MEDROXYPROGESTERONE AND MEGESTROL**

Medroxyprogesterone and megestrol are 17-OH-progesterone derivatives differing in a double bond between C6 and C7 positions in megestrol. Megestrol has been extensively evaluated for the treatment of anorexia-cachexia related to cancer or acquired immunodeficiency syndrome. Various dosages ranging from 160 to 1600 mg/d have been used. Prospective studies have demonstrated dose-response relationship with doses up to 800 mg/d. Low dosages of megestrol (40 mg/d) have been shown to be an effective means of reducing hot flashes in women with breast cancer and in men who have undergone androgen ablation therapy. Although megestrol historically had been commonly administered four times per day, the long terminal half-life supports that once per day dosing is reasonable.

Megestrol is a relatively well-tolerated medication, with its most prominent side effect being appetite stimulation and resultant weight gain. While this may be a beneficial effect in patients with anorexia-cachexia, it can be an important problem in patients with breast or endometrial cancers. Another side effect of megestrol acetate is the marked suppression of adrenal steroid production by suppression of the pituitary-adrenal axis. At a dosage of 320 mg/d. In addition, dosages of 160 mg/d are occasionally used as a hormonal therapy for prostate cancer. Megestrol has also been extensively evaluated for the treatment of anorexia-cachexia related to cancer or acquired immunodeficiency syndrome. Various dosages ranging from 160 to 1600 mg/d have been used. Prospective studies have demonstrated dose-response relationship with doses up to 800 mg/d. Low dosages of megestrol (40 mg/d) have been shown to be an effective means of reducing hot flashes in women with breast cancer and in men who have undergone androgen ablation therapy. Although megestrol historically had been commonly administered four times per day, the long terminal half-life supports that once per day dosing is reasonable.

Megestrol is a relatively well-tolerated medication, with its most prominent side effect being appetite stimulation and resultant weight gain. While this may be a beneficial effect in patients with anorexia-cachexia, it can be an important problem in patients with breast or endometrial cancers. Another side effect of megestrol acetate is the marked suppression of adrenal steroid production by suppression of the pituitary-adrenal axis. This appears to be an asymptomatic state in the majority of patients, reports suggest that this adrenal suppression can cause clinical problems in some patients. This drug has been abruptly stopped for decades without recognizing untoward sequelae in patients, and it seems reasonable to continue this practice. Nonetheless, if Addisonian signs or symptoms develop after drug discontinuation, corticosteroids should be administered. Furthermore, if patients receiving megestrol have a significant infection, experience trauma, or undergo surgery, then corticosteroid coverage should be administered. There may be a slight increased incidence of thromboembolic phenomena in patients receiving megestrol acetate. This risk appears to be higher in patients concomitant cytotoxic therapy is administered. There are conflicting reports regarding megestrol causing edema. If it does, it is generally minimal and easily handled with a mild diuretic. Megestrol may cause impotence in some men. The incidence of this is controversial, although it generally is agreed that this is a reversible situation. Megestrol can cause menstrual irregularities, the most prominent of which is withdrawal menstrual bleeding within a few weeks of drug discontinuation. Although nausea and vomiting have been attributed as a toxicity, there are good data to demonstrate that this drug has anantiemetic properties. In terms of magnitude, megestrol appears to decrease both nausea and vomiting in advanced-stage cancer patients by approximately two-thirds.

Medroxyprogesterone has many of the same properties, clinical uses, and toxicities as megestrol acetate. It is not used commonly in the United States, but has been used in Europe. Medroxyprogesterone is available in 2.5- and 10.0-mg tablets and in injectable formulations of 100 and 400 mg/L. Dosing for treatment of metastatic breast or prostate cancer is 400 mg/wk or more and for metastatic endometrial cancer, 1000 mg/wk or more. Smaller injectable or daily oral doses have been used for controlling hot flashes.

**PHARMACOLOGY**

The exact mechanism of antitumor effect of medroxyprogesterone and megestrol is unclear. These drugs have been reported to suppress adrenal steroid synthesis, suppress estrogen receptor levels, alter tumor hormone metabolism, enhance steroid metabolism, and directly kill tumor cells. In addition to this, progestins may influence some growth factors, suppress plasma estrone sulfate formation, and, at high concentrations, inhibit P-glycoprotein.
The oral bioavailability of these progestational agents is unknown, although absorption appears to be poor for medroxyprogesterone relative to megestrol. The terminal half-life for megestrol is approximately 14 hours \(^{60,99}\) with a \(t_{\text{max}}\) of 2 to 5 hours after oral ingestion. \(^{102}\) The AUC for a single megestrol dose of 160 mg is between 2.5- and 8-fold higher than that for single-dose medroxyprogesterone at 1000 mg. Of the radioactive dose of megestrol, 50% to 78% is found in the urine after oral administration, and 8% to 30% in the feces. Three glucuronide metabolites of megestrol have been identified in the urine: megestrol hydroxylated in the 2 position and the 6-methyl position, or both. They account for only 5% to 8% of the radioactive dose administered. Metabolism and excretion of megestrol have been incompletely characterized. In humans, 20% to 50% of a [3H] medroxyprogesterone dose is excreted in the urine and 5% to 10% in the stool following intravenous administration. \(^{125,126}\) Metabolism of medroxyprogesterone occurs via hydroxylation, reduction, demethylation, and combinations of these different reactions. \(^{127}\) The major urinary metabolite is a glucuronide. Less than 3% of the dose is excreted as unconjugated medroxyprogesterone in humans. Clearance of medroxyprogesterone has been reported to range between 27 and 70 L/h. \(^{144}\) The initial volume of distribution is between 4 and 8 L in humans. The mean terminal half-life is 60 hours. The \(t_{\text{max}}\) for medroxyprogesterone occurs 2 to 5 hours after oral administration. Medroxyprogesterone appears to be concentrated in small intestine, colon, and adipose tissue in human autopsy studies. \(^{145}\) Drug interactions of medroxyprogesterone have been reported with aminoglutethimide, which decreases plasma medroxyprogesterone levels. \(^{146}\) Medroxyprogesterone may reduce the concentration of the N-desmethyl-tamoxifen metabolite concentration. Progestational agents also may increase plasma coumadin levels. \(^{147}\) These reports are consistent with cytochrome P-450 3A being the site of interaction.

**AROMATASE INHIBITORS**

**AMINOGLUTETHIMIDE**

Aminoglutethimide was the first clinically used aromatase inhibitor. When it became available, it was used to cause a medical adrenalectomy. A 32% response rate in metastatic breast cancer has been reported. Aminoglutethimide is infrequently used for treating metastatic breast cancer because there are other available hormonal treatments with less toxicity. Aminoglutethimide has also occasionally been used to try to reverse excess hormone production by adrenocortical cancers. \(^{148}\)

For treatment of metastatic breast cancer before other aromatase inhibitors became available, aminoglutethimide was started at a dose of 250 mg/d, increasing doses every couple of days to twice a day, then three times a day, and sometimes four times a day. Replacement hydrocortisone was often started at 100 mg/d for a week and then decreased to 40 mg/d. Aminoglutethimide doses less than 500 mg/d did not require corticosteroid replacement. \(^{112}\) For suppression of hormone production by adrenocortical cancers, doses may be increased to 2 g/d.

Toxicities most frequently associated with aminoglutethimide are lethargy, orthostatic hypertension, nausea, vomiting, hypothyroidism, reversible agranulocytosis, and rash. \(^{116,117}\) The rash is generally self-limited and usually disappears despite the discontinuation of aminoglutethimide. However, a severe rash leading to a Stevens-Johnson syndrome can occur.

**Pharmacology**

Aminoglutethimide (Fig. 20.3-3) suppresses postmenopausal estrogen synthesis by inhibiting the conversion of circulating androgens into estrogens. Androstenedione is peripherally converted to estrone by cytochrome P-450 aromatase. Estrone can be further converted to estradiol by the enzyme, hydroxysteroid dehydrogenase. Aromatase inhibitors block estrogen production in postmenopausal women or oophorectomized premenopausal women by 90% inhibition of peripheral conversion of androstenedione to estrone, whereas ovarian estrogen synthesis is maintained by gonadotropin release in the premenopausal women with intact ovarian function. Another biochemical effect of aminoglutethimide includes the inhibition of several enzymes in adrenal steroid synthesis, which may lead to mineralocorticoid deficiency. \(^{118,119}\) Aminoglutethimide effect on adrenal steroid synthesis is complex. \(^{120}\) Suppression of circulating plasma cortisol may occur, but a compensatory increase in pituitary corticotropin (previously adrenocorticotropic hormone) levels may overcome this suppression. Because aminoglutethimide is a competitive inhibitor of aromatase, increased adrenal steroid synthesis may compete with aminoglutethimide at the level of the aromatase. Concomitant replacement doses of hydrocortisone addresses both potential effects on adrenal steroid synthesis. Aminoglutethimide is administered as a racemic mixture with different biologic effects. \(^{119}\) The \(d\) form is the more potent inhibitor of adrenal steroid synthesis and aromatase activity. The pharmacokinetic characteristics of the separate enantiomers have not been characterized. Aminoglutethimide is absorbed well, with 80% to 98% of a radioactive dose recovered in the urine within 72 hours. Only 1% of the drug is excreted unchanged in the feces. Of the administered aminoglutethimide dose, 12% to 20% is excreted unmetabolized in the urine, and 3% to 7% is excreted as the N-acetyl-aminoglutethimide. \(^{121}\) The \(t_{\text{max}}\) occurs 0.5 to 4.0 hours after oral administration in fasting patients. The clearance of the drug ranges from 1.5 to 6.0 L/h with a mean of 3 L/h. The volume of distribution is 66 to 70 L. Aminoglutethimide undergoes acetylation \(^{122}\) and is cleared more rapidly in fast acetylators [half-life \(t_{\text{1/2}} = 12.6\) hours] than in slow acetylators \(t_{\text{1/2}} = 19.5\) hours. After 7 days of treatment, the half-life in slow acetylators decreased from 19.5 to 14.3 hours and in fast acetylators, from 12.6 to 8.6 hours. This was associated with an increased apparent systemic clearance of chronically administered aminoglutethimide and indicates autoinduction of this drug’s metabolism. \(^{122}\) Lønning and associates have reported a decrease in volume of distribution on repeated dosing, which may also contribute to the decreased terminal half-life. Aminoglutethimide is approximately 25% bound to plasma proteins. Little is known about aminoglutethimide tissue distribution in humans. The erythrocyte to plasma concentration ratio is 0.83:1. Aminoglutethimide induces mixed function oxidases, enhancing the metabolism of coumarin, dexamethasone, theophylline, and digitoxin. Also, aminoglutethimide has been reported to decrease concentrations of progestational agents and tamoxifen. \(^{123}\) These drug interactions implicate cytochrome P-450 3A in aminoglutethimide metabolism. The increased clearance of progestational agents and tamoxifen in the presence of aminoglutethimide makes the interpretation of studies that combine this aromatase inhibitor with tamoxifen or progesterone difficult. Alterations in the blood levels of antiestrogen or progestational agents may have decreased their contribution to any therapeutic benefit.

![Figure 20.3-3. Structure of aminoglutethimide.](image)

A series of second-generation aromatase inhibitors have been synthesized and many are undergoing clinical trials. These include rologlutimide, formestane, fadrozole, letrozole, exemestane, vorozole, and anastrozole. \(^{124,125,127}\)

**LETROZOLE AND ANASTROZOLE**

Letrozole and anastrozole are available in the United States for women with metastatic breast cancer. These second-generation aromatase inhibitors have basically replaced aminoglutethimide for breast cancer given their better toxicity profile. Headaches were the most common toxicity in a phase I trial. \(^{128}\) It is not necessary to give replacement doses of corticosteroids as was previously done with aminoglutethimide. Letrozole and anastrozole appear to be similar drugs in clinical practice. Randomized trials have demonstrated that they are better hormonal agents for treating tamoxifen-resistant breast cancer than is megestrol acetate.
Letrozole is a nonsteroidal aromatase inhibitor with a high specificity for inhibition of estrogen production. Letrozole is 180 times more potent than aminoglutethimide as an inhibitor of aromatase in vitro. Aldosterone production in vitro is inhibited by concentrations 10,000 times higher than those required for inhibition of estrogen synthesis. In a normal male volunteer study, letrozole was shown to decrease estradiol and serum estrone levels to 10% of baseline with a single 3-mg dose. In phase I studies, letrozole caused a significant decline in plasma estrone and estradiol within 24 hours of a single oral dose of 0.1 mg. Following 2 weeks of treatment, the blood levels of estradiol, estrone, and estrone sulfate were suppressed by up to 80% and returned to normal within 12 weeks of therapy. There was no apparent alteration in plasma levels of cortisol and aldosterone with letrozole or following corticotropin stimulation.

In postmenopausal women with advanced breast cancer, the drug did not have any effect on follicle-stimulating hormone (FSH), luteinizing hormone (LH), thyrotropin (previously thyroid-stimulating hormone), cortisol, 17-α-hydroxyprogesterone, androstenedione, or aldosterone blood levels.

Anastrozole is an aromatase inhibitor that is 200-fold more potent than aminoglutethimide. No effect on the adrenal glands has been detected. In human studies, the t1/2 is 2 to 3 hours after oral ingestion. Elimination is primarily via hepatic metabolism, with 85% excreted by that route and only 10% excreted unchanged in urine. The main circulating metabolite is triazole after cleavage of the two rings in anastrozole by N-dealkylation. Linear pharmacokinetics have been observed in the dose range of 1 to 20 mg and do not change with repeat dosing. The terminal half-life is approximately 50 hours and steady-state conditions are reached in approximately 10 days with once a day dosing and are three to four times higher than peak concentrations after a single dose. Plasma protein binding is approximately 40%. Anastrozole 1 mg and 10 mg daily inhibits in vivo aromatization by 96.7% and 98.1%, respectively, and plasma estrone and estradiol levels were suppressed 86.5% and 85.3% regardless of dose. Thus, 1 mg of anastrozole achieves maximal inhibition in plasma and estrogen suppression in breast cancer patients.

VOROZOLE

Vorozole is another aromatase inhibitor that is not currently available for clinical use, but is undergoing clinical trial evaluation.

Pharmacology

Vorozole, a racemic mixture of (+) and (-) enantiomers, is approximately 1000 times more effective than aminoglutethimide in the inhibiting human placental aromatase. The aromatase inhibitory activity is primarily due to the (+) enantiomer. This drug does not appear to affect cytochrome P-450–dependent cholesterol synthesis, cholesterol side-chain cleavage, 7-α-hydroxylation of cholesterol, or 21-hydroxylation. In rat ovarian, testicular, and adrenal cell cultures, vorozole affects progesterone, androgen, and glucocorticoid production at concentrations at least 1000 times greater than that required to inhibit aromatase.

In initial human studies, doses of 5 mg of the racemic mixture of vorozole resulted in 94.4% inhibition of peripheral aromatization, and, in healthy male volunteers, a single dose of the racemic mixture lowered plasma estradiol levels to the detection limits of the assay between 4 and 8 hours after drug administration. Johnston and associates reported a similar inhibition of plasma estradiol, estrone, androstenedione, and estrone sulfate with no significant effect on aldosterone, testosterone, androstenedione, 17-α-hydroxyprogesterone, and thyroid-stimulating hormone. Vorozole is rapidly absorbed, with peak plasma concentrations obtained 1 hour after oral intake. Peak plasma concentrations and area under the concentration-time curve of vorozole are proportional to the dose. Vorozole displays a biphasic disposition curve with a mean terminal half-life ranging from 4.7 to 7.5 hours. The total body clearance ranges from 6.1 to 11.8 L/h in a single dose study in normal healthy male volunteers.

GONADOTROPIN-RELEASING HORMONE ANALOGUES

Gonadotropin-releasing hormone (GnRH) analogues result in a profound inhibition of the pituitary-gonadal axis.

Letrozole is a nonsteroidal aromatase inhibitor with a high specificity for inhibition of estrogen production. Letrozole is 180 times more potent than aminoglutethimide.

Gonadotropin-releasing hormone analogues result in a medical orchectomy in men and are used as a means of providing androgen ablation for metastatic prostate cancer.

Because the initial agonist activity of GnRH analogues can cause a tumor flare from temporarily increased androgen levels, concomitant use of the antiandrogen, flutamide, has been used to prevent this effect. GnRH analogues can also cause tumor regressions in hormonally responsive breast cancers and have recently received U.S. Food and Drug Administration approval for treatment of metastatic breast cancer in premenopausal women. Emerging data suggest that these drugs may be useful as adjuvant therapy of premenopausal women with resected breast cancer.

The primary toxicities of GnRH analogues are secondary to the ablation of sex steroid concentrations and include hot flashes, sweating, and nausea. These symptoms can be reversed with low doses of prostaglandins.

These drugs are administered intramuscularly or subcutaneously in a parenteral sustained-release microcapsule preparation because parenteral administration of the parent drug otherwise is associated with rapid clearance. The GnRH analogues are metabolized in the liver, kidney, hypothalamus, and pituitary gland by neutral peptidase cleavage of the peptide bond between the tyrosine in the 5 position and the amino acid in position 6, and a postproline cleaving enzyme that cleaves the peptide bond between proline in the 9 position and the amino acid in position 10. These changes increase the affinity of the D-amino acid for the GnRH receptor and decrease the susceptibility to enzymatic degradation. There is an amino acid structure of GnRH with the substitutions for leuprolide and goserelin. Initial administration of these compounds results in stimulation of gonadotropin release. However, prolonged administration has led to profound inhibition of the pituitary-gonadal axis. Plasma estradiol and progesterone are consistently suppressed to postmenopausal or castrate levels after 2 to 4 weeks of treatment with goserelin or leuprolide. These drugs are administered intramuscularly or subcutaneously in a parenteral sustained-release microcapsule preparation because parenteral administration of the parent drug otherwise is associated with rapid clearance. The GnRH analogues are metabolized in the liver, kidney, hypothalamus, and pituitary gland by neutral peptidase cleavage of the peptide bond between the tyrosine in the 5 position and the amino acid in position 6, and a postproline cleaving enzyme that cleaves the peptide bond between proline in the 9 position and the amino acid in position 10. Substitutions at the glycine 6 position and modification of the C-Terminal make these analogues more resistant to this enzymatic cleavage.

Leuprolide is approximately 80 to 100 times more potent than the naturally occurring GnRH. It induces castrate levels of testosterone in men with prostate cancer within 3 to 4 weeks of drug administration after an initial sharp increase in LH and FSH. The mechanisms of action include pituitary desensitization following reduction in pituitary GnRH receptor-binding sites and possibly a direct antitumor effect in estrogen receptor-positive human breast cancer cells. The depot form results in a dose rate of 210 μg of leuprolide per day. Plasma concentrations of the depot form that are achieved at approximately 3 hours after drug administration have been reported to range between 13.1 and 54.5 μg/L. There appears to be a linear increase in the AUC for doses of 3.75, 7.5, and 15.0 mg in the depot form. The parenteral bioavailability of subcutaneously injected leuprolide is 94%. The volume of distribution ranges from 27.4 to 37.1 L. In human studies, leuprolide urinary excretion as a metabolite was the primary route of clearance.

Goserelin is approximately 100 times more potent than the naturally occurring GnRH. Like leuprolide, it causes stimulation of LH and FSH acutely, and with subsequent administration, GnRH receptor numbers decrease and the pituitary becomes desensitized with decreasing LH and FSH levels. Castrate levels of testosterone are achieved within 1 month. In women, goserelin inhibits ovarian androgen production, but serum levels of dihydroepiandrosterone sulfate, and to a lesser extent androstenedione, are preserved. In vitro, goserelin has demonstrated antitumor activity in estrogen-dependent MCF-7 human breast cancer cells and LNCaP-2 prostate cancer cells. The drug is released at a continuous mean rate of 120 μg/d in the depot form, with peak concentrations in the range of 2 to 3 μg/L. The mean volume of distribution in six patients has been reported to be 13.7 L, consistent with extracellular fluid volume. Goserelin is principally excreted in the urine, with a mean total body clearance of 8 L/h in patients with normal renal function. The total body clearance is reduced by approximately 75%, with renal dysfunction and the elimination half-life increased two- to threefold. However, dose adjustment for renal insufficiency does not appear to be necessary. The 5 to 10 hexapeptide and the 4 to 10 hexapeptide were detected in urine in animal studies. The terminal half-life of goserelin is approximately 5 hours after subcutaneous injection. Protein binding is low, and no known drug interactions have been documented.

ANTIANDROGENS

FLUTAMIDE

The antiandrogen flutamide is used in men with metastatic prostate cancer either as initial therapy, combined with GnRH analogue administration, or when the
metastatic prostate cancer is unresponsive despite androgen ablation therapy. The recommended dosage is 250 mg orally three times a day. In patients whose prostate cancer is growing despite flutamide use, stopping flutamide can clearly cause a flutamide-withdrawal response.

The most common toxicity seen with flutamide is diarrhea with or without abdominal discomfort. Gynecomastia, which can be tender, frequently occurs in men who are not receiving concomitant androgen ablation therapy. Flutamide can rarely cause hepatotoxicity, a condition that is reversible if detected early, but can also be fatal. There is no accepted clinically recommended testing schedule to screen for flutamide-induced hepatotoxicity other than being aware of this phenomenon and testing for liver function if hepatic symptoms develop.

**Pharmacology**

Flutamide is a pure antiandrogen with no intrinsic steroidal activity. Flutamide's mechanism of action is as an androgen-receptor antagonist. This binding prevents the dihydrotestosterone binding and subsequent translocation of the androgen-receptor complex into the nuclei of cells. Because it is a pure antiandrogen, it acts only at the cellular level with no progesterational effects. Administration by flutamide alone leads to increased LH and FSH production and a concomitant increase in plasma testosterone and estradiol levels. Plasma protein binding of flutamide ranges between 94% and 96%, and for 2-hydroxy-flutamide, its major metabolite ranges between 92% and 94%. When the drug is administered three times a day, steady-state levels are achieved by day 6. The steady-state C_{max} is 112.7 ng/L and occurs at approximately 1.13 hours after drug administration. The steady-state C_{min}s between three and five times higher than after the first dose. The elimination half-life at steady state is 7.8 hours. 2-Hydroxy-flutamide achieves concentrations 50 times higher than the parent drug at steady state and has a potency equal to or greater than that of flutamide. The mean C_{max} averaged 1719 ng/mL at steady state and was achieved 1.5 hours after drug administration. The elimination half-life for the metabolite is 9.6 hours. The high plasma concentrations of 2-hydroxyflutamide, as compared with flutamide, suggest that the therapeutic benefits of flutamide are mediated primarily through its active metabolite.

**BICALUTAMIDE (CASODEX)**

Casodex is another nonsteroidal antiandrogen that has been approved by the U. S. Food and Drug Administration for use in the United States. The recommended dose is one 50-mg tablet per day. One randomized trial reported that Casodex compared favorably with flutamide in patients with advanced prostate cancer. Casodex appears to be relatively well tolerated and is associated with a lower incidence of diarrhea than is flutamide.

**Pharmacology**

Casodex has a binding affinity to the androgen receptor in the rat prostate that is four times greater than that of 2-hydroxy-flutamide. In vivo, Casodex caused marked inhibition of growth of accessory sex organs in rats with a potency five to ten times greater than flutamide. Unlike flutamide, Casodex did not cause a significant increase in LH or testosterone in rats. Casodex bioavailability in humans has not been defined. The drug has a long plasma half-life of 5 to 7 days such that the drug may be administered on a weekly schedule. Pharmacokinetics of the drug showed a dose-dependent increase in mean peak plasma concentrations, and the AUC increased linearly with dose. The half-life of Casodex in humans was approximately 6 days, and the drug clearance was not saturable at plasma concentrations up to 1000 ng/mL. Daily dosing of the drug led to an approximately ten-fold accumulation after 12 weeks of administration. In contrast to rats, serum concentrations of testosterone and LH increased significantly from baseline at all dose levels tested in humans. Whereas serum FSH concentrations remained essentially unchanged, the median serum estradiol concentrations increased significantly.

**NILUTAMIDE**

Nilutamide represents the third variation of antiandrogens available for use in patients with prostate cancer. Although it may be less expensive than the other antiandrogens, it has two unique toxicities, night blindness and pulmonary toxicity, which limit its utility.

**Pharmacology**

Nilutamide is a newer nonsteroidal antiandrogen that has a high bioavailability with moderate plasma protein binding. It is extensively metabolized with less than 2% of parent drug accumulating in urine over 5 days. Oxidation of a methyl group forms two stereoisomeric metabolites whose pharmacokinetics and pharmacodynamics are not characterized. Sixty-two percent of oral drug is eliminated in the urine as metabolites. The terminal half-life varies from 38 to 59 hours. Steady-state levels are achieved in 2 to 4 weeks with 150 mg given twice a day with approximately a twofold accumulation of drug over that time.

**FLUOXYMESTERONE**

Fluoxymesterone is an androgen that has been used in women with metastatic breast cancer who have hormonally responsive cancers and who have progressed on other hormonal therapies such as tamoxifen, an aromatase inhibitor, and megestrol acetate. The usual dose is 10 mg given twice daily. Although the overall response rate is low for fluoxymesterone used in this clinical situation, there are some patients who have substantial antitumor responses lasting for months or even years.

Toxicities associated with fluoxymesterone are those that would be expected with an androgen: hirsutism, male-pattern baldness, voice lowering (hoarseness), acne, enhanced libido, and erythrocytosis. Fluoxymesterone can also cause elevated liver function test results in some patients and rarely has been associated with hepatic neoplasms.

**PHARMACOLOGY**

Fluoxymesterone is a chlorinated synthetic analogue of testosterone with potent androgenic and anabolic activity in humans. Limited pharmacologic information is available on this agent. Colburn, using a radioimmunoassay, studied two subjects after a single oral administration of a 50-mg dose. Peak serum concentrations were achieved between 1 and 3 hours after administration, with the average peak concentrations being 335 ng/mL. By 5 hours after drug administration, serum levels had declined to approximately 50% of the peak concentration. Urinary excretion of a 10-mg dose can be detected for 24 hours; and at least 6-hydroxy, 4 ene, 3 β, and 11 hydroxy metabolites of fluoxymesterone have been detected.

**DIETHYLSTILBESTROL AND ESTRADIOL (ESTRACE)**

Diethylstilbestrol (DES) used to be the primary hormonal therapy for postmenopausal metastatic breast cancer. Randomized comparative trials demonstrated that it had a similar response rate as tamoxifen. However, based on these trials, DES use was supplanted by tamoxifen primarily because DES has more toxicity. DES is occasionally used in metastatic breast cancer patients who have hormonally sensitive cancers that have failed to respond to multiple other hormonal therapies. The usual dose in this situation is 15 mg/d (either as a single dose or as divided doses). DES was also used as androgen ablation therapy in men with metastatic prostate cancer. Doses of approximately 3 mg/d result in testosterone levels that are seen in an anorchid state.

In women, DES may cause a number of toxicities. One of the most common is nausea and vomiting. It also can cause breast tenderness and a thickening of the nipple-areolar complex. DES increases the risk of thromboembolic phenomenon, and this may result in life-threatening complications. In men, DES results in increased thromboembolic events and mortality, thus limiting its use. It also causes painful gynecomastia. Although breast irradiation before DES administration appears to prevent this toxicity, it does not appear to help if it is given after the toxicity develops.

DES has not been clinically available in the United States in recent years but similar antitumor effects and toxicities are seen with Estrace, 1 mg orally three times a day.

**PHARMACOLOGY**

DES disposition studies in humans have been limited. In animal studies, the oral absorption is approximately 20%. The drug undergoes hepatic metabolism and is excreted as diestrol and hydroxydiestrol in urine. The parent compound has been detected in feces. After administration of a radioactive dose of DES,
approximately 40% of the drug was found in urine in the first 24 hours, with 87% of this being in the form of glucuronides. The peak plasma concentrations were achieved approximately 20 hours after ingestion and the terminal half-life for the radioactivity ranged between 2 and 3 days.

Estrace is a micronized form of estradiol. The pharmacology of estradiol has been extensively described in other texts.

**OCTREOTIDE**

Octreotide is an octapeptide analog of the 14 amino acid peptide somatostatin. Octreotide has a similar high affinity for somatostatin receptors as does its parent compound, with the exception of the C₂ receptor by 50% (IC₂₀) in the supranuclear region. Octreotide inhibits insulin, glucagon, pancreatic polypeptide, gastrin inhibitory polypeptide, and gastrin secretion. It has a much longer duration of action than the parent compound because of its greater resistance to enzymatic degradation. Its absorption following subcutaneous administration is rapid, and bioavailability is 100% after subcutaneous injection. Peak concentrations of 4 ng/ml are reached 30 minutes after an oral dose due to 20-40% of the corresponding intravenous injection. Both peak concentration and AUC for octreotide increase linearly with dose. The total body clearance in healthy volunteers is 9.6 L/h. Hepatic metabolism of octreotide accounts for 30% to 40% of the drug's disposition, and 11% to 20% is excreted unchanged in the urine. The volume of distribution ranges between 18 and 30 L and the terminal half-life is reported to be between 72 and 98 minutes. Sixty-five percent of the drug is protein bound primarily to the lipoprotein fraction. Because of the short half-life, classic octreotide is administered subcutaneously two or three times per day. A slow-release form of octreotide, designed for once per day administration, is now available.

**Pharmacology**

Octreotide is an 8 amino acid synthetic analogue of the 14 amino acid peptide somatostatin. Octreotide has a similar high affinity for somatostatin receptors as does its parent compound, with the exception of the C₂ receptor by 50% (IC₂₀) in the supranuclear region. Octreotide inhibits insulin, glucagon, pancreatic polypeptide, gastrin inhibitory polypeptide, and gastrin secretion. It has a much longer duration of action than the parent compound because of its greater resistance to enzymatic degradation. Its absorption following subcutaneous administration is rapid, and bioavailability is 100% after subcutaneous injection. Peak concentrations of 4 ng/ml are reached 30 minutes after an oral dose due to 20-40% of the corresponding intravenous injection. Both peak concentration and AUC for octreotide increase linearly with dose. The total body clearance in healthy volunteers is 9.6 L/h. Hepatic metabolism of octreotide accounts for 30% to 40% of the drug's disposition, and 11% to 20% is excreted unchanged in the urine. The volume of distribution ranges between 18 and 30 L and the terminal half-life is reported to be between 72 and 98 minutes. Sixty-five percent of the drug is protein bound primarily to the lipoprotein fraction.

**References**


INTRODUCTION

Chemotherapy treatment of certain tumors (notably germ cell cancers and neuroblastoma) is occasionally associated with persistence of residual tumors that on biopsy reveal only differentiated cells. These clinical observations, combined with in vitro data that morphologic differentiation can be induced in many cancer cell lines, have led to a resurgence of interest in the concept of induced cytodifferentiation as a means of cancer treatment. The identification of drugs that can induce an irreversible commitment to terminal differentiation (and consequently programmed cell death) has yielded some noteworthy successes.

RETINOIDS

Retinoids, which are natural or synthetic derivatives of vitamin A (retinol), induce cellular differentiation, suppress carcinogenesis, or inhibit proliferation of a number of cell lines, including epithelial cancers, melanoma, neuroblastoma, leukemia, germ cell, bone, and breast cancers. These findings have generated widespread interest in these agents for cancer treatment and prevention. Several retinoids (all-trans retinoic acid [RA] and 9-cis RA) are normally found in plasma at nanomolar concentrations. Most retinoids bind to nuclear proteins that are RA receptors (RARs). Cofactors, called retinoid X receptors (RXRs), dimerize with RARs (Fig. 20.4-1), as well as receptors for thyroid hormone, vitamin D, and peroxisome proliferation activators. These receptor dimers bind specific DNA segments within target genes known as retinoid response elements. Activation of the receptor requires binding of its ligand, which then regulates transcription in part via recruitment of histone acetyltransferases. Importantly, nonactivated receptors have important roles in silencing basal transcription of target genes via interaction with nuclear corepressor proteins that recruit histone deacetylases.

FIGURE 20.4-1. Metabolism of all-trans retinoic acid (RA). RA enters the cell by simple diffusion or by conversion from retinol (vitamin A) that has been absorbed from the gastrointestinal tract. In the cell, RA is bound in circulating form to retinol-binding proteins (CRBP), and rebound intracellularly to cellular retinol-binding proteins (CRBP). RA can be immediately metabolized on binding to cellular retinoic acid–binding proteins (CRABP) and oxidized by cytochrome P-450 enzymes located in smooth endoplasmic reticulum. Alternatively, RA (or its isomers) enter the cell nucleus and bind to retinoic acid receptors (RARs) or retinoid X receptors (RXRs). On dimerization of these receptors (i.e., formation of a RAR-RXR heterodimer or RXR-RXR homodimer), RA-activated receptors bind with high affinity to specific DNA segments (the retinoid acid response element [RARE]) and effect messenger RNA (mRNA) transcription. Ultimately, the retinoid response is mediated by primary target genes, by interference with other transcription factors, or by control of certain posttranscriptional actions. (From ref. 1, with permission.)

ALL-TRANS RETINOIC ACID

The most striking success of the clinical application of differentiation therapy has been in acute promyelocytic leukemia (APL) (7) (see Chapter 46.2) where all-trans RA induces complete remission in a high proportion of patients with APL. Resistance to all-trans RA in a previously untreated patient is exceptionally rare, and failure is almost exclusively because of early death. In APL, reciprocal translocations between the long arms of chromosomes 15 and 17 result in a fusion between genes that encode a RAR (RAR-a) and a transcription factor known as PML. The resulting fusion protein, PML-RAR-a, blocks myeloid differentiation at the promyelocyte stage, which is relieved by pharmacologic (but not physiologic) concentrations of all-trans RA.

The initial response to all-trans RA in APL is associated with induced differentiation of leukemic cells. This process is obvious, both in the bone marrow and in the peripheral blood, with the appearance of cells that are intermediate in maturation between promyelocytes and neutrophils. Prominent features of these intermediate cells are indented nuclei, loss of azurophilic granularity, and nuclear and cytoplasmic vacuolation. Cell surface immunophenotyping of the neoplastic cells shows progression from a pattern of immature antigen expression at presentation toward the appearance of mature granulocytic markers during remission.

The plasma half-life of all-trans RA is approximately 40 minutes, and continuous dosing induces a progressive decrease in the plasma drug concentration. Remissions induced by all-trans RA in patients with APL who do not receive additional anticancer therapy are brief and average 3 to 5 months in duration. The mechanisms of clinically acquired retinoid resistance may be multifactorial, but point mutations in the ligand-binding domain of the PML-RAR-a have been described in a few patients. Combined sequential treatment programs that use all-trans RA (with or without chemotherapy) for induction, followed by anthracycline-based chemotherapy for consolidation, have yielded a two- to threefold increase in the proportion of patients cured of this disease. Further administration of all-trans RA as maintenance therapy during the first year of remission makes a further, albeit modest, contribution to relapse-free survival. Regrettably, the high single-agent activity of all-trans RA observed in APL has not been replicated in other neoplastic diseases.

13-CIS RETINOIC ACID

Of all retinoids, 13-cis RA has undergone the most extensive clinical examination; however, the single-agent activity of this drug in established cancer is quite limited. In the hematologic cancers, modest single-agent activity has been observed in patients with cutaneous T-cell lymphoma (mycosis fungoides); however, responses are usually partial and limited in duration. Studies of 13-cis RA in patients with myelodysplastic syndromes, chronic myelocytic leukemia, and germ cell cancer and...
neuroblastoma, and carcinomas of the head and neck, lung, and bladder have had negative results. Modest activity has been observed in patients with epidermoid skin cancers, and in combination with interferon-a.

The drug has also been explored as a means of cancer prevention, either as primary (to prevent an initial cancer) or secondary (to reduce the risk of recurrence) therapy. Treatment with 13-cis RA (1 to 2 mg/kg/d for 3 months) in heavy tobacco users reverses oral leukoplakia, a known precursor to squamous carcinoma of the oral cavity. Because this dose causes considerable mucocutaneous toxicity, follow-up studies have used a high-dose induction course followed by a lower dose (0.5 mg/kg/d) maintenance program. However, the duration of the clinical response is frequently brief, and most patients relapse when the drug is withdrawn. In an important preliminary study, adjuvant treatment with 13-cis RA (1 mg/kg/d) in patients who had undergone primary surgical excision, radiation treatment, or both for head and neck cancer significantly reduced the incidence of second primary tumors of the aerodigestive tract. However, a large randomized multicenter study has not confirmed these findings.

OTHER RETINOIDS

The natural ligand of the RXRs is 9-cis RA, an isomer of all-trans RA (see Fig. 20.4-1). Because 9-cis RA also binds to RARs, this property as a receptor pan-agonist suggested potentially broad biologic effects. Early clinical trials of 9-cis RA showed activity comparable with all-trans RA in APL, but the drug has not reversed clinically acquired retinoid resistance in this disease. Toxicity of the two compounds has also been similar (see Adverse Effects of Retinoids, later in this chapter). The drug was recently approved for topical use in patients with Kaposi's sarcoma related to acquired immunodeficiency syndrome. A number of relatively selective retinoid receptor agonists have also been synthesized and are under active development. In contrast, fenretinide (N-[4-hydroxyphenyl], Retinamide) is a synthetic retinoid whose receptor has not yet been identified, but that has exhibited some chemopreventive activity against carcinomas of the breast, prostate, oral cavity, and bladder. A large Italian study showed that fenretinide did not reduce the incidence of contralateral breast cancer, although an unexpected reduction of ovarian carcinoma was observed. Fenretinide lowers serum retinol levels, which can cause temporary night blindness.

ADVERSE EFFECTS OF RETINOIDS

Retinoids share many common side effects (Table 20.4-1). Most reactions are relatively mild; however, serious and occasionally fatal reactions have occurred. Headache that occurs several hours after drug ingestion is the most common side effect of all-trans and 9-cis RA. This effect is less prominent with 13-cis RA in which mucositis is the most common reaction. Although narcotics are occasionally required, mild analgesics generally control the headaches, and tolerance to this effect develops within the first week of dosing. Pseudotumor cerebri has been documented in several patients (especially children) who have required treatment with lumbar punctures and high-dose corticosteroids.

### TABLE 20.4-1. Adverse Clinical Effects of the Retinoids

<table>
<thead>
<tr>
<th>Effect</th>
<th>Description</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>Occurs several hours after drug ingestion</td>
<td>Usually mild; tends to occur early, remits with continued therapy, but can be quite severe</td>
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<tr>
<td></td>
<td></td>
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<tr>
<td>Dry skin, itching, flaking,</td>
<td>Common side effect of all-trans and 9-cis RA</td>
<td>Controlled with topical corticosteroids</td>
</tr>
<tr>
<td>nasal stuffiness, xerostomia,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>keratitis, and cheilitis</td>
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<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Leukocytosis</td>
<td>Occurs in approximately one-half of APL patients</td>
<td>Treated with full-dose chemotherapy (excluding an anthracycline)</td>
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<tr>
<td></td>
<td></td>
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</tr>
<tr>
<td>Cardiotoxicity</td>
<td>Occurs in approximately one-half of APL patients</td>
<td>Treated with full-dose chemotherapy (excluding an anthracycline)</td>
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<td></td>
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<tr>
<td>Hypercalcemia</td>
<td>Common side effect of all-trans RA</td>
<td>Treated with full-dose chemotherapy (excluding an anthracycline)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immunologic phenomena</td>
<td>Eosinophilia, neutrophilia, lymphocytosis</td>
<td>Treated with full-dose chemotherapy (excluding an anthracycline)</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Hepatitis</td>
<td>Occurs in approximately one-half of APL patients</td>
<td>Treated with full-dose chemotherapy (excluding an anthracycline)</td>
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<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td>Occurs in approximately one-half of APL patients</td>
<td>Treated with full-dose chemotherapy (excluding an anthracycline)</td>
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<td></td>
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<tr>
<td>Cardiovascular complications</td>
<td>Early recognition of the syndrome before the onset of dyspnea (usually fever or weight gain) is critical.</td>
<td>Treated with full-dose chemotherapy (excluding an anthracycline)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARSENIC TRIOXIDE</td>
<td>Recovery of the peripheral leukocyte and platelet counts usually follows cessation of drug therapy. One or more additional treatment courses, each of a fixed duration of 25 cumulative days, is usually started approximately 3 weeks after discontinuing the initial series of infusions. These later infusions have been administered at a weekdays-only schedule without any apparent decrease in efficacy to date.</td>
<td>Treated with full-dose chemotherapy (excluding an anthracycline)</td>
</tr>
</tbody>
</table>

Arsenic trioxide has proved surprisingly potent in APL; indeed, the proportion of patients who achieve a molecular remission (as manifest by a negative reverse transcriptase–polymerase chain reaction result for the PML-RAR-a rearrangement) considerably exceeds that of patients on all-trans RA. In APL, the drug is associated with induction of partial nonterminal differentiation, degradation of the PML-RAR-a fusion protein, and caspase activation. The drug is currently being studied in other conditions and in different dosing schedules.
When administered in the low-dose daily schedule described previously, the drug has generally been well tolerated. Fatigue is common. Lightheadedness during the infusion can be ameliorated by increasing its duration. A characteristic maculopapular skin eruption over the neck and torso occasionally occurs that resolves on discontinuation of the drug. Arsenic can cause peripheral neuropathy when administered for prolonged periods or higher doses, and severe neuropathic reactions, including quadriaparesis, have been reported from overdose. Prolongation of the QT interval may occur, which may require treatment with parenteral potassium and magnesium supplements, especially in patients after amphotericin B therapy. APL patients treated with arsenic trioxide may also develop leukocytosis and the RA syndrome. Management of these problems is identical to that described previously.

HISTONE DEACETYLASE INHIBITORS

The enzymatic addition of acetyl groups to histones, nuclear proteins closely associated with DNA, is known to have a permissive effect for messenger RNA transcription. Histone hyperacetylation may induce site-specific conformational relaxation of tightly coiled DNA that facilitates binding of transcription factors. Conversely, histone deacetylation has been linked to gene repression, and a number of oncoproteins (as well as normal genes) silence transcription by recruiting histone deacetylases. Furthermore, a link between gene methylation, a recognized mechanism of transcriptional repression, and histone deacetylation has now been established (Fig. 20.4-2). Thus, DNA demethylation and inhibition of histone deacetylation offer potential targets for anticancer therapy. Azacytidine is the best-studied agent that induces demethylation, and the drug has shown modest single-agent activity in patients with various myelodysplastic syndromes. Trichostatin A is the prototyic inhibitor of histone deacetylation, but the agent has not been used clinically. In addition to the drugs noted in the following sections, other inhibitors include the trapoxins, depudecins, and depsipeptides.

![FIGURE 20.4-2. Mechanism of transcriptional repression by DNA methylation and histone deacetylation. In a transcriptionally inactive state, DNA is tightly coiled around core histones in the nucleosome. To activate transcription, the compact inactive nucleosome must undergo conformational relaxation, which may facilitate the binding of transcription factors (TF). Chromatin relaxation is associated with histone acetylation by histone acetyltransferases (HAT). A variety of normal DNA-binding proteins or oncogene products can complex with other proteins, and these complexes recruit histone deacetylases (HDACs), which cleave acetyl groups from histones, thereby preventing chromatin relaxation and blocking gene transcription. Treatment with a HDAC may prevent such cleavage, thereby yielding a less accessible nucleosome whose DNA is then accessible for gene activation and transcription. Last, gene methylation (Me) in the promoter region has long been known to suppress gene expression in cancer. These two processes (i.e., gene methylation and histone deacetylation) have now been linked by the discovery of a protein (MeCP2) that forms a bridge between HDAC and methylated DNA. Inhibition of both processes may be required in cases wherein inhibition of only one process is insufficient to activate the target gene.]

BUTYRATES AND OTHER FATTY ACIDS

Butyric acid induces differentiation in various cell lines, but high concentrations (0.3 mM) have been required to reliably induce these effects. Butyrates have been widely studied as a treatment for thalassemia and certain hyperammonemic states in children. Several clinical studies have suggested that sodium phenylbutyrate has little single-agent activity in patients with advanced cancer or myelodysplasia.

Histone deacetylase was shown to mediate transcriptional repression in APL, as well as other cancers. One report has shown that sodium phenylbutyrate reversibly induced histone hyperacetylation in leukemic cells and induced complete remission in a child with retinoid-resistant APL when used in combination with all-trans RA. Studies have suggested that these drugs act synergistically to induce cytodifferentiation, and this combination is currently undergoing additional clinical testing. The major side effects of sodium phenylbutyrate are fluid overload and central nervous system depression, including transient somnolence and confusion.

Phenylbutyrate exhibits pleiotropic effects, and the agent is a produg for phenylacetate, which promotes in vitro differentiation of certain cell lines. High doses of phenylacetate itself (250 to 550 mg/kg/d) have been used clinically with low single-agent activity in malignant gliomas and prostate cancer. Tributyrin is a major constituent of dietary butterfat, which yields three molecules of butyrate after hydrolysis. The relatively high butyrate concentrations that are achievable in the colon have suggested a potential chemopreventive utility for colon cancer.

HYBRID POLAR COMPOUNDS

Certain hybrid polar compounds have broad in vitro activity as differentiating agents. The prototype compound of this class, hexamethylene bisacetamide, has required relatively high concentrations (1 to 5 mM). Renal insufficiency, central nervous system toxicity, and thrombocytopenia were dose-limiting in early studies, but some responses were observed in patients with myelodysplastic syndromes using 10-day infusion schedules. Newer synthetic derivatives have more potent activity than hexamethylen bisacetamide, and several are potent inhibitors of histone deacetylase.

VITAMIN D

1,25-Dihydroxyvitamin D, the active form of the hormone, facilitates differentiation in a variety of cell types. Vitamin D receptors have been identified in a variety of cell types. Circumstantial evidence has suggested that vitamin D can decrease the incidence of some tumor types. Vitamin D decreases growth of leukemia, breast, colon, and prostate cancer cell lines. In HL60 cells, vitamin D induces differentiation into monocytes and macrophages, unlike retinoids and dimethyl sulfoxide, which induce granulocytic differentiation.

Few clinical trials of vitamin D have been conducted. Several responses were observed in a study of patients with myelodysplastic syndromes treated at a dose of 2 mg/d, but intolerable hypercalcemia proved limiting. New analogues of vitamin D have become available that retain differentiating activity while causing minimal effects on calcium metabolism.

CYTOKINES AND OTHER PROTEINS

Colony-stimulating factors induce a variety of responses in their target cells, including a commitment to terminal differentiation. Both granulocyte colony-stimulating factor (filgrastim) and granulocyte-macrophage colony-stimulating factor (sargramostim) have been studied clinically. Neither agent has proved dramatically effective in either myelodysplastic syndromes or acute myeloid leukemias; however, mature populations of granulocytes and monocytes can be regularly increased in many patients, sometimes with clinical benefit (e.g., reduced infectious complications).


92. Freeman JJ. Effects of differing concentrations of sodium butyrate on 1,2-dimethylhydrazine-induced rat intestine neoplasia. Gastroenterology 1986;91:590.
Antibody-based therapeutics are coming of age. Antibodies have provided an important means to exploit the capacity of the immune system to specifically recognize and direct antigen responses. Antibody therapy studies were among the earliest attempts to explicitly target cancers based on the structural and biologic properties that distinguish neoplastic cells from their normal counterparts. Although the early clinical studies yielded inconsistent and often disappointing clinical results, more recent work has identified a number of important and useful applications for antibody-based cancer therapy. Unconjugated antibodies directed against the lymphocyte antigen CD20 have significant clinical activity in patients with low-grade lymphomas. The U.S. Food and Drug Administration (FDA) has approved one of these antibodies, rituximab, for clinical use. Radiolabeled antibody conjugates directed against CD20 demonstrate significant clinical activity in patients with chemotherapy-pretreated lymphomas as well. A chimeric antibody containing an anti-CD3 antibody and calicheamicin has impressive activity in acute myelogenous leukemia (AML). Finally, the anti-HER2/neu antibody trastuzumab has single-agent activity in metastatic breast cancer and potentiates the antitumor effects of Taxol chemotherapy. This antibody also received FDA approval for clinical use. These results provide ample evidence that a number of strategies using unconjugated antibodies or antibody conjugates carrying toxic payloads, such as radiotherapy or chemotherapy agents, have clinical benefits. At this time, the mechanisms underlying the clinical benefits of rituximab and trastuzumab are not understood, but both antibodies mediate antibody-dependent cellular cytotoxicity (ADCC) in vitro and may do so in the clinical setting as well.

Antibodies are produced by B cells. These proteins arise in response to exposure to a variety of structures, termed antigens, as a result of a series of recombinations of V, D, and J germline genes. Somatic hypermutation occurs with each subsequent exposure to the antigen and introduces further variation that can increase binding affinity or alter target antigen specificity. The resulting proteins exhibit selective targeting of a variety of potential antigens and can direct the clearance or immune recognition of such antigens. Various isotypes of antibodies have specialized functions (e.g., immunoglobulin A (IgA) molecules play important roles in mucosal immunity, and IgE molecules are involved in anaphylaxis). IgG molecules are most commonly used as the working backbones of current therapeutic monoclonal antibodies (MAbs).

Before 1975, the ability of antibodies to specifically target immunogens for therapeutic applications was inconsistently exploited because the available antibody preparations were derived from polyclonal antiserum obtained from immunized animals. The advent of hybridoma technology by Kohler and Milstein made it possible to produce large quantities of antibodies with high purity and monospecificity for a single binding region (epitope) on an antigen.
FACTORS REGULATING ANTIBODY-BASED TUMOR TARGETING

Although great progress has been made since initial treatment trials of MAB therapy, a number of obstacles to treatment efficacy have been identified in preclinical studies and in clinical trials. It is not surprising that obstacles have been identified for a concept that attempts to introduce an unprecedented degree of targeting specificity while using large proteins whose sizes greatly exceed those of conventional pharmaceuticals. It should be emphasized that the identification of obstacles is not a reason for discouragement, but rather is a necessary prelude to the cycles of molecular and strategy refinements that are inherent in the development of any new therapeutic modality.

IMPAIRED DISTRIBUTION AND DELIVERY OF ANTIBODY TO TUMOR SITE

IgG molecules are large proteins of approximately 150 kDa in mass; most chemotherapy agents have a molecular weight of less than 1 kDa. Accordingly, MABs would be expected to have significantly slower kinetics of distribution and severely limited tissue penetration properties as compared to small molecules. Indeed, nonuniform uptake of systemically administered antibody is generally observed in biopsied specimens of solid tumors. Although inhomogenous tumor antigen expression can be a factor, physiologic barriers to MAB penetration bear the greatest responsibility for the limited distribution of MABs within a tumor mass. Heterogeneous tumor blood supply limits uniform antibody delivery to tumors, and elevated interstitial pressures in the centers of tumors oppose inward diffusion. Furthermore, the relatively large transport distances in the tumor interstitium combine with the above factors to increase the time required for these large macromolecules to reach target cells. For example, the diffusion of an intact IgG molecule into a solid tumor is limited to 100 μm in 1 hour, 1 mm in approximately 2 days, and 1 cm in approximately 7 to 8 months. These physiologic barriers pose substantial obstacles to antibody penetration in the majority of solid tumors and bulky lymphomas. Thus, it can be anticipated that the therapy of patients with large tumors using MABs will be compromised. These concepts also hold true for potentially cytotoxic leukocytes to accumulate at tumor sites; as a result, physiologic barriers can represent a major limitation to the effective clinical exploitation of ADCC.

The poor tumor penetration of MABs has been addressed by using the smaller antibody-based constructs and fragments (discussed earlier in Immunoglobulin Structure, Structural and Functional Domains). As shown in Figure 20.5-1, commonly used antibody-based structures include F(ab')2 [fragment (of IgG) after digestion with the enzyme pepsin], Fab [fragment (of IgG involved in) antigen binding], and scFv molecules. These derivative structures usually exhibit binding affinity for target antigen that is of the same order of magnitude as the intact parental immunoglobulin. These molecules exhibit systemic clearance that accelerates with decreasing size, and the smaller antibody molecules have the advantages of improved tumor penetration, rapid systemic clearance, and improved specificity of tumor targeting during the terminal phases of elimination. These advantages are counterbalanced by decreased quantitative tumor targeting. The ideal size of tumor-targeting antibodies will most probably depend on the intended therapeutic application. When prolonged inhibition of a tumor-associated function is intended, larger molecules with slow clearance might be preferred, whereas the administration of a highly potent immunotoxin might be facilitated if the molecule is small and rapidly clears from normal organs.

TUMOR ANTIGENS

The properties of the tumor antigen can be a major factor in regulating the success or failure of antibody-based therapies. Heterogeneity of antigen expression by tumor cells can restrict the percentage of cells that can be reliably targeted by antibodies. This is manifested not only as the presence or absence of antigen on a cell, but also by the degree of its expression on a given cell. The density of antigen expression may be a critical determinant of therapeutic effect for a variety of antibody-based applications. The ultimate fate of a cell surface antigen (e.g., whether it is shed from the membrane or internalized) can also impact on the degree of targeting and therapeutic efficacy of an antibody. For example, large concentrations of shed antigen in the tumor microenvironment may saturate the antibody’s binding sites and prevent binding to the cell surface. In contrast, a rapidly internalized antigen may deplete the quantity of cell surface MABs capable of initiating ADCC or cytotoxic signal transduction events. Finally, additional obstacles relate to the tumor specificity of the targeted antigens. Antibody targets may be tumor-associated or tumor-specific. Tumor-associated targets have most frequently been identified and typically are oncoprotein antigens or overexpressed growth factor receptors with extracellular membrane domains. Tumor-associated antigens usually are relatively overexpressed on tumor cells but are found to a lesser extent on normal cellular counterparts and by other normal cells. Potential consequences of targeting this class of antigens with toxic immunocomplexes can include decreased targeting specificity and unacceptable normal tissue cytotoxicity. Tumor-specific antigens that exhibit high levels of expression limited to malignant tissue are both highly desirable and rare. Typically, these antigens arise as a result of unique genetic recombinations that are the cause or consequence of oncogenic transformation. Examples of tumor-specific antigens include clonal immunoglobulin idiotypes expressed on the surface of B-cell lymphomas and tumor-specific mutations, such as the epidermal growth factor receptor (EGFR)-VIII deletion mutant of the EGFR that is present in a small proportion of tumors, including glioblastoma and non-small cell lung carcinoma. The advent of new techniques for identifying genetic abnormalities in malignancies will no doubt uncover numerous tumor-specific mutations, some of which will provide accessible protein targets for antibody therapy.

IMMUNOLOGIC RESPONSES TO MONOCLONAL ANTIBODIES

The initial clinical trials of MABs used murine proteins produced by hybridoma technology. Treatment with murine MABs and their derivatives often induces human antimouse antibody (HAMA) responses within 2 to 3 weeks after the initial infusion. These responses, which are directed to any portion of the antibody, can impair targeting and accelerate MAB clearance. The induction of HAMA has precluded the continued successful application of MAB therapy in several instances.

Considerable effort has been expended to overcome HAMA by creating human or nearly human antibodies (discussed earlier in Immunoglobulin Structure, Structural and Functional Domains) or by suppressing the human immune response to the mouse MAB. As a result, the majority of the MABs currently entering the clinic bear human or humanized structures.

Although the field of antibody therapy is progressing beyond murine MABs and their associated drawbacks, analysis of the HAMA responses in clinical trials has led to the development of a novel therapeutic strategy. Although most of the HAMAs generated during these immune responses recognize conserved sequences, a small percentage of the antibodies are specific for the idiotypic or hypervariable sequences that comprise the active binding site of the antibody. Some of these antidiotyptic antibodies mimic the original antigen completely enough to be capable of inducing an immune response that is capable of reacting with the original tumor antigen. Stimulation of this “idiotypic network,” originally postulated by Jerne, offers some specific advantages when compared with immunization strategies that directly make use of the tumor antigens.

UNCONJUGATED ANTIBODIES

ANTIBODY-DEPENDENT CELLULAR CYTOTOXICITY

In the process of ADCC, the antibody Fab domains engage tumor antigen and the Fc domain binds to cellular Fc receptors to bridge effector and target cells. This interaction triggers cellular cytotoxicity. For example, BsAb can target tumor antigens and human effector cell trigger molecules on T cells via CD3/TcR and

BISPECIFIC ANTIBODIES

In the years since the pioneering work of Segal and colleagues, numerous BsAb targeting tumor antigens and effector cell trigger molecules have been developed and shown to redirect cellular cytotoxicity. For example, BsAb can target tumor antigens and human effector cell trigger molecules on T cells via CD3/TcR and...
CD28, B7 and B7-1 costimulates are present on activated T cells and B7-1 is known to costimulate T cells. Therefore, CD28–B7 interactions may act as a positive signal for T-cell activation and proliferation. In fact, the costimulatory signal provided by B7–CD28 interactions is essential for efficient T-cell activation and proliferation.

In summary, CD28–B7 interactions play a crucial role in T-cell activation, proliferation, and differentiation. They are critical for the development and function of the adaptive immune system, and disruptions in these interactions can lead to immune deficiencies and autoimmunity. Understanding the mechanisms underlying CD28–B7 interactions is essential for the development of novel therapeutic strategies to modulate T-cell responses in various pathological conditions.
number of tumor antigens have been generated and are under investigation as cancer vaccines. This approach offers the practical advantages of an abundant supply of highly purified immunogen that stimulates an immune response against carefully defined tumor antigen epitopes. This approach may be preferable to immunization with tumor antigens, because the immune response to the whole antigen may include reactivity with epitopes on the antigen that are shared by other structures that are not selectively expressed by tumors.

Results are available for several clinical trials of antibody-toxins. Helyan and colleagues treated 30 patients with advanced colorectal cancer with serial injections of polyclonal goat antibody induced by immunizations with murine 17-1A MAB. Six patients experienced brief clinical responses, and all 30 developed antibodies directed against the immunizing goat antibody. Miltelm and colleagues treated 15 patients with metastatic melanoma using a murine antitoxinotype Mycobacterium leprae body recognizing a high-molecular-weight human melanoma-associated antigen. Seven of these patients developed AB3, and three patients exhibited partial responses (PRs) to therapy. Similar findings have been observed using antibodies directed against the carcinogenic mycobacterial (CEA) system. It is noteworthy that these strategies induce not only the desired immunologic responses, but also possess clinical activity in some patients with advanced solid tumors. If these results hold up with further testing, this general strategy will merit testing in the adjuvant, high-risk setting.

An antibody-toxin, created using an antibody directed against the gp72 antigen, has been used to treat patients with advanced colorectal cancer, as well as rectal cancer patients in an adjuvant setting. The antibody 105AD7 was produced by fusion of plasma cells from patients treated with an anti-gp72 antibody 791T/36 with EL4, a mouse-human heterohybrid. The 105AD7 hybridoma was found to produce a human IgG1 that bound to the binding site of the 791T/36 antibody. In 13 patients, a percent decrease in colorectal cancer tumors was observed as compared to 4 control patients in a randomized study. The clinical significance of this increase in survival is unknown because this was not a prospectively randomized study. In vitro immunologic correlates demonstrated evidence of cellular responses as indicated by lymphocyte proliferation to gp72-expressing tumor cells and IL-2 production. In the adjuvant setting, patients were vaccinated preoperatively. In a follow-up study, the immunologic responses and progression-free survival rate in patients were superior in patients who received a 100-µg versus a 200-µg dose of vaccine.

Foon has evaluated an anti-idiotypic vaccine strategy for CEA expressing tumors. The antiidiotypic antibody 3H1 was derived from a murine antibody that targets a highly restricted epitope of CEA, which is not found on normal adult tissues or hematopoietic cells. Patients with advanced colorectal cancer treated with 3H1 injections developed both humoral and cellular responses against CEA. This response was not abrogated by concurrent chemotherapy. An ongoing phase II randomized study is evaluating 3H1 plus granulocyte-macrophage colony-stimulating factor (GM-CSF), or alum-precipitated 3H1 antibody with GM-CSF, in patients with stage II or stage III colorectal cancer. This trial is the first to evaluate an antibody as a vaccine in the adjuvant setting. Patients were found to have a cellular, but not a humoral, response to the immunization.

The impact of antiidiotypic vaccines remains to be clarified. Most of the vaccines use human antibodies against the vaccine, which may help stimulate an immune response against the antibody. However, as has been seen with intravenously administered antibodies, multiple administrations of the antiidiotypic vaccine may be limited by the immune response against the constant regions of the antibody (e.g., HAMA response). Also, although in vitro data supporting the induction immune responses have been demonstrated, no clear evidence exists for the induction of clinically meaningful responses. Clinical trials with various antibodies have demonstrated antiidiotypic cascades after therapy. There are also examples of antibodies with specificity for the tumor antigen that are being used as vaccines. The infused antibody may allow for in vivo immunization, and the induction of these antiidiotypic antibodies may serve to amplify the antigenic stimulus to the immune system. For example, ovarian and breast cancer patients receiving high-dose chemotherapy followed by stem cell transplantation have been immunized with Therotope STn-KHL, an antibody directed against a MUC-1 epitope. Eleven of 26 patients developed STn-specific T-cell responses. It remains to be determined if such responses are components of therapeutic responses.

**IMMUNOCONJUGATES**

The use of antibodies as "magic bullets" has captured the scientific and public imagination for some time. In contrast to the immunologically oriented strategies already described, antibodies used in immunomuc conjugates are designed to provide targeting specificity to cytotoxic processes. The toxic payloads used in clinically tested immunomuc conjugates have included catalytic toxins, chemotherapy agents, and radionuclides.

**RADIOIMMUNOCONJUGATES**

To a large extent, both immunomuc toxins and drug immunomuc conjugates kill by single-cell mechanisms. Thus, less opportunity exists for the destruction of "innocent bystander" antigen-negative tumor cells at the tumor site. Radiomuc conjugates address this potential deficiency by virtue of the long track lengths of many of the commonly used radionuclides, so that toxic effects can extend over several cell diameters from the radiation source. Most radiomuc conjugates do not require internalization to be effective, and the cytotoxic effects do not require the presence of an intact, functional immune system. Radiomuc therapy (RIT) has been the most extensively studied immunomuc conjugate treatment strategy and has been the source of several exciting clinical results, particularly in the treatment of chemotherapy-refractory lymphomas. In the past, most RIT studies used iodine 131, but improvements in chelation technology have enabled the study of yttrium 90 conjugates. Y is preferred because of its long track length, high-energy b-emissions, lack of volatility, and the relative ease and safety of its conjugation to antibodies and subsequent patient administration. Early studies of RIT have shown that partial, short-lived clinical responses can be achieved in some patients with advanced, solid tumors. Hematologic neoplasms are more responsive than are solid tumors. Bone marrow suppression is the common dose-limiting toxicity of RIT. The HAMA response can limit the use of multiple rounds of treatment. Lymphocytes are highly toxic tumor targets for RIT, presumably because of their intrinsic sensitivity to radiation and the relatively good access of radiomuc conjugates to the malignant cells that comprise these neoplasms. Patients with hematologic neoplasms are less likely to mount HAMA responses and frequently can be re-treated with MAB.

**IMMUNOTOXINS**

One approach to immunomuc conjugates involves coupling MAB (or fragments) to highly lethal cellular toxins. A number of plant and bacterial catalytic toxins have been used, but most clinical trials to date have been conducted using immunotoxins containing either the plant toxin ricin or the bacterially derived Pseudomonas exotoxin. These toxins require transport and intracellular processing to exert their effects and, generally, act by inhibiting protein synthesis via interruption of ribosomal elongation factor-2. Toxins of this type are extremely efficient and potent and usually contain two chains. One chain facilitates cell binding and intracellular transport, whereas the other chain is responsible for the cytotoxic activity of the toxin. Substituting an antibody binding domain for the cell binding chain of the catalytic chain of the toxin creates immunoconjugates that specifically direct the cellular targeting of the catalytic chain of the toxin. Immunotoxins have been prepared by chemical conjugation of antibodies or their fragments to the catalytic toxin chains, or by the creation of recombinant fusion proteins linking either Fab or sFv antibody fragments to native or modified catalytic toxin chains. Nanomolar concentrations of immunotoxins are capable of eradicating tumor cells in vivo, and low doses are extremely effective in preclinical animal models.

Clinical trials have been performed using immunotoxins in patients with breast cancer, ovarian cancer, colorectal cancer, melanoma, and lymphoproliferative disorders. In a landmark study, Vitetta and colleagues treated 14 patients with B-cell lymphoma using an anti-CD22 MAB conjugated to ricin A chain and observed clinical responses in five patients. In a separate study, patients with B-cell lymphomas were treated using a continuous infusion of an immunotoxin composed of an anti-CD20 MAB conjugated to whole ricin with a blocked B chain, so that the toxin's entrance into cells was conferred solely by the antibody binding specificity. In 34 patients with B-cell neoplasms, two complete and three PRs were noted.

The results of trials in patients with solid tumors have been less impressive. Toxicities have limited the doses of immunotoxins that have been used, and such dose limits must be overcome before the full therapeutic benefit of this highly potent therapy approach can be obtained. These toxicities include vascular leak syndrome, fevers, rashes, malaise, occasional hepatotoxicity, rhodanemysis, and rare but potentially devastating central nervous system effects. These effects are thought to arise from uncontrolled release of the toxins by normal cells and can be caused by local levels of targeted antigen expression by such cells, or by poorly understood nonspecific uptake. Further improvements in toxin selection and design, coupled with more knowledgeable selections of tumor antigen targets and the development of recombinant antibody-based proteins, are likely to address many of the impediments to effective therapy that have been observed to date. It may prove more difficult to overcome the potent human antitoxin immune response that these plant or bacterial proteins elicit. However, overcoming this response is necessary to permit multiple cycles of therapy.
CHEMIOIMMUNOCONJUGATES

One of the major potential advantages of immunotoxins is that such toxins work catalytically, so that the antitumor effects can be amplified in situ. Paradoxically, the potent toxicity of these molecules may make it difficult to identify an appropriate therapeutic window that permits efficacy within the tolerable host range. An alternate strategy is to use antibody-based targeting to deliver conventional chemotherapy agents to tumor sites. These molecules have well-understood pharmacology and can be administered safely in native form, so that it should be feasible to administer high, tumor-cytotoxic doses of antibody-conjugated agent within acceptable host toxicity ranges. For example, promising preclinical results were obtained using the immunonconjugate BR60-doxorubicin, with exceptional activity in vitro and in a variety of preclinical rodent models. This agent has been examined in a series of phase I clinical trials, and the dose-limiting toxicity was gastritis, possibly related to the Fc domain of the intact IgG BR6 molecule. More recently, highly potent calicheamicin-antibody conjugates have been tested in leukemia and other cancers and are undergoing clinical evaluation.

THERAPEUTIC APPLICATIONS

HEMATOLOGIC MALIGNANCIES

Initial studies using antibodies directed against B-cell determinants showed that the passive administration of these antibodies led to clearance of circulating tumor cells and rare objective clinical responses. In a series of landmark studies, Levy and colleagues prepared customized antibodies reactive with a given lymphoma patient's idotype that was uniquely expressed on the surface of the malignant B-cell clone. Each patient's idotype served as a tumor-specific signature that could be targeted by a customized MAB. The procedures for preparing such antibodies for each patient were laborious, but approximately 50% of treated patients experienced significant clinical responses, with some patients achieving durable complete remissions. The addition of chemotherapy agents, interferon (IFN), or other cytokines did not appreciably improve treatment outcomes. Effective therapy had to overcome circulating lymphoma idioytye proteins that diverted antibodies from their cellular targets, and resistance to therapy resulted in part from the emergence of idotype-negative variants. The mechanisms underlying responses to these antibodies have not been completely elucidated, but may include mechanisms such as ADCC and perturbation of signal transduction through idioytye engagement. Because of the immunosuppression of lymphoma patients, relatively few patients developed HAMAs that interfered with repeated therapeutic antibody administration. This exciting approach was very cumbersome, because it required the generation of patient-customized reagents. These results could not be replicated by using antibodies that recognize shared idiotypes expressed by a large proportion of lymphoma patients. Despite this set of impediments, these important observations have informed much of the subsequent work in this field.

Other antibodies directed against B-cell surface determinants have been developed and clinically tested. For example, Lym-1 recognizes an HLA-DR10 determinant and promotes ADCC. Clinical trials with this antibody have shown interesting response profiles in low-, intermediate-, and high-grade lymphoma, respectively.

CAMPATH-1

The CAMPATH-1 antibody has specificity for CD52, a glycopeptide that is highly expressed on T and B lymphocytes. It has been tested as a therapeutic agent for chronic lymphocytic and prolymphocytic leukemias, as well as other non-Hodgkin's lymphomas, and as a means to deplete T cells from allogeneic transplantation grafts. One-half of the patients with fludarabine-resistant chronic lymphocytic leukemia or B-prolymphocytic leukemia exhibited clinical responses to CAMPATH-1.

A phase II multicenter study of CAMPATH-1H in previously treated patients with low-grade non-Hodgkin's lymphomas has been reported. Fifty patients with relapsed or refractory disease were treated with 30 mg of CAMPATH-1H three times weekly for up to 12 weeks. Infection, anemia, and thrombocytopenia were common, and myelodysplasia occurred in a patient with a prior history of angina and congestive heart failure. A 16% PR rate and a 4% complete response (CR) rate were reported, for an overall response rate of 20%. Responses were short in duration, with a median time to progression of 4 months. Patients with mycosis fungoides responded more frequently and had a longer time to progression (10 months) than did patients with low-grade non-Hodgkin's lymphoma (4 months).

Treatment was associated with reactivation of herpes simplex, oral candidiasis, Pneumocystis carinii pneumonia, cytomegalovirus pneumonitis, pulmonary aspergillosis, disseminated tuberculosis, and seven cases of pneumonia and septicemia.

CAMPATH-1 has also been used to deplete T cells from allogeneic transplantation grafts in patients with hematologic malignancies. The initial study suggested that the addition of CAMPATH-1 can significantly decrease graft rejection and graft-versus-host disease compared with conventional therapy. However, the frequency of graft rejection and graft failure may be lower. A retrospective review of patients with acute lymphocytic leukemia or AML who underwent allogeneic transplantation with CAMPATH-1-purged marrow suggested no impact on the graft-versus-leukemia effect, because no increase in leukemia relapse was found. Additionally, the development of Epstein-Barr virus-related lymphoproliferative disorders was decreased in allogeneic transplantation patients who had T-cell depletion with CAMPATH-1 therapy compared with other methods of T-cell depletion (e.g., E-rosettes or other MABs). CAMPATH-1 eliminates B cells within the graft, thus eliminating a potential reservoir of Epstein-Barr virus or targets for subsequent infection.

Anti-CD20 Antibodies

The testing and evaluation of the chimeric anti-CD20 antibody, IDEC-C2B8, also known as rituximab, has led to significant excitement within the field. Rituximab was the first antibody therapy approved by the FDA for use in treating human malignancy. Other anti-CD20 antibodies had demonstrated responses of low-grade non-Hodgkin's lymphomas; however, therapy was limited because of the induction of HAMAs. By reducing immunogenicity through the substitution of human for murine constant domain sequences, rituximab allows for the safe administration of multiple doses of therapy. The phase I study that set out to determine the maximum tolerated dose used four weekly infusions. Thrombocytopenia and B-cell lymphocytopenia were observed. The lymphocytopenia persisted for 3 to 6 months. Six of 18 patients (33%) demonstrated PRs. Phase II studies using the maximum tolerated dose, 375 mg/m², confirmed the efficacy of this therapy, demonstrating 46% and 48% response rates in two separate studies. Although the numbers of circulating B cells were reduced by therapy, no changes were documented in serum immunoglobulin levels. Viral and bacterial infections were seen in patients with relapsed indolent lymphomas, but in contrast to the CAMPATH-1 experience, treatment with rituximab did not result in significant morbidity to infections. However, patients with small lymphocytic B-cell lymphoma had lower response rates, likely related to the lesser expression of CD20 on these tumor cells. A different multiminstitutional phase II study using a 375-mg/m² dose for eight weekly treatments in low-grade or follicular non-Hodgkin's lymphoma with relapsed or primary refractory disease also demonstrated minimal toxicity, with an overall response rate of 57%.

In another phase II trial, 54 patients with relapsing or refractory diffuse large B-cell lymphoma, mantle cell lymphoma, or other intermediate- or high-grade B-cell non-Hodgkin's lymphoma were treated. The study randomized patients to either eight weekly treatments of 375 mg/m² intravenous rituximab, or to 375 mg/m² rituximab intravenously in week 1 followed by seven weekly intravenous infusions of 500 mg/m². Five CRs and 12 PRs were observed, for an overall response rate of 31%; no evidence of superiority of either treatment regimen was demonstrated. Patients with refractory disease and those with histologies other than diffuse large B-cell lymphoma appeared to have lower response rates.

Peak levels of circulating antibody inversely correlate with pretreatment B-cell counts and the bulk of tumor. Greater numbers of peripheral lymphocytes or larger tumor bulk serve as an antigen sink and therefore remove antibody from the circulation. For patients with bulky disease, future consideration of a higher antibody dose or a greater number of cycles may be warranted, because patients with lower serum antibody concentrations have had statistically significant lower response rates. In some patients with circulating blood tumor cells, however, rituximab therapy has induced an infusion-related syndrome characterized by fever, rigors, thrombocytopenia, tumor lysis, bronchospasm, and hypoxemia requiring discontinuation of the antibody infusion. Symptoms typically resolve with supportive care, and patients may continue further therapy without sequelae. Another case report has documented rapid tumor lysis in a patient with B-cell chronic lymphocytic leukemia with a pretreatment lymphocytosis of more than 100 × 10⁹ cells per liter.

Rituximab therapy rarely selects for the emergence of an antigen-negative population of tumor cells. This phenomenon has been documented in a patient with a follicular mixed small and large cell lymphoma treated with rituximab after progression through multiple chemotherapy regimens.

Rituximab has been tested in conjunction with chemotherapy. Preclinical data have shown this antibody can sensitize chemotherapy-resistant cell lines to the cytotoxic effects of chemotherapy. Forty patients with low-grade or follicular non-Hodgkin's lymphoma received six cycles of the cyclophosphamide,
doxorubicin, vincristine, and prednisone (CHOP) regimen every 21 days, with six infusions of rituximab at a dose of 375 mg/m² given before, during, and after the completion of chemotherapy. Thirty-eight patients received therapy, with three patients not completing treatment because of intercurrent infections (n = 2) and patient choice (n = 1). The overall response rate was 95% (38 of 40) with a 55% CR and a 40% PR, with fewer CRs noted in patients with bulky disease. Median response duration and time to progression had not been reached after more than 29 months of follow-up. Seven of eight patients initially positive for the bc-2 translocation became negative for the translocation by polymerase chain reaction assay after therapy; this finding has not been seen previously with CHOP chemotherapy alone. Unconjugated antibodies directed against CD20 and other B-lymphocyte antigens have exhibited exciting and clinically important antitumor activity in patients with low-grade lymphomas (Table 20.5-1).

**Radiolabeled Antibodies**

Press and colleagues used high, marrow-ablative RIT doses in patients with biodistributions that predicted favorable tumor dosimetry within tolerable host toxicity ranges in the setting of autologous bone marrow transplantation. In a group of 42 patients with chemotherapy-refractory lymphomas, 24 had favorable biodistributions and 19 received high-dose RIT. A remarkable 64% of these patients experienced complete remissions, and an additional 11% had partial remissions. More recent updates suggest that many of the complete remissions are durable, with a 62% progression-free survival rate at 2 years. Preliminary studies in patients with AML suggest that RIT may be useful as a conditioning regimen before bone marrow transplantation. These exciting results illustrate the potential of RIT in appropriately selected patients, and they certainly contradict any pessimism regarding the role of antibody-based targeted therapies in the management of cancer. Further advances in antibody design, chelation chemistry, choice of radionuclide, and selection of appropriate candidates and clinical setting for therapy can be safely predicted to expanded indications for antibody-based RIT in the treatments of patients with hematologic neoplasms.

**Table 20.5-1. Antibody Therapy of B-Cell Lymphomas: Selected Results**

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Route of Administration</th>
<th>LD (mg/m²)</th>
<th>Dose (mCi/m²)</th>
<th>Response Rate</th>
<th>CR (%)</th>
<th>PR (%)</th>
<th>MR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-CD20</td>
<td>IV</td>
<td>375</td>
<td>131</td>
<td>95</td>
<td>55</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Anti-CD20 conjugated to gelonin</td>
<td>IV</td>
<td>375</td>
<td>131</td>
<td>95</td>
<td>55</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Anti-CD20 conjugated to TAC</td>
<td>IV</td>
<td>375</td>
<td>131</td>
<td>95</td>
<td>55</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Anti-CD20 conjugated to IL-2</td>
<td>IV</td>
<td>375</td>
<td>131</td>
<td>95</td>
<td>55</td>
<td>40</td>
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</tbody>
</table>

**Other Approaches**

CD15 and CD33 have been used as targets in AMLs. CD15, also known as CD15 (Lewis Y), is an IgM with specificity for CD15. It was evaluated before induction therapy in patients with AML. The number of peripheral blasts decreased transiently. Two patients at the highest dose level, 1.5 mg/m², had grade 4 toxicities of hypotension or hypothermia. Unconjugated HuM195 recognizes CD33. Patients with persistent disease after chemotherapy were treated with daily infusions 4 days a week for 2 weeks. Ten of one patients had a CR. More recently, this antibody has been conjugated to a recombinant form of gelonin, a single-chain plant catalytic toxin that inactivates the 60S ribosomal subunit. CD33 is expressed on leucemic and myeloblastic leukemia cells and is at low levels on normal hematopoietic stem cells. M195, a murine anti-CD33 MAb, has been used to deliver therapeutic doses of 111In in combination with busulfan or cyclophosphamide to eliminate residual leukemia before bone marrow transplantation. More recently, a humanized form of M195, HuM195, has been radiolabeled and used as a single agent in the treatment of AML and chronic myeloid leukemia. In these studies, 8 of 12 patients treated with 111In-conjugated MAB and 13 of 18 patients treated with bismuth 213-conjugated MAB exhibited minor responses.

**Breast Cancer**

HER-2/neu (c-erbB-2), a member of the EGFR family, has been targeted for antibody therapy because it is overexpressed on 25% of adenocarcinomas. Recombinant human MAB (rhuMAB) HER-2-2, also known as trastuzumab, is a humanized antibody derived from 4D5, a murine MAB that recognizes HER-2/neu. In a phase II trial in women with metastatic breast cancer, Baselga and associates reported an objective response rate of 11.6%, with responses seen in the liver, mediastinum, lymph nodes, and chest wall metastases. Patients typically received ten or more treatments with the antibody, and none developed an antibody response against trastuzumab. Cobleigh and coworkers treated 222 women with metastatic breast cancer, finding an objective response rate of 16%. The median response duration
was 9.1 months with a median overall survival rate of 13 months, which is superior to results reported for second-line chemotherapy in metastatic breast cancer. Preclinical data with trastuzumab suggested enhanced clinical activity in combination with cisplatin chemotherapy. A phase II study in patients with chemotherapy-refractory breast cancer that overexpressed HER2/neu has been completed. Nine of 37 assessable patients achieved a PR, and nine additional patients exhibited a minor response or stable disease. The median response duration was 3.3 months. Toxicities were largely attributable to cisplatin. No evidence was found for cisplatin-related alteration of antibody pharmacokinetics.

A large, randomized, phase III trial comparing cytotoxic chemotherapy alone or with trastuzumab (anti-HER-2/neu) has been completed. Patients receiving initial therapy for metastatic breast cancer were treated with doxorubicin or epirubicin and cyclophosphamide, or with paclitaxel. They had received an anthracycline in the adjuvant setting. Patients were randomized to receive chemotherapy alone or in combination with weekly antibody therapy. The addition of trastuzumab improved response rates for combination therapy from 42.1% to 64.9% for the anthracycline-based regimens and from 25.0% to 57.3% for the taxane regimen. Myocardial dysfunction seen with anthracycline therapy was observed with increased frequency in patients receiving antibody alone or with doxorubicin or epirubicin, and therefore trastuzumab is not recommended in combination with anthracyclines.

**Colorectal Cancer**

Ep-CAM is a glycoprotein normally found on the basolateral surface of the nonsquamous epithelium of the lung, gastrointestinal tract, pancreas, ovary, kidney, sweat glands, biliary tract, and thymus. Most recently it has been detected in prostata intraepithelial neoplasia and prostatic adenocarcinoma. 17-1A, a murine antibody that targets an extracellular epitope of this antigen, has undergone extensive clinical trials in metastatic colorectal cancer and pancreatic cancer as a single agent. The human chimeric antibody Ch14.18 has been tested in neuroblastoma and osteosarcoma.

The therapeutic administration of 17-1A has also been shown to induce potentially effective antidiagnostic antibodies with increased titers when GM-CSF was coadministered with the 17-1A. T-cell responses against antidiagnostic epitopes have been demonstrated by in vitro proliferation assays, IFN-g production, and in vivo delayed-type hypersensitivity responses. In a small study of ten patients, those with T-cell proliferation against antidiagnostic antibodies demonstrated clinical responses, contrasting with patients without a T-cell response who had no clinical response.

Initial phase I studies with 17-1A demonstrated occasional responses in metastatic cancers of the gastrointestinal tract after only one intravenous dose of antibody. Therapy was well tolerated, with mild side effects of nausea, vomiting, or diarrhea. Phase II studies in colon and pancreatic cancers were less encouraging. The overall lack of efficacy seen in these studies may have resulted from the large tumor burden or the associated immunosuppression seen in these patients with metastatic disease.

**Antiganglioside Antibodies**

Significant promise has been associated with MAB directed against ganglioside antigens in patients with melanoma and neuroblastoma. 17-1A, a murine antibody that recognizes a polymorphic epithelial mucin, has been evaluated in patients with stage Ic to IV ovarian cancer after standard chemotherapy. The decreased death rate persisted at 7 years—43% versus 63% in the observation group. This result translated to a 30% reduction in death (P = .04) and a 27% reduction in recurrence (P = .03). This study has been criticized for the higher than expected death rate in the observation group and the lack of adjuvant chemotherapy. Currently, a clinical trial is comparing 17-1A to observation in patients with lymph node–negative cancers. Another ongoing study is evaluating lymph node–positive colorectal cancer patients, randomizing patients to standard adjuvant chemotherapy alone or in conjunction with 17-1A. These trials will define the role of this antibody therapy in the adjuvant setting. If the encouraging outcomes of the original randomized study are confirmed, it will signify a paradigm shift. In this new paradigm, high objective response rates in patients with metastatic disease will not be required to provide an activity signal that warrants testing in the adjuvant setting when the agent involved acts to stimulate immune responses.

**Ovarian Cancer**

The majority of patients with ovarian cancer relapse even after receiving adjuvant chemotherapy and even when they present with limited disease. RIT using HMFG1, which recognizes a polymorphic epithelial mucin, has been evaluated in patients with stage Ic to IV ovarian cancer after standard chemotherapy. The radiolabeled antibody was given once as an intraperitoneal injection. Compared with a retrospective matched control group, the estimated survival at 10 years was superior for the patients treated with RIT. Further prospective studies are needed to confirm this initial observation.

**TABLE 20.5-2. Selected 17-1A Clinical Trials**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patient Characteristics</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial I</td>
<td>Patients with colorectal cancer treated with 17-1A for 5 months after 5 years</td>
<td>Death rate in the 17-1A group was 36% versus 51% in the observation group. The decreased death rate persisted at 7 years—43% versus 63%. This result translated to a 30% reduction in death (P = .04) and a 27% reduction in recurrence (P = .03).</td>
</tr>
<tr>
<td>Trial II</td>
<td>Patients with metastatic colorectal cancer treated with 17-1A and GM-CSF</td>
<td>T-cell responses against antidiagnostic epitopes have been demonstrated by in vitro proliferation assays, IFN-g production, and in vivo delayed-type hypersensitivity responses. In a small study of ten patients, those with T-cell proliferation against antidiagnostic antibodies demonstrated clinical responses, contrasting with patients without a T-cell response who had no clinical response.</td>
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GD3 ganglioside has been targeted by the R24 antibody, which promotes ADCC and complement-dependent cell lysis. Treatment with R24 has induced occasional tumor regressions in patients with metastatic melanoma. 34桅Soiffer and associates reported on a trial in metastatic melanoma combining IL-2 at both high and low doses with R24. Treatment was limited by IL-2–related toxicities, particularly cathereter-related infections. Treatment led to the expansion and activation of NK cells and T lymphocytes. In spite of this in vitro immune activation, only one PR was observed.

IFN-α given in an adjuvant setting may decrease the risk of melanoma recurrence in patients free of disease after the resection of lymph node–positive primary disease. The combination of IFN-α, R24, and IL-2 was studied in patients with metastatic melanoma. 35Patients were treated with R24 by continuous intravenous infusion for 3 weeks, followed by 3 weeks of IL-2. The cytokine therapy was designed to enhance the proliferation and cytotoxicity of T lymphocytes infiltrating melanoma lesions after R24 MAB therapy. However, pre- and posttreatment biopsies of these lesions showed no evidence of augmentation in the composition or biologic features of the effector cell population after the combination therapy in comparison with cytokine or MAB therapy alone. No objective tumor responses were observed. M-CSF has also been administered in combination with R24. 36In this study, M-CSF was given as a 14-day continuous intravenous infusion on days 1 to 14 followed by R24 on days 6 to 10. Three of 20 patients had minimal tumor regression in metastases in the breast, liver, and lymph nodes. In yet another study evaluating combination treatments with R24, treatment combining R24 and GM-CSF demonstrated increased ADCC in vitro after therapy. Two PRs were seen in 20 treated patients. Similar results have been obtained with ch14.18. 37

FUTURE DIRECTIONS

The initial clinical studies using antibodies and their derivatives have identified a number of applications that promise to make significant impacts in the management of patients with cancer. Patience was required to acquire the results, understand the reasons for disappointment or success, and refine the treatment strategies to obtain results that provide legitimate causes for encouragement. These promising results represent the most advanced clinical antibody therapy programs, but a wealth of innovative strategies using antibodies to human immune prepared antibodies to molecules with novel effector functions are in earlier stages of clinical evaluation. Some of these approaches, such as modulating growth factor receptor function or inducing immune responses using BsAbs, show considerable promise and are expected to add to the list of novel agents available for the treatment of malignancies in which previously conventional therapeutic strategies have proven inadequate.

In the past, antibody development has focused on identification of targets on the cancer cell itself. There are now an increasing number of targets in the extracellular matrix and local tumor environment. The most developed approach targets the vascular endothelial growth factor, a mediator of tumor neovascularization. An understanding of the mechanisms by which antibodies can activate the immune system and the potential for antibody-therapy to induce a T-cell response directed against the tumor has led to the development of bispecific antibodies (BsAbs). These antibodies are composed of two separate single-chain Fv fragments, one specific for the tumor cell and the other for an cell that would mediate the tumor regression.

Additional strategies to be developed in the future would include using BsAbs to target immune checkpoint inhibitors such as PD-L1/2 and CTLA-4 blocking antibodies. These checkpoints are expressed on immune cells and are involved in the regulation of the immune response. By blocking these checkpoints, BsAbs can enhance the immune response against tumors.

Several clinical trials have been conducted using BsAbs that target immune checkpoints. These trials have shown promising results in terms of tumor regression and improved survival. However, more research is needed to fully understand the mechanisms of action and to identify the optimal dosing and scheduling of these agents.

As the field of antibody therapy continues to evolve, it is likely that new agents and strategies will be developed to further enhance the therapeutic potential of this approach. The future promises exciting developments in the treatment of cancer using antibodies.

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SECTION 20.6
Antiangiogenesis Agents

JUDAH FOLKMAN

GUIDELINES TO THE BIOLOGIC BASIS OF ANTIANGIOGENIC THERAPY

INTRODUCTION

The second half of the twentieth century witnessed an explosion of knowledge about the cause and development of cancer at the biochemical, genetic, and molecular levels. Numerous studies have revealed the elegant wiring plan of the normal cell and have uncovered the subtle but complex events that transform normal cells into the neoplastic state. Virtually all of these studies have focused on the cancer cell. Therapy also has been directed almost exclusively against the cancer cell. When taken together, these results give hope that eventually molecular solutions to the cancer problem will be found. An example of such a molecular therapy would be some manipulation that would revert cancer cells to normal cells or would selectively cause cancer cells to undergo apoptosis without damage to normal cells. However, no one knows how far off such therapy is, or if it is even possible. I do not believe that we can ever paint a complete picture of cancer by the reductionist approach alone.

Therefore, it has seemed prudent to explore the cancer problem at a different level. Linus Pauling taught his students that an intractable problem may yield to a change in the level of exploration. Furthermore, Alvin Feinstein emphasizes that, in medical practice, a disconnect often exists between understanding the cause of a disease and having effective therapy for it. Compare, for example, appendicitis to sickle cell anemia. In the former, epidemiology, genetics, and direct cause are poorly understood, but the cure rate is very high. In the latter, a precise molecular cause is known, but therapy is unsatisfactory.

To examine the cancer problem at a different level, consider a cancer cell that has progressed through numerous checkpoints and through a long series of mutations so that many of its oncogenes are overexpressed and its suppressor genes are mutated or deleted. Assuming that this cancer cell is immortal in vitro and tumorigenic in vivo, we can ask, Are these neoplastic properties necessary and sufficient for a cancer cell to expand into a population that is detectable, symptomatic, or lethal? Experimental evidence now argues that these neoplastic properties may only be necessary, but not sufficient for a cancer cell to be lethal. This evidence shows that the microvascular endothelial cell acts as a critical control point in tumor growth and dictates to a microscopic in situ population of tumor cells whether they can continue to expand the primary tumor, metastasize, or kill their host. In the final analysis, the capacity of a tumor to switch to the angiogenic phenotype and to recruit its own private blood supply determines whether a tumor remains undetectable or becomes symptomatic and potentially lethal. Nonangiogenic tumor cells may not be inherently dangerous; they usually remain in situ.

Because it is now understood that the microvascular endothelial cell is a critical determinant of tumor growth in vivo, this cell has become a second target for cancer therapy. It is the target for which novel angiogenesis inhibitors have been developed as therapeutic anticancer agents. At this writing, at least 20 angiogenesis inhibitors are currently in clinical trials in the United States, and seven of them are in phase III (see Clinical Trials of Angiogenesis Inhibitors, later in this chapter) (Fig., 20.6-1).

GUIDELINES TO THE BIOLOGIC BASIS OF ANTIANGIOGENIC THERAPY

Because a wide variety of different angiogenesis inhibitors are currently being evaluated in clinical trials for patients with advanced cancer in the United States, the United Kingdom, and Europe, it is important for clinicians to understand certain fundamental principles of the angiogenic process that form the scientific basis of this translation from laboratory to clinical application.

TUMORS AND THEIR METASTASES ARE ANGIOGENESIS-DEPENDENT

I first proposed the hypothesis that tumor growth is angiogenesis-dependent in 1971. In its simplest terms, this hypothesis predicted that, beyond the size of a microscopic in situ cancer in humans or a “tumor take” in experimental animals, every further increase in tumor population must be preceded by the growth of new microvessels that congeal on the tumor. Since 1971, many experiments that support this hypothesis have been reported. The first evidence was mostly indirect, because it was based on in vitro studies of tumor spheroids, measurements of the prevascular stage of tumors in vivo, and mechanical separation of tumors from their vascular bed. Direct experimental evidence did not appear until the late 1980s, when it first became possible to inhibit angiogenesis by biochemical and molecular methods. These experiments were based on: (1) administration of molecules that inhibited angiogenesis specifically or selectively, (2) blockade of tumor-derived angiogenic factors, (3) transfection of dominant-negative receptors for an angiogenic factor into endothelial cells in the tumor bed, (4) transfection of angiogenesis inhibitor proteins into tumor cells, and (5) antiangiogenic therapy of spontaneous tumors in transgenic
Three decades after publication of the hypothesis that tumors are angiogenesis-dependent, elegant proofs continue to be published. Two such studies appeared in 1999. One of these is a gene knockout experiment. Mice deficient in one allele of Id1 and two alleles of Id3 are unable to mount an angiogenic response to 100 million inoculated tumor cells. The tumors take, but remain dormant and nonangiogenic and do not metastasize. Placental angiogenesis is unaffected. In a second experiment, human cancer cells are transfected with thrombospondin-1 and/or thrombospondin-2, both of which inhibit angiogenesis. The transfected cells are then inoculated into immunodeficient mice. Tumor growth is inhibited in direct proportion to the level of thrombospondin secreted. Tumor cell apoptosis is inversely proportional to tumor angiogenesis (i.e., apoptosis increases as angiogenesis decreases). Tumor cell proliferation, however, is independent of angiogenesis and apoptosis (Fig. 20.6-2).

**MICROVASCULAR ENDOTHELIAL CELLS CONTROL A TUMOR'S SUPPLY OF OXYGEN, NUTRIENTS, AND GROWTH FACTORS**

**Oxygen and Nutrients**

Virtually every cell in the body lives adjacent to a capillary endothelial cell, or at least a distance no greater than the oxygen diffusion limit of 100 to 200 μm. This arrangement permits perfused vessels to deliver oxygen and nutrients and to remove catabolites over short distances. This proximity of tissue cells to microvessels is accomplished by at least three common configurations and some rare configurations (Fig. 20.6-3). One category includes cells such as pancreatic islet cells, fat cells, and certain skeletal muscle cells, which are surrounded by two or more microvessels. A second category includes hepatic cells and cells of other solid organs. Each hepatic cell abuts a microvessel on one side and another hepatocyte on the other side. Epithelial cells exposed to the environment make up a third category (e.g., keratinocytes in the skin; mucosal cells in the gastrointestinal tract and bladder; and cells that line a wide variety of ducts, such as those in the breast or prostate). These cells exist in an avascular compartment (e.g., epidermis) separated from underlying microvessels (e.g., in the dermis) by a basement membrane. The basal cells lying on the basement membrane are closest to the microvessels beneath it and receive oxygen and nutrients across a short distance defined by the limits of oxygen diffusion (100 to 200 μm). However, the cells in the upper layers lie beyond the oxygen diffusion limit and are undergoing apoptosis. In contrast, tumor cells form multiple layers that encircle a microvessel until these cell layers (three to six or more), reach the absolute limits of oxygen diffusion. In the outermost cell layer, tumor cells are completely anoxic and are dying. This has been quantified by infrared spectroscopy in transparent skin chambers in experimental animals. A gradient of tumor cell proliferation also is present in these multiple layers. The highest rate of proliferation is found in tumor cells closest to the microvessel. Tumor cells may continue to proliferate and die in this in situ configuration, but they cannot expand the tumor mass beyond 0.2 to 2.0 mm until they have induced endothelial cell migration, proliferation, and sprout formation. Therefore, a general rule is that any expansion of tumor mass beyond a microscopic size is dependent on two cell compartments growing in tandem: tumor cells and microvascular endothelial cells.

**Growth Factors and Antiapoptotic Factors**

Endothelial cells not only guard the entry of oxygen and nutrients as well as the exit of catabolites, these cells also elaborate mitogens and survival factors for tumor cells. This paracrine activity of microvascular endothelial cells includes the mobilization of basic fibroblast growth factor (bFGF), platelet-derived growth factor, insulin-like growth factor-1 and -2, and cytokines such as interleukin-6 and granulocyte-macrophage colony-stimulating factor. At least 20 paracrine factors are known to be produced by vascular endothelial cells.

Antiangiogenic therapy can cause either arrest or regression of growing blood vessels, which would shut down the supply of endothelial-derived paracrine factors and other cell growth factors. In an in vitro experiment, the withdrawal of insulin-like growth factor-1 from myeloid lymphoma cells caused them to undergo apoptosis. Because one microvascular endothelial cell can support up to 5 to >100 tumor cells, antiangiogenic therapy directed solely against endothelial cells is amplified in contrast to conventional chemotherapy, which attacks tumor cells directly.

**ANTIANGIOGENIC THERAPY OPERATES OVER A WIDE THERAPEUTIC WINDOW**

In animal studies and in human clinical trials, antiangiogenic therapy generally has fewer side effects than conventional cytotoxic chemotherapy. Endostatin, for example, showed no detectable side effects in tumor-bearing animals. At this writing, no significant side effects have been reported during the first 6 months of a phase I clinical trial of endostatin in five cancer centers.

**Turnover Times of Endothelium in a Tumor Bed versus Endothelium in Other Regions of the Vasculature**

One reason for this predicted lack of toxicity in antiangiogenic therapy is that, under normal conditions, vascular endothelial cells, which form a monolayer of approximately 1000 μm², are not dividing. Their turnover time is more than 1000 days. In contrast, bone marrow cells and mucosal cells in the gastrointestinal tract are among the most rapidly proliferating cells in the body. Bone marrow cells undergo approximately 6 billion cell divisions per hour, and the entire bone marrow is turned over in 5 days. During ovulation and in wound healing, microvascular endothelial cells may grow almost as rapidly as bone marrow cells, but for short periods (days). During tumor angiogenesis, microvascular endothelial cells undergo sustained rapid proliferation that persists for as long as the tumor is present. In
Angiogenic response to the same dose of an angiogenic protein (bFGF) that induces a low angiogenic response in mice of a different genetic background (SJL/J).

**Genetic Differences in Host Angiogenic Response**

Differences in the specificities of angiogenesis inhibitors and the fact that the same dose of a given angiogenic protein may induce different angiogenic responses in different genetic backgrounds have implications for the development of angiogenesis inhibitors as therapeutic agents. For instance, repeated therapy is required for inhibition of metastases in different organ sites. Conversely, different doses of inhibitor may be required for inhibition of metastases at different organ sites. If this finding applies to patients, metastases in different sites (e.g., lung vs. bone), may respond differently to a given dose of angiogenesis inhibitor. Conversely, different cells, tissues, or organs may respond differently to the same angiogenesis inhibitor.

**Differences in Angiogenic Response at Different Sites in the Host**

The more specifically that an angiogenesis inhibitor targets growing endothelial cells to the exclusion of resting endothelium or other cell types, such as smooth muscle or fibroblasts, the less is the risk of side effects. Although the pharmaceutical industry generally prefers to develop small synthetic molecules instead of proteins as therapeutic anticancer agents, certain proteins are advantageous because they inhibit angiogenesis specifically. Endostatin is an example of such a protein. This 20-kD fragment of the carboxy-terminus of collagen XVIII is one of the most highly specific and least toxic of the known angiogenesis inhibitors. Doses of endostatin that produce tumor dormancy or tumor regression have no effect on pregnant mice. Normal babies are born and their growth is not delayed by treating them with endostatin (R. Rohan and R. D’Amato, personal communication, 1998). Furthermore, wound healing is not delayed by endostatin (J. Marier, personal communication, unpublished data, 1999). Therefore, endostatin is not only a specific angiogenesis inhibitor, but it also appears to be a selective inhibitor of tumor neovascularization. Not all angiogenesis inhibitors are free of effects on healing wounds. For example, the fumagillin analogue TNP-470 slows tumor growth by approximately 65% to 75% in a wide variety of tumor-bearing mice, but it also delays wound healing by at least 15% to 17%. In addition, it causes 5% weight loss.

**Differences in Specificity of Angiogenesis Inhibitors**

Because a drug is an angiogenesis inhibitor per se does not guarantee its freedom from side effects. Certain synthetic small molecules designed to inhibit an angiogenic target (such as a receptor for an angiogenic factor), may induce side effects that are related to the structure of the molecule and not to its antiangiogenic function. Differences in the specificities of angiogenesis inhibitors and the fact that the same dose of a given angiogenic protein may induce different angiogenic responses in different genetic backgrounds have implications for the development of angiogenesis inhibitors as therapeutic agents. For instance, repeated therapy is required for inhibition of metastases in different organ sites. Conversely, different doses of inhibitor may be required for inhibition of metastases at different organ sites.

**Differences in Types of Angiogenesis Generated by the Host**

Why should tumor and wound vessels respond differently to a specific angiogenesis inhibitor such as endostatin? A possible explanation is that these two types of neovascular beds may be controlled in part by different ratios of certain endothelial regulatory proteins, such as the angiopoietins. Angiopoietin-1 is a 70-kD ligand that binds to a specific tyrosine kinase expressed only on endothelial cells, called Tie2 (also called Tek) (A ligand for Tie1 has not been elucidated.) Like vascular endothelial growth factor (VEGF), angiopoietin-1 is an endothelial cell-specific growth factor. Angiopoietin-1 is not a direct endothelial mitogen in vitro, but it induces endothelial cells to recruit pericytes and smooth muscle cells to appose themselves to the wall of a microvessel. This process can convert a capillary vessel to a venule. Pericyte and smooth muscle recruitment are mediated by endothelial production of platelet-derived growth factor-BB (and probably other factors) when Tie2 is activated by angiopoietin-1. In mice that overexpress angiopoietin-1 in the skin, increased vascularization is noted. The vessels are significantly larger than normal and the skin is reddened. The vessels are not leaky and no skin edema is present, in contrast to dermal vessels of mice overexpressing VEGF. Transgenic mice expressing both angiopoietin-1 and VEGF in the skin, dermal angiogenesis is increased in an additive manner, but the vessels do not leak. This model closely approximates angiogenesis in healing wounds (i.e., relatively nonleaky vessels coated by pericytes and some perivascular smooth muscle cells). In contrast, tumor vessels are leaky and thin-walled with a paucity of pericytes. Angiopoietin-2 blocks the Tie-2 receptor on endothelial cells, which initiates a chain of events so that pericytes and smooth muscle cells are repelled. Angiopoietin-2 is produced by vascular endothelium in a tumor bed, but a putative “angiopoietin-inducing factor” from tumor cells is unknown. Nevertheless, tumor vessels remain as thin “endothelial-lined tubes,” even though some of these microvessels reach the diameter of venules. Angiopoietin-2 and VEGF acting together increase angiogenesis. However, if VEGF is antagonized or withdrawn at this point, endothelial cells may undergo apoptosis and new microvessels can regress. In summary, endostatin may regress tumor angiogenesis that is under the control of angiopoietin-2, but it may have little or no effect on wound neovascularization regulated by angiopoietin-1.

**Differences in Angiogenic Response at Different Sites in the Host**

In animals, it has been shown that the same tumor type may elicit different intensities of angiogenesis when implanted at different sites in the body. For example, subcutaneous tumors implanted on the dorsum between the scapulae may grow at four to five times the rate of tumor implanted more caudally between the iliac crests. Colon cancer implanted subcutaneously (in immunodeficient mice) do not become neovascularized and remain dormant at a microscopic size. In contrast, when these tumors are transplanted to the surface of the colon, they become neovascularized and grow to a large size. This tumor uses bFGF as its major angiogenic mediator but is unable to induce angiogenesis in the subcutaneous position because of high levels of interferon-β in the keratinocytes, which is not found in the colon wall. Interferon-β, like its commercially available relative interferon-α, down-regulates bFGF messenger RNA and protein production by colon cancer cells, thus acting as a natural suppressor of any angiogenesis mediated by bFGF. In this experiment, the colon cancer cells lacked a receptor for bFGF. If these findings apply to patients, metastases in different sites (e.g., lung vs. bone), may respond differently to a given dose of angiogenesis inhibitor. Conversely, different doses of inhibitor may be required for inhibition of metastases at different organ sites.

**Genetic Differences in Host Angiogenic Response**

D’Amato and Rohan in our department of surgery at Children’s Hospital, Boston, demonstrated that certain strains of mice (e.g., 129/SvJ) produce an intense angiogenic response to the same dose of an angiogenic protein (bFGF) that induces a low angiogenic response in mice of a different genetic background (SJL/J). At least a tenfold difference is seen between the high and low responders, with other strains of mice responding in the middle range (Fig. 20.6-5).
MICROVESSEL DENSITY IS A USEFUL PROGNOSTIC INDICATOR BUT MAY NOT BE A USEFUL INDICATOR OF EFFICACY OF ANTIANGIOGENIC THERAPY

The first quantitative method for histologic grading of tumor angiogenesis was reported by Steven Brem and colleagues\(^2\) from my laboratory in 1972. They correlated neovascularization in human brain tumors with tumor grade. It was not until 13 years later that a second report describing histologic quantification of tumor angiogenesis was published.\(^3\) This report was followed 3 years later by the first report of the use of tumor vascularity as a prognostic marker (cutaneous melanoma).\(^4\) In 1991, Noel Weidner and I used specific antiendothelial antibodies to highlight tumor vasculature and showed that microvessel density was a prognostic marker for human breast cancer.\(^5\) Since then, the majority of reports (52 different studies) have confirmed that microvessel density is a powerful and often an independent prognostic indicator for many different types of human cancer. However, other reports fail to show that microvessel density is a prognostic indicator (seven studies), especially for certain types of tumors. Many of the negative reports may be methodological. Others may result from poorly understood biologic differences, such as the possible existence of angiogenesis inhibitors and stimulators in certain tumors. Gasparini and Harris\(^6\) analyzed the variables in quantitation of tumor angiogenesis in histologic sections, and they have summarized the reports up to 1999. These reports are also summarized in tabular form.\(^7\) The basis of the prognostic value of quantifying the areas of highest microvessel density (“hot spots”) in a tumor may be that these areas represent the most angiogenic clones of tumor cells. Such clones have the highest probability of being angiogenic metastases.

However, because microvessel density of a tumor is a prognostic marker for the risk of metastasis or death of a patient does not necessarily make it a useful indicator of efficacy of antiangiogenic therapy. Microvessel density is largely determined by intercapillary distance, which itself is governed by the thickness of the cuff of tumor cells surrounding a microvessel (50 to 200 μm). In experimental animals, microvessel density may remain constant as a tumor is regressing under antiangiogenic therapy. Despite ongoing capillary dropout in a shrinking tumor mass, residual tumor cells can assemble around the remaining microvessels, thus leaving the microvessel density relatively unchanged. Furthermore, microvessel density may not distinguish between certain benign and malignant tumors. For example, normal human pituitary has a higher microvessel density than a pituitary adenoma, which has a higher microvessel density than a pituitary carcinoma.\(^8\) One explanation of this apparent paradox is that, in most normal tissues, the perivascular cuff is usually one or two cells thick. In some normal tissues, therefore, intercapillary distance is small, leading to a high microvessel density. In contrast, in many tumors the perivascular cuff thickness increases as tumor cells adapt to lower oxygen tension and survive at an increasing distance from the nearest open capillary. The cuff thickness of a murine breast carcinoma (MCA-IV) reaches 100 μm or more, which approaches the limit of oxygen diffusion.\(^9\) For other tumors, such as breast carcinoma, microvessel density is significantly higher in the cancer than in normal breast.\(^10\) In certain animal tumors, angiogenic output appears to exceed the growth capacity of the tumor cells so that treatment with an angiogenesis inhibitor initially induces a significant decrease in microvessel density as tumor growth is inhibited or arrested. Because all of these variables are not fully understood, it may

The effect of antiangiogenic therapy on slowly growing (RT4) (A,B) versus rapidly growing (MGH-U1) (C,D) human bladder cancer in mice.
not be prudent at this time to use microvessel density as a surrogate marker for efficacy of antiangiogenic therapy. **STABLE DISEASE OR TUMOR DORMANCY MAY BE SUSTAINED BY BLOCKED ANGIOGENESIS**

Increasing evidence shows that experimental tumors can be maintained at a stable size or at a microscopic dormant size by uninterrupted antiangiogenic therapy or by blocked angiogenesis. For the purpose of this chapter, stable disease may be defined as tumor that has stopped expanding but is grossly visible or radiologically detectable. A definition of tumor dormancy is nonexpanding tumor that can be detected only microscopically. In either event, recruitment of new vessels is sufficiently restricted that tumor cells surviving on residual vessels exist in a steady state of proliferation and apoptosis that prohibits further expansion of tumor mass, regardless of whether it is a primary tumor or a metastasis. It is too early to say whether prolonged stable disease or durable tumor dormancy can be achieved by antiangiogenic therapy in cancer patients. Nevertheless, it may be prudent to include these states as possible end points in clinical protocols for antiangiogenic therapy. A close approximation to tumor dormancy in experimental animals may be the regression of a recurrent giant cell tumor of the mandible by interferon-α administered at a low dose of 3 million units per day for 1 year. Interferon-α is an angiogenesis inhibitor by virtue of its ability to block overproduction of bFGF.

**LEUKEMIA IS ANGIOGENESIS DEPENDENT**

The conventional wisdom has been that, because leukemia is regarded as a liquid tumor, it does not require angiogenesis. However, in children with newly diagnosed untreated acute lymphoblastic leukemia, bone marrow biopsies revealed a six- to sevenfold increase in microvessel density in the leukemic marrows in contrast to control bone marrows from children undergoing staging evaluations at the time of diagnosis of solid tumor. Microvessels in leukemic bone were surrounded by a perivascular cuff of tumor cells not unlike solid tumors. This configuration was best observed by confocal microscopy. bFGF was approximately sevenfold higher in the leukemic children than in controls. Interestingly, acute myeloid leukemia in adults is also associated with intense bone marrow neovascularization.

Cellular levels of the angiogenic factor VEGF are abnormally elevated and provide an independent predictor of outcome. The myeloproliferative diseases polycythemia vera, chronic myelocytic leukemia, and myelofibrosis also have significantly increased neovasculature. The close configuration of bone marrow cells and microvessels may permit a two-way paracrine pathway between vascular endothelial cells, which can release granulocyte colony-stimulating factor (a mitogen for bone marrow cells), and bone marrow cells, which release bFGF (a mitogen for vascular endothelial cells).

These results show that leukemia (and other proliferative diseases of the bone marrow) are angiogenic. They do not, however, prove that leukemia is angiogenesis dependent. The first experimental evidence in support of this concept is by Browder and colleagues, who demonstrated that L1210 leukemia can be eradicated by an antiangiogenic schedule of chemotherapy, but not by the conventional schedule of maximum tolerated dosing. Unpublished preliminary data by Browder suggests that endostatin, a specific angiogenesis inhibitor, can significantly prolong survival of mice bearing murine leukemias.

These observations provide a conceptual basis for the potential future use of angiogenesis inhibitors in leukemia, perhaps first in patients for whom all conventional therapy has been unsuccessful, and later as an adjunct to conventional therapy.

**CLINICAL PATTERNS OF METASTASIS PRESENTATION MAY BE ANGIOGENESIS DEPENDENT**

Cancer metastases may present at least four common clinical patterns and one rare pattern (Fig. 20.6-7). These clinical observations have previously been unrelated to each other, but we can now propose that they may all be explained on the basis of angiogenic principles.

![Figure 20.6-7. Clinical presentation of metastases.](image)

1. The patient whose metastases appear a few months after surgical removal of a primary tumor may have undergone a decrease in a circulating angiogenesis inhibitor that was generated by the primary tumor. A murine Lewis lung carcinoma that generates angiostatin is a model of this type of clinical presentation.
2. When metastases are already present at the first diagnosis of a primary tumor (i.e., parallel tumor growth), the primary tumor may have lost or down-regulated its ability to generate a circulating angiogenesis inhibitor and therefore is incapable of suppressing distant metastases. The experimental analogue would be a line of Lewis lung carcinoma that has lost the ability to generate angiostatin.
3. When metastases present in the absence of a primary tumor (i.e., a pattern known as the occult primary), this finding may be similar to mice in which tumors cells are injected intravenously and are allowed to take as lung metastases before a primary tumor is implanted subcutaneously. In this experiment, growth of the subcutaneous tumor appears to be inhibited by the extensive metastatic growth. However, it has not yet been ascertained whether the inhibition was mediated by a circulating inhibitor. In a patient presenting with this metastatic pattern, the total mass of metastases would need to expand faster than the primary tumor to produce sufficient quantities of circulating angiogenesis inhibitor that could suppress the primary tumor.
4. The patient whose metastases do not appear until years after removal of a primary tumor may harbor dormant metastases that are not angiogenic for many years but eventually switch to the angiogenic phenotype. This is more than just speculation, because we have developed an animal model that behaves exactly in this way. The surgical removal of a B-16 melanoma from C57Bl/6 mice leaves numerous viable lung metastases of approximately 0.1 to 0.2 mm diameter that are nonangiogenic and do not expand further throughout the life of the animal. However, the microscopic metastases can be stimulated to grow by trauma to the lung or by transplanting a piece of lung to the subcutaneous tissue of another mouse (M. O'Reilly, unpublished data, 1998).
5. A rare event is for metastases to disappear completely or to undergo partial regression after removal of a renal cell carcinoma. An animal model that most closely resembles this clinical pattern is V2 carcinoma in the rabbit. Lung metastases grow in parallel with a primary tumor in the thigh. However, lung metastases regress after the primary is completely resected (H. Verheul, R. D'Amato, and D. Panigrahy, unpublished data, 1998). This finding does not appear to be an immune reaction, because fresh tumor can be successfully grown in the same rabbit. One explanation may be that the metastases were dependent on high production of a circulating angiogenic factor(s), such as the high tissue levels of bFGF that have been found to correlate with high mortality in renal cancer.

By describing these patterns of metastatic presentation in patients, I have tried to provide a possible unifying mechanism to explain them. The experimental evidence for the animal models is discussed in more detail by Holmgren et al. It must be emphasized that the similarity of such animal models to human patterns of metastatic presentation does not prove that the human patterns are based on the same angiogenic principles as the animal models. However, this arrangement of the human metastatic patterns will hopefully stimulate other investigators to find additional clinical or experimental evidence to support or refute the general hypothesis. Thus, the heuristic value of the clinical patterns of angiogenesis inhibitors. These observations also provide an alternative to the widely held assumption that tumor cells in a dormant microscopic tumor are not cycling and remain in G0. In fact, dormant animal tumors with blocked angiogenesis maintain a high apoptosis rate balanced by a high proliferation rate in the tumor cells.

**CYTOTOXIC CHEMOTHERAPY MAY BE ANGIOGENESIS-DEPENDENT**

Conventional cytotoxic chemotherapeutic drugs target tumor cells, but the effect of these drugs on microvascular endothelial cells has received little attention until the 1990s. Baguley et al. demonstrated in 1991 that vinblastine caused more than 90% necrosis of drug-resistant solid tumors within hours but had no direct effect on the tumor cells as demonstrated when the cells were grown as ascites. In 1992, Steiner showed that vincristine, vinblastine, doxorubicin, mitoxantrone, and etoposide...
had short-term antiangiogenic activity in the chick embryo. 97 Also, in vitro antiendothelial effects have been reported for cyclophosphamide, 98 5-fluorouracil, 99 and
mitomycin C.99,100 Short-term in vivo antiangiogenic effects have been reported for paclitaxel, 101,102 and 103 6-methylmercaptopurine,104 tegafur,105
9-amino-20(S)-camptothecin, 106 topotecan,106 and combretastatin A-4.107,108
The question was raised by Browder as to why those cytotoxic chemotherapeutic agents with antiangiogenic activity still induced acquired drug resistance. Specific
angiogenesis inhibitors do not usually induce drug resistance. 39,72 Vascular endothelial cells, like bone marrow cells, do not develop drug resistance, in part because
of their low mutation rate. Browder hypothesized that the usual dose-schedule regimen for chemotherapeutic agents is not conducive to sustained blockade of
angiogenesis. Conventional chemotherapy is traditionally administered at maximum tolerated doses followed by an extended treatment-free interval to permit recovery
of hematopoietic progenitors and gastrointestinal tract mucosa. Browder proposed, however, that during this off-therapy interval, microvascular endothelial cells in the
tumor bed could also resume growth and nourish tumor recurrence . Virtually all animal experiments show that antiangiogenic therapy is most successful when it is
given over short intervals (e.g., daily or every other day) without off-therapy gaps. Browder demonstrated that 5-fluorouracil and 6-mercaptopurine are nearly devoid
of antiangiogenic activity when given as bolus injections, but they reveal potent antiangiogenic efficacy when the same dose is given as a continuous infusion. 74
He further showed that a standard cytotoxic agent, cyclophosphamide, can be administered to animals bearing Lewis lung carcinoma at a dose and schedule that is
optimized for more sustained apoptosis of endothelial cells but not of tumor cells. This was named the antiangiogenic schedule. The conventional schedule is a
maximum tolerated dose administered every other day for three doses followed by 21 days off-therapy to rescue bone marrow. The antiangiogenic schedule consists
of a lower dose administered every 6 days. A drug-sensitive Lewis lung carcinoma became drug resistant on the conventional schedule and killed all mice, but it was
eradicated on the antiangiogenic schedule. No detectable tumor was detected after 657 days, when the animals reached the end of their natural lifespan. When the
tumor was made drug resistant before therapy, the antiangiogenic schedule suppressed tumor growth three times more effectively than the conventional schedule.
When an angiogenesis inhibitor, TNP-470, was added at a dose 86% lower than its effective dose alone, the drug-resistant tumor was eradicated in 84% of mice. 74
This finding is provocative because TNP-470 alone, even at its full dose, slows Lewis lung carcinoma by only 65% and cannot cause regression. Thus, a cytotoxic
chemotherapeutic agent administered in an antiangiogenic dose schedule can more effectively control tumor growth in mice, whether or not its tumor cells are drug
resistant, an improvement that has come from using new logic for an old drug. In summary, the new logic is that the antiangiogenic properties of certain conventional
cytotoxic agents are not revealed unless the drugs are administered frequently, without a prolonged off-therapy period. Frequent administration requires lower doses.
Klement et al. 109 in Robert Kerbel's laboratory have demonstrated this new logic with a different experimental system. For a commentary on antiangiogenic
chemotherapy, see Hanahan et al. 110 They showed that continuous low-dose therapy with vinblastine and an antibody to VEGF receptor-2 induced sustained
regression of neuroblastoma without overt toxicity. No evidence of acquired drug resistance was found throughout the 6 months' course of treatment.
When taken together, these results in mice may help to explain why some patients who are receiving long-term maintenance or even palliative chemotherapy continue
to have stable disease beyond the time that the tumor cells would have been expected to develop drug resistance. However, because conventional schedules of
combination chemotherapy have led to profound increases in the survival of children with cancer and have improved the survival of adults with certain types of cancer,
we do not believe that these clinical protocols should be changed for the sake of increasing the antiangiogenic efficacy of any given drug. 74 Formal clinical trials with
patients whose tumor has become refractory to conventional chemotherapy or radiotherapy will be necessary to find an optimum antiangiogenic dose and schedule
and to demonstrate whether it is an improvement over conventional chemotherapy dose schedules.

CLINICAL TRIALS OF ANGIOGENESIS INHIBITORS
At this writing, 20 angiogenesis inhibitors produced by the biotechnology and pharmaceutical industry are in clinical trial for patients with advanced metastatic cancer,
and seven are in phase III trials (see Fig. 20.6-1).
Three general strategies have been used to develop these inhibitors. A target molecule in the angiogenic pathway is identified and then is counteracted by a synthetic
inhibitor or by an antibody (e.g., an antibody to the angiogenic factor VEGF or its receptor). A second approach is to identify antiangiogenic activity in a drug
previously used for a different effect. Examples are thalidomide and interferon-a. Slamon showed that Herceptin has antiangiogenic activity in addition to its direct
antitumor effect on breast cancer cells: It interferes with the activity of at least three angiogenic proteins produced by breast cancer cells (D. Slamon, Plenary Address
before the American Association of Cancer Research, San Francisco, April 2000). A third approach is to discover specific endogenous angiogenesis inhibitors that
are already in the circulation or in matrix. In fact, several of these are internal fragments of larger proteins that have different functions. Some examples are
thrombospondin-1, a 140-kD protein under the control of p53 111; angiostatin, a 38-kD fragment of plasminogen 35; endostatin, a 20-kD fragment of collagen XVIII 37;
pigment epithelium-derived factor, a 50-kD serine protease inhibitor 112; antiangiogenic antithrombin III, a 53-kD cleaved or latent conformation of the 58-kD
antithrombin III 40; restin, a 22-kD internal fragment of collagen XV 113; canstatin, a 24-kD fragment of the a 2-chain of type IV collagen 114; and maspin, a 42-kD gene
product of normal breast epithelium, also under the control of p53 and silenced during breast cancer progression. 115,116 A longer list would include SPARC (secreted
protein acidic and rich in cysteine), 117 VEGI (vascular endothelial cell growth inhibitor),118 IP-10 (interferon- g–inducible protein-10), 119 interleukin-18, 120 and 16-kD
prolactin.121
The angiogenesis inhibitors operate by quite different mechanisms, which reveal that multiple pathways in the angiogenic process are vulnerable to attack. 4 As of this
writing, it is too soon to say which of the angiogenesis inhibitors currently in clinical trial will receive U.S. Food and Drug Administration approval. However, because
angiogenesis inhibitors can be added to chemotherapy, radiotherapy, immunotherapy, or gene therapy, as well as to each other, there is likely to be a future need for
a group of angiogenesis inhibitors from which physicians can choose. The eventual possibility also exists that antiangiogenic therapy may be used as long-term
maintenance therapy, like tamoxifen, to reduce the risk of recurrences.
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SECTION 21.1
Design and Analysis of Clinical Trials

RICHARD SIMON

Introduction
Phase I Clinical Trials
Phase II Clinical Trials
Patient Selection
Design of Single-Agent Trials
Trials of Combination Regimens
Design of Phase III Clinical Trials
Randomization
Stratification
Sample Size
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Ethics/Drug Efficacy/Dosage
Analysis of Phase III Clinical Trials
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Reporting Results of Clinical Trials
Epidemiology of Clinical Trials
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INTRODUCTION

Clinical trials are experiments to determine the value of treatments. There are two key components to the experimental approach. First, results rather than plausible reasoning are required to support conclusions. Second, experiments should be prospectively planned and conducted under controlled conditions in order to provide definitive answers to well-defined questions. Comparing the survival rates (based on tumor registry data) of prostate cancer patients treated with surgery to those of patients receiving radiotherapy is an example of an observational study, not a clinical trial. In an observational study, the investigators are passive observers. Treatment assignments, staging workup, and follow-up procedures are out of the control of the investigators and are conducted with no considerations about the validity of the subsequent attempt at comparison. The statistical associations resulting from such studies are, consequently, a weak basis for causal inferences about relationships between the treatments administered and the outcomes observed. Treatments usually are selected on the basis of subjective assessment of the prognosis of the patient, specialties of the physician, and various diagnostic evaluations. Unknown patient selection factors generally are more important determinants of patient outcome than are differences between treatments.

Observational studies are generally the only feasible approach for epidemiologic assessment of disease etiology. Acute observations in poorly structured therapeutic settings can also lead to the development of valuable ideas that can be tested in the laboratory and in clinical trials. However, observational studies rarely are satisfactory substitutes for clinical trials. 12,13 As pointed out by MacMahon and Pugh: 14

“Only a minority of statistical associations are causal. . . . Once a statistical association has been demonstrated, how can it be determined whether or not it is causal. . . . The most satisfactory procedure is a direct experiment. . . . The evaluation of the causal nature of a relationship, in the absence of direct experiment, is neither easy nor objective. . . . The field of cancer therapy is replete with examples of new modalities that were taken up with enthusiasm and proved worthless only after they had resulted in many years of futile cost and suffering.”

Clinical trials require careful planning. The first result of the planning process is a written protocol. Typical subject headings for the protocol are shown in Table 21.1-1. The protocol should define treatment and evaluation policies for a well-defined set of patients. It also should define the specific questions to be answered by the study and should directly justify that the number of patients and the nature of the controls are adequate to answer these questions. Some clinical trials are really only guidelines for clinical management supplemented by lofty objectives with no scientific meaning and no realistic chance of providing a reliable answer to a well-defined medical question. Such studies do not warrant the expenditure of limited clinical research dollars and represent a disservice to the patients who may be willing to undergo some inconvenience in order to contribute to the welfare of future patients. In this section, we attempt to provide information that will help to avoid such clinical trials.

TABLE 21.1-1. Subject Headings for a Protocol

PHASE I CLINICAL TRIALS

The objective of a phase I trial is to determine a dose that is appropriate for use in phase II trials. Patients with advanced disease that is resistant to standard therapy are included in such trials, but it is important that the patients have normal organ function.

There are several different types of phase I trials. The most common is the phase I trial of a new cytotoxic drug. Such studies usually are performed by starting with a low dose not expected to produce serious toxicity in any patients. A starting dose of one-tenth the lethal dose (expressed as milligrams per square meter of body surface area) in the most sensitive species usually is used. 15 The dose is increased for subsequent patients according to a series of preplanned steps. Dose escalation for subsequent patients occurs only after sufficient time has passed to observe acute toxic effects for patients treated at lower doses. Cohorts of three to six patients are treated at each dose level. Usually, if no dose-limiting toxicity (DLT) is seen at a given dose level, the dose is escalated for the next cohort. If the incidence of DLT is greater than 33% at a given level, then dose escalation also stops. The phase II recommended dose often is taken as the highest dose for which the incidence of DLT is less than 33%. Usually, six or more patients are treated at the recommended...
The dose levels themselves commonly are based on a modified Fibonacci series. The second level is twice the starting dose; the third level is 67% greater than the second; the fourth level is 50% greater than the third; the fifth is 40% greater than the fourth; and each subsequent step is 33% greater than that preceding it. Escalating doses for subsequent courses in the same patient is generally not done, except at low doses before any DLT has been encountered.

There is no compelling scientific basis for the approach just outlined, except that experience has shown it to be safe. Traditional phase I trials have three limitations: (1) They sometimes expose too many patients to subtherapeutic doses of the new drug; (2) the trials may take a long time to complete; and (3) they provide very limited information about interpatient variability and cumulative toxicity. New trial designs have been developed to address these problems. One class of designs, accelerated titration designs, permit within-patient-dose escalation and use only one patient per dose level until grade 2 or greater toxicity is seen. Doses are titrated within patients to achieve grade 2 toxicity. The analysis consists of fitting a statistical model to the full set of data that includes all grades of toxicity for all courses of a patient’s treatment. The model may parameterize that the steepness of the dose-toxicity curve, the degree of interpatient variability in the location of the dose-toxicity curve, and the degree (if any) of cumulative toxicity. All these parameters are estimated from the data.

In developing the accelerated titration designs, Simon et al. 7 fit a stochastic model to data from 20 phase I trials of nine different drugs. New data then were simulated using the model with the parameters estimated from the actual data, and the performance of alternative phase I designs on this simulated data was evaluated. Four designs were evaluated. Design 1 was a conventional design using cohorts of three to six patients with 40% dose-step increments and no intrapatient dose escalation. Designs 2 through 4 included only one patient per cohort until one patient experienced dose-limiting toxicity or two patients experienced grade 2 toxicity (during their first course of treatment for designs 2 and 3 or during trials for design 4). Designs 3 and 4 use 100% dose steps during this initial accelerated phase. After the initial accelerated phase, designs 2 through 4 resort to standard cohorts of three to six patients with 40% dose-step increments. Designs 2 through 4 use intrapatient dose escalation if the worst toxicity is grade 0 to 1 in the previous course for that patient.

Only three of the actual trials showed any evidence of cumulative toxicity. The average number of patients required was reduced from 39.9 for design 1 to 24.4, 20.7, and 21.2 for designs 2, 3, and 4, respectively. The average number of patients who had grade 0 to 1 toxicity as their worst toxicity grade over three cycles of treatment was 23.3 for design 1 but only 7.9, 3.9, and 4.8 for designs 2, 3, and 4, respectively. The average number of patients with a worst toxicity grade of 3 increased from 5.5 for design 1 to 6.2, 6.8, and 6.2 for designs 2, 3, and 4, respectively. The average number of patients with a worst toxicity grade of 4 increased from 1.9 for design 1 to 3.0, 4.3, and 3.2 for designs 2, 3, and 4, respectively. Accelerated titration designs appear to be effective in reducing the number of patients who are undertreated, speeding the completion of phase I trials, and providing increased information. These advantages are achieved with some increase in the number of patients experiencing grade 3 and 4 toxicities.

Some phase I trials are very complex in that they involve the simultaneous escalation of two or more drugs. The design of such trials has been discussed by Korn and Simon.11

So-called phase IB trials attempt to determine the relationship between dose of a biologic agent and both toxicity and immunologic effect. Such trials often suffer from two flaws. One is that it is assumed that cohorts of three to six patients are sufficient for relating dose to immunologic effects, without consideration of interpatient variability and measurement error of the immunologic assays. The second problem is that there is often little information about what immunologic end points actually are relevant for antitumor effects. Such studies have little potential for producing meaningful information about the dose of a biologic that should be used for subsequent trials.

Some phase I trials attempt to answer comparative questions. For example, should paclitaxel be administered before or after doxorubicin in a two-drug combination? Because of the small sample sizes of phase I trials, the maximum tolerated doses (MTDs) generally are determined imprecisely. This, combined with the nonrandomized nature of such trials, means that reliable comparative conclusions can be expected only if the differences are large.

PHASE II CLINICAL TRIALS

PATIENT SELECTION

Whereas phase I trials need not be performed separately by tumor type, this is not the case for phase II trials, because the biologic response of interest is that of the tumor itself. When a drug enters phase II trials, it should be tested in the patient group that is most likely to show a favorable effect but for whom no effective therapy is available. This is best accomplished by patients with maximum performance status and a minimum amount of prior chemotherapy. Full-dose chemotherapy is often impossible in patients debilitated by prior treatment, and lack of chemotherapeutic activity in previously treated patients may not indicate lack of clinical usefulness in earlier disease. This issue was well illustrated by etoposide in small cell lung carcinoma. For the less chemosensitive cancers, chemotherapy offers little or no palliative benefit, and initial phase II trials should be conducted in patients with no prior chemotherapy. In more sensitive tumors, such as breast, small cell lung, or ovarian carcinoma or non-Hodgkin’s lymphoma, it is desirable to evaluate new drugs in patients with no more than one prior treatment for advanced disease. For very chemosensitive tumors, the window-of-opportunity design sometimes is used, in which patients who are not previously treated are given one or two courses of a phase II drug and then are switched to a standard combination. In general, agents should be shown to be active in a favorable population of patients before they are given to a less favorable group. Adherence to this principle saves patients with advanced disease from exposure to inactive agents for which the likelihood of toxicity is much greater than the likelihood of benefit.

TRIALS OF SINGLE AGENTS

There is much confusion about the appropriate objectives of phase II trials. It often is useful to distinguish between phase II trials of single agents and phase II trials of combinations. Both are called phase II trials because eligibility is limited to patients with a specific diagnosis and there is no internal control group. For most single-agent phase II trials, however, the objective is simply to determine whether the drug has activity against the tumor type in question. For this objective, response rate is an appropriate end point for evaluating the question posed by the trial. It is important to recognize, however, that tumor response is not a direct measure of patient benefit and, hence, it cannot be assumed that response rate is an appropriate end point for drawing conclusions about treatment efficacy. A treatment that causes partial responses is not necessarily beneficial to the patient, and analyses that demonstrate that responders live longer than nonresponders are invalid for concluding that a treatment extends survival. First, responders, by definition, have lived long enough to achieve that status. Second, responders may have more favorable prognostic factors. Finally, treatment may shorten survival of nonresponders while not influencing survival of responders. To demonstrate that treatment extends survival, it must be demonstrated that the treated group as a whole lives longer than an appropriate control group. Phase II trials do not have an internal control group and, hence, drawing conclusions about survival from such trials is very problematic.

A variety of statistical accrual plans and sample size methods have been developed for phase II trials. Many have been reviewed by Simon. One of the most popular approaches is the optimal two-stage design. A number (n,) of evaluable patients is entered into study in the first stage of the trial. If fewer than a specified r1 responses are obtained among these n1 patients, then accrual terminates and the drug is rejected as being of little interest. Otherwise, accrual continues to a total of n evaluable patients. At the end of the second stage, the drug is rejected if the observed response rate is less than or equal to r1/n, where r and n are determined by the design employed. Tables 21.1.2 and 21.1-3 illustrate some of these optimized designs. To select a design, researchers must specify a target activity level of interest, , and also a lower activity level, . The first row of each triplet of optimal designs provides designs with probability 0.10 of accepting drugs worse than , and probability 0.10 of rejecting drugs better than . Subject to these two constraints, the optimal designs minimize the average sample size. The average sample size is calculated at the lower activity level in order to optimize protection of patients from exposure to inactive drugs. The tables show for each design the optimal values of , , r, and n, the average sample size, and the probability of stopping after the first stage for a drug with activity level .
TRIALS OF COMBINATION REGIMENS

Many so-called phase II trials of combination regimens are conducted. The objectives of such trials are often unclear. One reasonable objective is sometimes merely to ensure that the combination is feasible and tolerable when used in a multiinstitution setting before embarking on a phase III trial. Achieving this objective does not require many patients. An alternative objective is to determine whether the new regimen is promising enough to warrant a phase III trial. Achieving this objective does not require considerable planning. Consequently, many phase II trials of this type are not adequately planned and analyzed to serve any real scientific objective.

Investigators often do not distinguish between phase II trials of combinations of active agents and phase II trials of new single agents. Consequently, protocols often are written to distinguish between inactivity of the combination (e.g., \( p_1 = .05 \) or .10) and some modest level of activity (e.g., \( p_1 = .20 \) or .25). Since the drugs being combined are generally already known to be active, this makes little sense. If response rate is the primary end point, then the level of no interest (\( p_0 \)) should generally represent the level of activity of the most active single-agent component or the level of activity of previously studied combination regimens (as presumably the new regimen would be considered promising only if it is promising relative to other existing regimens).

With the lower limit of activity, \( p_0 \), defined as described earlier, Tables 21.1-2 and 21.1-3 can be used for the design of phase II trials of combination regimens. One problem with this approach, however, is the uncertainty in specifying a meaningful value of \( p_0 \) to be used for trial design and analysis. Because the conclusions of phase II trials of combinations are essentially comparative, it is important that the comparison be based on a prognostically similar group of patients given standard treatment. Hence, the planning of such a trial should include the prospective identification of such a group of patients. Although such historical control comparisons are not considered reliable enough to eliminate the need for phase III trials, if done carefully they will provide better decisions about which new regimens are worthy of phase III evaluation. For comparative trials of response rates using historical controls, appropriate tables for sample size planning are given by Makuch and Simon. When sufficient numbers of patients and several treatments are available to test, there are advantages to randomized phase II trials. Although phase II trials are not comparative, in selecting the most promising treatment or schedule to pursue, it is advantageous to evaluate the candidates on comparable patients. Table 21.1-4 shows the number of patients per treatment arm required to ensure that the best treatment will have the highest observed response rate. This calculation assumes that the true response probability for the best treatment is 10 percentage points better than for the others. Simon et al. provide similar tables for 15% differences. This selection approach is useful when one treatment will be carried forward and the treatments are similar with regard to cost and toxicity.

**TABLE 21.1-2.** Simon Two-Stage Phase II Designs for \( p_1 - p_2 = .20 \)

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<th>Sample Size</th>
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These tables also show the "minimax" designs, which provide the smallest maximum sample size \( n \) that satisfies the two constraints just described. Although minimax designs have somewhat larger average sample sizes than do optimal designs, in some instances they are preferable because the small increase in average sample size is more than compensated for by a large reduction in maximum sample size.

The designs shown in Tables 21.1-2 and 21.1-3 are two-stage designs with the potential for early stopping for lack of activity. Other two-stage designs have been described that provide for early termination for inactivity or for early evidence for activity. Also, optimized three-stage designs have been described.

When sufficient numbers of patients and several treatments are available to test, there are advantages to randomized phase II trials. Although phase II trials are not comparative, in selecting the most promising treatment or schedule to pursue, it is advantageous to evaluate the candidates on comparable patients. Table 21.1-4 shows the number of patients per treatment arm required to ensure that the best treatment will have the highest observed response rate. This calculation assumes that the true response probability for the best treatment is 10 percentage points better than for the others. Simon et al. provide similar tables for 15% differences. This selection approach is useful when one treatment will be carried forward and the treatments are similar with regard to cost and toxicity.

**TABLE 21.1-3.** Simon Two-Stage Phase II Designs for \( p_1 - p_2 = .15 \)

<table>
<thead>
<tr>
<th>Sample Size</th>
<th>( (C) ) Probability</th>
<th>( (A) ) Probability</th>
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<tr>
<td>20</td>
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**TABLE 21.1-4.** Number of Patients per Treatment Group for Selecting Better Treatment When True Response Probabilities Differ by 10 Percentage Points *

<table>
<thead>
<tr>
<th>Relative Response Probability</th>
<th>( P_1 ) Probability of ( C ) Success</th>
<th>( P_2 ) Probability of ( C ) Success</th>
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<tr>
<td>.05</td>
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* Number of patients required to ensure that the best treatment will have the highest observed response rate. This calculation assumes that the true response probability for the best treatment is 10 percentage points better than for the others. Simon et al. provide similar tables for 15% differences.

TRIALS OF COMBINATION REGIMENS

Many so-called phase II trials of combination regimens are conducted. The objectives of such trials are often unclear. One reasonable objective is sometimes merely to ensure that the combination is feasible and tolerable when used in a multiinstitution setting before embarking on a phase III trial. Achieving this objective does not require many patients. An alternative objective is to determine whether the new regimen is promising enough to warrant a phase III trial. Achieving this objective requires considerable planning. Consequently, many phase II trials of this type are not adequately planned and analyzed to serve any real scientific objective.

Investigators often do not distinguish between phase II trials of combinations of active agents and phase II trials of new single agents. Consequently, protocols often are written to distinguish between inactivity of the combination (e.g., \( p_1 = .05 \) or .10) and some modest level of activity (e.g., \( p_1 = .20 \) or .25). Since the drugs being combined are generally already known to be active, this makes little sense. If response rate is the primary end point, then the level of no interest (\( p_0 \)) should generally represent the level of activity of the most active single-agent component or the level of activity of previously studied combination regimens (as presumably the new regimen would be considered promising only if it is promising relative to other existing regimens).

With the lower limit of activity, \( p_0 \), defined as described earlier, Tables 21.1-2 and 21.1-3 can be used for the design of phase II trials of combination regimens. One problem with this approach, however, is the uncertainty in specifying a meaningful value of \( p_0 \) to be used for trial design and analysis. Because the conclusions of phase II trials of combinations are essentially comparative, it is important that the comparison be based on a prognostically similar group of patients given standard treatment. Hence, the planning of such a trial should include the prospective identification of such a group of patients. Although such historical control comparisons are not considered reliable enough to eliminate the need for phase III trials, if done carefully they will provide better decisions about which new regimens are worthy of phase III evaluation. For comparative trials of response rates using historical controls, appropriate tables for sample size planning are given by Makuch and Simon and are summarized in Table 21.1-5. This table is for achieving 80% power with a one-sided 5% significance level. If the historical control group of 50 patients showed a response rate of 30%, and the target level of improvement is a 50% response rate, then 59 patients should be treated with the experimental regimen. If there were 100 appropriate historical control patients, then only 48 new patients are required. If there were only 30 historical control patients, then 137 new patients are needed for the experimental treatment. If the uncertainty in the level of response achievable with standard treatment is substantial because of the limited number of appropriate historical controls, then it is not efficient to conduct a phase II trial of the new regimen. It would be more efficient to conduct a randomized phase II or phase III trial of the new regimen and the standard treatment.
Thall et al.\textsuperscript{12,20} have developed Bayesian methods for planning and conducting trials in which the precision in the response probability \( p_1 \) is quantified by a "prior probability distribution." These Bayesian designs provide for continual analysis of results after evaluation of response for each patient. This is difficult logistically for multistitutional trials but provides a valid statistical basis for the intensive monitoring of cancer center or pharmaceutical industry trials in which patients may be limited or time may be critical. One begins with a prior probability distribution of response for \( p_1 \) that is flat over the range 0 to 1. After each patient is evaluated on the experimental regimen, the "posterior probability distribution" for \( p_1 \) is updated. This permits calculation of the posterior probability distribution for \( p_1 - p_0 \).

Let \( d \) denote the difference in response probabilities that is of interest. If, at some point during the trial, the posterior probability that \( p_1 - p_0 \leq d \) becomes small—say less than 0.05—one might terminate the trial and conclude that the new regimen is not promising. If, at some point during the trial, the posterior probability that \( p_1 - p_0 \geq d \) becomes large—say greater than 0.95—one might terminate the trial and conclude that the new regimen appears better than the historical control. In this case, one could continue entry of patients if it were desirable to study the regimen further in a phase II setting.

The trial is designed with a maximum number of patients, \( n_{	ext{max}} \), that limits sample size even if neither early termination condition occurs. Table 21.1-6 shows an example of the operating characteristics of a design of this type. In this example, the historical data indicate that the expected response probability for the control regimen is 0.20, and that the width of the 90% confidence interval around 0.20 for the true value is approximately 0.20. The table also represents targeting a 20–percentage point improvement in response probability (\( d = 0.20 \)). The maximum sample size is set at 65, and it is assumed that the trial is arbitrarily not terminated before ten patients are evaluated. As can be seen from the table, the median number of patients required is 12 under the null hypothesis that the response probability for the experimental regimen is 0.20 and is only 13 under the alternative hypothesis. The table also indicates that 75% of the time the trial will terminate by the evaluation of 20 to 22 patients. Bayesian continuing-monitoring phase II designs have also been developed for simultaneously monitoring multiple end points, including efficacy and toxicity. Designs of this type used in actual clinical trials have been illustrated in the work of Thall et al.\textsuperscript{12}

Some investigators and statisticians do not like to use approaches based on explicit comparison to historical controls. Phase II trials of combinations are inherently comparative, however. Going through the exercise of explicitly quantifying the basis of comparison, which these methods require, clarifies beforehand whether the uncertainty in outcome for the control group is so great that a phase II trial is not useful. Phase II trials of combinations are problematic. Only by using methods that provide more careful statistical planning of such trials can we streamline the drug development process.

Many reports in the literature of phase II trials of combination regimens conclude that the treatment is effective. As noted, response rates generally are not a measure of patient benefit. Such reports generally fail to make any meaningful attempt at determining outcome on standard treatment for a prognostically comparable set of patients. Often these trials are not conducted as a prelude to a phase III evaluation, and hence their value to clinical therapeutics is difficult to identify.

For some diseases, it has been noted that combination regimens that produce high response rates in phase II trials do not result in improved survival in phase III trials as compared to standard treatment. This has led to interest in using survival directly as an end point for phase II trials to evaluate the promise of a regimen. In some types of cancer, response rate is difficult to measure, and many patients do not have measurable disease (e.g., brain, ovarian, gastric, and prostate cancer). Dixon and Simon\textsuperscript{12} have developed tables for planning historically controlled phase II comparative studies with a survival or time-to-progression end point.

### DESIGN OF PHASE III CLINICAL TRIALS

Good clinical therapeutic research requires asking important questions and getting reliable answers. This chapter attempts to provide guidance on the components necessary for getting reliable answers. As noted earlier in Trials of Combination Regimens, many phase II trials of combination regimens do not provide reliable answers. Some phase III trials, however, do not ask important questions. The most important clinical trials are often the most difficult to conduct.\textsuperscript{22} They may involve withholding a treatment established by tradition, potentially transferring patient management responsibility across specialties, standardizing procedures among physicians who believe that their way is best, and sharing recognition with a large group of collaborators.

Phase III trials attempt to provide guidance to practicing physicians to help them make treatment decisions with their patients. Consequently, the trials should provide reliable information concerning end points of relevance to the patients. The major end points for evaluating the effectiveness of a treatment should be direct measures of patient welfare. Survival and symptom control are two such end points. The latter is not routinely used because of the difficulty of measuring it reliably and because it may be influenced by concomitant treatments. As stated, tumor shrinkage usually is not an appropriate end point for phase III trials because it may have little or no relation to patient benefit. Torri et al.\textsuperscript{23} performed a metaanalysis of the relationship between difference in response rates and difference in median survivals for randomized clinical trials of advanced ovarian carcinoma. They found that large improvements in response rates corresponded to very small improvements in median survival. Hence, use of response rate as an end point results in giving patients increasingly intensive and toxic therapy with little or no net benefit to them.

It is usually important that the results of phase III trials be applicable to patients seen in the community outside of clinical research settings. This is accomplished by conducting the trials in multistitutional settings that include community physician participation. The eligibility criteria established for the trial also has a bearing on the generalizability of the conclusions; the trials conducted with narrow eligibility criteria tend to be less generalizable. Narrow eligibility criteria also complicate trials logistically. Narrow eligibility criteria tend to require extensive and expensive patient worksup and thereby do not facilitate broad participation, especially in an era of closely monitored medical costs. For these and other reasons, there is a trend toward broadened eligibility criteria for phase III clinical trials. In the United Kingdom, many trials are designed using the uncertainty principle, an approach that leaves much of the decision making about eligibility to the treating physician. There may be guidelines for eligibility, but the ultimate decision will be made by the treating physician; if he or she is uncertain about which treatment is more appropriate for the

### TABLE 21.1-6. Thall-Simon Bayesian Phase II Design

<table>
<thead>
<tr>
<th>Sample Size (Patients)</th>
<th>Probability of Benefit</th>
<th>Probability of Regimen</th>
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RANDOMIZATION

To determine whether a new treatment cures any patients with a disease that is uniformly and rapidly fatal, history is a satisfactory control. Once we leave this setting of complete determinism, however, the definition of an adequate nonrandomized control group becomes problematic. In studies using nonrandomized controls, often diagnostic and staging procedures, supportive care, secondary treatments, and methods of evaluation and follow-up are different for the controls and for the new patients. There is generally differential bias in the selection of patients to be treated resulting from judgments by the physicians, self-selection by the patients, and differences in referral patterns. There may be bias in treatment ineligibility rates. Current patients sometimes are excluded from analysis for not meeting eligibility criteria, not receiving "adequate" treatment, refusing treatment, or committing a major protocol violation. The control group, on the other hand, generally contains all the patients. There may be differences in the distribution of known and unknown prognostic factors between the controls and the current treatment group. Often there is inadequate information to determine whether such differences are present, and current known prognostic factors may not have been measured for the controls. It generally is difficult or impossible to determine whether the controls would have been eligible for the current study and in what way they represent a selection of all eligible patients.

Formation of the control group by random treatment assignment as an integral part of the planned study can avoid most of the systematic biases just mentioned. Randomization does not ensure that the study will include a representative sample of all patients with the disease, but it does help to ensure an unbiased evaluation of the relative merits of the two treatments for the types of patients entered.

It is sometimes said that randomization is unnecessary because matched historical or concurrent controls can be selected. However, matching can be done only with regard to known prognostic factors, and these generally are not sufficient for the construction of prognostically homogeneous groups of patients. Matching with regard to known factors gives no assurance that the distributions of unknown factors are similar between the groups. It also is sometimes said that randomization is not effective in ensuring that the treatment groups are similar with regard to unknown prognostic factors unless the number of patients is large. This is true but reflects a misunderstanding of the purpose of randomization. Randomization does not ensure that the groups are medically equivalent, but it distributes the unknown biasing factors according to a known random distribution so that their effects can be rigorously allowed for in significance tests and confidence intervals. This is true regardless of the study size. A significance level represents the probability that differences in outcome can be the result of random fluctuations. Without a randomized treatment allocation, a "statistically significant difference" may be the result of a nonrandom difference in the distribution of unknown prognostic factors.

Many investigators today see a useful role for both nonrandomized and randomized clinical trials. The nonrandomized format is used for determining which regimens are sufficiently promising for randomized phase III evaluation and for use in clinical settings where outcome is uniformly poor. For major questions of public health importance, unless the treatment effects are huge, the need for reliable answers dictates the use of randomized phase III trials.

Randomization of a patient should be performed after the patient has been found eligible and has consented to participate in the trial and to accept either of the randomized options. A truly random and nondeceivable randomization procedure should be used and implemented by calling a central randomization office staffed by individuals who are independent of participating physicians.

STRATIFICATION

When important prognostic factors are known for patients in a randomized trial, it is often advisable to stratify the randomization to ensure equal distribution of these factors. This usually is accomplished by preparing a separate randomization list (or set of cards in sealed envelopes) for each stratum of patients. Each list must be balanced so that after each block of four to ten patients within the stratum, the treatment groups contain equal numbers of patients. Within the blocks, the sequence of treatment assignments is random. The stratification factors must be known for each patient at the time of randomization.

It generally is best to limit stratification to those factors definitely known to have important independent effects on outcome. If two factors are closely correlated, only one need be included. Peto1-11 believes that stratification is an unnecessary complication because adjustment for imbalances of known factors can be made in the analysis. This is true for large trials. Stratification helps to ensure balance for interim analyses when the sample sizes may be limited and provides the medical audience with confidence in the results, which often is unavailable when depending on complex adjustment methods to deal with prognostic imbalances. Stratification also is a convenient way of specifying a priori what are considered the important prognostic factors. Subsequent "subset analyses" can then be limited to the patient subsets determined by the stratification factors.

Many clinical trials use adaptive stratification methods. These methods permit effective balancing by many prognostic factors, although they typically require a computer program for their use. Simon12 and Kalish and Begg13 have reviewed the various stratification methods that are available. Kalish and Begg13 have also studied analytic aspects of adaptive stratification methods.

SAMPLE SIZE

The protocol for a phase III trial should specify the number of patients to be accrued and the duration of follow-up after the close of accrual when the final analysis will be performed. Methods of sample size planning are based on the assumption that at the conclusion of the follow-up period, a statistical significance test will be performed comparing the experimental treatment to the control treatment with regard to a single primary end point. A statistical significance level of .05 has the following meaning: If there is no true difference in treatment effectiveness, the probability of obtaining a difference in outcomes as extreme as that observed in the data is .05. The significance level does not represent the probability that the null hypothesis is true; it represents a probability of an observed difference, assuming that the null hypothesis is true. Conventional statistical theory ascribes no probabilities to hypotheses, only to data.

A one-sided significance level represents the probability, by chance alone, of obtaining a difference as large as and in the same direction as that actually observed. A two-sided significance level represents the probability of obtaining a chance difference in either direction as large in absolute magnitude as that actually observed. The two-sided significance level is usually twice the one-sided significance level. Controversy exists over the appropriateness of one-sided or two-sided significance levels. Although this is a somewhat trivial issue, a two-sided significance level of .05 has become widely accepted as a standard level of evidence.

With few patients in the trial, the difference in observed outcomes must be extreme in order to obtain statistical significance. Consequently, the probability of obtaining a statistically significant result may be low even when a substantial true difference in effectiveness exists. The probability of obtaining a statistically significant result when the treatments differ in effectiveness is called the power of the trial. As the sample size and extent of follow-up increases, the power increases. The power depends critically, however, on the size of the true difference in effectiveness of the two treatments. Generally, one sizes the trial so that the power is either .80 or .90 when the true difference in effectiveness is the smallest size that is considered medically important to detect.

A number of statisticians have developed useful methods for planning sample size to compare survival curves or disease-free survival curves in phase III trials. Table 21.1-7 demonstrates results that are valid whenever the hazard ratio, the ratio of forces of mortality for the two treatment groups, is constant over time.14,15 The table shows the total number of deaths that must occur in a given cohort to reflect 90% power for detecting a specified reduction in the hazard for the experimental treatment relative to the control treatment. For exponential distributions, the percentage reduction in hazard of death can be expressed as a ratio of median survivals, which is displayed in the second column of Table 21.1-7. For comparing disease-free survival curves, deaths should be replaced by events, wherein death, disease recurrence, or development of second cancer usually are considered events. The translation of the number of deaths or events required among the number of patients depends on the actual shape of the survival distributions, the rate of accrual, and the duration of follow-up after close of accrual. Generally, however, it is best to specify the time of the final analysis as the time when the specified number of deaths or events are obtained, not in terms of absolute calendar time.
If standard frequency regarding interactions, it provides for the specification of intermediate positions. The Bayesian approach also avoids a preliminary test of interaction having poor encouragement of prior belief about the size of interactions that may exist. Rather than forcing the investigator to adopt one of two extreme positions assumptions that interactions either do or do not exist and provides a flexible approach to the design and analysis of such clinical trials. The Bayesian method assume with confidence that there will be no interactions between the effects of the factors and can determine sample size on the basis of that assumption. All the patients are randomly allocated to either treatment A or placebo, with no use of treatment B. Consequently, factorial designs often are used only when one can noted that the power for detecting an effect of treatment A is substantially impaired by a negative interaction with treatment B, as compared to an experiment wherein the effects of the two factors do interact, then the analysis of main effects may not be meaningful. Usually, the sample size for a two-by-two factorial trial is computed assuming that there is no interaction between the effects of the factors. This sample size will not provide enough patients to test adequately the assumption of no interactions, but not by separate analyses for each level of the other factor). The usefulness of this analysis of average effects is proportional to whether the comparison between the two levels of one factor depends in any important way on the level of the other factor. If the effects of the two factors do interact, then the analysis of main effects may not be meaningful. Usually, the sample size for a two-by-two factorial trial is computed assuming that there is no interaction between the effects of the factors. This sample size will not provide enough patients to test adequately the assumption of no interaction between the factors. Consequently, the factorial design offers the possibility of answering two questions for the cost of one, but there is a risk of ambiguity in the interpretation of results. For situations in which interactions are unlikely or in which it is unlikely that both factors will have substantial effects, the factorial design can provide a substantial improvement in the efficiency of clinical trials.

In a two-by-two factorial design, there are actually four treatment groups. The first factor represents two alternative interventions, such as amputation and resection. The second factor represents two other alternatives superimposed on the first factor, such as adjuvant chemotherapy and no chemotherapy. In another example, the first factor might be chemotherapy regimen A or B, and the second factor might be the duration of treatment, 6 or 12 months. Although there are actually four treatment groups, the average effect of each treatment factor can be evaluated using all of the patients and pooling with regard to the other factor (or by accounting for the influence of the other factor in the analysis by stratification, but not by separate analyses for each level of the other factor). The usefulness of this analysis of average effects is proportional to whether the comparison between the two levels of one factor depends in any important way on the level of the other factor. If the effects of the two factors do interact, then the analysis of main effects may not be meaningful. Usually, the sample size for a two-by-two factorial trial is computed assuming that there is no interaction between the effects of the factors. This sample size will not provide enough patients to test adequately the assumption of no interaction between the factors. Consequently, the factorial design offers the possibility of answering two questions for the cost of one, but there is a risk of ambiguity in the interpretation of results.

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The use of a factorial design for a clinical trial is often controversial. Proponents sometimes indicate that factorial designs are ideal for studying interactions. Others have questioned how factorial trials can provide meaningful information about interactions when the trials are sized only to detect main effects. Britain and Wittes noted that the power for detecting an effect of treatment A is substantially impaired by a negative interaction with treatment B, as compared to an experiment wherein all the patients are randomly allocated to either treatment A or placebo, with no use of treatment B. Consequently, factorial designs often are used only when one can assume with confidence that there will be no interactions between the effects of the factors and can determine sample size on the basis of that assumption.

Simon and Freedman developed a Bayesian method for the design and analysis of factorial clinical trials. Their approach avoids the need to dichotomize one’s assumptions that interactions either do or do not exist and provides a flexible approach to the design and analysis of such clinical trials. The Bayesian method encourages the quantification of prior belief about the size of interactions that may exist. Rather than forcing the investigator to adopt one of two extreme positions regarding interactions, it provides for the specification of intermediate positions. The Bayesian approach also avoids a preliminary test of interaction having poor...
power.

The Bayesian model suggests that in planning a factorial trial where interactions are unlikely but cannot be excluded, the sample size should be increased by at least 30% as compared to a simple two-arm clinical trial for detecting the same size of treatment effect. This is less extreme than doubling the sample size but is a recommendation that differs greatly from current usage. The 30% figure allows for a 5% prior probability of a medically important, qualitative interaction between the treatment effects.

Factorial designs can also be useful in phase II trials when an internal control is needed. For example, consider the investigation of antiangiogenic agents A and B for patients in partial remission after induction chemotherapy. With a factorial design, there would be four treatment groups. One group would receive neither agent, one would receive A, one group would receive B, and one group would receive both A and B. Patients are randomized to the four groups. For analyzing the effect of A, the time to progressive disease for the two arms that received A are compared to the time to progressive distribution for the two arms that did not receive A. Analyzing the effect of B is performed analogously. The single-arm phase II trial is problematic when the end point is disease stabilization or time to progression. It is easy to come up with a definition of disease stabilization, but just defining it does not make it valid for measurement of treatment effect. Data are needed that demonstrate that such stabilization does not occur in the absence of treatment in a comparable group of patients. This is difficult to do reliably because of the usual difficulties of identifying comparable historical controls and because of special difficulties involved with documenting stabilization or measuring time to disease progression in a consistent manner. Stabilization is not established by historical controls. Consequently, the use of disease stabilization or time to progression as an end point in single-arm phase II trials is particularly problematic. A better approach is use of the factorial design, because the factorial design is internally controlled for evaluating the effects of the factors and, hence, the use of time to progression is not problematic.

**THERAPEUTIC EQUIVALENCE TRIALS**

The objective of a therapeutic equivalence trial is generally to demonstrate that a new treatment is equivalent to a standard therapy with regard to a specified clinical end point. This is contrasted to bioequivalence trials in which the objective is to demonstrate equivalence of serum concentrations of the active moiety. In some cases, investigators would like to demonstrate that the new treatment is effective as compared to no treatment but, because use of a no-treatment arm is not feasible, they attempt to demonstrate therapeutic equivalence to a standard treatment.

Therapeutic equivalence trials are problematic because it is impossible to demonstrate equivalence. If the outcomes for the two treatments are similar, one can only conclude that results are consistent with differences within specified limits.

In conventional trials, rejection of the null hypothesis leads to change in the treatment of future patients. The implications of failure to reject the null hypothesis are more difficult to interpret. Failure to reject the null hypothesis often is interpreted as a demonstration of therapeutic equivalence and grounds for adoption of the new regimen but may merely reflect inadequate sample size or ineffectiveness of the standard treatment for the patients in the clinical trial.

Large sample sizes often are needed for meaningful therapeutic equivalence trials. For example, consider a cancer trial evaluating tumor resection as an alternative to patients' resection of the organ containing the tumor in a setting in which amputation is the standard therapy known to be curative in a large number of cases. Tumor resection may have clear advantages with regard to quality of life, but few patients would be interested in these advantages unless they were assured that any reduction in the chance of cure would be very small. Hence, the appropriate trial should focus on distinguishing the null hypothesis in which the difference in efficacy is expressed as D = 0 from that in which the difference in efficacy is expressed as D = d, where d is very small. Consequently, this trial would have to be very large.

In a therapeutic equivalence trial, there is no internal validation of the assumption that the control treatment C is actually effective for the patient population at hand. It is not enough for the experimental treatment E to be therapeutically equivalent to C; we want equivalence coupled with the effectiveness of E and C relative to no treatment or to whatever was standard before the adoption of C.

None of the conventional approaches to the design and analysis of therapeutic equivalence trials is satisfactory. These approaches depend on the specification of a minimal difference (d) in efficacy that one is willing to tolerate but do not address how d should be determined. Simon has recently developed a general Bayesian approach to the utilization of information from previous trials in the design and analysis of therapeutic equivalence trials. The effectiveness of the control treatment C relative to no treatment or to the previous standard before C was adopted is represented by a parameter \( b \). We will denote the previous standard by P. The effectiveness of C relative to P will not be known with certainty and may vary among trials. The information about b is summarized by a prior distribution, which is normal with mean \( \mu_b \) and standard deviation \( s_b \). The parameter g represents the effectiveness of the new experimental treatment E relative to P. Usually, it is assumed that there is no prior information about g.

The result of the therapeutic equivalence trial is summarized by a value \( y \), which estimates the effectiveness of E relative to C.

Two major objectives of active controlled trials can be distinguished. The first is to determine whether the experimental treatment is effective relative to P. This requires explicit use of prior information about outcomes of trials comparing P to the active control. Meaningful interpretation of active control trials is impossible without consideration of such information. Establishing whether or not the experimental treatment is effective relative to P is a first requirement. The second objective is to determine whether any medically important portion of the treatment effect for the active control is lost with the experimental treatment. In some cases, this objective is unrealistic because the size of the treatment effect (relative to P) for the active control is imprecisely determined. Simon has recently developed a general Bayesian approach to the utilization of information from previous trials in the design and analysis of therapeutic equivalence trials. The effectiveness of the control treatment C relative to no treatment or to the previous standard before C was adopted is represented by a parameter \( b \). We will denote the previous standard by P. The effectiveness of C relative to P will not be known with certainty and may vary among trials. The information about b is summarized by a prior distribution, which is normal with mean \( \mu_b \) and standard deviation \( s_b \). The parameter g represents the effectiveness of the new experimental treatment E relative to P. Usually, it is assumed that there is no prior information about g.

The result of the therapeutic equivalence trial is summarized by a value \( y \), which estimates the effectiveness of E relative to C.

where \( z \) is the \( z \) value for comparison of the active control C to P in the previous trial (or metaanalysis of previous trials), with a positive value of \( z \) corresponding to superiority of C. The parameter \( r \) represents the ratio of the required sample size of the therapeutic equivalence trial to the effective sample size of the previous trials demonstrating the superiority of C to P. When the parameter \( r \) is 3 (corresponding to a two-sided significance level of .0027 for the effectiveness of C relative to P), the ratio \( r \) equals 1.25, indicating a 25% larger therapeutic equivalence trial. Hence, the ratio \( r \) equals 10, indicating that the therapeutic equivalence trial needs to be ten times as large as the previous trial that established the effectiveness of C. Consequently, unless the evidence for the effectiveness of C is highly statistically significant, the therapeutic equivalence trial is not feasible or appropriate.

An important implication of the new approach is that reliable therapeutic equivalence trials are not practical unless evidence of the effectiveness of the control treatment is substantial and consistent. Conventional methods for planning therapeutic equivalence trials often miss this point, because they take the maximum likelihood estimate of the effectiveness of the control treatment as if it were a value known with certainty. This ignores the fact that the degree of effectiveness of the control treatment is known only imprecisely unless the effect is overwhelmingly significant. For example, if the effect is of borderline significance, then the confidence interval for the size of the effect almost includes zero. Consequently, many planned therapeutic equivalence trials, even large multicenter trials, cannot demonstrate clinically relevant objectives. Superiority trials, rather than therapeutic equivalence trials with marginally effective control treatments, are strongly preferred whenever possible.

**ANALYSIS OF PHASE III CLINICAL TRIALS**

**INTENTION-TO-TREAT ANALYSIS**

One of the important principles in the analysis of phase III trials is called the intention-to-treat principle. This indicates that all randomized patients should be included in the primary analysis of the trial. For cancer trials, this has often been interpreted to mean all “eligible” randomized patients. Because eligibility requirements sometimes are vague and unverifiable by an external auditor, excluding “ineligible” patients can itself result in bias. However, excluding patients from analysis...
because of treatment deviations, early death, or patient withdrawal can severely distort the results. Often, excluded patients have poorer outcomes than do those who are not excluded. Investigators frequently rationalize that the poor outcome experienced by a patient was due to lack of compliance to treatment, but the direction of causality may be the reverse. For example, in the Coronary Drug Project, the 5-year mortality for poor adherents to the placebo regimen was 28.3%, significantly greater than the 15.1% experienced by good adherents to the placebo regimen. In randomized trials, there may be poorer compliance in one treatment group than the other, or the reasons for poor compliance may differ. Excluding patients, or analyzing them separately (which is equivalent to excluding them), for reasons other than eligibility is generally considered unacceptable. The intention-to-treat analysis with all eligible randomized patients should be the primary analysis. If the conclusions of a study depend on exclusions, then these conclusions are suspect. The treatment plan should be viewed as a policy to be evaluated. The treatment intended cannot be delivered uniformly to all patients, but all eligible patients should generally be evaluable in phase III trials.

INTERIM ANALYSES

If statistical significance tests are performed repeatedly, the probability that the difference in outcomes will be found to be statistically significant (at the .05 level) at some point may be considerably greater than 5%. This probability is called the type I error of the analysis plan. Fleming et al. have shown that the type I error can be as great as 26% if a statistical significance test is performed every 3 months of a 3-year trial that compares two identical treatments. Many trials are published without stating the target sample size, without indicating whether a target sample size was stated in the protocol, and without describing whether the published analysis represented a planned final analysis or was one of multiple analyses performed during the course of the trial. In such cases, one must suspect that the investigators were not aware of good statistical practices and the dangers of informal multiple analyses. Consequently, the statistical significance reported in such trials must be discounted as uninterpretable.

Interim analyses can be very misleading, and the significance levels of interim analyses cannot be taken at face value. Nevertheless, the random trends often seen in interim analyses can destroy accrual to a clinical trial and interfere with a physician’s attempt to state honestly to the patient that there is no reliable evidence indicating that one treatment option or the other is preferable. For these reasons, it has become standard in multicenter clinical trials to have a data-monitoring committee review interim results, rather than having the monitoring done by participating physicians. This approach helps to protect patients by having interim results carefully evaluated by an experienced group of individuals and helps to protect the study from damage that ensues from misinterpretation of interim results. Generally, interim outcome information is available only to the data-monitoring committee. The study leaders are not part of the data-monitoring committee, because they may have a perceived conflict of interest in continuing the trial. The data-monitoring committee determines when results are mature and should be released. These procedures are used only for phase III trials.

A number of useful statistical designs have been developed for monitoring interim results. The simplest is that of Haybittle. Interim differences are discounted unless the difference is statistically significant at the two-sided \( P < .0025 \) level. If the interim differences are not significant at that level, the trial continues until its originally intended size. The final analysis is performed without regard to the interim analyses, and the type I error is almost unaffected by the monitoring.

Others have developed group-sequential methods for interim monitoring based on a prespecified number of planned interim analyses. The critical \( P \) value for determining whether an interim difference should be judged statistically significant depends on the number of analyses that will be performed during the trial. For a five-stage trial—four interim analyses and one final analysis—the critical \( P \) values are shown in Table 21.1-10.

### TABLE 21.1-10. Nominal Two-Sided Significance Levels for Interim Monitoring Methods That Maintain an Overall Type I Error Level of .05

<table>
<thead>
<tr>
<th>Analysis Number</th>
<th>Pre et al.</th>
<th>Other and Haybittle</th>
<th>Fleming and Others</th>
<th>Fleming et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.05</td>
<td>0.0075</td>
<td>0.0068</td>
<td>0.0065</td>
</tr>
<tr>
<td>2</td>
<td>0.05</td>
<td>0.0075</td>
<td>0.0068</td>
<td>0.0065</td>
</tr>
<tr>
<td>3</td>
<td>0.05</td>
<td>0.0075</td>
<td>0.0068</td>
<td>0.0065</td>
</tr>
<tr>
<td>4</td>
<td>0.05</td>
<td>0.0075</td>
<td>0.0068</td>
<td>0.0065</td>
</tr>
<tr>
<td>Total</td>
<td>0.05</td>
<td>0.0100</td>
<td>0.0100</td>
<td>0.0100</td>
</tr>
</tbody>
</table>

Extreme treatment differences at an interim analysis are unusual in cancer clinical trials. It is more common to find that interim results do not support the hypothesis that the experimental treatment is substantially better than the control. The method of stochastic curtailment was developed for evaluating such a circumstance. At any interim analysis, the probability of rejecting the null hypothesis at the end of the trial is computed. This probability is calculated as being conditional on the data already obtained and on the assumption that the alternative hypothesis of superiority of the experimental treatment used initially in planning the sample size for the trial is true. If this conditional power is less than approximately 0.20, then the trial may be terminated with acceptance of the null hypothesis. The 0.20 cutoff can be raised substantially to at least 0.40 if this type of interim analysis is performed only a few times during the course of the trial. With stochastic curtailment, interim analyses need not be equally spaced, and the number of interim analyses need not be specified in advance.

Several investigators have developed other designs for early termination of the clinical trial if results are not promising for the experimental treatment. For example, Table 21.1-11 shows some of the two-stage designs developed by Thall et al. for clinical trials with dichotomous end points. The first two columns show the hypothesized success rates for the control and experimental treatments. The remaining columns show the first-stage sample size per treatment and the maximum sample size per treatment. In all instances, the clinical trial is terminated after the first stage, and the experimental treatment is rejected as superior, if the one-sided significance level for comparing success rates is no less than approximately .38. If the one-sided significance level is less than .38, then a second stage of patient accrual is conducted to give the maximum sample size per group shown. When the treatments are equivalent, the chance of early termination is generally 60% to 65% with this design.

### TABLE 21.1-11. Two-Stage Early Termination Designs

Schaid et al. and Wieand et al. developed designs for early termination when results are not promising in survival studies. Schaid’s design provides for multiple experimental treatment arms, as do the designs of Thall et al. Such designs have been reviewed by Simon. Jennison and Turnbull have presented methods for calculating confidence intervals for treatment differences at interim analyses. Such confidence intervals can be useful in deciding when to terminate the trial.
Stochastic curtailment is based on computing the conditional probability of rejection of the null hypothesis calculated under the alternative hypothesis of the trial. The probability is conditioned on the data available at that point but, because the probability is computed under the originally specified alternative hypothesis that the new regimen \(E\) is superior, stochastic curtailment is conservative. Bayesian biostatisticians have argued that the conditional probability should be computed under a distribution of the treatment difference that itself reflects the data available at that point. That distribution is called the posterior distribution. The Bayesian predictive probability is the probability of rejecting the null hypothesis if the trial is continued to its target number of events, conditional on the data available at that point and computed and averaged with regard to a range of hypotheses about the true difference \(d\) as determined by the posterior distribution of \(d\) given the data at that point. Computing the posterior distribution of \(d\), however, requires specification of a prior distribution for \(d\) before the trial begins. The need to specify a prior distribution in a satisfactory manner has limited the applicability of Bayesian methods in clinical trials.

Phase III trials are supposed to be definitive and objective; if we could believe the subjective opinions of experts, we would not need to conduct phase III clinical trials. Recently, it has been realized that a single prior distribution is not necessary for using Bayesian monitoring. It has been found useful to think in terms of one prior distribution for “enthusiasts” for the experimental regimen \(E\) and a different prior distribution for “skeptics.” The investigators conducting the trial often are enthusiasts, whereas other investigators or practicing physicians may be more skeptical. If a trial is to terminate early with a claim that \(E\) is more effective than \(C\), then the data from the trial should be strong enough to convince skeptics. On the other hand, if the trial is to terminate early with a claim that \(E\) is not more effective than \(C\), then the data from the trial should be strong enough to convince enthusiasts. Although this is a somewhat oversimplified view (some enthusiasts or skeptics will never be convinced), it serves as a useful basis for interim monitoring. For computing the Bayesian predictive probability of rejection of the null hypothesis at the end of the trial if it is continued, it would be useful to use an enthusiast’s prior distribution to ensure that the data are sufficiently compelling.

Stopping trials when the experimental regimen \(E\) is not appearing more effective than \(C\) but is not statistically significantly worse than \(C\) is sometimes controversial. Statisticians tend to want data as definitively as possible. One must also be cautious that with survival or disease-free survival end points, early parts of the survival curve may not reflect latter parts. Another argument for continuing such trials even if it is clear that \(E\) will not be found to be significantly better than \(C\) is that additional data will provide narrower confidence intervals for the true difference \(d\). The alternative point of view is that it is not appropriate to continue to expose patients to a more toxic and debilitating treatment \(E\) if the essential outcome of the trial is well assured. Data-monitoring committees are charged with helping to make these difficult judgments.

### SIGNIFICANCE LEVELS, HYPOTHESIS TESTS, AND CONFIDENCE INTERVALS

Medical decision making is complicated, and clinicians frequently misinterpret statistical significance tests in search of clear-cut answers from ambiguous data. A statistical significance level for comparing outcomes represents the probability of obtaining a difference as large as that actually observed if the treatments were actually equally effective. Differences of this type occur merely by chance. If differences in either direction and differences of this magnitude as large as or larger than the one actually obtained are included, the significance level is called two-sided. If the probability is calculated only for differences in the same direction as that actually obtained, the significance level is called one-sided. Generally, the two-sided significance level is twice the one-sided level.

After significance tests had been used for many years, Neyman and Pearson formalized a mathematical theory of hypothesis testing. In this theory, a study must specify a null hypothesis, an alternative hypothesis, and a decision rule for accepting one hypothesis and rejecting the other based on the data obtained. The theory has appealed to clinicians because it simplifies complex medical decision making by providing yes or no answers; either the difference is statistically significant or it is not. The distinction between one- and two-sided decision rules becomes crucial because a one-sided \(P = .05\) is simply nonsignificant if a type I error of .05 based on a two-sided decision rule is specified.

The concept of prespecification of hypotheses is important for medical experimentation. However, the accept-reject nomenclature of the Neyman-Pearson theory provides an oversimplified and sometimes misleading interpretation of the results. It is misleading to interpret results, but qualification about whether a one-sided \(P = .04\) is significant makes little sense. Significance levels are influenced by sample sizes, and failure to reject the null hypothesis does not mean that the treatments are equivalent. There is no simple index for interpreting results. Some attempt to use the notion of statistical significance in this way, but thorough presentation, skeptical evaluation, and cautious interpretation of results always are required.

Confidence intervals are generally much more informative than are significance levels. A confidence interval for the size of the treatment difference provides a range of effects consistent with the data. The significance level tells nothing about the size of the treatment effect because it depends on the sample size. However, it is the size of the treatment effect, as communicated by a confidence interval, that should be used in weighing the costs and benefits of clinical decision making. Many so-called negative results are actually noninformative, and confidence intervals help to determine when this is the case. Simon has presented a nontechnical discussion of how to calculate confidence intervals for treatment differences with the types of end points commonly used in cancer clinical trials.

### CALCULATION OF SURVIVAL CURVES

Most cancer trials display survival results by showing survival curves or disease-free survival curves. Survival curves display the probability of surviving beyond any specified time, with time shown on the horizontal axis. Time of disease-free survival, however, is the time until recurrence or death that is shown. Other time-to-event distributions can be similarly represented using the same methods. The usual statistical methods are not appropriate for analyzing survival because they ignore the fact that surviving patients have a limited follow-up period after which their survivals are “censored.”

The most satisfactory way of representing such data is to estimate the survival function \(S(t)\). This function represents the probability of surviving more than \(t\) time units. Time \(t\) is measured from diagnosis, start of treatment, or some other meaningful time point. For randomized studies, it is best to measure time from the date of randomization. There are basically two satisfactory methods for estimating \(S(t)\). The first is the life-table or actuarial method. It is frequently attributed to Berkson and Gage and is appropriate when the number of patients is large. The other method is the product limit method of Kaplan and Meier. This method is appropriate for any number of patients, but it involves more effort than the life-table method when the number of patients is large.

The first step in the application of either method is the calculation of survival time for all patients. Survival is the duration from the chosen baseline (e.g., date of randomization) until death or date last known to be alive for patients who are not known to have died. To use the life-table method, intervals for the grouping of survival times are determined. The life table, shown in Table 21.1-12, is then filled out. This sample life table is prepared with yearly intervals in the first column. The number of patients alive at the beginning of the interval is entered in column 2. The number who died in the interval is entered in column 4. Patients dying exactly at a time that represents a boundary between two intervals (e.g., 365 days) are considered to have died in the preceding interval (e.g., 0 to 1 year). Column 3 contains the number of patients who are lost to follow-up during the interval or who are alive with maximum follow-up duration included in the interval. These latter patients are referred to as censored patients; they are alive with maximum follow-up duration included in the interval. These latter patients are referred to as censored patients; they are alive with maximum follow-up duration included in the interval. These latter patients are referred to as censored patients; they are alive with maximum follow-up duration included in the interval.

<table>
<thead>
<tr>
<th>Time (Years)</th>
<th>Number at Risk</th>
<th>Number Lost</th>
<th>Number Dead</th>
<th>Number Alive</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>100</td>
<td>5</td>
<td>1</td>
<td>94</td>
</tr>
<tr>
<td>1-2</td>
<td>95</td>
<td>4</td>
<td>2</td>
<td>89</td>
</tr>
<tr>
<td>2-3</td>
<td>91</td>
<td>3</td>
<td>3</td>
<td>85</td>
</tr>
<tr>
<td>3-4</td>
<td>88</td>
<td>2</td>
<td>4</td>
<td>82</td>
</tr>
</tbody>
</table>

The life-table method assumes that patients lost to follow-up or withdrawn alive during the interval are at risk of death for half of the interval. Hence, column 5, the number alive at the start of the interval minus half the number lost or withdrawn during the interval, represents an approximate number of patients at risk of death during the interval. Column 6 gives the ratio of the number of patients who died during the interval to the number at risk during the interval. Column 7 gives the estimated probability of surviving the interval for patients alive at the start of the interval.

**TABLE 21.1-12. Life-Table Method for Estimating a Survival Distribution**
Column 8 should be studied carefully, because it provides the life-table estimate of the survival distribution and indicates the logic behind the method. The probability of surviving more than 3 years after randomization, for example, equals the entry in the third row of column 8 (0.50). The logic is as follows: To survive 3 full years, the patients must survive through the first year; and given that they have survived the first year, they must survive the second year; and given that they have survived the second year, they must survive the third year. Consequently, the probability of surviving for at least 3 years is estimated by the product \( P \cdot P \cdot P \) of factors in column 7. By using this product, the life-table method takes maximal advantage of the mortality experience of patients with limited follow-up. The entry \( S_x \) in column 8, row \( x \), represents the life-table estimate of the probability of surviving more than \( x \) years from randomization. Computational shortcuts to observe are those for column 8—\( S_x = P \cdot P \cdot P \cdot P \) —and for column 2—\( l_{x+1} = l_x - w_x - d_x \).

The product limit method of Kaplan and Meier is similar in concept to the life-table method. With the Kaplan-Meier approach, however, the intervals are defined by the actual survival times of patients who have died. Suppose, for example, that the survivals are 3, 3, 3+, 5, 6, 8+, 8+, 10, 10, and 12+ months, where a plus sign follows survivals for patients still alive. Then the intervals are 0 to 3, 3 to 5, 5 to 6, and 6 to 10 months, as shown in Table 21.1-13. With the Kaplan-Meier method, deaths occur only at the ends of intervals. The entry in column 5 equals \( l_x - w_x \) rather than \( l_x - 2w_x \) for the life-table method. This is because deaths occur only at the ends of intervals here, and the number of patients at risk of death just before the interval end is \( l_x - w_x \). In the entry \( w_x \) in column 3 for the Kaplan-Meier method, patients who are lost to follow-up or withdrawn alive at the end of an interval are considered not lost or withdrawn until the following interval. These differences between the Kaplan-Meier and life-table methods render the former more appropriate for studies with fewer patients.


<table>
<thead>
<tr>
<th>Component</th>
<th>Probability of at Least One Survival Event (Estimated %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25</td>
</tr>
<tr>
<td>2</td>
<td>50</td>
</tr>
<tr>
<td>3</td>
<td>75</td>
</tr>
<tr>
<td>4</td>
<td>83</td>
</tr>
<tr>
<td>5</td>
<td>92</td>
</tr>
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<td>6</td>
<td>83</td>
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<tr>
<td>7</td>
<td>25</td>
</tr>
<tr>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>10</td>
<td>5</td>
</tr>
</tbody>
</table>

TABLE 21.1-14. Probability of Obtaining at Least One Statistically Significant (\( P < .05 \)) Difference by Chance Alone in Multiple Comparisons of Two Equivalent Treatments

For any time \( t \), the Kaplan-Meier curve is an estimator of the true unknown value of \( S(t) \). The estimator is approximately normally distributed in large samples. If \( m \) patients remain alive at time \( x \), the standard error of the estimate can be conservatively estimated \( \text{SE} \) as

\[
\frac{S_x \sqrt{1 - S(x)}}{m}
\]

The Kaplan-Meier estimate of a survival distribution is based on the assumption that censoring is noninformative, which means that the censoring time is independent of the prognosis of the patient. Most censoring in a randomized clinical trial results from the fact that some patients are alive and still being followed at the time of analysis. This is noninformative censoring. However, if patients are lost to follow-up, if they fail to return to clinic when they are too sick to travel, then the censoring is informative and all the usual methods of survival analysis are invalidated. Consequently, it is essential to obtain follow-up information actively on all patients before analysis. If some patients have not been contacted for many months and their status is unknown, that information should be obtained before any analysis is performed. Examining the distribution of time since the last contact for patients not known to have died is a good way to examine the adequacy of follow-up.

The issue of informative censoring also arises in considering end points other than death. For example, one may be attempting to estimate the distribution of time until tumor recurrence in the central nervous system (CNS) in a pediatric leukemia trial. How should one handle patients whose disease recurs in the marrow without
evidence of CNS recurrence? One may be tempted to censor the time to CNS recurrence of such patients at their time of marrow recurrence, but that implicitly assumes that the censoring is noninformative. Because CNS and marrow recurrence may be biologically linked, the assumption of noninformative censoring may not be valid. Other issues of informative censoring can be similarly problematic. Clearly, one should never censor patients because of lack of compliance with therapy, as this can severely bias results.

More extensive, but fairly nontechnical, discussions of statistical methods for the analysis of clinical trial data are given by Anderson et al. and by Harrington and Anderson.

MULTIPLE COMPARISONS

Table 21.1-14 shows the probability of obtaining one statistically significant (P < .05) difference by chance alone as a function of the number of independent comparisons of two equivalent treatments. With only five comparisons, the chance of at least one false-positive conclusion is 22.6%. When the number of end points, interim analyses, and patient subsets are considered in the analysis of clinical trials, these results are disturbing. The comparisons performed in clinical trials are not entirely independent, but this does not have much effect on ameliorating the problem. Fleming and Ware[25] performed a computer simulation to determine the chance of obtaining a statistically significant treatment difference when two equivalent treatments in six subsets determined by three dichotomous variables are compared. The chance of a statistically significant difference between treatments in at least one subset was 20% at the final analysis and 39% in the final or one of the three interim analyses. Subset analyses, comparison of treatments with regard to multiple end points, and multiple interim analyses are common sources of erroneous conclusions. The primary end point should be defined in the protocol. Subset analyses and analyses with regard to secondary end points should be specified in advance, and statistical significance should be declared only for significance levels much more extreme than the conventional .05. The simplest approach to the problem is to declare statistical significance only if the observed result is < .05/n, where n denotes the number of comparisons to be made. For example if n = 10, then .005 should be the threshold for declaring significance for a secondary analysis. The number of comparisons planned in the protocol is represented by n. Comparisons not preplanned should not be considered significant in any case and represent hypothesis generation to be tested in subsequent trials.

Interaction tests are statistical procedures that test for lack of homogeneity of treatment effect across subsets of patients. A statistically significant interaction should be documented before claiming that treatment effects vary among subsets. Such tests are described by Simon and Gail and Simon.

REPORTING RESULTS OF CLINICAL TRIALS

Effective reporting of results is an integral part of good research. Unfortunately, numerous reviews have indicated that the quality of reporting of clinical trial results is poor. Pocock et al. concluded that “overall, the reporting of clinical trials appears to be biased toward an exaggeration of treatment differences.” Barr and Tannock[26] have given a clear illustration of how this is easily done. Simon and Wittes developed a set of methodological guidelines for reports of clinical trials, and these guidelines have been adopted by major cancer journals. These nine guidelines are summarized below:

1. Authors should discuss briefly the quality control methods used to ensure that the data (including response assessments) are complete and accurate.
2. All patients registered on study should be accounted for.
3. The study should not have an inevaluability rate of greater than 15% for major end points.
4. In randomized trials, the report should include a comparison of survival and other major end points for all eligible patients as randomized, with no exclusions other than those not meeting eligibility criteria.
5. The sample size should be sufficient to establish or conclusively rule out the existence of effects of clinically important magnitude. For “negative” conclusions in clinical trials, the sample size should be sufficiently large to obtain at least 80% power to reject the null hypothesis of no difference between two treatments when the true difference is at least 20%.
6. The report should indicate the initial target sample size. It should specify how many interim analyses were performed and how the decisions to stop accrual and report results were made.
7. Claims of therapeutic efficacy should not be made based on nonrandomized phase II trials, unless the disease is so rare or the prognosis so poor that properly controlled randomized trials are not feasible. In the latter case, nonrandomized trials should use explicit historical controls for which comparability of patients can be thoroughly evaluated. Comparison of survival between responders and nonresponders is not a valid way of establishing therapeutic efficacy.
8. All patients should be adequately described. Applicability of conclusions to the general population of patients should be carefully discussed. Claims of subset-specific treatment differences should be carefully documented statistically as more than the random result of multiple significance testing.
9. The methods of statistical analysis should be described in detail sufficient that a knowledgeable reader could reproduce the analyses if the data were available.

EPIEDEMILOGY OF CLINICAL TRIALS

Several authors have pointed out that many of the positive results reported from small trials are expected to be false-positive results. In 100 trials, suppose that there are 10 in which the experimental treatment is significantly better than the control such that there is an 80% chance of the difference being detected in a small or moderate-sized clinical trial. Of these 10 trials, obtaining a statistically significant difference in 8 cases (0.80 ¥ 10) is expected. Of the remaining 90 trials, it is assumed that the treatments are approximately equivalent to the control. We would expect to obtain a statistically significant difference in 5% (4.5) of these cases. Hence, 10 of the 12.5 (8 + 4.5) trials that yield statistically significant results, the finding is false-positive in 4.5 or 36% of the cases (4.5/12.5). The 36% false-positive result is striking. It depends on the assumption that only 10% of the trials represent important advances, but this assumption does not seem overly pessimistic.

An additional factor to consider is that of publication bias, which denotes the preference of journals to publish positive rather than negative results. A negative result may not be published at all, particularly from a small trial. If it is published, it is likely to appear in a less widely read journal than it would if the result were positive. These observations emphasize that results in the medical literature often cannot be accepted at face value. It is essential to recognize that “positive” results need confirmation, particularly positive results of small studies, before they can be believed and applied to the general population.

METAANALYSIS

A metaanalysis is a quantitative summary of research in a particular area. It is distinguished from the traditional literature review by its emphasis on quantifying results of individual studies and combining results across studies. Key components of this approach are to include only randomized clinical trials, to include all relevant randomized clinical trials that have been initiated, regardless of whether they have been published, to exclude no randomized patients from the analysis, and to assess therapeutic effectiveness based on the average results pooled across trials.

Attention is restricted to randomized trials, because the bias from nonrandomized comparisons may be larger than the small to moderate therapeutic effects likely to be present. Including all relevant randomized trials that have been initiated in a geographic area (e.g., the world, or the Americas and Europe) represents an attempt to avoid publication bias. Avoiding exclusion of any randomized patients also functions to avoid bias. Assessing therapeutic effectiveness based on average pooled results is an attempt to make the evaluation on the totality of evidence rather than on extreme isolated reports. In calculating average treatment effects, a measure of difference in outcome between treatments is calculated separately for each trial. For example, between treatments of the hazard ratio can be computed for each trial. A weighted average of these study-specific differences then is computed, and the statistical significance of this average is evaluated. This approach to metaanalysis requires access to individual patient data for all randomized patients in each trial. It also requires collaboration of the leaders of all the relevant trials and is very labor-intensive. Nevertheless, it represents the gold standard for metaanalysis methodology.

A major issue of concern in metaanalyses is whether the individual trials are sufficiently similar to make calculation of average effects medically meaningful. If the therapeutic interventions or control treatments differ too greatly or if the patient populations are too different, then the results may not be medically meaningful as a basis for decision making. However, decisions for individual patients. Often in cancer therapeutics, the studies will not be identical in their treatment regimens or their patient populations, but they will not be so different as to make the results meaningless. In this case, the metaanalysis may be useful for answering important questions about a class of trials that the individual trials cannot address reliably. For example, trials evaluating adjuvant treatment of primary breast cancer often are designed to detect differences in disease-free survival, and a metaanalysis is often required to evaluate survival. Similarly, subset analysis can usually be meaningfully evaluated
only in the context of a metaanalysis, because individual trials are not sized for this objective.

Metaanalysis is not an alternative to properly designed and sized randomized clinical trials. Because most investigators would prefer to "do their own thing," this would lead to a proliferation of diverse trials and increase the risk of inconsequential trials and the evaluation of sufficient large, randomized clinical trials of very similar treatment regimens have been conducted, metaanalysis can provide supplemental information about a given class of treatments that is not available from the individual trials.

**CHAPTER REFERENCES**

SECTION 21.2
Research Data Management

INTRODUCTION

Historically, discussions of data management have focused on an inherently manual process. Questions pertaining to data collection form layout, transport of information, and the role of computers were paramount. Now the questions relate to information technology’s assumed role in research data management. Data can be collected in real time from study sites worldwide. Data quality can be verified at time of input or collection. The human interface between clinical care data (the hospital-clinic systems) and clinical research data (the subset of clinical data dictated by protocol) can be significantly assisted by the electronic interchange of data between computers. Still, the fundamentals of data management remain fairly constant and can be applied throughout the steps in the clinical trial life cycle. The clinical trial life cycle begins with protocol development and continues through patient recruitment, screening and registration, protocol implementation, and analysis and publication.

PROTOCOL DEVELOPMENT

Data management begins with the protocol document and the events prescribed in that document. The protocol defines study objectives, patient selection and eligibility, and the temporal sequence of events. Data to be collected must be prospectively identified. Common elements in treatment protocols include a précis or summary of the protocol, schema, protocol objectives, study design, definition of patient population, the protocol intervention, drug information, toxicities and dosage modifications, methods of evaluation against study end points, data collection, and statistical considerations (see protocol outline in Table 21.2-1).

Each component has an impact on research data management and defines requirements to be carried out during the study. In fact, data management begins with the process of authoring, reviewing, and approving the protocol document itself. This process often depends on coordination with associate investigators, internal review committees, institutional review boards, and external sponsors. It is often time-consuming and driven by multiple levels of review. Document templates, electronic document routing, electronic signature, and the use of structured text in the protocol-authoring step of the life cycle could mean that protocols can be conducted more quickly with higher-quality information at every level. The National Cancer Institute (NCI) is pursuing development of information systems that may help to evolve this lengthy process into a faster one.

TABLE 21.2-1. Protocol Outline, National Cancer Institute Division of Clinical Sciences, Bethesda, MD

PHASE OF PROTOCOL

The protocol phase determines the type of data collected to evaluate study end points. Phase I is not disease-specific. Major end points are maximum tolerated dose of the treatment. The data collection will be focused on measurement and categorization of toxicities. The study size will be small, composed of groups (usually fewer than six participants) at each dose level until maximum tolerated dose is reached.

Phase II is tumor- and diagnosis-specific. The major end points are response of the tumor to the intervention. Phase II studies do not require a control group. The data collection will be to evaluate biologic effect and tumor response.

Phase III is disease- and diagnosis-specific, and its major end points are efficacy, survival, and symptom control. Phase III studies yield results that can be generalized to the population. This imposes the need for a dramatically larger sample size and, possibly, randomization of study subjects to create a control group. The implications for data management are huge: To achieve protocol accrual in a reasonable time, phase III studies are usually conducted in multiple centers. A coordinating center is responsible for the management and monitoring of study accrual and conduct of the randomization process. Phase IV studies are designed for postmarketing surveillance of approved drugs.

STUDY OBJECTIVES
This section includes scientific background and defines study. The end points will drive study conduct as well as determine the data required.

**STUDY DESIGN**

The study design specifies study population, sample size, enrollment, treatment administration and schema, data collection, and analysis. Each component will require specific data management events or tasks.

The study population is determined by the use of inclusion and exclusion criteria: what patient diagnoses or characteristics are required to participate in the study (inclusion) and which will eliminate someone from participating (exclusion). Data management tasks include the evaluation and recording of these criteria for each prospective patient.

**TREATMENT ADMINISTRATION AND SCHEMA**

Treatment administration and schema outline the study intervention and the temporal sequence in which events must occur. The impact on data management is the resultant schedule sequence for data collection. Schedule delays and intervention modification will be described in sufficient detail to render these directives operational.

**PROCEDURAL ISSUES**

The protocol should identify procedural issues for the study conduct, such as documentation of eligibility, enrollment and registration procedures, study schedule, and detailed data collection and handling methods. The tools (forms, procedures, computer applications) for data collection will be included, as well as documentation about computerized systems used to handle trial data. All processes, data requirements, sequence of events, data collection instruments, database, and electronic system usage in a study should be identified prospectively as intended, to support the stated study objectives.

**PATIENT RECRUITMENT, SCREENING, AND REGISTRATION**

Once the protocol is approved and ready for patient accrual, the life cycle moves to the step of patient recruitment. The goal here is to apply the study population strengths—inclusion or exclusion criteria—in a way that can be supported by recruitment and retention of participants. Matching eligibility criteria with a particular patient requires that criteria be expressed in a standard way. As appropriate within the study design, rendering the entrance criteria as nonspecific as possible will facilitate study accrual. An additional challenge is the display of protocol information based on very specific patient characteristics. Without this capability, information may not narrow study choices sufficiently for patients and their physicians to make informed preliminary decisions. For example, one test using the NCI’s Physician Data Query protocol search at [http://cancernet.nci.nih.gov/trialsrch.shtml](http://cancernet.nci.nih.gov/trialsrch.shtml) to enter a search for breast cancer trials returned 140 trials, but when the search was limited to only phase III trials for stage II breast cancer, the return dropped significantly. To the extent that the patient population specified in the protocol can be expressed via minimal criteria, the study-patient matching can be facilitated.

Prospective registration (before study intervention) ensures that the patient selection process does not bias the results. Given the methodologic issues and the administrative challenges associated with tracking study accrual, an independent registration office or coordinating center is recommended. A common model is for a coordinating center to record patient registration to a study. After registration, notification to the pharmacy allows study agents to be released to the patient. Additionally, randomization assignments can be made by the coordinating center at time of registration, independently of the study team.

**PROTOCOL IMPLEMENTATION**

The protocol life cycle approach allows the researcher to reap the benefit of advance planning at the point of protocol implementation (Table 21.2-2). Study design and questions drive the collection of research data and the creation of study-specific data management tools, while U.S. Food and Drug Administration (FDA) recommendations and international guidelines define good clinical practices (GCPs) that must be operational in clinical research.

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Clinical research data constitute a subset of the patient’s medical information, so the requirement in the design of data management tools and processes is to be selective. The desire to capture interesting but unused data will dilute the ability to answer the study’s scientific questions and will overwhelm study personnel with unnecessary workloads.

A data management approach that supports the protocol life cycle will reuse elements identified in the concept and protocol documents, maintaining focus on the study design. It also supports minimal redundancy of data entry, using data harmonization to add standardized meaning to terminology. Researchers understand the strength of this approach in their long-term ability to share information with other investigators and to apply the same analytic procedures across protocols, and in their ability to enroll patients and conduct clinical trials across organizational and geographic constraints.

The heart of data management is the effort of personnel using a set of tools and work processes. Processes must support the sophistication of the tools (electronic or paper-based) used and facilitate the collection and entry of clinical research data.

**DATA COLLECTION**

Case report forms (CRF’s) represent the industry’s standard approach that has been adopted by most research institutions for the collection of clinical research data. The CRF is a layout, or template, of the data elements that are to be captured by personnel working with clinical research data. Items may be categorized and grouped in a logical work flow and order. Items collected or abstracted from source documents should be contiguous on the forms; encouraging the capture of complete data sets and lessening the risk of missing elements. Consistency across protocols will be reflected in a similar display of generic items on forms, use of the same coding conventions across studies, and standardized definition of terms across protocols and across forms for a single study. Figure 21.2-1 is an example of a CRF used for collecting a patient’s prior therapy information. Notice that acceptable choices for certain categories (prior therapy type and response) are identified at the top of the form, in addition to other specific instructions supplied at the bottom of the form.
Monitoring and audit activities fit the traditional profile of quality assurance activities. Whether it is the submission of current data or the retrospective audit of source data, the approach is not approached as an additional requirement. This view of quality control within an organizational philosophy, a union of the United States, the European Union, and Japan. This group has formulated global standards for the conduct of clinical trials. The International Conference on Harmonisation defines a GCP as “A standard for the design, performance, monitoring, auditing, recording, and reporting of clinical trials to provide assurance that the data and reported results are credible and accurate.”

GCPs are codes, regulations, and guidelines that supply structure and requirements to the clinical research process. Scientific questions and data that must be collected add the direction and level of detail required for personnel to conduct clinical research. International standards have emerged from the International Conference on Harmonisation, a union of the United States, the European Union, and Japan. This group has formulated global standards for the conduct of clinical research that have been adopted by many industry and academic groups worldwide.

In recent years, many institutions have moved to the use of electronic CRFs to enter, view, and monitor clinical research data. The automated approach offers such advantages as the ability to aggregate data for reports, the ability to search for patient-specific data as needed, and the ability to share information rapidly. The use of paper CRFs as retrievable, auditable signs of data abstraction is a powerful reminder of the benefits of a paper approach.

Electronic CRFs that are customized for a protocol yet retain some measure of generic content to support cross-study aggregate views of the data are appealing to investigators and clinical trial teams. A presentation of data collection needs that is driven by the study, and not a cloned set of data points used for all trials, supports principles of data integrity. The electronic replacement of paper CRFs and data discrepancy forms with computers requires the same attention to coding conventions, work flow, and consistency as do approaches with paper tools. Additionally, the electronic approach permits front-end validation processes, such as range checking, simple edit checks, and cross-validation between variables measured on repeated occasions.

The decision to move from paper to electronic CRFs and automated data management processes requires an organizational commitment to reengineer work processes. Hammer and Champy noted that most organizations view technology through the “lens of existing processes.” They should not ask how they can use technology to do what they are doing now but rather how they can improve what they are doing now and achieve entirely new goals. Electronic CRFs may enable organizations to streamline their work flow, introduce new data quality practices, or prepare auditors before monitoring visits. In 1996, 95% of all clinical trials still used paper. Moving to the electronic arena requires personnel to overcome fears about change, to reengineer processes, and to create radically new goals. It is possible to redefine data management to make the paper CRF obsolete and create electronic access for personnel to enter clinical data directly from the source document into the computer. Auditors could review an activity log and electronic CRFs as well as view aggregate data before a site visit.

In 1996, 95% of all clinical trials still used paper. This technologic advancement must be accompanied by process reengineering, so that personnel are comfortable with these changes and the benefits they offer. They may enable geographically distant sites, patients, and researchers to collaborate on clinical trial accrual, using Internet-based technologies and multi-site-consistent work practices.

A collection of data values from the conduct of clinical research is a logically coherent, meaningful collection of related data. It is designed and populated for a specific purpose. Data are entered and stored so that they may be retrieved and used in meaningful ways. Clinical research data are composed of discrete pieces of raw material gathered through investigation. If the data are ambiguous, incomplete, or erroneous, processing cannot turn the data into valid information. There are strategies an institution can adopt to validate data at the point of abstraction and entry.

Data must be accurate, precise, current, and complete. CRFs (electronic or paper) must be constructed to encourage correct entries, supplying user instructions and cues. Instructions should be unambiguous and written in terminology useful for personnel completing the forms. Form identifiers and landmarks must be consistent and clearly defined required items. When choice lists are used to code or list items, they must be readily available for review. The sequence of items on a form must be logical and mimic source documents or work processes used to capture these items. Elements captured together must be contiguous on the CRFs, to enter a complete set of data points.

Duplication must be avoided. To increase efficiency and eliminate the need to cross-check items across forms, data should be collected without redundancy. Data should be entered once and reused, not reentered. To indicate the presence of mandatory items, elements can be set in bold-face type or displayed in some consistent manner.

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PROTOCOL QUESTIONS AND END POINTS

Data must be targeted to answer protocol questions. Forms must focus on the data needed to answer questions central to the study conduct. Study end points must be defined with specificity and then decomposed to yield the components needing collection on a defined schedule. Element definitions and coding conventions must be recorded consistently across the protocol, to ensure that outcomes can be replicated and results generalized and to attest to the proper conduct of the protocol. Data harmonization and standardization should be reflected in data validation approaches that focus on the interpretation of results across single or multiple protocols. The use of a data dictionary or inventory of well-defined data elements could help to impose standards critical for study outcomes.

Whether in paper or electronic form, data collection instruments combined with quality control offer an integrated approach to the capture and entry of clinical research data.

QUALITY CONTROL

GCPs are codes, regulations, and guidelines that supply structure and requirements to the clinical research process. Scientific questions and data that must be collected add the direction and level of detail required for personnel to conduct clinical research. International standards have emerged from the International Conference on Harmonisation, a union of the United States, the European Union, and Japan. This group has formulated global standards for the conduct of clinical research, which have been adopted by many industry and academic groups worldwide.

The International Conference on Harmonisation defines a GCP as “A standard for the design, performance, monitoring, auditing, recording, and reporting of clinical trials to provide assurance that the data and reported results are credible and accurate.” Study performance, monitoring, and auditing are components of quality control activities pivotal to the conduct of clinical research. Long impugned as undesirable or even noncontributing measures of research integrity, quality control topics have found new disciples in an environment sensitized to the disasters that can occur when they are missing.

Quality control activities merit a plan for each level of personnel to handle clinical research data according to guidelines. Clinical data systems and processes have the potential to improve the quality and costs of research by influencing medical decisions at the point they are being made. Quality control procedures must be integrated into daily work assignments, not approached as an additional requirement. This approach views quality control within an organizational philosophy, a continuum of events resulting in process improvement and the professional development of personnel.

MONITORING AND AUDITS

Monitoring and audit activities fit the traditional profile of quality assurance activities. Whether it is the submission of current data or the retrospective audit of source documents and forms, these activities reflect an ongoing process and the expectation of never reaching perfect compliance. Monitoring activities reflect the scientific and administrative rigor an organization imposes on itself to measure the quality of its research programs.
Monitoring is a primary means of quality control for clinical research studies. It is an activity performed by the study monitor of a clinical research organization with the formal responsibility of monitoring the conduct of research trials. Monitoring visits can focus on a variety of protocol-centered elements. Data can be inspected for their completeness and comparison to expected values. Values that fall outside the range of acceptance as well as missing values will generate data clarification forms for the submitting organization. The creation of clarifications or data discrepancy reports and the resolution of clarifications with resultant resubmission of corrected and validated data back to the monitoring agency creates a continual loop for process improvement at the organizational level. Monitoring activities can focus on protocol administrative and regulatory aspects, the availability and completeness of standard operating procedures, institutional and regulatory approvals and reviews, and adverse-event reporting or can even compare electronic data entry screens to reports submitted by the institution.

An audit is one means of quality assurance, to assess the quality of the research process, and must be conducted by personnel independent of a clinical trial. While the terms audit and monitoring often are used interchangeably, most literature conveys the relationship to be many audits or auditing activities within the realm of a monitoring plan. Analysis and publication

DATA VALIDATION

Validation can be easily applied in a computer-based system. These include detection of missing data, data artifacts (outside the usual range), data that contradict answer computer-driven queries, a preferred process would be to record queries centrally and ensure that they be addressed later (i.e., batch edit). Several types of data corrections or other actions can be simple range checking or algorithms that alert users when certain conditions are present. One example of this is the application of the NCI Cancer Therapy Evaluation Program's adverse event reporting requirement, which uses Common Toxicity Criteria (CTC) and the Medical Dictionary for Regulatory Activities (MedDRA). Classification of diagnoses, procedures, morphology, and medications are areas in which fairly mature internationally or commercially maintained vocabularies exist.

DATA CLASSIFICATION

As information is collected from multiple studies, sites, investigators, and the like, the issues of data standards and data classification become more important. If data are to be collected or aggregated across multiple patients at different centers or multiple studies over time, concepts and terms must be expressed with as little ambiguity as possible. While there is still no consensus on national or international standards for medical vocabularies, there are some dominant candidates to consider, depending on the medical concept being described. One example is the NCI Cancer Therapy Evaluation Program's adverse event reporting requirement, which uses Common Toxicity Criteria (CTC) and the Medical Dictionary for Regulatory Activities (MedDRA). Classification of diagnoses, procedures, morphology, and medications are areas in which fairly mature internationally or commercially maintained vocabularies exist.

Realizing that there is much change occurring in classification of medical terminology, there is no guarantee that a standard used today will be the universally accepted standard tomorrow. However, implementation of a current classification standard is highly recommended over using a home-grown standard or no standard at all. Using an existing standard brings a high likelihood that it will be accounted for should a master thesaurus, such as the Unified Medical Language System, become the standard. Whichever particular scheme is used for data classification on one or a group of studies, adherence to the chosen classifications, enforced by a data system dictionary, will ensure consistent use.

U.S. FOOD AND DRUG ADMINISTRATION RECOMMENDATIONS

The FDA has adopted guidelines for clinical trial computer systems that report data to that agency. Data management systems should provide validation logic to be applied to data at time of entry or in batch edit, a process that records data that fail built-in validation rules. Validation can be simple range checking or algorithms that alert users when certain conditions are present. One example of this is the application of the NCI Common Toxicity Criteria; the software prompts the user to file an adverse event report based on a laboratory value falling sufficiently out of range. Data corrections or other actions taken at time of entry are enforced in real time, but this may or may not be desirable. If the person entering data does not have the expertise or documentation to answer computer-driven queries, a preferred process would be to record queries centrally and ensure that they be addressed later (i.e., batch edit). Several types of validation can be easily applied in a computer-based system. These include detection of missing data, data artifacts (outside the usual range), data that contradict other data and data trends (conflicting data from one encounter to the next)
Validation checks for the presence of data in these fields should be displayed to personnel using clear instructions. When using electronic CRFs, data that fail validation attempts should generate a message in natural language that will identify delinquent items.

Simple edit checks can verify that text fields are not filled with numbers or dates, that future dates are detected, and that values fall within specified acceptable ranges. Because it is difficult to apply edit check logic to free text, responses translated into coding lists can help in the application of edit check rules.

Cross-checks can be used in the context of relationships between data points. The value in one field may constrain the entry of a value in another field, so that the content of these fields can be compared. For example, if the response to “Prior Chemotherapy?” is yes, the CRF may require that details of a chemotherapy treatment regimen be entered on the CRF. Other cross-validation would occur between variables measured on repeated occasions (e.g., lesion measurements on repeated cycle visits) and other context-specific checks.

Double data entry is another form of validation used to minimize data entry. However, double entry procedures may not be sufficient or even necessary for the production of high-quality clinical research data. Day et al. 12 used exploratory data analysis techniques on simulated clinical data measurements and found that while the double entry approach does detect some errors, many others occur during the transcription process that are not detectable by double entry procedures. The use of systems with computerized CRFs to enter data directly from source documents also lessens the benefit of a double entry approach. While the double data entry practice may offer some benefit, other methods to validate data integrity and validity should be mandatory.

DIRECT DATA CAPTURE

Electronic transfer of data from hospital laboratory or other systems into the research data management system is known as direct data capture. When direct data capture is used, it can result in higher-quality data through reduction of the errors produced when data are rekeyed. Where this model is used, the data management system must be able to indicate whether and where data have been changed after import. 13

SECURITY

Data management systems should control security at the physical and logical levels. Physical security applies to controlling and safeguarding the physical computer resources and data storage, enforced via off-site storage of backup data and firewalls that prevent unauthorized access to data and computing resources. Logical access refers to those persons who have access to data through the assignment of system-based roles. 14 Spriet and Dupen-Spriet described required security as (1) operational (proper maintenance, virus protection, and proper use); (2) physical (protection against physical harm by fire, water damage, and the like); and (3) safeguarding backup data; and (3) safeguarding backup data; and (3) safeguarding backup data. 15

SUMMARY

Each step of the clinical trial life cycle creates distinct data management tasks and processes specified during protocol development. Supporting these tasks can be accomplished with manual (paper-based) processes, completely automated with computer systems, or through some combination of both. The model chosen at the organizational level will depend on principles of good clinical practice and quality control need. The acceptance and use of Internet systems is increasing the acceptance of computer systems as data management facilitators. The product of clinical research is data, and proper data management can help to turn the data into information.

CHAPTER REFERENCES

CHAPTER 22
Cancer Prevention: Preventing Tobacco-Related Cancers

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INTRODUCTION

Tobacco addiction ranks as the greatest public health catastrophe of our time. The practice of inhaling cigarette smoke, which gained widespread acceptance only during the twentieth century, has generated devastating cancer outcomes for our society. Specifically, lung cancer, previously rare, has risen to become the leading cancer killer in American men and women. Worldwide estimates suggest that the annual deaths attributable to smoking, currently 2.5 million, will rise to 12 million by the year 2050. Future medical historians undoubtedly will recall the 1900s as the Tobacco and Cancer Century.

A healthier twenty-first century requires a societal commitment to reducing and eradicating tobacco addiction. This chapter reviews the impact of tobacco on cancer and individual and societal strategies for tobacco control.

TOBACCO AND NICOTINE ADDICTION

Tobacco and tobacco smoke contain at least 4000 chemicals, of which 55 are known carcinogens identified by the International Agency for Research on Cancer. The most notable carcinogen classes include polycyclic aromatic hydrocarbons (PAHs), N-nitrosamines, and miscellaneous organic compounds. Of the PAHs, benzo(a)pyrene (BaP) is the most extensively studied lung carcinogen. Of the N-nitrosamines, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) is best known. Metabolic activation of these agents can incite DNA adduct formation, gene mutations, and a sequence of events that can lead to cancer. The balance between detoxification and metabolic activation determines, in part, the susceptibility of smokers to cancer.

Though nicotine in tobacco is itself not carcinogenic, addiction to nicotine exposes the user to carcinogens, which increases the likelihood of cancer. Nicotine addiction fulfills the physiologic, behavioral, and social characteristics of a dependence syndrome. The American Psychiatric Association’s Diagnostic and Statistical Manual of Mental Disorders (DSM, third edition) requires a minimum of three of seven diagnostic symptoms for drug dependency: (1) tolerance, (2) withdrawal, (3) greater use than intended, (4) persistent desire to quit, (5) great amounts of time spent smoking, (6) activities given up or reduced due to smoking, and (7) continued smoking despite knowledge of having persistent physical or psychological problems with the substance.

HEALTH EFFECTS

As early as 1928, Lombard and Doering reported higher smoking rates among patients with cancer than among controls. Later, the pioneering epidemiologic work of Doll and Hill, Wynder and Graham, and Hammond and Horn led to further investigations, which culminated in the 1964 U.S. Surgeon General’s report on smoking and health. This report concluded that cigarette smoking was the major cause of lung cancer in men and was causally related to laryngeal cancer and oral cancer in men.

In total, more than 60,000 studies and two dozen additional reports of the Surgeon General have confirmed the devastating impact of tobacco use on human health. Tobacco use, causing approximately 30% of all deaths and more than 400,000 deaths annually, is the leading cause of preventable death in this country.
Smoking causes more than 85% to 90% of lung cancers, with a clear dose-response relationship between risk and daily cigarette consumption. People who smoke more than a pack of cigarettes per day have a risk that is as much as 20 times that of nonsmokers. In smokers exposed to other carcinogens in the workplace (e.g., pipefitters exposed to asbestos; uranium workers exposed to radon), the risk for lung cancer is raised in a synergistic fashion.

Lung cancer is the leading cause of cancer mortality in both men and women. U.S. estimates for 2000 include approximately 157,000 lung cancer deaths. Lung cancer incidence rates vary widely by race and ethnicity, from a high of 73.9 per 100,000 in African Americans to a low of 27.6 among Hispanics. Gender differences exist as well. Male lung cancer incidence rates peaked in 1984 (86.5 per 100,000) and have decreased since then. Similarly, male lung cancer mortality rates peaked in 1990 at 75.2 per 100,000. In contrast, female lung cancer incidence and mortality continue to rise. Of note, in the late 1980s, lung cancer surpassed breast cancer as the leading cause of cancer death among U.S. women.

The histologic profile of lung cancer has shifted, with declining rates of squamous cell carcinoma but increasing rates of adenocarcinoma.

In addition, smoking is accepted as the major cause of cancers of the larynx, pharynx, oral cavity, and esophagus, and is a contributory factor in cancers of the pancreas, bladder, kidney, stomach, colon, and uterine cervix and in acute leukemia. A synergistic, multiplicative effect appears to exist between smoking and drinking. For example, the risk for developing cancer of the larynx is as much as 76% higher in people who use tobacco and alcohol as compared with people using either substance alone.

The use of pipes, cigars, and spit tobacco in its various forms (plug tobacco, loose-leaf tobacco, twist tobacco, and moist snuff) also causes cancers of the oral cavity. Tobacco use is responsible for more than 90% of tumors of the oral cavity among men and 60% among women. Spit tobacco is a significant cause of leukoplakia, an abnormal thickening and keratinization of the oral mucosa that is recognized as a precursor of malignancy. Even after cessation of tobacco exposure, the "field cancerization effect" elevates the risk of cancer of the entire epithelium of the upper aerodigestive tract for years.

Other adverse health outcomes from tobacco addiction include increased risks of cardiovascular disease. The Nurses' Health Study found a 2.5-fold increased risk of fatal coronary heart disease and nonfatal myocardial infarction and up to three times the risk of cerebrovascular disease in smokers as compared to nonsmokers. Smoking also contributes to peripheral vascular disease, aortic aneurysm, impotence, Buerger's disease (thromboangiitis obliterans), and skin aging.

Americans spend an estimated $50 billion annually on direct medical care for smoking-related illnesses. Lost productivity and forfeited earnings due to smoking-related disability account for another $47 billion per year.

### SMOKING RATES AND TRENDS

With the vigorous promotion of the blended cigarette in the twentieth century, the annual adult per capita consumption of cigarettes has skyrocketed from 54 cigarettes in 1900 to 4345 cigarettes in 1963, the peak of American consumption per individual smoker. Although consumption has declined, approximately 500 billion cigarettes were sold in the United States in 1995. Historically, smoking rates in men have far exceeded those in women, but the gender difference has narrowed as male rates declined and female rates rose. Rates for most races and ethnic groups have decreased since 1978, although the rate of decrease recently has ebbed (Fig. 22-2). The tobacco industry's attempts to recruit women range from the American Tobacco Company's advertising campaign, "To keep a slender figure, reach for a Lucky Strike instead of a sweet" (1920s) to Philip Morris's Virginia Slims slogan, "You've come a long way, baby."

**FIGURE 22-2.** Current cigarette smoking among adults, National Health Interview Surveys, United States 1978–1995 aggregate data.

### ADULTS

Approximately 1 billion smokers are found worldwide. According to the 1995 National Health Interview Study, in the United States, nearly 47 million adults (24.7%) currently smoke, either daily (20.1%) or on some days (4.6%). Currently, men (27.0%) are more likely to smoke than are women (22.6%). Among racial and ethnic groups, American Indians and Alaska Natives had the highest prevalence (36.2%), whereas Asian Americans and Pacific Islanders had the lowest (16.6%). Educational level is the most important predictor of smoking prevalence. High school dropouts had the highest prevalence (41.9% and 33.7% for men and women, respectively), whereas college graduates had the lowest (14.3% and 13.7%, respectively).

Since the landmark 1964 Surgeon General's report, overall U.S. smoking prevalence has declined by half, from 50.2% (1965) to 25% (1998), although adult smoking rates reached a plateau in the 1990s. Declines in smoking prevalence were greater among African American, Hispanic, and white men who were high school graduates than among those with less education. In fact, in the United States during 1965 through 1994, smoking prevalence in adults younger than 65 years declined in every demographic category except those with less than 12 years of education.

### CHILDREN, ADOLESCENTS, AND COLLEGE STUDENTS

Tobacco use qualifies as a pediatric disease. Its current prevalence among adolescents (cigarettes, cigars, or smokeless tobacco) is an astonishing 42.7%. The 1997 Youth Risk Behavior Survey showed smoking rates for girls and boys as 69.3% and 70.9% for lifetime cigarette use and 34.7% and 37.7% for current cigarette use. Nearly 90% of adult smokers begin smoking by the age of 18 years. Even by grade 9, 67% of children have experimented with cigarettes. It is estimated that of nearly 3000 young people who start smoking each day, 1 in 3 will die prematurely. At least 3 million American teenagers smoke regularly.

Numerous surveys document increased smoking among children in recent years. The national 1997 Youth Risk Behavior Survey indicated that cigarette smoking prevalence among U.S. high school students increased from 27.5% in 1991 to 36.4% in 1997. This rise occurred in all racial and ethnic groups [e.g., whites (30.9% to 39.7%), African Americans (12.6% to 22.7%), and Hispanics (25.3% to 34.0%)]. In 1997, the prevalence of current cigarette use was 22.0%. Monitoring the Future Project data (an analysis of high school seniors from 1976 to 1995) show that the smoking rate among high school seniors (defined as smoking in the past 30 days) rose from 28.3% in 1991 to 34% in 1996, and rates for grades 8 and 10 show similar or larger increases.

Notably, the age of smoking initiation has declined over the past four decades, for both whites (by 2.4 years) and African Americans (by 1 to 3 years). The decline is particularly striking for girls (5.4 years and 4.6 years for whites and African Americans, respectively). Also, half of the nation's 6 million smokeless tobacco users were younger than 21 years, and several national surveys show an increase in prevalence, especially among boys.

Predictors of future tobacco use include a number of behavioral risk factors. These factors include the child's own certainty about smoking or not...
smoking in the future, low self-image, poor academic career, receptivity to tobacco advertising, peer pressure, and the use of promotional items. Individual personality traits such as risk taking and deviant behaviors and perceptions of maturity, attractiveness, and independence also play a role in a child's susceptibility to tobacco use. In white youngsters, peer pressure (estimated by the number of friends who smoke) and a low grade point average were important risk factors. Among African Americans, a greater risk-taking attitude was an important predictor of tobacco use. Acculturation or integration into American society is associated with increased smoking by Latin and Asian women.

Tobacco use in children is linked to alcohol and illegal drug use. Among boys especially, aggressive or disruptive classroom behavior as early as first grade has been found to predict later tobacco and other heavy drug use, as well as antisocial behavior and criminality. The National Household Study on Drug Abuse from 1985 showed children who smoke are 3 times more likely to drink alcohol, 8 times more likely to smoke marijuana, and 22 times more likely to use cocaine. Children's tobacco and alcohol use also were associated with less effective parenting behaviors in the children's families and with parental use of tobacco and alcohol.

Newer data point to increasing smoking rates among college students. In serial surveys of nearly 15,000 randomly selected college students, Wechsler et al. found that the prevalence of current cigarette smoking rose by 27.8% (from 22.3% to 26.5% during the period 1993 through 1997). Defying earlier trends, 11% of college smokers had their first cigarette and 28% began to smoke regularly at or after age 19 years. Half of current college smokers tried to quit in the previous year; 18% had made five or more attempts to quit.

CIGARETTE PRODUCT MODIFICATION

In the 1990s, confronted with declining cigarette sales after studies linked smoking to lung cancer, tobacco companies began producing filter-tip brands designed to remove certain smoke components that manufacturers had not heretofore acknowledged to be harmful. Methods used to decrease the tar and nicotine content in cigarettes were filter tips, porous cigarette paper, reconstituted tobacco, and filter-tip ventilation. Today, almost all cigarettes on the market have filters, most with perforations to dilute tar, nicotine, and carbon monoxide, thereby decreasing their delivery to a smoker's lungs. As a result, in 1995, 72.7% of cigarettes delivered no more than 15 mg of tar, as compared to only 3.6% of cigarettes in 1970. Cigarettes contain 6 to 11 mg of nicotine, of which a smoker typically absorbs 1 to 3 mg, irrespective of nicotine yield rates. To satisfy the level of nicotine needed, smokers modified their smoking behavior by inhaling more deeply and blocking filter vents with their fingers or lips to increase nicotine yield. These behaviors now are suspected to be linked to rising rates of adenocarcinoma of the lung, which currently is the most common type of lung cancer in the United States. Nevertheless, the tobacco industry has continued to suggest health benefits to consumers through the creation and promotion of "light," "ultralight," "mild," "medium," "slim," and "superslim" cigarettes.

SPIT TOBACCO

Spit tobacco (smokeless tobacco), available as snuff or chewing tobacco, has gained great popularity over the last few decades. Snuff dipping, the practice of sucking on a pinch of powdered, flavored tobacco in the cavity between gum and cheek, has increased. Consumption of snuff products nearly tripled between 1972 and 1991. The 1997 Youth Risk Behavior Survey documented a 9.3% prevalence of current spit tobacco use among high school students, with 21% of boys ages 11 to 19 defined as experimenters. The consumption of chewing tobacco, which involves a "chaw" held in the inner cheek area, has also increased.

Use of both snuff and chewing tobacco requires continual expectoration—hence the term spit tobacco. Manufacturers prefer the term smokeless tobacco, to imply a safe alternative to smoking. However, the nicotine in snuff is 2 times the dose in cigarettes, whereas the nicotine in chewing tobacco is 15 times that found in cigarettes. Users tend to be white male adolescents aged 16 to 24 years, persons of low socioeconomic status, current cigarette smokers, residents of the southern United States, baseball players, and American Indians.

Spit tobacco can accelerate a litany of destructive oral changes, from local nonmalignant effects (gingival recession, loss of periodontal attachments, periodontal bone and soft tissue destruction, halitosis, tooth staining, tooth abrasion) to leukoplakia and frank oral cancer. Leukoplakia typically occurs on the cheek mucosa, alveolar ridge, and gingiva, where the snuff is placed. In contrast, tobacco chewers tend to have bilateral lesions of leukoplakia, which is associated with a 3% to 6% progression to squamous cell carcinoma.

CIGARS

Cigar smoke, which contains the same carcinogenic and toxic compounds as cigarettes, also increases risk of cancer, coronary heart disease, and pulmonary pathologic processes. Cigar smoking is potentially addicting and is associated with cancers of the oral cavity, larynx, esophagus, and lung. Reversing a 20-year decline, cigar sales increased by 50% from 1993 to 1997, prompted by industry marketing and the belief that cigars are less dangerous than cigarettes. Young to middle-aged men of high socioeconomic status, teenagers, and women are the groups responsible for the increased consumption of cigars. The overall prevalence of current cigar use among high school students was 22% in 1997. Teenagers most at risk of smoking cigars were male and those students who smoke cigarettes.

ENVIRONMENTAL TOBACCO SMOKE

The 1986 U.S. Surgeon General's report defined environmental tobacco smoke (ETS), also called secondhand smoke, as the combination of sidestream smoke (released from a burning cigarette between puffs) and the fraction of mainstream smoke exhaled by the smoker. The more hazardous sidestream smoke has double the amount of nicotine than mainstream smoke and a higher concentration of carcinogens. Most people spend 90% of their time in the two microenvironments of home and work, where ETS exposure usually occurs. Those at greatest risk for harm from ETS are those who live with smokers in homes where smoking is allowed. Levels of serum cotinine, a nicotine metabolite, are increased in nonsmokers who live with smokers and are correlated to the number of cigarettes smoked.

An increasing number of studies have documented the health risks of the nonsmoker exposed to ETS. Case-control studies first noted that nonsmoking wives of smoking husbands had increased risk of lung cancer. In 1992, the U.S. Environmental Protection Agency (EPA), in the most thoroughly documented analysis ever undertaken of the effects of exposure to ETS, concluded that secondhand smoke can cause lung cancer in nonsmoking adults and can impair the respiratory systems of children. The EPA classified ETS as a group A carcinogen, a designation reserved for agents such as asbestos. Of 30 studies analyzed in the EPA report, 24 found an increased risk of lung cancer for nonsmoking wives of husbands who smoked, and each of the 17 studies that examined risk based on exposure level reported increased lung cancer among those most exposed.

The EPA report and other ETS studies now attribute approximately 3000 deaths to lung cancer, up to 62,000 deaths to ischemic heart disease, and up to 2700 deaths to sudden infant death syndrome. The 1997 California Environmental Protection Agency Report also notes that ETS is responsible for new cases of low-birth-weight infants (up to 18,600 cases per year), new cases of childhood asthma (up to 26,000 new cases per year), exacerbation of childhood asthma (up to 1 million new cases per year), and bronchitis or pneumonia in children aged 18 months and younger (up to 300,000 cases per year). Workers at great risk for harm from ETS include flight attendants, casino workers, and restaurant and bar workers, among others.

TOBACCO INDUSTRY ADVERTISING STRATEGIES

Tobacco companies have dedicated considerable resources to corner new markets, because an estimated 3500 Americans quit smoking and an additional 1200 customers die of smoking-related illness each day. During the last two decades, the tobacco industry has nearly quadrupled its marketing expenditures. The 1994 U.S. Surgeon General's report, "Preventing Tobacco Use Among Young People," summarized the research on the impact of tobacco advertising and promotional activities on youth.
The Agency for Health Care Policy and Research (AHCPR) smoking cessation guidelines incorporate the National Cancer Institute's (NCI's) four pamphlets: ask, advise, assist, and arrange. Physicians and health professionals should view smoking cessation as a cornerstone of their practice. The 1989 and 1993 Teenage Attitudes and Practice Surveys did show that nearly 75% of 12- to 18-year-olds had seriously thought about quitting smoking; more recent surveys found that 73% of young smokers had tried to quit smoking. Of all smokers that attempt to quit each year, fewer than 10% are successful. Cigarette smokers who have successfully quit made, on average, seven serious attempts before achieving abstinence.

Even young smokers want to quit. The 1989 and 1993 Teenage Attitudes and Practice Surveys did show that nearly 75% of 12- to 18-year-olds had seriously thought about quitting smoking; more recent surveys found that 73% of young smokers had tried to quit smoking. Of all smokers that attempt to quit each year, fewer than 10% are successful. Cigarette smokers who have successfully quit made, on average, seven serious attempts before achieving abstinence.

Smoking cessation restores a chance of living a full, healthy life. Quitting smoking reduces the risk of lung cancer by 50% at 5 years, and by 10 years, lung cancer risk drops almost to the rate for nonsmokers. After a year, mortality from heart disease decreases by half, and by 5 years it equals the rate for nonsmokers.

**FIGURE 22-3.** Cigarette advertising and promotion expenditures in the United States have more than quadrupled in 22 years.
NICOTINE REPLACEMENT THERAPY

Approximately 300 cessation methods are reported in the literature, ranging from group therapy, hypnosis, and self-help manuals to acupuncture. The introduction of nicotine-based medications in the form of chewing gum or a transdermal patch, combined with counseling, now provides cessation rates roughly double that of a control group (a factor of 1.4 to 2.6) as compared to placebo treatments. However, 70% to 80% of smokers who use these therapies still start to smoke again.

By providing a substitute source of nicotine, NRT lessens the withdrawal symptoms associated with quitting and improves the cessation process. As dozens of published studies have demonstrated its efficacy, safety, and utility, the Smoking Cessation Clinical Practice Guideline of AHCPR recommends NRT as a first-line treatment for tobacco dependence "except in the presence of special circumstances." Most commonly, NRT is used in the form of nicotine (polacrilex) gum [first approved by the U.S. Food and Drug Administration (FDA) in 1984] or the transdermal nicotine patch (FDA-approved in 1991). In 1996, both of these medications became available as over-the-counter products, greatly increasing access. In a metaanalysis, Fiore et al. studied 42 randomized controlled trials of nicotine gum, as well as trials with fewer subjects using a transdermal patch and nasal spray inhaled nicotine. From their studies of nearly 18,000 persons, the authors concluded that NRT was effective, either as a sole therapy or as an adjunct to other therapeutic approaches. Dosing of nicotine gum should initially be titrated by the level of nicotine dependence and then adjusted if withdrawal symptoms are not relieved. The Fagerstrom Test for Nicotine Dependence (which features such questions as “How soon after you wake up do you smoke your first cigarette?”) helps guide dosing decisions.

Other agents also show promising results. Recent attention has focused on bupropion, an antidepressant, in combination with the nicotine patch. A recent double-blind, placebo-controlled smoking cessation trial found 12-month abstinence rates of 15.6% for placebo, 16.4% for the nicotine patch alone, 30.3% for sustained-release bupropion (Zyban) alone, and 35.5% for bupropion in conjunction with the nicotine patch. Treatment consisted of 9 weeks of bupropion (150 mg/d) for the first 3 days and then 150 mg twice daily.

COMMUNITY LEVEL AND STATE INTERVENTIONS

The Community Intervention Trial for Smoking Cessation (COMMIT) and the American Stop Smoking Intervention Study for Cancer Prevention (ASSIST), two NCI-funded efforts to change social norms regarding tobacco use in the community, marked a societal shift toward viewing tobacco control as a public health

TABLE 22-1. Good Reasons to Stop Smoking

Clinicians should determine and document the tobacco use status of every patient treated in a health care setting. To remind physicians, Fiore has recommended that smoking status be included as part of a routine patient vital sign assessment. Other researchers recommend flagging smokers' charts to ensure necessary smoking interventions (Fig. 22-4). Ahluwalia et al. have found that placing a smoking stamp on patients' charts significantly increases (from 45.6% to 78.4%) the likelihood that a physician will ask patients whether they smoke.

The AHCPR guidelines also stipulate that effective cessation treatments should be offered to every patient who smokes. Brief cessation treatments are effective. At least a minimal intervention should be provided for every patient who uses tobacco.

As described in the AHCPR guidelines, a dose-response relationship exists between the intensity and duration of treatment and its effectiveness. In general, more intense intervention leads to more effective long-term abstinence from tobacco. The success of an intervention also is maximized by proper training and education of physicians and medical students, by increasing the number of modalities used and the number of professionals involved, and by the creation of office-based systems. Although only 2% to 3% of smokers become nonsmokers each year, some studies report that up to 15% of patients seen by trained physicians have quit smoking.

Finally, three particularly effective elements of smoking cessation treatment are (1) nicotine replacement therapy (NRT), (2) social support (clinician-provided encouragement and assistance), and (3) skills training and problem-solving techniques for achieving and maintaining abstinence. Individualizing the message to the patient increases the likelihood for success. Studies have shown that 3 minutes or less of advice increased quit rates from 7.9% to 10.2%. For example, quit rates of 50% to 63% 6 months after a myocardial infarction can increase to 65% to 75% for those patients who received additional interventions in addition to physician contact. Blum recommends that physicians ask nonthreatening questions, such as “What brand do you buy?” and “How much do you spend on cigarettes?” The term inhalation count can remind a pack-a-day patient that he or she will breathe in as many as 1 million doses of cyanide, ammonia, carcinogens, and carbon monoxide in less than 15 years. To the construction worker, the physician could link smoking cessation to the likelihood of fewer lost paydays, greater physical strength, and greater ability to work. A high school student, unresponsive to discussions of future emphysema and lung cancer, might be more receptive to the cosmetic unattractiveness of yellow teeth, bad breath, loss of athletic ability, or the financial drain of cigarettes (with costs for a pack-a-day smoker in excess of $1460 a year, calculated at $4 per pack).

Also, the physician needs to tailor the message to the patient's readiness to change, according to the Prochaska and DiClemente model: precontemplation, contemplation, action, and maintenance. During precontemplation, the patient has not considered quitting. During the contemplation phase, the patient is thinking about quitting. In the action phase, the patient is preparing and attempting to quit, and, during maintenance, the patient is avoiding relapse. Patients do not necessarily pass through each stage in orderly fashion; they may skip a stage or regress.

FIGURE 22-4. Smoking status included in the vital signs (a proposal by Fiore).
prevention issue. The 4-year COMMIT study involved 11 matched pairs of communities, randomly assigning one community to active intervention while the other served as the control site. The hypothesis was that a community-level, multichannel intervention (involving media, public education, work-site intervention, and other means) would increase quit rates among smokers, particularly heavy smokers. In 1995, the trial concluded with equal smoking prevalence rates in both intervention and control communities.

From 1991 through 1999, the NCI (with logistic support from the American Cancer Society) conducted ASSIST, a nonrandomized study. The project funded health departments in 17 states to implement tobacco control programs that included cessation classes, mass media campaigns, and public policy such as clean indoor air campaigns, efforts to prohibit youth access to tobacco products, and tax increases. Though the goal of reducing adult smoking prevalence to 15% by the year 2000 was not reached, the ASSIST initiative helped public health officials to gain valuable knowledge in statewide tobacco control planning and to move toward statewide denormalization of tobacco use.

Restricting smoking in workplaces has the potential to decrease greatly human exposure to ETS. Data show that in 1994, of 122 million full-time workers in the United States, nearly 100 million worked indoors. The 1994 National Health Interview Survey showed that smoking prevalence of indoor workers was 26%, and 59% of workers (59 million) worked in buildings where smoking was not permitted. A review of 19 studies of the impact of smoke-free workplaces found that all almost reported declines in daily smoking rates and smoking prevalence. Approximately 13% of the national decline in cigarette consumption in the United States between 1988 and 1994 was attributed to smoke-free workplaces.

An ongoing challenge is to guarantee that smoke-free policies have strength at the local level and are not subject to preemption (i.e., legislation that prevents any local jurisdiction from enacting restrictions that are more stringent than the state law). The Centers for Disease Control and Prevention (CDC), by including tobacco control laws and policies as part of their surveillance efforts, note that from 1993 through 1996, the number of tobacco control laws with a preemption provision increased significantly to cover 30 states currently.

TOBACCO TAXES THAT FUND DEDICATED, COMPREHENSIVE STATEWIDE TOBACCO CONTROL PROGRAMS

Many public health experts regard tobacco taxes to be the single most effective measure for decreasing tobacco consumption. Economic research documents price elasticity (i.e., a 10% increase in cigarette price generally reduces overall consumption by 4%). Studies show that youth, lower-income smokers, young adults, and minority smokers are more likely than others to be encouraged by a price increase to quit smoking. Government has traditionally taxed tobacco to fund government services, but public health professionals support increased taxes on tobacco products to deter consumption. The Canadian tobacco tax experience in the 1980s and early 1990s demonstrated the potential health impact. The combined average federal and provincial tax reached close to $3.00, pushing the average price per pack to more than $4.00. As a result, per capita cigarette consumption (adjusted for estimates of tobacco smuggling) dropped by 36% (1982 to 1992).

In contrast, among the world's industrialized countries, the United States has one of the lowest cigarette tax rates, with an average combined federal and state tax on cigarettes in 1993 of 53¢ per pack, as compared to countries such as Denmark and Norway, where taxes exceed $3.00 per pack. U.S. federal cigarette taxes, currently 24¢ per pack, will rise to 39¢ by 2002. Other forms of tobacco such as snuff, chewing tobacco, and pipe tobacco also are taxed.

To some degree, the state's dependence on tobacco production determines the level of state tax, which currently ranges from 2.5¢ in Virginia to $1.00 per pack in Alaska and Hawaii (nationwide average, 38.9¢ per pack). The cigarette tax–to–price ratio, which assesses the relative contribution of the total (state and federal) taxes to the full price of cigarettes, has declined from 49.8% in 1960 to 29.6% in 1997.

In general, the public is willing to increase tobacco taxes if those extra revenues are earmarked for specific purposes such as health programs. To date, four states—Arizona, California, Massachusetts, and Oregon—have passed tobacco tax initiatives and used the revenue to develop statewide comprehensive tobacco control programs. The CDC recently studied state experiences and disseminated best practices for comprehensive tobacco control programs.

CALIFORNIA

California voters approved a 1988 ballot initiative that increased the state cigarette tax by 25¢, allocating 20% of the revenue to establish a comprehensive statewide tobacco education and prevention program. The initiative also funded mass media antitobacco campaigns, assistance to local health agencies for providing technical support and monitoring adherence to antismoking laws, community-based interventions, smoking cessation services (including a statewide quit-smoking telephone hot line), and enhancement of school-based prevention programs. As a result, an analysis of per capita cigarette consumption indicated that the start of the California Tobacco Control Program in 1989 was associated with a 50% more rapid rate of decline in cigarette consumption than was seen in the rest of the country. Both the tax increase and the funded tobacco control program contributed to this decline. However, the post-1993 rate of decline, while still significantly more rapid in California than in the rest of the United States (where the decline in consumption halted), slowed to less than one-third of the rate seen in 1989 through 1993. Pierce et al. attributed the slowing to reduced program funding, increased tobacco industry expenditures for advertising and promotion, industry pricing, and political activities.

MASSACHUSETTS

Massachusetts voters approved a special 25¢ tax that helped to fund the Massachusetts Tobacco Control Program (MTCP). The MTCP had three major goals: to prevent onset of tobacco use by children, to assist smokers in quitting, and to guard against the harm of ETS. Like California's program, the MTCP consisted of funding for local cessation efforts and local coalitions, a statewide quit-smoking telephone hot line, funding of local boards of health, a statewide public awareness and counter-advertising campaign, and comprehensive school-based programs. Adult per capita tobacco consumption in Massachusetts declined by 20% from the program's inception in 1992 through 1996, reflecting a threefold increase over the reduction observed at the national level. The number of cities and towns that have adopted ordinances restricting youth access to cigarette vending machines has doubled. Recently, data showed the prevalence of current smoking among adults in Massachusetts was 19.1% in 1999, down from 23% in 1993, one of the lowest rates in all the 50 states.

OTHER STATES

Similar results accompanied a successful 1996 ballot measure in Oregon that increased the excise tax by 30¢ per pack of cigarettes. After passage, per capita consumption has declined 11.3% in Oregon, or the equivalent of 200 cigarettes per capita. Arizona's ballot initiative in 1994 raised cigarette prices by 40¢. Funds from a settled Medicaid lawsuit launched the Florida Pilot Program on Tobacco Control, which is credited with sparking significant declines in tobacco use among middle school and public high school students, declines attributed primarily to a youth-oriented, counter-advertising media campaign, community partnerships in all 67 Florida counties, and enhanced enforcement of youth access laws. From 1998 to 1999, the prevalence of cigarette use among middle school students declined from 18.5% to 15.0% (P < 0.01); among high school students, declines ranged from 27.4% to 25.2% (P = .02).

MASS MEDIA AND COUNTER-ADVERTISING

All the statewide tobacco control programs just cited have incorporated counter-advertising efforts through mass media. Minnesota (1986) and Michigan (1994) also...
have initiated limited tax-funded media campaigns. Such efforts counter the tobacco industry's efforts to normalize a lethal product through advertising and promotional cigarette sales. A counter-advertising public health approach aims to reduce tobacco use by degrading and de-normalizing the use of the product. To be effective, such mass media antismoking campaigns should provide consistent messages from multiple sources, repeatedly and over a long period, and should work in concert with other interventions and policies, with the goal of changing societal norms.

The effects of these counter-advertising media campaigns, especially those in California and Massachusetts, have been striking. Of the California Tobacco Control Program's decline in cigarette consumption, approximately 20% was estimated to be attributable to the media campaign. One study of California adults who successfully quit smoking (1990 and 1991) found that in 41%, the media counter-advertising campaign had influenced their decision to stop.

The effectiveness of counter-advertising first emerged in 1967 when the Federal Communications Commission invoked the Fairness Doctrine to require broadcasters to air one antismoking message for every three cigarette commercials aired. When such antismoking advertising prompted a decline in per capita cigarette consumption of at least 5%, the tobacco industry then agreed (in 1970) to Congressional legislation to ban all tobacco advertising on television and radio, thereby eliminating the need for free antismoking ads.

Later, research in Vermont and Minnesota showed that community- and school-based interventions highlighted by prominent mass media campaigns could reduce smoking in young persons by up to 40%. However, such mass media campaigns before 1988 usually occurred on a sporadic basis. Also, institutionalizing counter-advertising campaigns has posed a public health challenge, as funding for such campaigns can be subjected to legislative diversion. Typically, public service announcements on television did not air during prime time and therefore reached smaller audiences.

Goldman and Glantz have concluded that messages challenging social norms are more successful than are those aimed at changing individual behavior to improve health. Focus group analysis by these researchers found that the most effective themes stressed the tobacco industry's manipulation of young persons, the negative impact of secondhand smoke, and the burden of cigarette addiction. Such advertisements can be controversial yet memorable and, ultimately, effective.

TOBACCO LITIGATION AND TOBACCO SETTLEMENT

Public health lawyers have advocated bringing suits against tobacco companies as a cancer prevention strategy. The last half century of tobacco litigation can be divided into three waves. Wave 1 (1954 through 1973) featured a number of individual lawsuits against an industry that maintained that tobacco products had never been proven to cause disease. The industry claimed that smokers chose to smoke, hence assuming risk for themselves. In essence, the 1965 Federal Cigarette Labeling and Advertising Act, which requires warning labels on all cigarette packaging and labeling, ironically served as a shield from liability. Wave 2 (1983 through 1992) featured Cipollone v. Liggett Group, Inc., a suit brought by a smoker and continued by her husband after her death. Although the original jury verdict of $400,000 favored the plaintiff, it was reversed on appeal and the case finally was dropped after years of litigation.

Wave 3 (1994 to the present) capitalizes on the release of internal industry documents and subsequent industry concessions that tobacco is addictive and causes cancer and that tobacco companies engaged in conduct that the U.S. Department of Justice characterized as a giant fraud. These concessions include the creation of an increasing number of individual lawsuits against class action suits brought on behalf of flight attendants injured by ETS and was settled for $345 million. The money realized from this suit will establish a foundation for the study of diseases associated with tobacco.

Engle v. R. J. Reynolds is a suit brought on behalf of addicted and sick smokers in Florida. In the first phase of this massive class action suit, the industry was found liable for punitive damages, with the award potentially in the hundreds of billions of dollars. In addition, in 1999, the Justice Department filed a $20 billion lawsuit against the nation's tobacco companies to recover federal costs of treating smoking-related illness.

The most notable litigation to date has been lawsuits brought by states' attorneys general against the tobacco industry to recoup Medicaid costs for the treatment of ill smokers. In a remarkable turn of events, the major tobacco manufacturers first settled individually with Mississippi, Texas, Minnesota, and Florida at a cost of $40 billion over 25 years. Then the industry signed a Master Settlement Agreement with 46 state attorneys general in November 1998, agreeing to pay $206 billion over 25 years in exchange for no future state litigation. Other conditions included some advertising restrictions (e.g., bans on billboard advertisements) and the establishment of a national foundation to reduce teen smoking.

As the twentieth century ends, states are embroiled in historic discussions of how best to spend the settlement money. The Master Settlement Agreement expressly states that parties "have agreed to settle their respective lawsuits and potential claims pursuant to terms which will achieve for the Settling States and their citizens significant funding for the advancement of public health, the implementation of important tobacco-related public health measures, including the enforcement of mandates and restrictions related to such measures, as well as funding for a national foundation dedicated to significantly reducing the use of tobacco products by youth." However, to date, in most states, the debate has been dominated by proposals to fund civic projects such as debt reduction, school construction, teacher retirement funds, prison construction, and sidewalk repair. As the suits were launched and settled for reasons of tobacco and health, the most fitting outcome would be to dedicate such funds to tobacco control and health programs.

PROPOSED U.S. FOOD AND DRUG ADMINISTRATION REGULATION

Under Commissioner David Kessler, the FDA first investigated whether to regulate nicotine as a drug. The Federal Food, Drug and Cosmetic Act defines a drug as "an article (except for food) intended to affect the structure or function of the body." Universal scientific consensus indicates that nicotine is an addictive drug. Evidence of the intent of the industry had been supported by the release of internal documents showing that tobacco manufacturers knew that nicotine causes significant pharmacologic effects and designed their products to provide pharmacologically active doses.

In 1996, the FDA proposed strategies to restrict access to tobacco products and advertising to youth. The first step, effected in part in 1997, involved stricter enforcement of laws affecting minors. The remaining proposed steps included banning free samples, restricting advertising within 1000 feet of schools and playgrounds, and limiting to black and white text print advertising in youth publications. The U.S. Supreme Court recently rejected these proposals, saying the FDA had never received authority from congress to regulate tobacco products.

CONCLUSION

The dawn of the twenty-first century offers us a new opportunity to create a smoke-free society. All health care professionals, and indeed all citizens, can work to achieve this goal and prevent cancer. At the individual level, we must maximize access to cessation services for all smokers and promote further research into improving nicotine replacement therapies and other pharmacologic approaches. Health care professionals can raise awareness and promote cessation with every clinical opportunity. Reducing and even eliminating nicotine from cigarettes is also technically feasible and may hold the future to eradicating the potential for addiction.

On a broader societal level, communities can commit to changing permanently to a non-smoking social norm. Such efforts include restricting tobacco advertising and promotion to children, prohibiting tobacco access by youth and teenagers, enhancing public education, raising tobacco excise taxes, and controlling tobacco exports. Dedication of tobacco settlement funds to statewide tobacco control programs nationwide can reduce cigarette consumption and promote prevention, as has been done in California and Massachusetts. Key to such comprehensive programs are programs that reduce counter-advertising programs that glamorize tobacco use.

On the legal front, multiple individual and class action suits ultimately may change the tobacco industry's ability to conduct business as usual. In light of the U.S. Supreme Court's decision as to the authority of the FDA to regulate tobacco, we now await study of this issue by the U.S. Congress.

It is hoped that all these combined efforts will cause the decline and prevention of tobacco-related cancers in the new millennium. Medical historians then can mark the end of the so-called Tobacco and Cancer Century and celebrate the beginning of a new smoke-free chapter in public health.

CHAPTER REFERENCES


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SECTION 23.1
Fat

WALTER C. WILLET

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Fat and Breast Cancer
Case-Control Studies
Cohort Studies
Different Types of Fat
Fat and Age at menopause
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INTRODUCTION

In recent years, reduction in dietary fat has been at the center of cancer prevention efforts. In the landmark 1982 National Academy of Sciences review of diet, nutrition, and cancer, a reduction in fat intake to 30% of calories was the primary recommendation; this objective has been echoed in subsequent dietary recommendations as well.3

Interest in dietary fat as a cause of cancer began in the first half of the twentieth century when studies by Tannenbaum and colleagues indicated that diets high in fat could promote tumor growth in animal models. In this early work, energy (caloric) restriction also profoundly reduced the incidence of tumors. A vast literature on dietary fat and cancer in animals has subsequently accumulated (reviewed elsewhere).14,16,21 Diet fat has a clear effect on tumor incidence in many models, although not in all; however, a central issue has been whether this is independent of the effect of energy intake. An independent effect of fat has been seen in some animal models,16,21 but this has been either weak2 or nonexistent12 in some studies designed specifically to address this issue.

In the 1970s, the possible relation of dietary fat intake to cancer incidence gained greater attention as the large international differences in rates of many cancers were noted to be strongly correlated with apparent per capita fat consumption.14 Particularly strong associations were seen with cancers of the breast, colon, prostate, and endometrium, which include the most important cancers in affluent countries not caused by smoking.26 These correlations were observed to be limited to animal, not vegetable, fat.29 Complementing these correlational observations, studies of populations migrating from low- to high-incidence areas indicated that the migrating groups adopted the cancer rates of the new environment. This provided powerful evidence that the large international differences in cancer incidence were not due to genetic factors and therefore that the high rates of specific cancers in affluent countries were potentially avoidable. Although such evidence did not directly implicate dietary factors, the animal studies noted previously made the area of diet a strong suspect.

A principal limitation of both the international correlational and migrant studies is the potential for confounding; many other differences besides dietary fat exist between the low-fat (less affluent) and high-fat (more affluent) countries. Indeed, the correlations with gross national product are similar to those for fat intake.5,25 Among the many factors that differ between low- and high-fat countries, reproductive behaviors, physical activity level, and body fatness are particularly notable and are strongly associated with specific cancers.29,30 The quality of dietary data used in the international correlations has also been problematic; this information is not based on actual intakes, but rather on estimated production figures.

Despite their limitations, the suggestive findings of at least some animal models as well as the international correlations and migrant studies have clearly indicated the need for more detailed studies in humans. In particular, studies that can control for the confounding influences of lifestyle factors other than fat intake are important. Two general approaches, discussed elsewhere in detail,36 are available: case-control or cohort epidemiologic studies and randomized trials. Both case-control and cohort studies are dependent on a reasonably valid assessment of dietary intake. Although for some nutrients, biochemical measurements can be used to assess intake, for total fat consumption a useful biochemical indicator does not exist. Since 1980, considerable effort has been given to the development of standardized questionnaires for measuring intake of fat and other dietary factors and numerous studies have been conducted to assess the validity of these methods.37,38,39 These investigations have clearly demonstrated that an informative range of fat exists within the populations of the United States and other countries and that standardized food frequency questionnaires can reasonably measure differences among subjects. Although the range of fat intake that can be studied is restricted to the range of diets in the study population, this typically includes both the levels that have often been recommended (less than 30% of energy) as well as more traditional U.S. levels (more than 40% of energy). Moreover, by combining the data from multiple large prospective studies, the range of fat has been extended from less than 20% of energy to more than 45% of energy, which is similar to the current range observed internationally.38

In principle, the most definitive approach to evaluate the relation between fat intake and cancer is to conduct a large randomized trial. However, many practical problems exist in conducting such a trial. The most important being the need to maintain a difference in fat intake between the intervention and control groups for many years; the experience of the Multiple Risk Factor Intervention Trial heart disease prevention study and the pilot studies for the Women's Health Initiative37 indicates this may be difficult. Moreover, the necessary duration for such a trial is not known; much evidence suggests that factors acting from childhood through postmenopausal years can influence breast cancer risk. Because trials of cancer prevention require tens of thousands of subjects to be randomized and the costs of instruction in dietary change is high, such studies are extremely expensive; for example, the Women's Health Initiative will cost well over half a billion dollars.38

Since 1985 information on fat intake and cancer has grown rapidly and will continue to accrue exponentially as the populations of ongoing cohort studies age and as recently started cohort studies begin to report their findings. In the following sections, current data on the relation of fat intake to cancers of the breast, colon, and prostate are briefly reviewed as these are the cancers for which the current evidence is most abundant.

FAT AND BREAST CANCER

Breast cancer is the most frequent malignancy among women in Western countries, and incidence rates have been increasing for decades.4,26 Rates in most parts of Asia, South America, and Africa have been only approximately one-fifth as high as that of the United States.24 but in almost all these areas rates of breast cancer are also increasing. Populations that migrate from low- to high-incidence countries develop breast cancer rates that approximate those of the new host country.5,26 However, among Japanese immigrants to the United States, not until the second or third generation do rates approach those of the general U.S. population.4 This slower rate of change for Japanese immigrants may indicate delayed acculturation, although a similar delay in increase is not observed for colon cancer.

A major rationale for the dietary fat hypothesis has been the international correlation between fat consumption and national breast cancer mortality.4 However, in a study of 65 Chinese counties,5 in which both dietary assessment and mortality were measured using standardized methods, and per capita fat intake varied from 6% to 25% of energy, only a weak positive association was seen between fat intake and breast cancer mortality. Notably, four counties consumed approximately 25% of energy from fat, yet experienced rates of breast cancer far below those of U.S. women with similar fat intake,5 thus providing strong evidence that factors other than fat intake account for the large international differences.

Breast cancer incidence rates increased substantially in the United States during the twentieth century, as have the estimates of per capita fat consumption based on food disappearance data. However, surveys based on reports of individual actual intake, rather than food disappearance, indicate that consumption of energy from fat, either as absolute intake
or as a percentage of energy, has actually declined in the last several decades,\textsuperscript{23-25} a time during which breast cancer incidence has increased.\textsuperscript{26}

\section*{CASE-CONTROL STUDIES}

A number of case-control studies have been performed to investigate the dietary fat effect on breast cancer. The largest study so far is that of Graham et al.,\textsuperscript{2} who used a food-frequency questionnaire to compare the fat intake of 2024 women with breast cancer with that reported by 1463 women controls entering the hospital with benign conditions. Both animal fat and total fat intake were essentially identical in the two groups. The results from 12 smaller case-control studies have been summarized in a metaanalysis by Howe et al.,\textsuperscript{3,4} which included 4312 cases and 5978 controls. The pooled relative risk was 1.35 (\(P < 0.0001\)) for a 100-g increase in daily total fat intake, although the risk was somewhat stronger for postmenopausal women (relative risk = 1.48; \(P < 0.001\)). This magnitude of association, however, could potentially be compatible with biases due to recall of diet or the selection of controls.\textsuperscript{5}

\section*{COHORT STUDIES}

A substantial body of data from cohort studies is now available to assess the relation between dietary fat intake and breast cancer in developed countries. Because of the prospective design, most of the methodologic biases of case-control studies are avoided. In a pooled analysis of the seven prospective studies with more than 200 cases of breast cancer, which included 337,000 women who developed 4980 incident cases of breast cancer,\textsuperscript{6} no overall association was seen for fat intake over the range of less than 20% to greater than 45% of energy (Fig. 23.1-1). A similar lack of association was seen among postmenopausal women only and for specific types of fat. Only among the small number of women consuming less than 15% of energy from fat was a significant association seen; breast cancer risk was elevated twofold in this group. An update of the Nurses' Health Study included 14 years of follow-up, during which 2956 women developed breast cancer.\textsuperscript{7} Because repeated assessments of diet were obtained at 2- to 4-year intervals, this provided a particularly detailed evaluation of the fat intake over an extended period in relation to breast cancer risk. For total fat intake, the overall association was weakly inverse and statistically significant. There was no suggestion of any reduction in risk at intakes below 25% of energy. These cohort findings therefore do not support the hypothesis that dietary fat is an important cause of breast cancer.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure231-1.png}
\caption{Pooled relative risks and 95\% confidence intervals for various levels of energy from fat. A level of 30\% to less than 35\% of total energy from fat was designated as the reference category. (From ref. 25, with permission.)}
\end{figure}

Estrogen level in blood has now been established as a factor for breast cancer.\textsuperscript{8} Thus, the effects of fat and other dietary factors on estrogen levels are of potential interest. Vegetarian women, who consume higher amounts of fiber and lower amounts of fat, have lower blood levels and reduced urinary excretion of estrogens, apparently due to increased fecal excretion.\textsuperscript{9} A metaanalysis has suggested that reduction in dietary fat may reduce plasma estrogen levels,\textsuperscript{10} but the studies included were plagued by the lack of concurrent controls, short duration, and confounding by negative energy balance.\textsuperscript{11} In a large randomized trial among postmenopausal women with a previous diagnosis of breast cancer, reduction in dietary fat did not affect estradiol levels when appropriately analyzed.\textsuperscript{12}

\section*{DIFFERENT TYPES OF FAT}

In animal mammary tumor models, the tumor-promoting effect of fat intake has been observed primarily for polyunsaturated fats when fed in the presence of high-fat diets containing approximately 45\% of energy.\textsuperscript{13-15} In a metaanalysis of animal studies, monosaturated fat had no significant effect on mammary carcinogenesis, and the effect of saturated fat was weak.\textsuperscript{16}

In several prospective cohort studies, an inverse association between monounsaturated fat and breast cancer has been present.\textsuperscript{17-19} This is an intriguing observation because of the relatively low rates of breast cancer in Southern European countries with high intakes of monounsaturated fats due to the use of olive oil as the primary fat. In case-control studies in Spain, Greece, and Italy, women who used more olive oil had reduced risks of breast cancer.\textsuperscript{20,21} Also, olive oil has been protective relative to other sources of fats in several animal studies.\textsuperscript{22} Further examination is needed of the hypothesis that monounsaturated fats, and perhaps olive oil in particular, may protect against breast cancer.

\section*{FAT AND AGE AT PUBERTY}

An earlier age at menarche is an established risk factor for breast cancer. Although the relative risks associated with early menarche are generally modest, usually less than approximately 1.5 for the earliest compared with the latest age groups within a population, this is likely to be due to the limited range of age at menarche within a population. For example, in the United States, the average age is between 12 and 13 years,\textsuperscript{23} but in rural China the typical age is approximately 17 to 18 years.\textsuperscript{24} Further, the average age at menarche has been declining worldwide for the last 200 years,\textsuperscript{25} thus suggesting that increasing breast cancer rates that occur with increasing industrialization are in part due to a decreasing average age at menarche.

For this reason, nutritional factors that influence age at menarche are of particular interest. Nutritional factors have been examined as potential predictors of age at menarche in several prospective cohort studies. Body mass index, height, and weight have consistently been strong determinants of age at menstruation.\textsuperscript{26-28} In the United States,\textsuperscript{29} as well as in the Canadian cohorts,\textsuperscript{30} no association was found between the fat composition of the diet and occurrence of menarche, but a suggestion of earlier onset with higher fat intake was seen in the German study.\textsuperscript{31} Collectively, these studies provide strong evidence that rapid growth rates before puberty play an important role in determining future risk of breast cancer, but that overall energy balance rather than fat intake is most important.

\section*{FAT AND BREAST CANCER SURVIVAL}

High intake of dietary fat has been hypothesized to affect survival adversely in patients with breast cancer, in part because of observations that, adjusted for stage, survival is lower in the United States than in Japan.\textsuperscript{32} However, obesity has often been associated with adverse survival from breast cancer, which provides an alternative hypothesis as Japanese women tend to be substantially leaner than U.S. women, and other dietary and lifestyle factors have differed substantially between the United States and Japan.

At present, studies of dietary fat intake and survival from breast cancer are few and have substantial limitations. Most were not specifically designed for this purpose, but instead are based on the follow-up of the control series of case-control or cohort studies of breast cancer incidence. Thus, they usually refer to premorbid diet assessed either before or at about the time of diagnosis rather than to diet after diagnosis and, moreover, most studies have been small in terms of the failure end points. Mixed results have been seen in the published work; positive associations have been seen in several studies,\textsuperscript{33-35} but not in others.\textsuperscript{36-38} In a report from the Nurses' Health Study,\textsuperscript{39} fat intake after diagnosis was not significantly associated with survival, but a modest effect could not be excluded. Unexpectedly, higher protein intake was associated with improved survival. A randomized trial has been started to evaluate the effect of a diet low in fat (15\% of energy from fat is the dietary goal) on survival of breast cancer patients.\textsuperscript{40}
FAT AND COLON CANCER

In comparisons among countries, rates of colon cancer are strongly correlated with national per capita disappearance of animal fat and meat, with correlation coefficients ranging between 0.6 and 0.9. Rates of colon cancer rose sharply in Japan after World War II, paralleling a 2.5-fold increase in fat. Based on these epidemiologic investigations and animal studies, a hypothesis has developed that dietary fat increases excretion of bile acids, which can be converted to carcinogens or promoters. However, more recent evidence from many studies that obesity and low levels of physical activity increase risk of colon cancer risk means that at least part of the high rates in affluent countries previously attributed to fat intake are probably due to sedentary lifestyle.

With some exceptions, case-control studies have generally shown an association between risk of colon cancer and intake of fat, or red meat. A positive association between total energy intake and risk of colon cancer has also been observed. raising the question of whether it is general overconsumption of food or the fat composition of the diet that is etiologically important. A metaanalysis by Howe of 13 case-control studies found a significant association between total energy and colon cancer, but saturated, monounsaturated, and polyunsaturated fat were not associated with colon cancer independently of total energy.

Prospective cohort studies of colon cancer are less prone to selection and recall bias. Earlier prospective data have shown positive, inverse, and null associations with fat or meat consumption. These studies were limited by small number of cases or crude assessments of diet. More recent cohort studies have largely avoided these limitations (Table 23.1-1). The Nurses’ Health Study showed approximately a twofold higher risk of colon cancer among women in the highest compared with those in the lowest quintile of animal fat intake. In a multivariate analysis of these data, which included red meat and animal fat intakes in the same model, red meat intake remained significantly predictive of risk of colon cancer, whereas the association with animal fat was eliminated. A cohort study from the Netherlands showed a significant direct association between intake of processed meats and risk of colon cancer, but no relationship was observed for fresh meats or overall fat intake. A cohort study in Iowa women also found a direct association with processed meats, although this was not statistically significant.

Among a large cohort study of men, a direct association between red meat consumption and risk of colon cancer was seen, but no association was observed with other sources of fat. In this study, no overall relationship existed between total or saturated fat and colon cancer despite a substantial range in fat intake. A similar association was noted for colorectal adenomas in the same cohort of men. In large American Cancer Society Cohort, little relation was seen between either meat or fat intake and mortality caused by colon cancer, but the dietary questionnaire was brief and of uncertain validity. As noted in Table 23.1-1, other cohort studies have also failed to support an association with fat intake, even though positive associations with red meat were usually observed.

**TABLE 23.1-1.** Large Prospective Studies of Colon Cancer: Energy, Fat, and Meat

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Total</th>
<th>Saturated</th>
<th>Meat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hawaii</td>
<td>1,000</td>
<td>65</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>California</td>
<td>2,000</td>
<td>70</td>
<td>10</td>
<td>15</td>
</tr>
</tbody>
</table>

The apparently stronger association with red meat compared with fat intake in most recent cohort studies needs further confirmation, but could result if the fatty acids or nonfat components of meat (e.g., the heme iron or carcinogens created by cooking) were the primary etiologic factors. This issue does have major practical implications as current dietary recommendations support the daily consumption of red meat as long as it is lean. Virtually no data exist on the relation of dietary fat to survival from colon cancer.

FAT AND PROSTATE CANCER

Consumption of animal fat, but not vegetable fat, is strongly correlated with prostate cancer mortality internationally. Associations with fat intake have been seen in many case-control studies, but sometimes only in subgroups. In a large case-control study among various ethnic groups within the United States, consistent associations with prostate cancer risk were seen for saturated fat, but not with other types of fat.

The association between fat intake and prostate cancer risk has been assessed in only a few cohort studies (Table 23.1-2). In a cohort of 8,000 Japanese men living in Hawaii, no association was seen between intake of total or unsaturated fat. However, diet was assessed with a single 24-hour recall in this study so the lack of association may not be informative. In a study of 14,000 Seventh-Day Adventist men living in California, a positive association between the percentage of calories from animal fat and prostate cancer risk was seen, but this was not statistically significant. More recently, three large prospective studies have been published. In the Health Professionals Follow-up Study of 51,000 men, a positive association was seen with intake of red meat and total and animal fat, which was largely limited to aggressive prostate cancers. No association was seen with vegetable fats. In another cohort from Hawaii, increased risks of prostate cancer were seen with consumption of beef and animal fat. In contrast, no relation was seen between intakes of either total or saturated fat and incidence of prostate cancer in a large Dutch cohort.

**TABLE 23.1-2.** Prospective Studies of Dietary Fat and Prostate Cancer Risk

Although further data are desirable, the evidence from international correlations, case-control, and cohort studies provides some support for an association between consumption of fat-containing animal products and prostate cancer incidence. This evidence does not generally support a relation with intake of vegetable fat, which suggests that either the type of fat or other components of animal products are responsible. Some evidence also suggests that animal fat consumption may be most strongly associated with aggressive prostate cancer, which suggests an influence on the transition from the widespread indolent form to the more lethal form of this malignancy. No data are available on fat intake in relation to the probability of survival after the diagnosis of prostate cancer.
OTHER CANCERS
Rates of other cancers that are common in affluent countries, including those of the endometrium and ovary, are, of course, also correlated with fat intake internationally. Although these have been studied in a small number of case-control investigations, consistent associations with fat intake have not been seen.

In a prospective study among Iowa women, no evidence of a relation between fat intake and risk of endometrial cancer was observed. Positive associations have been hypothesized between fat intake and risks of skin cancer and lung cancer, but relevant data in humans are limited.

SUMMARY
Based largely on the results of animal studies, international correlations, and a few case-control studies, great enthusiasm developed in the 1980s that modest reductions in fat intake would have a major effect on breast cancer incidence. However, as the findings from large prospective studies have become available, support for this relationship has weakened considerably. For colon cancer, the associations seen with animal fat intake have been confirmed in numerous case-control studies. However, many of the previous findings in this area have not been explained by associations in rodent models in red meat other than simply its content of fat. Further, the importance of physical activity and leanness as protective factors against colon cancer indicates that international correlations probably overstate the contribution of diet to differences in colon cancer incidence. At present, the available evidence most strongly suggests an association between animal fat consumption and risk of prostate cancer, particularly the aggressive form of this disease. As with colon cancer, the possibility remains that other factors in animal products contribute to risk.

Despite the large body of data on dietary fat and cancer that has accumulated since 1985, all conclusions should be regarded as tentative because we are dealing with disease processes that are poorly understood, but that are likely to take many decades to develop. As most of the reported literature from prospective studies is based on less than 15 years of follow-up, further evaluation of the effects of diet earlier in life and at longer intervals of observation will be needed to understand fully these complex relationships. Nevertheless, persons interested in reducing their risk of cancer could be advised, as a prudent measure, to minimize their intake of foods high in animal fat, particularly red meat. Such a dietary pattern is also likely to be beneficial from the standpoint of cardiovascular disease. On the other hand, unsaturated fats (with the exception of trans fatty acids) reduce blood low-density lipoprotein cholesterol levels and risk of cardiovascular disease and little evidence suggests that they adversely affect cancer risk. Thus, efforts to reduce unsaturated fat intake do not appear to be warranted at this time and may have adverse effects on cardiovascular disease. As excess adiposity adversely affects risks of several cancers and cardiovascular disease, balancing calories from any source with adequate physical activity is extremely important.

CHAPTER REFERENCES
Dietary Fiber and Other Cancers

INTRODUCTION

The hypothesis linking high intakes of dietary fiber with reduced risk of colorectal cancer in humans was advanced in the early 1970s by Burkitt, who observed that certain chronic diseases common to westernized societies, including colon cancer, diverticular disease, gallstones, and ischemic heart disease, were rare among African populations whose diets consisted predominantly of high-fiber foods. Since that time, a compelling body of epidemiologic evidence, experimental data, and clinical research has found that diets high in fiber, grains, cereals, and fresh vegetables and fruits are associated with reduced risk of several cancers, including cancers of the colon, rectum, and breast, and possibly with lowered risk for additional cancers of the alimentary canal (mouth, esophagus, pharynx, stomach) and other hormone-sensitive cancers (ovarian, endometrial, and prostate cancers).

Despite a substantial body of research suggesting that diets high in fiber-rich foods protect against certain cancers, results from epidemiologic and animal studies investigating the effect of dietary fiber on cancer risk are not entirely consistent. The type or source of fiber consumed, temporal nature of consumption (current versus past intake), overall eating patterns, familial predisposition to certain cancers, cancer site, and other nutrients found in high-fiber foods (e.g., folate; antioxidants such as vitamins C and E and selenium; and phytochemicals such as carotenoids, phytoestrogens, organosulfides, and isothiocyanates) may all influence cancer risk. Also at issue are the complexities of fiber and the lack of standardized analytical methods for extracting and quantifying the fiber content of food; the differential effects of the various types of fiber on gut physiology; the effect of storage, processing, and food preparation on the physical and chemical nature of fiber; the lack of comprehensive food composition data on types of dietary fiber and total fiber; and problems with dietary assessment methods, such as recall bias. Inconsistencies in animal studies may be related to the species and strain of animal used; the type (i.e., an initiator versus promoter) and amount of carcinogen administered; the type and amount of fiber; the overall composition of the animal's diet; the timing of administration of fiber, in relation to the carcinogenic process; and the length of the study.

SOURCES AND TYPES OF DIETARY FIBER

Dietary fiber is a heterogeneous mixture of complex, plant-based carbohydrates that are resistant to digestion by human intestinal enzymes. High-fiber foods include whole grains, vegetables, fruits, beans, nuts, and seeds. The skins of many vegetables and fruits and the bran layers of grains also are good sources of fiber. Components of dietary fiber in plant foods vary with plant species, stages of maturity, and parts of the plant. Further, although one or two types of fiber may predominate in a particular food, most plants contain a variety of fiber types or components. Grains, roots, green leafy vegetables, legumes, and some fruits such as apples contain high levels of cellulose and hemicelluloses. Another component of fiber, lignin, is found in the walls of plant cells and increases as the plant matures. Most fruits contain pectin, but citrus fruits and apples contain high levels of cellulose and hemicelluloses. Another component of fiber, lignin, is found in the walls of plant cells and increases as the plant matures.

The two primary types of fiber are categorized as soluble and insoluble, according to their degree of solubility in water. Fibers also are described in terms of their fermentability characteristics (Table 23.2-2). Soluble fibers attract water, form a gel during digestion, and generally are fermentable. Insoluble fibers, in contrast, are insoluble in water and usually are nonfermentable. Different types of dietary fibers in commonly consumed plant foods are grouped further according to their chemical structure, as nonstarch polysaccharides and lignin, a polymer of aromatic alcohols. Nonstarch polysaccharide plant fibers include cellulose, hemicelluloses, pectins, gums, muclages, and other miscellaneous polysaccharides. Soluble, fermentable gel-forming fibers include pectins, gums, starches, some hemicelluloses, and other polysaccharides and are present at the highest levels in fruits, oats, beans, and vegetables. Whole grains and whole-grain foods are primary sources of insoluble, nonfermentable structural fibers such as cellulose, most hemicelluloses, and lignins.
TABLE 23.2-2. Benefits and Examples of Good Sources of Both Soluble and Insoluble Fiber

| Fiber Source | Soluble Fiber | Insoluble Fiber | Example
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Wheat bran</td>
<td>10% to 15%</td>
<td>70%</td>
<td>Rich in lignin and pentosans.</td>
</tr>
<tr>
<td>Oat bran</td>
<td>3%</td>
<td>20%</td>
<td>Rich in lignin and phenolic acids.</td>
</tr>
<tr>
<td>Lentils</td>
<td>2%</td>
<td>25%</td>
<td>Rich in lignin and phytic acid.</td>
</tr>
<tr>
<td>Corn bran</td>
<td>2%</td>
<td>50%</td>
<td>Rich in lignin and phytic acid.</td>
</tr>
</tbody>
</table>

DIETARY FIBER AND COLORECTAL CANCER

SUMMARY OF EPIDEMIOLOGIC AND EXPERIMENTAL EVIDENCE

International colon cancer incidence rates vary by a factor of 20 or more, and a large proportion of that difference is believed to be a result of various dietary factors, including certain types of fiber. Overall, results of international comparisons and correlation and case-control studies support the hypothesis that high-fiber intakes reduce risk for colorectal cancer. In these studies, total dietary fiber intake and consumption of cereal fiber and whole grains show a consistent reduction in risk for colorectal cancer. A meta-analysis of data from 13 case-control studies reported a 50% reduction in risk for colorectal cancer when the highest versus lowest quintiles of fiber intake were compared. Results of prospective cohort studies are mixed, with most showing either only weak protective associations or no statistically significant relationship. Differences between fiber intake and risk of cancers of the colon or rectum. Differences in the findings of these and other epidemiologic studies likely result in part from the heterogeneous nature of fiber, the way in which fiber is measured, and the problems associated with collection of dietary intake data, but also with the relatively homogeneous fiber intakes across the study cohorts. Data from both epidemiologic and basic research studies suggest that the various types of fiber confer a differential effect on colorectal cancer risk. One international study of 20 populations in 12 countries reported a strong inverse relationship between starch consumption and risk for colorectal cancer. Another study found that soluble but not insoluble fiber, and fiber from fruits but not vegetables, had a protective effect on the development of distal colon adenoma in men. Results of a case-control study of nearly 2000 patients with confirmed colorectal cancer and more than 4100 controls with no history of cancer indicated that total fiber intake, and particularly intake of cellulose, soluble noncellulose polysaccharides, and fiber of vegetable and fruit origin, was associated with a reduction in the risk of cancers of the colon and rectum. Reviews of animal studies investigating the effect of different types of dietary fiber on colon tumorigenesis generally report that the greatest protective effect, as measured by lowered incidence (number of animals with tumors) and multiplicity (number of tumors per animal with tumors) of small intestine and colon tumors, is conferred by insoluble fibers, in particular wheat bran, whereas soluble fibers may increase risk.

The growing interest in the potential effect of wheat bran fiber on colorectal cancer risk has been the focus of several reviews, Wheat bran, which contains more than 70% of the fiber of the whole grain, is rich in lignin and polysaccharides. Numerous animal studies show wheat bran fiber to be as or more effective than other fiber sources, such as corn and oat, in inhibiting or preventing colon tumor growth. In some studies, however, dietary wheat bran fiber either had no effect on the development of colon tumors in rats or increased colon tumorigenesis. Several epidemiologic studies and clinical interventions also have investigated the effect of different dietary fibers, including wheat bran, on factors associated with increased risk for colorectal cancer, including colonic or rectal cell proliferation, bile acid excretion, fecal mutagens, and activity of several intestinal bacterial enzymes linked to the production of carcinogenic substances. Results of these studies indicate that wheat bran has a favorable, and sometimes more favorable, effect when compared with other sources of fiber, on these factors. The cancer-protective effects of wheat bran may be the result, at least in part, of various compounds, including the fermentation product butyrate and certain constituents of wheat bran, including phytic acid, phenolic acids, and phytoestrogens, all of which have shown a cancer-protective effect in either, or both, epidemiologic and animal studies.

POTENTIAL INFLUENCES OF DIETARY FIBER ON GENETICALLY LINKED COLORECTAL CANCERS

Approximately 10% to 15% of all cases of colorectal cancers are believed to result from genetic predisposition to these cancers. Two inherited genetic forms of colorectal cancer, familial adenomatous polyposis and hereditary nonpolyposis colon cancer, are associated with up to an 80% lifetime risk of developing the disease. The potential of a high-fiber diet, or fiber supplementation, to modify colorectal cancer risk in at-risk or high-risk individuals who have a genetic predisposition to colorectal cancer has been studied and further investigations are under way. One clinical trial found that supplementing the diet with at least 11 g of wheat bran fiber per day significantly reduced the recurrence of rectal adenomas in patients with familial adenomatous polyposis. Results of the Australian Polypl Prevention Project indicated that consuming high levels of dietary fiber supplementation (25 g wheat bran fiber per day) or a low-fat diet (25% of total calories) for 2 to 4 years reduced risk (but not to a level of statistical significance) of developing new, large adenomas (diameter greater than or equal to 10 mm) in healthy individuals who had at least one colonic polyp removed before the start of the study. Participants following a combined low-fat, high-fiber diet had no large adenomas at both 2 and 4 years, a finding that was statistically significant (P <.03). The European Concerted Action Polypl Prevention studies are examining the role of a variety of preventive strategies, including daily dietary supplementation with resistant starch, in high-risk persons with a family history of either familial adenomatous polyposis or hereditary nonpolyposis colon cancer.

PROPOSED MECHANISMS OF ACTION

Several mechanisms by which dietary fiber may protect against colon cancer have been proposed. These mechanisms include both direct and indirect actions on the alimentary and gastrointestinal canals that are related to properties of fiber, such as solubility and fermentability; actions may occur at the physical, chemical, cellular, and/or molecular levels.

One direct mechanism by which fiber may reduce the risk of colorectal cancer is through the absorption of water by insoluble dietary fiber; this action increases fecal bulk, diluting the concentration of carcinogens in the feces, and decreases transit time, reducing the effective interaction of carcinogens with colonic mucosal cells. The direct binding of carcinogens to insoluble dietary fibers, such as wheat bran, cellulose, and lignin, similarly reduces the potential interaction between carcinogens and cells within the bowel. Indirect mechanisms by which dietary fiber may lower colorectal cancer risk include stimulation of microbial growth, which increases fecal bulk and the production of short chain fatty acids (SCFAs); alteration of bile acid production; influence on the production of factors that affect cell proliferation, such as diacylglycerol, p21, and protein kinase C; and reduction of luminal pH, largely as a result in increases in SCFAs, especially butyrate.

Products of fiber fermentation, particularly butyrate, appear to have a beneficial, antineoplastic effect in the bowel. Several studies suggest that, compared with other SCFAs, butyrate most consistently protects against the development of colon tumors in the rat by acting through a variety of mechanisms, including blocking the proliferative action of carcinogens and other cancer-promoting agents such as bile acids, inducing cell differentiation, lowering concentrations of secondary bile acids, reducing the mutagenicity of fecal water, and enhancing programmed cell death (apoptosis) in human colorectal cancer cell lines. Acting at the molecular level, butyrate stimulates histone acetylation by inhibiting the enzyme histone deacetylase, which, in turn, makes certain sections of the DNA molecule more accessible to transcription factors known to control gene expression. The effects of butyrate on histones appear to be through induction of the p21 gene and subsequent production of the p21 protein, which slows the growth of cancer cells. Butyrate also decreases the expression of the transcription factors c-fos and c-jun, acting, in turn, to reduce proliferative activity.

Experimental data show that dietary wheat bran fiber reduces the formation of early markers of colon cancer associated with carcinogen-induced disease, such as the number of aberrant crypts or foci, and alters the colonic environment in several other ways, such as increasing fecal bulk, decreasing transit time, adsorbing to carcinogens, and stimulating the production of butyric acid. In epidemiologic and clinical intervention studies, wheat bran fiber supplementation favorably modified several putative makers of colorectal cancer, including fecal mutagenicity, concentrations of total and secondary fecal bile acids, the activity of bacterial enzymes associated with the production of carcinogenic substances, and rectal proliferation in high-risk individuals.
PROPOSED MECHANISMS

One possible role for dietary fiber in differential risk for cancers in the proximal versus distal colon is suggested primarily from animal studies. Soluble fibers, such as guar gum, oat bran, and pectin, are fermented by anaerobic bacteria in the proximal colon, producing large amounts of SCFAs, which are absorbed almost entirely in the proximal colon. In contrast, insoluble and poorly soluble fibers, such as wheat bran, cellulose, and lignin, are fermented along the length of the gut, providing a more continuous supply of SCFAs throughout the intestine, which, in turn, assists in maintaining normal colonicocyte proliferation and differentiation. Such fiber-related maintenance of normal cell function and activity likely contributes to the inhibition of tumors in the distal colon in rats fed wheat bran compared with other fiber sources, such as oat bran.

Results of dietary epidemiologic studies have not consistently found similar associations. One case-control study found no difference in risk of cancers of the right colon, transverse and descending colon, sigmoid colon, rectosigmoid junction, or rectum according to total fiber intake. Another case-control study reported the strongest inverse associations between consumption of dietary fiber, whole grains, and vegetables and risk of proximal tumors in both men and women; and between soluble fiber, insoluble fiber, and pectin intake and risk of proximal tumors in women. In contrast, a prospective study of 16,448 men from the Health Professionals Follow-up Study reported a reduced risk of distal colon adenoma as intake of fiber from fruit increased (P < .03 for trend) and an inverse association between soluble, but not insoluble, fiber intake and distal colon adenoma (P for trend, .007). This study did not examine or compare associations according to other intestinal subites.

Dietary fiber and calcium: Potential interactions

An association between dietary calcium or calcium supplementation and reduced colorectal cancer risk has been suggested from the results of epidemiologic, clinical, and experimental research studies. Mechanisms by which calcium may inhibit colorectal carcinogenesis are similar to those of dietary fiber and include the ability of calcium to bind potentially carcinogenic compounds, such as secondary bile acids; slow proliferation of colonic epithelial cells; and enhance cell differentiation. These effects of calcium have been reported in both animal and human studies and in vitro experiments. Animal experiments further suggest that calcium and fiber may act synergistically in their effect on the colonic environment.

The roles of calcium and fiber on markers for colorectal cancer risk are being studied in several clinical trials. The multicenter European Cancer Prevention Calcium Fibre Polyp Prevention Study is testing the efficacy of oral calcium (2 g/d) or oral dietary fiber supplements (as 3.8 g ispaghula husk, a mucilaginous substance) on adenoma recurrence, colonic cell proliferation, and stool concentration. Participants include patients from nine European countries who are between 35 and 75 years old at study entry and have at least two adenomas greater than 5 mm in diameter. Preliminary results of another clinical trial showed that high doses of wheat bran fiber (13.5 g/d) or calcium (1500 mg/d), or high doses of fiber plus high doses of calcium, increased both fecal bile acid concentrations and excretion rates. The strongest statistical effect, reflecting an approximate 50% reduction in fecal concentrations of total bile acids and deoxycholic acid, was seen in the high-fiber group. The effect of the combined high-fiber and high-calcium diet on mean fecal bile acid parameters was less than that for either factor alone; the reason for this lack of additivity between the two supplements is not clear but may be caused by cross-interference with each agent's putative effects on bile acids. A subsequent analysis of the same study reported that neither level of wheat bran fiber or calcium supplementation significantly reduced [3H]thymidine labeling index percentages in rectal mucosal crypts. These preliminary findings suggest that a primary mechanism by which wheat bran fiber and calcium may protect against colon cancer is through reducing fecal bile acid concentrations.

Ongoing national cancer institute clinical trials

The National Cancer Institute (NCI) is evaluating the role of dietary fiber in the prevention of colorectal cancer in humans through several clinical trials. The Polyp Prevention Trial, for example, allows for the simultaneous investigation of the effect of three dietary components on recurrence of polyps in the large bowel. Polyp Prevention Trial study participants include men and women at least 35 years old who have had one or more adenomas removed within 3 months of randomization. The primary objective of the Polyp Prevention Trial is to determine whether a diet that is low in fat (20% of calories from fat), high in fiber (18 g/1000 calories), and high in vegetable and fruit intake (five to eight daily servings) will decrease the recurrence of large bowel polyps. The trial also is evaluating the relationship between dietary modification and biochemical markers in the blood and validating promising intermediate endpoint markers of large bowel carcinogenesis with respect to polyp recurrence.

Another NCI-supported study, the Women's Health Initiative Clinical Trial and Observational Study, is investigating several strategies for the prevention and control of cancer, cardiovascular disease, and osteoporotic fractures in postmenopausal women 50 to 79 years old. The Clinical Trial, which anticipates an enrollment of 64,500 participants, is randomized, controlled evaluation of three interventions: (1) a goal of a low-fat (20% of calories) eating pattern that includes at least five servings of vegetables and fruits and six or more servings of grain products per day, hypothesized to prevent breast cancer and colorectal cancer and, secondarily, coronary heart disease; (2) hormone replacement therapy; and (3) calcium (1000 mg/d) and vitamin D3 (400 IU/d) supplementation (or placebo), hypothesized to prevent hip fractures and, secondarily, other fractures and colorectal cancer. A prospective surveillance (the Observational Study) will enroll an additional 100,000 women to identify new etiologic factors and biologic predictors of disease and community-based interventions. The Women's Health Initiative was initiated in 1992 and is scheduled to end in 2007.

The double-blind, placebo-controlled Arizona Phase III cancer prevention trial, also funded by NCI, is examining how supplementing the diet with large versus small doses of wheat bran fiber (13.5 vs. 2.0 g/d) alters the molecular genetics of polyp tissue in patients with previously resected adenomatous colon polyps. Genetic changes will be compared with dietary factors and bile acid profiles. Approximately 945 participants have fulfilled all aspects of the study protocol in this 3-year dietary intervention, which is nearing completion.

Dietary fiber and breast cancer

Summary of epidemiologic and experimental research

Evidence from both epidemiologic and experimental studies suggests a protective role for fiber in the prevention of breast cancer, although the exact role of fiber on breast cancer development is not yet clear. One review, a metaanalysis of the original data from 12 case-control studies of populations with widely varying breast cancer risks and dietary habits, reported a significant reduction in breast cancer risk among women in the highest versus lowest quintiles of fiber intake, both before and after adjusting for fat intake. A more recent review found that four of four ecological studies and nine of ten case-control studies showed an inverse correlation between either cereal consumption or fiber intake and breast cancer risk; in the five case-control studies reporting a statistically significant decrease in breast cancer risk among women consuming a high-fiber diet, the odds ratios ranged from 0.46 to 0.60. All four prospective cohort studies included in this review reported either no change in breast cancer risk or a nonsignificant decrease in risk in association with cereal or fiber intake. The combination of a high-fiber, low-fat diet also has been associated with reduced risk for breast cancer, with evidence from both epidemiologic and animal studies suggesting that the proposed protective effect of fiber may occur independently of dietary fat content. It also has been postulated that a high-fiber diet may modulate the risk of breast cancer associated with a high-fat diet. Experiments in rats support the hypotheses that dietary fiber, including wheat bran and psyllium, protects against breast cancer and that dietary fiber may block the promotion of mammary tumors by fat.

Proposed mechanisms
Results indicate that reproductive hormones, especially estrogens, are involved in the development of breast cancer. The mechanisms by which fiber alters hormone production, metabolism, and bioavailability focus on the ability of fiber to bind estrogen in the small intestine, thereby both increasing the excretion and reducing the enterohpatic circulation of hormones. And on the biologic activity of phytoestrogens, compounds present in fiber-rich foods that possess weak estrogenic and antiestrogenic activity.

High-fiber intake and diets rich in legumes and whole grains in the diet significantly reduce breast cancer risk. The mechanisms by which fiber alters breast cancer risk include the following:

1. Inhibiting the proliferation of human breast cancer cells that require estrogen to replicate.
2. Increasing the excretion and reducing the bioavailability of both estrogens and androgens in the body.
3. Inducing the production of sex-hormone binding globulin.
4. Modulating the activity of estrogen and androgen receptors.

Dietary phytoestrogens (i.e., isoflavonoids and plant lignans) are found in a variety of high-fiber foods such as fruits, berries, seeds, soy products, and vegetables. Two common isoflavonoids are genistein and daidzein; two mammalian lignans, enterolactone and enterodiol, are formed from plant lignans by the action of intestinal bacteria. Urinary concentrations of these lignans have been found to correlate directly with consumption of foods containing phytoestrogens. A review of 26 animal studies in which the animals’ diets were supplemented with soy or soybean isoflavonoids found a cancer-protective effect in 65% of the studies, as reflected by reductions in tumor incidence, latency, or number. Results of both in vitro and in vivo animal studies suggest that phytoestrogens mimic the activity of estrogen in inhibiting the growth of estrogen-dependent cancer cells. Although the affinity of phytoestrogens to estrogen receptors is tens of thousands of times lower than that of endogenous estrogens, the ability of these plant-based compounds to bind to estrogen receptors permits a dual, dose-dependent effect on mammary tumor initiation and growth. At lower doses, in vitro experiments show that phytoestrogens can increase the mitogenic activity of breast cancer cells. In contrast, higher doses of phytoestrogens inhibit mammary tumor development, suppress the growth of established tumors, and inhibit the growth of hormone-dependent breast cancer cells.

Dietary fiber may protect against these alimentary canal cancers through many of the same mechanisms suggested for the modulation of colorectal cancer risk and influence risk of these hormone-dependent cancers by affecting the bioavailability of both estrogens and androgens.

PUBLIC HEALTH IMPLICATIONS

In addition to its proposed protective effects against colorectal cancer, breast cancer, and possibly other cancers, dietary fiber as total fiber, whole grains, cereal fiber, soluble fiber, and fiber-rich foods, psyllium, or dietary flavonoids has been associated with reduced risk of other conditions important to public health, including cardiovascular diseases, and type II diabetes. Because of the significant health benefits afforded by fiber-rich foods, individuals and the public are encouraged to consume a diet that includes a wide variety of vegetables, fruits, and whole grains, with a goal of meeting the NCI’s recommended 20 to 30 g of fiber per day. Results of the 1992 National Health Interview Survey, cosponsored by the Census Bureau, the National Center for Health Statistics, and the NCI, indicate that adult Americans consume an average of 10.4 g of fiber per day. The U.S. Department of Agriculture’s (USDA) Nationwide Food Consumption Survey found a higher overall consumption rate for fiber among American adults, with a mean intake of 14 g. Although these values are below the recommended intake levels, it is encouraging that fiber intake increased among all Americans and in all subgroups in the National Health Interview Survey between 1987 and 1992 and among all surveyed in the USDA’s Continuing Survey of Food Intake by Individuals between 1989 through 1991 and 1994.

Several national programs have been instituted to increase fiber intake and consumption of fiber-rich foods and vegetables. For example, the 5 A Day for Better Health Program, sponsored by the NCI in partnership with the Produce for Better Health Foundation, includes retail, community, and research components as well as a national media campaign that encourages Americans to eat five or more servings of vegetables and fruits each day as part of a low-fat, high-fiber diet. The USDA’s Food Guide Pyramid suggests that fiber-containing breads and grains, followed by vegetables and fruits, should form the foundation of an individual’s diet. Recommended are 6 to 11 servings of breads and grains per day, 2 to 4 servings of vegetables, and 2 to 4 servings of fruits per day. The 1989 through 1991 USDA Continuing Survey of Food Intakes in Individuals found that, overall, Americans met the minimum basic recommended intakes for breads and grains (mean, 5.7 servings per day) and vegetables (mean, 3.3 servings per day), but failed to meet the recommended intake for fruits (mean, 1.3 servings per day). The subsequent 1994 USDA survey reported significant (P < 0.005) increases in intakes of vegetables, fruits, and grains when compared with data from the 1989 through 1991 survey. A comprehensive review of seven nationally representative surveys of food and nutrient consumption among Americans similarly reported significant (P < 0.001) increases in per capita intakes of vegetables (19%), fruits (22%), and grain products (47%) during the 24-year period from 1970 to 1994.

To help consumers increase fiber intake, the Food and Drug Administration required fiber content to be included on the nutrition facts panel on food labels. In 1991, the USDA’s 1991 Food Consumption Survey found that, overall, Americans met the minimum basic recommended intakes for breads and grains. The 1991 USDA report indicates that adult Americans consume an average of 10.4 g of fiber per day. The U.S. Department of Agriculture’s (USDA) Nationwide Food Consumption Survey found a higher overall consumption rate for fiber among American adults, with a mean intake of 14 g. Although these values are below the recommended intake levels, it is encouraging that fiber intake increased among all Americans and in all subgroups in the National Health Interview Survey between 1987 and 1992 and among all surveyed in the USDA’s Continuing Survey of Food Intake by Individuals between 1989 through 1991 and 1994.

Cancer research also shows that fiber-containing foods and vegetables, fruits, and whole grains, should be considered as part of a healthy diet. Research indicates that fiber-containing foods and vegetables, fruits, and whole grains should be considered as part of a healthy diet. Research indicates that fiber-containing foods and vegetables, fruits, and whole grains, should be considered as part of a healthy diet. Research indicates that fiber-containing foods and vegetables, fruits, and whole grains, should be considered as part of a healthy diet. Research indicates that fiber-containing foods and vegetables, fruits, and whole grains, should be considered as part of a healthy diet. Research indicates that fiber-containing foods and vegetables, fruits, and whole grains, should be considered as part of a healthy diet.
Cancer chemoprevention can be defined as pharmacologic intervention with specific nutrients or other chemicals to suppress or reverse carcinogenesis and to prevent the development of invasive cancer. Two basic concepts support this cancer control strategy: multistep and field carcinogenesis. Carcinogenesis is a chronic, multistep process characterized by the accumulation of specific genetic and phenotypic alterations that can evolve over a 10- to 20-year period from the first initiating event. The premise of human chemoprevention is that one can intervene (and suppress) at many steps in the carcinogenic process and over many years. Field carcinogenesis is a concept that was first described in the early 1950s in the head and neck site as field cancercization and subsequently found to apply to many epithelial sites. The concept is that patients at high risk for an epithelial cancer have a wide surface area of carcinogenic tissue change that can be detected at the gross (oral premalignant lesions, polyps), microscopic (metaplasia, dysplasia), and molecular (gene loss or amplification) levels. More recent molecular studies detecting profound genetic alterations in histologically normal tissue from high-risk individuals have provided strong support for the field carcinogenesis concept. The implication is that multifocal, genetically distinct premalignant lesions can progress across a broad tissue region. The clinical importance is best illustrated in head and neck squamous cancer, for which both synchronous and metachronous second primary tumors are common. The latter develop at an annual rate of 5% to 7% in prospective studies and account for the principal cause of cancer death in early-stage disease and in long-term survivors of head and neck cancer, regardless of stage of diagnosis of the first cancer. The essence of chemoprevention, then, is intervention within the multistep carcinogenic process and throughout a wide field.

To date, retinoids (the natural derivatives and synthetic analogues of vitamin A) and one member of the carotenoid class, β-carotene, are among the best-studied agents in human chemoprevention. This review focuses on these compounds, with a brief discussion of other micronutrients that have often been evaluated for chemopreventive efficacy along with the retinoids and carotenoids, namely vitamins E and C and the trace mineral selenium.

**HISTORICAL PERSPECTIVE**

Vitamin A was first recognized as an essential nutrient in 1913 and has been the subject of considerable research in the ensuing years. In 1925, Wolbach and Howe described the histopathologic changes in epithelia associated with vitamin A deficiency. This led to the identification of retinol and some of its naturally occurring retinoid derivatives (see Fig. 23.3-1) and a large body of research aimed at understanding the role of vitamin A and retinoids in cellular differentiation and in neoplastic transformation. Epidemiologic studies of vitamin A and cancer began to emerge in the 1970s, when it was shown that computed indices of total vitamin A intake were associated significantly with lower cancer risk, particularly for lung cancer.

Vitamin A is a nonspecific term embracing two families of dietary factors: preformed vitamin A (chiefly retinyl esters, but also retinol and retinal) and the other family consisting of the various provitamin A carotenoids (β-carotene and those other carotenoids that can be metabolic precursors of retinol). Preformed vitamin A is found predominantly in foods of animal origin, whereas provitamin A carotenoids are found predominantly in fruits and vegetables.

Epidemiologic studies conducted in the 1980s and 1990s evaluated the independent associations of preformed retinol and provitamin A carotenoids with cancer in humans. Dietary intake of provitamin A carotenoids, such as β-carotene, but not of retinol, was associated with a lower risk of cancer. Interpretation of observational epidemiologic studies is difficult as carotenoids are consumed in the form of fruits and vegetables, which contain numerous other substances, many of which may have cancer preventive properties. In contrast, the primary dietary sources of retinol are animal products, consumption of which tends to be associated positively with cancer risk. Also, blood levels of carotenoids increase with increasing dietary intake, whereas blood levels of retinol are regulated homeostatically. Thus, in evaluating the chemopreventive efficacy of carotenoids and retinoids, one must consider evidence from epidemiologic studies, clinical trials, animal models, and mechanistic considerations. This chapter reviews briefly the biology and pharmacology of retinoids and carotenoids and then focuses on randomized cancer prevention clinical trials involving carotenoids, retinoids, and other selected micronutrients.

**RETINOID BIOLOGY AND PHARMACOLOGY**

Retinoids are required for the maintenance of normal cell growth, differentiation, and loss within epithelial tissues. Various retinoids have been shown to suppress or reverse epithelial carcinogenesis and prevent the development of invasive cancer in many animal systems, including skin, lung, oral cavity, esophagus, bladder,
mammary gland, cervix, stomach, prostate, pancreas, and liver. Retinoids act primarily in the postcarcinogen (postinitiation) phases of promotion and progression, which are most relevant to human cancer chemoprevention. Significant single-agent activity has been observed with natural [e.g., all-trans-retinoic acid (ATRA), 13-cis retinoic acid (13cRA), 9-cis retinoic acid (9cRA), retinyl palmitate] and synthetic [e.g., N-(4-hydroxyphenyl) retinamide or fenretinide (4HPR)] retinoids. Additive or synergistic increases in chemopreventive activity have been achieved by combining retinoids with other agents, such as the combination of 4HPR or 9cRA with tamoxifen in mammary carcinogenesis systems.

The term retinoid was redefined in 1985 by Sporn and Roberts to include a substance that binds and activates one or more specific receptors, the latter producing a biologic response. Much has been learned about the specific receptors and mechanisms of action for the retinoids. The retinoid molecular mechanism of action is similar to that of steroid/thyroid hormones in that retinoid nuclear receptors are members of the steroid receptor superfamily. These elusive nuclear receptors were discovered simultaneously by two groups of investigators and reported in 1987. The subsequent studies indicate that retinoid receptors are unique from other members of the steroid receptor family in that there are two receptor classes, RARs and RXRs. Each receptor contains a, b, and g subtypes, and several of these subclases have multiple isoforms. These receptors are DNA-binding transcription factors that can activate or suppress the expression of many genes, the products of which mediate retinoid effects on cell growth, differentiation, and apoptosis. Different retinoids bind to the different receptor classes and subclasses with different affinities. This receptor complexity and great diversity in ligand binding, activation, and receptor function has important preventive and therapeutic implications.

As with other members of the steroid family, retinoid receptors are active only as dimers. Two retinoid receptor dimer types have been identified. RAR-RXR heterodimers, and RXR-RXR homodimers (RAR-RAR homodimers have not been identified). Part of the retinoid receptor binds to the ligand, and part binds to specific DNA sequences (RARE or RXRE) and either induces or suppresses gene transcription. The best characterized pathway involves RAR-RXR heterodimers. RXRs have been shown to form heterodimers with the retinoid receptor family, including the vitamin D receptor and thyroid hormone receptor. RXRs and their ligands, therefore, can modulate the activities of other steroid hormones. The different ligand-binding patterns can be illustrated with the three major natural retinoic acid derivatives, 13cRA, ATRA, and 9cRA, which are found endogenously in human plasma, albeit at low physiologic levels. RARs bind ATRA and 9cRA, and RXRs bind only 9cRA. 13cRA does not bind directly to nuclear receptors, but is rapidly isomerized to ATRA. Ligand binding stabilizes the receptor dimers and activates gene transcription.

The retinoid receptor distribution pattern in normal and neoplastic human tissue is under intense study. The tissue distribution of these receptor classes, subclasses, and isoforms varies greatly in normal and pathologic conditions and in different sites within the human body. In normal tissue, RAR-a is expressed in most tissues, RAR-b expression is more limited (e.g., not expressed in the skin), and RAR-g is expressed predominantly in the skin. In cancer, these normal tissue patterns can change (e.g., RAR-b is lost in aerodigestive tract carcinogenic progression).

More than 1000 retinoids have been synthesized. Current intensive efforts to develop more active and less toxic retinoids for cancer prevention and therapy are directed to the study of which retinoid receptors mediate retinoid effects on cell growth, differentiation, and apoptosis in different systems and the synthesis of more selective ligands to obtain the desired retinoid pharmacologic effect. An exciting development for chemoprevention is the finding that certain retinoids can interfere with the activity of certain transcription factors such as AP-1 and, therefore, inhibit neoplastic cell proliferation. Mechanistic studies of retinoid pharmacology provide a basis for rational retinoid development programs for chemoprevention.

**CAROTENOID BIOLOGY AND ACTIONS**

As described by Krinsky, carotenoids have both biologic functions and actions. Carotenoids function as accessory pigments in photosynthesis, via singlet-excited carotenoid; offer protection against photosensitization, via triplet excited carotenoid; and some serve as provitamin A compounds, via central and eccentric cleavage. Mechanisms for these functions are reasonably well characterized. Carotenoids also have been reported to have a number of biologic actions, including antioxidant activity, immunoenhancement, inhibition of mutagenesis and transformation, and regression of premalignant lesions. In contrast to the carotenoid functions, mechanisms of carotenoid action are far from clear. Some of the actions of carotenoids, such as regression of premalignant lesions, are shared by the retinoids, with the potential for a similar mechanism of action. The identification of retinoid cleavage products from carotenoids certainly suggests that retinoids and carotenoids may share not only structural similarities and vitamin A activity, but perhaps other mechanisms of action that are not fully appreciated at present. However, carotenoids and retinoids also have distinct differences in action, the most notable of which includes antioxidant activity.

Many carotenoids including b-carotene have the ability to quench singlet oxygen, a highly reactive form of oxygen. The quenching involves a physical reaction in which the energy of the excited oxygen is transferred to the carotenoid, forming an excited state molecule. Quenching of singlet oxygen is the basis for b-carotene's well-known therapeutic efficacy in erythropoietic protoporphyria, a photosensitivity disorder. The ability of b-carotene and other carotenoids to quench excited oxygen, however, is limited, because the carotenoid itself can be oxidized during the process (auto-oxidation). Burton and Ingold and others have shown that b-carotene auto-oxidation in vitro is dose dependent and dependent on oxygen concentrations.

In addition to singlet oxygen, carotenoids are also thought to quench oxygen free radicals. A relatively large body of literature has linked oxygen free radicals with carcinogenesis, thus there is considerable interest in antioxidant compounds and antioxidant activity as a mechanism for cancer prevention. Despite the focus on antioxidants and cancer and clear evidence of chemopreventive efficacy of b-carotene in some animal carcinogenesis models, it is not clear that antioxidant activity is responsible for the chemoprotective effects observed in the animal studies. For example, b-carotene–induced immunologic enhancement could have a significant role in tumor inhibition by increasing natural killer cells and activating immunoregulatory lymphocytes important in host defense. Various carotenoids have been reported to affect gap junctional communication, related to their ability to up-regulate the expression of the connexin43 gene. This activity was not related to the antioxidant activities of the various carotenoids. Supplementary b-carotene also has been reported to increase the expression of transforming growth factor-b in cervical biopsy specimens. These and other potential mechanisms reviewed elsewhere suggest that it is biologically plausible that carotenoids may have chemopreventive activity, although we know far less about mechanisms of action for the carotenoids than the retinoids.

Given the interest in antioxidant activity as a potential mechanism for chemopreventive effects, it is not surprising that other dietary antioxidants have been studied for chemopreventive efficacy, particularly vitamins E and C and selenium. These agents are often evaluated in combination. However, as is the case with b-carotene, these micronutrients may have biologic actions independent of antioxidant activity.

**CLINICAL TRIALS**

A number of randomized cancer prevention trials involving carotenoids and retinoids and a few of other micronutrients are ongoing or have been completed. Completed trials involving retinoids are summarized in Table 23.3-1 and those involving carotenoids in Table 23.3-2. Retinoid trials have tested efficacy of several retinoids, including retinol, retinyl palmitate, ATRA, 13cRA, etretinate, and 4HPR. Cancer prevention trials with carotenoids, however, are limited to b-carotene at present. The focus on b-carotene, one of more than 600 carotenoids thus far identified, is based on practical considerations: b-carotene has been the only carotenoid that is commercially available in large quantities for which human data supporting safety existed. Several other carotenoids (e.g., lycopene) have been suggested to have chemopreventive efficacy in animal models, but are only beginning to be evaluated in human chemoprevention studies (see New Retinoids and Carotenoids, later in this chapter).
head and neck trials: premalignancy

Oral premalignant lesions include leukoplakias and erythroplakias. Small hyperplastic leukoplakia lesions have a 30% to 40% spontaneous regression rate, and less than a 5% risk of malignant transformation. Erythroplakia and dysplastic leukoplakia lesions, however, are associated with a low rate of spontaneous regression and a 30% to 40% long-term risk of oral cancer. High-risk, diffuse, and multifocal disease, accounting for 10% to 15% of all oral premalignant lesions, is not controlled adequately by local therapy. Oral premalignant lesions are markers of field carcinogenesis, since patients with oral premalignancy develop squamous cancers at the site of the lesions as well as in distant sites within the upper aerodigestive tract. Thus, regression of oral premalignant lesions can be used to screen agents that may have utility in the prevention of upper aerodigestive tract cancers. The frequency of micronuclei (an indicator of genotoxic damage) in exfoliated cells from buccal mucosa is another premalignant end point that has been used in head and neck chemoprevention trials. 0

Studies in the 1980s in populations at high risk of oral cancer (tobacco chewers, betel quid chewers) demonstrated that supplemental b-carotene and retinol significantly reduced the frequency of oral micronuclei. As for premalignant lesions, nine trials have investigated the effects of supplemental b-carotene, alone or in combination with other agents, on regression of oral leukoplakia. Six nonrandomized studies reported response rates ranging from 44% to 97%. The response rates from these uncontrolled studies, however, must be interpreted cautiously for three reasons: (1) leukoplakias can regress spontaneously; (2) varying response criteria were used; and (3) there was no apparent dose-response relationship. Three placebo-controlled trials of b-carotene and oral leukoplakia are available. Stich et al. reported that the combination of b-carotene plus retinol produced complete remissions in 27.5%, b-carotene alone in 14.8%, and placebo in 3.0% of subjects (partial remissions were not reported) with a 6-month intervention. Sankaranarayanan et al. got better response rates with an even longer duration of intervention (12 months), consisting of 33% complete regression with b-carotene and 52% with retinyl palmitate versus 10% in the placebo arm. In a trial in Uzbekistan, 6 months of treatment with the combination of retinol, b-carotene, and vitamin E led to a significant reduction in the prevalence odds ratio of oral leukoplakia (odds ratio = 0.62; 95% confidence interval (CI) = 0.39 to 0.98). The risk of progression or no change versus regression was also reduced by 40% by this intervention, although not statistically significant (odds ratio = 0.60; 95% CI = 0.23 to 1.63). Vitamin E was evaluated by itself in a single-arm trial in oral leukoplakia in which both clinical and histologic responses were observed.

Retinoids have been studied extensively in the reversal of oral premalignant lesions. One of the first such trials, reported in 1986, was a 3-month placebo-controlled study of 13cRA (2 mg/kg/d). The complete plus partial response rate in the 44 evaluable patients was 67% in the retinoid arm and 10% in the placebo arm (P = 0.002). The histopathologic improvement rate (e.g., reversal of dysplasia) was also higher in the retinoid arm (54% vs. 10%, P = 0.01). There were two major problems, however, with this high-dose, short-term approach. First, high-dose 13cRA toxicity was substantial and not acceptable in this clinical setting. Second, over one-half of the responders had recurrences or developed new lesions within 3 months of stopping the intervention.

Based on the results of this placebo-controlled trial, a randomized maintenance trial was designed. In this trial, patients initially received a 3-month induction course of high-dose 13cRA (1.5 mg/kg/d), followed by a 9-month maintenance course with low-dose 13cRA (0.5 mg/kg/d) or b-carotene (30 mg/d) in patients with responding or stable lesions during the high-dose induction phase. The induction-phase response rate was 55% (95% CI = 42% to 67%). During the maintenance phase, 2% of the patients in the retinoid group progressed versus 16% (55%) in the b-carotene group (P < .001). Toxic effects of low-dose 13cRA maintenance therapy were mild, although greater than for b-carotene, with no patients discontinuing therapy because of toxicity.

4HPR, a promising new retinoid, is also being evaluated in oral premalignancy. A randomized study was begun in 1988 at the Milan Cancer Institute to evaluate the efficacy of 52 weeks of systemic 4HPR maintenance therapy (vs. no intervention) after complete laser resection of oral premalignant lesions. The most recent report on this ongoing study included data from 153 randomized patients. A 3-day drug holiday at the end of each month was prescribed to avoid the adverse effects (night blindness) of lowering serum retinol by 4HPR treatment. The rate of treatment failure (recurrence plus new lesion rate) among those patients who completed the 12-month intervention was 6% in the 4HPR group and 30% in the control group.

Two other randomized studies involving retinol and another involving the retinoid N-4-(hydroxycarbophenyl) retinamide (4HCR) have been reported; all observed significant retinoid chemopreventive activity.

head and neck trials: malignancy

There have been only two phase III adjuvant chemoprevention trials of retinoids in head and neck cancer. The first, reported by Hong et al., tested high-dose 13cRA in 103 head and neck cancer patients. Following definitive local therapy of stage I to IV (M0) disease with surgery, radiotherapy, or both, patients were assigned randomly to 12 months of 13cRA (50 to 100 mg/m²/d) or placebo. At a median follow-up of 32 months, there were no significant differences in primary disease recurrence (local, regional, or distant) or survival. The rate of second primary tumors, however, was significantly lower in the retinoid arm than in the placebo group, developing in two (4%) of the 13cRA-treated patients compared with 12 (24%) of the placebo-treated patients (P = .005). More than 70% of second primary tumors occurred in the carcinogen-exposed aerodigestive tract fields of the head and neck, lungs, and esophagus. Side effects were substantial and included skin dryness and peeling, chelitis, conjunctivitis, and hypertri glyceridemia. Approximately 30% of the retinoid-treated patients required dose reduction and 18% did not complete the 12-month intervention because of toxicity.

This trial has been reanalyzed with a longer median follow-up of 55 months. With the additional follow-up, each group had one more second primary tumor in the aerodigestive tract, resulting in a cumulative total of three of the retinoid group and 13 of the placebo group (P = .008).

Based on this high-dose adjuvant trial and the low-dose 13cRA trial in oral premalignancy, a multicenter large-scale phase III National Cancer Institute trial was designed and is ongoing to evaluate low-dose 13cRA as adjuvant chemoprevention in stage I and II head and neck cancer.

The other randomized trial studied the synthetic retinoid etretinate in 316 patients following definitive therapy of stage I to III (T1,2, N0,1) squamous cell carcinoma of the oral cavity and oropharynx. In this French trial, the etretinate dose was 50 mg/d for 1 month, then 25 mg/d for 2 years. The etretinate was well tolerated. At a median follow-up of 41 months, the rate of second primary tumor development in the two arms was not significantly different. The lack of a retinoid effect on second primary tumors in this trial is in contrast to the result of the earlier high-dose 13cRA trial and could be attributable to differences in the patient populations and differing dose levels. A more likely reason for the difference, however, involves the pharmacokinetics and mechanisms of action of the two retinoids studied. 13cRA leads to transcriptional activation via rapid isomerization to ATRA. In contrast, etretinate is known not to be transcriptionally active and is not known to isomerize to ATRA or...
LUNG TRIALS: PREMALIGNANCY

The Tyler (Texas) Chemoprevention Trial randomized 755 asbestos workers to receive b-carotene (50 mg/d) and retinol (25,000 IU every other day) versus placebo, to see if the nutrient combination could reduce the prevalence of atypical cells in sputum. After a mean intervention period of 58 months, there was no difference in the two groups in the prevalence of sputum atypia. In another randomized, placebo-controlled trial, 14 weeks of supplemental b-carotene (20 mg/d) significantly reduced microround cells in sputum from heavy smokers. b-Carotene was not found, however, to reduce oxidative damage as measured by urinary excretion of 8-oxo-7, 8-dihydro-2'-deoxyguanosine, suggesting that antioxidant activity was not responsible for the reduction in micronuclei.

In a French trial, chronic smokers with squamous metaplasia of the bronchial epithelium detected in initial bronchoscopy specimens were treated with etretinate (25 mg/d) for 6 months. In this uncontrolled trial, a decline in the extent of squamous metaplasia was observed in most treated patients. The positive result of this French study has been confirmed in trials in the U.S. and Japan. One of 4HPR in Chinese patients with squamous cell carcinoma of the lung who were randomized to receive either supplemental b-carotene (20 mg/d), a-tocopherol (50 mg/d), the combination, or placebo for 5 to 8 years. Unexpectedly, participants receiving b-carotene (alone or in combination with a-tocopherol) had a statistically significant 18% increase in lung cancer incidence (relative risk [RR] = 1.18; 95% CI = 1.03 to 1.36) and a 38% increase in total mortality (relative risk [RR] = 1.08; 95% CI = 1.01 to 1.16) relative to participants receiving placebo. Supplemental b-carotene did not appear to affect the incidence of other major cancers occurring in this population. Although not the primary outcome of this trial, an interesting observation was made with regard to vitamin E and prostate cancer: Men randomized to receive a-tocopherol had a 32% decrease in prostate cancer incidence and a 41% decrease in prostate cancer mortality. This promising finding will be followed up in future trials (see Conclusions, later in this chapter).

The finding of an increased incidence of lung cancer in b-carotene–supplemented smokers was apparently replicated in another major trial. The Carotene and Retinol Efficacy Trial was a multicenter lung cancer prevention trial of supplemental b-carotene (30 mg/d) plus retinol (25,000 IU/d) versus placebo in asbestos workers and smokers. The Carotene and Retinol Efficacy Trial was terminated nearly 2 years early in January 1996, because interim analyses of the data indicated that should the trial have continued for its planned duration, it is highly unlikely that the intervention would have been found to be beneficial. Furthermore, the interim results indicated that the supplemented group was developing more lung cancer, not less, consistent with the results of the Finnish trial. Overall, lung cancer incidence was increased by 28% in the supplemented subjects (RR = 1.28; 95% CI = 1.04 to 1.57) and total mortality was also increased (RR = 1.17; 95% CI = 1.03 to 1.33). The increase in lung cancer following supplementation with b-carotene and retinol was observed for current but not former smokers. Major findings of one additional trial, the Physicians’ Health Study of supplemental b-carotene versus placebo in 22,071 male U.S. physicians, are also now available. There was no significant effect, positive or negative, of 12 years of supplementation of b-carotene (50 mg every other day) on total cancer, lung cancer, or cardiovascular disease. The relative risk for lung cancer in current smokers randomized to b-carotene was 0.90 (95% CI = 0.58 to 1.40). Among nonsmokers, the relative risk was 0.78 (95% CI = 0.34 to 1.79). The lack of a significant effect of long-term supplementation of b-carotene on lung cancer incidence, even in baseline smokers who took the supplements for up to 12 years, is noteworthy and is discussed further here. A similar lack of effect of supplemental b-carotene on overall cancer incidence was seen in the Women’s Health Study, although the duration of intervention was short (median, 2.1 years).

In contrast, more encouraging results for lung cancer prevention come from an esophageal and gastric cancer prevention trial in China (see Esophagus and Stomach Trials, later in this chapter). The relative risk of death from lung cancer was 0.55 (95% CI = 0.26 to 1.14) among those receiving the combination of b-carotene, a-tocopherol, and selenium. However, this result is not statistically significant, based on only 31 total lung cancer deaths.

A clear mechanism to explain the apparent enhancement of lung carcinogenesis by supplemental b-carotene, alone or in combination with retinol, in smokers has yet to emerge. As detailed elsewhere, it should be noted that the two trials that observed this enhancing effect had higher median plasma b-carotene concentrations in their intervention groups than did the trials that did not observe this enhancing effect. Thus, it is possible that high tissue concentrations of b-carotene in the presence of strongly oxidative tobacco smoke cause an interaction that affects carcinogenesis. Wang et al. have used the ferret to model b-carotene/tobacco interactions in lung and noted a relative lack of both retinolic acid and RAR-b expression in the lung of smoke-exposed ferrets given high-dose b-carotene. The authors suggested that oxidative metabolites of b-carotene might cause diminished retinoid signaling and thus increase tumorigenesis. Other groups are also studying b-carotene oxidation products, for example Salgo et al. reported that under some conditions b-carotene oxidation products, but not 13cRA, enhanced binding of cytochrome P-450-catalyzed metabolites of benzo[a]pyrene to DNA. While mechanistic studies continue, it is prudent to recommend that heavy smokers, particularly those with well-nourished populations, should avoid high-dose supplements of b-carotene for lung cancer chemoprevention.

Retinoids have not been tested as single agents in primary prevention trials of lung cancer; however, one trial of retinyl palmitate in adjuvant chemoprevention of lung cancer has been reported. In a phase I trial conducted by NCI (1986–1991), 452 males with non– small-cell lung cancer (n = 307) were assigned randomly to treatment with retinyl palmitate (300,000 IU) for 1 year of observation. At a median follow-up of 46 months, survival trends favored retinyl palmitate over no therapy in estimated 5-year-disease-free survival (64% vs. 51%, P = .054) and overall survival (62% vs. 54%, P = .44). Eighteen patients in the retinyl palmitate arm developed a second primary tumor compared with 29 patients developing 33 second primaries in the control group. Reduction of tobacco-associated second primary tumors was more pronounced. At a median follow-up of 46 months, tobacco-associated second primary tumors developed in 13 patients in the retinyl palmitate arm compared with 25 control patients. The time to development of tobacco-related second primary tumors also favored the retinyl palmitate arm (P = .045). Retinyl palmitate toxicity was frequent, occurring in the majority of treated patients; however, more than 80% of patients maintained regular drug intake during the first 12 months, indicating that the intervention was tolerable.

Based on the encouraging second primary tumor results and retinoid activity in related carcinogenic systems, two large-scale phase III retinoid trials were implemented in the second primary tumor prevention. One of these trials, called Euroscan, has been completed in Europe. Euroscan was an open-label multicenter trial designed to demonstrate a two-by-two factorial design to test 2 years of retinyl palmitate and N-acetylcysteine in preventing secondary primary tumors in 2582 patients. Patients had completed definitive therapy of early-stage head and neck cancer (larynx, Tis, T1 to 3, N0 to 1; oral cavity T1 to 2, N0 to 1) and non– small-cell lung cancer (T1 to 2, N0 to 1, and T3, N0). Retinyl palmitate, N-acetylcysteine, or both produced no improvement in event-free survival, survival, or incidence of second primary tumors. The other related trial is still ongoing in the United States. This is a multicenter trial (intergroup NCi 191-0001) of low-dose isoretinoxin to prevent second primary tumors after definitive therapy of stage I non–small-cell lung cancer. Currently, new phase III chemoprevention trials in the non–small cell and small cell lung cancer settings are being designed. In addition, new retinoid formulations and delivery systems (e.g., aerosolized) and potential secondary lung benefits...
BREAST TRIALS

The retinamide 4HPR is a potent apoptosis-inducing retinoid with retinoid receptor-dependent and receptor-independent activities. Moon and colleagues first showed that 4HPR was among the most active cancer chemopreventive agents for the breast, having a high therapeutic index and synergistic interaction with tamoxifen in mammary carcinogenesis model studies. This laboratory work led to a large-scale randomized trial of 4HPR (vs. no treatment) for 5 years to prevent contralateral breast cancer in women aged 30 to 70 years with a history of resected early breast cancer and no prior adjuvant therapy. The intervention produced no significant overall effect. Subset analyses suggested that reduced contralateral and ipsilateral breast cancer rates occurred in premenopausal women. Promising new retinoids for breast cancer prevention include other potent apoptosis-inducing retinoids and RAR-subtype-selective, RXR-selective, and anti-AP1 retinoids.

As for b-carotene, observational data have suggested that higher intake of b-carotene from foods is an important prognostic factor in breast cancer. Given this, randomized trials aimed at increasing vegetable intake to prevent breast cancer recurrence are under way. These interventions clearly influence circulating carotenoid concentrations and illustrate a food-based approach to investigate potential chemopreventive efficacy.

SKIN TRIALS

Data suggest that topical ATRA has significant dose-related activity in reversing premalignant skin lesions (e.g., actinic keratoses, which undergo a malignant transformation rate of 5%). Systemic retinoid therapy has produced significant activity in the two reported randomized trials. Several small, single-arm studies have found that 13cRA and etretinate can reduce skin cancer incidence significantly in high-risk patients with xeroderma pigmentosum (XP) and in renal transplant recipients, respectively.

The XP trial, published in 1988, was a landmark trial for the field of chemoprevention in general in that it was the first human trial to establish a significant reduction in tumor development. Although including only five XP patients, the extremely high rate of skin cancer development and rigorous documentation of skin tumor rates before, during, and after the 2-year high-dose (2 mg/kg/day) 13cRA intervention provided statistically valid results. The overall average reduction in skin cancer incidence during therapy was 83% (P < .019). Two major problems were evident from this trial: Severe, acute mucocutaneous toxicity occurred with this high 13cRA dose, and the preventive effect of the retinoid was lost after stopping retinoid therapy, as indicated by a mean 8.5-fold increase in the annual rate of skin tumor development (P < .007). The retinoid chemopreventive effect in this study was greatest in the XP patients with the highest frequency of new skin tumor development, and, in subsequent studies, was found to be dose related.

Based on positive single-arm retinoid data, a randomized, placebo-controlled trial of the retinoid acitretin (30 mg/d for 6 months) was conducted in 38 renal transplant recipients. The retinoid group had significant reductions in (1) premalignant lesions (P = .008); (2) the number of patients with skin cancer (P = .01); and (3) the number of skin cancers (P = .009). Nine of the 19 placebo patients developed a total of 18 skin cancers and 2 of the 19 retinoid patients developed skin cancer, one each. After completing the intervention, the rate of skin cancer incidence in the retinoid arm increased and became similar to that of the placebo arm. Toxicity in the retinoid group was frequent but mild in degree, and the retinoid had no adverse effect on renal function.

Greenberg and colleagues conducted a large randomized clinical trial of supplemental b-carotene (50 mg/d for 5 years) in 1805 persons with a previous nonmelanoma skin cancer. There was no difference between the two groups in the rate of occurrence of the first new nonmelanoma skin cancer (RR = 1.05; 95% CI = 0.91 to 1.22).

Selenium is another nutrient that has been evaluated for efficacy in the prevention of second skin cancers. Clark et al. randomized a total of 1312 patients with a history of nonmelanoma skin cancer to 200 mg selenium per day or placebo. Selenium did not affect the incidence of second skin cancers (RR = 1.10 for basal cell carcinoma and RR = 1.14 for squamous cell carcinoma). However, there was a significant reduction in total cancer mortality (RR = 0.50; 95% CI = 0.31 to 0.80), mainly due to reductions in incident lung, colorectal, and prostate cancers. Other selenium trials are now getting under way (see Controversies, later in this chapter), given these promising results.

BLADDER TRIALS

Data from in vivo animal, in vitro, and epidemiologic studies suggested efficacy of retinoids for bladder cancer prevention. Three randomized clinical trials have tested the retinoid etretinate in patients following resection of their superficial (noninvasive) bladder tumors, which recur in 40% to 90% of cases. All three studies were limited substantially because of mucocutaneous toxicity. However, in two of the three trials, prolonged (greater than 1 year) low-dose etretinate (25 mg/d) apparently was effective. These positive results require a cautious reading, because of small patient numbers and short-term follow-up.

Another chemoprevention trial randomized 65 patients with biopsy-confirmed transitional cell carcinoma of the bladder to a multivitamin (recommended dietary allowance levels) alone or supplemented with 40,000 IU of retinol, 100 mg of pyridoxine, 2000 mg of ascorbic acid, 400 IU of a-tocopherol, and 90 mg of zinc. The 5-year estimate of tumor recurrence was 91% in the recommended dietary allowance arm versus 41% in the megadose arm (P = .0014). These results are promising in that the intervention was essentially nontoxic, with only one patient (3%) requiring dose reduction for mild stomach upset. Further research is needed to identify which vitamin(s) were responsible for chemopreventive efficacy.

Studies in the bladder of newer synthetic retinoids with better therapeutic ratios are also anticipated. One such leading candidate is 4HPR, which tests as one of the strongest anticarcinogenic retinoids in the rodent bladder, is less toxic than either etretinate or isotretinoin in humans, and has produced promising results in a phase IIa trial.

CERVICAL TRIALS

Many randomized and nonrandomized chemoprevention studies have been conducted in cervical dysplasia. Randomized trials include two studies of folic acid, four of interferons, three of b-carotene, and one of ATRA. Only one of these trials, using topical ATRA, found a significant treatment effect. Three hundred one patients with moderate (cervical intraepithelial neoplasia 2) and severe (cervical intraepithelial neoplasia 3) dysplasia were randomly assigned to topical ATRA versus placebo. This trial administered a 0.372% b-ATRA solution by collagen sponge in a cervical cap delivery system for 4 days initially, then for 2 days at months 3 and 6. Patients were evaluated by serial colposcopy, Pap cytology, and cervical biopsy. The ATRA dose, schedule, and delivery system were determined by prior single-arm phase I and II studies. The major finding was a higher complete response rate (43%) than in the placebo group (27%, P = .041) among the 141 patients with moderate dysplasia. No significant differences in dysplasia regression rates between the two study arms were detected in patients with severe dysplasia. Acute toxicity was infrequent, mild, and reversible consisting primarily of local (vaginal and vulvar) irritation occurring in less than 5% of treated subjects. Major problems with compliance (e.g., 52 patients lost to follow-up), however, have limited somewhat the interpretation of this trial.

Three randomized trials involving b-carotene have been published. The first was a trial from the Netherlands that randomized women with a histologic diagnosis of cervical dysplasia to either 10 mg of b-carotene per day for 3 months or placebo. After 3 months of intervention, there was no detectable effect of supplemental b-carotene on the regression and progression of cervical dysplasia. Romney et al. randomized women with cervical dysplasia to 30 mg of b-carotene per day (n = 38) or placebo (n = 30). After 9 months of intervention, there was no beneficial effect of b-carotene supplementation. An Australian trial used a factorial design to investigate the effects of supplemental b-carotene (30 mg/d) or vitamin C (500 mg/d) in 141 women with minor cervical abnormalities. There was no significant effect of either agent in this trial. In contrast are results from a nonrandomized phase II intervention trial of cervical dysplasia that reported a striking 70% response rate following 6 months of supplementation with 30 mg of b-carotene per day. The results of the randomized trials suggest that this impressive response rate may.
reflect spontaneous regression rather than an effect of the b-carotene.

**ESOPHAGUS AND STOMACH TRAILS**

Certain regions of China (Huixian and Linxian) have strikingly high incidence rates of esophageal and gastric cancers; moreover, intake and blood levels of various micronutrients are consistently low in these populations. These observations have led to three esophageal and esophagostestinal cancer prevention trials in China. 

The first was in high-risk Chinese subjects from Huixian and tested the combination of retinol, riboflavin, and zinc for 13.5 months. After the intervention, there was no overall difference between the two arms in the occurrence of premalignant lesions or the prevalence or severity of dysplasia. However, esophageal (but not oral) mucosal frequency decreased in the intervention arm.

Two more recent trials were done in Linxian county. The first trial was conducted in residents from the general population. Nearly 30,000 men and women aged 40 to 69 took part in the study, which tested the efficacy of four different nutrient combinations at inhibiting the development of esophageal and gastric cancers. The nutrient combinations included retinol plus zinc, riboflavin plus niacin, ascorbic acid plus molybdenum, and the combination of b-carotene, selenium, and a-tocopherol. After a 5-year intervention period, those who were given the combination of b-carotene, vitamins E and selenium had a 13% reduction in total cancer deaths (RR = 0.87; 95% CI = 0.75 to 1.00), a 4% reduction in esophageal cancer deaths (RR = 0.96; 95% CI = 0.78 to 1.18), and a 21% reduction in gastric cancer deaths (RR = 0.79; 95% CI = 0.64 to 0.99). None of the other nutrient combinations reduced gastric or esophageal cancer death significantly in this trial. The finding that b-carotene reduced cancer deaths supports the conclusion that cancer prevention via nutrients; however, the applicability of these results for populations with adequate nutritional status and for other tumor sites may be limited. Also, it is unclear which nutrient(s) (b-carotene, vitamin E, or selenium) was responsible for the observed protection. It is of interest that selenium was not deficient in this population.

The other Linxian trial was done to determine whether a multivitamin and mineral preparation plus b-carotene (15 mg) reduced esophageal and gastric cancer in 3318 residents with esophageal dysplasia. Cumulative esophageal and gastric cancer death rates after the 6-year intervention period were 8% lower (RR = 0.92; 95% CI = 0.67 to 1.28), esophageal cancer mortality was 16% lower (RR = 0.84; 95% CI = 0.54 to 1.29), and total cancer mortality was 4% lower (RR = 0.96; 95% CI = 0.71 to 1.29) in the supplemented group. Surprisingly, stomach cancer mortality was 18% higher (RR = 1.18; 95% CI = 0.76 to 1.85) in the supplemented group. None of the results were statistically significant.

Repeat endoscopic surveys were carried out 2 and 6 years after randomization in a subsample of participants in the dysplasia trial. At baseline (1983, 2 years before randomization), all of the subjects had a cytologic diagnosis of dysplasia (98% squamous). In the 1987 survey (n = 768), 61.3% of the participants who were endoscoped and on the active arm were found to have normal cytology, compared with 57.6% of those on the placebo arm. In the 1991 survey (n = 396), 17.8% of the participants who were endoscoped and on the active arm were found to have normal cytology, compared with 20.6% on the placebo arm. The striking degree of apparent regression observed in the placebo arm, particularly in the 1987 survey, again underscores the importance of placebo controls in trials of intermediate endpoints.

In addition to the Chinese trials, a trial from Uzbekistan used a factorial design to study the combination of b-carotene, retinol, and a-tocopherol, with and without riboflavin, in subjects with chronic esophagitis. The risk of progression or no change versus regression was nonsignificantly decreased by 34% in those receiving retinol, b-carotene, and a-tocopherol (OR = 0.66; 95% CI = 0.37 to 1.16) versus those who did not receive these agents.

**COLORECTAL TRIALS**

Three randomized trials aimed at the prevention of recurrent colorectal adenomas with supplemental b-carotene have been completed. The largest trial studied 751 patients who had an adenoma diagnosed and removed within the previous 3 years. Participants were randomized using a two-by-two factorial design, with the active treatments being b-carotene (25 mg/d), and the combination of 1 g of vitamin C plus 400 mg of vitamin E. There was no evidence that either b-carotene or vitamins C and E reduced the incidence of adenomas in this 4-year trial. The relative risk for b-carotene was 1.01 (95% CI = 0.85 to 1.20), for vitamin C and E it was 1.05 (95% CI = 0.87 to 1.26), and for the combination it was 1.29 (95% CI = 1.04 to 1.29). The Australian PolyPrevention Project evaluated the efficacy of reducing dietary fat to 25% of total calories, and supplementing the diet with 25 g of wheat bran, 20 mg of b-carotene, or both daily, in a factorial design. b-Carotene did not reduce the incidence of adenomas; at 24 months 50% of patients on the b-carotene arm had adenomas versus 36% patients on the placebo arm. However, patients taking b-carotene had a statistically significantly lower proportion of positive nuclei in the upper rectal crypt compartments than those taking placebo, suggesting that b-carotene modified preneoplastic mucosal proliferation rather than adenoma growth. Another trial (n = 291) using a lower dose of 15 mg of b-carotene per day also failed to see a reduction in adenomas with supplementation.

**TRANSLATIONAL AND INTERMEDIATE END POINT STUDIES IN RETINOID CHEMOPREVENTION**

Clinical-laboratory translational research is critical for developing new and better chemopreventive agents and for moving them more quickly into standard care; the oral premalignancy model appears to be an excellent model for translational studies. Advanced oral lesions can be visualized, biopsied, and monitored prospectively; they are linked to carcinogenesis throughout the aerodigestive tract; and activity of retinoids and b-carotene has been demonstrated in randomized trials in the retinoid oral premalignancy model. 

Basic research in the retinoid oral premalignancy model will increase our knowledge of the biology of epithelial carcinogenesis and agent mechanisms, and, it is hoped, will lead to intermediate end point biomarkers. As reviewed in detail elsewhere, intermediate end point biomarkers are short-term markers of chemopreventive agent activity. Criteria include (1) differential expression in high- and low-risk tissue, (2) pattern and degree of expression correlating with histopathologic stage (e.g., hyperplasia, degree of dysplasia, cancer), (3) low rate of spontaneous change, (4) ability to be modulated, and (5) technical and logistic feasibility. The most substantial work in the retinoid oral premalignancy model involves RAR-b and p53.

The discovery and early descriptions of nuclear receptors came from molecular data suggest a molecular model of retinoid chemoprevention in the head and neck (Fig. 3). These translational RAR-b findings in the retinoid and oral premalignancy system are consistent with preclinical data. The RAR-b promoter has a DR5 response element in situ transfection studies in lung 

These translational RAR-b findings in the retinoid and oral premalignancy model are consistent with in vitro data. The RAR-b promoter has a DR5 response element and is the most tightly retinoid-regulated receptor. Mutations, deletions, or structural changes in the RAR-b gene or its promoter, however, have not been identified. More recent data suggest that loss of RAR-b expression in oral premalignant lesions is related to a defect in intracellular vitamin A metabolism (and reduced levels of retinoic acid in premalignant cells), which can be corrected by pharmacologic doses of retinoic acid. These translational findings are consistent with preclinical data in vitamin A-deficient animals.

The available in vitro and in vivo data suggest a molecular model of retinoid chemoprevention in the head and neck (Fig. 23). In vivo transfection studies in lung cancer and other experimental systems suggest that RAR-b, which is located on chromosome 3p, may have tumor suppressor activity. Contributing to
p53 chromosomal instability and loss of heterozygosity are also under intensive study in aerodigestive tract carcinogenesis. As indicated previously, translational research in the oral retinoid premalignancy model is a paradigm for chemoprevention research in general. Future goals include increasing our knowledge of the biology of carcinogenesis and agent mechanisms of action, establishing effective screens for response and resistance to agents, and establishing valid intermediate end point biomarkers. Valid intermediate markers will be necessary for reducing the size and duration, and therefore, the tremendous costs, of future chemoprevention trials. Perhaps of greater importance, valid intermediate markers will help focus limited research resources on only the most promising candidate agents.

NEW RETINOIDS AND CAROTENOIDS

The retinamide 4HPR is a promising new retinoid now in clinical trials for human chemoprevention. Data support RXR-selective ligands for use in cancer prevention. RXRs have a unique role in controlling apoptosis and as obligate heterodimer partners for RARs and many other intracellular receptors (e.g., vitamin D receptor and peroxisome proliferator-activated receptors). Via versatile dimer-partnering behavior and other complex effects, RXR agonists can modulate other endocrine-signaling pathways. The potential importance of RXR antagonists in breast carcinogenesis was first illustrated by mammary carcinogenesis studies suggesting that the RXR-RXR panagonist 9dRA is more active than RXR agonists. Findings of subsequent prevention studies of selective RXR agonists in a rat mammary carcinoma model were as follows: less toxic and more active than 9dRA; inhibited estrogen- and tamoxifen-stimulated uterine proliferation; activity in tamoxifen-resistant disease and similar to that of tamoxifen; and supra-additive effects when combined with tamoxifen. This study of RXR agonists has led to intensive study of their combination with selective estrogen receptor modulators.

Several carotenoids also appear to have promising chemopreventive activity. For example, epidemiologic studies (in vitro and in vivo) suggest that a-carotene may have chemopreventive efficacy. Lycopene, a carotenoid found primarily in tomato and tomato products, is of great interest as a potential agent for the prevention of prostate and other cancers. In one article, 57 of 72 studies reviewed reported inverse associations between tomato intake or blood lycopene levels and the risk of cancer; 35 of these inverse associations were statistically significant. Small intervention trials of lycopene in men with prostate cancer have been initiated. Other carotenoids including crocetin, canthaxanthin, fucoxanthin, and a-carotene have been found to inhibit tumorigenesis in animal models. While there is considerable interest in these and other carotenoids for cancer prevention, large-scale human trials should be undertaken with great caution, given the lack of a clear understanding of the apparent mechanism of b-carotene in promoting lung carcinogenesis.

CONCLUSIONS

A number of chemoprevention trials involving retinoids and the carotenoid b-carotene are ongoing or have been completed. Although many of the trials have reported chemopreventive efficacy for various retinoids and for b-carotene, particularly in oral premalignancy, other trials have been negative or have even suggested promotional effects. This suggests that the patient population, tumor site, histopathology, choice of agent(s), dose, duration, and timing of intervention may be critical in determining efficacy. Although our understanding of mechanisms of action for retinoids has increased dramatically in the last decade, the same is not true for the carotenoids, and additional research is needed in this area. Nonrandomized phase I and II trials provide useful information regarding toxicity, feasibility, and suggestions of drug activity; however, randomized phase III and IV trials are clearly necessary for rigorous evaluation of efficacy. This is particularly true for trials using intermediate end points, as uncontrolled trials are difficult to interpret and may produce spurious findings. Several large randomized trials of retinoids in the prevention of cancer will be concluded by 2003. Others involving b-carotene, alone or in combination with other agents such as vitamins E, C, and selenium, also are ongoing. Trials will soon be initiated to evaluate single-agent efficacy of some of the less-studied micronutrients, such as the planned Selenium and Vitamin E Chemoprevention Trial (select), which will examine selenium and vitamin E in a factorial design aimed at the prevention of prostate cancer in 32,400 healthy male participants in the United States. In the meantime, the use of retinoids, carotenoids, vitamins E, C, and selenium for cancer prevention remains investigational.

CHAPTER REFERENCES

SECTION 23.4
Naturally Occurring Dietary Anticarcinogens

PETER GREENWALD

INTRODUCTION

Experimental research has identified hundreds of food-derived compounds as having inhibitory effects on carcinogens. In humans, these cancer-protective compounds are typically consumed as components within a complex diet, rather than as high-dose supplements. Because the variety and complexity of the diet of free-living humans limits direct experimental intervention of food intake, observational studies of eating patterns are often used to infer the role of particular dietary components. Epidemiologic studies emphasizing overall dietary intake or consumption of specific foods, rather than investigation of a particular nutrient or dietary supplement, do, however, provide consistent evidence that populations consuming higher levels of fruits and vegetables are at decreased risk of various cancers relative to populations with lesser intakes. A growing body of research indicates that certain nonnutritive phytochemicals, including those found in the everyday diet, have marked cancer-preventive properties. This chapter examines some of the current evidence for the link between dietary anticarcinogens and cancer risk, with particular emphasis on selected nonnutritive phytochemicals.

CAROTENOIDS

Commonly consumed green, yellow-red, and yellow-orange vegetables and fruits contain more than 40 carotenoids, including β-carotene, lutein, lycopene, and the xanthins. Various carotenoids may serve as cancer-preventive agents, and a comprehensive review of experimental and epidemiologic studies examining their properties has been published. Among the most promising of these carotenoids is lycopene, commonly found in tomatoes and tomato-based products; the biochemical and metabolic characteristics of lycopene have been summarized. Epidemiologic studies have found an inverse relationship between intake of tomatoes or plasma lycopene level and risk of cancer at various sites, particularly the prostate, lung, and stomach. In vitro studies have found a synergistic inhibitory effect of lycopene and α-tocopherol on growth of two human prostate carcinoma cell lines. Mechanisms of action of carotenoids that may explain their potential cancer-preventive effects include antioxidant activity; modulation of carcinogen metabolism; and effects on cell transformation, differentiation, and communication. More definitive conclusions regarding the role of lycopene in cancer prevention await controlled clinical trials.

Lutein displays anticarcinogenic properties that include enhancement of immune function, inhibition of the auto-oxidation of cellular lipids, and protection against oxidant-induced cell damage. In mice, dietary lutein inhibited mammary tumor growth, and, among humans, high plasma lutein is associated with increased expression of estrogen receptors in breast cells and better survival rates and response to hormone therapy.

PHYTOESTROGENS

Sources for two major categories of phytoestrogens, isoflavonoids and lignans, include legumes, whole grains, fruits, and berries. Phytoestrogens exhibit both weak estrogenic and antiestrogenic effects. Evidence for the role of phytoestrogens as cancer-preventive agents, from experimental and epidemiologic studies, has been the subject of a number of reviews. Evidence supports the role of isoflavonoids in cancer prevention.

ISOFLAVONOIDs

Isoflavonoids, common in soy-based foods, inhibit angiogenesis, cell-cycle progression, and aromatase enzyme; stimulate sex hormone-binding globulin synthesis; and have antioxidant properties. The primary isoflavonoid associated with cancer prevention is genistein. Although the specific molecular mechanisms have yet to be elucidated, genistein displays multiple biochemical properties that inhibit the proliferation of cancer cells in various tissue cultures. Genistein also possesses nonestrogenic properties, including inhibition of ribosomal S6 kinase activity and induction of differentiation of malignant cells. Epidemiologic studies of populations that regularly consume soy-based foods reveal markedly lower incidence rates for breast, colon, and prostate cancer, when compared with populations with lesser intake of soy products.

LIGNANS

In addition to their estrogen-like properties, lignans possess a wide range of other biologic activities, including antioxidant, antiproliferative, antiangiogenic, antiaromatase, antiestrogenic, antiinflammatory, and antiviral properties. High-fiber diets in Western countries provide a substantial proportion of lignan precursors, and the lower incidence of cancer in countries consuming high vegetarian or semi-vegetarian diets may be partially attributable to such fiber-associated substances. Flaxseed flour is a particularly good source of certain lignans, and dietary flaxseed is being investigated as a potential anticancer agent in humans.

The relationship between phytoestrogens and breast cancer has been of particular interest, given the ability of phytoestrogens to mimic the properties of natural estrogens and the hormonal factors determining disease risk, respectively. Numerous animal and human studies indicate that increased consumption of phytoestrogens, particularly soy-based products, is associated with decreased breast cancer risk. The traditional Western diet, having as a component low soy consumption, may adversely affect risk of certain hormone-dependent cancers. For example, the risk of breast cancer is less among Asian women born in Asia, where soy consumption is higher, relative to Asian women born in the United States, where soy consumption is lower. In experimental studies, soy positively affects various physiologic parameters (e.g., menstrual cycle length, hormone levels of follicle-stimulating hormone and luteinizing hormone), and inhibits the proliferation of human breast cancer cells. One potential mechanism for the protective effect of phytoestrogens involves inhibition of ras gene expression.

Like breast cancer, prostate cancer risk may also be influenced by dietary consumption of phytoestrogens. Men living in Asian countries where consumption of soy-based foods is higher display a lesser risk of disease relative to men in Western countries where soy consumption is lower. More research into the molecular and biochemical characteristics of the various phytoestrogens, and valid data on their consumption in the typical diet, are required.

ORGANOSULFUR AND ORGANOSELENIUM COMPOUNDS

Both experimental and epidemiologic studies support the cancer-preventive ability of certain organosulfur compounds. Garlic, a member of the genus Allium, is rich in organosulfurides, and diallyl sulfide (DAS) is the most frequently investigated sulfur compound found in garlic. In animals and humans, DAS and related compounds inhibit chemical carcinogenesis through an array of mechanisms, in various tissues, and against a variety of specific carcinogens. For example, studies
have demonstrated protective effects of DAS against human colon tumor cells, and murine skin carcinogenesis. Studies of the related compound diallyl disulfide (DADS) have noted that it suppresses human colon, skin, and lung tumor cell proliferation; the effect possibly being attributable to the ability of DADS to induce G1 arrest and depress p34cdc2 kinase activity. Epidemiologic studies have found an inverse association between garlic consumption and risk of gastric cancer, possibly a result of the antibacterial properties of garlic that inhibit conversion of nitrate to nitrite in the stomach, thereby limiting formation of carcinogenic nitrosamines. Organosulfide preventive agents also are present in Brassica vegetables (e.g., broccoli, cabbage, cauliflower, and Brussels sprouts). Sulforaphane, for example, inhibits carcinogen-induced mammary tumorigenesis in rats, and induced phase 2 enzymes in murine hepatoma cells. Selenium inhibits various types of tumors in rodents, and, in humans, low plasma levels of selenium are associated with increased risk of polyps and possibly prostate cancer. A sampling of additional studies of organosulfur and organoselenium compounds is found in Table 23.4-1.

### PHENOLIC COMPOUNDS

Almost all fresh fruits, vegetables, and grains contain measurable amounts of natural plant phenolics, some of which display cancer-inhibitory properties. The metabolic, bioavailability, antioxidant, and chemical properties of phenolic compounds have been reviewed, as have potential mechanisms accounting for their anticarcinogenic activity. For example, resveratrol, a triphenolic common in grapes, displays strong antioxidant and antiinflammatory properties and has received considerable attention as a potential cancer-preventive agent in humans. Although the exact mechanism(s) for its antimutagenic effects are not fully known, its growth inhibitory and antiproliferative properties may be attributable to induction of apoptotic cell death. Resveratrol exhibits a chemical structure similar to diethylstilbestrol, and thus may also be classified as a phytostrogen. Resveratrol has shown variable amounts of estrogen receptor agonism in different test systems. Resveratrol inhibited the development of preneoplastic lesions in carcinogen-treated mouse mammary glands in culture, and inhibited tumorigenesis in a mouse skin cancer model.

### SIMPLE PHENOL AND PHENOLIC ACIDS

The simple phenols include the monophenols, found in fruits (e.g., raspberry, blackberry); the diphenols; and vanillin. Ellagic acid, a phenolic acid found in nuts and berries, possesses a number of anticarcinogenic properties, and different parts of the ellagic acid molecule may be responsible for assorted putative anticarcinogenic effects. In animal studies, ellagic acid inhibited DNA-carcinogen adduct formation, lung tumorigenesis induced by nicotine-derived nitrosamine in mice, and development of an esophageal-specific carcinogen. Other phenolics also have shown antioxidant, antimutagenic, and anticarcinogenic effects (Table 23.4-2).

### FLAVONOIDS

Flavonoids represent the most important single group of phenolics in food, more than 4000 different types have been identified. Potential mechanisms for the anticancer effects of flavonoids include interaction with the cytochrome P-450 mixed function oxidase system and inhibition of tyrosine protein kinase activity and phosphoinositide phosphorylation. Like phytostrogens, flavonoids display structural properties that allow them to bind to estrogen receptors, potentially decreasing the risk of certain estrogen-dependent cancers.

Experimental and epidemiologic studies of quercetin, the most common and biologically active dietary flavonol, have been reviewed. Quercetin has multiple biochemical effects in mammalian cells and has shown antiproliferative activity against ovarian, breast, and stomach cancer cell lines in vitro and against human ovarian cancer primary cultures. In a phase I clinical trial, quercetin inhibited tyrosine kinase activity and showed evidence of antitumor activity. Other flavonoids, particularly tangeretin and nobletin, appear to inhibit proliferation of the human breast cancer cell lines MDA-MB-435 and MCF-7.

Long-term studies of the preventive ability of silimarins, a flavonoid isolated from artichoke or milk thistle, indicate its ability to protect against tumor promotion in mouse skin models of carcinogenesis. Protective effects of common citrus flavonoids (e.g., naringen, hesperitin, hesperidin) include actions against B16F10 melanoma cells in mice, inhibition of MDA-MB-435 human breast cell cancer proliferation, and a preventive effect against oral carcinogenesis in rats. Additional studies involving the anticarcinogenic properties of the flavonoids are summarized in Table 23.4-2.

### GREEN TEA POLYPHENOLS

Experimental studies supporting the antimutagenic and anticarcinogenic activities of tea polyphenols, and epidemiologic data indicating an association between tea consumption and cancer risk, have been reviewed. Studies on the catechin (-)-epigallocatechin-3-gallate, the primary green tea polyphenol (GTP), indicate that its growth inhibitory effects are selective, operating on cancerous but not on normal cells. Although various GTPs individually exhibit inhibitory effects, certain catechins act synergistically to reduce cancer risk, indicating that green tea is a more effective protective agent than any of its individual components. Studies of the anticarcinogenic properties of green tea and its constituents are summarized in Table 23.4-2.

Characteristics of GTPs that may account for their anticarcinogenic properties include scavenging of carcinogenic electrophiles, inhibitory action against nitrosation, modulation of carcinogen-metabolizing enzymes, trapping of ultimate carcinogens, inhibition of growth-related signal transduction pathways, modulation of enzymes...
associated with cell proliferation, and stimulation of phase II detoxifying enzymes. Epidemiologic studies support the potential preventive effect of green tea against cancer at a number of sites, including the lung, esophagus, stomach, and skin. Although GTPs have been the focus of most studies, black tea is consumed more commonly in the West; its potential cancer-protective properties, however, have yet to be fully explored. Animal studies indicate that certain black tea polyphenols, the theaflavins, are associated with significant inhibition of lung adenomas, both in vivo and in vitro. Additional research involving black tea polyphenols may be warranted.

CURCUMINOIDS
Curcumin, the major yellow pigment in turmeric and curry, is a common spice, coloring agent, and herbal drug, particularly in Asia. Curcumin has multiple effects on the carcinogenic process, including antioxidant activity, reduction in polyamine synthesis, and inhibition of tumor initiation and promotion. The molecular mechanism explaining the action of curcumin is complex and varies, but it is known to inhibit cyclooxygenase- and lipoxigenase-dependent metabolism of arachidonic acid to prostaglandins and hydroxyeicosatetraenoic acids and to moderately enhance interleukin-4 production. Additional work has shown that curcumin inhibits colon carcinogenesis during the postinitiation phase and has a cytostatic effect at G2/M against MCF-7 human breast tumor cells.

MONOTERPENES
Monoterpenes are found in the essential oils of citrus fruits and other edible plants. The most common monocyclic monoterpene, d-limonene, and its metabolite perillyl alcohol have shown effectiveness as cancer-protective agents against rodent cancers of the mammary, skin, liver, lung, forestomach, pancreas, and prostate. In human breast cancer cell lines, limonene-related monoterpenes exhibited a dose-dependent inhibition on cell proliferation. Multiple mechanisms may account for the activities of these compounds on tumor cells. The blocking effects of d-limonene and other monoterpens in prostate during the initiation phase of mammary carcinogenesis may result from induction of phase II carcinogen-metabolizing enzymes and subsequent carcinogen detoxification, in the postinitiation phase, tumor-suppressive activity may be a result of induction of apoptosis and inhibition of the posttranslational isoprenylation of proteins that regulate cell growth. Other cancer-preventive mechanisms include actions on the mevalonate  and ras signal transduction pathways.

ISOTHIOCYANATES AND INDOLES
Epidemiologic studies have consistently found strong, inverse relationships between high consumption of cruciferous vegetables and cancer incidence. Cruciferous vegetables are a group of glucosinolate-containing plants known to be cancer-protective: indole-3-carbinol (I3C) and related indole compounds, phenethyl isothiocyanate (PEITC) and related isothiocyanates, such as benzyl isothiocyanate (BITC) and diethylthiourea and other thiol-containing compounds. The mechanism by which cruciferous vegetables exert their anticarcinogenic effects have been reviewed. The isothiocyanates and indoles have shown promising results against cancer at a number of sites, in both animals and humans. For example, indoles reduce mammary tumor formation in laboratory animals; PEITC inhibits the initiation phase of mouse-induced esophageal cancer in rats  and may be protective against lung cancer among smokers, and diethylthioureas reduce mammary and pulmonary tumorigenesis in rodents. Mechanisms for the cancer-preventive actions of the isothiocyanates and indoles include induction of phase II detoxifying enzymes.

PROTEASE INHIBITORS
In vivo, in vitro, and epidemiologic studies examining the suppression of neoplastic growth by soy-based protease inhibitors (PIs) have been summarized. Actions of protease inhibitors include alteration of the expression of certain oncogenes and proteolytic activities that are elevated in carcinogen-exposed tissues; interference with tyrosine phosphorylation by normal cells; and modulation of adenosine diphosphate ribosyltransferase, possibly through the induction of synthesis and distribution of endogenous PIs by dietary PIs. The soybean-derived Bowman-Birk inhibitor (BBI), a major protease inhibitor, may be at least partially responsible for the differences noted in the incidence of breast cancer between Asian and Western populations. BBI and its concentrated form (BBIC) have exhibited suppressive effects in a number of carcinogenic models, including animals with a known genetic susceptibility to cancer.

IMPLICATIONS FOR CANCER PREVENTION
Primary prevention represents the most desirable and cost-effective means of reducing cancer incidence. Toward this end, the human diet contains anticarcinogens capable of reducing cancer risk, but substantial basic science research will be required to elucidate the mechanisms by which any particular phytochemical exerts its anticancer effect. In the absence of specific knowledge of anticarcinogenic dietary components and their mechanisms, consumption of a wide variety of fruits and vegetables is highly encouraged, because several agents having weak effects in vitro may, in combination, prove more effective than any single agent. Such a “polypharmacological” approach to cancer prevention is most likely to minimize cancer risk.

Because phytochemicals are consumed, not in the form of high-dose supplements, but rather as constituents within a complex matrix of nutrients, the difficulty in identifying any particular component as being “a” primary preventive agent can be profound, particularly given the attendant problems of valid dietary assessment, confounding, and interaction with other factors. This is not to say, however, that such research cannot, or should not, be conducted. The further elucidation of naturally occurring dietary anticancer agents represents a key element in efforts to decrease cancer incidence through primary preventive measures. Additional epidemiologic and experimental research involving dietary anticarcinogens holds great potential for future cancer prevention efforts.
37. Gehm BD, McAndrews JM, Chien JY, Jameson JL. Resveratrol, a polyphenolic compound found in grapes and wine, is an agonist for the estrogen receptor. Proc Natl Acad Sci U S A 1997;94:1418.
SECTION 23.5
Dietary Carcinogens

PETER GREENWALD

Introduction
Naturally Occurring Dietary Carcinogens
Natural Pesticides
Mycotoxins
Products of Food Preparation and Processing
Tetrahydrofuranic Aromatic Amines
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INTRODUCTION

With the exception of tobacco, no environmental exposure to potential carcinogens is comparable to sources in the diet. Although the public often attributes the source of carcinogens in the food supply to food additives, synthetic pesticides, and various environmental contaminants, these chemicals are estimated to represent less than 1% of the carcinogens found in foods. In fact, most known dietary carcinogens either occur naturally in plants or are produced during food preparation. Dietary carcinogens in both groups are discussed, with a review of common food sources, mechanisms of action, human exposure, and degree of human risk. A brief overview of issues regarding synthetic carcinogens in the diet is also provided.

In many cases, current knowledge is incomplete and does not allow reliable estimates of risk. First, no concentration data exist for many potentially carcinogenic constituents of foods. In addition, determining human exposure levels is difficult and sometimes inconclusive. Dietary assessment tools are subjective and often biased, the food levels of some substances can vary from year to year, and exposure to mixtures of substances at low doses might be more important than exposure to single agents. High-dose animal testing has been used to approximate human risk, and the Carcinogenic Potency Database currently includes results for approximately 1288 chemicals tested in long-term animal experiments (http://poisdata.berkeley.edu/app414.html). However, this information cannot predict human risk with a high degree of confidence. Extrapolation from the near-toxic doses used in animal tests to human risk at low-dose exposure is difficult, and some critics believe its use has sometimes led to overestimation of potentially minimal risks. One challenge relates to differences in the carcinogenic mechanisms involved. For example, mitogens likely act by increasing cell proliferation, but only at near-toxic levels, whereas mutagens can damage DNA at low doses. As a result, animal tests involving mutagens may have more significance for human risk.

To increase the reliability of exposure estimates, biomarkers are being developed to mark internal dose, putative early response, and susceptibility. For example, DNA-carcinogen adducts have been used as measurable end points in laboratory studies and, to a more limited extent, in humans, to assess dietary carcinogen exposure, carcinogen metabolism, mutagenesis, and tumorigenesis. In addition, genetic and acquired susceptibility traits have been shown to affect carcinogen metabolism, DNA damage, and repair. In fact, more than a dozen polymorphisms related to the metabolism of dietary carcinogens are possible actors in the complex process of carcinogenesis at many sites. Although related technology is just emerging and more study is needed, approaches such as these have already affected understanding of the substances discussed in the following sections.

NATURALLY OCCURRING DIETARY CARCINOGENS

Most naturally occurring dietary carcinogens are either “natural pesticides,” produced by plants for protection against fungi, insects, and animal predators, or mycotoxins, secondary metabolites produced by molds in foods. Table 23.5-1 lists some of the most common substances in both categories.

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<tr>
<th>Table 23.5-1. Food Sources of Naturally Occurring Dietary Carcinogens</th>
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NATURAL PESTICIDES

Animal studies have provided evidence for the carcinogenicity of a large number of individual plant constituents fed at high doses. However, no firm conclusions can be drawn about the overall effects of most of these substances on human health. Plant foods contain thousands of phytochemicals representing various chemical classes and exhibiting diverse molecular structures, and only a small fraction of potential carcinogens produced by plant foods have been tested systemically. In addition, the difficulties previously described in assessing human risk are well illustrated by naturally occurring pesticides. Caffeic acid, which has been shown to cause forestomach squamous cell carcinomas in rats as well as renal tubular cell hyperplasia and adenomas in mice, is a good example. The relevance of the animal findings to humans is uncertain, because data are not available on carcinogenicity in humans, very high doses were used in the animal studies, humans do not have a forestomach, and the renal lesions were related to toxic lesions. In addition, in vitro, caffeic acid may act either as a pro- or antioxidant, and it has been observed to be both protective and enhancing when administered orally in combination with known carcinogens. Another confounding factor is the fact that many foods containing caffeic acid also contain compounds believed to be protective, which might affect its ultimate human impact.

Despite such challenges, with additional information on factors such as exposure levels, concentration levels, mechanisms of action, and human clinical experience, researchers can draw conclusions on human risk from natural pesticides. For example, studies of coumarin—a substance with many food sources (particularly cinnamon) that has been found to be carcinogenic in rats and mice—have concluded that it poses no health risk to humans. Known exposure levels and differences in coumarin metabolism between susceptible rodent species and humans contributed to this finding. Other studies are elucidating some of the important factors in assessing human risk, particularly regarding mechanisms of action in animals. For instance, researchers rationalized the restriction of allyl isothiocyanate–related bladder tumors to male rats compared with female rats and both sexes of mice on the basis of a species difference in metabolism and a sex difference in exposure to allyl isothiocyanate metabolites. Other studies have found that the hepatocarcinogenicity of hydrazine is linked to the hypomethylation of total target organ DNA that occurs with chronic exposure and that the hypomethylation is dose-related to the development of liver cancer. Methylation is believed to be a factor in aberrant gene expression and the development of tumors.
From a public health perspective, dietary exposure to natural pesticides can generally be controlled by selecting genetic strains of plants that produce lower concentrations and by reducing plant stress during the growing season. Particular natural pesticides that are carcinogenic in animals might be bred out of crops if research indicates they could be hazardous to humans. Increasing the level of natural pesticides by breeding as an alternative to synthetic pesticides must be considered cautiously in view of their potential health effects. Consumers also could be informed of the relative risks associated with food products such as herbal teas, for which both protective and toxic effects have been documented.

**MYCOTOXINS**

Mycotoxins are structurally diverse toxic fungal metabolites that are common contaminants of ingredients in animal feed and human food; to date, more than 300 mycotoxins have been identified. The mycotoxins listed in Table 23.5-1 are among those shown to have carcinogenic potential in animals. However, only aflatoxin B₁ (AFB₁) and naturally occurring mixtures of aflatoxins are known to be genotoxic and carcinogenic to humans. Fumonisins and ochratoxin A have been shown to be possibly carcinogenic to humans.

**Aflatoxins**

AFB₁ is a potent carcinogen in many species of animals, including rodents, nonhuman primates, and fish. Epidemiologic studies show a strong direct association between AFB₁ intake in Africa and China and risk for primary liver and lung cancer in humans. Synergistic interactions of AFB₁, with both viral B hepatitis and alcohol consumption in humans also have been demonstrated. High levels of AFB₁, produced by the Aspergillus species, are found in regions of Africa, southeast Asia, and southern China, where the foods they contaminate are dietary staples for humans and animals. In fact, human exposure to AFB₁ in southern China (either directly or through eating the products of animals that ate contaminated feed) can be as high as 75 to 250 µg/d, compared with 25 to 75 ng/d in the United States, where aflatoxin contamination levels are lower.

The aflatoxins have been extensively characterized with respect to chemistry, biology, and toxicology. Like most other mycotoxins with the exception of fumonisins, aflatoxins are genotoxic agents, and substantial research has been conducted on the genetic damage created by AFB₁ in liver and lung tumors. A key biomarker, the predominant AFB₁-DNA adduct (AFB₁-N⁷-Gua), has been identified and correlated with the incidence of hepatic tumor in trout and rats. Formation of the AFB₁-DNA adduct requires metabolic activation of AFB₁ to its carcinogenic form, the 8,9-epoxide. A review of data from animal and human studies that measured urinary excretion of aflatoxin-DNA adducts by molecular dosimetry suggested that these adducts are useful markers of exposure. For instance, a prospective study of more than 18,000 men in Shanghai, China, demonstrated a significant increase in risk [relative risk (RR) = 3.4] for liver cancer in individuals in whom aflatoxin-DNA adducts were detected.

Striking species differences exist in the oncogenic mutations involving AFB₁. For example, a considerable amount of evidence shows that dietary AFB₁ exposure can produce codon 249 (AGG to AGT) p53 tumor suppressor gene mutations during human liver carcinogenesis. In rat liver tumors, however, codon 12 of K-ras appears to be the "hot spot" for AFB₁-induced mutations. In mice exposed to AFB₁, preneoplastic lesions contained mutations in codon 61 of the Ha-ras gene, and in vitro studies show that metabolically activated AFB₁ in humans is capable of mutating this protooncogene to its oncogenic form, although no such mutations have been reported in vivo. Thus, although these mutations are clearly associated with exposure, their significance in terms of mechanistic involvement in tumorigenesis needs further elucidation.

Elimination of exposure to aflatoxins is not possible given the ubiquitous nature of the molds that produce them. Primary prevention methods have included developing aflatoxin-resistant plants, building better storage facilities for grains, and establishing regulatory and testing programs around the world.

**Fumonisins and Ochratoxin A**

Of the six fumonisins identified, fumonisin B₁ has been shown to be carcinogenic in rats and mice at high doses, primarily targeting the liver and kidneys. It also has been linked in ecologic studies to esophageal cancer in humans in high corn-consuming regions of China and Africa where high levels of contamination are documented, but no convincing evidence of causality has been presented to date.

Fumonisins, which are produced by Fusarium moniliforme, do not appear to be genotoxic, but they may induce cancer through disturbing the signal transduction pathways. As with other dietary carcinogens, difficulties exist with available technologies for assessing exposure, and the search for biomarkers is a rapidly growing area of research. Fumonisins in urine and altered sphingolipid metabolism (sphinganine-sphingosine ratio) in urine and blood are two potential markers currently under investigation. The co-occurrence of fumonisins and aflatoxins in corn-based foods has been demonstrated and a synergistic effect postulated.

Ochratoxins are produced by Aspergillus ochraceus and related species. Ochratoxin A (OA) has induced renal adenomas and kidney cancers in mice and rats. Carcinogenic effects in humans are suspected based on findings of high levels of OA in the blood of patients with Balkan endemic nephropathy, who also have a high incidence of varied carcinomas. The search for DNA adducts as biomarkers of OA also is ongoing. The relative lack of information on fumonisins, ochratoxins, and other mycotoxins compared with aflatoxins does not mean that their public health risk is necessarily less. Rather, it indicates that more investigation of these mycotoxins is needed.

**PRODUCTS OF FOOD PREPARATION AND PROCESSING**

Food preparation and preservation are major sources of dietary carcinogens, including heterocyclic aromatic amines (HAA), formed during frying, broiling, and grilling high-protein foods and more prevalent in well-done meats; polycyclic aromatic hydrocarbons (PAH), formed during broiling and smoking food; and N-nitrosocompounds (NOC), formed in smoked, salted, and pickled foods cured with nitrate or nitrite. NOCs are also formed endogenously at sites such as the stomach from nitrites and amines in the diet. Table 23.5-2 lists common carcinogens produced during food preparation and related food sources and cooking methods. Although human risk from these compounds is not always well understood, it may be prudent to minimize exposure by modifying meat cooking methods and eating fewer foods containing NOCs.

<table>
<thead>
<tr>
<th>Table 23.5-2. Dietary Carcinogens Produced During Food Preparation: Sources and Cooking Methods</th>
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<tbody>
<tr>
<td><strong>HETEROCYCLIC AROMATIC AMINES</strong></td>
</tr>
<tr>
<td>HAAs are potent mutagens and animal carcinogens, causing cancers of the liver, colon, mammary gland, skin, Zymbal gland, large intestine, prostate, lymphoid</td>
</tr>
</tbody>
</table>
FUTURE RESEARCH NEEDS

The National Research Council classifies synthetic chemicals as genotoxic, which directly affect DNA, form DNA adducts, and increase cancer risk, and studies of animal tumors have begun to relate AIA-DNA adduct-induced mutagenic events with the mutations found in critical genes associated with oncogenesis, and AIA-DNA adduct levels in target tissues are strongly related to tumor incidence. Dietary fat also has been implicated as a promotional factor in HAA-related carcinogenesis in animal studies, but the data remain difficult to interpret.

Although HAA-DNA adducts can be useful biomarkers, their detection in humans has proved difficult. Some adducts have been detected in human tissue samples, but not in others, who were both rapid N-oxidizers and rapid acetylators had a greater risk of colon cancer than those who were both slow N-oxidizers and slow acetylators. In one study, rapid acetylators had an increased risk only with a high intake of meat. Some data suggest that variations in susceptibility to pancreatic and prostate cancer also are associated with genetic differences of carcinogen-metabolizing enzymes, although these areas require further investigation. In breast cancer, differential susceptibility in rapid versus slow acetylators has been found in some studies, but not in others.

There is wide interindividual variation in the capacity of human tissues to activate HAAs, and polymorphisms of related enzymes in humans have been investigated for potential relationship to cancer risk. In some studies, but not in others, individuals who were both rapid N-oxidizers and rapid acetylators had a greater risk of colon cancer than those who were both slow N-oxidizers and slow acetylators. In one study, rapid acetylators had an increased risk only with a high intake of meat. Some data suggest that variations in susceptibility to pancreatic and prostate cancer also are associated with genetic differences of carcinogen-metabolizing enzymes, although these areas require further investigation. In breast cancer, differential susceptibility in rapid versus slow acetylators has been found in some studies, but not in others.

Urinary excretion of cooking-associated HAAs and their metabolites is being investigated as a possible biomarker of human exposure, and studies have shown measurable excretion of MeIQx and its metabolites after consumption of proteins cooked at high temperatures. Although researchers found a dose-response relationship between the bacon intake of African American, white, and Asian American men and MeIQx excretion, no such relationship was seen in the same group of men for consumption of any type of cooked meat and PhIP.

POLYCYCLIC AROMATIC HYDROCARBONS

PAHs, several of which have been found to be carcinogenic in animal studies, have a widespread distribution throughout the environment, both as a by-product of cooking meats over an open flame and as a contaminant in animal and human foods. However, available exposure and carcinogenicity data are insufficient to allow a reliable estimate of dietary PAH risk for humans at this time. It is clear that fat dripping onto the coals and the subsequent deposition of PAHs that rise with smoke onto the meat contribute significantly to PAH exposure. Benzo(a)pyrene, the most carcinogenic PAH, has been reported at levels of up to 50 µg/kg in charbroiled steaks and ground beef, five times greater than levels in some less fatty pork cuts and chicken.

In addition, several studies have demonstrated a consistent association between recent consumption of charbroiled foods and increased PAH-DNA adduct concentrations in peripheral white blood cells and excretion of 1-hydroxypyrene in urine. One review suggests a correlation between PAH-DNA adducts and ras oncogene mutations. Some evidence points to an antioxidant response element playing a significant role in PAH carcinogenesis. It also has been suggested that the hGSTP1 gene, which has been shown to be polymorphic in humans, may be an important factor in differential susceptibility to PAH-related cancers, although study conclusions differ. The chemical composition of the PAH mixtures to which humans are exposed can include cigarette smoke and industrial emissions as well as dietary sources, and differences in mixtures may affect the involvement of the hGSTP1 gene.

N-NITROSOCOMPOUNDS

NOCs administered orally in animals, including nonhuman primates, consistently elicit carcinogenic responses. These compounds also may be a significant risk factor for human cancers of the stomach, esophagus, colon and rectum, nasopharynx, urinary bladder, and liver. One review found that, although the epidemiologic evidence overall remains inconclusive, an association between NOCs and human cancer cannot be ruled out. The author postulated that inadequate available data may be obscuring a small to moderate carcinogenic effect of NOCs.

The formation of endogenous NOCs may be inhibited by naturally occurring compounds in foods, such as ascorbic acid, tocopherols, retinoids, phenolic compounds, sulfhydryl compounds, tea, orange peel, and certain fruits and vegetables. This may in part explain the generally protective effect of vegetables and fruits consistently observed in epidemiologic studies.

SYNTHETIC CARCINOGENS IN THE DIET

Animals and humans also are exposed to a variety of synthetic chemicals in their foods from food additives. Direct (intentional) synthetic additives include antioxidants, colorants, flavor ingredients, artificial sweeteners, solvents, and humectants. Regulation of synthetic or natural chemicals intentionally added to food has led to extensive data on exposure. Indirect (unintentional) synthetic additives include pesticides, solvents, and packaging-derived chemicals. These chemicals, which number more than 2000, enter the food supply during production, processing, packaging, and storage from a variety of sources. Very little data exist on exposure to these chemicals. Pesticides are of major concern to the public and regulatory agencies compared with other indirect food additives. Most, if not all, pesticides have possible human toxicity, including carcinogenic potential. In general, levels encountered are below allowable tolerances, although actual estimates of risk are problematic.

Packaging materials, including vinyl chloride, and several phthalate esters used as plasticizers have gained attention from researchers as another possible unintentional addition to packaged foods with potential risks to human health. Synthetic chemical contamination of water has been another concern, principally focused on trihalomethanes, which are disinfection by-products, in public water supplies and pesticides in well water.

The National Research Council classifies synthetic chemicals as genotoxic, which directly affect DNA, form DNA adducts, and increase cancer risk, and nongenotoxic, which do not directly affect DNA, but which may affect carcinogenesis through other posited mechanisms. Some synthetic chemicals can exhibit both genotoxic and nongenotoxic activity.

The metabolic pathways involved in the biotransformation of both synthetic and naturally occurring chemicals are similar, and evidence to date suggests that the processes of carcinogenesis also are similar, if not identical. Not surprisingly, the difficulties that complicate risk prediction for naturally occurring dietary carcinogens also apply to the synthetic carcinogens.

FUTURE RESEARCH NEEDS

It is clear from human epidemiologic data that diet contributes to an appreciable portion of cancer; however, continuing research is needed for better identification of...
**SECTION 23.6**

**Aspirin and Other Nonsteroidal Antiinflammatory Drugs and the Risk of Cancer Development**

MICHAEL J. THUN  
CHARLES H. HENNEKENS

**INTRODUCTION**

Since the late 1970s, researchers have been interested in whether regular ingestion of aspirin or other nonsteroidal antiinflammatory drugs (NSAIDs) can decrease the risk of cancer, especially colorectal cancer. This hypothesis was stimulated by basic research and uncontrolled clinical observations beginning in the mid-1970s. Further support derives from numerous observational epidemiologic studies and mechanistic insights in the 1990s, and from several randomized clinical trials showing that the aspirin-like produg sulindac, 23,24,27,28 and 29 and the novel selective cyclooxygenase-2 (COX-2) inhibitor celecoxib,20 suppress adenomatous polyps among patients with familial adenomatous polyposis (FAP). More recent data indicate that NSAIDs increase apoptosis, 30,31,32 and inhibit angiogenesis, 33,34 and reduce metastasis in various experimental models of carcinogenesis. 35,36 No randomized trials have been completed to test whether aspirin or other NSAIDs inhibit colorectal cancer. The Physician’s Health Study, a randomized trial of aspirin designed to evaluate the primary prevention of cardiovascular end points, 37 found no reduction in colorectal cancer among male physicians randomized to 325 mg aspirin or placebo every other day for 5 years and followed for 12 years. However, the short duration and low dose of randomized treatment limit the interpretability of this finding. At least five ongoing randomized clinical trials are testing whether nonselective NSAIDs, such as aspirin and sulindac, or novel selective inhibitors of inducible COX reduce the recurrence of adenomatous polyps among patients with previous sporadic polyps. Trials of intermediate endpoint and ends in high-risk populations have the advantage of decreasing the necessary sample size and duration of treatment but have the disadvantage of not directly measuring the effect of NSAIDs on cancer.

This chapter reviews the experimental, clinical, epidemiologic, and randomized trial evidence relevant to NSAIDs and cancer, particularly colorectal cancer. We also consider the limited evidence available on lowest effective dose, treatment criteria, and the balance of potential benefits to risk of prolonged NSAID treatment. Although extensive evidence now indicates that NSAIDs inhibit neoplasia in several experimental settings and in the clinical context of FAP, we believe that aspirin and other NSAIDs are presently promising but unproven candidates for the chemoprevention of colorectal and perhaps other cancers in high-risk populations.

**PHARMACOLOGY AND TOXICITY OF NONSTEROIDAL ANTIINFLAMMATORY DRUGS**

NSAIDs are a chemically diverse group of drugs effective in the relief of pain, inflammation, and fever. The analgesic, antiinflammatory, and antipyretic properties of salicylate in willow bark and other plant extracts were recognized in ancient Egypt and Greece. NSAIDs also have dose-related toxicity to the gastrointestinal (GI) tract and kidney. The chemist Felix Hoffmann was reportedly motivated to synthesize aspirin (acetyl salicylic acid) from sodium salicylate in the late nineteenth century because of the GI toxicity experienced by his father during treatment with salicylate for arthritis. NSAIDs can also affect hemostasis, reproduction, childbirth, and asthma. Efforts to minimize stomach irritation and to prolong the half-life of these drugs have motivated the development of many new NSAIDs in addition to aspirin. Nonselective NSAIDs, such as ibuprofen, indomethacin, naproxen, piroxicam, and sulindac, now compete with novel, selective COX inhibitors that are reputed to lack major GI toxicity.

The common pharmacologic action of NSAIDs is to inhibit COX, the initial and rate-limiting enzymatic step in the metabolism of arachidonic acid into a complex group of signaling proteins termed prostaglandins. 38,39,40,41,42,43 Arachidonic acid derives from meat or linoleic acid in the diet. It is normally tightly bound to cell membranes until being hydrolyzed by phospholipases as free arachidonic acid (arachidonate). Arachidonate can then be metabolized through COX pathways into prostaglandins and thromboxanes; through lipoxigenase into leukotrienes and other lipid mediators; or by nonenzymatic pathways. Metabolites of arachidonic acid are called eicosanoids.

Prostaglandins and their derivatives modulate many functions within cells (autocrine) or across neighboring tissues (paracrine). They differ from systemic hormones in that they are produced and destroyed almost instantaneously. Most tissues produce only a few prostaglandins in abundance. The function of the same prostaglandin may differ in different organs. Thromboxane-A2 (TXA2) produced by platelets enhances platelet aggregation, clot formation, and hemostasis; prostacyclin (prostaglandin I2) from vascular endothelial cells enhances vasodilatation and prevents the aggregation of platelets. Prostaglandin E2 (PGE2) is a potent vasodilator in most vascular beds and also relaxes tracheobronchial and uterine muscle and protects gastric epithelium from acid. Prostaglandin G and prostaglandin D2 contract smooth muscle and modulate renal blood flow and sodium and water retention by the kidney.

The diverse homeostatic and reactive functions of prostaglandins have prompted pharmacologists to seek drug and treatment regimens that improve NSAID specificity. One such strategy is to use low-dose aspirin (40 to 100 mg daily) to inhibit COX activity and TXA2 production by platelets as they pass through the enterohepatic circulation. Aspirin is the only NSAID that covalently acetylates and permanently inhibits COX. Platelets lack a nucleus and cannot synthesize new enzyme during their 7- to 10-day lifespan. At antplatelet doses, virtually all of the absorbed aspirin is metabolized by the liver and does not reach the systemic circulation.

A second strategy is to develop new NSAIDs that selectively target a single isoform of the COX enzyme. Until 1991, only one isoform of COX was recognized. Then a second isoform was identified that increased in many tissues during inflammation, wound healing, and neoplasia. These isoforms were named COX-1 and COX-2, reflecting the sequence with which their structure was characterized by x-ray crystallography. The original enzyme, COX-1, is expressed constitutively in nearly all tissues of the body. It plays a central role in gastric cytoprotection and reduces platelet aggregation. It also has a central role in postnatal development. COX-2 expression increases in response to cytokines and other stimuli in many tissues during inflammation, wound healing, and neoplasia. It has a central role in chondrocyte and osteoblast proliferation and also has a central role in the development of many new NSAIDs in addition to COX-2,
Most conventional NSAIDs inhibit both COX-1 and COX-2 with variable potency. Aspirin is a relatively selective COX-1 inhibitor, except at antiinflammatory doses of 1 g/d or more. Novel selective COX-2 inhibitors have been introduced that cause GI symptoms but are thought not to cause serious GI ulceration. Prototypes of these, such as celecoxib (SC-58635) and rofecoxib, are considerably more expensive than conventional NSAIDs. These drugs are proving informative in mechanistic studies to identify the enzymatic target(s) by which NSAIDs inhibit carcinogenesis in experimental models.

**HISTORICAL EVOLUTION OF THE HYPOTHESIS THAT NONSTEROIDAL ANTIINFLAMMATORY DRUGS INHIBIT CANCER**

**EICOSANOIDS IN HUMAN TUMORS**

The hypothesis that certain cancers might overproduce specific prostaglandins and thereby promote their own growth arose in the mid-1970s when Bennett and colleagues observed higher concentrations of PGE₂ in some human colorectal carcinomas than in surrounding normal mucosa. Subsequent studies confirmed that certain human colon cancer cell lines and tumor tissues overproduce PGE₂. The idea that tumor prostaglandins might accelerate the growth and invasion of the cancer was further supported by the observation of Narisawa et al. that PGE₂ in venous blood draining human colorectal carcinomas is higher in vivo when the cancers are large and locally invasive.

**NONSTEROIDAL ANTIINFLAMMATORY DRUGS AND CHEMICALLY INDUCED CANCER IN RODENTS**

Extensive experimental evidence confirms that many NSAIDs suppress tumor development in animal models and cell culture. More than 40 experiments in rodents show that aspirin, other nonaspirin NSAIDs, and selective COX-2 inhibitors suppress intestinal tumorigenesis in rats and mice exposed to chemical carcinogens. Colorectal cancers produced in these rodent experiments resemble human cancer, except for a lower tendency to metastasize. Tumor inhibition is greatest when NSAID treatment is begun before exposure to the carcinogen and continued without interruption throughout the experiment.

**UNCONTROLLED CLINICAL STUDIES OF SULINDAC IN PATIENTS WITH FAMILIAL ADENOMATOUS POLYPOSIS**

The early rodent experiments prompted Waddell and Loughry to test whether the prodrug sulindac inhibits adenomatous polyps in the rare hereditary condition of FAP. Adenomatous polyps are the precursor to most human colorectal cancers. Patients with FAP inherit a germline mutation inactivating one allele of the adenomatous polyposis coli (APC) gene. Loss of the remaining functional APC allele results in hundreds to thousands of adenomatous polyps by the second or third decade of life. Patients who do not undergo prophylactic colectomy almost invariably develop colorectal cancer by the age of 40 to 50 years. FAP patients who have undergone total colectomy still have increased risk of adenomatous polyps; cancer of the rectal stump and small intestine; and nonmalignant, primitive desmoid tumors.

In FAP, sulindac reduces the number and size of new polyps and even causes existing polyps to regress. This finding has been reported in thirteen case studies and in three small randomized crossover trials. Sulindac also suppresses the formation of desmoid tumors in these reports. However, sulindac does not prevent all polyp growth in FAP patients. Just as conventional NSAIDs do not inhibit all chemically induced colorectal cancer in the rodent model, some polyps may grow during treatment or be transformed into carcinoma. Most adenomatous polyps typically increase in number and size after sulindac is discontinued.

**EPIDEMIOLOGIC STUDIES OF NONSTEROIDAL ANTIINFLAMMATORY DRUGS IN THE GENERAL POPULATION**

At least 25 observational epidemiologic studies have compared people who regularly use aspirin or other NSAIDs to those who do not with respect to colorectal cancer. All but one of the published studies finds 30% to 50% lower incidence or mortality rates from colorectal cancer (Fig. 23.6-1) or lower incidence of adenomatous polyps (Fig. 23.6-2). The consistency of these observational studies is striking, despite different researchers using varied study designs in different parts of the world. Interestingly, the single observational study that did not find reduced risk of colorectal cancer or adenomatous polyps among aspirin users also did not find reduced risk of myocardial infarction among the elderly subjects (median age of 70 years at enrollment) who reported taking one aspirin daily.

**TABLE 23.6-1.** Cohort Studies on the Use of Nonsteroidal Antiinflammatory Drugs and the Risk for Colorectal Cancer in General Populations

**TABLE 23.6-2.** Case-Control Studies on the Use of Nonsteroidal Antiinflammatory Drugs (NSAIDs) and the Risk for Colorectal Cancer in the General Population
Homozygous inactivation of either COX-1 or COX-2 produces an equivalent 70% to 80% reduction in intestinal tumors compared to Min mice with both COX isoforms.

More limited experimental and epidemiologic evidence suggests that COX-1 activity may also contribute to the development of colorectal and other cancers.

Studies Implicating Cyclooxygenase-2

Several observational studies report a dose-response gradient of decreasing risk of colorectal cancer or adenomatous polyps among individuals who report more prolonged or frequent NSAID use. Factors that influence self-selection for or against NSAID use could, in principle, confound this observation. Perhaps a more important limitation of the analyses by dose and duration is that none of the studies have simultaneously taken into account both aspirin and nonaspirin NSAIDs, prescription and nonprescription medications, and changes in the frequency or dose of NSAID use over time. Two large prospective studies and one case-control study found the largest reductions in colorectal cancer in persons who have used aspirin for at least 10 or even 20 years. Another large prospective study based on prescription drug records in the United Kingdom between 1994 and 1997 found reduced risk of colorectal cancer in patients prescribed at least 300 mg aspirin daily compared to nonusers, but not among current users of less than 300 mg aspirin daily. The U.K. study lacked information on long-term use of aspirin or other NSAIDs. It is important to define the lowest effective dose and optimal duration, because the GI toxicity of NSAIDs increase with dose, and risk accumulates with duration. The use of antplatelet doses of aspirin (100 mg or less) to prevent cardiovascular events did not begin until the late 1980s and cannot yet be evaluated with respect to colorectal cancer. However, even antplatelet doses of aspirin (80 to 100 mg/d) causes some increase in GI and intracerebral bleeding especially with prolonged treatment of large numbers of healthy people. If NSAIDs are proven to be effective in preventing colorectal cancer in the future, it is likely that long-term prophylaxis could produce a net benefit only in persons with substantially increased risk of colorectal cancer, or because of a combination of other factors that may affect individual risk and benefit.

COMPLETED AND ONGOING RANDOMIZED TRIALS

Several randomized clinical trials show that sulindac and the novel selective COX-2 inhibitor celecoxib reduce the number and size of adenomatous polyps in FAP patients and causes existing polyps to regress. Only one randomized clinical trial of aspirin in the primary prevention of cardiovascular end points has been sufficiently large to measure incidence or death rates from colorectal cancer, although the aspirin arm of this trial was terminated after 5 years. The Physicians’ Health Study showed no reduction in either invasive or in situ colorectal cancer incidence, nor a reduction in colorectal cancer mortality among 22,071 male physicians randomized to 325 mg aspirin or placebo every other day for 5 years and followed for 12 years. The short duration of randomized treatment and relatively low dose of aspirin limit the interpretability of these results.

Several randomized clinical trials are now testing whether aspirin or other NSAIDs inhibit adenomatous polyps among patients with previous sporadic polyps or FAP. Trials of intermediate end points in high-risk populations have the advantage of decreasing the necessary sample size and duration of treatment, but have the disadvantage of not directly measuring the effect of NSAIDs on cancer.

STUDIES OF MECHANISM

Debate is ongoing over the mechanisms by which NSAIDs inhibit carcinogenesis in various experimental and clinical models. This debate is further complicated in that NSAIDs may affect several stages in the adenoma-carcinoma sequence, perhaps by different mechanisms. Most evidence suggests that COX, particularly the inducible COX-2 isoform, is probably the major enzymatic target by which NSAIDs inhibit cancer in various models. Effects mediated through COX could explain why numerous NSAIDs with diverse chemical structures all inhibit COX activity and nearly all suppress colorectal carcinogenesis. There is also debate about which cellular targets and functions may be most relevant to NSAID tumor inhibition in humans.

Studies Implicating Cyclooxygenase-1

Circumstantial evidence that the inducible isoform of COX contributes to colorectal neoplasia is that COX-2 is up-regulated as normal intestinal mucosa progresses to invasive colorectal cancer in humans. COX-2 protein and messenger RNA are undetectable in normal colon mucosa, yet are present in approximately 40% of human adenomatous polyps and more than 80% of colorectal cancers. COX-1, in contrast, is expressed at constant basal levels in all of these tissues. COX-2 is expressed constitutively by at least one human colon cancer cell line (HT-116) and can be induced in four other human tumor cell lines by exogenous agonists. COX-2 concentration in human colorectal carcinomas has been reported to increase with larger tumor size and deeper invasion, although not with evidence of metastases. In rodent models, COX-2 expression is up-regulated after exposure of rats to azoxymethane (AOM). COX-2 is also expressed at an early stage in APC- and APC mice. Intestinal cells from murine models of FAP overproduce COX-2 and PGE, even in mucosa in which no adenomatous polyps are visible.

Direct laboratory evidence that COX-2 affects colorectal cancer comes from genetic knockout studies that eliminate specific isoforms of COX in Min mice and from selective drug inhibition in several rodent models. Min mice that have been genetically altered to lack COX-2 activity develop 70% to 80% fewer intestinal tumors than do Min mice with normal activity of both isoforms. AOM-exposed rats treated with the selective COX-2 inhibitor celecoxib (1500 ppm) develop virtually no intestinal tumors and 50% fewer aberrant crypt foci than those exposed to the chemical carcinogen alone. Celecoxib also reduces the number and size of intestinal tumors in Min mice and variant Apc mice and in mice implanted with human colon cancer transplants.

Studies Implicating Cyclooxygenase-1

More limited experimental and epidemiologic evidence suggests that COX-1 activity may also contribute to the development of colorectal and other cancers. Homozygous inactivation of either COX-1 or COX-2 produces an equivalent 70% to 80% reduction in intestinal tumors compared to Min mice with both COX isoforms intact. No experimental studies have tested selective COX-1 inhibitors in various rodent models of carcinogenesis. However, participants in several epidemiologic studies
studies who report taking 365 mg of aspirin daily experience fewer adenomatous polyps or colorectal cancers than those who do not take NSAIDs. Aspirin is predominantly a COX-1 inhibitor at this dosage. Epidemiologic studies cannot yet assess whether prolonged use of aspirin at doses of 100 mg or less is also associated with reduced incidence of colorectal cancer or adenomatous polyps. Clinical studies report that people given low-dose aspirin (80 mg) for up to 3 months, or 325 mg daily for 60 days, have lower concentrations of PGE₂ and PGF₂α in rectal mucosa than were present in biopsy specimens taken before aspirin administration. These studies are limited in interpretability, however, in that rectal epithelial specimens are likely to have been contaminated by platelets, possibly accounting for the observed changes in eicosanoid levels.

Evidence for Nonsyncoxygenase Mechanisms

Some research suggests that NSAIDs may inhibit neoplasia through pathways other than COX or that a mix of prostaglandin-independent and -dependent mechanisms may exist. Sulindac sulfone, the sulfone metabolite of sulindac, is believed to have little inhibitory activity against COX, yet high oral concentrations (1000 and 2000 ppm in food) inhibit intestinal tumors and aberrant crypt formation in AOM-exposed rats, and inhibit chemically induced mammary cancer in mice. In one of these studies, no suppression was found in PGE₂ or the activity of COX, lipoxygenase, and phospholipase A₂. In other studies, supraphysiologic concentrations of sulindac sulfone in cell culture inhibit the growth of human HT-29 tumor cells, as well as other human cell lines that do not express COX or produce prostaglandins. NSAIDs also have been postulated to inhibit colorectal cancer by influencing nitric oxide metabolism or binding with the peroxisome proliferator-activated receptor (PPAR). The latter is postulated to be a common target by which NSAIDs can mimic the effects of the APC gene and down-regulate transcription. The relevance of these mechanistic studies to human colorectal cancer remains uncertain.

CELLULAR MEDIATORS OF TUMOR INHIBITION

ENHANCED APOPTOSIS

Accumulating evidence suggests that loss of apoptosis (programmed cell death) contributes to the development of human colorectal cancer and that NSAID treatment can restore normal apoptosis in several clinical and experimental settings. Apoptosis is impaired in adenomatous polyps from FAP patients, in sporadic colorectal polyps, and in human intestinal epithelial cells altered to overexpress COX-2. Normal apoptosis can be restored in FAP patients by a 3-month treatment with sulindac. Apoptosis can also be increased in cultured HT-29 human colon cancer cells by salicylate, sulindac or sulindac sulfide, and by other conventional NSAIDs. NSAIDs increase apoptosis in rats exposed to chemical carcinogens and in nontransformed rat intestinal epithelial cells altered to overexpress COX-2 constitutively. Although the mechanisms by which NSAIDs affect apoptosis are unknown, Takeo proposes that they may involve some critical interaction between the induction of COX-2 and homoygous loss of function of the APC gene. Apoptosis can be induced in HT-29 human colorectal cancer cells that lack APC activity by restoring APC function in these cells.

Additional evidence that apoptosis may be an important cellular mediator of the anticancer effects of NSAIDs is that the combination of NSAIDs and lovastatin is a more potent stimulus for apoptosis, experimentally, than either agent alone. Lovastatin is a cholesterol-reducing hepatic 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor. The combination of lovastatin and sulindac amplifies several-fold the stimulatory effect of sulindac alone on apoptosis in three human colon cancer cell lines (HCT-116, SW 480, and LoVo) and in AOM-exposed rodents. Agarwal et al. suggest that combining NSAIDs with an HMG-CoA reductase inhibitor may increase the effectiveness of chemoprevention or allow the use of lower, less toxic doses of NSAID.

Furthermore, experimental evidence suggests that NSAIDs cause cell-cycle arrest and accumulation of cells in the G₀/G₁ phase, potentially contributing to enhancement of apoptosis. Indomethacin has long been known to induce reversible cell-cycle arrest in the G₁ phase in cultured, transformed rat hepatoma and nontransformed human fibroblast cells. NSAIDs such as sulindac and sulindac sulfide also reduce the level and activity of several cyclin-dependent kinases that regulate cell-cycle progression and induction of apoptotic cell death in human HT-29 colon cancer cells. These effects on cell-cycle progression require concentrations of salicylate between 1 and 5 mM/L; thus, the extent to which these effects are relevant to human colon cancer remains unclear.

INHIBITION OF ANGIogenesis

Another cellular function by which NSAIDs may inhibit cancer involves the suppression of angiogenesis and neovascularization. A selective COX-2 inhibitor (NS-398) suppresses production of angiogenic factors such as vascular endothelial growth factor, basic fibroblast growth factor, transforming growth factor-β, platelet-derived growth factor, and endothelin-1 by human cultured colon cancer cells that express COX-2. COX-2 expression greatly increases the production of angiogenic factors by these cells. In the same experiment, aspirin at concentrations thought to inhibit COX-1 selectively suppressed endothelial tube formation by human umbilical endothelial cells exposed to these growth factors. The inhibitory effect of NSAIDs on angiogenesis may involve several mechanisms, such as a COX-2 pathway that affects the production of angiogenic factors by tumor cells and a COX-1 pathway involving the endothelial cell response.

EFFECTS ON METASTASIS

Relatively little research has examined the effect of NSAIDs on cancer metastases, although this area of experimental research has been active. Also limited has been research on the potential of aspirin or other NSAIDs as adjuvant therapy in treating cancers. A small randomized clinical trial found no improvement in the survival of 66 patients with Duke's class B2 or C invasive colorectal cancer with aspirin treatment of 600 mg twice daily.

NONSTERoidal ANTIINFLAMMATORY DRUGS AND CANCErS OTHER THAN COLORECTAL CANCer

A few studies have examined the relationship between the use of aspirin and other NSAIDs and the digestive tract cancers other than that of the large intestine. Table 23.6-3 lists the studies pertaining to cancers of the esophagus and stomach. In the American Cancer Society study, aspirin use was inversely associated with fatal cancers of the esophagus and stomach as well as colon and rectum, but not generally with fatal cancers outside the GI tract. The limited evidence that NSAIDs may inhibit cancers throughout the digestive tract is interesting in light of the common embryologic derivation of GI tissues and observations that COX-2 is also prominently expressed in cancers of the esophagus and stomach.

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<th>Study</th>
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The results of nonrandomized studies relating breast cancer to NSAID use have been less consistent, with two case-control studies reporting some reduction in risk, but other large prospective studies finding no association. Extensive evidence indicates that eicosanoids affect several aspects of carcinogenesis in mouse models of mammary carcinomas, and that both COX-1 and COX-2 are moderately up-regulated in some human breast tumors. However, the current
DOSE AND DURATION ISSUES IN CHEMOPREVENTION

Because the GI toxicity of NSAIDs is dose-dependent, at least two strategies have emerged for minimizing the toxicity of NSAID treatment while maintaining therapeutic effectiveness. One has been the development of "designer" drugs, such as the novel selective COX-2 inhibitors that are thought to be less ulcerogenic than conventional NSAIDs. A second approach, used effectively in preventing cardiovascular disease with aspirin, has been to identify a sufficiently low dose of NSAID that is effective therapeutically yet has minimal GI toxicity. Antiplatelet doses not exceeding 100 mg aspirin daily have the largest absolute benefit in populations at high risk of cardiovascular events, because the large, immediate reduction in cardiovascular risk far outweighs the small increase in GI bleeding that occurs even with low-dose aspirin.

With respect to the chemoprevention of colon cancer, researchers have not yet identified the lowest effective dose or optimal NSAID treatment regimen. Resolving these uncertainties becomes critically important when large numbers of people might consider taking a chemopreventive drug for several decades. In this context, balancing the potential benefit to risk is highly susceptible to the lowest effective dose of the drug, the toxicity at this dosage, the probability of serious adverse effects in a particular individual, and the probability of the event being prevented. None of these clinical questions has yet been adequately answered with respect to NSAIDs and colorectal or other cancers.

CHAPTER REFERENCES


SECTION 23.7
Physical Activity and Body Weight
GRAHAM A. COLDITZ

INTRODUCTION
The 1994 report of the U.S. Surgeon General concludes that lack of physical activity is causally related to increased risk of coronary heart disease, diabetes, and colon cancer. Other cancers are listed as having a suggestive relation, including breast cancer, whereas there is lack of evidence for a relation between activity and either rectal or prostate cancers. The evidence for colon and breast cancers is therefore summarized in detail.

COLON CANCER
Numerous studies have illustrated a relation between physical activity and colon cancer. Higher levels of physical activity are related to lower rates of colon cancer, the fourth most common cancer diagnosed in the United States.

The rates of colon cancer vary considerably among countries. During the 1960s and 1970s, there was a gradual increase in colon cancer in most industrialized countries, and in European countries with low rates there was an increase in the rates observed in high-risk countries, such as the United States and England. Low incidence is reported from India and China, whereas high rates are observed in the United States, Australia, and Western Europe. Numerous lifestyle factors have been proposed to explain this large international variation.

PHYSICAL ACTIVITY
Epidemiologic studies have measured activity in two ways: by occupation and by leisure-time activities. These measures may represent somewhat different patterns of energy expenditure. Activity demanded by employment in a certain occupation may be relatively constant from week to week and year to year, whereas leisure-time activity is far more labile, changing from week to week, season to season, and year to year. In the epidemiologic study of a disease like colon cancer, long-term patterns of activity may be the relevant factor in determining disease risk. Therefore, occupational activity may be a better marker of cancer-determining activity level than is self-reported leisure-time activity. Both the methods used to measure activity and the validity or accuracy of the methods vary considerably. Similar methodologic issues arose in the study of heart disease. When poor measures of activity were used, studies tended to underestimate the true impact of activity on health. In other words, studies using poor measures of physical activity fail to measure true activity levels and then fail to provide data showing a strong association with activity, even though physical activity is, in truth, protective against heart disease.

Likewise for colon cancer, when less accurate measures of physical activity are used, the estimated benefit from this activity is smaller than its probable true benefit. Thus, the protection by physical activity is underestimated. Nonetheless, as summarized in the following section, the most precise studies using validated measures of physical activity have shown, overall, that higher levels of physical activity are related to lower levels of colon cancer.

Validity of Activity Measures
The validity of activity measures has been assessed and is quite variable. Among the better measures, one observes a correlation between the self-reported measure of activity and an independent gold standard (such as 28 days of activity diary) in the range of 0.5 to 0.7. Thus, the epidemiologic associations observed with these measures of activity and disease outcome are considerably attenuated, perhaps by as much as one-half. For example, Giovannucci et al. reported a relative risk that was 0.68 [95% confidence interval (CI), 0.81 to 0.95] per 10 metabolic equivalent of task (MET) increase in physical activity. After correcting for measurement error, the relative risk was strengthened to 0.65 (0.48 to 0.88).

A systematic review of published literature through March 1997 identified studies that reported a measure of physical activity and outcomes of colon cancer or colorectal cancer. A review of these studies presents summary data for each, including the relative risk for each level of activity.

CASE-CONTROL STUDIES. Overall, the published case-control studies suggest a consistent inverse relation between both occupational and leisure-time activity and colon cancer risk among men and women. These results have been replicated across a wide range of countries, including China, Japan, New Zealand, Spain, Sweden, Turkey, and the United States.

COHORT STUDIES. Cohort studies generally enroll healthy individuals to assess elements of lifestyle, behavior, environment, and occupation that are thought to influence later development of disease. The initial follow-up of college athletes by Polednak did not show any protection against colon cancer, although data were not available on lifestyle characteristics (including family history, diet, smoking, etc.). The other 17 studies through 1997 show a reduction in risk similar to that observed in the case-control studies. Higher activity in adult life is generally related to reduced risk of colon cancer, although the cohort results are less consistent than those from the case-control studies. Inconsistency may, in part, be attributed to studies that focused on college activity and cancer risk many years later, or that included both colon and rectal cancer in a single outcome category. An inverse association between activity and rectal cancer is generally not seen when rectal cancer is analyzed as a separate outcome variable.) When occupation was used to categorize activity in a study of Swedish men, those with higher activity had a lower risk of colon cancer [relative risk (RR) = 0.8]. In that study, the strongest contrast was based on a joint classification of occupation and recreational activity. Men in the highest activity group for both occupation and recreation had a relative risk that was 0.3 (0.1 to 0.8) representing a 70% reduction in risk compared with men who were inactive at work and engaged in little recreational activity.

Leisure-time activity is addressed separately in the Harvard Alumni Study, a cohort of graduates from Harvard College followed since 1960 to study activity and chronic diseases. Lee and colleagues observed a strong inverse association among men who were active both in the 1960s and in 1977 when surveys were administered. Men expenditure more than 2500 kcal per week in leisure activity had a 50% reduction in risk of colon cancer compared with those spending less than 1000 kcal per week.

Overall, the cohort studies conducted in Denmark, Norway, Sweden, Switzerland, and the United States support a dose-response relation across increasing activity levels: Higher activity levels are related to lower levels of colon cancer risk. Those in the highest activity category have approximately a 40% to 50% reduction in risk of colon cancer compared to the least active category.

Although historically data have suggested that the association between physical activity and reduced risk of colon cancer is stronger in men than in women, this finding may, in part, reflect the small number of women in the high-activity category. Data from Norway show a stronger relation between total physical activity and colon cancer among women than among men, and data from the Nurses’ Health Study show similar magnitude of reduction in risk in women as observed among men in a parallel study using comparable methods for activity assessment.

SITE-SPECIFIC RISK. Studies that examined activity in relation to site of cancer in the colon suggest that the relation between higher activity and lower risk of cancer...
may be stronger for the left than for the right colon. One large case-control study shows no difference in the strength of association between vigorous activity and proximal or distal colon cancer. The association is stronger for the colon than it is for the rectum, for which activity is at best only very weakly associated.

**Interpretation**

Despite the variable and often poor measures of activity used, a consistent reduction in risk is observed across different study design and different populations and across occupational and leisure-time activity. A consistent dose-response relation emerges, indicating that those at higher levels of activity are at reduced risk of colon cancer. Across the studies, the evidence suggests that the relation is stronger for the left colon and weaker or absent for rectal cancer. Few studies have addressed the relation between specific activities and cancer risk—that is, they control for other lifestyle factors (food mass index [BMI], alcohol, and diet) that may be related to higher levels of physical activity and could therefore bias or distort the protection attributed to physical activity. Activity is independent of dietary fat and fiber intake in these studies and is also independent of BMI, a measure of adiposity. Although not all studies examined for the independence of activity from other lifestyle factors, the magnitude of the inverse relation is not materially altered when investigators have controlled for diet, BMI, and other factors. The one exception is the analysis of Whittimore et al., who saw a shift in the magnitude of association for activity but not control data from the People’s Republic of China, but no substantial change in effect after control for diet in the United States. In a detailed analysis of the Health Professionals Follow-Up Study, a cohort of some 50,000 men followed to study relations between diet and chronic diseases, Giovannucci et al. showed that individuals with higher physical activity were more likely to use multivitamins, had lower intake of saturated fat, higher intake of fiber, lower prevalence of cigarette smoking, and lower BMI (men were leaner). After controlling for these risk factors, as well as use of aspirin and family history, the protection was reduced from 56% to 47% [the relative risk changed from 0.4 (0.3 to 0.7) to 0.5 (0.3 to 0.9)]. In other words, the protection remained at almost 50% despite controlling for all the other factors known to relate to colon cancer risk. The inverse trend in risk with increasing activity remains statistically significant. Thus, we conclude that activity is not merely a marker of healthier lifestyle, but exerts an independent protective effect.

**Mechanisms**

Several biologic mechanisms have been proposed for the protective effect of physical activity, reflecting changes in physiologic measures after physical activity. Among these is the bowel transit time that decreases with physical activity. It is then proposed that the reduced transit time alters the environment within the colon and thereby reduces exposure to carcinogens. A second mechanism may be that abdominal obesity and low physical activity are independently related to insulin resistance. Across a gradient of physical activity, insulin sensitivity improves with exercise. Furthermore, insulin is a strong growth factor for colon mucosal cells in laboratory studies and an animal model of colon cancer. Thus, it is possible that activity exerts its protective effect through reduced insulin levels.

Another possible mechanism is the effect of prostaglandins on colon cell proliferation. Physical activity produces an increase in prostaglandin $F_2\alpha$, which increases intestinal motility, and a decrease in prostaglandin $E_2$, which in cell culture can act to stimulate colon cell proliferation. Further support for this possible mechanism comes from laboratory studies on rats and evidence in humans that aspirin and nonsteroidal antiinflammatory drugs, also inhibitors of prostaglandin synthesis, reduce risk of colon cancer.

With this large body of epidemiologic data and supporting laboratory studies, it appears that low levels of physical activity are causally related to increased risk of colon cancer. Causal considerations include a consistent decrease in risk with higher levels of physical activity, either measured as occupational in the activity or leisure-time activity, a dose-response relation with hours of activity per week or level of occupational physical activity, specificity for the relation with colon and not rectum, and a temporal relation such that activity measures precede the onset of colon cancer by years, although relations are stronger for more recent activity rather than distant past activity.

**BREAST CANCER**

Regular physical activity has been hypothesized to prevent breast cancer, largely by reducing circulating levels of sex hormones. The mechanisms by which physical activity reduces exposure to hormones vary by period of life. Young girls participating in strenuous athletic training such as running and ballet dancing have delayed menarche, which is known to reduce the risk of breast cancer, and even moderate-intensity physical activity may also delay menstruation. A later menarche is associated with a later onset of regular ovulatory cycles and lower serum estradiol concentrations during adolescence. Once menstruation has been established, anovulatory and irregular menstrual cycles may be more frequent among moderately and strenuously active women than among inactive women, although there is disagreement regarding the degree to which the intensity of physical activity influences menstrual abnormalities. Among older women, levels of past and current physical activity influence fat stores, which after menopause are the locus of conversion of androstenedione to estrogen.

Despite the evidence that higher levels of physical activity are associated with lower levels of circulating ovarian hormones, epidemiologic studies relating physical activity to risk of breast cancer are inconsistent. Methodologic differences in physical activity assessment are likely to have contributed to these inconsistencies. Studies have differed in the ages at which physical activity was assessed; methods for measuring intensity, frequency, and duration of physical activity; definition and categorization of physical activity levels; and age of breast cancer diagnosis. Furthermore, the ranges of physical activity that are typically studied are very limited in comparison with the levels of hard labor typically practiced by women in traditional agrarian societies. To date, the strongest reduction in breast cancer risk associated with increased physical activity has been reported in a population-based case-control study of women younger than age 40 years in Southern California. The RR was 0.42 (95% CI, 0.27 to 0.64) when comparing women with a lifetime average of 3.8 hours or more of physical activity per week to those with an average of 0 hours per week. This has been the only study explicitly devoted to the relationship between physical activity and breast cancer, and it used a detailed physical activity assessment instrument to quantify the average number of hours per week of recreational physical activity over the reproductive life span, beginning at menarche. Activities such as housework, gardening, and easy walking not for the explicit purpose of physical exercise were not counted in the measure of physical activity. Bernstein et al. concluded from their various analyses that lifelong physical activity is the critical exposure of interest with regard to breast cancer risk.

In contrast to the detailed measurement instrument previously described, a relatively simple measure of physical activity was used in a prospective cohort study of Norwegian women aged 20 to 54 years at baseline. Over a period of 3 to 5 years, women were administered two surveys about their patterns of physical activity during the previous year. The RR was 0.42 (95% CI, 0.22 to 0.79) for women who were physically active in comparison with sedentary women, who were defined in the same way. These data are second-strongest inverse association reported in the literature. This study is also the only prospective cohort study of the five reported to date to find a substantial inverse association between physical activity and breast cancer risk.

Most studies fall between these two studies with regard to the detail of physical activity measurement and categorization. For instance, in two population-based case-control studies conducted among younger women, physical activity both early in life and in the period immediately before the interview was assessed. However, neither of these studies found an association between physical activity (in either period) and breast cancer risk, despite defining physical activity categories in various ways.

Because of the potential public health significance of a relationship between a modifiable lifestyle risk factor such as physical activity and breast cancer, future
studies will need to address important methodologic issues surrounding physical activity measurement.

Although the relation between physical activity and risk of breast cancer remains unsettled, indirect evidence relating higher physical activity to risk of postmenopausal breast cancer is strong because of the important role of activity in controlling weight gain, an important cause of postmenopausal breast cancer. This, in addition to many other benefits of staying lean and fit, provide sufficient justification for including regular physical activity in daily life.

**OBESITY**

A strong and consistent relation has been reported between obesity and mortality from all cancers among men and women. Due to the relationship of obesity with postmenopausal breast cancer and endometrial cancer, the relation is stronger among women than among men.

Attained weight and weight change in adults provide sensitive measures of the balance between long-term energy intake and expenditure. Although the relation between these variables and breast cancer risk has been complex and confusing, findings provide a coherent picture and indicate a major contribution of weight gain to risk of postmenopausal breast cancer risk. Findings have been particularly intriguing: (1) in affluent Western populations with high rates of breast cancer, measures of body fatness have been inversely related to risk of premenopausal breast cancer, and (2) body fatness has been only weakly related to postmenopausal breast cancer risk despite strong associations between body fat and endogenous estrogen levels.

The inverse relation between body weight (typically defined as BMI, calculated as weight in kg divided by height in meters, to account for variation in height) and incidence of premenopausal breast cancer has been consistently seen in recent prospective studies and in a meta-analysis of both case-control and cohort studies. Little relation between BMI and breast cancer mortality has been observed in premenopausal women, probably because delayed detection and diagnosis in heavier women counterbalances the lower incidence among heavier women. Heavier premenopausal women, even at the upper limits of what are considered to be healthy weights, have more irregular menstrual cycles and increased rates of anovulatory infertility, suggesting that their lower risk may be due to fewer ovulatory cycles and less exposure to ovarian hormones. Increased rates of menstrual irregularity and anovulatory infertility also are seen among very lean women, but such women are uncommon in Western populations. In case-control studies, a consistent relation between menstrual cycle regularity and breast cancer risk has not emerged, which could cast doubt on this explanation, but this may be due to the indirect relation between menstrual regularity and ovulation and to difficulties in remote recall. In a prospective study among younger women, compared with regular cycles of approximately 28 days, both short and longer or irregular cycles were associated with reduced risk of breast cancer, lending support to irregular anovulation as the explanation for the lower risk in heavier women.

In both case-control and prospective studies conducted in affluent Western countries, the association between BMI and risk of breast cancer among postmenopausal breast cancer has been only weakly positive or nonexistent. The lack of a stronger association has been surprising because obese postmenopausal women have plasma levels of endogenous estrogens nearly twice as high as lean women, due to conversion of androstenedione to estrogens in adipose tissue and also lower levels of sex-hormone binding globulin. However, the lack of a stronger positive association now appears to be due to two factors.

First, like the protective effect of early pregnancy, the reduction in breast cancer risk associated with being overweight in early adult life appears to persist throughout later life. Thus, an elevated BMI in a postmenopausal woman represents two opposing risks: a protective effect due to the correlation between early weight and postmenopausal weight and an adverse effect due to elevated estrogens after menopause. For this reason, weight gain from early adult life to after menopause should be more strongly related to postmenopausal breast cancer risk than would be elevated weight. Indeed, the relation between weight gain and risk of postmenopausal breast cancer has been consistently supported by both case-control and prospective studies.

A second reason for failing to appreciate a greater adverse effect of excessive weight or weight gain on risk of postmenopausal breast cancer is that the use of postmenopausal hormones obscures the variation in endogenous estrogens due to adiposity and elevates breast cancer risk regardless of body weight. To appreciate fully the impact of weight or weight gain, an analysis should be limited to women who never used postmenopausal hormones. Thus, among women who never used postmenopausal hormones in the Nurses' Health Study, those who gained 25 kg or more after age 18 years had double the risk of breast cancer compared with women who maintained their weight within 2 kg. In this population, the combination of either using postmenopausal hormones or gaining weight after age 18 years accounted for one-third of postmenopausal breast cancer cases.

The relation between body weight and breast cancer risk among low-risk, mainly non-Western, countries has been observed to be somewhat different in higher risk countries. In general, the inverse relation between weight and premenopausal breast cancer risk has not been observed, and the association between weight and breast cancer risk has been stronger. This difference is likely to be due to the lower prevalence of obesity among premenopausal women in these low-risk countries; few women are likely to be sufficiently overweight so as to cause anovulation and a reduction in premenopausal breast cancer risk. As a result, BMI after menopause would only reflect the adverse effects of high endogenous estrogens, opposed by a residual protective effect due to correlation with overweight in early adult life.

**RELATIONSHIP BETWEEN OBESITY AND CARCINOMA**

As in animal studies, energy balance appears to play an important, but complex role in the causation of human breast cancer. During early adult life, obesity is associated with a lower incidence of breast cancer before menopause, but no reduction in breast cancer mortality. However, weight gain after age 18 years is associated with a lower incidence of breast cancer among women who maintained their weight within 2 kg. However, the lack of a stronger positive association now appears to be due to two factors.

The relationship between obesity and endometrial cancer follows from the excess exposure to estrogen that is associated with adiposity. This direct relation has been long observed.

The relationship between obesity and colon cancer has been observed among both women and men and persists even after control for physical activity and dietary patterns. It is postulated that excess weight gain may act through increased insulin resistance and hyperinsulinemia to promote colon carcinogenesis.

Evidence for a relationship between obesity and prostate cancer is less consistent. At this time, the inconclusive evidence precludes a definite assertion of any important relation.

**CONCLUSIONS**

Lack of physical activity and adult weight gain are harbingers of our Western culture and both act to increase risk of major malignancies. Through numerous mechanisms, these two lifestyle factors contribute substantially to the risk of colon and breast cancer. The evidence is strong for obesity and endometrial cancer, and less consistent for other major malignancies.

**CHAPTER REFERENCES**

**INTRODUCTION**

Prophylactic is a word derived from Greek (pro- “before” and phylassin “to guard”) meaning “advanced guard.” The current status of prophylactic surgery to prevent malignant disease is limited and often controversial. Clinicians have long recognized that certain conditions, such as inflammatory bowel disease and cryptorchism, confer on patients an increased risk of developing fatal organ-specific malignancies. Advances in molecular biology coupled with an increased appreciation that cancer is a genetic disorder have made accurate risk evaluation with genetic screening a reality for certain malignancies. As our understanding of cancer susceptibility has advanced, so too has our appreciation of the complexity of the associated social and clinical issues. Progress in the laboratory has often outpaced our ability to use these new insights in the clinic. These factors have created a new impetus to develop practical strategies to prevent cancer.

That surgery can and should be used to prevent cancer is obvious (Table 24-1). The fact that colonoscopic polypectomy can help prevent colorectal cancer is now accepted and largely taken for granted. Nevertheless, the efficacy of many other interventions is not as convincing. Although the role of prophylactic surgery is largely undefined, it is certain to evolve. The focus of this chapter is the current use of surgery to prevent cancer.

**TABLE 24-1. Prophylactic Surgery for the Prevention of Cancer**

**MULTIPLE ENDOCRINE NEOPLASIA 2 AND FAMILIAL MEDULLARY THYROID CARCINOMA**

Multiple endocrine neoplasia (MEN) is characterized by the development of multiple tumors in endocrine organs in a patient and close relatives. The syndrome is divided into three types: MEN 1, MEN 2a, and MEN 2b. MEN 2 is defined by the combination of tissues affected and the presence of developmental abnormalities and has been the focus of extensive genetic analysis. MEN 2a is associated with medullary carcinoma of the thyroid and with hyperparathyroidism. Individuals with MEN 2b have medullary carcinoma of the thyroid, pheochromocytoma, and developmental abnormalities involving hyperplasia of intestinal autonomic nerve plexuses and growth of nerve axons in the lips, oral mucosa, and conjunctiva, which give rise to the characteristic facies. A syndrome related to MEN 2 is familial medullary thyroid carcinoma, in which patients have only medullary carcinoma of the thyroid. MEN 2a, MEN 2b, and familial medullary thyroid carcinoma have an autosomal dominant pattern of inheritance and account for approximately 25% of all cases of medullary carcinoma of the thyroid. ²

In 1993, it was established that mutations in the RET protooncogene were responsible for the hereditary predisposition to medullary thyroid cancer. ³ This genetic breakthrough has allowed accurate identification of kindreds at high risk for developing medullary carcinoma of the thyroid and has permitted families to consider the risks and benefits of prophylactic thyroidectomy.

In 1994, Wells et al. ⁴ reported the first experience with prophylactic thyroidectomy based on identification of RET protooncogene mutations. Thirteen patients were confirmed to carry a mutation in the RET protooncogene in association with MEN 2a and underwent immediate thyroidectomy. In each patient, the resected thyroid gland demonstrated C-cell hyperplasia. No metastases were found in regional nodes, and all patients had normal postoperative stimulated plasma calcitonin levels. Subsequent reports have confirmed the validity of this approach, and prophylactic thyroidectomy is now recommended for these patients at approximately 6 years of age.

Kebebew et al. ⁵ reported a review of ten published series of patients that had prophylactic thyroidectomy for RET protooncogene germline mutations. Two hundred and nine patients were included in this review, and only 3.4% of these patients had normal thyroid histology. A central node dissection was performed on 139 of these patients, and 12 individuals (8.6%) were found to have cervical node metastases. These 12 patients ranged in age from 14 to 70 years. Overall, the morbidity from total thyroidectomy was low. These investigators have recommended that a central node dissection be included when prophylactic total thyroidectomy is performed for patients with RET protooncogene mutations.

A second technical issue is whether to include the routine use of total parathyroidectomy and parathyroid autotransplantation in asymptomatic children with MEN 2a. Decker et al. ⁶ reported on the strategy of leaving parathyroid tissue preserved in situ. These authors recommended this approach because only 10% to 20% of these individuals develop parathyroid disease, and when parathyroid disease does develop in this population, it is usually focal. ⁷

Prophylactic thyroidectomy has become the treatment of choice for patients with RET protooncogene mutations and, if done at an early age, the cure rate should be 100%. The identification and management of these patients is perhaps the best example of prophylactic surgery in patients known to be at risk for an inherited malignancy. Genetic testing allows the accurate identification of patients at high risk of developing an invasive cancer, and the organ at risk is removed surgically with low morbidity.
BARRETT'S ESOPHAGUS AND ESOPHAGEAL CANCER

Barrett's esophagus is a premalignant condition in which the stratified squamous epithelium in the distal esophagus is replaced to a variable extent by metaplastic columnar epithelium. It is significant from an oncologic perspective because of the close association between Barrett's esophagus and the development of adenocarcinoma of the esophagus. Barrett's esophagus develops as a sequela of chronic inflammation caused by reflux of gastric contents, including acid, pepsin, and bile acids. Esophageal motility studies and pH monitoring suggest that these patients exhibit weak lower esophageal sphincter tone and slow clearance of gastric acid.13,14,15 Although Barrett's esophagus can be recognized or suspected by its appearance on endoscopy, a definitive diagnosis of Barrett's esophagus must be based on biopsy and histologic analysis. The histologic features of Barrett's esophagus should include a demonstration of goblet cells interspersed among mucin-type columnar cells. This represents the so-called specialized columnar epithelium and is pathognomonic of the process.12

It is difficult to determine the incidence of Barrett's esophagus. The majority of individuals with Barrett's esophagus in the general population are probably asymptomatic and therefore do not seek medical attention.12

Historically, Barrett's esophagus has been taken to mean specialized columnar epithelium that was determined to be more than 3 cm in length, and consequently, much of the published information regarding the incidence and natural history was generated by analyzing patients with long segments of the disease. It is now recognized that intestinal metaplasia of less than 3 cm in length should be classified as Barrett's. It has been reported that up to 33% of all patients undergoing upper endoscopy may have histologic evidence of Barrett's esophagus.15,16,17 Approximately 10% of patients with frequent reflux symptoms will have a long segment of Barrett's esophagus identified.12

Numerous reports have confirmed that patients with Barrett's esophagus are at increased risk to develop adenocarcinoma of the esophagus.20,21,22,23 In a review of 18 published series, Tytgat24 estimated the median incidence of esophageal adenocarcinoma in patients with the disease to be approximately 1 cancer per 100 patient-years of follow-up. The overall risk was approximately 40 times higher than that of the general population.22 The annual rate of cancer development in these patients is estimated to be approximately 0.8%.22 Information on the risk of developing adenocarcinoma in short segments (less than 3 cm) of Barrett's esophagus is more limited, but the available data suggest it is associated with significant potential for malignant degeneration.22

The detection of esophageal epithelial dysplasia is an important clinical factor used to stratify patients with Barrett's esophagus. Dent et al.22 reviewed eight published series and reported the outcome of 50 patients with high-grade dysplasia in Barrett's esophagus. These individuals were followed for up to 5 years, and adenocarcinoma developed in 16 patients (32%). Eleven patients had a resection for dysplasia where no malignancy was found in the specimen.22 Hameeteman et al.22 published a prospective study of 50 patients with Barrett's esophagus. All patients were without carcinoma at entrance to the study and were followed for a mean of 5.2 years. Six patients had low-grade dysplasia, and one patient had high-grade dysplasia at the start of the study. By the end of the observation period, five patients had developed adenocarcinoma, ten scored as low-grade dysplasia, and three were scored as high-grade dysplasia.22 Thus, it is suggested that low-grade dysplasia may be helpful in identifying individuals who are likely to progress to high-grade dysplasia or adenocarcinoma. It is clear, however, that not all high-grade dysplasia progresses to cancer, and regression of a short segment of Barrett's esophagus that contained high-grade dysplasia has been reported.25,26

The optimal management of Barrett's esophagus has not been established. No prospective randomized trials have compared alternative treatment strategies. Comparing published series can be problematic because of biopsy sampling errors, differences in pathologic interpretation, and variations and improvements in endoscopic and surgical techniques. Although complete agreement has not been reached regarding the best approach for these patients, most experts depend on the degree of dysplasia associated with Barrett's esophagus to guide treatment recommendations.

BARRETT'S ESOPHAGUS WITHOUT DYSPLASIA

No role for esophagectomy has been established in patients with Barrett's esophagus and no evidence of dysplasia. The clinical issues surrounding these patients involve questions about the efficacy of screening and the effects of medical or surgical therapy to prevent progression to dysplasia. The exact risk of a patient with Barrett's esophagus without dysplasia for developing cancer is unknown, but it has been estimated to be 0.2% to 2.1% per year, which is an incidence 30 to 125 times that of the general population.23 Consequently, most patients who are surgical candidates are enrolled into surveillance programs. Currently, most patients are treated medically with weight reduction, head of bed elevation, and H2-receptor antagonists or protein pump inhibitors. The goal of therapy is symptomatic relief of gastroesophageal reflux. Although symptoms of reflux often improve with therapy, no evidence suggests that medical therapy consistently induces regression of the metaplastic columnar epithelium.25,26 In addition, there is little evidence to suggest that antireflux surgery has an important impact on this process. DeMeester27 reported a review of 11 published series that followed patients with Barrett's esophagus after an antireflux procedure. A total of 340 patients were followed for a mean of 4.4 years. Seventy-four percent of these patients showed no change in their Barrett's mucosa, 17% showed progression, 12% showed partial regression, and only 4% achieved a complete regression of Barrett's esophagus.

The current recommendation for patients with Barrett's esophagus without dysplasia is to have endoscopic surveillance and biopsy performed every 1 to 2 years. This recommendation assumes that the patient is a satisfactory surgical candidate.24

BARRETT'S ESOPHAGUS WITH LOW-GRADE DYSPLASIA

There is no role for esophagectomy in patients with low-grade dysplasia associated with Barrett's esophagus. Clearly, the risks of developing severe dysplasia or adenocarcinoma of the esophagus are significant. Medical therapy and antireflux procedures do not appear to influence the natural history of the condition. The current recommendation for healthy patients with low-grade dysplasia associated with Barrett's esophagus is to undergo histologic surveillance every 6 to 12 months. Innovative techniques, such as mucosal ablation, photodynamic therapy, and chemoprevention, are under active investigation.

BARRETT'S ESOPHAGUS WITH HIGH-GRADE DYSPLASIA

The treatment of patients with high-grade dysplasia associated with Barrett's esophagus is controversial. Most experts recommend that healthy patients undergo esophagectomy by an experienced surgeon. The pathologic diagnosis should be independently confirmed.24,25,26 Because a wide spectrum of mortality has been reported after esophagectomy (1.4% to 21.0%) and because not all patients with high-grade dysplasia develop adenocarcinoma, some experts have made a case for aggressive surveillance for these patients. Levine et al.28 described and reported on an aggressive biopsy protocol with up to 12 biopsy specimens per centimeter of Barrett's mucosa in patients with high-grade dysplasia. Seventy patients with high-grade dysplasia were followed, and 12 were found to have early-stage adenocarcinomas of the esophagus within an average of 2 months after the diagnosis. In the remaining 58 patients, 15 (23%) progressed to early-stage cancer after an average of 1.1 years of follow-up. None of the remaining 43 patients (74%) developed cancer when followed an average of 2.5 years. These results have not been confirmed at other institutions. It should be noted that more than 25% of these patients developed esophageal adenocarcinoma. In addition, the described surveillance protocol may be impractical for most physicians to follow. Physicians managing healthy patients with severe dysplasia associated with Barrett's esophagus should seriously consider prophylactic esophagectomy.

The recommendation for surgery or surveillance should take into account the mortality and morbidity of esophagectomy weighed against the risk and expected prognosis associated with invasive cancer. Most surgical series report an operative mortality of less than 10% when esophagectomy is performed for malignant disease. The mortality for prophylactic esophagectomy may be less than the mortality associated with surgery for malignant disease, because many patients with malignant disease are debilitated. In addition, prophylactic esophagectomy does not require an extensive nodal dissection. Either a transhiatal or multiepipscopal approach with cervical anastomosis appears to be appropriate. The reported 5-year survival rate for patients undergoing esophagectomy for known invasive cancer is estimated to be 18% to 32%.29 The survival of patients with invasive adenocarcinoma detected during a rigorous surveillance program may be higher.

BREAST CANCER

It has been estimated that 5% to 10% of women with breast cancer have hereditary breast cancer.30,31,32 BRCA1 was identified on the long arm of chromosome 17 (17q21) in 1990, and more than 500 different mutations in this gene have been identified.33,34,35 BRCA1 is transmitted as an autosomal dominant gene with high penetrance, so that 50% of the children of carriers inherit the trait. It has been estimated that women with a BRCA1 gene mutation have between a 56% to 85%
A second breast cancer susceptibility gene, BRCA2, was identified and localized to the long arm of chromosome 13 (13q12-13). Women with BRCA2 germine mutations are estimated to have a lifetime risk of breast cancer that is similar to that of BRCA1 carriers.

The optimal management strategy for patients with BRCA1 and BRCA2 mutations has not been established. The clinical options for managing a patient known to have a BRCA1 or BRCA2 mutation are obvious and include increased surveillance or prophylactic bilateral total mastectomy. No prospective trials have compared these options. Furthermore, serious questions remain regarding the efficacy of both surveillance and prophylactic mastectomy in this patient population.

Chemoprevention using tamoxifen has been shown to reduce the incidence of breast cancer in women at high risk for breast cancer, but the results in women with an inherited susceptibility to breast cancer are not known. Clearly, counseling regarding any option must take into account the uncertainties associated with the estimation of cancer risk; the lack of definitive research regarding risk; and the social, medical, and psychological status of the patient. Ideally these factors should be reviewed during counseling that occurs before genetic screening.

The most obvious management strategy, and one that appears currently to be most popular among clinicians, is for patients with BRCA1 or BRCA2 mutations to depend on increased surveillance. This strategy is based on the assumption that an invasive cancer will be detected at an early stage, which is associated with a good prognosis. The current recommendations for surveillance in these women include monthly self-examination beginning by age 18, annual or semiannual clinician breast examination, and annual mammography beginning at age 25 to 35 years.

These recommendations reflect a commonsense approach to attempt to reduce the risk of breast cancer–related mortality. However, the evidence to support such a strategy is limited. The one randomized trial that assessed the efficacy of breast self-examination showed no difference in the stage of detected cancers and no reduction in mortality from breast cancer in the trained cohort. The sensitivity of clinician breast examination was highly based on tumor size, breast density, and experience of the clinician. Palpation of a breast mass of less than 10 mm is problematic, even for the most experienced clinician.

Mammography has been firmly established to reduce breast cancer mortality by up to 30% to 40% when used for women 50 to 70 years of age. For women 40 to 49 years of age, the benefit of mammography has been inconsistent. Screening mammography has not been effective in younger women, because the density of their breast tissue limits the quality of x-rays. The sensitivity and specificity of mammography for detecting nonpalpable breast cancers in young women with BRCA1 or BRCA2 mutations is unknown.

Prophylactic mastectomy is a second option for reducing breast cancer risk. This procedure had fallen out of favor because of multiple case reports of breast cancer after prophylactic mastectomy, combined with a lack of credible evidence to support the efficacy of the intervention. Breast tissue can be detected in the chest wall, axilla, and abdomen, which are distant to the typical surgical field during subcutaneous or total mastectomy. Residual breast tissue remains after mastectomy, with larger amounts of breast tissue presumed to be present after subcutaneous mastectomy compared to total mastectomy.

Hartmann et al. published a retrospective study based on the Mayo Clinic experience with prophylactic mastectomy (Table 24-2). This report represents the first indication that prophylactic mastectomy may reduce the incidence of breast cancer in women at high risk for developing invasive cancer. The study included 639 women who had undergone prophylactic mastectomy between 1960 and 1993. Patients were assigned into either a high- or moderate-risk group based on family history. A high-risk cohort had a family history that suggested an autosomal dominant predisposition to breast cancer. All other women were considered to be at moderate risk for developing breast cancer. A control study group of sisters was used for the analysis of the high-risk probands. The Gail model was used to predict the expected number of breast cancers and breast cancer–related deaths for women in the moderate-risk group. The authors concluded that bilateral prophylactic mastectomy was associated with at least a 90% reduction in the incidence of breast cancer for these women. Women in both the high-risk and moderate-risk cohorts appeared to have a significant reduction in the risk of dying from breast cancer after prophylactic surgery.

Interestingly, all seven women who developed breast cancer after prophylactic surgery had undergone bilateral subcutaneous mastectomy. No patient who had bilateral total mastectomy developed breast cancer (7 of 575 vs. 0 of 64; P = .38). Most experts recommend bilateral total mastectomy as the procedure of choice for patients who choose prophylactic mastectomy.

Additional support for preventative surgery can be found in a report by Robson et al. These investigators followed women of Ashkenazi Jewish descent who underwent lumpectomy and radiation therapy for invasive breast cancer. Outcomes were compared for women with or without BRCA1 or BRCA2 mutations. Women with BRCA1 or BRCA2 mutations were more likely to develop ipsilateral local recurrence, although this finding was not statistically significant. Women with mutations were also significantly more likely to have cancer before the age of 50, were more likely to develop contralateral breast cancer, and were more likely to have metastatic nodal involvement. Distant disease-free survival and breast cancer–specific survival rates were shorter at 10 years for women with BRCA1 or BRCA2 mutations.

Two reports of the estimated benefit of prophylactic mastectomy for women with BRCA1 or BRCA2 mutations have been based on decision analysis using a Markov model to determine survival. Grann et al. estimated the probability of developing breast cancer based on a literature review of women with BRCA1 or BRCA2 gene mutations and based on the mortality rates associated with breast cancer from Surveillance, Epidemiology, and End Results data. They assumed a 90% reduction of risk with the procedure and concluded that a 30-year-old woman would improve her survival by 2.8 to 3.4 years. Schrag et al. using a similar model, estimated an 85% reduction in breast cancer incidence with prophylactic mastectomy and concluded that a 30-year-old woman with a BRCA1 or BRCA2 mutation would gain 2.9 to 5.3 years of life expectancy from the surgery.

The psychological effects of prophylactic surgery in patients have not been thoroughly evaluated. Reconstructive surgical techniques that include autologous tissue transfer have dramatically improved the cosmetic results of breast surgery. Although the surgical morbidity associated with bilateral mastectomy is low, it is inevitably increased when breast reconstruction is added. There is a clear need to define the efficacy of surveillance strategies, as well as the efficacy of chemoprevention and prophylactic surgery in this challenging population. Until more accurate clinical information is available, women must be counseled based on the limited information available.

**LOBULAR CARCINOMA IN SITU**

Lobular carcinoma in situ (LCIS) is a histopathologic entity characterized by cellular proliferation originating in the lobules and terminal ducts of the breast. Women found to have LCIS on breast biopsy are known to be at increased risk of developing invasive ductal and lobular carcinoma of the breast. The critical clinical features of LCIS are that it is a noninvasive process, frequently found to be multifocal and bilateral, and it generally lacks clinical and mammographic signs. The precise
incidence of LCIS is unknown, but it is estimated to be identified in approximately 0.5% to 1.5% of all benign breast biopsies and in approximately 2% of breast specimens obtained for mammographic abnormalities. Women with LCIS are clearly at increased risk for developing subsequent invasive carcinoma. Six series of women with LCIS who were followed for an average of at least 15 years have been published. These series reported that between 12.5% and 34.5% of women with LCIS developed invasive breast cancers. A metaanalysis of 389 cases of LCIS followed for a mean of 10.3 years noted that invasive breast cancers developed in 16.4% of these women, and the breast cancer mortality rate was 2.8%. Treatment options for patients with LCIS remain controversial. Close observation with or without tamoxifen is currently the most popular choice. Evidence from the National Surgical Adjuvant Breast Project tamoxifen prevention trial noted that women with LCIS treated with tamoxifen demonstrated a decrease in the incidence of invasive cancer from 12.99 per 1000 to 5.69 per 1000. Bilateral prophylactic mastectomy is an appropriate choice for healthy women who are unwilling to accept the risks associated with LCIS or with tamoxifen chemoprevention.

OVARIAN CANCER

Women identified as carrying the BRCA1 or BRCA2 mutation are at high risk for developing ovarian cancer as well as breast cancer. The lifetime risk of developing ovarian cancer for a woman with a BRCA1 mutation is approximately 30% to 60%, although some estimates are as high as 85%. Patients with BRCA2 mutations have an estimated lifetime ovarian cancer risk of approximately 10% to 20%. The optimal management strategy for a woman with an inherited susceptibility to ovarian cancer is unclear. To date, no convincing evidence demonstrates that surveillance for ovarian cancer is effective. This may reflect the low ovarian cancer incidence associated with the general population. Screening for ovarian carcinoma has been hampered by the low sensitivity and specificity of the available techniques, which include pelvic examination, serum CA-125 determinations, and transvaginal ultrasound. In addition, a laparoscopy or a laparotomy is required to make the diagnosis. Currently, routine screening in the general population has not been shown to impact on the morbidity and mortality associated with ovarian cancer, and it is not recommended. The utility of increased surveillance for patients with BRCA1 and BRCA2 mutations has not been thoroughly investigated. It is known, however, that approximately 70% of patients diagnosed with ovarian cancer have stage III or IV disease and that these patients generally have poor 5-year median survival rates.

Faced with a lack of effective screening for ovarian cancer and the poor prognosis of advanced disease, prophylactic oophorectomy has been suggested as a reasonable alternative for women considered to be at high risk for invasive cancer. The National Institutes of Health Consensus Panel on Ovarian Cancer and the American College of Obstetricians and Gynecologists have concluded that prophylactic bilateral oophorectomy should be recommended to women older than 35 or after childbearing is completed if there is an inherited predisposition for ovarian cancer. The Cancer Genetics Consortium reviewed the same information and concluded that the evidence is insufficient to recommend for or against prophylactic oophorectomy as a measure to reduce ovarian cancer risks.

It is clear that prophylactic bilateral oophorectomy does not completely eliminate the risk of developing abdominal carcinomatosis that histologically resembles ovarian cancer. Tobacman et al. reported that, among the 16 potentially inherited ovarian cancer families studied at the National Cancer Institute, prophylactic oophorectomy had been performed on 28 women. Three of these women developed ovarian-like carcinomatosis 1 to 11 years after oophorectomy. This finding may reflect the fact that the peritoneum has the same embryologic origin as the ovarian epithelium and that the entire peritoneum may be at risk for malignant degeneration. Alternatively, occult ovarian cancer may have been present at the time of surgery. Struwing et al. reported an analysis of 12 families with inherited breast/ovarian cancers and noted a reduction in ovarian cancer in oophorectomized women compared with women who had not undergone surgery. Compared with adjusted Connecticut Tumor Registry data, a 24-fold excess of ovarian cancer was found among nonoophorectomized women, and a 13-fold excess of “ovarian-like” cancer was found among the women who had undergone oophorectomy. These results were not statistically significant.

Patients with BRCA1 and BRCA2 mutations are obviously at risk for both breast and ovarian cancer. Clinical decisions regarding prophylactic surgery are difficult when breast and ovary are considered independently, and the decisions become more challenging when they are considered together. Rebbeck et al. analyzed 43 women with BRCA1 mutations who underwent bilateral prophylactic oophorectomy and had not had bilateral prophylactic mastectomy. Control subjects included women with BRCA1 mutations who had not had oophorectomy and had no prior history of breast or ovarian cancer. These authors reported a statistically significant reduction in breast cancer risk after oophorectomy when compared to the control cohort. The reduction in breast cancer risk appeared to increase over time. The use of hormone replacement therapy did not negate the reduction in breast cancer risk after oophorectomy in these patients.

Evidence indicates that the use of oral contraceptives is associated with a decreased risk of ovarian cancer. The use of oral contraceptives has not been analyzed in patients with BRCA1 and BRCA2 mutations, and what effect, if any, these medications would have on the incidence of breast cancer in these patients is unknown.

COLORECTAL CANCER

Approximately 75% of all colorectal cancers occur in patients with no known risk factors for colon cancer. Individuals with ulcerative colitis, familial adenomatous polyposis (FAP), and hereditary nonpolyposis colorectal cancer (HNPCC) are at increased risk for developing the disease, but these patients probably account for fewer than 10% of all colorectal cancer cases. Despite the low incidence of these conditions in the general population, understanding and managing these patients has provided insights into the etiology of cancer and the potential role of surgery in the prevention of cancer.

ULCERATIVE COLITIS

Ulcerative colitis is a nonspecific inflammatory bowel disease of unknown etiology that involves the rectum, usually all or part of the colon, and, frequently, the distal terminal ileum as a result of colonic reflux. The clinical course of ulcerative colitis is variable, ranging from intermittent to chronic, and the severity of attacks also vary widely from mild to fulminant. The incidence of ulcerative colitis is relatively low at approximately 8 to 15 cases per 100,000 people. From an oncologic perspective, ulcerative colitis is important because of its association with colorectal cancer. Although only a small fraction of colon cancer occurs in the setting of ulcerative colitis, colorectal cancer is the major cause of the increased morbidity and mortality of patients with this inflammatory disease.

It is difficult to precisely determine the risk of colorectal cancer in patients with ulcerative colitis. Most but not all studies have noted a significant increase in the risk of colorectal cancer in this population. The duration of disease and the extent of colonic involvement at the time of diagnosis are the two most important clinical factors that determine the degree of increased cancer risk. In patients with pancolitis, the cancer risk is approximately 0.5% to 1.0% per year after 10 years of disease. A disease duration of 20 years in patients with pancolitis is associated with an estimated cumulative incidence of malignancy of between 5% and 35%. The cumulative risk of malignancy increases over time and is reported to be as high as 75% after 40 years of disease.

Patients with pancolitis are known to be at higher risk of developing cancer compared with patients with left-sided colitis. Ulcerative colitis, when limited to the left colon, is associated with an estimated cumulative incidence of cancer between 1% and 5% at 20 years. Patients with only proctitis appear to be at only average risk for colorectal cancer compared with the general population. The impact of other related clinical factors, including the age of onset of the disease and family history of colon cancer, is not known.

The optimal management strategy for patients with long-standing ulcerative colitis remains controversial and varies from prophylactic colectomy after 10 to 20 years of disease to vigilant surveillance with colonoscopic examination and multiple random biopsies to exclude dysplasia. In the latter strategy, colectomy is recommended based on the presence and degree of dysplasia. The differences in management strategies are not surprising given the heterogeneous nature of inflammatory bowel disease and the patient population and the absence of randomized clinical trials to support one strategy over another.

There is widespread agreement that colorectal dysplasia is a strong but imperfect marker for identifying patients likely to develop colorectal cancer. Colonic surveillance is performed with the assumption that a dysplastic lesion can be detected before invasive cancer has developed. Invasive cancer can be found in approximately 10% of patients with ulcerative colitis at initial screening. Patients with no dysplasia identified on biopsy have a 3% cumulative risk of developing cancer when followed over time. Patients found to have indefinite or low-grade dysplasia are thought to progress to invasive cancer or severe dysplasia between 16% and 54% at the time. Forty percent to 45% of patients with ulcerative colitis identified to have high-grade dysplasia or dysplasia associated with a mucosal mass develop colorectal cancer.
Many of these patients already have evidence of nodal metastasis. It is also important to recognize that although the risk of developing colorectal cancer if there is no histologic evidence of dysplasia appears to be low, up to 25% of patients with ulcerative colitis–associated invasive cancer demonstrate no dysplasia in the resected specimens.

No well-controlled trials have been conducted that confirm the efficacy of colon surveillance to reduce the mortality of ulcerative colitis–associated colorectal cancer. Leonard-Jones reported a review of four published series that included 423 patients who were screened regularly by colonoscopy over a period of 12 to 15 years. Eleven patients were operated on for precancerous lesions, and only three Duke’s class A lesions and one Duke’s class B lesion were found. No cancer deaths were reported during the surveillance period. The author suggested that surveillance colonoscopy should be performed only in individuals with long-standing ulcerative colitis involving the entire colon.

Despite the limitations and lack of data to support the efficacy of colon surveillance for patients with long-standing ulcerative colitis, the fact that surgery eliminates the symptoms of ulcerative colitis, including bleeding, diarrhea, anemia, steroid dependence, and cyclosporin therapy, as well as eliminating the risk of colorectal cancer may be underappreciated. Several surgical alternatives are available for patients undergoing colectomy, and the operation should be tailored to the individual and the clinical situation. In the setting of acute colitis, for example, most surgeons recommend a subtotal colectomy and ileostomy. In the elective surgical setting, many options are available, including proctocolectomy and ileostomy, colectomy and ileorectal anastomosis (assuming the rectum is free of inflammation), proctocolectomy and Kock continent ileostomy, or ileal pouch–anal anastomosis. Each procedure is associated with reported complications; however, surgery for ulcerative colitis is extremely safe for most patients, and the reported operative mortality is less than 1%, even in the emergency setting. Although comparing the outcomes of each procedure is difficult and controlled studies do not exist, most patients report a high quality of life regardless of the procedure performed.

It is evident that some consideration of colectomy should be taken 10 years after the diagnosis of ulcerative colitis in patients with pancolitis. After a 20-year disease interval, a stronger case for prophylactic colectomy can be made for patients, even in the absence of dysplasia. Colon surveillance for dysplasia is an option favored by many clinicians, and it is most appropriate for patients with disease limited to the left colon or rectum and for patients with a short duration of disease. Any surveillance strategy that recommends colectomy based on histologic evidence of dysplasia will miss some patients with invasive cancer. The precise number of patients in this situation is unknown. If surveillance is the adopted strategy, then it is recommended that, in the absence of dysplasia, colonoscopy and multiple biopsies should be performed every 2 years until 20 years of disease. At 20 years of disease, surveillance colonoscopy should be performed annually.

**HEREDITARY COLORECTAL CANCER**

It is estimated that up to 20% of patients with colorectal cancer may have some form of inherited susceptibility. Hereditary colon cancer currently includes FAP and HNPCC. Although many of the clinical issues surrounding these syndromes are similar, each syndrome is considered separately because of differences in the genetics, in the phenotypic presentations, and in the accepted management strategy.

**FAMILIAL ADENOMATOUS POLYPSY**

FAP is a rare autosomal dominant inherited disease in which patients develop hundreds to thousands of adenomatous polyps. The clinical diagnosis is based on the histologic confirmation of at least 100 adenomas. These polyps are similar on histologic examination to sporadic adenomatous polyps and usually appear during the second or third decade of life. The genetic cause of FAP is a mutation of the adenomatous polyposis coli (APC) gene located on chromosome 5 (5q21). The genetic alterations found in patients with FAP are similar to those identified in sporadic colon cancer, except an APC mutation is present as a germline mutation.

Genetic tests for APC mutations are commercially available.

The obvious phenotypic appearance of FAP coupled with the fact that more than 90% of patients with FAP develop colon cancer by age 40 has helped to establish standard treatment for this disease. Elective prophylactic colectomy is the current mainstay of therapy and has been performed for FAP since the 1930s. No trials have compared surgery with surveillance. The current recommendations for treatment of this genetic disorder include annual sigmoidoscopy beginning by age 10 years and prophylactic colectomy in the teen years or when colon polyps are detected at endoscopy. Patients that elect to have colectomy and ileorectal anastomosis face the risk of subsequently developing rectal cancer. Estimates of the risk of rectal cancer after subtotal colectomy vary widely and have been reported to be as high as 55% at 30 years. Patients with ileorectal anastomosis require lifelong endoscopic surveillance.

The choice of operations for patients with FAP includes proctocolectomy with ileostomy, proctocolectomy with ileal distal rectal anastomosis, and proctocolectomy with ileal-anal anastomosis. Each of these operations has strengths and weaknesses. Overall, these procedures are performed with low morbidity. The choice of operations should be tailored to patient preference and the experience of the operating surgeon.

FAP is associated with extracolonic manifestations of disease, which include desmoid tumors and osteomas. Polyps may occur at other intestinal locations, and carcinomas of the upper intestine have been reported as the most common fatal malignancy in patients after prophylactic colectomy. It is recommended that these patients undergo upper endoscopy every 6 months to 3 years starting by age 20. Many agents, including sulindac, vitamin C, and indomethacin, have been investigated as chemopreventive agents. Although some agents have shown promise, none has been proven to be effective in reducing the number of polyps or the risk of cancer in FAP patients.

**HEREDITARY NONPOLYPSY COLORECTAL CANCER**

HNPCC describes a clinical syndrome of colorectal cancer that occurs with early onset and in multiple family members. In contrast to FAP, HNPCC has no antecedent phenotype, and malignancy develops in the absence of adenomatous of the colon and rectum. The expression of disease may be limited to the colorectum (Lynch syndrome I) or coexist with extracolonic tumors, typically endometrial cancer (Lynch syndrome II). Other associated malignancies include stomach, small intestine, hepatobiliary, pancreas, breast, ovary, brain, and skin cancers.

In 1991, the International Collaborative Group on HNPCC established the minimum clinical criteria required to help identify families with HNPCC. The so-called Amsterdam criteria are: (1) colorectal cancer in three or more relatives, one of whom is the first-degree relative of the other two; (2) at least two generations of affected individuals with colorectal cancer; and (3) one or more of the cancers has been diagnosed before the age of 50. FAP must be excluded.

Additional loci have since been identified as sites at which increased risk of cancer may be inherited, including 8q21, 14q21, 17p12, 18q11–12, 22q11. The genetic basis of HNPCC has been identified as a germ-line mutation in a subset of genes responsible for DNA mismatch repair. Additional loci have since been identified. More than 90% of the identified mutations are in two genes, MSH2 (MutS homologue 2) and MLH1 (MutL homologue 1), located on chromosome 2p and 3p, respectively. These genes are dominantly inherited, with a penetrance of approximately 90%. Consequently, gene carriers have a 90% likelihood of developing colorectal cancer. Patients suspected of carrying an APC mutation can be tested for at least two mismatch repair gene mutations in commercial laboratories.

HNPCC gene carriers develop colorectal cancer at an average age of 45 years. These tumors occur more commonly in the right colon and tend to be more poorly differentiated. Synchronous and metachronous cancers are frequent, and should a segmental colectomy be performed for a primary cancer, there is a 45% risk for a new primary cancer within 10 years. Lynch and Smyth have reported that colorectal polyps can be identified in up to 17% of first-degree relatives during colonoscopic screening. Adenomas are more likely to grow and progress to invasive cancer in this patient population than in the general population.

The optimal management strategy for HNPCC gene carriers has yet to be established. Substantial evidence from uncontrolled studies suggests that surveillance colonoscopy and polypectomy are effective in reducing the risk of invasive cancer in these patients. Jarvinen et al. reported a 62% decrease in the diagnosis of colorectal cancer in HNPCC patients in a screening program at a medium follow-up of 117 months compared with patients not followed by colonoscopy at 10 years. Below et al. reported a decreased incidence of cancer and improved survival rate of patients with HNPCC who had surveillance and experiments compared with probands. Therefore, it has been recommended that surveillance colonoscopy be performed on gene carriers starting at age 20 and be repeated every 1 to 2 years. Patients older than 35 years of age should have annual colonoscopy.

Currently, no consensus among experts has been reached regarding the role of prophylactic subtotal colectomy for patients with HNPCC. Given the high penetrance of the disorder and the high rate of synchronous and metachronous disease among mutation carriers, a strong case can be made for prophylactic surgery in patients with this disease. A subtotal colectomy is currently the procedure of choice, and it can be performed with minimal morbidity and mortality. Patients who....
elect to undergo a subtelcule cotection require colonsoscopic surveillance of the remaining rectum. Patients undergoing prophylactic surgery may still face the risk of extracolonic cancers. Patients eleoting not to consider prophylactic surgery must commit to lifelong surveillance, and should a colon cancer be detected, a subtelcule cotection is then indicated. No prospective clinical trials in patients with HNPPC have been conducted, and given our current understanding of the increased risk of colorectal and extracolonic malignancy in these patients, the suggested benefit of surveillance colonscopy, and the low morbidity of prophylactic subtelcule cotection, either vigilant surveillance or prophylactic surgery are reasonable management strategies.

TESTICULAR CANCER AND CRYPTOCHIDISM

Cryptorchidism, or undescended testes, is characterized by absence of at least one testis in the scrotum and is the most common genitourinary disorder of childhood. Approximately 3% of children born at term and up to 30% of children born prematurely will have an undescended testis. A well-known but poorly understood association has been made between cryptorchidism and testicular cancer. In 1929, Cooper noted that the longer a testis remained cryptorchid the higher the testes lay from the scrotum, the more likely it was to be histologically abnormal. The reported risk for malignancy in cryptorchidism is 48.6 per 100,000, which is more than 100 times the risk of testicular cancer in the general population. It has been estimated that approximately 10% of testicular tumors arise from an undescended testis.

Either orchiopepysy in association with observation or observation alone is recommended for patients with cryptorchidism. There are multiple reasons for correcting an undescended testis, including the presence of a child, the risk of a future child, the risk of a genetic problem associated with the child's failure to descend, to prevent psychological and social difficulties, and to enhance the possibility of future fertility, and to place the testes in a site where it can be easily examined. Correction of an undescended testis might be achieved using hormonal therapy or surgery. Most experts agree that this should be accomplished as early as 12 months of age.

It is not clear that correction of an undescended testis alters the risk of developing testicular cancer. Reports in the literature conflict regarding the protective effects of correcting cryptorchidism, and virtually no information is available on patients who had an undescended testis corrected at younger than 2 years of age. and Most reports are population-based case-controlled studies. It is known that with uninilateral cryptorchidism have been found to have an increased risk of testicular cancer in both the undescended and the normally descended testis.

Management of an undescended testis in a postpubertal patient has been extensively addressed by Farrer et al. These authors concluded a statistical analysis comparing the estimated risk of death from a germ cell testis cancer in patients with cryptorchidism to the risk of death from an undescended testis. They concluded that the risk of death from orchectomy is greater than the risk of death from testicular cancer in patients with cryptorchidism. The authors recommended that orchiopepysy be considered only for patients younger than 32 years with postpubertal unilateral cryptorchidism. Other experts recommend orchiopepysy or observation in older patients, depending on patient preference and assessing the testis to be palpable. General agreement exists that a palpable undescended testis is a surgical indication.

CHAPTER REFERENCES

CHAPTER 25
Cancer Screening

Barbara K. Rimer
Joellen Schildkraut
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Measures of Effectiveness
Positive and Negative Consequences of Screening
Cancer Screening Randomized Clinical Trials
Evidence for Microinvasive Breast Cancer Screening Guidelines
Cervical Cancer Screening
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INTRODUCTION

The goal of cancer screening is a very practical one—to detect cancer at an early stage when it is treatable and curable. However, the reality is quite complex. For a screening test to be useful, the test or procedure should detect cancer earlier than would occur otherwise and there should be evidence that earlier diagnosis results in an improved outcome. Advances in genetics and molecular biology herald the era when it may be possible to detect cancer at earlier and earlier stages along the carcinogenesis pathway. Because of this progress, the line between prevention and screening may narrow further. Moreover, screening will be used to detect susceptibility as well as early markers of disease. Yet, in spite of the promises of molecular diagnostics, screening still must be evaluated according to its present reality, which is to detect asymptomatic disease when it is potentially curable.

The purpose of this chapter is to provide an overview of cancer screening—what it is, key terms, measures of effectiveness, and consequences. We also review briefly the status of screening for several prevalent cancers (breast, cervical, skin, prostate, colorectal, and lung). The recommendations are for the general population, but not for people with identified mutations in cancer susceptibility genes. Generally, it is recommended that people with these and other relevant mutations (e.g., HNPCC, p53) be screened at an earlier age, and more frequently, for the cancers to which they are predisposed.

This chapter cannot provide comprehensive information on any of the cancer sites reviewed, because the literature for each is vast. Rather, the chapter provides a succinct summary of the field and a perspective for clinicians to use in determining the efficacy of particular screening tests. Several texts provide good overviews of the issues related to screening for specific kinds of cancer. The National Cancer Institute's (NCI) Physician Data Query (PDQ) [World Wide Web site http://cancernet.nci.nih.gov/pdq.htm] also is an excellent source for the latest data on the specific screening tests discussed here.

WHAT IS CANCER SCREENING?

Appropriate cancer screening should lead to the early detection of asymptomatic or unrecognized disease by the application of acceptable, inexpensive tests or examinations in a large number of persons. The results of a screening test should then be applied expeditiously to separate apparently well persons who probably have disease from those who probably do not. The main objective of cancer screening is to reduce the morbidity and mortality from a particular cancer among the persons screened. The screening procedure itself is not diagnostic, and positive or suspicious findings must be evaluated further to determine diagnosis and appropriate treatment. Characteristics that distinguish screening tests from diagnostic tests are listed in Table 25-1.

Several characteristics make particular cancers suitable for screening. These include (1) substantial morbidity and mortality; (2) a high prevalence in a detectable preclinical state; (3) the possibility of effective and improved treatment because of early detection; and (4) the availability of a good screening test with high sensitivity and specificity, low cost, and little inconvenience and discomfort. Although there are more than 100 different cancers, most of them lack proven screening interventions. Only cancers of the breast, cervix, skin, colon-rectum, prostate, and testes have widely accepted screening interventions, and there is controversy over some aspects of each. Only breast, cervical, and colorectal screening have met the rigorous criteria of the U.S. Preventive Services Task Force.

The benefits of the investment in cancer screening occur over many years. Cancer screening affords both benefits and disadvantages; therefore, it is important to evaluate the effectiveness of screening programs by specifying criteria to meet the program's objectives. For screening to be a benefit, treatment given during the detectable preclinical phase must result in a better prognosis than therapy given after symptoms develop. Also, disclosure of disease or abnormality may cause emotional distress or economic hardship. Cervical cancer is a good example of a disease with a preclinical phase that can be detected in a preinvasive stage, in this case, using the Papanicolaou (Pap) smear. Finally, there are economic costs associated with cancer screening, and these should be evaluated before a cancer screening test is recommended on a population basis.

EVALUATION OF A SCREENING TEST

In the evaluation of a screening test, it is essential to answer questions concerning the test's ability to accurately predict the presence or absence of disease. If the
test is abnormal, what are the chances that disease is present? If the test result is normal, what are the chances that the disease is absent? The validity of a screening test is measured by its ability to classify correctly those persons who have preclinical disease as test-positive and those without the preclinical disease as test-negative.

Sensitivity and specificity address the validity of the test. Sensitivity is the probability of testing positive if the disease is truly present. As the sensitivity of the test increases, the number of persons with the disease who are classified as test-negative (false-negative) decreases. Specificity is the probability of screening negative if the disease is truly absent. A highly specific test rarely is positive in the absence of disease and therefore results in a lower proportion of persons without disease who are incorrectly classified as test-positive (false-positive). Two measures that directly address the estimation of probability of disease are the positive predictive value (PPV) and the negative predictive value (NPV). The PPV is an estimate of the accuracy of the test in detecting the presence of disease, and the NPV is an estimate of the accuracy of the test in predicting the absence of disease. The predictive value is a function of the sensitivity, specificity, and prevalence of disease. The accuracy of a test is a measure of the percent of all results that are true results, whether positive or negative, or the total correct test results. Table 25-2 summarizes the relationship between results of a screening test and the actual presence of disease as determined by an appropriate diagnostic test.

Sources of bias are of particular importance in the evaluation of a screening program. People who choose to participate in screening programs (volunteers) are likely to be different from the general population in ways that pertain to survival; thus, volunteer bias is a concern. Lead-time bias is defined as the interval between diagnosis of disease at screening and when it would have been detected due to the development of symptoms. If lead-time bias is not taken into account, survival may appear to be erroneously increased among screen-detected cases as compared to unscreened cases. Finally, length bias is the overrepresentation among screen-detected cases of those with a long preclinical period (thus less rapidly fatal), leading to the incorrect conclusion that screening was beneficial.

MEASURES OF EFFECTIVENESS

Several measures have been used to judge the effectiveness of screening. The most definitive measure of the efficacy of a breast cancer screening program and the one that is most relied on is the breast cancer mortality as determined by the comparison of screened and unscreened groups in a randomized clinical trial. There are excellent epidemiology texts and reviews that discuss the measures in more detail than can be presented here.

Other outcome measures have been proposed, including case finding and survival. Each has limitations. The problem with case finding is that it is subject to lead-time bias. Survival may appear to have been advanced, but only because cancer is found earlier in the screened group. Because of length bias, screening may appear effective, but in fact, it has not made a difference in mortality; slow-growing cancers may contribute to the apparent success of the screened group. Thus, length bias limits the value of survival data as outcome measures. Survival, in itself, does not establish that the natural history of the disease has been altered or that mortality has been reduced.

Another potential outcome is improved quality of life (QOL). However, none of the international breast cancer screening trials have good QOL data. These data are being collected as part of the NCI’s Prostate, Lung, Colorectal, Ovarian Cancer (PLCO) screening trial. This is an important area for further exploration and, in future trials, QOL should be measured. Cost per quality-adjusted life-years saved would be a good measure, but it has been used rarely. QOL may include a reduction in psychologic morbidity for a woman and her family. QOL also may be enhanced by providing better or more acceptable treatment choices. For example, Tabar and colleagues have argued that even if mammography does not reduce breast cancer mortality for women in their 40s, it may be beneficial because it avoids disfiguring and debilitating surgery. And de Koning and colleagues showed that breast cancer screening could reduce health care costs and improve QOL by preventing advanced disease, which also could be true for cervical and colorectal cancer screening. However, Harris has expressed concern that a woman’s QOL could be diminished by living longer with breast cancer.

In assessing the effectiveness of screening technologies, the randomized clinical trial (RCT) has been the gold standard. It is the most powerful methodology for demonstrating the value of screening in comparison to an unscreened group. RCTs overcome the biases inherent in other designs. The RCT with the end point of mortality avoids almost all important biases noted earlier, lead-time and length bias, as well as selection bias and overdiagnosis. However, case-control studies also can provide useful information, and at less cost than RCTs, and may be used to supplement RCT data. In addition, increasingly sophisticated statistical modeling techniques may be appropriate to assess the impact of screening, especially in situations where large RCTs cannot be conducted. The U.S. Preventive Services Task Force, the PDQ system, and others have ranked levels of evidence; the RCT is uniformly regarded as the highest level of evidence.

POSITIVE AND NEGATIVE CONSEQUENCES OF SCREENING

Every medical activity has positive and negative consequences, and screening is no exception. The benefits include: (1) improved prognosis for those with screen-detected cancers, (2) the possibility of less radical treatment, (3) reassurance for those with negative test results, and (4) resource savings if treatment costs are reduced because of less radical diagnosis. The optimal outcome is a reduction in cancer mortality. The assumption is that screening can detect cancer when it is early and curable, if cancer is present, or indicate that cancer is not present, if that indeed is the case. But because no medical test is perfect, there are several potential negative consequences of screening that also must be considered. These include the economic and psychologic consequences of false-positives and false-negatives, the potential for overdiagnosis, and the labeling phenomenon.

Screening in the community usually means that many people will require additional tests for what will later be recognized as false-positives. This is one of the predictable costs of cancer screening. A consideration of the negative consequences of screening is essential, because screening is offered to presumably healthy people. The negative consequences should not override the potential benefits. However, accumulating evidence in the area of breast cancer screening suggests that although there are negative psychologic consequences of abnormal test results, they appear to be relatively short-lived. On the plus side, abnormal results may increase the likelihood that women will be screened in the future. However, the data regarding negative psychologic consequences are still sparse and related primarily to breast cancer. More data are needed in other areas, such as colorectal cancer screening. Overdiagnosis is an important area that has not been well studied. As understanding of cancer biology increases, it will become easier to classify overdiagnosis.

For all kinds of cancer screening, physicians should engage patients in discussions of the risks and benefits of cancer screening. Because most people overestimate the risks for certain types of cancers (e.g., breast), they may inflate both the need for screening and the potential benefits. For some cancers, such as colorectal cancer, people may underestimate their personal susceptibility and may need encouragement to consider screening, with both the positive and negative consequences. In the case of prostate cancer, where the evidence is still equivocal and population-based screening is not recommended, it is especially important that men understand the limitations of screening. Harris encouraged that screening discussions begin with the possible outcomes of screening, making sure the patient’s information is accurate. Then, the physician should define and clarify the patient’s perceptions and values. Together, the patient and physician then weigh the benefits of screening versus the costs and benefits. This has been called shared decision making.
Austoker 42 outlined the topics that should be included when helping patients to make informed decisions about cancer screening. These include the purpose of screening; the likelihood of positive and negative findings and the possibility of false-positive or false-negative results; the uncertainties and risks involved; any significant medical, social, or financial implications of screening; and follow-up plans.

**BREAST CANCER SCREENING**

In 1999, 176,000 new invasive cases of breast cancer and approximately 43,700 deaths due to the disease were reported in the United States. 43 Widely accepted techniques for breast cancer screening, but with differing levels of evidence, include mammography, clinical breast exam (CBE), and breast self-examination (BSE). As with other screening techniques, the purpose of breast cancer screening is to find breast cancer early, while the disease is curable, to reduce mortality for breast cancer. As Tabar et al. 44 and others have shown, tumor size, lymph node status, and malignancy grade are major prognostic factors in survival. No cancer screening test has been studied more than mammography (with or without CBE). Yet, after more than 35 years of trials, many questions remain regarding at what age and at what interval women should be screened. The breast cancer screening trials provide clear evidence of benefit for screening women older than age 50 until approximately age 70, and increasing evidence of a small but statistically significant benefit of mammography for women aged 40 to 49 years.

Eight randomized trials have been conducted over more than 35 years to assess the impact of mammography. Together, these trials have included more than 500,000 women, with 180,000 women aged 40 to 49.

The eight international randomized clinical trials have varied greatly 45 (Table 25-3). Most trials have included women in their 40s, although two trials began accrual at 45, and one of the Canadian trials [the first National Breast Cancer Screening Study (NBSS1)] was designed to examine mammography and CBE versus usual care for women in their 40s, with a separate study (NBSS2) to assess mammography and CBE versus CBE only for women aged 50 to 59. The studies also varied in (1) whether they used one-view or two-view mammography; (2) the screening interval, which varied from 12 to 24 months; and (3) the level of compliance achieved. The problems in the trials also have varied. For example, cluster randomization resulted in socioeconomic status differences with the study groups in the Edinburgh trial. 46 Other trials experienced higher than desired contamination, most often because of higher than expected levels of screening in the control groups. For most of the studies, women’s breast cancer risk factors were not known; only the Health Insurance Plan of New York (HIP) and NBSS assessed and published data on the breast cancer risk factors for women in the study. 47

**TABLE 25-3. Selected Characteristics of Eight Randomized Controlled Trials of Breast Cancer Screening**

<table>
<thead>
<tr>
<th><strong>TRIAL</strong></th>
<th><strong>DESIGN</strong></th>
<th><strong>SCREENING INTERVAL</strong></th>
<th><strong>RANDOMIZATION</strong></th>
<th><strong>MAMMOGRAPHY/ CBE</strong></th>
<th><strong>COMMENTS</strong></th>
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<tr>
<td><strong>BCDDP</strong></td>
<td>Randomized</td>
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<td>By age cohort</td>
<td>Mammography/CBE</td>
<td>One of only two trials that began screening at age 45, and it stopped entry at age 69. It used two-view mammography every 18 to 24 months for five rounds; randomization was by cluster based on birth cohort. Approximately 59,000 women were enrolled in this trial.</td>
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**RANDOMIZED CLINICAL TRIALS**

Although mammography was first reported in 1913, it was not until 1963 that the first RCT— and the only U.S. RCT—commenced at HIP. HIP included women aged 40 to 64 at entry. Nearly 62,000 women were randomized to the study (two-view mammography and CBE or control group (usual care). Two-view mammography and physical examination were offered every 12 months during the 4-year study period, and follow-up was continued for 18 years. 42

The Swedish Two-County Trial in Kopparberg and Ostergotland began in 1977–1978 with an enrollment of almost 135,000 women randomized to one-view mammography every 24 months (younger than age 50) or 33 months (older than age 50). Within those geographic areas, all women were invited to enroll by letters of invitation, using the population registry list. Screening continued for four rounds for younger women and three rounds for older women. 43 The Kopparberg arm used single-view mammography without grids; Ostergotland used a grid. 44

The Malmö Trial was begun in 1976 in one city in Sweden. 45 It was one of only two trials that began screening at age 45, and it stopped entry at age 69. It used two-view mammography every 18 to 24 months for five rounds; randomization was by cluster based on birth cohort. Approximately 59,000 women were enrolled in this trial.

The Stockholm Study began in 1981 and enrolled approximately 43,000 women aged 40 to 64 who received single-view mammography every 28 months. Like the Malmö trial, randomization was by birth cohort within clusters. 45

The final Swedish study was conducted in Gothenburg, starting in 1982. The trial began with nearly 50,000 women aged 40 to 59 who received two-view mammography plus CBE on either a 24- or 36-month schedule. Randomization of women aged 40 to 49 was by individual, whereas clustered randomization was used for women aged 50 to 59. Verifled results have not yet been published, 46 but additional data were provided in 1997 for the National Institutes of Health Consensus Conference on Breast Cancer Screening in women aged 40 to 49.

The Edinburgh Trial began in 1978 as a randomized component of the larger, nonrandomized United Kingdom trial of The Early Detection of Breast Cancer. Approximately 25,000 women aged 45 to 64 were randomized to two-view mammography plus CBE on either a 12- or 24-month schedule. The purpose was to assess the impact of mammography and CBE in reducing mortality from breast cancer. 47, 48, 49

The National Breast Cancer Screening Study (NBSS1) was designed to examine the value of two-view mammography and CBE compared to usual care in women aged 40 to 49. Nearly 53,000 women were enrolled, starting in 1980, and received follow-up yearly for 5 years. Unlike the other trials, the women were recruited as volunteers and then randomized. As Miller and colleagues 50 have reported, these women were different from the Canadian population in several ways—for example, they were less likely to smoke, and they had higher levels of education.

The second Canadian study, the NBSS2, also began in 1980, enrolled nearly 43,000 women aged 50 to 59 and was designed to compare two-view mammography and CBE against CBE only. In other words, the question was whether there is a benefit of mammography over and above CBE in this age group. This is the only trial planned to assess the additive impact of mammography in addition to CBE. 51, 52 Critiques of this trial have appeared by several authors. 53, 54, 55 The criticisms are probably overstated, and the results should not be discounted.

**NONRANDOMIZED CLINICAL TRIALS**

A number of nonrandomized trials have been conducted around the world. Much can be learned from these studies. However, because of a number of design limitations, they should not be used alone in establishing screening guidelines and policies. 56 The largest study of mammography and CBE was the U.S. Breast Cancer Detection Demonstration Project (BCDDP): 280,000 women aged 35 and older were recruited and screened in 28 centers annually with mammograms and CBE during the 1970s. 57 The BCDDP was sponsored jointly by the NCI and the American Cancer Society (ACS). Because the BCDDP participants were not a random sample of the population, there were some important differences from women in the general population. Most notably, the BCDDP population was at much higher risk, with a substantially higher incidence of breast cancer. Moreover, because it was not an RCT, the case fatality rate was used to assess the impact of...
A subset of women were followed as part of a case-control study conducted by Morrison and colleagues to examine case fatality rates within the BCDDP. Breast cancer mortality was approximately 20% less than expected from national data. There was a benefit for younger women, but it was less than for older women.

**EVIDENCE FOR MAMMOGRAPHY**

More than 3.5 million women-years of observation have been recorded for women of all ages, and more than 2.7 million women-years for women aged 40 to 49 at entry from the breast cancer screening RCTs. One of the challenging aspects of tracking these trials is the constantly shifting nature of the data. The trialists provide updates at different points in time, and some reports use nonverified data. Thus, at any given point, review articles may vary substantially in the numbers they report. Figure 25-1 and Figure 25-2 illustrate the mortality outcomes for women of all ages and for those younger than age 50, with 18 years of follow-up for HIP, 14 years for the Edinburgh trial, 10.5 years for the Canadian trials, and 7 to 13 years for the Swedish trials.

**FIGURE 25-1.** Mortality impact of the randomized clinical trials (all ages) by relative risk and upper and lower confidence intervals. Adjusted for socioeconomic status differences. HIP, Health Insurance Plan of New York; NBSS2, second Canadian National Breast Cancer Screening Study.

**FIGURE 25-2.** Mortality impact of the randomized clinical trials (women aged 40 to 49 years at entry) by relative risk and upper and lower confidence intervals. Adjusted for socioeconomic status differences. HIP, Health Insurance Plan of New York; NBSS1, first Canadian National Breast Cancer Screening Study.

In 1993, the International Workshop on Breast Cancer Screening created considerable controversy when it concluded that for women aged 40 to 49, randomized controlled trials consistently demonstrated no benefit from screening in the first 5 to 7 years after entry and a marginal benefit after that. More recently, in reviewing the same trials, Kerlikowske and colleagues confirmed this conclusion and suggested that the same benefit could be achieved by screening women after age 50. However, several years later, with most of the international RCTs now having more than 10 years of follow-up, the trends are clearer: Six of the trials show reductions in mortality for women who were in their 40s at entry. But a large variability remains in the relative risk of dying from breast cancer for women younger than 50. There also is significant controversy over many of the reported numbers.

Although the randomized trials have included too few women older than age 70 to offer guidance about screening for older women, the Forum on Breast Cancer Screening recommended regular mammograms for women aged 70 years who are otherwise healthy. A case-control analysis in the Nijmegen study confirmed the benefit of mammography for women older than 70.

Six different published metaanalyses, including the two mentioned earlier, have examined the effect of the mammography trials on women aged 40 to 49 (Table 25-4). When Elwood and colleagues conducted a metaanalysis and included all the data except for the controversial Canadian study, they found an overall relative risk of 0.99, suggesting no difference between the screened and control groups. With the Canadian data included, there was a slight increase in the relative risk for the experimental group (relative risk, 1.08). The overall relative risks found in the metaanalyses have ranged from 0.85 to 0.99 without the NBSS data and 0.93 to 1.08 with the NBSS data. Eckhardt and colleagues found a nonsignificant 7% reduction in mortality. In a 1995 metaanalysis, Smart and colleagues found a significant 24% mortality reduction for women in their 40s. Hendrick et al. combined recent follow-up data on women aged 40 to 49 at entry. They found a statistically significant 18% mortality reduction. This is similar to the 18% reduction Berry found when an assumption of homogeneity was made. However, the benefit was not statistically significant when he assumed heterogeneity. The benefit occurs approximately 15 years after the start of screening. The benefit for women in their 50s is larger and also significant: an approximately 25% to 30% reduction in mortality. It is reasonable to conclude that there is a small but statistically significant reduction in mortality in their 40s. Nevertheless, most of the benefit actually is achieved when they are in their 50s. For women in their 50s and 60s, there is general agreement about the benefits of mammography.

**TABLE 25-4.** Metaanalyses of Trials for Women Aged 40 to 49 Years

**BREAST CANCER SCREENING GUIDELINES**

The question, "At what age should women begin getting regular mammograms?" has been one of the most contentious in science and medicine. The issue became even more inflamed after a 1997 National Institutes of Health Consensus Conference on Breast Cancer Screening for Women Aged 40 to 49. The report, contrary to
expectations, found insufficient data to recommend that women in their 40s get regular mammograms. Disagreement still exists over whether the modest reduction in mortality warrants a recommendation that all women in their 40s be screened. The argument turns primarily on the small population benefit achieved. Most of the benefit occurs when the screened women are in their 50s. As Ransohoff and Harris noted, only 1 to 2 women's lives would be extended per 1000 women of 40 to 50 years of age who are screened annually for 10 years. However, in agreeing on a reduction in breast cancer mortality of 18%, both the ACS and the NCI changed their screening recommendations, with the ACS now advising annual mammograms for women aged 40 and older. Annual screening for women in their 40s is based on the assumption of a shorter lead time for younger women. The NCI recommends mammograms every 1 to 2 years for average-risk women aged 40 and older. For the first time since 1993, however, the recommendations are compatible; both organizations now endorse regular mammograms for women older than age 40 (Table 25-5).

### TABLE 25-5. Screening Guidelines for Breast, Colorectal, Prostate, and Cervical Cancers for Selected Health Care Organizations

The evidence suggests that a 5% to 20% additional benefit in mortality reduction can be achieved by adding a high-quality CBE. Although the recommendations of different medical organizations vary, it seems prudent to encourage women to have a CBE yearly (see Table 25-3).

### CERVICAL CANCER SCREENING

In 1999, an estimated 12,800 new cases of invasive disease and 4800 deaths resulted from cervical cancer. A steady decline in mortality was observed after the initiation of widespread Pap testing in the mid-twentieth century. From 1970 through 1995, mortality continued to decrease by 40%. This decline represents a major success in cancer control in the United States. Mortality associated with invasive cervical cancer is no longer common compared to other cancers. However, cervical cancer is the second most common cancer worldwide, and fatalities from this disease in developed countries should be entirely avoidable with currently available technology. Continued efforts to improve cervical cancer screening practices are, therefore, well justified both nationally and internationally.

Dr. George Papanicolaou introduced the test that bears his name in the 1930s. An RCT has never been conducted to confirm its efficacy because wide-scale adoption and diffusion of the Pap test into medical practice made assignment to a nonscreened control group unethical and, therefore, untenable. Nevertheless, one would expect screening to be effective because cervical cancer is accessible and has a relatively long preclinical detectable phase. Numerous observational studies have demonstrated its efficacy beyond a reasonable doubt. Large national screening programs in Nordic countries, Canada, and the United States have been associated with marked drops in mortality from cervical cancer. Analysis of these studies and others suggested that the probability of invasive cancer could be reduced up to 90% for frequencies up to every 3 years. Controversy remains about the appropriate screening interval for Pap testing. Guidelines from major expert groups have continued to recommend annual screening, with less frequent intervals after three normal smears (at the discretion of the physician). However, after its review of the evidence, the U.S. Preventive Services Task Force left the interval from 1 to 3 years (see Table 25-5). The literature that bears on this question is limited.

Inadequate data are available to recommend an upper age limit for regular screening. Because mortality increases with advancing age and 40% to 50% of all women who die from cervical cancer are older than 65 years of age, it seems prudent to screen older women. However, national survey data document a marked fall-off in regular screening for older women. There is concern that Pap testing is less sensitive in older women who have a receded squamocolumnar junction of the cervix. However, it is likely that the primary reason for invasive cervical cancer in older women is lack of screening.

For women who have had hysterectomies, the practice of cytologic screening with vaginal smears is still common. However, at least for women who have had a hysterectomy for benign conditions, the likelihood of detecting vaginal dysplasia is extremely low and the false-positive rate is high, thus suggesting that the practice is unnecessary.

### SKIN CANCER SCREENING

The incidence of skin cancer has increased worldwide, with U.S. incidence data mirroring this trend. In the United States, the incidence rate of melanoma has increased approximately 4% per year since the early 1970s, with a 162% increase in male melanoma cases and 95% in women. It is unclear whether this increase is due to actual changes in prevalence or is a function of increased awareness with subsequent diagnosis, improved reporting by tumor registries, or both. In 1999, 54,000 new cases of skin cancer were projected, with 44,200 new cases of melanoma and 7300 deaths. Melanoma now ranks sixth in incidence among cancers in males and seventh in incidence among cancers in females. Approximately 800,000 nonmelanoma skin cancers are diagnosed each year. The United States lags behind many other countries in the creative application of interventions to reduce the incidence of and mortality from melanoma and other skin cancers. Australia, which has the highest reported incidence of melanoma anywhere, has mounted successful population-based programs that have had dramatic effects.

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### PROSTATE CANCER SCREENING

Prostate cancer is the most commonly diagnosed cancer among men in the United States and is the second leading cause of male cancer deaths. In 1999, 179,000 new cases of prostate cancer were identified, and there were 37,000 deaths. However, consensus is lacking concerning recommendations for prostate cancer screening. There are several reasons for the controversy surrounding screening tests for prostate cancer. First, no definitive evidence suggests that prostate cancer...
screening results in improved clinical outcomes, especially a reduction in mortality from the disease. Second, the incidence of prostate cancer is on the rise largely due to the detection of latent, asymptomatic cases with uncertain clinical relevance, thus putting the value of screening in doubt.

SCREENING TESTS FOR PROSTATE CANCER

The three main screening modalities for prostate cancer include digital rectal examination (DRE), serum prostate-specific antigen (PSA), and endorectal (transrectal) ultrasonography (TRUS). The most widely used and oldest technique for detection of prostate cancer is the DRE. Wide ranges in estimates of sensitivity (33% to 69%) and specificity (49% to 97%) of the DRE have been reported. Ultimately, only one in three patients with a positive DRE has prostate cancer. With the development and application of intraluminal (rectal) probes with high resolution, studies have shown that small, nonpalpable malignant lesions of the prostate could be detected. TRUS has fallen short of expectations, with a large variation in reports of sensitivity and specificity, both ranging from 41% to 77% and 50% to 95%. Despite this, TRUS is considered an excellent ancillary modality to increase accuracy of biopsy over the digital guidance alone. The PSA test is a blood test that allows for earlier detection of many prostate cancers. Interest in the PSA grew in the late 1980s. Impressively, PSA levels were shown to drop to undetectable levels after prostatectomy. However, normal PSA values are found in approximately one-third of men with localized cancers, and PSA levels are often elevated in men with noncancerous conditions, such as benign prostatic hyperplasia. Some investigators have argued that integration of the DRE with determination of PSA levels and the use of TRUS in selected cases would improve prostate cancer detection. A new approach for using PSA based on age-dependent thresholds has been suggested and may be promising.

Nonrandomized Studies

Two nonrandomized studies are ongoing to evaluate screening tests for prostate cancer (the ACS National Prostate Cancer Detection Project and a multicenter study headquartered at Washington University involving six university medical centers). Results of these trials will not be available until the first decade of the twenty-first century. Thus, clinicians and patients must make decisions in the absence of RCT data. Table 25-6 summarizes the sensitivity, specificity, and predictive value of these data.

TABLE 25-6. Estimates of Screening Test Performance for Prostate Cancer

Randomized Clinical Trials

The NCIs PLCO trial is a 16-year randomized control study that began on November 16, 1993. It is accruing 74,000 men 60 to 74 years of age and has a design power of 90% to determine 20% reduction of prostate cancer mortality. This trial will provide important information about the efficacy of screening.

Trends and What They Mean

National data from 1990 to 1996 show that prostate cancer incidence peaked in 1992 at 190.8 per 100,000 and declined at an average rate of 8.5% from 1992 to 1996. A series of related reports in the Journal of the National Cancer Institute, based on data from the Surveillance, Epidemiology and End Results Cancer Registry Program, indicates a decline in the incidence of distant stage disease, as well as a decline in incidence-based mortality of distant stage disease and flat incidence-based mortality trends of localized and distant-stage disease. Statistical methods were applied to consider the effect of screening by limiting some analyses to the contribution from cases diagnosed since 1987 when widespread screening using the PSA test had begun. Thus, some evidence shows improved prognosis for the screen-detected cases. However, alternative interpretations, such as the possibility that cause-of-death misclassification could explain these findings, cannot be ruled out.

PROSTATE CANCER SCREENING RECOMMENDATIONS

In light of the limitations of prostate cancer screening, it is important to consider the natural history of this disease and subgroups of men at high risk for developing prostate cancer. These considerations are critical for determining public health policy.

Not surprisingly, no consensus has been reached about prostate cancer screening (see Table 25-5). Several groups, including the U.S. Preventive Services Task Force, American College of Physicians, and Canadian Task Force on the Periodic Health Examination, have recommended against routine PSA screening. The NCIPDQ does not recommend PSA screening to the general population. The ACS has modified its guidelines and now recommends that men age 50 and older who have at least a 10-year life expectancy should talk with their health care professionals about having a DRE of the prostate gland and a PSA blood test every year. Men who are at high risk for prostate cancer (African Americans or men who have a history of prostate cancer in close family members) should consider beginning these tests at an earlier age.

COLORECTAL CANCER SCREENING

Increased emphasis on the importance of screening for colorectal cancer during the 1990s has followed studies documenting the efficacy of both fecal occult blood testing (FOBT) and sigmoidoscopy. Cancers of the colon and rectum account for the third largest number of new cancer cases after lung, with 94,700 and 34,700 cases estimated, respectively, in 1999. Substantially fewer people now die from the disease, indicating the promise of screening and treatment (47,900 and 8700 estimated deaths in 1999 for colon and rectum, respectively). A slow decrease has been seen in both incidence and mortality since the late 1970s. Incidence has decreased at a rate of approximately 1.4% per year for the period from 1991 to 1995. As with cervical and prostate cancers, the long preclinical and detectable phase makes colorectal cancer ideal for screening. Like cervical (but unlike prostate) cancer, the specificity of existing screening procedures minimizes the necessity of additional procedures necessary for the follow-up of false-positives. Increased risk for colorectal cancer is found for persons with personal histories of colorectal cancer, adenomatous polyps, or inflammatory bowel disease, as well as those with family histories of adenomas, colorectal cancer, or hereditary colorectal cancer syndromes (i.e., familial adenomatous polyposis and hereditary nonpolyposis colorectal cancer).

SCREENING TESTS FOR COLORECTAL CANCER

Four tests are currently in use for colon cancer screening: FOBT, sigmoidoscopy, colonoscopy, and high-contrast barium enema. RCT data are not available for colonoscopy or barium enema. A fifth test, the DRE, is a low-cost, low-harm practice that is well ingrained into routine medical evaluation, but no evidence from controlled studies indicates that it is useful in preventing mortality from rectal cancer. The FOBT, based on the use of guaiac to detect hemoglobin in the stool, can detect occult bleeding from early-stage colorectal cancers. Flexible sigmoidoscopy involves the use of a 60-cm fiber-optic endoscope that can view up to the splenic flexure
of the colon and at the same time provide access for biopsy and removal of polyps. A comprehensive review of colorectal cancer screening with clinical guidelines has been developed by a multidisciplinary panel under the aegis of the Agency for Health Care Policy and Research.

**Fecal Occult Blood Test**

Support for the use of FOBT comes from several large randomized controlled trials, including a Minnesota trial of 46,501 participants between the ages of 50 and 80 years of age. This study found that annual FOBT with rehydration of the samples decreased the 13-year cumulative mortality from colorectal cancer by 33% and biennial screening by 21%. Most (75% to 84%) of this reduction resulted from the test rather than from incidental discovery of cancers by follow-up colonoscopy. Earlier RCTs in England of 152,850 individuals, as well as a large study of 62,000 persons in Denmark, demonstrated that biennial FOBT without rehydration reduced mortality by 15% to 18%. An additional study of 27,000 persons in Sweden, aged 60 to 64 years of age, is ongoing. A fifth trial in the United States evaluated FOBT as a supplement to annual rigid sigmoidoscopy in 21,750 subjects and found no significant decrease in colorectal cancer mortality. Data from case-control studies are generally consistent with the conclusions of these trials. In a health plan population, a decreased mortality of 31% was associated with having had at least one screening FOBT in the previous 5 years. Other case-control studies in Japan and Washington also have demonstrated protective effects on mortality.

When used in unscreened populations the FOBT is positive in 1% to 5%; 2% to 10% of these have cancer and 20% to 30% have adenomas. Concern remains about the lack of specificity of FOBT and the necessity to follow positive results with colonoscopic examination or barium enema. However, the evidence is mounting that FOBT saves lives from colorectal cancer. Physicians must weigh the benefits of possible early detection of colorectal cancer against the possible complications and expense of follow-up procedures.

**Flexible Sigmoidoscopy**

The advantage of sigmoidoscopy screening over FOBT is that it frequently includes the actual removal of cancer or a precancerous lesion in a biopsied polyp, thus combining prevention (through removal of polyps), screening, and treatment in one step. Another advantage is that it needs to be performed infrequently, perhaps every 5 to 10 years.

At least two large randomized trials of flexible sigmoidoscopy screening are in progress. The NCIs PLCO trial is evaluating the efficacy of examinations every 3 years in 74,000 men and women, 55 to 74 years of age, with an equal number of controls. A trial in the United Kingdom, year 2000, evaluations the efficacy of one sigmoidoscopy delivered for reducing colorectal cancer mortality.

Meanwhile, supporting evidence for efficacy comes from several case-control studies. In the first, screening sigmoidoscopy, primarily with the rigid sigmoidoscope, reduced mortality from cancer of the rectum and distal colon by 60% (adjusted odds ratio, 0.41, 95% confidence interval, 0.25 to 0.69) in a large Kaiser Permanente California health plan population. Confirmation came from a smaller second study of 66 cases and 196 controls in another health plan population in Wisconsin. A third large case-control study in American veterans, with 4358 cases and 16,199 matched controls, reported a 59% reduction in mortality from any prior colorectal procedure. The first two case-control studies were judged sufficiently convincing that the U.S. Preventive Services Task Force upgraded the evidence and recommends screening with sigmoidoscopy or FOBT annually for persons older than 50.

**LUNG CANCER SCREENING**

Lung cancer screening is not currently recommended due to lack of evidence that any available screening procedure, even for smokers, can identify tumors early enough to reduce mortality. This remains a major challenge to research and technology because of the tremendous burden caused by this cancer. In 1999, an estimated 171,600 new cases of disease and 158,900 deaths were due to lung cancer, making it by far the most common killer from cancer in both men and women and accounting for 28% of all cancer deaths.

The decision to actively discourage lung cancer screening by x-ray was made based on the results of RCTs performed in the 1970s. None of four randomized trials showed any benefit of reducing mortality from lung cancer. The Mayo Lung Project, the primary trial contributing to this evidence, demonstrated that screening with either chest x-rays or chest x-rays plus sputum cytology could lower the stage at presentation and increase survival. Neither approach had any effect on lung cancer mortality. The lack of connection between improved survival and the absence of a mortality benefit can be attributed to lead-time and length biases. This study and its contemporaries have, however, been criticized because of study design and analytic issues, including a lack of statistical power. Recent preliminary results from the Early Lung Cancer Action Project in New York indicated that low-dose spiral computed tomography used in 1000 symptom-free former smokers older than age 60 detected 27 cancer cases versus 7 cases detected by chest radiograph. Although this is not an RCT and, therefore, susceptible to lead-time and length-bias, these preliminary results suggest that never smoking imaging technologies may hold promise. Efforts to prevent initiation of smoking, especially by young people, and cessation of tobacco use remain the physician's main tools for combating this most common of all cancers.

**THE FUTURE OF SCREENING**

Many challenges lie ahead for cancer screening. Better detection methods are urgently needed, and molecular detection methods may surpass current techniques. At the same time, more effort is required to encourage adherence to the proven cancer screening modalities. Adherence to screening is less than optimal for all the major recommended screening techniques. With the discovery of mutations in susceptibility genes that predispose for cancer, new challenges in cancer screening arise. There is a need for appropriate screening recommendations and programs for high-risk subgroups. Not only are those who have inherited a mutation for cancer susceptibility at higher risk for developing some cancers, but often the age at onset among such individuals is younger than the age at onset in the general population. This creates challenges for those who recommend and promote screening regimens. The example of the BRCA1 susceptibility gene for breast cancer illustrates a perplexing situation in which recommendations for screening with mammography do not address the early age at onset of this disease. Moreover, there are no good population data on which to base guidelines. Further study is needed to establish efficacious screening protocols for those who are genetically predisposed to cancer. Finally, there are new screening modalities on the horizon, such as low-dose helical computed tomography scans for detecting early lung cancers. Among the challenges of the future is how to evaluate new screening technologies in a world where large RCTs may be increasingly difficult to conduct. In screening, as in other areas of medicine and public health, the inclination to recommend screening tests on the basis of an intriguing and promising study must be balanced by a careful assessment of the evidence.

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CHAPTER 26
Cancer Diagnosis: Molecular Pathology

José Costa
Carlos Cordon-Cardo

INTRODUCTION

The traditional role of the surgical pathologist has been the morphologic evaluation of human tumors in a search for clues of their histogenesis and anticipated behavior. Over the years, this quest has benefited from the application of specialized techniques, which have become part of the pathologist's armamentarium. The diagnosis of cancer involves the analysis of tissue and cytology samples for features correlated with malignant transformation. Specimens of tissues and cells are obtained through several procedures, including surgical biopsy, endoscopic biopsy, core or aspirational needle biopsy, venipuncture, spinal tap, scraping of tissue surfaces, and collection of exfoliative cells from urine or sputum. The acquired tissue or cell specimens are subjected to a series of analytic modalities for diagnostic purposes.

Light microscopy, assessing morphologic features of the procured specimens, was used as almost the sole approach for many years, and it remains the standard diagnostic method to which all novel methods must be compared. The use of enzyme histochemistry and electron microscopy expanded the primary microanatomic evaluation to include biochemical and subcellular structural features. More recently, cytogenetics, analysis of DNA content, molecular genetic assays, and immunohistochemistry (IHC) have been added as valuable adjuncts to light microscopy in cancer diagnosis. These methods, particularly the latter, have greatly enhanced our ability to precisely define the lines of differentiation of human tumors, which constitutes the basis for the current classification schemes. As important as the "histogenetic" categorization provided by these techniques is, it addresses only indirectly other aspects of human neoplasia that are more relevant to their biologic behavior and response to therapy. These include rate of proliferation, capacity for invasion and metastases, and development of resistance mechanisms to certain treatment agents. This chapter reviews the contributions of novel approaches to the diagnosis and classification of tumors.

ROLE OF MOLECULAR PATHOLOGY IN CLINICAL ONCOLOGY AND TRANSLATIONAL RESEARCH

Molecular pathology studies the origins and pathogenesis of disease at the molecular level. Because cancer is a hereditary disease of the cell, much of the mechanistic studies of the cancer cell are based on the characterization of acquired or somatic mutations and subsequent structural or regulatory alterations of the gene products. In this regard, it differs from medical genetics, in which the main objective is to determine the genetic abnormalities associated with inherited disorders and carried as germline mutations. Molecular pathology of neoplasia aims at identifying and understanding those aberrations involved in the development and progression of neoplastic diseases. Clinically relevant objectives include (1) establishing a definitive diagnosis and classification of tumors based on the recognition of complex profiles ("fingerprints") or unique molecular alterations that occur in specific tumor types; (2) providing early detection of tumor cells using sensitive molecular techniques, thus anticipating therapeutic intervention; (3) rendering prognostic information of clinical relevance through the assessment of molecular predictors of outcome, and (4) assisting in the selection of individualized treatment regimens, saving unnecessary drug toxicity. Protocols based on molecular markers increase the chances for cure by opting for the right management approach, and they improve the quality of life of patients with cancer.

Molecular pathology also serves as a bridge between clinical and basic biomedical sciences. The translational aspects of research in molecular pathology are bidirectional, involving both the active transfer of relevant observations that are a result of the analysis of primary tumors and clinicopathologic correlations to basic laboratory studies, as well as the effective transfer of laboratory findings into clinical analyses and protocols. In promoting such transfers, molecular biology facilitates and maximizes the transfer of biologic discoveries into diagnostic, prognostic, and therapeutic applications.

The use of molecular techniques has led to remarkable progress in the understanding of cell growth, differentiation, maintenance of genomic integrity, and programmed cell death, these being key issues in tumor development and progression. Biologic markers, such as alterations of TP53, which correlate with tumor behavior when detected in specific tumor types, await validation studies. Similarly, prospective clinical analyses using well-characterized cohorts of patients and properly selected pairs of normal and tumor samples are needed to better delineate the role of mutations occurring in these genes, because they may impact on the management of patients affected with cancer. The implementation of objective predictive assays to the diagnostic and prognostic tools will enhance the ability to assess tumor biologic activities and to design effective treatment regimens.

USE OF HUMAN TISSUE SAMPLES FOR MOLECULAR ANALYSES

Discrepancies of reported results aimed at the identification of gene mutations and altered patterns of gene expression in primary tumors could be explained by the use of distinct probes and methods. Critical caveats include assurance for the presence of viable tumor, extent of necrosis, normal cell to tumor cell ratio, and the stage and grade of the lesion being studied. Often, distinct methods are available to detect a given marker, these approaches differing in specificity, sensitivity, speed and cost, and appropriateness for particular clinical situations.

Strategies have been developed whereby, from a single tissue sample, different techniques can be performed in search of the molecular phenotype and genotype. One of these strategies is illustrated in Figure 26-1. Briefly, using consecutive tissue sections cut at different thicknesses and deposited either on glass slides or microtubes, one can (1) evaluate morphology (i.e., hematoxylin and eosin staining), (2) perform expression assays (i.e., IHC and in situ hybridization (ISH)), (3) identify molecular alterations (i.e., Southern blot, polymerase chain reaction/single-strand conformation polymorphism (PCR-SSCP), and sequencing), and (4) conduct high-throughput assays (i.e., expression array technologies). Tissue microdissection assays can be implemented to remove normal contaminating cells, enriching the neoplastic cell content of the tumor sample when needed. This method can also be used to study low-grade and high-grade tumor foci in a single tissue sample or to analyze minimal lesions, such as carcinoma in situ. Evaluation of gene mutations and altered patterns of expression can be performed using a combination of techniques, including deletion studies by restriction fragment length polymorphism and comparative multiplex PCR, point mutation screening by PCR-SSCP and confirmation by direct sequencing, and assessment of altered expression by IHC and ISH. More recently, the introduction of microchips and other technologies allows the detection of missense mutations in certain genes with great sensitivity.
Figure 26-1. Use of tissue for research and diagnostic purposes can be prepared to yield a variety of tissue-derived products that can be treated using different technological approaches. The ability to analyze nucleic acids and proteins from small numbers of cells makes it possible to obtain a comprehensive profile of the tissue. These data can then be correlated to the histopathologic appearance and to clinical characteristics of the lesion. Properly annotated samples stored in a tissue bank constitute a precious resource to test the efficacy of newly discovered biomarkers and diagnostic or predictive tests. F/U, follow-up; H&E, hematoxylin and eosin; IHC, immunohistochemical; NB, Northern blot; PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism; Rx, medication; SB, Southern blot; WB, Western blot.

Manual microdissection of tumor samples, to enrich neoplastic cell aliquots to be used in specific techniques, is achieved by the use of a magnifying lens and sterilized scalpels. It can be also performed using scraping devices mounted on specially designed stereoscopic microscopes. More refined, laser-based, microdissection instruments have been developed and are commercially available (Fig 26-2). One of the strategies, the laser-capture method, is based on adhering cells to a material after it is thermally activated by a laser beam. Tissues to be microdissected are viewed through a video microscope, and the position of the slide is adjusted so that the desired cells are under the targeting light. Activation of the laser causes the desired cells to adhere to the special coverslip, which is mounted on a plastic cap and positioned over the targeted cells. The cap is then separated from the tissue section, pulling the desired cells for study. The dissected material can be reviewed for morphology and nonspecific transfers before placing it in a tube containing the appropriate digestion buffer for nucleic acid extraction. Protocols for the dissection of tumor cells from frozen and formalin-fixed paraffin-embedded tissue have been developed that allow the extraction of nucleic acids, mainly DNA. It is possible to select cell populations based on their phenotypic features determined by IHC. Isolation of intact RNA transcripts is difficult, if not impossible, to achieve through this procedure. The distortion produced during the application of the laser beam appears to be responsible for the partial degradation of most RNA species.

Figure 26-2. Laser microdissection enables researchers to capture and characterize microscopic normal or pathologic structures. The efficacy of the approach can be appreciated in genotyping a single crypt obtained from colonic epithelium. Verification of the donor section after capture clearly demonstrates the ability to precisely capture well-defined groups of cells making up a structure. In this manner, specific regions from the DNA from cells constituting a single crypt profile can be amplified and analyzed.

The application of the full spectrum of molecular-based methods to the evaluation of tissue and cell specimens, and the implementation of novel therapeutic modalities aimed at specific molecular targets, has led to changes in the established patterns of tissue procurement, processing, and tissue banking. Advanced diagnostic technology should be included in tissue analysis carried out during the diagnostic investigation of any potentially neoplastic lesion. Diagnosticians should “think molecular.” Protocols should be implemented and constantly updated to guarantee that samples are handled in a way that will not preclude optimal application of molecular testing. In daily practice, this means that part of the specimen, whenever possible, should be set aside prospectively for advanced diagnostics. The advent of advanced diagnostics is forcing operational changes that ensure fast delivery of specimens to the laboratory, where pathologists can select an aliquot of tissue or cells that will be used to resolve questions pertinent to the management of the lesion or set aside a sample “in reserve” for molecular analysis if necessary. The one of the most common ways to preserve samples is by snap freezing in liquid nitrogen. However, this procedure does not allow for preservation of microanatomic detail. Rapid freezing of tissue in a block with cryopreservative solution maintains morphology and yields frozen sections that can be used for different assays. This method is favored in building frozen tumor banks from which enough genomic DNA or complementary DNA (cDNA) can be generated from a thick section to produce useful reagents for subsequent analyses. In addition, monoclonal antibodies, purified antisera, and riboprobes can easily be used on thin sections, usually 5 µm, by implementing IHC or ISH protocols. In today’s practice, one of the ideal moments to procure tissue is at the time of an intraoperative consultation, when tissue is sampled for diagnostic frozen section examination. It is important to realize that the tissue procured for advanced diagnostics remains usable when and if required for routine morphologic analysis. Tissue procurement and tissue banking are different tasks that should be well delineated if this kind of valuable resource is to be implemented with maximum efficiency.

When using archival tissue for research, including both discovery and validation studies, issues of patient confidentiality and informed consent should be carefully considered and resolved through established institutional and national guidelines. Institutional review boards and human investigation committees must be made aware of the ever-growing complexities involved in the use of human tissues for research. These issues grow in complexity because of the rapid development of new technology and bioinformatics. The existence of large databanks containing comprehensive information on disease susceptibility, pharmacogenomics, and other biologic data that can be potentially linked to an individual are of obvious concern to researchers and ethicists.

Overview of the Technological Approaches to Molecular Diagnostics

The value of molecular markers for cancer diagnosis and patient management depends on their accessibility to detection by various analytic methods. Often, several strategies are available to detect the same marker, and these strategies differ in several aspects, including specificity, sensitivity, and appropriateness for particular clinical situations. With the exception of DNA content, there are two broad categories of strategies for the detection of molecular markers: biochemical molecular techniques that can be applied to analyze carefully chosen tissue samples or, alternatively, reagents can be applied on tissues, cells, or chromosomes to detect and demonstrate the presence and spatial distribution of the marker. At present, the development of new clinical tests depends mainly on low-throughput assays, but it seems likely that the high-throughput, comprehensive analytic techniques described in the following sections will have a major impact in the near future. Some understanding of these techniques is central for the appreciation of their capabilities, advantages, and limitations when analyzing clinical material.

Low-Throughput Techniques

DNA Content and Flow Cytometry

Individual cells harboring many genetic alterations, including genes regulating growth and apoptosis programs, often contain an abnormal amount of nuclear DNA that can be measured by flow cytometry. Deviations in cell DNA content relative to normal cells (DNA index) may indicate duplications or losses of individual chromosomes.
DNA Alterations and Detection Assays

Native DNA extracted from either tissues or cells can be directly sequenced or analyzed by Southern blotting, restriction fragment length polymorphism, and comparative genomic hybridization (CGH). These techniques are capable of detecting alterations present in the genome of neoplastic cells that serve as markers, including point mutations, translocations, amplifications, deletions, microsatellite length instability, and altered methylation. Point mutations are the most common DNA changes found in neoplastic cells, and can be identified by the mutations can be identified by the presence of nucleotide substitution when paired DNA samples are compared. Hybridization with the transformed state of the cell. Amplification of an oncogene is usually associated with protein overexpression and is another mechanism for gain of function. Amplification constitutes an easily detectable and measurable change; thus, it is a good diagnostic and potential prognostic marker. In translocations, protooncogenes are subjected to a strong promoter-enhancer or removed from a physiologic regulatory control element. The net effect is an inappropriate increase in product that provides excess function.

Alternatively, a translocation can produce a novel gene by fusion of the two partners participating in the translocation and generate a chimeric product with aberrant function. Missense or nonsense point mutations can cause loss of function of tumor suppressor genes that are important in maintaining control of cell growth and differentiation. In the case of a dominant-negative tumor suppressor gene, the product of the allele inactivated by mutation suffices to contribute to the neoplastic state by binding and abrogating the function of the wild-type product. For the majority of tumor suppressor genes, however, inactivation of the second allele is necessary to completely lose function. The second hit is often effected by the deletion of genomic information, often registered by loss of heterozygosity assays. Loss of function can also be produced by hypermethylation of the promoter or fragile regions, resulting in silencing or extinction of its expression. The genetic instability inherent to many cancer cells can be manifested by microsatellite instability. Changes in the length of repeats can be caused by lesions in the DNA repair genes (i.e., hMSH1, hMSH2, hMPS1, hMPS2) giving rise to the so-called mutator phenotype.

An additional category of markers is based on the clonal nature of neoplastic proliferations. When there is a question about whether abnormal cells are the consequence of non-tumoral tissue response (regenerative atypia) or represent a neoplastic proliferation, clonality assays may provide the answer. If the suspicious cells or tissue can be shown to be clonal, they are likely to represent a neoplastic process, because cells in hyperplastic or reactive lesions are polyclonal. Assays of clonality can be used to identify the cells within a tissue or cytology sample that carry the same form of mutation or alteration of function than that of the transformed state of the cell. Amplification of an oncogene is usually associated with protein overexpression and is another mechanism for gain of function. Amplification constitutes an easily detectable and measurable change; thus, it is a good diagnostic and potential prognostic marker. In translocations, protooncogenes are subjected to a strong promoter-enhancer or removed from a physiologic regulatory control element. The net effect is an inappropriate increase in product that provides excess function.

Fluorescence In Situ Hybridization

Fluorescence in situ hybridization (FISH) overcomes many of the practical problems of conventional cytogenetics by permitting the specific staining of any given region of the genome. In addition, the staining can be done using metaphases or interphase nuclei. ISH of DNA probes to metaphase chromosomes deposited on microscopic slides or to chromatin within intact interphase cells in smears or tissue sections is usually monitored by fluorescence, and it is therefore referred to as FISH. The DNA probes used for FISH may consist of mixtures of DNA fragments covering whole chromosomes, fragments containing chromosome-specific repeated sequences, or fragments containing unique nonrepetitive sequences. The lower limit of fragment size for unique sequence fragments is approximately 4 kilobases (kb), but in practice, fragments of approximately 25 kb, such as those propagated in bacterial cosmids or in yeast artificial chromosomes, give the most consistent results. The probes labeled to specific chromosomal regions with a marker (digoxigenin or biotin) that can be detected with an antibody specific to the tag and labeled with a fluorochrome. Up to seven probes can be used simultaneously, and changes not detectable in expanded banding preparations can be identified with this approach. The number of simultaneous probes that can be applied is growing, and with the aid of confocal microscopy and image processing, this methodology is becoming an increasingly valuable tool for genetic findings. The advantage of FISH over traditional karyotyping, a feature not shared by the analysis of metaphase chromosomes. FISH is well suited for the detection of numerical changes in chromosomes or regions of chromosomes, including microdeletions. In addition, chromosomal translocations can be detected by the simultaneous use of two probes containing DNA sequences known to reside on either side of a translocation breakpoint in one of the two reciprocal translocation products. Apposition of two of the four dots present in diploid cells indicates the presence of a translocation. Identification of such a result is labeling the two probes with different tags that are recognized with antibodies conjugated to different fluorochromes. When used in interphase cells, for the diagnostic or monitoring purposes discussed in the following section, FISH has the advantage over PCR that it is a quantitative technique, because the results can be expressed as the percentage of a class of cells containing the diagnostic abnormality.

The limitation of FISH—providing information only on the regions covered by the probe(s) used—is partially overcome by CGH. In this procedure, tumor DNA ultimately recognized by a red fluorochrome and normal DNA recognized by a green fluorescent dye are mixed at equimolar concentrations and then allowed to hybridize to metaphase chromosomes. If a region of the genome appears painted in an orange-yellow signal. If a gene is missing in the tumor, it is painted green. In contrast, if a region of the genome is amplified many-fold in the tumor, this region appears in red. CGH allows assessment of the entire genome, albeit at a relatively rough scale, but it is a technologically demanding and lengthy procedure. Although it constitutes a powerful research and discovery tool, it is unlikely to receive widespread diagnostic application as a clinical test.
include ultraclean and separate rooms for pre-PCR, PCR, and post-PCR manipulation of the samples; use of pipetting devices containing aerosol barriers; and UV irradiation of the reaction mixture before addition of the polymerase and template DNA. Additionally, control reactions from which template DNA is omitted should always be performed and analyzed in parallel with any PCR test to ensure that the reagents, other than the template, are not contaminated. Products can also be precisely sized on gels, analyzed by Southern blot hybridization, or subjected to nucleotide sequence analysis to distinguish bona fide products expected for a specific amplification reaction from artificial products that may have been amplified during the reactions. The advantages of PCR, however, far outweigh the disadvantages. The amplification capabilities of the procedure mean that very small numbers of total cells are sufficient for analysis. The small size of the amplification target (as small as 40 to 50 base pairs) makes PCR possible on partially degraded DNA or on the highly fragmented DNA normally obtained when extracting from formalin-fixed paraffin-embedded tissue. PCR is a fast procedure, because standard amplifications that comprise 25 to 30 cycles can be completed in a few hours, facilitating timely turnaround of tests. Furthermore, if maximum sensitivity is not a concern, analysis can be carried out with nonradioactive probes. For all these reasons, PCR has been used in most of the molecular diagnostic tests relevant to cancer. It is the sensitivity of PCR that makes it the method of choice for the staging of cancer, as well as for the monitoring of residual disease after therapy.

A productive application of PCR has been to amplify specific genomic sequences obtained from paraffin sections by microdissection (Fig. 26-3). By using random primers, the entire DNA extracted from a small number of cells can be amplified in an unbiased fashion. Efficient protocols for “whole genomic amplification” make it possible to perform CGH experiments, starting from a microscopic lesion.

**TABLE 26-1.** Selected Antigens Analyzed by Immunohistochemistry in the Diagnosis and Characterization of Tumors

IHC is a powerful tool to dissect the different cell components present in tumoral tissues. It can show two different phenotypes of tumor cell differentiation most dramatically when two antigens specific for each cell type are shown simultaneously on the same slide, and thus, it has contributed to the elucidation of the composition of tumors showing diverse lines of differentiation. It can also separate reactive cells infiltrating the tumor when distinction of tumor cells from reactive cells...
is unreliable using routine histologic stains. Such an instance is seen in the so-called T-cell-rich B-cell lymphomas, which consist of neoplastic lymphocytes of B lineage accompanied by a heavy infiltrate of nonneoplastic T cells. The latter sometimes constitute the majority of the cellular elements visible on a slide. At least some of the cases classified as malignant histiocytosis on the basis of finding neoplastic cells admixed with “atypical” histiocytes demonstrating erythrophagocytosis have been shown to be T-cell lymphomas infiltrated by activated histiocytes.

IHC can sometimes contribute to the distinction between benign and malignant tumors. The demonstration of the ectopic chorionic gonadotropin-b subunit in subset I lymphomas of the pancreas strongly suggests malignancy. Many tumor markers can be localized in tumorous tissues, contributing to both tumor classification and identification of tumor cells in distant sites. Demonstration of cells containing neuron-specific enolase antigenic determinants in their cytoplasm has increased the sensitivity of detecting very small numbers of neoplastic cells in brain metastases, thereby widening the choice of therapeutic agents that may have value in this setting.

Pathologic staging has become more precise when the involvement of lymph nodes is established using IHC to detect breast tumor cells in axillary lymph nodes. IHC is a very useful diagnostic adjunct to resolve controversial cases in cell type and to unequivocally identify the presence of small numbers of tumor cells. To maximize the efficiency and usefulness of IHC in clinical practice, it is best to use batteries of antisera chosen to solve specific problems in a critical and systematic fashion. Together with the availability of automated staining devices, this algorithmic approach helps manage the laboratory and facilitates periodic evaluation of test performance and efficiency of operations.

With the explosion of molecular medicine, IHC used mostly to investigate disease in a correlative mode is progressively being applied to attack mechanistic questions. Monoclonal antibodies are capable of recognizing subtle structural changes that are directly related to the function of the molecule and are thus excellent tools for molecular analysis. An example of dissection of molecular function using antibodies is provided by monoclonal antibodies directed to the phosphorylated peptides of growth factor receptors. The erbB-2 receptor is phosphorylated on activation. Antibodies that discriminate between the phosphorylated and nonphosphorylated producing a ladder sequence. Besides the technological restraints, including the resolution of the bands and the “compressed” or clustered migrated bands in the top and bottom of the gel. New, automated high-throughput genotyping blood gene sequencing have been developed to increase the sensitivity and speed the analysis of gene sequencing. Incorporating a fluorescent-labeled nucleotide in the newly synthesized DNA strand and coupling a fluorescence emission detector next to gel, fluorescence can be identified while the gel runs. Instead of a photographic image, electrophorograms are automatically read and printed. The use of capillary machines and four-color automated fluorescent sequencing produce well-defined peaks in a highly sensitive and reliable fashion. Several genetic analyzers, or automated sequence detection systems, are commercially available that greatly enhance the analytical ability with respect to mutation detection. Moreover, the use of fluorescent-labeled dNTPs allows laboratories to move away from radioactive, gel-based systems. Using fluorescent-labeled microsatellite markers, some of these apparatus also have the capability of detecting genetic losses.

**HIGH-THROUGHPUT TECHNIQUES**

The manual sequencing method most widely used is the Sanger dideoxy sequencing technique. This procedure uses base-specific termination during in vitro synthesis of DNA and is also known as the chain termination method. The basis for terminating the elongation of the DNA chain is the use of a nucleotide triphosphate containing a reduced (dideoxy) nucleotide triphosphate (dNTP). When such dNTPs are mixed with the four intact dNTPs at the appropriate concentrations, chain termination occurs. The four normal dNTPs are mixed with the respective dNTPs in four different test reactions, and reactions are compared for the growing DNA chain. In these reactions, the normal dNTPs are labeled at the a position, usually with phosphorus 32, to incorporate the radioactive signal needed for detection. These products are separated using acrylamide gel electrophoresis. The gels are dried and then imaged using autoradiography, producing a “ladder” sequence. Besides the technological restraints, including the resolution of the bands and the “compressed” or clustered migrated bands in the top and bottom of the gel. New, automated high-throughput genotyping blood gene sequencing have been developed to increase the sensitivity and speed the analysis of gene sequencing. Incorporating a fluorescent-labeled nucleotide in the newly synthesized DNA strand and coupling a fluorescence emission detector next to gel, fluorescence can be identified while the gel runs. Instead of a photographic image, electrophorograms are automatically read and printed. The use of capillary machines and four-color automated fluorescent sequencing produce well-defined peaks in a highly sensitive and reliable fashion. Several genetic analyzers, or automated sequence detection systems, are commercially available that greatly enhance the analytical ability with respect to mutation detection. Moreover, the use of fluorescent-labeled dNTPs allows laboratories to move away from radioactive, gel-based systems. Using fluorescent-labeled microsatellite markers, some of these apparatus also have the capability of detecting genetic losses.

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The acquisition and processing of hybridization intensity data obtained by probe arrays is being applied in multiple areas, including the study of differential expression patterns and genotyping or analysis of polymorphisms. The potential for generating a novel molecular nosology of tumors, selecting the most effective therapy for an individual patient, determining molecular staging and grading, and discovering new therapeutic strategies is great and, to many, self-evident. For the data to be analyzed, correlated, and exchanged, however, a unified informatics platform must exist for collecting, storing, retrieving, and interrogating the databases. The development of a specific branch of bioinformatics designed to handle a large volume of data, create appropriate clusters to define entities, and find ways to display the results is common to many of the comprehensive technologies, such as proteomics and even tissue arrays.

Two-dimensional gel electrophoresis of proteins has held the promise of comprehensive analysis of the protein constituents of a tissue or a population of living cells. The development of immobilized pH gradients lowered the barrier to the widespread application of two-dimensional gel analysis to tumors. The potential value of proteomics for the accurate classification of tumors was well demonstrated in the mid-1980s by the use of polypeptide phenotyping of acute leukemia in children. Advances in two-dimensional gel analysis and biophysical instrumentation suggest that comprehensive analysis of the proteins expressed in a tissue or population of cells will yield information capable of differentiating different tumor types. As in the case of mRNA profiling, it is hoped that this technique may help select therapies and identify novel targets for therapy. A promising advance is the use of MALDI-TOF (matrix-assisted laser desorption/ionization–time of flight) technology and variations thereof to construct "protein chips" that detect and identify proteins at the femtomole scale directly from their native environments. By using modified surfaces to capture molecules on the basis of specific binding kinetics, this type of approach can probe the function of some molecules in an exquisite way, thus significantly contributing to the knowledge of functional genomics. Technological platforms for nucleic acid identification can be modified to greatly enhance the sensitivity of IHC, and molecular counting can be made possible on the basis of rolling circle amplification (RCA) technology.

As a consequence of genomics and proteomics, antibodies will be raised against a very large number of novel antigenic determinants. The task of characterizing the patterns of tissue reactivity and the prevalence of the potential marker in even the most common tumor types appears out of reach of most laboratories. Although still in its early stages of development, tissue microarrays may enable investigators to rapidly characterize novel antigens. Tissue microarrays (Fig. 26-4) make it possible to analyze hundreds, even thousands, of tissue specimens from patients in different stages of disease and to assess the diagnostic, prognostic, and therapeutic importance of emerging cancer gene candidates. In situ detection of DNA, RNA, and protein can be performed on consecutive sections of tissue microarrays. In this fashion, hundreds to thousands of samples can be analyzed simultaneously. Although the labor needed to construct a tissue microarray is considerable, and many issues in array design, image acquisition, and data storage are yet to be resolved, it is clear that all barriers will be lowered to facilitate the widespread use of this approach. One of the advantages of tissue arrays is that each human tissue sample is greatly expanded. A regular paraffin block can easily yield twenty 0.2-mm cores, and 300 sections can be obtained from a microarray master block. Thus, 6000 sections can be analyzed from each tumor block. Mutation detection in cyto logic specimens and in tissues is now a possibility using a new reporter system, the RCA. RCA is an isothermal amplification driven by a polymerase that replicates circularized oligonucleotide probes. The reaction can be set up to take place with either linear or geometric kinetics and is amenable to use in a variety of formats ranging from surface immobilized DNA to cytotytic specimens (Fig. 26-5).

APPLICATIONS OF MOLECULAR MARKERS: DIAGNOSTIC MOLECULAR PATHOLOGY

Molecular markers and the techniques to demonstrate them in cells and tissues can be exploited for a series of paradigmatic clinical purposes that are succinctly discussed in the following paragraphs. As knowledge of the basic pathogenesis of human tumors advances and technology develops, new applications will come to the fore and molecular diagnosis can be truly described as a rapidly evolving and expanding field.

RISK ASSESSMENT

A significant number of inherited predispositions to develop tumors has been identified, and the genetic defect underlying the predisposition has been fully characterized for many of the inherited tumor syndromes (see Chapter 13). Assessing inherited risk of developing a tumor because of a germline mutation is the province of clinical geneticists and of cancer prevention programs. Many of the genetic defects causing inherited tumor syndromes are also the rate-limiting initiating events for the sporadic tumors of the same histotype. The adenomatous polyposis coli (APC) gene altered in familial polyposis is found mutated in more than 90% of sporadic adenomatous polyps of the colon. An analogous situation exists for the Rb gene responsible for initiating the mutation of both inherited and sporadic retinal neoplasms. Thus, finding these genes mutated in acquired preneoplastic conditions could possibly contribute to assessing the risk of a given tissue for developing a tumor. Evidence is emerging that lesions preceding adenocarcinoma of the lung harbor cells that show loss of alleles in chromosomes 3p and 9p and that these events are followed by mutations in the ras gene that occur at more advanced morphologic stages (carcinoma in situ). Studies in Barrett's esophagus suggest that the subset of patients showing an increased G1 fraction or aneuploidy is at increased risk for progression to high-grade dysplasia and cancer and should therefore be under closer surveillance. It will be of interest to see if patients known to be at increased risk for certain tumors can be screened to detect the lesions at an early stage. Studies suggest that detection of microsatellite expansion in cells sloughed from translational epithelium lining the urinary tract may fulfill this goal.

For patients
with severe, long-standing ulcerative colitis, microsatellite instability has been more prevalent than in patients with dysplasia.

DIAGNOSIS

In the proper hands, cytology and histopathology are highly efficient diagnostic tests, but in a number of instances, these tests do not provide a decisive answer as to whether a lesion is a tumor or not. In many instances, determining the specific tumor type is facilitated by IHC; however, because of suboptimal material in some cases, the interpretation of the test results may be rendered difficult. Molecular markers can in many instances contribute to the reliable characterization and diagnosis of a sample.

Among the most useful markers are the different translocations that are specific for certain tumor types. Among the cancers on which molecular diagnostics has had the greatest impact is chronic myelogenous leukemia (CML). The marker of this disease has been the Philadelphia chromosome (Ph1) t(9;22) (q34;q11), demonstrable in 95% of cases of CML. The translocation is demonstrable by conventional cytogenetics, FISH, Southern blot hybridization, and PCR. The Philadelphia translocation joins the S’ portion of the BCR gene located on chromosome 22 to the 3’ portion of the ABL gene on chromosome 9. The chimeric gene is transcribed into a novel 8.5-kb mRNA, which in turn is translated into a 210-kD protein. The precise position of the breakpoints within the DNA varies considerably from case to case. This is due to the fact that the breaks occur within introns, the sequence of which is excised from the initial forms of the BCR-ABL transcript to produce a mature 8.5-kb mRNA. The variability in the positions of the breaks in DNA preclude the use of a single pair of primers to amplify DNA across the breakpoint. To circumvent this problem, investigators have devised the so-called reverse PCR. In the first step of the procedure, BCR-ABL mRNA is transcribed with an ABL primer into single-stranded cDNA using reverse transcriptase. Nucleotide sequences in the cDNA are then amplified with primers for the BCR and ABL exons. It is important to perform control amplifications using primers for an omnipresent mRNA to ensure that the quality of the RNA to be tested is adequate.

Up to 6% of children and 20% of adults with acute lymphoblastic leukemia (ALL) also have a Ph1 chromosome indistinguishable cytogenetically from the one found in CML. However, the precise position of the breakpoints in DNA differ between CML and ALL, and molecular techniques are the only way to reliably distinguish a lymphoblast crisis of CML from de novo ALL. Other practical contributions of the demonstration of the Ph chromosome in ALL is that ALL patients with the translocation seem to have a poorer prognosis than those with Ph-negative ALL. Protocols for the demonstration of an increasing number of translocations linked to the pathogenesis of hematolymphoid neoplasias are available and constantly being improved.

A group of tumors that very often presents a diagnostic challenge is the so-called small round cell tumors of childhood. By light microscopy, it is often very difficult to distinguish rhabdomyosarcoma from lymphoma and from primitive neuroectodermal tumors or Ewing’s sarcoma. Translocations that are specific for a number of malignant tumors of the soft tissues (Table 26-2) are beginning to bring the resolute power of molecular diagnostics to this area. Defining the underlying genetic defects in these tumors not only clarifies their pathogenesis, but also provides information of how they can be distinguished from case to case. This is due to the fact that the breaks occur within introns, the sequence of which is excised from the initial forms of the BCR-ABL transcript to produce a mature 8.5-kb mRNA. The variability in the positions of the breaks in DNA preclude the use of a single pair of primers to amplify DNA across the breakpoint. To circumvent this problem, investigators have devised the so-called reverse PCR. In the first step of the procedure, BCR-ABL mRNA is transcribed with an ABL primer into single-stranded cDNA using reverse transcriptase. Nucleotide sequences in the cDNA are then amplified with primers for the BCR and ABL exons. It is important to perform control amplifications using primers for an omnipresent mRNA to ensure that the quality of the RNA to be tested is adequate.

MOLECULAR GRADING AND STAGING

The purpose of grading is to predict the risk for local and distant spread of a tumor. Improving the capacity to predict whether a tumor has metastasized will have a significant impact on therapy and prognosis. The concept that neoplasia is accumulation of mutations makes it possible to think that, if the molecular pathways of tumor progression are defined, determining the alterations present in a tumor could provide accurate indication of the stage of progression and, thus, complement and refine the prognosis based on conventional grading and staging. It has been suggested that a certain class of mutations of the Ki-ras gene encountered in colorectal cancer could identify the more aggressive neoplasms. The demonstration that a mass lesion is composed of cells issued from a single progenitor cell is the single most reliable sign that the mass is a tumor. Hence, methods to demonstrate clonality are important adjuncts to the morphologic evaluations of biotic tissues. The first tumor in which clonality as assessed by molecular methods had a significant diagnostic impact was lymphoma. Clonal rearrangement of B- and T-cell receptors indicates that a lymphoid mass is a tumor, although not necessarily malignant, and also provides information as to the lymphoid cell lineage of the neoplasm. PCR protocols to demonstrate monoclonal populations are available for both B- and T-cell receptors. This technique makes it possible to determine clonality in small tissue samples, and the demonstration of monoclonality helps to establish the neoplastic nature of lymphoid proliferations of the stomach.

Clonality assays applied to cell smears promise to greatly enhance the diagnostic efficiency of cytology. The differential diagnosis between reactive mesothelial cells and mesothelioma can be resolved by showing clonality of the cells by FISH.

Demonstration of point mutations in the Ki-RAS gene can be an important diagnostic feature of malignant pancreatic tumors. Determining that mutated alleles of the Ki-ras gene are present in cells aspirated from a pancreatic mass strongly suggests a malignant tumor, and the efficiency of diagnosis of pancreatic masses by fine-needle aspiration is significantly increased by the simultaneous use of Ki-ras assessment and carcinoembryonic antigen levels.

Microsatellite DNA markers are useful clonal markers for the detection of cancer, and microsatellite changes matching those found in the primary tumor can be detected in the urine sediment of 95% of patients diagnosed with bladder cancer. It is of interest that, in the same series of patients, conventional cytology was positive in only 50% of the patients. Thus, microsatellite analysis might possibly be a viable method to screen for bladder cancer.

MOLECULAR GRADING AND STAGING

The purpose of grading is to predict the risk for local and distant spread of a tumor. Improving the capacity to predict whether a tumor has metastasized will have a significant impact on therapy and prognosis. The concept that neoplasia is accumulation of mutations makes it possible to think that, if the molecular pathways of tumor progression are defined, determining the alterations present in a tumor could provide accurate indication of the stage of progression and, thus, complement and refine the prognosis based on conventional grading and staging. It has been suggested that a certain class of mutations of the Ki-ras gene encountered in colorectal cancer could identify the more aggressive neoplasms.

Evaluation of the expression of proteins linked to cell division, such as Ki-67 (MB) and PECAN, have been extensively used to evaluate the percentage of proliferating cancer could identify the more aggressive neoplasms. The demonstration that a mass lesion is composed of cells issued from a single progenitor cell is the single most reliable sign that the mass is a tumor. Hence, methods to demonstrate clonality are important adjuncts to the morphologic evaluations of biotic tissues. The first tumor in which clonality as assessed by molecular methods had a significant diagnostic impact was lymphoma. Clonal rearrangement of B- and T-cell receptors indicates that a lymphoid mass is a tumor, although not necessarily malignant, and also provides information as to the lymphoid cell lineage of the neoplasm. PCR protocols to demonstrate monoclonal populations are available for both B- and T-cell receptors. This technique makes it possible to determine clonality in small tissue samples, and the demonstration of monoclonality helps to establish the neoplastic nature of lymphoid proliferations of the stomach.

Clonality assays applied to cell smears promise to greatly enhance the diagnostic efficiency of cytology. The differential diagnosis between reactive mesothelial cells and mesothelioma can be resolved by showing clonality of the cells by FISH.

Demonstration of point mutations in the Ki-RAS gene can be an important diagnostic feature of malignant pancreatic tumors. Determining that mutated alleles of the Ki-ras gene are present in cells aspirated from a pancreatic mass strongly suggests a malignant tumor, and the efficiency of diagnosis of pancreatic masses by fine-needle aspiration is significantly increased by the simultaneous use of Ki-ras assessment and carcinoembryonic antigen levels.

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Evaluation of the expression of proteins linked to cell division, such as Ki-67 (MB) and PECAN, have been extensively used to evaluate the percentage of proliferating tumor cells in biopsies or resection specimens. In lymphomas, for example, when the percentage of Ki-67–positive cells is high, the prognosis is significantly worse. For many tumors, a high percentage of cycling cells correlates with bad prognosis. This finding is not surprising and is in keeping with the number of mitotic figures, one of the classic parameters used for tumor grading.

Genotypic characteristics can sometimes predict the behavior of a lesion, as illustrated in the case of fibromatosis. Trisomy of chromosome 8 is found in lesions that recur, whereas lesions with low potential for recurrence have a balanced genetic complement. The status of TP53 (wild-type vs. mutated) has been found to contribute prognostic information in bladder, colon, and breast carcinoma. Abrogation of TP53 function can lead to a loss of G1 arrest in response to DNA damage or can interfere with apoptosis. In the first instance, mitosis without repair could fix mutations contributing to the cumulation of genetic lesions in the same cell. Loss of apoptosis could contribute to an increase in cell number and lack of responsiveness to therapy. The concept that loss of competence for apoptosis could contribute to tumor recurrence has led to investigation of the pathogenic role of genes involved in cell survival, such as BCL-2. Overexpression of BCL-2 has been found to correlate with lymph node metastases in ductal carcinoma of the breast.

Neuroblastoma is perhaps the tumor that is most often graded by molecular means in many centers. The status of N-MYC amplification and the level of expression of TRK-A are among the most significant prognostic parameters for tumors of matched stage and morphology. Together with ploidy and loss of chromosome 1p, they
Gene expression array profiling studies are being reported, disclosing the potential contributions they may be able to make in the molecular classification of neoplastic diseases. They also offer significant new information regarding differentiation states; global alterations affecting particular cellular programs, such as growth regulation; and host response mechanisms. If current classification schemes still lump together different diseases with distinct clinical phenomenologies, differential gene expression will distinguish molecular heterogeneity and produce biologically more accurate, and probably clinically more useful, diagnostic and predictive information.

Few original studies have been reported as proof of principle for the approach using specific entities as “test cases.” For example, Golub et al. attempted to produce a molecular classification of acute leukemias based on gene expression monitoring by DNA microarrays and containing 6817 human genes. After producing a teaching set of genes highly correlated with acute myeloblastic leukemia (AML)-ALL class distinction, these investigators then tested the validity of such a class of predictors. The final 50-gene set of predictors derived from cross-validation tests correctly assigned 36 of 38 samples as either AML or ALL, the remaining two cases resulting in “uncertain” phenotypes. The authors concluded that class prediction provides an unbiased general approach to prognostic tests. They also cautioned that sample collection, appropriate histopathologic documentation, and integrity of data sets are critical requirements for reaching robust conclusions. In a more recent study, Alizadeh et al. reported the distinct molecular nature of diffuse, large B-cell lymphomas (DLBCLs), an aggressive malignancy of mature B lymphocytes. This group of investigators had previously produced a specialized microarray, the so-called lymphochip, which holds selected genes preferentially expressed in lymphoid cell lines and their derived malignancies. Using a modification of this basic tool, they were able to molecularly subclassify DLBCLs into two groups: germinal-center B-like tumors and activated peripheral B-like neoplasms. Moreover, this molecular classification not only pointed out what was previously an ill-defined histogenesis, but it also incorporated novel data relating to proliferation and state of differentiation. Patients with germinal-center B-like DLBCL had a significant prolonged overall survival when compared to those with activated B-like DLBCL, revealing the clinical significance of molecular subtyping of neoplastic diseases.

To reach acceptance and clinical applicability, individual tumor markers and “class prediction sets” of biologic determinants must undergo methodical analysis. However, stringent criteria for the development of such studies, which should bring basic laboratory findings to clinical investigations and finally to standard of care, have not been well delineated. Certain groups of clinical investigators have proposed a protocol similar to the one used by the study for evaluating and implementing new therapeutic agents. In this exercise, phases of development and clinical application are well defined (see Chapter 17). Briefly, phase I deals with toxicity, phase II determines dose escalation and definition of therapeutic index, phase III is designed to ascertain efficacy, and phase IV is finalized after validation before commercialization and routine use. A similar analogy could be implemented that would take into account the process of discovery through validation of any given biologic predictor. Phase I should deal with issues regarding biologic properties of the marker and the methodologies that could better identify the marker in the context of using clinical material. Phase II should include pilot studies aimed at determining the specificity and sensitivity of such an assay; the definition of the cutoff value, if needed; and the potential clinical significance of detecting the marker as an adjunct to the already available clinicopathologic information. Phase III should include randomized trials where the marker is compared against other standard investigational (and, prospectively accepted in specific clinical settings) systems designed for such a purpose. Finally, phase IV studies should incorporate multifunctional efforts to delineate intra- and interlaboratory variability, define and implement a standardized assay (using the selected cutoff value, if required), and demonstrate the clinical usefulness of the marker. This does not signify a final proposal of the sequential steps that must be fulfilled by a potentially clinical significant tumor marker or set of markers. It is just meant to draw attention to the lack of specific criteria for such an exercise and the need to reach some generally approved system if it is thought that such applications deserve to be translated to the routine clinical practice.

DETECTION OF MINIMAL DISEASE

Detection of minimal disease has benefited greatly from the availability of molecular markers and, perhaps with diagnosis, is one of the most fruitful areas of expansion in molecular diagnostics. It plays a role in three clinical circumstances: (1) evaluation of minimal residual disease, (2) early detection of recurrence, and (3) evaluation of local extension. These applications are based on the high specificity of the molecular markers and the very high sensitivity afforded by the PCR-based techniques.

Detection of circulating cells harboring the bcl-2 translocation is an important prognostic indicator of relapse in patients with t(14:18)-positive B-cell lymphoma treated with aggressive chemotherapy and autologous bone marrow or peripheral blood stem cell support. A correlation exists between the relapse rate and both the degree of contamination of the autograft and the efficacy of purging, suggesting that contamination is in part responsible for treatment failures. Similar strategies are being explored for other malignancies. Detection of cytokeratin 19 transcripts by RT-PCR in a sample of bone marrow, peripheral stem cells, or peripheral blood, indicates the presence of epithelial cells for patients with breast carcinoma. Other tumor-specific transcripts, such as tyrosinase for melanoma, prostate-specific antigen for prostate cancer, and thyroglobulin for thyroid cancer, also have been exploited for the detection of circulating cells. In general, these assays achieve the detection of one tumor cell in a background of 10^11 cells. Circulating soluble Ki-RAS DNA bearing the same mutated sequences as the primary tumor can be detected in plasma and other fluids of patients with pancreatic carcinoma or ovarian cancer. The clinical significance of these findings is not yet established, but when quantitative assays become available, the level of circulating tumor-specific DNA can perhaps be used as a marker to follow therapy and for early detection of recurrence.

A different use of the ability to detect tumor cells with high sensitivity is the analysis of tissues for the presence of a specific mutation that identifies the primary tumor primary. It is indeed possible to verify the close link between the spread of a tumor by testing the surgical margins, not just by light microscopy but also using the sensitive PCR. Moreover, the worthiness of the workhorse of molecular biology is pointed out by the following facts. Many studies in head and neck cancer that show that “molecular margins” are superior in predicting local recurrence when compared to the conventional approach of assessing resection margins by intraoperative frozen section. Should sequencing of short cDNA fragments in minutes become feasible, intraoperative molecular assessment of margins for tumors genotyped at the time the first diagnostic biopsy is obtained may possibly become a real option.

RECURRENT versus SECOND PRIMARY

With cure rates and survival rates of patients with malignant tumors increasing, it is more important in clinical practice to identify second primary tumors. When a second tumor has its presentation in the same organ system as the first, the question invariably arises about distinguishing between a recurrence and a second primary. Morphologic comparison and an extended immunophenotypic profile of the two lesions can sometimes resolve the question, but the presence of a clonal mutation or a broader constellation of genetic alterations is the most direct way to establish a link between the two lesions or to strongly suggest that the molecular nature of the recurrent event. An adenocarcinomatous lesion in the lung of a patient in long-term remission for a primary adenocarcinoma elsewhere is another situation that benefits from a molecular approach to distinguish between a second primary and a metastasis. Clearly, is it best not to rely on the alterations present on a single gene but to attempt to establish a broad genotypic characterization of the two lesions to maximize the effectiveness of the interpretation of the results. Microsatellite alterations at multiple loci can be useful. Relying on differences or similarities in gene sequence in genes that show a wide spectrum of mutations (e.g., TP53) clearly is more effective than using genes exhibiting a limited repertoire of mutations (e.g., Ki-RAS). Molecular analysis of multiple tumors of the transitional epithelium in the urinary bladder has demonstrated that the multiple lesions arise from a single progenitor cell that seeds the bladder mucosa, explaining the high risk for recurrence encountered in these patients.

CONSIDERATIONS FOR THE FUTURE

The practice of conventional histopathology based on light microscopy was changed and complemented in the second half of the twentieth century by three technological advances: ultrastructure, IHC, and molecular diagnostics. The first two represented incremental gains in diagnostic power and efficiency but did not fundamentally change the practice of molecular medicine is profuse. However, the practice of molecular medicine is changing. Perhaps more important, molecular medicine is altering the pathway for advancement. The elucidation of the molecular pathogenesis of tumors has led directly to the discovery and application of molecular tumor markers. Diagnosis and prognosis have, in many cases, been enhanced by the use of the marker(s). Finally, the marker (e.g., HER2/neu) may constitute a therapeutic target. With the advances in biotechnology and bioinformatics, the preceding sequence of events can be predicted to change. Rather than elucidating a molecular pathway, we will have a complete view of the molecular biology of a given tumor type. This comprehensive understanding will lead to the development of specific therapies and to the rational selection of therapeutic modalities for a specific patient. Molecular tests will allow an accurate assessment of the response and modification of therapy when required. The detailed molecular knowledge of the natural history of tumors will yield markers for inherited and acquired risks, and these, in turn, will make improved design and monitoring of prevention a reality.
INTRODUCTION

Computed tomography (CT) has long been a mainstay of diagnostic imaging in cancer patients. CT offers noninvasive and accurate results for most disease processes and is both widely available and relatively low in cost. The number of CT examinations performed in the United States continues to increase at a rate of approximately 10% per year. CT has remained a vital and important imaging modality because it has continued to evolve, with spiral (helical) CT, multiphase imaging, and multidetector scanning being the notable recent innovations. The current diagnostic capabilities and the accuracy of CT continue to improve. With spiral CT, data acquisition can be timed with the administration of contrast material during multiple phases of enhancement, optimizing cancer detection and diagnosis. In addition, new techniques centered on three-dimensional (3D) and virtual CT imaging are being refined to take advantage of some of the capabilities of spiral CT. These techniques will prove valuable in planning surgical procedures and radiation therapy. CT is also ideally suited for the guidance of interventional procedures often necessary to confirm malignancy and allow subtyping of tumors. This section reviews some of the key current applications of CT scanning and defines its role in patient treatment and management.

LIVER

Spiral CT currently is the study of choice for the evaluation of the liver and biliary tree. Spiral CT can both detect and characterize hepatic pathology by providing detailed information as to the presence, extent, and vascularity of a lesion. Accurate localization of tumor to specific hepatic segments can be performed when key vascular structures are defined. The enhancement pattern, as well as lesion attenuation values, allow specific classification of a lesion as benign (cyst or hemangioma) or malignant (primary vs. metastases) in most cases. Specific CT characteristics may also suggest whether a lesion is a primary or metastatic lesion, although there is significant overlap in many cases. Identification of the characteristics that differentiate benign from malignant lesions is critical because many smaller liver lesions (1 cm or less), even in oncology patients, are benign (Fig. 27.1-1, Fig. 27.1-2).

FIGURE 27.1-1. Adenocarcinoma of the liver. Cystic tumor mass grows through the liver capsule. Ascites is also seen.

FIGURE 27.1-2. Cholangiocarcinoma of the liver. A: A 10-cm intrahepatic mass is partially calcified on non–contrast-enhanced scans. B: After infusion of contrast, the vascularity and necrotic nature of the tumor are best defined.

There has been much discussion over the last several years, with various conclusions, as to the optimum imaging protocol for the detection of hepatic tumors. Before the introduction of spiral CT, the optimal CT technique for imaging the liver was CT during arterial portography. The limitations of that technique include the need for catheterization of the superior mesenteric artery as well as problems with flow-related defects in up to 25% of patients. Newer CT techniques have essentially the same detection rate (or better) but without the related limitations. Kuszyk et al. found that with portal-phase contrast-enhanced spiral CT, 91% of lesions larger than 1 cm can be detected. Hollett et al. found that by using a dual-phase CT technique, almost 10% more lesions were detected than with portal-phase images only. As CT technology is constantly evolving, the prospect of greater accuracy in the ability to detect lesions is fairly optimistic. The most recent work, utilizing multidetector spiral CT scanning, uses very narrow collimation (2.5 mm) for optimal lesion detection, with excellent results.

In addition to the detection of tumor, CT coupled with 3D reconstruction of data represents the next step in CT imaging. The image data are presented in a form that combines the best of angiography and CT scanning. These 3D images can be displayed in real time and can be supplemented by stereoscopic displays to optimize lesion definition and extent. The information generated can help with surgical planning. By combining a vascular map from the arterial phase with a venous map from the portal phase, the radiologist can generate key road maps and vascular anatomy in a noninvasive format. With technical advances such as this, curative resection of some primary and metastatic tumors is now possible. In addition, the number of relatively invasive preoperative studies often needed to document tumor resectability, including conventional angiography and CT portography, have been markedly reduced.
CT is also valuable in monitoring patient treatment. Accurate tumor volumetrics can be accomplished and captured to measure and quantify therapeutic response accurately. Three-dimensional size measurements have been shown to be reproducible and clinically useful for following up response of liver tumors to treatment. Enhancement pattern changes as well as changes in normal liver volumes also are often helpful in assessing treatment success. New techniques to measure liver enhancement after intravenous (IV) injection of contrast material can be used to quantify arterial blood flow to the liver and may be useful in determining which patients are at risk for subsequent development of liver metastases.

PANCREAS

The role of CT in the evaluation of the pancreas typically centers on the detection and staging of pancreatic adenocarcinoma. Although the 5-year survival rate for pancreatic cancer in general remains poor, in selected patients, survival can be increased. Patients with a mass of 2 cm or less limited to the pancreatic head or patients without major vessel encasement or spread to lymph nodes who are treated with a pancreaticoduodenectomy (Whipple procedure) have a 30% or greater 5-year survival. The key roles for CT in this patient population are accurate staging and triage.

The use of spiral CT has increased the accuracy of CT in staging pancreatic cancer by allowing detection of smaller lesions and by its ability to improve definition of vascular encasement. With modern spiral CT scanners, tumor detection approaches 96%. The number of indeterminate cases (i.e., the inability to distinguish between glandular enlargement due to inflammation and carcinoma) based on spiral CT findings has also decreased substantially. Pancreatic adenocarcinoma is usually a hypodense lesion relative to the normally enhancing pancreatic gland. In the past, a pancreatic mass was typically detected based on a gross contour change within the pancreatic gland. However, such an obvious contour change usually indicated a relatively large mass. With the optimal IV contrast delivery of spiral CT, smaller lesions can now be detected. The key roles for CT in this patient population are accurate staging and triage.

Optimal IV contrast enhancement also provides for better assessment of key arterial and venous structures, such as the portal vein, celiac axis, and superior mesenteric artery, to help to determine their patency and relation to tumor extension. The degree of major vascular involvement by pancreatic cancer is useful in predicting which patients will have surgically resectable tumors. Major vessels with less than one-fourth of their circumference involved by tumor are almost always resectable; tumors that surround more than three-fourths of the circumference are almost always unresectable. Hommeyer et al. analyzed the caliber of the peripancreatic veins and found that dilation of these vessels to more than 7 mm also suggests early vascular invasion and unresectability. Conventional angiography is no longer necessary for preoperative planning in most cases, since the sensitivity of CT and that of angiography are nearly identical, and 3D imaging can produce angiography-like images. Metastatic disease to the liver and lymph nodes is easier to detect, particularly for lesions that are hypodense and measure at least 1 cm in diameter. The characteristic CT appearance of other pancreatic masses may allow a diagnosis on the basis of appearance alone. CT can also be used to monitor response to adjuvant therapy and to detect any potential sites of tumor recurrence.

KIDNEY

One of the major roles of CT in the oncology patient is in detecting, classifying, and staging renal tumors. Common diagnostic problems in renal imaging are the detection and the characterization of a renal mass. Spiral CT has been shown to be accurate for the evaluation of renal masses and accurately can distinguish between a simple cyst and a solid tumor. In a small percentage of cases, there is an overlap, and an indeterminate diagnosis is made. In these cases, ultrasonography or magnetic resonance imaging (MRI) may be helpful, although usually these techniques are subject to the same limitations as CT.

FIGURE 27.1-5. Renal cell carcinoma. Computed tomography demonstrates a vascular tumor of the left kidney, with paraaortic nodes. Metastases to the mediastinal nodes are also seen.
FIGURE 27.1-6. Renal cell carcinoma. Sequence of computed tomography scans demonstrates tumor extension into the renal vein and the inferior vena cava. Tumor extends up to but does not involve the right atrium.

FIGURE 27.1-7. Non-Hodgkin's lymphoma involving the kidneys. Multiple solid bilateral renal masses are due to lymphoma. The kidneys are not enlarged.

One of the current controversies in imaging the kidney is the timing of data acquisition in relation to contrast injection. Specific acquisitions can be obtained during the arterial phase, nephrogenic phase, or delayed phase of renal enhancement. Most authors now agree that scans during two, if not all three, of these phases are necessary for optimal CT imaging of renal masses. Lesion detection approaches 100% with modern CT scanners. Arterial-phase images (20 to 30 seconds after IV contrast administration) are crucial for evaluating renal artery and tumor vascularity. Nephrogenic phase imaging (90 to 120 seconds after IV contrast administration) is ideal for lesion detection in the central portions of the kidney. Suspected renal vein or inferior vena cava involvement and collecting system opacification require a more delayed scan (3 to 5 minutes after IV contrast administration).

In addition, spiral CT serves as an excellent modality for multiplanar reconstruction and 3D imaging of the kidneys. These techniques are important if such procedures as partial nephrectomy are being considered. The 3D spiral CT study provides a valuable tool to define the location of the renal mass and its relationship to the renal vasculature and perinephric tissues (Fig. 27.1-8). The 3D images assist the surgeon by providing preoperative information in a flexible display that aids in determining whether nephron-sparing surgery is possible.

FIGURE 27.1-8. Renal cell carcinoma. Three-dimensional image demonstrates mass in the upper pole of the right kidney (curved arrow). The renal vein (straight arrow) is patent. Three-dimensional images such as this are valuable for preoperative planning.

CT is also useful for evaluation of tumors in the renal pelvis and collecting system, such as transitional cell carcinoma. In these cases, delayed CT scans are necessary to define accurately the true extent of tumor infiltration. Metastases to the kidney from such processes as lymphoma or lung cancer are best detected on these delayed scan examinations, especially since these tumors may not distort the renal outline and are best seen only with differential contrast enhancement.

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ADRENAL GLAND

CT scanning can clearly identify the adrenal glands in nearly all patients. The normal adrenal has two limbs, which have a maximum thickness of 3 to 4 mm. Adrenal enlargement can be due to a wide range of pathologies, from adrenal adenoma and hyperplasia to primary and metastatic adrenal tumors. The specific clinical criteria used to characterize an adrenal mass include patient history, age, medical history, and the presence of any biochemical or physiologic abnormalities. The specific CT criteria used include mass size, whether it is unilateral or bilateral, the density of the mass, the presence of calcification or fat within the lesion, and the presence of other signs suggestive of malignancy.

Even in the oncology patient, the most common adrenal mass is a benign adrenal adenoma. Adenomas range in size from 1 to 5 cm and are typically of low CT attenuation (–20 to 20 Hounsfield units) values. Several articles have reported successfully differentiating benign from malignant adrenal masses based on CT attenuation of the mass. In these studies, all small adrenal masses with CT attenuation below 18 HU on noncontrast evaluation were benign. In practice, then, adrenal masses that are 4 cm or less and are of low CT attenuation can be followed up conservatively with follow-up CT scanning. In the remaining patients with a potentially significant indeterminate adrenal mass, chemical shift MR imaging can be used to characterize the lesion confidently. Percutaneous biopsy may still be necessary in some patients.

Malignant adrenal lesions can be divided into primary and metastatic lesions. It may be impossible to distinguish a primary adrenal carcinoma from a metastatic lesion based on its CT appearance alone. Other adrenal tumors that can be confused with a primary adrenal malignancy include pheochromocytoma (which is malignant in up to 10% of cases), neuroblastoma (usually in younger patients), and myelolipoma (usually containing fat and calcification).
FIGURE 27.1-9. Primary adrenal carcinoma. A 12-cm, left upper quadrant mass with foci of calcification can be seen. The left kidney (not shown) was displaced inferiorly.

FIGURE 27.1-10. Bilateral adrenal metastases from a non–small cell lung cancer. The masses are unusually cystic.

SMALL BOWEL AND COLON

CT is typically not the first study to suggest the presence of a small bowel or colon neoplasm. Nevertheless, with the increased use of CT as the initial study for bowel obstruction or an acute abdomen, there has been an increased detection rate of primary gastrointestinal tract tumors. In most cases, CT is used in tumor staging to define the extent of the primary mass and to define spread to adjacent structures. Although the CT appearances of small bowel tumors may overlap, several signs are indicative of the etiology of the mass. Small bowel carcinoid tumor, for example, will typically present with an associated calcified mesenteric mass with a desmoplastic reaction. Small bowel adenocarcinoma is variable in appearance and may be an infiltrating lesion, a bulky mass, or an ulcerating lesion. Lymphoma of the small bowel also varies in appearance but is usually bulkier and more extensive than an adenocarcinoma (Fig. 27.1-11).

FIGURE 27.1-11. Small bowel lymphoma. Large ulcerating mass involves the proximal jejunum. The differential diagnosis would include a small bowel adenocarcinoma.

Adenocarcinoma of the colon is a diagnosis usually made by colonoscopy or barium enema, with CT typically reserved for staging spread of disease (Fig. 27.1-12). In some centers, double-contrast CT of the colon is performed, to stage better the extent of tumor locally and local spread. In other centers, the key role of CT is the detection of extracolonic disease, particularly to the liver or lung.

Recent advances in rapid volumetric CT scanning, combined with 3D imaging and computer graphics, have extended CT imaging into the “virtual” realm. Perhaps no other area has generated as much clinical interest and promise as that of virtual colonoscopy. With this technique, CT combined with 3D visualization provides a virtual endoscopic view of the mucosal surface of the colon (Fig. 27.1-13). This rapidly growing application has gained attention as a noninvasive test for screening of colon polyps and cancer. It has also proven effective in evaluating portions of the colon not accessible or readily seen at conventional colonoscopy. Authors have reported 84% to 100% sensitivity for the detection of polyps larger than 10 mm and 70% to 95% sensitivity for polyps ranging from 6 to 9 mm. Sensitivity remains poor for polyps measuring less than 5 mm but, with such technologic innovations as rapid-speed multidetector CT scanning and improved computer processing, there is great hope for improvement in the detection of tiny polyps.
FIGURE 27.1-13. Virtual colonoscopy. Data from spiral computed tomography can be manipulated with three-dimensional imaging to produce images that simulate the appearance of a barium enema (A) or colonoscopy (B). The virtual colon view demonstrates a small polyp (arrow).

ESOPHAGUS AND STOMACH

The role of CT in evaluating the upper gastrointestinal tract is somewhat controversial. Published results on the accuracy of CT for staging esophageal and gastric cancer have been variable and depend in large part on the extent of disease and the specific parameter evaluated. For example, in the evaluation and staging of esophageal cancer, CT has been shown to be fairly accurate in detecting invasion of the trachea and airway as well as in detecting nodes in the region of the gastrohepatic ligament. Recently, CT has been used increasingly for the follow-up and monitoring of patient status after therapy for esophageal cancer, whether with surgery, chemotherapy, or radiation therapy. Recent progress suggests that CT can be used not only to monitor response but for treatment planning.

Technologic advances have expanded the clinical role of CT in evaluation of the stomach (Fig. 27.1-14, Fig. 27.1-15, and Fig. 27.1-16). The use of double-contrast spiral CT produces a more detailed evaluation of the stomach than conventional CT. Initial studies suggest that this technique permits earlier detection and more accurate staging of small gastric tumors. The most commonly encountered stomach tumor is adenocarcinoma. Less common malignancies include lymphoma, leiomyosarcoma, and metastases. The CT appearance of each of these lesions has findings that are often helpful for diagnosis. Despite these features, there may be some overlap between all these tumors and other malignancies, such as metastatic disease to the stomach, or benign processes, such as Helicobacter pylori, which can simulate a malignant process.

FIGURE 27.1-14. Adenocarcinoma of the stomach. The patient presented with gastric outlet obstruction. Tumor encases the gastric antrum, with carcinomatosis seen.


FIGURE 27.1-16. Gastric leiomyosarcoma. Large necrotic mass arises off the gastric fundus. A small focus of calcification is seen in the mass.

LUNGS AND MEDIASTINUM

CT remains the study of choice for a wide range of oncology challenges in the thorax. Spiral CT has further enhanced the potential of CT in thoracic studies because of the single breath-hold capability, which essentially eliminates the problem of patient motion and breathing misregistration responsible for suboptimal examination. There are four major indications for CT scanning in the oncology patient with thoracic pathology: (1) staging a known tumor, such as lung cancer, lymphoma, or thymoma; (2) detecting possible lung metastases from an extrathoracic primary tumor, such as a renal cell carcinoma; (3) evaluating a known or suspected mediastinal mass (i.e., widened mediastinum on a routine chest radiograph); and (4) evaluating by high-resolution CT the lung parenchyma in suspected complications of therapy, including radiation injury, drug reactions, and such secondary infections as in the immunosuppressed bone marrow.
For staging most chest tumors, IV contrast material is required (Fig. 27.1-17, Fig. 27.1-18, and Fig. 27.1-19). Contrast delineates the normal vascular structures and defines the presence and extent of tumor and lymphadenopathy. Spiral CT can accurately depict the hilar lymph nodes and their major anatomic relationships. In lung cancer staging, we can determine the extent of disease, including vascular encasement or chest wall involvement. CT scans can also be used as a guide for fiber-optic bronchoscopy to optimize tissue sampling. CT combined with 3D visualization can provide a virtual endoscopic view of the trachea and can be useful for evaluating areas beyond high-grade tumor stenoses (Fig. 27.1-20).

**FIGURE 27.1-17.** Superior vena cava syndrome due to small cell lung cancer. Spiral computed tomography demonstrates tumor encasement of the superior vena cava. The azygous vein is enlarged.


**FIGURE 27.1-19.** Metastatic breast cancer. Computed tomography demonstrates lymphangitic spread of tumor into the right upper lung.

**FIGURE 27.1-20.** Virtual bronchoscopy. Three-dimensional image from spiral computed tomography data can produce images that can see the inside of the trachea and bronchi.

CT evaluation of primary mediastinal masses is useful in defining the extent of disease and can suggest a specific diagnosis in many cases. Specific CT findings, including location of the mass (anterior, middle, or posterior mediastinum), the presence of fat or calcification, enhancement characteristics, and mass size and other sites of disease are often helpful in diagnosis. Clinical history (e.g., myasthenia gravis), patient age, and medical history are also critical for achieving the correct diagnosis. CT can stage most of these processes and is a useful guide for planning appropriate therapy, such as surgery, radiation therapy, or chemotherapy. CT also plays a major role in monitoring response to therapy.

Another major advantage of CT is the ability to display an entire cross section of anatomy. This is especially important when staging such disease processes as lymphoma. Studies have shown a change in therapy or treatment protocol in approximately 10% of patients based on information from chest CT, as compared with information from chest radiographs only.

Spiral CT provides a more accurate detection rate for pulmonary nodules than conventional chest radiography. Small nodule detection is important clinically, as lesions 1 cm or smaller are malignant in a large percentage of patients, especially in patients with a history of previous malignancy. Spiral CT also allows for accurate density readings of lesions to aid in detecting the presence of fat or calcification, which is helpful in determining the nature of any given nodule. Enhancement characteristics of pulmonary nodules can also be used to characterize and predict their malignant potential. Recently, much attention has been focused on the use of “low-dose” spiral CT as a screening test for patients at high risk for the development of lung cancer. Spiral CT with dose reduction to 10% to 25% of standard CT has been shown to be very accurate in the detection of pulmonary nodules and can be used to exclude or confirm the presence of a nodule in a
patient with an equivocal chest radiograph. 72

Finally, the use of what is commonly referred to as high-resolution CT scanning is particularly valuable in detecting and defining the presence of parenchymal lung injury, whether from radiation therapy (radiation pneumonitis) or from infections, such as invasive pulmonary aspergillosis after a bone marrow transplant. This CT technique uses very thin sections and has a high spatial resolution algorithm. It is important to remember that the high-resolution CT scanning may be positive for disease even with a "normal" plain radiograph.

MUSCULOSKELETAL SYSTEM

The role of CT in the musculoskeletal system changed significantly with the introduction of MRI. It became the dominant examination for staging musculoskeletal tumors, largely because of its superior soft tissue definition and evaluation of the bone marrow. CT, however, has continued to have specific advantages, especially when evaluation of the bony skeleton is required. CT is particularly useful when there is a conflict between radiographic studies (i.e., plain radiographs and bone scans) and pathologic studies and should be considered in any patient complaining of tumor. CT is especially good at defining bone destruction in purely lytic lesions where lesion aggressiveness may produce less than optimal bone scans. Specific areas where CT is invaluable are the bony pelvis, scapula, and the shoulder girdle (Fig. 27.1-21). Similarly, imaging the thoracic and lumbar spine can be successfully performed with CT. Three-dimensional volumetric reconstruction can be useful for preoperative planning and surgical simulation.

CENTRAL NERVOUS SYSTEM

CT became the dominant force in neurooncologic imaging in the early 1980s, before the introduction of clinical MRI. However, with the diffusion of MR technology, MRI is now the dominant force in the imaging centered nervous system. CT, however, still has specific applications, particularly when a detailed analysis of the calvarium or spine is required. CT, with high-resolution bone detail algorithms, provides an optimal anatomic region, such as the base of the skull, the temporal bone, or the maxillofacial region. Subtle destruction or invasion by adjacent tumor is easily defined on these studies. Similarly, involvement of the spine by primary or metastatic disease may be detected with CT. In these cases, CT may be used when there is a question as a result of bone scan findings or when clinical symptoms and other study results are contradictory.

SUMMARY

CT scanning is a mainstay in oncology imaging because of its ability to survey multiple organs and organ systems in a single examination with both high sensitivity and specificity. The introduction of spiral CT has provided rapid advancements in 3D imaging technologies. CT is now the mainstay in the detection and staging of diseases. Future progress likely will center on organ-specific contrast agents as well as blood pool agents. Newer technologies, such as real-time 3D imaging and virtual reality displays, will surely expand the role of CT and move it from a diagnostic to a therapeutic modality.

CHAPTER REFERENCES

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Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is based on the effect of large magnetic fields on the spinning motion of certain nuclei within biologic tissues. Due to the laws of electrodynamics, spinning nuclei with odd mass numbers have a net charge and align themselves in the presence of an external magnetic field. In the human body, the hydrogen nucleus (mass number of 1) is most often used in clinical MRI due to its abundance in water and lipid tissues. When a patient is placed in the bore of a magnet, the hydrogen nuclei partially align themselves with the direction of the external magnet, which generates the net magnetization vector (NMV) of the patient. In addition, these hydrogen molecules are spinning (a process called precession) at a specific frequency that varies with the strength of the external magnetic field. This frequency is called the Larmor frequency. Based on the principle of resonance, a radiofrequency pulse emitted by a transmitter at the Larmor frequency can displace the alignment of the hydrogen nuclei NMV through a flip angle that depends on the amplitude and duration of the radiofrequency pulse. Once the pulse is turned off, the hydrogen nuclei relax back into their previous alignment with the external magnetic field. It is during this process of relaxation that the spinning hydrogen nuclei produce a radiofrequency electromagnetic signal, which can be detected by a receiver coil placed on or around the patient. The information from this signal can be processed by a computer to generate an image via a mathematical algorithm known as a Fourier transform.

The magnetization of the NMV exists in the planes of three-dimensional space. When the NMV is aligned with the external magnetic field, the magnetization is said to be in the longitudinal plane. After a radiofrequency pulse, the NMV is usually flipped into the transverse plane. When the pulse is turned off, the relaxation of the NMV back into the longitudinal plane is called T1 relaxation. The decay of transverse plane magnetization is called T2 relaxation. Different tissues in the body relax at different rates. Fat has very short T1 and T2 relaxation times, whereas water has considerably longer T1 and T2 relaxation times. Neoplastic tissue also generally relaxes at rates different from the tissues surrounding it. The varying relaxation times of tissues generate different strengths of signal at specific points in measurement times. Hence, it is the difference in relaxation between tissues and the varying strength of the signals they generate that determine the contrast between tissues on MR images. Tissues that appear bright on MR images are said to have high signal intensity, whereas dark-appearing tissues demonstrate low signal intensity. In addition to relaxivity times, the strength of tissue signal also depends on the number of hydrogen nuclei present in the tissue (i.e., “proton density”). The ability of MRI to demonstrate superior contrast between different tissue types (Table 27.2-1) constitutes a major advantage over other cross-sectional imaging modalities, such as computed tomography (CT).

It is possible to “weight” an image by varying the repetition time (TR) between radiofrequency pulses and varying the time to sample the signal, called the echo time (TE) (Fig. 27.2-1). One can choose the weighting of an image to emphasize the T1 relaxivity properties of tissues, the T2 relaxivity, or the proton density. Tissues with short T1 relaxivity times, such as fat, appear brighter on T1-weighted images. Tissues exhibiting long T2 relaxivity, such as water, appear brighter on T2-weighted images (Table 27.2-2). In general, T1 weighting is useful for demonstrating anatomic detail, whereas T2 weighting may be preferred when imaging pathology, such as neoplastic tissue.

![Table 27.2-1. Relative Signal Intensities of Tissues](image)

![Figure 27.2-1. The basis of T1 and T2 weighting. A: Because fat has a shorter T1 relaxivity than does water, a short repetition time (TR) can maximize the T1 signal difference between fat and water, prior to full recovery of longitudinal magnetization. Hence, a short TR [and a short echo time (TE), which minimizes T2 effects] results in T1 weighting of a magnetic resonance image. B: The T2 signal decay of fat is faster than that of water; hence, a long TE can maximize signal differences from T2 signal between fat and water. As a result, a long TE (in combination with a long TR, which minimizes T1 effects) results in T2 weighting of an image.](image)
The use of contrast agents can also improve the detection of tumors and other pathology by MRI. The most commonly used agent is gadolinium, a paramagnetic rare earth metal that slows the tumbling of adjacent hydrogen molecules. This results in a large reduction in the T1 and T2 relaxivities of the tissues that take up the contrast. Hence, tissues into which gadolinium diffuses appear bright on T1-weighted images. MRI of tumors exploits this property of gadolinium because tumors are often hypervascular and demonstrate increased contrast agent uptake relative to the surrounding normal tissues. Further, tumor vessels are disorganized and “leaky,” so that there is increased extracellular fluid in the tumor. Hence, many tumors “enhance” after contrast administration. The distinct enhancement pattern of some tumors on sequential images taken at multiple time points after contrast administration (known as dynamic MRI) can also separate tumor from surrounding tissues. The risks and side effects of gadolinium are minimal as compared with those of iodinated contrast agents used for CT.

An ever-increasing number of different radio frequency pulse sequences are available for use in MRI. The gold standard for most imaging is the spin-echo pulse sequence, in which an initial variable flip-angle pulse is rephased by a magnetic gradient to produce an echo signal. Gradient echo sequences reduce scan times and are particularly useful for demonstrating flow on MR angiograms. The most recent advances have been made in developing very fast pulse sequences that can acquire several image slices in a single breath hold. Faster imaging reduces artifacts from breathing and other movements, and new ultrafast sequences are continually expanding the applications and widening the range of anatomy that can be accurately imaged by MRI.

The basic MR imager consists of the gantry, operating console, and computer with software that coordinates the acquisition and processing of images. During imaging, the patient is placed inside the gantry, surrounded by the primary magnetic coils that generate the main external magnetic field and by the secondary magnetic coils that generate various magnetic field gradients. These magnetic gradients are what allow signal to be localized to precise locations within the patient. The use of gradients also allows MR images to be obtained in multiple planes, including coronal, axial, sagittal, and oblique. Most commercially available “high-field” MRI magnets use field strengths of 1.0 or 1.5 tesla. “Low-field” and “open” MRIs use magnetic strengths from 0.2 to 0.5 tesla. Different radiofrequency receiver coils are available, depending on the anatomy to be imaged, and commonly include shoulder, body, or head coils placed on the patient. Exposure to the magnetic fields of an MR imager is generally considered much safer than exposure to the ionizing radiation of some other imaging modalities. MRI workup of brain tumors is the imaging technique of choice for evaluating brain tumors. MRI has significant advantages over CT, such as multiplanar capabilities, which allow better assessment of the origin of tumors and their involvement of adjacent structures. In addition, MRI offers both better imaging detail of posterior fossa tumors and superior tissue contrast. MRI can also show the secondary effects of some brain tumors, such as hydrocephalus, hemorrhage, and edema. MRI is also useful in identifying the best location for surgical biopsy. Two disadvantages of MRI are difficulties in detecting calcifications that occur in some tumors, such as oligodendrogliomas, and decreased ability to delineate tumor invasion into bone. In such cases, a CT scan, which can detect these phenomena, can be complementary to MRI.

The characteristic MRI appearance of the majority of brain tumors is a hyperintense signal on T2-weighted images. In addition, gadolinium contrast is used in every MRI workup of brain tumors. Most normal brain tissue does not take up contrast, owing to the integrity of the blood-brain barrier. However, with malignancy, there is breakdown of the blood-brain barrier and neovascularity and, hence, most tumors enhance. Some tumors would not be seen without contrast administration. Gadolinium contrast administration can also help to distinguish tumor margins from surrounding edema on T1-weighted images. The intensity of contrast enhancement correlates in a rough sense with the tumor grade, probably because generally higher-grade lesions have increased neovascularity. Therefore, higher-grade lesions may enhance more intensely than well-differentiated brain tumors. In addition, the amount of vasogenic edema and hemorrhage adjacent to tumor may roughly correlate with the degree of malignancy. Hence, a low-grade fibrillary astrocytoma may demonstrate little contrast enhancement and no edema or hemorrhage, whereas a high-grade glioblastoma may show intense heterogeneous contrast enhancement, with prominent edema and hemorrhage. However, this rule is not always reliable. An exception is low-grade pilocytic astrocytoma, which shows a paradoxical marked contrast enhancement (Fig. 27.2-2). Hence, MRI can help to assess the aggressiveness of brain tumors, but tumor diagnosis and grading must depend on the histopathologic analysis of surgical material.

Other brain tumors may demonstrate some distinguishing characteristics on MRI. Meningiomas are isointense to normal brain on all pulse sequences but enhance intensely with contrast administration. Meningiomas can also demonstrate a focal thickened collar of enhancement adjacent to the tumor’s dural attachment, known as the dural tail sign. Ependymomas and choroid plexus papillomas may be associated with hydrocephalus seen on MRI. Metastatic lesions often appear at the gray-white interface, enhance intensely, and can demonstrate edema. MRI is the most sensitive modality for imaging brain metastasis. 2 and single lesions on CT can sometimes be revealed as multiple intracranial lesions when imaged with contrast-enhanced MRI.

MRI is also useful in assessing patients after surgery, irradiation, or chemotherapy. However, changes secondary to both surgery and irradiation can cause findings that may mimic residual or recurrent tumor. One solution is to reimage the postoperative patient within 4 days after surgery to establish a baseline prior to the development of postoperative processes simulating tumor. In addition, positron emission tomography scanning may be able to differentiate recurrent tumor from the changes of radiation injury.

**TABLE 27.2-2. Characteristics of Image Weighting**

**FIGURE 27.2-2.** Pilocytic astrocytoma. A large enhancing mass is present, arising from the region of the hypothalamus. Gadolinium contrast has been administered, resulting in heterogeneous enhancement of the mass. The extent of the tumor is well depicted on magnetic resonance imaging, as is the adjacent mass effect on the brain, with mild dilatation of the lateral ventricles.

**SPINE**
MRI is the primary imaging technique used to evaluate neoplastic disease of the spine. MRI is preferred over CT and plain-film myelography and does not require the infusion of intrathecal contrast. Intramedullary tumors appear with decreased signal intensity relative to cord on T1-weighted images. Cord expansion by tumor can also be seen. Contrast enhancement aids in the detection and characterization of tumors and is also helpful in detecting “drop metastases” that have spread from intracranial and extracranial tumors to the spine via the subarachnoid space. Common extradural-intradural tumors (e.g., schwannomas and meningiomas) and extradural tumors (e.g., osseous hemangioma, myeloma) can also be detected on images. MRI accurately assesses for the presence of spinal cord compression by neoplasm (Fig. 27.2-3), with a reported sensitivity of 92% and specificity of 90%.!

**Fig. 27.2-3.** Breast cancer metastatic to spine. The T2-weighted sagittal view of the spine shows areas of increased signal intensity diffusely throughout the spine, owing to metastatic disease (e.g., small arrows). In the lower thoracic spine, a pathologic compression fracture has occurred (large arrow), resulting in mild compression of the spinal cord at this level.

**HEAD AND NECK**

MRI is now a primary imaging modality for evaluating many tumors of the head and neck, including tumors of the sinuses, oropharynx, nasopharynx, salivary glands, and larynx. The abilities of MRI to image in multiple planes and to detect subtle differences in soft tissue boundaries render MRI superior to CT in staging and localizing many tumors for guidance in therapeutic decision making. The main advantage of MRI of the sinuses is that malignant tissue can be distinguished from adjacent inflammatory disease and secretions in the sinuses. This is because on T2-weighted images, most sinus tumors have little intercellular and intracellular free water and appear hypointense, whereas inflammatory tissues are high in free water and appear hyperintense. Squamous cell carcinomas of the sinuses can erode into bone, a critical finding that affects treatment choices. MRI can demonstrate bony erosion by the absence of signal void normally present within cortical bone. However, in evaluating certain critical areas, such as the orbit, pterygopalatine fossa, and central skull base, a CT should be ordered to improve detection of small focal bony erosions. In the oropharynx, MRI can image without artifacts from dental amalgam and without beam-hardening artifacts from the mandible, both of which limit CT examination of this area. In the nasopharynx, MRI is superior to CT at identifying tumor infiltration beyond the pharyngobasilar fascia, detecting enlarged retropharyngeal lymph nodes, and demonstrating possible intracranial involvement. MRI has replaced CT for imaging major salivary glands. MRI is often used to determine the location of salivary gland tumors relative to the facial nerve so as to optimize treatment approaches that will preserve facial nerve function. The larynx and hypopharynx are regions that are readily accessed by clinical examination, which makes possible the diagnosis of malignancy through endoscopy and biopsy. However, coronal MRI images can complement clinical examination by delineating the depth of extension and submucosal involvement of laryngeal and hypopharyngeal tumors.

**BREAST**

Contrast-enhanced MRI is the most sensitive imaging modality for detecting breast pathology and can improve the detection of breast cancer in selected patient populations. The majority of invasive carcinomas are hypervascular and demonstrate intense enhancement with contrast administration. When morphologic criteria are combined with characteristic tumor enhancement patterns, MRI in many studies demonstrates greater than 90% sensitivity for detecting invasive breast carcinomas. Despite the improved sensitivities of MRI over mammography for detecting breast cancer, MRI should not be used for cancer detection in unselected patient populations, owing to false-positive rates and the higher cost of the examination. Instead, MRI is primarily indicated for detecting malignancy in high-risk patients when mammography is compromised owing to radiographically dense breasts, silicone-augmented breasts, or scarring due to remote surgery or trauma. MRI can detect many tumors that mammography may miss in these patients. When combined MRI and conventional imaging are used in these patients, sensitivities greater than 98% can be routinely achieved for detecting invasive breast carcinomas. MRI may also be useful in the search for a primary tumor when a patient presents with positive axillary nodes but no evidence of breast cancer on conventional imaging or physical examination (Fig. 27.2-4).

**Fig. 27.2-4.** Breast cancer. On a sagittal image of the breast, an intensely enhancing focus of invasive ductal carcinoma is present. This patient had enlarged lymph nodes in the axilla, which were subjected to biopsy and were found to be positive for breast cancer. However, mammogram results were negative. In this circumstance, magnetic resonance imaging is useful for detecting the primary lesion. Although magnetic resonance imaging should not be used for screening for breast cancer, it is useful in younger patients with dense breast tissue and, in certain cases, in determining the extent of the lesion before planned lumpectomy versus mastectomy.

There are also a number of emerging indications for the use of MRI in the preoperative staging and posttreatment monitoring of breast cancer, based on preliminary investigations. In considering breast conservation therapy, it is important to determine preoperatively whether a detected breast malignancy is unifocal, multifocal, or multicentric, as multicentric disease is a contraindication for breast conservation therapy. MRI appears to be markedly more sensitive than mammography in detecting multifocality or multicentricity within breast carcinomas. MRI also has shown promise in assessing the results of induction chemotherapy in reducing tumor burden prior to breast conservation surgery. A recent review has suggested using MRI prior to lumpectomy to help to decrease the number of reexcisions due to positive pathologic margins. In addition, the use of high-resolution RODEO (rotating delivery of off resonance) MRI has recently been demonstrated to improve the evaluation of ductal carcinoma in situ. After conservative breast surgery, MRI has been shown to be superior to mammography in diagnosing recurrent malignant foci. In one study, 4 of 11 local recurrences were detected only by MRI. However, MRI should be performed not less than 6 months after surgery and 12 months after irradiation to reduce false-positive rates.

**LIVER**
With the development of fast breath-hold scanning techniques that reduce motion artifact, the role of MRI in detecting and characterizing focal hepatic lesions has advanced greatly. MRI may be superior to CT and sonography in detecting hepatocellular carcinoma (HCC), as T2-weighted images may demonstrate characteristic morphologic features of HCC, such as mosaic or nodules-in nodule patterns of signal intensity. In addition, HCC demonstrates a pattern of dynamic signal enhancement distinct from the surrounding liver after bolus injection of contrast agents, owing to a prominent arterial blood supply for HCC. MRI can also detect early HCC arising within regenerating nodules associated with cirrhosis, even when the α-fetoprotein level is normal and biopsy is negative for tumor.

Metastatic lesions can appear mildly hypointense on T1-weighted images and hyperintense on T2-weighted images (Fig. 27.2-6) and can contain areas of central necrosis of different intensity from the surrounding tumor. New contrast agents containing superparamagnetic iron oxide particles have recently been approved for clinical use and have improved the accuracy of hepatic metastasis detection. These particles are taken up selectively by Kupffer cells within the liver, causing a size dropout in the signal of normal liver. Metastatic lesions, which do not contain Kupffer cells and do not take up the particles, appear as high-intensity signal against the low signal of the surrounding liver.

Cavernous hemangiomas are the most common benign tumors of the liver. They are often incidentally discovered on various abdominal imaging studies and must be distinguished from malignant lesions. MRI can make this distinction with greater than 90% sensitivity and specificity, owing to the inherently higher T2 values of hemangiomas (Fig. 27.2-6) and to the characteristic appearance of hemangiomas on dynamic gadolinium-enhanced images.

ADRENAL GLANDS

With the use of chemical shift imaging, MRI has become the most effective noninvasive method for distinguishing between commonly found benign adrenal adenomas and malignant masses. MRI can accurately make this distinction, owing to the fact that, unlike malignant adrenal tumors, most adrenal adenomas contain a large amount of cytoplasmic lipid. On application of chemical shift imaging techniques to MRI of the adrenals, tissues that contain both lipid and water demonstrate low signal intensity relative to other tissues containing mostly water. This is because fat and water protons have different precessional frequencies, owing to the size differences in the electron clouds surrounding them. When the appropriate TE is chosen, fat and water are maximally out of phase, and their radiofrequency waves cancel each other, resulting in signal loss. Most adenomas, which contain both fat and water, demonstrate signal loss on chemical shift imaging (Fig. 27.2-7), whereas both primary adrenal malignancies and metastatic lesions, which do not contain fat, have signal intensities similar to other organs, such as liver and spleen. Exploiting this difference, chemical shift MRI has been reported to have a sensitivity for identifying benign adrenal lesions of 80% and a specificity of 100%.

MRI is particularly useful for characterizing incidental adrenal masses found in patients with known malignancies. In these patients, the finding of a metastatic lesion to the adrenals may profoundly influence treatment of the primary tumor. To date, no lesion metastatic to the adrenals has demonstrated signal loss with chemical shift imaging comparable to that demonstrated by benign lesions. This allows accurate differentiation of metastases from adenomas. In the case of fat detected on chemical shift MRI, an adrenal biopsy is unnecessary. In addition to this application, MRI is the imaging modality of choice in localizing pheochromocytoma and
extraadrenal paraganglioma and for evaluating vascular invasion by adrenal carcinoma.

**KIDNEY**

In staging renal cell carcinoma (RCC), CT and MRI are comparably accurate, their accuracy ranging from 67% to 96%. Hence, given its lower cost, CT is generally the preferred modality for staging RCC. However, because of its high tissue contrast and multiplanar imaging capabilities, MRI offers improvement over CT for delineation of RCC extension into the renal veins, inferior vena cava, and right atrium (Fig. 27.2-8). MRI can also distinguish tumor thrombus from bland thrombus in the inferior vena cava and offers improved detection of venous wall invasion. Hence, MRI is the preferred modality for RCC staging when iodine contrast is contraindicated, CT results are inconclusive, or it is necessary to determine the extent of venous invasion by tumor to guide surgical approaches for thrombectomy.

**UTERUS**

T2-weighted images depict three distinct zones of signal intensity within the uterus. A central hyperintense stripe corresponds to the endometrium. This is surrounded by a hypointense zone representing the junctional zone, which is the inner myometrial layer. The remaining segment of the myometrium is of intermediate signal intensity. Endometrial carcinoma can be identified as tissue with signal intensity intermediate between normal endometrium and myometrium. By use of MRI, tumor can be seen confined to the endometrium (Fig. 27.2-9), extending into the junctional zone, or invading into the deep myometrium.

**CERVIX**

On T2-weighted images, the normal cervix demonstrates an inner hyperintense signal zone representing the endocervical canal. Adjacent to this is a hypointense zone that corresponds to the cervical stroma. The outer zone, which is continuous with the myometrium, is isointense to myometrium. Parametrial tissues (composed of vessels, ligaments, and fat) surround the cervix and are hypointense. Most cervical carcinomas have at least intermediate or high signal intensity on T2-weighted images, which provides good contrast between tumor and the hypointense cervical stroma.

MRI is considered the most reliable imaging modality for staging cervical cancer and planning its treatment. In a comparative study, the overall staging accuracy of MRI (83%) was higher than CT (63%) or clinical staging (70%). Although preinvasive microscopic disease (stage IA) is not well identified on T2-weighted images, MRI can accurately depict the depth of stromal invasion (stage IB), the presence of parametrial extension (stage IB), invasion of the vagina or pelvic wall (stages IIA and III), and bladder or rectal invasion (stage IV). Of particular importance is determining whether tumor has extended to the parametrium, as patients who present with parametrial invasion are not usually surgical candidates. The presence of a completely intact ring of hypointense cervical stroma excludes parametrial involvement. However, there are false-positive outcomes associated with disruption of the stromal ring. MRI is also useful for distinguishing recurrent tumor from fibrosis if imaged 12 months or more after treatment. The use of MRI has been shown to decrease the number of procedures and invasive studies ordered (e.g., excretory urography, barium enema, lymphography), with a resultant cost benefit.

**OVARY**

In the evaluation of ovarian masses, MRI is useful in delineating the internal architecture of ovarian tumors. MRI can depict complex tumor structures, such as irregular mural thickening, septations, and solid components, as well as associated findings, such as ascites, visceral lesions, adenopathy, and peritoneal implants. Such findings can be associated with malignancy. However, these findings can be nonspecific; hence, the differentiation of benign from malignant ovarian masses can be difficult for all cross-sectional imaging modalities, including MRI. Accuracy rates for contrast-enhanced MRI in identifying malignancy have ranged from 78% to 95%. MRI can accurately identify some benign ovarian masses, such as dermoid cysts, endometriomas, and fibromas. MRI identifies dermoid cysts with an accuracy of 99% by demonstrating the presence of intraluminal fat. In addition, MRI can determine whether a mass is truly ovarian in origin and can accurately differentiate subserosal leiomyomas from ovarian masses. In the preoperative staging of ovarian malignancy, MRI and CT demonstrate generally equivalent accuracy; hence, CT is the primary imaging modality for preoperative staging, given its lower cost and ready availability. Regarding postoperative monitoring, MRI can often
detect macroscopic recurrent tumors larger than 2 cm (considered nonresectable), thus eliminating the need for second-look surgery in such patients. However, MRI is less successful in detecting smaller implants or microscopic disease.

PROSTATE

The most common indication for MRI of the prostate is for staging prostate cancer after a biopsy diagnosis has been made (Fig. 27.2-10). The use of an endorectal surface coil alone or with anterior phased-array coils allows MRI identification of the tumor, the prostate capsule, the neurovascular bundles, and the seminal vesicles. Capsular penetration is demonstrated on MRI with the finding of gross tumor extension into the periprostatic fat or with capsular thickening, irregularity, or bulging. Tumor invasion of the neurovascular bundles can manifest as asymmetric enlargement of the bundle. Signs of seminal vesicle invasion on T2-weighted images include a low-signal-intensity mass within the seminal vesicle or wall thickening. MRI can also screen for the presence of enlarged pelvic lymph nodes and bone metastases but cannot detect the presence of tumor in normal-sized nodes. Because MRI offers superior anatomic detail, owing to improved soft tissue contrast, it is considered by some to be superior to CT and ultrasonography in staging prostate cancer. However, there have been wide ranges of sensitivities and specificities reported for MRI staging of prostate cancer, with accuracy ranging from 81% to 92%. These variations are in part dependent on the experience of the radiologist performing the readings. Some have proposed that MRI data are best used in combination with other clinical parameters, such as patient’s age, prostate-specific antigen, digital rectal examination, and the biopsy Gleason score. In particular, D’Amico et al. have reported that MRI improves staging accuracy for patients at intermediate clinical risk for invasive disease, as indicated by prostate-specific antigen levels of 10 to 20 ng/mL and Gleason scores of 5 to 7. Similar to CT and ultrasonography, MRI is not recommended for initial cancer detection and screening because of its low sensitivity for demonstrating central zone cancers and its difficulty in distinguishing malignant from benign lesions.

BLADDER

The use of dynamic imaging after the administration of gadolinium has improved the evaluation of bladder carcinoma with MRI. The tumor usually enhances prior to enhancement of the remainder of normal bladder wall after contrast administration. MRI is the most accurate imaging modality for staging bladder carcinoma and has superior ability to detect perivesical spread and to assess the penetration of tumor through the deep muscle layers of the bladder (Fig. 27.2-11). Precise staging is critical to the selection of the therapy most appropriate for bladder cancer. Recent studies have demonstrated MRI staging accuracy of 84% to 93%. A challenge for MRI has been the differentiation between postbiopsy or irradiation changes and tumor. However, the use of dynamic, fast gradient-echo sequences has recently improved the ability of MRI to make this distinction.

MUSCULOSKELETAL SYSTEM

Plain film, MRI, and nuclear medicine play complementary roles in the evaluation of bone tumors. When a bone tumor is suspected, plain film is the initial study to show the lesion and its origin, location, morphology, and aggressivity. After plain film, if the lesion may be something other than an inactive asymptomatic benign tumor, MRI can confirm the initial plain-film findings and add additional diagnostic information. In known malignant lesions, MRI is the best study to determine accurate tumor localization and staging, which is critical to optimizing the success of limb salvage techniques and other surgery. MRI can accurately determine the intraosseous extent of lesions, as bone marrow demonstrates high contrast with tumor. MRI can delineate tumor from adjacent fascia and muscle. “Skip” lesions, which can occur with osteosarcomas, can be detected with sagittal and coronal views that image long bones in their entirety. The detection of neurovascular bundle involvement and the determination of lesion distance from the joint are also MRI capabilities useful in surgical planning. MRI can show the response of tumor to adjuvant chemotherapy prior to resection and can detect residual or recurrent tumor after resection. T1-weighted images are very accurate for detecting metastatic lesions within the marrow compartment (Fig. 27.2-12). Hence, MRI is indicated in symptomatic patients with suspected bony metastases or positive bone scans but with negative or inconclusive plain films. MRI is also extremely sensitive in detecting marrow replacement by metastases, leukemia, or lymphoma on T1-weighted images and can differentiate these lesions from osteoporosis. MRI is, however, similar to CT in that it is generally nonspecific in determining tumor cell type. A common pitfall of MRI is that it is possible for some bony lesions to appear benign when, in actuality, the lesion represents a high-grade malignancy. This is particularly true in patients older than 40, in whom even benign-appearing lesions commonly represent metastases or myeloma. In younger patients, however, lesion morphology correlates in a very rough sense with its malignancy potential, though MRI still at times over- or underestimates tumor malignancy.
FIGURE 27.2-12. Bone metastasis. This patient had a primary leiomyosarcoma in the abdomen and presented with pelvic pain. T1-weighted magnetic resonance images show a large lesion (arrows) involving the left iliac bone as well as extension to the adjacent iliacus and gluteal muscles. The extent of bone involvement is precisely delineated on the magnetic resonance images. T1-weighted images are extremely sensitive for bone metastasis in adult patients and are frequently used in conjunction with nuclear medicine bone scans to determine precisely the extent and location of metastatic bone lesions. Magnetic resonance imaging is particularly useful in the pelvis, where overlapping structures can render diagnosis on plain radiographs difficult.

Owing to excellent soft tissue contrast, MRI displays outstanding anatomic detail of soft tissue lesions and is, therefore, the imaging modality of choice for evaluating soft tissue tumors. Plain films, however, should still be additionally obtained. MRI is diagnostic of several common benign tumors, including lipomas (Fig. 27.2-13), ganglion cysts, some hemangiomas, and simple neurofibromas. There is some debate about whether MRI can consistently distinguish lipoma from liposarcoma. In general, a thin-rimmed homogeneous high signal on T2-weighted images may represent a simple cyst. Heterogeneous high internal signal on T2-weighted images may indicate a solid lesion with high water or mucin content, a complex thick-walled lesion, calcification, necrosis, or hemorrhage, all of which can be associated with malignancy. MRI can be indeterminate in many of these cases, and MRI is helpful in determining the need for biopsy in suspicious-appearing lesions. In cases of known sarcoma, MRI is the best imaging modality to stage the mass accurately, determining its location relative to fleshy planes and muscular structures, invasion into neurovascular or osseous tissues, and the distance of lesions from joints. It is possible for some high-grade sarcomas, however, to display a nonaggressive, benign appearance.

FIGURE 27.2-13. Lipoma of the posterior thigh. This patient felt an enlarging mass in the thigh, which was palpable on clinical examination. Magnetic resonance imaging examination showed a high-signal-intensity mass (arrow) on this T1-weighted image. The appearance on magnetic resonance imaging examination is chemically specific for lipoma due to the presence of macroscopic fat. In the case of a characteristic soft tissue mass, such as lipoma, a biopsy is not necessary for diagnosis, given the magnetic resonance imaging findings.

CHAPTER REFERENCES

SECTION 27.3
Functional and Metabolic Imaging

MARTIN G. POMPER

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Techniques for Functional and Metabolic Imaging
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INTRODUCTION

Unique to functional imaging is the provision of unperturbed physiologic information. While pathologists increasingly apply the highly sensitive and accurate techniques of molecular biology to histologic examination, those techniques, when applied to functional imaging, promise even more relevant and timely data. Together with advances in molecular biology, advances in the generation of new imaging agents and in imaging science compel us to rethink cancer diagnosis and treatment. Soon, cancer patients will no longer be categorized according to the primary organ involved; rather, their disease will be diagnosed and treated according to their predominant underlying genetic abnormality. In this fashion and in the spirit of molecular medicine (i.e., the idea that human disease proceeds from biochemical imbalance), the diagnosis and staging of cancer will be tailored to each patient. Tumor characterization will consequently become more accurate and treatment more effective.

The uses of functional imaging in current cancer practice include (1) detection of malignancy, particularly if the primary site is unknown; (2) differential diagnosis of lesions found on anatomic imaging studies; (3) tumor grading; (4) disease staging; (5) assessing for recurrence; and (6) therapeutic monitoring. Table 27.3-1 lists metabolic processes amenable to measurement in humans by functional imaging. Only 18F-fluorodeoxyglucose–positron emission tomography (FDG-PET) and proton magnetic resonance spectroscopy (MRS) are used in routine clinical practice for oncology. Optical imaging techniques are also being developed but have been applied to humans on a limited basis to date.

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<th>TABLE 27.3-1. Physiologic Processes Accessible in Humans by Functional and Metabolic Imaging</th>
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| **PET** is the most sensitive functional imaging technique used in clinical practice, with the ability to quantify processes that occur at subnanomolar concentrations. Although its resolution is an order of magnitude inferior to that of magnetic resonance imaging (MRI), that obtained with current PET scanners approaches 4 mm. As with many other functional techniques, the initial application of PET was to the study of brain physiology and pathology. ^2^ PET relies on the detection of coincident photons that result from the annihilation of a positron and an electron. ^3^ Because the annihilation event occurs up to several millimeters away from the site of decay and the coincident photons do not separate at an angle of precisely 180 degrees, physical and geometric constraints limit the resolution of imaging with PET. ^4^ Nevertheless, neither clinical nor even high-resolution small-animal imaging systems have reached the resolution limit imposed by those constraints. ^5^ Radionuclides most commonly used include ^15^C, ^18^F, ^11^O, and ^13^N, all of which are isotopes of atoms that are found in molecules of biologic importance ( ^15^C, ^13^N, and ^18^O) or that can be substituted without significant disruption of molecular structure ( ^11^C). Because the physical half-lives of radionuclides for PET range from 2 minutes ( ^11^C) to 110 minutes ( ^18^F), a premium is placed on synthetic algorithms. Images are generally reconstructed using algorithms, such as filtered back-projection. PET imaging is performed increasingly frequently on dual-head coincidence (DHC) gamma cameras. ^6^ Although FDG-DHC imaging is less expensive than is dedicated FDG-PET, the resolution of the former system is lower (13.5 mm vs. 4 mm), suggesting that FDG-DHC not be recommended for detection of lesions less than 1.5 cm in size. FDG is the mainstay of PET oncologic imaging. As with all radiopharmaceuticals, distribution of FDG throughout the body obeys the tracer principle: It is administered in such small amounts (<10 µg) that while portraying the pathway of interest, it leaves that pathway completely intact. There is no pharmacologic or toxic effect. Neoplastic cells undergo accelerated glycolysis, even under aerobic conditions, a phenomenon known as the Warburg effect. ^7^ That metabolic difference between normal and cancer cells is exploited in FDG-PET imaging. Increased levels of glucose transporters and hexokinase and decreased levels of glucose-6-phosphatase contribute to the relatively increased glucose metabolism of cancer cells. ^8^ Unlike glucose, because FDG lacks a hydroxyl group at the 2 position, it cannot undergo further metabolism (phosphorylation) and remains trapped within the cell. Because glucose competes with FDG for glucose transporters and hexokinase, elevated blood glucose levels tend to decrease FDG uptake. ^9^ Patients are fasted for 4 hours before intravenous administration of FDG (370 MBq, 10 mCi) and for 12 hours to reduce interfering myocardial uptake when searching for mediastinal adenopathy. The study is not performed if blood glucose levels exceed 200 mg/dL. Careful measurement and titration of blood glucose levels with insulin are unnecessary and may actually confound the study, owing to propagation of errors in blood glucose measurement. ^10^ Patients are scanned approximately 1 hour after FDG administration. Deep organs may experience a 5-fold attenuation in photon detection relative to those at the surface. ^11^ Transmission scans using a 68Ge source are accordingly performed to account for such geometric distortions. Transmission scans are time-consuming, particularly for whole body imaging that requires 10 gantry positions (for a 15-cm axial field-of-view scanner), each in turn requiring an 8- to 10-minute transmission scan. Transmission scans are not generally obtained for whole body imaging, and their use is controversial. Nevertheless, attenuation correction is necessary for coregistration of PET images with other modalities and for application of semiquantitative measurements, such as the standard uptake value (SUV). ^12^ True quantification of FDG-PET data, including kinetic modeling and arterial blood sampling or other surrogate methods for determining the input function, is noted frequently in the recent literature. ^13^ ^14^ For those reasons, attenuation correction will likely be applied increasingly to clinical imaging. Furthermore, acquiring postinjection transmission scans or using iterative reconstruction methods, such as
An important issue in clinical PET imaging centers around the necessity of reporting quantitative information (i.e., regional glucose metabolic rate). Currently, PET images are interpreted in a fashion similar to that of other nuclear medicine studies (i.e., areas of increased radiopharmaceutical uptake are reported as abnormal, accounting for the known physiologic distribution of tracer). Along with its high sensitivity, the quantitative capabilities of PET are constantly showcased, but the latter are seldom used clinically, particularly in oncology. As suggested, truly quantitative data are difficult to acquire because tracer uptake reflects more than merely what can be seen and measured by the PET scanner. The images produced also depend on blood flow to the organ of interest, metabolism of the tracer, dispersion of the activity bolus, and the compartmental residence of the tracer (i.e., blood pool vs. target receptor vs. nonspecific binding). To uncover the true concentration of tracer in the region of interest (ROI), requires arterial blood from the patient, which is nontrivial to obtain. Quantitative PET techniques were originally developed for the brain, a homogeneous structure as compared to a tumor. Tissue heterogeneity renders quantification more challenging in tumors. Zasadny and Wahl developed the SUV as somewhat of a compromise between the extremes of true quantification and visual inspection. The SUV is the activity in the lesion (expressed in milliCuries per milliliter) divided by the weight of the patient (in kilograms) and the dose of FDG (in milliCuries). Because of initial concerns over its inappropriate use, the SUV has been refined to account for lean body mass, since FDG distribution differs between fat and muscle. Also, using the maximum intensity pixel, rather than the average value distributed throughout an ROI, and carefully accounting for the time after injection at which the ROI was analyzed, have improved use of the SUV as an objective, semiquantitative measurement. As long as a baseline study is obtained, quantitative PET data may not be necessary for therapeutic monitoring.

**Clinical Applications**

FDG-PET is superior to anatomic imaging for a variety of tumors and indications (Table 27.3-2). Notable is that PET can identify metastatic deposits in lymph nodes that are still small (<1 cm) and considered benign by computed tomography (CT). In contrast, PET may recognize large masses, such as posttherapy fibrotic tissue, as benign if minimal FDG uptake is demonstrated. The most serious limitation to tumor detection with PET is that increased FDG uptake can also be demonstrated in inflammatory tissue. In areas endemic to fungal infections of the lung, the specificity of PET for detecting malignancy is decreased.

**TABLE 27.3-2. Comparison of [18F] Fluorodeoxyglucose-Positron Emission Tomography and Anatomic Techniques**

| PET | PET may be used in therapeutic monitoring after chemotherapy or radiotherapy, with a classic indication being assessment for recurrent tumor versus radiation necrosis. Conventional imaging cannot differentiate recurrent tumor from radiation necrosis. Although the specificity for PET in this regard may seem unacceptably low (see Table 27.3-2), an earlier report indicated a sensitivity of 94%. Combining PET with MR techniques, such as perfusion-weighted imaging and magnetic resonance spectroscopy–spectroscopic imaging (MRS(I)), will likely improve the specificity of detecting recurrent brain tumors.

PET is the most accurate noninvasive technique for detecting and staging lung cancer (Fig. 27.3-1; see Table 27.3-2). Accordingly, it was initially for lung cancer that PET was reimbursed. Low background activity in the thorax renders the chest ideal for study, and visual analysis tends to be equivalent to calculating SUVs. By improving staging, unnecessary thoracotomies, estimated at 30%, may be avoided. The management of their disease is changed after whole body PET in 41% of patients with lung cancer.

**FIGURE 27.3-1.** Coronal (A) and sagittal (B) whole body [18F] fluoro-2-deoxyglucose–positron emission tomography images in a patient with lung cancer and left upper lobe atelectasis (white arrow in A). The patient was originally thought to have had left hilar and left apical lung masses on CT and was to undergo radiation therapy to the left upper lobe and mediastinum; however, subsequent [18F] fluoro-2-deoxyglucose–positron emission tomography confirmed absence of tumor in the left apex and detected a metastasis in the right mediastinum (diagonal arrow in A). Horizontal arrows in A and B depict the left hilar masses. After positron emission tomography, the patient was treated with a different radiation port that spared the left apex but included the left and right mediastinum. (Courtesy of Richard L. Wahl, M.D., Ann Arbor, MI.)

**FIGURE 27.3-2.** Positron emission tomography–computed tomography (PET-CT) images of a patient with head and neck cancer. CT: 160 mAs; 130 kV; pitch = 1.6; 5-mm slice thickness. PET: 7 mCi [18F] fluoro-2-deoxyglucose (FDG); 2 × 15 min; 3.4-mm slice thickness. False color (yellow) depicts the increased FDG uptake on PET. A: Sagittal image depicts increased FDG uptake in the anterior larynx (arrow). B: Axial image depicts increased FDG uptake in the right neck (arrow) due to adenopathy. Tumor is also present to a small extent in the left laryngeal mucosa (curved arrow). C: Axial image at the level of the true vocal cords shows tumor in the right larynx (arrow) and, to a lesser extent, in the midline involving thyroid cartilage (curved arrow). (Courtesy of David Townsend, Ph.D., Pittsburgh, PA.)
PET has changed surgical management in 28% of patients with colorectal cancer by identifying resectable or unresectable metastasis not identified on clinical examination or CT. PET is of higher sensitivity (see Table 27.3-2) than is CT arterial portography (80% to 90%) in detecting intrahepatic metastases.

PET has not proved as useful for breast cancer as for lung cancer, primarily owing to lower glucose utilization in the breast and background activity from concurrent mastopathy. Although PET demonstrates the highest accuracy for axillary staging of breast cancer for any noninvasive test (see Table 27.3-2), node dissection is still required for planning adjuvant therapy.

Anatomic complexity in the head and neck region, particularly after surgery, renders PET evaluation of this area a boon to therapeutic monitoring. Tumors as small as 4 mm have been detected in the head and neck with PET. Detection and localization of head and neck tumors may be improved by applying SUVs and anatomic coregistration (Fig. 27.3-2), in part because significant amounts of FDG are distributed to the salivary glands and adenoids.

Care must be taken when applying PET after radiation therapy because of false-positive results due to inflammation and false-negative results due to metabolic "stunning" that might occur. Postirradiation PET is, therefore, recommended 40 days to 4 months or longer after therapy.

PET has been successfully applied to detecting subclinical involvement of lymph nodes in melanoma (see Table 27.3-2). It has proved somewhat less fruitful when applied to pancreatic cancer, likely owing to the presence of concurrent inflammation and high blood glucose levels; however, correction for serum glucose did not significantly improve the accuracy of PET in several studies. PET was more accurate than CT for pancreatic cancer, and surgical management was altered in 43% of cases when PET and CT were used together. PET has also proved useful, even superior to gallium imaging, in staging lymphoma and detecting residual disease after therapy. PET may be useful to evaluate adjuvant therapy in osteosarcoma and in assessing prognosis in malignant pleural mesothelioma.

It has proved less useful for genitourinary cancers, primarily because of high background activity in the bladder. Nevertheless, recent applications of PET to cervical and prostate cancers, primarily for detecting local disease recurrence (cervix) and for staging (prostate), show promise.

### Tracers Other Than FDG

As stated, FDG has limitations. Its tissue uptake may be dictated by factors other than viable tumor cell fraction, such as degree of hypoxia, inflammation, and recent therapy. High FDG levels in cerebral cortex can cloak tumors and metastases. Processes germane to cancer other than glucose uptake (e.g., blood flow, proliferation rate, protein synthesis rate, or tissue oxygenation) may be sought, as they may have prognostic and therapeutic implications as well. For those reasons, new tracers have been developed and include radionuclide amino acid analogs, thymidine analogs, markers of tissue oxygenation (imidazoles and thiosemicarbazones), substrates for multidrug resistance efflux pumps, and such metabolites as choline and acetate. Radiolabeled analogs of chemotherapeutic agents, such as [18F]fluorouracil, have been synthesized to assess for their pharmacokinetics and metabolism. The concentration of [18F]fluorouracil in metastatic colorectal cancer correlated with patient survival.

Sex steroid receptor–based imaging agents enable measurement of estrogen receptor status in vivo and may be useful in therapeutic monitoring of certain subtypes of breast and prostate cancers.

Among the amino acid analogs, [11C]methionine (MET) and [11C]tyrosine (TYR) have received the most attention. MET may be superior to FDG for brain tumor imaging, particularly for low-grade tumors, owing to minimal brain background activity. Recent studies compared MET and FDG in a variety of tumors. MET demonstrates a high negative predictive value (94%) for mediastinal node staging of lung cancer. Because it undergoes less metabolism than MET, TYR may be used to measure protein synthesis rate and has been applied to head and neck cancers and soft tissue sarcomas. For metastases due to head and neck cancer, TYR demonstrated higher specificity than FDG.

Developed in search of a noninvasive marker of tumor proliferation, carbon 11–labeled thymidine analogs, particularly those labeled at the 5-methyl moiety, undergo extensive, rapid metabolism, thereby prohibiting routine use. More stable 18F–labeled analogs have been synthesized and have shown promise in an initial study (Fig. 27.3-3).

**FIGURE 27.3-3.** Computed tomography (A) and 3'-deoxy-3'-[18F]fluorothymidine–positron emission tomography (FLT-PET) (B) images in a patient with breast cancer metastatic to the mediastinal lymph nodes (arrows in A, arrowheads in B). The FLT-PET image was obtained 30 to 60 minutes after injection. FLT is retained in normal sternal and vertebral marrow (top, bottom arrows, respectively, in B) and ribs as well as within mediastinal tumor. (Courtesy of Anthony F. Shields, M.D., Detroit, Mi.)

**Future Developments in Oncologic Positron Emission Tomography**

Chemists have synthesized a vast array of selective, high-affinity radiopharmaceuticals in positron-emitting form; however, combinatorial chemistry and phage display libraries will generate even more promising lead molecules for oncologic imaging. More generalized use of old probes, such as [18F]fluoroethylspiperone, may enable gene transcription imaging in tumors with a variety of genetic perturbations. Based on a principle similar to imaging with FDG (i.e., metabolic trapping), radiolabeled herpes simplex virus (HSV) thymidine kinase substrates for imaging gene transfer and expression are nearing clinical trials. Generator-produced PET radionuclides, such as [64Cu], which can render PET available to imaging facilities without a cyclotron on site, have been incorporated into appropriate ligands and used for tumor imaging. Improvements in whole body PET are being sought by performing three-dimensional acquisition, routine attenuation correction, and application of statistical, iterative methods to reconstruct imaging data. If PET is to reach its true potential in oncologic imaging (i.e., measuring genomic events), quantitative techniques developed over the last 15 years for brain imaging must be adapted to tumor imaging. Concurrent recent advances in other imaging modalities and in understanding the microenvironment of tumors (Fig. 27.3-4) are serving to demystify the heterogeneity problem and will facilitate quantitative PET for oncology in the future.
FIGURE 27.3.4. Multimodality, functional radiologic-pathologic correlation of the mammary tumor model MDA-MB-435 in the mammary fat pad of a severe combined immunodeficiency mouse. A: Hematoxylin-eosin stain shows a pink hue centrally indicative of dead and dying cells. B: Vascular volume map [snapshot–fast low-angle shot (FLASH) magnetic resonance image] with gadolinium-albumin contrast (40 mL/g) shows decreased volume centrally in the area of necrosis. C: Vascular endothelial growth factor (VEGF) map generated from polyclonal antibodies to VEGF depicts increased VEGF protein in areas of necrosis. VEGF is a potent modulator of vascular permeability. D: Vascular permeability map (snapshot-FLASH magnetic resonance image; 1.27 mL/g/min) shows increased vascular permeability (arrow) where vascular volume is lowest (i.e., centrally). Such multimodality correlation enables better understanding of the tumor microenvironment. (Courtesy of Dmitri Artemov, Ph.D., Meiappan Solaiyappan, B.E., and Zaver M. Bhujwalla, Ph.D., Baltimore, MD.)

MAGNETIC RESONANCE IMAGING

MR-based techniques are less well established for functional imaging than are those based on PET. They include diffusion-weighted imaging (DWI), perfusion or cerebral blood volume imaging, MRS(i), and functional MR imaging (fMRI). In many ways, those techniques complement PET and attempt to measure similar physiologic phenomena (see Table 27.3.1). Apart from the obvious advantages related to logistics (e.g., no need for synthesis of short-lived radiotracers or for an on-site cyclotron), the MR techniques benefit from not needing anatomic coregistration. The resolution of clinical MR is submillimeter, at least one order of magnitude superior to clinical PET. Quantification of the MR-based techniques is in its infancy, but progress is being made, particularly in the assessment of blood flow and metabolite concentrations. As was the case for PET, the brain has been the primary organ of initial inquiry for MR-based techniques, and most of that work, except for MRS(i), has been dedicated to hemodynamics and stroke rather than cancer.

SPECIFIC MAGNETIC RESONANCE–BASED TECHNIQUES

MRS(i) is applied in medicine to determine the concentrations of a relatively few metabolites that are altered in disease. In MRS(i), the high-resolution morphologic imaging capabilities of MRI are sacrificed to provide metabolic data that, in many cases, precede structural abnormality. Molecules containing a limited number of nuclei may be imaged, including $^3$P, $^2$Na, $^7$F, and $^1$H. Among those, $^3$P-MRS and especially $^1$H-MRS(I), or MRS(I) have found the most applications in oncology.

Early work focused on $^3$P-MRS; however, owing to large volumes (voxels) required for analysis, reducing sensitivity, MRS(i) has been developed and used to a greater extent more recently. $^3$P-MRS still finds applications in oncology because $^3$P is incorporated into adenosine triphosphate, phosphocreatine, and pyridine nucleotides (i.e., molecules that reflect tumor energetics). Intraacellular tumor pH can be derived from $^3$P-MRS spectra. Tumors have elevated phosphomonooesters and phosphodiesters. $^3$P-MRS may find its greatest application in therapeutic monitoring of soft tissue sarcomas, where metabolite changes, which occur soon after the initiation of treatment, correlate with clinical response. $^3$P-MRS has also been used to detect non-Hodgkin’s lymphoma to study liver metabolism in cancer patients, and to follow up after therapy in patients with breast cancer.

MRS(i) is the most commonly used MR spectroscopic technique because of the high natural abundance of protons. Key metabolites include choline and lactate, which tend to be elevated in tumors. Choline is a membrane constituent, its increase hypothesized to be due to increased cell membrane synthesis in rapidly proliferating tissue. Lactate is generally present only in pathologic tissue, such as necrotic tumors and abscesses, and reflects abnormal carbohydrate metabolism. Preoperative diagnosis and grading are the goals of brain tumor MRS(i); however, MRS(i) currently is best at merely differentiating normal from malignant tissue. Preul et al. obtained remarkable success in grading gliomas by using pattern-recognition analysis rather than simply peak ratios. Nevertheless, that technique is rather sophisticated mathematically and not widely available. MRS(i) is becoming useful in therapeutic monitoring, challenging PET for diagnosis of recurrent tumor versus radiation necrosis in patients with gliomas. One recent study showed no false-positive results when using MRS(i) to assess for radiation injury (Fig. 27.3.5). MRS(i) has more recently been applied to head and neck, breast, and prostate cancers (Fig. 27.3.6). Each of those tumor types displays increased choline that, in the case of head and neck tumors, reflects tissue oxygenation status. Cystic ovarian tumors demonstrated higher levels of lactate and amino acids than their benign counterparts. The high-resolution, multivoxel capabilities of MRS(i) are important in prostate tumor assessment, because the lesions tend to be small and their precise intraglandular location has important therapeutic implications. Difficulty in suppression of lipid peaks outside of the ROI and in shimming continue to challenge extracranial MRS(i).

FIGURE 27.3.5. Patient with partial resection of a grade III astrocytoma in 1996 followed by radiotherapy (60 Gy) and chemotherapy. In February 1999, imaging showed a large butterfly-like enhancing mass on magnetic resonance imaging. Magnetic resonance spectroscopy–spectroscopic imaging [MRS(i)] single slice point-resolved spectroscopy (PRESS) sequence; repetition time $= 1500$; echo time $= 136$; slice thickness $= 20$ mm, nominal resolution of 2 mL (field of view $= 160$ $\times$ 160; matrix $= 32$ $\times$ 16) demonstrated that the enhancing areas contained large lipid peaks; there were no areas of abnormally elevated choline within or outside the lesion. The diagnosis of radiation necrosis was made, and 1 year later, the lesion remained stable by magnetic resonance imaging and MRS(i). (Courtesy of Alberto Bizzi, M.D., Bologna, Italy.)

FIGURE 27.3.6. Patient with stage pT3a prostate cancer (Gleason score, 5). A: Fast spin-echo T2-weighted (repetition time $= 5000$; echo time $= 102$) axial magnetic resonance image through the midprostate obtained using an endorectal coil. A tumor focus (arrows in A) is seen as an area of decreased signal intensity in the peripheral zone of the right gland. B: Histopathologic section (hematoxylin-eosin stain) confirmed tumor in the peripheral zone of the right midgland that abuts the inked prostatic margin (a) and is interspersed between normal prostatic glands (b). C: 0.24-cm$^3$ spectrum obtained from area 1 in the image in A demonstrates elevated choline and reduced citrate, consistent with cancer. D: Magnetic resonance spectrum within the normal left peripheral zone, area 2 in the image in A, that shows dominant citrate, as expected. (Modified from ref. 80, with permission.)
Clinical studies using 19F-MRS have centered around studying the tumor pharmacokinetics of 5-fluorouracil analogs and effects of other chemotherapeutic agents on 5-fluorouracil tumor uptake. These studies are performed with a view to individualizing chemotherapeutic regimens for specific patients. Several groups have used 23Na imaging to characterize brain tumors, with new pulse sequences and high-field systems contributing to furthering the sensitivity and resolution for this nucleus.

DWI is among the triad of functional MRI techniques, a triad that also includes perfusion imaging and fMRI. Water diffusion is a random event; however, certain structures, such as intracellular organelles and white matter tracts within the brain, may impede diffusion. Applying appropriate pulse sequences and magnetic field gradients, those differences in diffusion may be detected. Resembling free water, necrotic or cystic portions of brain tumors display high apparent diffusion constants (ADCs), while the solid (enhancing) portions have lower ADCs, demonstrating the ability of DWI to distinguish various portions of a single heterogeneous lesion. Coupled with the high resolution of MR systems, that finding suggests that DWI may direct biopsies, an important function, as sampling errors now lead to approximately 25% of brain tumors being undergraded. Huang et al. used DWI in conjunction with MRS and perfusion imaging to assess the effects of intracavitary chemotherapy on brain tumors in patients with gliomas or primary central nervous system lymphoma, showing a normalization of ADC values after treatment. In the periphery, hemangiomias (high ADC) can be differentiated from hepatocellular carcinomas (low ADC) of the liver using a turbo-fast low-angle shot sequence with DWI. That technique enabled differentiation of malignant (low-ADC) from benign (high-ADC) ovarian cysts. Other fast MR techniques, such as echo-planar imaging, are beginning to be applied to extracranial regions, further allowing the calculation of ADC values in abdominal organs.

Once only a function of PET, perfusion imaging is now possible, in some cases quantitatively, with MRI. Perfusion imaging enables calculation of blood volume, which is likely related to tumor angiogenesis, or new blood vessel formation. Angiogenesis is a strong indicator of tumor grade. Biopsy of tumor subregions with increased perfusion may prove superior to biopsy of regions of enhancement, the current practice. Areas of perfusion and enhancement often do not coincide, the latter being due to breakdown of the blood–brain barrier in the case of brain tumors. Extracranial studies using perfusion imaging are rare, although several studies of cervical cancer have appeared recently. In the latter study, the cervical microcirculatory parameters determined with perfusion imaging did not always correlate with histology; however, they did correlate with patient outcome. Several groups have performed dynamic contrast-enhanced imaging of the breast or prostate in attempting to take advantage of the temporal signature of contrast uptake in tumors relative to neighboring tissue. Dynamic CT with Patlak analysis enabled measurement of perfusion in prostate tumors during therapy.

**FIGURE 27.3-7.** Patient with a left parietal glioma. Postgadolinium T1-weighted image (A) [repetition time (TR) = 415; echo time (TE) = 18] demonstrates minimal enhancement (arrow) in the left posterior parietal lobe, where a large region of high signal intensity is identified (B, arrow) on the fluid-attenuated inversion recovery (FLAIR) image (TR = 8800; TE = 130; inversion time(TI) = 2200). The diffusion-weighted image (C) (TR = 9999; TE = 99; B = 1000), calculated apparent diffusion constants map (D), and cerebral blood volume perfusion image (E) all demonstrate increased signal in the region of the mass favoring the diagnosis of tumor. The time–to–peak perfusion image (F) shows delayed perfusion of the mass relative to the neighboring gray matter.

fMRI detects signals based on the difference in blood oxygen tension that occurs between active and inactive brain regions (i.e., the blood oxygen level dependence effect). Several centers are beginning to use fMRI for preoperative planning of brain tumors because eloquent, or essential, brain regions, such as motor cortex or language areas, may be mapped preoperatively and avoided during surgery for tumors and other lesions. Similarly, the nonrandom orientation (anisotropy) of white matter tracts may be exploited by diffusion tensor imaging, a variant of DWI, for preoperative planning. In diffusion tensor imaging, deep structures, such as the corticospinal tract, well beyond the domain of intraoperative cortical mapping, may be delineated and, consequently, avoided during tumor surgery.

**FIGURE 27.3-8.** Optical coherence tomography (OCT) images were obtained from fresh tissue samples, within 5 minutes of excision by a loop electrosurgical excision procedure. Image acquisition time was 2.5 seconds. The instrument used delivers and collects 850-nm broadband light via an optical fiber probe that is placed in contact with the sample. Shown is a clinically normal site in the tissue sample. From the top down, the image shows a dark band corresponding to the quartz shield (S) of the optic fiber probe. Next, the surface of the sample is observed (1), followed by a layer of low-scattering epithelial tissue (E) 150 µm deep in this image. Immediately below, approximately 325 µm deep in the image, is the interface with a layer of highly scattering connective (C) tissue (2). This layer occupies the rest of the image, and the signal fades approximately 400 to 500 µm into the tissue. This technique may also be used to demonstrate the optical properties of tissue in situ.
Either endogenous or exogenous fluorophores may be used to detect fluorescence of malignant tissues. Igamah and Hashimoto recently applied the former to characterizing oral carcinomas, demonstrating that tumors vary in the amount of a porphyrin-like substance responsible for fluorescence. Anderson-Engels et al. used a porphyrin to delineate basal cell carcinomas. Schantz et al. exploited the endogenous fluorescence of head and neck cancers and demonstrated a correlation between fluorescence maxima and tumor grade and likelihood of recurrence. Tromberg et al. accomplished quantitative functional imaging of breast tumors using near-infrared light in conjunction with photon migration spectroscopy. Low-level (0.5- to 1-cm) images of tissue hemoglobin concentration, oxygen saturation, blood volume, and water and fat contents are capable with that technique.

Subtle differences in redox status, oxygenation, and intracellular pH are normally significant to normal tissues and malignant tumors. Redox status and oxygenation can be measured by electron paramagnetic resonance. The detection of nitrooxide, redox-sensitive probes, has been accomplished using electron paramagnetic resonance-enabled imaging of tumor heterogeneity in a rodent model, with clinical studies on the horizon.

**SUMMARY**

The use and cost-effectiveness of PET are finally being recognized in the clinic. The proliferation of satellite suppliers of FDG to sites that use DHC gamma cameras and reimbursement for an increasing number of indications may account for the anticipated 30% increase in PET use over the next 5 years. PET techniques are largely used as replacing PET indications for other than receptor- or enzyme-based imaging (i.e., blood flow) and can provide important complementary information to other imaging techniques. A current challenge is the creation of large clinical datasets of malignant tumors using FDG PET. Wahl et al. have argued that PET is not an alternative to the question: a review. Nucl Med Commun 1997;18:979.

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SECTION 27.4
Interventional Radiology

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Introduction
Diagnostic Procedures
Percutaneous biopsy in the Thorax
Biopsy of Other Organ Systems
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Percutaneous Transcatheter Therapeutic Interventions
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INTRODUCTION

The field of interventional radiology has continued its rapid expansion into the world of clinical medicine and oncology. In doing so, its focus has shifted from an essentially diagnostic to a primarily therapeutic subspecialty. The interventional radiologist is now involved in direct patient care and, in many instances, has become the patient's primary care physician. This growth of interventional radiology is especially extraordinary in the field of clinical oncology, where many procedures, such as placement of tunneled central venous catheters for infusion of chemotherapy or nutritional support, inferior vena cava (IVC) filters to prevent pulmonary embolism, and catheterization of the biliary or urinary tract to decompress obstructed systems, are now performed by interventional radiologists. In addition, new procedures developed by interventional radiologists, such as transarterial chemoembolization of liver tumors, percutaneous ethanol infusion, radiofrequency ablation, or embolization techniques, have become suitable therapeutic alternatives to other traditional forms of therapy, including systemic chemotherapy, irradiation, or surgery and, in some instances, have become the mainstay of therapy. A wide range of cancer patients benefit from the services of interventional radiology. This chapter first reviews some of the well-established procedures still performed to help diagnose cancer and then addresses the many contributions of interventional radiology in the treatment of cancer patients.

DIAGNOSTIC PROCEDURES

Percutaneous and intraluminal biopsies of suspicious lesions are relatively easy and reliable methods of obtaining tissue for histologic or cytopathologic diagnosis. The lungs, breast, liver, pancreas, adrenal glands, kidney, and retroperitoneum (especially lymph nodes) are the most commonly targeted organs. Ultrasonography, magnetic resonance imaging, and computed tomography (CT) provide excellent image guidance and have made it possible to safely sample focal lesions as small as 5 mm.1 The majority of percutaneous biopsies can be performed on an outpatient basis. By alleviating the need for diagnostic surgery, biopsy is cost-effective and can have a great impact on patient management.1 Numerous types and sizes of biopsy needles are commercially available. They vary from the small aspiration needle (19- to 23-gauge), which provides a cellular slurry for cytologic examination when confirmatory diagnosis of malignancy is sought, to the large-core biopsy cutting needle and biopsy gun (18-gauge or less), which provide an actual piece of tissue for cytotologic and histopathologic analysis.2,3,4 The choice of a specific needle should be made according to the type of tissue to be sampled. Other considerations include the type and vascularity of the target organ, the coagulation status of the patient, and the anticipated course of the needle. Percutaneous biopsy is most commonly performed to provide a definitive diagnosis of malignancy. It can also be used for tumor staging and assessment of tumor response to therapy.

PERCUTANEOUS BIOPSY IN THE THORAX

Despite persistent controversy about its usefulness, transthoracic needle biopsy is still commonly performed to diagnose both benign and malignant disease of the thorax.2,3,5,6 Aspiration or cutting needles can be used to evaluate suspicious lesions adequately in the lung parenchyma, pleura, or mediastinum. Although cutting or core needles generally provide better quality samples than those provided by aspiration needles, they are usually not required to sample parenchymal abnormalities of lung nodules and, in most instances, provide no substantial advantage over needle aspiration.1,7,8,9 Only when the diagnosis of malignancy cannot reliably be established by fine-needle aspiration is the use of core needles indicated.3,10 It is helpful to have the pathologist in attendance during the procedure to determine whether the collected sample can yield a definitive diagnosis. If the initial biopsy sample is negative, the positioning of the needle tip should be checked to ensure that it is within the lesion. Once the needle tip is appropriately redirected, further samples should be collected. Both established and more recent series have shown that the sensitivity of transthoracic needle aspiration for the detection of pulmonary parenchymal, hilar, or pleural malignancy to vary between 74% and 97%, its diagnostic accuracy to range from 76% to 99%, and its specificity to approach 100%.12,13,14,15 Only when the diagnosis of malignancy cannot reliably be established by fine-needle aspiration is the use of core needles indicated.3,10 It is helpful to have the pathologist in attendance during the procedure to determine whether the collected sample can yield a definitive diagnosis. If the initial biopsy sample is negative, the positioning of the needle tip should be checked to ensure that it is within the lesion. Once the needle tip is appropriately redirected, further samples should be collected. Both established and more recent series have shown that the sensitivity of transthoracic needle aspiration for the detection of pulmonary parenchymal, hilar, or pleural malignancy to vary between 74% and 97%, its diagnostic accuracy to range from 76% to 99%, and its specificity to approach 100%.12,13,14,15 Only when the diagnosis of malignancy cannot reliably be established by fine-needle aspiration is the use of core needles indicated.3,10 It is helpful to have the pathologist in attendance during the procedure to determine whether the collected sample can yield a definitive diagnosis. If the initial biopsy sample is negative, the positioning of the needle tip should be checked to ensure that it is within the lesion. Once the needle tip is appropriately redirected, further samples should be collected. Both established and more recent series have shown that the sensitivity of transthoracic needle aspiration for the detection of pulmonary parenchymal, hilar, or pleural malignancy to vary between 74% and 97%, its diagnostic accuracy to range from 76% to 99%, and its specificity to approach 100%.12,13,14,15

Fluoroscopy, CT scanning, and ultrasonography are the preferred imaging modalities for guidance of needle biopsy in the thorax. All available radiographic studies of the lesion to undergo biopsy should be reviewed before the procedure. For lung nodules, fluoroscopy is the imaging guidance of choice because it provides immediate identification and, thus, rapid sampling of the lesion. If the lesion cannot be identified by fluoroscopy, CT scanning guidance should be used. CT images provide exquisite anatomic details, and vital structures, such as major blood vessels, can thus be avoided. These attributes render CT scanning the imaging guidance of choice for lesions involving the mediastinum, hila, or pleura. Finally, the use of ultrasonography should be reserved for superficial chest wall masses.

Although no absolute contraindications to percutaneous pulmonary biopsy exist, there are several relative contraindications, such as an uncooperative patient, pulmonary hypoxia, hypotension, coagulopathy, and severe bullous emphysematous disease. Severe complications from transthoracic pulmonary biopsy are extremely rare, and the overall mortality ranges from 0.01% to 0.05%.12,14,15 On the other hand, the incidence of pneumothorax (by far the most common complication) varies between 14% and nearly 60%, but only 4% to 13% of these cases require treatment by placement of a chest tube.12,13,14,15 Note that the incidence or size of a pneumothorax is not related to either the size of the biopsy needle or the number of passes made during the biopsy.12 Other complications include hemoptysis (5% of cases) and pleural pain, especially if a pneumothorax is present.12,13,14,15

BIOPSY OF OTHER ORGAN SYSTEMS

With the advent of high-quality cross-sectional imaging, percutaneous biopsy of suspicious abdominal masses has become a relatively easy, safe, and reliable method of obtaining definitive tissue diagnosis. CT guidance remains by far the most common imaging guidance modality, because it provides superb anatomic details and excellent evaluation of internal structures, thus allowing the operator to plan and choose the safest approach to a biopsy. It is clearly the modality of choice for biopsy of the pancreas, adrenals, lymph nodes, retroperitoneal masses, and liver lesions not seen well by ultrasonography. On the other hand, ultrasonography is the guidance modality of choice for biopsy of the thyroid and breast and is frequently used for biopsy of the liver (especially if the lesions are relatively large and superficial), the pancreas, kidneys, and pelvic organs. Ultrasonography offers the advantage of real-time, multplanar imaging as well as Doppler analysis, which makes it very practical and improves safety by allowing the operator to identify and thus avoid major vessels. The role of magnetic resonance imaging in biopsy guidance remains limited by the high cost of nuclear medicine examinations and the need for specialized biopsy needles owing to the magnetic field. Although both fine-needle aspiration and larger cutting needles can theoretically be used for biopsy of abdominal lesions, a fine needle is often preferred because the risk of injury to adjacent vital structures is minimized. Indeed, such structures as the liver, stomach, small bowel, and colon can safely be traversed by a fine needle. Cutting needles should be used if a definitive diagnosis cannot be established with fine-needle aspiration and only if a clear, safe pathway...
Percutaneous biopsy of abdominal or pelvic masses generally yields high diagnostic accuracy rates. In the liver, it ranges from 60% to 84% with fine aspiration needles to 90% to 100% with core or cutting needles. In the pancreas, diagnostic accuracy has greatly improved over the last 10 years and now ranges between 85% using fine-needle aspiration and 92% using core needles. The diagnostic accuracy for biopsy of the kidney and adrenal is greater than 90%. The use of large cutting needles for biopsy of the adrenal glands is not recommended because major vital structures, which surround the adrenal glands, could be transgressed during the procedure, thus causing major complications. For abdominal biopsies, the diagnostic accuracy is directly related to the number of needle passes made during the biopsy.

The complication rate for percutaneous biopsy in the abdomen is low (1% to 3%). It is lowest in the liver (0.1%) and highest in the adrenals (8.4%). Major complications, though extremely rare, include hepatic or renal hemorrhage, pancreaticitis, and pneumothorax. They can usually be treated effectively by transcatheter or tract embolization (hemorrhage) or insertion of a drainage catheter (pancreatitis or pneumothorax).

More invasive techniques, such as transjugular liver biopsy and percutaneous transhepatic biopsy of the biliary tree can also be performed to obtain tissue diagnosis in the liver. In cancer patients, transjugular liver biopsy is used mainly to obtain core-like samples of liver tissue to establish the diagnosis of graft-versus-host disease. It is performed via a right internal jugular approach and requires selective hepatic vein catheterization. Once seeded within the hepatic vein, either a biopsy gun or forceps is directed inferiorly and advanced through a vascular sheath directly into the liver parenchyma to collect tissue samples. This technique is especially useful in coagulopathic patients with diffuse liver disease.

Traditional image-guided percutaneous biopsy or endoscopic brush biopsy of the biliary tract have diagnostic yields ranging only from 40% to 70%. Benign and malignant biliary strictures have similar cholangiographic appearances, and distinguishing between the two entities can be extremely difficult. Percutaneous transhepatic biliary drainage allows direct access to the biliary tract once satisfactory decompression of the biliary tree has been achieved. Biopsy forceps catheters can then be used through the existing tract to obtain tissue samples of suspicious areas within the biliary tree. Sensitivity and specificity with this technique hover near 85% and 95%, respectively, and are highest when a scope, introduced percutaneously through the established tract, provides direct visualization of the biliary tree.

**VISCERAL ANGIOGRAPHY**

The role of angiography in the diagnostic evaluation of hepatobiliary or pancreatic neoplastic disease has greatly diminished in the last decades. The advent of sophisticated noninvasive fast imaging modalities, such as CT, ultrasonography, and nuclear medicine, has fulfilled most of the clinician’s diagnostic needs. However, angiography continues to be important not only as a visceral diagnostic test but as it provides the basis for many therapeutic interventional procedures. Visceral angiography requires selective catheterization of the celiac axis and superior mesenteric artery after which digital subtraction imaging is performed. Filming should be carried out long enough to visualize the portal venous phase. Visceral angiography is used for detailed evaluation of the splanchic arterial anatomy, particularly the numerous potential anatomic variations in the arterial supply to the liver. Documenting patency of the portovenous system, and determination of vascular encasement. When intraarterial chemotherapy administered via a surgically placed pump is being considered for treatment of liver metastases, thorough evaluation of the hepatic arterial anatomy is especially important to ensure appropriate delivery of the chemotherapy to all segments of the liver involved by the tumor. In cases of pancreatic cancer or cholangiocarcinoma, if surgical resection is contemplated, assessment of vascular encasement is critical, since surgery offers the only hope for cure. Encasement of the celiac axis, the superior mesenteric artery, portal vein, or superior mesenteric vein usually indicate that the tumor is not amenable to surgical resection for cure, although in some cases and, depending on the surgeon's experience, such findings may not preclude surgical exploration.

![Diagnostic visceral arteriogram in a patient with pancreatic adenocarcinoma: venous encasement.](image1)

**FIGURE 27.4-1.** Diagnostic visceral arteriogram: variant arterial anatomy. A: Replaced right hepatic artery (arrow) off the superior mesenteric artery. B: Replaced left hepatic artery (black arrow) off the left gastric artery (open arrow).

![Diagnostic visceral arteriogram in a patient with pancreatic adenocarcinoma: venous encasement.](image2)

**FIGURE 27.4-2.** Diagnostic visceral arteriogram in a patient with pancreatic adenocarcinoma: venous encasement. A: Venous phase from splenic arterial injection demonstrates narrowing of the main portal vein consistent with encasement (arrow). B: Venous phase from superior mesenteric arterial injection demonstrates encasement of main portal vein (arrow).

**PORTAL VENOUS SAMPLING**

Islet cell tumors of the pancreas can be elusive, and their detection by noninvasive imaging or by conventional angiography often fails. Percutaneous transhepatic portal venous sampling is used to localize islet cell tumors by measuring hormonal levels in the superior mesenteric, splenic, and portal veins. This method has a sensitivity exceeding 95% for localization of islet cell tumors. Detection and localization of islet cell tumors is important because patients can be cured once the tumor is resected. Precise anatomic mapping of the hormonal collections is, therefore, essential to accurately locate the tumor, thereby avoiding blind surgical resection and enabling the surgeon to resect the affected segment (head, body, or tail) of the pancreas. When the sampling procedure is completed, the transhepatic tract should be embolized with Gelfoam pledges to prevent excessive bleeding.

**THERAPEUTIC INTERVENTIONS**

The second part of this chapter focuses on the most important contributions of interventional radiology in the treatment and management of hepatic, pancreatic,
biliary malignancies; other gastrointestinal tract cancers; genitourinary tumors; superior vena cava (SVC) syndrome, as well as pulmonary thromboembolic disease.

**LIVER CANCER**

The management of primary and secondary malignancies of the liver constitutes one of the most difficult challenges for oncologists. First, primary hepatic malignancies frequently escape detection because most patients remain asymptomatic for long periods. Then, if clinical symptoms are present, they may be masked by the patient’s underlying liver disease and may, therefore, be difficult to attribute to a malignancy. In addition, clinical outcome is typically poor, with median survival of less than 1 year for all patients and between 3 and 6 months for unresectable presentations. Hepatocellular carcinoma (hepatoma) is one of the most common malignant tumors in the world (1.2 million deaths per year) and accounts for approximately 90% of all liver cancers. It is most commonly encountered in Asia and sub-Saharan Africa, where it constitutes 20% to 40% of all malignancies. The high incidence of hepatoma in these regions can be attributed to hepatitis B, which is endemic in these regions of the world. In Europe and North America, the incidence of hepatoma is markedly lower (10,000 to 14,000 cases per year in the United States) and largely related to alcoholism, but it is climbing rapidly and expected to increase further given the recent rise in hepatitis C and its association with hepatoma.

Metastatic malignant tumors of the liver are by far the most common type of hepatic malignancies in the United States (at least 20 times that of hepatoma) and occur most often secondary to colorectal carcinoma (155,000 cases and 60,000 deaths per year in the United States). Followed by ocular melanoma, neuroendocrine tumors of the pancreas, including carcinoid tumors, as well as both functional and nonfunctional islet cell tumors, and some sarcomas. In many of these conditions, the liver is the only site of metastatic involvement, thus justifying a role for locoregional therapy.

Although rare, carcinoid tumor represents the most common of all endocrine tumors of the gastrointestinal tract, and the incidence of metastatic carcinoid tumor is 0.32 to 0.7 per 100,000 with the majority arising from the small bowel. The tumor is usually slow growing and, therefore, associated with longer survival than hepatoma or colorectal metastatic disease, but patients can be plagued by severe symptoms due to excessive secretion of serotonin and bradykinin as part of the carcinoid syndrome (4% to 9% of cases). In cases of carcinoid syndrome, the liver is almost always involved, and locoregional palliative therapy with chemoembolization constitutes the only therapeutic option.

Ocular melanoma is a very aggressive and highly lethal disease. It usually progresses very rapidly and commonly metastasizes to the liver. Once the liver is involved, fatal hepatic disease ensues. Median survival ranges from 2 to 6 months. As for the other tumors involving the liver, locoregional therapy offers the best option.

For both primary and metastatic liver cancers, such surgical options as resection or transplantation offer the only hope for cure and, at the very least, have a definite impact on survival. Although a cure has been achieved in a small percentage of patients, survival rates ranging from 55% to 80% at 1 year and 25% to 50% at 5 years, only a minority of patients are surgical candidates (15% to 20% of all patients with either primary or secondary liver cancers). Cited criteria used to determine resectability include the size, location, and volume of the lesion to be resected; multivisceral involvement; as well as the presence of limited hepatic reserve due to advanced cirrhosis or chronic hepatitis and significant concurrent disease (especially cardiac or pulmonary disease). In addition, surgical resection continues to be plagued by fairly high morbidity and mortality rates, especially when surgery is performed in patients with underlying liver failure (15% to 30% perioperative mortality), as well as high recurrence rates (75% of patients). Liver transplantation remains limited by the scarcity of liver donors (although the development of living-related liver transplantation could remedy this problem) and by a surprisingly high recurrence rate. Other therapeutic options, such as systemic chemotherapy and external-beam radiotherapy, have been disappointing. The response rate from single-agent or multidrug chemotherapy is poor, as it does not exceed 15% to 20% and a clear survival benefit has not been demonstrated. External-beam irradiation is limited by the extensive damage it causes to the radiosensitive hepatocytes.

The limitations of the traditional weapons against cancer (surgery, chemotherapy, and radiotherapy), combined with the fact that the immense majority of patients afflicted by primary or metastatic liver cancer have liver-only disease, have led to the hunt for and development of various locoregional therapies. In addition, patients afflicted by hepatoma usually die of hepatic failure and cachexia as a result of local growth and resultant liver tissue destruction but not of extrahepatic metastatic disease. Thus, control of the tumor at the regional level is essential.

The goal of locoregional therapy is to destroy the tumor while preserving as much of the normal liver tissue as possible. This can be accomplished either by direct percutaneous ablative therapies, such as percutaneous ethanol injection and radiofrequency ablation, or by intraarterial delivery of embolic material with or without chemotherapeutic agents, such as transarterial chemoembolization, which is by far the most widely performed procedure in the treatment of unresectable liver cancers.

**Transcatheter Arterial Chemoembolization**

Transcatheter arterial chemoembolization has truly become the mainstream of therapy for unresectable hepatoma and carcinoid tumors and has shown great promise against colorectal metastases. The concept of chemoembolization evolved from practical experience obtained with two partially effective therapies, intraarterial chemotherapy and embolotherapy. Although many different chemoembolization regimens can be used, the principles and theoretic advantages of chemoembolization are based on three combined factors: the particulate nature of the embolic drugs mixed with the selected chemotherapy and an embolic agent directly into the hepatic artery. It is well established that the normal liver draws most of its blood supply from the portal vein (approximately 75%), whereas primary or metastatic liver tumors draw most of their oxygen supply from the hepatic artery (>90%). Targeting the hepatic artery for regional delivery with a mixture of chemotherapeutic agents and embolic material is, therefore, not only safe and possible but also extremely effective in destroying the tumor. The theoretic beneficial effects of chemoembolization include delivery of a high concentration of chemotherapy to the tumor bed, marked increase in contact time between the drugs and the tumor cells, and high first-pass extraction. These factors combine to increase the drug concentration and the retention rate within the tumor even further (100- to 400-fold increases in drug concentration have been reported), thereby minimizing the systemic toxicity of the chemotherapeutic drugs. Although many different chemoembolization protocols are being used throughout the world without any compelling evidence of the superiority of one over the other, a generally accepted rule is that the chemoembolization infusion should include a mixture of iodized oil (Ethiodol) and chemotherapeutic agents. Doxorubicin is most commonly used alone in Europe, whereas the combination of cisplatin, doxorubicin, and mitomycin C is favored in the United States. Ethiodol plays a key role in the process since it not only acts as a carrier for the chemotherapeutic agents by creating an emulsion with the agents but it also prolongs contact time between the tumor cells and the agents by clogging the presinusoidal and portal shunts, thus allowing the agents to slowly diffuse into the tumor. Particulate emulsion materials (Gelfoam or Ivalon) should also be injected toward the end of the procedure to reduce arterial inflow and, thus, prevent washout of the chemotherapeutic agents.

Since chemoembolization is currently only used as a palliative therapy, its impact on patients’ quality of life should be given high priority. The benefits of the procedure should be weighed against the potential complications that could worsen patients’ quality of life. Thus, proper patient selection should be conducted to exclude patients who could be adversely affected by the procedure, such as those with clinically apparent jaundice, hepatic encephalopathy, extensive extrahepatic metastases, poor liver function (combination of >50% liver replacement by tumor, aspartate transaminase >100, markedly elevated lactate dehydrogenase, and hyperbilirubinemia), or biliary obstruction.

Patients scheduled to undergo chemoembolization are required to fast before surgery. The day of the procedure, vigorous hydration with normal saline, prophylactic antibiotics, antihistamines, and sedatives are administered. A visceral arteriogram is then performed to define the arterial anatomy and to assess portal venous patency. With the advent of hydrophilic guidewires and catheters as well as coaxial systems with smaller diameter catheters, it is now possible to perform superselective catheterization of third- or fourth-order branches. Once the catheter has been advanced beyond the gastroduodenal artery to avoid nontarget embolization and is located within striking distance of the tumor, the chemoembolization material can be injected. The infusion should be stopped before thrombosis of the hepatic artery occurs. Patients are then admitted for pain management, continued antibiotic coverage, and hydration. The vast majority of patients requires only a 24- to 48-hour hospital stay. Although most patients experience some degree of pain, nausea, vomiting, and fever as part of the embolization syndrome, which typically lasts 3 to 10 days, chemoembolization is generally relatively well tolerated. True complications, such as liver failure, liver infarction, abscess formation, cholecystitis, nontarget embolization to the gastrointestinal tract, and biliary necrosis, are rare (3% to 4% of cases).
is no doubt that outcome and survival are primarily directly related to these factors, regardless of whether treatment is administered and regardless of the form of treatment. Patients with hepatoma experience a wide spectrum of diseases directly related to the extent of tumor involvement and preexisting nonneoplastic liver disease. There is no doubt that outcome and survival are primarily directly related to these factors, regardless of whether treatment is administered and regardless of the form of therapy selected.

Recent prospective randomized trials conducted by Pelletier et al., Madden et al., the Groupe d’Etude et de Traitement du Carcinome Hepatocellulaire, and Bruix et al. (the only four randomized trials to date) failed to show a significant survival advantage of chemoembolization over supportive care, although a trend to improved survival was observed (63% vs. 44% at 1 year). Each of these studies had significant flaws in their methodology and design, severely limiting their validity. However, they managed to question the utility of chemoembolization in prolonging survival. In a landmark article published in 1991, Vetter et al. reported a case-control study comparing chemoembolization to supportive care, which clearly demonstrated the superiority of chemoembolization over supportive care. Survival at 1 and 2 years was 59% and 30%, respectively, in the treatment arm, whereas it was 0% at 1 year in the supportive care group. Another study by Bartolozzi et al. confirmed the survival benefits of chemoembolization in a group of 53 patients with 91% survival at 1 year, 70% and 43% overall survival rate at 1, 2, and 3 years, respectively. Nakan et al. measured survival as a function of tumor size and found that patients with tumor less than 9 cm had a better survival than those with tumor greater than 9 cm. Overall survival at 1 and 4 years was 67% and 31%, respectively. Solomon et al. focused on the effectiveness of chemoembolization in an exclusively Western population and found cumulative survival of 60% at 1 year, 41% at 2 years, and 16% at 3 years similar to that obtained by studies in Asian populations. Despite the impact of these studies, the search is still on for one or more specific niches that would help to establish chemoembolization as an uncontested treatment option for hepatoma. For example, the issue of high recurrence after liver transplantation or surgical resection is perplexing, and adequate therapy against such recurrence is lacking. Recent studies exploring the role of chemoembolization as a neoadjuvant treatment modality have shown markedly improved disease-free survival when chemoembolization was performed before surgery. Patients treated with chemoembolization before surgical resection had survival rates of 87%, 70%, and 39% at 1, 3, and 5 years, respectively, whereas patients treated with surgical resection alone had survival rates of 79%, 38%, and 19%. Disease-free survival was also better in the chemoembolization than in the surgery-only group (40% and 28% vs. 20% and 11% at 3 and 5 years, respectively). When chemoembolization was used before liver transplantation, the 1- and 2-year disease-free survival rates were 91% and 84%, respectively. Survival was also significantly improved when chemoembolization was used to treat intrahepatic tumor recurrence that had occurred postoperatively (Fig. 27.4-4, Fig. 27.4-5). The 1-, 3-, and 5-year survivals were 75%, 46%, and 30%, respectively, as opposed to 20%, 4%, and 0% when no chemoembolization was administered.

Patients with hepatoma experience a wide spectrum of diseases directly related to the extent of tumor involvement and preexisting nonneoplastic liver disease. There is no doubt that outcome and survival are primarily directly related to these factors, regardless of whether treatment is administered and regardless of the form of therapy selected. However, the available data published to date have clearly helped to define a role for chemoembolization as an effective adjuvant therapy either

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**FIGURE 27.4-3.** Transhepatic arterial chemoembolization in a patient with multifocal hepatocellular carcinoma. **A:** Extensive staining of the tumor foci after chemoembolization indicating excellent uptake of the chemoembolization material by the tumor. **B:** Superselective catheterization. The catheter has been advanced to within striking distance of the tumor.

**FIGURE 27.4-4.** Transhepatic arterial chemoembolization in a patient with recurrence of hepatocellular carcinoma in the left lobe of the liver 1 year after wedge resection of a solitary hepatocellular carcinoma in the right lobe of the liver. **A:** Two low-density nodules are clearly identified within the left lobe of the liver, consistent with recurrent hepatoma. **B:** Arterial phase from a celiac arteriogram demonstrates hypervascular tumor foci within the left lobe of the liver (arrows) consistent with the computed tomography findings.

**FIGURE 27.4-5.** Computed tomography scan of the abdomen without contrast 1 day after chemoembolization in the patient from Figure 27.4-4. Excellent distribution of the chemoembolization material throughout the two tumor nodules (arrows).
preoperatively or postoperatively and establish its efficacy as a palliative therapy against unresectable hepatocellular carcinoma.

No controversies exist about the use of chemoembolization in the treatment of metastatic neuroendocrine tumors, such as carcinoid and islet cell tumors, with survival ranges from 27 to 48 months from the time of therapy. These tumors are usually hypervascular, thus making them ideal candidates for treatment with chemoembolization; and, unlike patients with hepatoma, patients affected by neuroendocrine tumors are frequently symptomatic. The goal of therapy is clear and consists of alleviating symptoms (pain, anorexia, early satiety) related both to hormonal release and the tumor bulk itself resulting from intrahepatic involvement. Multiple studies by Therasse, Winkelbauer, Mavligit, Stokes, and Perry have clearly demonstrated the effectiveness of chemoembolization against such tumors. Therasse and Stokes reported a 100% symptomatic response, which lasted for an average of 28 months, and a 90% decrease in hormonal levels after treatment with chemoembolization. Although earlier reports with embolization alone demonstrated high response rates, symptom-free intervals of 5 to 10 months achieved with embolization do not compare favorably with chemoembolization.

The role of chemoembolization in the treatment of colorectal liver metastases is still under investigation at several centers in the United States, and published studies remain sparse. Colorectal carcinoma is especially lethal once it has metastasized to the liver. Indeed, median survival is only 6 months after the diagnosis of hepatic metastasis is made. Systemic chemotherapy with 5-fluorouracil or combination regimens have produced mediocre response rates rarely exceeding the 20% range and have caused significant systemic toxicity. Hepatic artery infusion of chemotherapy with either 5-fluorouracil or 5-fluorodeoxyuridine has been shown to improve response rates to 45%. However, despite encouraging response rates, seven separate randomized phase III studies failed to show survival benefit. Chemoembolization has, therefore, become a form of last-resort therapy for patients who have liver-dominant disease and have failed to respond to systemic chemotherapy. Enrolling patients with such a deadly disease into clinical trials to demonstrate the worth of chemoembolization is, thus, understandably difficult. Tellez et al. conducted a phase II clinical trial in which 30 patients with colorectal metastases to the liver were treated with chemoembolization. Median survival was 9 months after the initiation of chemoembolization and 29 months after the initial diagnosis of liver metastasis was made. In the largest study to date involving 52 patients, Daniels et al. reported a 78% response rate using biologic criteria (decrease in carcinoembryonic antigen) accompanied by median survival of 11 months from the time of treatment. Despite evidence of promising response rates with chemoembolization, the survival benefit of the procedure is still in question. Only well-designed randomized clinical trials comparing chemoembolization to systemic chemotherapy can answer this question. Such a multicenter trial is now under way in the United States.

**Percutaneous Ethanol Injection**

Since 1983, when it was first described, percutaneous ethanol injection has been used primarily against unresectable hepatoma and occasionally against colorectal metastases. Ethanol diffuses into the tumor cells, where it causes cellular dehydration and induces coagulative necrosis. Ethanol is more effective against hepatoma lesions because they are usually softer than colorectal lesions, thus allowing greater diffusion of the ethanol throughout the tumor. Although no significant limitations to the size or number of lesions exists, percutaneous ethanol injection is most effective against tumors measuring less than 3 cm in diameter and large lesions. In patients with three or fewer lesions, the presence of multifocal or diffuse hepatoma, extrahepatic metastases, or severe coagulopathy constitutes absolute contraindications to treatment with percutaneous ethanol injection.

The procedure is usually performed under ultrasonography or CT guidance. A 20- to 22-gauge needle is inserted directly into the tumor, and tumor volume (estimated from the formula on the volume of a sphere) is then calculated to determine the exact amount of ethanol required. As ethanol diffuses throughout the tumor, the tumor becomes hyperemic on ultrasonography owing to the presence of microbubbles within the tumor. Nontarget injection into blood vessels or biliary ducts must be avoided. The procedure can be performed over multiple sessions if necessary, depending on the size of the tumor and the number of lesions to treat. Typically, 4 to 12 sessions are required to treat solitary lesions and large lesions. In patients with the least underlying liver disease fare best in terms of long-term survival. Large series mostly from Japan and Italy (where percutaneous ethanol injection is most commonly used) have demonstrated that percutaneous ethanol injection can be very effective against hepatoma. These studies have also helped to establish clear prognostic factors, such as the volume of ethanol.

![FIGURE 27.4-6. Percutaneous ethanol injection into liver tumor. (Courtesy of Matrix Pharmaceutical, Inc., Fremont, CA.)](image-url)

When comparison between percutaneous ethanol injection and supportive care or surgery was made, survival rates achieved with percutaneous ethanol injection were found to be markedly better than those obtained with supportive care and nearly equal to those obtained at surgery. These studies, although retrospective and thus not randomized, attempted to closely match patients between groups based on tumor size, number of lesions, and underlying liver condition. For example, Livraghi et al. found no significant difference in 3-year survival between ethanol injection (79%) and surgical resection (71%) in 391 patients who all had a solitary lesion measuring less than 5 cm. Similar results were reported by Castella et al. who compared clinical outcomes between surgery and ethanol injection in 63 patients with solitary lesions measuring up to 4 cm. Patients treated with ethanol injection had overall survival rates at 1 and 4 years (83% and 34%) nearly equal to those treated with surgical resection (81% and 44%). The high rate of recurrence, which typically varies between 64% and 98% within a 5-year period and is actually similar to recurrence rate after surgery, constitutes a nagging problem. However, when recurrence does occur, these tumors can be treated repeatedly with ethanol injection (unlike surgery) without damaging liver functions.

The effects of percutaneous ethanol injection and chemoembolization on liver tumors can be synergistically enhanced when the two techniques are combined. Several recent reports have demonstrated the efficacy and potential benefits of such tandem therapy. In a study by Lencioni et al., 86 patients with mild cirrhosis and a large hepatoma (5 to 6 cm in diameter) were treated with a single cycle of chemoembolization followed by percutaneous ethanol injection. Survival rates were 92% at 1 year, 70% at 3 years, and 47% at 5 years. Tanaka et al. reported 100% and 75% survival rates at 3 and 5 years, respectively, in patients with a 3- to 5-cm
CANCERS OF THE BILIARY TRACT AND PANCREAS

Cancers of the biliary tract, which include gallbladder and bile duct carcinoma or cholangiocarcinoma, are the second most common primary hepatobiliary cancers after hepatocellular carcinoma. \(^{123}\) Cholangiocarcinoma is more common in men, whereas gallbladder carcinoma is seen more frequently in women. \(^{123}\) These differences can be explained by the higher incidence of sclerosing cholangitis in men and gallstones in women, which are well-known risk factors for cholangiocarcinoma and gallbladder carcinoma, respectively. \(^{123}\) Although gallbladder carcinoma is encountered twice as frequently as cholangiocarcinoma (7500 vs. 2000 to 3000 new cases per year), most patients requiring intervention radiology procedures experience cholangiocarcinoma. \(^{123}\)
Cholangiocarcinoma is a slow-growing tumor with a peak incidence in the sixth and seventh decades. The tumor is notorious for invading the liver parenchyma as well as hepatic arteries and portal venous system, which renders surgical resection especially difficult. As a result of its infiltrating growth pattern within the biliary ductal system, patients with cholangiocarcinoma usually present with symptoms (jaundice, pruritus, and color-altered stools and urine) caused by obstruction of the biliary tree. When the tumor involves the common hepatic duct, the common bile duct, or the ampulla, symptoms will occur early in the course of the disease. On the other hand, when the tumor involves the perihilar region, which is the most common area of tumor involvement (approximately two-thirds of the cases), the occurrence of symptoms may be delayed significantly. Other symptoms, such as pain, fatigue, general malaise, and weight loss, are typically seen in advanced disease. Surgical resection is the only therapeutic option associated with improved survival in patients with cholangiocarcinoma. Systemic chemotherapy and external-beam radiotherapy have not significantly improved survival or quality of life. Therefore, palliative therapy plays a critical role in the management of patients who are not surgical candidates.

Carcinoma of the exocrine pancreas carries a dismal prognosis, with median survival from time of diagnosis approaching 6 months. There are no curative treatments, and even surgery, which can be performed only in 10% to 20% of patients with pancreatic carcinoma, does not appear to increase survival. Thus, as for cholangiocarcinoma, the need for effective palliation is critical.

The diagnosis of cholangiocarcinoma or pancreatic carcinoma is usually established by cross-sectional imaging (ultrasonography and CT scanning). Diagnostic visceral angiography and cholangiography are reserved for determining tumor resectability. Depending on the location of the tumor, cholangiography can be performed from a percutaneous transhepatic or an endoscopic approach. The cholangiographic appearance of cholangiocarcinoma is again directly related to the infiltrating-scirrhous nature of its growth pattern. Thus, cholangiocarcinoma generally presents as a focal stricture, often without a mass, which may mimic sclerosing cholangitis if tumor involvement is diffuse. The cholangiographic appearance of pancreatic carcinoma is similar to that of cholangiocarcinoma with a short and irregular stricture, resembling a rat tail, causing massive biliary ductal dilatation. Access into the biliary tree also provides an avenue for collection of biopsy samples, which can be extremely useful to differentiate benign from malignant disease. This diagnostic technique is especially useful to distinguish biliary ductal strictures caused by pancreatic carcinoma from those due to pancreatitis. However, in the case of bile duct tumors, establishing a definitive diagnosis of cholangiocarcinoma can be difficult owing to the intense desmoplastic reaction that the tumor generates. The use of brush biopsies and cytologic examination has increased the diagnostic yield to approximately 40% to 70%.

The goal of palliative therapy is to relieve the symptoms associated with biliary tract obstruction. This can be accomplished via endoscopic placement of plastic stents or via percutaneous transhepatic placement of external-internal biliary drains or metallic stents. Given the less invasive nature of endoscopic techniques, endoscopic stent placement is preferred as the first line of therapy, especially when the tumor involves the extrahepatic biliary tree, and is successful in 80% to 90% of the cases. However, it is usual for these endoscopic stents to become occluded fairly quickly after placement, thus requiring frequent stent replacement (approximately every 3 months). Percutaneous transhepatic biliary drainage is the procedure of choice in cases of unsuccessful endoscopic stent placement, prior biliary-enteric surgical reconstruction, or high level of biliary obstruction (i.e., above the confluence of the ductal systems). In some centers, such as the Johns Hopkins Hospital, percutaneous biliary drainage is also routinely performed preoperatively to facilitate surgical reconstruction of the biliary tract. Indeed, these biliary drainage catheters aid in the creation of biliary-enteric anastomoses by providing anatomic landmarks of the intra- and extrahepatic biliary ducts during surgery, which can be particularly helpful in patients with extensive tumor involvement. Several studies have shown that preoperative percutaneous biliary drainage reduces operative time as well as operative morbidity and mortality. One of the critical benefits offered by percutaneous biliary drainage remains the possibility of rapid intervention to decompress the biliary tree. The procedure can even be life-saving in cases of acute cholangitis or biliary sepsis. Reestablishment of bile flow usually causes rapid recovery of hepatic function, with decrease in liver enzymes, which in turn leads to relief in patient's symptomatology and improvement in overall health of the patient. Percutaneous biliary drainage can also relieve obstruction in patients with occluded endoscopically placed plastic stents. These stents either can be removed percutaneously (snare technique) or can be pushed into the small bowel. Once access into the biliary tree is secured, either internal-external biliary stents or permanent self-expanding metallic internal stents can be placed to maintain biliary-enteric flow.
Internal-external biliary stents are preferred if surgical resection or debulking of the tumor is contemplated, because they provide immediate access to the surgical site for evaluation of possible complications during the perioperative period and prevent stricture formation at the biliary-enteric anastomosis, which can occur during the late postoperative period. Internal-external biliary stents offer several other advantages, such as allowing for the careful monitoring of the surgical site for possible tumor recurrence in those patients who underwent curative surgery and the exchange of stents when they become occluded. In fact, patients with internal-external stents generally have to undergo routine biliary tube changes every 2 to 3 months to maintain biliary-enteric flow and prevent biliary sepsis. On the other hand, placement of permanent metallic stents is recommended for patients with a limited life expectancy and for whom no surgical options exist. Debilitated or nursing-home patients who cannot care for their internal-external biliary tubes should also be treated with permanent stents if at all possible. These patients usually experience marked improvement in their quality of life owing to the absence of external tubes and their associated risk of skin infection, pericatheter bile leakage, and catheter obstruction or dislodgment. Metallic stents can be deployed atraumatically, since they go through small delivery systems. Once released from the guiding catheter, they self-expand to reach a diameter approximately three times that of plastic stents. Thus, with their larger diameter and inherent radial expansile force, metallic self-expanding stents are favored over endoscopic plastic stents because they tend to stay open longer than endoscopic stents (see Figs. 27.4-12 and 27.4-13). Several series by Boguth et al., Schima et al., and others have reported patency rates for metallic stents of approximately 6 months. In addition, metallic stents are very flexible, rendering them especially well suited for tortuous courses. This is particularly useful when the tumor involves the confluence of hepatic ducts (Klatskin tumor). In such cases, massive dilatation of both the right and left intrahepatic bile ducts occurs, and bilateral access into the biliary tree is necessary to properly relieve the obstruction. Effective palliation with internal stents can then be provided only by self-expanding, flexible stents deployed from above the level of obstruction and extending into the common hepatic duct.

Patients scheduled to undergo percutaneous biliary drainage should receive prophylactic broad-spectrum antibiotic coverage, and any coagulopathy should be corrected. Percutaneous transhepatic cholangiography is first performed via a 22-gauge needle inserted from a right midaxillary line. Contrast opacification of the biliary tree, a duct within the right posterior ductal system is selected based on its position and course relative to the location of the tumor and accessed using a slightly larger needle (21-gauge). A guidewire is then advanced through the needle into the biliary tree to secure access into the biliary system. Steerable guidewires are then used to cross the obstruction and, thus, gain access into the duodenum. To maintain adequate biliary-enteric flow, a multi-side-hole catheter is placed across the obstruction. The tube is typically left to external drainage for 12 to 24 hours before it is capped and functions as an internal-external biliary stent. Two major types of biliary drainage catheters are available, a plastic (Percuflex), somewhat stiffer catheter, which is necessary for initial placement, or a softer, silastic catheter, which is much more comfortable for the patient and is generally favored if long-term intubation is required. If access into the duodenum cannot be achieved, the biliary tube must be connected to a drainage bag indefinitely, and oral bile salt replacement must be initiated.

Percutaneous transhepatic biliary drainage performed for palliation is markedly safer than surgical decompression. The mortality rate associated with biliary drainage varies between 0.5% and 3%, as opposed to 20% to 30% for surgery. However, the complication rate is not insignificant, since it ranges from 5% to 25%. The most common complications include tube occlusion, tube dislodgment, cholangitis-sepsis, hemobilia, and pseudoaneurysm. Biliary tubes become occluded because of continued tumor growth, blood clots, or bile. As a result, biliary ductal dilatation ensues, leading to bile stasis and cholangitis or sepsis. This process, which has been reported to occur in 23% of cases, constitutes the major indication for performing biliary tube exchange.

**GENITOURINARY TRACT TUMORS**

Obstruction of the urinary tract is a common urologic problem that requires prompt intervention to avoid permanent damage to the kidney. Renal obstruction may be caused by the tumor itself (transitional cell carcinoma), blood clots, fungal infection, fibrotic changes that can occur after radiotherapy,
retroperitoneal fibrosis (Fig. 27.4-14), or extrinsic compression due to either enlarged lymph nodes or a tumor mass, such as lymphoma. In these instances, percutaneous interventional techniques play a significant role to alleviate some of the symptoms and, more important, relieve the obstruction. In fact, percutaneous drainage of the kidney or percutaneous nephrostomy is the treatment of choice for malignant obstruction of the urinary tract and has completely replaced surgical nephrostomy. 174-176 The diagnosis of obstruction, which can be somewhat challenging to establish, is usually made with CT scanning or ultrasonography. Cross-sectional imaging studies also provide information about the level of obstruction, the anatomy of the retroperitoneal space, and whether the obstruction is unilateral or bilateral. 174-176

There are no absolute contraindications to percutaneous nephrostomy other than noncorrectable coagulopathy. Prophylactic antibiotic therapy should be administered before the procedure and continued for at least 24 hours after the procedure. However, in cases of known pyonephrosis or urinary sepsis, antibiotic therapy should be continued for 5 to 7 days. Whether performed under CT, ultrasonography, or fluoroscopy guidance, the goal of the procedure remains the same and consists of gaining access into the renal collecting system via a posterior calyx. Entering the kidney via the posterior calyx is critical to avoid major bleeding complications, since the posterior calyx is less well vascularized than the other calyces. Once the needle is placed within the posterior calyx, an antegrade nephrostogram should be performed to define the nature of the obstructing lesion and determine the precise level and extent of the obstruction or stricture. A small-caliber guidewire is then inserted through the needle to secure access into the renal collecting system. Eventually, after successive dilation of the tract, a pigtail-type nephrostomy catheter is placed and locked into position within the renal pelvis. Initially, a small catheter (8 to 10 Fr.) is typically placed, but it can be safely up-sized to a larger caliber catheter (up to 16 Fr.) if necessary. The nephrostomy catheter usually requires minimal care and drains the urine directly into an external drainage bag, which should be emptied three to six times per day, depending on urine output. Since nephrostomy catheters provide adequate urinary decompression, they can be used indefinitely in chronically obstructed patients without damaging the kidney or altering renal function (see Fig. 27.4-14). However, conversion to a nephroureteral stent, which extends from the renal pelvis through the ureter into the bladder, is desirable and should be attempted whenever possible. The main advantage of nephroureteral stents is that they can function as an internal-external system similar to that described in the biliary system and, therefore, do not require an external bag. These stents can be used only if the obstruction is successfully crossed and require a functioning bladder or reconstructed bladder, such as an ileal loop. 178 The main portion of the stent is located within the patient, and the small portion of catheter residing outside the patient is usually capped off. Multiple side holes exist throughout the entire length of the catheter, allowing urine to bypass the obstruction and collect in the bladder. If fever or flank pain develops, it usually indicates stent occlusion. In such cases, the stent can first be externalized (by attaching a drainage bag) to relieve the symptoms prior to exchanging it for a new one. Common indications for the placement of nephroureteral stents include (1) ureteral strictures, which may develop after pelvic or retroperitoneal surgery or radiotherapy or at the anastomosis after creation of a neobladder and ureteral reimplantation; (2) ureteral fistulae; (3) healing of ureteral injuries postoperatively or after radiotherapy; and (4) reestablishment of urine flow from kidney to bladder in patients with urinary tract obstruction scheduled for definitive surgical repair. 178

Internal-external nephroureteral stents can also be converted to internal double-J nephroureteral stents. These internal stents can be placed from a percutaneous approach via the kidney or from a cystoscopic approach. They offer the advantage of being entirely within the patient, thus relieving the patient of any catheter care and reducing the risk of local or systemic infection. On the other hand, when occluded, they are much more difficult to exchange than internal-external stents. Placement of double-J stents is mostly indicated when long-term drainage of the urinary system is required, such as patients with unresectable malignant urinary tract obstruction, or ureteral injury from surgery or radiotherapy. Internal stents should also be used when patients cannot tolerate or care for them.

Percutaneous nephrostomy is performed successfully in 85% to 98% of the cases and is generally well tolerated, with an incidence of major complications ranging from 4% to 6%. The mortality rate is low (0.2%) as opposed to that of surgical nephrostomy (6%). The most common complications are due to massive hemorrhage requiring surgical treatment or transcatheater embolotherapy (1%), pneumothorax (1%), and peritonitis. 174-176 178-179 and 180 Minor complications occur in 10% to 28% of the cases and include microscopic or gross hematuria, which usually clears within 24 to 48 hours, unsuspected retroperitoneal or perirenal hematoma, extravasation of urine (>2%), and infection (1.4% to 21%). Infection can be caused by inadequate drainage due to occlusion of the catheter secondary to encrustations or a preexisting urinary tract infection. Flushing the catheter routinely with normal saline solution is useful in preventing catheter occlusion. Finally, if the catheter becomes dislodged, the track should stay open for 72 hours, thus allowing successful reaccess into the renal collecting system.

SUPERIOR VENA CAVA SYNDROME

Venous thrombosis or occlusion is not an uncommon occurrence in cancer patients. It may be due to direct tumor involvement, extrinsic compression by tumor, or lymphadenopathy. Fibrosis secondary to radiotherapy, or long-term indwelling central venous catheters, which are often needed for systemic chemotherapy or nutritional support. 181-183 184-186 and 187 The central veins, such as the subclavian, innominate, SVC, and IVC, are most commonly affected. The severity of symptoms is directly related to the degree of venous obstruction. In the SVC syndrome, most often caused by lung carcinoma with extension into the mediastinum, symptoms are often dramatic. Patients typically present with swelling of the face and neck as well as dilated collateral venous channels readily visible coursing throughout the upper thorax. 182-183 185-186 and 188 If the degree of obstruction is severe, additional symptoms may be encountered, such as respiratory distress, edema of the conjunctiva, and neurologic disturbances. 181-183 188-189 and 190 Radiotherapy is the treatment of choice for SVC syndrome, and most patients respond well to therapy. 182 However, when radiotherapy is unsuccessful (failure to clear symptoms, recurrence of symptoms, or presence of benign postirradiation fibrotic changes), percutaneous venous interventions, such as percutaneous transluminal angioplasty or stenting, become the treatment of last resort. 188 A diagnostic study, such as central venogram or magnetic resonance venography should first be performed to delineate the extent of the thrombosed or stenosed segment of SVC (Fig. 27.4-15A). If concurrent thrombosis of the SVC is present, catheter-directed thrombolytic therapy can be used to reduce the clot burden and allow for better evaluation of the unmasked underlying stenosis. Once the stenosis is successfully crossed, angioplasty of the stenosis is usually first performed (see Fig. 27.4-15B). Although some success has been reported with angioplasty alone, 182-184 the recurrence or failure rate after percutaneous transluminal angioplasty is quite high because of the elastic recoil that takes place secondary to the compressing tumor or fibrosis. Therefore, stenting has become the most reliable method of establishing venous continuity. Two types of stent, a self-expandable and a balloon expandable, exist for this purpose. Because of its expansile radial force, the self-expandable stent is more commonly used (Fig. 27.4-16). Improvement in patients’ symptomatology may be dramatic and usually occurs within 24 hours of therapy, with complete resolution taking place within 3 days. 181-183 185-186 and 191 Complications include stent migration or thrombosis and vessel injury or perforation during placement.
Although the technical success rate approaches 100%, long-term results are difficult to evaluate since many of these patients have advanced malignant disease and a limited life expectancy. Percutaneous venous stenting should, therefore, be regarded as a palliative therapy and a successful outcome viewed as a patent SVC at the time of death.

PULMONARY THROMBOEMBOLIC DISEASE AND INFERIOR VENA CAVA FILTERS

The association between venous thrombosis and malignancy has been known for more than a century and is strongest in cancers of the lung, breast, pancreas, colon, stomach, prostate, and uterus. A complicating factor is the deep system of the lower extremities, the risk of pulmonary embolism is markedly increased. In fact, the incidence of pulmonary embolism in cancer patients is three times that in the general population. There are approximately 570,000 to 630,000 cases of pulmonary embolism annually in the United States, nearly one-third of which are fatal events. Despite initial management with anticoagulation, a significant number of cancer patients develop recurrent pulmonary thromboemboli. Furthermore, anticoagulation therapy is contraindicated in many cancer patients because of the associated risk of hemorrhage. It is for these reasons that the use of IVC filters, which prevent thrombi from reaching the lungs, is strongly advocated in cancer patients.

Multiple IVC filter designs are commercially available, including the Greenfield stainless steel and titanium filters, the Vena-Tech, the Simon Nitinol, and the Bird's Nest. These filters can be deployed from a femoral or internal jugular approach. A venogram is first performed to measure the diameter of the IVC, to determine the location of the renal veins, and to detect the presence of potential thrombus within the IVC. Filters should be placed immediately below the lowest renal vein, but they can also be placed above the renal veins if thrombus extends to the level of the renal veins. If the diameter of the IVC exceeds 30 mm, the Bird's Nest filter is the only filter that can be placed; otherwise any of the filters can be used. Each filter has advantages and disadvantages, and selection of a specific filter often depends on the filter availability and experience of the radiologist. Note that the Simon Nitinol filter is the most versatile of the filters since, because of its small delivery system, it can be deployed from virtually any peripheral access site.

IVC patency rates vary between 91% and 97% after filter placement. Recurrence of pulmonary embolism occurs in approximately 2% to 4% of the cases. Other complications include filter migration (0% to 30%) and perforation of the IVC (0% to 40%).

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INTRODUCTION

Advances in radiologic techniques have allowed the radiologist to make significant contributions in the diagnosis and management of cancer patients. The applications of ultrasonography (US) in oncology have rapidly increased in recent years, due to development of new technologies and therapeutic regimens as well as easy availability and noninvasiveness of US. This chapter gives an overview of the current role of US in the evaluation of the oncologic patient, with particular emphasis on the sonographic diagnosis, staging, and follow-up of superficial or deep masses and discusses US guidance and techniques for abdominal, thoracic, and superficial interventional procedures.

ULTRASONOGRAPHY APPLICATIONS

An evaluation of the diagnostic role of US includes three particular aspects: (1) detection of a mass or lesion, (2) definition of the nature of the lesion, and (3) estimation of the extent of the lesion. Although a large number of organs can be studied by US with good sensitivities, the staging accuracies of US are limited and depend on the site of the organ. Superficial organs (thyroid, parathyroid, breast, testicles) are better evaluated than deep-seated organs. Nevertheless, tumors in the liver, biliary tree, gallbladder, pancreas, and kidney, prostate, and bladder can be detected by US with quite good sensitivities. The results are less favorable in the retroperitoneum and adrenal glands. In deep-seated tumors, US does not provide detailed evaluation of tumor spread, with exception of hepatic hilar node involvement or vascular invasion of the hepatic veins in hepatocellular carcinoma and the renal veins in renal cell carcinoma.

US may also play an important role in the follow-up of the oncologic patient in a search for or monitoring of liver metastases as well as for the assessment of response in patients with primary or secondary malignancies treated by intraarterial infusion of cytotoxic drugs. The areas wherein US plays an important role include urologic oncology, gynecologic oncology, medical oncology, and as a guidance modality for interventional diagnostic or therapeutic procedures.

UROLOGIC ONCOLOGY

Ultrasound plays a major role in the oncologic workup of tumors of the kidney, bladder, prostate, and seminal vesicles as well as testes.

KIDNEY

When a renal mass is discovered on an intravenous urogram, further evaluation with US is usually performed. A benign renal cyst has a characteristic US appearance, defined as an echo-free fluid-filled lesion with a thin wall and posterior acoustic enhancement (Fig. 27.5-1A). Any doubt about the benign nature of a renal mass or the presence of a complex lesion demands further evaluation with computed tomography (CT) to exclude a renal cell carcinoma (see Fig. 27.5-1B).

Renal lymphoma is usually metastatic or from direct extension from lymphoma in adjacent retroperitoneal lymph nodes. Transitional cell carcinoma arises in the renal pelvis or ureter and presents sonographically as a filling defect in the renal collecting system (Fig. 27.5-2). Doppler and color Doppler US (CDUS) are useful to assess renal vein or inferior vena cava invasion (or both) by tumor (Fig. 27.5-3).

FIGURE 27.5-1. A: Sagittal sonogram of a right renal cyst (arrow). Note the echo-free appearance and smooth wall. B: Solid mass arising from the lower pole of the left kidney (arrows), compatible with renal cell carcinoma.
BLADDER

Transabdominal US permits gross evaluation of the bladder to assess for focal masses. US may have difficulty differentiating a hypertrophied median lobe of the prostate from a bladder mass. Cytoscopy is usually performed in cases of hematuria. Transurethral US may be used for staging of bladder cancers.

PROSTATE AND SEMINAL VESICLES

Analysis of transrectal ultrasonography as a screening tool for prostate cancer has been disappointing, due to the low specificity of a hypoechoic lesion for cancer. Likewise, sonographic criteria to predict extracapsular extension of disease or spread into the seminal vesicles have not been reliable, with sensitivities of 65% and 33%, respectively, in some series. Transrectal ultrasonography, however, is an excellent tool to detect mimics of cancer on digital rectal examination, such as cysts, calcification, or abscess, as well as a guidance modality for prostate biopsies and staging biopsies into the seminal vesicles.

TESTES

US can detect scrotal masses with an accuracy approaching 100%. The majority of intratesticular masses are malignant, whereas the majority of extratesticular lesions are benign or inflammatory in nature. Testicular tumors account for 1% to 2% of all malignant neoplasms in men and are the most common cancer in 25- to 35-year-olds. The majority of patients present with painless or mildly painful testicular enlargement. Between 90% and 95% of testicular neoplasms are of germ cell origin and include seminomas, embryonal cell cancer, teratomas, chorionicarcinomas, or mixed germ cell tumors. Leukemia and lymphoma are the most common metastatic tumors to the testis. Malignant lymphoma is the most common secondary neoplasm and most common testicular tumor in men older than 60 years. Most are non-Hodgkin’s lymphomas, and 50% of patients have extension into the spermatic cord. Leukemia is the most common metastatic testicular neoplasm. Leukemic infiltrates are common in children during bone marrow remission. The testis acts as a sanctuary during chemotherapy because of a blood–gonad barrier inhibiting concentration of chemotherapeutic agents. Other metastases to the testicle are prostate, melanoma, lung, kidney, colon, and pancreas. US is also used for the surveillance of contralateral testicles in patients with testicular tumors and to detect masses in patients with retroperitoneal masses of unknown origin.

FIGURE 27.5-2. Echogenic mass (arrows) filling the left renal collecting system, compatible with transitional cell carcinoma.

FIGURE 27.5-3. Tumor thrombus (arrow) extending into the inferior vena cava in a patient with metastatic leiomyosarcoma to the kidney.

FIGURE 27.5-4. Well-defined hypoechoic mass in the left testicle (arrows), compatible with seminoma. Note small, bright, echogenic foci of microlithiasis in the remainder of the testicle.

FIGURE 27.5-5. Transverse sonogram of both testicles demonstrating heterogeneous enlargement of the left testicle due to infiltration by B-cell lymphoma.
GYNECOLOGIC ONCOLOGY

OVARY

Ovarian cancer is the least frequent but the most lethal of the three common gynecologic malignancies. US has played an increasingly important role in the evaluation of the oncologic patient with an ovarian mass. Scoring systems to differentiate between benign and malignant masses have been reported to provide encouraging results in terms of sensitivity and negative predictive values (95% to 100%); however, significant limitations exist in terms of specificity (73% to 83%) and positive predictive values (32% to 46%). The likelihood of malignancy in an ovarian mass increases with size and complexity of the lesion. Simple cysts are almost always benign. The role of US for screening of early ovarian carcinoma needs yet to be defined. Doppler and CDUS endovaginal techniques to assess blood flow parameters are encouraging; however, the role of endovaginal CDUS for the evaluation of ovarian cancer is controversial, with limited sensitivity and specificity of this technique due to overlaps of flow velocity indices in benign and malignant ovarian masses. US is useful to assess local or distant spread and detect ascites. In clinical practice, US is most often used to confirm the presence of an adnexal mass, often with characteristics of malignancy.

ENDOMETRIUM

Endometrial cancer is the most common gynecologic malignancy in the United States. Most patients present with postmenopausal bleeding. On endovaginal US, the endometrium is thickened, inhomogeneous in echotexture, and with irregular hypoechoic areas throughout. Endovaginal US is helpful in staging the degree of myometrial invasion: The presence of an intact subendometrial halo suggests superficial carcinoma without myometrial penetration. With advanced invasive cancers, the myometrium becomes heterogeneous, with echogenic areas, and the uterus may have a lobulated appearance. Hysterosonography (instillation of sterile saline into the uterine cavity) allows better detection and characterization of underlying pathology in a patient with a thickened endometrium.

GESTATIONAL TROPHOBlastic DISEASE

US has long been the first imaging study to diagnose molar pregnancy, demonstrating hypoechoic grape-like intrauterine structures during the first or second trimester. Recent studies have also demonstrated the use of endovaginal Doppler and color Doppler flow studies in assessing myometrial invasion in patients with persistent human chorionic gonadotropin elevation after dilatation and curettage.

BREAST

Breast US with high-frequency probes (7 to 13 mHz) is most often used to differentiate a cystic from a solid mass detected on palpation or mammography. Recent reports have demonstrated the utility of US to differentiate benign from malignant masses, therefore limiting the need to perform a biopsy on lesions with benign features, such as sharp margins, circumscribed borders, homogeneous internal echotexture and a horizontal orientation of the lesion. Doppler and CDUS studies to differentiate benign from malignant masses are under way. US is an exquisite guidance modality for preoperative needle localization or core biopsy of sonographically visualized and nonpalpable breast masses.

MEDICAL ONCOLOGY

LIVER

Liver and biliary cancers account for only 1.5% of all gastrointestinal malignancies in the United States. Liver cancers are more common in China and Africa, because of higher endemic hepatitis B carrier rates. In the United States, 60% of hepatocellular carcinoma are associated with underlying liver cirrhosis. Hepatic US in conjunction with serum a-fetoprotein has been used to screen patients in Asia and Europe. Sonography in high-risk patients can detect lesions as small as 1 cm in diameter. The sonographic appearance varies with the histologic composition and size. Tumor invasion of the hepatic and portal veins may be demonstrated by CDUS. Most often, biopsy is necessary to make the definitive diagnosis and differentiate these from other benign and malignant liver masses. Hepatic lymphoma is an infiltrative neoplasm, sonographically presenting as focal, multifocal, or diffuse infiltration, often as hypoechoic masses or ill-defined areas of mixed echogenicity. Metastases to the liver may be hypoechoic, hyperechoic, or show a diffuse infiltrative pattern. Most common primary tumors are gastrointestinal, renal, pancreas, breast, lung, and thyroid cancer.

FIGURE 27.5-7. Sagittal sonogram of the right hepatic lobe containing a heterogeneous mass in this patient 9 years after heart transplantation. Biopsy demonstrated hepatic lymphoma.
GALLBLADDER–BILIARY TREE

Gallbladder carcinoma usually presents with advanced disease. Sonographically, a focal wall mass protruding into the lumen or a diffuse infiltrative mass in the bed may be seen (Fig. 27.5-8). Cholangiocarcinoma may be intrahepatic, nodular, and mass-forming, or it may be infiltrative along the intra- and extrahepatic bile ducts. On US, it is seen as a heterogeneous hypoechoic mass, with or without ductal dilatation.

**FIGURE 27.5-8.** Sagittal sonogram of the gallbladder in patient with gallbladder carcinoma demonstrating thickening of the fundal wall, with mass protruding into the lumen (arrows).

PANCREAS

Pancreatic cancers include exocrine, endocrine, and cystic neoplasms and most commonly an adenocarcinoma of the exocrine duct. The tumor invades adjacent structures and vessels and commonly metastasizes to the liver. Patients most frequently present with obstructive jaundice. On US, a pancreatic mass, frequently hypoechoic, and a dilated common bile duct and pancreatic duct are identified. Sonography is less sensitive in imaging carcinoma of the body and tail of the pancreas because of overlying bowel gas. Pancreatic endocrine tumors, usually islet cell tumors, may present as small, hypoechoic masses in the gland. Mucinous cystic neoplasms may contain central calcifications. Pancreatic cancers are usually best imaged with CT and biopsied preferably by US, sometimes, however, with CT guidance (Fig. 27.5-9).

**FIGURE 27.5-9.** Focal mass in the pancreatic head (cross-hair) proven to be metastatic rhabdomyosarcoma. Linear echogenic lines represent indwelling biliary stent.

ENDOCRINE

Thyroid nodules are not infrequently detected during US performed to evaluate the carotid arteries or in patients with abnormal thyroid function tests or palpable abnormalities. Solitary or suspicious, complex masses are usually biopsied under US guidance. Local lymph node involvement in thyroid malignancies can be exquisitely demonstrated with high-resolution US. Postthyroidectomy local recurrence or lymph node spread can be imaged and proven by US guided biopsy.

Adrenal malignancies are most commonly adrenocortical carcinoma and pheochromocytoma. CT is usually the mainstay for the evaluation of adrenal masses because of its high sensitivity and simultaneous ability to accurately stage extension into adjacent structures. US may be the study on which an adrenal mass is detected incidentally. Small masses are homogeneous, and tumors become progressively heterogeneous with enlargement, due to necrosis and hemorrhage. Right adrenal masses can cause anterior displacement of the inferior vena cava. Metastases from lung primaries are common to the adrenal gland. However, in larger series, one-third to two-thirds of patients with adrenal masses and lung cancer had incidental nonfunctioning adenomas. Fine-needle aspiration biopsy is normally performed in these patients to establish the diagnosis of metastases.

BONE MARROW TRANSPLANT

Sonography is frequently used to evaluate complications of high-dose therapy in bone marrow transplant patients, such as hepatic venoocclusive disease or hemorrhagic cystitis.

**Hepatic Venoocclusive Disease**

Hepatic venoocclusive disease is caused by high-dose chemotherapy prior to bone marrow transplant salvage. Toxicity to the liver results in hepatic edema, venous compression, and stagnation, with ultimately occlusion of the small hepatic veins. Imaging with CDUS may demonstrate a heterogeneous and enlarged liver, ascites, a thick-walled gallbladder, elevated hepatic artery resistive index (>0.8), decreased hepatic vein flow, and pulsatile or reversal of portal vein flow.

**Hemorrhagic Cystitis**

Hemorrhagic cystitis is caused by the toxic effect of high-dose steroids to the urothelium, resulting in severe cystitis, hemorrhage, and bladder necrosis. On US, the bladder wall is thickened, and blood clots can be seen as intravesical masses. US is also useful to assess the effectiveness of therapy.
FIGURE 27.5-10. Vesical ultrasonography in a patient with hemorrhagic cystitis. Note bladder wall thickening and heterogeneous mass in the bladder compatible with a large blood clot.

ACQUIRED IMMUNODEFICIENCY SYNDROME MALIGNANCIES

The most common neoplasms related to acquired immunodeficiency syndrome (AIDS) are Kaposi’s sarcoma and non-Hodgkin’s lymphoma. Other malignancies include cervical carcinoma, bronchogenic carcinoma, and Hodgkin’s lymphoma with an unusual or aggressive presentation. AIDS patients are also at higher risk to develop testicular neoplasms, such as germ cell tumors or AIDS-related lymphoma (ARL).

Kaposi’s Sarcoma

In AIDS, Kaposi’s sarcoma is an aggressive multifocal neoplasm arising from lymphatic endothelial cells. It can involve skin, lymph nodes, gastrointestinal tract, liver, spleen, lung, and pleura. On US, focal liver or splenic masses or infiltrative lesions can be seen. Infiltrative lesions may also be present in the kidney, adrenal, bladder, or prostate.

Acquired Immunodeficiency Syndrome–Related Lymphoma

Isolated or bulky adenopathy is rare and favors chronic infections, such as Mycobacterium avium–intracellulare and tuberculosis. Extranodal disease usually involves the gastrointestinal tract, liver, spleen, lung, and adrenal gland. Chest wall disease involving the spine and sternum as well as pleural effusions are common. On US, hepatic and splenic involvement present as solitary or multiple hypoechoic nodules, which may appear cystic. Renal involvement may demonstrate bilateral parenchymal or perirenal masses. The differential diagnosis for such lesions includes renal cell carcinoma, tuberculosis, candidiasis, aspergillosis, or pyogenic abscesses.

VENOUS COMPLICATIONS

US has become the standard primary imaging technique for the initial evaluation of patients with the clinical suspicion of deep venous thrombosis (DVT) of the extremity veins. Predisposing factors for DVT in the oncologic patient include paraneoplastic syndrome; immobilization; compression or direct invasion by the primary tumor or metastatic masses (pelvis, chest, Pancoast tumor); radiotherapy; and indwelling catheters or stents. The hallmark finding of acute DVT on gray scale, Doppler, and CDUS include distention and noncompressibility of vessels and direct visualization of tumor thrombus. In long-standing venous occlusion, abundant collateral vessels may be seen on US.

ULTRASONOGRAPHICALLY GUIDED INTERVENTIONAL PROCEDURES

Accurate characterization and staging of malignancies has become increasingly important for cancer patients to avail themselves of the increasing advances in treatment options. Precise localization of disease process by fluoroscopy US, CT, and magnetic resonance imaging have made possible percutaneous biopsies, aspirations of fluid collections, abscess drainages, nephrostomy, and stent placement as well as vascular access in many organ systems of the oncology patient. Advances in cytopathology diagnostic techniques and the development of smaller and safer needles coupled with cross-sectional image guidance, particularly US, facilitate accurate and safe needle placement in formerly inaccessible sites. Most biopsies in the oncology patient are performed to confirm malignancy in a radiographically suspicious lesion or to obtain a tissue diagnosis in an indeterminate lesion. Growing experience with US as a guidance modality has greatly expanded the role and scope of US-guided interventional masses in deep abdominal and superficial masses, thoracic and mediastinal applications. Specific biopsy applications include liver (Fig. 27.5-11) and pancreas; renal, adrenal, retroperitoneal, splenic, neck, and musculoskeletal masses; as well as selected thoracic lesions when pleura-based or mediastinal (Fig. 27.5-12); breast lesions; endocavitary biopsy (endorectal, endovaginal); and recently intraoperative or percutaneous ablations (ethanol, cryosurgery, radiofrequency, laser, and microwave) for hepatic, renal, and prostate lesions.

FIGURE 27.5-11. Ultrasonographically guided percutaneous biopsy of a small mass in the liver proved to be metastatic pancreatic carcinoma. Note biopsy trajectory (dotted lines).

FIGURE 27.5-12. A: Computed tomography scan of the chest demonstrating small, left-sided posterior pleural-based lung nodule. B: Same nodule imaged by ultrasonography as a hypoechoic mass (between dotted lines). Ultrasonographically guided biopsy revealed metastatic squamous cell carcinoma to the lung.
US is an ideal guidance modality for interventional procedures for various reasons. It allows real-time display throughout the procedure with unlimited scan plans, thus allowing creative patient positioning. Speed of the procedure; CDUS for vessel visualization; direct pressure over the lesion with the transducer in case of bleed; portability; lower cost; and nonionizing irradiation are other advantages of US. Future applications include percutaneous US-guided delivery of chemotherapy agents, drug delivery, and gene therapy as well as organ-specific delivery of substances in conjunction with contrast agents and directed local bubble destruction.

SUMMARY
US plays an important role in the diagnostic evaluation and management of cancer patients. With further advances in technology and an ever-increasing variety of therapeutic options, its use in the oncology patient will expand in the future.

CHAPTER REFERENCES
SECTION 27.6
Radionuclide Imaging

E. EDMUND KIM

INTRODUCTION

The development of molecular biology and genetics since the late 1970s has provided medical science with an unprecedented chance to understand the molecular basis of disease. Although disease is usually defined as gross structural or histopathologic abnormality, it can now be defined on the basis of abnormal deviation from normal regional biochemistry. Molecular derangements occur at the very beginning of disease processes, and anatomically detectable abnormalities occur much later.

Cancer is viewed as a failure of multiple chemical processes or genetic disease. The care of cancer patients has become a cooperative multidisciplinary endeavor. A multidisciplinary approach to the diagnosis, staging, treatment, and follow-up of cancer takes a great deal of effort, but the rewards to patients and oncologists are tremendous. It is critical for imaging specialists to embrace and participate in the multidisciplinary environment so that they are considered valued and equal partners.

Advanced imaging techniques have made it possible to diagnose localized abnormalities, often before they have produced irreversible damage. Cancers too small to be detected by physical examination can be pinpointed by imaging and treated before metastasis has occurred. Most imaging methods reveal the anatomic extent of an organ or of an abnormality within an organ. Many masses cannot be characterized clearly with imaging studies. This may be a problem when attempting to distinguish residual viable tumor from fibrosis.

Many radionuclide studies have been performed for the detection of primary and metastatic tumors. Most are organ- or receptor-specific but not tumor-specific. A few studies are highly tissue-specific, such as thyroid scans using iodine 131 sodium iodide and adrenal scans using 131I metaiodobenzylguanidine (MIBG) or 6-b-iodomethyl-19-norcholesterol. Radiolabeled antibodies and peptides are potentially tumor-specific. With nonspecific limited agents, abnormalities on scans represent alteration or displacement of normal tissue, and additional scans with other agents are often necessary to evaluate potential involvement of other organs. Extensive effort has been directed toward the development of specific general agents that ideally would be taken up specifically by tumor and that could be used for a broad spectrum of tumor types.

INDIRECT RADIONUCLIDE TUMOR IMAGING

NUCLEAR BONE SCANS

The bisphosphonate bone scan is the most frequently performed radionuclide study, and it is used for the early detection of metastatic bone disease. The positive bone scan (Fig. 27.6-1) reflects levels of blood flow and osteoblastic formation. Magnetic resonance imaging (MRI) has a greater sensitivity and specificity than bone scans in detecting metastatic foci, but bone scans remain the choice for initial screening of bony metastasis because of its ability to easily assess the whole body and because of its availability. In the follow-up of bony metastases, the flare phenomenon, in which the patient's clinical condition is improving but the bone scan is worsening, has been described in up to 20% of patients after a therapeutic intervention. Bone single photon emission computed tomography (SPECT) has been helpful and complementary in differentiating degenerative joint disease or facet syndrome from metastasis. Extraskeletal uptake of technetium 99m methylene diphosphonate (MDP) has been reported in many malignant tumors with calcification or increased vascularity. Severe bone pain can be a particularly debilitating effect of metastatic disease. Strontium 89 chloride, samarium 153 ethylene diamine tetramethane phosphoric acid (EDTMP), and rhenium 186 hydroxy ethylene diphosphonic acid (HEDP) and Sn-117m DTPA (diethyleneetriamine pentaacetic acid) have been effective in reducing pain in breast and prostate cancer patients.

FIGURE 27.6-1. Whole body anterior (A) and posterior (P) images of follow-up bone scans using technetium 99m methylene diphosphonate show focal areas of abnormally increased activities in the left humeral head, T7, T8, T12, left sacrum, and left anterior second rib end, indicating active metastatic lesions. Note also the diffusely increased renal activities suggesting nephrotoxicity in a patient with breast cancer.

NUCLEAR LIVER SCANS

Cavernous hemangioma is the most common benign tumor of the liver and consists of dilated endothelium-lined blood-filled spaces. Increasing focal activity over 1 to 2 hours after injection of 99mTc red blood cells is a typical diagnostic finding. SPECT is cost effective in demonstrating hemangiomas greater than 1 cm when CT or MRI findings are questionable.

Hepatic adenoma and focal nodular hyperplasia show a contrast enhancement on CT or MRI. The adenoma presents as a cold defect on 99mTc sulfur colloid liver-spleen scans but shows an uptake of 99mTc iminodiacetic acid hepatobiliary agent because no Kupffer cell is present. On the other hand, focal nodular hyperplasia demonstrates uptake of 99mTc sulfur colloid because of the presence of Kupffer cells.

HEPATIC PERFUSION SCANS

The technetium 99m iminodiacetic acid hepatobiliary agent is taken up by the liver. Magnetic resonance imaging (MRI) has a greater sensitivity and specificity than bone scans in detecting metastatic foci, but bone scans remain the choice for initial screening of bony metastasis because of its ability to easily assess the whole body and because of its availability. In the follow-up of bony metastases, the flare phenomenon, in which the patient's clinical condition is improving but the bone scan is worsening, has been described in up to 20% of patients after a therapeutic intervention. Bone single photon emission computed tomography (SPECT) has been helpful and complementary in differentiating degenerative joint disease or facet syndrome from metastasis. Extraskeletal uptake of technetium 99m methylene diphosphonate (MDP) has been reported in many malignant tumors with calcification or increased vascularity. Severe bone pain can be a particularly debilitating effect of metastatic disease. Strontium 89 chloride, samarium 153 ethylene diamine tetramethane phosphoric acid (EDTMP), and rhenium 186 hydroxy ethylene diphosphonic acid (HEDP) and Sn-117m DTPA (diethyleneetriamine pentaacetic acid) have been effective in reducing pain in breast and prostate cancer patients.

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Intraarterial chemotherapy has been used to treat many tumors in an effort to obtain better results than with systemic chemotherapy. Hepatic tumors derive 99% of their blood supply from the hepatic artery. \(^{99m}\text{Tc}\) macroaggregated albumin, usually 10 to 90 mm, is trapped in the first capillary bed and has been useful to detect misplaced or displaced hepatic arterial catheters that require repositioning.

**NUCLEAR CARDIOVASCULAR IMAGING**

In patients undergoing chemotherapy with doxorubicin (Adriamycin), one risk is developing cardiotoxicity. Radionuclide ventriculography using \(^{99m}\text{Tc}\) red blood cells provides the left ventricular ejection fraction, and a 10% to 15% decrease of left ventricular ejection fraction or a decrease to less than 45% is considered significant.

Chemotherapy or catheterization increases the risk for thrombus formation in cancer patients. Radionuclide venograms using \(^{99m}\text{Tc}\) macroaggregated albumin for lower extremities and \(^{99m}\text{Tc}\) sulfur colloid or DTPA for upper extremities have been useful in screening hemodynamically significant venous obstruction. \(^{99m}\text{Tc}\) P-829 peptide accumulated in the platelet receptor is now being used to detect acute venous thrombosis.

**LYMPHOSCINTIGRAPHY**

Approximately 20% of melanoma patients do have clinically undetectable micrometastases in the lymph nodes, and the presence of metastases in the sentinel (first draining) node indicates the need for a regional lymph node dissection. A dose of 0.5 mCi \(^{201}\text{Tl}\) sulfur colloid in 0.25 mL is injected intradermally around the melanoma site, and the lymphatic flow is imaged dynamically for 30 minutes. Subsequent static images demonstrate the draining regional node basin and the location of the sentinel node. The status of regional lymph node remains the most powerful predictor of survival in women with invasive breast cancer. Approximately 14% to 37% of small (less than 1 cm) invasive cancers may have axillary nodal metastases. Lymphatic drainage from breast cancer can be mapped to regional lymph nodes pre- or intraoperatively. The technique involves peritumoral injection of 0.5 mCi \(^{99m}\text{Tc}\) sulfur colloid and gamma camera imaging or gamma detection probe. In one study, the sentinel lymph node was identified in 92% of patients, and 32% of them were found to have metastatic diseases.

**DIRECT RADIONUCLIDE TUMOR IMAGING**

**GALLIUM 67 CITRATE SCANS**

Gallium 67 citrate has been known to be taken up in varying degrees by many other tumors, and \(^{67}\text{Ga}\) scans have been useful as a marker of tumor viability and for evaluating the effectiveness of radiotherapy or chemotherapy. \(^{67}\text{Ga}\) citrate binds to serum transferrin, ferritin, and lactoferrin. Approximately 15% to 25% is excreted by kidneys within 24 to 48 hours, and 30% to 40% is cleared slowly through the intestinal tract. \(^{67}\text{Ga}\) citrate localizes normally within the reticuloendothelial system and lacrimal and salivary glands. A dose of 5 to 10 mCi is usually recommended for tumor imaging. High-resolution whole body images (Fig. 27.6-2) and SPECT of chest or abdomen are obtained at 48 to 72 hours.

**THALLIUM 201 AND TECHNETIUM 99M SESTAMIBI SCANS**

Thallium 201 behaves in a manner that is biologically similar to potassium. Tumor blood flow influences the uptake of \(^{201}\text{Tl}\) by tumors, probably related to the action of the adenosine triphosphatase system in the cell membrane. \(^{201}\text{Tl}\) is accumulated by viable tumor tissue, and its uptake correlates with the grade of histopathologic differentiation. Planar and SPECT imaging of the lesion is usually obtained at 10 to 30 minutes after the injection of 3 mCi. \(^{201}\text{Tl}\) chloride. \(^{201}\text{Tl}\) scans have been used to determine viability when CT or MRI cannot differentiate residual or recurrent brain or lung tumors from posttreatment changes or infectious lesions (Fig. 27.6-3). \(^{201}\text{Tl}\) indices, count-density ratios of tumor to nontumor area, were significantly higher in high-grade tumors than in those patients with low-grade tumors. \(^{201}\text{Tl}\) is usually taken up only by tumors, whereas \(^{99m}\text{Tc}\) is taken up in both tumor and inflammatory lesions. \(^{201}\text{Tl}\) appears valuable in detecting low-grade non-Hodgkin’s lymphoma and also Kasabian’s sarcoma. Some studies have found the \(^{201}\text{Tl}\) scan to be more sensitive than the \(^{131}\text{I}\) scan in the detection of thyroid cancer, although \(^{201}\text{Tl}\) is not specific for thyroid cancer and does not give predictive information on the therapeutic potential of 1 sodium iodide.

**FIGURE 27.6-2.** Whole body anterior (A) and posterior (P) images of follow-up gallium scans show focal areas of abnormally increased uptake of gallium 67 citrate (arrows) in the right upper and lower lungs, indicating active lymphomatous lesions confirmed by biopsy.

**FIGURE 27.6-3.** A: Axial T1-weighted magnetic resonance images of the head show a contrast-enhanced lesion (arrow) in the right frontal lobe in a patient who had a treatment for anaplastic astrocytoma. B: Selected coronal (upper left), sagittal (upper right), and axial (lower left) single photon emission computed tomography images using thallium 201 chloride show a focal area of markedly increased activity (arrow) in the right frontal lobe, indicating active malignant tumor. Biopsy confirmed a recurrent anaplastic astrocytoma.
**NUCLEAR THYROID AND ADRENAL IMAGING**

During the 1990s, it has become apparent that the most cost-effective diagnostic workup of a thyroid nodule is fine-needle aspiration. However, histologic and cellular details of endocrine tumors do not always establish the diagnosis of carcinoma. Both papillary and follicular cancers retain, to varying degrees, the ability to concentrate radioiodine. Medullary and anaplastic carcinomas do not concentrate radioiodine. All types of thyroid cancer do not concentrate radioiodine as avidly as normal thyroid tissue. To enhance radioiodine uptake by thyroid cancer, high levels of circulating thyroid-stimulating hormone are desired (more than 30 µIU/mL).

Radioiodine uptake is ideal for imaging because of short physical half-life (13 hours) and optimal photon energy (159 keV). However, it is relatively expensive, and the thyroid imaging is usually performed at 4 to 6 hours after the oral administration of 0.2 mCi. 99mTc sodium pertechnetate is cheap and ideal for early (30 minutes) imaging with good physical properties (6-hour half-life: 140 keV optimal photon energy), although it is only trapped and not organified. Indications of radionuclide thyroid imaging are functional evaluation of palpable nodules, detection of the primary tumor in patients with known regional or distant thyroid metastases, detection of thyroid cancer metastases, and assessment of thyroid treatments. Nonfunctioning cold nodules are common, and 6% to 20% of them are usually malignant. 12

Phaeochromocytoma is a tumor of adrenal medulla or sympathetic nervous tissues. Approximately 10% occur in children, 10% are familial, 10% are malignant, 10% are multifocal, and 10% are extraadrenal. CT or MRI is useful in detecting intraadrenal or other abdominal masses. MIBG is an analogue of guanethidine and localizes in cytoplasmic storage vesicles in presynaptic adrenergic nerves through the active amine transport mechanism. 125I- or 131I-labeled MIBG has been useful in surveying the entire body for the localization of phaeochromocytoma or paraganglioma. 12

**ANTIBODY AND PEPTIDE IMAGING**

Antibodies are glycoproteins produced by plasma cells after exposure to a foreign antigen. Many tumors have antigens expressed on their cell surfaces, thus allowing antibody targeting. Major roles of immunoscintigraphy using indium 111 anti-Tag-12 (Oncoscint, CytoGen Co., Princeton, NJ) or 99mTc anti–carcinoembryonic antigen (CEA) (CEA-scan, Immunomedics Co., Morris Plains, NJ) (Fig. 27.6-4) in colon cancer are: (1) detection of recurrent disease in patients with elevated serum CEA level, and either negative workup or equivocal findings on CT or MRI; (2) differential diagnosis of residual or recurrent disease from posttreatment changes; and (3) exclusion of extraabdominal disease before planned resection of a presumably isolated recurrence. 111In antiprotein hormone antibody (ProstaScint, CytoGen Co.) scans are indicated for patients with proven prostate cancer thought to be localized clinically after standard diagnostic evaluation who are at risk for pelvic node metastasis. It is also indicated in prostate cancer patients with a rising prostate-specific antigen level and negative or equivocal standard metastatic evaluation. Antibody scans generally revealed 70 to 80 T diagnostic sensitivities and should be interpreted in conjunction with CT or MRI studies. 12 Natural somatostatin is a tetradecapeptide produced by hypothalamus and pancreas. Five subtypes of human somatostatin-release inhibiting factor receptors, termed somatostatin type receptors (SSTRs), are expressed on many tumors, and SSTR2 is the predominant subtype. Tumors that have been found to express SSTRs include small cell lung cancer, endocrine pancreatic tumor, carcinoïd, pilar adenoma, paraganglioma, lymphoma, and meningioma. Octreotide is a synthetic somatostatin-release inhibiting factor analogue that has been used for treating gastroenteropancreatic tumors. 111In pentetreotide (Octreoscan, Mallinckrodt Co., Hazelwood, MO) has been helpful for detecting neuroendocrine tumors and evaluating their therapeutic response. 99mTc-P-829 peptide has been approved to image somatostatin receptors in lungs. 12

**FIGURE 27.6-4.** Anterior whole body images at 2 (left) and 20 (right) hours after the injection of technetium 99m anti–carcinoembryonic antigen (CEA) show focal areas of abnormally increased activity in the left inguinal (closed arrow) and iliac (open arrow) lymphatic chains in a patient with colon carcinoma and rising serum CEA levels. Note the cystic lesions in the left kidney.

**CHAPTER REFERENCES**

CHAPTER 28
Cancer Diagnosis: Endoscopy

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Upper Gastrointestinal Endoscopy
Diagnostic Upper Gastrointestinal Endoscopy
Therapeutic Upper Gastrointestinal Endoscopy
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Indications and Results
Endoscopic Ultrasonography
Principles
Indications and Results
Diagnostic Endoscopy
Therapeutic Endoscopy: Polypectomy
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Laparoscopy
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Complications
Endoscopic Retrograde Cholangiopancreatography
Therapeutic Endoscopic Retrograde Cholangiopancreatography
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Anterior Mediastinotomy (Chamberlain Procedure)
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Therapeutic Upper Gastrointestinal Endoscopy
Diagnostic Upper Gastrointestinal Endoscopy
Complications
Upper Gastrointestinal Endoscopy

UPPER GASTROINTESTINAL ENDOSCOPY

Endoscopy is a rapidly advancing field. Video-recording or electronic instruments use microchip technology to capture high-resolution digitized endoscopic images, leading to more accurate diagnoses and greater ease in documentation and analysis. Many internal organs can be examined by endoscopy with video documentation, endoscopic biopsy, cytology, and endoscopic sonography to determine diagnosis, operability, and staging.

Although diagnostic endoscopy remains the major component of any endoscopy program, therapeutic endoscopy is rapidly catching up. Endoscopic removal of polyps, tumor ablation with laser therapy, luminal stents, control of hemorrhage, relief of biliary obstruction, and enteral nutritional support through endoscopically placed tubes are but some of the therapeutic uses of endoscopy available at large medical centers.

Upper gastrointestinal (GI) endoscopy is the procedure of choice for the diagnosis of symptomatic esophagogastric neoplasia. Benign upper GI conditions that can mimic or complicate cancer are accurately diagnosed. Endoscopy is often the initial diagnostic procedure rather than a follow-up to radiologic examination. Upper GI endoscopes are thin and highly maneuverable, making upper endoscopy comfortable and rapid. Upper GI endoscopy requires only mild sedation and is safe for the patient. Although upper GI endoscopy is more invasive and more expensive than barium upper GI radiography, it is also more accurate and may avoid multiple procedures, with their associated added costs. There is no exposure to radiation, and complications are rare. The ability to perform guided mucosal biopsy and cytology provides tissue diagnosis to complement high-resolution observation and photography.

DIAGNOSTIC UPPER GASTROINTESTINAL ENDOSCOPY

The diagnostic accuracy of endoscopy and biopsy for primary and metastatic upper GI cancer is in the range of 95%. Infiltrating cancers may be less successfully subjected to biopsy, although a tissue diagnosis is still achieved in most cases with large biopsy forceps and needle aspiration cytology. Endoscopy is recommended in all patients with gastric ulcers found on upper GI series, because some benign-appearing gastric ulcers are malignant. If suspicion remains, repeat endoscopy is indicated in 6 to 8 weeks. This is not the case in duodenal ulcer disease, which is only rarely due to cancer, and endoscopy solely to diagnose Helicobacter pylori infection is not recommended.

Patients with an identifiable high risk for upper GI cancer, such as those with Barrett's esophagus, prior gastric adenomas, or previous partial gastrectomy, may be considered for periodic screening endoscopy, although the benefits of such screening remain controversial. When high-grade dysplasia is identified on endoscopic biopsy of either the stomach or Barrett's esophagus, surgical management should be considered because there is a high likelihood of developing invasive cancer.

In northern China, where chronic esophagitis and epidermoid carcinoma of the esophagus are endemic, population screening programs for esophageal cancer have been carried out on a large scale with promising results. Screening has been based on esophageal cytology and confirmation with endoscopy. Using these methods, early-stage esophageal cancers with good probability for surgical cure have been detected in asymptomatic persons. Similar screening programs, carried out in heavy smokers and drinkers in the United States, have not proven effective. Endoscopy has identified early asymptomatic esophageal cancer in up to 5% of patients with cancers of the head and neck who are also at risk for esophageal cancer. Endoscopic staining of the esophagus with Lugol's iodine solution before endoscopy may help in detecting small areas of squamous cell malignancy.

In Japan, where gastric cancer is a leading cause of death, mass population screening with radiography and endoscopy has led to a major improvement in the detection of early disease and subsequent survival. Distal gastric cancer in America and Europe has been decreasing in incidence, but there is an increase in cancers affecting the proximal stomach and an increasing incidence of early gastric cancer detection. Mass screening is not practical or economically feasible in low-incidence Western countries; the increased detection of early gastric cancer has been attributed to greater physician sensitivity to suggestive symptoms and more aggressive application of radiologic and endoscopic methods.
Whether patients with partial gastrectomy for benign disease are at long-term risk for gastric cancer and merit endoscopic screening is also an open question but, in patients who have dysplasia on endoscopic biopsy, endoscopic surveillance is indicated. 13

Periodic endoscopic surveillance of the stomach and duodenum in patients with familial adenomatous polyposis (FAP) and Gardner’s syndrome is recommended, including the use of a side-viewing duodenoscope for better visualization of the periampullary area. Adenomas of the duodenum are common in patients with FAP. In such cases, the adenomas tend to be very flat and may be numerous. 14 Carcinoma in the duodenum, most often periampullary, has become a major cause of death in patients with FAP who have had a colectomy.

New endoscopic technology is continually being developed. Fluorescence spectroscopy is one such advance currently in clinical trials. Laser-generated light of a specific wavelength is used to stimulate tissue during endoscopy. Differential fluorescence can be detected from benign, dysplastic, and malignant GI tissues. This technology may become a complement to histopathology, especially in sampling large areas of the GI tract before endoscopic biopsy. 17

As a rule, endoscopy is most effective in evaluating intraluminal GI disease, focal and diffuse, benign and malignant. The procedure can be informative but is less effective in assessing abnormal motility, extrinsic compression by contiguous structures, and degree of luminal obstruction. Barium radiologic and computed tomography (CT) scans provide not only better evaluation of extrinsic lesions that are causing compression and contour defects in the GI tract but better assessment of the degree of obstruction.

**THERAPEUTIC UPPER GASTROINTESTINAL ENDOSCOPY**

Therapeutic applications of endoscopy include the placement of guidewires, stents, and balloons for the following purposes 18-20:

1. Dilation of benign and malignant strictures
2. Removal of foreign bodies
3. Removal of polyps by electrocautery
4. Endoscopic strip biopsy of small cancers
5. Vaporization and coagulation of cancerous tissues with neodymium:yttrium aluminum garnet (Nd:YAG) laser or with photodynamic therapy
6. Control of bleeding with electrocautery, heat, or laser probes
7. Injection of epinephrine and sclerosant solutions via needle-tipped catheters for tumor necrosis or treatment of bleeding

In patients with advanced, unresectable cancer of the esophagus or gastric cardia that is unresponsive to primary treatment, endoscopic therapy has assumed a major role in the palliation of concomitant dysphagia. The mainstays of endoscopic palliation have been the placement of endoprostheses, using either plastic stents or self-expanding metallic stents, and laser ablation with Nd:YAG laser energy. There are advantages and disadvantages to both methods. In approximately 70% of patients, laser therapy is more likely to allow a normal diet, but it must be repeated at frequent intervals. Although outpatient treatment is possible, laser sessions become increasingly time-consuming and uncomfortable for the patient as the cancer progresses. Esophageal strictures ideally provide a longer-lasting palliation, and they are the treatment of choice for tumors that are primarily infiltrating, submucosal, or extrinsic. They can be used anywhere in the esophagus except near the proximal sphincter. Endoluminal stents are also useful for sealing fistulas into the tracheobronchial tree. In most centers where an Nd:YAG laser is available, laser therapy is performed first, particularly if there is bulky intraluminal tumor. However, some groups preferentially palliate esophageal and esophagogastric malignant stenoses with stents. This is especially true with the advent of self-expanding metal stents, which are easier to insert, cause less trauma, carry a lower perforation rate, but are more expensive initially than polyvinyl stents. Complications, mostly perforations, occur in approximately 5% of those treated with laser and 5% to 18% of those treated with stents. 18-20

Photodynamic therapy (PDT) uses both photochemical sensitizers that preferentially concentrate in neoplastic tissue and low-powered laser light activation. This technique is, in theory, more selective and safer than the Nd:YAG laser treatment. However, one multicenter study 21 of advanced esophageal cancer showed no difference when the cancers were treated with either PDT or Nd:YAG laser. Perhaps the most effective use of PDT will be in the management of early cancers or premalignant conditions such as Barrett’s esophagus. 21-22

**COMPLICATIONS**

Upper GI endoscopy is a very safe procedure with few contraindications and only rare complications. The probability of GI perforation is less than 0.1%. 2 This procedure can be performed safely even in patients on anticoagulants or with nadir blood counts, although therapeutic options in these patients may be limited. In weakened or comatose patients, there is an increased risk of aspiration pneumonia.

**ENDOSCOPIC ULTRASONOGRAPHY**

**PRINCIPLES**

Endoscopic ultrasonography (EUS) is an important new extension of diagnostic GI endoscopy. Using this modality, it is possible for the endoscopist to assess not only mucosal lesions but intramural disease processes deep to the mucosa and extrinsic abnormalities in proximity to the wall of the GI tract. 22-24

EUS uses high-frequency ultrasound (more than 7 MHz) for high resolution, producing detailed views of the GI wall and surrounding structures that are unmatched by other imaging methods. The higher the ultrasound frequency, the shorter the penetration depth of ultrasound and the more limited the field of view. However, with EUS a limited field is acceptable, because the transducer can be placed immediately adjacent to the area of interest.

Using EUS, the wall of the GI tract can be imaged as a five-layer structure of alternating bright (hyperechoic) and dark (hypoechoic) bands (Fig. 28-1). The echogenic layers consist in part of interface echoes produced as the sound waves travel between tissues of differing densities. 2 For clinical purposes, the first two layers correspond to the superficial and deep mucosa, the third layer to the submucosa, the fourth to the muscularis propria, and the fifth to the serosa or adventitia.

**FIGURE 28-1.** Endosonographic image of the normal gastric wall. The concentric circles in the center represent the transducer and water-filled balloon in the lumen of the stomach. From the lumen, the first two wall layers correlate with the superficial and deep mucosa (m), the third wall layer represents the submucosa (sm), the fourth layer is the muscularis propria (mp), and the fifth layer is the serosa (s).

Most clinical studies have been carried out using mechanical sector scan instruments manufactured by the Olympus Corporation, Melville, NY, principally the GF-UM3 instrument. These instruments are combination endoscopes and ultrasound probes that use an acoustic mirror rotating around a transducer with switchable 7.5- and
12-MHz frequencies and produce a 360-degree image. In the tubular GI tract, this greatly facilitates orientation of the image. Optics are forward oblique, but the 4-cm rigid tip and the 13-mm diameter make the instrument somewhat difficult to use and limit passage through tightly stenotic areas.

Instruments using linear- or phased-array technology have the advantages of forward-viewing optics and an absence of moving parts but provide a slice-like image, which can make orientation more difficult. Pentax Precision Instruments, Orangeberg, NY, manufactures a linear-array 5- and 7.5-MHz ultrasound endoscope (FG-32UA). Doppler ultrasound technology, to aid in evaluation of vascularity and blood flow, is easily obtained on ultrasound instruments. Blind endosonography probes, rigid and flexible, mechanical and electronic, have been used in the rectum and in the esophagus. Ultrathin miniprobeS that can be passed through an endoscope biopsy channel have also been developed. They have a restricted field of view and often produce less-than-satisfactory images.

INDICATIONS AND RESULTS

EUS has been applied most extensively to the staging of esophageal, gastric, and rectal cancer. Data show that EUS is the most accurate imaging modality for staging depth of tumor invasion (T), with preoperative accuracy in the 80% to 90% range when compared with surgical pathology. For staging esophageal and gastric cancer, T1 cancers invade the mucosa to submucosa and are imaged as a disruption of the first three endosonographic wall layers (Fig. 28-2). T2 cancers invade the muscularis propria to the subserosa and show a hypoechoic invasion of the fourth layer. T3 cancers invade the subserosa and can be seen to penetrate the fifth layer. T4 cancers directly invade adjacent organs or structures.

FIGURE 28-2. Endosonographic image shows a polypoid hypoechoic disruption involving only the first three wall layers of the stomach at the angularis. A T1 cancer invading to the submucosa, but not involving the muscularis propria, was confirmed by surgical pathologic examination.

At the Memorial Sloan-Kettering Cancer Center (MSKCC), a prospective study used EUS in 50 patients for preoperative staging of esophageal cancer (Fig. 28-3) and in 50 patients for preoperative staging of gastric cancer (Fig. 28-4). Results were compared for accuracy with surgical pathology and with CT using rapid scanners, oral contrast, and dynamic technique. EUS was significantly more accurate than dynamic CT in staging tumor extent in esophageal and gastric cancer. Most studies comparing EUS with CT for staging esophageal, gastric, and rectal cancer have found EUS superior for evaluation of tumor extent.

The greatest strength of EUS is in identifying the location of tissues and not the specific histology. Biopsy and histopathologic evaluation are still required to identify the nature of any abnormality. EUS cannot reliably distinguish an inflammatory from a neoplastic process (e.g., determining whether a gastric ulcer is benign or malignant). EUS has proved less accurate in staging lymph nodes than in staging depth of tumor invasion because the node must not only be located but be characterized as benign or malignant. Lymph nodes in the 2- to 3-mm range can be detected with EUS. Some investigators use the echo character of nodes for staging. Nodes that are rounded, sharply defined, and hypoechoic are more likely to be malignant (Fig. 28-5). Using such criteria, staging regional lymph node metastases has been more accurate than other imaging modalities, such as CT scan, and is accurate in the range of 70% to 80%. EUS is a sensitive method of detecting recurrent upper GI cancer in the area of the surgical anastomosis. There have been false-positive results due to inflammation, and specificity should be improved.
Patients who have had a colon cancer or adenomatous polyp resected are at risk for metachronous lesions. Various estimates have placed the risk for metachronous adenomatous polyps. These rates increase as the age of the study population increases.

Asymptomatic patients with a positive fecal occult blood test should also undergo colonoscopy. Data from the New York occult blood screening trial enemas that were either negative or showed only diverticula. In 29 patients (11.2%), cancer was found during colonoscopy.

Hemorrhage in their patient population. Tedesco et al. found six (13.6%) with unexpected cancer; he was unable adequately to examine the colon in a similar number of patients. One of the most difficult areas of barium enema interpretation is the differentiation of strictures due to diverticular disease from colon cancer. Barium enema may underestimate the degree and intensity of diverticular inflammation. Colonoscopy, with associated biopsy and cytology, is the most important tool to use in making this distinction. In 44 patients with diverticular disease, Hunt found six (13.6%) with unexpected cancer; he was unable adequately to examine the colon in a similar number of patients. Hematochezia and melena thought not to be from an upper GI source should be evaluated by colonoscopy. Cancer of the large bowel, particularly in the rectum and left colon, often causes rectal bleeding, whereas cancers involving the right colon are more likely to produce melanic stools or occult bleeding, with the gradual onset of iron-deficiency anemia. Brand et al. studied by colonoscopy more than 300 patients with recent rectal bleeding and found that the bleeding was due to cancer in approximately 8% of their patients, though in more than 20% it was due to benign colon polyps. Angiodysplasia was also an important cause of large-bowel hemorrhage in their patient population. Tedesco et al. performed colonoscopy in 258 patients with rectal bleeding, negative proctosigmoidoscopy, and barium enemas that were either negative or showed only diverticula. In 29 patients (11.2%), cancer was found during colonoscopy.

Asymptomatic patients with a positive fecal occult blood test should also undergo colonoscopy. Data from the New York occult blood screening trial show that, of patients initially tested for occult blood, approximately 50% have a colonic neoplastic lesion. Approximately 12% of these lesions are cancers, and the rest are adenomatous polyps. These rates increase as the age of the study population increases.

Patients who have had a colon cancer or adenomatous polyp resected are at risk for metachronous lesions. Various estimates have placed the risk for metachronous adenomatous polyps. These rates increase as the age of the study population increases.
cancer between 5% and 10%, whereas the risk of developing a metachronous adenoma can be as high as 60%, as defined in a study of 383 patients by Foxler and Hedberg. The National Polyp Study (NPS), a multicenter randomized trial, demonstrated a polyp recurrence rate of 29% to 35%, depending on the number of colonoscopies performed and the interval between them. It is clear that these patients should be kept under surveillance by follow-up colonoscopy. Published NPS data have demonstrated that at a follow-up interval of 3 years, as many important colonic lesions were detected as were found at a 1-year interval. Therefore, it is recommended that postpolypectomy surveillance colonoscopy be performed every 3 years.

Colonscopic polypectomy, although long thought to help prevent colon cancer, now has been proven to do so. Winawer et al. analyzed the NPS cohort of 1418 patients who had a complete colonoscopy during which at least one polyp was removed. The colon cancer incidence in the study population was compared with the incidence in three reference groups, and reductions in cancer incidence of 76%, 88%, and 90%, respectively, were observed (P < 0.001).

Surveillance for colon cancer in patients with long-standing chronic ulcerative colitis represents a special problem. Although there is disagreement as to the magnitude of the cancer risk in ulcerative colitis, most investigators agree that cancer is unusual during the first 8 to 10 years of the disease and that thereafter the endoscopic findings and the incidence of cancer is approximately 5% at 20 years and 12% at 25 years. Annual surveillance colonoscopy should begin after 10 years. The aim of colonoscopy is to identify those patients who are especially likely to develop colon cancer by finding high-grade dysplastic changes in the colonic mucosa on endoscopic biopsy. Dysplasia is clear-cut neoplastic change in the colonic mucosa, and high-grade dysplasia is generally what triggers intervention. Several studies of colonoscopic surveillance were summarized by Waye. Fifteen percent of patients studied were found to have dysplasia, and 20% of these were found to have colon cancer. However, 10% of colitis patients with cancer had no evidence of dysplasia and were more likely to have the neoplastic lesion in the rectum.

Studies have confirmed that colorectal cancer occurs in first-degree relatives (i.e., parents, children, siblings) of patients with colorectal cancer, with three to four times the frequency expected by chance. There is also an increased risk for adenomatous polyps in first-degree relatives of patients with bowel cancer and an increased risk for colorectal cancer in first-degree relatives with adenomatous polyps. Many physicians now recommend colonoscopy, in conjunction with annual fecal occult blood testing, as the primary diagnostic tool for first-degree relatives in colon cancer families.

Screening colonoscopy has been studied in average-risk, asymptomatic patients with negative fecal occult blood studies. In one such study, adenomatous polyps were detected at a rate that was twice that expected from flexible sigmoidoscopy alone. Of 210 patients, 53 (25%) had adenomas, and two had cancers. The larger adenomas and both cancers were found in patients older than 60 years. A follow-up report by the same investigators confirmed the substantial prevalence of colonic neoplasia in asymptomatic people, particularly elderly men, with negative fecal occult blood tests.

THERAPEUTIC COLONOSCOPY: POLYPECTOMY

After a polyp is identified, colonoscopic polypectomy should be performed. If possible, the polyp is totally removed and submitted for histologic assessment. Complete colonoscopy should be performed at polypectomy to identify and remove any synchronous polyps. Biopsy of polyps is not recommended, because the results may be misleading. Small polyps (≤7 mm in diameter) are often removed by “hot biopsy” technique. Electric current is passed through a special biopsy forceps to cauterize the base of the polyp; then the tissue in the forceps is sent to pathology. Larger polyps are removed by snare-cautery technique. A wire loop is passed around the polyp base, and an electric current transsects and cauterizes the polyp base. The entire polyp is then retrieved and submitted to pathology for analysis. Most colonic polyps can be managed in this fashion. Large sessile polyps (>2 cm in diameter) may need to be removed with a piecemeal approach. Submucosal saline injection has made this process safer. Occasionally, a large sessile polyp may not be removed safely during colonoscopy, and surgical resection is necessary. Marking the polypectomy site with an injection of sterile india ink has been recommended as an accurate and permanent method for future endoscopic or surgical identification.

COMPLICATIONS

The major complications of colonoscopy are bowel perforation and hemorrhage. In 4713 diagnostic colonoscopies reported by the American Society for Gastrointestinal Endoscopy, perforation occurred in 0.17%. These perforations are usually the result of the mechanical force of the colonoscope shaft on the sigmoid colon, especially a sigmoid colon affected by diverticular disease or adhesions. In 1901 polypectomy was described by the American Society for Gastrointestinal Endoscopy, the perforation rate was 0.11%. Perforation almost always occurred at the polypectomy site and was usually related to the removal of a sessile polyp. Hemorrhage occurred more commonly after polypectomy than after diagnostic colonoscopy (2.16% vs. 0.01%). Patients should avoid aspirin for up to 2 weeks after polypectomy. Postpolypectomy abdominal pain, leukocytosis, and fever do not always represent bowel perforation and may be due to a transmural electrocautery burn. Conservative management in this setting is appropriate.

LAPAROSCOPY

PRINCIPLES

Laparoscopy or peritoneoscopy involves the creation of a pneumoperitoneum and the insertion of a thin telescope through a puncture in the anterior abdominal wall. Additional punctures are commonly used for insertion of probes, biopsy needles, and other instruments. For diagnosis and for guided biopsy, laparoscopy can be performed using local anesthesia and mild sedation, similar to that used for other GI endoscopic procedures. This type of laparoscopy should be differentiated from therapeutic procedure involved in laparoscopic cholecystectomy and other laparoscopic abdominal surgery, which requires general anesthesia. During laparoscopy, the anterior peritoneal space is visualized, with a view of the parietal peritoneum on the anterior abdominal wall and the diaphragm. Most of the liver surface and gallbladder can be examined, along with much of the greater omentum and visceral surfaces of the stomach, small bowel, and colon. The pelvic organs can be visualized. Less commonly seen are posterior structures, such as the porta hepatitis, pancreas, and spleen. The retroperitoneal lymph nodes and renal system are usually not evaluable.

INDICATIONS AND RESULTS

The ability to see large areas of parietal and visceral peritoneum and to evaluate the cause of ascites have been major indications for laparoscopy. CT scans have a low yield in imaging small peritoneal metastases. Paracentesis and blind peritoneal biopsy are frequently nondiagnostic. Deposits of even a few millimeters in size on CT scans have made this process safer. Occasionally, a large sessile polyp may not be removed safely during colonoscopy, and surgical resection is necessary. Marking the polypectomy site with an injection of sterile india ink has been recommended as an accurate and permanent method for future endoscopic or surgical identification.

LAPAROSCOPY
approximately 0.2% and with mortality of 0.05%. Subcutaneous emphysema and pneumomediastinum are not serious and require no treatment. Mediastinal emphysema, pneumothorax, and air embolism are rare. Abdominal wall bleeding and laceration of blood vessels, organs, or bowel occurs uncommonly but may require surgical management. Biopsy, especially of the liver, accounts for most complications. Tumor implantation at the laparoscopy or biopsy needle insertion site is well described.

**ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY**

**DIAGNOSTIC ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY**

The technique of endoscopic retrograde cholangiopancreatography (ERCP) was first reported in 1968 and has been an important diagnostic tool for more than 25 years. The skilled endoscopist working with a cooperative patient can often perform a diagnostic ERCP in less than 20 minutes. Success rates for cannulating the common bile duct and pancreatic duct are well in excess of 90%.

A side-viewing electronic duodenoscope is used to afford excellent visualization of the ampulla of Vater. Cannulization of the biliary and pancreatic ducts is then accomplished, and a contrast agent, such as diatrizoate (Renograffin-60), is injected into the desired duct under fluoroscopic control, and radiologic films of the duct anatomy are subsequently obtained. Duct cytology can be obtained, and biopsy of the ampulla, duodenum, and stomach may also be performed.

Evaluation of the jaundiced patient was one of the more important indications for ERCP. Imaging procedures, such as transabdominal sonography, high-quality CT scans, and magnetic resonance cholangiopancreatography, are replacing diagnostic ERCP (Fig. 28-6). Today, therapeutic ERCP is most commonly performed for endoscopic sphincterotomy, removing bile duct gallstones, or placement of an endobiliary stent across the obstructed bile duct segment.

![FIGURE 28-6. An endoscopic, retrograde cholangiogram demonstrating a short distal common bile duct stricture caused by a primary bile duct cancer.](image)

ERCP may be useful when the patient's symptoms suggest pancreatic cancer and the sonogram or CT scan is not diagnostic. ERCP may be difficult to interpret in the setting of chronic pancreatitis, and cancers can be missed. ERCP is a sensitive and specific diagnostic test for pancreatic cancer. At MSKCC, ERCP had a sensitivity of 92% and a specificity of 97% in the evaluation of 116 patients. In a report by Freeney of 530 patients with pancreatic cancer, normal pancreatograms were seen in only 15 (2.8%). Typical findings include complete occlusion or stenosis of the main pancreatic duct, narrowing or cutoff of the intrapancreatic portion of the common bile duct, and the double-duct sign of stenosis or obstruction of both the main pancreatic duct and the common bile duct. There may also be endoscopic abnormalities, such as a duodenal mass or ulcer that, when subjected to biopsy, document pancreatic cancer.

ERCP is not necessary when the diagnosis appears clear-cut. Frick et al. reported on ERCP used to evaluate 26 patients with indeterminate CT scans and found that ERCP aided the preoperative diagnosis in 25. One pancreatic cancer was missed by ERCP. In an English study of 140 patients with undiagnosed severe chronic abdominal pain, the ERCP was abnormal in 25 (18%). In approximately one-fourth of the patients, diagnoses were made. These diagnoses included gallstones, peptic ulcer disease, pancreatic cancer, and chronic pancreatitis.

**THERAPEUTIC ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY**

The therapeutic use of ERCP is growing rapidly. The major therapeutic procedures performed are endoscopic sphincterotomy, stone extraction, and placement of endobiliary stents for the palliative nonsurgical treatment of biliary obstruction. Approximately 75% of ERCPs done in our endoscopy unit at MSKCC are therapeutic.

Endoscopic sphincterotomy is performed by inserting into the distal common bile duct through the ampulla a specialized cannula containing an electrosurgical cutting wire. When the electrical current is passed through the exposed wire, a controlled incision is made in the sphincter, opening the distal bile duct to allow the endoscopic removal of bile duct stones or the placement of endobiliary stents. Biopsy of ampillary tumors is facilitated by endoscopic sphincterotomy, and the associated obstructive jaundice may be temporarily relieved by this procedure. Bourgeois et al. obtained the correct histologic diagnosis in all 55 patients with perianpillary cancer after endoscopic sphincterotomy but in only one-half before sphincterotomy.

Nonsurgical biliary drainage has become an important tool in the palliative management of patients with malignant biliary obstruction. Endoscopic biliary drainage (EBD) (Fig. 28-7) and percutaneous transhepatic drainage (PTD) complement each other and are selected on the basis of the level of the biliary obstruction. In a prospective randomized study comparing EBD with PTD in 75 high-risk patients with malignant biliary obstruction, EBD was significantly more successful in relieving jaundice (81% vs. 61%) and had a significantly lower 30-day mortality rate (15% vs. 33%). The complication rate of EBD was 19%, whereas the morbidity of PTD was 67%.

![FIGURE 28-7. An endoscopically placed biliary stent is seen in the common bile duct across the malignant stricture shown in Figure 28-6.](image)

The location or level of the malignant biliary stricture is very important in determining success and complication rates with nonsurgical biliary drainage. Seventy patients with malignant hilar strictures were stratified by Deviere et al. into three groups. Twenty patients had common hepatic duct lesions (type I), and 50 patients had bifurcation or intrahepatic strictures (types II and III). The type I patients were likely to experience complete drainage, whereas in only approximately 50% of the type II and III patients was drainage adequate. These patients had a higher 30-day mortality, a higher rate of early cholangitis, a higher death rate from sepsis, and a shorter postprocedure survival. Success in adequately draining common bile duct and common hepatic duct strictures should be approximately 90% with large-bore endoprosthesis placed during ERCP. The success rate for establishing drainage by ERCP in bifurcation or intrahepatic strictures is much lower. Using an aggressive
approach with multiple attempts and combining EBD with PTD increased the success rate of insertion of two or more stents to only approximately 50% of patients with hilar strictures. 59

EBD has been prospectively compared to surgical biliary bypass. Fifty-two patients with distal common bile duct obstruction were randomly assigned to either EBD or surgical biliary bypass. 60 Survival data for both groups were similar, as was the 90% success rate in relieving jaundice. Patients treated with EBD had a significantly shorter initial hospital stay (6 vs. 13 days; \( P < .002 \)). Readmissions to the hospital were more frequent in the EBD group, but the total hospital stay in days per patient until death was shorter in the EBD group (8 vs. 13 days; \( P < .01 \)). In patients with pancreatic cancer and jaundice who are not candidates for surgical resection, because of either advanced disease or other medical problems, EBD should be the biliary drainage procedure of choice. Metal endobiliary stents are replacing polyethylene stents, especially in those patients who can reasonably be expected to live more than 6 months. The use of metal endobiliary stents should reduce the number of stent replacements. Although EBD affords good palliation for advanced cancer cholestasis, studies have shown that there is no role for preoperative biliary drainage. 61

COMPLICATIONS

The most common complications of ERCP are cholangitis and sepsis. The rate of cholangitis and sepsis varies, depending on the reason for the ERCP and the underlying pathology. For example, therapeutic ERCP done for biliary obstruction may have a sepsis rate as high as 14%. 62

The level of the biliary obstruction affects the rate of sepsis. In an MSKCC series 63 looking at PTD after failed EBD, the rate of sepsis for patients with intrahepatic and bifurcation strictures was significantly greater than for those with common hepatic or common bile duct lesions (75% vs. 17%; \( P = .04 \)). Another MSKCC study 64 compared the microbiologic data for septic episodes after EBD with septic episodes after PTD. Although enteric gram-negative organisms predominated in both groups, there were significantly more gram-positive organisms noted in the PTD group ( \( P = .0005 \)).

Acute pancreatitis is another common complication of ERCP, and it is related to the injection of contrast material into the pancreatic duct. Its frequency varies but generally occurs in fewer than 7% of patients. It is usually self-limited and rarely presents as a serious clinical problem. Clinical trials with such agents as octreotide have not shown a reduction in ERCP-associated pancreatitis. 65

SMALL INTESTINAL ENDOSCOPY: ENTEROSCOPY

Evaluation of the small intestine beyond the fourth portion of the duodenum is commonly accomplished by barium studies or angiography. Two endoscopic techniques for studying the small bowel have been developed. Dedicated push enteroscopes (Olympus Corp., SIF-10) often can be passed rapidly to approximately 100 cm distal to the ligament of Treitz. Biopsy, polypectomy, diathermy, and Nd:YAG laser treatment can be performed through this instrument. In a study of 56 patients, the median depth of insertion into the small intestine was 45 cm (range, 15 to 90 cm), and procedure times varied from 10 to 45 minutes. 66 Push enteroscopy has been very useful in the evaluation and treatment of GI bleeding due to occult proximal small intestinal sources and in the evaluation of abnormalities seen on barium small intestinal radiographs.

The sonde-type enteroscope is slender and approximately 2.7 m long. It has an inflatable balloon at its tip that helps in passage through the small intestine. Among the several disadvantages of this instrument is its lack of a biopsy channel, the absence of tip deflection, a limited field of view, the need for fluoroscopy, and the 8 hours required for its use.

In using enteroscopy in the evaluation of obscure GI bleeding, one study of push enteroscopy identified the source of bleeding in 15 of 39 patients (38%). 67 The most common cause found was an arteriovenous malformation. The diagnostic yield in a study of 35 patients with obscure GI bleeding using a sonde-type enteroscope was 26%. 68 A study of 258 patients identified nine malignant and four benign tumors to be the cause of the obscure bleeding (5%). 69

PERCUTANEOUS ENDOSCOPIC GASTROSTOMY

Since its original description by Ponsky and Gauderer 70 in 1981, percutaneous endoscopic gastrostomy (PEG) has become a routine procedure, done in an outpatient setting without general anesthesia, in patients either unable to take oral feedings or in whom parenteral nutritional support is not feasible. PEG and percutaneous endoscopic jejunostomy (PEJ) are rapid and safe endoscopic methods for establishing enteral feeding routes and can eliminate the need for long-term nasal feeding tubes. In a study of 42 patients with dysphagia and cancers of the head and neck, successful use of PEG and PEJ was accomplished in 39. 71 No immediate complications occurred. After a mean follow-up of 4.5 months, only one patient developed pneumonia presumed to be due to aspiration. Complication rates for surgical gastrosomies have been reported to be as high as 75%. 72

When patients have had previous gastric resections, PEJ may be used. In 115 patients, Shike et al. 73,74 had a success rate with PEJ of more than 90%. PEJ was used in gastric outlet and small bowel obstruction, gastroparesis, and anorexia. Only two patients experienced severe complications of bleeding and abscess formation. Significant caloric intake ranging between 900 and 2400 calories per day could be administered.

BRONCHOSCOPY

Bronchoscopy (Table 28-1) is the single most useful modality for accurately diagnosing lung cancer. With the advent of fiber-optic equipment introduced more than 25 years ago, 75 this procedure has been used for diagnosis with increasing frequency.

| Table 28-1. Comparison of Rigid and Flexible Fiber-Optic Bronchoscopy Technique |
|--------------------------|--------------------------|
| Rigid Fiber-Optic Bronchoscopy | Flexible Fiber-Optic Bronchoscopy |
| Advantages | Disadvantages | Advantages | Disadvantages |
| - Excellent visualization of airways | - Limited visualization due to rigid nature | - Better maneuverability | - Limited visualization due to flexible nature |
| - High diagnostic accuracy | - More difficult to perform complex procedures | - Good for endoscopic procedures | - Limited for deep intubation |

INDICATIONS

The most common oncologic indication for bronchoscopy is to diagnose and assist in staging lung cancer by direct observation and by obtaining material for cytologic and histologic evaluation. 76 In investigating other upper aerodigestive tumors, bronchoscopy rules out extension of laryngeal and esophageal carcinomas to the upper airway. Flexible bronchoscopy has been especially important in localizing occult sites of malignancy when sputum cytology results are positive.

Therapeutically, bronchoscopy has been extensively used to remove retained secretions in the postoperative period, to relieve obstructed airways due to malignancy (in conjunction with laser destruction), and to arrest bleeding. This technique is used to deliver anticancer therapy (cauterization, cryotherapy, photocoagulation, and brachytherapy) in the definitive or palliative treatment of endobronchial malignancies. 77,78 Bronchoscopy is also used to insert intraluminal stents when required to maintain airway patency.
**Technique**

**Rigid Bronchoscopy**

The open-tube rigid bronchoscope, although used less frequently for diagnosis, remains a valuable therapeutic tool. It is especially important in controlling airway hemorrhage and is favored by most endoscopists for mechanical removal and laser coagulation of tumors (Fig. 28-8). It also has the advantages of a large lumen, allowing suctioning of blood or fumes developing during laser coagulation and obtaining larger biopsies. Although the rigid bronchoscope can be introduced under local anesthesia, the preferred approach is general anesthesia.

**Flexible Bronchoscopy**

Flexible bronchoscopy has become the mainstay of endoscopic airway examination. The flexible equipment is small enough to be introduced transnasally or transorally under local anesthesia with or without sedation. Because of its small diameter (6 mm or smaller), the average flexible bronchoscope can enter all segmental orifices of the tracheobronchial tree. Newer instruments (with an external diameter as small as 2.0 mm) can now extend the visible range to the periphery of the lung and have been used for biopsy of peripheral nodules or infiltrates (Fig. 28-9). These newer instruments no longer use fiber-optics for visualization: Electronic signals are now transmitted from the tip of the bronchoscope to a television monitor.

**Diagnostic Bronchoscopy**

Malignant lesions of the tracheobronchial tree and pulmonary parenchyma are most often diagnosed using flexible bronchoscopy. Tumors that involve the proximal airways as distal as subsegmental bronchi can usually be seen at the time of flexible bronchoscopy, and specimens can be obtained for histopathology or exfoliative cytology. Those lesions beyond the range of the flexible equipment can be subjected to biopsy under fluoroscopic control, passing biopsy forceps or brushes into the lesion that has been localized using an image intensifier. Diffuse pulmonary infiltrates requiring diagnosis can be easily sampled using similar radiologic techniques, passing biopsy forceps into the pulmonary parenchyma to obtain representative samples (transbronchial biopsy). Wang et al. have popularized the technique of transbronchial needle aspiration for diagnosing malignancy in mediastinal lymph nodes as well as in submucosal lesions inaccessible to direct biopsy or brushing. More recently, localization of mediastinal lymph nodes has been attempted using bronchoscopic ultrasonography. This has proven to be somewhat difficult because the air-containing airway cannot transmit the ultrasound waves, and obstruction of the airway is required to fill the lumen with a fluid-filled balloon to perform the examination. However, subcarinal lymph nodes can be easily accessed by performing endoesophageal ultrasonography with guided endobiopsy.

The success of these techniques is operator-dependent. It is rare for lesions that can be visualized not to yield a diagnosis. Intrapulmonary lesions located more peripherally may be more difficult to diagnose, especially if they are small (<3 cm in diameter) and are probably best diagnosed by percutaneous transthoracic needle aspiration biopsy using radiologic techniques. However, bronchoalveolar lavage with saline and postbronchoscopy sputum samples can provide cytology for examination.

Identification of occult in situ malignancies can be enhanced with the use of tumor fluorescence aided by laser light excitation. Injected hematoporphyrin derivatives fluoresce at a specific wavelength (640 nm) emitted by the argon laser beam and, most recently, autofluorescence of tumors using specific wavelengths can identify areas of dysplasia and frank neoplasia (lung imaging fluorescent endoscopy bronchoscopy). This technique is extremely important in identifying occult cancers detected by sputum cytology. This autofluorescence technique is being investigated also as a method of early diagnosis of lung cancer in high-risk individuals (especially patients with previous aerodigestive tumors).
The most common oncologic indication for therapeutic bronchoscopy is bronchopulmonary toilet after major pulmonary resections for malignancy. This has become an invaluable bedside tool in the postoperative management of thoracic surgical patients since the introduction of flexible instruments. Bronchoscopy has also been used with success in relieving endobronchial obstruction and in dealing with significant airway hemorrhage.

Endobronchial tumors can be mechanically débrided using the tip of the rigid bronchoscope or a large biopsy forceps. Techniques of tumor coagulation and destruction have been introduced that avoid unnecessary or excessive bleeding. These techniques include cryosurgery, electrocautery and, most recently, carbon dioxide, Nd:YAG, or argon laser destruction. These modalities require significant training in the use of lasers and are best applied when visible endobronchial tumors are present. Extrinsic compression by enlarged mediastinal lymph nodes does not respond to this type of treatment. When extrinsic compression is a major problem, endobronchial stents similar to those used for obstructing esophageal lesions can be inserted. A variety of Silastic and self-expanding metallic stents have been devised. The Silastic stents have the disadvantage of frequent migration. Self-expanding metallic stents, once inserted, cannot be removed but rarely migrate. These stents can be coated with Silastic to avoid growth of tumor through the interstices of the stent. With the expandable metallic stents, instances of tracheoesophageal fistulization have occurred. In properly selected patients, however, these expandable stents are replacing the plastic stents in the management of malignant disease. When either external-beam radiation or internal brachytherapy is added to endobronchial tumor destruction or in conjunction with stents, longer periods of palliation can be achieved, avoiding tumor regrowth and overgrowth. With these techniques, approximately 80% of patients can be relieved of their obstructing symptoms for a median of 3 months.

PDT has also been used to destroy endobronchial tumors. This technique is used as definitive therapy for \textit{in situ} carcinoma and is effective in totally destroying such tumors in approximately 50% of cases. It is now being used with increasing frequency to destroy inoperable tumors obstructing the airway. Most tumors respond to this therapy, and up to 90% of patients obtain some palliation. With the U.S. Food and Drug Administration release of hematoporphyrins for therapy in North America, significant activity has occurred in investigating this approach for palliation of obstructing tumors and treatment of \textit{in situ} and inoperable stage I proximal tumors. A newer hematoporphyrin, porfimer (Photofrin II), is currently the drug of choice. It is administered 24 to 48 hours before laser illumination of the tumor. This causes an intense and immediate destruction of the tumor, which requires mechanical débridement. In most instances, a second bronchoscopy 24 or 48 hours later completes the débridement. When compared to Nd:YAG laser destruction, it fares very well. Currently, all of these endobronchial-reaching methods are effective, and a combination of two of these (e.g., PDT plus radiotherapy, mechanical or Nd:YAG destruction plus radiotherapy) seems to produce the longest periods of palliation. Metastatic endobronchial tumors are also amenable to these therapies.

COMPLICATIONS

The complications of diagnostic rigid and flexible bronchoscopy are minimal, with fewer than 1.0% of patients experiencing any significant postprocedure problems. Rigid bronchoscopy has the disadvantage of trauma to the teeth, lips, and mouth as well as the larynx. This is completely avoided by using flexible bronchoscopy. Biopsy of lesions can lead to hemorrhage, although bleeding rarely is excessive. As with any other surgical procedure, care must be taken, before bronchoscopy is performed, to evaluate and correct any coagulation abnormalities. Transbronchial biopsy of lung parenchyma can lead to bleeding and pneumothorax; the latter complication occurs rarely if routine precautions are taken to avoid biopsy at the extreme periphery of the lung. In a series from the Cleveland Clinic, only 58 episodes of bleeding occurred in almost 7000 flexible bronchoscopies. Transbronchial biopsy showed a higher incidence of bleeding, though no deaths ensued. In two other large bronchoscopy series, the death rates were 0.1% and 0.3%, respectively. In a series of 4000 patients, major complications (pneumothorax, pulmonary hemorrhage, or respiratory failure) occurred in 0.53% of flexible bronchoscopies. After transbronchial biopsy, however, 6.8% of patients experienced either...
hemothage (2.8%) or pneumothorax (4%), and there were no deaths. 121

MEDIASTINOSCOPY

INDICATIONS

Mediastinoscopy is used most frequently to obtain lymph node samples from the superior mediastinum to assist in the clinical staging of lung cancer. It can be extremely valuable in identifying metastatic malignancy in these lymph nodes, thereby providing histologic evidence of N2 and N3 (stage IIIa and IIIb) disease in patients with lung cancer. 122 Less frequently, this technique is used to diagnose other lesions presenting with mediastinal adenopathy. Lymphomas, primary lung cancers with mediastinal involvement, and a host of benign lesions can be diagnosed using this approach. The procedure can also identify direct mediastinal invasion by a lung tumor and, by extending the mediastinal dissection, can be used for biopsy of lesions in the anterior mediastinum. Either pleural space can be entered through the mediastinum to detect abnormalities, especially in the paramediastinal regions. 122

TECHNIQUE

The mediastinoscopy technique (Fig. 28-13) is simple and safe in the hands of well-trained thoracic surgeons. A short suprasternal transverse incision is made, dissecting down to the pretracheal fascia, which is opened. Finger dissection in the pretracheal plane precedes the insertion of the mediastinoscope. Direct visualization of all areas of the superior mediastinum then allows appropriate biopsies of tissue in the various mediastinal nodal stations.

FIGURE 28-13. Technique of mediastinoscopy. A: Make a 3- to 4-cm incision just above the manubrium. B: Use the finger to dissect bluntly the loose fibrofatty tissue in front of the trachea down to the level of the pulmonary artery. C: Introduce the endoscope and take biopsies of suspicious tissues. Needle aspiration of structures before biopsy helps to reduce hemorrhagic complications. (Modified from PA Kerschner. Transcervical approach to the superior mediastinum. Hosp Pract 1970;5:61.)

Mediastinoscopy is performed under general anesthesia but is usually performed on an outpatient basis. It can also be used just before thoracotomy for final clinical staging in patients suspected of possibly harboring inoperable disease by virtue of mediastinal spread.

RESULTS

With the ability to biopsy mediastinal lymph nodes directly, the accuracy of mediastinoscopy approaches 90% when assessing the mediastinal involvement of lymph nodes in lung cancer. 123 Virtually no false-positive examination results should occur. Because of the inaccessibility of certain areas of the mediastinum, a 10% false-negative rate can be expected. However, those inaccessible mediastinal lymph nodes are usually resectable at the time of surgery. When mediastinoscopy fails to reveal metastatic disease in patients with otherwise operable lung cancer, the resectability rate of such patients approaches 95%. Mediastinoscopy remains the most accurate method of assessing mediastinal involvement by lung cancer and is usually used when CT scanning suggests enlarged mediastinal lymph nodes (>1 cm) to confirm the presence of metastatic disease to the mediastinum.

Since the introduction of positron emission tomography (PET) scanning, many centers have used this technique of staging the superior mediastinum instead of the invasive technique of mediastinoscopy. There are differences of opinion as to whether PET scanning can be depended on to be accurate. Certainly, “positive” PET scans denoting mediastinal spread of tumor should be confirmed by histologic proof. “Negative” PET scans do not rule out microscopic metastatic disease to the superior mediastinum. 124 125

In expert hands, mediastinoscopy is safe. One retrospective review from Washington University demonstrates the safety of the technique. In more than 2000 mediastinoscopies, there was one treatment-related death in a patient with very extensive mediastinal disease and very few significant complications: Only three patients required a thoracotomy for bleeding and, in all of those patients, the primary tumor was surgically treated at the time of thoracotomy. 126

ANTERIOR MEDIASTINOTOMY (CHAMBERLAIN PROCEDURE)

Tumors situated in the anterior mediastinum (e.g., lymphomas, germ cell tumors, thymomas) are often diagnosed by percutaneous transthoracic needle aspiration biopsy. The most direct approach to the anterior mediastinum, when incisional biopsies are required, is a modification of the technique of anterior mediastinotomy described by MacNeill and Chamberlain. 127 A small transverse incision is made in the second intercostal space or over the second or third costal cartilage. The anterior mediastinum is entered, usually without transgressing the pleura, and a biopsy can be obtained. Frequently, left upper lobe tumors do not metastasize to superior mediastinal lymph nodes but to the lymph nodes in the paraaortic area, most accessible by anterior mediastinotomy.

THORACOSCOPY

Thoracoscopy (pleuroscopy) is used most frequently to investigate and treat pleural effusions when simple thoracentesis fails. Until recently, open-tube instruments (e.g., mediastinoscopes) were used for inspection and biopsy. However, the use of thoracoscopy has been extended significantly with the introduction of miniaturized video-recording equipment and improved instrument technology (Fig. 28-14). Learning from the experience developed with laparoscopic surgery, video-assisted thoroscopic surgery has become a burgeoning enterprise. 128 129 Thoracoscopy has now been used not only for diagnosing pleural disease but for assessing mediastinal spread of lung and esophageal cancer and diagnosing lung disease. 130 The diagnosis of indeterminate pulmonary nodules, previously requiring a thoracotomy, can now be accomplished with relatively minimal invasion using video-assisted techniques. This has become especially important in identifying those nodules so frequently seen on CT scan, only a few millimeters in diameter, inaccessible by any other technique short of thoracotomy. Advanced thoroscopic techniques can allow partial and total lung resection as well as dissection and removal of mediastinal structures (esophagus, thymus gland, mediastinal lymph nodes, etc.). The ultimate indications for video-assisted thoroscopic surgery in the treatment of oncologic disease await further investigation and long-term follow-up of efficacy. 131
Simple thoracoscopic (pneumonectomy) can be performed using a small incision and inserting an open-lung scope (e.g., mediastinoscope) for removal of fluid and small biopsy of abnormal lesions on the pleural surface. Video-assisted thoracoscopic surgery usually requires the development of a pneumothorax using one-lung anesthesia, three to four small intercostal incisions, and the insertion of several trocars to allow the introduction of a videoscope plus a variety of instruments for surgical dissection. With this technique, the total visceral and parietal pleural surfaces can be examined and subjected to biopsy, the mediastinum can be entered and dissected as well as subjected to biopsy, and portions of the lung can be removed, taking advantage of mechanical stapling and cutting devices designed for the purpose.

With very small lesions, difficult to identify at the time of thoracoscopy, transbronchial needles placed radiologically before thoracoscopy can localize the area for resection, similar to the localization techniques used in performing breast biopsies.

RESULTS
Thoracoscopy is an excellent tool to diagnose pleural disease definitively and yields almost a 100% success rate. Peripherally placed lesions of the lung can usually be localized and can be resected for diagnosis, avoiding a major thoracotomy and its attendant morbidity. For this reason, hospital stays are shortened, and the use of expensive medical resources is diminished. The long-term results of thoracoscopic resectional surgery for oncologic disease have yet to be determined. When used judiciously for diagnostic purposes, thoracoscopy is an extremely safe technique, surgery in patients with pleural disease. However, with appropriate techniques, these problems are avoidable. As yet, there is no real evidence of major cost savings or significant long-term benefit using this approach in treating thoracic malignancies. However, the diagnostic abilities of video-assisted thoracoscopic surgery have allowed firm diagnosis to be established with minimal morbidity.

CHAPTER REFERENCES
INTRODUCTION

Laparoscopy has become an important tool in the diagnosis and treatment of many diseases worldwide since the late 1980s. However, the procedure has been available for nearly 100 years, used mostly by gynecologists, hepatologists, and a few pioneer general surgeons. The first report is from a gynecologic procedure performed by Ol in Russia in 1901. Later, in 1901 by Kelling, in a dog model. The Veress needle was developed in 1938. Older instruments consisted of a metal tube fitted with lenses, which allowed one person at a time to see the hazy images provided. One of the major reasons for the new popularity of laparoscopy is the availability of high-quality images on video monitors, making it easy for a team of surgeons to work together, each with the same view. In addition, the development of long-handled tools that function through ports has rapidly and widely expanded the scope of laparoscopic surgery.

One of the earliest applications of laparoscopy to patients with cancer was by Bagley and coworkers in 1973 who reported on the laparoscopic evaluation of 23 patients with pancreatic carcinoma. These pioneers were able to investigate the lesser sac with their primitive instruments and thought that laparoscopy might be used to obviate the need for laparotomy in patients with advanced disease. First, as with any procedure, laparoscopy should not be performed simply because it can be done. Second, when laparoscopy is used in the care of the cancer patient for diagnosis, staging, treatment, or palliation, the laparoscopic conduct of the operation should compromise neither the nature of the procedure nor the amount or source of the tissue obtained.

In 1978, Cuschieri and colleagues reported on the laparoscopic evaluation of 23 patients with pancreatic carcinoma. These pioneers were able to investigate the lesser sac with their primitive instruments and thought that laparoscopy might be used to obviate the need for laparotomy in patients with advanced disease. Although laparoscopy is applied widely to a large number of surgical conditions and has become the standard surgical approach for cholecystectomy since its introduction to the United States in 1986, its application to patients with cancer remains less well defined. In fact, there are no specific indications for the use of laparoscopy in patients with malignancies. Two principles guide the use of laparoscopy in the care of the cancer patient. First, as with any procedure, laparoscopy should not be performed simply because it can be done. Second, when laparoscopy is used in the care of the cancer patient for diagnosis, staging, treatment, or palliation, the laparoscopic conduct of the operation should compromise neither the nature of the procedure nor the amount or source of the tissue obtained.

Surgeons have been involved in the diagnosis, staging, treatment, and palliation of malignancies for centuries. Laparoscopy is assuming a role in each of these areas. Laparoscopy has a role in establishing the diagnosis of cancer in some situations, allowing biopsy of intraperitoneal and retroperitoneal masses and lymph nodes, biopsy of visceral lesions, and the examination of abdominal contents with ultrasound probes. Laparoscopy is useful in the staging of established malignancies, such as pancreatic cancer, Hodgkin’s lymphoma, and esophageal cancer. Laparoscopy also has a role in the surgical treatment of a variety of malignancies, including gastric carcinoma, pancreatic cancer, renal tumors, adrenal tumors, colon cancer, and gynecologic tumors. Laparoscopy may be the appropriate approach for the definitive therapy of these lesions or may be a way to provide a palliative procedure, such as a cholecystectomy, in a patient with unresectable carcinoma of the pancreas. Lastly, laparoscopy can play an important role in the palliative care of the cancer patient as a way of performing procedures such as feeding tube placement or intestinal stoma creation with decreased hospitalization and recovery time.

Although many procedures have been performed successfully using laparoscopic technology, the results obtained should be analyzed objectively and critically. There are advantages and disadvantages to both the open and laparoscopic conduct of many procedures. Most important, the technique selected should benefit the patient maximally. This must be viewed from many angles, including patient comfort, tissue obtained, cost-effectiveness, surgical morbidity, and surgical mortality. At the present time, for most laparoscopic procedures applied to the care of the patient with cancer, insufficient data are available to make quantitative judgments about most of these issues. Therefore, only by critically analyzing the existing data can a practitioner begin to make decisions about what techniques to use for a specific patient.
One of the most notable sequelaes of laparoscopic surgery is the generally significant decrease in the amount of pain when compared with open procedures. This may easily be attributed to the use of smaller incisions and the lack of retractors holding these incisions open for hours. However, patients who undergo laparoscopic splenectomy and then require an incision for removal of the intact specimen (see later, Lymphoma) also note decreased pain in their incisions. West and colleagues investigated the effect of different insufflation gases on murine peritoneal macrophage intracellular pH and correlated these alterations with changes in lipopolysaccharides stimulated inflammatory cytokine release. Peritoneal macrophages were incubated for 2 hours in air, helium, or carbon dioxide (CO2), and the effect on tumor necrosis factor (TNF), interleukin (IL)-1, and cytosolic pH were determined. Macrophages incubated in CO2 produced significantly less TNF and IL-1 compared with incubation in air or helium. In addition, exposure to CO2, but not air or helium, produced a marked cytosolic acidification. These authors conclude that cellular acidification induced by peritoneal CO2 insufflation contributes to the diminished local inflammatory response seen in laparoscopic surgery.

**EFFECTS ON HEPATIC BLOOD FLOW**

Changes in hepatic blood flow can be significant because the liver plays a central role in the removal of a wide variety of substances from the circulation. Changes in hepatic blood flow could significantly alter the biokinetics of anesthetic and other agents. In an effort to investigate the effect of CO2 pneumoperitoneum, Turhon and colleagues evaluated the pharmacokinetics of indocyanine green, an anionic dye frequently used to estimate hepatic blood flow in experimental systems. They found a significantly decreased clearance of indocyanine green in the insufflation and laparoscopic surgery groups compared with the open surgery group, corresponding to a significantly decreased hepatic blood flow in these two groups. They concluded that dose adjustments of many agents may be necessary for patients undergoing laparoscopic procedures, especially those with limited hepatic reserve.

**CARIDOPULMONARY EFFECTS**

The use of laparoscopy in patients with sepsis may be a significant physiologic challenge. In an effort to assess this experimentally, Greif and Forse studied cardiopulmonary physiologic parameters in a population of adult respiratory distress syndrome (ARDS). After inducing ARDS, animals were divided into two groups: 1. One underwent laparoscopy and the other the conventional laparotomy. The laparoscopic group demonstrated a significantly decreased pulmonary compliance compared with the laparotomy group, had a higher pCO2, and was more acidic. Animals with ARDS demonstrate further compromise in pulmonary physiologic parameters when undergoing laparoscopy, but overall, cardiopulmonary function was preserved.

In a subsequent study, Greif and Forse used a porcine sepsis model to evaluate interventions to ameliorate the effect of laparoscopy on cardiovascular hemodynamics. Specifically, they found that the adverse effects may be mediated by increased pulmonary vascular resistance, diminished venous return, or both. They found that insufflation with air instead of CO2, to manipulate arterial pH did not improve cardiovascular hemodynamics. Aggressive fluid administration, and administration of prostacyclin or indomethacin, had positive effects on the hemodynamic effects of pneumoperitoneum.

**LAPAROSCOPIC AND THE SYSTEMIC IMMUNE RESPONSE**

The effect of laparoscopy on the activation of the systemic immune response has been studied by a number of investigators. Cytokine levels provide us with one method of evaluating the systemic immune response. The cytokines IL-1, IL-6, C-reactive protein, and TNF are known mediators of the acute-phase response. Peak C-reactive protein levels have been shown to be significantly higher after open cholecystectomy compared with laparoscopic cholecystectomy. Furthermore, these investigators found a significantly prolonged elevation in C-reactive protein levels in patients undergoing open cholecystectomy compared with those undergoing laparoscopic cholecystectomy.

Serum IL-6 levels are early and sensitive markers of tissue damage because they increase proportionally to degree of injury. IL-6 levels also have been shown to correlate with the development of significant complications and mortality. Serum IL-6 levels have been shown to be reduced in patients undergoing laparoscopic cholecystectomy compared with those undergoing open cholecystectomy. There remains a distinct lack of consensus about the meaning of the decreased IL-6 response, and further study is indicated.

The immunosuppression induced by open surgery has been studied in the past and has been well described. More recent studies have looked at the effect of laparoscopic surgery on the cellular components of the immune system. Previous studies have shown significant decreases in the CD4 and CD8 cell counts in patients undergoing open cholecystectomy. Vallina and Velasco studied peripheral lymphocyte populations in 11 patients undergoing laparoscopic cholecystectomy and found a transient decrease in the CD4 to CD8 ratio, with no difference in absolute CD4 and CD8 cell counts and a return to preoperative ratio within 1 week of surgery. These studies suggest that laparoscopic surgery may impact less on the cellular components of the immune system than open surgery, but further study is necessary to determine the significance of this information.

**PORT-SITE METASTASES**

Soon after the laparoscopic treatment of malignancies began throughout the world, a number of reports appeared describing “port-site metastases”—that is, tumor recurrence at the sites of trocar placement—in the postoperative period. A large number of such anecdotal reports were published, which subjectively seemed far more common than wound recurrences after open colon resection. The true extent of the problem was difficult to determine. In a large series of open colon resections, Hughes et al. reported 3 recurrences in a series of 208 laparoscopic colon cancer resections. Of these three patients, two had widespread disease. Between 1993 and 1996, 35 cases of port-site recurrence after laparoscopic colectomy for colorectal carcinoma were reported. These observations led to a number of consequences. First, these reports prompted careful scientific evaluation of the procedure and its application to malignancies. Registrars were developed to monitor the occurrence of port-site recurrences. Second, a number of investigators began to examine possible mechanisms for this phenomenon in the laboratory.

A retrospective study of 372 patients who underwent laparoscopic colon resection for malignancy was conducted by Nelson and colleagues. This study had relatively short follow-up, with a mean follow-up of just 23 months. The incidence of port-site metastases was 1.1%, which is similar to published data for open surgical resection of colon cancer. This study also demonstrated a 3-year survival rate that was similar, stage for stage, with open colon resection data. In a large prospective study of 533 patients with a variety of intraabdominal malignancies who underwent laparoscopic investigation, port-site recurrences were identified in just four patients (0.8%). The investigators in this study looked at the extent of disease as well, identifying port-site recurrences in 3 of 71 patients with advanced disease compared with just 1 of 462 without advanced disease (P < .003), further supporting the concept that this phenomenon may be an indicator of advanced disease.

A number of investigators have attempted to explain this phenomenon using clinical studies and laboratory models of port-site recurrences, specifically looking at the effects of the insufflation gases. In a clinical study of 15 patients with malignancies by Ikrumuddin et al., the insufflation gas effluent was directed through saline. Macroscopic specimens from only two patients, both of whom had carcinomatosus, in specimens concluded that tumor cell aerosolization is unlikely to contribute to port-site metastases. In a study of effluent CO2, another group reported very low levels of tumor cells in the gas, but they did find large numbers of tumor cells on trocars and instruments that were used. They suggest that port-site metastases might be reduced with avoidance of mechanical contamination. In another clinical study, labeled red blood cells were injected in the gallbladder bed in two groups of patients, one with standard CO2 pneumoperitoneum and one with gasless laparoscopy. Radioactivity was observed in the area of trocar insertion in all patients who underwent standard laparoscopic surgery but was rare in patients who underwent gasless laparoscopy. In a rat model of laparoscopy, peritoneal tumor growth was greater after laparotomy than after CO2 laparoscopy. The investigators in this study also found that insufflation of CO2 promotes tumor growth at the peritoneal surface and is associated with more abdominal wall metastases than gasless laparoscopy. Others also have shown that CO2 pneumoperitoneum significantly increases tumor implantation at trocar sites in a hamster model. In a rat study, the influence of the trocar itself was studied, and investigators found an increase in port-site metastases from the act of withdrawing the port and seeding the wound site. Several studies have looked at the role of the gas used for insufflation with contradictory results. In one study, the gas used was not a contributing factor, comparing CO2, helium, and air. In another study, helium was associated with reduced tumor growth. Both of these studies suggest the use of gasless laparoscopy...
for patients with malignancies.

Other investigators have looked at the influence of tissue trauma on the formation of port-site metastases. In a rat experiment, tissue trauma was induced at the port sites, and a significantly greater amount of tumor grew there after insufflation than at port sites without induced trauma. These authors also identified leakage of insufflating gas as a contributing factor. Other investigators also have looked at the influence of tissue injury and found that peritoneal injury enhances peritoneal implantation of tumor cells. A number of investigators have used laboratory models to compare laparotomy and laparoscopy. In the absence of tumor manipulation, no difference was seen in intraperitoneal tumor growth and spread between laparotomy and laparoscopy in a rat model. The possibility of immune mediation has been investigated by one group. These authors also found that tumors were established and grew more readily and larger after laparotomy than after insufflation. In one of their studies, altered levels of TNF were found, suggesting an association. The relative immunosuppression of laparotomy may play a role.

A number of explanations have been put forth to explain the phenomenon of port-site metastases. These are outlined briefly in Table 29.1-1. The potential causes of this problem suggest that technical modifications of the procedure may minimize the likelihood of this problem occurring. Early data clearly suggest that the incidence of port-site recurrences after laparoscopic tumor resection is similar to the wound recurrence rate after open resections for colon cancer. Further clinical and experimental studies are in progress to determine the true extent of this problem. Laparoscopic resection of malignancies performed outside of clinical trials should be undertaken "with circumspection" until the true incidence of this problem is known as a result of prospective randomized trials.

### TABLE 29.1-1. Possible Causes of Tumor Cell Dissemination in Laparoscopic Surgery for Cancer

<table>
<thead>
<tr>
<th>Possible Cause</th>
<th>Intervention to Potentially Minimize This Cause</th>
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<tbody>
<tr>
<td>Digestive tract injury</td>
<td>Avoid iatrogenic trauma to bowel</td>
</tr>
<tr>
<td>Tissue injury from manipulation</td>
<td>Avoid iatrogenic trauma to bowel</td>
</tr>
<tr>
<td>Tumor rupture at extraction</td>
<td>Incise the tumor capsule</td>
</tr>
<tr>
<td>Immunoinhibitory effects</td>
<td>Decrease temperature during extraction</td>
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LAPAROSCOPY IN THE DIAGNOSIS OF MALIGNANCY

GENERAL CONSIDERATIONS

Patients often present with constitutional symptoms and undergo evaluation by imaging studies in the hopes of identifying an underlying cause. Figure 29.1-1 shows a computed tomography (CT) scan image from a 70-year-old woman who presented with fever and malaise and no evidence of peripheral adenopathy on physical examination. Celiac lymph nodes were sampled laparoscopically (Fig. 29.1-2), establishing the diagnosis of NHL. In this case, the patient underwent a diagnostic procedure and was discharged home the same day with minimal postoperative pain. The use of diagnostic laparoscopy in the evaluation of abdominal malignancies has been reported. In a series by Easter et al., of 25 patients with suspected malignancies, 17 (68%) had a positive study for cancer; these investigators concluded that patient management had been altered by the laparoscopic finding in 25 patients (100%).

FIGURE 29.1-1. A 70-year-old woman presented with fevers and nonspecific abdominal pain. Workup revealed a negative physical examination, with an enlarged celiac lymph node seen on computed tomography scan. (From ref. 2, with permission.)

![Figure 29.1-1](image1)

FIGURE 29.1-2. The celiac node was identified laparoscopically and excised. Histopathologic evaluation revealed non-Hodgkin's lymphoma. (From ref. 109, with permission.)

![Figure 29.1-2](image2)

BIOPSY OF MASSES

Masses identified on preoperative imaging studies are often amenable to laparoscopic biopsy. Some studies have evaluated the tactile sensation afforded by laparoscopic instruments and have found it to be almost comparable with open palpation. Techniques available for the biopsy of masses under laparoscopic control include:

- Percutaneous insertion of a core biopsy needle with direct puncture of the mass; this is easily performed under the direct vision afforded by the laparoscope.
- Wedge biopsy using the electrocautery; this method should be used cautiously to avoid thermal destruction of the specimen.
- Cup forceps biopsy; careful use of these forceps allows removal of adequate tissue for histopathologic examination while avoiding destruction of the specimen. This technique is extremely useful for the biopsy of small lesions such as those present on peritoneal surfaces (Fig. 29.1-3).
were unresectable. Conversely, 12% of patients who had laparoscopic findings suggesting resectability were found at laparotomy to be unresectable. Sites missed performed in 37% of cases. In 36% of cases, laparoscopy yielded information that prevented unnecessary laparotomy because of the identification of lesions that underwent laparoscopic staging.

A series of 162 patients with a variety of malignancies, including 98 patients with hepatic lesions and 64 patients with nonhepatic intraabdominal malignancy, lesions is shown in disease are often found in patients with negative CT scans, supporting the use of laparoscopy to identify these lesions. Laparoscopy is extremely accurate for the identification of peritoneal disease, which is often missed by standard noninvasive imaging studies such as CT scanning, ultrasonography, and magnetic resonance imaging. The results of these studies and others demonstrate that effective use of laparoscopy for tumor diagnosis requires the use of LICU as a complementary technique to evaluate the true extent of disease.

**Liver Biopsy and Evaluation of Liver Tumors**

Laparoscopic investigation of hepatic lesions can include inspection, palpation (with a probe), intraoperative ultrasound (discussed later in Laparoscopic Intracorporeal Ultrasound), and directed biopsy. Lesions that are located on the thin edge of the liver may be easily biopsied using two applications of the linear stapler to avoid destruction of the tissue as shown in Figure 29.1-4. This method is also useful in obtaining blind liver biopsies requiring larger specimens than those available with a core biopsy needle.

**LAPAROSCOPIC INTRACORPOREAL ULTRASOUND**

One of the most important developments in the laparoscopic evaluation of malignancies is the laparoscopic intracorporeal ultrasound (LICU) probe. Intraoperative ultrasound was first described in 1958 and, with advancements in the technology, has had significant impact on the intraoperative management of a number of complex problems. The laparoscopic application of these devices is limited by the size and location of the access ports used. The direct contact of the probe to the liver affords superior resolution compared with that obtained with transabdominal ultrasound imaging. When searching for lymphadenopathy, it is critical to adapt the technique to the specific area being studied, assuring good acoustic contact between the probe and the tissue. Saline solution may be instilled to aid in this process. Doppler techniques are useful to identify blood vessels that will aid the identification of lymph nodes.

The ability to examine the biliary tree with LICU has been described. This report establishes the accuracy of this technique compared with cholangiography in determining common duct size and presence of choledocholithiasis. The use of LICU in 176 patients was reported. In this series, 145 patients underwent laparoscopic cholecystectomy, and 31 patients underwent staging laparoscopy with examination of the liver. From these preliminary studies, it appears that LICU has potential in the intraoperative evaluation of patients with malignancies. It is also clear that the value of this procedure is limited by operator skill.

The use of LICU is clearly complementary to laparoscopy alone, particularly in the evaluation of hepatic lesions. In a study of 50 patients with potentially resectable liver tumors, laparoscopy alone demonstrated factors that rendered the patient unresectable in 23 patients (46%). Of the remaining patients, LICU identified nine patients as unresectable. Patients in this study who underwent combined laparoscopic/LICU staging ultimately had a 93% resectability rate among a historical group who did not have laparoscopic staging. In another study of 420 patients with a wide range of upper gastrointestinal malignancies, laparoscopy/LICU staging precluded laparotomy in 20% of patients deemed resectable by preoperative imaging studies, with an overall sensitivity of 70%. The results of these studies and others demonstrate that effective use of laparoscopy for tumor diagnosis requires the use of LICU as a complementary technique to evaluate the true extent of disease.

**LAPAROSCOPY IN THE STAGING OF MALIGNANCY**

GENERAL CONSIDERATIONS

Perhaps the most important benefit of laparoscopic staging is the exclusion of patients with disease that is not resectable for cure from further invasive procedures. It is, however, difficult to assess the utility of this approach. Table 29.1-1 lists the indications for laparoscopic diagnosis and staging at the University of Dundee. This approach was analyzed by a 2-year prospective evaluation, and the parameters assessed were diagnostic yield, management benefit, and management disadvantage. The results of this trial showed a 90% diagnostic yield. The authors concluded that 30% of patients had their management affected by the performance of a laparoscopic staging procedure. Only two cases (4%) in which laparoscopy failed to identify disease that signaled unresectability were reported—a missed hepatic lesion in segment eight, and portal vein involvement by a tumor of the head of the pancreas.

Laparoscopy is extremely accurate for the identification of peritoneal disease, which is often missed by standard noninvasive imaging studies such as CT scanning, ultrasonography, and magnetic resonance imaging. Lesions that are only a few millimeters in size can be biopsied with extreme accuracy. Liver and peritoneal disease are often found in patients with negative CT scans, supporting the use of laparoscopy to identify these lesions. A representative laparoscopic view of such lesions is shown in Figure 29.1-3.

A series of 162 patients with a variety of malignancies, including 98 patients with hepatic lesions and 64 patients with nonhepatic intra-abdominal malignancy, underwent laparoscopic staging. All of these patients were believed to be resectable for cure based on a number of preoperative imaging studies. Biopsies were performed in 37% of cases. In 36% of cases, laparoscopy yielded information that prevented unnecessary laparotomy because of the identification of lesions that were unresectable. Conversely, 12% of patients who had laparoscopic findings suggesting resectability were found at laparotomy to be unresectable. Sites missed...
included positive lymph nodes, hepatic vein involvement, and missed peritoneal metastases. This study supports the use of laparoscopy to prevent unnecessary laparotomy in those patients who will not benefit from resection.

Laparoscopy is facilitated in patients with tense ascites by repeated paracentesis begun 24 hours before surgery. In a series of 47 patients with ascites, laparoscopy revealed metastatic disease in 22; ovarian carcinoma in 11; three patients each with mesothelioma, hepatoma, and hepatic myelofibrosis; two patients with pancreatic cancer; and one patient each with squamous cancer, chronic lymphatic leukemia, breast cancer, and lymphoma. The accuracy of laparoscopy in the evaluation of malignant disease presenting as ascites has been reported in one series as 100%.

**PANCREATIC CANCER**

Laparoscopy has been used in the staging of patients with carcinoma of the pancreas for some time. In fact, the first report of laparoscopy in the United States was the evaluation of a patient with carcinoma of the pancreas. The goal of laparoscopy in the staging of patients with carcinoma of the pancreas is to avoid laparotomy in those patients deemed resectable by preoperative imaging studies. An early report describes the experience of 23 patients with pancreatic cancer. This study was carried out before the widespread use of abdominal CT scan and the advent of quality optics for laparoscopy. This report emphasized the utility of biopsy under direct vision.

In a report of 40 patients with carcinoma of the pancreas, Warshaw and coworkers found 26 patients without evidence of metastatic disease and 14 patients with metastatic disease that precluded a curative resection. Laparoscopy was performed as the final study before laparotomy, but only if the imaging studies were negative for metastatic disease. The negative findings at laparoscopy were confirmed in 23 of 28 patients at laparotomy. The positive laparoscopic findings in 14 of 40 patients altered the therapeutic course of all 14 patients. Findings in these patients were single, small (1 to 2 mm) nodules in the liver (n = 6), peritoneal surfaces (n = 7), and omentum (n = 1), all of which were verified histologically. The three instances of false-negative findings were due to incomplete examination of the liver (n = 2) and a central liver lesion (n = 1). The overall accuracy was 93% and, with negative findings, 88%.

Another application of laparoscopy in the staging of patients with carcinoma of the pancreas is the ability to obtain specimens for cytologic examination. In 40 patients with lesions that were resectable according to the results of preoperative imaging studies, peritoneal washings were obtained (27 at laparoscopy and 13 at laparotomy). Malignant cells were found in 12 (30%) of the specimens. Liver metastases were seen in six patients, all of whom had negative cytology. Interestingly, positive cytology was found in six of eight patients who had previously undergone needle biopsy and in 6 of 32 patients who had not, suggesting that intraperitoneal spread may be enhanced by needle biopsy. Laparoscopy is described as an excellent method to obtain cytologic washings, which may be of importance in the evaluation of patients with carcinoma of the pancreas.

The ability of laparoscopy to detect metastatic disease not otherwise identified has been reported by others. The use of laparoscopy and laparoscopic ultrasonography has been described in the evaluation of 40 consecutive patients felt to have a resectable pancreatic lesion. Resectability was confirmed in 12 patients with negative laparoscopic examinations, for a sensitivity of 100%. Occult metastatic disease was identified in 14 patients, including liver lesions (n = 10), disease on peritoneal surfaces (n = 8), and hilar lymphadenopathy (n = 2). Laparoscopy failed to demonstrate metastatic disease in three patients. As for predicting resectability, laparoscopy alone did not identify the 12 patients with locoregional tumor unresectability, with an overall specificity of only 50%. However, the combined use of laparoscopy and laparoscopic ultrasonography resulted in a sensitivity of 92%, a specificity of 86%, and an accuracy of 89%.

The careful exploration of the abdominal cavity was emphasized in a study by Conlon and coworkers. These investigators performed laparoscopy on 115 patients with radiologically resectable lesions. Unresectability was determined by the presence of any of the following: metastatic lesions, extrapancreatic tumor extension, celiac and portal node involvement, and vascular encasement of the celiac or superior mesenteric vessels. Resection was performed in 76% of patients with a negative laparoscopic evaluation, compared with a historical series of radiologic evaluation only with a resectability rate of 35%.

The importance of laparoscopy combined with LICU was emphasized in a report by John et al. that demonstrated that this combined approach was significantly better than either CT in predicting resectability (87% vs. 79%, P < 0.05). LICU was considered indispensable for the detection of occult metastases. Furthermore, these investigators found that LICU is a reliable predictor of tumor unresectability. Others also have affirmed the importance of combined laparoscopy and LICU to evaluate extent of disease.

More recently, several investigators have suggested that laparoscopy be used in a highly selective manner in patients with carcinoma of the pancreas rather than as a standard staging modality. Of 398 patients who underwent laparotomy for pancreatic or periampullary carcinoma at one center, 172 patients underwent resection, 150 had a palliative bypass, and 76 underwent exploratory laparotomy only. Local signs of unresectability, identifiable only at laparotomy, were found in 47, leaving 29 patients (7%) who did not require palliation and whose signs of unresectability could have been determined by laparoscopy. The authors of this study concluded that laparoscopy (with or without LICU) should be used selectively in patients considered probably unresectable who do not require a palliative surgical procedure. The laparoscopic conduct of palliative bypass procedures may make laparoscopy somewhat more applicable than these data imply, however. In a retrospective study of 148 patients with pancreatic cancer, survival of patients with clinically resectable pancreatic cancer that was deemed unresectable at laparotomy was evaluated to determine the utility of staging laparoscopy. The importance of staging laparoscopy is enhanced if one believes that endoscopic stenting is the best palliation. The authors of this study concluded that extensive laparoscopic evaluation is not necessary, because they contend that operative palliation is superior to endoscopic palliation. Staging laparoscopy is useful only to identify those patients with liver or peritoneal metastases who have an expected survival of approximately 6 months and for whom endoscopic palliation is sufficient.

The use of laparoscopy or combined laparoscopy and laparoscopic ultrasonography appears to be helpful in the identification of lesions that suggest unresectability in patients with negative imaging studies. Although some suggest that laparoscopy be used in a fairly routine manner, data suggest that laparoscopy be used more selectively.

**ESOPHAGEAL AND GASTRIC TUMORS**

Early laparoscopic studies of the staging of esophageal cancer were usually characterized by little manipulation of the abdominal contents to identify disease and were commonly limited to observation of the parietal peritoneal surfaces. A prospective trial was undertaken to compare the accuracy in diagnosing intraabdominal metastatic disease by scintigraphy, ultrasound scanning, and laparoscopy. Of the 50 patients studied, 23 had esophageal carcinoma, 14 had gastric carcinoma, and 13 had suspected intraabdominal metastatic spread from other lesions. The accuracy of identification of metastatic disease was determined by laparoscopic biopsy, laparotomy, and autopsy. The overall accuracy was 72% for scintigraphy, 75% for ultrasound, and 96% for laparoscopy. Thirteen patients without hepatic metastatic disease that precluded a curative resection had no peritoneal disease diagnosed only by laparoscopy. This study demonstrates the value of laparoscopy and its ability to obviate the need for laparotomy in patients with lesions not resectable for cure.

In another study, 369 patients with carcinoma of the esophagus and cardia of the stomach underwent laparoscopy, revealing single or multiple intraabdominal metastases in 52 patients (14%). This study suggested that intraabdominal metastases become more common as the location of the primary tumor becomes more distal, being greatest in lesions of the cardia. More recent data suggest that abdominopelvic lymph node metastases may be present despite the location of the primary tumor.

As for predicting resectability, laparoscopy alone did not identify the 12 patients with locoregional tumor unresectability, with an overall specificity of only 50%. However, the combined use of laparoscopy and laparoscopic ultrasonography resulted in a sensitivity of 92%, a specificity of 86%, and an accuracy of 89%.

The use of laparoscopy or combined laparoscopy and laparoscopic ultrasonography appears to be helpful in the identification of lesions that suggest unresectability in patients with negative imaging studies. Although some suggest that laparoscopy be used in a fairly routine manner, data suggest that laparoscopy be used more selectively.

The sensitivity, specificity, and accuracy of laparoscopy, ultrasound, and abdominal CT scan were compared in 90 patients with biopsy-proven carcinoma of the esophagus or carcinoid cardia. Laparoscopy was found to be significantly more sensitive and more accurate (P < 0.05) than either ultrasound or abdominal CT scanning in diagnosing hepatic disease. Peritoneal disease was not identified by ultrasound or CT scan, but laparoscopy identified it in eight (89%) of nine cases. Lymph node metastases were identified most accurately by laparoscopy, although the difference between laparoscopy and CT scanning did not achieve statistical significance. The authors of this study concluded that laparoscopy offers an accurate, reliable, and safe method of preoperative assessment in patients with carcinoma of the esophagus.

Thoracoscopic lymph node staging has not been shown to provide accurate pre-resection staging of thoracic node status. More recently, laparoscopic lymph node assessment in patients with carcinoma of the esophagus has been combined with thoracoscopic lymph node staging. The use of thoracoscopy in staging accuracy has been validated in a trial comparing thoracoscopy to noninvasive staging techniques that found greater accuracy with thoracoscopic staging. Laparoscopic evaluation of intraabdominal disease was correct in 17 of 18 patients (94%) in a prospective trial. A positive lymph node was not identified in a single patient. Three patients were downstaged as a result of laparoscopic evaluation of intraabdominal lymph nodes. Six of 18 patients (33%) had unsuspected cervical lymph node
involvement. Lymph nodes near the diaphragm may be difficult to evaluate without extensive dissection. Furthermore, the laparoscopic staging procedure can be combined with placement of an enteral feeding tube at the same time.

The value of combined laparoscopic and laparoscopic ultrasound has been demonstrated in a number of other studies. In 56 patients with carcinoma of the esophagus (n = 28), rectosigmoid (n = 18), or rectum (n = 18), the preoperative staging of disease was altered by laparoscopy in nine (17%) of the overall group of patients. Of the patients with tumors of the gastric cardia (n = 18), laparoscopy altered the stage in seven (41%), but of patients with esophageal tumors (n = 38), stage was altered in just two (6%). The authors of this study concluded that the approach was better suited to tumors of the gastric cardia than of the esophagus. In this study, no attempt was made to perform thoracoscopic staging for lesions of the esophagus, however, and lymphatic drainage patterns may have precluded their ability to identify intrabdominal metastatic disease in patients with more proximal lesions of the esophagus.

In a study of 71 patients with potentially resectable gastric cancer, laparoscopy identified distant disease in 16 patients (23%). The combination of preoperative CT and laparoscopic evaluation resulted in a 93% resectability rate. These authors advocate staging laparoscopy for all patients with potentially resectable gastric cancer. Future studies may use the combination of laparoscopy and laparoscopic ultrasound to improve the results further.

HEPATIC TUMORS

The accurate evaluation of the liver is a critical component of tumor staging for many malignancies of interest to the surgeon, because the presence of metastatic disease in the liver often obviates the need for major resections. Radiologic imaging alone is imperfect, and several studies have demonstrated the scope of the problem. In one series, 63 of 150 of patients (42%) with colorectal carcinoma were found to have unresectable hepatic disease at laparotomy after an imaging evaluation demonstrated resectable lesions. In another series, 132 patients referred to the National Cancer Institute for liver tumor resection, 107 had negative staging evaluation but were brought to laparotomy. Extrahepatic disease was identified in 28 of these 107 patients (26%). These studies demonstrate one of the major potential benefits of laparoscopic staging—the ability to exclude from laparotomy those patients with unresectable lesions in a way that minimizes postoperative pain and hospitalization.

Of interest, one of the early applications of laparoscopy was for the staging of hepatic lesions, which had been reported as early as 1966 and in 1973 was reported in the evaluation of patients with Hodgkin’s lymphoma. Before the advent of modern video systems and laparoscopic instrumentation, it was estimated that 80% of the liver surface could be visualized laparoscopically and, of note, performed in the endoscopy clinic. The sensitivity of laparoscopy in the detection of hepatic metastatic disease was estimated at 70% to 90%.

In a study of 29 patients with hepatic malignancies (12 with hepatoma and 17 with metastatic disease), laparoscopy was undertaken before laparotomy to evaluate the resectability of the lesions. Laparoscopy alone demonstrated unresectability in 14 (48%) of 29 patients evaluated. Unsuspected cirrhosis was identified in four, and unsuspected extrahepatic metastases were found in ten. Not surprisingly, these investigators found that patients who underwent laparoscopy had shorter hospital stays than historical controls who underwent laparotomy that identified unresectable disease, and they concluded that laparoscopy should precede laparotomy for planned resection of hepatic malignancies.

The gold standard for evaluation of the liver is intraoperative palpation combined with intraoperative ultrasonography (LICU). In an experimental study to evaluate the effectiveness of laparoscopy and laparoscopic ultrasonography, liver lesions were induced in 18 pigs. Laparoscopic ultrasound identified the lesions in 17 of 18 animals, for a 94% sensitivity. Two false-negatives were obtained, for a specificity of 78%. In a study of 30 patients undergoing planned hepatic resection and 32 patients undergoing resection of a gastrointestinal primary malignancy, intraoperative ultrasonography was compared with CT angiography. Of the 30 patients planned to undergo hepatic resection, the procedure was changed or guided by the ultrasonographic result in 20 cases (67%). Of the 32 patients undergoing resection of their primary tumor, five patients (16%) had the stage of their disease altered by the results of intraoperative ultrasonography.

Having demonstrated the value of laparoscopy and intraoperative ultrasonography, combining the two procedures is a natural extension of the technology. In a study of 50 patients undergoing laparoscopic evaluation of hepatic tumors, laparoscopic ultrasonography was performed in 43 patients. Laparoscopy alone demonstrated that lesions shown resectable by preoperative imaging studies were unresectable in 23 patients (46%). Hepatic lesions not visible by laparoscopic examination alone were identified by laparoscopic ultrasonography in 14 patients. Furthermore, the use of laparoscopic ultrasonography provided staging information in addition to that gained by laparoscopy in 18 patients (42%).

In a study combining laparoscopic with laparoscopic ultrasonography, 50 patients were evaluated. Of these, 28 patients were deemed resectable on the basis of the laparoscopic studies. At laparotomy, 26 were resectable, for a false-negative rate of 4%. Of the 22 patients deemed unresectable after laparoscopy, 11 were identified by laparoscopy alone, but 11 more were deemed unresectable after laparoscopic ultrasound. Nodal involvement and vascular invasion were identified by ultrasound, emphasizing the importance of the combined approach for accurate staging.

A study of 420 patients with upper gastrointestinal malignancies evaluated the utility of combined laparoscopy and laparoscopic ultrasonography in staging these tumors. Patients underwent routine imaging studies and were thought to have resectable disease, then underwent laparoscopy and laparoscopic ultrasound. The use of combined laparoscopic staging avoided laparotomy in 20% of patients, with a sensitivity of 70%, although it was of little use in esophageal tumors—avoiding laparotomy in just 5% of patients and a 42% sensitivity—it appeared beneficial in patients with proximal bile duct tumors, liver tumors, and pancreatic tumors. This study supports the use of combined laparoscopy and laparoscopic ultrasonography in the staging of patients with a variety of upper gastrointestinal malignancies.

Up to 90% of metastatic lesions can be seen on the liver surface using laparoscopy. Furthermore, although CT can reliably detect lesions that are at least 10 mm in size, laparoscopy can detect lesions as small as 1 mm. Laparoscopy also facilitates the identification of lesions in areas often missed by CT scan, such as peritoneal, omental, and mesenteric surfaces. Accurate sampling of hepatic lesions with biopsy instruments is greatly facilitated by the direct vision afforded by laparoscopy, and hepatic metastatic disease can be accurately staged. Finally, the technical problems caused by loops of bowel are avoided when laparoscopy is used compared with conventional laparotomy or CT scanning. Thus, laparoscopy is extremely important in the staging of hepatic malignancies of all types.

PROSTATE CANCER

The definitive final staging procedure in the evaluation of prostate cancer is now considered to be pelvic lymphadenectomy. In the past, open bilateral pelvic lymphadenectomy was routinely performed, even with its associated significant morbidity, which included a lengthy recovery time. More recently, laparoscopic pelvic lymph node dissection (LPLND) has become standard practice for many urologists, affording their patients the benefits of decreased hospitalization and recovery times. The technique for this procedure has been described, including the extraperitoneal laparoscopic approach.

Laparoscopic detection of positive pelvic lymph nodes may alter the management of patients with prostate cancer. Patients with positive pelvic lymph nodes have been advised to undergo a wide range of therapies, ranging from endocrine treatment to a combination of radical prostatectomy and radiation therapy. An early series of 11 patients found metastatic disease in five, with a resultant change of therapy.

The findings for LPLND have evolved over time, particularly with the advent of widespread prostate-specific antigen (PSA) testing. Before PSA testing, lymph node
disection was indicated in all prostate cancer patients considered candidates for curative therapy. Many urologists limit the conduct of LPLND to patients at high risk for metastatic disease based on clinical stage, a PSA level of greater than 10 mg/dL, and tumor grade (Gleason score 7).

TESTICULAR TUMORS

Patients with early-stage nonseminomatous testicular cancer have a 20% to 30% incidence of retroperitoneal spread of disease to paraaortic nodes at the time of diagnosis. Laparoscopic retroperitoneal lymph node dissection has been described to evaluate these patients. At this time, few cases of this procedure have been reported in the literature. No studies to date have carefully compared this technique with its open counterpart. Therefore, this procedure is appropriate only in patients who have a low likelihood of nodal disease based on clinical risk factors.

LYMPHOMA

Lymphomas are a diverse group of malignant disorders of the lymphatic system that arise in nodal tissues. Typically, they are categorized by histology into Hodgkin’s lymphoma and NHL. The present role of surgery in the management of lymphoma is to establish a tissue diagnosis or to serve as a diagnostic adjunct when noninvasive diagnostic studies do not accurately define the extent of disease. Definitive treatment based on staged disease then follows.

The histologic type and regional extent of the disease are the primary factors used to determine the prognosis and the treatment selection. Histologic type is usually determined by a regional lymph node biopsy. Evaluating or staging the true extent of the disease has proven more elusive by noninvasive modalities. This is especially true in the determination of an intrabdominal component to the spread of lymphoma. The spleen, for example, is involved in approximately one-third of all cases of Hodgkin’s lymphoma. Most involved spleens, however, are of normal size or contain malignant foci whose size is beyond the resolution of present imaging technology. Likewise, lymph node size is a poor determinant of involvement by lymphoma. Many involved lymph nodes are of normal size, whereas normal lymph nodes may be enlarged secondary to a reactive response. Because of this lack of sensitivity and specificity of noninvasive modalities, surgical staging still has a key role in the staging of selected patients with lymphoma. This places the lymphoma staging procedure in the unique position of being one of the few major abdominal surgical procedures that is undertaken strictly for diagnostic purposes.

Indications and techniques for the performance of the staging laparotomy, in attempts to influence the associated morbidity and mortality, have undergone considerable evolution. Although previously performed on 85% of all patients with Hodgkin’s disease, staging laparotomy is performed in at most, only 30% of patients. With refinement of noninvasive imaging techniques, and changes in the medical management of the disease, the value of surgical staging of lymphoma has been reevaluated. Consequently, the subset of patients for whom surgical staging appears to be of value has become much smaller. This reduction has resulted in significant decreases in the proportion of splenectomies performed for staging lymphoma. In a study of the frequency of splenectomy for Hodgkin’s lymphoma, Marble et al. reported a rate of 44% during the period from 1979 to 1985, compared with only 26% during the period from 1986 to 1991. The role of splenectomy, however, is still in evolution. Some evidence suggests that combined chemoradiation therapy for Hodgkin’s lymphoma may be associated with a significantly increased risk of developing a second malignant disease. If this risk proves to hold true, it follows that surgical staging may again provide significant benefits for patients with Hodgkin’s lymphoma by reducing their need for combination therapy. Conversely, some centers are treating every patient with Hodgkin’s disease using chemotherapy as a first-line modality, obviating the need for surgical staging.

The role of the surgeon in patients with Hodgkin’s lymphoma includes lymph node biopsy to establish a diagnosis and staging laparotomy in a very select group of patients, usually limited to those patients with stage IIB disease after imaging evaluation. Patients with obvious stage III or IV disease should rarely be subjected to staging laparotomy because they will be treated with chemotherapy, and patients with stage I disease are usually treated with radiation alone, obviating the need for staging laparotomy. In some centers, chemotherapy is used to treat all patients with Hodgkin’s lymphoma, almost entirely eliminating the need for any surgical staging procedure.

Surgical staging of Hodgkin’s lymphoma has been reported to change the pathologic stage of the disease in 30% to 40% of patients, resulting in significant alterations in both prognosis and treatment selection. Staging laparotomy is associated with 18% morbidity and up to 0.7% mortality. Late complications occur in 5% to 15% of patients. These include partial small bowel obstruction in 9.6% of patients, requiring lysis of adhesions in 6.8% of these, and overwhelming post-splenectomy sepsis (OPSS) in 6.8% of patients. Horowitz et al. reported a 52% overall morbidity and a 9% mortality rate after splenectomy for hemolymphatic diseases. Spleenic size was the only preoperative factor found to be predictive of postoperative complications.

The conventional technique for the conventional staging for lymphomas has been well described. With the smaller incisions used in minimal-access surgery, several potential advantages can be offered to patients undergoing laparoscopic staging of abdominal lymphoma. These include less postoperative pain, earlier ambulation, better breathing, and shorter recovery time. These can be translated into fewer postoperative complications and possibly earlier administration of definitive therapy.

However, the procedure remains a technically demanding operation with which no single surgeon will probably gain vast experience. With further advances in laparoscopic technology and refinements in techniques, laparoscopic staging of abdominal lymphoma will become an important tool in the surgical armamentarium.

The laparoscopic approach to this procedure follows the same principles as those delineated for the open procedure. There are no true contraindications to laparoscopic staging. Relative contraindications to laparoscopic staging include abdominal wall sepsis, gastrointestinal distention, intraabdominal sepsis, and extensive adhesions. Laparoscopic staging of abdominal lymphoma has been successfully performed by several groups. A comparison of laparoscopic and open staging of Hodgkin’s disease has demonstrated equivalent oncologic results, and functionally superior results with laparoscopic staging. These investigators found a slightly longer operative time (202 vs. 144 minutes), but significantly shortened postoperative ileus and postoperative hospitalization times. These data strongly support the use of laparoscopy for accurate staging of Hodgkin’s disease when indicated.

Techniques for the laparoscopic exploration of other abdominal malignancies, with lymph node retrieval, laparoscopic splenectomy, and laparoscopic wedge biopsy of the liver, were developed. When combined, these procedures complete a laparoscopic staging procedure. The ports, or trocars, are positioned as in Figure 29.1-5. All five ports are 12 mm in diameter. Using identical large ports enables the surgeon the versatility to switch instruments between the different anatomic sites required in this procedure. A sixth port may be, but is not always, necessary for access to the iliac nodes.

FIGURE 29.1-5. Port placement for laparoscopic splenectomy. The operating ports are on the left side, whereas the two upper midline ports are used for retraction. (From ref. 108, with permission.)
The laparoscopic dissection of lymph nodes can be very challenging because nonpathologic nodes are small and difficult to identify. LPLND is widely used in genitourinary surgery for the staging of prostate cancer and has become well accepted. The magnification afforded by the use of laparoscopic instrumentation has proven to be very helpful. All abnormal nodes on preoperative lymphangiogram should be removed and clips applied as markers. Oophoropexy is then performed in young females by suturing the ovaries to the back of the uterus. The spleen is then removed intact, within the plastic bag, through a small midline incision incorporating the umbilical port site.

The accurate histologic diagnosis of lymphoma requires assessment of the nodal architecture, which requires an intact node capsule. Therefore, whenever possible, one should excise an entire intact lymph node. The use of formalin precludes the assessment by flow cytometry, which has become crucial for complete and accurate classification of lymphomas and on which therapeutic decisions may ultimately be based. Therefore, each lymph node should be sent for examination in saline in a fresh state. As mentioned above, the spleen should be sent to the pathologists intact and, usually, in a fresh state. The liver tissue may be placed in formalin for transport to the pathology department. The planning and conduct of the staging procedure involves close cooperation between surgeon, radiologist, medical oncologist, and pathologist.

The morbidity and mortality associated with staging laparotomy is well established. A review of staging laparotomy by Multani and Grossbard demonstrated a mortality of 0.3% to 1.0%, major morbidity of 3% to 18%, and minor morbidity of 6% to 19%. Delays to definitive treatment occurred in 5% to 10% of patients. Jockovitch et al. reported surgical complications in 26% of 133 consecutive patients. Complications included atelectasis in 13%, small bowel obstruction in 10% (requiring reoperation in 7%), subphrenic abscesses in 2%, and wound dehiscence in 1%.

OPSS, which can follow any procedure that removes the spleen, remains a serious potential complication. The incidence of OPSS can be decreased by the preoperative administration of the polyclonal pneumococcal vaccine. In addition, vaccinations for Haemophilus influenzae and Neisseria meningitidis are often administered. These precautions should provide some protection against the three organisms most commonly responsible for OPSS. The optimal timing of such vaccinations remains difficult to define but should probably be administered as long as possible before operation. Patient education is also vitally important. They should be alerted that a low-grade fever might be a harbinger of a serious infection. Although some recommend prophylactic oral penicillin in children, this practice is somewhat controversial. In general, although some question the value of splenectomy because of the risk of OPSS, patients whose therapy depends on accurate staging should undergo splenectomy.

Causes for conversion to an open procedure during splenectomy include densely adherent adjacent structures, technical errors, and cardiopulmonary instability. The most troubling technical errors are those associated with excessive bleeding that makes delineating anatomic structures very difficult. Conversion rates from 0% to 19% have been reported in series of laparoscopic splenectomy alone. Patients about to undergo laparoscopic staging must be apprised of these data as part of the process of informed consent.

Whereas the use of laparoscopic splenectomy in the treatment of idiopathic thrombocytopenia purpura (ITP) has become the standard, some still question the use of laparoscopic approaches in the staging of Hodgkin’s disease. More recent data, such as that reported by Baccarini and coworkers, suggest that the laparoscopic operation is equivalent to the open procedure. They demonstrated equivalent lymph node harvest, and on reasonable postoperative follow-up, they found fewer subdiaphragmatic relapses in the laparoscopy group. Although these data are not prospectively randomized, the results are very compelling in support of laparoscopic staging.

The use of laparoscopy in the management of a variety of abdominal lymphoproliferative diseases has been reported by Silecchia et al. These investigators performed laparoscopic investigation on 64 patients with a number of diseases, including retroperitoneal adenopathy, Hodgkin’s disease, and non-Hodgkin’s disease. Laparoscopic ultrasound was used extensively. They concluded that the interval between diagnosis and treatment was significantly shortened by using a laparoscopic approach. Although this series does not necessarily provide the final word, it again demonstrates the utility of laparoscopy in the evaluation of these patients and suggests the need for further study.

NHL is a diverse group of diseases with a wide range of biologic behaviors. They may be very aggressive and rapidly fatal or behave as one of the most indolent and well-tolerated malignancies affecting humans. Because the clinical course is variable, the pattern of spread is also unpredictable. NHL is classified into low, intermediate, and high-grade pathologic groups according to the National Cancer Institute’s working formulation. Each of these groups is further subdivided based on cell type (e.g., small cell, large cell). The therapy for these patients is still evolving, and surgical staging is generally reserved for the very small minority of patients with localized disease who receive radiation therapy alone. The role of the surgeon in the care of patients with NHL is usually limited to the biopsy of a single peripheral lymph node to establish a tissue diagnosis. In patients with NHL, the precise definition of disease location, unlike Hodgkin’s lymphoma, has less impact on therapeutic decision making. In general, NHLs are systemic diseases at the time of diagnosis and require the use of systemic therapy (e.g., chemotherapy) rather than regional therapy (e.g., radiation) for treatment.

Laparoscopy can play a beneficial role in the diagnosis of NHL in a select subgroup of patients. For example, a 70-year-old woman presented to her primary care physician with general malaise, weight loss, and occasional fevers. In the absence of positive findings on physical examination, she was evaluated with an abdominal CT scan (see Fig. 29.1-1), which demonstrated peri-aortic lymphadenopathy. The diagnosis of NHL was made in this patient by laparoscopic lymph node excision as shown in Figure 29.1-2, performed on an outpatient basis, and systemic chemotherapy was begun.

Staging laparoscopy in patients with NHL is restricted to those few patients with clinically limited disease (stage I and II) who are to be treated with radiation therapy alone with curative intent. In these very unusual cases, a staging procedure similar to that performed for patients with Hodgkin’s lymphoma may be undertaken laparoscopically. Splenectomy may be omitted from the surgical staging of abdominal NHL because splenic involvement usually does not affect the therapy used. Laparoscopy and its removal increases toxicity to patients given combination chemotherapy. Laparoscopy may have a role in the evaluation of treatment efficacy because persistent disease is often overdiagnosed by routine imaging studies.

The gastrointestinal tract is involved in 20% of advanced NHL and represents 1% to 4% of all alimentary tract malignancies. When large or small bowel is involved, the typical presenting signs and symptoms are consistent with a bowel obstruction secondary to external compression or intussusception. The most frequent site of involvement is at the ileocecal valve. Complete, curative resection is generally indicated for localized lesions. If the lymphoma is of a diffuse submucosal pattern where systemic therapy is required, resection should be limited to the correction of the mechanical obstruction. Should the lesion be discovered during a laparoscopic exploration or a laparoscopic staging procedure, laparoscopic resection of the lesion may be feasible if the surgeon has the technical ability and experience.

Laparoscopic localization and laparoscopic-assisted resection of the tumor is another alternative. The entire bowel, however, should be evaluated because skip...
lesions may exist. Gastric lymphoma, on the other hand, may be diagnosed after esophagogastroduodenoscopy, which is usually performed for upper gastrointestinal bleeding or anemia. If the lesion is localized, then laparoscopic resection may be technically feasible. Most patients with NHL are upstaged by staging laparotomy. This upstaging, however, results in no significant impact on the modality of treatment. Therefore, staging laparotomy for NHL has fallen out of favor except for the small, select group of patients whose treatment would be intensifed should the liver be involved. The liver can be involved in 20% of patients with NHL. The role of the surgeon for patients with NHL is generally limited to the minimum procedure needed to establish the diagnosis.

GYNECOLOGIC MALIGNANCIES

Although gynecologists have used laparoscopic instrumentation for many years, the use of laparoscopy for the management of gynecologic malignancies is more recent. Several reports of laparoscopic staging for apparent early-stage ovarian cancer have been published. However, the follow-up remains short at this time, and the utility of this technique in ovarian cancer remains unproven. A prospective trial sponsored by the Gynecologic Oncology Group is under way to evaluate the utility of laparoscopy in these patients. The utility of the second-look laparotomy in the assessment of patients who have been treated for ovarian cancer is well established. Several reports of second-look laparoscopy with apparently good results have been published. Further evaluation of this application is currently in progress.

Laparoscopy also has been used in the staging of advanced ovarian disease. Patients with cervical cancer have undergone laparoscopic-assisted radical vaginal hysterectomy with LPLND. The utility of this procedure remains to be proven with prospective trials. Patients with early endometrial cancer have been staged by combining laparoscopy with vaginal hysterectomy in a procedure that has been named laparoscopic-assisted surgical staging. Laparoscopy provides the ability to assess the peritoneal cavity, obtain peritoneal washings, and guarantee the removal of the adnexae. Lymph node sampling can also be performed laparoscopically when necessary in these patients. Although laparoscopy has been used in the management of ovarian, cervical, and endometrial malignancies, its potential is unconfirmed at this time. Reports of complications and long-term results are not yet available. The results of ongoing clinical trials must be evaluated before this technique is widely applied in the management of gynecologic malignancies.

LAPAROSCOPY IN THE TREATMENT OF MALIGNANCY

GENERAL CONSIDERATIONS

Laparoscopic approaches have been used to treat a wide variety of malignancies. Many of these techniques were applied with a curative intent, whereas some were conducted as palliative procedures. At the time of this writing, the use of laparoscopic techniques to treat patients with malignancy remains controversial. In an attempt to afford patients with cancer the same benefits afforded patients with cholelithiasis, many investigators have conducted laparoscopic surgery for cancer with curative intent, particularly for carcinoma of the colon. However, this development may have been somewhat premature. The two major concerns about an operation performed laparoscopically for the treatment of cancer are (1) to be sure that the laparoscopic operation meets the same “oncologic” goals of the open procedure (e.g., margins of resection, lymph node harvest, recurrence rate, evaluation of other intraabdominal organs) and (2) to demonstrate an advantage to the patient for having undergone the procedure laparoscopically (e.g., decreased hospital stay, decreased cost, more rapid return to work). To date, few data convincingly demonstrate the validity of these two laparoscopic principles in the treatment of cancer.

GASTRIC CANCER

The application of laparoscopic techniques to gastric resection has been made possible by the rapid advances in staple technology. The first laparoscopic gastric resection using a Billroth II reconstruction performed intrabdominally was reported in 1992. Since that time, the same group has continued to apply laparoscopic surgical techniques to gastric surgery. In a series of 16 patients, all were operated on for benign disease, although two patients had foci of cancer found at the time of histologic examination. These two patients underwent open lymphadenectomy. Laparoscopic gastric resection remains a technically demanding procedure, with precise identification of anatomic structures essential to its successful completion.

The use of laparoscopic techniques in the treatment of gastric cancer requires careful selection of patients. Early gastric cancer involving the submucosa requires gastrectomy with removal of the greater omentum and level 1 lymph nodes. Techniques for this procedure have been fully described. More advanced tumors, which require further node dissections, are not amenable to laparoscopic resection. Patients with stage IV disease who require palliative gastric resections are good candidates for laparoscopic resection. Gastric lymphoma and gastric polyps requiring resection are also suitable for laparoscopic resection. The inability to perform extensive lymphadenectomy may limit the applicability of laparoscopic gastric resection to malignancies, but it is clear that advances in technology may make this more feasible.

COLON CANCER

Carcinoma of the colon is a very common disease in the United States, making it an attractive candidate for laparoscopic treatment. Surgical resection of carcinoma of the colon is a well-established procedure. Thus, any surgical approach that can potentially treat this disease with decreased postoperative pain and hospitalization may result in considerable advantages, generating great interest in the laparoscopic resection of colon cancer. It is clear that laparoscopic colon resection is an “advanced” procedure requiring more training, experience, and time than that for procedures such as appendectomy or cholecystectomy. The use of animal models has facilitated the testing of some of these techniques and may be an important educational tool. Intracorporeal anastomotic techniques may be used but remain a greater technical challenge than extracorporeal anastomoses.

Indications for laparoscopic colon resection at this time include segmental resections for diverticular disease, polyps, rectal prolapse, and intestinal volvulus. The role of laparoscopic resections in the management of colonic malignancies remains undefined at this time and should be carried out only in the setting of a prospective trial. It is reasonable to laparoscopically resect colonic malignancies with synchronous hepatic or pulmonary metastases as a palliative procedure. When performed appropriately, laparoscopic colon resection for cancer should include the following components, just as in open surgical resections: (1) resection of tumor in the bowel wall and adjacent soft tissues, (2) resection of an adequate margin of normal bowel, and (3) an adequate lymph node resection with associated vascular pedicle.

The preoperative factors affecting suitability for laparoscopic colonic surgery are similar to those important in other laparoscopic procedures. The role of laparoscopic colon surgery is similar to those important in other laparoscopic procedures. The lack of ability to use palpation in the abdominal cavity prompts some to perform a more thorough preoperative evaluation with colonoscopy and CT scan. In general, the surgeon and assistant stand on the side opposite the bowel to be resected. Some prefer the dorsolithotomy position, and others prefer the patient in the supine position. The use of the dorsolithotomy position has two potential advantages. First, intraoperative colonoscopy, facilitated by the use of low stirrups, may be necessary for the colorectal anatomy, obtain peritoneal washings, and guarantee the removal of the adnexae. Lymph node sampling can also be performed laparoscopically when necessary in these patients. Although laparoscopy has been used in the management of ovarian, cervical, and endometrial malignancies, its potential is unconfirmed at this time. Reports of complications and long-term results are not yet available. The results of ongoing clinical trials must be evaluated before this technique is widely applied in the management of gynecologic malignancies.

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The preoperative factors affecting suitability for laparoscopic colonic surgery are similar to those important in other laparoscopic procedures. The lack of ability to use palpation in the abdominal cavity prompts some to perform a more thorough preoperative evaluation with colonoscopy and CT scan. In general, the surgeon and assistant stand on the side opposite the bowel to be resected. Some prefer the dorsolithotomy position, and others prefer the patient in the supine position. The use of the dorsolithotomy position has two potential advantages. First, intraoperative colonoscopy, facilitated by the use of low stirrups, may be necessary for localizing the lesion in the operating room. Second, one technique demonstrates the utility of the colonoscope in dissecting the hepatic and splenic flexures. The zero-degree laparoscope is used for these procedures.

In general, for a right hemicolectomy, two left-sided and one right-sided port are used in addition to the umbilical camera port (Fig. 29.1-7). The abdomen is explored thoroughly, with special attention paid to the liver, just as is performed with open surgical approaches. Ports are best placed as they are needed, which allows for flexibility, rather than using a static pattern placing all ports synchronously. The bowel is then mobilized and the vascular pedicle to the sigmoid colon divided using a stapler. The bowel is then exteriorized and an extracorporeal anastomosis fashioned.
Technical limitations can hinder the performance of laparoscopic colon resections. In an attempt to define them, Pandya and colleagues examined indications for intraoperative conversion of a laparoscopic colon resection to an open procedure. Two hundred patients who underwent laparoscopic colon resection were reviewed, with 47 (23.5%) converted to an open operation. Indications for conversion included technical problems in 15 patients (hypercarbia, unclear anatomy, and stapler misfire), laparoscopic complications in nine patients (bleeding, cystotomy, and enterotomy), and problems that “exceeded the limits of laparoscopic dissection” in 23 patients (phlegmon, adhesions, obesity, and tumor invasion of adjacent organs). The investigators noted a decreasing conversion rate with experience. After the “learning curve,” indications for conversion have included excessive tumor bulk, adhesions, and a massive diverticular phlegmon.

The safety and efficacy of laparoscopic colectomy has been studied retrospectively. A summary of a large number of studies is shown in Table 29.1-2. In a series of 51 laparoscopic colon resections, 24% of patients who underwent open colon resection. Mean postoperative hospital stay was significantly less in patients with laparoscopic sigmoid and right colectomies than for those patients converted to open operation or for those procedures performed using conventional open techniques. Total hospital cost for patients undergoing conventional open right hemicolectomy was less than that for the converted group but not for those having a laparoscopic resection. Lymph node harvest was comparable in all three groups. The authors of this study concluded that these data demonstrate that laparoscopic colectomy can be performed with acceptable morbidity and mortality, but that there is no definite cost savings.

Laparoscopic colon resection was performed in 80 patients and compared with a control group of 53 patients undergoing conventional open colectomy by the same group of surgeons. Analysis included complications, rate of conversion, length of procedure, duration of postoperative ileus, hospital stay, hospital cost, and adequacy of the specimen obtained. Operations were converted to open procedures in 23% of patients, which decreased to 15% in the second half of the series. The length of procedure was greater in those undergoing laparoscopic resection (mean, 221 minutes) than in those undergoing open colectomy (mean, 183 minutes). Operating room and total hospital charges were also greater in those patients undergoing laparoscopic resection compared with those having open colectomy. Patients having a laparoscopic colectomy had an average postoperative stay of 5.2 days, compared with 7.8 days for those having open colectomies. The pathology specimens were similar in all groups. This study further validates that laparoscopic colectomy can be performed safely with shorter hospitalization, but at higher overall cost. Perhaps with greater experience, operating times will decrease, as was suggested by this study.

A number of trials have compared laparoscopic colon resection to traditional open resection. Thirty-eight laparoscopic colon resections were compared with 39 open resections. The authors of this study found slightly longer operative time (161 minutes vs. 131 minutes) in the laparoscopic group, with lower estimated blood loss (122 mL vs. 192 mL) and significantly shorter length of stay (3.3 days vs. 7.4 days), with similar complication rates. They concluded that laparoscopic colon resection for benign disease affords the patient the advantages of laparoscopic surgery and gives surgeons the opportunity to develop requisite skills while results of trials of laparoscopic surgery for malignancy are awaited. In a prospective trial of 194 patients in San Antonio, Texas, patients selected their own method of resection. Open colon resection was selected by 110 patients and laparoscopy by 84 patients. The authors of this study looked at a number of outcome variables and observed that laparoscopic resection allows adequate margins and lymph node harvests no different from open resection. In brief follow-up, survival in the two groups was similar. In a study of 14 patients undergoing laparoscopic colon resection for diverticular disease, patients were compared with a similar group who had undergone open resection. Estimated blood loss, days to oral liquids, and length of stay were significantly less in the laparoscopic group. Mean total hospital charges and costs were also less, suggesting the benefits of laparoscopic colon resection. In a randomized prospective trial, 51 patients underwent colon resection by laparoscopic means or by traditional open techniques. Similar lymph node harvests were reported in the two groups, as were resection margins and adequacy of specimens. Patients were discharged earlier from the hospital in the laparoscopic group as well. Although follow-up was not long, this study suggests that the laparoscopic approach is preferable for patients requiring colon resection. Similar results have been observed by a number of authors.

Some of the trials reported to date demonstrate excellent results but lack lengthy follow-up. Hoffman et al. reported 238 patients who underwent laparoscopic colon resections, with 39 patients who underwent resection available for just 24 months of follow-up. They concluded that survival rates were similar to those observed for patients who underwent open colectomy. A single-arm, retrospective multicenter study reported a 10.5% conversion rate, an average of 12.1 lymph nodes resected, and a mean follow-up of 16 months. The authors of this study admitted the need for longer follow-up. In a study of 100 patients, median operative time for laparoscopic resection was 180 minutes, and the conversion rate was 31%, although the conversion rate decreased relatively along the learning curve. Median follow-up was just 15 months in this study, which demonstrated four distant recurrences and one pelvic recurrence. These authors asserted the importance of longer follow-up and a randomized trial to truly establish the benefit of this procedure. In an excellent study of 172 patients who underwent laparoscopic resection for adenocarcinoma of the colon, 25 patients underwent colon resection and 12 patients were lost to follow-up, leaving 135 patients in the study. Median follow-up was 24 months, with observed 2-year survival rates of 100% for stage I, 86% for stage II, 81% for stage III, and 29% for stage IV. Survival rates at 4 years were 100% for stage I, 80% for stage II, 54% for stage III, and 0% for stage IV. No port-site recurrences were observed. Although the authors of this study correctly concluded that early survival curves for patients undergoing laparoscopic resection do not differ from historical controls, they also assert that “further validation is needed.”

That laparoscopic colon resection is feasible goes unquestioned. Some studies have pointed out that it remains a technically demanding procedure, considerably more difficult than laparoscopic cholecystectomy, and has a lengthy learning curve. However, the use of laparoscopic resection of the colon for the treatment of malignancies is currently under study. The American Society of Colon and Rectal Surgeons does not endorse the application of laparoscopic technology to cure cancers at this time. The studies just described have shown that laparoscopic colon resection is safe, feasible, and obtains pathologic specimens similar to those obtained from open surgery. Although it is tempting to obtain the same benefits of decreased hospitalization and recovery for patients undergoing colon resection as has been shown in patients undergoing cholecystectomy through the use of laparoscopy, there is no evidence at this time to definitively conclude that this is the case. We must also consider the issue of the possibility of compromised cancer control and complications in this discussion. Cancer control issues include extent of lymph node resection, port-site recurrences, and adequacy of intraperitoneal staging in the absence of tactile sensation. The series reviewed above suggest that a lymph node resection similar to that in open surgery is possible. Others have made similar observations regarding lymph node harvests. The issue of port-site metastases is discussed above in the section Port-Site Metastases, but rates from 0% to 3.2% have been reported, compared with fewer than 1% in open surgery.
colon resection. The problem with many of the anecdotal reports in the literature is that the overall denominator is not known, and only through a prospective trial can these issues be adequately studied. The 1-year post-surgical recurrence rate has been reported at less than 1% in the first 252 patients in the registry of the American Society of Colon and Rectal Surgeons. In this series, all of the recurrences were in patients with node-positive disease. Sugarbaker has advocated the use of intraperitoneal chemotherapy based on his work with disseminated gastrointestinal malignancies.

Although laparoscopic surgery has the potential to save hospitalization time and recovery time, such savings must not be made at the expense of overall survival. The prospective trial currently under way at many centers throughout the United States and funded by the National Institutes of Health should address the issues of cancer control, costs, and quality of life. The surgical community is awaiting the results of this trial. This carefully designed prospective trial will answer the significant questions regarding laparoscopic resection of colon cancer. The approach of waiting for the results of this study has been endorsed by a number of authors. 

GALLBLADDER CANCER

Although it is rare, the presence of a gallbladder malignancy is a possibility that must always be in the mind of the laparoscopic surgeon while performing a routine laparoscopic cholecystectomy. This disease, most common in older women, is the fifth most common malignancy of the gastrointestinal tract and is associated with a dismal prognosis. It is estimated that carcinoma is present in 1% of all cholecystectomy specimens. Laparoscopic cholecystectomy is the procedure of choice for patients with symptomatic cholelithiasis, but the presence of gallbladder carcinoma remains a contraindication to the laparoscopic conduct of this procedure. Preoperative diagnosis of this disease is difficult, because the sensitivity for ultrasonography in early cases is only approximately 20%. In view of the difficulty with which preoperative diagnosis can be made, it is not surprising that the diagnosis is often made only after histologic examination of the surgical specimen.

The optimal treatment for this rare disease remains elusive. In a large retrospective study of 724 patients from a number of European centers, only 4% of patients presented with Tis lesions, but these were the only patients with any hope of long-term survival. Prognosis in stage T1 and T2 was markedly worse, although no data support the use of extended surgical resections in these patients. Furthermore, others have shown that, at the present time, the use of adjuvant chemotherapy or radiation therapy does not significantly affect survival.

The treatment of patients suspected of having carcinoma of the gallbladder preoperatively should include a definitive procedure performed through conventional open surgical techniques as the initial procedure. Clinical data from ten patients with laparoscopically discovered gallbladder carcinoma have been reported. All ten patients were believed to have resectable disease based on preoperative studies and intraoperative findings. The interval to exploration at the referral center was 14 to 74 days, with a median of 30 days. Gross intraperitoneal dissemination was found in four patients. The investigators concluded that patients in whom gallbladder carcinoma was found preoperatively using either visual examination of the gallbladder during attempted laparoscopic cholecystectomy should be converted immediately to an open procedure or the procedure terminated and the patient referred for definitive therapy. During the conduct of a laparoscopic cholecystectomy, any evidence for the presence of a carcinoma is cause for conversion to an open procedure. Routine examination of the specimen with frozen section if suspicious areas are present should also be carried out, with conversion to an open procedure if positive for malignancy.

In summary, any patient with a lesion that is preoperatively suspect for malignancy should undergo cholecystectomy by conventional open cholecystectomy. If the diagnosis is suspected during a laparoscopic cholecystectomy based on the appearance of the gallbladder, frozen section should be obtained and the procedure converted to an open cholecystectomy if the histology demonstrates malignancy. If the diagnosis is made only after laparoscopic cholecystectomy is completed, then port sites should be excised at a second procedure. Further surgical or adjuvant therapy may also be indicated.

HEPATIC TUMORS

Whereas the use of laparoscopy in the staging of hepatic lesions, either primary or metastatic, has become fairly widespread, laparoscopic treatment of hepatic malignancies is rarely performed. This is because of the technical difficulty of this procedure as well as the scarcity of patients with lesions amenable to laparoscopic resection. The laparoscopic treatment of hepatic lesions has been reported. A benign liver cyst was fenestrated under laparoscopic guidance and provided effective therapy for this benign condition while avoiding the potential morbidity of a laparotomy. A large series of 43 patients with benign solid and cystic lesions treated laparoscopically has been reported by Kakhouda et al. These authors concluded that laparoscopic surgery is indicated for patients with giant solitary hepatic cysts and select patients with small, benign solid tumors located in anterior liver segments.

A number of techniques can be performed laparoscopically, including wedge excisions using a stapling device or even laparoscopic hepatic segmentectomy. The anterolateral areas of the segments in the Couinaud classification are amenable to laparoscopic resection because of their accessibility.

Although a number of techniques are available for liver resection, the ultrasonic dissector is preferred by some. A randomized prospective trial has shown that a laparoscopic version of this device is effective in laparoscopic cholecystectomy. It is natural that this device may be used for hepatic resection. An animal trial has been reported, demonstrating hepatic resection on pigs using the ultrasonic dissector. The ultrasonic dissector was effective in dissecting the intraparenchymal structures, including vascular structures. A single case of a left lateral segmentectomy in a human performed laparoscopically has been reported. With improved instrumentation becoming available, perhaps more hepatic resections will be performed laparoscopically.

Another application of laparoscopic technology to the treatment of liver lesions is cryotherapy. Cryosurgery has been shown to be effective in the treatment of some hepatic malignancies. Ultrasound monitoring of this procedure is essential. With the advent of laparoscopic ultrasound probes and cryotherapy probes, it is possible to perform cryotherapy of hepatic lesions. However, anatomic limitations may prevent the use of this technology because of limited exposure of certain lesions.

More recently, radio frequency ablation of tumors has been performed for metastatic and primary lesions of the liver. This technique is often performed percutaneously, but situations exist in which a lesion is accessible only by using laparoscopic techniques to position the treatment probe accurately. Of 30 patients who underwent radio frequency ablation for primary and metastatic lesions of the liver in one series, 12 were treated laparoscopically, 12 at laparotomy, and six percutaneously.

As laparoscopic technology improves and new modalities are applied to the treatment of hepatic lesions, more applications of minimally invasive surgery may be found for these patients. The role of laparoscopy in the management of malignant lesions of the liver remains undefined.

PANCREATIC CANCER

Resection with the intent for cure is possible in only approximately 10% to 20% of patients who present with carcinoma of the pancreas, and 5-year survival rates of all patients presenting with the disease are only approximately 3%. However, several more recent series have reported 5-year survival rates as high as 20% to 25% for patients who undergo resection for cure. Patients with pathologically negative lymph nodes have an even higher survival rate. Many of the patients who are not resectable for cure often require surgical palliation. Laparoscopic surgery has the potential to provide this palliation while minimizing postoperative pain and length of hospital stay, both especially important considerations in patients with limited life expectancy.

The laparoscopic resection of pancreatic tumors is technically feasible but unlikely to become widely practiced. Gagner and Pomp, reporting having performed a pylorus-preserving pancreaticoduodenectomy in a patient with chronic pancreatitis and pancreas divisum. Reconstruction was performed with a gastrojejunostomy, hepaticojejunostomy, and pancreatojejunostomy. The patient's postoperative course was complicated by delayed gastric emptying, and he was discharged on the 30th postoperative day.

Laparoscopic distal pancreatectomy, with or without splenic salvage, has been well described. It is often combined with splenectomy, as described by Cuschieri and colleagues, who reported a series of five patients who underwent laparoscopic distal pancreatectomy and splenectomy using a five-port technique. This procedure is indicated for benign tumors in which the splenic vein cannot be separated from the pancreatic lesion, or in palliative resections of the distal pancreas for lesions such as cystadenoma, neuroendocrine tumors, cysts, and adenocarcinoma of the tail of the pancreas. It is unlikely that minimally invasive surgery will play a large role in the curative resection of malignancies of the head of the pancreas in the near future.
RENAL CELL Carcinoma
The use of laparoscopic surgical approaches for patients with renal cell carcinoma has been described, with investigators demonstrating that nephrectomy can be safely performed using existing laparoscopic instrumentation. In this early series, the procedure took a mean of 5.6 hours to complete, and patients had an average hospital stay of 4.6 days. The kidney is morcellated with an electric morcellator placed through a 10-mm port and extracted using a sturdy bag.

In some cases, preservation of renal parenchyma may be indicated. The laparoscopic enucleation of a renal cell carcinoma also has been described. These investigators concluded that this procedure is relatively easy to perform compared with nephrectomy and, when indicated, may be preferable to perform by a laparoscopic approach.

Spleen
Although the spleen rarely harbors primary or secondary tumors in humans, the surgical oncologist is often called on to perform a splenectomy for hematologic diseases. The spleen is well within the reach of the laparoscopic surgeon, and by applying laparoscopic techniques, the patient is afforded the benefits of laparoscopic surgery, including shortened hospitalization and decreased postoperative pain. A number of series in the literature report laparoscopic removal of the spleen. These procedures have been performed for a number of indications including staging of Hodgkin’s lymphoma, ITP, thrombotic thrombocytopenia purpura, acquired immunodeficiency syndrome-related thrombocytopenia, hereditary spherocytosis, autoimmune hemolytic anemia, leukemia, and splenic abscesses. There may be particular subsets of patients for whom laparoscopic splenectomy is particularly beneficial. A case report of successful laparoscopic splenectomy on a patient who is human immunodeficiency virus–positive, a devout Jehovah’s witness refusing transfusion, and with a preoperative hematocrit of 8.8% highlights the attractiveness of this technique. In general, laparoscopic splenectomy represents the gold standard for removal of the spleen.

Splenectomy was commonly performed for the staging of lymphomas in the past, and in one series demonstrated a significant increase in the period 1963–1982 compared with 1946–1962. However, more recent trends show that splenectomies are now being performed more often for cytopenic and anemic diseases and less often for Hodgkin’s disease. The consequences of splenectomy are poorly understood at an immunologic level, but it is clear that the spleen plays a major role in a wide range of immune responses. Patients should receive a pneumococcal vaccine preoperatively to help avoid the infectious complications of the asplenic state. The patient can be positioned in several ways for this procedure, with some groups preferring a right decubitus position.

In one large series, 43 patients were brought to the operating room for laparoscopic splenectomy, and 35 (81%) were successfully completed. The remaining 19 underwent conversion to open splenectomy, usually for bleeding. Laparoscopic splenectomy has become the standard method for splenectomy in some centers. Conversion rates in other series have been reported as 2 (9%) of 22 cases, 12 (12%) of 17, 15, and 3 (19%) of 13. The details of the technique have been adequately described by Flowers et al.

It is important to make a thorough search for accessory splenic tissue, identified in 10% of the patients in one series. Accessory spleens are identified in up to 18% of patients undergoing splenectomy. The magnification afforded by the laparoscope may aid in this task. In a series of 100 patients undergoing open splenectomy for ITP, 13 patients had a poor response to splenectomy, five of which required accessory splenectomy. In one large series of laparoscopic splenectomies for ITP, a positive response was observed in 18 (82%) of 22 patients with ITP. It is difficult to predict who will respond to splenectomy, with no predictive factors being identified, even in large series of patients with ITP.

In a prospective study of operative outcomes, laparoscopic splenectomy using the lateral approach was performed on 147 patients and open splenectomy performed on 63 matched patients at three teaching centers. Laparoscopic splenectomy resulted in longer operative times (145 minutes vs. 77 minutes), reduced blood loss (162 mL vs. 380 mL), shorter postoperative stay (2.4 days vs. 9.2 days), and fewer complications compared with the open procedure. The authors of this study also reported that the mean operative time for laparoscopic splenectomy was lower than the open procedure ($3311 vs. $3861). The conversion rate in this series was 2.7%.

Although laparoscopic splenectomy is a technically demanding procedure, it offers the patient the potential for decreased postoperative pain and hospitalization with more rapid return to normal activities of living. Further prospective data are needed to confirm these observations. Surgical alternatives to splenectomy, such as partial splenectomy, have been offered as a way to reduce the incidence of postoperative infections. These techniques may also be approachable with laparoscopic techniques in the future.

ADRENAL Tumors
Laparoscopic techniques have been used for the resection of adrenal lesions. Although the anterior transabdominal approach is considered by some to be a source of postoperative morbidity, the laparoscopic approach may offer some advantages. Adrenal tumors are fairly common, having been found in 2% of patients in autopsy series. Small, asymptomatic tumors are reported in as many as 0.6% of abdominal ultrasonograms and CT examinations. Those discovered that are less than 4 cm in diameter and in the absence of endocrine syndromes can be observed after a careful evaluation. However, a fair proportion of these lesions may require extirpation, a procedure that has been performed laparoscopically with the apparent advantages of decreased pain and more rapid return to full activity.

Furthermore, a number of laparoscopic approaches have been described. The anterior laparoscopic approach requires mobilization of the colon and, occasionally, other intraabdominal organs. A retroperitoneal laparoscopic approach also has been described, which may be more attractive. One study has compared the two approaches and found no difference in operative time, analgesia requirements, hospital time, recovery time, or complication rate. The retroperitoneal laparoscopic approach may ameliorate some of the negative effects of pneumoperitoneum on the cardiovascular hemodynamics of the patient. However, most surgeons prefer the anterior approach at this time.

In one series of four patients, three patients had unilateral tumors and one had a bilateral pheochromocytoma. Single right adrenalectomy was performed in 2.0 to 2.5 hours, whereas bilateral adrenalectomy lasted 5.5 hours. The hospital stay was 3 to 4 days postoperatively.

Over a 14-month period, Takeda and coworkers removed seven left adrenal glands and three right adrenal glands from ten patients in operations ranging from 165 to 572 minutes (mean, 295 minutes). Conversion to open adrenalectomy was reported in one case (10%). They concluded that laparoscopic adrenalectomy is applicable to cases of primary hyperaldosteronism, but application to other lesions requires further study.

Twenty-five consecutive laparoscopic adrenalectomies performed on 22 patients in a 1-year period were reported by Gagner et al. These surgeries were performed through a lateral decubitus flank approach and four 11-mm trocars and included 12 right and 13 left adrenal glands. The mean operative time for single adrenalectomy was 2.3 hours and for bilateral adrenalectomy was 5.3 hours. Diseases in this series included nonfunctional adenoma, pheochromocytoma, Cushing’s disease, aldosteronism, primary aldosteronism, angiomylipoma, and medullary cyst. Lesions ranged in size from 1 to 15 cm, with a mean of 4.1 cm. Conversion to open laparotomy was required in one patient for lack of exposure, resulting in completion of the procedure in 96% of patients. The median postoperative stay was 4 days. Gagner et al. concluded that laparoscopic adrenalectomy results in less postoperative pain and more rapid return to normal activity compared with open adrenalectomy.

A study compared laparoscopic adrenalectomy with a historical group of posterior adrenalectomies. The two groups were comparable for patient demographics. The median time for posterior adrenalectomy was 120 minutes versus a median of 160 minutes for laparoscopic adrenalectomy. Patients who underwent laparoscopic adrenalectomy had a mean hospital stay of 3 days, a shorter time to return to work, and a lower blood loss than those patients who underwent posterior adrenalectomy with a mean hospital stay of 5 days. The authors of this study concluded that laparoscopic adrenalectomy is the procedure of choice.

One study reported the results of a case-controlled study of 40 laparoscopic and 40 open adrenalectomies. Statistically significant differences were found (laparoscopic vs. open) in operative blood loss (40 mL vs. 172 mL), operating time (147 minutes vs. 79 minutes), hospital stay (12 days vs. 18 days), and late morbidity (0% vs. 48%). The authors of this study found no statistically significant differences in time to oral intake, total cost, and early morbidity. The late morbidity in the open group consisted of wound complications that were absent in the laparoscopic group. The authors concluded that the laparoscopic approach is the method of choice.
choice for adrenal masses less than 6 cm in diameter.

A series from the National Cancer Institute reported the learning curve for laparoscopic adrenalectomy. In the first five patients, median operating time was 255 minutes, which dropped to 207 minutes in the second group of five patients and to 143 minutes in the third group of five patients. The use of minimally invasive surgery for adrenal malignancies remains controversial. The SAGES Manual states that laparoscopy is not to be used in the treatment of patients with malignant lesions. Other contraindications to laparoscopic adrenalectomy include masses larger than 10 cm, untreated coagulopathies, and surgeon inexperience. Further study of this technique is clearly needed.

GYNECOLOGIC MALIGNANCIES

The use of laparoscopy in the treatment of gynecologic malignancies has begun relatively recently, particularly in the treatment of endometrial and cervical cancer with the laparoscopic-assisted surgical staging and laparoscopic-assisted radical vaginal hysterectomy trials (described earlier in Gynecologic Malignancies under Laparoscopy in the Staging of Malignancy). At this time, the utility of laparoscopy in the treatment of gynecologic malignancies is unclear, and the results of ongoing prospective trials are awaited.

LAPAROSCOPY IN THE PALLIATION OF MALIGNANCY

PANCREATIC CANCER

The use of laparoscopy in the staging of patients with carcinoma of the pancreas is discussed earlier in Pancreatic Cancer under Laparoscopy in the Staging of Malignancy. In addition, laparoscopic techniques may be useful for palliative surgical procedures. Unfortunately, palliative therapy is all that is indicated for many patients with this disease. It is possible to palliate the three symptoms of this disease—biliary obstruction, gastrointestinal obstruction, and pain—using laparoscopic techniques. As many as 57% of patients who present with this disease undergo palliative surgery. A particularly attractive concept is to stage patients using laparoscopic techniques, and then perform palliative bypass surgery at the same time using a laparoscopic approach in patients found to have unresectable disease. Nonoperative palliation of obstructive jaundice using an endoscopically placed stent has been shown effective when compared with surgical palliation, and it also is associated with lower complication rates than surgical palliation.

Palliation for obstructive jaundice may be performed nonoperatively using an endoprosthesis, or it may be carried out using a number of bypass procedures that can be performed laparoscopically. The simplest technique is choledochojejunostomy, which has been described using both sutured and stapled techniques. Choledochooduodenal or choledochojejunal anastomoses may also be fashioned laparoscopically. The biliary bypass is then combined with a gastroenterostomy, which is performed at the surgeon's discretion. Similarly, the celiac plexus may be injected under laparoscopic guidance to provide pain relief. Such a combined approach was used by Mouti in 12 patients with excellent results.

FEEDING TUBE PLACEMENT

Enteral feedings are preferable to parenteral feedings in patients who can tolerate them, yet not all patients with cancer are able to take in enough calories by mouth, thereby necessitating placement of a feeding tube. Open surgical gastrostomy is most often performed in the United States by the method of Stamm. This was the only method available until 1980, with the development of the percutaneous endoscopic gastrostomy (PEG). However, placement of a PEG requires upper endoscopy, which is not possible in all patients. Furthermore, the use of a PEG tube, necessitating pulling the tube through the tumor-bearing area, has been reported to result in implantation of the tumor at the PEG site in three cases. In select patients, including patients with head and neck tumors, Zenker's diverticula, and large hiatal hemias, open surgical gastrostomy remains the preferred method of enteral access.

The technique for laparoscopic gastrostomy has been described. Importantly, although formal laparotomy is not needed, the stomach is directly visualized using this technique. A retrospective review established the usefulness of this technique. In this study, 32 patients who underwent laparoscopic gastrostomy and 37 patients who underwent open gastrostomy were reviewed. The underlying illnesses and contraindications to PEG placement were similar in both groups. Operative time was significantly greater in the open gastrostomy group (62 ± 19 minutes) compared with the laparoscopic gastrostomy group (58 ± 7 minutes). Complication rates were 11% in the open group and 6% in the laparoscopic group. The investigators concluded that laparoscopic gastrostomy is a safe and effective alternative procedure in patients unable to undergo placement of a PEG. Laparoscopic placement of jejunostomy tubes also has been described.

LAPAROSCOPIC STOMA CREATION

Decompression of the intestinal tract may be an important procedure in the cancer patient, especially in those with carcinomatosis and resulting intestinal obstruction. The importance of colonic decompression in patients with obstructing carcinomas of the colon has been described. The initial presentation of carcinoma of the colon is obstruction in 15% to 21% of patients, most commonly in the left colon. The 5-year survival rate in these patients is significantly less than that in patients without obstruction. This common situation underscores the importance of palliative procedures that may decrease postoperative pain, incidence of ileus, and recovery time.

Laparoscopic creation of a loop colostomy has been described. In this technique, after the sigmoid colon is mobilized, a drain is passed through its mesentery and is then used to extract the colon through a special 3.5-cm trocar placed in the left lower quadrant. This procedure was modified and described with an associated decrease in postoperative pain and ileus with a rapid recovery.

The use of small laparotomy incisions may be used for the creation of intestinal stomas; however, the presence of metastatic disease or peritoneal implants may make such procedures difficult to perform. The use of a laparoscopic approach makes possible the inspection of the abdominal cavity for other lesions and results in discharge from the hospital within 24 to 48 hours of surgery. In one study, 17 (89%) of 19 patients were successfully diverted using laparoscopic techniques. The remaining two patients had extensive adhesive disease that could not be managed laparoscopically and required conversion to open laparotomy. Other procedures, such as laparoscopic gastrostomy, may also be carried out as needed.

THE FUTURE OF LAPAROSCOPY IN THE CARE OF THE PATIENT WITH CANCER

Exciting technology for laparoscopic surgery now under development will soon be in operating rooms. Cuschieri has pointed out that we need to "see better, feel better, increase the precision of maneuverability and handling, reduce contamination, facilitate specimen extraction and bring order to the present ergonomic chaos in our operating rooms." New developments in the technology of imaging are being applied to laparoscopic surgery. Although head-mounted displays have been tested, they are probably less than optimal for the laparoscopic surgeon because of the isolation created by these devices. Current three-dimensional imaging systems are not without their limitations, but new systems may provide a true improvement in tissue visualization. Continued improvements in instrumentation will certainly be an important part of the evolution of laparoscopic surgery. New methods of tissue extraction include a sleeve system and an extracorporeal pneumoperitoneal access bubble. Both of these systems have potential advantages, especially for the removal of large tumor specimens.

Training of surgeons in these newly emerging techniques remains a complicated problem. Because hospitals decide what procedures may be performed by surgeons, criteria for training and furnishing credentials must be developed. The Society of American Gastrointestinal Endoscopic Surgeons (SAGES) has suggested criteria for training and awarding credentials. It remains to be shown whether some advanced laparoscopic procedures result in a true cost savings when the increased cost of instrumentation and operating room time are factored into the total expenses incurred.

The surgeon has traditionally been involved in the diagnosis, staging, treatment, and palliation of patients with malignancies. Laparoscopy is rapidly becoming an important tool in each of these areas of cancer patient care. The ultimate application of laparoscopic techniques depends on the imagination of surgical investigators and on careful analyses of risks and benefits. Over time, it may be discovered that certain uses for this technology are not ultimately advantageous to the patient compared with traditional open surgical techniques. Only by the conduct of carefully controlled studies, however, will the facts be elucidated, allowing this methodology to be used when it will benefit the patient and avoided when it will not.
SECTION 29.2
Vascular Access and Specialized Techniques of Drug Delivery

INTRODUCTION

The complex management of the cancer patient frequently relies on the ability to deliver a variety of intravenous or intraarterial agents over a prolonged period. Chemotherapy, anesthesia, analgesics, and total parenteral nutrition may be required alone or in combination. Certain drug delivery systems may be more appropriate than others, depending on the particular situation. Since their introduction in the early 1970s, significant changes and improvements have been made in indwelling catheters and infusion devices. All physicians who are involved in caring for cancer patients should have a basic understanding of the uses and limitations of these devices. An understanding of the issues involved in catheter selection, techniques of insertion, routine maintenance, and treatment for catheter-related complications, allows the physician and the patient to optimize the use of these devices.

CATHETER TYPES

A variety of catheter types are available, each with its own intrinsic advantages and disadvantages. The choice of which one to use is based on a variety of factors, including type of agent to be infused, length of time the catheter is to be used, number of concurrent therapies requiring intravascular routes, need for blood draws, desirability of continuous infusion, and patient (or physician) preference. Given the number of available systems, it is convenient to divide catheters into two broad categories. The first group are those catheters having an external component, represented by devices such as the Hickman, Groshong, or Broviac (Bard Access Systems, Salt Lake City, UT). The second group are devices that can be completely internalized or implanted, such as Portacaths and infusion pumps. (Sims Deltec, Inc., St. Paul, MN).

EXTERNAL DEVICES

The simplest and most straightforward central venous access catheter is a single-lumen 16-gauge catheter positioned in either the subclavian, internal jugular, or femoral vein. When inserted using sterile technique, these catheters can generally remain in place for 7 to 10 days, and they allow for the acute infusion of a variety of agents. The catheter is not tunneled, and therefore it is at risk for both infection and migration. Although a simple central line can be very useful, these catheters are not appropriate for long-term or outpatient intravascular therapy.

The Hickman- or Broviac-type catheters are made of barium impregnated silicone rubber (Silastic, Dow Corning Corporation, Midland, MI) and are available as single- or double-lumen devices in both pediatric and adult sizes. These catheters can be tunneled under the skin and have a Dacron cuff, which is implanted in the subcutaneous tissue just above the exit site. This cuff is intended to promote fibrous ingrowth and scarring, which serves to lessen the likelihood of catheter migration and infection. Although some early suggestion was made that silver ion impregnation of the cuff might further reduce the incidence of catheter-related bacteremia, prospective randomized studies have not supported any benefit of silver ion impregnation. It appears that the mechanical barrier provided by the fibrous reaction to the cuff is sufficient. The Groshong-type catheter is similar to the Hickman and Broviac designs in all respects except for the tip. The Groshong tip is modified with a slit valve to prevent the passive reflux of blood into the lumen (Fig. 29.2-1). The valve only opens when positive or negative pressure is applied to it, such as during infusion or withdrawal of fluid, thereby reducing the frequency with which the catheter must be flushed. These catheters can normally be flushed with saline alone. However, Mayo et al. have shown that the addition of a weekly heparinized saline flush decreased the presence of intraluminal adherent clots and improved the catheter function. This study also demonstrated that the slit valve is frequently incompetent.

Considerable interest has been focused on peripherally inserted central catheters (PICC lines). These lines can be inserted in a peripheral vein in the arm using a Seldinger technique or a “through the needle” technique and threaded into the subclavian vein. Advantages include ease of insertion and the low risk of serious complication. Skilled nurses trained in the insertion technique can perform the procedure at the bedside with results similar to those obtained by interventional radiologists. For initial insertions, this approach has proven very cost-effective. If maintained properly, these lines can last for as long as 1 year and can be used for chemotherapy or total parenteral nutrition.

IMPLANTED DEVICES

Since their introduction, implantable ports have become popular with patients and clinicians alike. These devices are constructed from a variety of materials, including titanium and plastic, and can be made compatible with magnetic resonance imaging (MRI) and computed tomography (CT). The general design includes a compressed silicone diaphragm, which can withstand repeated punctures with a Huber needle. A comparison of a typical external catheter device with an implantable port is shown in Figure 29.2-2. The device shown is a single-lumen port; however, dual-lumen models are also available. These ports are typically inserted in the operating room. The technique used for the insertion of the catheter itself is identical to that used for external catheters and is described in detail in the section Insertion Technique. The port housing is placed in a subcutaneous pocket on the chest wall. Care needs to be taken to make sure that the diaphragm of the port can be palpated through the overlying tissue to allow for access to the device. The port housing is anchored to the underlying fascia by several interrupted sutures. Unlike external catheters, removal of a port generally requires a repeat trip to the operating room to perform a cutdown over the port and a removal of the device from the
subcutaneous pocket. If the device is removed because of infection, the pocket should be left open to close by secondary intention to prevent the formation of an abscess.

FIGURE 29.2-2. A: Dual-lumen 10 Fr. Hickman catheter showing the Dacron cuff. B: Implanted venous access device. A noncoring Huber needle is also shown. The housing of the port can be made of titanium (pictured) or plastic.

Comparisons have been made between external catheters and implanted ports with respect to infection rates, patency, and long-term complications such as vessel thrombosis. Most studies have demonstrated comparable rates of infection between external and implanted devices, with the implanted devices having a longer durability of usage. Overall, the majority of studies have not demonstrated one system to be overwhelmingly superior to the other. The main determinants of catheter survival, regardless of whether the device is external or implanted, are still careful placement and careful maintenance.

Improvements in port design have allowed for the construction of very low profile, small devices that can be implanted in the subcutaneous tissue of the arm with the catheter threaded in a similar fashion as a PICC line. These devices, referred to by their trade name as Pasports (Sims Deltec, Inc., St. Paul, MN), can be inserted in the operating room or imaging suite using local anesthesia. Comparisons between these devices, standard Portacaths, and external catheters have shown that both the Portacath and Pasport have a reduced incidence of infectious complications when compared to external catheters.

Implantable Infusion Pumps

Although the implantable ports have been an advance in convenience and comfort for patients, they still must be connected to an external infusion system. This is true whether the port is placed for intravenous or intraarterial access. The reliance on the external pump has been partially supplanted by completely implanted subcutaneous infusion pumps.

The implantable devices are larger, but they resemble infusion ports in many respects. The earliest devices were used to deliver long-term heparin therapy for patients with thrombotic complications. Using such a system, patients were able to receive long-term continuous intravenous therapy for periods of up to 1 year.

FIGURE 29.2-3. A: The implantable infusion pump (Arrow International, Reading, PA), which comes in various sizes. The smaller pump is used for the infusion of narcotic analgesics either intravenously or via an intraspinal route. B: A schematic representation of how the pump system works. Body heat causes the propellant to shift from a liquid to a gaseous phase, which compresses the bellows and allows for the drug to be dispensed. When the drug reservoir is refilled, the propellant is compressed and shifts back into a liquid phase.

The first implantable pump to be introduced was manufactured by Infusaid and was known by the same name (it is now produced by Arrow International (Reading, PA)). This system weighed slightly less than 200 g when it was empty and was positioned in the subcutaneous tissues of the abdominal wall. The pump delivers a constant rate, determined by internal flow resistors, and is powered by the pressure generated from the expansion of a liquid fluorocarbon to the gaseous phase at body temperature. As the drug reservoir is filled percutaneously through a septum, the surrounding fluorocarbon chamber is recharged as gas is compressed and condensed into the liquid phase. The newest models have a side-access septum that bypasses the infusion system and allows for direct delivery of a flush or bolus of medication.

Although its main use has been in the delivery of intraarterial chemotherapy via the gastroduodenal artery for the regional treatment of liver metastases, the Infusaid pump has been used to deliver insulin intravenously, as well as morphine for intractable pain. The current models are smaller than their predecessors, resulting in improved patient comfort (see Fig. 29.2-3). Other implantable systems using battery-powered peristaltic or solenoid pump mechanisms are also available. A telemetry system transmits or receives signals from the totally implanted device, which can turn the pump on or off, adjust the delivery rate, and determine battery voltage. Although these implantable pumps can save patients the inconvenience of carrying an external device and free them from the need to be attached to an intravenous line, they can be expensive. As the number of uses for these devices increases, however, the costs will undoubtedly decline.

INSERTION TECHNIQUE

The single most important aspect of catheter insertion is to strictly adhere to sterile technique. To do this, it is important to have adequate light and space to perform the procedure. Therefore, the preferred setting for the insertion of long-term indwelling catheters is the operating room or interventional radiology suite. The availability of real-time fluoroscopy is also extremely helpful for confirming catheter position. In a patient who is not cognitively impaired and who is able to follow direction, local anesthesia is all that is required. Monitored sedation can be used in certain cases and with pediatric patients.

The most common insertion technique used today is the one described by Seldinger, using a percutaneous approach over a guidewire. This technique has been shown to be superior to open cutdown approaches. This technique can be used to insert a catheter into any vein; however, the preferred locations are the subclavian or internal jugular veins. The approach to the subclavian vein is described in greater detail.

The precordium is prepared steriley, and a local anesthetic is infiltrated infraclavicularly. The patient is placed in Trendelenburg's position, and a shoulder roll positioned longitudinally between the shoulder blades will sometimes facilitate insertion. A finder needle attached to a 5-cc syringe is advanced into the vein under the clavicle with the bevel of the needle facing up. Gentle aspiration is applied until blood freely flows into the syringe. If there is any question as to whether the needle is
in an artery or a vein, a central venous pressure line can be connected to confirm a venous insertion.

Once the needle is in the vein, it is rotated 90 degrees and the syringe is disconnected, taking care not to allow air into the vein through the needle. A flexible guidewire is then advanced into the needle. If advancement of the guidewire meets with any resistance, it is not intraluminal and the wire should be removed. The needle should then be repositioned and aspiration of venous blood confirmed.

Once the wire has been successfully inserted, its position can be confirmed with fluoroscopy. At this point, a site on the precordium is selected for the catheter exit site (Fig. 29.2-4). After infiltrating the tissues with local anesthetic, a small incision is made at the exit site as well as adjacent to where the wire enters the skin. The catheter is then tunneled under the skin subcutaneously until the Dacron cuff is situated approximately 1 cm from the exit site. A peel-away sheath dilator is then advanced over the wire into the vessel by intermittently advancing the sheath and withdrawing the wire to check for resistance (see Fig. 29.2-4 inset). It is possible for the sheath dilator to bend the wire and result in the dilator penetrating the wall of the vessel. This can result in fatal hemorrhage.

Once the dilator is in place, the catheter is inserted into the lumen of the dilator and the catheter is advanced as the dilator is peeled apart (see Fig. 29.2-4 inset). The ideal catheter tip position is just inside the right atrium. The surgeon must keep in mind that, when the patient is upright, the catheter tip migrates back from 1 to 3 cm.

A high rate of catheter failure can occur from thrombotic complications if the tip is in the subclavian vein rather than in the right atrium. To avoid this, the catheter is cut to its estimated desired length, which is determined from external bony landmarks. Typically, the right superior vena cava/right atrial junction lies approximately 4 to 6 cm inferior to the angle of Louis (Fig. 29.2-5). The final position of the catheter tip can be confirmed with fluoroscopy. After the procedure is completed, the patient should have an upright chest x-ray to confirm position and to rule out a pneumothorax. The incidence of pneumothorax after percutaneous placement of a central venous catheter by either a subclavian or jugular approach has been shown to be less than 1%. 24

In certain situations the subclavian vein may not be suitable for catheter insertion. In such an instance, the internal jugular vein is the preferred location. This site, however, is less desirable given its anatomic position and difficulty in keeping the area aseptic. Other insertion sites have included the saphenous vein, gonadal vein, intercostal vein, or azygous vein, or direct placement into the inferior vena cava. 25-27 After the successful placement of a long-term indwelling central venous catheter, certain routine postoperative maintenance procedures should be performed to increase the durability of the catheter. Careful attention should be paid to the maintenance of catheter patency and to the catheter exit site to ensure it is kept clean. Although there is some discrepancy among catheter manufacturers, external catheters are typically flushed daily or every other day with a heparin solution or saline when they are not in use.

SELECTING THE APPROPRIATE CATHETER

The selection of the right catheter for a particular patient must be based on an assessment of a number of factors. Consideration must be given to the intended use of the catheter and how long the catheter will be needed. For example, a patient who needs 2 weeks of intravenous antibiotics as an outpatient will probably be best served by having a single-lumen external catheter placed, which can be more easily removed when the course of therapy is completed. Some evidence suggests that single-lumen catheters pose less of an infection risk than dual-lumen devices. 28 In contrast, a patient expected to receive several courses of chemotherapy over the next 3 months, who will also require frequent blood draws, may be best served by the placement of a double-lumen implantable Portacath.

At the National Institutes of Health, a team approach is used in the selection, insertion, and maintenance of intravenous access devices. The team is made up of surgeons, interventional radiologists, intensivists, and specially trained access nurses. When a physician requests a consult for a line placement, information about the patient and planned uses is obtained. The most important issues, in addition to type of agent to be infused and duration of planned use, are history of previous indwelling catheters, patency of central veins (duplex Doppler examinations are obtained if necessary), the patient's ability to maintain the catheter, age of the patient, size of the patient, and need for blood draws. All of these issues are factored into the selection of the appropriate device. The Vascular Access Device (VAD) Service then assists in patient teaching both before and after the device is inserted. Once the device is in place, the VAD Service then tracks information regarding outcome. Programs such as this have been shown to enable the patient and the physician to derive the longest possible benefit from the vascular access device and to minimize complications. 29

CATHETER-RELATED COMPLICATIONS

FIGURE 29.2-4. Insertion of a long-term indwelling central venous catheter via a subclavian approach using a percutaneous technique. A: After insertion of the guidewire, the catheter is tunneled from the chosen exit site to the venous cannulation site. B: The Dacron cuff is placed subcutaneously 1 cm above the exit site.

FIGURE 29.2-5. The length of the catheter can be estimated by simulating its course through the subclavian vein and superior vena cava along the clavicle and right border of the sternum. If the catheter is cut 6 cm inferior to the angle of Louis, it approximates a final position at the superior vena caval and atrial junction. Tip position should be confirmed using fluoroscopy.
CATHETER MALFUNCTION

Catheters leak or break because of defective construction or because they are pinched between the clavicle and first rib when the patient is upright. More commonly, infusion through a VAD may be difficult because of a kink in the catheter, a forgotten suture holding it in place, or precipitates of salts or medications obstructing the lumen. The latter can sometimes be removed with instillation of 0.1 N HCl or 70% ethanol.

The most common type of VAD malfunction, however, is the inability to withdraw blood from the catheter without difficulty infusing through it. Withdrawal occlusion not only prevents use of the VAD for blood sampling, but also is a sign that fluid injected through the catheter may not be entering freely flowing blood in the superior vena cava. Continuously bathing a small vein with a nonphysiologic solution may lead to chemical phlebitis. Withdrawal occlusion is caused by an obstruction at the catheter tip that acts as a one-way valve. It occurs when aspiration pulls the wall of a vein against the catheter orifice. This is especially likely if the catheter tip is in a vein smaller than the superior vena cava. Even if the VAD has been properly placed initially, the catheter tip can migrate into the contralateral innominate or a jugular vein as a result of postural changes. More commonly, it can be pulled back into the ipsilateral innominate vein by traction applied by the chest wall, or partially retracted so that the tip is held perpendicular to the superior vena cava wall.

Malpositioning of a catheter can often be identified by a chest x-ray. The problem can be relieved, at least temporarily, by having the patient stand, raise his or her arms, or use Valasalva's maneuver to move the catheter tip. Interventional radiologists can sometimes return a migrated catheter to the superior vena cava with a snare. In the long run, however, poor catheter position is typically associated with recurrent malfunction and ultimately requires replacement of the VAD.

Catheter tips that rub against the vein may stimulate local thrombosis, which can also cause withdrawal occlusion and sometimes anchor the tip to the venous wall. Even in good position, however, catheters virtually always accumulate a coat of fibrin. If this "sheath" extends to the catheter orifice, it can act as a one-way valve to obstruct withdrawal.

In extreme cases, these fibrin sheaths can extend from the tip of the catheter to the point where it enters the vein. This not only creates withdrawal occlusion but provides a channel for infusates to backtrack and possibly extravasate. Withdrawal occlusion that is not relieved by changing the patient's position, therefore, suggests the possibility that the obstruction is actually due to a fibrin sheath.

An effort can be made to dissolve the obstructing fibrin by instilling a thrombolytic agent through the obstructed catheter into the suspected sheath, where it is left to dwell for 1 to 2 hours before re-attempting withdrawal. Although the traditional thrombolytic agent for this indication has been urokinase, this drug is now unavailable and has been replaced by instillations of recombinant tissue plasminogen activator (rtPA) in a concentration of 1 mg/mL. Usually 2 to 3 mL are infused and left for 2 hours before withdrawal is attempted.

If this treatment is not successful, the cause of the withdrawal occlusion should be investigated further. If a chest x-ray has not already been taken, one should be performed to confirm that the catheter tip is properly positioned in the superior vena cava. Then x-ray contrast material should be injected through the obstructed lumen to look for a fibrin sheath, which is detected as a tubular structure filled with contrast encasing the catheter. If the presence of a fibrin sheath is confirmed, repeat instillations of rtPA can be tried. In the past, regimens of continuously infused urokinase were often successful in relieving obstructions refractory to routine instillations of the drug. Experience using rtPA in a similar manner, however, is quite limited.

Open-ended catheters have traditionally been flushed with low-dose heparin on a regular basis to reduce the risk of thrombotic obstruction of the catheter. However, the value of this technique has not been proven, except perhaps with dosing schedules that are not practical on a long-term outpatient basis. A reason not to use heparin flushes is the risk, albeit a low one, of heparin-induced thrombocytopenia and thrombosis. In addition, coagulation tests cannot be reliably performed with blood drawn through heparinized VADs, even with a large discard volume.

VENOUS THROMBOSIS

Thrombi usually originate at the point where a catheter enters the vein or at any point where it chronically rubs against the venous wall. Symptomatic thrombosis of the catheterized vein develops in 5% to 10% of patients with VADs. Most VAD-related venous thrombosis, however, is asymptomatic, occurring in approximately 30% to 70% of patients. Thrombi develop soon after the catheter is placed and usually remain clinically silent because abundant collateral veins relieve the pressure as the primary vein becomes obstructed. It is important to be aware of asymptomatic thrombosis as a potential nidus of infection as well as a source of pulmonary embolism. Furthermore, because thrombosis may leave the vein permanently obstructed, it may create a problem for an unsuspecting surgeon who attempts to re-catheterize the vein at a later time.

The management of symptomatic VAD-related thrombosis must be individualized. The catheter rarely must be removed immediately and does not necessarily have to be removed until the need for it has passed. Prompt relief of symptoms is often achieved by simply elevating the affected arm overnight. Most patients also receive systemic anticoagulation in the form of heparin, followed by warfarin for several months, with the rationale that this prevents the thrombus from extending. However, the risk of extension is unknown. Anticoagulation also is recommended to prevent pulmonary emboli, which are reported to occur in 10% to 15% of patients with upper extremity deep venous thrombosis and can be fatal. Small emboli, however, frequently occur when the catheters are removed, but the minimal morbidity from these does not justify routine evaluation or therapeutic intervention before explanation. The more threatening emboli appear to be much less commonly associated with the modern silicone and polyurethane catheters. The risk of chronic venous insufficiency due to thrombosis in the axillary-subclavian vein may also be a consideration. On the other hand, the most important issues are often the need for long-term venous access and the risks of antithrombotic treatment.

With the introduction of low-molecular-weight heparin, hospitalization is no longer necessary for initial anticoagulation. Subcutaneous low-molecular-weight heparin and oral warfarin can be started together and the heparin continued for at least 5 days and until the patient's international normalized ratio has been between 2 and 3 for 2 days. The necessary duration of warfarin therapy is unknown. It can be argued that warfarin should be continued as long as the VAD is in place but that 4 to 6 weeks of warfarin is sufficient if the VAD is removed after the thrombus is discovered. However, no clinical trials have tested this recommendation, and extenuating circumstances often dictate the anticoagulant regime for an individual patient.

Thrombolytic therapy of VAD-related thrombosis may be reasonable when salvaging the vein is a high priority because anticoagulation alone will probably not leave the vein patent enough to be used for subsequent VADs. A regimen using relatively low doses of rtPA has been published. Long-term patency, however, generally requires that the catheter be removed while anticoagulation is continued for several weeks or months.

FIGURE 29.2-6. A: Catheter-related subclavian vein thrombosis documented by venogram, which shows complete obstruction and collateral venous flow. The patient was treated with urokinase infusion through an ipsilateral forearm vein and, after 16 hours, (B) and 39 hours (C) of urokinase infusion, showed progressive resolution of the thrombosis.
Of course, effective prophylaxis would eliminate the problem of VAD-related thrombosis. This reportedly can be achieved with very low-dose warfarin (1 mg/day) or with low-molecular-weight heparin. However, the benefit of these regimens was demonstrated in patients with an unusually high incidence of symptomatic thrombosis, and therefore it is not clear that this will be generalized. The value of prophylactic warfarin was not apparent in a population of less hypercoagulable patients.

**INFECTIONS**

The organisms infecting VADs are most commonly derived from the patient's skin flora or from the hands of health care workers. They migrate along the internal (intraarterial and intravenous) lumen of the catheter, sequestering a biofilm that protects them from the host's immune system as well as from antibiotics. Before the catheter is inserted, some species add their own secreted proteins to this sleeve. In this matrix, the organisms are relatively protected from phagocytes and antibodies, as well as from antibiotics. Instillations of rPA into the catheter have been shown to improve the outcome in cases refractory to antibiotics alone. rPA would be expected to provide the same benefit and should be given in the same manner as for treating withdrawal occlusion associated with a fibrin sheath. Another consideration in assessing antibiotic-resistant bacteria is whether the patient has an infected venous thrombus. A venogram is necessary to evaluate this possibility. If thrombosis is found, the catheter must be removed and antibiotics continued for 4 to 6 weeks. In some cases, the infected clot may require surgical resection.

**CHAPTER REFERENCES**


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SECTION 29.3
Isolation Perfusion

H. RICHARD ALEXANDER

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Principles of Isolation Perfusion
Isolated Limb Perfusion
Isolated Hepatic Perfusion
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INTRODUCTION

Vascular isolation and perfusion of a cancer-bearing organ or region (i.e., extremity) using a recirculating extracorporeal perfusion circuit has been in clinical use for almost 50 years. It was originally applied to the limbs by Creech et al. in the 1950s for patients with high-grade unresectable extremity sarcoma or in-transit melanoma. In the early 1960s additional experience with isolated perfusion of the limbs or liver was reported by a small number of centers. More recently, the technique has been actively used to provide clinical evaluation of patients with these conditions and has also been used in isolation perfusion of the lung and kidney. Isolation perfusion was initially applied under normothermic conditions using chemotherapeutics alone and subsequently mild to moderate hyperthermia (38.5°C to 42°C) became a routine component of treatment. Over the past 6 years there has been considerable interest in the use of tumor necrosis factor (TNF) used in combination with melphalan and hyperthermia in isolation perfusion. This chapter reviews the principles and technique of isolation perfusion and the current status of this treatment modality in clinical practice. The role of the various components of therapy that are routinely used on efficacy and toxicity are reviewed.

PRINCIPLES OF ISOLATION PERFUSION

Isolation perfusion is a specialized surgical technique administered under a general anesthetic and usually for an interval of 60 to 90 minutes. Initially, the vascular supply of a cancer-bearing organ or region such as liver or extremity is identified and isolated and all collateral blood flow to the area is controlled to avoid any leak of perfusate into the systemic circulation or leak of systemic blood into the perfusion circuit. Once the vessels are cannulated they are connected to inflow and outflow lines of an extracorporeal bypass circuit, which consists of an oxygenator, reservoir, heat exchanger, and roller pump. The heat exchanger, which warms the perfusate, is connected to a closed water-recirculating circuit (Fig. 29.3-1). It has become routine practice during isolation perfusion to confirm that complete vascular isolation has been achieved using a continuous intraoperative leak monitoring technique with either radiolabelled human serum albumin or technetium 99–labeled red blood cells. Once the perfusion is complete, the vascular bed of the treated organ is flushed with several liters of saline and colloid solution to remove any residual intravascular therapeutic agents. Finally, the native vascular blood flow is reestablished to the site and therapy is completed. Because of the need to place indwelling vascular catheters during treatment, the patient must be systemically anticoagulated usually using heparin during perfusion. However, the anticoagulation effects can be effectively reversed with protamine sulfate and thawed fresh frozen plasma.

There are several advantages of isolation perfusion as a treatment technique. In practice, complete separation of the regional and systemic circulation can be achieved in most circumstances. This is particularly true for isolation perfusion of the liver and in patients undergoing isolated limb perfusion (ILP) for in-transit melanoma for high-grade unresectable sarcoma of the extremity. Small, less than 1%, leaks of perfusate into the systemic circulation can be detected using a leak-monitoring system. Klaas and coworkers reported the frequency of perfusate leak in 383 patients who underwent 438 ILPs using a standardized technique. The cumulative overall leak rate was 0.9%. A leak rate of greater than 5% was encountered in 6.2% of ILPs and a leak rate of greater than 10% was observed in only 1.4%. During ILP, leak of perfusate can usually be controlled with various maneuvers such as adjustments in flow rate or tightening of the extremity tourniquet. Because treatment is confined to an organ or region of the body, systemic exposure and toxicity secondary to the therapeutic agents can be eliminated or significantly limited. In addition, dose escalation of the therapeutic agents is limited largely by the tissue tolerance of the perfused organ or the extremity. Finally, isolation perfusion allows one to deliver clinically significant levels of hyperthermia, which has direct cytotoxic and synergistic antitumor effects with various chemotherapeutic and biologic agents.

ISOLATED LIMB PERFUSION

ILP of the lower extremity is most commonly performed via cannulation of the external iliac vessels and in the arm via the axillary vessels. However, in the lower extremity ILP can be performed via the femoral or popliteal vessels and in the arm via the brachial vessels under certain clinical situations. For the approach to the iliac vessels, a lower abdominal transplant incision and a retroperitoneal approach is made. The external iliac artery and vein are carefully dissected from their origin down to the inguinal ligament and small arterial branches and venous tributaries and ligated and divided. This is particularly important in the region of the inguinal ligament to prevent leak of perfusate into the systemic circulation. The hypogastric vein is ligated in situ and the hypogastric artery is temporarily occluded with a vascular occluding clamp. If possible, some of the branches of the hypogastric artery in the pelvis should be identified and ligated to prevent collateral flow across the pelvis. These vessels include the vesicular, pudendal, and obturator arteries. A Steinmann pin is anchored into the anterior superior iliac spine and the external iliac vessels are cannulated with the catheter tips positioned just below the inguinal ligament. An Esmarch tourniquel is snugly wrapped at the root of the extremity and the
cannulae are connected to the extracorporeal bypass circuit (Fig. 29.3-2).

FIGURE 29.3-2. Intraoperative photograph showing an isolated limb perfusion circuit in a patient with in-transit extremity melanoma. Note the leg is wrapped in warming blankets to facilitate tissue warming, and the leak-monitoring gamma detection camera is positioned over the patient’s precordium and connected to a strip chart recorder. The extracorporeal bypass circuit (not shown) is positioned by the patient’s side during therapy.

ISOLATED HEPATIC PERFUSION

Isolated hepatic perfusion (IHP) is a more complex treatment to administer and has not gained as widespread or consistent a clinical evaluation because of the major nature of the operative procedure, the associated morbidity associated with the treatment, and the fact that initial clinical studies did not clearly document efficacy of the therapy. The unique vascular anatomy of the liver, however, does make it an ideally suitable organ for isolated perfusion. The procedure starts with a right subcostal incision and once it has been determined that there are no contraindications to proceeding with IHP, the incision is extended and the liver is extensively mobilized. This includes division of the diaphragmatic attachments of the left and right hepatic lobes and complete dissection of the retrohepatic vena cava from the level of the renal veins to the diaphragm to prevent any leak of perfusate from the retrohepatic inferior vena cava (Fig. 29.3-3). A cholecystectomy is performed and the portahepatis structures are completely dissected and isolated. This includes complete dissection and division of the surrounding connective tissue and lymphatics, which can serve as a leak of perfusate into the systemic circulation during therapy. Cannulation for inflow to the liver is typically via the gastroduodenal artery alone or the gastroduodenal artery and portal vein. Splanchnic venous flow is shunted to the right atrium using a second veno-veno bypass circuit similar to that used in hepatic transplantation procedures with an inflow cannula positioned in the axillary vein. The venous effluent of the liver is collected from a cannula positioned in an isolated segment of retrohepatic inferior vena cava and, therefore, during treatment the inferior vena cava flow must also be shunted (see Fig. 29.3-3). Originally reports of IHP described the use of a passive double-lumen internal shunt system that may not have provided adequate venous return from the inferior vena cava and the portal vein to the heart. The external veno-veno bypass circuit results in flow rates of approximately 2 L/min and stable cardiac parameters during treatment.

FIGURE 29.3-3. Schematic illustration of the isolated limb perfusion circuit. The arterial inflow is via the gastroduodenal artery, and venous outflow is collected from a cannula positioned in an isolated segment of retrohepatic vena cava. The inflow and outflow cannulae are connected to a perfusion circuit as shown in Figure 29.3-1. On the patient’s left is the veno-veno bypass circuit that shunts portal splanchnic and inferior vena caval blood flow back to the systemic circulation during therapy. IVC, inferior vena cava.

PERFUSION PARAMETERS

The extracorporeal perfusion circuit typically contains 1 L of perfusate, which consists of 700 mL of a balanced salt solution, 1 U of type-matched packed red blood cells, and 1500 U of heparin. The resultant hematocrit of approximately 25% provides adequate tissue oxygen retention and perfusates containing higher hematocrits provide no additional benefit in preventing regional toxicity. Generally, flow rates in the range of 400 to 800 mL/min are achievable and adjusted depending on line pressure, changes in reservoir volume, or the presence of a systemic perfusate leak based on intraoperative monitoring.

Continuous intraoperative leak monitoring to assess for the presence of leak of the perfusate into the systemic circulation is being used more routinely and is an important component of isolation perfusion therapy when one considers that the perfusate often contains doses of therapeutic agents that are at least tenfold greater than maximally tolerated systemic doses. Careful monitoring of leak can reduce the severity of systemic complications and may improve response rates. Standard leak-monitoring techniques using 131I radiolabeled albumin or technetium 99–labeled red blood cells have been described for continuous intraoperative monitoring. A gamma detection camera is positioned either over the precordium of the heart for patients undergoing ILP or over the pump housing of the veno-veno bypass circuit for patients undergoing IHP, both of which serve as a stable reservoir of blood to measure radioactivity (see Fig. 29.3-2). The detection system provides continuous assessment of leak rates and can discriminate leaks less than 1%. Once the gamma detection camera has been positioned, a small dose of radionuclide is given systemically and a baseline level of radioactive counts is measured on a strip chart recorder. Then a tenfold higher dose is administered into the perfusion circuit. Therefore, if a 10% leak of perfusate into the systemic circulation occurs, there will be a doubling of the amount of radioactivity compared with baseline. Leak rates using this system have been correlated with measured leak rates with TNF or melphalan from the perfusate into the systemic circulation.

Despite careful preoperative preparation, during ILP the surgeon may encounter several situations that require adjustment in perfusion parameters to minimize a leak of perfusate out of or blood into the perfusion circuit. Flow rates that indirectly affect arterial line pressure, reservoir volume, and leak of perfusate are continuously monitored. If there is leak of systemic blood into the perfusion circuit this is reflected by an increase in the reservoir volume in the circuit and can be remedied by increasing flow rates to increase line pressure, tightening the extremity tourniquet, or increasing venous pressure in the circuit by placing a partial occluding clamp on the venous outflow line. If there is a perfusate leak into the systemic circulation this is manifested by an increase in radioactive counts detected by the gamma camera and the strip chart recorder. In addition, one may see a decrease in reservoir volume in the perfusion circuit, although this is a relatively late manifestation of a perfusate leak. Under these circumstances, one may decrease flow rates to lower the line pressure or tighten the tourniquet to stop systemic leak. Rarely, a two-way leak occurs that is evidenced by changes in reservoir volume (generally a gain) as well as an increase in radioactivity on the strip chart recorder. This can be a particularly difficult and tricky condition to adequately control, and typical steps would include decreasing flow rates to stop any systemic leak of perfusate, tightening the tourniquet, and then placing the partial occluding clamp on the venous outflow line of the perfusion circuit.

RESULTS OF ISOLATION PERFUSION

There are many perfusion and treatment-related factors that may affect efficacy and toxicity of isolation perfusion. The majority of clinical experience with isolation
perfusion has been with ILP using chemotherapeutics for in-transit melanoma or sarcoma of the extremity (Table 29.3-1). The early clinical trials of ILP using hyperthermia or chemotherapy for sarcoma were difficult to interpret because of the variability in treatment conditions and patient selection. Two early studies of adjuvant ILP using melphalan for patients with melanoma undergoing initial excision of all disease did show a significant reduction in local recurrences with ILP compared with excision alone but suffered from including high- and low-risk patients. A large multicenter trial of prophylactic ILP following excision of primary melanoma greater than 1.5 mm in depth showed a decrease in local recurrence with ILP from 6.6% to 3.3% compared with excision alone with no benefit for survival. Based on these results prophylactic ILP has been largely abandoned. There are other components of isolation perfusion that may have substantial effects on outcome including hyperthermia and biologic agents, most notably TNF.

### TABLE 29.3-1. Results of Selected Trials of Isolated Limb Perfusion for Melanoma or Sarcoma

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Primary Site</th>
<th>Treatment</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stehlin et al.</td>
<td>50</td>
<td>Extremity sarcoma</td>
<td>ILP with TNF, melphalan</td>
<td>89% complete response</td>
</tr>
<tr>
<td>Klaase and coworkers</td>
<td>165</td>
<td>Extremity sarcoma or melanoma</td>
<td>ILP with TNF, melphalan</td>
<td>70% complete response</td>
</tr>
<tr>
<td>Posner et al.</td>
<td>6</td>
<td>In-transit melanoma</td>
<td>ILP with TNF</td>
<td>20% transient response</td>
</tr>
<tr>
<td>Fraker</td>
<td>8</td>
<td>In-transit melanoma</td>
<td>ILP with TNF</td>
<td>20% transient response</td>
</tr>
</tbody>
</table>

### HYPERTERMIA

Hyperthermia has been used in isolation perfusion alone or in combination with chemotherapeutics and TNF. In experimental models it has direct cytotoxicity against tumor lines and has established synergy with various chemotherapeutics and TNF. This later feature is presumed to be the main contribution of hyperthermia in isolation perfusion. Under hyperthermic conditions tumor neovasculature responds differently than native blood vessels. At temperatures up to 46°C normal microvessels dilate and blood flow increases up to sixfold as a compensatory mechanism to diffuse local heat accumulation. In contrast, tumor-associated microvessels have a diminished capacity to vasodilate and at comparable temperatures there is stasis and diminution of blood flow, indicating a differential sensitivity between tumor-associated and normal microvasculature.

Following the original report of normothermic ILP using chemotherapeutics in 1957 by Creech et al., most investigators subsequently incorporated some degree of hyperthermia as closed circuit water-recirculating heat exchangers became available to replace the use of inefficient warm moist towels and infrared lamps to warm perfusate fluid. Stehlin et al. reported results of ILP in 50 patients in 1969 and a follow-up report in 1975 of 165 patients with extremity sarcoma or melanoma in whom significant hyperthermia was delivered to the perfused limb. In the initial series the perfusate was warmed to 46°C and average tissue temperatures of 42°C resulted in severe regional toxicity including pain, edema, blistering, and weakness observed in 70% of patients. When tissue temperatures were reduced to 40°C or less, regional complications were minimal. In 1967 Cavaliere and coworkers reported results of hyperthermia alone ILP with tissue temperatures ranging from 42°C to 44°C. The combination of this degree of hyperthermia, perfusion lasting more than 8 hours, and the lack of a proximal tourniquet resulted in severe regional toxicity and an unacceptable 28% mortality. Stehlin reported that compared with historic controls treated identically at one institution, the addition of hyperthermia during ILP with melphalan in patients with extremity melanoma resulted in an increase in response rates from 35% to 80%. Klaase and coworkers reported an analysis of factors associated with toxicity following ILP for melanoma in 425 patients. Tissue temperature greater than 40°C was the most significant factor associated with increased regional toxicity. In addition, female gender and a decrease in perfusate pH were also associated with worse regional toxicity.

Skibba et al. have reported data on eight patients with unresectable cancer confined to liver and treated with a 4-hour IHP using hyperthermia alone to 42.5°C. In 1975 Carswell et al. demonstrated that a circulating factor present in the sera of endotoxin-treated mice caused dramatic hemorrhagic necrosis of tumors when administered to tumor-bearing mice. This factor was termed TNF, and after it became available in recombinant form in the mid-1980s it was evaluated in multiple clinical trials via various methods of administration. However, it was found that humans are very sensitive to the toxic effects of TNF, and, at the maximum tolerated doses administered, it had little antitumor activity. Although interest in TNF as a systemically administered antitumor agent waned, enthusiasm for its administration via isolation perfusion grew remarkably in the early 1990s when Lienard et al. reported initial results in 29 patients treated with a combination of TNF, melphalan, and hyperthermia for in-transit melanoma or high-grade sarcoma of the extremity. The overall response rate in that initial trial was 100%, with 89% of patients having a complete response to treatment.

TNF is ideally suited for administration via isolation perfusion and is thought to exert its antitumor activity via effects on the tumor-associated neovasculature. TNF has significant known procoagulant activity and increases vascular permeability. In addition, several authors have published data showing selective obliteration of tumor neovascularization following ILP with TNF and melphalan for patients with high-grade unresectable extremity sarcoma (Fig. 29.3-1). However, there are few clinical data available using TNF alone via isolation perfusion. Three patients with high-grade extremity sarcoma were treated at our institution with hyperthermic ILP and TNF. One patient had angiographically documented obliteration of tumor-associated neovascularization following ILP; however, he experienced clinical and radiographic tumor progression within 6 weeks, suggesting that the vascular obliteration observed after TNF may not be sufficient for subsequent tumor regression. Posner et al. reported results of ILP with TNF alone in six patients with in-transit melanoma. One had a complete response of 7 months’ durations and two others had brief, less than 1 month, partial responses. TNF administered alone via IHP has little antitumor activity. Fraker reported a 20% transient response rate following IHP with escalating doses of TNF. Interestingly, the responses were seen only at the lowest doses of TNF and once perfusate pH was corrected with sodium bicarbonate during treatment, no further responses were seen despite dose escalation of TNF to 2 mg.

### FIGURE 29.3-4. Preperfusion and postperfusion magnetic resonance angiograms showing neovascularity in a large multiply recurrent Ewing’s sarcoma arising on the dorsum of a forearm. The patient had small volume pulmonary metastases and was treated with palliative 90-minute hyperthermic isolated limb perfusion using tumor necrosis factor and melphalan. He had a significant regression (top panel) that lasted for 2 years until death from systemic disease progression. Three days posttherapy complete obliteration of the tumor neovasculature was observed with no effect of perfusion on the native blood vessels in the extremity (bottom panel).
When TNF is used in ILP with melphalan it is associated with a rapid time course of response in tumors compared with ILP with melphalan alone, and large tumors form eschar reminiscent of the findings in murine models (Fig. 29.3-5). Because TNF causes increased endothelial permeability and has selective procoagulant effects on tumor-associated vasculature, it has been postulated that during ILP TNF may augment delivery of chemotherapeutics to the tumor by increasing vascular permeability. However, a study reported by Alexander and coworkers evaluated vascular permeability in tumor and unaffected liver tissue obtained from patients undergoing IHP with melphalan alone or TNF and melphalan. After IHP there was a significant increase in permeability in tumor vasculature compared with liver. However, the increase in permeability was similar in those treated with or without TNF, suggesting that the augmentation in permeability occurred via TNF-independent mechanisms.

**Figure 29.3-5.** Photographs of a patient treated with isolated limb perfusion using tumor necrosis factor and melphalan for in-transit extremity melanoma. A: In-transit site of disease before and (B) 5 days after isolated limb perfusion. Note the rapid eschar formation over tumor with sparing of overlying and adjacent normal skin, which is characteristic of the effect of tumor necrosis factor.

### CURRENT STATUS OF ISOLATED LIMB PERFUSION

The role of TNF in isolation perfusion is still under clinical evaluation and has no conclusively demonstrated benefit in properly designed and conducted prospective random assignment trials. In the initial report from Liénard and Lejeune, results from 29 patients treated with ILP using a combination of TNF, melphalan, and hyperthermia for in-transit melanoma or high-grade sarcoma of the extremity were presented. The overall response rate in that initial trial was 100%, with 86% of patients having a complete response to treatment. In subsequent reports from various institutions, including a follow-up report from Liénard and Lejeune of a larger series of patients, the complete response rates were lower and ranged between 70% and 79% (Table 29.3-2). A prospective random assignment trial was initiated at the National Cancer Institute and subsequently expanded to a multiinstitutional study but was closed prematurely in 1997 due to the lack of available clinical-grade TNF in the United States. The results of that trial showed no difference in overall or complete response rates between the groups. It is also noteworthy that in several trials of ILP using melphalan alone, complete response rates between 56% and 82% have been reported. A prospective random assignment trial comparing melphalan and TNF with melphalan alone administered via ILP for in-transit melanoma of the extremity was closed in Europe because of low accrual, suggesting a bias that TNF for most patients with this histology does not substantially contribute to efficacy compared with melphalan alone.

ILP has been used for patients with unresectable high-grade extremity sarcoma for palliation, for potential cure in cases of multifocal disease, and as a neoadjuvant therapy to convert an unresectable lesion to a resectable one. Most data reported on ILP using chemotherapeutics alone indicate limited antitumor activity against this histology. After the initial reports by Liénard and Lejeune using the combination of TNF, melphalan, and hyperthermia as a neoadjuvant treatment for high-grade unresectable sarcoma, a multiinstitutional trial using this regimen for patients with condition was conducted in Europe and the results reported in two papers by Eggermont and coworkers. In more than 219 patients, the overall clinical and pathologic response rate was more than 80% and the limb salvage rate was 84%. Based on these results TNF is now licensed for administration via ILP for high-grade sarcoma in Europe, but no trials are currently being conducted in the United States.

### CURRENT STATUS OF ISOLATED HEPATIC PERFUSION

Following the initial experience with TNF and melphalan in ILP several centers have reported results with this regimen used in IHP for patients with unresectable primary or metastatic cancers confined to liver (see Table 29.3-2). De Vries and coworkers reported results in eight patients treated with melphalan and TNF and one patient treated with TNF alone for 1 hour at 41°C. IHP was associated with a 33% mortality in the series but five of six evaluable patients treated with melphalan and TNF had radiographic evidence of antitumor efficacy. Hafström and coworkers reported results in 11 patients using melphalan and TNF and also reported a high morbidity and mortality of 45% and 18%, respectively. Three patients experienced a radiographic partial response to therapy. A German group reported results in six patients treated with a 60-minute IHP using melphalan and TNF at 40°C to 41°C and had no mortality in this series. Three of six patients had radiographic evidence of significant tumor regression. The largest series reported using TNF and melphalan via IHP comes from the National Cancer Institute; 34 patients underwent IHP with doses of melphalan and TNF that were derived from previously conducted phase I studies and were higher than those used at higher institutions. The treatment lasted for 1 hour and hyperthermia between 39.5°C and 40°C was used in all circumstances. The treatment-related mortality was 4% and the investigators observed an overall radiographic response rate of 75%. The group has presented follow-up data on 44 patients with metastatic unresectable colorectal cancer to the liver. The cohort of patients who had advanced and largely refractory disease had a median number of hepatic lesions of eight, the median diameter of the greatest lesion was 8.5 cm, and one-fourth of patients had more than 50% hepatic replacement by tumor. Furthermore, approximately 45% of patients who had failed prior systemic 5-fluorouracil-based chemotherapy in the 32 patients treated with TNF and melphalan there was a 74% radiographic partial response rate. The time to liver progression was 8.5 months, and median survival was 16.5 months. In a second cohort of patients, IHP with melphalan alone was administered followed by hepatic artery infusional therapy using floxuridine and leucovorin. The radiographic partial response rate was 90%, with 9 of 11 responses ongoing in the liver at a median follow-up of 11 months.

### Table 29.3-2. Selected Series of Isolation Perfusion Using Tumor Necrosis Factor and Melphalan

Although the morbidity and treatment mortality in some of these series are high, the data, for the most part, represent initial institutional experience with a highly...
technical procedure using agents that have known regional and systemic toxicity. With continued refinement and experience the morbidity and mortality associated with the therapy should decrease. Additional refinements in the technique of IHP, and when combined with potentially effective therapies tailored for specific histologies, the treatment may become a more widely used option for patients with unresectable hepatic malignancies from a variety of histologies (see Table 52.3.1).

### Literature References

SECTION 29.4
Intensity-Modulated Radiation Therapy

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CHANDRA BURMAN
MARGIE BURMAN
GIGAS MAGERAS
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ZHYI FUKES
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INTRODUCTION

In radiotherapy, the sum of experimental and clinical data indicates that the probabilities of local tumor control and normal tissue complications are dose dependent, and that the corresponding dose-response curves are sigmoidal in shape. For some disease sites the curves for local control are at lower dose levels relative to those for associated normal tissue toxicity, underpinning the success of radiotherapy in those cancers. For other sites, where these curves are closer to each other, or when the tumor control curve is less steep (the effect of population averaging due to heterogeneous radiosensitivity among individual tumors), the high doses required for tumor cure may cause unacceptable complications. In the last two decades, the development of three-dimensional conformal radiotherapy (3D-CRT), which substantially reduces the volume of critical organs irradiated to high doses, has partly addressed this issue. In 3D-CRT, patient immobilization, image-guided treatment planning, and computer-controlled treatment delivery have combined to conform the radiation dose to the tumor, while maximally excluding the adjacent normal organs. This approach has permitted the increase of tumor dose without concomitant increase in normal tissue complications. At Memorial Sloan-Kettering Cancer Center (MSKCC), a clinical trial in cancer of the prostate has accrued more than 1100 patients, and the prescription dose has been escalated to 81 Gy with 3D-CRT, and to 86.4 Gy using intensity-modulated radiotherapy (IMRT), with promising results.

3D-CRT involves the delineation of target and nontarget structures from patient-specific 3D image data sets [primarily computed tomography (CT), sometimes supplemented with magnetic resonance imaging, positron emission tomography, and so forth], the design of treatment portals using beam’s-eye view (BEV), the calculation and display of dose distributions, the analysis and evaluation of structure-specific dose-volume data (dose-volume histogram (DVH)), radiation delivery with computer-controlled multileaf collimators (MLC), and treatment verification with electronic portal images. However, the dose-distribution conformity achieved with 3D-CRT can be further improved by the use of computer-optimized intensity modulation. In addition, the treatment design phase of 3D-CRT involves several iterative steps and can be time-consuming, particularly when the anatomic geometry is complex. Thus, with the advance in computer technology, there has been much investigation on computer-aided treatment plan optimization.

IMRT is an advanced form of 3D-CRT with two key enhancements: (1) computerized iterative treatment plan optimization, and (2) the use of intensity-modulated radiation beams. Although the overall process of IMRT and 3D-CRT is quite similar, these two ingredients have implications in some aspects of treatment planning and implementation. In this chapter, we describe the process of IMRT as compared with 3D-CRT, identify how they differ, emphasize those features and benefits unique to IMRT, and point to current and future development. At present, there are two primary methods of IMRT delivery: (1) intensity-modulated radiation fields at fixed gantry angles delivered with MLCs, and (2) tomotherapy using beams from 360 degrees and modulated by a slit MLC. Most of our discussion focuses on the former approach.

PROCESS OF INTENSITY-MODULATED RADIOTHERAPY

The process of IMRT, as implemented at MSKCC, is schematically illustrated in Figure 29.4-1. The following is a discussion on each of the steps in the process, and in addition, other information that is pertinent to the development and application of IMRT.

**Figure 29.4-1:** A schematic illustrating step by step the intensity-modulated radiation therapy process. CT, computed tomography; EPID, electronic portal imaging device; MLC, multileaf collimators.
The use of simulators may be decreasing in 3D-CRT and IMRT, relative to its use in conventional radiotherapy. If a simulator is used, an initial (pre-CT) simulation may be carried out in conjunction with patient immobilization to establish fiduciary skin marks, define the tentative treatment isocenter, and obtain anteroposterior and lateral radiographic films. A second simulation may be performed, after the treatment plan has been accepted, to position the patient at the established isocenter and acquire reference radiographs of each field for comparison with the corresponding BEV digitally reconstructed radiographs and subsequently, the verification portal films.

A complete 3D CT image set is usually obtained with the patient in the treatment position on a flat couch. The number of CT slices and the interslice spacing are according to protocols, depending on the size, shape, and location of the target and the treatment technique. However, to produce high-resolution digitally reconstructed radiographs, the slices are contiguous with interslice spacing of 3 to 5 mm. For certain sites, magnetic resonance imaging and positron emission tomography are complementary to CT and helpful in defining the extent of disease, especially when used with image-correlation software.

The advent of CT simulation may make the process more efficient, by combining the simulation and CT imaging sessions into one. The CT simulator combines the capabilities of spiral (or helical) scanners for volumetric data acquisition and high-speed workstations for rapid image reconstruction and display. This permits the so-called virtual simulation, carried out on a computer workstation using the 3D CT data set (the virtual patient). In this process, a complete 3D CT data set is first obtained with the patient in the treatment position using 3- to 5-mm slice thickness. Then, corresponding to the specific treatment set-up parameters, patient anatomy is reconstructed from the CT data and displayed in BEV, and simulation fluoroscopic and radiographic images are digitally generated for viewing, decision-making, and documentation.

Aside from the improved efficiency, CT simulation eliminates or minimizes systematic uncertainties in the registration of simulation films to CT data sets, and in set-up errors when transferring the patient from one mechanical coordinate system to another. The disadvantage is the degraded image quality of reconstructed radiographs as compared with a conventional simulation film.

**DELINEATION OF TREATMENT VOLUME AND SELECTION OF TREATMENT BEAMS**

Treatment volumes are derived from the CT images according to the ICRU Report 50 nomenclature, with clinical target volume (CTV) being the visualized tumor plus the regions at risk, and planning target volume (PTV) to include setup and other uncertainties. The manual delineation of these and their adjacent critical organs are time consuming and would benefit from new and improved tools. However, human intervention will likely remain a necessary and important component for defining the CTV and PTV. Other contours needed for treatment planning and dose-distribution calculation such as the outer skin, bone, lungs, and air cavities can be outlined automatically with existing edge detection algorithms.

In 3D-CRT, to facilitate the selection of beam angles and field shapes, various display methods have been developed to represent the PTV and the adjacent critical organs in 3D perspectives. These objects are often displayed as wireframes or solid structures, using colors to differentiate between them and intensity to indicate depth. The treatment geometry is best visualized in the BEV, in which the anatomy is viewed from the perspective of the radiation source. Once the beam orientations are chosen, their shapes (apertures) can be determined, again facilitated by the BEV display.

3D image display is probably less critical in IMRT than in 3D-CRT. We believe that as long as there are a sufficient number of radiation fields (five to seven or more), the number of beams and their orientations are less important. This is because the many degrees of freedom in intensity modulation can effectively compensate the less optimal beam direction. Also, field size and shape can be completely defined by the assignment of intensity pattern in the optimization process (see Computer-Aided Plan Optimization in Intensity-Modulated Radiotherapy, later in this chapter). This is true at least for the treatment of cancers of the prostate and of head and neck at MSKCC and likely applies to other disease sites as well. Whether significant improvements in IMRT can be achieved via the use of noncoplanar beams is yet to be demonstrated, although this may likely prove advantageous for brain tumors and possibly other sites.

**COMPUTER-AIDED PLAN OPTIMIZATION IN INTENSITY-MODULATED RADIOTHERAPY**

The most distinguishing feature in IMRT planning is the use of intensity modulation to improve the dose distribution. An iterative process is invariably used, alternately adjusting the intensity pattern of the beams and assessing the resulting dose distribution until an acceptable plan is devised. The iterative process could be computer automated or could involve significant manual intervention. In general, computer automation is needed in the so-called inverse planning, while user experience and involvement are more important in the forward planning of IMRT. As widespread enthusiasm is primarily for the inverse method, we shall only briefly describe the forward process.

In forward planning, the starting point is a number of open beams and their field shapes. Based on the resultant dose distribution, the user adjusts the intensities in parts of some of the beams and recalculates the dose distribution. This is repeated until an optimal dose distribution is obtained. This approach is sensitive to the experience of the planner and may be restrictive in terms of the number of intensity levels and the complexity of the intensity-modulation pattern.

The inverse method of treatment planning was first proposed by Brahe in 1988. In this approach, the user specifies the number and orientations of the beams, and the desired objectives for the PTV and the critical organs. The computer algorithm divides each beam into individual rays and iteratively alters the ray weights until the composite 3D dose distribution conforms to the specified objectives. The beams derived by this method are intensity modulated (i.e., the pattern of radiation varies within each beam). It is easy to see why the field shapes need not be prespecified; the optimization process determines the edges as well as the intensity patterns within.

Central to the success of computer optimization is the specification of some quantitative measure of the goodness of a treatment plan. In inverse planning, the criteria are stated mathematically as objective functions that the optimization algorithm attempts to minimize. At present, most algorithms (including ours) are dose or dose-volume based (i.e., constraints are defined as doses to the target and normal tissues, or to volumes of interest). The use of biologically weighted objective functions is in principle more relevant, but is currently limited by the lack of validated biophysical models on tumor control and organ toxicity. The inverse planning method developed by Spirou and Chui at MSKCC is briefly summarized in the section Clinical Experience with the Use of Optimization Criteria, later in this chapter.

The starting point is the specification of the number of beams and their directions, and then the algorithm optimizes the intensities in the different parts of each of the beams. Suppose a patient is treated with three beams as shown in Figure 29.4-2, the computer program first calculates the doses to a matrix of points within the target and the normal organs from each individual rays of the three beams. If the point in question is in the target with a prescribed dose \( p \), the goodness of the current set of ray weights is given by the square of the difference between \( p \) and the current dose. This square of the difference is then summed over all the target points to determine the objective function that describes the goodness of the present set of beam weights. The weights of the individual rays and of each beam are then changed one at a time, with the change accepted if the objective function is reduced. The iterative process continues until the optimal plan is obtained, that is when the objective function is at its minimum.
resulting beams are intensity modulated (as shown by the profile of the vertical beam).

Constraints for critical organs can be incorporated as added term in the objective function. Dose-volume considerations are typically stated as "no more than q% of the particular organ may receive a dose greater than \(d_{\text{q\%}}\)." To impose such a constraint, at each iteration, the cumulative volume of the organ receiving doses greater than \(d_{\text{q\%}}\) is compared with \(q\). If it exceeds \(q\), a penalty in the form of constraint is added to the objective function, but only for those points that cause the constraint to be violated (i.e., the points beyond the volume \(q\)).

Several objective functions are illustrated graphically in Figure 29.4-3. For the treatment target, the graph illustrates the concept of the allowable inhomogeneity (i.e., if the dose is between a lower limit \(P_l\) and an upper limit \(P_u\), penalty is not assessed). Also, a larger weight can be assigned to penalize underdose as opposed to overdose. For the normal organ, penalty can be applied if dose exceeds a certain critical value (\(D_{\text{c}}\)) or based on dose-volume considerations, as discussed previously.

![Figure 29.4-3](Image)

**FIGURE 29.4-3.** Examples of possible objective functions, illustrated graphically. For the treatment target, doses within the allowable inhomogeneity are permitted, with different penalties (\(w\)) assessed for underdose as opposed to overdose. For the normal organ, penalty can be applied if dose exceeds a certain critical value (\(D_{\text{c}}\)) or based on dose-volume considerations. D, dose; V, volume.

**TREATMENT PLAN EVALUATION**

The process of treatment plan evaluation is continuing to evolve, particularly for IMRT with inverse planning. The tools by which plans are evaluated are largely the same for 3D-CRT and IMRT: two-dimensional (2D) dose distributions superimposed on CT images, 3D volumetric rendering of dose distribution and the PTV (and critical organs), structure-specific DVH, and biometric indices as a rough guide. Additionally, for IMRT plans, inspection of the intensity profiles either from an observer's point of view (like a relief map) or by the projection of isointensity lines on a BEV is often useful in evaluating an individual beam's contribution to the dose distribution. Even though the evaluation tools for 3D and IMRT plans are quite similar, the approach and action are quite different.

In the forward process of 3D-CRT or IMRT, the planner and the physician evaluate the initial treatment design(s) with a view to improve on it by altering some of the beam parameters (e.g., directions, weights, shapes, wedges, and so forth). The identification of deficiencies and the devising of remedies rely on the experience and intuition of the planner. The effort-intensive nature of this approach limits the practical number of iterations of evaluation and alteration. On the other hand, the application of class solutions to some disease sites minimizes the alterations needed and facilitates convergence to an acceptable solution within a few cycles.

In the inverse process of IMRT, to exploit the benefits of the increased degrees of freedom with modulated individual ray weights, a significant number of iterations (typically five to ten) are both needed and carried out. As the goal of the iterative adjustment of beam modulation by the optimization algorithm is to minimize the user-specified objective function, the resultant plan should satisfy the clinical criteria of acceptance. Thus, ideally the evaluation process should be primarily checking and approval. However, as discussed previously, this is usually not the case, at least in the developmental phase of IMRT.

Corrective action for an unacceptable IMRT plan would involve alteration of the parameters of the objective functions (instead of the beam parameters in a 3D-CRT plan). As alluded to previously, our observation is that such adjustments are not always consistent with our intuition or past experience in conventional or 3D-CRT treatment planning. One major difference is the lack of control in making coordinate-specific adjustment (i.e., it is difficult to alter the dose level to specific regions in the 3D space by changing the objective function parameters). At present, a trial and error (and time-consuming) approach is used to alter the input parameters and improve the IMRT. However, with improvement in software features and with experience in IMRT planning, we believe that this situation will improve.

**DELCERY OF INTENSITY-MODULATED FIELD WITH DYNAMIC MULTIPLEAF COLLIMATOR**

The intensity-modulated field can be delivered with an MLC. The 2D intensity distribution is divided into one-dimensional intensity profiles, with each profile delivered by one pair of leaves. In the dynamic MLC (DMMLC or sliding-window) method, the leaves are in continuous motion during radiation delivery. In Figure 29.4-4, the trajectory (the dotted lines) of the left and right leaves of one leaf pair is plotted as a function of beam-on time during radiation delivery, from their initial (instance a) to their final positions (instance d). As the beam is turned on (instance a), both leaves move, with different speeds, from left to right. The point P begins to receive radiation at instance b when the right leaf edge moves past it. It continues to receive radiation until instance c, when the left leaf begins to block the beam from P. By controlling the movement of the leaves and therefore the exposure duration (in this case, between b and c), one can deliver any desired intensity to point P, or any other point under this leaf pair. Extending this concept to multiple pairs of leaves, any desired intensity modulation can be produced with designed sequences of leaves positions.
The leaves' paths illustrated in Figure 29.4-4 (replotted here as dotted lines) are planned to produce the intensity profile indicated by the solid line in Figure 29.4-5A. In practice, a separate computer program (different from the inverse planning algorithm), sometimes called the leaf sequencer, is used to translate the intensity profiles of the intensity-modulated beam into the so-called DMLC file, that contains the data of the leaf position sequence as a function of monitor units (MU). In practice, not all desired intensity profiles are (exactly) achievable because of the constraints on leaf motion imposed by the design of the MLC and the clinical dose rate of the machine. The MLC manufactured by Varian Medical Systems, for example, is constrained by the maximum leaf speed ($v_{\text{max}}$ of 2.5 cm/s) and a maximum DMLC field of 14.5 cm (unless movement of the carriage is allowed). Beam delivery systems from other manufacturers may have similar or different limitations and constraints. Some leaf motion patterns may require a large number of MUs to deliver the desired dose (typically two to three times that for static beam delivery). Transmissions through the leaves are accounted for in the DMLC file.

To fully account for the intricacies of IMRT dose delivery, the calculation model must accurately predict the incident energy fluence and use a dose kernel that describes the transport of photons and electrons and energy spread in an inhomogeneous medium. One accurate method of dose calculation involves the convolution decomposition patterns for the 2D beams, and therefore the design of the most efficient MLC position sequence in the arc therapy is a challenging problem.

Yu proposed the intensity-modulated arc therapy method of IMRT delivery. In this method, the 2D intensity-modulated beams at many equally spaced gantry angles are approximated by a superposition of multiple-shaped radiation fields with uniform intensity. The increments of intensity level are delivered by individual arcs, with the pattern determined during treatment planning. Thus, each gantry arc treats a 2-cm long longitudinal strip of tissue. Treatment fields longer than 2 cm can be delivered by longitudinally translating the patient (with the treatment couch) between multiple arcs. Of extreme importance is the accuracy and stability of patient positioning as the treatment progresses from one axial slice to the next.

OTHER METHODS OF DELIVERY OF INTENSITY-MODULATED FIELD

A large number of IMRT treatments have been delivered using the MIMiC collimator from NOMOS. In this schema, a slit beam is used, typically 2-by-20 cm, and intensity modulation is achieved via 20 pairs of leaves. Each of the 40 leaves defines a pencil beam of 1 by 1 cm² that is either on or off at any given gantry position. As the gantry rotates through its 360-degree arc, all 40 leaves open and close (in a binary manner, either fully open or fully closed) according to the leaf motion pattern determined during treatment planning. Thus, each gantry arc treats a 2-cm long longitudinal strip of tissue. Treatment fields longer than 2 cm can be delivered by longitudinally translating the patient (with the treatment couch) between multiple arcs. Of extreme importance is the accuracy and stability of patient positioning as the treatment progresses from one axial slice to the next.

DOSE DISTRIBUTION CALCULATION

To fully account for the intricacies of IMRT dose delivery, the calculation model must accurately predict the incident energy fluence and use a dose kernel that describes the transport of photons and electrons and energy spread in an inhomogeneous medium. One accurate method of dose calculation involves the convolution of pencil beams. In our current dose model, inhomogeneity is accounted for by the traditional equivalent path length method, and pencil beam convolution is used only as a correction factor to account for the variation of intensity as opposed to a flat, uniform field. However, in a highly heterogeneous medium such as the lung, the accuracy of this calculation method needs improvement, for which development is in progress. The Monte Carlo method can provide the most accurate dose calculation, but because of the lengthy computation time, its routine use awaits faster computer speed. Nevertheless, the Monte Carlo method is relied on to derive accurate pencil beam kernel and the source function (which predicts the incident intensity pattern), with detailed accounting of the finite source size, extracranial radiation (from the flattening filters, primary and secondary collimators), beam spectrum, and so forth. For both the DMLC and the MSS methods of IMRT treatment delivery, because small aperture sizes are frequently used, accurate prediction of output factor is important.

Beam-on time calculation for IMRT treatment at MSKCC is an adaptation from our empirical-based method in which the dose D at a point $\{x,y,z\}$ is given as $D(x,y,z) = MU \times F$, where MU is the monitor unit of radiation beam, and F is a product of several factors, including the field size or output factor, the tissue maximum ratio, the off-center ratio, the inverse-square factor, and so forth. For IMRT, we modify the equation using a factor that accounts for the intensity modulation.

Figure 29.4-4. This graph depicts radiation delivery by the dynamic multileaf collimation (sliding window) method. The dotted lines are the positions of a leaf pair (x-axis) as a function of beam-on time (y-axis). As the beam is turned on (point a), both leaves move, with different speeds, from left to right. The point P begins to receive radiation when the right leaf edge moves past over it (point b). It receives radiation until the left leaf blocks the beam (point c). By controlling the motion of the leaves and therefore the beam-on-time duration between b and c, one can deliver any desired intensity to point P, or any other point under this leaf pair.

FIGURE 29.4-4. Illustrating the intensity profile delivered by the leaves' paths shown in Figure 29.4-4 (replotted here as dotted lines). In practice, a leaf-sequencing algorithm is used to translate the desired intensity profiles into computer data file of the leaf positions as a function of monitor units. B: Another method using the multileaf collimators to deliver intensity-modulated beams is by multiple static segment (the so-called step-and-shoot method). In the step phase, multileaf collimator travels to discrete positions, then beam-on in the shoot phase (i.e., alternate multileaf collimator movement and radiation delivery). The result is discrete intensity levels, the number of which depends on the step number.

The MLC can also be used to deliver intensity-modulated beams in the multiple static segment (MSS, or the so-called step-and-shoot) mode. In this mode, the MLC travels in a stepwise manner to discrete positions, with the beam turned off during the stepwise movement. As illustrated in Figure 29.4-5B, the leaf paths can be approximated by alternate horizontal step and vertical shoot segments, representing stepwise and alternate MLC movement and radiation delivery. As a result, the delivered intensity profile comprises discrete levels, with its number depending on the number of steps. In either mode, the total beam-on time for this leaf pair is T, and the MU needed for an intensity-modulated field is the largest T among all leaf pairs. It should be noted that there are other methods of MSS leaf sequencing to produce intensity-modulated beams.

OTHER METHODS OF DELIVERY OF INTENSITY-MODULATED FIELD

To deliver intensity-modulated beams, an MLC is used to deliver intensity-modulated beams in the multiple static segment (MSS, or the so-called step-and-shoot) mode. In this mode, the MLC travels in a stepwise manner to discrete positions, with the beam turned off during the stepwise movement. As illustrated in Figure 29.4-5B, the leaf paths can be approximated by alternate horizontal step and vertical shoot segments, representing stepwise and alternate MLC movement and radiation delivery. As a result, the delivered intensity profile comprises discrete levels, with its number depending on the number of steps. In either mode, the total beam-on time for this leaf pair is T, and the MU needed for an intensity-modulated field is the largest T among all leaf pairs. It should be noted that there are other methods of MSS leaf sequencing to produce intensity-modulated beams.

Yu proposed the intensity-modulated arc therapy method of IMRT delivery. In this method, the 2D intensity-modulated beams at many equally spaced gantry angles are approximated by a superposition of multiple-shaped radiation fields with uniform intensity. The increments of intensity level are delivered by individual arcs, with the leaf positions changing with gantry angle to produce the shaped fields. As has been pointed out, there are a large number of possible permutations of decomposition patterns for the 2D beams, and therefore the design of the most efficient MLC position sequence in the arc therapy is a challenging problem.
rate. In general, the more complex the intensity modulation, the larger the MU.

For conventional treatment, the independent MU check is typically calculated by hand. For IMRT, however, the intensity distribution is sufficiently complex that hand calculation is not feasible. At MSKCC, the independent check was initially provided by ionization chamber measurement, and subsequently by another computer program. Measurement is a direct assessment of the delivered dose, particularly valuable for new treatment techniques, but extremely time-consuming as a routine check. Our computer MU check software was programmed by an independent team. The program first constructs the delivered intensity distribution from the leaf-sequence files and the beam-on time. Doses to points or to planes at depth in a phantom are then calculated and compared with those of the original plan.

COMMISSIONING AND QUALITY ASSURANCE PROGRAM

Both mechanical and dosimetric measurements are required in the commissioning of IMRT delivery using DMLC. Because the dose delivered using DMLC is directly related to the gap widths between pairs of opposing leaves, precise leaf position is much more important in this approach than in treatments using static MLC. The positions of the leaf tips of the leaf positions can be accomplished using the recommended procedure and software supplied by the manufacturer. We have determined that a precision of 0.2 mm in leaf position is necessary, and that the Varian Mark II MLC satisfies this requirement. Dosimetric characterization of the MLC, using film, ion chambers, or both, includes measurements of radiation transmission through the leaves and their rounded ends, and the determination of head scatter. The dosimetric contribution of these factors, which can amount to as much as 15% of the dose, are accounted for in the leaf sequencer algorithm of the treatment planning system.

Another important consideration of DMLC is the monitoring of the performance of the MLC during treatment. While the beam is on, the Varian MLC control computer checks all leaf positions every 55 msec, compares them to the planned leaf positions in the DMLC file, and records them in a DMLC log file. If any leaf deviates from its planned position beyond a preset tolerance, the control computer invokes a beam holdoff, and radiation delivery is withheld until all the leaves are within tolerance again. Deviations that invoke beam holdoff should occur infrequently as the leaf sequencer algorithm, in generating the DMLC file, has duly considered the maximum MLC leaf speed and the nominal dose rate. Tests using clinical fields indicate that deviations of greater than 1 mm occur less than 1% of the time. For the initial group of patients, we tested the delivery of each field before treatment and examined the log files to ensure that there was no deviation that would significantly affect the dose. Based on those studies, a preset tolerance level of 2 mm was selected that mainly serves to insure against a potential hardware failure (e.g., a stuck leaf).

In addition, a comprehensive program to evaluate the routine performance of DMLC needs to be in place. This includes a quality assurance procedure and periodic dosimetric verification of intensity-modulated fields. Image patterns of predesigned fields are produced on radiographic films twice a week by radiotherapists to provide a quick visual assessment that the DMLC is functioning properly. Ion chamber and diode array measurements at different gantry and collimator angles are performed monthly by a physicist to ensure constancy of the DMLC output and to track long-term stability. Ion chamber measurements in solid phantom for patient fields provide an independent check on the MU calculations. Film dosimetry, with sufficient spatial resolution for the intensity-modulated patterns, efficiently compares the delivered and the planned dose distributions. It is also used intensively during the testing of new software and new treatment sites for IMRT, as well as for periodic spot checks. The general procedure is to irradiate the film in a homogeneous plastic phantom and to digitize the exposed film with a laser scanner.

TREATMENT DELIVERY WITH DYNAMIC MULTILEAF COLLIMATOR

For treatment implementation, the DMLC files of the intensity-modulated fields are transferred either via a floppy disk or electronically to the MLC control computer of the treatment machine. Also transmitted for each intensity-modulated beam is its fluence aperture, defined as the area with greater than 1% of the maximum intensity, or approximately the MLC aperture with the leading leaves and the trailing leaves at their respective final and initial positions. This fluence aperture is used for acquiring portal image (see Consideration of Treatment Uncertainties, later in this chapter) and for recording and verification purposes by that system.

Before the first treatment, portal localization electronic portal imaging device (EPID) images are taken of each intensity-modulated field with its fluence aperture. The portal localization films are then compared with the corresponding digitally reconstructed radiographs overlaid with the maximal DMLC apertures. This verifies that the radiation is directed properly, relative to the bony anatomy of the patient. During the treatment course, weekly portals are obtained for each field using the EPID. Using the EPID in combination with the MLC allows machine setup and image acquisition to occur without the therapist reentering the room between fields, thereby improving efficiency.

Before the dose delivery in patient treatment, the record and verify computer checks the initial leaf settings and the other machine parameters: the gantry angle, collimator angle, jaw positions, and MU setting. During radiation delivery, the MLC control computer monitors the leaf positions every 55 msec, compares them with the planned positions, and records the result in a DMLC log file. On completion of the first DMLC field, the record and verify system records the MU delivered and the final positions of the MLC. Without reentering the room, the radiotherapists rotate the gantry to the next orientation, program the accelerator and the MLC for the next intensity-modulated field, and then deliver the radiation. The process is repeated for each of the fields.

CLINICAL EXPERIENCE

CANCER OF THE PROSTATE

Since 1986 we have treated more than 1000 patients with cancers of the prostate using 3D-CRT. An analysis of 743 of these patients showed a significant effect of increased dose (from 64.8 Gy to 81.0 Gy) on response. With the capability of IMRT, we have further escalated the dose and have treated approximately 40 patients to 86.4 Gy. At the same time, a five-field IMRT treatment with a prescription dose of 81.0 Gy has become the standard of care for prostate of the cancer at MSKCC. This summary describes this experience and our preliminary clinical results.

Patients are immobilized in the prone position, simulated, and imaged on a CT simulator. With the CT data transferred electronically to the MSKCC planning system, the PTV, bladder, rectum, bowels, femors, and pelvis are contoured. IMRT planning is performed with the inverse method using a five-field technique (0, 75, 135, 225, and 285 degrees) as detailed previously. The present criteria for optimization are dose uniformity (within 12%) to the PTV, less than 34% of the rectal wall at 75 Gy, and less than 58% of the bladder wall at 81 Gy. The overlap region between the PTV and the rectal wall is separately constrained during optimization to exert greater control over the spatial dose distribution in that region. On approval of the optimized plan, BEV digitally reconstructed radiographs and the fluence apertures are generated, and the DMLC files transmitted to the MLC controller for treatment delivery using DMLC.

We reported the preliminary results of 171 IMRT patients, in comparison with those of 61 3D-CRT patients treated to the same 81 Gy. Because the dose delivered using DMLC is directly related to the gap widths between pairs of opposing leaves, precise leaf position is much more important in this approach than in treatments using static MLC. Measurement is a direct assessment of the delivered dose, particularly valuable for new treatment techniques, but extremely time-consuming as a routine check. For conventional treatment, the independent MU check is typically calculated by hand. For IMRT, however, the intensity distribution is sufficiently complex that hand calculation is not feasible. At MSKCC, the independent check was initially provided by ionization chamber measurement, and subsequently by another computer program. Measurement is a direct assessment of the delivered dose, particularly valuable for new treatment techniques, but extremely time-consuming as a routine check. Our computer MU check software was programmed by an independent team. The program first constructs the delivered intensity distribution from the leaf-sequence files and the beam-on time. Doses to points or to planes at depth in a phantom are then calculated and compared with those of the original plan.
Radiotherapy of head and neck cancers is often complex due to target doses of 70 Gy or higher and the close proximity of the spinal cord, brain stem, parotid glands, and optic pathway structures with tolerance doses of 45 to 55 Gy or less. Traditional treatments, consisting of parallel opposed photon fields (with blocks added to shield the spinal cord at 45 Gy) and electron fields to augment the dose to the cervical lymph nodes, are often inadequate in target coverage and in normal tissue sparing. We have previously used a multifield 3D-CRT approach, but since May 1998 have adopted IMRT and DMLC to deliver a uniform target dose with steep dose gradients at target-normal structure interfaces and reduced doses over normal tissues. Approximately one-half of 20 patients have received treatment for primary nasopharynx cancer, with 70 Gy to the gross disease and 54 Gy to the presumed microscopic disease.

Subsequent to CT simulation and image (3-mm increments) acquisition of the immobilized patient, the PTV (the gross disease and adjacent lymph nodes) and the normal structures (spinal cord, brain stem, optic nerves, chiasm, mandible, larynx, and parotid glands) are delineated. The beam arrangement, consisting of seven equally spaced beams directed from the posterior and lateral directions, attempts to create a concave dose distribution that encompasses the nasopharynx, skull base, and regional lymph nodes but encircles and spares the spinal cord and brain stem. When implemented with 3D-CRT, the technique is limited by excessive dose nonuniformity within the PTV (up to 140%) and by both planning and treatment complexities. These limitations are easily overcome with IMRT.

The dose-based criteria for optimization are for the nasopharynx and nodal target volumes to receive the prescription dose with a maximum of 120%, and dose constraints on the normal structures as follows: spinal cord, 40 Gy; brain stem, 50 Gy; optic structures, 50 Gy; and larynx, 45 Gy. The penalties for the spinal cord and brain stem are generally four to five times greater than the penalties for the PTV and other normal tissues. The derived IMRT plan, as assessed by dose distribution and DVH for the PTV and normal structures, demonstrates significant improvements over the traditional approach of parallel opposed primary plus 3D-CRT boost. The dose distributions are highly conformal and constrain the maximum spinal cord and brain stem doses to less than 40 and 50 Gy, respectively, well below maximum acceptable doses. Although there is no specific attempt to decrease the dose to the parotid glands for fear of underdosing nearby lymph nodes, the distribution of dose within the parotid gland is substantially different from that obtained with traditional opposed fields. With traditional parallel opposed beams, nearly the entire parotid gland volume would receive a dose of 70 Gy or more. With IMRT, approximately one-half the gland receives less than 50 Gy. Dose to the mandible is also substantially improved. Although the maximum mandible dose is still approximately 75 Gy, only 10% of the mandible receives more than 60 Gy.

In terms of clinical outcome, the combined rates of acute grade 1 and 2 rectal toxicity for IMRT were significantly less (45%) than that of 3D-CRT (61%) using the Radiation Therapy Oncology Group morbidity grading scale (P = .05). Similarly, there was a highly significant decrease in late grade 2 rectal bleeding to 0.5% with IMRT as compared with 13% for conventional 3D-CRT (P < .001). There was one grade 3 rectal toxicity (bleeding requiring laser cauterization) in each treatment group. Based on this experience, we have escalated the dose to 86.4 Gy and have successfully treated 40 patients using IMRT. We now await follow-up data on late reactions before additional patient accrual at this dose level.

Compared with our previous method of 3D-CRT planning for the 81-Gy treatment, IMRT planning is less labor intensive. The 81-Gy 3D-CRT plan was performed in two phases, a standard six-field plan to 72 Gy and a second one for the 9-Gy boost. In contrast, a single IMRT plan for both the 81-Gy or 86.4-Gy treatment course was judged acceptable for both tumor coverage and normal tissue sparing. Thus, the treatment planning effort has been reduced by a factor of two.

In terms of implementation, on average the length of treatment sessions was comparable for the five-field IMRT and the six-field 3D-CRT plans, even though the MUs of IMRT were approximately 2.5-fold higher. The average session for 136 patients treated (April 1995 to March 1996) with 3D-CRT to 75.6 Gy was 17.7 ± 0.1 minutes, compared with 16.5 ± 0.1 minutes for 140 IMRT patients treated (April 1997 to March 1998) to 81 Gy on the same machine, inclusive of the time for setup and weekly portal imaging.

**HEAD AND NECK CANCER**

FIGURE 29.4-6. An example of the dose distribution, in a color wash representation, for intensity-modulated radiation therapy prostate treatment to 81 Gy with 5 intensity-modulated beams. The dose distributions in the (A) transverse and (B) midsagittal planes are shown, with the planning target volume (PTV) (green) and rectum (yellow) outlined.

FIGURE 29.4-7. The cumulative dose volume histograms for the 81-Gy intensity-modulated radiation therapy plan illustrated in Figure 29.4-6. The dose-volume histograms for the planning target volume, rectal wall, and bladder wall are shown.

FIGURE 29.4-8. The intensity profile of the posterior beam, in the isocentric plane, from the 81-Gy intensity-modulated radiation therapy plan illustrated in Figure 29.4-6.
Radiation therapy after lumpectomy remains a primary method of treatment for primary breast cancer. Excellent local control is achieved in early-stage disease along with generally good cosmetic results and low toxicity. Nonetheless, improvements are needed, particularly for large-breasted patients with left-sided disease for whom cosmesis and potential cardiac toxicity remain significant issues. Since April 1999, we have treated selected patients with disease in the left breast and with large chest wall diameters with intensity modulation using a standard tangential beam arrangement. All patients undergo CT simulation during which the direction and size of the tangential beams are determined. The PTV is defined to be all tissue encompassed within 0.5 cm of the tangent field borders. The ipsilateral lung and coronary artery regions are defined by the physician using the CT.

The IMRT plan must deliver a uniform dose distribution in the PTV to within 10% of the prescription. Typically, this is achieved by setting an even tighter dose uniformity constraint for the target (of 5%) during optimization. The dose to the coronary artery region is minimized to the extent possible without sacrificing target coverage. Generally, a maximum dose constraint of 95% is used for this structure during optimization. Dose to the apex of the breast is controlled by separately contouring and constraining this region.

The advantages of tangential fields include treatment and setup simplicity and the ability to totally exclude critical structures such as the opposite breast from the treatment fields. Despite the limits imposed by this simple beam geometry, target dose uniformity and normal tissue doses have improved with IMRT. In a study comparing intensity modulation with conventional wedged tangents, an average improvement in target dose homogeneity of 5% was observed with IMRT. The mean dose to the coronary artery region and opposite breast decreased by more than 30% and 35%, respectively. The average volume of ipsilateral lung receiving doses in excess of the prescription decreased by 35%.

CONSIDERATION OF TREATMENT UNCERTAINTIES

To account for treatment uncertainties, arising from patient set-up variation and organ motion, a margin is added to the target in radiotherapy planning. As the dose distributions become more conformal in 3D-CRT and even more so in IMRT, the outcome of the treatment may become more sensitive to these uncertainties. Thus, it is important to quantify them, develop corrective methods to minimize them, and account for the residual component in treatment planning.

Ideally, patient-specific treatment uncertainty data should be used, but practically it would be difficult. Thus, approaches have been developed to quantify treatment uncertainties of a patient population. Set-up errors have been measured for several disease sites using serial portal images and interfraction organ motion by repeated CT scans. Based on such data, analysis can be performed to assess the potential effect of treatment uncertainties on treatment outcome using statistical sampling technique.

The previously mentioned population average uncertainty data can also be useful for the calculation of the dose distribution in treatment planning. Specifically, the frequency distribution of treatment uncertainties can be incorporated into the pencil beam kernel, which is equivalent to a convolution of the idealized dose distribution with the frequency distribution of treatment uncertainties. This yields an average dose distribution representing the effects of random, or daily, errors occurring over a treatment course.

DEVELOPMENT AND RESEARCH ISSUES

IMRT is in a developmental phase and there has been limited experience in the use of inverse planning in the radiotherapy community. Although we have had some experience of its use in the treatment of the prostate, each application to a new disease site (head and neck and breast) represented a new challenge, requiring adaptation or new custom features. For example, in the treatment of the breast, an extension of each intensity-modulated field to include a skin flash is needed. Given that our optimization algorithm is developed at MSKCC, we are able to modify the software to meet the unanticipated clinical requirement. We surmise that users of the emerging inverse planning systems may encounter similar experiences and will seek incremental improvement of their algorithms. The situation will likely be system specific and may vary widely among them due to the large number of variables in such systems and in the inverse process. In addition, better understanding in the use of optimization criteria is needed for the efficacious use of the inverse planning technique, and we have approached this by trial and error. Such criteria are certainly disease site specific and probably algorithm specific as well.

There are investigations on the use of biologic models of tumor tissue response as criteria for plan optimization. In general, biology-based score functions typically consist of some weighted combination of biologic indices. Two under current study are the normal tissue complication probabilities and tumor control probabilities. These indices condense structure-specific dose-distribution data to yield relative figures of merit for the respective objects of interest. However, both of these indices are at present based on rather rudimentary models with simplistic assumptions. Importantly, clinical data for validating the models and deriving the model parameters are lacking. Nevertheless, the advent of 3D treatment planning and the accrual of patients treated with this modality are beginning to provide clinical outcome data for which dose volume information are available. For example, analysis has been performed on clinical complication data of the lung, liver, and optic pathways. Such studies promise to improve the present biologic models, provide better estimates for the model parameters, or both. It is hoped that the iterative process of generating clinical data and refinement and validation of the models will incrementally improve the predictive power of the biologic indices and facilitate the quantitative evaluation of 3D treatment plans.

Certain technical aspects of inverse planning will continue to be investigated. For example, the advantages and disadvantages of gradient-based optimization as compared with simulated annealing. The latter method, though much slower computationally, is more likely to yield the global minimum (or the most optimal solution), but this theoretical advantage has not been demonstrated to be clinically important. Another often discussed issue pertains to the optimal number of intensity-modulated beams and their orientations. Again, our view is that given a sufficient number of equally spaced beams (five to seven or more) and the intensity-modulation capability, near optimal plans can be generated.

There is significant interest in developing methods to verify the delivery of intensity-modulated beams. These efforts are benefiting from the gradual maturation of the EPID technology, particularly using amorphous silicon detectors. The ability to verify directly the intensity pattern of the delivered intensity-modulated beams will greatly enhance the confidence in the use of IMRT and lead to wider acceptance of this modality. At present, the electromechanical monitoring of leaf positions during radiation delivery provides similar assurance, albeit indirectly and without providing measured data.
The ability of IMRT to deliver nonuniform dose patterns by design brings to fore the question of how to dose paint and dose sculpt, leading to the suggestion that biologic images may be of assistance. In contrast to the conventional radiologic images that primarily provide anatomic information, biologic images reveal metabolic, functional, physiologic, genotypic, and phenotypic data. Important for radiotherapy, the new and noninvasive imaging methods may yield 3D radiobiologic information. Studies are urgently needed to identify genotypes and phenotypes that affect radiosensitivity and to devise methods to image them noninvasively. Incremental to the concept of gross target volume, CTV, and PTV, we suggest the concept of biologic target volume and hypothesize that biologic target volume can be derived from biologic images and that their use may incrementally improve target delineation and dose delivery. We emphasize, however, that much basic research and clinical studies are needed before this potential can be realized.

In conclusion, IMRT is a powerful technique that provides extra degrees of freedom in customizing the dose distribution for photon radiotherapy. With the development of the computer-controlled treatment machines equipped with DMLC, it is now possible to deliver these treatments reliably. The clinical implementation of inverse planning and treatment delivery with DMLC is extremely complex and involves a substantial developmental effort. However, once accomplished, the process is efficient and capable of providing the dual benefits of improved dose distribution and cost savings. It is likely that this new modality will become widely accepted and applied in the future.

CHAPTER REFERENCES

**SECTION 30.1**

**Molecular Biology of Head and Neck Tumors**

DAVID SIDRANSKY

**INTRODUCTION**

Cancer is a complex genetic disease derived from the accumulation of various genetic changes. These genetic alterations include activation of protooncogenes and inactivation of tumor suppressor genes. Moreover, inactivation of tumor suppressor gene function requires inactivation of both parental alleles, usually by point mutation and a chromosomal deletion. The correlation of these specific genetic changes with the various lesions depicted in the histopathologic progression of colorectal cancer has led to the development of a molecular progression model for this disease. This molecular model now serves as a paradigm for the molecular progression of many other solid neoplasms.

A number of specific genetic events have been identified in the progression of head and neck squamous cell carcinoma (HNSCC). Primary tumor DNA can now be isolated and assessed directly for the presence of chromosomal deletions and amplification, as well as direct characterization of candidate oncogenes. Identification of the critical genetic changes that drive the neoplastic process has provided a preliminary progression model for head and neck cancer. This model now delineates appropriate genetic targets for novel diagnostic, prognostic, and therapeutic strategies.

**GENETIC SUSCEPTIBILITY**

It has been estimated that up to 10% of all cancers have a strong hereditary component. Generally, familiar clustering of cancer has suggested the possibility of genetic predisposing factors. A clustering of oral cancer has been seen in certain ethnic groups, and an increased risk of cancer has been noted among relatives of patients with one head and neck cancer. Several studies have suggested a threefold higher risk of developing an oropharyngeal cancer in populations that have a first-degree relative with HNSCC. There has also been some suggestion of a remarkable increase in the relative risk of cancer in relatives of individuals with multiple primary tumors. Except for the finding of head and neck cancer in some rare cancer syndromes, the basis of this genetic susceptibility has yet to be determined.

An emerging area of study centers on the prevalence of specific polymorphisms in enzymes that are involved in the detoxification of several tobacco smoke–derived carcinogens. One larger study of 162 patients with head and neck cancer and 315 healthy controls suggested that certain glutathione S-transferase (GST) genotypes represented independent risk factors for head and neck cancer. Some studies also have shown a two- to threefold risk for the GST M1 and GST T1 null genotypes, whereas others have shown no increase in HNSCC risk.

In all these studies, it is difficult to exclude other important risk factors, such as smoking, yet there appears to be a consistent susceptibility based on certain metabolic genotypes. Others also have found that the repair capacity of peripheral lymphocytes or their ability to repair carcinogen-induced chromatic breaks may also define a certain risk for head and neck cancer. A more precise contribution of these polymorphisms and other risk factors to the development of head and neck cancer will need to be elucidated in larger studies.

**CYTOGENETIC ALTERATIONS**

Statistical analysis based on the age-specific incidence of head and neck cancer suggests that HNSCC tumors arise after the accumulation of six to ten independent genetic events. Cytogenetic approaches have given us some insights into potential areas of deletion and amplification involved in the progression of head and neck cancer. Previously, karyotypic studies concentrated on established cell lines with complex chromosomal abnormalities. Unfortunately, different cell culture conditions added substantial variation to these observed chromosomal alterations. Moreover, cultured cells from the primary tumor may represent only a small clone derived from a very large number of different clones. Thus, the analysis of primary tumors is one of the major future challenges.

Additional studies have shown that the presence of important alterations in most of these studies, it is difficult to exclude other important risk factors, such as smoking, yet there appears to be a consistent susceptibility based on certain metabolic genotypes. Others also have found that the repair capacity of peripheral lymphocytes or their ability to repair carcinogen-induced chromatic breaks may also define a certain risk for head and neck cancer. A more precise contribution of these polymorphisms and other risk factors to the development of head and neck cancer will need to be elucidated in larger studies.

More recently, comparative genomic hybridization has emerged as a comprehensive method for genome-wide evaluation to detect deletions or amplification. In this approach, normal DNA is mixed and hybridized to metaphase spreads from normal cells. Labeling of tumor-normal DNA by different fluorescent colors allows direct visualization of increased or decreased chromosomal material in neoplastic tissue by fluorescence detection. This approach is complementary to other methods for assessment of both tissue culture and primary tumor material. In addition to the chromosomal areas previously noted, comparative genomic hybridization has demonstrated amplification of 3q, 5p, 11q13, and 19q.

**PROTOONCOGENES**

Protooncogenes were initially identified as activated cellular genes specifically altered in some human neoplasms. Despite the cloning of dozens of putative protooncogenes involved in the development of human neoplasms, few were found to be altered directly in the progression of primary tumors and cell lines. In addition to activation of oncogenes such as ras by point mutation, amplification is also a mechanism for activation of a protooncogene locus. Definitive studies suggested that the 11q13 amplification was associated with amplification of a critical protooncogene termed cyclin D1 (PRAD1; CCND1). Although other genes were also coamplified in the same region, only cyclin D1 was consistently amplified in approximately 30% of HNSCC and most other neoplasms. Moreover, amplification of this region correlated with increased expression of the cyclin D1 gene and may indicate a likelihood of progression in primary HNSCC.

As previously noted, amplification of 3q has been noted in many squamous cell carcinomas, including head and neck cancer. A p53 homologue (p40/p51/p63) has been cloned and localized to the distal arm of 3q. Although homologous to p53, this genetic locus was found to be amplified in a high frequency of squamous cell carcinomas, and this amplification correlated with increased expression at the RNA and protein level. Although there has been no evidence of activating point mutations in squamous cell cancers, functional evidence suggests that ASIS may in fact be a true oncogene in squamous cell cancers. Interestingly, dominant negative mutations are responsible for a specific hereditary syndrome called ectrodactyly–ectodermal dysplasia–clefting syndrome. Knockout mice display a lack of epidermal development consistent with the role of this gene in epithelial renewal. Further studies should establish the role of ais in the genetic progression of head and neck cancers.

The role of cyclin D1 in the progression of human cancer is now well established. Other tumor suppressor genes, including Rb and p16, are negative regulators of the cyclin D1 pathway and are often inactivated in human neoplasms. In head and neck cancer, p16 appears to be a major target of inactivation. Thus, abnormal cycling through this critical G1/S checkpoint may be a consistent genetic alteration in a majority of primary HNSCC. Although p16 and Rb inactivation are almost
always exclusive, cyclin D1 amplification is independent of p16 inactivation in head and neck cancers.  

Like other epithelial neoplasms, the role of other protooncogenes has been much less definitive. Few mutations in ras have been identified in primary head and neck tumors. Although epidermal growth factor receptor (EGFR) has been an interesting candidate, increased levels of the receptor at the RNA or protein level rarely correlate with primary DNA amplification. New evidence suggests that activation of signaling through Stat-3 leads to EGFR-mediated cell growth and that antiserum suppression of EGFR antibodies leads to apoptosis (apoptotic initiation factor) (e1F4E) binds to messenger RNA during initial protein synthesis, and its overexpression can result in the up-regulation of proteins essential for cell growth and division. Overexpression of e1F4E has been found in HNSCC, and there has been some evidence of gene amplification and protein overexpression in these tumors. Overexpression of the protein in cells can lead to oncogenic transformation and may facilitate the synthesis of angiogenic factors such as vascular epidermal growth factor by enhancing their translation. In at least one study, there was a correlation between increasing e1F4E and vascular epidermal growth factor levels, suggesting its possible role in angiogenesis.  

Additionally, several other genes or gene products have been found to be overexpressed in head and neck tumors. High levels of cyclooxygenase (COX)-2, have been seen in squamous cell carcinomas by a competitive reverse transcription assay. GST P1 messenger RNA levels are found to be high in most moderately and poorly differentiated tumors, but only a fraction of these had specific gene amplification. Newer cytogenetic techniques may lead to the identification of important protooncogenes more commonly involved in the progression of HNSCC.

SUPPRESSIVE GROWTH REGULATION

In addition to growth factors with “positive” regulation and augmentation of tumor growth, other growth factor pathways may suppress cell growth. Transforming growth factor-β (TGF-β) is one among these growth factors that have been implicated almost universally with suppression of tumor growth. Alterations of the type II TGF-β receptor, one target of TGF-β, were noted in primary colorectal cancers potentially involved in abrogation of this negative regulatory pathway. Initially, some head and neck cancer cell lines were also found to harbor TGF-β receptor mutations, and mutations in the conserved serine/threonine kinase domain were found in 6 of 28 primary tumors. The interaction of TGF-β with this critical receptor normally leads to an increase of negative regulators of the cell cycle (e.g., p15, INK4B) and G1/S arrest; thus, normal negative regulation may be abrogated by mutations in the type II TGF-β receptor.

Through a different mechanism, retinoic acid receptors (RARs) have been implicated in the negative growth regulation of HNSCC. This negative regulation has been the cornerstone of successful chemopreventive approaches to diminish the incidence of second primary tumors in head and neck cancer patients. Retinoic acid is a naturally occurring member of the vitamin A family and has activity that is directed toward differentiation and growth arrest in many cancer cell lines. Although the regulation of retinoids is complex, a critical end point may be down-regulation of RAR-β. Studies in patients with premalignant disease (leukoplaikia) have suggested that RAR-β levels are closely associated with response to retinoid acid. In particular, those patients with tumors demonstrating low RAR-β levels did not respond to retinoid acid. Further functional studies into the role of retinoid acid and RAR-β may yield important information regarding the role of this pathway in the progression of HNSCC and successful treatment of premalignant lesions.

TUMOR SUPPRESSOR REGULATION

Molecular analysis has now revolutionized the ability to look at primary neoplasms. Methods that required large amounts of DNA (e.g., Southern blot analysis) have now been supplemented by polymerase chain reaction (PCR)-based approaches that allow access to limited DNA samples. Minute primary specimens from paraffin can be evaluated by rapid and accurate techniques. DNA extracted from these samples can be amplified by PCR to reveal the presence of allelic losses. In practice, maternal and paternal alleles can be distinguished by testing highly polymorphic markers that occur naturally among DNA sequences.  

It is now generally believed that these allelic losses (or chromosomal deletions) are markers for inactivation of critical tumor suppressor genes contained within the regions of loss. Testing of highly polymorphic microsatellite markers (small 2– to 4–base pair repeats) from a specific chromosomal region allows rapid assessment of allelic losses in tumors that have normal DNA. Perhaps the best example of this association is derived from loss of chromosome 17p. These losses led to characterization of p53 as a candidate gene within the deleted area and subsequent identification of point mutations within the remaining allele. Inactivation of p53 now represents the best described and most common genetic change in all of human cancer. Approximately 50% of all primary HNSCCs harbor p53 mutations in the conserved regions (exons 5 to 9).

A comprehensive allelotype of head and neck cancer has now been completed and refined. The most commonly deleted region in head and neck cancer is located at chromosome 9p21-22. Loss of chromosome 9p21 occurs in the majority of invasive tumors and is also present at a high frequency in the earliest definable lesions, including dysplasia and carcinoma in situ. Furthermore, homozygous deletions in this region are frequent in HNSCC and represent one of the most common genetic changes identified in all human neoplasms. p16 (CDKN2) is contained within this critically deleted region and is a potent inhibitor of cyclin D1/CDK4 complexes. Thus, p16 has emerged as an excellent candidate tumor suppressor gene within the deleted area. Indeed, germline point mutations of p16 predispose to familial melanoma, and loss of p16 may be necessary for immortalization of keratinocytes.

Although initial enthusiasm for p16 as a target gene in head and neck cancer was diminished when sequence analysis revealed rare point mutation (approximately 10% to 15% of HNSCC tumors), alternative mechanisms of inactivation were identified suggesting that aberration of p16 function may be a common occurrence in head and neck cancer. Homozygous deletion (deletion of both gene copies) and methylation of the 5' CpG region of p16 have been identified, each detected in approximately one-fourth of primary head and neck cancers. This methylation is associated with complete block of p16 expression and appears to be a common mechanism for p16 inactivation. The notion that p16 inactivation is directly involved in the progression of primary tumors has been strengthened. Lack of p16 protein was detected by immunostaining in most primary invasive lesions, and tumors with absent p16 protein contained a homozygous deletion, methylation, or point mutation of p16. Loss of p16 protein has been observed in most advanced premalignant lesions.

It is also possible that a second critical tumor suppressor gene resides at 9p21. We and others have identified an alternative RNA transcript for p16 termed p16 beta. This unique transcript originates from an upstream initiating site in a novel exon 1 and codes for a protein through an alternative rating frame (ARF). Interestingly, introduction of p16 or p16 beta into head and neck cancer cell lines results in potent growth suppression. Although the human transcript is somewhat shorter than the murine protein, functional studies have suggested that ARF binds to MDM2, leading to a decrease in p53 degradation and a subsequent increase in p53 levels. Moreover, a knockout ARF mouse develops certain tumors at an increased frequency. In human tumors, homozygous deletion of the p16 locus correlates with loss of most of 17p. Inactivation of ARF in head and neck cancers is frequent, and knock-out of p16 beta results in an ARF protein. The absence of an ARF protein suggests that p53 mutations and p16 inactivation are not exclusive, suggesting that, at least on a genetic level, they do not function in the same pathway. Ultimately, further studies will have to be done in primary tumors and human models to establish the precise role of p16 beta inactivation in squamous cell carcinoma.

A second commonly deleted locus occurs on chromosome 3p. Several studies have suggested that this region of loss is complex in head and neck cancer and may in fact be composed of three distinct suppressor regions juxtaposed to one another. As for 9p21, analysis of 3p21 losses in HNSCC has revealed frequent loss in early lesions. The 3p21 region is also frequently lost in lung cancer and has been the target of an intensive search for the critical tumor suppressor gene. The 3p21 region is also frequently lost in lung cancer and has been the target of an intensive search for the critical tumor suppressor gene. The 3p21 region is also frequently lost in lung cancer and has been the target of an intensive search for the critical tumor suppressor gene. The 3p21 region is also frequently lost in lung cancer and has been the target of an intensive search for the critical tumor suppressor gene. The 3p21 region is also frequently lost in lung cancer and has been the target of an intensive search for the critical tumor suppressor gene. The 3p21 region is also frequently lost in lung cancer and has been the target of an intensive search for the critical tumor suppressor gene. The 3p21 region is also frequently lost in lung cancer and has been the target of an intensive search for the critical tumor suppressor gene. The 3p21 region is also frequently lost in lung cancer and has been the target of an intensive search for the critical tumor suppressor gene. The 3p21 region is also frequently lost in lung cancer and has been the target of an intensive search for the critical tumor suppressor gene. The 3p21 region is also frequently lost in lung cancer and has been the target of an intensive search for the critical tumor suppressor gene. The 3p21 region is also frequently lost in lung cancer and has been the target of an intensive search for the critical tumor suppressor gene. The 3p21 region is also frequently lost in lung cancer and has been the target of an intensive search for the critical tumor suppressor gene.

Loss of chromosome 17p is a frequent occurrence in most primary cancers, and head and neck cancer is no exception (occurring in 60% of invasive lesions). Although EGFR protein expression characterizes certain squamous cell carcinomas, it is quite rare in squamous cell carcinomas of smokers. Newer evidence from cell lines also suggests that a distinct breakpoint to p53 occurs in head and neck cancer. Together, these data suggest that a second tumor suppressor gene on 17p may be involved early in the progression of this neoplasm. p53 mutations, as in most tumors, generally rise in frequency between the preinvasive to the invasive state. This is consistent with a critical function for p53 in response to DNA damage. p53 mutant tumors are also less likely to respond to local radiation therapy.

This model is certain to become more complex, but offers an important insight into the role of p53 in the progression of head and neck cancer and many other tumors. Although only 10% of these cancers have been detected in primary tumors and cell lines, specific inactivating mutations of the second allele have not been forthcoming. This is consistent with a critical function for p53 in response to DNA damage. p53 mutant tumors are also less likely to respond to local radiation therapy. Ultimately, further studies will have to be done in primary tumors and human models to establish the precise role of p16 beta inactivation in squamous cell carcinoma.
inactivated gene, it seems to be more common in advanced tumors and may harbor a poor prognosis. 74, 75

Loss of 13q also occurs in approximately 60% of primary tumors and the minimal area of loss includes the tumor suppressor gene Rb. However, immunohistochemical analysis of Rb (which detects most Rb alterations) revealed inactivation of Rb in only small percentages of tumors with loss of 13q. 76, 77 Again, as in many other chromosomal regions, there appears to be another tumor suppressor gene near Rb, putatively inactivated in the progression of head and neck cancer.

More recent work has suggested that there may be one or more regions of specific loss on the short arm of chromosome 8 and on 7q31. 72, 73, 79 Loss of 18q has been seen, and one of these minimally deleted regions harbors two tumor suppressor genes. 80 Homozygous deletions of both DCC and DPC4 have been noted in cell lines but have been rarely seen in primary tumors. 81 Many other areas of chromosomal loss have been seen in head and neck cancer consistent with the occurrence of multiple genetic events in the progression of these neoplasms. Except for those previously noted, critical tumor suppressor genes have not been identified from these losses and remain to be isolated and characterized. Further fine-mapping of these deletions, amplifications, and translocations with characterization of critical genes within these areas may provide important information about the biology and clinical behavior of these neoplasms.

We have tested the ten most common allelic loss events in a large number of primary preinvasive lesions and invasive HNSCC to develop a molecular progression model. 82 As seen in Figure 30.1-1, the progression of head and neck cancer involves inactivation of many putative suppressor gene loci. Chromosomes 9p and 3p appear to be lost early, closely followed by loss of 17p. p53 mutations are seen in the progression of the preinvasive to invasive lesions, and many other genetic events occur later in progression. Other specific genetic events, such as amplification of cyclin D1 and inactivation of p16, have been tested predominantly in invasive lesions, and the precise order in the model cannot yet be determined. As noted in the molecular model for colorectal cancer, it is the accumulation and not necessarily the precise order of these genetic events that determine histopathologic progression. This is best exemplified by some early lesions that demonstrated a “late” event as the sole genetic alteration.

FIGURE 30.1-1. Preliminary progression model for head and neck squamous cell carcinoma. Genetic alterations have been ordered by testing a variety of preinvasive and invasive lesions and determining the frequency of these events at each stage in progression. Inactivation of p16 (chromosome 9p21) and amplification of cyclin D1 (chromosome 11q13q) have not been directly tested in preinvasive lesions. It is the accumulation and not necessarily the order of these genetic changes that determines progression.

To test this model directly, we were able to analyze lesions that demonstrated histologic progression from one area to another. In each of the cases, we confirmed that 9p and 3p loss were early events, with other genetic changes occurring in the more advanced histopathologic lesion. Moreover, losses biopsied in the same area over time in a few critical genes also demonstrated the same general order of these events. Molecular progression models such as this one allow direct characterization of early genetic events that might be important in diagnostic strategies. Critical events that occur in the progression from the preinvasive state to the invasive state (e.g., p53 mutations) may be useful as prognostic indicators in primary lesions. Losses occurring later in progression, such as 11q, 13q, 14q, and 18q, and loss of p27 protein (another cyclin-dependent kinase inhibitor) have been found to correlate with a decrease in survival. 83, 84, 85, 86 Early losses at 3p14 and 9p21 may persist in premalignant lesions exposed to chemoprevention agents and may predict those likely to relapse despite apparent histologic remissions. 85, 86

All of these genetic events may one day serve as appropriate targets for novel therapeutic approaches. This model also has given some interesting insights into the well-known phenomenon of field cancerization.

FIELD CANCERIZATION

Patients with head and neck cancer often present with second metachronous and synchronous tumors of the aerodigestive tract. Moreover, patients with primary lesions often have skip areas that are characterized by preinvasive lesions throughout the field. Slaughter originally coined the term field cancerization and attributed this to a field defect that allowed independent transformation of epithelial cells at a number of sites. Previous studies in bladder cancer demonstrated that multiple tumors arising in a single patient were derived from the uncontrolled spread of a single transformed cell. 87 These tumors then grew independently with variable subsequent genetic alterations. For head and neck cancer, our working progression model allowed direct assessment of the genetic changes in surrounding areas of histopathologic abnormality. In every case, surrounding lesions appeared to share the same genetic events (e.g., critical breakpoints at chromosomes 9p21 and 3p21) present in the primary tumor, suggesting that a single transformed cell gave rise to the independent and apparently geographically distinct skip areas seen in these patients. Thus, Slaughter's original observations can be explained as follows: A cell is transformed by a critical genetic event and begins to migrate through the mucosa. Additional genetic events in one critical lesion eventually give rise to the clinical tumor that is seen on presentation. However, direct molecular assessment of surrounding regions confirms the presence of clonal cell populations that are not yet fully transformed. Given time, these lesions then arise as other preinvasive or invasive lesions in the same patient.

Although investigators have reported a confirmation of this field cancerization effect in head and neck cancer by detection of discordant p53 mutations in multiple tumors, 88 our working model suggests that this conclusion may be premature. Other genetic events, including loss of 9p and 3p, precede inactivation of p53. Thus, one of these early events probably leads to initial cell transformation and replacement of surrounding mucosa, whereas subsequent genetic events including p53 appear to arise independently. Thus, these investigators identified the diversity of subsequent genetic events rather than established the distinct clonal origin of these clonal lesions. By examining the pattern of X-chromosome inactivation loss of chromosomes 9p21 in multiple tumors from female patients, we demonstrated a common clonal origin in most of these cases. 89 In support of this result, cytogenetic evidence in at least one patient identified the presence of a specific chromosomal marker in both primary neoplasms. More recently, apparent second primary tumors of the lung and even rare esophageal tumors were found to be clonally related to the initial primary HNSCC. 90

If minimally abnormal or benign-appearing premalignant lesions show clonal genetic changes adjacent to a primary HNSCC, it is conceivable that normal-appearing mucosal areas could harbor an occult neoplasm. Clinically detectable cervical lymph node metastases without identification of the primary tumor were assessed by molecular analysis of multiple surveillance biopsies. We investigated whether the site of origin of the primary tumor could be localized by detection of specific losses on some of the key chromosomes described in the molecular progression model. 35, 91 In 10 of 18 patients, at least one pathologically benign biopsy demonstrated a pattern of genetic alterations identical to that present in cervical lymph node metastases. Three of these patients went on to develop primary tumors in the identified or adjacent mucosal region between 1 to 13 years later. 92 These data further support the notion that histopathologically benign mucosa may harbor parishes of clonal preneoplastic cells that are genetically related to the metastatic HNSCC and that such mucosal sites are the sites of origin of unknown primary HNSCC.

MOLECULAR EPIDEMIOLOGY

The pattern of specific mutations within a given gene sequence may provide important information concerning the etiology (e.g., effect of a carcinogen) of that particular cancer. 93 The p53 gene can be inactivated by a large variety of distinct mutations and is frequently inactivated in many human cancers, providing an excellent model for this type of survey. Analysis of the pattern of p53 gene mutation in 129 HNSCC patients has demonstrated that the incidence of p53 mutations is much higher among premalignant lesions exposed to tobacco and alcohol than among those patients who abstained from both. 94 Moreover, we found that the alcohol appeared to augment the effect of smoking, consistent with models in which alcohol is not a carcinogen per se, but might lead to an increase in the absorbance of carcinogens contained within cigarette smoke. Furthermore, we found that CpG mutations are rare among mutations patients who smoke cigarettes, whereas they...
constituted most of the mutations found in nonsmokers and nondrinkers. C to T mutations at these CpG sites are important because, through methylation and deamination, they are thought to represent potential sites of "endogenous" mutations. These data thus support a growing body of epidemiologic evidence that abstinence from cigarette smoke may help decrease the overall incidence of head and neck cancer.

HUMAN PAPILLOMAVIRUS

Human papillomavirus (HPV) has long been thought to play a role in some head and neck cancers. One study of more than 250 patients used PCR followed by definitive techniques such as sequencing and in situ hybridization to search for the presence of HPV in head and neck tumors. HPV was detected in approximately 25% of the lesions and virtually all were "high-risk" oncogenic types (HPV 16). Remarkably, most HPV-positive tumors were in the oropharynx. For these HPV-positive oropharyngeal cancers, they were less likely to occur among heavy smokers and drinkers, less likely to harbor a p53 mutation, and had an improved disease-specific survival. Another group suggested that HPV-positive tumors may also inactivate Rb and harbor a better prognosis. These new data are consistent with previous studies with a smaller number of patients or those that used less definitive determine techniques. It appears that HPV-positive oropharyngeal tumors compose a distinct clinical and pathologic disease entity causally associated with HPV.

DIAGNOSTICS

Clonal genetic alterations can be identified in clinical samples including bodily fluids. These clonal genetic alterations are generally considered to represent specific markers for the presence of neoplastic cells. In many clinical samples, however, the number of neoplastic cells are greatly outnumbered by normal cells within the same specimen. Therefore, we and others have developed very sensitive and specific techniques to detect these rare clonal genetic alterations among many "normal" or wild-type DNA molecules. Clonal ras gene mutations have been detected in the stool of patients with colorectal cancer and p53 mutations in the urine of patients with bladder cancer. Moreover, both ras and p53 oncogene mutations were used as targets to detect neoplastic cells in the sputum of patients with lung cancer. In one case, the same clonal cell population containing the identical mutation eventually identified in the primary tumor was detected 1 year before clinical diagnosis in a patient with lung cancer. Analysis of p53 mutations also has confirmed the ability to detect neoplastic clones in the saliva of patients with head and neck cancer.

Telomerase is a ribonucleoprotein that maintains telomere length, and reactivation of its activity is associated with escape from cellular senescence. Using a modified PCR-based assay for telomerase activity, 80% to 100% of primary head and neck cancers were found to display telomerase activity. Some authors have suggested that most dysplastic lesions and preneoplastic lesions also display telomerase activation. Interestingly, 14 out of 44 (32%) of oral rinses from HNSCC patients were found to harbor telomerase activity, but a small percentage of normal controls also exhibited this telomerase activity. Using a panel of 21 microsatellite markers, clonal genetic changes (loss of heterozygosity or microsatellite instability) were detected in 80% of the saliva samples from the patients with head and neck cancer. Moreover, exfoliative cell samples were subjected to microsatellite analysis and found to contain the identical changes observed in the primary tumors. It is still unknown if these changes can be identified in early lesions or if they can detect recurrence, as has been seen in bladder cancer through urinalysis. Clearly, the continued identification of molecular markers will lead to improved diagnostic techniques for squamous cell carcinoma.

A more pressing problem in HNSCC is the high incidence of local-regional recurrence despite aggressive surgical therapy. We used a similar molecular approach as previously described to probe surgical margins and lymph nodes from patients with primary head and neck cancer after surgical resection. A segment of the p53 gene is amplified by PCR from DNA extracted from the clinical sample. The PCR products are then cloned into phage, transferred to nylon membranes, and probed with a specific oligomer (small DNA strand) able to recognize the same mutation initially identified in the primary tumor. Thus, a unique DNA probe was synthesized and used to test the resected surgical margins and lymph nodes from affected patients. Perhaps not surprisingly, many of the apparently normal margins and lymph nodes by light microscopy were found to contain infiltrating tumor cells by this sensitive molecular analysis.

In an initial pilot trial that contained 30 patients, the results were quite interesting. Although all patients were thought to be completely negative by light microscopy, final pathology revealed at least one positive margin in five patients. These five patients had markedly positive margins by molecular analysis and were further excluded from this study. There were 25 remaining patients who were still completely negative by light microscopy. Of these, 13 were positive by molecular analysis and five have recurred within 2 years (average, 9 to 12 months). Of the 12 patients who were completely negative by molecular assessment, none has recurred at 2-year follow-up. As expected, there is a significant improvement in survival for those patients initially negative by molecular analysis. Other markers have been used to assess possible recurrence in tumor-free margins. e14FE (previously described) is associated with increasing overexpression in the progression of head and neck cancer and also has been detected in apparently tumor-free margins.

Although the previous results must be confirmed by a larger prospective trial, the results are already intriguing. Perhaps patients with negative molecular assessment may be spared adjuvant radiation therapy. Moreover, patients with positive margins will benefit from more aggressive chemotherapeutic approaches and perhaps...
The identification of new genes and other molecular factors will help in the early detection of head and neck cancer and may already provide prognostic information. The identification of novel targets for blocking tumor behavior will improve the genetic understanding of these cancers, and improved molecular pathways in the genetic therapy of these tumors. Chemotherapeutic, pharmacologic, and biologic approaches may all be useful in either reestablishing or abrogating newly established pathways that lead to tumor growth. These discoveries will eventually lead to improved surgical techniques, chemotherapeutic approaches, and novel therapeutic approaches.


SECTION 30.2
Tumors of the Nasal Cavity and Paranasal Sinuses, Nasopharynx, Oral Cavity, and Oropharynx

STIMSON P. SCHANTZ
LOUIS B. HARRISON
ARLENE A. FORASTIERE

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Natural History
Staging
Treatment
Lip
Epidemiology
Anatomy
Pathology
Natural History
Treatment
Alveolar Ridge and Retromolar Trigone
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Pathology
Natural History
Treatment
_floor of mouth_
Epidemiology
Anatomy
Pathology
Natural History
Treatment
Hard Palate
Epidemiology
Anatomy
Pathology
Natural History
Treatment
Buccal Mucosa
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INTRODUCTION

The analysis of cancers within the upper aerodigestive tract reveals a heterogeneity of neoplastic processes. Each bears its own unique set of epidemiologic, anatomic, pathologic, and treatment considerations. This chapter reviews such considerations based on four anatomically defined regions: the nasal cavity and paranasal sinuses; nasopharynx; oral cavity; and oropharynx.

However, there exist general principles regarding these cancers that may be considered here. Such principles involve anatomy (i.e., primarily the anatomy of regional lymph nodes within the head and neck), pathology, staging, and screening, as well as general principles of treatment involving either single modality or multimodality therapy, which are relevant to all sites.

ANATOMY

An understanding of the regional lymph node anatomy is critical to the care of head and neck cancer patients. There are several major lymphatic chains in the neck containing nearly 200 lymph nodes that run parallel to the jugular veins, spinal accessory nerve, and facial artery and into the submandibular triangle (Fig. 30.2-1). To facilitate communication regarding cervical lymph node anatomy, the regions of the neck have been characterized by levels (Fig. 30.2-2).

Level I includes nodes within the submental triangle and the submandibular triangle. The submental triangle extends from the midline anteriorly to the anterior belly of the digastric muscle posteriorly. Its third border is formed by the hyoid bone inferiorly. The submandibular triangle is bounded by the mandible superiorly. The anterior and the posterior belly of the digastric muscle complete the triangle.

Level II includes the jugular nodes extending from the subdigastric area down to the carotid bifurcation and the nodes surrounding the spinal accessory nerve from the jugular foramen to the posterior border of the sternocleidomastoid muscle. It includes the lymph nodes in the upper posterior cervical triangle above the entrance of the spinal accessory nerve into this triangle.

Level III represents the nodal area principally along the jugular vein between the carotid and its bifurcation, the posterior border of the sternocleidomastoid muscle, and the omohyoid muscle.

Level IV constitutes nodal areas below the omohyoid muscle above the level of the clavicle and between the carotid vessels anteriorly and the omohyoid muscle posteriorly.

Level V represents nodes in the posterior cervical triangle. Its borders are formed by the posterior edge of the sternocleidomastoid muscle, the level of the entrance of the spinal accessory nerve, the trapezius muscle, and the posterior belly of the omohyoid muscle.

Specific sites within the aerodigestive tract have a predetermined drainage pattern. A knowledge of this pattern aids in diagnosis. It also affects therapy. Drainage patterns are addressed in each of the anatomic subsites detailed in this chapter.

PATHOLOGY
The predominant lesion within these anatomically defined regions is squamous cell carcinoma. Squamous cell carcinoma can be categorized into three classic differentiations. Well-differentiated disease shows greater than 75% keratinization; moderately differentiated disease contributes to the bulk of squamous cell carcinoma and is characterized by 25% to 75% keratinization; and poorly differentiated disease demonstrates less than 25% keratinization. Other variants of squamous cell carcinoma include verrucous carcinoma, sarcomatoid squamous cell carcinoma, and lymphoepithelioma. Additional pathologic criteria of squamous cell carcinoma that is believed to be clinically relevant were developed by Jacobsson and others. \(^5\) and \(^6\) This includes the number of mitoses, presence of vascular invasion, size of nuclei, degree of inflammatory infiltrate, and pushing or infiltrating borders (Table 30.2-1).

### TABLE 30.2-1. Jacobsson Classification System

<table>
<thead>
<tr>
<th>Differentiation</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>TUMOR CELL CHARACTERISTICS</td>
<td></td>
</tr>
<tr>
<td>Degree of Keratinization</td>
<td>1–4</td>
</tr>
<tr>
<td>Number of Mitoses</td>
<td>1–4</td>
</tr>
<tr>
<td>Number of Vessels</td>
<td>1–4</td>
</tr>
<tr>
<td>TUMOR AND SPREAD</td>
<td></td>
</tr>
<tr>
<td>Weight of Evidence</td>
<td>1–4</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>1–4</td>
</tr>
<tr>
<td>TOTAL MEASUREMENT</td>
<td></td>
</tr>
<tr>
<td>Score</td>
<td>1–6</td>
</tr>
</tbody>
</table>

The series of pathologic changes from premalignant disease to frank malignancy can occur in the oral cavity. Among the premalignant diseases are leukoplakia, erythroplakia, hyperplasia, and dysplasia. Each of these types has a propensity for malignant transformation. \(^7\) Histopathologic assessment of leukoplakia reveals hyperparakeratosis, which is variably associated with an underlying epithelial hyperplasia. Leukoplakia without underlying dysplastic changes is rarely associated with progression to malignancy (i.e., less than 5% probability of malignant changes). \(^9\) Erythroplakia is a condition within the oral cavity and pharynx characterized by red superficial patches adjacent to normal mucosa. Distinct from leukoplakic lesions as identified previously, erythroplakia is commonly associated with underlying epithelial dysplasia. Likewise, it can be associated with carcinoma in situ to frank malignancy in nearly 40% of lesions. \(^9\)

Dysplasia as compared with the previously mentioned two clinical descriptives is a true histopathologic term that is characterized by several morphologic changes, including the presence of mitoses, pleomorphism, and prominent nucleoli. When dysplasia involves the entire thickness of the mucosa, it is commonly referred to as carcinoma in situ. Dysplasia has been associated with a subsequent risk of progression to frank malignancy ranging from 15% to 30% of cases. \(^10\)

### STAGING AND SCREENING

#### STAGING

The role and current status of staging for head and neck cancer is undergoing continuous analysis. \(^14\) Although standard staging has been defined, there is a growing debate as to what the primary function of staging should be. The American Joint Committee on Cancer Staging (AJCC), however, has described the principal goal of staging as a means of defining the natural history of disease. Additional goals include the ability to judge therapeutic results between various centers as well as a means of defining patient prognosis. Revisions to standard staging have continually been offered, \(^15\) but today it is based on the TNM classification. T stage represents extent of primary disease. N represents the extent of regional lymph node metastasis and M is a measure of distant metastasis. The AJCC staging system, used for classifying TNM status, is periodically revised. \(^16\)

The current clinical staging system, although based principally on physical examination, has also incorporated specific radiographic observations of disease status. Thus, invasion through cortical bone by an oral cavity tumor up-stages a T2 or T3 lesion to T4 (i.e., from stage II or III to stage IV).

Radiographic assessment of cervical lymph node metastases has not been integrated into clinical staging. The benefits of these diagnostic techniques beyond that provided by standard physical examination are under investigation. \(^17\), \(^18\), \(^19\), \(^20\), \(^21\) and \(^22\) Most would consider the combination of radiographic and clinical assessment to be more accurate than either one alone. Furthermore, growing emphasis is being placed on the advantages of one imaging technique versus another [i.e., the relative merit of magnetic resonance imaging (MRI) vs. computed tomography (CT)]. \(^23\) Table 30.2-2 summarizes the relative value of these two techniques in head and neck imaging.


<table>
<thead>
<tr>
<th>Technique</th>
<th>Advantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT Scanning</td>
<td>Can detect soft tissue, bone, and disc herniation easily.</td>
</tr>
<tr>
<td>MRI</td>
<td>Can detect soft tissue, bone, and disc herniation easily.</td>
</tr>
</tbody>
</table>

The criteria for T staging within the upper aerodigestive tract differs depending on the primary site. N staging and M staging, however, are uniform and therefore are considered in Table 30.2-3. Table 30.2-4 represents the most current stage classification as defined by the AJCC. \(^24\)
TABLE 30.2-3. Staging within the Upper Aerodigestive Tract

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>T0</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>I</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>II</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIIE</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIIE</td>
<td>T4</td>
<td>N0</td>
<td>M0</td>
</tr>
</tbody>
</table>

TABLE 30.2-4. Stage Grouping Based on American Joint Committee on Cancer Staging Criteria

Additional data continue to accrue regarding the effect of comorbidities in prognostication. Data suggest that these host-related factors provide information beyond standard AJCC criteria alone. Host factors include the presence of significant heart disease, liver disease, and severe cerebrovascular disease. Survival rates are significantly reduced if comorbidities exist and are improved with their absence. In a study by Singh et al., involving 70 patients with squamous cell carcinoma of the upper aerodigestive tract, patients with Kaplan-Feinstein comorbidity index grades 2 and 3 had a significantly decreased disease-free survival as compared with those with comorbidity index of grade of 0 to 1. Stage distribution between the two groups was similar.

SCREENING FOR PRIMARY CANCERS

It is intuitive that detection of disease at its earliest stages would improve cancer mortality. Given the degree to which the oral cavity and upper aerodigestive tract can be easily examined, it would also seem that screening for head and neck cancers would be a readily achievable goal. Diminished mortality would be readily achievable. The significance of screening as a potentially significant modality is emphasized by a review by Smart, who reported that 94% of head and neck cancer patients had seen a physician at least 1 year before diagnosis. Each patient reported an average of 11 physician visits within a 3-year period before diagnosis. Smart's review emphasizes that with appropriate training and practice of systematic screening habits by examining physicians, head and neck cancer may be diagnosed considerably earlier. In that regard, a study by Prout et al. assessed the value of educational programs for health care providers in the Boston area and provided information that would reinforce that notion. These latter authors noted that health care providers schooled in the oral cancer educational program were significantly more likely to perform systematic oral screening in subsequent years. These studies emphasize the important role of the physician in the early detection of head and neck cancer and that such individuals, if properly motivated, are more likely to perform such screening than those less aware of the significance of oral cancer.

Despite the intuitive benefit that would come with more effective screening, confounding factors may limit success. First, head and neck cancer is a relatively sporadic disease. Mass screening procedures would detect cancer in only limited instances. Second, individuals at risk tend to be less health conscious. Compliance with health care advice such as avoidance of substance abuse, good nutritional habits, and regular physical evaluation is not readily achieved in this population. Third, head and neck cancer patients can often be characterized by diminished social support systems. Access to medical care is hindered, making routine follow-up by a health care provider difficult. Finally, although it is often stated that a readily identifiable premalignant condition exists (i.e., leukoplakia or erythroplasia), few head and neck cancer cases can be shown to progress through this premalignant clinical stage. Although head and neck cancers tend to occur late in life, these same cancers can occur at any time within a 20-year interval. Knowing which patient and when that patient will develop disease remains a conundrum. Furthermore, whether or not the identification of disease changes its natural history is not clear. We cannot state with certainty the interval required for a tumor to achieve its initially diagnosed stage. We do not know whether the biologic potential of a head and neck cancer follows the same time course within every individual. Ultimate tumor aggressiveness may be determined early in its natural history. The window of opportunity to detect the most lethal cancers may be small. No studies have yet demonstrated that systematic screening diminishes head and neck cancer mortality. Indeed, the Task Force for the Guide to Preventive Services has concluded that routine screening for oral cancer cannot be recommended.

It is not surprising, therefore, that various mass screening programs for head and neck cancer have demonstrated mostly negative results. Julien et al. and others have made it apparent that the identification of head and neck cancer is only one part of the process. In the assessment of nearly 1000 patients as reported by Jullien et al., only 67% of the 12 patients noted to have potentially malignant disease were compliant with follow-up recommendations. The experience in Cuba, likewise, showed similar discouraging results. Annual oral examination had been considered mandatory for all individuals over 15 years of age in Cuba since 1984. The proportion of early-stage disease was noted to increase during this period of more intensive screening. However, overall oral cancer mortality was not altered. As in the study by Jullien et al., a major problem was patient compliance in follow-up examinations once the disease has been diagnosed. The investigators of these large population-based studies conclude that systematic mass screening for head and neck cancer is not a cost-effective process and has little effect on overall cancer mortality.

Perhaps more significant than the screening process itself and in light of the development of more effective behavioral modification approaches, Cowan et al. have demonstrated that screening strategies are valuable in identifying the health care beliefs of the provider. Primary care dentists participating in this study were noted to routinely assess the oral cavity for evidence of disease. However, a minority of dentists routinely recorded information about tobacco and alcohol abuse. The implication of Cowan's study was that screening was already adopted. What should be developed in the primary care setting is a clearer understanding of the benefits of health promotion involving substance abuse modification.

There are, however, novel strategies under development that may enhance screening effectiveness. We have previously noted in this brief review that epidemiologic investigations continue to refine risk estimates. Current computer technology may allow for translating previous risk factor assessments into clinical strategies that enhance screening efforts. An example involves the use of neural networks. The Oral Cancer Screening Group in England has demonstrated its potential utility. The performance of the network to identify individuals at increased risk was compared with the results of oral screening by health care specialists. Over 2000 adults were entered into the study and were asked to fill out a questionnaire that identified ten input variables. The overall sensitivity and specificity of the screeners as compared with the neural network were comparable. The use of neural networks could be performed, however, at a fraction of the cost.

Other screening techniques under investigation include the use of genetic markers of increased risk, molecular cytology, serum tumor markers, as well as newer technologies involving optical engineering and the computer sciences.

SCREENING FOR SECOND PRIMARY CANCERS

Head and neck cancer patients are characterized by their high risk of developing second primary malignancies. The majority of these cancers occur within tobacco-exposed tissue, including the esophagus, lung, and remaining upper aerodigestive tract. This risk has been well characterized and is known to occur at a rate of 4% per year. Given the high rate of second malignancies within these individuals, numerous screening strategies have been described. Available screening modalities include laryngoscopy, esophagoscopy, contrast studies of the esophagus, chest radiography, sputum cytology, and bronchoscopy. Newer modalities are under investigation including the use of molecular assessments of cells within saliva and sputum. Despite this effort, no agreement exists as to the optimal screening means, including the timing and duration of follow-up. Perhaps the greatest controversy revolves around the role of panendoscopy at the time the patient presents for treatment of the index cancer. Proponents of this procedure, which includes laryngoscopy, esophagoscopy, and bronchoscopy, cite the high rate of identified second cancers, reported in one prospective study to occur in 10% of patients. Disease found in this setting is presumed to be of an earlier stage and more responsive to treatment. Opponents of routine panendoscopy cite the relatively low yield and questionable value in actually altering disease course and survival.
prospective study by Benninger et al. provided compelling evidence to support the use of screening procedures based principally on symptomatology (i.e., so-called symptom-directed selective endoscopy). A careful history and physical examination of all newly diagnosed head and neck cancer patients represents the most effective screening method. Although routine panendoscopy cannot be advocated, in certain individuals its use may be more beneficial. This, in our experience, includes patients whose index cancer resides within the pharynx and who admit to a long history of tobacco and alcohol abuse. Special attention should be given to the assessment of the esophagus in these individuals as well as the remaining upper aerodigestive tract.

TREATMENT

PRETREATMENT CONSIDERATIONS

The comprehensive care of the head and neck cancer patient begins with pretreatment considerations including the assessment of general medical conditions, nutritional status, dental health, and the appropriate choice of medical therapies designed to minimize treatment-related complications. It is beyond the scope of this chapter to detail the numerous associated medical illnesses that are typically identified in the head and neck cancer patient. Given the prolonged history of tobacco and alcohol abuse that can be typically identified, diseases involving the pulmonary, cardiovascular, and digestive systems are common. There remain, however, important considerations that should be stressed. This includes the significance of pretreatment dental care, nutritional support, the effect of therapy on the elderly patient, and the choice of preoperative medications (i.e., antibiotics for the patient about to undergo major surgical procedures).

The standard of care today for the head and neck cancer patient is the reduction of oral diseases before initiation of treatment. Periodontal diseases, infections, and caries are common in this patient population. This can lead to loss of integrity of the gingival-cervical tissues. Left unchecked, significant morbidity can result to structural elements of the oral cavity in the face of aggressive therapy. Following initial evaluation by the oncologic team, dentulous patients should be referred to the dental colleagues for preoperative evaluation and management appropriate to their disease. Preoperative surveys should identify patients with recalcitrant caries, oral mucositis, or exposed bone. Such cases are likely to continue smoking habits. In the execution of effective surgical management, the single most significant principle is the adequate preoperative assessment of disease extent. Precise and general medical condition that remains the most critical consideration, regardless of age. In a more recent article by Clayman, 43 patients who were 80 years of age or older were noted to have no increased postoperative complications than a stage- and site-matched population aged 65 years or less. Of note, the older patient was more likely to have a lesser surgical procedure, more likely to have positive pathologic margins, and less likely to receive postoperative radiation therapy (RT). Disease-free survival was also decreased in the older population. The perception of an increased risk of treatment-induced complications may compromise appropriate therapy.

Increasing attention recently has been given to the significance of continued tobacco use in the head and neck cancer population. The data would support the notion that continued tobacco use following diagnosis of the index cancer leads to an adverse patient outcome. This relates to not only the more obvious problem of progressive cardiopulmonary disease, but considerations related to head and neck cancer progression as well. Day et al. and others have provided more information regarding the risk of second primary malignancies in patients who continue to smoke following treatment of their index cancer. The risk of second primary malignancies was significantly higher in the smoking population as compared with those who achieved smoking cessation. This difference was apparent only after 5 years following initial treatment. In another study by Brown et al., continued tobacco use was associated with a decreased likelihood to respond to primary therapy. This latter study represents an initial report and is limited by its small population size. It does, however, raise an important consideration in the overall care of these patients, namely, the systematic approach toward achieving smoking cessation. In that regard, several studies have identified characteristics of patients who are likely to continue smoking habits. Interestingly, Ostroff et al. have reported that it is the patients with the best outlook who seem to be the most recalcitrant to modify smoking behavior. High-risk patients with high-stage disease continued to use tobacco at higher rates than patients with higher stage disease. Strategies are being explored in order to effectively support the patient through this critical period. The hallmark of any approach should include surgeon-delivered advice as well as the judicious use of nicotine replacement.

Finally, head and neck oncologists should critically assess the need for supportive therapies in the patient who is to undergo operative procedures. This has principally related to the choice of perioperative antibiotics. The use of prophylactic antibiotics can only be supported for those individuals undergoing clean-contaminated surgery (i.e., when it is anticipated that the aerodigestive tract is to be entered) or in those circumstances in which there is frank contamination. Postoperative infection complications may occur in up to 30% of these cases. Several studies have addressed risk factors for infectious complications and found that should be considered include defective restorations, ill-fitting prostheses, and impacted molars. It is generally considered prudent to perform necessary dental rehabilitation, including extractions, approximately 2 weeks before the initiation of any radiotherapy. This allows for the appropriate healing of extraction sites and mucosal coverage of exposed bone. In order to minimize delays in the initiation of radiation, dental care can be performed at the time of surgical resection in a patient who is to undergo multimodality therapy.

The assessment of nutritional status and the choice of pretreatment nutritional regimens is more controversial. Several authors report the common finding of malnutrition in the head and neck cancer patient. Severe malnutrition has been identified in over 25% of the patients. Furthermore, the presence of severe malnutrition was associated with increased operative morbidity. This has led to efforts to appropriately quantify nutritional status through the use of documentation of pretreatment weight loss, the measurement of triceps skin fold thickness, and the inclusion of various laboratory measures such as plasma protein levels and the creatinine and height index. To date there has been no conclusive randomized trial of pretherapy nutritional restoration in order to minimize treatment morbidity. However, Goodwin and Byers have stressed that in the severely malnourished patient, attention should be given to a 2-week pretreatment course of nutritional support. Such attempts can most often be achieved through enteral means with the placement of either a nasogastric tube or a percutaneously placed gastrostomy tube.

The care of the elderly patient represents a commonly occurring dilemma. The tendency to deny a patient optimal treatment because of the patient's advanced years should be avoided. In a study by McGuirt and Davis, operative mortality was 4% in 217 patients greater than 65 years of age and not significantly different from those less than 65 years. In a subset of patients over the age of 75 and with stage III or IV disease, however, the mortality increased to 6%. A prospective case-control study by Kowalski et al. on elderly patients undergoing head and neck surgery failed to identify any increased frequency of postoperative complications or mortality as compared with younger patients. The choice of treatment should not be predicated on the age of the patient. Rather, it is the patient's general medical condition that remains the most critical consideration, regardless of age. In a more recent article by Clayman, 43 patients who were 80 years of age or older were noted to have no increased postoperative complications than a stage- and site-matched population aged 65 years or less. Of note, the older population was more likely to have a lesser surgical procedure, more likely to have positive pathologic margins, and less likely to receive postoperative radiation therapy (RT). Disease-free survival was also decreased in the older population. The perception of an increased risk of treatment-induced complications may compromise appropriate therapy.

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An extension of adequate preoperative assessment is optimal intraoperative exposure of disease. The surgeon should consider appropriate means to achieve operative exposure. The choice of incision and the ability to mobilize surrounding anatomic structures to achieve exposure is considered later in the text for each anatomic subsite. Additionally, exposure is facilitated by careful hemostasis. Besides allowing for better operative exposure, minimizing blood loss prevents potential sequelae associated with blood transfusion. Weber et al. reported expected blood loss for various surgical procedures involving cancers of the upper aerodigestive tract. Electrocautery dissection has been used by Weber and colleagues, which may explain the relatively infrequent need for blood transfusion. Electrocautery dissection has been adopted by many experienced surgeons as the preferred extirpative technique. Additional methods of surgical excision have included the use of the Moh's technique and laser ablation. These techniques, however, cannot be considered standard surgical procedure at this time.

Surgical Management of the Cervical Lymph Nodes

General principles of surgery exist involving regional lymph nodes as well. The standard in the surgical control of cervical metastases by which various procedures
are judged is the radical neck dissection. The radical neck dissection involves complete removal of the lymphatic pathways within the neck. To ensure complete extirpation, anatomic structures including the sternocleidomastoid muscle, spinal accessory nerve, and jugular vein are routinely sacrificed.

Developments in the management of cervical lymph node disease involve more conservative surgical procedures. These procedures differ from the classic radical neck dissection principally in the sparing of specific anatomic structures (i.e., principally the spinal accessory nerve and the sternocleidomastoid muscle). Table 30.2-5 provides a classification of currently used selective neck dissection and details removed lymph node regions.

### Surgical Management of Disease in the Neck: N0 Neck

Multiple studies have determined that cancers of the upper aerodigestive tract are associated with an approximately 20% to 30% incidence of occult cervical lymph node metastases, despite clinically negative examination. The overall incidence of occult primary disease is influenced by multiple factors including size and location of the primary cancer within the upper aerodigestive tract, depth of invasion, and tumor differentiation. These observations have led to the generally accepted need for elective lymph node neck dissection as part of standard surgical management. Support for this approach has been provided by Spiro et al. Those patients who did not undergo elective dissection were more likely to present with more advanced neck disease when disease recurred as compared to those who underwent elective dissection. It should be emphasized, however, that randomized controlled clinical trials that conclusively support the role of elective cervical lymph node dissection have been limited. Indeed, a study by Vandenbrouck and colleagues failed to find a survival benefit in oral cavity cancer patients randomized to receive elective dissection. This study was limited by the small number of patients entered.

A debate exists as to the type of elective neck dissection that should be performed. The standard radical neck dissection that encompasses lymph node basins I through V as well as the spinal accessory nerve, internal jugular vein, and sternocleidomastoid muscle is not indicated in the treatment of occult disease, principally because of its associated shoulder dysfunction. The debate still exists as to whether to perform modified radical neck dissection versus a more limited selective procedure. Leemans et al., citing a metaanalysis, report a lower incidence of neck recurrence in those patients treated by a modified neck dissection. Others argue that a supraomohyoid neck dissection for cancers of the oral cavity is adequate given the limited likelihood of level V metastases and the limited likelihood of disease recurrence in level V region. In a randomized study conducted by the Brazilian Head and Neck Cancer Study Group, overall survival was the same in patients who underwent a supraomohyoid neck dissection as compared with patients who underwent a standard modified radical neck dissection. This is despite the observation that 50% more lymph nodes were identified in the surgical specimen from the population undergoing modified radical neck dissection. The standard supraomohyoid neck dissection is notable, however, encompassing nodes in levels I through IV only. Skip metastases may occur in level IV nodes and disease recurrence in this level has been identified. These two latter observations suggest that a selective lymph node dissection in oral cancer patients who are clinically N0 should include levels I to IV.

The value of elective dissection is further justified by its low risk ratio. When performed by an experienced head and neck surgeon, the procedure does not require excessively prolonged operative time and can be performed with minimal morbidity. The caveat should be the performance of careful dissection along the spinal accessory nerve. Indeed, advances in the performance of elective neck dissection have been reported by Kraus et al. The authors investigated the probability of metastases in the lymph nodes superior to the spinal accessory nerve in patients who were clinically N0. In 44 patients analyzed, only one individual had disease in this region.

### Surgical Management of Disease in the Neck: N+ Neck

The presence of cervical metastases dictates in most instances the use of combination surgery and RT. Surgery alone has been reserved for those situations in which only a single lymph node is involved with disease and in which there is no extension of disease beyond the lymph node capsule. For patients with evidence of disease within cervical lymph nodes the most commonly accepted surgical management involves radical neck dissection. A trend, however, is evolving toward a more oncologically conservative approach designed to preserve shoulder function. Traylor et al. reported the use of selective neck dissection in the management of the neck-positive neck. Twenty-nine patients were retrospectively reviewed in whom 16 had N2 disease or higher. Only one patient developed recurrence. Again, however, experience has been limited by the lack of controlled clinical trials designed to answer the question as to the optimal surgical procedure. Pellitari et al. reviewed their experience with selective neck dissection in 34 patients with multiple pathologically positive lymph nodes who underwent a selective neck dissection. Regional recurrence rates approximated 12%, indicating the adequacy of the surgical resection when used judiciously with postoperative radiation.

A major debate in the management of disease in the neck revolves around the handling of the carotid artery. This includes (1) indications for removal of the carotid as a part of an oncologic procedure and (2) indications and means of carotid artery reconstruction including preoperative assessment determination of cerebral blood flow reserve. There are those who advocate a less aggressive approach to the carotid, indicating that in the majority of circumstances, actual invasion of the carotid wall is rare and with careful dissection disease can be dissected away from the vessel without compromising cancer control. Furthermore, in those situations in which carotid invasion of the carotid artery actually exists, long-term disease control is limited, patients typically die from regional, distal, or both regional and distant metastatic disease. Finally, and most significantly, a conservative approach to the carotid artery minimizes significant incidence of cerebral vascular morbidity. Carew and Spiro reported experience with carotid artery resection at Memorial Sloan-Kettering Cancer Center. In their review of extended neck dissections, the authors noted that in only 3 instances in over 2500 cervical lymph node dissections performed in a 10-year period was carotid artery resection required. Regional disease control in this population of individuals with predominantly N3 cervical lymph node disease was 71% and comparable with those reports in which carotid artery resection is more liberally used. None of the three patients who underwent carotid resection was alive at 2 years. The approach at Memorial Sloan-Kettering Cancer Center also includes the use of brachytherapy implants on the carotid artery in those circumstances in which the surgical peel potentially left macroscopic or microscopic disease. Others use an intermediate approach for disease encasing the carotid. Adams et al., for instance, reserve resection for instances in which there is 70% encasement of the vessel. In those situations in which the patient was noted to tolerate preoperative balloon occlusion, survival was 30% at 2 years.

Snyderman et al. have performed a metaanalysis of the reported experience with carotid artery resection in patients with metastatic head and neck cancer. The overall (disease-free) survival for the group of patients reported was 22% and was similar between those who underwent carotid resection versus those who did not. Interestingly, survival has not changed in this group of patients over the last 20 years. The authors emphasize the high complication rate, with major cerebral vascular accidents occurring in 26% of the patients undergoing carotid artery resection. The rate of cerebrovascular accidents was 17% and no difference was seen between the two groups.

There are an increasing number of reports, however, that demonstrate that carotid artery resection in selected circumstances can be performed safely when preceded by appropriate presurgical assessment of collateral blood flow from the opposite cerebral hemisphere through the circle of Willis. This approach is justified by a classic pathologic report by Huvo et al., who showed that metastatic squamous cell carcinoma can be microscopically identified invading the carotid adventitia in up to 30% of cases in which disease is adjacent to the vessel. Vascular surgeons have used pressure flow studies that assess the patency of collateral blood flow, mostly contributed through the circle of Willis, to determine the safety of carotid occlusion. Hays et al. reported that back flow pressure of 50 mm Hg was safe for temporary occlusion and/or ligation. The current protocol of Adams et al. is to perform angiography to demonstrate nonstenotic patent carotid arteries, spontaneous crossover, and an intact circle of Willis. Patients also undergo an angiogram with controlled balloon inflation for 30 minutes. If tolerated, a xenon CT scan to assess

### Table 30.2-5. Classification of Neck Dissections

<table>
<thead>
<tr>
<th>Classification</th>
<th>Level(s) of Neck Region Removed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard radical neck dissection</td>
<td>I, II, III, IV, V</td>
</tr>
<tr>
<td>Modified radical neck dissection</td>
<td>I, II, III, IV, V</td>
</tr>
<tr>
<td>Selective dissection</td>
<td>I, II, III, IV, V</td>
</tr>
<tr>
<td>A</td>
<td>Supraomohyoid</td>
</tr>
<tr>
<td>B</td>
<td>Carotid type</td>
</tr>
<tr>
<td>C</td>
<td>V, VI</td>
</tr>
<tr>
<td>D</td>
<td>Carotid confluence type</td>
</tr>
<tr>
<td>E</td>
<td>Extended neck dissection</td>
</tr>
</tbody>
</table>

GENERAL PRINCIPLES OF RADIATION THERAPY

For early-stage disease, both radiation and surgery are frequently curative and can produce similar rates of cure. Selection of treatment must be individualized to each patient and must consider issues such as cosmetic and functional outcome, quality of life, speed with which treatment can be completed, sequelae of each modality, patient reliability, risk of subsequent cancers, and capacity of salvage therapy should there be a recurrence.

For advanced-stage disease, surgery and radiotherapy are often combined (for resectable cases). When this is done, radiation is usually delivered postoperatively. Peters et al. reported a prospective randomized trial evaluating various dose levels for postoperative radiation in locoregionally advanced head and neck cancer. They found that a dose of 57.6 Gy in daily fractions of 1.8 Gy were superior to doses of 54 Gy. For patients with extracapsular spread in the lymph nodes in the neck, doses of 63 Gy were superior to 57.6 Gy. Doses above 63 Gy did not appear warranted. Typical indications for postoperative radiation include T3 to T4 primary, close or involved margins for any primary, the presence of nodal metastases, especially extracapsular extension, and factors such as perineural invasion, soft tissue extension, and so forth. Ang updated this experience, assessing the effect of a variety of risk factors and total treatment time (surgery plus radiation) on outcome. High-risk features included extracapsular extension, oral cavity primary, positive mucosal margins, nerve invasion, more than one node involved, more than one nodal station involved, node size greater than 3 cm, and greater than a 6-week interval between surgery and radiation. Patients with none of these features did not receive RT. Those with one adverse feature in addition to extracapsular extension were considered intermediate and, those with more than one feature plus extracapsular extension were considered high risk. Locoregional control for low-risk patients (no RT) and intermediate-risk patients (57.6 Gy) was greater than 90%, compared with 68% for high-risk (63 Gy) patients ($P = .004$). Actuarial 4-year survival by risk was 83%, 66%, and 43%, respectively. Those who began radiation more than 6 weeks after surgery and whose total therapy time extended beyond 12 to 13 weeks also had worse outcomes.

There are other groups of patients with advanced disease that are treated differently, and these subjects are covered in this chapter. Those with small primary lesions and neck metastases can be treated with definitive RT to the primary and neck, plus a neck dissection. This is especially true for pharyngeal wall, oropharynx, and larynx cancers. Patients who have resectable larynx cancer but who would require total laryngectomy are often treated with organ-preserving therapy combining chemotherapy and radiotherapy. Either that approach or radiation alone (neck dissection) is often used for base of tongue and tonsil lesions, for the purpose of preserving organ function.

A variety of fractionation programs have been used by different groups. The Radiation Therapy Oncology Group (RTOG) reported a prospective trial looking at four different schedules: conventional fractionation (70 Gy/35 fractions/7 weeks) versus hyperfractionation (81.6 Gy/66 fractions/7 weeks) versus accelerated fractionation with split (67.2 Gy/42 fractions/6 weeks including 2 weeks rest after 38.4 Gy) versus accelerated fractionation with concomitant boost (72 Gy/42 fractions/6 weeks), which used a twice a day concomitant boost during the last 12 treatment days. The latter schedule provided better 2-year locoregional control than standard fractionation, and will be the standard treatment in future RTOG trials for locally advanced squamous cell carcinoma of the head and neck.

For unresectable disease, combined chemotherapy and radiotherapy has become the standard of care. Many of these trials are reviewed in this chapter. Interestingly, a combined modality experience using cisplatin and RT has been reported, using a concomitant boost schedule not dissimilar to the RTOG experience. Harrison et al. have reported long-term results of a program using 70 Gy/6 weeks using a concomitant boost during weeks 5 and 6, as well as cisplatin, 100 mg/m$^2$ on days 1 and 22. Three-year local control for unresectable sinonasal sinus cancers, T4 nasopharynx cancers, unresectable oropharynx cancers, and unresectable larynx and hypopharynx cancers were 78%, 78%, 64%, and 100%, although there were only six patients in the latter category. Unresectable oral cavity cancers fared poorly.

Merlano et al. reported a prospective, randomized trial comparing radiation alone with an alternating chemotherapy and radiation approach. This trial is reviewed later in this chapter, in Combination Chemotherapy and Radiotherapy, but revealed an improved outcome in the chemotherapy and radiation group.

Side effects of RT are usually separated into acute and late effects. Acute effects generally are related to inflammatory reactions in the tissues within the radiation field (i.e., epidermitis and mucositis). Irradiation of the taste buds can cause loss or diminution of taste. Irradiation of the salivary glands causes xerostomia, irradiation of the lacrimal glands can cause dryness in the eye, and epilation can result from irradiating hair-bearing skin. Whether these effects are temporary or permanent are usually dose related and site related. Because RT to the salivary glands and oral cavity can have a significant effect on dentition, all patients receiving this treatment should be seen by a dentist before RT. Any required dental work should be done before the initiation of radiation, and patients should be placed on dental prophylaxis with fluoride applications. It has been clearly shown that fluoride application significantly reduces dental sequela after RT. It has also been clearly shown that dental extractions in an irradiated mandible can lead to osteonecrosis.

Advances in radiotherapy techniques have had a significant effect on head and neck patients. For external-beam treatments, three-dimensional conformal radiation and stereotactic radiotherapy are particularly exciting new areas (Fig. 30.2-3). This allows the physician to plan RT based on three-dimensional reconstruction of the target area, and three-dimensional planning of the radiation beams. As a result, it is frequently possible to lower the dose to surrounding normal tissue while potentially escalating the dose to the tumor. Efforts to use this technique in nasopharyngeal cancer have been particularly interesting and are discussed in that section (see Nasopharynx, later in this chapter). The development of multileaf collimators and on-line portal imaging techniques should make the delivery of three-dimensional RT more efficient. Intensity-modulated radiation is also being developed.

![Dose distribution for a stereotactic radiotherapy plan for a boost for a patient with an unresectable squamous cell carcinoma of the frontal sinus. The microleaf collimator conforms nicely to the target. The optic chiasm is well protected, as is the contralateral orbit.](image)

**FIGURE 30.2-3.** Dose distribution for a stereotactic radiotherapy plan for a boost for a patient with an unresectable squamous cell carcinoma of the frontal sinus. The microleaf collimator conforms nicely to the target. The optic chiasm is well protected, as is the contralateral orbit.

Finally, there are biologic and treatment-related factors that have been emerging as clinically relevant. Anemia has been shown to have a significantly adverse effect on local control and is discussed in greater detail throughout Chapters 30.1, 30.3, 30.4, and 30.5. Attempts to overcome tumor hypoxia with hypoxic cell sensitizers concomitant with RT (mitomycin C) have also shown success, all suggestions that tumor oxygenation has significant importance in the success of radiotherapy. Also, with respect to reducing the side effects of radiotherapy, Brizel et al. have reported a clinical trial that shows that the daily administration of amifostine with radiotherapy reduced the incidence of acute and chronic xerostomia. This is an area under active investigation.

PRINCIPLES OF CHEMOTHERAPY: RECURRENT AND METASTATIC DISEASE

The median survival for patients with recurrent squamous cell carcinoma of the head and neck is 6 months and the 1-year survival rate is 20%. These statistics have not been affected by the use of chemotherapy. Consequently, patients with recurrent squamous cell carcinoma of the head and neck are candidates for phase I and II trials of experimental therapeutic.

SINGLE-AGENT CHEMOTHERAPY

The activity of older single agents commonly incorporated into combination regimens and newer drugs are listed in Table.
Methotrexate is the standard palliative therapy for recurrent squamous cell carcinoma of the head and neck. The standard dose for initiation is 40 mg/m² weekly to be escalated weekly by 10 mg/m² increments to 60 mg/m²/week or until dose-limiting toxicity or an objective response is reached. Therapy with this drug is relatively nontoxic, inexpensive, and convenient. Higher doses of methotrexate in single-arm studies were shown to produce higher response rates. Five randomized trials have shown no significant difference in survival rates between higher doses of methotrexate with leucovorin (as much as 5000 mg) and standard-dose methotrexate.

The methotrexate analogues trimetrexate, edatrexate, and piritrexim have all been tested in small numbers of patients and seem to be active, but have no particular advantage over methotrexate. In a randomized comparison of methotrexate and edatrexate, activity was similar but edatrexate was more toxic.

Bleomycin has been studied extensively as a single agent and in combination in recurrent and metastatic squamous cell carcinoma of the head and neck. Response rates as a single agent vary from 6% to 45%, with a pooled average of 21%. It has largely been replaced by continuous infusion 5-FU, which is synergistic and more active in combination with cisplatin.

Cisplatin is perhaps the most important chemotherapeutic agent for treating squamous cell carcinoma of the head and neck. Most of the studies have used a dose of 80 to 100 mg/m² every 3 to 4 weeks. Response rates have ranged from 14% to 41%, with a pooled average of 28%. Whether there is a dose-response relationship is not yet proven. Single-agent cisplatin in doses of up to 200 mg/m² produced higher response rates in pilot trials, but a randomized trial comparing 60 mg/m² doses with 120 mg/m² doses found no difference in response or survival.

Carboplatin has significantly less renal, otologic, neurologic, and gastrointestinal toxicity than does cisplatin, but response rates are lower, in the range of 14% to 30%, with an average of 22%. Carboplatin should be reserved for treatment of patients with peripheral neuropathy or renal dysfunction that prohibits use of cisplatin. Of the other platinum analogues, irinotecan trials have yielded much lower response rates and major toxicity in phase II trials. Oxaliplatin is under investigation in gastrointestinal and ovarian malignancies and nedaplatin is in early investigations in Japan. Each drug has its own toxicity profile; the relative advantage over cisplatin and carboplatin will need to be determined in appropriately designed trials in head and neck cancer patients. 5-FU was studied initially using intravenous daily bolus dosing for 5 days or weekly in recurrent squamous cell carcinoma of the head and neck as second- or third-line chemotherapy. Response rates ranged from 0% to 33%, with an average of only 15%. The dose-limiting toxicity of this method of administration was myelosuppression. Subsequent studies of 5-FU as a prolonged infusion for 96 to 120 hours at a dose of 1000 mg/m² showed mucositis to be dose-limiting, and antitumor activity was increased. 5-FU was synergistic with cisplatin, leading to the establishment of the now standard combination regimen of cisplatin plus infusional 5-FU.

Ifosfamide, a synthetic analogue of cyclophosphamide, was limited in early clinical trials by the occurrence of hemorrhagic cystitis. With the use of MESNA, a thiol antioxidant, ifosfamide is better tolerated and recommended. As with paclitaxel, a weekly dosing schedule of 30 to 40 mg/m², the dose-limiting toxicity of this method of administration was myelosuppression. Subsequent studies of ifosfamide have all been tested in small numbers of patients and seem to be active, but have no particular advantage over methotrexate. In a randomized comparison of methotrexate and edatrexate, activity was similar but edatrexate was more toxic.

The taxanes, paclitaxel and docetaxel, bind to the P subunit of tubulin, induce the formation of stable microtubule bundles, and inhibit microtubule depolymerization. Docetaxel is the more potent analogue. Docetaxel appears to be schedule independent, whereas paclitaxel appears to be more effective with prolonged exposure.

Paclitaxel and docetaxel are covered in more recent reviews.

<table>
<thead>
<tr>
<th>Chemotherapy</th>
<th>Side Effects</th>
<th>Regimen</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td>Nausea</td>
<td>10 mg/m²</td>
<td>194-207</td>
</tr>
<tr>
<td>Bleomycin 50</td>
<td>Nausea</td>
<td>10 mg/m²</td>
<td>194-207</td>
</tr>
<tr>
<td>Cisplatin 75</td>
<td>Nausea</td>
<td>10 mg/m²</td>
<td>194-207</td>
</tr>
<tr>
<td>Vinorelbine 75</td>
<td>Nausea</td>
<td>10 mg/m²</td>
<td>194-207</td>
</tr>
<tr>
<td>Pemetrexed 150</td>
<td>Nausea</td>
<td>10 mg/m²</td>
<td>194-207</td>
</tr>
<tr>
<td>Camptothecin 100</td>
<td>Nausea</td>
<td>10 mg/m²</td>
<td>194-207</td>
</tr>
<tr>
<td>Topotecan 40</td>
<td>Nausea</td>
<td>10 mg/m²</td>
<td>194-207</td>
</tr>
<tr>
<td>Oxaliplatin 75</td>
<td>Nausea</td>
<td>10 mg/m²</td>
<td>194-207</td>
</tr>
<tr>
<td>Nedaplatin 100</td>
<td>Nausea</td>
<td>10 mg/m²</td>
<td>194-207</td>
</tr>
<tr>
<td>Cisplatin 75</td>
<td>Nausea</td>
<td>10 mg/m²</td>
<td>194-207</td>
</tr>
<tr>
<td>Pemetrexed 150</td>
<td>Nausea</td>
<td>10 mg/m²</td>
<td>194-207</td>
</tr>
</tbody>
</table>

The older drugs include methotrexate, bleomycin, cisplatin, carboplatin, ifosfamide, and 5-fluorouracil (5-FU). The details of these phase II studies may be found in older reviews, whereas the activity of newer agents such as the taxanes, vinorelbine, gemcitabine, and topotecan are covered in more recent reviews.

Oxaliplatin is under investigation.
Three other relatively recent drugs with activity in lung cancer and other solid tumors are the semisynthetic vinca alkaloid vinorelbine, 125,126 and the pyrimidine antimetabolite gemcitabine, 127 and the topoisomerase I inhibitor topotecan. 128,129 These drugs appear to have only marginal activity in head and neck cancer with response rates under 20%.

Drugs with an uncertain level of activity because they were studied in broad phase I and II trials before uniform response criteria were established include doxorubicin, cyclophosphamide, and hydroxyurea. Response rates of less than 10% have been reported from phase II trials of the plant alkaloids vinblastine and etoposide. 122,123

COMBINATION CHEMOTHERAPY

Over the last two decades numerous phase II trials of cisplatin-based regimens have been published and detailed in reviews. 117,118 and 119-121 Most contain small numbers of patients and often the results suggest greater efficacy than would be expected with single-agent cisplatin or methotrexate. In the early 1980s, researchers at Wayne State reported a response rate of 70% and a complete response rate of 27% using cisplatin, 100 mg/m2 day 1, and 5-FU, 1000 mg/m2/day for 96 hours repeated every 3 weeks. 122 The compiled results of 12 trials including 365 patients with recurrent or metastatic squamous cell carcinoma show an average response rate of 50% and complete response rate of 16%. 123

Three large multicenter trials reported by Jacobs et al., 124 Forastiere et al., 125 and Clavel et al. 126 compared cisplatin and infusional 5-FU to the single agents cisplatin, 5-FU, or methotrexate. The results of the three trials were remarkably similar. The response rate to cisplatin plus 5-FU was 32% in two of the trials and 31% in the third; all studies demonstrated a significantly higher response rate for cisplatin plus 5-FU compared with the single agents. However, there were no differences in median survival rates (5 to 6 months) or 1-year survival (20%) for any of the treatment arms. These response and survival results serve as the benchmark for comparison of regimens incorporating new agents.

Attempts to improve on the cisplatin plus 5-FU regimen include the addition of leucovorin, continuous infusion bleomycin, 133,134 and 135 bleomycin and methotrexate, 136 interleukin-2, 137 and interferon. 138 These three- and four-drug combinations result in enhanced toxicity without indications of survival benefit. More recently, two- and three-drug combinations incorporating paclitaxel or docetaxel have been reported in phase II trials.

Table 30.2-7 and Table 30.2-8 list the results of uncontrolled trials of combination chemotherapy regimens that include paclitaxel or docetaxel. Many consist of preliminary findings presented in abstract form at oncology meetings. Some studies include only patients with recurrent or metastatic disease undergoing palliative treatment, whereas others include varying proportions of patients with locally advanced, untreated disease who received two to four cycles before proceeding to radiotherapy, surgery, or both. Nearly all studies were limited to patients with good performance status who had not received prior chemotherapy for treatment of recurrent disease. All paclitaxel studies used the 3-hour infusion schedule and docetaxel was infused over 1 hour.

### Table 30.2-7. Phase I and II Trials of Paclitaxel Combination Regimens

<table>
<thead>
<tr>
<th>Study</th>
<th>Regimen</th>
<th>Response Rate</th>
<th>Complete Response Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shin et al.</td>
<td>Paclitaxel + Carboplatin</td>
<td>71%</td>
<td>22%</td>
</tr>
<tr>
<td>Forastiere et al.</td>
<td>Paclitaxel + Carboplatin</td>
<td>63%</td>
<td>16%</td>
</tr>
<tr>
<td>Clavel et al.</td>
<td>Paclitaxel + Carboplatin</td>
<td>62%</td>
<td>15%</td>
</tr>
</tbody>
</table>

Trials testing paclitaxel in combination with either cisplatin or carboplatin in recurrent and metastatic disease patients (see Table 30.2-7) demonstrate response in 32% to 39% of patients and complete response rates of less than 10%. 127,128 and 129 In contrast, a phase I and II trial of escalating doses of paclitaxel and cisplatin, 75 mg/m2, reported by Hitt and associates in locally advanced, untreated patients resulted in a 78% overall response rate and 46% clinical complete response rate. 130 Similarly, Dunphy and associates evaluated paclitaxel in doses of 150 to 265 mg/m2 combined with carboplatin at area under the concentration-time curve (AUC) 7.5 in 33 locally advanced, untreated patients and observed a 54% overall response and 27% complete response rate. 131 The results were quite similar, adding paclitaxel to cisplatin and 5-FU: 38% in recurrent disease patients and 81% in locally advanced, untreated patients evaluated for primary site response before definitive local therapy. 132

Two successive trials adding ifosfamide to paclitaxel and either cisplatin or carboplatin (TIP or TIC regimens) have been reported by Shin and associates from the M. D. Anderson Cancer Center for the treatment of recurrent disease. 124,125 Both studies combined 175 mg/m2 of paclitaxel and 1000 mg/m2 of ifosfamide daily for 3 days with cisplatin, 60 mg/m2, or carboplatin, AUC 6, repeated at 3- to 4-week intervals. The overall response rate of 55% to 58% and complete response rates of 17% to 18% were encouraging.

Despite the low single-agent activity observed for gemcitabine in head and neck cancer, a 41% response rate was reported by Fountzilas et al. when it was combined with paclitaxel using a day 1 and 8 schedule every 3 weeks. 133

While the amount of life-threatening toxicity varies with each particular regimen, the data do not suggest that taxane-based regimens are less toxic than older regimens. Myelosuppression and neuropathy are common, particularly with 3-hour infusion paclitaxel combined with cisplatin while the substitution of carboplatin has the potential to augment myelotoxicity. All of the combination regimens should be reserved for patients with good performance status, while patients with poor performance status should be considered for either single-agent chemotherapy or supportive care. The results of these phase I and II series suggest response rates that are similar to what is reported for cisplatin plus 5-FU and certainly no better, for either untreated patients or for patients with recurrent disease. The only exception is the response data from the TIP and TIC regimens 124,125 for patients with recurrent disease that needs to be evaluated further in a larger multiinstitutional trial setting. A randomized trial directly comparing cisplatin plus 5-FU as the standard regimen to paclitaxel plus cisplatin completed accrual in January 2000 in the
ECOG. This trial will provide important comparative data on response, duration of response, survival, toxicity, and cost.

Phase II trials of docetaxel in combination with other cytotoxic drugs are shown in Table 30.2-8. Similar to the studies in Table 30.2-7 for paclitaxel, many include patients with locally advanced untreated disease for which the overall response rates and complete response are proportionately higher. Only one trial was designed to test docetaxel and cisplatin specifically in patients with recurrent and metastatic disease. A total of 33 patients were enrolled from Johns Hopkins, Vanderbilt, and M. D. Anderson, of whom 5 were previously untreated, presenting with far advanced locoregional disease or metastatic disease. The overall response rate was 52% including a 9% complete response. Toxicity was typical of docetaxel and cisplatin combination regimens with grade 3 to 4 neutropenia observed in 79% of patients, asthenia in 21%, and grade 3 peripheral neuropathy in 9%. Four other small phase II trials with previously untreated patients constituting one-half to all patients enrolled reported overall response in 48% to 73% of patients and complete response in 15% to 30%.

In separate trials, docetaxel has been combined with 5-day infusional 5-FU and with vinorelbine with response outcomes similar to that achievable with cisplatin plus 5-FU.

Two studies have evaluated the three-drug combination of docetaxel, cisplatin, and 5-FU with or without G-CSF support primarily in patients with locally advanced inoperable disease before treatment with radiotherapy. Each study enrolled under 30 patients and reported overall response of 75% and 80% after several cycles of chemotherapy. Whether or not this level of response is superior to cisplatin plus 5-FU in a comparable population of advanced head and neck cancer patients is unknown. The addition of docetaxel clearly leads to a substantial increase in life-threatening toxicities of neutropenia and infection. A large multicenter randomized trial is under way to address this question.

**RANDOMIZED TRIALS OF SINGLE AND COMBINATION CHEMOTHERAPY REGIMENS**

Randomized trials comparing combination regimens with either single-agent methotrexate or cisplatin are shown in Table 30.2-8. Survival benefit was reported in three trials. Morton et al. reported median survivals of 4.2 and 4.0 months for patients treated with cisplatin or cisplatin plus bleomycin, respectively, compared with a 2-month median survival for a no-treatment control group. Campbell et al. reported a significant improvement in survival of patients treated with cisplatin (6.7 months) compared with those treated with methotrexate (2.7 months). The Liverpool Head and Neck Oncology Group randomized 200 patients to receive cisplatin alone, methotrexate alone, cisplatin and infusional 5-FU, or cisplatin and methotrexate. Although there were no differences in response rate, survival was significantly better in the three cisplatin-containing arms. In contrast, the three large multicenter trials reported by Jacobs et al., Forastiere et al., and Clavel et al. comparing cisplatin plus 5-FU with single agents all showed a significantly increased response rate for combination chemotherapy but no benefit in median or 1-year survival rate. No other trials comparing combination regimens with single agents have been reported since 1994.

**TABLE 30.2-9. Phase III Trials of Combination Regimens versus Single-Agent Cisplatin or Methotrexate in Recurrent and Metastatic Squamous Cell Carcinoma of the Head and Neck**

Randomized trials comparing combination regimens are shown in Table 30.2-9. Kish et al. compared cisplatin plus infusional 5-FU versus cisplatin plus bolus 5-FU. The response rate was significantly higher for infusional 5-FU, but median survivals were 6.7 and 5.0 months, respectively. Response rates were also significantly higher for the methotrexate plus bleomycin plus vincristine plus cisplatin regimen compared with methotrexate, bleomycin, and vincristine reported by Clavel et al., but survival was similar.

**TABLE 30.2-10. Phase III Trials Comparing Combination Regimens in Recurrent and Metastatic Squamous Cell Carcinoma of the Head and Neck**

To gain perspective on the many trials that have been reported for palliation of patients with recurrent and metastatic squamous cell carcinoma of the head and neck, Bispin and 5-FU could be modulated by interferon-a as shown in preclinical experiments. A total of 244 patients with recurrent or metastatic disease were randomized to receive the standard cisplatin (100 mg/m^2^) and 5-FU (1000 mg/m^2^/d × 4) regimen with or without interferon, 3 million U subcutaneously, days 1 to 5 of...
each chemotherapy cycle, repeated every 3 weeks. There was no significant difference in response or survival rates between treatment groups.

In summary, cisplatin-based combination chemotherapy is more effective than single agents. Response to cisplatin plus infusional 5-FU occurs in approximately one-third of patients, with complete response in 5% to 15%. An advantage for choosing combination chemotherapy seems to be limited to patients with excellent performance status and chemotherapeutic sensitivity of the tumor burden. During recent years, complete responses and improved survival are possible in this small subset of patients. Randomized trials directly comparing docetaxel and paclitaxel combination regimens with cisplatin plus 5-FU are in progress. However, it is unlikely that the addition of the taxanes to other conventional cytotoxic drugs will produce substantial gains in survival, reduce toxicity, or otherwise improve patient quality of life. This underscores the need for new therapies to treat this population.

**BIOLOGIC TARGETED THERAPIES**

An understanding of the molecular and cellular pathways involved in normal and unregulated cell growth is leading to the development of biologically targeted therapies. These signal transduction agents in early clinical trials after a phase I dose-escalation study, cell-cycle traversal, programmed cell death, transcription regulation, matrix invasion, and angiogenesis. Three targeted therapies in head and neck cancer clinical trials with promising preliminary results are the epidermal growth factor receptor (EGFr) antagonists, cyclin-dependent kinase (cdk) inhibitors, and replication competent adenoviruses.

The EGFr is a transmembrane glycoprotein that is a member of the tyrosine kinase growth factor receptor family encoded by the c-erb-B. Activation of the protooncogenes results in overexpression of the receptor, which has been demonstrated to occur in over 90% of squamous cell head and neck cancers. Transforming growth factor-a, EGFr, and other growth factors bind to the extracellular domain of the EGFr-stimulating tumor growth through autocrine or paracrine pathways. Agents that block ligand binding could inhibit cell proliferation. Several monoclonal antibodies against the EGFr are in clinical development. The chimeric IgG antibody C225 developed by Mendelsohn has binding affinity that is equal to the natural ligand effectively blocking EGFr/transforming growth factor-a binding when administered using a weekly intravenous dosing schedule. Enhanced cytotoxicity is observed in combination with a number of chemotherapeutic agents including cisplatin and paclitaxel, and in combination with radiotherapy. The major toxicity is a follicular rash. Phase I and II trials of C225 with cisplatin are in progress in patients with recurrent disease and in combination with radiotherapy for patients with locally advanced disease. The preliminary response rates suggest enhanced antitumor activity, which has prompted the initiation of multicenter double-blind placebo-controlled trials in patients with advanced disease.

Another novel compound in clinical trials that affects signal transduction is the cdk inhibitor flavopiridol. Cdk5 phosphorylate key substances that regulate transition from one cell-cycle phase to the next. In vitro, inhibitors of cdk 1, 2, and 4 block cell-cycle progression at G1/S and G2/M boundaries. In preclinical testing, flavopiridol induces cell-cycle arrest and p53-independent apoptosis. Flavopiridol is a particularly suitable candidate drug for study in tumors in which cyclin D1 overexpression, and the endogenous inhibitor of cdk4 is deleted. The most commonly deleted chromosomal region in head and neck cancer is 9p21-22, the locus of p16, and p15 is commonly absent. A phase I trial has been completed by investigators at the National Cancer Institutes, and a phase II trial in head and neck cancer is under way.

A third area of promising clinical research for head and neck cancers involves replication competent viruses. Mutant adenoviruses have been developed that selectively replicate in and cause lysis of cells deficient in p53-suppressor activity. This takes advantage of the high rate (approximately 45%) of p53 mutations in squamous head and neck cancers. Phase I and II clinical studies of intralesional injection of the E1B-deleted adenovirus ONYX-015 have shown tumor cell necrosis and improvement in tumor-related symptoms. There appears to be enhanced antitumor efficacy in studies of systemic chemotherapy combined with ONYX-015 and perhaps more durable responses at the injected tumor sites. The status of other novel investigational bioreponse modifiers and gene therapies directly administered to local or regional tumor is discussed in reviews.

**PRINCIPLES OF CHEMOTHERAPY: PREVIOUSLY UNTREATED DISEASE**

**INDUCTION CHEMOTHERAPY**

Initial trials of cisplatin-based combination chemotherapy given to newly diagnosed patients before receiving local therapies showed dramatic tumor reduction in 70% to 80% of patients. This observation suggested that sequential therapies so traditional chemotherapy was administered before the tumor vasculature was disrupted might improve locoregional control and affect survival. Now, more than two decades since the first randomized trial evaluated induction cisplatin and bleomycin before surgery, we can conclude from many such trials that the induction strategy confers no survival advantage. A role in preservation of the larynx for patients with locally advanced cancers of the larynx or hypopharynx who would otherwise undergo total laryngectomy has emerged and is discussed in Chapter 30.3. Down-staging of the primary and regional node disease with three cycles of cisplatin plus 5-FU chemotherapy has successfully allowed for larynx preservation and a reduction in the rate of development of distant metastases.

**NONRANDOMIZED TRIALS OF INDUCTION CHEMOTHERAPY**

In the early 1980s, Wayne State University investigators reported high response rates with the regimen cisplatin and infusional 5-FU administered before local treatment. They achieved a response rate of 88% (complete response 19%) with two courses and 93% (complete response 54%) with three courses of the same regimen. Over the past two decades, thousands of patients have received this regimen (cisplatin, 100 to 120 mg/m2 days 1 and 5-FU, 1000 mg/m2 infused over 96 to 120 hours) in clinical research trials and in community practice. Response occurs in 85% of patients, on average, with complete response in approximately 40%. Two-thirds of clinical complete responses are pathologically confirmed in biopsy or resection specimens. Response varies by site, with the larynx and nasopharynx being most responsive and the oral cavity less responsive. Cisplatin and infusional 5-FU remains the most active regimen in previously untreated patients.

Modifications of this regimen to increase the complete response rate have been tested. This includes trials of cisplatin, 5-FU, and leucovorin, demonstrating overall and complete response rates ranging from 50% to 95% and 24% to 65%, respectively. The initial reports by Yokes et al., using oral leucovorin, and Dreyfus et al., using continuous infusion leucovorin appeared promising; however, long-term follow-up did not demonstrate any striking improvement in survival over cisplatin plus 5-FU. Severe myelosuppression, diarrhea, and mucositis occurred frequently, necessitating dose reductions in most patients.

Cisplatin-based combination regimens that include paclitaxel or docetaxel are being tested in patients with locally advanced, unresectable disease before receiving radiotherapy. The preliminary results of those small phase II studies are listed in Table 30.2-7. These trials compared induction chemotherapy followed by definitive local therapy, as dictated by initial resectability status, versus immediate surgery, radiotherapy, or both. Improved survival through a decrease in local and regional failure and distant metastatic rates was the primary goal. Studies designed in the latter half of the 1980s up to 2000 (not included in Table 30.2-7) have focused on organ preservation specifically for primaries in the larynx and hypopharynx. The results of these randomized trials are consistent and fail to demonstrate a survival advantage with the addition of induction chemotherapy.
Although many trials have been criticized for methodologic flaws, five used full doses of cisplatin and 5-FU for three to five courses and had adequate power to reach statistical conclusions.\textsuperscript{22,24,25,26,27} Only one of these trials found a significant improvement in survival for chemotherapy-treated patients and that was limited to a subset with unresectable disease.\textsuperscript{28} Several studies, however, have found a significant reduction in distant metastases,\textsuperscript{22,24,25,26} but in the absence of improvement in locoregional control this has failed to affect survival. It is noteworthy that both distant metastases and locoregional failure were reduced in the inoperable subset of patients achieving a survival advantage reported by Paccagnella et al.\textsuperscript{22}

The following conclusions can be drawn from two decades of experience with induction chemotherapy:

- Induction chemotherapy results in major response rates in 60% to 90% and complete response in 20% to 50% of patients with locally advanced squamous cell carcinoma of the head and neck.
- Pathologic complete response is documented in approximately two-thirds of complete responders determined by clinical assessment, and these patients appear to have a survival advantage.
- Response to induction chemotherapy is predictive of response to subsequent radiotherapy.
- There is no increase in morbidity from surgery or radiotherapy in patients who have received induction chemotherapy.
- Although cancers from all head and neck sites are lumped together in almost all the studies, there is evidence that biologic behavior differs with primary site.
- No significant difference in overall survival has been demonstrated with the use of induction chemotherapy compared with surgery alone.
- Organ preservation and improved quality of life can result from induction chemotherapy (see Chapter 30.3).

**POSTOPERATIVE ADJUVANT TREATMENT**

**ADJUVANT CHEMOTHERAPY**

Chemotherapy administered after a patient has been rendered disease free with surgery, radiation, or both has been evaluated in three large multicenter randomized trials.\textsuperscript{24,25,26} The rationale for this approach was threefold. First, definitive surgery is not delayed. Second, tumor margins may become blurred after response to induction chemotherapy, leaving the extent of required surgery uncertain. Third, up to 20% of patients receiving induction chemotherapy refused surgery once response was achieved and their symptoms abated.

The sequence of surgery followed by adjuvant chemotherapy and then radiation was a strategy developed to avoid these potential disadvantages of induction chemotherapy. The Head and Neck Intergroup tested this strategy using three cycles of cisplatin and infusional 5-FU as adjuvant chemotherapy.\textsuperscript{22} From 1985 to 1990, 499 patients with stage III and IV resected squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, and larynx were stratified into high- and low-risk groups; high-risk was defined as close surgical margins less than 5 mm, cancer in situ at margins, or extracapsular nodal extension. Randomization was to immediate radiotherapy or adjuvant chemotherapy followed by radiation. Although the overall comparison of the two treatments showed no significant differences in survival, disease-free survival, or time to locoregional failure, an analysis of treatment effect on high-risk patients suggested benefit. Improved survival and decreased locoregional failure that approached statistical significance was observed for the high-risk subset of patients who received adjuvant chemotherapy compared with those receiving radiation alone. No benefit for adjuvant chemotherapy could be detected for the low-risk patients. Had this trial been limited to high-risk patients, a significant positive outcome may have resulted.

The RTOG\textsuperscript{22} retrospectively analyzed survival and locoregional failure rates in three patient cohorts enrolled in RTOG clinical trials: those considered low risk, those at intermediate risk because of two or more involved regional lymph nodes or extracapsular extension of tumor, and those at highest risk because of a positive surgical margin with or without other risk factors. At 3 years, the locoregional recurrence rate was 14% for the low-risk group, 27% for those at intermediate risk, and 49% for the highest risk group. Median survival rates were 5.6 years, 2.6 years, and 1.5 years, respectively, for the three groups.

Two other large randomized trials have been performed by head and neck cancer study groups in Japan and France.\textsuperscript{24,25,26} Japanese investigators evaluated a combination of tegafur and uracil known as UFT, 300 mg/d, for 1 year.\textsuperscript{22} Three groups of patients were randomized to observation or adjuvant UFT: 424 patients with stage II to IV cancers treated surgically, 111 patients with stage III disease treated with definitive radiotherapy, and 25 patients with nasopharyngeal cancer treated with radiotherapy. Three-year survival results of surgically treated patients showed no significant difference in survival or relapse-free survival, but adjuvant UFT patients had a significantly lower rate of distant metastases (7.9% vs. 14.6%, \(P = .034\)). No benefit could be shown in the patients treated with primary radiotherapy.

Reported only in preliminary abstract form, French investigators randomized 287 patients with extracapsular nodal extension to receive postoperative radiation alone or adjuvant cisplatin, bleomycin, and methotrexate after completion of RT.\textsuperscript{22} Chemotherapy-treated patients had significantly worse overall survival and an increased rate of distant metastases, but better local regional control.

Several randomized trials that use both induction and adjuvant chemotherapy have been conducted in an attempt to further intensify therapy.\textsuperscript{22,24,25} The Head and Neck Contracts Program, a three-arm trial, compared surgery and postoperative radiation to neoadjuvant cisplatin and bleomycin and to treatment with induction chemotherapy plus adjuvant cisplatin for 6 months after surgery and radiation.\textsuperscript{22} No differences in overall survival were observed, but a significant decrease in distant metastases was reported for the adjuvant group.

Ervin et al. treated 114 patients with neoadjuvant cisplatin, bleomycin, methotrexate, and leucovorin.\textsuperscript{22} After definitive local treatment, patients were randomized to observation or three cycles of adjuvant chemotherapy. The 3-year disease-free survival rates were 55% and 88%, respectively; partial responders to induction chemotherapy showed the greatest benefit. The Southwest Oncology Group conducted a feasibility trial of postoperative radiotherapy and three cycles of concurrent cisplatin followed by three cycles of adjuvant cisplatin plus 5-FU. Compliance was poor, with only 37% of 72 patients completing all six chemotherapy cycles.\textsuperscript{22}

In summary, there is no role for adjuvant chemotherapy in low-risk patients (negative margins of resection, neck disease staged N0 or N1 without extracapsular extension). Patients with positive or close margins of resection, two or more involved regional nodes, or extracapsular extension of disease are at increased risk for both locoregional recurrence and distant metastases. It now seems clear from several studies that at least the rate of development of distant metastases can be reduced with systemic chemotherapy, but an effect on overall survival has not been shown perhaps because of the lack of large enough randomized trials enrolling only high-risk patients.

**ADJUVANT CHEMORADIOThERAPY**

Improvement in locoregional control through the use of concomitant chemotherapy and radiotherapy may be most feasible in the patient with locally advanced but resectable disease. Locoregional recurrence is the most frequent site of failure after surgery and postoperative radiation. Extracapsular extension of tumor in cervical
node metastases is well established as an adverse prognostic factor for recurrence. Before 1999, this experience was almost exclusively limited to patients with bulky unresectable disease. The RTOG conducted a small feasibility study treating 51 patients with resected stage IV disease, postoperative margins, or both, with postoperative RT and concurrent cisplatin, 100 mg/m² every 3 weeks for three cycles. Locoregional control was significantly better compared with matched historic controls. This pilot trial and the positive results of a randomized trial by Bachaud et al., led to a Head and Neck Intergroup Phase III trial now in progress. Resected patients with positive margins, metastases to multiple regional nodes, and the presence of extracapsular spread of disease were randomized to receive postoperative RT with or without concurrent cisplatin (100 mg/m² days 1, 22, and 43).

Four randomized trials of postoperative chemoradiation have been published. Bachaud et al. randomized 88 patients with extracapsular spread of disease in regional neck node metastases to receive postoperative RT alone or postoperative RT plus cisplatin, 50 mg intravenously weekly. After a minimum follow-up of 5 years, the median survival (22 months vs. 40 months) and 5-year survival (13% vs. 36%) were significantly better for the chemoradiotherapy group. Radiation-treated patients had a higher locoregional failure rate compared with the chemoradiotherapy group, while no differences were observed in the incidence of distant metastases. Randomized trials reported by Weissberg et al. and Haflty et al. evaluated mitomycin C and postoperative RT versus RT alone. Both investigators reported improvement in locoregional control but not survival. A third small trial conducted by Weisler et al. found no benefit for cisplatin and 5-FU plus RT compared with RT alone. These last three trials were not targeted to high-risk patients but included all resected patients with stage III and IV disease.

All postoperative chemoradiotherapy studies reported increased acute toxicity, primarily mucositis, and weight loss with combined therapy. Careful monitoring of patients receiving combined chemoradiotherapy along with psychosocial and nutritional support is essential for these therapies to be successful and to have a high level of patient compliance. Completion of the current Head and Neck Intergroup Trial is crucial to confirm the improved survival reported by Bachaud and to change standard of care.

CONCURRENT CHEMORADIOTHERAPY

The purpose of administering chemotherapy and radiotherapy together is to take advantage of the radiosensitizing capability of many of the active drugs for this disease and effect a substantial enough increase in locoregional control to significantly improve survival. The postulated mechanisms for enhanced cell kill with concurrent chemoradiation strategies have been described for decades and include interference with repair processes after sublethal or potentially lethal damage or with tumor cell synchronization. In addition, administering both modalities together may prevent or decrease the emergence of radioresistant or drug-resistant clonogens.

RESULTS FROM METAANALYSES

Since 1999, four metaanalyses evaluating the effect of chemotherapy on survival from randomized trials of induction, adjuvant, and concurrent chemoradiotherapy compared with definitive local therapy alone have been published. These analyses covered the period of publication up to 1993; three were literature based, while the largest and most comprehensive used updated individual patient data from 63 trials including 10,741 patients. The results of all four analyses were consistent in finding a small survival benefit favoring chemotherapy: 2.8%, 4.0%, 4.0%, and 6.5%. The reduction in risk of death was statistically significant in three of the metaanalyses. The survival benefit observed in all of the studies was associated primarily with the patient group receiving concurrent chemoradiation. In the Meta-Analysis of Chemotherapy in Head and Neck Cancer (MACH-NC) analysis based on individual patient data, the absolute survival benefit at 5 years from chemoradiation was 8%. It should be emphasized that the most impressive gains in locoregional control, disease-free survival, and overall survival have been reported since 1995 in large, multicenter randomized trials employing cisplatin-based chemotherapy and concurrent radiotherapy, either standard or altered fractionation.

SINGLE-AGENT CHEMOTHERAPY AND RADIOTHERAPY

Many randomized trials have been published combining the single agents hydroxyurea, methotrexate, bleomycin, 5-FU, mitomycin-C, and cisplatin with radiotherapy compared with radiotherapy alone. These older trials were limited to patients with extensive, locally advanced disease not considered resectable. The results of selected trials with adequate power to demonstrate outcome differences are shown in Table 30.2-12. Gupta and associates at the Christie Hospital and Holt Radium Institute in Manchester randomized over 300 patients to concurrent methotrexate or radiotherapy alone. There was a highly significant improvement in local control (P = .0019) and survival (P = .0089) for patients with oropharyngeal cancers in the methotrexate arm, while survival benefit did not reach statistical significance (P = .075) in the overall analysis.

The results of four trials with bleomycin and radiotherapy are conflicting. Only the trial reported by Shanta and Krishnamurthi in patients with T3 to T4, N0 to N2 squamous cell carcinoma of the buccal mucosa showed a significant beneficial effect of bleomycin on local control, disease-free survival, and overall survival. Local control and progression-free survival were improved in the Northern California Oncology Group trial reported by Fu et al., while large trials from the EORTC and the Norwegian Radium Hospital did not observe benefit for any outcome parameter.

Many studies have used 5-FU with concurrent RT. In the study by Lo and associates, local control and 5-year survival were superior in the combined treatment group, but only in patients with oral cavity cancers was the difference significant. Brown and associates of the National Cancer Institute Canada evaluated infusional 5-FU and radiotherapy. The complete response rate was significantly better with combined treatment, but only a trend for improved progression-free and overall survival was observed. Investigators in Barcelona randomized 658 patients with T3 to T4, N0 to N3 cancers to three treatment groups: radiotherapy, 60 Gy in 30 fractions within 6 weeks of radiation therapy, and 50 Gy in 30 fractions, plus concurrent 5-FU, 250 mg/m² every week. Local control and progression-free survival were significantly better for the 5-FU-treated group compared with the control group receiving 60-Gy radiotherapy alone, but there was no difference when compared with patients receiving 70.4-Gy radiotherapy. Mitomycin C has been shown in trials conducted at Yale to improve progression-free survival but not overall survival.

Cisplatin has been combined with RT because mucositis is not a primary toxicity and experimental data support its effectiveness as a radiosensitizer. As a single agent, cisplatin has been administered using two schedules in head and neck cancer: weekly low doses (20 mg/m²) or intermittent high doses (100 mg/m² every 3 weeks) concomitant with RT. The results of an intergroup randomized trial comparing low-dose weekly cisplatin (20 mg/m²) during radiation with conventional radiation were reported by Haselow et al. The overall response rate was significantly higher for the cisplatin-treated patients (73% vs. 59%, P = .007), but there was no difference in complete response rate (34% vs. 30%) or survival. The lack of benefit may be attributable to the low total dose of cisplatin received (120 to 140 mg/m²) over the 6 to 8 weeks of radiotherapy. The higher dose of cisplatin (100 mg/m² every 3 weeks) during radiotherapy resulted in significant survival benefit for
patients with nasopharyngeal carcinoma. 280

Al-Sarraf et al. reported the findings of an intergroup trial for patients with stage III and IV cancer of the nasopharynx. 282 Patients were randomized to receive standard radiotherapy or cisplatin (100 mg/m² days 1, 2, 22, and 43) during radiation followed by three cycles of adjuvant cisplatin and 5-FU. The trial was terminated early after an interim analysis showed a significant improvement in 2-year survival (80% vs. 55%) with combined treatment. Local and distant failure rates were also significantly reduced with combined treatment. These results cannot be generalized to other sites in the head and neck and the contribution of each component (concurrent chemoradiotherapy and adjuvant chemotherapy) to the improvement in survival cannot be determined.

The newer agents paclitaxel, docetaxel, and gemcitabine have radiation-enhancing properties. 231, 232, 233 Phase I and II trials are in progress to assess dose-limiting toxicities using various schedules of these drugs as single agents or combined with cisplatin or other drugs concurrent with radiation. The safe dose of gemcitabine for head and neck irradiation has not been determined. Initial dosing in a study at the University of Michigan of 150 to 300 mg/m² week was associated with severe late toxicity. 234 Paclitaxel has been studied in low dose as a prolonged infusion, 235 as a weekly low dose by 3-hour infusion, and in combination with cisplatin 236 or carboplatin. 237 The optimal schedule for radiosensitization has not been determined.

COMBINATION CHEMOTHERAPY AND RADIOTHERAPY

Administering multiple cytotoxic drugs during radiation substantially increases toxicity and often necessitates frequent interruptions in radiotherapy. Thus, investigators have developed regimens that use split-course RT providing planned breaks in therapy, or regimens that alternate chemotherapy and radiotherapy in order to minimize normal tissue toxicity. The mode of combining the two therapies is an important issue. For head and neck cancer, it has been demonstrated that protracted RT as single modality treatment results in decreased local control rates. 238,239 This is thought to be due to accelerated repopulation of tumor cells surviving the initial treatment. The failure of induction chemotherapy to show any survival benefit in randomized trials may have a similar cause. If RT is considered a non–cross-resistant tumor-killing agent, then alternating it with chemotherapy or simultaneous administration without breaks might circumvent the problem of heterogeneous tumor cell repopulation and primary drug resistance.

Many concomitant chemotherapy and radiation pilot trials have been reported. Some with the longest follow-up that use cisplatin-based combination chemotherapy report promising survival and response data but also severe mucosal toxicity. 230,231,232 The advantage of multiagent chemotherapy is that in addition to improved local regional control, distant metastases may also be decreased. Taylor and associates used a regimen of concurrent radiation and cisplatin and 5-FU chemoradiotherapy administered every other week. 233 After a median follow-up of 8 years, 31% of 68 patients had recurrences or progressed. The 5-year progression-free survival was 60% and overall survival 43%. Lavertu and associates reported their 8-year experience from the University Hospitals of Cleveland, Case Western Reserve University, using two courses of cisplatin and 5-FU concurrent with 65- to 72-Gy radiotherapy in 105 patients with stage II, III, and IV cancer. 235 At a median follow-up of 39 months, 66 patients (63%) were disease free. The 4-year disease-specific survival was estimated to be 74% and overall survival 60%. The overall survival with the primary site preserved was 54%. Investigators from the University of Chicago have reported their long-term results with concomitant hydroxyurea and fluorouracil for stage II and III head and neck cancer. 236 At a median follow-up of 52 months, 5-year survival, progression-free survival, and local regional control were 65%, 82%, and 86%, respectively. Only eight patients developed local or regional failure, and three were successfully salvaged with surgery. These results suggest a possible survival advantage over surgery or radiotherapy and the potential for preservation of organ function.

Randomized trials of concurrent or alternating chemotherapy and radiotherapy compared with the induction approach of sequential chemotherapy and radiotherapy are shown in Table 30.2-13. 235,236,237,238,239 Only one of the four trials reported a significant improvement in overall survival for the regimen of vinblastine, bleomycin, and methotrexate alternating with radiotherapy compared with sequential treatment. 237 However, the other three trials showed benefit in complete response rate, locoregional control, or progression-free survival with the concurrent strategy. 235,236,237

TABLE 30.2-13. Randomized Trials of Concurrent versus Sequential Chemotherapy and Radiation

More significant are the results of the randomized trials of concurrent platinum-based chemotherapy and radiotherapy compared with radiotherapy alone in patients with locally advanced disease shown in Table 30.2-14. 235,236,237,238,239,240,241,242,243,244 and 245 A significant improvement in overall survival has now been reported for three studies in patients with unresectable disease 238,239,240 and 241 and for one trial limited to patients with stage III and IV cancers of the oropharynx. 242 These positive results are reported for standard fractionation radiotherapy as well as altered fractionation radiotherapy. In all studies, toxicity was increased in patients receiving combined treatment, emphasizing the need for aggressive supportive care, ideally at a treatment center familiar with the expected severity of toxicity and potential complications.

TABLE 30.2-14. Randomized Trials of Concurrent Multilagent Chemotherapy and Radiotherapy versus Radiotherapy in Stage III and IV Disease

Only one study showed no benefit for any outcome parameter. 235 Investigators from the Princess Margaret Hospital compared continuous course radiotherapy with split-course radiotherapy, 50 Gy, and mitomycin and 5-FU in patients with advanced cancers of the larynx and hypopharynx. The lack of a difference may have been due to the 4-week planned break after 25 Gy in the chemotherapy arm, allowing tumor repopulation to occur. 235 The data from more recently matured trials shown in Table 30.2-14 support the use of concurrent chemotherapy and radiotherapy as the standard of care for the treatment of resectable cancers of the oropharynx when nonsurgical treatment is planned. It must be noted that no randomized trials have been performed or are planned comparing chemoradiotherapy to surgery with reconstruction. The large French cooperative group trial reported by Calais et al. 242 using three courses of carboplatin (70 mg/m² days 1 to 4) and 5-FU (600 mg/m²/d continuous infusion for 4 days) during 70 Gy showed significant survival benefit of 51% versus 31% ( P =
In contrast to the favorable results of chemoradiotherapy achieved with oropharyngeal cancers, oral cavity primaries continue to be managed by a surgical approach. Resection produces less relative organ dysfunction, and these cancers appear somewhat less responsive to cytotherapy. Site-specific trials have not been performed.

Aerodigestive tract epithelial carcinogenesis is an extremely complex, multistep process. The process begins with genetic alterations and proceeds to altered proliferation and differentiation. 

Aerodigestive tract epithelial carcinogenesis is an extremely complex, multistep process. The process begins with genetic alterations and proceeds to altered proliferation and differentiation. Histologic and molecular markers of this process are observable but not until late in the process. Molecular and cellular techniques have revealed specific genetic alterations in the process of epithelial carcinogenesis in which losses of genes on chromosomes 3p, 9p, 11q, 13q, and 17p are common.

The most recently completed trial is a randomized maintenance study of the retinoid fenretinide after laser resection of oral premalignant lesions. Of the various regimens tested in these positive trials, cisplatin, 100 mg/m$^2$ d, administered with vigorous hydration and diuretics on days 1, 2, 22, and 43 of standard fractionation radiotherapy (70 Gy) would be a reasonable recommendation for treating unselectable patients. Grade 3 or worse toxicities, particularly muco-cutaneous toxicity, can be expected in approximately 75% of patients and thus aggressive support is required with analgesics, oral care, and gastrostomy tube for nutritional support. Patients with poor performance status, complicating comorbid disease, or who lack the psychosocial resources to undergo these complex therapies should be managed with radiotherapy alone.

**PRINCIPLES OF CHEMOPREVENTION**

Patients at increased risk for developing upper aerodigestive tract cancer may be identified by a history of previous head and neck cancer or exposure to risk factors such as alcohol and tobacco. Because alcohol and tobacco are avoidable risks, there has been considerable interest in developing effective prevention strategies for these patients. One approach currently being tested is chemoprevention, which is the administration of natural or synthetic agents to reverse or suppress carcinogenesis before the development of an invasive cancer. Chemoprevention trials in the upper aerodigestive tract, guided by epidemiologic studies, have often evaluated dietary constituents, such as b-carotene and retinol. The retinoids, natural and synthetic analogues of vitamin A, have been studied extensively as chemopreventive agents.

Retinoids can modulate the growth and differentiation of normal, premalignant, and malignant epithelial cells in culture and can suppress carcinogenesis in vivo in various human epithelial tissues. Aerodigestive tract epithelial carcinogenesis is an extremely complex, multistep process. The process begins with genetic alterations and proceeds to altered expression of regulatory gene products and dysregulated tissue growth or proliferation and dysregulated differentiation. Gross histologic and cellular markers of this process are observable but not until late in the process. Molecular and cellular techniques have revealed specific genetic alterations in the process of epithelial carcinogenesis in which losses of genes on chromosomes 3p, 9p, 11q, 13q, and 17p are common. This step-wise process is an accumulation of genetic events that may be reversible or suppressed at various points. Advances in the biology of carcinogenesis are leading to the development of reliable intermediate biomarkers that can be quantitatively measured to assess modulation by chemopreventive agents.

**CHEMOPREVENTION OF ORAL PREMALIGNANCY**

The first chemoprevention studies in oral premalignancy began in the mid-1950s and used high doses of topical and systemic natural vitamin A derivatives. These early studies reported clinical and histologic activity and response, relapse, and toxicity patterns that are still relevant currently for the reversal of oral leukoplaikia. Agents that have been studied in oral premalignancy chemoprevention trials include selenium, a-tocopherol, b-carotene, and six retinoids.

Hong et al. reported the first randomized trial of oral premalignancy in 1986 in which 44 patients were entered into a 3-month placebo-controlled trial of 13- cis retinoic acid (isotretinoin), 2 mg/m$^2$d. Differences observed in clinical response rate (67% vs. 10%, P = .0002) and histopathologic reversal of dysplasia (54% vs. 10%, P = .01) were highly significant. Toxicity, however, was unacceptable in those patients receiving 2 mg/kg. Cheilitis, facial erythema, and skin dryness and peeling occurred in 88% and conjunctivitis in 76% of patients. Although reversal of the leukoplakic lesions was observed, a relapse rate of higher than 50% occurred within 3 months of stopping the drug.

Hong and coworkers designed a second study to prolong remission with less toxic maintenance therapy. After a 3-month induction phase with high-dose 13- cis retinoic acid (1.5 mg/kg/d), responding or stable patients were randomized to a 9-month maintenance program with low-dose 13- cis retinoic acid (0.5 mg/kg/d) or b-carotene (30 mg/d). Low-dose 13-cis retinoic acid was significantly more effective than b-carotene in maintaining clinicopathologic remission. Only 8% of patients in the 13-cis retinoic acid group had progression of their leukoplakia during maintenance, compared with 55% in the b-carotene group (P < .001). In addition, the low-dose 13-cis retinoic acid regimen was well tolerated, causing only mild and reversible toxicities. The long-term results of this study at a median follow-up of 66 months showed that 17 of 70 patients (24%) developed cancer with an annual rate of 5.8%. The rate of development of cancer in the two treatment groups was not different, 23% for 13-cis retinoic acid and 27% for b-carotene.

Four other randomized trials also demonstrated positive results. Stich et al. observed significant activity with natural vitamin A in Asian patients with leukoplaikia chewing betel nuts and enrolled in a 6-month placebo-controlled trial: 57.1% complete remission with vitamin A versus 30% for controls (P < .01). Benefit was also seen in a second trial from this group comparing b-carotene plus retinol with placebo. Han et al. also noted positive results with a synthetic Retinamide taken for 4 months in a placebo-controlled trial for oral leukoplaikia. The most recently completed trial is a randomized maintenance study of the retinoid fenretinide after laser resection of oral premalignant lesions. After 12 months of fenretinide, the relapse rate in 39 treated patients was 8% compared with 29% in 41 control patients. This results are similar to that observed with low-dose 13-cis retinoic acid maintenance therapy.

Current research efforts are focusing on the biochemoprevention therapies such as the combination of high-dose 13-cis retinoic acid, a-tocopherol, and interferon-a for the treatment of patients with advanced premalignant lesions defined as moderate to severe dysplasia.
favor of laryngeal lesions as compared with oral lesions, suggesting that this may be a promising approach for laryngeal dysplasia.

Chemoprevention of Second Primary Tumors

Regardless of their initial treatment, head and neck cancer patients remain at significantly increased risk for second primary tumor (SPT) development. SPTs occur after treatment for all stages of head and neck cancer, but their effect is most striking in patients treated for early disease. $^{32,33}$ SPTs, either synchronous or metachronous, develop conservatively at a constant yearly rate of 2% to 5% in previously treated patients. The long-term risk of developing additional aerodigestive tract malignancies is 10% to 40%.

Investigators at the M. D. Anderson Cancer Center evaluated the role of cis-retinoic acid in preventing SPTs. $^{34-36}$ Following surgery, radiotherapy, or both, 103 patients with stage I through IV (M0) squamous cell carcinoma of the head and neck were randomized in a double-blind fashion to receive 13-cis retinoic acid (100 mg/m²/d) or placebo for 12 months. After a median follow-up of 32 months, there was a significant difference in the development of SPTs (24% vs. 4%, $P = .005$), respectively, for placebo and treated patients. $^{37}$ At a median follow-up of 55 months, the retinoid-treated patients continued to have fewer SPTs, within the upper aerodigestive tract (7% vs. 33%, $P = .008$), although the difference in incidence for all SPTs had diminished (14% vs. 31%, $P = .004$).$^{35}$ Although these results are impressive, no survival advantage was seen. This may be due to the small sample size and the nature of the study population: One-half of patients had advanced disease.

Bolla and colleagues evaluated etretinate in a placebo-controlled trial to prevent SPTs in patients with squamous cell carcinoma of the oral cavity or oropharynx following local therapy. $^{38}$ After a median follow-up of 41 months, the rates of primary disease recurrence and SPTs were the same for both treatment groups.

Two National Cancer Institute–sponsored multicenter placebo-controlled randomized trials evaluating 13-cis retinoic acid for the prevention of SPTs were initiated in the early 1990s. Both trials are for patients with stage I or stage II squamous cell carcinoma of the oral cavity, pharynx, or larynx who have been rendered disease free with surgery or radiation. The trial, conducted jointly by M. D. Anderson Cancer Center and the RTOG, randomizes patients between placebo and low-dose 13-cis retinoic acid, 0.30 mg/kg for 2 years. Until these trials are analyzed, there is no role for retinoids in daily practice.

POSTTREATMENT REHABILITATION

Increasing emphasis on the posttreatment rehabilitation of the head and neck cancer patient has taken place over the last decade. No doubt as we see the limitations of current therapeutic strategies to improve on mortality for advanced disease, quality-of-life issues will become increasingly important. Specific approaches to the rehabilitation of the head and neck cancer patient have now been defined. $^{39-41}$ The majority of these approaches are based on quantitative assessment of various speech and swallowing parameters (Table 30.2-15).

Optimal rehabilitation approaches for the head and neck patient begin before the initiation of treatment. We have discussed the role of dental examination and hygiene. Another pretreatment assessment should be performed by a speech and swallowing therapist, especially in those circumstances in which resection of critical organs is anticipated, such as the tongue, palate, and pharyngeal wall. Posttreatment rehabilitation should generally be considered within 3 days after treatment depending on the healing and integrity of surgical wounds. Each site within the upper aerodigestive tract must be considered separately.

Appropriate rehabilitation of the oral cavity begins with choice of reconstruction. Resections contribute to intraoral sensory loss, which impairs the initial phases of deglutition. The optimal reconstruction in most circumstances involves primary closure, thereby minimizing large insensate contact surfaces. Teichgraeber et al., however, raised the important consideration of tongue mobility. $^{42}$ The degree of swallowing dysfunction correlates with the extent of tongue resection. In certain circumstances, approximation of the residual tongue to lateral soft tissue may suffice to serve further restrict tongue movement. In this setting the use of a split-thickness skin graft to cover the surgical defect may prevent this restricted function. Teichgraeber et al. noted that patients reconstructed with a split-thickness graft had improved articulation and improved swallowing. $^{43}$ Resections involving the base of tongue and pharyngeal wall may contribute to velopharyngeal dysfunction (i.e., the inability to build adequate intraoral pressure), which contributes to dysfunction of the pharyngeal phase of swallowing. Reduced capacity for generating normal food bolus propulsion results. Rehabilitation in such circumstances may require several means. The placement of an intraoral prosthesis obliterates the defect. The obturator also serves to lower the palate to allow for appropriate contact with the remaining tongue base. Logemann notes that patients with 50% or more of the tongue base resected are likely to benefit from prosthetic rehabilitation. $^{44}$ Other rehabilitation approaches initiated by the speech and swallowing therapist include the use of exercise programs to improve tongue-base motion. Barium swallow studies should be performed before and following rehabilitation efforts to document both the degree of dysfunction and the extent of improvement.

NASAL CAVITY AND PARANASAL SINUSES

EPIDEMIOLOGY

Cancers of the nasal cavity and paranasal sinuses are relatively infrequent cancers with an incidence of 0.75 per 100,000 individuals in the United States. $^{45}$ Lesions of the maxillary antrum are twice as frequent as those of the nasal cavity. Cancers of the ethmoid and sphenoid sinuses are the least frequently observed. Disease occurs more frequently in male than in female subjects (2:1 ratio) and primarily involves individuals in the sixth decade of life. It is noted that cancer of the paranasal sinuses is more frequently observed in other regions of the world including Japan and South Africa. $^{46}$

Etiologic factors involved in disease development are multifold. Exposure to nickel has been attributed to cancer development in the nasal cavity. $^{47}$ Occupations associated with a high incidence of nasal cavity cancers also include those within the furniture, textile, as well as boot and shoe industries. $^{48,49}$ Other workers considered at risk include those involved with production of chromium, mustard gas, isopropyl alcohol, and radium. $^{50}$ When considering cancers of the paranasal sinuses, the most frequently cited agent has been Thorotrast. $^{51}$ Some have attributed maxillary sinus carcinoma to chronic sinusitis.

ANATOMY

The nasal cavity comprises the nasal vestibule, nasal antrum, and turbinates. The paired nasal cavities are separated by septal cartilage. The nasal vestibule is the triangular region of the nasal cavity bounded by the palatine processes of the maxilla inferiorly, the nasal septum medially, and laterally by the fibrofatty tissue called the nasal ala. The nasal vestibule represents that portion of the nasal cavity composed of skin (i.e., bearing hair follicles and sweat glands). Its posterior border is demarcated by transition from skin to mucosa.

TABLE 30.2-15. Assessment of Swallowing Capacity after Oral Cavity and Oropharyngeal Surgery

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The nasal antrum represents the remaining portion of the nasal cavity and contains the inferior, middle, and superior turbinates. The superior and middle turbinates are composed of highly vascular tissue overlying fragile bony projections that inset onto the ethmoid air cell bony framework. The inferior turbinate is composed of a separate bone.

The paranasal sinuses include the maxillary, ethmoid, sphenoid, and frontal sinus. More detailed anatomy of this region is provided.

Primary lymphatic drainage of the maxillary sinuses is into the submandibular nodal basin. The ethmoid sinuses drain into the submandibular as well as retropharyngeal nodes. The nasal cavity drains into these regions as well as along the course of the facial blood vessels into the submandibular triangle and to periparotid nodes.

PATHOLOGY

The majority of tumors of the nasal cavity and paranasal sinus are squamous cell carcinomas. Distinct from other sites within the upper aerodigestive tract, however, squamous cell carcinoma is less predominant. A vast variety of histopathologically distinct cancers occur in this region. Tumors found in the superior portion of the nasal cavity include adenocarcinoma and esthesioneuroblastoma. In the paranasal sinuses, additional neoplasms include tumors of minor salivary gland origin including adenocarcinoma, adenoid cystic carcinoma, and mucoepidermoid carcinoma. Rare tumors of this region are lymphoma, mucosal melanoma, teratocarcinomas, angiosarcomas, and various odontogenic and bone tumors.

NATURAL HISTORY

The most common cancers (i.e., squamous cell carcinomas) are usually well differentiated and slow-growing, and the tendency to metastasize is infrequent. Common presenting symptoms include a nonhealing ulcer, occasional bleeding, and unilateral nasal obstruction.

Given the anatomic limitations in making early diagnosis, disease is usually far advanced at time of initial presentation. Other symptoms may reflect growth into the oral cavity causing dental pain, loose teeth, or ill-fitting dentures, or into the orbit leading to ocular symptoms such as diplopia, proptosis, and epiphora. Severe pain and trismus may occur with extension into the pterygoid fossa. Tumors in the superior nasal antrum and paranasal sinuses may invade the cribriform plate and extend into the anterior cranial fossa, causing anosmia or headache.

The regional lymph nodes most frequently involved with metastatic disease are nodes within the periparotid region or within the submandibular triangle. The propensity for spread to regional lymph nodes is dependent on the subsite in which primary disease may occur. Approximately 20% of patients with cancers of the nasal vestibule develop clinically evident lymph node disease. Nearly 15% of these patients have bilateral disease. Regional lymph node spread is less frequently seen from tumors of the ethmoid and maxillary sinus, approaching 10% to 15% of patients. The probability of lymph node spread increases with extension of tumors outside the normal confines of the nasal and paranasal cavities, especially with extension into the oral cavity.

Prognoses from nasal cavity lesions are directly proportional to size of the lesion and overall approximate 60% at 5 years. The principal determinant of survival is the presence of local recurrence, which is the most frequent site of disease failure. Prognosis for paranasal sinus cancers likewise depends on extent of primary disease at presentation and approximates 30% for advanced T4 lesions.

STAGING AND SCREENING

Given the infrequency in which primary cancers occur in this region, AJCC classification has been adopted only within the maxillary sinus. For the maxillary sinus, the definition of the TNM system is presented in Table 30.2-16. The regional lymph node (N) and distant metastases (M) staging are identical to other sites within the upper aerodigestive tract and are as stated previously (see Staging, earlier in this chapter).

TABLE 30.2-16. Staging for Cancer of the Maxillary Sinus

<table>
<thead>
<tr>
<th>TNM</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T1</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor is limited to nasal cavity and surrounding structures, including the hard palate, nasal septum, maxillary sinus, or teeth</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor invades any of the following: orbit, pterygoid plates, sphenoid sinus, ethmoid sinus, nasopharynx, skull bone, posterior nasal septum, or soft tissue of nasopharynx</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor directly invades, or is in continuity with, any of the following: maxillary sinus, ethmoid sinus, or sphenoid sinus</td>
</tr>
</tbody>
</table>

Careful examination of patients presenting with symptoms referable to the midface may minimize delay in diagnosis of these cancers. Likewise, considerable progress has occurred in the use of diagnostic radiology in the preoperative assessment of tumors of this region. Kraus et al. described how the judicious use of CT, MRI, or both may help to delineate the extent of disease. These authors and others show that CT scan may be optimal for the definition of tumor infiltration of bony architecture (Fig. 30.2-4). MRI, on the other hand, aids in the assessment of tumor invasion of soft tissue structures including orbit, dura brain, and cavernous sinus. Gadolinium-enhanced MRI is an additional tool to aid the therapist in the pretreatment of patients with paranasal sinus cancers by helping to distinguish inflammatory disease from neoplastic extension.

FIGURE 30.2-4. Coronal computed tomographic scan demonstrating bony involvement of the lamina papyracea (curved arrow) and intracranial extension (double arrow). (From ref. 361, with permission.)
TREATMENT

Treatment of Tumors of the Nasal Cavity

For tumors of the nasal cavity, the appropriate surgical procedure depends on location of the primary disease. Tumors of the nasal septum can be approached through a lateral rhinotomy or by a midface degloving technique.\textsuperscript{371} Cancers of the superior or lateral nasal cavity can be resected by a medial maxillectomy and an en bloc ethmoidectomy.\textsuperscript{372}

Early tumors of the nasal cavity do not require elective treatment of regional lymph nodes as regional spread of disease is relatively infrequent. RT and surgical resection yield roughly equivalent results for early lesions. Wong and Cummings have pointed out that most patients presented with lesions that are less than or equal to 5 cm, and less than 10% present with lymph node metastases.\textsuperscript{373} When RT is used, treatment can be given by either external-beam techniques, interstitial implants, or a combination of both.

The difficulty with advanced tumors is in obtaining adequate surgical margins. Given the high propensity for local recurrence, combined modality therapy consisting of surgery and radiation should be used in most circumstances.

Treatment of Paranasal Sinus Cancers

For cancers of the maxillary sinus, maxillectomy is the procedure of choice and generally is combined with postoperative radiation. For most lesions, maxillectomy entails a standard Weber-Ferguson incision through skin of the anterior face. The bone cuts used depend on the decision to preserve or resect the orbital floor and orbital contents. It should be recognized that multiple procedures are encompassed by the term maxillectomy dependent on the extent or resection of the bony framework (i.e., inferior, medial, anterior, and lateral walls). Spiro et al. have suggested classification schemes indicating limited, subtotal, and total maxillectomy.\textsuperscript{373}

Debate in the management of paranasal sinus cancers centers on extent of surgical resection as well as what constitutes resectability. Furthermore, the management of the eye in patients with paranasal sinus cancer remains controversial. For T1 or T2 lesions of the maxilla, the eye can be preserved. Surgeons would advocate resection of orbital contents in patients whose tumors transgress the orbital floor and infiltrate orbital contents. In certain circumstances, however, invasion of orbital floor by maxillary sinus cancers cannot be determined preoperatively.\textsuperscript{374}

Should disease involve orbital floor and yet not extend into the orbit, resection of the bony floor may be entertained with preservation of globe. However, ocular motion may be impaired and diplopia can result from such a procedure secondary to loss of structural support of orbital contents. This complication has led to numerous procedures for reconstructing the resected orbital floor including medial galeal pericranial flaps.\textsuperscript{376} The value of one surgical approach versus another is limited by the relative infrequency of these tumors. Tiwari et al. have provided additional insight as to the management of orbital contents in patients whose tumors involves periorbita.\textsuperscript{371} The authors, in a careful analysis of anatomic contents of the orbit, note that the periorbita is not the final barrier to tumor invasion, rather, a thin fascia around the periorbital fat. This fascial plane is rarely involved in their series, even in the presence of periorbital involvement. The authors note radiographic assessment cannot discriminate involvement of this fascial plane. The authors go on to note that ocular function with preservation of this fascial plane, even when combined with postoperative radiation, is good. Diplopia is not a complicating factor.

With advances in surgical technique and cumulative experience, factors that classically are considered to preclude surgical excision are continually evolving.\textsuperscript{377,378} Lund et al., for instance, presented results of craniofacial resection in over 200 patients with a wide variety of tumors of the paranasal sinuses.\textsuperscript{379} Actuarial survival in this population was 44%. Lund et al. describe acceptable survival results with acceptable morbidity in patients who underwent skull base resection. Disease involving dura, although associated with an adverse outcome, in selected instances can be controlled surgically. Similar results were noted by McCaffrey et al.\textsuperscript{380}

Results, however, are significantly influenced by histology. Survival of patients with olfactory neuroblastoma is far superior to those with adenocarcinoma. Involvement of brain parenchyma and extensive involvement of the infratemporal fossa from tumors of the maxillary sinus has not been considered amenable to surgical resection for cure. Each of the decisions regarding resectability should be tempered by the skill of the primary surgeon and availability of neurosurgical and reconstructive expertise.

A major decision in the treatment of paranasal sinus involves reconstruction of the surgical defects. Multiple methods of reconstruction have been advocated including temporal muscle slings, skin grafts, and even composite flaps containing bone.

In general, elective treatment of regional lymph nodes in patients without clinical evidence of lymph node metastases is not indicated.

RT alone is not commonly used for these lesions although it can be used when surgery is not feasible. Roa et al. have reported results of three-dimensional conformal RT for advanced paranasal sinus cancer.\textsuperscript{381} For unresectable lesions treated by radiation alone, local control was 32% at 3 years. For patients who had a grossly incomplete resection, local control was only 20%. The group of patients who had a grossly complete operation, leaving only microscopic residual, enjoyed 79% local control. These data suggest that there is considerable room for improvement. In fact, newer programs that combine this type of sophisticated RT with chemotherapy, either sequential or concomitant, have been promising.

Results of Treatment

NASAL CAVITY. Spiro et al. have reviewed the results of therapy for 27 patients with squamous cell carcinoma of the nasal cavity.\textsuperscript{382} Surgery alone was the treatment in 21 instances. Five-year determinate cure for nasal cavity lesions were 43%. Local failure remains the most frequent site of failure in the treated surgery, occurring at rates ranging from 10% to more than 40%, emphasizing the need for effective multimodality therapy.\textsuperscript{377,379,380}

Levendag and Pomp have reported a series of 63 consecutive patients with squamous cell carcinoma of the nasal vestibule who were managed with RT, principally with interstitial implantation.\textsuperscript{383} A mean dose of 62 Gy for T1 and 64 Gy for T2 lesions was used. Patients were grouped according to the classification system proposed by Wang.\textsuperscript{384} Local control was obtained in 97% of T1NO patients, and 79% of T2N0 patients. Similar results have been observed by others.\textsuperscript{381,383} Factors associated with an adverse outcome to primary RT include the presence of nodal metastases and local tumor extension into surrounding anatomic structures such as skin, lip, cartilage, or bone.

PARanasal sinuS. Results of surgical resection of paranasal sinus cancer have demonstrated local control rates ranging from 10% to 90%, depending on disease stage.\textsuperscript{377,387} Surgical series likewise demonstrated that limits of surgical resection could be extended into the anterior as well as the middle cranial fossa with 5-year
None of the complete responders have had a local recurrence, although median follow-up is only 1 year. These encouraging results for unresectable paranasal sinus tumors were 93% and 95.5%, respectively. These results compared favorably with a 40% survival rate for historic controls treated with surgery and radiotherapy.

Chemotherapy for Cancer of the Paranasal Sinuses

Information on the role of chemotherapy in treating paranasal sinus cancer is limited because these patients are usually reported as a subset of a larger series of head and neck cancer patients. For carcinomas of squamous cell histology, there are no data to suggest that the response rate to standard intravenous chemotherapy such as cisplatin and 5-FU is any different from that achievable at other primary sites.

One form of chemotherapy that is specific to paranasal sinus cancer is intraarterial drug delivery. Intraarterial chemotherapy has been studied for almost three decades. The rationale is based on the steep dose-response curve exhibited by most cytotoxic drugs. Regional or intraarterial drug delivery has the potential to increase tumor drug exposure while reducing systemic toxicity. The rationale for using this method of drug delivery for maxillary sinus cancers in particular is to increase local control and to preserve the orbit.

Most of the literature is from trials performed in the 1970s and 1980s using intraarterial bleomycin or 5-FU. As an example, Japanese investigators reported cannulating the superficial temporal artery in 68 patients with paranasal sinus cancer to avoid the need for general anesthesia and to avoid postoperative problems. In 57 patients, 38 showed disappearance of tumor, and among these, 22 required no further treatment. In 19 cases of residual tumor after surgery, partial resection of the orbit was performed to avoid orbital exenteration.

More recent trials used intraarterial cisplatin alone or combined with other agents in sequence or simultaneously with radiotherapy. In one trial, intraarterial cisplatin, bleomycin, and intravenous 5-FU infusion were used as an induction regimen. Of a total of 28 evaluable patients, 6 complete and 13 partial responses were observed. After chemotherapy, 13 patients had RT alone and 11 had surgery followed by RT. Overall, 21 patients were rendered free of disease. Of 18 patients who were initially judged to need orbital exenteration, only 7 required it. The median disease-free survival was 42 months. Mortimer et al. employed external carotid artery catheterization to treat 25 patients with intraarterial cisplatin, 100 mg/m² every 7 to 14 days for three cycles. The complete response rate was 32% and partial response rate was 50%, which is comparable with that reported for combination chemotherapy administered intravenously.

Wayne State reported its 10-year experience with intravenous cisplatin-based chemotherapy in 24 patients. The response rate was 82% (complete response, 44%; partial response, 38%) for previously untreated patients and 88% (complete response, 36%; partial response, 50%) for patients with recurrent disease. The median survival of untreated patients who achieved complete response was 21 months; for those achieving partial response it was 13 months, and for those achieving no response it was 3 months. For patients treated for recurrent disease who achieved a complete response, the median survival was 16 months; for those who achieved a partial response it was 13.5 months; and for those who achieved no response it was 5 months.

Lee and colleagues from the University of Chicago Hospitals published the results of treatment of 19 consecutive patients with stage III and IV paranasal sinus cancer with multimodality protocols over a 12-year period. Patients received cisplatin-based induction chemotherapy, followed by resection and then concomitant radiotherapy and hydroxyurea and 5-FU. The disease-free survival rate at 5 and 10 years was 66.6% and local control was 76%. Regional and distant control rates were 93% and 95.5%, respectively. These results compared favorably with a 40% survival rate for historic controls treated with surgery and radiotherapy.

Harrison and associates reported the results of a prospective study evaluating concomitant chemotherapy with RT for advanced unresectable head and neck cancer. Eight of the ten patients with unresectable paranasal sinus tumors had a complete response to the combined chemotherapy with RT treatment program. None of the complete responders had a local recurrence, although median follow-up is only 1 year. These encouraging results for unresectable paranasal sinus cancer raise the issue as to whether this combined modality approach could be successful in earlier stage disease. Larger numbers of patients and longer follow-up are needed before this could be considered an alternative to standard treatment with surgery and RT.
Interesting results have come from Robbins and colleagues using their Rad-Plat protocol of 150 to 200 mg/m² of cisplatin weekly for up to four doses through a microcatheter angiographically to selectively encompass the dominant tumor supply. Concurrent with the intraarterial cisplatin, intravenous bolus sodium thiosulfate was administered to neutralize the systemic effects of cisplatin. The response rate in 22 patients in a phase I trial was 62%. This intraarterial regimen is continuing to be studied by this group in patients with locally advanced head and neck cancer, and high complete response rates have been achieved.

Based on the information published to date, it seems that intraarterial chemotheraphy with radiation in locally advanced maxillary sinus tumors may achieve results similar to surgery and RT without the effects of major surgery. For patients with paranasal sinus cancer who need orbital exenteration or major craniofacial resection, the option of intraarterial chemotheraphy as induction therapy to preserve the eye should be considered as an alternative treatment.

NASOPHARYNX

EPIDEMIOLOGY

The epidemiology of nasopharyngeal carcinoma suggests multiple determinants including diet, viral agents, and genetic susceptibility. Endemic areas include Southern China, North America, and regions within the far northern hemisphere. The population diets of these regions are what contributes a link to disease development. Populations in endemic areas are characterized by intake of salt-cured fish and meat. The cooking of such food releases volatile nitrosamines that are distributed over nasopharyngeal mucosa when carried by steam.

In addition to diet, considerable epidemiologic evidence incriminates Epstein-Barr virus (EBV) in nasopharyngeal carcinoma development. Old and colleagues first demonstrated the presence of anti-EBV antibodies within the sera of nasopharyngeal carcinoma patients. Knowledge about EBV serology has rapidly progressed, reinforcing the potential causal relationship. More recent advances in molecular biology have provided more direct evidence of the carcinogenic properties of this herpesvirus, including the identification of EBV-related peptides capable of inducing malignant transformation of lymphoblastoid cell lines in vitro.

Potential genetic determinants of nasopharyngeal carcinoma have been suggested by the increased incidence of disease in individuals with specific major histocompatibility complex profiles. Loci associated with increased relative risk include the H2 locus antigen. Likewise, Simons et al. noted the so-called Singapore antigen, BW46, was associated with a high risk of nasopharyngeal carcinoma. The risk of disease increases significantly in individuals with both the H2 and BW46 antigen. An increased odds ratio of disease was also demonstrated in individuals who carry the B17 antigen. In the latter instance, the disease is associated with an earlier age of onset. The peak incidence of disease occurs in the fourth and fifth decades. The male to female ratio is 2.2:1.

ANATOMY

The nasopharynx is a cuboidal structure covered by stratified mucociliary columnar epithelium. Anteriorly it is in continuity to the nasal cavity by way of the posterior choanae. The roof is formed by the basiocciput, the basiocciput, and the anterior arch of the atlas. The roof gradually slopes inferiorly to become the posterior wall. The latter is formed by the first two cervical vertebrae. The lateral walls of the nasopharynx contain the eustachian tube openings, which lie within the elevations of the torus tubarii (i.e., the cartilaginous portions of the internal auditory canal). Behind the torus is the lateral pharyngeal recess or fossa of Rosenmüller, which is the most common site of nasopharyngeal carcinoma development. The floor of the nasopharynx is the upper surface of the soft palate.

Lymphatic drainage from the nasopharynx encompasses all levels within the neck as it proceeds along the jugular vein and spinal accessory nerve. Extensive lymphatics within the nasopharynx also drain into the retropharyngeal nodes medial to the carotid artery. It is of note that involvement of these nodes rarely can be detected clinically. Radiologic assessment, either CT or MRI, is the most sensitive diagnostic technique for detecting retropharyngeal node enlargement.

PATHOLOGY

The World Health Organization (WHO) has divided nasopharyngeal carcinoma into three types: type 1, keratinizing squamous cell carcinoma; type 2, nonkeratinizing carcinoma; and type 3, the undifferentiated carcinoma. The latter is the most frequently identified neoplasm. It characteristically is associated with a lymphoid infiltrate that accounts for its more familiar description, lymphoepithelioma. The proportion of type 1 nasopharyngeal carcinoma among the North American population is higher than found in other localities.

Additional cancer types noted include lymphoma, juvenile angiofibroma, plasmacytoma, and adenocarcinomas. The latter is of minor salivary gland origin.

NATURAL HISTORY

Nasopharyngeal cancer grows either by infiltration or by expansion with the former growth pattern predominating. Frequently, mucosal abnormalities may reflect only a small portion of tumor extent. On occasion, no abnormalities of the mucosa are identifiable. In such instances, tumors may extend submucosally and extend into sites outside the confines of the nasopharynx proper.

The most common presenting complaint of nasopharyngeal carcinoma is a mass in the neck occurring in nearly 90% of patients. Additional frequently encountered symptoms include alterations in hearing associated with serous otitis media, tinnitus, nasal obstruction, and pain. Patients may present with symptoms that reflect growth of the disease into the many significant surrounding anatomic structures. Tumors can access the parapharyngeal space through the sinus of Morgagni, an opening in the lateral nasopharyngeal wall through which the eustachian tube courses. Infiltration laterally into the parapharyngeal space may lead to pterygoid muscle involvement and trismus. Frequently, cranial nerve involvement is manifested with more extensive growth into the skull base. Growth into the cavernous sinus under such circumstances can lead to impairment of cranial nerves II to VI. Additionally, cancer may break through the pharyngobasilar fascia and spread along vascular sheaths (i.e., fascial planes surrounding the jugular vein and carotid artery). Disease extending along these planes may also extend within skull base and lead to cranial nerve involvement.

Any description of the natural history of nasopharyngeal carcinoma must take into account its metastatic potential. Furthermore, the metastatic potential of these tumors is governed by the WHO histopathologic classification. WHO type 1 has a greater propensity for uncontrolled local tumor growth and a lower potential for metastatic spread than the WHO type 2 or 3 cancers. Clinically advanced nodal metastases from WHO type 1 approximates 80%. For WHO type 2 and 3 disease, clinical evidence of metastatic disease ranges from 80% to 90%. Distinct from cancers of the oral cavity and oropharynx, metastatic disease frequently presents itself in the posterior triangle. Bilateral neck nodes are present in 53% of patients. Another common location for metastatic disease is in the lymph nodes in the retropharyngeal space, the so-called nodes of Rouviere. Thus, multiple nodal chains can be involved with disease including chains along the special accessary nerve, jugular vein, and the retropharyngeal pathway.

Prognosis for the various WHO classifications of nasopharyngeal carcinoma vary from approximately 15% 5-year survival for type 1 lesions to 60% for type 3 lesions dependent on disease stage.

STAGING AND SCREENING

The regional lymph node (N) and distant metastases (M) staging are identical to other sites within the upper aerodigestive tract (see Staging and Screening, earlier in this chapter; Table 30.2-17).
All patients with cancer of the nasopharynx require treatment to both sides of the neck. The overwhelming majority present with either unilateral or bilateral

**TREATMENT**

RT is the standard treatment of almost all nasopharyngeal carcinomas. Surgery is usually not feasible and cannot provide adequate margins of resection. There is also considerable morbidity to nasopharyngeal surgery, even in the most selected patients.

Modern imaging techniques, including CT and MRI, have dramatically changed RT for this disease. Yu et al. and others have shown that CT scans up-stage more than 50% of T2 and T3 patients. In addition, these investigators found that CT identified parapharyngeal extension in more than 60% of T2 patients. They found that patients who were treated with CT treatment plans had improved local control and 5-year survival. This result will not come as a surprise to most radiation oncologists. Because CT and MRI scanning have identified disease extensions that were not previously known, the RT plans can now be modified accordingly. An example is shown in Figure 30.2-7. The patient in the figure has parapharyngeal extension. A standard, bilateral opposed field arrangement for the nasopharynx and upper neck would significantly compromise the treatment to the parapharyngeal space. In particular, when the spinal cord block was added, the parapharyngeal extension would be under the block and thereby underdosed. It is not surprising that this would lead to treatment failure. Indeed, Sham and Choy have studied the importance of parapharyngeal extension in the management of nasopharyngeal cancer. This group demonstrated that the degree of parapharyngeal space extension was an important prognostic factor that influenced local tumor control. Using CT scans, they identified four categories of parapharyngeal extension. Type 1 extension involves disease extending up to a line that extends from the medial pterygoid plate to the lateral carotid artery. Type 2 extension goes beyond type 1, up to a line from the medial pterygoid to the styloid process. Type 3 extension goes beyond type 2, up to a line from the lateral pterygoid to the posterior aspect of the ascending ramus of the mandible. Sham and Choy reported that the degree of extension was important, but also that the degree of extension within the T4 group was statistically significant (type 0 and 1 vs. 2 and 3) and approached statistical significance for the T3 group.

In addition to the benefits of target-volume delineation that these new imaging techniques have provided, the advent of three-dimensional RT treatment planning has been vital. Kutcher et al., as well as the experience at Memorial Sloan-Kettering Cancer Center, revealed that multifield conformal plans were able to achieve excellent coverage of tumor, while reducing the normal tissue doses compared with standard treatment techniques. An example of a treatment plan is shown in Figure 30.2-8. It should be pointed out that this is complicated RT. Anywhere from seven to ten fields might be necessary to provide the best dose distribution to the primary site. This needs to be matched to upper neck fields, which then needs to be matched to lower neck fields. The spinal cord must be protected at each junction. Electron beams are required for the posterior neck and these are matched to the photon fields. The result is that up to 15 fields might be required in a single patient. There is some suggestion that RT in a concomitant boost during the last 2 to 2.5 weeks of radiation may provide better local control. This allows for the total dose to be increased with a shortened overall treatment time, yielding an enhanced biologic effect. Total doses in the 70-Gy range are usually given to the primary site. The addition of chemotherapy for selected patients with advanced primary and neck disease is discussed later in this section.

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**TABLE 30.2-17. Staging for Nasopharyngeal Cancer**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>Tumor limited to one side of nasopharynx</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor extends more than 1 cm outside of nasopharynx</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor extends into only, oropharynx, or both</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor extends, mandible, or both</td>
</tr>
</tbody>
</table>

In addition, these investigators found that CT identified parapharyngeal extension in more than 60% to 80% of cases. Cellai et al. attempted to study the effect that CT staging and treatment planning had on therapeutic results. They found that patients who were treated with CT treatment plans had improved local control and 5-year survival. This result will not come as a surprise to most radiation oncologists. Because CT and MRI scanning have identified disease extensions that were not previously known, the RT plans can now be modified accordingly. An example is shown in Figure 30.2-7. The patient in the figure has parapharyngeal extension. A standard, bilateral opposed field arrangement for the nasopharynx and upper neck would significantly compromise the treatment to the parapharyngeal space. In particular, when the spinal cord block was added, the parapharyngeal extension would be under the block and thereby underdosed. It is not surprising that this would lead to treatment failure. Indeed, Sham and Choy have studied the importance of parapharyngeal extension in the management of nasopharyngeal cancer. This group demonstrated that the degree of parapharyngeal space extension was an important prognostic factor that influenced local tumor control. Using CT scans, they identified four categories of parapharyngeal extension. Type 1 extension involves disease extending up to a line that extends from the medial pterygoid plate to the lateral carotid artery. Type 2 extension goes beyond type 1, up to a line from the medial pterygoid to the styloid process. Type 3 extension goes beyond type 2, up to a line from the lateral pterygoid to the posterior aspect of the ascending ramus of the mandible. Sham and Choy reported that the degree of extension was important, but also that the degree of extension within the T4 group was statistically significant (type 0 and 1 vs. 2 and 3) and approached statistical significance for the T3 group.

**FIGURE 30.2-7.** A patient with squamous cell carcinoma of the nasopharynx that was staged as T2N0. A: A computed tomographic (CT) scan shows disease extension posteriorly in the parapharyngeal space. If bilateral opposed portals were used for the nasopharynx, the posterior extent of the disease would be undertreated when the spinal cord block is placed. This demonstrates the need for CT scan in all nasopharynx patients. B: Another CT scan shows retropharyngeal adenopathy (arrow). Again, this disease would be undertreated significantly by conventional, opposed lateral portals with a spinal cord block. C: This patient was treated before there was three-dimensional treatment planning. A three-field arrangement was used, which included two posterior oblique portals that protected the spinal cord but treated the posterior extent of disease. A small portion of the posterior aspect of the disease is undertreated by 20%, even with this plan. This area was boosted with an 125I implant. The patient had no evidence of disease at 5 years.

**FIGURE 30.2-8.** A patient with a T4N0 squamous cell carcinoma of the nasopharynx. The patient has a bulky disease, extending into both retropharyngeal areas. A: Computed tomographic scan shows target volume outlines. If bilateral opposed lateral portals were used to treat the nasopharynx, and a spinal cord block was placed at 4500 cGy, the posterior aspect of the target volume is underdosed. The retropharyngeal disease cannot be treated with this technique. B: Using a three-dimensional treatment plan, it is possible to encompass the entire retropharyngeal area adequately and still protect the brainstem and the spinal cord. This patient has a complete response to radiation therapy and is doing well 10 months after completion of treatment.

All patients with cancer of the nasopharynx require treatment to both sides of the neck. The overwhelming majority present with either unilateral or bilateral
metastases. Those with clinically negative necks still require elective neck irradiation. It is the pattern of nodal spread that is quite orderly with the upper jugulodigastric nodes being involved in the great majority, and the low neck involved far less frequently. It is interesting to note the ability of RT to control neck disease without the need for neck dissection. Neck control is high, even in patients with bulky cervical lymphadenopathy. All patients with nasopharyngeal disease require radiation treatment to regional cervical lymph nodes. Patients with N0 necks are usually treated to 5000 cGy to the entire neck in 180- to 200-cGy daily fractions. Patients with involved necks receive at least 6000 cGy to the region of the involved neck, with boost to higher doses to the gross disease itself. For N1 disease, an additional 500 to 1000 cGy is given. For bulkier necks, doses in the 1000 to 1500 cGy range are added. These additional boost dosages are usually done with electron beams. There has been increasing interest and development of more sophisticated treatment techniques. The role of multileaf and micro-multileaf collimators in conformal therapy has allowed for increasing customization and automation of treatment. In particular, micro-multileaf systems (leaves less than 5 mm) may be particularly valuable. Three-dimensional intensity-modulated radiotherapy may also be helpful in attempts to maximize tumor dose while decreasing normal tissue dose.

Treatment of Recurrent Disease

For patients with local recurrence, a second course of RT can usually be delivered to the nasopharynx. This can be quite rewarding in selected patients. Wang has shown the importance of high-dose reirradiation in obtaining good results. Five-year survival was 45% in patients who received greater than or equal to 6000 cGy, as compared with zero 5-year survivors in those who receive less than 5000 cGy. Also, the interval of time between the original treatment and the recurrence was of prognostic significance. For patients who had recurrences more than 2 years after their original treatment, 5-year survival could be obtained in 66%. However, only 13% of patients who failed within 2 years of the original treatment were 5-year survivors. Wang emphasizes the importance of combining external beam and brachytherapy in the management of recurrent disease.

Brachytherapy alone has been used for selected patients with local recurrence. Harrison et al. have reported the use of permanent 125I implants for discreet local recurrences in the nasopharynx. Either the transoral or the transpalatal approaches can be used. Figure 30.2-9 shows a transpalatal approach. The transnasal approach can also be used. If patients are selected with localized, discreet lesions that are limited to the mucosa, permanent implants can be quite successful. It also has the advantage of limiting the normal tissue that is reirradiated.

FIGURE 30.2-9. A patient with a discrete mucosal recurrence of a nasopharyngeal cancer. The recurrence was superficial and at the root of the nasopharynx. It was not accessible through the opened mouth or through the nose. He was treated with an 125I implant via the transpalatal approach. A: This view looks into the mouth from above the patient's head, under general endotracheal anesthesia. A mouth retractor holds the mouth open. The tongue is at the top of the figure retracted by the tongue blade. The soft palate is exposed for the incision. B: The soft palate has been incised and reflected to expose the interior of the nasopharynx. The torus tubarius is seen, and the glistening mucosa of the nasopharynx is directly visualized. Using this access, 125I seeds are directly implanted into the roof of the nasopharynx. C: Localization films of the implant show the position of the seeds in the roof of the nasopharynx.

In most situations, because the recurrent lesion is not discreet and localized, a combination of external-beam and intracavitary irradiation is important. The field size should be kept as small as possible, preferably smaller than 8 cm in maximum diameter. It would be typical to deliver 4500 to 5000 cGy with external-beam RT, and then boost the nasopharynx with an intracavitary implant with an additional 1000 to 1500 cGy. The techniques for these different brachytherapy approaches have been reviewed by Harrison et al. and Erickson and Wilson. It is important to tailor the implant to the specific location within the nasopharynx that one wants to irradiate. This can help maximize the dose to the target area and minimize the dose to the surrounding normal tissue. The use of charged particle irradiation as well as stereotactic radiosurgery and combining chemotherapy with radiotherapy has been reported. The relative roles of these techniques for patients with recurrent nasopharyngeal carcinoma remain to be determined. The chemotherapy approaches are discussed later in this section.

The role for surgery in nasopharyngeal carcinoma is limited principally to treatment of residual or recurrent disease. Small locally recurrent disease within the nasopharynx has been shown to be amenable to surgical resection with 5-year survival rates of 50% in 5 small patient series. Morton et al. have reviewed the various techniques involved in the surgical management of recurrent disease. Various approaches include transpalatal, palatocystic, maxillary swing, infratemporal, and the transcervicocaudalbiulinal approach. Complications of such surgery include injury to cranial nerves, cerebral spinal fluid leaks, and hemorrhage secondary to vessel injury.

Management of regional recurrence entails the same considerations as regional recurrence from squamous cell carcinomas elsewhere within the upper aerodigestive tract. If the disease is resectable, an attempt at surgical ablation is indicated. In most instances this requires a radical neck dissection. Brachytherapy can supplement the neck surgery if there is concern about residual disease.

Chemotherapy for Nasopharyngeal Cancer: Metastatic or Recurrent Disease

The natural history of nasopharyngeal carcinoma, WHO types 2 and 3, differs from that of other sites in the head and neck. Local control rates are high, while distant failure is more common and is often the cause of death. The distant metastatic rate at presentation is reported to be 5% to 11%. However, a thorough extent of disease evaluation that includes CT scans of chest and abdomen, a bone scan and bone marrow aspiration, and biopsy reveal distant metastases in up to 40% of patients. Those presenting with bulky or fixed nodes, disease low in the neck, or bilateral involvement are at the greatest risk.

Bone is the most common site of metastases followed by lung, liver, and extraregional nodes. Autopsy series report distant metastases in up to 87% of patients with nasopharyngeal carcinoma, which is substantially more than found for any other primary site in the head and neck.

Reports of chemotherapy for treating recurrent and metastatic disease have usually been included with outcome data for other sites. The single agents, cisplatin, doxorubicin, epirubicin, bleomycin, and melphalan have been shown to be active for this disease, whereas the evidence for the activity of 5-FU, cyclophosphamide, and the vinca alkaloids is less certain.

The most effective combinations are cisplatin-based. Using these regimens to treat patients with metastatic disease consistently results in a small proportion of long-term disease-free survivors. The results of phase II trials generally show higher complete and partial response rates than are attainable for squamous cell carcinoma from other sites. Selected trials are shown in Table 30.2-18.
Choo and Tannock treated 40 patients with single agents or non-cisplatin-containing combinations and reported response in 25%, three complete and seven partial responses. In contrast, the response to cisplatin-based combination chemotherapy in 30 patients was 70%, 7 complete and 14 partial responses. A multicenter collaborative group led by investigators from the Institut Gustave Roussy-La Grange, France, has performed a sequence of studies evaluating cisplatin-based combination chemotherapy. The best results were achieved with a regimen of cisplatin, bleomycin, and 5-FU that resulted in a 20% complete response rate and 79% overall response rate in 49 patients with metastatic or recurrent undifferentiated nasopharyngeal carcinoma. A total of 165 patients with metastatic undifferentiated nasopharyngeal carcinoma were treated on four consecutive protocols between 1985 and 1996. Twenty patients (12%) were long-term disease-free survivors (42+ to 208+ months), demonstrating the chemosensitivity of this disease in patients with visceral or bone metastases.

Investigators from the Prince of Wales Hospital, Hong Kong, evaluated carboplatin, 300 mg/m^2 day 1, and 5-FU, 1000 mg/m^2/d, days 1 to 3 every 3 weeks, in 42 patients with metastatic disease. Complete responses were observed in lung, liver, and distant nodal sites of metastases. The overall response rate of 38% was lower than reported for cisplatin-based combinations; however, both agents were administered in lower total doses than customarily used in the United States. This same group subsequently evaluated paclitaxel, 135 mg/m^2 (3-hour infusion), and carboplatin, AUC 6 dosing every 3 weeks. One-third of the 27 patients enrolled had received prior chemotherapy and yet a 59% response rate was observed with acceptable toxicity. Similar results were reported by Fountzilas and associates using a more intensive regimen of paclitaxel, 200 mg/m^2 (3-hour infusion), carboplatin, AUC 7 dosing, and G-CSF support repeated every 4 weeks.

**Combined Modality Therapy for Locally Advanced Disease**

Although local control and survival rates are excellent for T1 to T2, N0 to N1 undifferentiated nasopharyngeal carcinoma treated with RT alone, the 5-year survival rate of patients with more advanced disease is unsatisfactory, ranging from 10% to 40%. Because of the high rate of distant metastases, integrating chemotherapy into the primary management is logical. A number of nonrandomized trials evaluating induction, adjuvant, or concomitant chemotherapy and radiotherapy have been performed. Selected trials are shown in Table 30.2-19. These studies and others from older literature may be found in several excellent reviews.

**Induction Chemotherapy**

Reports of two to three cycles of cisplatin-based induction chemotherapy followed by radiotherapy in patients with locally advanced nasopharyngeal carcinoma suggested survival improvement compared with historic controls. Complete response rates of 82% to 98% and complete responses in up to 66% of patients were observed. Geara et al. reported the results of a single institution study of 61 patients treated with the standard cisplatin and 120-hour infusion of 5-FU for three courses followed by definitive radiotherapy. The 5-year cumulative incidence of distant metastases was 19% for the chemotherapy patients compared with 34% for the matched historic controls receiving radiotherapy alone. This effect on distant metastases was most notable for patients with N2 to N3 disease. Five-year disease-free and overall survival were also improved (84% vs. 42% and 69% vs. 48%, respectively). However, locoregional control rates were not different.

A retrospective comparison was reported by Teo and associates from Hong Kong that also suggested that benefit from chemotherapy was limited to those with advanced disease. Between 1984 and 1989, 209 patients with bulky or low cervical or suprACLAVICULAR nodes (less than or equal to 4 cm) were treated with two courses of cisplatin, 100 mg/m^2, and 3 days of infusional 5-FU followed by radiotherapy. In contrast to the findings of Geara et al., a multivariate analysis, after 5.5 years of follow-up, showed significantly fewer local failures in the chemotherapy group for node-positive T3 and stage IV patients when compared with historic controls, but no difference in survival, relapse-free survival, or distant metastases. There was no apparent benefit for stage II or T1 and T2 disease. These divergent results with induction cisplatin and 5-FU may be due to the difference in the number of treatment courses and intensity of the regimens or simply the nature of retrospective comparisons. These findings emphasized the need for randomized trials.

Three prospective randomized trials of induction chemotherapy have been reported and the results are shown in Table 30.2-20. The International Nasopharyngeal Cancer Study Group compared three cycles of bleomycin, epirubicin, and cisplatin (BEC) chemotherapy followed by radiotherapy with radiotherapy alone in 339 patients with N2 and N3 staged nasopharyngeal carcinoma (WHO types 2 and 3). This BEC regimen consisted of bleomycin, 15 mg/m^2 intravenous bolus day 1 followed by a 4-day continuous infusion of 12 mg/m^2/day; epirubicin, 70 mg/m^2 day 1; and cisplatin, 100 mg/m^2 day 1 repeated every 3 weeks for three courses. Conventional fractionation radiotherapy was used to a total dose of 65 to 70 Gy to the primary. The overall response rate to chemotherapy was 91%, with 47% complete response. The updated 6-year results showed significant improvement in disease-free survival for chemotherapy patients (41% vs. 30%, P < 0.02) for the control group. BEC induction chemotherapy was associated with substantial toxicity including 8% treatment-related deaths. Fewer distant and local recurrences occurred in the chemotherapy arm, but the magnitude of the effect coupled with severe toxicity was insufficient to produce a statistically significant improvement in overall survival.
The second randomized trial was reported by Chan and associates from the Prince of Wales Hospital. From 1988 to 1991, 82 patients with WHO type 3 carcinoma, Ho's N3, or any nodal disease greater than or equal to 4 cm were randomized to receive RT alone or two cycles of cisplatin, 100 mg/m² day 1, and 3 days of infusional 5-FU, 1000 mg/m², followed by RT. Conventional fractionation radiotherapy was given, 66 Gy to the primary with or without brachytherapy. The response rate to chemotherapy was 61% (95% complete response) and 100% after radiation compared with 95% (19% after radiotherapy alone. An updated analysis after a median follow-up of 60 months showed no difference in survival, disease-free survival, or pattern of failure. Only 55% of patients completed the adjuvant chemotherapy phase of treatment. The less intensive nature of this regimen may account for the lower complete response rate and the absence of any difference in survival outcomes.

The third randomized comparison of induction chemotherapy was reported by the Asia-Pacific Clinical Oncology Association, which included centers from Hong Kong, Thailand, Malaysia, and Indonesia. This study enrolled 334 patients (286 evaluable) with stage III and IV disease or any nodal involvement greater than or equal to 3 cm. All patients had WHO types 2 or 3 histology. The investigational treatment consisted of cisplatin, 60 mg/m², and etoposide, 110 mg/m² day 1, repeated every 3 weeks. Chemotherapy was assessed after two cycles and patients demonstrating at least a partial response to the first cycle of chemotherapy received a third cycle before radiotherapy. The total dose of radiotherapy was 70 Gy to the primary tumor; however, the treatment technique was not standardized but left to each participating center. The response rate to chemotherapy was 84%, with 16% complete. There was a trend for improved relapse-free survival for the chemotherapy-treated patients (59% vs. 47%, P = 0.06) at 3 years, but no difference in overall survival, and local or distant failure rates. In a subset analysis of patients with nodal disease greater than or equal to 6 cm, significantly improved survival and relapse-free survival was apparent for the chemotherapy group. This trial has been criticized for the lack of standardized radiotherapy technique, nonuniform use of CT for staging and response assessment, and the high number of ineligible patients.

In summary, the only induction chemotherapy trial with a positive result was the International Nasopharyngeal Cancer Study Group (INSGC) trial of three cycles of BEC followed by radiotherapy in which disease-free survival but not overall survival was improved. Although a high response rate was achieved with BEC, it cannot be recommended because of the associated toxicity and failure to sufficiently improve overall survival. Induction chemotherapy, therefore, remains investigational.

Concurrent Chemotherapy and Radiotherapy

The RTOG conducted a phase II trial of concurrent radiotherapy and cisplatin, 100 mg/m² day 1, 22, and 43, in patients with unresectable squamous cell carcinoma from multiple sites. A subset of 27 patients with nasopharyngeal carcinoma had an 89% complete response rate after completing concurrent treatment and a 5-year survival rate of 55%, which was superior to historic controls.

This concept was then tested by the Head and Neck Intergroup. Concomitant chemoradiotherapy and adjuvant chemotherapy (cisplatin, 100 mg/m² every 3 weeks for three doses during radiotherapy followed by three cycles of adjuvant cisplatin, 80 mg/m², and 5-FU, 1000 mg/m² × 4) were compared with radiotherapy alone. Conventional radiotherapy total dose 70 Gy, was administered in both arms. This trial was closed in November 1995 when an interim analysis of 138 randomized patients showed a highly significant difference in progression-free survival (52% vs. 13 months) and 2-year survival (80% vs. 55%) favoring the chemotherapy-treated patients. Sixty-three percent of patients received all three doses of cisplatin during radiotherapy and 55% completed adjuvant chemotherapy. When all 185 patients enrolled were included in the analysis, the survival results remained significant: 3-year overall survival was 76% versus 46% (P < 0.001), and progression-free survival was 66% versus 26% (P < 0.01). The population of patients in this study differed from other trials in that approximately one-half had WHO type 1 squamous cell carcinoma, a reflection of the U.S. population. WHO type 1 nasopharyngeal carcinoma is associated with lower sensitivity to chemoradiotherapy as compared with types 2 and 3 found in endemic areas. Because of the small sample size, a subgroup analysis of these two populations was not feasible. For similar reasons, it is impossible to dissect the contribution of adjuvant chemotherapy to these positive results.

A second randomized trial of concurrent cisplatin and radiotherapy was completed by Chan and colleagues at the Prince of Wales Hospital in Hong Kong. A total of 321 patients with advanced nodal disease were enrolled between 1994 and 1999 and randomized to receive conventional fractionation radiotherapy, 62.5 Gy, plus paraplatin boost when indicated, or the same radiotherapy plus concurrent cisplatin, 40 mg/m²/week for up to eight doses. The preliminary results indicate a significant difference in 2-year disease-free survival (62% vs. 78%, P = 0.01). Further follow-up will be needed to ascertain the effect on overall survival.

Adjuvant Chemotherapy

Adjuvant chemotherapy after radiotherapy is another strategy that is logical to pursue to improve survival given the propensity of this disease for distant spread. Several small institutional phase II adjuvant chemotherapy trials from the 1980s are listed in Table 30.2-19. Survival comparisons with historic controls indicated significant improvement in disease-free survival, supporting the need for a prospective randomized trial.

One multicenter randomized trial was reported by Rossi et al. for the Italian National Research Council. A total of 229 patients were treated with radiotherapy or chemotherapy and six cycles of adjuvant vincristine, doxorubicin (Adriamycin), and cyclophosphamide. Seventy-four percent completed the adjuvant chemotherapy. No differences in relapse-free survival, overall survival, or pattern of failure were observed. The results of this single trial of adjuvant chemotherapy are inconclusive regarding the potential benefit of this strategy to reduce the incidence of distant metastases. The vincristine, Adriamycin, and cyclophosphamide regimen may not be considered ineffective for this disease. Adjuvant chemotherapy for nasopharyngeal carcinoma requires further formal study using more efficacious regimens.

In summary, three randomized trials evaluating cisplatin-based induction chemotherapy have been performed. Only the INSGC trial used an active regimen optimally (three cycles of BEC) and observed significant improvement in disease-free survival. None of the induction trials, however, could demonstrate a survival advantage. The role of adjuvant chemotherapy is unclear as only one randomized trial was designed to specifically address this question, but an ineffective chemotherapy regimen was tested. In contrast, the U.S. Head and Neck Intergroup trial of concurrent cisplatin and radiotherapy was highly positive, and the early, preliminary results of the Prince of Wales Hospital, Hong Kong, trial using concurrent cisplatin on a weekly schedule are supportive. These results now suggest that radiotherapy alone is insufficient treatment for patients with T3 to T4 or node-positive nasopharyngeal cancer. Chemoradiotherapy followed by adjuvant chemotherapy as used in this intergroup trial should be considered the standard of care for this disease.

Results of Treatment

External-beam RT alone has shown to provide excellent local control for T1 and T2 lesions of the nasopharynx. Wang reported better results when intracavitary RT is added to external-beam treatment alone. However, results with external-beam plus intracavitary RT are equivalent to the results of external-beam RT alone in other large centers. Well-documented external-beam RT should provide local control in at least 90% of patients with T1 lesions, and between 85% and 90% of patients with T2 lesions. Doses in the 6500 and 7000 cGy range are used.

For T3 and T4 disease, local control rates have been significantly lower than the earlier stages, ranging from 62% to 73% for T3 lesions and 44% to 71% for T4 lesions. There is a suggestion of a dose response curve for RT. Vikram et al. reported a 90% local control rate for T4 patients receiving more than 7600 cGy, although few patients have been followed beyond 4 years. With the use of three-dimensional treatment planning and delivery, dose escalation to 7500 cGy and
beyond may be feasible. Investigators at Memorial Sloan-Kettering Cancer Center have had ongoing experience with both three-dimensional conformal radiation alone and in conjunction with concomitant chemotherapy and concomitant boost radiotherapy. Comparison of the outcomes for patients treated with once-daily RT versus concomitant boost RT, both with concurrent chemotherapy, showed a significant advantage to the concomitant boost technique. The implication of these data is that dose escalation alone is not adequate. However, the combination of three-dimensional treatment planning, concomitant boost fractionation, and concurrent chemotherapy are important in improving the outcome.

Results from M. D. Anderson Cancer Center show control of neck disease in all 35 N0 patients, 27 of 30 (90%) for N1, 24 of 26 (92%) for N2a, and 28 of 33 (85%) for N2b. However, patients with N3a metastases in the neck did worse, with only 10 of 16 (63%) being controlled. Today, most patients with N3 neck disease receive chemotherapy along with irradiation. Neck dissection is reserved for salvage for residual disease that persists after radiation or chemoradiation.

ORAL CAVITY

EPIDEMIOLOGY

Oral cavity cancer represents a multiplicity of diseases. Epidemiology as it relates to each of these disease processes likewise differs. However, given that squamous cell carcinoma represents the preponderance of cancers that occur in this region, greater attention is focused on its etiologic determinants.

It is estimated that 30,000 new cases of oral cavity cancer occur annually. The relationship between tobacco exposure and disease development has been clearly demonstrated. A clear dose-response relationship has been identified with a greater risk being directly proportional to intensity and duration of exposure. Alcohol has been identified as a coagent, most probably through a topical effect. The mucosal areas that are exposed to prolonged contact with alcohol are at greatest risk of cancer development. Readers are referred to reviews on mechanisms of tobacco-induced carcinogenesis for in-depth understanding. Likewise, reviews regarding the role of alcohol in cancer development are available.

Cigarette smoking cannot be considered the sole etiologic agent for oral cavity cancer. This fact is made evident by the observation that over 50 million individuals in the United States consume cigarettes. The percentage of the total population that uses tobacco in its various forms is even greater. As mentioned, however, only 30,000 individuals develop oral cavity cancer annually. Other factors must therefore be considered. Arguably it is genetic susceptibility that may be the most significant. Genetic factors associated with increased risk include mutagen sensitivity, which is potentially reflective of an underlying DNA repair deficiency. Syndromes that are characterized by mutagen sensitivity including xeroderma pigmentosum, Fanconi’s anemia, and ataxia-telangiectasia have all been associated with oral cavity cancers. Other relevant genetic markers may include inducibility of the cytochrome P-450 enzyme system.

Additional risk factors for oral cavity cancer include diet. Patients with vitamin A deficiency have been considered at high risk of malignant transformation of oral mucosa. High dietary consumption of fruits and vegetables have been found to provide a protective effect. Chronic irritants have been considered an etiologic factor, including mouthwash, poor dental hygiene, and syphilis. Reports have incriminated marijuana smoking as a contributing factor to oral cavity cancer.

Studies have focused on the viral etiology of cancers within the upper aerodigestive tract. Herpes simplex virus type 1 has long been considered an etiologic agent. The inability to identify herpes simplex virus type 1–related proteins within oral cavity cancers has, however, raised questions as to the significance of this virus. Investigations have identified human papilloma virus within head and neck cancers, specifically types 2, 11, and 16. Papilloma transcriptional factors, when inserted within human DNA, can alter normal gene replicative control mechanisms.

ANATOMY

The anatomy of the oral cavity is covered for each specific site.

STAGING

T staging for oral cavity cancer applies to all subsites within the oral cavity unless otherwise stated. For the oral cavity the definition of T staging is presented in Table 30.2-21. The regional lymph node (N) and distant metastases (M) staging are identical to other sites within the upper aerodigestive tract (see Staging and Screening, earlier in this chapter).

<table>
<thead>
<tr>
<th>T</th>
<th>Primary cancer site</th>
<th>T staging for oral cavity cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tis</td>
<td>No evidence of primary tumor</td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>Carcinoma in situ</td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>Tumor less than 2 cm or locally permeation</td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>Tumor more than 2 cm but not more than 4 cm or gross disease</td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>Tumor more than 4 cm or gross disease</td>
<td></td>
</tr>
</tbody>
</table>

N staging for oral cavity cancer:

<table>
<thead>
<tr>
<th>N</th>
<th>Lymph nodes</th>
<th>N staging for oral cavity cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0</td>
<td>No evidence of nodal disease</td>
<td></td>
</tr>
<tr>
<td>N1</td>
<td>Single involved node</td>
<td></td>
</tr>
<tr>
<td>N2</td>
<td>Multiple involved nodes</td>
<td></td>
</tr>
<tr>
<td>N3</td>
<td>Positive mediastinal nodes</td>
<td></td>
</tr>
</tbody>
</table>

M staging for oral cavity cancer:

<table>
<thead>
<tr>
<th>M</th>
<th>Distant metastases</th>
<th>M staging for oral cavity cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>No evidence of distant metastasis</td>
<td></td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
<td></td>
</tr>
</tbody>
</table>

TABLE 30.2-21. Staging for Oral Cavity Cancer

PATHOLOGY

The most common cancer within the oral cavity is squamous cell carcinoma. Additionally, cancers can arise from minor salivary glands; these latter cancers include adenoid cystic carcinoma, mucoepidermoid carcinoma, and adenocarcinoma. Rare soft tissue neoplasms include mucosal melanoma, plasmacytoma, and soft tissue sarcomas. Also found within the oral cavity are cancers arising from bone including osteosarcomas.

There also exist neoplastic lesions that are not truly malignant disorders of bone growth such as ameloblastoma. These lesions, however, have a propensity for local expansion and destruction. The principles of sound oncologic surgery and radiation thus apply to these processes.

NATURAL HISTORY

Earliest changes associated with squamous cell carcinoma are associated with erythema and slight mucosal surface irregularities. Many times a punctate lesion also is identified. As disease progresses, several growth patterns emerge that can be typically characterized as exophytic or infiltrative. The latter is more characteristically associated with destruction of surrounding anatomic structures. The exophytic lesions have a less aggressive growth pattern. It should be realized that both patterns are capable of producing metastasis and disease progression. Therapy should be planned accordingly.

Characteristics of the disease are reflected in certain histopathologic criteria. When considering tumor differentiation it has been reported that poorly differentiated disease has a greater propensity for metastasis than well-differentiated disease. This has, however, not been universally accepted. Jacobsson’s criteria, as outlined in Table 30.2-1, likewise reflects the natural history of the disease. More specific information regarding natural history is covered in each anatomic subsite.
EPIDEMIOLOGY

Carcinoma of the lip is second only to skin cancer as a site of neoplasia within the head and neck region. It is noted to occur in approximately 3600 cases per year (i.e., 1.8 persons per 100,000 population annually). The majority of these lesions occur on the lower lip and 95% occur in male subjects. A principal etiologic factor, similar to other upper aerodigestive cancer, has been the use of tobacco, including both pipes and cigars. Sun exposure has also been incriminated and may represent the most significant factor. The latter fact is of potential relevance given the increased incidence of other skin cancers as well as lip cancer. Patients genetically susceptible to skin cancers following sun exposure (i.e., patients with xeroderma pigmentosum) are likewise susceptible to lip cancer. Such an observation emphasizes ultraviolet radiation as an etiologic agent. Disease has likewise been noted in renal and homograft recipients, implicating immune suppression as a determinant.

ANATOMY

The lip is composed of the orbicularis oris muscle and is delineated by the junction of the vermilion border with the skin. Blood supply and sensory nerve supply are by means of the labial artery (a branch of the facial artery) and by cranial nerve V, respectively. The primary lymph node drainage is to levels I and II.

PATHOLOGY

The principal cancer involving the lip is squamous cell carcinoma. Another common lesion is basal cell carcinoma. Rarely, minor salivary gland cancers can occur.

NATURAL HISTORY

Patients most frequently present with either an exophytic or ulcerative lesion of the lower lip. Occasionally, these lesions are associated with bleeding and pain. The latter symptom, however, is a late feature of the disease. These lesions are typically slow-growing lesions. With progression there may be associated numbness of the skin of the chin secondary to involvement of the mental nerve, a branch of the third division of cranial nerve V. Furthermore, progression of disease along the mental nerve may extend into the mental foramen of the mandible. Such involvement leads to enlargement of the foramen with bone destruction and widening of the inferior alveolar canal. A Panorex examination of the mandible is recommended as part of each diagnostic evaluation.

Lymphatic spread occurs relatively infrequently in lip cancer; approximately 5% to 10% of patients develop evidence of nodal involvement. Lymph node spread is typically to submandibular nodes or submental nodes. Lesions in the midline may spread bilaterally. The incidence of metastases has been related to histologic grading, with high-grade lesions being at greatest risk. The upper lip tends to metastasize earlier than the lower lip. Upper lesions metastasize to parotid nodes (i.e., preauricular nodes, in addition to submandibular nodes).

The prognosis from lip cancer is principally dependent on the size of the primary tumor. T1N0 squamous cancers of the lower lip have a 5-year survival of 90%. T2 survival is 84%. With evidence of lymph node metastases, survival decreases to 50%. Perineural invasion represents a bad prognostic sign. Likewise, prognosis appears worse in younger adults. Tumors have a greater tendency to metastatic spread in these latter patients.

TREATMENT

Early Disease

Surgery or radiotherapy are the mainstays of therapy. Dysplasias and carcinoma in situ can be handled by lip shave (i.e., vermilionectomy with advancement of a mucosal flap). Those lesions that involve less than 30% of the lip can be resected with a V excision and primary closure of resulting defects. For larger lesions transposition flaps are required for reconstruction.

Undoubtedly the challenge in the surgical management of lip cancer resides in the best means of reconstruction. Oral competence remains the primary goal. Those lesions that require resection of 30% to 50% of the lip, can be best handled with a transposition flap drawn from the uninvolved opposing lip. This reconstruction technique is termed Abbe-Estlander. When the near total lip is involved (i.e., 50% to 75%), the Karapandzic advancement flap can be used. This has the benefit of providing a competent oral sphincter with an associated neurovascular integrity.

The problem with the Karapandzic reconstruction is the reconstructed lip is tight and significantly foreshortened. Other methods have been devised. These vary from simple nasolabial flaps based inferiorly or superiorly to more formal fan-type flaps such as the Gillies flap and Webster cheek advancement flap.

Most T1 to T3 squamous cell carcinomas of the lip can be managed by either RT or surgery. The choice of radiation or surgery may depend on the size and location of disease. If the lesion is quite small and can be easily excised without functional sequelae, surgery would be the chosen treatment. Lesions involving commissures can be irradiated, without the functional sequelae of surgery. However, involvement of the commissure under such circumstances is rare. Brachytherapy alone can be used for early T1 and small T2 lesions. Temporary implantation with localized electron-beam irradiation can be used. Implant doses of 60 Gy over 6 days, or external-beam doses of 50 Gy in seven fractions to 60 Gy can be used. Figure 30.2-10 shows a clinical example of the brachytherapy procedure.

\[ \text{Figure 30.2-10. A: A patient with a T1N0 squamous cancer of the lower lip. The lesion measured 2 cm in greatest diameter and involved the commissure. B: An } \]

Given the infrequency in which early cancers spread to regional lymph nodes, elective treatment of the neck is not necessarily required.

Advanced Disease

Stage III and IV lip disease are optimally managed with combined surgery and postoperative RT. Selected T3 lesions can be managed with either radiotherapy alone or surgery alone. Reconstructive options are as described in the previous section. Doses in the 6000- to 6300-cGy range, delivered at 180 to 200 cGy per fraction over 6 to 7 weeks, is preferred. If the patient has lymph node metastases in the neck, a neck dissection would be done along with the resection of the primary site. The postoperative RT would then be delivered to both the neck and the primary site. Even if the patient were N0, one should still use elective RT or elective node dissection as part of the management, given the increased risk of microscopic lymph node metastases in these patients.
For patients with T1 to T3 disease who have had an operation, sometimes the radiation oncologist is faced with a positive margin of resection. This can either be managed with brachytherapy alone, or localized superficial external-beam irradiation, with similar doses and techniques as when RT alone is used.

**Results of Treatment**

The RT results are similar to the reported results of surgical management. Jorgensen et al. have reported a series of 869 lip cancers. In 766 patients, treatment was performed entirely with brachytherapy. The remaining cases had external-beam radiation, mainly with orthovoltage beams. The majority of patients had either T1 or T2 lesions, with only 75 having T3 lesions. Local control was in the 90% range. External-beam radiation can also be used. Petrovic et al. reported on 250 patients, most receiving 5100 cGy in 3 weeks with daily fractions of 330 cGy. There were a total of 896 patients in the study, most of whom were treated with orthovoltage beams. Local control was obtained in 94% of T1 and T2 lesions and in 90% of T3 lesions. For T4 disease, 47% of the patients obtained local control with radiation alone, pointing to the need for combined modality treatment for this subset. Sykes et al. reported 26 patients with T1 to T2 squamous cell cancers of the lip treated with electron-beam radiation. With median follow-up of 31 months (range, 1.5 to 60.0 months), there was 100% local control.

**ALVEOLAR RIDGE AND RETROMOLAR TRIGONE**

**EPIDEMIOLOGY**

Cancers of the alveolar ridge and retromolar trigone account for approximately 10% of all oral cancers. Male subjects are more frequently affected at a ratio of 4:1. An increased frequency in rural women in the southeastern United States has been stated to occur.

**ANATOMY**

The alveolar ridge consists of an upper and lower portion. The lower alveolar ridge has as its structural basis the alveolar process of the mandible, extending from the alveolar crest to the pterygoid process. The upper alveolar ridge, also known as the maxilla, is an integral part of the craniofacial skeleton. The alveolar ridge is bounded superiority by the hard palate, inferiorty by the alveolar ridge, medially by the anterior tonsillar pillar, and laterally by the gingival-buccal sulcus.

Lymphatic drainage of the alveolar ridge and retromolar trigone is principally to levels I and II.

**PATHOLOGY**

Squamous cell carcinoma represents the near total majority of lesions in this area. Minor salivary gland lesions (i.e., mucoepidermoid carcinomas and adenoid cystic carcinomas) can occur.

**NATURAL HISTORY**

Squamous cell carcinoma of the alveolar ridge grows in patterns similar to other squamous cell carcinomas of the oral cavity (i.e., either as exophytic lesions or as infiltrative disease). The latter is commonly associated with bony destruction, which occurs in up to 58% of cases. The presenting symptom is primarily pain, which is exacerbated by chewing. Other symptoms include intermittent bleeding as well as loose teeth. In those patients who are edentulous, the principal complaint relates to ill-fitting dentures. The lower alveolus is affected most often in the molar and premolar region. Delay in diagnosis is characteristic because of confusion with inflammatory conditions such as gingivitis or periodontitis.

These lesions have a higher probability of regional lymph node metastases than other cancers within the oral cavity, with the exception of tongue cancer. Overall, the probability of lymph node metastases increases directly with the size of the primary and averages 30%. It may increase up to 70% for T4 cancers. It is of note, however, that lymph node metastases tend to occur more frequently from mandibular alveolar ridge cancers than maxillary alveolar ridge disease. Metastatic disease is primarily to lymph nodes in levels I and II. Byers et al. noted that less than 5% of patients develop disease in the posterior cervical triangle.

The prognosis from alveolar ridge carcinoma is reflected by the extent of primary and regional lymph node metastatic disease. Sykes et al. reported approximately 90% local control for T1, T2, and T3 lesions associated with 80% and 60% survival, respectively. Prognosis with T4 lesions is poor, approximating 20%.

**TREATMENT**

**Early Disease**

Surgical management of carcinomas of the alveolar ridge reflects the management principles of cancers of other sites within the oral cavity. The fundamental feature remains the achievement of tumor-free surgical margins with the preservation of critical anatomic structures.

Early T1 or T2 lesions of the alveolar ridge can be managed successfully by surgery alone. With minimal cortical involvement or with involvement by cancer confined to the mucoperiosteum, resection may include a marginal (coronal) mandibulectomy that preserves structural integrity of the mandible. The ability to preserve segments of the mandible is in part dependent on dental status. Not infrequently, edentulous patients present with thin alveolar mandibles that preclude all but a segmental resection.

The tendency for bone invasion by alveolar ridge carcinomas through thin mucoperiosteum or through tooth sockets makes primary radiation less feasible. In general, lesions of the gingiva are best managed by surgery. Studies by McGregor and MacDonald have reinforced the notion that a conservative approach to the management of the mandible can only be justified by a thorough understanding of patterns of spread of squamous cell carcinoma into bone.

The need for neck dissection for alveolar ridge carcinomas is enhanced secondary to its tendency to regional nodal spread. The considerations for elective neck dissection as well as the type of neck dissection have been discussed previously in this chapter (see Surgical Management of the Cervical Lymph Nodes, earlier in this chapter). The infrequency of tumor spread to levels IV and V has led to acceptance of selective neck dissection of levels I through III in instances of a clinically N0 neck.

**Advanced Disease**

Advanced staged tumors generally require multimodality therapy including surgery and radiation. Segmental mandibulectomy is required. Advances in the management of such disease has related to improved reconstructive techniques, principally the use of osteomyocutaneous free-tissue transfer.

**Treatment Results**

In those studies that report primary surgery results, the actuarial survival for stage I and II was 77% at 5 years, compared with approximately 60% for stage III, and 24% for stage IV.
There are relatively few patients reported in the literature with gingival carcinoma who have been managed with primary RT. Fuchihata et al. reported a group of patients treated with external-beam irradiation and chemotherapy (bleomycin or peplomycin). Major responders were treated definitively using this approach, whereas others underwent surgery. Responders with T1 and T2 lesions who were not operated on had local control at 3 years of 95%, while those who had surgery had local control of 86%. For T3 and T4 lesions, the nonsurgical group had local control of 45%, while the surgery group had local control of 75%. Thus, there may be a role for nonsurgical management in selected early lesions, but more advanced lesions definitely benefit from surgery followed by postoperative radiation. Early retromolar trigone tumors can be treated successfully by primary radiation, especially when they are superficial. Figure 30.2-11 shows a clinical example.

FIGURE 30.2-11. A: A patient with a T2N0 squamous cancer of the right retromolar trigone. The patient was treated with definitive external-beam radiation therapy to the primary and ipsilateral neck. B: The treatment plan involved a wedged photon pair. The boost field is shown. The contralateral parotid area received less than 10% of the dose, thereby avoiding xerostomia. The primary site received 7020 cGy, at 180 cGy per fraction. The right low neck received 5000 cGy over 5 weeks with an ipsilateral low neck field (not shown). C: The patient had no evidence of disease at 6.5 years.

FLOOR OF MOUTH

EPIDEMIOLOGY

The annual incidence of cancers of the floor of mouth is 0.6 cases per 100,000 in the United States. It occurs in male subjects approximately three times as frequently as female subjects. Reports, however, have demonstrated an increasing incidence of the disease among women. The median age of individuals developing squamous cell carcinoma is approximately 60 years.

ANATOMY

The floor of mouth is delineated by the free margin of the mucosa as it extends from the junction of the mobile tongue to the alveolar process. This margin extends from one anterior tonsillar pillar to the other. Within the floor of mouth anteriorly are the openings of bilaterally located submandibular salivary glands, Wharton's ducts. These ductal openings are significant because anterior lesions of the floor of mouth can frequently obstruct associated salivary flow, leading to tenderness and enlargement of the respective submandibular gland. Also within the floor of mouth are minor salivary glands and the sublingual glands. Distinct from mucosa of the tongue, mucosa of the floor of the mouth is nonkeratinizing stratified squamous epithelium under nonpathologic situations. Musculature making up the floor of mouth include the genioglossus, geniohyoid, and mylohyoid muscles. Blood supply and nerve supply are principally from the paired lingual arteries and lingual nerves, respectively.

PATHOLOGY

Cancers of the floor of mouth account for approximately 10% to 15% of all oral cavity cancers. Squamous cell carcinoma constitutes the majority of lesions within the floor of mouth, with the majority of these lesions being moderate to well differentiated. There are several variants of squamous cell carcinoma of the floor of mouth. This includes verrucous and sarcomatoid squamous cell carcinoma. Cancers derived from salivary gland tissue also are encountered including mucoepidermoid carcinomas, adenocarcinomas, and adenoid cystic carcinomas.

NATURAL HISTORY

Squamous cell carcinomas of the floor of mouth typically present as infiltrative lesions that are characteristically painful. These lesions may extend anteriorly to invade bone, deep to infiltrate muscles of the floor of mouth, or posteriorly to invade tongue. On occasion, an enlarged lymph node in the neck is the presenting symptom. Floor of the mouth cancers can grow to massive size without metastasizing to cervical lymph nodes. However, approximately 12% of T1 lesions are associated with occult metastatic disease, depending on the thickness of lesion. Metastatic rates to cervical lymph nodes occur in 30%, 47%, and 53% of T2, T3, and T4 cancer, respectively. Lymph nodes in the submandibular and submental triangles represent the first echelon of metastatic sites. Distant metastases is infrequently observed in patients who present with previously untreated disease. Prognosis is influenced principally by disease stage and presence or absence of histopathologically confirmed regional lymph node metastases. The overall 5-year survival for stage I disease approximates 85% to 90%. For stage II, III, and IV disease, 80%, 66%, and 32% of patients are alive at 5 years, respectively. Other factors considered to reflect a worse prognosis include evidence of perineural invasion, depth of primary tumor invasion, and poor tumor differentiation.

TREATMENT

Early Disease

Treatment of floor of the mouth cancers has been principally surgical resection, but may either be surgery or radiation alone. As is true for cancers of the alveolar ridge, superficial involvement of the mandible can be handled by marginal mandibulectomy (Fig. 30.2-12).

When radiation is used for early disease, it has been shown that results are improved when at least a portion of the treatment is delivered by an interstitial implant.\textsuperscript{544} Interstitial implant alone can also be used.\textsuperscript{542} Prostheses can be designed to protect the mandible for brachytherapy (Fig. 30.2-13). Lesions that abut or are tethered to the periosteum of the mandible or lesions that extend onto the gingiva are not good candidates for primary radiotherapy. Implants against the mandible can lead to osteonecrosis.

\textbf{FIGURE 30.2-13. Prosthesis with lead lining that fits onto the lower teeth and serves as mandibular protection for brachytherapy. (Compliments of Dr. Joshua Verona, Dental Service, Beth Israel Medical Center.)}

The treatment of the neck for early cancer of the floor of the mouth is controversial. Most advocate elective neck treatment for clinically N0 disease. The value of this approach as compared with observation with neck dissection and RT being performed for clinically developing disease remains unproven. Some have advocated performing neck dissection depending on the thickness of the primary lesion (i.e., greater than 4-mm thickness).

\textbf{Advanced Disease}

For advanced lesions, combined therapy of surgery and radiation is the treatment of choice. Surgical resection generally entails partial glossectomy and segmental mandibulectomy. Identification of the inferior alveolar nerve and frozen section histopathologic assessment should be performed during the operation. This is to ensure that disease has not extended beyond surgical margins by perineural spread. Resection for most advanced lesions requires removal of the entire thickness of the floor of mouth.

New reconstructive techniques have greatly facilitated rehabilitation following surgical excision of advanced tumors. Techniques include myocutaneous flaps as well as osteomyocutaneous free flaps with microvessel anastomoses.\textsuperscript{540}

Elective, therapeutic, or both kinds of neck dissections are considered necessary in each case. Bilateral neck dissections are indicated for those lesions that approach or cross the midline.

Postoperative radiation entails doses in the range of 6000 to 6300 cGy at the primary site. In instances of positive surgical margins, our policy is to treat the area of positive margins to 6300 cGy. Certain patients with positive margins may be treated with adjuvant brachytherapy instead of external-beam RT.\textsuperscript{542}

\textbf{Results of Treatment}

Local recurrences after surgical resection of T1 and T2 floor of the mouth cancers are noted in no less than 10% of the patient population.\textsuperscript{541,542} As tumors increase in size, the pattern for failure becomes predominately a regional problem. Nearly 40% of failures are solely within regional cervical lymph nodes.\textsuperscript{541}

Mazeron et al. have reported a large radiotherapy series.\textsuperscript{541} The majority of patients were treated to 65 Gy with \textsuperscript{192}Ir brachytherapy alone. Local control was 94% for T1 N0, and 74% for T2 N0 lesions and was dependent on size of the lesion as well as the presence or absence of gingival extension. For T2 lesions between 2 and 3 cm, local control was 58%. For lesions with gingival extension, local control was 50%. There is an interest in using high dose-rate brachytherapy for floor of the mouth lesions. Inoue et al. reported 2- and 5-year local control of 94% and 94% for a cohort of mainly T1 to T2 lesions treated with high dose-rate brachytherapy alone or combined with 30- to 40-Gy external-beam RT.\textsuperscript{540}

Wang et al. have reported excellent results with the use of intraoral cone electron boost and no brachytherapy.\textsuperscript{544} The daily dose of radiation via the cone is frequently greater than the conventional 180- to 200-cGy range. Local control was obtained in all 13 patients with T1 lesions, and in 19 of 20 (95%) with T2 lesions.\textsuperscript{542}

Fu et al. have published an extensive RT experience with floor of the mouth cancer.\textsuperscript{544} When implant was either the only treatment or a part of the treatment, local failure occurred in only 2% (1 of 39 patients) with T1 lesions, 7% (4 of 54 patients) with T2 lesions, and 14% (5 of 35 patients) with T3 lesions. The use of primary radiation may be associated with improved functional outcome as compared with surgery, but this requires more investigation.\textsuperscript{540,541,544}

There is a cohort of patients who undergo surgery and are referred for postoperative radiotherapy because the pathology reveals positive or close margins. In this setting, certain patients may be treated with brachytherapy alone, thereby limiting the high-dose region to the area at risk. This is not always technically or oncologically feasible. When it is, it can provide the patient with local control in excess of 80%\textsuperscript{542} and can avoid the sequelae of wide-field external-beam irradiation to the oral cavity.

\textbf{TONGUE}

\textbf{EPIDEMIOLOGY}

Tongue cancer is estimated to occur in 6200 individuals per year in the United States.\textsuperscript{54} Excluding lip, it exceeds all other sites in the oral cavity. The median age for individuals with tongue cancer is approximately 60 years. The male to female ratio is similar to other disease sites, approximately 5:1. It is of interest that an increase in tongue cancer has been reported among young adult men.\textsuperscript{539,547} Some have suggested marijuana use as a contributing factor in this latter population.\textsuperscript{547}

\textbf{ANATOMY}

The oral tongue represents the mobile portion of the tongue musculature that extends from the line demarcated by the circumvallate papilla posteriorly to the junction of the floor of mouth anteriorly. It is made up of the genioglossus, hyoglossus, styloglossus, and palatoglossus muscles. All of these muscles are innervated by the hypoglossal nerves. Taste and sensation within the tongue are provided by the lingual nerve, a branch of the third division of the cranial nerve V. Blood is supplied principally from the external carotid artery through the paired lingual arteries. Lymphatic drainage is principally to level II, III, and I in decreasing order.

\textbf{PATHOLOGY}
The primary cancer of the tongue is squamous cell carcinoma. Other cancers are frequent and include minor salivary gland cancers such as adenoid cystic carcinoma and adenocarcinoma. Myeloblastoma represents a rare tumor of the tongue.

**NATURAL HISTORY**

These cancers can grow in both an exophytic and an infiltrative fashion. The primary presenting symptom is pain, although many of these lesions can be painless. Difficulty in speech and deglutition is occasionally elicited. It tends to be more rapid in its onset than other cancers within the oral cavity. There may be a history of long-standing leukoplaikia before the development of symptoms, especially in younger female subjects.

As compared with other cancers within the oral cavity, tongue cancers have a greater propensity for lymph node metastases. This occurs in ranges from 15% to 75% depending on the extent of primary disease. Lymph nodes most frequently involved lie within level II (i.e., jugulodigastric nodes). Nodes within level I, III, and IV are involved in decreasing order. It is of note, however, that all nodes can be involved. The incidence of bilateral nodal metastases occurs in up to 25% of cases. Contralateral nodal metastases are present in 3% of cancers.

Prognosis is principally reflected in extent of nodal metastases, ranging from 75% in early-stage node-negative disease to 30% in those with advanced lesions. Other factors portending more aggressive disease include perineural and vascular invasion and infiltrative versus pushing borders. Depth of invasion has likewise been considered significant. Whether or not tongue cancer in young adults represents a worse disease has not been demonstrated.

**TREATMENT**

**Early Disease**

Early stage I and II lesions can usually be removed introrally. Excision usually entails an hemiglossectomy. Special attention to surgical margins should be exercised as disease may spread along muscle bundles that extend beyond clinical assessment. The 5-year local control was 93% for T1, 65% for T2, and 49% for T3 lesions. For T2 lesions managed by postoperative RT, this can frequently be done with brachytherapy. This is especially true for the smaller lesions. The 5-year local control for T2 lesions managed by postoperative RT was 80% for T2, 65% for T3, and 49% for T4 lesions.

Most T1 lesions can be managed with brachytherapy alone. This generally consists of an Ir implant, although high dose-rate implants are also being used. Whether low dose-rate or high dose-rate is used, the catheters themselves are placed in the operating room under general anesthesia. The Ir is loaded 1 to 2 days postoperatively. Localization films are taken, and computerized dosimetry is performed. The usual dose rate is in the 40 to 60 cGy/h range, and the usual total dose is 6000 to 7000 cGy. The patient wears a tongue prosthesis during the dwell time of the implant to protect the hard and soft palate as much as possible. For high dose rate, 60 Gy fractions given twice a day over 6 days has yielded good results.

As the lesion increases in size when using radiation as primary therapy, it is preferred to combine external-beam irradiation with implant. First, the external beam can be used as elective neck irradiation simultaneous with irradiation to the tongue. The implant then serves as the boost to the tongue. Second, the external beam allows a wider margin of tongue to be treated than does the implant. In these situations, it is typical to treat the primary site and the neck to doses in the 5000- to 7000-cGy range, followed by a 2000- to 3000-cGy implant boost to the tongue.

For N0 patients, this treatment program manages both the primary site and the neck. For those patients with palpable neck nodes, a neck dissection can be performed at the same as anesthesia for the implant, thereby completing the treatment to the primary site and the neck. This can usually be done approximately 3 weeks after the completion of the external-beam irradiation.

**Advanced Disease**

The surgical management of more extensive lesions requires either a mandibulotomy or a lingual-releasing procedure to gain access to disease. The latter procedure entails removal of neck contents before primary cancer resection. The tongue is delivered into the neck by releasing musculature attachments posteriorly and mucosal attachments within the oral cavity. Large lesions with mandibular involvement require composite resection. The term composite resection refers to the removal of tissue involving multiple anatomically defined structures, one of which includes the mandible (Fig. 30.2-14). Typically, it refers to resection of a portion of tongue, floor of the mouth, and segment of mandible.

For patients who require postoperative RT to the primary site alone, this can frequently be done with brachytherapy. This is especially true for the smaller lesions. The decision of how to deliver this irradiation is integrated with the management of the neck. We prefer to use neck dissection as part of the management of all deeply infiltrative or advanced tongue lesions. For the N0 patients, this generally means a staging procedure or a functional neck dissection. For patients who have involved lymph nodes, this means either a radical neck dissection or one of its modifications. Yamazaki et al. have shown a clear relationship between tumor thickness and neck failure in a cohort of patients treated with brachytherapy alone: The incidence of neck metastases was 50%, 40%, and 30% for tumors greater than 11 mm, 6 to 10 mm, and less than or equal to 5 mm, respectively. T stage also correlated with tumor thickness.

Results of Therapy

Decroix and Ghosein from the Curie Institute in Paris have reported on over 600 patients treated with primary RT for T1, T2, or T3 squamous cell carcinoma of the oral tongue. Although the majority of patients had implants alone, a large cohort had combined external-beam irradiation plus implant. Almost all patients at this center received RT as their primary treatment. Primary control was obtained at 86% for T1, 80% for T2, and 68% for T3. These data compare quite favorably with the results obtained with partial glossectomy.

Pernet et al. have reported a series of 448 patients with brachytherapy alone with or without neck dissection (181 patients) or combined external beam plus brachytherapy (267 patients) for oral tongue cancer. The 5-year local control was 93% for T1, 65% for T2, and 49% for T3 lesions. For T2 lesions managed by...
brachytherapy alone, local control was 90% versus 50% for those managed by external beam plus implant. These data emphasize the importance of using brachytherapy as a major part of the radiation program, but patient selection factors clearly play a role as well. The 5-year overall survival for T1, T2, and T3 lesions (all N stages) was 69%, 41%, and 25%, respectively. Severe complications were uncommon. While 15% experienced grade 1 soft tissue injury, and 3% had grade 1 bone necrosis, only 1% and 2% had grade 3 soft tissue and bone complications, respectively. Spiro et al. have reviewed the Memorial Sloan-Kettering Cancer Center experience using partial glossectomy as primary management. As was true for the Curie Institute series, the Memorial Hospital series is also relatively unselected, with primary surgery being offered to the great majority of patients at that institution. Local control was obtained in 85% for T1, 77% for T2, and 50% for T3. These data serve to highlight the similarity in local control rates for surgery or irradiation for most early tongue lesions.

Although the traditional brachytherapy approach has involved low dose-rate implants, there has been an emergence of interest in high dose-rate brachytherapy for oral tongue. Either high dose-rate alone or in combination with moderate doses of external-beam irradiation have been used. Inoue et al. compared low dose-rate versus high dose-rate implants in a small randomized trial of T1 to T2 oral tongue lesions, finding no major differences. A program of 60 Gy in 10 fractions given twice a day over 6 days with high dose-rate yielded 100% local control at 2 years. All tumors had a thickness of 1 mm or less. Leung et al. reported similar local control using the same fractionation program. Mucositis related to these implants can last up to 20 weeks.

There are relatively few recent studies that report the results of therapy for surgery alone for advanced disease. RT is generally used in the postoperative setting. Failure is most often within regional lymph nodes and leads to a 5-year determinate survival of 35% for stage III and IV disease.

A program of 60 Gy in 10 fractions given twice a day over 6 days with high dose-rate yielded 100% local control at 2 years. All tumors had a thickness of 1 mm or less. Leung et al. reported similar local control using the same fractionation program. Mucositis related to these implants can last up to 20 weeks.

Surgical salvage of radiation failures in the oral tongue can be difficult. Yuen et al. reported 47 patients who underwent attempted salvage for either local recurrence, locoregional recurrence, or regional recurrence. Overall, 62% failed their salvage procedure. The 5-year actuarial survival was 39% for local recurrence alone, 27% for locoregional recurrence, and 68% for regional recurrence alone.

HARD PALATE

EPIDEMIOLOGY

Hard palate cancers account for approximately 5% of all oral cavity cancers. The incidence of the disease in the United States approximates 0.4 per 100,000 population. The male to female ratio is 8:1.

PATHOLOGY

Squamous cell carcinoma accounts for approximately 50% of hard palate tumors. The majority of these lesions are well differentiated. Other cancers occurring in this area include the minor salivary gland lesions such as adenoid cystic and adenocarcinomas, which may be as frequent as squamous cell carcinoma.

NATURAL HISTORY

Cancers of the hard palate grow in a multiplicity of patterns including deeply infiltrating, destructive lesions versus diffuse superficial lesions associated with microscopic invasion.

When considering metastatic squamous cell carcinoma of the hard palate, lymph node metastases is less frequently encountered than cancers of other sites within the oral cavity, ranging clinically from 6% to 29%. Likewise, distant metastasis is infrequent. Prognosis in patients with squamous cell carcinoma is 75%, 46%, 36%, and 11% for stage I through stage IV disease, respectively.

TREATMENT

Early Disease

Surgical management of early disease involves infrastructure maxillectomy (i.e., resection of the palatine process of the maxillary bone). Exposure for such resections is generally obtained through a Weber-Ferguson–type incision.

As stated earlier, carcinoma in situ and microinvasive disease can involve a significant portion of the hard palate with extension of disease onto the soft palate and retromolar trigone. Under such circumstances, primary radiation may be used.

Elective treatment of the neck is not generally required unless disease extends beyond the anatomic confines of the hard palate. Selective neck dissection under such circumstances is adequate. Such dissection includes removal of lymph nodes in levels I, II, and III.

Advanced Disease

Surgical resection of advanced disease may involve a near total palatpectomy. Generally, however, lesser operations are required. Advances in the surgical therapy of hard palate cancers involve the immediate use of prophylactic obturators that allow for early restoration of adequate speech and swallowing. The need for postoperative radiation is based on the closeness or involvement of tumor margins by tumor, perineural involvement, the presence of regional lymph node metastases, or all three conditions.

Results of Treatment

Generally, incorporating the treatment philosophy described previously, Evans and Shah report an overall survival of 75% for stage I, 46% for stage II, and 36% and 11% for stage III and IV, respectively. The majority of patients who die of disease do so in the face of advanced local recurrence.

BUCCAL MUCOSA

EPIDEMIOLOGY

Cancer of the buccal mucosa accounts for approximately 8% of oral cavity cancers in the United States. The disease may be seen much more frequently in other parts of the world such as India depending on tobacco consumption patterns. Indeed, in the southeastern United States, the incidence of buccal mucosal cancer is much higher in women; an observation attributed to the common use of snuff. The median age of individuals with buccal mucosal cancer may be slightly higher than noted in patients with cancers of other sites within the oral cavity.

ANATOMY

The buccal mucosa is composed of a mucous membrane that extends from the lips anteriorly to the retromolar trigone posteriorly. Inferiorly it extends from the lateral alveolar sulcus of the mandible to the lateral sulcus of the maxillary alveolar ridge. Its blood supply and nerve supply are from the facial artery and the third division of cranial nerve V. Lymphatics from the buccal mucosa drain primarily into level II and level I in decreasing order.
NATURAL HISTORY

Cancers of the buccal mucosa are more frequently exophytic than other cancers within the oral cavity. They are also relatively silent in their presentation and thus present rarely as T1 lesions. Pain is the initial presenting complaint and is subsequently followed by bleeding and difficulty chewing. With extension of the disease outside the confines of the buccal mucosa into the pterygoid musculature, patients may present with trismus. Disease not infrequently invades the mandible, maxillary alveolar ridge, or both.

Lymph node metastases are most frequently observed within levels I and II and are observed clinically in 10% of presenting patients.

Five-year survival ranges from 77% to 18% depending on the stage of disease. Urist et al. have shown that tumor thickness is a significant prognostic factor. Patients with tumors less than 6 mm in thickness have significantly better survival rates than those with tumors greater than 6 mm in thickness, regardless of tumor stage.

TREATMENT

Early Disease

Small lesions (T1 and early T2) can be managed with equal effectiveness by either surgery or RT. If the tumor can be excised easily through the open mouth, with minimal functional sequelae, then small lesions are probably best managed in that fashion. Larger T1 lesions and lesions that approach the commissure are best managed with RT. T2 lesions can be managed with RT if they are exophytic or relatively superficial. Deeper lesions are probably best managed by surgery.

In patients with small lesions and a clinically negative neck, the neck can be observed. Neck failure occurs in less than 10% of patients. However, for more advanced lesions, the neck is treated electively with the same therapeutic modality that is used for the primary lesion.

RT can be used with a variety of different techniques. Interstitial brachytherapy, ipsilateral electrons, intraoral cone, or external-beam photon irradiation can all be employed. The exact technique depends on the clinical situation and the expertise of the radiation oncologist.

Advanced Disease

More advanced disease requires surgery as the principal therapeutic modality, usually with postoperative radiation. The initial factor in such treatment relates to adequate operative exposure. This is generally facilitated by dividing the lip in the midline and resecting the cheek postilaterally in order to gain optimal exposure.

Postoperative radiotherapy is used for patients with close or positive margins, high-grade lesions, positive nodes, bone invasion, and thick (greater than 10 mm) lesions. Adequate locoregional treatment at initial diagnosis is essential, as locoregional failure is a major cause of death for patients with buccal mucosa cancer and few patients can be salvaged.

Care must be taken in assessing the need for resection of surrounding anatomic structures such as skin of face, upper alveolar ridge, and mandible. Invasion of tumor into buccal fat pad and into dermis of cheek skin occurs not infrequently. Such invasion generally requires full-thickness resections including oral mucosa and cheek skin. Such defects can be repaired with myocutaneous flaps. Free-tissue transfer is a relatively recent option for reconstruction.

Ipsilateral neck dissection is advocated in all instances of T3 or T4 primary disease, regardless of the nodal status.

Results of Treatment

Nair et al. have reported on 234 patients with buccal mucosa cancer treated with RT. Disease-free survival at 3 years was 85% for stage I, 63% for stage II, 41% for stage III, and 15% for stage IV disease. All 13 patients with T1 N0 disease were controlled with radiotherapy. Fifty percent of patients with T4 disease failed locally.

The presence of nodal metastases clearly affected the local regional failure rate.

Lapeyre et al. reported an experience using definitive brachytherapy for epidermoid cancer of the buccal mucosa. A variety of techniques were employed from 1973 to 1991. The loop technique provided the best results, with only 1 of 22 patients with T1 to T3 lesions having local recurrence. Bloom and Spiro reported the results for 90 patients with buccal mucosa cancer treated by surgery. The 5-year survival rate by stage was 77%, 65%, 27%, and 18% for stages I, II, III, and IV, respectively. Local failure was noted in 47% of patients. Regional failure was observed in 37%.

Dixit et al. performed a comparative study on 176 patients with buccal mucosa cancer, comparing surgery alone with surgery plus postoperative radiation. Postoperative radiation was found to improve local control for patients with positive nodes, close or positive margins, high-grade lesions, bone invasion, and thick tumors greater than 10 mm. Mishra et al. reported a randomized trial comparing surgery alone versus surgery plus postoperative radiotherapy. There was improved disease-free survival (68% vs. 38%, P < .005) in those who received radiation. This trial only included patients with stage III and IV disease.

REHABILITATION OF THE ORAL CANCER PATIENT

Over the last decade there has developed an increased effort to address the rehabilitation of the oral cancer patient, the major considerations reflected in speech and swallowing disorders. There is no question as to the effect of surgical resection of anatomic components of the oral cavity including the mandible, tongue, and other soft tissue components. The need to preserve function through appropriate reconstructive measures is becoming increasingly apparent. Likewise, rehabilitation efforts have been enhanced by improved quantitative assessments of functional outcomes, as well as through improving rehabilitation techniques. No medical center or treating physicians can truly be considered as providing state-of-the-art therapy unless they are prepared to systematically address these issues.

OROPHARYNX

EPIDEMIOLOGY

The pharynx is divided into three regions: the nasopharynx, oropharynx, and hypopharynx. Our discussion is limited to the oropharynx and its encompassing sites (i.e., the base of tongue, tonsil and tonsillar fossa, soft palate, and posterior pharyngeal wall). Cancer of the oropharynx is expected to occur in approximately 4000 patients annually in the United States. Most commonly, the disease involves patients in the fifth through seventh decades of life. Men are afflicted three to five times as frequently as women. The etiology of the disease, to the greatest extent, cannot be distinguished from cancers of the oral cavity. Tobacco and alcohol abuse constitute the most significant risk factors.

STAGING

As was true for staging of oral cavity cancers, staging of tumors of the oropharynx relies on both physical examination as well as a variety of imaging procedures, including CT scan. Staging of the primary tumor is presented in Table 30.2-22. The regional lymph nodes (N) and distant metastases (M) staging are identical to other sites within the upper aerodigestive tract and are as stated in the beginning of this chapter (see Staging and Screening, earlier in this chapter).
TABLE 30.2-22. Staging of Tumors of the Oropharynx

BASE OF TONGUE

ANATOMY

The base of tongue is bounded anteriorly by a line demarcated by the circumvallate papillae. Posteriorly, it ends with the epiglottis. Laterally, it extends to the glossopalatini sulcus and includes the pharyngoepiglottic and glossoepiglottic folds. Tongue musculature is composed of the genioglossus, styloglossus, palatoglossus, and hyoglossus muscles. The blood supply and nerve supply are identical to that of the oral tongue and consist of the lingual artery and the hypoglossal nerve, respectively.

Lymphatics are extensive within the base of tongue. Drainage is into numerous node levels including levels II, III, IV, and V in decreasing order. Indeed, disease may involve retropharyngeal lymph nodes in certain instances such as with progression to lateral pharyngeal wall.

PATHOLOGY

Base of tongue cancers are less frequent than cancers of other anatomically defined areas of the tongue. Squamous cell carcinoma represents nearly 95% of those cancers that occur in this subsite. Other cancers in this area include those of minor salivary glands origin (i.e., adenoid cystic and mucoepidermoid carcinoma) and lymphomas.

NATURAL HISTORY

Cancers of the base of tongue are frequently advanced at the time of presentation. This is partly a reflection of the relatively silent location of such disease as well as its aggressive tendencies. Patients usually present with symptoms of pain and dysphagia. Not infrequently, as is true for nasopharyngeal carcinomas, individuals present with a mass in the neck. A history of weight loss is common. Likewise, referred otalgia secondary to cranial nerve involvement is common. With progressive laryngeal involvement, a muffled quality of the voice may become apparent.

As is true for other squamous cell carcinomas of the head and neck, cancers of the base of tongue can grow either in an infiltrative or exophytic pattern. Careful physical examination delineates such growth. An important component of that evaluation should include digital and bimanual palpation. This delineates the extent of base of tongue involvement as well as determines whether or not disease has infiltrated into the preepiglottic space. Figure 30.2-15 shows routes of spread for squamous cell cancers for the base of tongue.

Base of tongue tumors have a high propensity for metastatic spread to lymph nodes. Nearly 70% of patients with T1 lesions have clinically palpable disease in the neck. The risk of nodal metastases increases with T stage, approaching 85% for T4 cancers. Likewise, tumors of the base of tongue have a high propensity for bilateral cervical lymph node spread, occurring in approximately 30% of patients. Therapy should account for this propensity even in circumstances of early primary disease. Lymph nodes commonly involved include levels II and III. Levels IV, V, and VI, however, are more frequently involved than many other cancers of the head and neck such as oral cavity lesions.

Prognosis for tongue base tumors is generally poor secondary to their advanced stage at presentation. Stage I and II 5-year survival approximates 60% and 40%, respectively. Five-year survival for patients with stage III disease approximates 30%. For stage IV disease, survival diminished to 15% at 5 years.

TREATMENT

Early Disease

Early-stage cancers of the base of the tongue are readily treated by surgery or RT. Results are equivalent. Surgery for early unilateral lesions entails a hemiglossectomy. Surgical approaches can be transoral or by lateral pharyngotomy. The former approach entails a midline labiobulngeal split.

RT has a high prospect of cure without the functional deficit that occurs with operation. In general, treatment consists of 5000 to 5400 cGy with external-beam radiation and 2000 to 3000 cGy boost to the base of the tongue via an 192Ir implant. There is debate in the radiation oncology literature as to whether or not to use an interstitial implant as the boost treatment. Altered fractionation programs can also be used, with either twice a day treatment or concomitant boost having its advocates.

Regional lymphadenectomy is recommended regardless of the primary size because of the high propensity for metastatic spread. Bilateral neck dissection is recommended for those lesions approaching midline structures.
Advanced Disease

For larger lesions involving the tongue base, primarily T4 lesions, total resection of tongue base, and total laryngectomy may be required. The addition of total laryngectomy may be dictated for several reasons. Tumor may infiltrate through the relatively thin hypoglossal ligament and extend well into the preepiglottic space. Laryngectomy is required as part of an en bloc procedure necessary to ensure complete extirpation of disease. Additionally, the removal of tongue and soft tissues of the neck (i.e., the preepiglottic space) impairs normal deglutition. With such surgery, chronic aspiration represents a major long-term complication. Total laryngectomy may represent the only means to isolate critical air exchange passages from oral secretions. The need for laryngectomy is increased in patients with diminished cardiopulmonary reserve. Restoring bulk of the base of tongue with myocutaneous flaps or free tissue transfer may minimize aspiration problems. Nowadays, patients who would require a total laryngectomy can be managed with an organ-sparing program of chemotherapy and RT, reserving surgery for salvage.

Extended supraglottic laryngectomy may be performed for smaller lesions involving the vallecula. Disease in such circumstances should not extend along the pharyngoesophageal fold to involve lateral pharyngeal wall. In the circumstances in which such a procedure is performed, pretreatment assessment must in all circumstances confirm adequate cardiopulmonary reserve.

The need for mandibulectomy as part of the surgical procedure for tongue base tumors is controversial. The traditional surgical management involves the composite (jaw, tongue, neck) resection. Such an en bloc procedure ensures more adequate tumor removal, including tumor within surrounding lymphatics. Furthermore, closure of surgical defect is facilitated by such resection (i.e., soft tissues are able to collapse with removal of mandible).

Advances, both surgical and in our understanding of patterns of tumor spread, mitigate against the need for mandibulectomy. Soft tissue defects can be repaired with free-tissue transfer, thus facilitating wound closure. Studies of lymphatic spread of oropharyngeal tumors have shown that cancer not approximating periosteum rarely infiltrates mandible. Resection of bone is thus not required for oncologic reasons.

Results of Treatment

Surgical results of early base of tongue cancers have been encouraging, with local control rates approximating 85%. The major determinant of control rate is reflective in tumor growth patterns. Exophytic tumors are controlled in 84% of instances as opposed to 58% with ulcerative-infiltrative disease.

With advanced disease, initial surgery is associated with a high probability of positive margins (25%), thus emphasizing the need for combined modality therapy.

Data from Harrison et al., Goffinet et al., and Puthawala et al. show that the local control rate for T1 to T2 base of tongue tumors is in the 90% range when treated with external-beam RT plus implant. Harrison et al. have reported long-term results on 68 patients treated between 1981 and 1995 with combined external-beam RT (54 Gy) plus 192Ir implant (20 to 30 Gy), combined with neck dissection for patients presenting with positive nodes (Fig. 30.2-16 shows a clinical example; Table 30.2-23). Actuarial 5- and 10-year local control is 89% and 89%, distant metastasis-free survival is 91% and 76%, disease-free survival is 80% and 67%, and overall survival is 86% and 52%. All T stages (T1, 17 patients; T2, 32 patients; T3, 17 patients; T4, 2 patients) were combined together, as there were no differences when analyzed by T stage. When survival salvage is included, local control rises to 92%. Lee has reported that all 58 patients who underwent external-beam RT plus neck dissection (all of whom presented with palpable nodes) were regionally controlled at 10 years, and the majority had negative surgical experiences. Harrison et al. reported detailed quality-of-life assessment on these patients, reporting that the majority of patients could maintain their incomes, employment status, and socioeconomic quality of life despite having advanced tongue cancer.

Understanding of speech and eating in public were excellent, but xerostomia was a major problem. Horowitz et al. also reported excellent performance status scores for eating in public, understandability of speech, and normalcy of diet for their patients treated with external-beam RT plus brachytherapy.

Finally, a comparison of the performance status outcomes of eating in public, understandability of speech, and normalcy of diet showed significant advantages in each category to primary radiotherapy over primary surgery.

![FIGURE 30.2-16. A patient with a T2N2 squamous cancer of the left side of the base of the tongue. The treatment plan consisted of initial external-beam radiation therapy to the primary site and the entire neck bilaterally. This was followed by a left radical neck dissection and an implant, both done with the same anesthesia. A. The simulation film shows the primary site outlined and the neck node with wire around it. A bite block is in place. A total of 4500 cGy was given to the primary site and 67%, and overall survival is 86% and 52%. All T stages (T1, 17 patients; T2, 32 patients; T3, 17 patients; T4, 2 patients) were combined together, as there were no differences when analyzed by T stage. When survival salvage is included, local control rises to 92%. Lee has reported that all 58 patients who underwent external-beam RT plus neck dissection (all of whom presented with palpable nodes) were regionally controlled at 10 years, and the majority had negative surgical experiences. Harrison et al. reported detailed quality-of-life assessment on these patients, reporting that the majority of patients could maintain their incomes, employment status, and socioeconomic quality of life despite having advanced tongue cancer. Understanding of speech and eating in public were excellent, but xerostomia was a major problem. Horowitz et al. also reported excellent performance status scores for eating in public, understandability of speech, and normalcy of diet for their patients treated with external-beam RT plus brachytherapy. Finally, a comparison of the performance status outcomes of eating in public, understandability of speech, and normalcy of diet showed significant advantages in each category to primary radiotherapy over primary surgery.]

![TABLE 30.2-23. Treatment of Carcinoma of the Base of Tongue with External-Beam Irradiation Plus Brachytherapy.](image)

External-beam RT alone has its advocates. However, the only study that sought to compare external-beam RT alone, external-beam RT plus implant, versus surgery plus postoperative radiation was done by Houssuet et al. They found that the local control rate for both external-beam RT plus implant or surgery plus postoperative radiation was in the 80% range for T1 and T2 lesions, as opposed to 50% for external-beam RT alone. Survival for external-beam RT alone was 17%, as opposed to more than 50% for the other two approaches.

Various hyperfractionated and accelerated fractionated regimens have been updated. Mendenhall reported 5-year local control of 98% for T1, 91% for T2,
81% for T3, and 38% for T4, and advocated that radiotherapy was a better alternative than primary surgery. Moore et al. reported quality-of-life data on the same group of patients, suggesting excellent outcomes with respect to eating in public, understandability of speech, and good outcomes for normalcy of diet. Neck dissection did not have a major effect on the performance status measurements. Morrison has also reported good outcomes using an accelerated fractionation, concomitant boost technique for oropharynx carcinomas of all subsites. However, all patients developed severe mucositis, and there was a growing risk of bone complications and swallowing problems and gastrostomy tube dependence with longer follow-up. Mak et al. reported that this concomitant boost program of 72 Gy in 6 weeks produced local control at 5 years of 76% (T1 = 100%, T2 = 96%, T3 = 67%), with disease-specific survival of 65% and overall survival of 59%. Implants have also been used for patients who have received prior RT to the oropharynx, who developed either recurrent base of tongue cancers or a second primary cancer in the base of tongue. Housset et al. reported on 55 patients who had received prior irradiation and in whom they performed 10½ implants. The local control rate was in the 50% to 60% range. Vikram et al. reported on ten patients who had previously treated base of tongue lesions. All ten received implants in an attempted salvage maneuver. Local control was obtained in 60% of the patients, with size being the most important prognostic feature. No local failures occurred in patients who had lesions less than or equal to 4 cm, whereas most of the patients with lesions larger than 4 cm were not salvaged. Overall survival in the entire group was poor, mainly due to uncontrolled recurrent neck disease.

TONSIL, TONSILLAR PILLAR, AND SOFT PALATE

ANATOMY
The tonsillar pillars anteriorly (the palatoglossal muscle) and posteriorly (the palatopharyngeal muscle) and the glossopalatini sulcus inferiorly constitute a triangular region that houses the lymphoid tonsillar tissue. Extending from the tonsillar pillars is the soft palate. The latter demarcates the oral cavity from the oropharynx as well as the oropharynx from the nasopharynx. It is composed of the following muscles: palatoglossus, palatopharyngeus, levator veli palatini, tensor veli palatine, and the muscular uvulae.

Nerve supply to this region is via the trigeminal nerve. Lymphatics from the tonsillar region drain into the jugulodigastric basin as well as the submandibular triangle. Lymphatics from the soft palate drain into the upper jugulodigastric lymph nodes as well as the retropharyngeal lymph nodes.

PATHOLOGY
As in other sites within the upper aerodigestive tract, the near total lesions involving this region are squamous cell carcinoma. Occasionally, lymphoepitheliomas have been identified within the tonsillar fossa. Other cancers include lymphomas and those derived from minor salivary glands.

NATURAL HISTORY
Cancers of these three sites may present and spread in a variety of means. Cancers of the tonsillar pillar tend to be more superficial than those of the tonsillar fossa. Tonsillar pillar cancers progress over a broad region including lateral soft palate, retromolar trigone and buccal mucosa, tonsillar fossa, as well as the glossopalatini sulcus.

Tonsillar fossa cancers more often present in advanced-stage disease than either cancers of the tonsillar pillar or soft palate. Approximately 75% of patients present as stage III or stage IV disease. Disease in this area tends to be bulky and can progress to involve the base of tongue as well as lateral pharyngeal wall. Symptoms include pain, dysphagia, weight loss, and a mass in the neck. Should disease extend posteriorly and involve pterygoid muscles, trismus may be a presenting sign.

Primary disease of the soft palate, however, may behave in a more indolent manner. Tumors in this region may remain in the early stages. Likewise, disease in this area may remain superficial, presenting as diffuse erythroplakia extending into the hard palate or inferiorly along the tonsillar pillar.

Tonsillar pillar cancers metastasize less frequently to regional lymph nodes than cancers of the tonsillar fossa. Patients present with clinical evidence of nodal metastases in 38% of T2 tonsillar pillar cancers, while 66% of T2 tonsillar fossa lesions are associated with clinically evident lymph node disease at presentation. Contralateral metastases are common for tonsillar fossa cancers. Nodal disease in tonsillar fossa cancer, likewise, most often presents in an advanced stage with nearly 55% of patients presenting with N2 or N3 disease. Soft palate tumors are more commonly associated with bilateral lymph node metastases. Approximately 20% of patients present with bilateral disease.

Prognosis for tonsillar fossa cancers ranges from 93% for stage I disease to 17% for stage IV disease. For soft palate lesions, 5-year survival ranges from 21% to 85% depending on disease stage.

TREATMENT

Early Disease
Except in circumstances of early disease, the distinction between cancers arising in the tonsillar fossa versus tonsillar pillar cannot be made. Early cancers of this region can be treated by single modality therapy, either surgery or RT.

Surgical resection of early disease can occasionally be done transorally. Such an approach, however, should be performed only in circumstances in which free surgical margins can be ensured. Better exposure to early cancers of this region may also be obtained through a combined lip-splitting incision coupled with an anterior midline or lateral mandibulectomy. Careful dissection thus proceeds by first identifying anterior lateral margins. If tumors extend to the periosteum of the ascending ramus of the mandible, trismus may be a presenting sign. Careful dissection thus proceeds by first identifying anterior lateral margins. If tumors extend to the periosteum of the ascending ramus of the mandible, trismus may be a presenting sign. Careful dissection thus proceeds by first identifying anterior lateral margins. If tumors extend to the periosteum of the ascending ramus of the mandible, trismus may be a presenting sign. Careful dissection thus proceeds by first identifying anterior lateral margins. If tumors extend to the periosteum of the ascending ramus of the mandible, trismus may be a presenting sign.

Early squamous cell carcinomas of the tonsillar region can, likewise, be treated with RT. Radiation can be delivered with either external beam, interstitial implant, or a combination of both. In general, radiation is preferred because it offers excellent cure rates and more comprehensive treatment of primary site, retropharyngeal nodes, and neck, all with a potentially better functional outcome.

Given the high propensity for even early cancers of this region to metastasize to cervical lymph nodes, cervical lymphadenectomy should be included as part of the surgical resection. The various types of neck dissections that could be used have been discussed (see Surgical Management of the Cervical Lymph Nodes, earlier in this chapter). Our choice for early lesions in which cervical lymph nodes are not clinically involved with disease would include a modified supraomohyoid neck dissection. Debate exists as to whether or not such dissection should be performed in continuity with extirpation of the primary disease. Where possible, in continuity dissection should be advocated.

When applying RT as the primary treatment modality, it is usually possible to treat the ipsilateral neck alone and avoid contralateral neck irradiation. With such treatment, radiation dosage to the contralateral salivary gland is minimized, thereby reducing the incidence of xerostomia. Due to the rich lymphatic network in the oropharyngeal region, it is standard practice to radiate the neck in all patients. This includes the retropharyngeal nodes. In fact, one advantage of using radiation is the inclusion of these nodes in the treatment, which is not included in primary surgical management.

Early-stage soft palate tumors are readily treated with RT. Treatment can be delivered with external beam, brachytherapy, or a combination of both. Figure 30.2-17 shows the external-beam technique in a typical patient. Most patients do not have palpable cervical lymph node metastases on presentation. It is unclear whether or not all patients require prophylactic neck treatment. Both prophylactic neck irradiation and observation alone have been used by various authors. With a successful outcome. Of course, this is retrospective and subject to the selection factors inherent in retrospective reviews. Small superficial lesions can probably be treated locally, with observation of the neck. Larger T1 and all T2 lesions should receive elective neck treatment.
Advanced Disease

Advanced cancers (i.e., stage III and stage IV disease) generally require combined modality therapy (i.e., surgery and postoperative RT). However, there has been increasing interest in radiation alone for the primary site, combined with neck dissection. Clearly, the choice of treatment relates to the exact T and N stage. For early (T1 to T2) primary lesions with neck metastases, definitive radiation to the primary neck, followed by a neck dissection, is commonly used. For T3 lesions, external-beam radiation alone combined with an implant can be used for the primary site, with a neck dissection added for those with involved nodes. This approach for T3 lesions is reserved for the exophytic lesions, or those that do not demonstrate highly infiltrative characteristics. The endophytic T3 and T4 lesions are best managed by surgery followed by postoperative RT. Clearly, optimal management requires individual assessment of each patient and close collaboration between the surgeon, radiation oncologist, and patient. If the primary lesion can be managed by radiation, however, the functional outcome with regard to speech and swallowing is usually better than surgically managed patients. The extent of surgical resection should be governed by the size of the primary disease and its pattern of spread. Tumor-free surgical margins generally entail a segmental mandibulectomy in most circumstances of advanced disease in the tonsillar region.

Results of Treatment

TONSILLAR PILLARS AND FOSSA. Surgical resection as the sole modality of therapy for early disease is not frequently used in most series. However, studies have demonstrated that when used, local control rates are excellent. Indeed, even for advanced tumors in highly selected instances, effective local control can approach 80%. The degree to which local control can be obtained depends on disease extension outside the tonsillar fossa. When disease extends to lateral pharyngeal wall or base of tongue, local recurrence approaches 33% and 47%, respectively.

Wong et al. have reported the results of definitive external-beam irradiation for 150 patients with previously untreated squamous cell carcinoma of the tonsillar fossa. Most patients were treated with conventional fractionation with total doses in the 6400 to 7200 cGy range. Local control was obtained in 15 of 16 (94%) patients with T1 lesions, and 51 of 52 (79%) patients with T2 lesions. Other series have reported local control rates for T2 lesions approximating 60%.

When surgical salvage is added, local control was 100% for T1 and 85% for T2. Wang has used an accelerated hyperfractionation program for oropharyngeal tumors. During an earlier time period, patients received 1.6 cGy per fraction, two fractions per day, to a total of 38.4 cGy. Due to acute toxicity, a 2-week break was then given. Treatment was then resumed at 1.8 cGy per fraction, one fraction per day, to a total of 65 cGy. This was called the BID-GD program. More recently, the treatment regimen was changed. The initial treatment remained the same, as did the 2-week break. However, when the patient returned for the second part of the treatment, they were resubmitted at 1.8 cGy per fraction, two fractions per day, to a total of 64 cGy. This was called the BID-BID program. For tonsillar lesions (T1 to T4), the 36-month actuarial local control after irradiation therapy was 93% versus 64% for the BID-GD program.

There has been increasing interest in brachytherapy for selected tonsillar lesions. Levendag et al. used fractionated high-dose-rate or pulsed-dose-rate brachytherapy as a boost, combined with external-beam irradiation for a cohort of tonsillar and soft palate lesions. There were 5 T1, 22 T2, 10 T3, and 1 T4 lesions. Local failure occurred in 13% of cases. These authors believed that this approach was superior to external-beam alone when compared with their data for external-beam RT alone. Puthawala et al. reported the results of 80 patients with previously untreated squamous cell carcinoma of the tonsillar region who received 4500 to 5000 cGy with external-beam irradiation, followed by an interstitial Ir implant.

Patients with T1 or T2 disease received an implant boost to 2000 to 2500 cGy, and those with T3 to T4 lesions received a boost of 3000 to 4000 cGy. Overall local control was 84%, and absolute 3-year disease-free survival was 72%. When looked at by stage, all three T1 patients obtained local control. For T2, T3, and T4 patients, local control was obtained in 14 of 15 (93%), 32 of 43 (74%), and 11 of 19 (58%), respectively.

Mazeron et al. reported the results of external beam, implant, or a combination of the two, for lesions of the tonsillar and soft palate. For tonsillar lesions, most patients were treated with 45-Gy external beam plus 31-Gy interstitial brachytherapy. A protraction was made for each of the radiotherapeutic techniques for T1 and T2 lesions. Almost all T1 lesions were controlled regardless of technique. However, for T2 disease, 7 of 26 patients failed locally after external-beam RT alone, compared with only 1 of 43 patients managed by external-beam RT plus implant. Behar et al. evaluated combined external-beam RT, brachytherapy, and adjuvant neck dissection (neck surgery mainly for N2 and N3 disease) for a group of 37 patients with cancers of the tonsillar and soft palate.

Thirty-two percent had T3 or T4 disease, and 49% had N2 or N3 neck metastases. Local control was obtained in 90% of cases, and neck control was achieved in 87%. Actuarial 5-year survival was 64%, and approximately 25% of the patients developed a second primary cancer.

Pernet et al. accumulated a large series of 361 patients with cancers of the tonsil and soft palate who were managed either by brachytherapy alone or a combination of external-beam irradiation (50 Gy) plus a brachytherapy boost (20 to 30 Gy). In total, 64% of patients had T1 to T2 lesions, and 64% were N0. Only two patients had T4 disease. A select group of 18 patients with small T1 lesions were managed by brachytherapy alone, and all were locally controlled. All others received combined external-beam RT plus implant. Local control was 89% for T1, 85% for T2, and 67% for T3 lesions. The group with lesions on the soft palate, tonsillar fossa, and posterior pillar had a better outcome than those with lesions on the anterior pillar and glossectomised tonsil. For T3 lesions, the local control with external-beam irradiation falls considerably. However, it would appear that the subset of T3 tumors with tongue involvement have the highest local failure rate. Tong et al. reported that 18 of 39 (46%) T3 patients ultimately had failures in the primary site after external-beam RT. Interestingly, all 18 patients who failed had lesions that extended into the base of tongue. Mendenhall has reported that the addition of interstitial implant to the base of tongue, after external-beam irradiation, can improve the local control in their T3 patients with base of tongue extension, only five of nine patients were controlled with external-beam RT alone, as compared with 13 of 17 who had full-dose external-beam RT plus a localized base of tongue implant.

Puthawala et al. reported local control in 16 of 19 patients with T3 N0 lesions, and 5 of 6 patients with T3 N1 lesions, all treated with external-beam RT and implant. Wong et al. reported local control in only 58% of patients with T3 treated with external-beam RT plus implant. Leborgne analyzed 140 patients with tonsil cancer who received definitive radiation. The subgroup of patients with lingual extension who had an implant as part of their treatment had better local control than those who received external-beam RT alone. Thus, it appears that many T3 lesions and those with lingual extension may be best served with the addition of an implant, if radiation is used as the primary modality. It would therefore appear that the results of external-beam radiation alone for T3 tonsillar cancer are suboptimal. The addition of an interstitial implant may improve the results in selected patients. There may also be a role for a combination of surgery and radiation.

For T1 to T2, N0 to N1 patients, it is usually possible to treat the ipsilateral neck alone and avoid contralateral neck irradiation. By doing this, the irradiation dosage to the contralateral salivary gland tissue is minimized, and the incidence of xerostomia is significantly reduced. Murthy and Hendrickson reported that none of their 20 patients with T1 to T2 N0 or N1 disease failed in the untreated contralateral neck when the primary and ipsilateral neck were controlled. Tong et al. reported that none of their patients with either T1 N0 or T2 N0 lesions failed in either neck despite the fact that approximately 40% of the cases had ipsilateral treatment only. It is
considered safe to omit contralateral neck treatment in most of these early lesions, as long as there is no extension into the base of tongue or significant extension onto the soft palate.

The management of patients with more advanced lesions is somewhat controversial. There are advocates of RT alone, reserving surgery for salvage only. Others advocate a approach involving surgery and postoperative radiation. Perez et al. analyzed 296 patients with epidermoid carcinoma of the tonsillar fossa. In this group, 127 received radiation alone, 133 were planned to have preoperative RT, and 36 received surgery plus postoperative radiation. There was no statistically significant difference in 3-year disease-free survival for T1 to T2, N0 to N2 patients with radiation alone versus radiation combined with surgery. In patients with T4 or N3 disease, there was an advantage to combined treatment over radiation alone, suggesting a benefit for those who had surgery. The authors concluded that radiation alone was the treatment of choice for early-stage lesions, but there might be an advantage in selected advanced stage patients for a combination of surgery and postoperative irradiation. Dasmahapatra et al., likewise, report that the 5-year survival for patients who had combined radiation and surgery was better than those who had radiation alone in the stage III and IV categories. Spiro and Spiro could not demonstrate a benefit in survival when patients with stage III and IV disease were treated with either radiotherapy alone, surgery alone, or combined surgery and irradiation. This may be a reflection of selection bias, with more advanced and less favorable patients being treated with surgery and radiation combined. The RTOG has performed a prospective randomized trial and analyzed various combinations of radiation and surgery for patients with advanced squamous cell cancer of the oropharynx. Patients with oropharynx tumors were randomized to receive preoperative RT (5000 cGy) plus surgery, surgery plus postoperative RT (6000 cGy), or RT alone (6500 to 7000 cGy) with surgery reserved for salvage. This study revealed that the overall survival, as well as the estimated 4-year local regional control rate, was not statistically different in any of the arms. One of the weaknesses of this study is that it did not stratify the results by subsite within the oropharynx. It is therefore impossible to determine what the specific results would be for tonsil patients. Clearly, treatment must be individualized from patient to patient and should attempt to provide the highest rate of cure as well as the best functional and quality-of-life outcome.

SOFT PALATE: There have been emerging data over the past few years advocating the use of brachytherapy for small soft palate lesions. Mazeron et al. reported on 59 T1 and T2 squamous cancer of the soft palate and uvula treated with definitive irradiation. Sixteen patients had external-beam RT alone, 14 had implantation alone, and 29 had a combination of external-beam RT plus brachytherapy. Local failure occurred in 25% (4 of 16) after external irradiation alone, 18% (5 of 19) after combined external-beam RT and implant, but in 0% (0 of 14) in the group selected for implant alone. This group preferred the plastic tube technique over the guide gatter technique for implantation. It is unclear exactly how the patients were selected for each of the treatment strategies. The authors believed that severe dry mouth was less frequent in those patients who received all or part of the treatment by implantation compared with those who had external-beam irradiation alone. Similarly, Sealy et al. reported excellent control rates in patients with early squamous cell cancer of the soft palate and uvula treated with implant alone. Pernet et al. have reported on 277 patients treated for carcinoma of the oropharynx by exclusive RT. The group (212 patients) lumped soft palate and tonsil and posterior pillar lesions together in the reporting of results. Nine percent of these patients had soft palate lesions. In this group, 7% (8 of 121) of the T1 and T2 lesions exhibited recurrence; 27% (23 of 85) recurred in the T3 category. The overall local control at 5 years was 83%. This series has been updated (361 patients) and already quoted in the section on tonsil cancer. Local control was 89% for T1, 85% for T2, and 67% for T3 lesions. All 18 patients managed by brachytherapy alone for small T1 lesions had local control.

The results of the study by Levendag et al. have already been described in the section on tonsillar cancer. Amdur et al. reported an analysis of 75 patients with squamous cell carcinoma of the soft palate, uvula, or both treated with RT alone or in combination with neck dissection. Most patients received 6000 to 7550 cGy. Local control was obtained in all 8 patients with T1 disease, and 14 of 19 patients with T2 disease. Including surgical salvage, 16 of 19 T2 patients obtained ultimate local control (84%). The results were far worse for T3 and T4 disease, with local control being 45% and 25%, respectively, for continuous course external-beam irradiation. This series highlights the poor results achieved with RT for advanced disease, with quite good results for early-stage disease with external-beam RT alone. Clearly, from an oncologic point of view, there is no definitive proof that brachytherapy is required for early-stage soft palate tumors. However, there may be a rationale for using implant as all or part of the treatment in an effort to improve the functional outcome with regard to salivary gland function. Obviously, brachytherapy spares the major salivary glands from receiving significant doses of radiation and decreases the risk of xerostomia. Proper patient selection is required, and the radiation oncologist must have expertise in performing a palatal implant.

Although the local control is excellent for early-stage disease, the overall survival may not necessarily reflect the high local control rate. Intercurrent illness as well as the problem of second primary malignancies represent a significant cause of mortality in this population.

Complications from RT are in the 10% range, with severe complications, principally osteonecrosis of the mandible requiring surgical resection, occurring in 5% or less. Whether elective neck treatment is required remains an open question. The probability of neck recurrence in patients with early disease is low, regardless of whether or not the neck is treated prophylactically.

Most advanced soft palate tumors should be treated with combined surgery and postoperative radiation. Amdur et al. reported that the results of external-beam RT alone for T3 and T4 disease were suboptimal.

PHARYNGEAL WALL

Epidemiology

Epidemiologic considerations are as discussed for oropharyngeal cancers.

Anatomy

The pharyngeal wall within the oropharynx extends from the nasopharynx at a line demarcated by the soft palate to the level of the vallecular. It comprises the posterolateral surfaces of the oropharynx. The pharyngeal constrictor muscles constitute the structural framework of the pharyngeal wall. Nerve supply is from the pharyngeal branches of the ninth and tenth cranial nerves. Blood supply is largely from the ascending pharyngeal and superior thyroid arteries, both emanating from the external carotid artery.

The pharyngeal wall is rich in lymphatics. Primary drainage is to retropharyngeal lymph nodes as well as nodes in levels II and III.

Pathology

The near total majority of lesions on the pharyngeal wall are squamous cell carcinomas. Occasional minor salivary gland lesions have been identified.

Natural History

Tumors of the posterior pharyngeal wall are generally identified in the late stages. This is due to the silent location in which they develop. Symptoms at presentation include pain and bleeding. Weight loss is common. Likewise, patients may present with a mass in the neck as their initial symptom. Disease spread can be superiorly to involve the nasopharynx. Posteriorly, disease may infiltrate the prevertebral fascia. Inferiorly, disease spreads to involve the pyriform sinuses and hypopharyngeal walls.

Pharyngeal wall tumors have a propensity for cervical lymph node metastases. Clinically palpable disease is identified in 25% of patients with T1 lesions, 30% of T2 lesions, 66% of T3 lesions, and over 75% of patients with T4 disease. Given that most pharyngeal wall tumors extend past the midline, bilateral cervical metastases are common.

Prognosis for pharyngeal wall cancers ranges from 75% for stage I disease, 70% for stage II, 42% for stage III, to 27% for stage IV disease.
TREATMENT

Early Disease

Early-stage disease of the pharyngeal wall can be treated by either surgery or radiation. Given the functional impairment that may result from surgical resection, RT is generally preferred. Surgical resection generally entails a (trans)hyoid approach to gain access to the lesion. Wide excision of such lesions includes underlying prevertebral fascia. Split-thickness skin graft coverage is required. A significant morbidity following surgical resection is impaired swallowing secondary to resection of pharyngeal wall musculature.

Bilateral modified neck dissections are indicated in patients with early pharyngeal wall cancers.

An important issue in planning the RT for posterior pharyngeal wall tumors is the proximity of the spinal cord to the primary tumor volume. When opposed lateral fields are used, and the spinal cord block is placed, the posterior edge of the field is dangerously close to the posterior aspect of the tumor. It is important to use a sharp beam edge, so as to avoid underdosing the posterior aspect of the tumor, which can fall in the penumbra of the beam. This is best accomplished by avoiding cobalt 60 and using a 4- or 6-MeV photon beam. Cerrobend blocks are used to define the posterior border. It is also important to make this border as posterior as possible. It has been our practice to place this border at the most posterior aspect of the spinal cord. This is much closer to the spinal cord than in most other head and neck situations. Frequent portal films must be taken to ensure the accuracy of this field, and for maximal spinal cord protection. This situation represents a difficult challenge to the radiation oncologist. One of the potential advantages of brachytherapy is the delivery of high doses to the tumor with relative sparing of the spinal cord. However, in order for this technique to be useful, tumors have to be relatively small and discrete. Often, this is not the situation.

Advanced Disease

Advanced disease of the posterior pharyngeal wall is best handled by multimodality therapy. Surgery generally involves a total laryngopharyngectomy. Reconstruction under such circumstances includes either a pectoralis major myocutaneous flap, gastric pull-up, or free-flap transposition with microvascular anastomoses. Free-flap transposition entails a jejunoplasty and is becoming the procedure of choice. Rehabilitation and swallowing with the latter procedure is hastened. This allows for more expeditious use of postoperative radiotherapy.

The use of radiotherapy postoperatively is generally recommended. The high incidence of retropharyngeal lymph node metastases and the associated increased local regional failure rate mandates aggressive multimodality treatment.

Results of Treatment

Guilmondegui et al. have reported on the surgical management of pharyngeal wall carcinomas. Twenty-eight percent of the entire patient population developed local regional recurrence. Local recurrence predominated. It was of note in that series that salvage therapy consisting of either surgery or radiation was successful in 9 of 22 patients. The success of therapy was governed by the presence of retropharyngeal nodes, with only 25% of such patients disease free at 2 years.

Mezo-Mendes et al. have reported on 164 patients with squamous cell carcinoma of the pharyngeal walls who were treated with definitive RT at the M. D. Anderson Hospital. Their report included patients with both oropharynx and hypopharynx lesions. The primary sites were generally irradiated to a dose of 7000 to 7500 cGy in 7 to 7.5 weeks. Local control was 71% for T1, 73% for T2, 61% for T3, and 37% for T4. The authors recommended RT alone for T1 and T2 lesions. They concluded that resectable T3 and T4 lesions should be treated with combined surgery and radiation.

Marks et al. reported the experience from Washington University on 51 patients with pharyngeal wall cancer treated between 1964 and 1974. Survival was no different between patients treated with low-dose preoperative radiation plus surgery versus those treated with high-dose radiation alone. However, this was not randomized, and the surgical techniques were not standardized. Survival was also poor, with actuarial 3-year survival of 17%. There was a greater complication rate in the patients receiving surgery, with 31% having pharyngocutaneous fistula, 14% having carotid rupture, and an operative mortality of 14%. Marks et al. updated this series with a total of 89 patients treated between 1964 and 1981. Their update led to the suggestion that combined surgery and radiation might yield better results than high-dose radiation alone. Again, definitive conclusions are difficult to make.

Fein et al. analyzed the treatment factors for 99 patients with pharyngeal wall cancer treated with definitive external-beam irradiation at the University of Florida between 1964 and 1990. The main issues relate to the fractionation schedule (once daily vs. twice daily) and the location of the posterior border of the irradiation field (midvertebral body vs. posterior edge of the vertebral body). Local control is clearly improved when the posterior border of the field is maximally posterior, thus allowing better coverage of the posterior wall. This places significant technical demands on the radiation oncologist, who must verify the safety of this border with respect to the spinal cord on the daily treatment setup. Local control with the border at midvertebral body versus posterior was T1, 100% for both; T2, 57% versus 100%; T3, 46% versus 73%; and T4, 29% versus 75%. Local control for continuous course once daily versus twice daily fractionation was T1, 100% for both; T2, 67% versus 82%; T3, 43% versus 80%; and T4, 17% versus 50%. Clearly, the technical and fractionation parameters were less significant for early lesions, but increasingly important for more advanced lesions.

Spiró et al. reported a 12-year experience from the Memorial Sloan-Kettering Cancer Center. A variety of operations were used over this time. There was no standardization, and at least eight different treatment approaches were used during this time period, representing various combinations of surgery, radiotherapy, and chemotherapy. This heterogeneity of treatment approaches highlights the uncertainty as to the optimal management of this disease and the variety of disease presentations. Five-year survival was 32%, and the overall complication rate was 50%. A small group of patients were treated with 40 Gy to the primary site, followed by external-beam RT. The implants were done using surgery for access. Local control in this small group of patients was excellent. Son and Kacinski reported 14 patients treated with a combination of implant and external-beam radiation. This heterogeneity of treatment approaches highlights the uncertainty as to the optimal management of this disease and the variety of treatment approaches used in this time period.

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Overall survival was 73%, and the overall complication rate was 50%. A small group of patients were treated with 40 Gy to the primary site, followed by external-beam RT. The implants were done using surgery for access. Local control in this small group of patients was excellent. Son and Kacinski reported 14 patients treated with a combination of implant and external-beam radiation. This heterogeneity of treatment approaches highlights the uncertainty as to the optimal management of this disease and the variety of treatment approaches used in this time period.

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RELEVANT ANATOMY

LARYNX

Cancers of the larynx are considerably less frequent than malignancies of other sites, such as lung, breast, prostate, and colon; despite this fact, however, a substantial amount continues to be written on the subject. This seemingly disproportionate body of writing probably reflects the perceived importance of these neoplasms relative to their potential impact on people’s communicative skills. It would seem that the mere threat to a person’s vocal organ is associated with profound psychological and socioeconomic overtones, and curing the cancer at any cost no longer is accepted casually. More than ever before, a premium is placed on returning the patient to a productive and useful lifestyle (i.e., quality of life after cancer treatment). This attitude is demonstrated more keenly in the treatment of larynx cancer than with almost any other malignancy. In the past, treatment of laryngeal cancer focused predominantly on cure by relentless surgical aggressiveness. That era was followed by the emergence of conservation through larynx-sparing operations, the development of sophisticated radiation methods, and most recently, organ-sparing strategies in which chemotherapeutic, radiotherapeutic, and surgical methods are used in a variety of combinations and sequences. The overall 5-year cure rate for patients with laryngeal squamous cell carcinoma (SCC) is almost 70%, and although those data have not changed dramatically during the last decade, the treatment options and their sequencing have. As a result, a higher percentage of contemporary patients are retaining their larynx.

EPIDEMIOLOGY AND ETIOLOGY

Although considerable geographic differences exist in the incidence of larynx cancer, the distribution of the disease is consistent within each country. For example, regardless of the culture, this disease most commonly affects middle-aged or older men who have smoked tobacco and have consumed excessive alcohol. Laryngeal cancer rarely occurs in people who have done neither. In the United States during the year 2000, more than 12,000 new larynx cancers will be diagnosed, and approximately 10,000 of those cases will be in men. Although this disease has always been more common in men, the gender ratio is changing; in 1956, the ratio was 15:1, whereas current studies show an approximately 5:1 ratio of men to women. This trend is probably due to the predictable effects of the changing smoking patterns of the sexes. Racial differences also exist. Compared with whites, African Americans in the United States have a significantly higher incidence of larynx cancer. Overall, the peak incidence of larynx cancer is in the sixth decade. The disease occurs in young people only rarely. The etiologic factors that have been implicated in laryngeal cancer are voice abuse and chronic laryngitis, dietary factors, chronic gastric reflux, and exposure to wood dust, nitrogen mustard, asbestos, and ionizing radiation. The carcinogenic effect on the larynx that results from smoking tobacco—whether by pipe, cigarette, or cigar—is, however, the factor most widely held responsible for this malignancy. Larynx cancer only occasionally occurs in patients who have never smoked. Possibly, human papillomavirus is an important cofactor in aerodigestive carcinogenesis in general, and it may be especially significant in the larynx. Heavy alcohol intake appears to be associated with larynx cancer, and it appears to enhance the already present risk factors associated with smoking. On the other hand, some studies have failed to demonstrate an interdependent causal effect for alcohol intake and larynx cancer. The issue of alcohol, smoke, and carcinogenesis is complicated by the nutritional deficiencies that usually occur in alcoholics. In the larynx, this complex issue is more specifically defined by the fact that whatever the role of alcohol, it is apparently more significant in supraglottic than in glottic cancers. With the maturation of the current generation of those youngsters using smokeless tobacco, some alteration of the relative incidence in the United States of supraglottic and glottic cancers may be noted. Those worldwide data that show large variations of laryngeal cancer statistics consistently reflect the smoking and drinking habits of the individual country. Also, the sites within the larynx affected by cancers vary considerably between countries. This distribution is shown in Table 30.3-1, which represents a compendium of worldwide data that addresses the relative distributions of cancer within the larynx.

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>Etiology</th>
<th>Percentage</th>
<th>Smoking</th>
<th>Alcohol</th>
<th>wood dust</th>
<th>mustard</th>
<th>Asbestos</th>
<th>Ionizing Radiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supraglottic</td>
<td>62.5%</td>
<td>49%</td>
<td>54%</td>
<td>58%</td>
<td>14%</td>
<td>4%</td>
<td>25%</td>
<td>52%</td>
</tr>
<tr>
<td>Glottic</td>
<td>37.5%</td>
<td>47%</td>
<td>32%</td>
<td>63%</td>
<td>6%</td>
<td>4%</td>
<td>77%</td>
<td>52%</td>
</tr>
<tr>
<td>Supraglottic</td>
<td>75%</td>
<td>82%</td>
<td>55%</td>
<td>63%</td>
<td>12%</td>
<td>4%</td>
<td>75%</td>
<td>37%</td>
</tr>
<tr>
<td>Glottic</td>
<td>25%</td>
<td>18%</td>
<td>63%</td>
<td>52%</td>
<td>6%</td>
<td>8%</td>
<td>25%</td>
<td>63%</td>
</tr>
</tbody>
</table>

**TABLE 30.3-1. Geographic Variations in Larynx Cancer Sites**

Koufman and Burke make a strong case for a multifactorial etiology, and they have proposed a model that involves tobacco, environmental factors, alcohol, reflux, viral activation, dietary deficiency, and altered host immunity.

RELEVANT ANATOMY
The larynx is a uniquely complicated organ that is strategically located so that significant alteration of its anatomy by either surgery or cancer can have a noticeable impact on vocal, respiratory, and swallowing function. The organ consists of three subsites: glottis (paired true vocal cords), supraglottis, and subglottis. Thus, clarification of the subsites within the larynx is essential. Because of different embryologic development and different lymphatic patterns that are subsite-specific, to discuss larynx cancers without specific reference to the exact location(s) within that structure invites inaccuracies in staging and miscalculations in treatment planning. Additionally, certain embryologic and anatomic facts are relevant to understanding the natural history of cancers that occur in the larynx. For example, the adjacency of the paraglottic space to the thyroid and cricoid cartilages and to the hypopharynx is critical to the subtle differences between the increasing stages of glottic lesions.

The larynx consists of a complex variety of muscles, an overlying mucous membrane, and a skeletal structure of four cartilages—the cricoid, the epiglottis, the paired arytenoids, and the shield-like thyroid cartilage. Suspended within the endolarynx are the mobile true vocal cords, which are collectively known as the glottis. That portion above the glottis, the supraglottis, consists of the false vocal cords, the epiglottis, and the aryepiglottic folds. These folds form the junction (i.e., common partition) between the endolarynx and the hypopharynx. The medial wall of these folds is within the endolarynx, and the lateral wall is actually the medial wall of the adjacent pyriform sinus (Fig. 30.3-1). Those lesions that arise on the rim of the aryepiglottic folds, therefore, have been appropriately referred to as marginal cancers, because they bridge the junction between the larynx and the hypopharynx. Those marginal lesions that extend predominantly into the endolarynx behave more like supraglottic cancers, whereas those lesions that spill into the pyriform sinus tend to follow the natural history of the hypopharyngeal malignancies. The subglottis is that portion of the larynx between the underedge of the true vocal cords and the cephalic border of the cricoid cartilage. Although the subglottis is the laryngeal site least likely to harbor a primary cancer, it is critical to the pathogenesis and natural history of glottic (i.e., vocal cord) cancer because it provides an important route of inferior tumor extension.

The true vocal cords are remarkably engineered, although they are somewhat misnamed; rather than cord-like structures, they really are folds of mucosa that cover vocal muscles. These vocal cords (folds) are attached anteriorly to the inner surface of the thyroid cartilage and posteriorly to the arytenoid cartilages. The vocal muscles are complex in their activity, and their dynamic relationship with overlying mucosa is critical to voice production. Any loss of mucosal mobility relative to the underlying muscle, such as that produced by cancer, surgery, or, even to a lesser extent, by radiation therapy, alters the voice. An appreciation of this fundamental fact is an important component in the selection of treatment of vocal cord cancer.

The lining of the endolarynx consists of respiratory epithelium except on the vibratory edges of the true vocal cords, which typically are lined with pseudostratified squamous epithelium.

The paired arytenoid cartilages each sit on the cephalic rim of the cricoid cartilage and rotate in a relatively horizontal axis around a pivot point. Each arytenoid is attached anteriorly to a true vocal cord, and the clockwise and counterclockwise rotation of these cartilages pulls the respective vocal cord attachment with it, causing abduction and adduction of those structures. Invading cancer can damage any or all of the muscles that are responsible for arytenoid rotation and also the recurrent laryngeal nerve fibers that innervate them. The posterolateral aspect of the larynx is particularly vulnerable to the invasion of cancer because of the adjacency of the medial wall of the pyriform sinus. When cancers of this part of the pyriform sinus extend through the mucosa, they gain direct access to the important laryngeal compartment known as the paraglottic space, which leads to all parts of the endolarynx, including the vocal muscles and the preepiglottic space (Fig. 30.3-2). Treatment options for such a tumor are altered significantly because of paraglottic space involvement. Tumors that invade the endolaryngeal muscles or the nerve fibers that innervate them usually create a noticeable effect on vocal cord motion. Of all the findings on laryngeal examination during cancer evaluation, the state of endolaryngeal mobility is one of the most important. This fact has been substantiated by the separate designation that the American Joint Committee on Cancer (AJCC) has assigned to the immobile vocal cord in the staging categorization of this disease. 2

Another more subtle type of motion alteration pertains to the anatomic relation between the vocal cord musculature and the overlying mucosa. An awareness of this relatively recent knowledge has enhanced the understanding of the pathogenesis and treatment of early glottic cancer. 2 The vibratory mechanism that produces the voice is due to the mobility of the mucous membrane overlying the musculature of the vocal cords. The free edge of the true vocal cord consists of a pseudostratified squamous epithelium, under which is a lamina propria of fibroelastic and gelatinous consistency. This arrangement allows a sliding motion of the mucous membrane, which creates a mucosal wave, the fluidity of which is a direct reflection of the freedom of that layer from the underlying muscle. Any surface cancer that invades through the basement membrane, such as any cancer deeper than carcinoma in situ (CIS), affects the mucosal wave by creating a tethering effect. These subtle differences are usually not appreciated by routine laryngeal examination but are obvious with stroboscopic evaluation. An appreciation of these subtleties can translate into the practical matter of determining whether to radiate or microscopically excise certain minimal vocal cord cancers. Because of the different embryologic origins of the supraglottic from the glottic and subglottic larynx, and also because of the independent lymphatic drainage patterns from each of these subsites, the larynx can be thought of as a compartmentalized structure. These features are important influences in determining the spread of various cancers within that organ. 2

The lymphatics of the supraglottic larynx are profuse, and the frequency of metastasis associated with cancers of this subsite reflects that fact. 2 Lymphatic spread...
from the epiglottis to the false cords, and these channels are directed bilaterally. The drainage from the false cords and the remainder of the supraglottic larynx is lateral and superior, and these channels exit the larynx bilaterally through the thyrohyoid membrane. They then proceed to the adjacent deep cervical nodes. The lymphatics of the infraglottic larynx drain laterally and inferiorly, out of the cricothyroid membrane into the lower deep cervical lymph nodes. The true vocal cords, on the other hand, are unique because they possess little or no lymphatic drainage. From a lymphatic drainage standpoint, the left half of the larynx is essentially independent from the right half, and the supraglottic larynx is independent from the structures below it. These facts are clinically demonstrated: Early-stage supraglottic cancers have little affinity for extension into the lower structures, and those beginning on the true vocal cord do not tend to extend cephalad into the supraglottis. Knowledge of this unique pathogenesis has substantial impact on the ability to predict metastasis into various parts of the neck as well as on the planning of the various partial laryngectomies known as conservation operations. These techniques combine the removal of laryngeal parts with the preservation of vocal and swallowing functions. Additionally, radiation therapy planning, especially for occult cervical metastasis, is predicated on a thorough knowledge of these and other drainage tendencies of laryngeal cancers.

PATHOLOGY, PATHOGENESIS, AND NATURAL HISTORY

A variety of laryngeal malignancies, most of which are primary to the larynx and others that are metastatic from other sites, have been reported. A comprehensive classification is shown in Table 30.3-2.

Table 30.3-2. Classification of Laryngeal Malignancies by Histologic Type

<table>
<thead>
<tr>
<th>Histologic Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCC</td>
<td>Squamous cell carcinoma</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>Adenocarcinoma</td>
</tr>
<tr>
<td>Neuroendocrine</td>
<td>Neuroendocrine</td>
</tr>
<tr>
<td>Others</td>
<td>Others</td>
</tr>
</tbody>
</table>

More than 95% of all primary laryngeal malignancies are SCCs, with the remainder being sarcomas, adenocarcinomas, neuroendocrine tumors, and other types. Both spindle cell and verrucous carcinomas probably are variants of SCC.

It should be noted that knowledge and recognition of the neuroendocrine family of malignancies has changed considerably over time, and the exact percentage of these within the overall population of larynx cancers is unknown. In the past, certain tumors were vaguely classified as poorly differentiated malignancies when, in fact, they were neuroendocrine in origin. Modern techniques of immunohistochemical and morphologic analysis will almost certainly lead to the recognition and accrual of more of these tumors in the future, and as a result, they will make up a higher relative percentage of laryngeal malignancies.

Laryngeal SCC accounts for approximately one-fourth of all head and neck SCCs. Some variability is seen between series from different institutions and different patient populations; however, more than one-half of laryngeal SCCs present as localized disease without metastasis, one-fourth present as local disease with regional metastases, and approximately 15% are first seen at an advanced stage with or without distant metastasis. As with other aerodigestive carcinomas, metachronous and synchronous cancers are ongoing considerations in developing appropriate diagnostic and therapeutic strategies. The incidence of metachronous (i.e., second primary aerodigestive SCC) is reported to be between 5% and 35% of all aerodigestive cases, with the esophagus being the most common second site overall. The larynx, however, seems to demonstrate a more frequent association with lung rather than esophageal carcinoma. This is a logical sequel to the carcinogenic impact of inhaling rather than ingesting offensive chemicals.

Separate consideration must be given to the spectrum of cellular disarray that includes premalignant squamous lesions, CIS, and superficially invasive carcinomas. To discuss the epithelial changes that precede and probably lead to carcinoma of the larynx is of considerable importance because it is with this group of lesions that cancer prevention and conservative management methods are most effective. As our knowledge of this subject has increased, so too has our sophistication in applying the minimal techniques necessary to achieve excellent cure rates in these disorders. The obvious value of a philosophy of preemptive strategies and treatment minimalism is the achievement of an outcome with the least physiologic change. Important also is that, by applying the appropriate minimal treatment, one is able to save radiation in reserve for potential future cancers of the adjacent aerodigestive tissues.

Because the appropriate management strategy for early laryngeal neoplasia depends greatly on a dialogue that is understood by both oncologist and pathologist, the description of the various alterations of the surface epithelium, although not exclusively applicable to the larynx, is important to this discussion. The term leukoplakia describes any white lesion on a mucous membrane and does not automatically refer to an associated or underlying malignancy. Erythroplasia, on the other hand, is a clinical term that describes any red lesion on a mucous membrane and, in contrast to the white lesions, is often indicative of an underlying malignant tumor. The term hyperkeratosis represents an increase in the amount of surface keratin. In the case of the larynx, which normally is lined with a nonkeratinizing epithelium, the use of the term hyperkeratosis is redundant; instead, the preferable term is keratosis.

Investigators have studied the occurrence of aberrant squamous epithelium in various areas of the larynx, and a predilection seems to exist for carcinogenesis in those respective sites. However, because only those lesions that begin on the true vocal cords are likely to produce early symptoms and signs, the opportunity to treat small cancers on other aerodigestive sites is infrequent. With true vocal cord lesions, however, the early warning symptoms frequently lead to early diagnosis and extraordinary cure rates for glottic malignancies.

The mucosal changes that lead to cancer take years to develop, and that evolution probably follows a consistent pattern. Most laryngeal SCCs result from prolonged exposure to recognized carcinogens that stimulate mucosal hyperplasia and metaplasia. Some of these changes are associated with keratosis, and others are not. In some situations, epithelial atypia or dysplasia may exist, the degree of which probably determines whether a lesion is destined to become malignant. In one large study by Slamniku and colleagues, 3% of patients with vocal cord keratosis unassociated with atypia and 7% with mild atypia developed invasive carcinoma. In those patients with moderate and severe atypia, however, 18% and 24%, respectively, developed carcinoma. Another study by Hjelst and colleagues showed a similar probability of cancer evolution in the group with less atypia and a strikingly higher probability in those patients with severe atypia.

In addition to the morphologic appearance of mucosal alteration, DNA changes seem to show a correlation between cancer potential and cellular aneuploidy. In a study by Munich-Wirtland and coworkers, for instance, all of those patients with dysplastic laryngeal lesions that later went on to become carcinoma demonstrated an aneuploid DNA pattern.

Mucosal lesions, whether premalignant or not, have an inconsistent gross appearance; some are white and others are hyperemic. Many investigators believe the risk for cancer development is substantially higher in lesions that are soft and red in appearance. Without histologic study, however, even the most experienced diagnostician cannot consistently predict the presence of cancer or the likelihood of its evolution in any of these lesions. Furthermore, any given point within a lesion does not necessarily represent the balance of that lesion. The facts that CIS is often surrounded by dysplastic epithelium and that many areas of invasive carcinoma are surrounded by zones of both CIS and dysplastic epithelium lend credence to the concept that these morphologic categories of epithelial disturbance are each part of a dynamic spectrum of disorders, each probably related to and possibly representing different stages of the same process. This rationale suggests that dysplasia leads to CIS, which in turn leads to invasive carcinoma.

On the other hand, this concept is challenged vigorously, and contrary thought suggests that the spectrum of abnormal epithelial maturation and individual cellular aberrations can occur in circumstances that may or may not precede invasive carcinoma. Dysplasia is a term that is synonymous with atypia, and the degree of dysplasia is graded as mild, moderate, or severe, depending on the extent of involvement of the surface epithelium. In general, the less the degree of dysplasia, the
less likely is the transformation to invasive carcinoma. Conversely, the higher the degree of dysplasia, the more likely is such a progression. In the opinion of some investigators, however, severe dysplasia, especially in the larynx, is not a prerequisite for the development of an invasive SCC. In fact, invasive carcinoma can develop in an epithelium with only mild dysplastic changes.

As classically defined, CIS represents full-thickness, mucosal, epithelial, dysplastic change without violation of the basement membrane. For all intents and purposes, severe dysplasia can be synonymous with CIS. Also, CIS is known to arise from the basal epithelial layer in the absence of overlying dysplastic changes. In this setting, therefore, the definition of CIS can be expanded to include those lesions in which the mucosal alterations are so severe as to signal a high probability for the progression to an invasive carcinoma if left untreated. Extension of the dysplastic process to involve the mucouserous glands should still be considered CIS and not invasive carcinoma. Such is not the case with transgression across the basement membrane, which is the point at which CIS becomes invasive carcinoma.

It is unknown whether those lesions that have achieved the status of carcinoma continue to grow at the same rate as they did during their premalignant state or whether their growth is accelerated. The growth of a cancer through the basement membrane into the lamina propria constitutes the transition from CIS to microinvasive carcinoma, and accompanying this development is a tethering of vocal cord mucosal motion. The degree of this membrane motion restriction is in direct proportion to the extent of invasion into the underlying lamina propria of the vocal cord. Failure to appreciate these subtle changes can result in the administration of suboptimal treatment. For example, high failure rates that have been reported with mucosal stripping in CIS patients almost certainly represent underestimation of these lesions. Some of those lesions that had been classified in the prestroboscopic era as CIS probably contained areas of invasive carcinoma, and the stripping left behind foci of cancer that resulted in recurrence.

The gross appearance of a given laryngeal lesion is suggestive of its general type. SCCs originate within the mucous membrane and are exophytic or ulcerative, are of surface origin (Fig. 30.3-3), and are frequently adjacent to or surrounded by keratoses. Neuroendocrine cancers and tumors metastatic to the larynx are rarely submucosal and, as such, do not resemble lesions of surface origin. Metastatic lesions of various types and neuroendocrine tumors are seen throughout the various subsites within the larynx, although the latter group shows a predilection for the supraglottic area. The distribution of SCC within the various laryngeal subsites varies between different countries, a fact that reflects the different social habits within those cultures. In the United States, for example, the ratio of supraglottic to glottic SCCs is 1:2, whereas the reverse is true in certain European countries (see Table 30.3-1).

![Figure 30.3-3. Squamous cell carcinoma (C) of the true vocal cord (TVC). Notice the “surface” appearance of the lesion.](image)

The major differences in the natural histories of the various SCCs of the larynx are related largely to the area anatomy and to the lymphatic drainage patterns of the respective subsite(s).

Cellular characteristics vary by site. In the supraglottis, lesions are more likely to be nonkeratinizing and poorly differentiated, and they have more aggressive local behavior in general. Those lesions of the true vocal cords, on the other hand, are more often well differentiated and tend to be less aggressive locally. Although the degree of cellular differentiation is not thought to be the most significant fact in tumor grading, it does seem to correlate with the probability of cervical metastasis, which in turn strongly impacts on survival. Other local characteristics, such as tumor-host interface, peritumor inflammatory response, and vascular and perineural invasion, also seem important in determining performance. Finally, the actual tumor thickness and depth of invasion almost certainly have an influence on metastasis and, ultimately, on survival.

A variety of studies have attempted to standardize the predictive value of thickness in SCCs of the upper aerodigestive tract with the probability of cervical metastasis and, therefore, the prognosis. Although head and neck oncologists have for some time intuitively favored a direct correlation between the two, a number of studies have failed to demonstrate a statistically significant association between tumor thickness and nodal metastasis. Also, it should be noted that those studies demonstrating a correlation between thickness and metastasis generally focused on sites other than the larynx, and because of the anatomic complexity and embryologic uniqueness of the larynx, one cannot necessarily transpose such data from other head and neck organs.

SPECIFIC SITES

Supraglottis

Lesions of the supraglottic larynx tend to spread locally. If they begin on the epiglottis, they can extend onto the false vocal cords and into the ventricles. Inferior extension beyond the ventricle is initially thwarted, but as growth continues, these cancers can penetrate into the paraglottic space. From there they gain full access to the length of the endolarynx. These cancers often exit the paraglottic space at the top and bottom of the larynx to enter directly into the neck.

Most supraglottic lesions arise on the epiglottis, with fewer being seen on the false vocal cords and aryepiglottic folds. Those lesions that occur on the suprahypopharynx or upper part of the epiglottis are more often exophytic, whereas those that occur on the lower portion of that structure are likely to be endophytic or ulcerative. An endophytic growth pattern is especially significant in this particular area of the epiglottis because of the presence of foramina that lead directly through the cartilage into the preepiglottic space. This space is a compartment continuous with the tongue base. What would appear to be a localized tumor in the endolarynx, therefore, can actually involve considerable unrecognized extralaryngeal extension. Tumors are confined initially to the preepiglottic space by the ligamentous boundaries of that compartment, but once those barriers are overcome, the loosely arranged skeletal muscle fibers of the tongue provide no restriction to further tumor extension. Modern imaging, especially magnetic resonance imaging (MRI), has greatly improved the ability to recognize tumor extension into the preepiglottic space and base of the tongue.

Those lesions that occur on the laryngeal surface of the epiglottis are capable of invading and destroying the cartilage of that structure. Supraglottic cancers, on the other hand, almost never destroy the thyroid cartilage. This feature has an influence on the design of treatment plans. For example, an ossified and invaded thyroid cartilage poses a substantial problem for surgeons attempting to perform partial laryngectomy and also for radiation oncologists attempting to deliver curative therapy.

 Aryepiglottic fold cancers are somewhat different in their behavior, more commonly following the tendencies of pyriform sinus lesions by spreading in a more diffuse fashion and metastasizing more frequently than their endolaryngeal counterparts. The particularly ominous natural history of these lesions probably relates as much to the abundant and multidirectional lymphatic drainage of the area as it does to individual cellular peculiarities.

Because of the profuse lymphatic network of the supraglottic larynx, carcinomas of this area metastasize frequently to the cervical lymph nodes, and failure of treatment is usually a result of metastasis rather than local disease. The incidence of patients with clinically positive lymph nodes at the time of diagnosis is 23% to 50% for all supraglottic sites and stages combined. A substantial number of those patients with clinically negative necks turn out to have histologic disease as demonstrated when a neck dissection is done, or, if left untreated, they convert to clinically positive necks. In supraglottic cancers, the probability of cervical metastasis and the probability of delayed contralateral metastasis increase in direct proportion to the size of the primary (i.e., the T stage). Lindberg reported impressive overall metastatic rates with various supraglottic carcinomas: Sixty-three percent of T1, 70% of T2, 79% of T3, and 73% of T4 cases.
In that group of patients with supraglottic lesions that present with a clinically positive cervical node 2 cm in diameter or more, the possibility for contralateral neck metastasis is 40% or higher. The epiglottis is particularly prone to bilateral metastasis, and even in smaller lesions of that site, the incidence of contralateral metastasis is more than 20%. Much of the data on clinically positive necks and on occult metastasis were compiled before the routine use of computed tomography (CT) and magnetic resonance imaging (MRI) of the necks. With the use of these more sophisticated staging methods added to the already 75% to 85% accuracy of physical examination, the overall incidence of metastasis noted at the time of diagnosis will probably become higher than that reported previously.

**Glottis**

Glottic, or true vocal cord (fold), carcinoma is the most common of all laryngeal cancers encountered in the United States. Although these lesions are usually well differentiated, they can demonstrate an infiltrative growth pattern, even when they appear exophytic and well organized. Most true vocal cord cancers occur on the anterior two-thirds of that structure; a small percentage of them develop on the anterior commissure; and they rarely occur on the posterior commissure.

To a large extent, growth characteristics and the natural history of glottic carcinomas are determined by the unique anatomy of the true vocal cords. First, the sparsity of the lymphatic drainage of the true vocal cords in all areas other than the posterior commissure makes metastasis of early lesions extremely unlikely. Second, the elastic layers (conus elasticus) within the larynx often divert cancers that begin on the free edge of the vocal cord and continue into the underlying vocalis muscle and paraglottic space, which is an interlateral pathway that leads out of the larynx through the cricothyroid space. With penetration into the underlying tissues, all degrees of motion impartation, from subtle mucous membrane stiffness to frank fixation of the vocal cord, can follow. That increasing impairment of motion has a telling effect on local control and survival data, a fact that is reflected in AJCC staging designations. Much discussion continues about mobility change and its therapeutic implications, and it is in the group of glottic cancers that demonstrate this change that the clinical judgment of the physician is most tested. The final anatomic factor unique to the glottis that influences the growth pattern of certain cancers is the anterior commissure ligament, which forms the bridge between the anterior ends of the true vocal cords. This structure lies immediately against the inner lamina of the thyroid cartilage, and its presence initially retards penetration of cancers into that area, often causing their diversion upward onto the epiglottis or downward onto the cricothyroid membrane. From there, these lesions can escape the larynx into the anterior neck. If the cancer overcomes the ligamentous barrier at the anterior commissure, the cartilage is penetrated. This event is particularly likely in thyroid cartilages that are ossified, and when this does occur, substantial therapeutic implications compromise the effectiveness of radiation therapy and dictate specific surgical approaches.

**Subglottis**

Carcinomas of the subglottic larynx are unusual, making up only approximately 1% to 8% of all laryngeal cancers. These lesions tend to be poorly differentiated and often demonstrate an infiltrative growth pattern unimpeded by tissue barriers. These tumors are, therefore, frequently circumferential and can extend down the trachea. The incidence of cervical metastasis in this group of cancers is reported to be 20% to 30%, but that figure is somewhat obscured by the fact that the primary drainage pattern of these lesions is to the less detectable pretracheal and paratracheal nodes. The actual incidence of metastasis may, therefore, be significantly higher.

**UNUSUAL AND RARE NEOPLASMS**

The pathology and pathogenesis of verrucous carcinoma are unique and deserve special consideration. This unusual tumor is poorly understood, and its origin, classification, and response to treatment are controversial. Verrucous carcinoma is described as a distinct neoplastic entity of squamous origin that occurs in the oral cavity, larynx, esophagus, and nose and on the genitilia. Some authorities have suggested the human papillomavirus as its cause. Although there are views to the contrary, most investigators consider verrucous carcinoma to be an entity unto itself. Just because some tumors originally thought to be verrucous carcinomas are discovered to have features of SCC and can metastasize does not, in their opinion, justify combining the two diagnoses (actually, they think that such tumors were always low-grade SCCs rather than verrucous carcinoma). Other investigators, although conceding verrucous carcinoma to be unique, believe it to be only a variant of well-differentiated SCC. Different authors believe that because verrucous carcinomas neither fulfill the histologic and cytologic criteria of malignancy nor possess the capability to metastasize, they should be renamed verrucous acanthoma. When this lesion does occur in the larynx, it usually is on the true vocal cord, where it grows slowly and can cause significant local destruction by expanding gradually. Although these lesions often destroy cartilage, they do not tend to metastasize; instead, aggressiveness is directed locally.

Verrucous carcinoma is consistently difficult to diagnose, even when the clinical index of suspicion is high. This observation relates to the fact that these tumors microscopically demonstrate an exuberant and keratinizing hyperplasia that is benign by pure histologic and cytologic criteria. The diagnosis is largely a clinical one and is most effectively achieved by concert between pathologist and surgeon, but usually only after multiple biopsies have been taken.

Verrucous carcinoma is typically a slow-growing but relentless mass, exophytic and wary in appearance, and broad based at its interface with the mucosa. Its surface is often necrotic and infected, and the associated inflammation of adjacent tissues can be remarkable. This tendency to cause inflammation can erroneously influence treatment planning. For example, the patient with verrucous carcinoma can demonstrate enlarged adjacent cervical lymph nodes that are worrisome when in fact the adenopathy is only secondary to the inflammatory process. Although this finding has been described in other aerodigestive tumors, the mere presence of lymphadenopathy in the primary drainage area of an impressive primary tumor is worrisome, no matter how benign its histology looks. In such a circumstance, clinical judgment is enhanced greatly by modern imaging and cytopathologic techniques.

**FIGURE 30.3-4.** Verrucous carcinoma of the true vocal cord.

This discussion of the nature of verrucous carcinoma has substantial therapeutic implications, especially when the lesion occurs in the larynx. Essentially, SCC is a radiosensitive cancer, a fact that provides treatment options to the oncologist. On the other hand, verrucous carcinoma seems to be somewhat radioresistant, whether found in the mouth or the larynx. Additionally, anecdotal information suggests radiation-induced dedifferentiation into anaplastic cancer in these lesions. This transformation seems to occur in fewer than 10% of verrucous carcinomas and may involve alteration of the DNA that facilitates the integration of the human papillomavirus into host cells. Both the concept of radiation resistance and the transformation into anaplastic cancers are vigorously disputed. The neuroendocrine family of tumors represents an evolving database. This is true largely because newer diagnostic techniques have allowed pathologists specifically to label as neuroendocrine a variety of previously undefined cancers. Almost certainly, an immunohistochemical reexamination of laryngeal cancers previously diagnosed as atypical or undifferentiated malignancies would result in the reclassification of many of them as neuroendocrine tumors. The small cell tumors look and act much like their counterpart oat cell lung lesions and, as such, are generally managed by chemotherapy and radiation therapy. Surgical procedures do not seem to enhance the likelihood of survival in patients with these tumors. The other neuroendocrine tumors that occur in the larynx—carcinoids...
and parangliomas—are rare and are best managed surgically. Cartilaginous malignancies, adenosarcomas, sarcomas, malignant fibrous histiocytomas, plasmacytomas, granular cell tumors, and primary lymphomas have all been reported but are rare. Primary melanomas of the larynx are equally rare. Of all of the laryngeal cancers reported from Memorial Sloan-Kettering Cancer Center between 1949 and 1983, only three were melanomas.

**DIAGNOSIS AND EVALUATION**

Cancers of the supraglottic larynx usually do not produce early symptoms or signs, and it is common for the first hint of such a cancer to be cervical adenopathy. When symptoms do occur, they are often subtle; pain perceived in the primary site or in the ear (otalgia), a scratchy sensation when swallowing, or merely an alteration of one's tolerance for hot or cold foods may be all that is noticeable. Airway alteration, hoarseness, or a tendency to aspirate liquids are all produced by more advanced lesions.

Cancers of the glottis, on the other hand, are often detected early in the course of the disease because even a slight alteration of the vibratory surface of the true vocal cords produces voice change. Smokers are often hoarse, however, and such alteration of the voice may not alarm them. Anyone with a voice change that persists longer than 2 weeks should have a laryngeal examination. Different than in supraglottic lesions, it is unusual for glottic cancer patients to seek medical attention because of cervical adenopathy. In the latter group, metastasis generally occurs late in the course of the disease, long after the early warning signals.

Subglottic cancers are uncommon, but when they do occur, they do not produce early symptoms; therefore, the disease is often advanced by the time of diagnosis. Almost all laryngeal cancers are squamous carcinomas and, as such, are surface lesions. Most are obvious with routine laryngeal inspection, but a small percentage are located in obscure areas and, therefore, not readily visible. The modern generation of flexible endoscopes has provided the capability of examining the larynx to a broad range of physicians; thus, the overall process of screening and follow-up after treatment has been enhanced. Importantly, these methods allow the occasional laryngeal examiner to see areas that previously had been visually inaccessible.

**FIGURE 30.3-5.** Flexible laryngeal endoscope in use.

It is essential that the larynx be examined in the awake patient who is sitting upright. Direct laryngoscopy under anesthesia should be reserved for biopsy and a more detailed tumor mapping. Even when done under local anesthesia, the introduction of a direct laryngoscope distorts the natural position and the relaxed motion of the larynx and, by doing so, tends to disguise subtle motion changes that are important in staging of these tumors. Certain subtleties of contour, such as bulging and tethering, are visually not appreciable during direct laryngoscopy.

**FIGURE 30.3-6.** Diagrams of laryngopharynx used for mapping and recording tumors.

The earliest stage of invasive glottic carcinoma through mucosa into the underlying lamina propria is visible as a tethering of the mucous membrane that normally slides over the underlying structures, and the mucosal wave is lost. Although the gross abductive capabilities of the vocal cord may be intact, the early invasive character of a lesion can be appreciated when a stroboscopic examination is used to demonstrate this restrictive feature. As the process of invasion continues into the underlying vocalis muscle, the actual lateral excursion of the vocal cord is limited and eventually lost. The ability of the clinician to view and interpret this scenario is critical to the sophisticated management of vocal cord cancer. Essentially, lesions of the true vocal cord that do not transgress the basement membrane do not cause tethering of the mucosa, and those that enter the underlying lamina propria do cause tethering. Benign lesions and even CIS, therefore, may look extensive topographically, but their lack of depth is revealed by appropriate diagnostic technology. Although contemporary methods of staging tend to emphasize the bulk and topographic size of tumors rather than depth, investigators have begun to focus more on this third dimension. As data are accumulated, more emphasis will be placed on this important matter.

 Imaging should not be relied on to detect early larynx cancer, because the routine methods of physical examination are far more suitable. The primary care physician should not, therefore, initially resort to CT or MRI when a laryngeal cancer symptom persists. Instead, someone skilled in the appropriate techniques should examine that patient. Once a lesion is discovered, however, the evaluation of its depth, bulk, and possible cartilage invasion and the status of the regional lymph nodes are often enhanced by CT or MRI. It is not clear which of the two imaging methods is better for larynx cancer evaluation. Both have certain advantages over the other, and both are of limited usefulness in evaluating the radiated larynx. CT of the larynx is most effectively achieved in the axial plane, and because of this, the images are especially efficient in showing lateral tumor extension and the relation of that extension to cervical nodal disease. The axial projection is, therefore, effective in demonstrating the important paraglottic space. CT also effectively demonstrates the vertical extension of tumor, especially in the subglottic and anterior commissure areas. MRI offers the advantages of multiplanar visualization of the larynx and, therefore, is especially valuable in evaluating the preepiglottic space and the adjacent base of the tongue.

Invasion of laryngeal cartilage is important in treatment planning. Determining whether this feature exists has always been difficult because of the inconsistency of the ossification that occurs in the laryngeal framework. Generally, cartilage is vulnerable to tumor invasion in those areas where it is ossified, and it is somewhat resistant where it is not ossified. In fact, healthy, nonossified cartilage provides a considerable natural barrier to cancer invasion. Writings by Castelijns et al. and Towler and Young have suggested that MRI is the method of choice for delineating the important finding of cartilage invasion. Other investigators would dispute this claim. One study correlated MRI findings of cartilage invasion with the effectiveness of radiation treatment, and in so doing, the authors found a surprising number of small glottic
lesions with foci of cartilage invasion. Significantly, it was from this group that most of the radiation failures of the series occurred. Other imaging methods, such as tomography and laryngography, have been surpassed by more elaborate technology and are only of historic interest.

STAGING

The AJCC last updated larynx staging in 1997, and that version is presented in Table 30.3-3. Staging provides a commonality of language that is essential for effective outcomes analysis. The larynx is a complex structure because it involves many anatomic and physiologic factors that impact on performance and, therefore, on staging. Although it is essential that pathologic findings always be compared with preoperative analysis, it should be remembered that the staging referred to and that reported by the AJCC is a clinical one, which is based on performance. The accuracy of clinical staging is periodically updated on the basis of better recognition of performance. For example, Pillbury and Kirchner studied this question by comparing whole-organ sections of nonradiated larynges and compared the actual pathologic findings with the preoperative staging. They found that 40% of cases had been categorized incorrectly, and most of these inaccuracies reflected understaging. Most commonly, the depth of invasion had been underestimated, and the frequency of cartilage invasion was much higher than previously had been realized. Certainly, as imaging technology improves, so will the ability to stage more accurately. As clinicians make use of adjuvant chemotherapy treatment protocols for which the assessment of complete versus partial response is required, modern imaging hopefully will enhance the accuracy of that assessment.

TABLE 30.3-3. Tumor (T), Node (N), Metastasis (M) Staging System for Larynx

Survival in larynx cancer decreases in a linear fashion with increasing stage. The most remarkable change is between stages II and III, the zone that generally represents the occurrence of cervical metastasis.

TREATMENT AND SURVIVAL

Supraglottis

Because the supraglottic larynx is composed of multiple sites, referring to it as one unit is not always accurate when discussing treatment results. Because all of the subsites are intimately related and because the supraglottic is continuous with its neighboring glottic larynx, the hypopharynx, and the oropharynx, it can be difficult to determine the exact site of many large cancers. For example, when one encounters a lesion that involves the pharyngoepiglottic fold, the aryepiglottic fold(s), and the pyriform sinus(es), it can be difficult to know whether this is a primary hypopharynx cancer extending superiorly or a supraglottic cancer extending inferiorly.

Unlike glottic cancer, in which cervical metastasis is relatively uncommon in early-stage disease, the probability of nodal spread in all supraglottic lesions is substantial. A contralateral metastasis is significantly probable in these lesions, and this probability increases in direct proportion to primary tumor size. This finding is especially true for epiglottic lesions, which make up most of the supraglottic carcinomas. It is essential to recognize that the site of treatment failure in supraglottic cancer is usually the neck; therefore, treatment strategies require neck management for virtually all lesions. For the N0 neck, this implies selective neck dissection and/or postoperative radiation, or elective radiation only. For patients with a clinically positive neck(s), this implies neck dissection, therapeutic radiation, or both.

Early-stage supraglottic cancers have equivalent cure rates with either conservative (partial laryngectomy) surgery or primary radiation therapy. This is especially true for those lesions on the most cephalic part of the epiglottis (i.e., the suprahypoid epiglottis), but not for those lesions on the lower part of that structure where there are foramina that lead through the cartilage into the preepiglottis space and, ultimately, into the tongue base. For more advanced lesions, a variety of treatment options are available, including radiation therapy alone, supraglottic laryngectomy with or without postoperative radiation therapy, and chemoradiation therapy programs for patients who would otherwise require a total laryngectomy.

The results of primary radiation for supraglottic cancer are well established. Mendenhall and colleagues reported 5-year local control of 100% for T1, 83% for T2, 68% for T3, and 56% for T4 lesions. Wang and associates reported 5-year local control of 96% for T1, 86% for T2, 76% for T3, and 43% for T4 lesions. In this particular study, when laryngectomy was added for salvage, local control was 96% for T1, 93% for T2, 88% for T3, and 51% for T4 lesions.

Different criteria create T3 designation of supraglottic laryngeal cancer, and in selected circumstances of this stage in which there is no vocal cord fixation, supraglottic laryngectomy can be applied efficiently; thus, voice sparing is achieved. Three different studies have applied strict standards to the patient selection for supraglottic laryngectomy in T3 lesions, and disease-free survival of approximately 75% at 3 years can be expected.

Parsons and coworkers reported on 26 T4 invasive SCCs of the larynx treated with radiation therapy. Only 38% achieved local control at 5 years in this report. Other series also demonstrate the similarity of outcomes of primary radiation therapy and surgery, even for moderately advanced disease. Supraglottic lesions that cause vocal cord fixation (T3), those that involve the postcricoid region (T3), those that invade the laryngeal cartilage (T4), or those that extend into extralaryngeal sites (T4) can often be effectively managed with total laryngectomy and postoperative radiation therapy. Today, however, it is the exception rather than the norm to offer a patient a total laryngectomy as an initial treatment option in these advanced-stage cancers. Instead, the organ-sparing strategy of chemoradiation, with laryngectomy reserved for unsuccessful cases, is generally the standard of care. It should be emphasized, however, that each case must be individualized, and certain lesions in certain patients warrant the traditional approach whereby laryngectomy is performed first.

For patients who undergo supraglottic laryngectomy, postoperative radiation therapy is occasionally considered. Excellent local control has been reported with this sequencing in selected T3/T4 lesions; however, the combination of these two treatments is morbid, with increased gastrostomy or tracheostomy dependence, airway problems, and delayed independent swallowing. In general, it is best to choose one or the other (i.e., radiation or surgery) as the definitive local therapy. However, because of the extremely low rate of local recurrence after supraglottic laryngectomy, postoperative radiation to the laryngeal segment is not often used after this operation.

An advantage to radiation as the initial treatment of early-stage supraglottic disease is that bilateral elective neck radiation can be included in the plan with minimal morbidity. If an adequate dose of elective neck radiation is given, neck relapse should be less than 5% in the absence of clinically obvious disease. If surgery is chosen as the treatment for a T1 or T2 supraglottic lesion, the supraglottic laryngectomy should be combined with bilateral selective neck dissections, even when the neck is N0. Postoperative radiation therapy is added to the necks of those patients in whom these staging procedures show metastatic disease. The obvious disadvantage to this approach is that it becomes necessary to use two different treatment modalities compared with the strategy in which radiation therapy is used initially to the primary tumor and necks. The disadvantage to the plan that uses radiation therapy initially is that, when it is unsuccessful, total laryngectomy is needed. Such is the case because supraglottic laryngectomy is contraindicated after full-course radiation therapy to the larynx (complications such as persistent swelling,
failure of wound healing, radiation chondritis, and swallowing difficulties are strikingly frequent in this setting). Pretreatment CT scans can be helpful in predicting outcomes for supraglottic lesions treated with primary radiation therapy. Herrmans and colleagues\textsuperscript{133} reported that tumor volume derived from CT analysis was the strongest predictor of locoregional failure and that the degree of paraglottic space involvement, subglottic extension, and preepiglottic space involvement were important prognostic factors demonstrated by this imaging method. Mancuso et al.\textsuperscript{134} was able to quantify the correlation between CT findings and local control. For patients with a tumor volume of less than 6 cm\textsuperscript{3} who were treated by radiation therapy alone, local control was achieved in 89%. When the tumor volume was 6 cm\textsuperscript{3} or greater, the local control was only 52%. A decreased rate of local control and voice preservation was also noted if 25% or more of the preepiglottic space was involved with tumor. A study conducted by Lo and associates\textsuperscript{135} also correlated CT tumor volume with radiation failure, but this analysis was unable to demonstrate such a correlation with surgery.

When comparing one type of operation (supraglottic laryngectomy) to the other (total laryngectomy), it is important to note that the former of the two is physiologic and allows retention of vocal and swallowing functions. Furthermore, because of the unique lymphatic drainage patterns of the organ and the presence of certain natural anatomic barriers to tumor spread, this operation is oncologically sound, yielding the same local control rates as achieved by total laryngectomy in comparable lesions.\textsuperscript{136,137} Ogura and Biller\textsuperscript{138} reported an 85% 3-year control for epiglottis cancers treated with supraglottic laryngectomy, but this result decreased to 71% with extension onto the false cord(s). These figures are comparable to those produced by total laryngectomy for similar lesions.

It is not the mission of this text to provide an elaborate description of the various partial laryngeal surgical techniques used to manage supraglottic cancer; however, the student of this disease should have at least a summary knowledge of the methods known collectively as conservation laryngeal surgery. The compartmentalization of the larynx and the directional drainage patterns of the lymph channels within it provide surgeons with the unique opportunity for removing that portion of the larynx above the true vocal cords, and with proper reconstruction, swallowing and vocal functions are retained in the process. Essentially, this procedure is a horizontally directed hemilaryngectomy in which the surgeon removes the upper half of the thyroid cartilage and the contents within it (the false vocal cords, the epiglottis, and the aryepiglottic folds). The edge of the thyroid cartilage is brought up to and attached to the transected base of the tongue. Because the motor nerve supply of the vocal cords comes from below (recurrent laryngeal nerves) and is not in the surgical field, the important vocal cord functions of abduction and adduction are retained, and because of this, voice and the important airway protective functions of glottic closure are preserved.

The supraglottic laryngectomy is, however, physiologically challenging, and patients with chronic pulmonary disease often have difficulty tolerating the aspiration that can follow. Essentially, this elegant technique is oncologically sound in appropriate tumors, but certain patients are not good candidates for its implementation. The correct use of the supraglottic laryngectomy is accomplished only by surgeons properly trained in this methodology and who have the experience to apply the right methods in the right situations. A succinct discussion of the method of selection for all conservation procedures and which patients are suitable for them was developed by Sessions and Parish.\textsuperscript{139} Although certain chemoradiotherapy options have been popularized since that discussion was published, the fundamental principles are the same and can be applied to the current philosophy. As those alternative chemoradiation schemas are used more frequently, the number of surgeons accomplishing conservation laryngeal surgery will diminish. Although the idea of saving more larynges without compromising cure is meritorious, it is worrisome that those subtle skills necessary for achieving excellent functional results with the partial laryngectomies is to some extent being lost by the current generation of head and neck surgeons. A variety of conservation surgery procedures are applied to variations of laryngeal cancer, and although a description of each is beyond the scope of this text, the following classification of these operations should be helpful in placing this important surgical methodology into the proper perspective:

1. Hemilaryngectomy
   a. Horizontal hemilaryngectomy (supraglottic)
   b. Vertical hemilaryngectomy
   i. Lateral hemilaryngectomy
   ii. Frontal hemilaryngectomy
2. Cordectomy
3. Supracricoid laryngectomy\textsuperscript{133}
4. Partial laryngopharyngectomy

Just as with the description of specific surgical methods, elaborate details of radiation therapy technique are not appropriate here. In general, patients with early-stage laryngeal disease are treated with once daily continuous course radiation therapy. Opposed lateral fields are used for the primary site and upper neck(s), and a separate anterior field is used for the lower neck(s). In selected total laryngectomies, the stoma is included in this neck treatment plan. The total dose to the primary site is in the 65 to 70 Gy range.\textsuperscript{133,134} For more advanced disease, a variety of fractionation schemes have been used, including once daily, twice daily, and concomitant boost techniques.\textsuperscript{133,134} A Radiation Therapy Oncology Group randomized trial compared four different fractionation schedules for advanced head and neck cancers treated with primary radiotherapy: once daily radiation to a total of 70 Gy in 7 weeks; twice daily radiation using 1.2 Gy per fraction to a total dose of 81.6 Gy; accelerated hyperfractionation technique with a planned break using 1.6 Gy per fraction twice daily up to approximately 38.4 Gy, followed by a 2-week break, and a combination of both with once daily 1.6 Gy and a concomitant boost technique using once daily fractionation in the beginning of the program, followed by twice daily fractionation for the concomitant boost during the final 12 treatment days, up to a total of 72 Gy. The results show better 2-year locoregional control and disease-free survival using the concomitant boost approach. Acute and late toxicity was acceptable, although increased, over standard fractionation.

**Glottis**

CIS of the true vocal cord is highly curable with equal efficiency by microexcision, laser vaporization,\textsuperscript{132} or radiation therapy.\textsuperscript{133} Pure CIS lesions are unusual, and a frequent association exists, more often than not, between such lesions and invasive carcinoma. Those series that have been reported in which numerous recurrences developed after stripping of vocal cord CIS almost certainly consisted of a heterogeneous group that included lesions containing areas of unrecognized invasive cancer. For this reason, we favor microexcision of the involved membrane over laser vaporization, which destroys the specimen and does not allow for the pathologic analysis needed to identify areas of microinvasion. True CIS, by definition, remains superficial to the basement membrane, and if mucosal excision techniques are confined to that group of patients, the cure rate should be the same as the best that can be achieved by radiation therapy. The advantages of microexcision over radiation is that it is simpler and that radiation therapy is held in reserve for future use. Considering the incidence of metachronous and synchronous second primary, cancers that occur in the aerodigestive tract, the policy of holding radiation in reserve whenever possible is prudent. The advantages of radiation therapy are that the voice is at least as good and often better than with surgery, and it is a more definitive treatment for invasive cancer that may exist within the lesion. In both microexcision and radiation, when treatment fails, a surgical procedure can still salvage most patients and, in the majority of cases, with a voice-sparing operation.

All things considered, if the diagnosis of pure CIS of the vocal cord(s) is fairly certain, microexcision is probably the treatment of choice. So-called vocal cord stripping often has a crippling effect on the voice and is in violation of the contemporary standard of care. Such is not the case with microexcision, which has minimal impact on vocal quality.

The value of a properly excised piece of tissue to complete a histopathologic analysis cannot be overrated. Importantly, microexcision should include a wide zone around the obvious trouble, followed by a thorough pathologic evaluation of the specimen to look for microinvasive areas. Procedures that excise the underlying vocal cord muscle (i.e., cordectomy) produce a crippling vocal effect and do not offer any oncologic improvement over microexcision or radiation; thus, such a procedure should not be considered as one of the treatment options for vocal cord CIS.

Radiation therapy is used either as the definitive treatment for CIS when microexcision is not possible or is refused, or as a salvage treatment for patients with recurrent CIS following prior surgical procedures.\textsuperscript{135,136} Series of CIS patients show that, when radiation therapy is used, it is very effective. Medini and coworkers\textsuperscript{136} reported the outcomes with 68 CIS treated with radiotherapy, using a dose of 1.75 Gy per fraction to a maximum total dose of 68.4 Gy. The 4-year disease-free survival rate was 95%. Improved voice was reported in 16 of 20 patients, with no change noted in the other 4. In summary, the standard of care for CIS of the vocal cord consists of a strategy that uses primary surgery for most patients and selective radiation therapy in others.

These authors rely heavily on the preoperative evaluation by videostroboscopy\textsuperscript{137} to estimate the depth of the surface cancer. Normal membrane motion (i.e., a normal mucosal wave)\textsuperscript{138} suggests confinement of the lesion to that area superficial to the basement membrane (i.e., CIS). On the other hand, if stroboscopy demonstrates tethering of the membrane to the underlying tissue, we consider that a sign of microinvasion (more advanced than CIS). Such a patient receives radiation therapy. If
we believe the lesion is entirely superficial to the basement membrane, we do microexcision and examine the specimen carefully for microinvasion. The understaging of CIS in past studies could probably have been avoided by the appropriate use of stroboscopic analysis.

Finally, certain CIS lesions, such as those on the anterior commissure, in the subglottis, or some that extend into the laryngeal ventricle, do not lend themselves to these surgical methods; in these cases, radiation is a better means of initial treatment. For T1 or T2 invasive glottic cancer, excellent local control is achieved by either radiation therapy or conservation surgery procedures. It is generally agreed, however, that vocal quality is better after radiation therapy. Harrison and colleagues reported an ultimate return to normal voice in nearly all biopsied T1 and T2 glottic cancer patients. Even though several patterns of vocal dysfunction existed before, during, and immediately after radiation therapy, normalization of these alterations occurred within 3 months after completion of radiotherapy. Dagli, however, showed that the postradiation voice, although better than the surgically treated counterpart, remains abnormal with respect to various subtle parameters, such as maximum vocal intensity, dynamic vocal intensity range, jitter, and mean fundamental frequency. De Graeff and associates also reported objective improvement of speech after radiotherapy but pointed out that there was short-term, temporary deterioration of physical functioning and fatigue. Tsunoda and coworkers stroboscopically studied the changes of the mucous membrane motion after radiation of early glottic cancers. They demonstrated ultimate return to normal motion in all patients studied. Furthermore, these authors suggested the potential value of stroboscopy for detecting early cancer recurrence, thus corroborating the findings of Sessions et al. in a previously reported study.

Finally, there seem to be predictors of poor vocal quality: Vocal cord stripping (instead of biopsy only) before radiotherapy and continued smoking after radiation therapy predicted worse voice quality as well as substandard stroboscopic performance. It is important to note that, in those lower-staged (i.e., T1 and T2) glottic lesions that are unsuccessfully treated with radiation, salvage partial laryngectomy (hemilaryngectomy) can be performed successfully in a significant number of patients, thus achieving excellent overall cure rates while retaining voice.

Whether achieved by radiation therapy or by surgery, local control rate decreases with increasing tumor bulk. Dickens and coworkers reported the results for early glottic tumors of various sizes and extent. The lesions were categorized by the type of surgical procedure that would have been necessary had surgery been used. This type of analysis provides an excellent basis for comparing the results of surgery and radiation. In patients suitable for hemilaryngectomy, the local control with radiation alone was 94%. This figure increased to 100% when surgical salvage was added. On the contrary, for patients managed by radiation therapy who would have required total laryngectomy, local control rate was only 65%, but it increased to 91% when surgical salvage was added. Extension of these glottic carcinomas onto the anterior and posterior aspects of the larynx lessens the local control rates achieved with radiation therapy. In this study, the surgical procedure required for salvage usually was a total laryngectomy rather than a hemilaryngectomy.

Essentially, the 5-year survival rates for primary surgery (cordectomy or hemilaryngectomy) and primary radiation for T1 lesions are comparable, and local control obtained in this same-stage glottic group using conservation surgical procedures is reported to be 78% by Kirchner and Owen and 87% by Ogura et al. Results obtained for comparable T1 lesions treated by radiation therapy show local control of 91% by Harwood and 93% by Pellitteri.

Sessions and colleagues reported a 5-year survival rate of 74% for T1 and T2 lesions that originated in the anterior commissure of the glottic larynx. This study demonstrated that survival and recurrence rates of anterior commissure lesions correlated with the size and stage of the tumor. Olofsson and associates reported an 80% survival rate at 5 years for early-stage anterior commissure lesions, but this study included those recurrences that had been salvaged by surgery. Those anterior commissure lesions that are thin and of low volume and that do not have substantial subglottic extension are probably treated with equal efficiency by partial laryngectomy or radiation therapy. As lesions become more advanced, the natural barrier of the anterior commissure ligament is overcome and the thyroid cartilage is frequently invaded; therefore, radiation therapy becomes less appealing than surgery as the front-line treatment. Most tumors involving the anterior commissure occur as a result of spread from the true vocal cord. Lesions actually arising in the anterior commissure are unusual, making up 1% to 2% of glottic cancers. In summary, the standard for treating T1 glottic cancers is radiation therapy, and partial or total laryngectomy is used as a salvage operation in those patients for whom this first line of treatment is unsuccessful.

The management of T2 lesions, on the other hand, is somewhat more complicated because this group is more heterogeneous. Surgical management usually consists of vertical hemilaryngectomy and is associated with 3-year survival rates of 83% and 82% in two major series. Primary radiation therapy with surgical salvage yields a net 5-year survival rate of 92% in Pellitteri et al.’s series. 72% in Wang’s series, and 90% in Fletcher et al.’s series. Because of the heterogeneity of the T2 group, Wang has suggested subdividing these lesions into those with normal mobility (T2A) and those with impaired mobility (T2B). He showed that local control was obtained in 86% of the former and 63% of the latter when primary radiation was used. Similar observations were made by Harwood, whose series yielded 77% and 51% local control rates for T2A and T2B lesions, respectively. Medini and colleagues reported a 5-year disease-free survival rate of 80% for T2A and 64% for T2B lesions. Klintenberg and associates reported a 73% for T2 lesions, with subglottic extension being the most significant factor. In summary, radiation therapy is usually recommended as the primary treatment modality for T2 lesions with no vocal cord mobility impairment (T2A); however, in those lesions that demonstrate impairment of motion (T2B), hemilaryngectomy is preferred. These criteria are variable, however, depending on tumor bulk, and in those less bulky T2B lesions, radiation can be used. It should be noted also that, when vocal cord motion is restricted by actual surface tumor bulk rather than by invasion of the underlying muscle, radiation is often ineffective.

Those conservation surgical procedures that can be applied to the management of glottic cancer are time honored and tested, and when used in the properly selected patient, can yield an 80% survival rate at 5 years for early-stage anterior commissure lesions, but this study included those recurrences that had been salvaged by surgery. Those anterior commissure lesions that are thin and of low volume and that do not have substantial subglottic extension are probably treated with equal efficiency by partial laryngectomy or radiation therapy. As lesions become more advanced, the natural barrier of the anterior commissure ligament is overcome and the thyroid cartilage is frequently invaded; therefore, radiation therapy becomes less appealing than surgery as the front-line treatment. Most tumors involving the anterior commissure occur as a result of spread from the true vocal cord. Lesions actually arising in the anterior commissure are unusual, making up 1% to 2% of glottic cancers. In summary, the standard for treating T1 glottic cancers is radiation therapy, and partial or total laryngectomy is used as a salvage operation in those patients for whom this first line of treatment is unsuccessful.

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Those conservation surgical procedures that can be applied to the management of glottic cancer are time honored and tested, and when used in the properly selected case of laryngeal cancer, they consistently yield excellent results functionally and oncologically. The most commonly used of these procedures is the vertical hemilaryngectomy, in which the surgeon bisects the larynx and, to a varying degree, removes a portion or all of the true and false vocal cord along with the respective half of the thyroid cartilage. Because most of the lesions for which this operation is performed are located on the anterior two-thirds of the vocal cord, the most posterior resection line usually is in front of the arytenoid cartilage. In those circumstances in which the cancer extends onto the posterior larynx, this cartilage can be resected (Fig. 30.3-7). By using the perichondrium from the external surface of the half of the thyroid cartilage that has been removed, the operated side of the larynx heals in the midline, forming a firm buttress (pseudocord) against which the opposite and normal true vocal cord vibrates.

FIGURE 30.3-7. Axial and frontal views of larynx show that portion of the organ removed by a horizontal hemilaryngectomy ( shaded).

Just as with surgery, radiation therapy of T2 glottic cancer need not include elective neck treatment. Fein and coworkers reported that, in this group, the incidence of neck failure was 3.7% with elective neck radiation, and 2.6% when no elective treatment was given. The radiation field arrangement is similar to the technique used for T1 disease. The field size must be large enough to encompass the entire extent of disease, and the total dose is usually approximately 70 Gy range. Various factors seem to be important prognostically for all glottic cancer treated with radiation. Several series strongly correlate anemia with poorer outcomes for T1 and T2 glottic cancer treated with radiation, with one series revealing a 6% drop in local control for every 1 g drop in hemoglobin. Similar studies have not been accomplished with surgically treated patients.
Data on other potential prognostic markers include contradictions on whether p53 correlates with radiation failure; some suggest such an ability, whereas others fail to demonstrate a significant relationship. Growth factor markers such as Ki-67, an indicator of the proliferation index, may be important and may also be prognostic for surgically treated cases.

Radiologic imaging is playing an increasingly important role. CT derived tumor volume correlates with outcome for radiation patients and may become increasingly important. Emerging data likely suggest that position emission tomographic scanning may be very useful in assessing patients after radiation therapy and in differentiating radiation-related changes from recurrent tumor.

A continued evolution of radiation techniques is largely responsible for the excellent control of early glottic disease in many reported series. Lower-energy photon beams (cobalt 60, 4-MV linear accelerators) may have an advantage over higher-energy beams, although proper treatment planning may make 6-MV beams acceptable.

Much has been written about the time-dose relationships and the variety of fractionation schemes used. The optimal fractionalization schedule is not known, although many different programs have been successfully conducted. Most authors agree that dose per fraction of 2 Gy or more is preferable to lower dose per fraction. Most institutions use a dose per fraction of 2 Gy or more and a total dose in the 60 to 66 Gy range, with lower total doses in those with higher doses per fraction. It seems clear that longer overall treatment times are associated with worse outcomes.

Individualized treatment planning, isodose contours, and beam compensation are mandatory to optimize local control. Lower-energy photon beams (cobalt 60, 4-MV linear accelerators) may have an advantage over higher-energy beams, although proper treatment planning may make 6-MV beams acceptable.

It seems clear that longer overall treatment times are associated with worse outcomes. It also is similar to a comparably poor performance for those larynx cancer patients with hypopharyngeal extension.

Several strategies, the concept of organ preservation is today widely accepted as standard therapy in selected advanced larynx and hypopharynx cancers. Most institutions use a dose per fraction of 2 Gy or more and a total dose in the 60 to 66 Gy range, with lower total doses in those with higher doses per fraction. It seems clear that longer overall treatment times are associated with worse outcomes.

The cure rate for these tumors is poor, despite combination therapy. Total laryngectomy and appropriate neck surgery, including thyroidectomy, are probably the surgical treatment most recommended, and postoperative radiation therapy should probably be administered.

Subglottis

Although the preponderance of subglottic tumors are SCCs, adenocarcinomas and adenosquamous carcinomas are seen occasionally. The cure rate for these tumors is poor, despite combination therapy. Total laryngectomy and appropriate neck surgery, including thyroidectomy, are probably the surgical treatment most recommended, and postoperative radiation therapy should probably be administered. Mediastinal dissection of the paratracheal nodal groups does not seem to add substantially to survival rates.
Chemotherapy for Preservation of Laryngeal Function—Organ Preservation

Surgical management of locally advanced SCCs of the larynx and hypopharynx has often required total laryngectomy. Organ-preservation trials in the form of uncontrolled feasibility series and prospective randomized controlled trials are now available to guide appropriate use of chemotherapy. In general, two nonsurgical strategies—induction chemotherapy followed by definitive radiation therapy in responding patients, and concurrent radiation therapy and chemotherapy—are the alternatives to laryngectomy.

Recent chemoradiation has been used for the treatment of unresectable head and neck cancer for decades. Trials of multiagent cisplatin-based chemoradiation strategies have demonstrated improved locoregional control and survival compared with radiation therapy alone in cancers of the nasopharynx, oropharynx, and in unresectable cancers of all aerodigestive sites. For resectable stage III and IV cancers of the larynx and stage II, III, and IV cancers of the hypopharynx, mature data is available on the induction chemotherapy strategies as a means of preserving the larynx. Randomized trials evaluating concurrent chemoradiation are nearing completion in the United States and are in progress in Europe.

The concept of induction chemotherapy as a primary strategy evolved for two main reasons. First, high response rates could be achieved with the standard cisplatin (100 mg/m² day 1) and infusional 5-fluorouracil (5-FU) (1000 mg/m²/d, days 1 to 5) regimen: an 85% overall response rate (complete and partial) and a clinical complete response rate ranging from 30% to 50%. A pathologic complete response was confirmed by biopsy or by resection in two-thirds of clinical complete responders. Second, the response to chemotherapy was generally predictive of radiosensitivity. These observations led to a number of uncontrolled trials, mostly in patients with advanced laryngeal and hypopharyngeal cancers that were destined for total laryngectomy. These small published series confirmed the feasibility of the concept of induction chemotherapy followed by definitive radiotherapy to preserve speech and swallowing function, and importantly, they suggested that survival was not compromised in the process. Three randomized controlled trials and a metaanalysis provide data from which to draw conclusions and recommend guidelines for patient management. The general scheme for organ preservation protocols that was conceptualized by Hong and colleagues is outlined in Figure 30.3-8.

FIGURE 30.3-8. Posterior view of pharynx and great vessels shows retropharyngeal lymph nodes commonly involved in hypopharyngeal cancer. a, artery; int., internal; n, nerve; v, vein.

Randomized Trials

The first randomized trial using induction chemotherapy for organ preservation was started in 1985 by the Department of Veterans Affairs Laryngeal Study Group in which 332 patients with stage III or IV (M0) cancer of the glottis or supraglottis were analyzed (Table 30.3-4). These were randomly assigned treatments with either surgery (total laryngectomy) and radiation therapy, or induction chemotherapy and radiation therapy. In the experimental arm, partial or complete responders after two cycles of cisplatin and 5-FU received a third cycle of chemotherapy followed by definitive radiation therapy. Laryngectomy was reserved for salvage of persistent or recurrent disease. Patients demonstrating less than a partial response at the primary site after two cycles of chemotherapy underwent immediate laryngectomy.

Various prognostic factors were analyzed for response to chemotherapy, organ preservation, and survival. For surgically treated patients, the one factor in multivariate analysis that was significant for decreased survival was extracapsular extension of nodal disease, whereas no independent predictive factor of survival emerged for chemotherapy-treated patients. Low T class (T1–T3 vs. T4) was the best predictor of response to chemotherapy (relative risk ratio, 5.6; \( P = .01 \)). T class, p53 overexpression, and elevated proliferating cell nuclear antigen index were independent predictors of successful organ preservation with induction chemotherapy and radiotherapy.

The second randomized induction chemotherapy trial of larynx preservation was conducted by the European Organization for Research and Treatment of Cancer (EORTC) in patients with resectable cancers of the pyriform sinus or the aryepiglottic fold (lateral epiglottis) (see Table 30.3-4). A total of 194 patients with stage T2–T4, N0–N2b were randomized to surgery (total laryngectomy plus partial pharyngectomy) and radiation therapy in one study arm or induction chemotherapy (cisplatin + 5-FU) and radiation therapy in responders. A clinical complete response at the primary site after two or three cycles of chemotherapy was required to proceed to radiation, and this was achieved in 54% of patients. Survival equivalence was demonstrated at 3 and 5 years, and a functioning larynx was preserved in 48% at 3 years. A delay in development of distant metastases was noted for the chemotherapy-treated patients, whereas no differences were observed in the rates of local or regional failure between treatment groups.

A third randomized trial of patients with locally advanced larynx cancer was conducted by the Groupe d'Etude des Tumeurs de la Tete et du Cou in France (see Table 30.3-4). This study was limited to patients with T3 tumors and consisted predominately of patients with glottic primaries. This was in contrast to the Veterans Affairs trial in which a majority of the lesions were supraglottic lesions. Laryngectomy was avoided in 41% (15 of 36 patients); however, the trial has been criticized for the small number of patients enrolled, the lack of imaging studies to assess tumor extent before treatment, and the lack of proper response evaluation after chemotherapy and after radiotherapy.

A metaanalysis by Lefebvre of chemotherapy in head and neck cancer limited to the 602 patients enrolled in these three trials shows a statistically nonsignificant difference in survival after a median follow-up of 5.8 years (45% for surgery patients vs. 39% for the induction chemotherapy group). The larynx was preserved in...
From these three randomized schemes, one can conclude the following for induction chemotherapy as a strategy to preserve the larynx: Survival is not jeopardized; laryngeal function can be preserved in approximately one-half of surviving patients; and the risk of requiring salvage surgery increases with bulky primary and nodal disease extension. In the context of these trials, these results indicate the following: First, these trials confirm a role for induction chemotherapy using the cisplatin plus 5-FU regimen followed by radiation therapy as an alternative, nonsurgical treatment for patients with locally advanced cancers of the larynx (stage III and IV) and hypopharynx (stage II, III, and IV) who would otherwise undergo total laryngectomy. A team approach that includes the surgical, radiation, and medical oncologists; nutritionist; and experts in lifestyle behavior modification is critical to the success of combined modality treatment. So that surgery can be performed promptly in nonresponders and for salvage of recurrent disease, it is essential that the surgeon be involved throughout and after the induction chemotherapy and radiation phases of treatment.

Left unanswered by these trials are the following important questions: (1) What is the precise role of induction chemotherapy? (2) What is the comparative efficacy of radiation therapy as a single modality for preservation of the larynx?, and (3) What is the potential of concurrent chemotheraphy and radiation therapy to improve locoregional control? These questions are particularly important in the United States and Europe in which cisplatin plus 5-FU induction chemotherapy followed by radiation therapy in responding patients (partial response of the primary tumor) serves as the control arm. The U.S. intergroup trial (R91-11) will complete accrual of 546 patients in the year 2000. This trial will provide data on two treatment alternatives: concurrent radiation therapy plus cisplatin compared to the control group, and radiation therapy alone compared to the control group. Until those trial results mature for larynx cancer specifically, induction chemotherapy and radiation therapy remains the standard of care. The consistent survival benefit observed in recent multisite and oropharynx randomized trials comparing concurrent chemotherapy and radiotherapy to radiotherapy alone is impressive. This suggests that the concurrent rather than the sequential strategy may emerge as the preferred treatment strategy for larynx and hypopharynx primaries as well.

Chemotherapy in the Treatment of Far Advanced (Unresectable) Locoregional Disease

There is no role for induction chemotherapy in the management of patients with advanced locoregional disease in which clear margins cannot be achieved by resection. Many randomized trials of patients with unresectable disease were carried out in the 1980s, which directly compared induction chemotherapy followed by radiation to radiation therapy alone. Survival benefit was reported in a subset analysis of patients with unresectable disease in only a single randomized trial. In contrast, prospective randomized trials of patients with unresectable disease clearly demonstrate a substantial increase in locoregional control and significantly improved survival with the use of concurrent chemotherapy and radiation therapy regimens when compared to either standard or altered fractionation schedules of radiation therapy alone. Thus, concurrent chemotherapy and radiation therapy can be recommended as the standard of care in this disease setting, provided the patient has sufficient performance status and psychosocial resources to undergo the generally more toxic treatment. At present, the most widely used regimen with proven survival benefit in a multicenter comparative trial is cisplatin 100 mg/m² on days 1, 22, and 43, during which radiation is taken to 70 Gy at a rate of 2 Gy per day. This is followed by an interval of 3 weeks during which a variety of doses under hyperfractionation or a schedule in fractionation and using cisplatin radiation therapy fractionation schedules. These reports indicate that even the smallest supraglottic tumors require elective neck dissections. For patients with poor performance status, radiation therapy alone or, in some situations, supportive care alone may constitute appropriate management.

In summary, the selection of a treatment strategy for T4 supraglottic and glottic larynx cancers is dependent on a variety of factors, including the following:

1. If there is bulky neck disease and if the primary tumor does not have extensive hypopharyngeal extension, induction chemotherapy followed by radiation therapy to the primary tumor and neck can be used in chemosensitive tumors. This should be followed by a neck dissection(s). In such lesions that are not chemoresponsive, laryngectomy and neck dissection(s) plus postoperative radiation therapy should be used.
2. If substantial hypopharyngeal extension is present, laryngectomy or laryngopharyngectomy plus neck dissection and postoperative radiation therapy is recommended.
3. If no clinical neck disease is present (i.e., T4, N0), induction chemotherapy followed by radiation therapy to the primary tumor and neck in chemosensitive tumors should be considered. If such a lesion does not respond adequately to induction chemotherapy, then the logical course should be a laryngectomy. The laryngectomy should probably be accompanied by appropriate selective neck dissection for staging and, depending on the result of the histologic analysis of the neck nodes harvested, postoperative radiation therapy.
4. In these large lesions, especially lesions that demonstrate subtotal extension, radiation therapy must be directed to the tracheal stoma, because recurrence here can be seen in a substantial percentage of these patients. Other indications for postoperative radiation are cartilage and extensive soft tissue invasion.

Most of these strategies for treating patients with advanced larynx or hypopharynx cancer and clinically positive necks must be analyzed in light of the dynamic state of the knowledge and experience with the organ-preservation concepts. Hitherto, we have been comfortable with the notion that substantial neck disease usually required surgery of some sort at some stage in the treatment plan. Armstrong and colleagues, however, have published data that parallel the concept of larynx preservation and that suggest that patients with clinically palpable cervical nodal metastases who have a complete response to chemotherapy and who receive high-dose radiation therapy have excellent neck control and may not need neck dissection. To address this issue, they reviewed the neck management of the first 80 patients treated in the larynx preservation trials at Memorial Sloan-Kettering Cancer Center. Of these, 54 patients presented with clinically positive nodes. Of these, 44% had a complete response and 20% had a partial response in the neck to induction chemotherapy. In 63% of the major responders, surgery to the neck was completely omitted, and radiation therapy alone was used. Neck control was obtained in 77% of patients with negative elective neck dissections. This suggests that, based on their observations of clinical failures, induction chemotherapy combined with radiation therapy may possibly avoid neck dissection. These data require supplementation, and data for concomitant chemotherapy and radiotherapy must also be generated before it can be decided if this observation is sustained. Even if these preliminary suggestions are substantiated, however, the definitive question to be asked is whether the morbidity endured with high-dose radiation is justified when moderate-dose neck radiation plus a tailored neck operation is so well tolerated.

Considerations for Neck Surgery

Management of the neck is critical to successful therapy of supraglottic cancer. Levendag and associates studied elective surgical management of the neck in a group of patients with stage I and II supraglottic carcinoma treated with surgery alone at the Memorial Sloan-Kettering Cancer Center. In those patients who underwent elective neck dissection (i.e., the group with clinically negative necks), 32% were found to have histologically positive cervical lymph nodes. One-half of the patients with involved nodes eventually had cancer recurrence in the dissected neck. Additionally, 19% of patients with negative elective neck dissections had cancer recurrence in the contralateral neck. Finally, in a group of 48 patients who did not have elective neck dissection, 29% had cancer recurrence in the neck. Therefore, a total of 35% of the T1, N0 and T2, N0 patients ultimately developed cervical lymph node metastases. Importantly, nearly two-thirds of those who relapsed in the neck eventually died from their cancer. On the other hand, none of the patients without neck relapse died from supraglottic cancer. These investigators compared their experience with a similar patient group from the other studies that showed similar neck failure rates with surgery alone and when radiation therapy was administered to the necks. Less than 5% failure follows electively radiated necks. These reports indicate that even the smallest supraglottic tumors require elective neck management.

A variety of neck dissections are currently used in the various treatment plans for laryngeal cancer; the classic radical neck dissection, the modified radical neck dissection, and a group of regional dissections collectively known as selective neck dissections. This group of operations has been standardized and endorsed by the American Academy of Otolaryngology–Head and Neck Surgery and the American Head and Neck Society. The monograph outlining the recommended terminology should be studied, and oncologists are strongly urged to incorporate this classification into their lexicon to facilitate interinstitutional data recording and appropriate comparisons.

Considerable diversity of opinion exists in the surgical community as to which of these procedures should be applied to which situation. Exact guidelines are not consistently substantiated by the data available, however. The radical neck dissection is almost never used in the clinically negative neck, even in those lesions in which the probability for metastasis is extraordinary. This procedure is usually reserved for necks in which there is gross metastasis, and even then the selective procedures are often used. Most of the time, however, these selective neck dissections are used as staging procedures in which the goal is to harvest and sample the nodal groups at highest risk for metastasis. This philosophy has evolved as a result of our increasing reliance on radiation therapy as the second half of neck treatment whenever disease is discovered in the neck. Only in very limited circumstances is the selective neck dissection thought to be therapeutic; that is to say, in most necks in which any neck disease is present, postoperative radiation is recommended.

The choice of the appropriate selective neck dissection in larynx cancer is based on a knowledge of the consistent patterns of metastasis that are exhibited by the various subsites within the larynx; for example, lesions of the supraglottis are prone to metastasis bilaterally and to levels II and III. Rarely, however, do they spread to all subsites within the larynx; for example, lesions of the supraglottis are prone to metastasis bilaterally and to levels II and III.
level. Based on this knowledge, the logical staging operation for a supraglottic laryngeal cancer with a clinically negative neck would be designed specifically to clean out those various compartments at highest risk. This is but one example of a tailored approach, and the reader is referred to the classic work by Lindberg, in which he mapped the patterns of metastases of the various aerodigestive SCCs. More recently, Shah and Andersen applied the modern classification to this process of selectivity and have established recommendations for the use of these neck operations.

**HYPOPHARYNX**

**GENERAL**

The hypopharynx is the area of the pharynx that lies behind and below the oropharynx, just outside the view provided by tongue blade and flashlight; as such, it is visually inaccessible by routine office examination. Hypopharyngeal cancers are usually aggressive in their behavior, grow in an area of abundant lymphatic drainage, do not produce early symptoms or signs, and usually occur in people who are nutritionally depleted and immunologically compromised. It is not surprising, then, that the survival rates for these cancers are poor and that their treatment is difficult at best.

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The hypopharynx extends from the oropharynx above to the esophageal inlet below, is cone shaped, and consists of three regions or subsites: the paired pyriform sinuses, the posterior pharyngeal wall, and the postcricoid area. The larynx is located at the anterior aspect of the hypopharynx, indenting it to create the two lateral sulci that are the pyriform sinuses. Although these sulci lie partially within the framework of the thyroid cartilage, they are actually part of the hypopharynx, and cancers that develop within them behave differently than do those of the larynx. The lateral wall of each pyriform sinus continues around to blend with and become the posterior pharyngeal wall. The apex of the pyriform sinuses extends down to a level just inferior to those endolaryngeal muscles of the adjacent true vocal cord. Above, the medial walls of the pyriform sinuses each form the pharyngeal side of the corresponding aryepiglottic fold, which is the partition between the hypopharynx and endolarynx. Laterally, the pyriform sinuses extend superiorly to the glossoepiglottic fold. The posterior aspect of each pyriform sinus is open and connects with the hypopharyngeal cavity. In effect, each pyriform sinus is a three-walled space that opens into the general hypopharyngeal cavity (see Figs. 30.3-1 and 30.3-2).

The funnel-shaped postcricoid area begins just below the arytenoids and extends to the level of the cricopharyngeus muscle below. It is lined with the mucosa that overlies the posterior lamina of the cricoid cartilage and that continues to the cervical esophagus. Laterally, the postcricoid mucosa blends with that of the pyriform sinuses, and because of this, the same cancer often affects these two areas.

Approximately 70% of hypopharyngeal lesions occur in the pyriform sinuses, and the remaining 20% to 30% occur on the posterior pharyngeal wall and in the postcricoid area. Postcricoid cancers make up a small percentage of the latter group. Cancer of the hypopharynx is uncommon; approximately 2500 new cases are diagnosed in the United States each year. Overall, these lesions occur more often in men by a significant ratio, but there does seem to be a higher incidence of lower hypopharynx or postcricoid, cancers in women. The upper hypopharyngeal lesions are more common in men, whereas those lower lesions are more often associated with nutritional abnormalities, whereas the lesions in the remainder of the hypopharynx seem to be associated more with heavy smoking and drinking.

Those ratios vary somewhat in different countries and change in accordance with the incidence of vitamin deficiencies. For example, a higher incidence of carcinoma of the postcricoid area is seen in patients with Plummer-Vinson syndrome, a condition that includes an iron deficiency anemia. This condition is especially prevalent in northern Europe and is seen in nonsmoking women. Also, other metabolic deficiencies, such as vitamin B12 malabsorption, may play a role in the development of these lesions.

**PATHOLOGY, PATHOGENESIS, AND NATURAL HISTORY**

Almost all hypopharynx malignancies are SCCs that have developed in an environment of deranged mucosa. The generalized effects of the carcinogens encountered over a lifetime can lead to the occurrence of multiple mucosal sites of epithelial disturbances that range from dyskeratosis to frank cancer. The concept of field cancerization is in part responsible for the multiple, synchronous primary malignant lesions that occur in approximately 12% to 20% of hypopharyngeal cancers.

Cancers of the hypopharynx are generally aggressive in their behavior and demonstrate a natural history that is characterized by diffuse local spread, early metastasis, and a relatively high rate of distant spread. The anatomy of the area is such that, once a cancer has penetrated the mucosa, little restriction is placed on diffuse tumor extension in the submucosal plane. Because of this fact and also because of the abundant lymphatic network of the region, a localized hypopharyngeal tumor is exceptional rather than expected. An important study by Harrison demonstrated pathologically that, in 40% of hypopharynx lesions, the true extent of the cancer had been underestimated initially. Tumors of the pharyngeal walls are more often ulcerative than exophytic and are particularly prone to an insidious and deceptive growth pattern characterized by skip metastasis and ill-defined margins; once submucosal, these lesions can resurface at various locations remote from the primary site. They can extend upward in this fashion and can travel all the way to the base of the skull. Cancers of the postcricoid area also tend to spread laterally, and can cause vocal cord paralyzis by invading the recurrent laryngeal nerve just as it enters the larynx. Postcricoid lesions can extend inferiorly and can develop skip metastases in the cervical esophagus. Gross involvement of the esophagus with postcricoid cancer is uncommon. These lesions usually do not produce early symptoms, and when discovered, they often have caused cricoid cartilage destruction.

It is significant that the lateral walls of the pyriform sinuses lie against that area of the thyroid cartilage that is often ossified, a state that renders the cartilage vulnerable to tumor invasion. See (see Fig. 30.3-2). In Kirchner and Owen's series of 500 whole-organ larynx sections, more than 50% of the pyriform sinus cancers demonstrated cartilage invasion. This fact is relevant to the strategies of radiation oncologists and surgeons, because cancer involvement in the cartilage probably explains radiocurability and substantially compromises the potential for conservation laryngeal surgery. Depending on the degree of ossification present, tumor that has invaded the thyroid or cricoid cartilage in one area can permeate the entire framework by extending within the cartilage and can even travel all the way to the opposite lamina of the structure.

Overall, the distribution of metastatic hypopharyngeal cancer is to all levels of the neck, with the level II (jugulodigastric) nodes being most common; level III the next most common site; and level I, IV, and V the least likely sites of metastasis. Overall, the risk for cervical metastasis from pyriform sinus cancer is 75%; from posterior pharyngeal wall, 60%; and from the postcricoid area, 40%. Because the pyriform sinuses are located laterally, only 10% of these lesions present with bilateral metastasis. Such a pattern of spread occurs more commonly in posterior pharyngeal cancers, and it is the norm in posterior pharyngeal cancer. Approximately 60% of patients with pyriform sinus wall lesions demonstrate bilateral cervical lymphadenopathy. Metastasis occurs early in the course of hypopharynx cancers. Approximately 60% of pyriform sinus lesions are associated with clinically positive necks at the time of diagnosis, and many of those that have clinically negative necks turn out to have occult metastasis in the thyroid gland or in the paratracheal node chain.

Because a significant number of postcricoid and pyriform sinus apex lesions metastasize to the less obvious paratracheal and thyroid gland lymphatics, the incidence of occult metastasis from those sites is somewhat greater than in the higher pyriform sinus and posterior pharyngeal wall lesions that typically metastasize to the deep jugular nodes. Because of this fact, calculating occult metastatic rate is a problem in hypopharyngeal cancers.

The retropharyngeal lymph nodes that are located high in the neck are primary drainage sites for hypopharyngeal cancers and are involved in more than 40% of patients with posterior pharyngeal wall and pyriform sinus lesions. It is, therefore, especially important in the staging and treatment of this particular group of tumors to include these nodes in the field of dissection, radiation, or both. These lymphatics are part of the deep jugular chain, are outside of the constrictor muscles, and are readily visible by imaging (see Fig. 30.3-1). Involvement of the retropharyngeal nodes may produce a symptom complex characterized by pain and stiffness in the neck, with pain radiating to the ipsilateral eye and forehead.

The incidence of distant metastasis from hypopharyngeal cancer is substantial, occurring in 24% of all sites and in all stages. This incidence is initially lower, rising in those subpopulations that live longest.
Hypopharyngeal cancer is usually not diagnosed in its early stages. In fact, most series reported include few T1 lesions. This finding is due, in part, to the fact that many patients with these cancers have abused their health by smoking and drinking heavily and therefore they have a high tolerance for throat symptoms; however, it is also true that these lesions are often indolent and produce few symptoms until they are substantial in size. This is especially so for posterior pharyngeal wall cancers. More than 50% of patients with hypopharyngeal cancer have clinically obvious cervical metastasis at the time they are first encountered, and in one-half of these individuals, the neck mass is actually the presenting symptom. Pyriform sinus and posterior pharyngeal wall lesions can cause a sensation of irritation and mucus retention that is felt only with swallowing. Otalgia is characterized by pyriform sinus lesions and is a manifestation of cancer compromising the sensory fibers of the superior laryngeal nerve, the axons of which synapse with sensory nerves of the external auditory canal. The pain generated is typically dull and is perceived by the patient in the posterior and inferior aspects of the canal and on the posterior aspect of the auricle. In the absence of ear findings, persistent pain in these areas must be viewed with suspicion, and a careful examination of the upper aerodigestive tract must be done by someone skilled in the appropriate methods. Voice change associated with pyriform sinus or postcricoid lesions is a late symptom and usually represents impairment of vocal cord function by invasion into the endolarynx or of a recurrent laryngeal nerve. Patients often have lost their ability to swallow comfortably or have a lack of willingness to swallow because of fear of aspiration. Therefore, they often become debilitated during the course of this disease.

Many patients with hypopharyngeal cancer are chronically ill before the development of their lesion, having the pulmonary and hepatic diseases that accompany a lifetime of tobacco and alcohol excesses. Recognition of the compounding nature of these associations with hypopharyngeal cancer is essential in the formulation of an appropriate treatment plan.

Physical examination of the hypopharynx has become much less problematic since the development of the flexible, fiberoptically lighted endoscopes that are easily included in basic outpatient facilities (see Fig. 30.3-5). The crevices and partially hidden areas of the laryngopharynx are effectively visualized using these instruments; however, the conventional hand-held mirror examination is still the state of the art when used by the experienced head and neck diagnostician. For the occasional examiner, however, the benefits of the flexible endoscopes are significant. What is most essential is that the primary care physician not be reassured falsely by a normal tongue blade and light examination. In those patients with persistent symptoms of swallowing alteration or discomfort, otalgia, or voice change, such an examination is inadequate, because only a small part of the hypopharynx and none of the larynx is visualized in such an examination.

Examination of the hypopharynx can reveal pooling of secretions in all lesions of the area, but this finding is especially impressive in postcricoid and pyriform sinus cancers because of impairment of the passage of food and secretions into the esophagus. Often, such pooling is the only sign of a small lesion. In larger tumors, the abundance of secretions sometimes obscures the actual lesion. Occasionally, small and less obvious lesions of the medial wall and apex of the pyriform sinuses cause subglottic edema in the adjacent larynx. Postcricoid carcinomas generally produce esophageal obstructive symptoms sooner than tumors in other areas of the hypopharynx.

In deeply invasive postcricoid or posterior pharyngeal wall cancers, fixation of the larynx and the pharyngeal wall to the prevertebral fascia often is associated with a loss of normal laryngeal crepitation when the examining physician attempts to move the thyroid cartilage from side to side. As with other sites in the head and neck, the importance of lesion thickness and depth is becoming more obvious, especially as the search continues for nonsurgical means of treating these cancers. The thickness, or third dimension, of hypopharyngeal tumors: their lateral extension into the neck; and finally, the status of the adjacent lateral cervical and retropharyngeal nodes are visualized well by CT or MRI.

Barium esophagogram is a relatively effective tool for detecting second primary cancers in the esophagus and also for evaluating postcricoid lesions; however, this study is limited by the fact that it visualizes only the surface of the area and does not accurately demonstrate the total tumor volume. Because of tissue edema and the resulting image distortion that can be caused by instrumentation, these studies should be obtained before endoscopy and biopsy whenever possible.

Each hypopharyngeal cancer should be examined, staged, and carefully mapped on a permanent record (see Fig. 30.3-6); importantly, this should be accomplished on the awake and upright patient. Direct endoscopy and biopsy should then be done on all patients under general anesthesia, so that adequate tissue can be sampled and the third-dimensional appreciation for the tumor better achieved. Finally, considering the significant incidence of multiple synchronous primary tumors that occur with hypopharyngeal cancer, esophagoscopy and bronchoscope should be done at this time.

STAGING SYSTEM

As with most cancers, a workable staging system is critical to the evaluation of treatment methods and for the comparison of data between institutions (Table 30.3-5). This is especially true now that the use of sophisticated imaging allows for a relative quantification of tumor volume and extension. Although staging based on physical examination alone is fairly accurate, imaging is especially important in those lesions treated by nonsurgical means, because pathologic positivity or negativity of the neck is never proved unless a recurrence develops. Although considerable effort has been expended to develop workable and descriptive terminology, there continue to be limitations to current staging for hypopharyngeal cancers. For example, the system is satisfactory for disease of the pyriform sinuses, but it cannot be applied to all lesions of the posterior pharyngeal wall, because they usually do not invade the larynx, and fixation is not part of the natural history. Rather, posterior pharyngeal wall tumors would be more appropriately staged by tumor diameter, as is the case with oropharyngeal lesions. According to the current system, a 5 × 4–cm posterior pharyngeal lesion without laryngeal fixation would still be classified as a T1 lesion, but in fact, it would have a prognosis similar to that for a T3 lesion.

The nodal staging and the stage grouping for the hypopharynx are the same as with other head and neck sites.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>Tumor limited to mucosa of hypopharynx and a T1 or T1b carcinoma has no more than 4 cm in greatest dimension.</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor invades muscle planes, or adheres to, or invades bone, or has more than 4 cm in greatest dimension, or invades larynx, or involves the pyriform sinus.</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor with extensive invasion of the posterior pharyngeal wall.</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor with extension to other head and neck structures.</td>
</tr>
</tbody>
</table>

The nodal staging for hypopharyngeal cancer is as follows:

<table>
<thead>
<tr>
<th>Node</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0</td>
<td>No cervical nodal involvement</td>
</tr>
<tr>
<td>N1</td>
<td>Positive cervical nodes</td>
</tr>
<tr>
<td>N2</td>
<td>Positive cervical nodes with direct extension to other head and neck structures</td>
</tr>
</tbody>
</table>

The nodal staging and the stage grouping for the hypopharynx are the same as with other head and neck sites.

TREATMENT AND SURVIVAL

A variety of prognostic factors have been identified for squamous carcinomas of the hypopharynx. Women and patients younger than 50 years of age seem to have a more favorable outcome. Because these tumors can affect swallowing, significant weight loss can occur, and extreme nutritional deficiency and debilitation may even prevent the delivery of curative therapy. Because many of the symptoms of this disease result from an advanced state, most patients are stage III or IV when diagnosed, and therefore, most are candidates for combined-modality treatment. This treatment involves surgery, radiation therapy and, more recently, chemotherapy programs. Surgeon, radiation oncologist, and medical oncologist must collaborate closely in the multidisciplinary evaluation and treatment of patients with hypopharyngeal cancer.

The fact that most patients with hypopharyngeal cancers currently are managed with combined-treatment modalities probably is not entirely explained by an inherent biologic difference between these tumors and other SCCs in the upper aerodigestive tract; rather, it may also reflect the fact that only a small number of these patients present with T1 or T2 disease. Higher percentages of poorly differentiated carcinomas are seen in the hypopharynx, but cell for cell, it is not entirely clear that these cancers are different from other poorly differentiated SCCs found in other sites. What makes hypopharyngeal cancers particularly ominous is probably related in large part to the anatomy of the area that allows extensive spreading of these tumors. On the other hand, even early-stage lesions do not do as well as other aerodigestive SCCs, and furthermore, in all larynx preservation protocols, the hypopharyngeal lesions fare worse than the larynx lesions. Finally, poor performance relates to debilitation, chronic anemia, to the extensive lymphatic drainage of the area, and to the fact that the diffuse carcinogenic effects that led to the initial problem also
create an environment of condemned mucosal multifocality and de novo carcinoma formation.

The appropriate therapy for tumors of the hypopharynx is predicated on several factors, such as the patient's performance status, extent of disease, laryngeal involvement, and the presence and extent of metastasis. If, for example, the only surgical option available for removal of a given lesion of the hypopharynx involves a total laryngectomy, then organ preservation strategies using chemotherapy and radiation therapy become mandatory. However, total laryngectomy should not always be necessary with resection of hypopharyngeal cancers, and a few selected patients who have tumors of the pharyngeal wall and pyriform sinuses are candidates for partial laryngopharyngectomy. The physiologic stress imposed on older and debilitated patients by these partial operations, however, can be unacceptable. Thin, early-stage cancers of the hypopharynx are probably as curable with radiation therapy as with surgery.

Excision of postcricoid carcinomas always involves a total laryngectomy. In a subset of patients, lesions of the posterior pharyngeal wall can be resected even while retaining laryngeal integrity. Even in the smaller of these lesions, however, the larynx can be preserved in only a few cases. Because of the tendency of pharyngeal wall lesions to have ill-defined margins, generous resections are necessary; with such liberal tissue removal, much of the sensory innervation normally used to localize the site of origin is violated. Because of this, the addition of T4 tumors and the presence of surgical margins and to avoid the significant chronic aspiration that usually follows pharyngectomy in these cases. With the contemporary techniques of reconstruction in head and neck surgery being as sophisticated as they are, the limitations of this form of surgery do not relate to anatomic realignments; rather, they are physiologic, and an ill-conceived larynx preservation procedure may cure the cancer but may not permit a sustainable lifestyle. Newer techniques of hypopharyngeal reconstruction are being developed that use reinnervated free flaps. This reconstitution of the sensory apparatus so important to deglutition may to some extent solve the problems currently limiting the ability to resect this area radically.

Limited T1 and T2 lesions on the medial wall of the pyriform sinus may be removed by partial laryngectomy, but either extension to the apex of the sinus or involvement of the adjacent postcricoid area mandates total laryngectomy. These medial wall lesions are particularly prone to penetrate the paraglottic space of the larynx (see Fig. 30.3-2), and when this does occur, laryngectomy becomes oncologically unsafe. In a pyriform sinus lesion, any motion change noticed in the vocal cord suggests invasion into the larynx. Some notable surgeons are skeptical of any indication for the use of partial laryngectomy for cancers of the pyriform sinuses. However, whatever the indications, it is fundamental that any attempt to remove a pyriform sinus cancer with less than a total laryngectomy should be done only by those surgeons with considerable experience in making the subtle judgments so often involved in this type of surgery. With the alternatives to surgery that are now available to treat these tumors, and considering our consistent ability to restore voice function after laryngectomy, any oncologic gamble associated with inadvisably trying to save the larynx is unacceptable. Overall, partial laryngopharyngectomy with preservation of voice and swallowing can be justifiably performed in fewer than 5% of all hypopharyngeal cancers.

Radiation therapy is effective for early lesions of the hypopharynx, especially when they are exophytic. Mendenhall and associates reported local control in 79% of T1 and 59% of T2 lesions treated with radiation therapy; however, the 5-year survival rate was only 60%. Vandenbranden and coworkers reported a 5-year survival rate of only 40% in an extensive series of smaller lesions treated with radiation therapy. Itami et al. reported local control of 49% for T1/T2 lesions of the pyriform sinus, which fell to 25% for T3/T4 disease. Doses of 70 Gy or higher are generally used, depending on the fractionation program. Pameijer and colleagues evaluated the role of CT scans in predicting the outcome for patients treated with definitive radiation for T1/T2 disease. Tumor volume was found to be prognostic. For tumors larger than 6.5 cm, local control was 25% compared with 85% for tumors of less than 6.5 cm. These data are similar to those achieved surgically for early disease. For instance, Shah et al. reported 5-year survival rates of 43% and 38%, respectively, for surgically managed T1 and T2/T3 (N0) hypopharyngeal disease.

Control drops significantly for more advanced lesions. In the series by Mendenhall et al. and Bataini and colleagues, T3 lesions treated with primary radiation therapy had approximately a 40% local control rate but a dismal 5-year survival rate of less than 20%. Results of surgery for advanced disease are not any better. Shah and coworkers reported a 16% 5-year survival rate for patients with T3 disease. When comparing single-modality therapy of hypopharyngeal cancers, results of surgery and radiation therapy are roughly associated with both yielding suboptimal outcomes.

Because of the consistently poor survival data associated with the single-modality methods of treating more advanced hypopharyngeal cancer, combined therapy consisting of radiation administered after pharyngectomy or laryngopharyngectomy is the method currently being practiced in most centers. The sequencing of the modalities is fairly standard, with the radiation generally administered postoperatively in all but selected circumstances. Essentially, this sequence allows the safe delivery of radiation doses in the 6000- to 7000-cGy range. Various trials from the Radiation Therapy Oncology Group and others have compared preoperative with postoperative therapy, and those data suggest better locoregional control and a trend toward better survival in the group treated with postoperative therapy.

Select circumstances exist, however, in which radiation therapy is recommended before surgery. For example, in those circumstances in which the primary tumor is small and exophytic and is therefore suitable for definitive radiation therapy, but in which the degree of neck disease precludes management with radiation alone, curative therapy to both the primary tumor and neck followed by neck dissection is an acceptable treatment plan. Mendenhall and associates have reported an 80% 2-year control rate for disease above the clavicle in patients with advanced neck disease and early primary tumors that have been treated in this fashion. Just as with other head and neck sites, the clonal progeny in cervical metastasis is often more prominent than in the primary tumor.

Several groups have reported results of a treatment strategy that consists of primary radiation with surgery being used only for salvage. Keane and colleagues reported 41% disease control using this approach. Most patients (75%) in this series had been staged as T3 or T4. Approximately two-thirds had palpable nodal metastases, and the 5-year survival rate was only 15%.

Traditional treatment programs of surgery and radiation therapy for hypopharyngeal carcinomas have been augmented by organ-preservation induction-chemotherapy strategies. Organ preservation for hypopharyngeal cancer may be feasible, but the percentage of patients who preserve their larynx term long is unsatisfactory. Future trials exploring concomitant chemotherapy and radiotherapy are more likely to yield better locoregional control and to affect survival.

Two randomized trials of organ preservation for patients with cancer of the hypopharynx have been published. The EORTC randomized 202 patients with operable squamous cancers of the pyriform sinus or the aryepiglottic fold (stage T2, T3, or T4 and N0, N1, N2a, or N2b) to receive either induction chemotherapy and radiation or standard treatment with total laryngectomy, partial pharyngectomy, and radiation. In the experimental treatment group, only patients achieving a clinical complete response of the primary tumor proceeded to radiotherapy; all others underwent resection. The preliminary results after a median follow-up of 51 months show no difference in survival for the two treatment groups; 3- and 5-year survival estimates are 57% and 30% for patients randomized to chemotherapy and 43% and 35% for those randomized to surgery. Fifty-four percent of patients had a clinical complete response at the primary site and 52% in the neck after chemotherapy. Three- and 5-year estimates of survival with a functional larynx were 28% and 17%, respectively. If only the deaths from local progression are considered, to account for patients who died with a functional larynx, then these survival estimates with a preserved larynx are 42% and 35%, respectively. The EORTC is now embarking on a trial that will compare sequential to simultaneous chemotherapy and radiotherapy for organ preservation of patients with cancer of the hypopharynx.

Mahe and colleagues evaluated the role of surgery for patients with T3/T4 or N2/N3 cancer of the hypopharynx. Ninety-one patients were randomly assigned treatment with induction chemotherapy followed by surgery and radiation or induction chemotherapy followed by radiation. Median and 5-year survival rates were significantly better with resection: 40 versus 20 months, and 37% versus 19%, respectively. This difference was explained by a significantly higher local failure rate in the nonsurgical group of 61%, compared with 37% in the surgical group. Because of the nature of the study design, no conclusions regarding the impact of induction chemotherapy can be made.

Survival data vary considerably between sites within the hypopharynx. Few postcricoid cancers are treated by radiation, but anecdotal experience suggests that a small subset of patients with smaller thin lesions are treatable with curative therapy. In almost all postcricoid lesions, extensive surgery consisting of laryngopharyngectomy or laryngopharyngoesophagectomy with reconstruction is followed by postoperative radiation and yields a 20% to 25% 5-year survival rate. Radiotherapy produces remissions of earlier stages of disease but results in 10% to 20% local failure rate. More advanced lesions are best treated by combined surgery followed by postoperative radiation. Mendenhall and colleagues reported that 91% of T1 and 73% of T2 lesions of the pharyngeal wall can be controlled with primary radiation, requiring a dosage greater than 6500 cGy. For T3 and T4 disease, similar doses controlled 61% and 37%, respectively. Pyriform sinus lesions of early stage are curable by radiation, whereas the much more common advanced lesions are best treated by combined therapy. Data accumulated by Vandenbranden and coworkers showed a 3-year survival rate of 48%, which dropped to 33% at 5 years for lesions treated with total and partial laryngectomy plus postoperative radiation therapy. In that same series, the 3-year survival rate was 67% in the group treated by partial laryngectomy plus postoperative radiation therapy. This latter statistic probably reflects the increased survival expected in lesser-stage disease.

All treatment plans for hypopharyngeal cancer must consider certain facts: The overwhelming majority of these lesions metastasize to cervical lymph nodes, and in the case of the posterior pharyngeal wall, bilateral metastasis is the rule rather than the exception; 40% of posterior pharyngeal wall lesions and probably an equal
number of upper pyriform sinus lesions metastasize to the retropharyngeal nodes; in those patients with clinically negative necks, the incidence of occult metastasis is 13-19.


Kjær J. One of five hundred cancers of the larynx and pyriform sinuses. Laryngoscope 1977;87:1288.


MAJOR SALIVARY GLAND TUMORS

The same neoplasms affect all salivary gland tissue, but with predictable variations for the different anatomic sites. The major salivary glands consist of paired parotids in the preauricular area, paired submandibulars deep and inferior to the mandible, and paired sublinguals in the floor of the mouth. The minor salivary glands, on the other hand, are ubiquitous in the upper aerodigestive tract, occurring throughout the oral and nasal cavities and the paranasal sinuses. The probability of any given salivary neoplasm being malignant is highest in the sublingual glands, next highest in the submandibular glands, and least in the parotid glands. Overall, salivary cancers make up approximately 3% of all head and neck malignancies that are diagnosed in North America each year; most of these are in the parotid glands. Sublingual and minor salivary gland cancers are unusual.

ANATOMY

The parotid gland is tightly compacted in the area immediately anterior and inferior to the external ear. It is best thought of in three dimensions, with the deep portion extending medially behind the posterior rim of the ascending ramus of the mandible into the parapharyngeal space. The superficial part of the gland lies on the masseter muscle and extends inferiorly to overlie the sternocleidomastoid and digastric muscles. The same fascia that engulfs both of these muscles also forms a substantial capsule around both the parotid and submandibular glands, thus forming a barrier that confines tumors to their site of origin. The most inferior extent of the parotid gland extends a variable distance, and in those necks in which this extension is exaggerated, the glandular tail overlies the transverse process of the second cervical vertebra as well as the deep jugular lymph nodes adjacent to this level. Not infrequently, a prominent transverse process or an enlarged lymph node in this area is misinterpreted as a parotid tail mass. This circumstance is encountered less frequently today, however, because contemporary imaging has helped to define that which is abnormal.

FIGURE 30.4-1. Representation of parotid gland and facial nerve anatomy. Lower part of diagram shows details of the relation of the nerve to the surrounding gland. Various branches of the nerve are directed to various parts of the facial musculature. (CIBA Collection, Frank Netter.)

The facial nerve leaves the stylomastoid foramen at the base of the skull and almost immediately penetrates the posterior capsule of the parotid gland. Once within that structure, the nerve divides into five main branches—temporal, zygomatic, buccal, mandibular, and cervical—all of which extend in a consistent direction and depth, and all of which gradually become more superficial as they extend anteriorly. In addition to being more superficial, the more anterior branches of the nerve are more delicate; thus, increased risks are associated with dissection of tumors located more anterior in the gland.

Although no actual lobes are defined by fascial planes, that part of the parotid gland superficial to the facial nerve is arbitrarily referred to as the superficial lobe. That portion deep to the nerve is called the deep lobe. These facts have considerable bearing on dissections done within the parotid gland (see Fig. 30.4-1). The deep lobe of the parotid gland extends into the parapharyngeal space; thus, tumors of that portion of the gland can come into contact with the carotid sheath and its contents, which form the posterior boundary of that space. These deep lobe tumors can press against the constrictor muscles of the pharynx that normally form the medial wall of the parapharyngeal space (Fig. 30.4-2). A large deep lobe parotid tumor can, therefore, present as a submucosal bulge of the tonsil pillar, a finding that is easily misinterpreted by the inexperienced diagnostian as an oropharyngeal neoplasm (Fig. 30.4-3). The distinction between a deep lobe parotid tumor and an oral lesion becomes clear on either magnetic resonance imaging (MRI) or computed tomography (CT). There is some difficulty, however, in distinguishing these deep lobe neoplasms from tumors that have their origin in the parapharyngeal space. Correct diagnosis depends on the presence or absence of a fat plane between the deep lobe and the tumor. The distinction between the two is important, because the differential diagnosis of tumors that originate in the parapharyngeal space must include lymphomas, neurogenic tumors, and paragangliomas, none of which is likely to occur primarily in the parotid gland. Most parotid tumors originate in the superficial lobe, probably because that portion of the gland is considerably larger than the deep lobe. Because no identifiable histologic differences exist between deep and superficial lobes, no reasonable explanation can be provided for this distribution of tumors other than the amount of salivary gland tissue available for tumor development. The distribution of different types of tumors is probably the same in the various parts of the gland.
The lymphatics in and around the parotid gland consist of two groups, and a knowledge of that distribution is essential to the understanding of the natural history of these tumors. The preauricular (periparotid) nodes lie superficially to the gland capsule and drain the external auditory canal, the facial and auricular skin, and the temple scalp. They are especially important drainage sites for squamous carcinomas and melanomas of adjacent skin. Parotid gland cancers usually do not drain into these nodes. The second nodal group consists of five to seven intraparotid lymph nodes that do play a role in the pathogenesis of parotid cancer. The efferent channels of the superficial nodes drain into the superficial jugular chain, whereas the intraglandular nodes drain into the upper and middle deep jugular lymph nodes. The extraparotid (periparotid) nodes are readily palpable and are distinguished easily from primary parotid tumors; however, nodes within the substance of the gland are not easily palpated and become noticeable only when they are enlarged. Distinguishing them from primary parotid gland tumors by palpation or by imaging can be difficult.

The submandibular gland lies in the submandibular triangle of the neck with its posterior extent adjacent to, but not contiguous with, the tail of the parotid gland. The deep surface of the submandibular gland lies against the muscular diaphragm of the floor of the mouth and is best examined bimanually, with one finger in the mouth and the external hand on the surface of the gland. Lymph nodes do not exist within the submandibular gland, but instead they lie around its surface. A mass outside the submandibular gland may represent a metastatic node from some other site, such as the lateral tongue or the floor of the mouth. Drainage from the submandibular gland goes into the adjacent nodes and upper deep jugular chain. Three important nerves, the marginal mandibular branch of the facial nerve (motor) and the lingual (sensory) and hypoglossal (motor) nerves to the tongue all lie in close proximity to the submandibular gland.

The sublingual glands are located submucosally in the floor of the mouth, just superficially to the muscular diaphragm. They are oval and lie along the inner table of the mandible. The sublingual glands drain into submandibular lymphatics and then into the deep jugular nodes.

ETIOLOGY, PATHOLOGY, AND CLASSIFICATION

The causes of salivary gland cancer have not been determined. Certain factors have been etiologically suggested, including ionizing radiation with all salivary cancers, a familial predisposition in parotid cancer, and chronic wood dust inhalation in certain individuals who develop minor salivary gland adenocarcinomas of the nasal and paranasal sinuses. Proof of cause and effect does not exist, however, in any of these postulated associations, and the etiology of most salivary gland cancers cannot be determined.

Overall, the majority of salivary gland neoplasms are benign, a fact that reflects an overwhelming predominance of parotid tumors, three-fourths of which are nonmalignant. Different classifications of salivary gland neoplasms have been established, but the one that seems to be the most consistently workable is shown in Table 30.4-1.

<table>
<thead>
<tr>
<th>CLASSIFICATION</th>
<th>DESCRIPTION</th>
</tr>
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<tbody>
<tr>
<td>BENIGN</td>
<td></td>
</tr>
<tr>
<td>Pleomorphic adenoma</td>
<td>Also known as the benign mixed tumor, the pleomorphic adenoma is the most common of the neoplasms that originate in the major salivary glands. This tumor is more correctly referred to by its formal name, which describes its multiple histologic components, including myxoid, mucoid, chondroid, and other elements. Although these lesions can occur in all salivary gland tissues, most often they are seen in the parotid gland. The distinction between this tumor and its malignant counterpart, malignant mixed tumor, is often difficult, but the histologic features that most reliably separate the two include a tendency in the malignant version for perivascular and perineural invasion and significant cellular atypia and mitosis. Malignant lesions can be</td>
</tr>
</tbody>
</table>

TABLE 30.4-1. Classification of Salivary Gland Neoplasms
Benign lymphoepithelial lesion (BLL) was first described in association with systemic conditions such as Sjögren's and Mikulicz's.

Papillary cystadenoma lymphomatosum (Warthin's tumor) is a slow-growing, often cystic, and at times troublesome because they are locally aggressive and are prone to invasion of nerves and vessels as well as to early metastasis. Spiro and Spiro have developed a compendium of the various series of salivary gland cancers reported and, in their survey, have outlined the relative occurrence rates of the various cancers in both the parotid and submandibular glands. The various reports from nine studies total 1778 parotid gland cancers, the distribution of which is abbreviated and summarized in Table 30.4-2. Summarized in Table 30.4-3 are comparative data for the submandibular gland that are taken from eight studies and that, when combined, reflect the relative distribution by type of 383 submandibular gland cancers.

RAPIDLY PROLIFERATING, HIGH-GRADE LESIONS. Rapidly proliferating, high-grade lesions reveals an incidence of nodal metastasis from all salivary gland sites that is probably even higher.

PAPILLARY CYSTADENOMA LYMPHOMATOSUM (WARTHIN’S TUMOR). Papillary cystadenoma lymphomatosum (Warthin's tumor) is a slow-growing, often cystic, and usually innocuous tumor that almost always occurs in older men, seems to favor the tail of the parotid gland, and occurs bilaterally in 10% of cases. Because of its benign nature and because it can be easily diagnosed cytologically, surgical removal is not always necessary, especially in older or unhealthy patients.

MONOMORPHIC ADENOMA. The monomorphic adenomas are a group of benign lesions that can have a variety of growth patterns. The most common monomorphic patterns are the basal cell and the oxyphilic adenomas (oncocytomas). Other monomorphic adenomas are the sebaceous lymphadenomas and sebaceous adenomas. The parotid gland is the most common site of these lesions.

BENIGN LYMPHOEPITHELIAL LESION. Benign lymphoepithelial lesion (BLL) was first described in association with systemic conditions such as Sjögren's and Mikulicz's syndromes. An apparent increase in its incidence has been seen in patients with human immunodeficiency virus (HIV). BLL now encompasses a spectrum of cystic changes seen in the parotid glands of HIV-infected persons, the common denominator of which is atypical lymphoid hyperplasia. It is thought that these changes are the direct result of HIV infection of intraparotid lymph nodes.

Several reports of HIV-associated malignancies of the parotid have been published, including non-Hodgkin's lymphoma, Kaposi’s sarcoma, and adenoid cystic carcinoma. Some of these have arisen on a background of BLL. Malignancy in association with prior BLL, however, was described before the acquired immunodeficiency syndrome (AIDS) epidemic, and it remains unclear whether HIV infection predisposes this lesion to malignancy.

Treatment of BLL in HIV-infected patients is controversial. Some clinicians cite the association of malignancy as justification for parotidectomy.

Malignant Tumors

Spiro and Spiro have developed a compendium of the various series of salivary gland cancers reported and, in their survey, have outlined the relative occurrence rates of the various cancers in both the parotid and submandibular glands. The various reports from nine studies total 1778 parotid gland cancers, the distribution of which is abbreviated and summarized in Table 30.4-2. Summarized in Table 30.4-3 are comparative data for the submandibular gland that are taken from eight studies and that, when combined, reflect the relative distribution by type of 383 submandibular gland cancers.

TABLE 30.4-2. Relative Prevalence of Histologic Types of Parotid Gland Cancer

<table>
<thead>
<tr>
<th>Histologic Type</th>
<th>Prevalence (%)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucoepidermoid</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Mucoepidermoid</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Malignant mixed</td>
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<td>Adenocarcinoma</td>
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<td>Acinic cell</td>
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</tr>
<tr>
<td>Malignant mixed</td>
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<td>Acinic cell</td>
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<tr>
<td>Malignant mixed</td>
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<td></td>
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<tr>
<td>Acinic cell</td>
<td>9</td>
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<tr>
<td>Adenocarcinoma</td>
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</tbody>
</table>

Notes: (a) Total of 1778 cases from various series of parotid tumors. (b) Table 30.4-2 is based on a survey of nine studies. (c) Table 30.4-3 is based on a survey of eight studies.

<table>
<thead>
<tr>
<th>Histologic Type</th>
<th>Prevalence (%)</th>
<th>Notes</th>
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<td>Acinic cell</td>
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<tr>
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Notes: (a) Total of 1778 cases from various series of parotid tumors. (b) Table 30.4-2 is based on a survey of nine studies. (c) Table 30.4-3 is based on a survey of eight studies.

ACINIC CELL CARCINOMA. Acinic cell carcinoma is an uncommon malignancy that probably accounts for fewer than 10% of all salivary gland cancers. Although acinic cell lesions usually are seen in the parotid gland, they occasionally occur in the submandibular gland. They are low grade, only infrequently invade the facial nerve, and are late to metastasize. When they do metastasize, however, it is usually to the lungs, and under these circumstances, death usually follows. Because of their slow growth, survival data are good when generous surgical excision is performed.

MUCOEPIDERMOID CARCINOMA. In major salivary glands, mucoepidermoid carcinoma occurs more frequently than any other malignancy. It is relatively more common in the parotid than in the submandibular gland, where it is third in prevalence after adenoid cystic carcinoma and adenocarcinoma (see Table 30.4-2 and Table 30.4-3).

Mucoepidermoid carcinoma is unique in that it demonstrates a broad spectrum of aggressiveness, from the low grade that rarely kills to its high-grade counterpart that frequently does. Low-grade mucoepidermoid carcinomas tend to create mostly local problems and can have a long natural history. A locally aggressive surgical approach is usually associated with cure. Although metastasis can occur from these lesions, it is the exception rather than the rule. In fact, such a striking performance gradient is apparent between low- and high-grade mucoepidermoid carcinomas that some investigators believe that the former should be referred to as mucoepidermoid tumor rather than carcinoma. When low-grade mucoepidermoid cancer metastasizes, however, it can be lethal, and to diminish the appreciation of its potential seriousness by this name change seems ill advised. The high-grade and, to a great extent, the intermediate-grade mucoepidermoids are often troublesome because they are locally aggressive and are prone to invasion of nerves and vessels as well as to early metastasis. Spiro and Spiro have reported that 44% of the previously untreated patients with intermediate- or high-grade mucoepidermoid parotid tumors develop nodal involvement at some stage. Analysis of only the high-grade lesions reveals an incidence of nodal metastasis from all salivary gland sites that is probably even higher.

Because of the propensity for regional...
ADENOCARCINOMA. Adenocarcinomas make up approximately 16% of parotid gland and 9% of submandibular gland cancers (see Table 30.4-2 and Table 30.4-3). These lesions are encountered more frequently in the minor salivary glands of the nose and paranasal sinuses. A difference in survival seems to correlate with grade, with the high grade having a poorer prognosis and the low grade a much more favorable one. In the higher-grade tumors, treatment failures result predominantly from distant metastasis. Along with the overall poor performance, this fact is important in helping to judge the degree of aggressiveness with which locoregional disease should be treated.

SQUAMOUS CELL CARCINOMA. Squamous cell carcinomas are uncommon in salivary tissue, making up approximately 7% of parotid gland and 10% of submandibular gland cancers. Individuals with high-grade tumors do poorly and usually present with an advanced stage of cancer. Squamous cell carcinomas of the parotid gland frequently are not primary to that gland but instead represent metastasis into parotid nodes from adjacent sites, such as temple, auricular, and facial skin. Skin lesions that originate from virtually any site on the face tend to metastasize to the superficial lymph nodes that lie external to the parotid capsule.

MALIGNANT MIXED TUMOR. Malignant mixed tumors make up approximately 14% of parotid gland and 12% of submandibular gland cancers (see Table 30.4-2 and Table 30.4-3). The diagnosis is often difficult because of the similarities with the tumor's benign counterpart, the pleomorphic adenoma. Many of the malignant mixed tumors seem to originate in previous pleomorphic adenomas (carcinoma ex-pleomorphic adenoma), but just how often they occur de novo is not known. Thus, controversy has continued for some time. Those proponents of the malignant transformation theory believe that the evolution of malignancy within a pleomorphic adenoma is the explanation for the circumstance encountered periodically in which a longstanding and stable tumor begins to grow significantly. When this does occur, they believe the assumption of malignant development should be made and management tailored accordingly. Although growth acceleration of a previously dormant salivary mass is not pathognomonic of malignancy, we agree that this behavior pattern dictates such a treatment strategy. The exact probability of any given benign mixed tumor becoming malignant is unknown but probably occurs in approximately 5% of pleomorphic adenoma cases. Survival from malignant mixed tumor must be measured over a lengthy period, because the natural history of this lesion can be characterized by protracted but inexorable growth. Metastasis to regional lymph nodes occurs in more than one-fourth of cases.

ADENOID CYSTIC CARCINOMA. In most series, adenoid cystic carcinoma accounts for almost one-fourth of the malignant salivary gland tumors treated and constitutes approximately 10% to 15% of all parotid gland malignancies (see Table 30.4-2). This cancer is relatively more common in minor than in major salivary glands. It is unique because it possesses a natural history, even when local recurrence or distant metastasis has developed. For instance, patients are known to live 10 to 20 years despite pulmonary metastasis, the most frequent manifestation of distant spread. When visceral or bone metastasis occurs, however, death usually follows within a relatively short time. The actual cure rate of adenoid cystic carcinoma is poorly defined, because long-term follow-up often is not included in data analyses. Also clouding the issue of cure is the fact that some 10- to 20-year studies have shown disease-related deaths that continue to occur throughout the follow-up period. Some investigators believe that most adenoid cystic carcinomas recur if followed long enough. Overall, the rate of pulmonary metastasis from these cancers is approximately 40%.

Adenoid cystic carcinoma has an exceptional capability to invade nerve tissue, and when this occurs, local control and survival are compromised. Such a morphologic finding is the rule rather than the exception in this cancer, and recognition of the tendency is essential in planning treatment, which usually consists of wide surgical excision and radiation therapy. Treatment failure most often occurs in the primary tumor site. Some authors have drawn a correlation between histologic patterns of adenoid cystic carcinoma and clinical behavior. Others, although conceding certain behavior pattern differences in the different histologic variants of adenoid cystic carcinoma, do not believe a correlation exists between these features and long-term outcome.
the low and high grades. Adenocystic carcinoma, on the other hand, must be analyzed with the realization that 5-year survival rates are always better than 10-year figures, which in turn are better than those at 15 years, and so on. Most series show 50% to 90% 5-year survival rates, 30% to 67% 10-year survival rates, and 25% 15-year survival rates for treated adenocystic carcinoma.\[24\] Patients with adenocarcinomas of major salivary glands show gradual deterioration of survival statistics with the passage of time; 76% to 85% survival at 5 years and 34% to 71% at 10 years.\[25\] Patients with malignant mixed tumors do not do well; only 31% to 65% survive 5 years and 23% to 30% survive 10 years.\[26\]

Distant metastasis is predictive of a poor prognosis, and it occurs in approximately 20% of parotid malignancies.\[27\] Distant metastasis is a significant concern in most higher-grade salivary gland malignancies. At least 40% of patients with adenocystic carcinoma and 26% to 32% with malignant mixed tumors demonstrate this feature.\[28\] Even with lower-grade tumors, such as acinic cell carcinoma, a measurable incidence of distant metastasis is found.\[29\] In all of these lesions, the site of distant metastasis is most often the lung(s).\[30\] Overall, the likelihood of metastasis from the submandibular gland is almost twice that from the parotid gland.\[31\]

Regional lymphatic metastasis is a subject of considerable importance in relation to malignant salivary gland tumors. In the extensive series reported from Memorial Sloan-Kettering Cancer Center, 14% of patients presented with palpable nodal metastases. Thirty-four percent of the patients with high-grade tumors demonstrated this finding, compared to only 2% of patients with low-grade lesions. Additionally, in the group of patients who had clinically negative necks but underwent elective neck dissections, 49% of the high-grade and 7% of the low-grade tumors turned out to have histologically positive necks.\[32\] These statistically significant figures suggest that the rates of occult and clinically positive node disease are increased with higher-grade malignant salivary gland tumors.

With submandibular gland malignancies, as with parotid tumors, prognosis is dependent on a number of factors, the most significant of which seem to be clinical stage and perineural invasion.\[33\]

Spiro and associates believed that the most important prognosticator for survival is tumor stage. Accordingly, in 1975, they proposed a staging system that was later incorporated into the current American Joint Committee on Cancer staging system.\[34\] This system addresses the size of the primary lesion and the presence or absence of fixation or facial nerve dysfunction. It was first applied only to parotid sites but seems to serve all salivary sites. Table 30.4-4 describes the American Joint Committee on Cancer staging system. According to Spiro,\[35\] cumulative survival exceeds 90% at 10 years for patients with stage I or II disease, whereas only 22% of stage III or IV patients are alive after 10 years.

### TABLE 30.4-4. Staging System for Major Salivary Gland Malignancies

<table>
<thead>
<tr>
<th>Stage</th>
<th>Characteristics</th>
<th>Survival Rate</th>
</tr>
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<tbody>
<tr>
<td>I</td>
<td>Tumor limited to salivary gland</td>
<td>90% at 10 years</td>
</tr>
<tr>
<td>II</td>
<td>Tumor extends beyond salivary gland</td>
<td>70% at 10 years</td>
</tr>
<tr>
<td>III</td>
<td>Tumor invades adjacent structures</td>
<td>50% at 10 years</td>
</tr>
<tr>
<td>IV</td>
<td>Tumor invades distant metastases</td>
<td>20% at 10 years</td>
</tr>
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</table>

CT and MRI are helpful in analyzing the important third dimension of larger tumors, especially those that involve the deep lobe of the parotid gland. Imaging technologies are especially important in studying malignant and/or benign tumors, but these expensive methods are not necessary for the evaluation of all parotid or submandibular gland tumors. As it pertains to tumors, sialography is of historic interest only and is superfluous.

### TREATMENT

The initial treatment for salivary gland neoplasia, whether benign or malignant, whether of minor or major gland origin, is almost always surgical, and whenever possible, removal of parotid, submandibular, and sublingual gland tumors should be excisional rather than incisional. The diagnosis of parotid tumors usually is established by removal of the involved part of the gland, thus avoiding lumpectomy whenever possible. In the case of a lesion of the parotid superficial lobe, for instance, the least extensive or most conservative operation should be superficial parotidectomy. With benign tumors, the diagnostic operation and the definitive operation are, therefore, usually the same. Before surgery, it is helpful for the surgeon to have a sense of whether the tumor is benign or malignant, and this is achieved by physical examination, history, and technological aids such as FNA and imaging.

An important general principle of management that applies particularly to higher-grade adenocarcinomas, malignant mixed tumor, and adenocystic carcinoma is that, by combining postoperative radiation therapy with moderate locoregional surgery, mutilation and physiologic compromise are often avoided. The preoccupation with liberal resection of facial nerve, mandible, and other important structures solely because they are in the field no longer dominates surgical philosophy. Instead, the realization that "more" does not necessarily improve survival has spawned a form of surgical minimalism. When failure does occur, it is frequently at a distant site and is probably not influenced by the degree of the local treatment. Important anatomic structures are rarely sacrificed unless obviously invaded by tumor. The surgeon's reliance on postoperative radiation therapy to manage histologic disease has dramatically altered the surgical feats required to deal with many malignant salivary gland tumors. It should be pointed out, however, that although local and regional control of these tumors is enhanced by this combined therapy, its impact on the development of distant metastasis and, therefore, on survival is less clear.

Some investigators have proposed the routine use of postoperative radiation therapy for almost all malignant tumors of the parotid,\[36\] but the absence of randomized data complicates the issue. Armstrong and associates\[37\] performed a matched-pair analysis comparing surgery alone versus surgery plus postoperative radiotherapy. Patients with stage III/IV disease and those with positive nodes experienced improved locoregional control and survival with postoperative radiation. A trend also was seen toward improved local control for high-grade lesions treated with postoperative radiation (63% vs. 44%). The 5-year determinant survival rate tended to be better for high-grade lesions treated with adjuvant radiotherapy than with surgery alone (57% vs. 28%). No benefits were achieved for lower-grade or lower-stage tumors. Malata and coworkers\[38\] reported 51 patients with malignant parotid tumors, most of whom (73%) received postoperative radiation. The crude 5- and 10-year survival rates were 86% and 49%, respectively, and 10-year actuarial local control was 79%.

Surgical resection is the mainstay of the management of benign pleomorphic adenoma. Reneman et al.\[39\] reported the cumulative experience of more than 1400 salivary gland tumors treated at Christie Hospital between 1947 and 1992. For 551 patients with previously untreated parotid pleomorphic adenoma treated by surgery, the recurrence rate (median follow-up of 12.5 years) was 1.6%. The recurrence rate rises to 15% in patients undergoing surgery for recurrence. Dawson and
On31 reported long-term outcomes for pleomorphic adenomas treated by "lumpectomy" plus radiotherapy. The 10-year local recurrence rate was 1.5%, with cumulative risk rising to 8% at 20 years. Most late recurrences were malignant, with one of four developing malignant recurrence at 15 years, and three at 18 years. The possibility of radiation-induced malignancy, therefore, must be added to the known possibility of malignant transformation when considering treatment options. Given these considerations, surgery alone seems to be the obvious initial treatment of choice.

Management of parotid pleomorphic adenomas that recur despite surgical removal can be particularly challenging. Generally, recurrences develop slowly, and frequently their appearance is not noted for years after surgery. Furthermore, recurrences often present in the form of multifocal nodules, all of which are inevitably engulfed in scar tissue from the previous surgery, and in this setting, the identification and protection of the facial nerve is substantially more difficult than in the nonoperated circumstance. Leverstein and colleagues32 reported on 40 patients with recurrent pleomorphic adenomas of the parotid. In three patients, no tumor resection was performed. Two received radiotherapy, and both were controlled. In the remaining 37 cases, en bloc resection was done. Pathology remained benign in 36 cases, and 16 received postoperative radiotherapy. None of the patients developed local failure with a median follow-up of 106 months. One patient experienced facial nerve paralysis and two developed malignant transformation. It would seem, therefore, that in high-risk circumstances, such as multifocality, positive surgical margins, and certain deep lobe tumors, selective use of radiation therapy after appropriate surgical excision should be the treatment of choice.

Cervical metastasis is an ominous event in salivary gland malignancy, and the standard management approach is to do a modified radical neck dissection followed by postoperative radiation. In malignant parotid and submandibular tumors in which no clinical adenopathy is present, the first echelon lymph nodes should be sampled because of a surprisingly high rate of occult metastasis. In a multivariate analysis, Armstrong et al.33 reported that the risk of occult metastasis is 20% in primary malignancies larger than 4 cm, with a 49% risk for high-grade tumors. Frankenthaler and colleagues34 found a 33% risk of occult metastases for parotid malignancies associated with facial nerve paralysis and 18% risk for high-grade tumors in general. At the present time, however, no compelling data support the benefit of elective neck dissection for the clinically negative neck in malignant high-grade tumors.35

Other series consistently have shown improvement in locoregional control when patients with major salivary gland cancers received postoperative radiation therapy.36-40 These consistent data are a marked improvement over the substantial local failure rates (39% for parotid gland and 60% for submandibular gland) reported for patients treated by surgery alone.41

Specifically, the indications for adding radiation to surgery for management of malignant tumors are positive surgical margins, advanced primary tumor stage (including facial nerve involvement, positive neck nodes, high-grade histology, and deep lobe involvement), and tumor spillage during the operation.

Other data suggest that, for lesions that are locally advanced at the time of initial treatment and for patients with involved margins, intraoperative brachytherapy plus postoperative external-beam radiation therapy might be useful in improving local control.42 Fu and associates43 showed that, with positive resection margins, local control improved with the addition of radiation. Overall, only 14% of those with microscopic disease at or close to the surgical margin experienced local recurrence when postoperative radiation therapy was given, as compared with 54% who recurred locally in the surgery-only group. Most patients in this series received total doses between 5000 and 7500 cGy.

Although a detailed technical description of parotidectomy is inappropriate here, several points should be made about this meticulous but safe surgical technique. Were it not for the presence of the facial nerve within the substance of the parotid gland, the procedure would be far less challenging; however, this important motor nerve, along with all of its branches, weave through the parotid parenchyma in such a way that almost all tumor operations involve nerve identification, isolation, and dissection. The approaches vary somewhat, but consistent with all parotid operations is the fundamental surgical tenet of generous and well-planned incision, skin flap elevation, and wide exposure. When well designed, the parotidectomy incision, even though long, leaves little obvious scarring. The incision usually is begun anterior to the auricle, extends behind the edge of the external ear canal to minimize its exposure, then swings along the lower edge of the ear lobe down to the first horizontal crease of the cervical skin and then anteriorly for some distance (Fig. 30.4-4). A skin flap is then lifted anteriorly to an extent that exposes the entire external surface of the parotid gland. The gland is separated from the anterior border of the sternocleidomastoid muscle, and the posterior belly of the digastric muscle is identified lying deep to the sternocleidomastoid. The diagastric muscle and the cartilaginous ear canal serve as landmarks for identification of the main trunk of the facial nerve as it exits the stylohyoid foramen and extends anteriorly. The various branches of the nerve are dissected and, in the case of the tumors within the superficial lobe of the parotid gland, that lobe and the tumor within it are removed without violating the capsule of the neoplasm. To remove tumors that lie within the deep lobe (i.e., under the nerve), the superficial lobe of the gland is often removed, and various manipulations of the nerve are necessary to remove the tumor under it. For a large, deep lobe neoplasm, other techniques of deep lobe exposure, such as submandibular gland excision, with or without mandibulotomy, may be necessary to accomplish safely and effectively the important goal of en bloc tumor removal.

**FIGURE 30.4-4. Typical parotidectomy incision.** A: The drawing of the incision is designed to blend into natural skin folds and minimize visibility. B: One-year postoperative result of an actual parotidectomy incision like the one depicted in A.

Often, the oncologic principles of wide excision with ample surrounding normal parenchyma are not attainable in deep lobe tumors, and the adequacy of the surgery must be sternly questioned. Generally speaking, one should apply liberal criteria in this circumstance for the use of postoperative radiation therapy. Modern imaging provides the means by which the surgeon can be forewarned about deep lobe involvement, its size, and the probability of needing extended methods, such as mandibulotomy, to eradicate the tumor from the parapharyngeal space. Whether partial or total parotidectomy is done, the defect incurred is usually reasonable. With proper attention to detail, dissection of the facial nerve and removal of most tumors can be accomplished with minimal risk of postoperative facial weakness. Closure of the skin incision usually is followed by a pleasing esthetic result.

Radiation therapy techniques vary, depending on the anatomic and pathologic situation. Submandibular lesions are usually treated with parallel opposed ports to cover the entire tumor bed and submandibular/submental area. The cervical lymph nodes are included for node-positive patients, and the occasional, high-risk, node-negative patient. For parotid, treatment-planning CT scans should routinely be done. A variety of techniques have been reported.32,44 Yaparpalvi and coworkers32 reported a comparison of nine different techniques using dose-volume histogram analysis of exit dose to contralateral parotid, hot spots in mandible and temporal lobe, and other key parameters. They concluded that an ipsilateral wedged pair; a three-field anteroposterior (wedged), posteroanterior (wedged), and lateral, using a 6-MV photon; and a mixed 6-MV photon beam with a 16-MeV electron beam (1:4 weighting) provided the best target coverage with minimal normal tissue dose. Garden et al.45 reported a preference for ipsilateral mixed beam over the wedged pair technique with respect to complications. Modern conformal techniques should provide excellent coverage of the target area and minimum dose to surrounding normal tissue using either approach.

The exact dose required for postoperative radiation therapy has not been determined. In a study in which patients who received doses of at least 5750 cGy were compared with patients who received smaller doses, Harrison and colleagues32 compared dose with outcome. The 10-year local control rate for the higher-dose group was 72%, compared with 53% for those in the lower-dose group. However, despite the suggestion of a trend in favor of high doses, the difference was not statistically significant. In another important study, Garden and associates32 reported no clear dose-response relationship, except in patients with positive margins or tumor involving the facial nerve, in whom he noted better results with doses of more than 60 Gy. Hosokawa and coworkers46 reported that patients with mucoepidermoid cancer of salivary gland origin experienced no local recurrences with postoperative doses of more than 55 Gy, whereas 3 of 17 patients recurred locally with doses of less than 55 Gy. The difference was statistically significant. McNaney and coworkers47 reviewed treatment failure and the total dose for patients
who received at least 6000 cGy or more. The doses that were associated with treatment failure did not lend themselves to a specific dose-response relation. In general, doses in the 6000 to 6500 cGy range given over 6 to 7 weeks are used for postoperative radiation therapy, except in patients with involved margins or T4 disease, who may require even higher doses. In this subset of patients, the expected high local failure rate that has been reported supports the need for dose intensification with either conformed external-beam techniques or intraoperative brachytherapy/radiotherapy approaches.

Because of the unique natural history of adenoid cystic carcinoma and because of its affinity for neural involvement, this tumor deserves special and separate consideration. Data from three different studies consistently show that postoperative radiation therapy should be added for almost all adenoid cystic carcinomas. When regional nodes are involved, the neck should be included in the treatment planning. When these nodes are uninvolved, elective neck radiation generally is not recommended.

Management of the neck in general includes the consideration of important variables such as T stage and grade. In a study by Armstrong and associates, 474 patients with major salivary gland cancers were reviewed. High-grade tumors had a 49% risk for occult metastases, as compared with only 7% for intermediate- or low-grade tumors. The risk for epidermoid cancers was 41%, but only 10% for all other histologies combined. Submandibular tumors had a higher risk for occult metastases, occurring in 21% as compared with 9% for parotid tumors. Occult disease was found in 7% of T1 and T2 tumors, 16% of T3 tumors, and 24% of T4 tumors. Most agree that, in patients with clinically positive regional nodes, postoperative radiation therapy should be administered. The question of how to manage the clinically negative neck is less clear, but the thinking is aided by Armstrong’s data. In patients who would otherwise need postoperative radiation therapy because of concerns about the primary site, elective neck treatment with radiation can be used. It is appropriate to electively harvest the first echelon nodes in high-risk patients as a means of staging the neck. If histologic examination reveals disease, postoperative radiation therapy to the neck should be added. In Armstrong’s study, the periparotid nodes were the ones most commonly involved, and in those that were positive, 25% had positive nodes at levels III and IV. This was because of skip metastases to level IV and IV without level II metastases. This point emphasizes the need for treatment of the entire neck when involved nodes are found.

For patients with a clinically positive neck, surgery and postoperative radiation therapy are indicated. Although with squamous cell carcinoma of the head and neck, nodal disease in one side of the neck frequently places the contralateral neck at risk, this does not appear to be the case with major salivary gland cancers. King and Fletcher 62 and Harrison et al. 29 showed that elective contralateral neck radiation is not necessary in this circumstance.

The role of chemotherapy in the management of both the major and minor salivary gland malignancies is limited to treating distant metastasis that is progressing and to circumstances of palliation of local/regional disease not amenable to either salvage surgery or radiation therapy. Although a few patients have been reported who have been given combination chemotherapy in the neoadjuvant setting or as adjuvant therapy after surgery, too few patients are available for study. Similarly, no data has been published evaluating concurrent chemotherapy and radiotherapy administered in an attempt to improve outcome by increasing radiation cell kill.

The interpretation of response data from phase II trials of single agents and combination chemotherapy regimens is limited by the heterogeneity of histologic types of salivary gland cancer, by the fact that response probably differs by histologic type, and by the small numbers of patients enrolled in any one study. Mucoepidermoid, adenoid cystic, and adenocarcinomas histologies constitute the bulk of patients referred to medical oncologists and therefore those that are included in clinical trials. Patients with other salivary gland malignancies, such as malignant mixed tumors, epithelial-myoepithelial carcinomas, salivary duct carcinomas, acinic cell carcinomas, and squamous cell carcinomas, are rare and therefore not separated out in the chemotherapy literature.

Mucoepidermoid and squamous cell carcinomas are thought to arise from the salivary excretory duct and generally respond to cisplatin-based chemotherapy regimens used for other sites in the head and neck. Adenoid cystic carcinomas and adenocarcinomas arise from the intercalated ducts of the salivary glands and tend to be lumped together in study reports but often have a different clinical course; adenoid cystic carcinoma may be surprisingly indolent and only manifested by the chronic pain of perineural tumor infiltration. Metastatic adenocarcinoma, on the other hand, generally has a more aggressive course that is reflected in proportionately more obvious responses to chemotherapy.

Table 30.4-5 lists single-agent and combination regimens reported to have activity in salivary gland cancers. Cumulative response rates to single agents range from 10% to 40%, with the higher rates reported from older literature. Retrospective reviews of patients treated for adenoid cystic carcinoma before 1980 at both the M. D. Anderson and Princess Margaret hospitals indicated that Adriamycin and 5-fluorouracil were the most effective single agents, whereas mitomycin C, vincristine, and cyclophosphamide showed little activity. A review published by Suen and Johns in 1982 noted clinical efficacy for cisplatin as well.

TABLE 30.4-5. Single Agents and Combination Regimens with Activity in Salivary Gland Malignancies

In the 1990s, three new agents were tested in multicenter trials with adequate numbers of patients with adenoid cystic carcinoma. The European Organization for Research and Treatment of Cancer (EORTC) conducted a phase II evaluation of epirubicin in 20 patients and reported two responses that lasted 7.5 and 20 months, respectively, and ten patients with disease stabilization. Symptomatic improvement was documented in 29% in this particular study. Phase II trials of mitoxantrone in adenoid cystic carcinoma patients were carried out by the EORTC and the Southwest Oncology Group. EORTC investigators observed four partial responses and 22 with stable disease in a total of 32 patients; the Southwest Oncology Group investigators reported one complete response and 12 patients with stable disease out of the 18 treated.

Paclitaxel at a dose of 200 mg/m² over 3 hours every 3 weeks was tested in the Eastern Cooperative Oncology Group, using a standard two-stage statistical design, in three patient cohorts: individuals with adenoid cystic carcinoma, adenocarcinoma, or mucoepidermoid carcinoma. The trial was closed for the adenoid cystic carcinoma cohort after no responses were observed in 15 patients, but patients with adenocarcinoma and mucoepidermoid carcinoma continue to be enrolled, with both arms demonstrating responses.

A fourth new drug studied was vinorelbine. Airoldi et al. conducted a phase II trial in 20 patients with salivary gland malignancies (13 adenoid cystic carcinomas, five adenocarcinomas, one malignant mixed tumor, and one undifferentiated carcinoma). Four patients achieved a partial response and nine demonstrate stable disease. In summary, modest activity has been shown for epirubicin, mitoxantrone, and vinorelbine in patients with adenoid cystic carcinoma. Paclitaxel does not appear to be active for adenoid cystic carcinoma, but preliminary findings from the Eastern Cooperative Oncology Group suggest activity for adenocarcinoma and mucoepidermoid carcinoma.

Combinations that include cisplatin, Adriamycin, or 5-fluorouracil (5-FU) have been the cornerstone of palliative treatment for salivary gland malignancies, a fact particularly true in adenoid cystic and adenocarcinomas. Complete and partial response rates in the 30% to 60% range have been reported. In addition, some trials note prolonged disease stabilization and relief of pain among patients with adenoid cystic carcinoma. Median response duration is in the range of 6 to 9 months, with some responses lasting more than 1 year. It is unknown whether survival is improved with chemotherapy. Two- and three-drug regimens combining cyclophosphamide with Adriamycin and cisplatin (CAP), cisplatin with Adriamycin or epirubicin plus 5-FU (OAF or OFE), cisplatin plus 5-FU (PF), or cisplatin, Adriamycin, and bleomycin (PAB) all appear equally effective. Combinations that incorporate mitomycin C or vincristine or use more than three drugs do not seem to offer any advantage.
In summary, no standard drug therapy has been established for treatment of salivary gland cancer because of the lack of formal trials with adequate numbers of patients. For the treatment of adenoid cystic carcinoma, the information at hand would suggest that combination chemotherapy is superior to single-agent strategies and that two- or three-drug combinations of cisplatin, doxorubicin, and 5-FU would be reasonable initial treatment. The slow growth rate of adenoid cystic carcinoma may be one of the factors that account for the lack of response observed in some studies. Relief of symptoms and stabilization of disease may be more achievable palliative end points for evaluating drug efficacy. Adenocarcinomas of salivary gland origin may be treated with the same regimens. High-grade mucoepidermoid carcinoma appears to be sensitive to the same spectrum of drugs that are commonly used to treat squamous malignancies (cisplatin, bleomycin, methotrexate, and 5-FU). Therefore, the combination of cisplatin and 5-FU or taxane-based combinations are reasonable regimens to use. No data are available about treatment of the less common malignancies, such as acinic cell carcinoma and malignant mixed tumors. All patients should be considered candidates for trials of investigational new drugs. Studies of adjuvant chemotherapy, particularly for high-grade mucoepidermoid carcinoma, have not been undertaken because of the small number of patients available for study. The optimal way to assess new therapies for salivary gland carcinoma is in a multistitutional setting in which patient resources can be pooled and treatments made uniform.

MINOR SALIVARY GLAND TUMORS

Minor salivary gland tumors can occur in any age group, and they have no particular gender predilection. The glands are ubiquitous in the upper aerodigestive tract, so tumors originating in minor glands can occur anywhere in the head and neck; however, the palate is the most common site for both benign and malignant lesions. Rarely, ectopic salivary gland tissue can lead to tumors in such diverse locations as the middle ear or the thyroid area. Table 30.4-6 shows the distribution by site of origin in the Memorial Sloan-Kettering Cancer Center’s experience with these tumors. Minor salivary gland lesions occur in the nasal cavities and paranasal sinuses, nasopharynx, larynx, lip, floor of the mouth, trachea, and other sites in the head and neck, but overall, they are most frequently seen in the oral cavity. It is often impossible to differentiate between a primary sublingual tumor and a minor salivary gland tumor in the anterior floor of the mouth.

Between 65% and 88% of all minor salivary gland tumors are malignant. Adenoid cystic carcinoma is the most common histologic type, occurring in as many as 55% of patients with minor salivary gland tumors. Otherwise, the presenting types are the same as for major salivary gland tumors, including mucoepidermoid carcinoma, adenocarcinoma, malignant mixed tumor, and anaplastic carcinoma. Small cell (oat cell) carcinoma of minor salivary gland origin also has been reported. Minor salivary gland tumors tend to present as painless submucosal masses and can be present for many years without change. Malignant tumors can persist without change, but more often they increase in size. Any submucosal mass in the head or neck should be considered a minor salivary gland tumor until proved otherwise. Malignancies can spread to invade local tissue, including bone and nerve. Tumors of the floor of the mouth or the tongue can extend into the neck and into the mandible. Adenoid cystic carcinoma has a particular tendency to grow along the perineural spaces and to extend great distances from the primary tumor along nerve pathways, and it is important for the surgeon to realize that skip areas of tumor involvement can occur along the nerve. For instance, when this lesion occurs in the lateral aspect of the palate, it can infiltrate the branches of the greater palatine nerve, extend centrally, and can ultimately occupy the gasserian ganglion in the middle cranial fossa. This fact should be taken into account, and treatment planning should include the ganglion. The presence of a negative frozen section taken from the nerve trunk proximal to the originally discovered peripheral nerve lesion does not rule out the possibility that the nerve is involved with tumor more centrally. Adenoid cystic carcinomas can also spread along the haversian canals of bone. Therefore, when involvement of the mandible is questionable in floor of mouth lesions, the surgeon must be prepared to deal with further extension than what is obvious.

Fewer than 20% of patients with minor salivary gland malignancies present with lymph node metastases, and approximately 10% who demonstrate a clinically negative neck subsequently develop nodal metastases. As with major salivary gland tumors, the incidence of nodal metastases is related to grade and tumor size (i.e., stage).

No uniform staging system has been developed for minor salivary gland tumors. Survival seems to correlate with clinical stage. Olsen and coworkers showed that tumor size was significant for mucoepidermoid carcinoma of the oral cavity. In their study, patients with lesions larger than 2 cm did much worse than those with lesions smaller than 2 cm. None in the latter group died from mucoepidermoid carcinoma.

TREATMENT

Surgery is usually the treatment of choice for minor salivary gland tumors, whether benign or malignant. Enucleation is considered inadequate and is associated with a recurrence rate in excess of 93% therefore, wide excision or regional excision must be performed whenever possible. The surgeon should not hesitate to remove underlying bone, such as palate or sinus wall(s), to achieve such excision. Paranasal sinus malignancies often require partial maxillectomy for complete removal. Speech and swallowing rehabilitation for head and neck defects that have been created by tumor resection is easily accomplished by prosthetic devices. Defects of the soft palate, however, are more problematic.

Limited information exists on the effectiveness of primary radiation treatment. Ellis and colleagues reported their results, in which a total of 20 patients with minor salivary gland malignancies received only radiation therapy for their disease. Seven had early-stage tumors and 13 had advanced tumors. Local control was obtained in six of the seven early-stage lesions (86%), a result that is comparable with those for surgical management. For more advanced lesions, however, radiation alone controlled only 2 of 13 (15%), a result considerably inferior to that following combined therapy. Parsons and associates reported local control in 13 patients treated with radiotherapy alone for adenoid cystic cancer, and five of these patients have follow-up longer than 10 years. A total of 20 of 51 cases treated with radiotherapy alone are locally controlled with follow-up ranging from 2.5 to 21.0 years. Several surgical failures were followed with radiotherapy as well. Although this and other limited studies suggest that radiation can be effective for small lesions, surgery usually is considered the treatment of choice whenever possible. Advanced lesions should always be treated initially with surgery, and usually that procedure is followed by postoperative radiation therapy. Exactly which patients should receive postoperative radiation therapy remains unclear. We tend to recommend the guidelines that have been established for major salivary gland tumors. Patients with advanced-stage disease, lymph node metastases, high-grade tumors, or inadequate surgical margins are treated with postoperative radiation. Many patients have a combination of these factors.

Long-term follow-up is now available for patients with minor salivary gland tumors. Parsons and associates reported 20-year local control of 57%. The most important factors affecting local control were tumor stage and combined modality therapy (surgery plus radiotherapy). It is significant that, with longer follow-up, the distant metastasis rate at 12 years was 40%.

Eapen and colleagues reported 70 patients with salivary gland carcinomas. Approximately one-third had minor salivary gland tumors, and the indications cited for postoperative radiation therapy were inconsistent. However, a significant decrease in locoregional recurrence was noted among patients who were given postoperative radiation therapy. The actuarial risk of locoregional recurrence in the nonradiated patients was 62%, as compared with 20% for the radiated group.

### Table 30.4-6. Incidence by Site of Origin of Minor Salivary Gland Tumors

<table>
<thead>
<tr>
<th>Site of Origin</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral mucosa</td>
<td>95%</td>
</tr>
<tr>
<td>Oral cavity</td>
<td>5%</td>
</tr>
<tr>
<td>Nasal cavity</td>
<td>0%</td>
</tr>
<tr>
<td>Paranasal sinuses</td>
<td>0%</td>
</tr>
<tr>
<td>Nasopharynx</td>
<td>0%</td>
</tr>
<tr>
<td>Larynx</td>
<td>0%</td>
</tr>
<tr>
<td>Lip</td>
<td>0%</td>
</tr>
<tr>
<td>Floor of mouth</td>
<td>0%</td>
</tr>
<tr>
<td>Trachea</td>
<td>0%</td>
</tr>
<tr>
<td>Other sites</td>
<td>0%</td>
</tr>
</tbody>
</table>

![Incidence by Site of Origin of Minor Salivary Gland Tumors](image_url)
Ninety percent of the patients received between 5500 and 6500 cGy over 5.0 to 6.5 weeks. In 95% of irradiated patients, the regional lymph nodes were treated along with the primary site.

Tran and coworkers\textsuperscript{11} reviewed the University of California, Los Angeles, experience with salivary gland tumors of the oral cavity. A total of 62 patients with previously untreated parotid tumors were analyzed, all of which received postoperative radiation therapy owning to advanced local disease, involved margins of resection, or both. Most of the lesions in this series were adenoid cystic carcinomas, and the palate was the most common primary site. Local tumor control in patients with positive margins was 50% for surgery alone, as compared with 71% with combined surgery and postoperative radiation therapy. A trend toward less successful disease control and poorer survival for patients with adenoid cystic carcinoma was noted as compared with the other malignant tumors.

The experience with minor salivary gland tumors of the nasal cavity and paranasal sinuses was also reported by Tran and coworkers.\textsuperscript{11} Thirty-five patients seen and treated between 1962 and 1985 were included, most of whom (66%) had adenoid cystic carcinoma. Adenocarcinoma was seen in approximately one-half the ethmoid and maxillary sinuses, and well over one-half the nasal cavity. Fifty percent of all patients with histologically confirmed adenoid cystic carcinoma were treated with primary surgery alone, and 84% with combined surgery and postoperative radiation therapy. A local or regional recurrence was noted in 10% of patients, and 5% died of disease. In addition, 7 patients had undergone a second resection for recurrent disease. The surgery alone group experienced a local recurrence rate of 12%, whereas the combined surgery and postoperative radiation therapy group experienced a local recurrence rate of 6%. This study thus reinforces the findings that surgery alone is not adequate for the treatment of adenoid cystic carcinoma.

Douglas and colleagues\textsuperscript{21} assessed fast-neutron radiotherapy for minor salivary tumors. They reported on 84 patients with adenoid cystic cancers of the nasal cavity, paranasal sinuses, and parotid region. A trend toward less successful treatment in the low-dose group was noted, which consisted of patients treated with doses of 4000 cGy in 5 weeks or less.

Koss and associates\textsuperscript{25} reported 14 patients with small cell carcinoma of minor salivary gland origin. Although no conclusive data were obtained from this or other series, these lesions may be managed optimally with resection, chemotherapy, and local radiation therapy.

The technique of radiation therapy for minor salivary gland tumors is similar to that for squamous cancer at the corresponding primary site. For postoperative radiation, doses in the 6000- to 6500-cGy range are used over 6 to 7 weeks. Wide portals are required, especially for adenoid cystic cancer. The nerve pathways up to and including the base of the skull should be included in the treated portals. When radiation alone is used for early-stage disease, doses of at least 7000 cGy in 7 to 7.5 weeks should be used. Brachytherapy can be used for a portion of the treatment, especially for oral cavity lesions. Effective nodal radiation usually is indicated only in selected circumstances, such as the occasional patient with minor salivary gland tumors of the nasopharynx. Whether elective nodal radiotherapy is required here is unclear, but it can certainly be justified on the basis of the rich lymphatic drainage of the nasopharynx.

**SPECIFIC STRATEGIES FOR SPECIAL SITUATIONS**

Deep lobe parotid tumors, whether benign or malignant, are often inaccessible in standard parotidectomy. In such a circumstance, a variety of mandibulotomy techniques are available to surgeons that provide excellent exposure to the area into which these tumors expand (i.e., the parapharyngeal space). Because deep lobe tumors often are not surrounded by parotid parenchyma, removing the lesion without fragmentation can be difficult. Additionally, this potential space is at the skull base, and the carotid sheath forms part of its perimeter.\textsuperscript{111} Although these mandibulotomy techniques are seldom required, in selected circumstances the technique and efficient and safe removal of deep lobe tumors is greatly enhanced by their use.

Occasionally, the facial nerve or one of its branches is exposed within (but not invaded by) a benign tumor; thus, sparing the nerve requires meticulous and painstaking removal of the neoplasm. Radiation therapy is not usually part of the primary management of benign lesions; however, for a lesion that enulates the nerve, for recurrent benign lesions, and when complete gross tumor removal is not possible, radiation therapy is often recommended.\textsuperscript{22} Postoperative radiation therapy is probably important for recurrent deep lobe parotid tumors, whether benign or malignant, even though all gross tumor has been removed. Even with gross tumor removal, large pleomorphic adenomas of the deep lobe are associated with a high local recurrence rate. To add radiation after routine and uncomplicated removal of a benign tumor of the superficial lobe of the parotid or from the submandibular gland seems unwarranted.

In cancers that involve the facial nerve or its branches, the involved segment is best resected and grafted with an interposition of nerve harvested from another site. In most cases, however, nerve can be dissected off a tumor surface and, with the use of postoperative radiation therapy, control results are achievable that are similar to those from a more radical approach. However, sacrifice of the facial nerve is rarely required, and postoperative radiation therapy has in large part been responsible for this more conservative approach to dealing with the facial nerve in parotid gland surgery. No prospective studies have been done that document the effectiveness of this approach, which has evolved from considerable anecdotal information. It is axiomatic that those patients who require nerve resection and grafting have advanced-stage disease and, therefore, require postoperative radiation therapy. Even though no definitive studies have been done to analyze the impact of external-beam radiation on nerve regeneration, it is generally felt that nerve grafts do equally well despite radiation. The important addition of postoperative radiation therapy for these advanced malignancies should not, therefore, be avoided or even delayed because of concern for neural regeneration.

Most data for major salivary gland cancers involve the parotid gland, selected reports have focused on submandibular tumors. Sykes and colleagues\textsuperscript{31} reported 30 cases of carcinoma of the submandibular gland treated with radiation therapy. Most patients were postoperatively treated, and 12 patients were irradiated after grossly negative biopsy alone. The 5- and 10-year local control rates were 85% and 73%, respectively. Cancer-specific survival was 79% and 57%, respectively. Late recurrences were seen, especially for those with adenoid cystic histology. Interestingly, 9 of 12 patients radiated for gross disease had local control.

Not infrequently, a particular situation arises in which a patient with a submandibular mass is explored, and for various reasons, only gland resection is done at the initial operation (i.e., none of the adjacent tissue is removed), and pathologic examination later reveals the existence of a malignancy. The literature is not clear in its recommendations, but the value of reoperation usually lies in the removal of gross disease such as that left behind at the primary site or metastatic nodes. To reoperate and radically remove regional nerves such as cranial nerve XII or to remove mandible in the absence of such gross disease does not seem warranted. Neck dissection or treatment of the bone is generally not recommended, and postoperative radiation to the primary bed and neck should be conducted. Considering the potential for locoregional control with this plan, and considering that more radical measures at the locoregional site do nothing to prevent distant metastasis, this moderate approach seems appropriate.\textsuperscript{32}

A unique accumulation of data has assessed the value of fast-neutron radiotherapy for malignant salivary gland tumors.\textsuperscript{123-126} Douglas et al.'s report\textsuperscript{123} of the results of neutron radiotherapy in 148 patients with major salivary gland malignancies is particularly noteworthy. The 5-year actuarial locoregional control rate for patients treated with curative intent for gross tumor was 59%. Tumor size was an important determinant of outcome. Tumors smaller than 4 cm were controlled in 80%, whereas larger tumors were only controlled in 35%. All patients who had complete resection followed by postoperative neutron therapy had local control. In yet another report,\textsuperscript{124} Douglas and colleagues assessed fast-neutron radiotherapy for minor salivary tumors. They reported on 84 patients with adenoid cystic cancers treated between 1965 and 1994. Overall 5-year actuarial locoregional control was 59%. For advanced lesions that involved the skull base, cavernous sinus, or nasopharynx, locoregional control was only 15%, whereas it was 63% when these sites were unreinvolved. Recurrence-free survival of 53% at 5 years also has been reported for adenoid cystic carcinoma in a European series.\textsuperscript{125}

Buchholz and coworkers\textsuperscript{126} also reviewed a limited experience of six patients with large, advanced, or recurrent pleomorphic adenoma who, because surgery was deemed excessively morbid, were treated with neutron beam therapy. With median follow-up of 52 months, all patients are locally controlled. Although the method is alluring, the unavailability of neutrons precludes most patients from receiving this therapy.

**PARAGANGLIOMAS**

Throughout modern medical literature, the paragangliomas are known by a variety of names, including glomus tumors, chemodectomas, nonchromaffin paragangliomas, glomocytomas, carotid body and tympanic body tumors, and rezeptomas. These names and others make up a heterogeneous and confusing list that addresses certain individual characteristics of various tumors but does not achieve the necessary consistency of classification.\textsuperscript{127-129}
Essentially, these tumors make up a family of neoplasms that develop from the paraganglia tissues, which are themselves chemooreceptor organs that are distributed throughout the body. These organs are of neural crest origin and have similar functions and histologic appearances. Their cells of origin are part of the diffuse neuroendocrine system (DNES), a name that has replaced the previous designation of amine precursor uptake and decarboxylase system. The newer terminology acknowledges that the primary products of the paraganglia, neuropeptides, and catecholamines may serve as neurotransmitters, neurohormones, and hormones, and parahormones.

Paragangliomas can be broadly categorized as either sympathetic or parasympathetic. The former arise from the adrenal medulla (pheochromocytomas), certain extradrenal sympathetic paraganglia, and visceral autonomic paraganglia. Parasympathetic paraganglia are found throughout the body, and it is this group that gives rise to almost all the paragangliomas of the head and neck.

The chief cell is probably the principal component of the paraganglioma, serving as its chemooreceptor. These cells contain acetylcholine, catecholamines, and serotonin. They are of neural crest origin and, hence, are neuroendocrine in nature. The chief cells render the paraganglioma receptive to hypoxia and pH changes, and to fluctuations in the blood carbon dioxide concentration.

As members of the DNES, the chief cells of the paraganglia are functionally and ultrastructurally linked with thyroid C cells, ultimobranchial cells, and adrenal/corticomedullary cells of the adrenal medulla. These chief cells migrate with autonomic ganglion cells and are, therefore, in close association with the autonomic ganglia around the aorta and its main branches. Many head and neck paraganglia, and their respective neoplasms, are distributed in relation to the vessels and cranial nerves of the primitive branchial arches and are therefore referred to as branchiomeric paraganglia.

For example, the jugulotympanic paragangliomas are branchiomeric by virtue of their relation to the third gill arch. The intravagral paragangliomas, on the other hand, are not associated with either the gill arches or their arterial derivatives.

Although paragangliomas can be seen in a variety of head and neck locations—orbit, maxilla, larynx, trachea—most are found on the carotid body, the vagus nerve, or in the jugulotympanic area. This follows the consistent sites occupied throughout the body by the paragangliomas. They can be classified as follows:

I. Branchiomeric paraganglia
   a. Temporal bone (tympanicum, jugulare)
   b. Carotid body
   c. Other head and neck (orbit, laryngeal, nasal)
   d. Subclavian, aortic, pulmonary
   II. Intravagral (upper mediastinal) paraganglia
   III. Aorticosympathetic (retroperitoneal) paraganglia
   IV. Visceral (pelvic, vagal, mesenteric) paraganglia

The term glomus was applied to paragangliomas because it was believed that the chief cells within the paraganglia were derived from specialized pericytes or from blood vessel walls, as is seen in true arteriogenous glomus complexes. Depending on whether they began in the ear or on the jugular bulb, those tumors that develop in the jugulotympanic paraganglia usually are referred to as glomus tympanicum or glomus jugulare tumors, respectively. The paraganglia from which these neoplasms arise are associated with the tympanic branch of the glossopharyngeal nerve and the auricular branch of the vagus nerve, respectively. The paragangliomas of the intravagral area are often referred to as glomus intravagral or vagal body tumors. Although the term glomus enjoys considerable name recognition, it is deceiving because of the suggestion of pathologic uniqueness. Such is not the case, however, because all the head and neck paragangliomas have similar histologic, ultrastructural, and cytochemical features, irrespective of the site of origin, post of fact, location and functional capabilities, rather than appearance, separate them from one another. It is noteworthy that the first description of a temporal bone glomus tumor by Lubbers was referred to a carotid body-like tumor that was thought to be metastatic from a contralateral carotid body tumor.

PATHOGENESIS

The word functional is used to describe paragangliomas that secrete catecholamines (epinephrine and norepinephrine) and serotonin. Even though the capacity for catecholamine synthesis and secretion has been documented for both jugulotympanic and intravagral paragangliomas, these two tumors actually have the lowest catecholamine content of all paragangliomas. Other functional capabilities have been documented in paragangliomas, but the significance of any secretory activity should be evaluated by its clinical impact. The incidence of clinically functional paragangliomas is only 1 to 3%, however, because of the potentially serious consequences of a catecholamine crisis during manipulations of a functional tumor, evaluation of patients with paragangliomas should include screening for symptoms and signs of catecholamine secretion and in selected circumstances, even the measurement of the appropriate blood and urine products.

Although all paragangliomas are chemically capable of secreting these products, no physiologic function of the jugulotympanic or the intravagral paraganglia has been established. For the carotid body paraganglia, however, a physiologic role is clearly defined. The carotid body and carotid sinus function as complementary chemooreceptor and baroreceptor, respectively, to effect homeostatic regulation of both ventilation and perfusion.

Overall, paragangliomas are uncommon neoplasms that occur as nonfamilial and familial tumors; the former develop more frequently in women and the latter in men. The mode of inheritance is thought to be autosomal dominant with incomplete penetration. The affected gene is probably located in the long arm of chromosome 11, but there have also been abnormalities found in chromosomes 5 and 7.

Multiple paragangliomas occur synchronously or metachronously, unilaterally or bilaterally, in 25% to 50% of the familial and in approximately 10% of the nonfamilial tumors. Any combination of two, three, or more sites of origin of synchronous tumors can occur, but the most frequent combination involves concurrent carotid body and jugulotympanic tumors. Synchronous occurrence is seen between paragangliomas and other DNES lesions, such as pheochromocytomas. Although this occurrence is unusual, the serious consequences of not being forewarned before surgery mandates screening for this tumor in all paragangliomas. Specifically, in patients with certain catecholamine profiles, the existence of a pheochromocytoma must be ruled out before any surgery is undertaken. Parathyroid adenomas, thyroid carcinomas, and certain other neural crest tumors also can be concurrent with jugulotympanic, intravagral, and carotid body paragangliomas.

Essentially, all paragangliomas of nonfamilial character carry the potential of being as potentially systemic afflictions, especially in patients with a family history of similar tumors. Carotid body tumors are much more common in people living at high altitudes than in those living at sea level.

CLINICAL BEHAVIOR AND NATURAL HISTORY

Although the clinical behavior of paragangliomas is determined somewhat by cellular characteristics, tumor location is the more influential factor. Malignancy is rare and typically is defined by the existence of metastasis rather than by cellular characteristics. Metastasis is usually to lungs, lymph nodes, liver, bone, or spleen.

Paragangliomas can be broadly categorized as either sympathetic or parasympathetic. The former arise from the adrenal medulla (pheochromocytomas), certain extradrenal sympathetic paraganglia, and visceral autonomic paraganglia. Parasympathetic paraganglia are found throughout the body, and this is this group that gives rise to almost all the paragangliomas of the head and neck.

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The jugulotympanic paragangliomas are extremely uncommon. Most originate in the supraglottic portion of that organ and, as such, do not present with early symptoms, such as hoarseness, or with airway compromise. When discovered, they present as a discolored, submucosal mass that is atypical in appearance and is often confused with other tumors, especially neuroendocrine carcinoma. These malignancies have a distinctly different behavioral pattern. Studies have concluded that laryngeal paragangliomas are benign neoplasms. Malignant behavior of these lesions is so unusual as to suggest misdiagnosis. These lesions are effectively managed by surgical excision.

Most commonly, carotid body paragangliomas present as painless masses located deep to the anterior border of the sternocleidomastoid muscle in the upper or midneck. These are generally slow growing and often have been obvious for years before diagnosis. They are usually nonfunctional, but they do have the capability of function. Carotid body paragangliomas actually can grow to impressive dimensions without creating neurologic or vascular findings. Large tumors occasionally produce compressive carotid artery symptoms. These facts are important in determining treatment philosophy, especially in older, asymptomatic patients. They begin in the arterial adventitia, usually at or around the bifurcation of the internal and external carotid arteries. Because these tumors generally develop from the medial aspect of the great vessels, the vessels are displaced laterally. This typical appearance of splayed and lateralized vessels distinguishes the carotid body tumors radiographically from vagal nerve paragangliomas (see Fig. 30.4-5). The radiography is important in diagnosis, because it is unique. As these neoplasms become larger, they can occupy the parapharyngeal space, actually presenting as a bulge in the tonsil area, and encroachment into this area can produce dysphagia.

EVALUATION

The diagnostic workup of paragangliomas must consist of CT or MRI and, in selected situations, angiography. Imaging should delineate bone destruction and complete tumor, intracranial and extracranial. CT scanning is more effective for imaging bone, but MRI offers a superior capability in accessing intracranial extension, as well as the relation of tumor to bone. With proper enhancement techniques, one or both of these images plus clinical evaluation can provide sufficient information to plan treatment of most paragangliomas. This point is relevant to overall management strategy; if radiation therapy is the planned treatment, the radiation oncologist must be comfortable enough with the diagnosis to proceed without a biopsy. FNA and cytologic analysis can be helpful, but because of the location medial to the carotid artery and because of the dense vascularity of most of these lesions, this study may not always be practical. Open biopsy becomes necessary when the diagnosis is not achieved by these other means.

Invasive arteriography is valuable in preoperative preparation because it provides a picture of contralateral vascular crossover and because it allows tumor embolization to be done before contemplated surgery. Paragangliomas are usually very vascular, and when surgery is planned, intraluminal embolization of the main arteries is helpful for safe and less morbid removal of large tumors. The continued concern for the purity of the commercial blood supply is such that surgeons should avoid transfusion whenever possible, and preoperative embolization can be extremely helpful in pursuing this goal. This technique has its most impressive impact in the removal of larger carotid body and jugular bulb tumors and is probably unnecessary for most small tumors. The techniques of embolization are beyond the scope of this chapter, and the reader is referred to the literature on the subject; it must be emphasized, however, that use of this technology carries significant risks and should be undertaken only by an experienced interventional radiology team. Finally, embolization of paragangliomas is only an adjunct to surgery and should not be considered primary treatment for these highly vascular tumors, no matter how successful the devascularization. If embolization is not followed promptly by tumor removal, undesirable collateral circulation and vascular shunting can develop, ultimately complicating an already challenging surgical process. In fact, the sooner the surgery follows the embolization, the more effective the hemostasis will be during surgery. If surgery is not to be the treatment of choice, then embolization should probably not be done.

TREATMENT AND RESULTS

Paragangliomas usually are considered benign, and although they can metastasize or be locally aggressive, such is the exception rather than the rule. Traditionally, the mainstay of treatment has been surgical removal, but repeated series of cases treated by radiation therapy have demonstrated its effectiveness in achieving local control of these tumors. Investigators have reviewed the literature and have compared surgical with radiation therapy results, which show no difference in local control achieved by either modality. Accordingly, treatment decisions should be based on a formula that considers tumor size, patient age and general health, symptoms and signs present before treatment, treatment-related mortality, and the expertise of those involved in the planned treatment.

Reluctance to use radiation therapy in paragangliomas probably stems from a historic bias against radiating benign tumors. Furthermore, series that have compared the two treatment methods have been somewhat biased because many tumors radiated in various series were not favorable lesions by virtue of their size and recurrent state. As in any study that compares treatment results, an accurate comparison of radiation and surgery should analyze comparable tumors. An important aspect of radiation therapy of paragangliomas relates to the definition of local control. In traditional cancer thinking, sustained complete response after radiation is the criterion by which local control is usually judged. Such cannot be the case, however, with paragangliomas. Instead, these tumors typically partially regress or remain stable after therapy. Because the tumors are composed predominantly of vascular tissue, the proliferative (i.e., neoplastic) elements make up but a minor portion of the overall tumor volume, and although successful radiotherapy kills the proliferative cellular component, the remaining vascular tissue typically does not change significantly. For purposes of assessing local control, therefore, the absence of disease progression with the resolution or even halting of symptoms after radiation is the ultimate goal. In fact, there may even be some short-term postradiation edema or swelling of the involved area, but this generally resolves within several months. When radiation is used as the treatment modality, therefore, it is important that both the treatment team and the patient understand this important aspect of local control, and all concerned should exercise patience in judging the outcome. Some investigators have been skeptical of the persistence palpable tissue after radiation, expressing concern for its capacity to proliferate after 20 to 30 years’ dormancy. However, it has never been demonstrated that this has occurred. In the future,
genetic mutations of p53, p161NK4A, and others may provide markers for local tumor progression and regression. 167

Cummings and coworkers168 have reported 45 patients treated for glomus tumors. Only three patients (6.6%) have had symptomatic recurrences, two of which were believed to be due to a “geographic miss.” The radiation therapy was effective in relieving the presenting symptoms of most patients. For example, 27 of 35 patients (77%) who received 3500 cGy in 3 weeks had complete relief of their tinnitus. The remaining 23% had partial relief or stabilization of symptoms. All patients with pain, vertigo, discharge, bleeding, and abnormalities of the fifth cranial nerve had complete relief of their symptoms with radiation therapy. All patients with abnormalities of cranial nerve IX through XII had partial relief or stabilization of their cranial nerve abnormalities. The authors of this study noted that symptomatic improvement often did not occur until many months after radiation therapy, highlighting the need to follow these patients for a lengthy period. As long as no clinical progression was noted, the authors believed there would be no need to intervene in the postradiation setting.

Kim and associates169 have analyzed the dose-response relation for radiation of paragangliomas. The literature was reviewed, and the rate of failure was correlated with dose. Overall, the recurrence rate was 25% when the radiation dose was less than 4000 cGy. With doses greater than 4000 cGy, local recurrence was rare. Of 93 patients, 43 (46.2%) received doses greater than 4000 cGy. Of these, 22 (51.2%) had no local recurrence. The authors recommended doses in the 4000- to 4500-cGy range delivered over 4.0 to 4.5 weeks. Cole and Beiter170 treated 39 glomus jugulare or vagal tumors with radiotherapy. The last 32 of those patients were treated with megavoltage radiotherapy (cobalt 60) or linear accelerator; the first seven patients had been treated with orthovoltage therapy. In the first seven patients, the results were unpredictable; however, 30 of the 32 later patients show no evidence of recurrence.

Everson et al.171 have reported the results of 15 patients with 23 paragangliomas treated with radiotherapy. Eighteen of these were previously untreated, whereas five had been unsuccessfully treated with prior therapy (one with radiation therapy, four with surgery). Most patients received doses in the 15-Gy range over 5 weeks. The local control for previously untreated patients was 100% at 10 years. The cause-specific survival rate was 100% for the 14 patients that were previously untreated, versus 92% for the group as a whole. Of those patients who developed radiation complications associated with radiation therapy are dose related. Bone and brain necrosis and abscess are the most serious of those reported. Each of these has occurred in approximately 1% of treated patients. These complications should occur as long as doses in the 4000- to 4500-cGy range are used. Fuller and colleagues172 reported one fibrosarcoma in their series that was considered a radiation-induced malignancy. Malignant transformation of tissue secondary to radiation has been reported in these tumors, and although unusual, this occurrence is a concern.

The decision to operate or radiate should be based on a formula that considers tumor size and location, patient age and health, symptoms or signs present before treatment, potential morbidity, and the expertise and availability of those involved in treatment. The decision should be made in consultation between the head and neck surgeon and the radiation oncologist and with an appreciation for the fact that this group of tumors is one of the most complex and dangerous head and neck tumors. Nothing is an absolute, and for a particular patient, the decision is often not clear. In general, a reasonable plan in patients with head and neck paragangliomas is to operate and remove those lesions (whether jugulotympanic, intravagal, laryngeal, or carotid body in origin) that are smaller and less likely to be associated with significant operative morbidity. For large tumors that demonstrate extensive bone destruction, intracranial extension, or both, in which considerable operative morbidity is expected, radiation therapy is probably the method of choice for achieving local control.

In young patients, radiation therapy should be avoided if a reasonable surgical option is available. On the other hand, the risk for radiation-induced cancer is small, and these authors do not hesitate to recommend it to young patients if the surgical procedure required is likely to be associated with unreasonable morbidity. Older patients are especially suited for radiation therapy, because local control usually is sustained throughout the balance of their lifetime.

Removal of jugulotympanic lesions should only be attempted by surgeons trained in otologic and skull base techniques. Those intravagal paragangliomas that are located high in the neck are often very challenging surgical endeavors, being too high to approach by conventional cervical exposure and too low to be approached from an infratemporal approach. There are true skull base lesions that are in the jugular foramen, often located in the carotid canal and other intercarotid paraganglia. Whereas the resection of unilateral carotid body paragangliomas, the input from both chemoreceptor and baroreceptor mechanisms is mediated via a common neural pathway; therefore, function of the entire system is affected by the resection of tumors involving the intercarotid paraganglia. Whereas the resection of unilateral carotid body lesions is generally well accepted, excision of bilateral tumors or of a unilateral carotid body lesion with a contralateral tumor may be more difficult. This is because the bilateral dysfunction that potentially can result from the bilateral denervation of the carotid sinuses. Labile hypertension and hypotension, headaches, diaphoresis, and emotional anxiety occur in a substantial percentage of patients who undergo bilateral excision.

Surgery of carotid body paragangliomas, although safe overall, is fraught with hazards, and only head and neck surgeons competent in vascular techniques should attempt to remove these lesions, especially in recurrent lesions. Carotid artery bypass or shunt, or even artery resection and reconstruction, are sometimes necessary. In addition, it is believed that a significant percentage of patients with vagal paragangliomas demonstrate a vagal nerve paralysis at the time of diagnosis, and that fact certainly alters the decision-making process for a vagal paraganglioma.

Because resection of vagal paragangliomas is almost always followed by complete vagal paralysis, the choice of a radiation versus a surgical strategy in these lesions should be based on a particular flexible paradigm. Rehabilitation after resection of midcervical vagal lesions is more easily accomplished than those at the base of the skull. Partly because of the fact that, in the latter group, multiple cranial nerve injuries are more common. Older individuals have much more physiologic difficulty after vagal nerve resection than do younger patients, regardless of the part of the nerve involved. One must factor into the decision process the fact that a significant percentage of patients with vagal paragangliomas demonstrate a vagal nerve paralysis at the time of diagnosis, and that fact certainly alters the decision process somewhat.

Surgery of carotid body paragangliomas, although safe overall, is fraught with hazards, and only head and neck surgeons competent in vascular techniques should attempt to remove these lesions, especially in recurrent lesions. Carotid artery bypass or shunt, or even artery resection and reconstruction, are sometimes necessary. In addition, it is believed that a significant percentage of patients with vagal paragangliomas demonstrate a vagal nerve paralysis at the time of diagnosis, and that fact certainly alters the decision-making process for a vagal paraganglioma.
SECTION 30.5
Rehabilitation after Treatment for Head and Neck Cancer

SUSAN D. MILLER
ROY B. SESSIONS

INTRODUCTION

In the 1980s and 1990s, concern for posttreatment function restoration became a primary part of management of head and neck cancer. Conservation surgery, radiation strategies, reinnervation of free flaps, and larynx-sparing protocols continue to be used under various circumstances in an attempt to maintain or reestablish functional speech, voice, and swallowing in head and neck cancer patients. The ideal multidisciplinary concept requires interactions, therefore, among the surgical, radiation, and medical oncologists, reconstructive surgeons, speech pathologists, maxillofacial prosthetists, dental oncologists, nutritionists, nurse oncologists, psychologists, audiologists, and social workers during pretreatment assessment and posttreatment intervention. To say the least, the standard for the complete head and neck team is complex.

Pretreatment counseling for persons with oral cavity and pharyngeal cancer is well established; the same should apply to organ preservation patients with laryngeal and hypopharyngeal cancers. Patients benefit from discussions with the speech pathologist regarding swallowing and voice and speech difficulties that can result from radiation therapy and chemotherapy regimens. Regrettably, however, patients entering organ preservation protocols often are inadequately counseled, if at all. Should failure of the treatment protocol occur, surgery is performed immediately, and the patient and family are forced to enter a frightening and stressful period unprepared for either the surgical experience or the rehabilitation that lies ahead. Optimal rehabilitation for all patients requires consideration of future strategies should one particular treatment plan fail.

PRETREATMENT ASSESSMENT

Preoperative consultation with the speech pathologist should be scheduled soon after the physician has made the final diagnosis and a treatment plan is formulated. During this consultation, the speech pathologist reviews what the patient already knows and further explains normal anatomy and physiology as well as the anticipated changes resulting from treatment. Patients with glottic carcinoma who are scheduled to be treated with radiation are counseled regarding vocal changes and swallowing difficulties that might occur during or after the treatment. Patients scheduled to undergo oral, pharyngeal cavity, or conservation laryngeal surgical procedures should be counseled in a special way, with an emphasis on their immediate postsurgical needs that relate to nasogastric, gastrostomy, and tracheostomy tubes. Additionally, short- and long-term rehabilitation strategies for speech, voice, and swallowing are summarily discussed in this initial consultation. The speech pathologist must be sensitive to the fine line between appropriate coverage and information overload; patients labor under a heavy emotional burden at this stage of their treatment and can easily be overwhelmed by someone insensitive to this potential. It is important, however, to accomplish as much of this as possible before the treatment. Depending on the specific treatment used, the patient’s ability to communicate may be largely or completely impaired afterward. Even though there are substitute means of communicating during this period, none are as effective as an interactive dialogue between patient and speech pathologist. If loss of oral communication is expected after treatment, patients will need information regarding augmentative or alternative communication methods or devices. Patients scheduled for total laryngectomy learn about alternatives to natural voice: the availability of the electrovocalyst and the mastery of esophageal or tracheoesophageal puncture speech (or both). Frequently, patients will consent to trial use of an electrolarynx and will order the recommended device before surgery. We have found that patients who are willing preoperatively to experiment with speech replacement devices feel more empowered and are relieved that they will be able to express their needs immediately after surgery. We frequently incorporate patient volunteers to meet patients and their families, thus allowing them to relate to and question a person who has had a similar treatment experience. Even candidates not scheduled for laryngectomy (i.e., laryngeal preservation protocol patients) should meet with the speech pathologist to discuss potential problems with voice and swallowing during or after the treatment.

DIAGNOSTIC EVALUATION

The correct rehabilitative effort after treatment is enhanced greatly by the initial evaluation of speech and swallowing. In matters pertaining to potential speech rehabilitation, baseline reading samples of standardized articulation sentences, nonnasal and nasal paragraphs, and conversational speech samples are audio-recorded from patients whose tongue, velum, or jaw will be affected by surgery. These recordings serve to establish baseline speech patterns of articulation, fluency, rate, dialect, intonation, and nasality. A spectrogram that portrays frequency, intensity, and format information descriptive of resonant frequencies of the vocal tract provides additional baseline data regarding tongue placement and resonance. Standardized articulation testing typically is not performed for patients undergoing treatment for early- or later-stage laryngeal carcinoma unless modification of the articulators (tips, tongue, cheek, etc.) is planned. The speech pathologist, however, should document any articulation, fluency, rate, or dialectal patterns observed during this conversation with the patient. Additionally, orofacial structures, sensation, and function should be carefully examined. Plans for pretreatment dental care or postoperative rehabilitation are discussed at this time because they also can have an impact on articulation, voice, and deglutition. Finally, because of the fact that patients with hearing deficiencies often have difficulty in monitoring the intelligibility and precision of their articulation, it is important to evaluate hearing before treatment.

If preexisting swallowing problems are present, a modified barium swallow (MBS), fiberendoscopic evaluation of swallowing (FEES), or FEES with sensory testing (FEESST) should be performed. If dysphagia does exist postoperatively, it is important that these studies be performed at the time to aid in the development of a management strategy. The MBS is a videofluoroscopic study of the motor aspects of the oral, pharyngeal, and esophageal stages of the swallow with varying food consistencies. This procedure permits measured amounts of barium bolus to be followed from the lips to the stomach and incorporates the effects of compensatory strategies, such as head position, chin tuck, and the like. Because of its clear documentation of the oral preparatory and oral stages of the swallow, the MBS is ideal for patients with oral-stage dysphagia; in fact, it is the diagnostic test of choice. If pharyngeal or laryngeal swallowing problems exist, however, the FEES or FEESST should be performed. The FEES uses a fiber-optic nasoendoscope to observe the pharyngeal and laryngeal structures directly during the pharyngeal phase of the swallow. A bolus of contrasting color is used to note premature spillage into the hypopharynx or laryngeal vestibule before swallowing and vocal fold closure and the presence of residuum in the hypopharynx and laryngopharynx after a swallow. Although penetration (i.e., aspiration) may be identified during a FEES or MBS examination, the primary purpose of these procedures is to analyze the motor components of swallowing. The FEESST combines the FEES with a technique that determines laryngopharyngeal sensory discrimination thresholds by endoscopically delivering air pulse stimuli to the mucosa that is innervated by the superior laryngeal nerve. Because vocal and aerodynamic parameters may be affected by the presence of a lesion or a biopsy (or both), baseline acoustic and aerodynamic analysis should be performed on all early glottic cancer patients, regardless of whether destined for radiation, microsurgery, or laser excision. Vocal measures of fundamental frequency, amplitude, frequency perturbation (jitter), amplitude perturbation (shimmer), and noise-to-harmonic ratio are obtained from a sustained vowel performed on all early glottic cancer patients, regardless of whether destined for radiation, microsurgery, or laser excision. Vocal measures of fundamental frequency, amplitude, frequency perturbation (jitter), amplitude perturbation (shimmer), and noise-to-harmonic ratio are obtained from a sustained vowel.
Pressure, and laryngeal resistance are measured using the Aerophone II (Kay Elemetrics), Glottal Enterprise MS-100 (Syracuse, NY), or Nagashima Phonatory Pressure Monitor. Vocal cord vibration is measured using stroboscopy. Vocal fold movement, shape, and position during sound production are determined by stroboscopy. A normal larynx displays smooth, symmetrical, and rhythmic vibration. Abnormalities may include asymmetry, irregularities, and loss of symmetry.

Therapy techniques, such as forced adduction exercises, digital pressure to the side of the thyroid cartilage, and vocal fold stripping before radiation and continued smoking during and after radiation therapy predicted worse voice quality. Nevertheless, as changes in vocal quality are common among patients after either radiation therapy or laser excision, patients should be seen by the speech pathologist for at least one posttreatment therapy session. Adherence to a vocal hygiene program with certain daily exercises results in a more efficient, resonant voice. Nevertheless, as changes in vocal quality are common among patients after either radiation therapy or laser excision, patients should be seen by the speech pathologist for at least one posttreatment therapy session. Adherence to a vocal hygiene program with certain daily exercises results in a more efficient, resonant voice.
For some laryngectomy patients, concerns regarding loss of speech are more important than survival itself. Alternative voice sources for the laryngectomee include the use of a pneumatic or an electronic speech aid, esophageal speech, or the gold-standard tracheoesophageal puncture (TEP) speech. Patients who have undergone a partial or total laryngectomy are unable to use these alternative voice sources, and they should be introduced to computerized speaking systems or talking keyboards.

**Artificial Larynges**

A 1987 study of voice rehabilitation practices revealed that the use of an artificial speech device was widely recommended by 90% of 400 head and neck surgeons surveyed, in many cases as a temporary means of communication after total laryngectomy. These battery-operated or pneumatic devices simulate vocal sound, are relatively inexpensive, are easy to operate, and can be used by a patient 1 to 2 days after surgery. These devices continue to serve a useful purpose, and surgeons and speech pathologists should encourage all patients to own an artificial device as a primary or auxiliary speech system. Pneumatic devices consist of a piece that fits over the tracheal stoma, a unit containing a reed that produces sound, and a tube that directs sound into the mouth to be articulated. These particular devices are less popular in the United States than they are in Europe.

On the other hand, a variety of battery-operated, hand-held artificial larynges (electrolarynges) are currently available. Examples are illustrated in Figure 30.5.1, The Cooper-Rand Electronic Speech Aid (Luminaud Inc., Mentor, OH) is an electrolarynx that is used exclusively with an intraoral adapter. This adapter directs sound into the oral cavity through a tube placed in the mouth. The NuVois 1 and NuVois 2 (Mountain Precision Manufacturing, Boise, ID), Servox Inton (Siemens Hearing Instruments, Inc., Prospect Heights, IL), Romet (Romet, Inc., Las Vegas, NV), OptiVox (Bivona Medical Technologies, Gary, IN), TruTone and SolaTone (Griffin Laboratories, Temecula, CA), Denrick (Denrick, Inc., Honolulu, HI), SPIKR (UNI Mfg. Co., Ontario, OR; not pictured), and Amplicord model 55 (Amplicord, Inc., Rome, Italy) are neck-type devices that transmit sound through the tissues of the neck into the oral cavity for speech production. These devices are activated with an on-off switch and are equipped with an adapter so that they can be used either as intraoral or when pressed against the neck. The availability of both options is important because patients can use the intraoral adapter immediately after surgery when the neck is edematous. The Amplicord model 95 is pressure-activated as it contacts the neck rather than being activated by a switch. The UltraVoice (UltraVoice, Ltd., Berwyn, PA; Fig. 30.5.2) is an intraoral electrolarynx custom-built into a denture or retainer and activated by a remote control switch.

**Esophageal Speech**

Esophageal speech involves learning to inject or inhale air into the esophagus through the reservoir created by surgical closure of the PE segment or gullet after laryngectomy. The trapped air is then released through the upper esophageal segment, which is the vibratory source for sound in the laryngectomee. Typically, the speech pathologist encourages the laryngectomee to attempt esophageal speech sound soon after the patient is able to swallow food comfortably. The details of the techniques taught by speech pathologists are beyond the scope of this text, but certain basic principles should be pointed out. The patient traps air in the mouth and forces it into the esophagus. Some patients learn the inhalation method, in which a lowered pressure in the esophageal segment relative to atmospheric pressure allows air to enter the gullet; thus, the source and the location of vibratory sound are fulfilled. Even though esophageal speech can be introduced to the patient 1 or 2 weeks after the total laryngectomy, the development of functional capabilities with this method may take from 6 months to 1 year to learn; in fact, some patients never master it. Previous reports regarding the success rate in learning esophageal speech have varied from 26% to 55%; however, Fujii found that 74% (51 of 69) of their patients successfully used esophageal speech in daily communication. Age was the most important factor in success and failure. Ninety percent of the patients in this study who were younger than 60 were successful in learning esophageal speech as compared to 10% of those older than 75. Although motivation and age appear to be important to the achievement of esophageal speech, abnormalities of the vibrating esophageal segment—tonic and hypertonic spasms—are the most common reasons cited for esophageal speech failure.

In patients in whom esophageal speaking has failed, the toxicity or relaxation of that esophageal segment that vibrates (the PE segment) can be accurately evaluated by simultaneous use of videofluoroscopy and esophageal insufflation. This is not routinely performed in the postoperative laryngectomee. An easier and reliable way to assess initial opening pressures of the PE segment is a portable manometry system that can be used 4 weeks after laryngectomy. An initial opening pressure of between 15 and 20 mm Hg has been found to correlate with the production of a good esophageal voice.

**TRACHEOESOPHAGEAL PUNCTURE**
Most head and neck surgeons and most professionals who rehabilitate laryngectomy patients think that in properly selected patients, TEP, introduced by Singer and Blom in 1980, is the standard of care for reconstitution of voice after laryngectomy. Rather than relying on the trapping of air in the esophagus, the creation of a permanent puncture through the tracheoesophageal wall permits the shunting of pulmonary air into and up the esophagus; thus, the basis for noise—vibration of the PE segment walls—is generated. Importantly, unlike esophageal speech, the reservoir of air does not depend on the gulping or trapping of air; instead it is limited only by expiratory capacity and, as such, more closely resembles normal voice. A valved prosthesis is placed into the puncture and, when the tracheal stoma is occluded, directs pulmonary air into the esophagus for speech. The one-way valve design of the prosthesis prevents aspiration from the esophagus into the trachea. An outer housing that contains a soft diaphragm allows normal respiration during silent periods; however, when speech is used, an alteration of the patient’s expiratory effort shuts off the diaphragm, thus diverting the air through the tracheoesophageal conduit into the esophagus. This external housing, called a tracheostoma breathing valve, was developed in 1982, and is of immeasurable value in rehabilitation of these patients because it eliminates the need for manual occlusion of the stoma during speech. A patient can, therefore, wear normal clothing over the lower neck to cover the apparatus, as there is no need for involvement of the hands. For a historical review of the evolution of voice restoration procedures and prostheses, the reader is referred to Singer and Singer and Blom.

Although TEP is the method of choice for voice and speech rehabilitation in the United States, some patients and some cultures are not so enthusiastic about its implementation.

Initially, TEP was performed as a second surgery in patients who had been laryngectomized; however, many surgeons and speech pathologists now prefer that TEP be done at the time of the laryngectomy. The controversy as to the value of the secondary versus primary TEP is ongoing and is unlikely to end. Recently, Chan performed a TEP as an outpatient office procedure using a flexible endoscope with local anesthesia and intravenous sedation. Those surgeons and speech pathologists who advocate secondary or delayed TEP think that waiting for 1 to 3 months after laryngectomy allows better control of factors, such as stoma size, vibration of the PE segment, and migration of the puncture site after radiation. Proponents of the primary puncture argue that patients are psychologically uplifted by the fact that they can speak 3 weeks after surgery. Furthermore, primary TEP proponents cite the value of technical simplicity, effectiveness, low morbidity, and cost-effectiveness of the one-stage procedure. Success rates for both primary and secondary TEP are to be reported between 73% and 95%, respectively.

Regardless of time of puncture, an average of 7 hours of speech therapy is needed to learn to manage the prosthesis and to obtain optimal communication using the TEP. Researchers have reported a decrease in TEP speech success rates from an initial 84% to 67% at 9 months and 65% at 10 years due to such “patient factors” as delays in seeking medical attention when the valve becomes dislodged and failure to care for the equipment properly. Although the Blom-Singer technique is popular in the United States, specialists in other parts of the world favor different methods to restore phonation. Most interesting was a study by Quer, who performed TEP at the time of the laryngectomy and also provided intensive esophageal speech instruction to 24 patients. Seventy percent of the patients (16 of 23) later chose to use esophageal speech rather than TEP speech even though they agreed that TEP speech was superior to esophageal speech.

**Candidacy for Tracheoesophageal Puncture**

The success of voice restoration depends on a multidisciplinary team committed to thorough patient assessment, consistent management, and flexibility in problem solving. Success with TEP depends on good stoma construction, adequate stoma size, and accurate placement and angle of the TEP. The tracheal stoma should be at least 1.5 cm and not retracted behind the manubrium. If sternal stenosis is a problem, a Bivona-Colorado stent can be used by the surgeon to create the puncture. A Bivona-Colorado prosthesis (Fig. 30.5-3), which is built into the tracheostome vent, is inserted into the puncture.

Patients with emphysema, severe allergies, or pulmonary complications are generally not good TEP candidates, owing to copious amounts of secretions and reduced air volume associated with these conditions. The patient’s cognitive status, physical health, and desire for communication should be considered before TEP. The presence or absence of radiation therapy does not seem to have a significant relationship to the success or failure of TEP.

Because of the development of low-resistance, self-retaining prostheses inserted by the speech pathologist or surgeon (or both) and composed of materials designed to last approximately 3 to 6 months, manual dexterity and visual acuity are no longer essential for the use of this technology. These prostheses include Inhealth Indwelling (Inhealth Technologies, Santa Barbara, CA; Fig. 30.5-4); Provox (Atos Medical, Sweden, Milwaukee, WI; see Fig. 30.5-4); Voicemaster (Amsterdam, Netherlands), and Nijdam (Sweden; not pictured). The Provox (Atos Medical), and Groningen prostheses (Groningen, Holland; not pictured) are popular indwelling prostheses in Europe.


In following up TEP patients over 13 years, Lavertu found that the absence of PE stricture was the only significant predictor of good to excellent speech. Because the toxicity of the PE segment in a primary puncture patient before the laryngectomy cannot be assessed, surgeons often perform a pharyngeal constrictor myotomy, a unilateral pharyngeal plexus neurrectomy, or a unilateral pharyngeal plexus neurectomy with a criopharyngeal myotomy at the time of surgery. Although all three
Several good books are available for the laryngectomee that may be provided to the patient preoperatively or postoperatively. These guides provide useful information about the treatment process. A variety of resources are available to laryngectomees and their families.

Significantly higher fundamental frequencies were found during reading in neurectomized primary TEP patients as compared to primary TEP patients receiving myotomy or a neurectomy with myotomy. In addition, TEP speakers using the tracheostoma-breathing valve demonstrated faster reading rates and a higher speaking fundamental frequency compared to the other methods. Methods are equally effective in preventing pharyngospasms, Singer et al. advocate use of the pharyngeal plexus neurectomy, as it preserves the vascular supply to the pharyngeal wall and preserves any residual resting tone in the PE segment, resulting in a higher speaking fundamental frequency compared to the other methods.

Many speech pathologists perform air insufflation testing before a secondary puncture, although the value of this has been challenged. Lewin reported greater than 90% success in predicting TEP failures when intraesophageal peak pressure levels are obtained in conjunction with the air insufflation test. The air insufflation test is performed by insertion of a transnasal catheter approximately 25 cm into the upper thoracic esophagus. The catheter is attached to a circular tracheostoma housing, which is secured to the patient's skin by an adhesive. As air is insufflated into the catheter, patients are instructed to inhale, occlude the stoma assembly, and sustain a vowel sound for as long as they can. Success is determined by the patient's ability to sustain a vowel for 15 to 20 seconds and count from 1 to 10. To ensure optimal results, it is important for the patient to feel relaxed and comfortable with the examiner. Multiple trials and a repeat visit are often necessary to confirm test results.

If insufflation testing fails but speech is achieved in a patient after a pharyngeal plexus nerve block with lidocaine, PE spasms is suspected. This should be confirmed via a videofluoroscopic MBS performed during rest and swallow and during speech with air insufflation. If the PE segment is confirmed to be highly resistant to airflow, botulinum toxin type A injection should be considered as a first-line treatment before consideration of surgical procedures, such as a pharyngeal constrictor myotomy, a unilateral pharyngeal plexus neurectomy, or a unilateral pharyngeal plexus neurectomy withcricopharyngeal myotomy. If speech during the air insufflation test is faint or whispery, the PE segment may be hypotonic. Digital pressure on the outside of the neck may help to produce a stronger sound. The existence of hypotonicity is not a contraindication for TEP, although it may indicate the need for a neck band or digital pressure postoperatively to enhance contact of intraluminal vibratory surfaces.

**Post-Tracheoesophageal Puncture Intervention**

With primary TEP, a catheter is placed in the newly created fistula that penetrates the posterior wall of the trachea and enters the esophageal lumen. The catheter provides a stent that keeps the fistula open during the weeks in which the tract is regenerating mucosa. Removal of the catheter and the fitting of the prosthesis is done in the hospital. In the first instance, the patient is admitted to the hospital for a period of monitoring. The patient is kept in bed on a supine position with a pillow under the head. The catheter is inserted into the catheter via the proximal opening of the fistula and is advanced into the esophagus. Once the catheter is in place, the patient is fitted with a 16-Fr. duckbill or lower-resistance prosthesis (see Figs. 30.5-3 and 30.5-4). The catheter is removed, and the patency of the tract is assessed by asking the patient to take a breath and say "Ah" on exhalation while the speech pathologist or patient occludes the stoma. If the tract is patent but sound cannot be attained, the patient can be fitted with a tracheoesophageal pull-up. Speech during the air insufflation test is performed by insertion of a transnasal catheter approximately 25 cm into the upper thoracic esophagus. The catheter is attached to a circular tracheostoma housing, which is secured to the patient's skin by an adhesive. As air is insufflated into the catheter, patients are instructed to inhale, occlude the tracheostoma assembly, and sustain a vowel sound for as long as they can. Success is determined by the patient's ability to sustain a vowel for 15 to 20 seconds and count from 1 to 10. To ensure optimal results, it is important for the patient to feel relaxed and comfortable with the examiner. Multiple trials and a repeat visit are often necessary to confirm test results.

Several researchers think that after extensive pharyngeal resection or cervical esophageal resection (or both), the tubed radial forearm free flap maximizes functional rehabilitation of the patient by providing the best swallowing and speech results. Free jejunal transfer also has gained wide acceptance in PE reconstruction because the jejunum is well vascularized and is associated with a low incidence of fistula formation and stenosis. Voice restoration has been successfully achieved in these jejunal interpositions with the creation of either a primary tracheojejunal shunt at the time of the surgery or a secondary procedure. Reconstruction with jejunal interposition and gastric pull-up have demonstrated better swallowing results than those with myocutaneous (pectoralis and latissimus dorsi) flaps, and colon interposition. Performance of a TEP in gastric pull-up patients has been successful in small but difficult laryngectomy or cervical esophageal surgery patients.

**SWALLOWING AND SPEECH AFTER EXTENSIVE RECONSTRUCTION OF THE PHARYNX OR CERVICAL ESOPHAGUS**

Several researchers think that after extensive pharyngeal resection or cervical esophageal resection (or both), the tubed radial forearm free flap maximizes functional rehabilitation of the patient by providing the best swallowing and speech results. Free jejunal transfer also has gained wide acceptance in PE reconstruction because the jejunum is well vascularized and is associated with a low incidence of fistula formation and stenosis. Voice restoration has been successfully achieved in these jejunal interpositions with the creation of either a primary tracheojejunal shunt at the time of the surgery or a secondary procedure. Reconstruction with jejunal interposition and gastric pull-up have demonstrated better swallowing results than those with myocutaneous (pectoralis and latissimus dorsi) flaps, and colon interposition. Performance of a TEP in gastric pull-up patients has been successful in small but difficult laryngectomy or cervical esophageal surgery patients.

**COMPARISON OF ESOPHAGEAL, TRACHEOESOPHAGEAL PUNCTURE, AND NORMAL SPEECH**

Acoustic and temporal studies indicate that TEP speech more closely approximates laryngeal speech in fundamental frequency, intensity, reading rate, percent silent pauses, and maximum phonation time, and maximum phonation time. Significantly higher fundamental frequencies were found during reading in neurotomized primary TEP patients as compared to primary TEP patients receiving myotomy or a neurectomy with myotomy. In addition, TEP speakers using the tracheostoma-breathing valve demonstrated faster speaking rates and fewer pauses. The valve prevents the escape of air sometimes observed with digital occlusion of the tracheostoma. Although TEP speech in general is more intelligible and preferred over esophageal speech, the monotonous tone, voice errors, and fricative errors are similar in TEP and esophageal speakers. When TEP speech after a total laryngectomy is compared to TEP speech after a laryngopharyngectomy with pectoralis major flap reconstruction, no significant differences were noted for soft and loud intensity levels, fundamental frequency for soft voice, and jitter, although perceptual analysis revealed significant differences. Speech in the tracheojejunal-esophageal puncture patients has even less pitch variation, more noise in the signal, shorter mean phonation time, a wet quality, and a softer intensity voice than TEP speech.

**VOLUNTEER AND SUPPORT ORGANIZATIONS**

The diagnosis and treatment of head and neck cancer may proceed quickly; however, a patient's adjustment to the diagnosis of a malignancy, its management, and the subsequent disability is not a short-term process. Patients and their families will require different information and support throughout various times of the treatment process. A variety of resources are available to laryngectomees and their families.

**WRITTEN MATERIALS**

Several good books are available for the laryngectomee that may be provided to the patient preoperatively or postoperatively. These guides provide useful information about the treatment process. A variety of resources are available to laryngectomees and their families.

**Self-Help for the Laryngectomee**, by Robert L. Keith

Lauder Enterprises, Inc., 11115 Whisper Hollow, San Antonio, TX 78230-3609

800-388-8642

E-mail: lauder@voicestore.com

http://www.voicestore.com

**A Handbook for the Laryngectomee**, by Robert L. Keith

PRO-ED, 8700 Shoal Creek Boulevard, Austin, TX 78701

512-451-8542

**Looking Forward by R. Keith, H. Shave, H. Coates, K. Devine.**

Thieme Medical Publishers, Suite 1501,
Booklets about cancer treatment and living with cancer can be obtained for free by calling of Cancer Communications, National Cancer Institute, Building 31, Room 1024, Bethesda, MD 20892, or calling 1-800-4-CANCER.

Volunteers

Patients are encouraged to meet before or after surgery with individuals who have undergone similar procedures. Some otolaryngology or speech pathology departments require that patient volunteers participate in formal volunteer training; other departments choose well-adjusted individuals and attend the patient visit with the volunteer. Many laryngectomees maintain a laryngectomy volunteer-patient visitation program coordinated with medical professionals in local hospitals and clinics.

Support groups

The various geographic, state divisions, and local units of the ACS assist IAL member clubs and sponsor field work of benefit to laryngectomees. Some ACS offices are able to lend equipment and other types of support. The ACS can be contacted at 1599 Clifton Road NE, Atlanta, GA 30329; 404-320-3333.

The American Speech-Language-Hearing Association (ASHA) is a professional organization that oversees certification of speech pathologists and audiologists. ASHA defines position statements and guidelines for practice standards within the profession. Several policy statements relate to the management of head and neck cancer patients and to instrumental diagnostic procedures for swallowing and evaluation and treatment of tracheoesophageal fistulization and puncture. ASHA can provide patient and their families with speech pathologist resources in their area. ASHA can be contacted at 10801 Rockville Pike, Rockville, MD 20852; 1-800-638-6868; or visit www.asha.org.

Chapter references

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**INTRODUCTION**

Lung cancer cells have accumulated a number of molecular genetic and epigenetic lesions, which appear necessary to transform normal bronchial epithelium to an overt lung cancer. There is complex interaction between the various molecular changes that ultimately result in the abrogation of key cellular regulatory and growth control pathways. Of the three major classes of human “cancer” genes, the protooncogenes and tumor suppressor genes (TSGs) are involved in lung carcinogenesis, whereas evidence implicating DNA repair genes is not yet conclusive. Many of the protooncogene and TSG changes are present in both major lung cancer subtypes: small cell lung cancer (SCLC) and non–small cell lung cancer (NSCLC), although certain mutations have subtype specificity (Table 31.1.1). Protooncogenes generally encode proteins that are positive effectors of the transformed phenotype and can simplistically be considered positive growth regulators. Their “activation” results in their functional deregulation, leading to a gain in function or “dominant” effect. Conversely, TSG products are negative growth regulators and their “inactivation” results in a loss of function that contributes to malignancy. Interacting with yet other biologic changes, these fundamental molecular events appear to underlie the characteristics of dysregulated growth, clonal expansion, and immortalization, which are typical of overt lung cancers. In addition, these, and yet other to be discovered molecular changes, may affect the processes of invasion, metastasis, and resistance against cancer therapy. In translating these laboratory discoveries into the clinic, it is important to identify these various changes, determine the frequency of occurrence, and test whether they have clinically important associations (e.g., with histologic type, stage, survival, response to therapy), as well as to determine if they could be used for early diagnosis, to monitor prevention and treatment efforts, and as targets for the development of new treatments. In addition, these abnormalities will probably also give us important understanding about lung development and differentiation.

### TABLE 31.1.1. The Most Frequent Acquired Molecular Abnormalities in Lung Cancer

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Frequency</th>
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<td>Chromosomal Abnormalities:</td>
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<td>Losses</td>
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<td>Gains</td>
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<td>Structural Alterations</td>
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<td>Microsatellite Instability</td>
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<td>Other Genetic Changes</td>
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### GENETIC AND EPIGENETIC ALTERATIONS IN LUNG CANCERS

#### CHROMOSOMAL ABNORMALITIES

Lung cancer cells display numerical abnormalities (aneuploidy) of chromosomes, which are suggestive of allelic loss or gain, as well as structural cytogenetic abnormalities. The latter include nonreciprocal translocations and deletions, whereas the presence of double minutes and homogeneously staining regions indicate gene amplification, such as for the MYC gene family. In SCLCs, losses from chromosomes 3p, 5q, 13q, and 17p predominate, but double minutes may be common late in disease. In NSCLCs, deletions of 3p, 9p, and 17p, together with +7, i(5)(p10), and i(8)(q10) are often seen. Molecular cytogenetic analysis with comparative genomic hybridization has identified hitherto unrecognized abnormalities, including deletions at 10q26, 16p11.2, and 22q12.1-13.1 and amplification at 1q24, 3q, 5p, 17q, and Xq26.

It has been proposed that human tumors may be genetically unstable at two levels: at the chromosomal level, including losses and gains (amplification), and at the DNA nucleotide level, including single- or several-base changes. It will thus be important to determine if aneuploidy and structural cytogenetic abnormalities, apart from targeting key genes, actually represent the phenomenon of chromosomal instability in lung cancers.

### MICROSATELLITE INSTABILITY

A genetic change that manifests itself as a mutator phenotype (often called the replication error repair phenotype) in human cancers results in widespread microsatellite instability. The result of microsatellite instability is a “laddering” of short-tandem DNA repeat sequences at multiple loci seen on high-resolution polyacrylamide electrophoretic gels. This phenotype is usually due to mutational inactivation of DNA mismatch repair enzymes, resulting in marked instability of these polymorphic DNA repeat sequences. This phenotype was initially reported in hereditary nonpolyposis colon cancer. Lung cancer frequently exhibits microsatellite instability; however, this occurs at only a few loci and results only in “shifts” of individual allelic bands (“microsatellite alterations”) compared to normal DNA in the same patient. The abnormal mechanism underlying this phenotype is currently unknown, and apparently mutations in DNA mismatch repair enzymes are very uncommon in lung cancer. The human 8-oxoguanine DNA glycosylase (OGG1) gene, involved in the repair of oxidative DNA damage, is another candidate for involvement in generating multiple lung cancer mutations. However, abnormalities in this gene only rarely occur in lung cancer, and mutations in other DNA repair genes have not yet been reported in lung cancer. Overall, approximately 35% (37 of 106) of SCLCs and 22% (160 of 727) of NSCLCs showed some examples of microsatellite alterations at individual loci. Microsatellite alterations in lung cancer have been reported to be associated with younger age, reduced survival, and advanced tumor stage. Regardless of the underlying mechanism, many groups are testing the possibility of using this microsatellite alteration phenotype for the early...
diagnosis of lung cancer by detecting these shifted DNA bands in sputum, bronchial washings, or blood.

ABERRANT DNA METHYLATION

DNA methylation involves covalent modification at the fifth carbon position of cytosine residues within CpG nucleotides of DNA, which tend to be clustered around the 5’ ends of many housekeeping genes (CpG islands). Hypermethylation in the 5’ promoter region of genes is associated with transcriptional silencing and is an alternative mechanism for down-regulating TSG expression rather than gene deletion or mutation.

Hypermethylation of the promoter region of the \( \beta \)-actin gene in a subset of NSCLCs results in its down-regulation and may be an early event in lung cancer pathogenesis.\(^5\) Other genes also have been found to be aberrantly promoter methylation in lung cancer but are not found in the normal lung associated with these tumors, including DAP (death associated protein) kinase, GSTP1 (glutathione S-transferase), and MGMT (O\(^6\)-methylguanine-DNA-methyltransferase).\(^6\) In addition, DNA containing these methylated sequences could be detected in the corresponding blood samples from the same patients, indicating that the tumor cells had shed DNA into the peripheral blood. Thus, aberrantly methylated DNA sequences, which can be selectively detected among a background of normal DNA, represent an attractive strategy for early molecular detection. Other sites of hypermethylation, including 3p, 4p34, 10q26, and 17p13, have been implicated in lung cancer pathogenesis, although the precise gene targets are uncertain. In addition to use as an early detection target, it may be possible to reverse methylation pharmacologically. In tissue culture systems, this is routinely done with the demethylating agent 5-aza-2’-deoxycytidine. Clinical trials with such agents have been attempted in other diseases, and agents with less toxicity need to be developed and tested in lung cancer.

Another acquired tumor abnormality is loss of imprinting (loss of methylation) to allow the expression of genes in lung cancer. Methylation plays a role in mediating genomic imprinting, which is a gamete-specific modification causing differential expression of the two alleles of a gene in somatic cells. Loss of genomic imprinting of the insulin-like growth factor-2 (IGF-2) gene and the H19 gene (associated with hypomethylation of its promoter region) also occurs in lung cancer.

PROTOONCOGENES AND GROWTH STIMULATION

The activation of protooncogenes requires mechanisms such as gene amplification or point mutation of a single allele leading to constitutive overexpression. In some cases, however, the mechanisms causing overexpression are still unclear. Protooncogene products include several growth factor receptors, such as epidermal growth factor receptor (EGFR), ERBB2, KIT, and MET. Indeed, many growth factor/receptor systems are expressed by either the lung tumor or adjacent normal cells, thus providing autocrine or paracrine growth stimulation loops (Fig. 31.1-1). For example, overexpression of the EGFR encoded by the ERBB1 gene is more common in NSCLC than SCC and may be related to tumor stage and differentiation. Coexpression of EGFR and its ligands, especially transforming growth factor-a (TGF-a), by lung cancer cells indicates the presence of an autocrine (self-stimulatory) growth factor loop. Overexpression of both EGFR and TGF-a occurs in 38%.\(^7\) Clinically, the presence of this loop had no significant impact on overall survival in early-stage NSCLCs and thus seems to play a role in lung tumor formation rather than tumor progression.\(^8\) ERBB2 (HER2/new) is highly expressed in more than one-third of NSCLCs, especially adenocarcinomas. Its expression correlates with a shorter survival in lung adenocarcinomas and may also be a marker for intrinsic multidrug resistance in NSCLC cell lines.\(^9\) KIT and its ligand, stem cell factor (SCF), are both preferentially expressed in many SCLCs. Activation of this putative autocrine loop may provide a growth advantage, or it may mediate chemotaxis. The SCF/KIT signal transduction pathway has been shown to be associated with Lck, a src-related tyrosine kinase.\(^10\) MET and its ligand, hepatocyte growth factor (HGF), are involved in fetal lung development. Coexpression of this putative loop is observed in most NSCLCs, and high HGF levels were associated with a poor outcome in resectable NSCLC patients.\(^11\) There are several clinical applications of these growth factor receptor abnormalities that have occurred in other cancers, which also need to be explored as new treatments for lung cancer. These include treatment with humanized monoclonal anti-HER-2/neu receptor antibody Herceptin alone or in combination with chemotherapy, treatment with monoclonal anti-EGF receptor antibody combined with radiotherapy, and new drugs that would inhibit the tyrosine kinase activity of these receptors.

Apart from protooncogene products, other growth stimulation loops are found in lung cancers. The best known is that governed by gastrin-releasing peptide (GRP) and other bombesin-like peptides, together with their receptors, which participates in lung development and repair as well as promoting SCLC growth via an autocrine loop.

DAP (death associated protein) kinase, GSTP1, and MGMT (O\(^6\)-methylguanine-DNA-methyltransferase).\(^6\) Another acquired tumor abnormality is loss of imprinting (loss of methylation) to allow the expression of genes in lung cancer. Methylation plays a role in mediating genomic imprinting, which is a gamete-specific modification causing differential expression of the two alleles of a gene in somatic cells. Loss of genomic imprinting of the insulin-like growth factor-2 (IGF-2) gene and the H19 gene (associated with hypomethylation of its promoter region) also occurs in lung cancer.

**FIGURE 31.1-1.** The common growth stimulation and inhibitory cascades involved in lung cancer cells. A single circle denotes growth stimulation molecules, and multiple circles denote activation caused by some tumor-acquired abnormality. A box denotes growth inhibitory molecules, whereas their inactivation is indicated by a cross within the box, again acquired (for example) by mutation in the tumor. Double arrows indicate transcriptional activation of target genes that regulate cell growth. cAMP, cyclic adenosine monophosphate; CDK4, cyclin-dependent kinase-4; EGFR, epidermal growth factor receptor; ERK, extracellular regulated kinase; GRP, gastrin-releasing peptide; HGF, hepatocyte growth factor; NSCLC, non–small cell lung carcinoma; RB, retinoblastoma protein; SCF, stem cell factor; SCLC, small cell lung carcinoma; TGF-a, transforming growth factor-a.

Because downstream effectors are needed to transduce incoming growth factor/receptor signals to the nucleus, it is not surprising that cytoplasmic signal transduction cascades are also implicated in carcinogenesis. For instance, the receptor tyrosine kinases initially signal the guanosine triphosphate–binding RAS protein. The RAS gene family (KRAS, HRAS, and N-RAS) can be activated by point mutations at codons 12, 13, or 61, and one member of this family is mutated in approximately 20% to 30% of NSCLC (particularly adenocarcinomas) but probably never in SCLC.\(^12\) KRAS accounts for 90% of the RAS mutations in lung adenocarcinomas, with approximately 95% of the KRAS mutations affecting codon 12. Characteristically, approximately 70% of KRAS mutation are G to T transversions, with the substitution of the normal guanine (G) with either cytosine (T) or thymine (C). Similar G to T transversions also affect the P53 gene in lung cancer and represent the type of DNA damage expected from bulky DNA adducts caused by the polycyclic hydrocarbons and nitrosamines in tobacco smoke. Further evidence for a causative role for tobacco use is the correlation of KRAS mutations with cigarette consumption. The presence of KRAS mutations portends a poor prognosis in both early- and late-stage NSCLCs,\(^13\) although the data conflict.\(^14\) Nonetheless, a metaanalysis of eight studies of 217 (of 881) NSCLC patients positive for KRAS mutations suggested a negative prognostic role.\(^15\) A prospective study has shown that neither chemosensitivity or survival correlated with KRAS mutation in advanced lung adenocarcinomas.\(^16\) New drugs, farnesyltransferase inhibitors, were developed to specifically kill or inhibit the growth of tumor cells with KRAS mutations. However, these drugs appear to be active against tumors with and without RAS mutations and are coming into clinical trials against lung cancer.

A direct downstream effector of RAS is the RAF1 protooncogene product. Unexpectedly, the experimental growth arrest of SCLC by activated RAF1 suggests that it has more of a TSG function.\(^17\) Although one copy of RAF1 is frequently lost; however, mutations in the RAF1 gene have not been detected in human lung cancers. Mutations downstream of RAF1 in the signal transduction pathway, such as MEK, MEK, and mitogen-activated protein kinase/extracellular-regulated kinase (MAPK/ERK), may also be involved occasionally in lung carcinogenesis. The PP2B(PP2A) gene, encoding the beta isofrom of protein phosphatase 2A (PP2A), which regulates the RAS/MAPK cascade, is also infrequently mutated in lung cancers.\(^18\)

Ultimately, signal transduction cascades result in the activation of nuclear protooncogene products such as those encoded by the myc family genes (MYC, MYCN, MYCL). MYC, when heterodimerized with a protein called MAX, functions as a transcription factor, necessary for normal cell cycle progression, differentiation, and programmed cell death. MYC is most frequently activated via gene amplification or transcriptional dysregulation in both SCLC and NSCLC, whereas abnormalities of
MYCN and MYCL generally occur in SCLC. Indeed, MYCL was originally isolated from a SCLC cell line. The myc family gene amplification has been differentially observed in the major lung cancer subtypes. In SCLC, one member of the MYC family was amplified in 18% of tumors and 31% of cell lines, compared to 8% of NSCLC tumors and 20% of cell lines, respectively. Amplification appears more frequent in patients previously treated with chemotherapy, the "variant" subtype of SCLC, and its presence correlates with adverse survival. In terms of therapy, all-trans-retinoic acid (RA) treatment inhibited the in vitro growth of a SCLC cell line overexpressing MYC, a process associated with increased neuroendocrine differentiation and increased MYCL and decreased MYC expression. Lastly, there have been reports of MYCL involvement in rearrangement in which MYCL fuses to the RLF gene causing a chimeric protein.

Occasional reports have implicated other oncoproteins, such as ERBB, MYB, JUN, and FOS in lung cancer, but data are relatively few. Tumor Suppressor Genes and Growth Suppression

p53 Pathway

p53 (or TP53) maintains genomic integrity in the face of cellular stress from DNA damage (for example caused by g- and UV irradiation, carcinogens, or chemotherapy). It functions as a transcription factor to activate the expression of genes that control cell-cycle checkpoints (e.g., p21WAF1/CIP1), apoptosis (BAX), DNA repair (GADD45), and angiogenesis (thrombospondin). The p53 gene is the most frequently mutated TSG in human malignancies, and mutations affect approximately 90% of SCLCs and 50% of NSCLCs. Most mutations occur in the evolutionarily conserved p53 exons S to 8. In NSCLCs, p53 alterations occurred more frequently in adenocarcinoma (52%) and large cell (53.7%) carcinomas than adenocarcinomas (38.8%). p53 mutations correlate with cigarette smoking and most are of the type of G to T transversions expected from tobacco smoke carcinogens. More evidence linking smoking damage with p53 mutations is the finding that a major cigarette smoke carcinogen, benzo(a)pyrene, selectively forms adducts at the p53 mutational hot spots. The types of p53 mutations are varied and include missense, nonsense, and splicing abnormalities as well as large deletions. Missense mutations (the most common type of mutation) often prolong the half-life of the p53 protein to several hours, leading to increased levels detectable by immunohistochemistry and thus the use of immunohistochemistry as a surrogate assay for p53 mutation. Whether the occurrence of p53 mutations (detected by either immunohistochemistry or molecular analysis) in a patient's tumor affects survival is controversial. Approximately 15% of lung cancer patients develop antibodies to the p53 protein, raising the possibility that mutant p53 protein overexpression can lead to a humoral immune response. Although p53 mutations have been proposed as a marker for early diagnosis and chemoresponsiveness, the development of these antibodies does not appear to improve prognosis in lung cancer. There have been several promising gene therapy clinical trials with objective response rates of approximately 10% to 15% in which lung cancers are treated by intratumoral injection (endobronchially, or by computed tomography (CT)-guided needle injection) with a normal (wild-type) p53 gene using retroviral or adenoviral vectors. These local injections are now being combined with chemo- and radiotherapy to test if gene therapy increases sensitivity to conventional treatments. Also, systemic methods (such as with lipid vesicles) of delivering p53 gene therapy to disseminated tumors are being developed. In another approach, clinical trials are being conducted to immunize patients against either mutant p53 or RAS proteins occurring in patients' tumors in attempts to generate a tumor-specific cytotoxic T-cell response.

p53 functions in a biochemical pathway; thus it is reasonable to consider that other components of this pathway may be mutated in lung tumors that are wild-type for p53. One of the upstream components is the kinase that phosphorylates p53 encoded by the ataxia telangiectasia (ATM) gene. However, this gene has not yet been found to be mutated in lung cancer. Other components are the MDM2 and p14ARF genes (see p16INK4A, later in this chapter), which regulate the levels of p53 protein, but so far they have not been implicated in lung cancer. Two proteins homologous to p53—p51 and p73—have been discovered, leading to the hypothesis that they may be mutated in p53 wild-type tumors. However, they are only infrequently, if ever, mutated in lung cancers. Finally, the Li-Fraumeni syndrome of inherited susceptibility to cancer determined by an inherited germline mutation of p53 may also lead to increased susceptibility to lung cancer in adults in these pedigrees.

The P16INK4A–Cyclin D1–Cyclin-Dependent Kinase 4–Retinoblastoma Protein Pathway

p16INK4A

The p16INK4A–cyclin D1–cyclin-dependent kinase 4 (CDK4)–retinoblastoma (RB) protein pathway is a key cell-cycle regulator at the G1/S phase transition, and one of the components of this pathway is abnormal in the majority of lung cancers. The activation of CDK4 by cyclins eventually leads to the phosphorylation (inactivation) of the growth-suppressive RB protein (see Fig. 31.1-1). As p16INK4A is an inhibitor of CDK4, especially CDK4 or CDK6 (which phosphorylate and keep RB in an "inactive" state), its normal role is to positively regulate RB's growth-controlling function by keeping RB unphosphorylated. However, if p16INK4A is inactivated by mutation, RB remains chronically phosphorylated and thus cannot function to regulate growth (see Fig. 31.1-1).

The p16INK4A (also called CDKN2) gene locus on chromosome 9p21 is frequently abnormal in human malignancies. In lung cancer, p16INK4A abnormalities are frequent in NSCLC but rare in SCLC (in which, by contrast, RB is mutated in 90% of SCLCs and 50% of NSCLCs). Thus, these two major histologic lung cancer types have this pathway inactivated by mutation of one or the other gene, and double mutants in the same tumor are very rare. A summary of 20 studies showed that p16INK4A point mutations in NSCLCs were observed in only 14% of primary tumors. However, homozygous or aberrant promoter methylation can also down-regulate p16INK4A. Indeed, aberrant methylation of the p16INK4A promoter may be the most frequent as well as an early preneoplastic event in the pathogenesis of squamous cell carcinomas. Taken together, these mechanisms ultimately result in absent p16INK4A expression in approximately 40% of primary NSCLCs, indicating that this may be the most common way to inactivate the p16INK4A–cyclin D1–CDK4–RB pathway in NSCLC. Because of the frequency of the abnormalities, p16INK4A is an attractive clinical trials candidate for replacement gene therapy or induction of re-expression with antimethylation drug therapy.

Complicating matters is the discovery of an alternative reading frame at the p16INK4A locus, p14ARF, which encodes a protein that binds p53/MDM2 complex, leading to p53 protein stabilization. If p14ARF is missing because of mutations in the p16 locus, p53 is less stable and its function diminished. It thus emerges that inactivation of the p53 pathway may also be triggered by abnormalities of the p16INK4A gene locus. Another CDK inhibitor gene, p15INK4B, is situated close to p16INK4A and can be co-deleted with p16INK4A in NSCLC. However, it appears that the majority of lung cancer abnormalities focus on p16INK4A and not on p15INK4B.

Cyclin D1 and Cyclin-Dependent Kinase-4

Because cyclin D1/CDK4 complex inhibits RB activity by stimulating its phosphorylation, cyclin D1 or CDK4 overexpression is an alternative way to disrupt this pathway. Immunohistochemically, cyclin D1 is overexpressed in 12% to 47% of primary NSCLCs and, in some cases, cyclin D1 overexpression is associated with a poor prognosis. How this overexpression occurs in lung cancer is unknown.

Retinoblastoma Protein

The RB gene (Rb), located at chromosomal region 13q14, encodes a growth-suppressive nuclear phosphoprotein. When active (i.e., hypophosphorylated), RB binds and inactivates proteins such as transcription factor E2F-1, which is essential for G1/S transition of the cell cycle (see Fig. 31.1-1). RB mutations (truncation by deletion, nonsense mutation, or splicing abnormalities), together with loss of the wild-type RB allele, have been demonstrated in lung cancers, particularly SCLC. The RB protein is absent or structurally abnormal in more than 90% of SCLCs and 15% to 30% of NSCLCs. Absent RB expression may be associated with poor prognosis in NSCLCs, although this is not a consistent finding. The relatively low frequency of RB abnormalities in NSCLC is consistent with the frequent disruption of the p16INK4A–cyclin D1–CDK4–RB pathway in these histologic types. Essentially, lung cancers can be characterized as having either RB mutation (mostly SCLC) or p16INK4A inactivation (mostly NSCLC). Gene therapy with replacement of RB function has been considered, but because of the large size of the RB coding region and the need for systemic delivery, in, for example, typical widely metastatic SCLCs, such therapy has not been actively pursued. Mutations of other RB-related genes, p107 and RB2/p130, have also been implicated in lung cancer. In the case of RB2, loss of protein expression and restoration of growth control by genetically re-introducing a normal copy of RB2 have been demonstrated. Finally, retinoblastoma patients or their relatives who carry a mutant RB in the germline have an excess risk of developing small cell lung cancer if they survive into adult life.

PTEN, FHT, RAR-β, PUTATIVE 3P TUMOR SUPPRESSOR GENES, AND OTHER TUMOR AND GROWTH-SUPPRESSIVE GENE SITES IN LUNG CANCER PATHOGENESIS

Besides the p53, p16INK4A, RB, and loci, cytogenetic and allelotyping studies show nonrandom, hemiallelic loss at many other chromosome regions in lung cancer. Such tumor-specific somatically acquired loss of heterozygosity is a hallmark feature of traditional TSG inactivation. In other words, the consistent identification of
multiple sites of loss of heterozygosity at various chromosomal regions suggests the existence of underlying TSGs in these regions. Usually the remaining allele is silenced by point or small mutations, epigenetic hypermethylation of the promoter region or, less frequently, by a larger deletion. These sites of allele loss are dispersed at more than 30 different chromosomal arms, although the molecular targets of most of these sites is not known. Although several of these chromosomal arms contain known TSGs, including VHL (3p25), APC (5q21), WTI (11p13), DCC (18q21), and NF1 (22q12), these genes are not known to be mutated in lung cancer. The TSG *PTEN*, which encodes a phosphatase, is located at chromosome region 10q23, another common area of allele loss in lung cancer. However, *PTEN* is mutated in only a subset of lung cancers. Frequent loss (60% to 80%) of several 4p and 4q regions were found in thoracic malignancies (particularly SCLC and mesotheliomas); however, the genes involved are not yet known.

Among these chromosomal locations, chromosome 3p allele loss (occurring at more than four different 3p regions) stands out as a very frequent and early event in lung cancer pathogenesis. 3p loss occurs in more than 90% of SCLCs and more than 80% of NSCLCs. In addition, it appears to be the earliest genetic change found in lung cancer development, occurring at frequent frequency in patches of normal epithelium accompanying lung cancer or in smokers, as well as in sites of hyperplasia, dysplasia, and carcinoma in situ of respiratory epithelium (see *Molecular Changes in Preneoplasia*, later in this chapter). Multiple distinct 3p regions have been identified by allelotyping, including 3p25-26, 3p21.3-22, 3p14, and 3p12. Furthermore, several homologous deletions are found in several lung cancer cell lines (at several 3p21.3 sites, as well as at 3p2 and 3p14.2). Several candidate TSGs have been identified in an approximately 600-kilobase 3p21.3 region homogeneously deleted in three SCLCs, and another 800-kilobase deletion region at 3p21 also has been described. The *FHIT* (fragile histidine triad) gene is found in the 3p14.2 homogeneously deleted region. Forty percent to 80% of lung cancer cells express abnormal *FHIT* messenger RNA transcripts but paradoxically almost always also express a normal-type *FHIT* transcript. Regardless of the transcript, the *FHIT* protein is absent in many lung cancers, particularly in the squamous cell type (75%) which compared to adenocarcinoma (57%) and may also be lost in some preneoplastic lesions. The loss of *FHIT* protein expression is also strongly associated with smoking. Functionally, *FHIT* may be involved in the regulation of apoptosis and in cell-cycle control. Transfection of wild-type *FHIT* into lung cancer induces apoptosis and blocks tumor formation in vivo in mouse models. Because of the occurrence of *FHIT* abnormalities early in lung cancer pathogenesis (e.g., in preneoplastic stages), it is possible to consider delivering *FHIT* gene therapy to airways containing multiple preneoplastic lesions by using aerosols.

TGF-β1 is a potent inhibitor of proliferation of most epithelial and hematopoietic cells, and its signal is mediated through TGF-β receptors and subsequently SMAD proteins. In SCLC cells, down-regulation of the type II receptor (*TGFBR2*) located in chromosome region 3p34, has been shown to correlate with the resistance to growth inhibition by TGF-β1. However, the TGFβRII or SMAD family genes are rarely mutated in lung cancer.

There is considerable evidence of dysfunction of retinoid acid receptor beta (RAR-b), located in chromosome region 3p24, in lung cancers, leading to resistance of lung cancer cells to retinoids and making it an excellent candidate 3p TSG. Although initial studies did not find RAR-b mutations, more recent studies have shown localization of the TAF7 and TAF4 genes in a subset of clinical samples. It is quite likely that this loss of expression without genomic changes occurs because of methylation of the promoter region. Because of the widespread testing of retinoids as chemoprevention agents, it will be important to characterize the timing of loss of RAR-b function in lung cancer preneoplasia. It is possible that loss of expression of RAR-b may occur at such an early stage that chemoprevention with retinoids cannot succeed.

**OThER BIOLOGIC ABNORMALITIES FOR LUNG CANCER DEVELOPMENT**

**TELOMERASE ACTIVITY**

During normal cell division, telomere shortening leads to cell senescence and thus governs normal cell “mortality.” Telomerases are maintained in normal stem cells by the enzyme telomerase. However, with abnormal expression of the enzyme in, for example, tumors, telomerase has been implicated in contributing to human cell immortalization and cancer cell pathogenesis. Telomerase is a ribonucleo complex, and ectopic expression in tumors of its catalytic subunit, human telomerase reverse transcriptase, appears critical for the cellular immortalization typical of cancer cells. Using the highly sensitive telomere replication amplification protocol assay, approximately 100% of SCLCs and 80% to 85% of NSCLCs were demonstrated to express high levels of telomerase activity. High telomerase activity was associated with increased cell proliferation rates and advanced stage in NSCLCs. Further tests must be performed to conclusively demonstrate that true telomerase-negative NSCLCs exist. If these telomerase-negative tumors truly exist, debulking therapy with surgery and radiotherapy should be considered, even for metastatic disease. It would be predicted that eventually such tumors would “senesce” and stop growing when their telomeres got too short. Telomerase activity and expression of its RNA component are also dysregulated in carcinoma in situ lesions associated with lung cancer, indicating that the timing of telomerase activation for lung cancer development can occur in preneoplasia. Because of the nearly ubiquitous expression of telomerase in human tumors, including lung cancer, there is much interest in developing anti-telomerase drugs as new therapeutic.

**APOTOPSIS**

Unlike normal cells, tumors have the ability to escape from programmed cell death (apoptosis), which usually occurs under adverse conditions such as DNA damage. In addition to p53, other molecules have the ability to escape from programmed cell death, which occurs in response to DNA damage. p53, however, is not absolutely required for apoptosis to occur, and other mechanisms, such as the mitochondria pathway, can contribute to the process. The mitochondria pathway involves the activation of caspases, which are proteolytic enzymes that play a critical role in the degradation of cellular proteins.

**METASTASIS AND ANGIGENESIS**

Many potential factors influencing metastasis from primary lung cancers have been studied, including cell adhesion molecules. For instance, reduced E-cadherin expression, which can occur by promoter hypermethylation, was associated with tumor dedifferentiation, increased lymph node metastasis, and poor survival in NSCLC patients. Reduced α3 integrin expression correlated with a poor prognosis of patients with lung adenocarcinoma. Specific CD44 isoforms may be associated with lung cancer metastasis. Meanwhile, matrix metalloproteinases inducing stromal degradation may also be involved in lung cancer invasion. Gelatinase A expression was observed in approximately 50% of SCLCs and 65% of NSCLCs, andstromelysin-3 overexpression was detected in stromal elements of primary NSCLCs. Because of this expression, several ongoing clinical trials of matrix metalloproteinase inhibitors in the treatment of lung cancer are ongoing. Finally, multiple other as yet unidentified genes may also be involved in lung tumor progression and metastases, as evidenced by the development of additional allelic losses (at 2q, 4p, 18q, and 22q) in brain metastases compared to the primary NSCLCs in the same patients.

**CARCINOGENS IN TOBACCO SMOKE AND GENETIC SUSCEPTIBILITY TO LUNG CANCER (GENETIC EPIDEMIOLOGY)**

The major cause of lung cancer, of course, comes from smoking, and tobacco smoke contains many substances, including carcinogens, co-carcinogens, and tumor promoters. Among them, 20 carcinogens convincingly cause lung tumors in laboratory animals or humans and are likely to be involved in lung cancer induction. The carcinogenic effects of tobacco smoke in the lung involve the induction of carcinogen-activating and inactivating enzymes, as well as covalent DNA adduct formation, which may cause DNA misrepair and mutation. DNA adducts have been identified in the bronchial tissue of lung cancer patients, and adduct levels correlate with the degree of tobacco smoke exposure. Of great importance is preventing children from starting to smoke. In this regard, it was found that, in former smokers, age at smoking initiation was inversely associated with DNA adduct levels. Thus, after controlling for the amount of smoking, the earlier one started smoking, the worse the long-term damage. In addition, for reasons that are not yet clear, it appears that women are more susceptible to developing lung cancer from cigarette smoking than men. Of the three major classes of carcinogens in tobacco smoke (polycyclic aromatic hydrocarbons, such as benz[a]pyrene; nitrosamines; and aromatic amines),
much interest focuses on the nitrosamines, especially 4-(methyl nitrosamino)-1-(3-pyridyl)-1-butane (NNK), partly because it induces tumors of the lung—primarily adenomas and adenocarcinomas—independent of the route of administration in mice. The finding that not every heavy smoker develops lung cancer has led to the concept of interindividual variation and the hypothesis that individuals may exhibit genetic polymorphisms in carcinogenic-metabolizing pathways that determine individual lung cancer risk. Clearly, such genetic susceptibility operates in close interaction with smoking and other external carcinogenic factors ("gene-environment" interaction, with smoking being the primary environment factor). Among genes for carcinogenic-metabolizing enzymes, polymorphisms in the cytochrome P-450 genes CYP1A1, CYP2B6, CYP2E1 and in microclass glutathione S-transferase (GSTM1) have received the most attention. Although studies have suggested that there may be a modest association of GSTM1 null polymorphism with lung cancer, studying single candidate genes may not be adequate to predict lung cancer risk due to complexity of carcinogen metabolism and gene-gene and gene-environment interactions. In addition to carcinogens, it also appears that persons may inherit different susceptibility to become addicted to nicotine, for example, through polymorphisms in one of the dopamine receptors. Overall, molecular epidemiology, aided by DNA microarray technology together with the Human Genome Project, should in the near future help to identify individuals at highest risk of developing lung cancer. Such information will be of great value in new lung cancer screening trials (for example with spiral CT scans) and in chemoprevention trials.

MOLECULAR CHANGES IN PRENEOPLASIA

Before clinically recognizable lung cancer develops, a series of morphologically distinct changes (hyperplasia, metaplasia, dysplasia, and carcinoma in situ) can be observed in the bronchial epithelium of smokers. It is felt that dysplasia and carcinoma in situ represent true preneoplastic (precancerous) changes. These sequential changes found with squamous cell cancers arising from central bronchi have long been recognized, whereas other changes in peripheral bronchioles and alveoli (adeno- and large cell cancers), such as adenomatous and alveolar hyperplasia, are more recently described.

It is now clear that preneoplastic cells contain several genetic abnormalities identical to some of the abnormalities found in overt lung cancer cells. Immunohistochemical analysis has confirmed abnormal expression of protooncogenes (cycillin D1) and TSGs (p53) in these lesions. Alleotyping of precisely microdissected, preneoplastic foci of cells shows that 3p allele loss is currently the earliest known change, suggesting that one or more 3p TSGs may act as "gatekeepers" for lung cancer pathogenesis. This loss is followed by 9p allele loss, 8p allele loss, and 17p allele loss (and p53 mutation) (Fig. 31.1-2). Even the histologically normal bronchial epithelium adjacent to cancers has been shown to have genetic losses. Similarly, atypical alveolar hyperplasia, the potential precursor lesion of adenocarcinomas, also harbors KRAS mutations. These observations are also consistent with the multistep model of carcinogenesis and a "field carcinogenesis" process, whereby the whole tissue region is repeatedly exposed to carcinogenic damage (toxic smoke) and is at risk for developing multiple separate foci of neoplasia. Although all types of lung cancers have associated molecular abnormalities in their normal and preneoplastic lung epithelium, small cell lung cancer patients in particular appear to have multiple genetic alterations occurring in their histologically normal-appearing respiratory epithelium. Molecular changes have been found not only in the lungs of patients with lung cancer but also in the lungs of current and former smokers without lung cancer. These molecular alterations are thus important targets for use in the early detection of lung cancer and for use as surrogate biomarkers in following the efficacy of lung cancer chemoprevention. In this regard, it appears that the smoke-damaged lung has thousands of multiple clonal or subclonal patches of approximately 90,000 cells each in the respiratory epithelium containing clones of cells with 3p and other allele loss abnormalities.

MOLECULAR TOOLS IN THE LUNG CANCER CLINIC

Our understanding of the molecular genetic changes in lung cancer pathogenesis is advancing rapidly. Some abnormalities also occur in other human cancers, whereas others appear more specific for lung cancer. Where their biochemical function is known, the proteins rendered abnormal appear to fall into several growth regulatory pathways. Thus, the "wiring" diagram of the lung cancer cell is becoming clear. There is a substantial effort to translate this current scientific knowledge of these abnormalities from the bench to the bedside. These approaches fall into four general categories:

1. Identification of persons at highest risk of developing lung cancer to enable chemoprevention and intensified smoking cessation efforts. In this regards, with improved methods of molecular identification of true precancerous lesions, our paradigm will become "treatment" of precancerous lesions rather than "chemoprevention." Obviously, because this treatment would occur in individuals without clinically evident cancer, the treatments must have low toxicity and high risk-benefit ratios.

2. Early detection tools to identify primary and recurrent disease (e.g., polymerase chain reaction-based molecular methods for testing body fluids). Again, such "early detection" of invasive but clinically occult disease would require careful analysis of risk-benefit ratios. Because only one out of ten cigarette smokers eventually develops lung cancer, the identification of persons with a genetic susceptibility to lung cancer should allow targeting and intensification of smoking cessation, early detection, and chemoprevention efforts. In this regard, the encouraging new information on spiral CT scanning for the early detection of lung cancer should be greatly targeted and enhanced by combining radiologic screening with identification of genetic epidemiology markers and acquired respiratory genetic alterations to identify the individuals at highest risk.

3. Identification of prognostic biomarkers that would also include markers that would predict the response to various therapies such as chemo- and radiotherapy.

4. The designing of new cancer-specific therapies based on knowledge of genetic abnormalities. This includes replacing mutant TSGs; developing drugs targeted to specific genetic abnormalities found in lung cancer cells, and creating new treatments for lung cancer by taking advantage of activated protooncogenes by interfering with autocrine, paracrine loops; and inhibiting angiogenesis, metastasis, and apoptotic pathways in cancer cells. Although new therapies may be dramatically effective, it is probably more reasonable to assume that they would complement rather than replace existing therapies.

CHAPTER REFERENCES

EPIDEMIOLOGY

INCIDENCE

Lung cancer is among the most commonly occurring malignancies in the world and is one of the few that continues to show an increasing incidence. In the United States, lung cancer is the leading cause of cancer death in men, and it surpassed breast cancer as the leading cause of cancer death in women in the latter part of the 1980s. In the year 2000, there will be approximately 164,100 new cases and approximately 156,900 deaths from this disease (Fig. 31.2-1).

Excluding this malignancy, most developed countries have shown declines in death rates from cancer in the last 20 years. During the same period in countries such as the United States and Canada, the death rate from lung cancer increased more than threefold but, in the last 5 years, it has finally begun to decline. In developing countries, the death rate from lung cancer continues to accelerate. These changes appear to be affected significantly by the observed difference in smoking habits and cigarette tar levels in developed and developing countries.

The incidence of lung cancer now exceeds 70 per 100,000 men in the United States. As we enter the twenty-first century, it is expected that the altered smoking habits of the nation's population during the last two decades and the decreased tar content of cigarettes consumed in the United States will lead to a further decline in lung cancer incidence.

MORTALITY

In the United States, only 14% of patients who develop lung cancer survive 5 years. These mortality rates (>150,000/year) far exceed those of the acquired immunodeficiency syndrome epidemic. However, this survival rate has only slightly increased in the last two decades, and it appears unlikely that marked
improvements will occur in the near future. With the anticipated decreased incidence, however, it is hoped that the lung cancer epidemic, at least in developed countries, will abate and that the total number of deaths per year attributed to this cancer will decline even further.

**LUNG CANCER CONTROL**

With the solid base of scientific information linking cigarette smoking habits to the development of lung cancer, many countries have launched programs to decrease tobacco use and educate the population. Included in these programs are legislative activity (e.g., increased taxes, smoke-free areas, banning tobacco advertisements), educational activities through mass media and schools, and interventional approaches (e.g., smoking-cessation clinics) targeted to groups at the highest risk for developing tobacco-related cancer. The greatest impact on decreased smoking habits appears to be the societal stigma directed at smokers. These activities have reduced the percentage of the U.S. population who smoke from a high of approximately 40% to approximately 30%. However, this decline has now leveled off. The only cohort that has demonstrated an increasing smoking habit in the United States is younger women. It is hoped, however, that with the societal pressures and the educational programs in developed countries, the incidence of smoking will continue to decrease. It is also hoped that a similar trend will occur in developing countries, where smoking activity continues to increase at present.

**SMOKING**

The epidemiologic data on smoking and lung cancer fulfill the following criteria for causal association: the consistency of results across studies, the strength of the relation and its specificity, the correct temporal sequence between exposure and disease, and the coherence of the association as evidenced by a dose-response relation.

It has been estimated that 80% of lung cancer deaths among men (approximately 65,000 deaths per year) and 75% of lung cancer deaths among women (approximately 27,000 deaths per year) are attributable to smoking. Mattson et al. calculated that a 35-year-old man who smokes 25 or more cigarettes per day has a 13% risk of dying of lung cancer before the age of 75 years, a 10% chance of dying of coronary heart disease, and a 28% chance of dying of smoking-related disease.

There is clear evidence for a dose-response relation between smoking and lung cancer. The risk of lung cancer increases with the number of cigarettes smoked, years of smoking duration, earlier age at onset of smoking, degree of inhalation, tar and nicotine content, the use of unfiltered cigarettes, and passive smoking. It decreases in proportion to the number of years after smoking cessation. These relationships to lung carcinogenesis are discussed in more detail in Chapter 11 and are incontrovertible.

**OCCUPATION**

Increases in lung cancer risk accompany exposure to carcinogens, such as asbestos, cigarette smoke, and polycyclic aromatic hydrocarbons (PAHs), benzene, and aromatic amines. The association with occupational exposure to these agents appears to be independent of cigarette smoking.

**DIET**

The role of dietary antioxidant micronutrients in the prevention of lung cancer is reviewed in Chapter 23.3. The presumed mechanism leading to prevention of carcinogenesis by these nutrients is that antioxidant micronutrients, including carotenoids, vitamins C and E, and selenium, have an important role in scavenging free radicals produced endogenously and exogenously by tobacco smoke, solvents, and pollutants. Carotenoids and vitamins C and E trap free radicals and reactive oxygen molecules, whereas selenium is a component of antioxidant enzymes. Analysis of the role of nutrients in the cause of lung cancer is confounded by methodologic problems and by the conflicting results of studies. However, to date, chemoprevention studies have failed to have an impact on lung cancer incidence. Several approaches have been adopted to detect a genetic association: studies of familial clustering, studies of naturally occurring antigens, and studies of the metabolism of drugs. Studies of familial clustering have been interpreted as showing no substantial genetic predisposition. Several approaches have been adopted to detect a genetic association: studies of familial clustering, studies of naturally occurring antigens, and studies of the metabolism of drugs. Studies of familial clustering have been interpreted as showing no substantial genetic predisposition. However, to date, chemoprevention studies have failed to have an impact on lung cancer incidence. Several approaches have been adopted to detect a genetic association: studies of familial clustering, studies of naturally occurring antigens, and studies of the metabolism of drugs. Studies of familial clustering have been interpreted as showing no substantial genetic predisposition.

**EVIDENCE FOR A GENETIC PREDISPOSITION**

There is limited evidence that genetic factors may contribute to lung cancer risk. Variations in the metabolism of carcinogens have been implicated. The pathways to create these toxic metabolites are genetically determined. The metabolism of the antihypertensive drug debrisoquin is genetically determined by a single gene. The metabolism of many drugs and chemicals correlate with that of debrisoquin, and this may also apply to carcinogenic components of cigarette smoke (Table 31.2-1), although this has not been proven for any one substance with respect to lung carcinogenesis. Several approaches have been adopted to detect a genetic association: studies of familial clustering, studies of naturally occurring antigens, and studies of the metabolism of drugs. Studies of familial clustering have been interpreted as showing no substantial genetic predisposition. Several approaches have been adopted to detect a genetic association: studies of familial clustering, studies of naturally occurring antigens, and studies of the metabolism of drugs. Studies of familial clustering have been interpreted as showing no substantial genetic predisposition. However, to date, chemoprevention studies have failed to have an impact on lung cancer incidence. Several approaches have been adopted to detect a genetic association: studies of familial clustering, studies of naturally occurring antigens, and studies of the metabolism of drugs. Studies of familial clustering have been interpreted as showing no substantial genetic predisposition. However, to date, chemoprevention studies have failed to have an impact on lung cancer incidence. Several approaches have been adopted to detect a genetic association: studies of familial clustering, studies of naturally occurring antigens, and studies of the metabolism of drugs. Studies of familial clustering have been interpreted as showing no substantial genetic predisposition. However, to date, chemoprevention studies have failed to have an impact on lung cancer incidence. Several approaches have been adopted to detect a genetic association: studies of familial clustering, studies of naturally occurring antigens, and studies of the metabolism of drugs. Studies of familial clustering have been interpreted as showing no substantial genetic predisposition.

![Reference Table]

| Table 31.2-1. Major Mutagens, Carcinogens, and Related Substances in Tobacco Smoke |

Although the molecular and genetic events underlying the pathogenesis of lung cancer are an area of active investigation, no genetic abnormality has conclusively defined the risk of lung cancer. In NSCLC, the most frequently identified abnormalities are deregulation of tumor suppressor gene p53, aberrant expression of the epidermal growth factor receptor (EGFR) and one of its ligands, and the presence of K-ras abnormalities in adenocarcinoma (discussed in New Potential Prognostic Markers). Clinical trials targeting adjuvant therapies for patients with resected NSCLC with K-ras point mutations are in progress. Monoclonal antibodies or other drugs blocking the action of epidermal growth factor are in clinical trials. The activation of cellular receptors for virtually all autocrine growth factors involves the activation of a protein kinase. This observation has given us a new therapeutic target, and the search for agents specifically inhibiting this enzyme is under way. The mutated sequences of p53 provide a unique, molecular target for the treatment of human cancers.

**APPLICATIONS OF ADVANCES IN LUNG CANCER BIOLOGY TO CLINICAL PRACTICE**

Advances in our understanding of the biology of lung cancer have the potential to affect all areas of lung cancer management. The identification of specific mutations related to tobacco exposure has elucidated the possible molecular foundation for the association of cigarette smoking and lung cancer and may allow us better to identify at-risk people for chemoprevention programs. The presence of autocrine growth factor receptors, specific mutations, or chromosomal deletions may provide additional or more accurate means for diagnosing, staging, choosing therapies, and establishing prognosis for patients with lung cancer. The presence of K-ras point mutations has been shown to be associated with a shortened survival in patients with completely resected NSCLC. Clinical trials targeting adjuvant therapies for patients with resected NSCLC with K-ras point mutations are in progress. Monoclonal antibodies or other drugs blocking the action of epidermal growth factor are in clinical trials. The activation of cellular receptors for virtually all autocrine growth factors involves the activation of a protein kinase. This observation has given us a new therapeutic target, and the search for agents specifically inhibiting this enzyme is under way. The mutated sequences of p53 provide a unique, molecular target for the treatment of human cancers.
tumor-specific antigen at which to direct therapeutic strategies. New treatment approaches using viral vectors to reverse discordant p53 mutations are in progress.

PATHOLOGY

The World Health Organization (WHO) classification of lung cancer is accepted worldwide (Table 31.2-2). NSCLC includes carcinoma, adenocarcinoma, and large cell (undifferentiated) carcinoma.

TABLE 31.2-2. World Health Organization Histologic Classification of Epithelial Tumors of the Lung

HISTOGENESIS

Evidence is increasing that lung cancer is derived from a pluripotent stem cell that is capable of expressing a variety of phenotypes. This epithelial stem cell, in normal histogenesis, differentiates to those cells found in the tracheobronchial tree, including pseudostratified reserve cells, ciliated goblet columnar cells, neuroendocrine cells, and type I and II pneumocytes seen lining the alveoli. Cells that are capable of division can express hyperplastic, metaplastic, or neoplastic change. Frequently, a lung cancer exhibits two or more histologic patterns. The frequency of this occurrence depends on the assiduity of the pathologist and the number of sections examined. In one study, when at least 10 blocks from each tumor were examined, 45 of the 100 cases demonstrated heterogeneity, and 10% of cases showed elements of both squamous cell carcinoma and adenocarcinoma.

It appears that squamous cell carcinoma and small cell carcinoma have a distinct dose-response relation, with increasing tobacco exposure producing increasing numbers of these histologic subtypes. Worldwide, however, adenocarcinoma appears to be increasing, especially in women, despite the fact that it does not have this significant dose-response relation with smoking. This increasing incidence of adenocarcinoma is especially seen in the United States and is less apparent in Europe and Japan.

Squamous Cell Carcinoma

Although at one time the most frequent of all lung cancers, squamous cell carcinoma in North America has not seen the marked increase observed with adenocarcinoma, the latter tumor accounting for most of the recent increased incidence of lung cancer. Some of these differences may be related to the change from nonfiltered to filtered cigarettes and their relation to site of deposition of the carcinogens. Squamous cell carcinoma arises most frequently in proximal segmental bronchi and is associated with squamous metaplasia. In its earliest form, carcinoma in situ, stratified squamous epithelium is replaced by malignant squamous cells without invasion through the basement membrane. Because of the ability of these cells to exfoliate, this tumor can be detected by cytologic examination at its earliest stage. With further growth, the tumor invades the basement membrane and extends into the bronchial lumen, producing obstruction with resultant atelectasis or pneumonia.

Histologically, the squamous cell tumor is composed of sheets of epithelial cells, which may be well or poorly differentiated. Most well-differentiated tumors demonstrate keratin pearls. The more poorly differentiated tumors, if determined to be squamous cell carcinoma, have positive keratin staining.

Adenocarcinoma

In North America, adenocarcinoma is the most frequent tumor, accounting for 40% of all cases of lung cancer. Some of this increase is due to the better identification of adenocarcinoma using immunohistochemical staining, with fewer tumors classified as undifferentiated large cell tumors. Most of these tumors are peripheral in origin, arising from alveolar surface epithelium or bronchial mucosal glands; they also can present as peripheral tumors arising in areas of previous infections, so-called scar tumors.

Histologically, these tumors form glands and produce mucin. Although they can be subdivided by light microscopy into the classic four types defined by the WHO classification, this has little clinical relevance except for bronchoalveolar carcinoma, which appears to be a distinct clinicopathologic entity. This latter tumor appears to arise from type II pneumocytes, grows along alveolar septa by lepidic growth, and shows little, if any, desmoplastic or glandular change. These tumors are interesting in that they present in three different fashions: a solitary peripheral nodule, multifocal disease, or a rapidly progressive pneumonic form, which appears to spread from lobe to lobe, ultimately encompassing both lungs.

FIGURE 31.2-4. Bronchoalveolar carcinoma. Columnar cells with minimal nuclear atypia are arranged along intact alveolar septa. The lepidic growth pattern is associated with no stromal reaction. Mucin vacuoles are present in the apical cytoplasm (arrows). A: Low-power magnification. B: High-power magnification.

Other than T1N0 tumors, it appears that adenocarcinoma has a somewhat worse prognosis, stage for stage, than does squamous cell carcinoma. Immunohistochemistry and electron microscopy have been used by pathologists with increasing frequency to identify adenocarcinoma. Using these techniques, adenocarcinoma cells stain positive for carcinoembryonic antigen and mucin. Specific monoclonal antibodies recognizing adenocarcinoma have been identified.

Large Cell Carcinoma

Large cell carcinoma is the least common of all NSCLC tumors, accounting for approximately 15% of all lung cancers. With immunohistochemical staining, electron microscopy, and monoclonal antibodies, many tumors previously diagnosed as undifferentiated large cell carcinoma can now be classified more appropriately as poorly differentiated adenocarcinoma or squamous cell carcinoma. For this reason, the incidence of this type of tumor continues to decrease.

METHODS OF SPREAD

After a variable period as a primary tumor growing within lung parenchyma or within the bronchial wall, the tumor ultimately invades the vascular and lymphatic channels, resulting in spread by these channels to regional draining lymph nodes and distant metastatic sites. Occasionally, airborne or lymphatic metastases (so-called satellite nodules) can be seen in the lung parenchyma near the primary tumor or in ipsilateral lobes other than that containing the primary tumor. These satellite nodules auger a worse prognosis, and their relation to small cell lung cancer remains to be defined.
Ultimately, all these lymphatic channels drain to the right lymphatic or left thoracic ducts. Metastatic lymphatic spread of lung cancer follows these lymphatic channels with tumor involving bronchopulmonary (N1), mediastinal (N2-3) and, ultimately, supraclavicular (N3) lymph nodes. Retrograde lymphatic spread to the pleural surface can occur, especially in peripheral tumors.

The primary tumor can also spread locally, ultimately invading contiguous structures, including mediastinal pleura or organs and the chest wall or diaphragm. Once vascular or lymphatic invasion occurs, metastatic spread to distant sites is common. The most frequent sites involved include bone, liver, adrenals, and brain. As demonstrated in autopsy studies, however, lung cancer metastases can be found in every organ system. Metastases within the lung are thought to result from a variety of mechanisms, including airborne spread by bronchi, retrograde lymphatic spread, and blood-borne spread.

**CLINICAL FEATURES**

The signs and symptoms manifested by patients suffering from lung cancer depend on the location of the tumor, its locoregional spread, or the effects of metastatic spread (Table 31.2-3). Lung cancer is associated with paraneoplastic syndromes more frequently than any other tumor. Many patients present with an asymptomatic lesion discovered incidentally on chest radiography.

<table>
<thead>
<tr>
<th>TABLE 31.2-3. Common Signs and Symptoms of Lung Cancer</th>
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<td><strong>Locoregional Manifestations</strong></td>
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| Tumors arising in the larger airways produce symptoms related to the growth of the tumor. Frequently, patients present with a persistent cough. In larger airways, with encroachment of the lumen, a wheeze or stridor may develop. As the tumor grows, areas of necrosis may develop, resulting in bleeding. Massive hemoptysis is a rare event, with most patients experiencing blood-streaked sputum. With continued tumor growth, airways may become obstructed, resulting in atelectasis, pneumonia and, occasionally, abscess formation. These obstructive complications often result in fever and the signs and symptoms of pulmonary infection. If pleural surfaces are involved in the infection, pleuritic pain may develop with or without a detectable pleural effusion. With endobronchial obstruction and the failure of ventilation of segments or lobes or even an entire lung, increasing shortness of breath can ensue. Depending on the location of the primary tumor, adjacent structures, such as the chest wall or mediastinum, may ultimately become involved by direct spread. Radicular chest wall pain then develops. With apical tumors, the classic Pancoast's syndrome (lower brachial plexopathy, Horner's syndrome, and shoulder pain) may become manifest, owing to local invasion of the lower brachial plexus (T1 and C8 nerve roots), chest wall, and stellate ganglion. Similarly, tumors invading or involving lymph nodes in the mediastinum may encase the phrenic nerve, vagus nerve, or recurrent nerve, resulting in malfunction of the specific end organs (e.g., diaphragm, vocal cord). It is not uncommon for patients to present initially with symptoms of a recurrent nerve palsy, including hoarseness and criopharyngeal dysphagia, especially with left upper lobe tumors. Superior vena cava syndrome usually results from mediastinal lymphadenopathy encroaching on this structure rather than primary tumor invasion. Direct invasion of the pericardium or metastases to this structure can occur and lead to a malignant pericardial effusion, with signs and symptoms of pericardial tamponade. Visceral pleural inversion or retrograde lymphatic spread can ultimately result in visceral and parietal pleural seeding. Pleuritic pain or increasing shortness of breath due to a massive pleural effusion can ensue. Nodal involvement or tumor invasion of the posterior mediastinum, usually from lower lobe tumors, can produce partial or complete obstruction of the esophagus, resulting in dysphagia and, with further invasion, symptoms of a tracheoesophageal fistula. Nodal involvement of the superior mediastinum can cause a nonproductive cough or, when extensive, superior vena cava obstruction. In addition to these specific symptoms related to the presence of tumor or lymphadenopathy in a locoregional area, nonspecific and vague chest pains, generally referred to as painless interstitial pneumonitis, are frequent occurrences in patients suffering from lung cancer. These pains are of visceral origin and are unrelated to invasion of local structures. Other nonspecific symptoms, including weight loss and a general unwell feeling, are common and usually indicate advanced disease. **Metastatic Manifestations**

Nearly all patients with advanced inoperable NSCLC demonstrate symptoms referable to their disease at the time of initial presentation. Most patients, in fact, have more than one symptom at the onset of their illness. Fatigue and decreased activity were reported by more than 80%, and most patients also experienced cough, dyspnea, decreased appetite, and weight loss. The high incidence of lung cancer symptoms, the occurrence of multiple symptoms in most patients, and the severity of these complaints demand both prompt treatment of the lung cancer and careful attention to the management of each symptom while definitive therapy is in progress.

Although lung cancer can metastasize to virtually any organ, the most common sites of spread that are clinically apparent are the pleura, lung, bone, brain, pericardium, and liver. The presenting complaints of a patient with metastatic spread are largely determined by the specific metastatic organ site involved. For example, bone metastases present with pain and limitation of function in the affected area.

We cannot explain the high incidence of adrenal metastases in NSCLC, detected in 41% of patients at autopsy. Most adrenal metastases are asymptomatic and are discovered incidentally during a staging evaluation or at autopsy. The computed tomographic (CT) scan is the most frequent method of diagnosis. Fine-needle aspiration provides a safe method to confirm the presence of metastatic disease in the adrenal gland if pathologic documentation is necessary, although other imaging studies, such as magnetic resonance imaging (MRI) and positron emission tomography (PET) can be confirmatory. Adrenal hormone insufficiency due to bilateral adrenal metastases from lung cancer is rare but can occur.
Pericardial complications are due to direct invasion, metastatic spread, or a cancer-associated but nonmalignant pericardial effusion. The presenting complaints of dyspnea, cough, and chest discomfort are identical to those of pulmonary tumors or pleural metastases. Because of its slow evolution, signs of pericardial tamponade are often absent. Electrocardiograms are usually not diagnostic. Enlargement of the cardiac silhouette on chest radiograph is often subtle and apparent only on review of multiple prior studies. The frequent association of a pleural effusion in patients with pericardial involvement further impedes the prompt diagnosis of this condition. The echocardiogram provides a safe and rapid diagnostic test for this condition as well as information on the presence and severity of associated cardiac compromise. Pericardial involvement should be considered in any lung cancer patient with dyspnea, cough, or chest discomfort and should be ruled out if a large pleural effusion is present.

**Nonmetastatic Features**

The anorexia-cachexia syndrome and generalized weakness and fatigue are the most common and least understood nonmetastatic complications of lung cancer. In addition, a variety of paraneoplastic syndromes associated with epithelial lung cancer have been identified. Many of these conditions are not specific to lung cancer but have been documented to occur frequently in lung cancer patients owing to the large number of patients with this disease (Table 31.2-4).

| Table 31.2-4. Paraneoplastic Syndromes in Patients with Lung Cancer |
| Hypertrophic pulmonary osteoarthropathy (HPO) occurs frequently in NSCLC patients. Symptoms of bone and joint pain herald the onset of this condition and can be the presenting signs of lung cancer. Clubbing of the digits is observed. The alkaline phosphatase level is commonly elevated, while serum hepatic enzyme levels are normal. Plain radiographs of affected bones demonstrate periosteal inflammation and elevation, and radionuclide bone scans reveal an intense and symmetric generalized increased uptake of the radiolabel, particularly in the distal end of long bones. Symptoms usually respond dramatically to aspirin and other nonsteroidal antiinflammatory agents and disappear after effective definitive treatment of the primary lesion. The digital clubbing is frequently present without other signs of HPO and resolve, as does HPO, with curative therapy. |

**DIAGNOSIS AND STAGING**

In 1985, the American Joint Committee on Cancer, the Union Internationale Contre le Cancer, and the Japanese Cancer Committee agreed to a worldwide tumor, node, metastasis (TNM) staging system. This has been rapidly accepted and is used extensively in the management of lung cancer. A revision of the 1985 version was accepted by the American Joint Committee on Cancer and Union Internationale Contre le Cancer in 1997.

The primary tumor is subdivided into four categories (T1–4), depending on size, site, and local involvement. Lymph node spread has been subdivided into bronchopulmonary (N1), ipsilateral mediastinal (N2), and contralateral or supraclavicular disease (N3), and metastatic spread is absent (M0) or present (M1; Table 31.2-5; Fig. 31.2-7). Four stages of lung cancer have been identified, with significant differences found in 5-year survival, depending on the stage of disease at diagnosis. The accuracy of these stages in predicting survival has been confirmed by many authors (Fig. 31.2-8). Although the 1979 staging system still lacks uniformity in definition and prognosis in certain subsets of locally advanced disease (T3 vs. T4 and N2 vs. N3), on the whole, it is a functional system that should be used for all patients.

| Table 31.2-5. Tumor, Node, Metastasis (TNM) Staging System for Lung Cancer; Including Proposed Changes |

| FIGURE 31.2-7. New International Staging System (ISS). Categories of stage IA, IB, IIA, IIB, IIIA, and IIIB disease. (From ref. 91, with permission.) |
An added advantage of CT scanning is the ability to detect abnormalities below the diaphragm, especially metastases to liver and adrenal glands. For the nodules, often undetected on plain films, may be evident on CT scans. CT scans may also suggest possible areas of local invasion of the primary tumor to chest wall, vertebrae, or mediastinal structures. Small pleural effusions or pleural should be investigated further by more invasive techniques.

In patients suspected of harboring lung cancer, accurate diagnosis with confirmatory cytology or histology is of supreme importance, as is an estimation of the clinical stage of the disease, since clinical staging will determine treatment. Since many of the modalities used for diagnosis are also important in clinical staging, these are discussed simultaneously (Fig. 31.2-9).

HISTORY AND PHYSICAL EXAMINATION

A detailed history and accurate physical examination remain the most important steps in assessing a patient with lung cancer. Smoking history, past exposure to environmental carcinogens, and family history may suggest a higher probability of lung cancer. New symptoms, including a change in cough, hemoptysis, or history of recurrent respiratory infection, are of concern. Symptoms suggesting locoregional spread include chest pain, symptoms of recurrent nerve palsy, or superior vena cava obstruction. Symptoms suggestive of metastatic disease frequently include focal neurologic symptoms, bone pain, or weight loss. Occasionally, patients suffering from NSCLC present with symptoms and signs of a paraneoplastic syndrome but not as frequently as with small cell tumors.

Physical examination should look for signs of partial or complete obstruction of airways, atelectasis or pneumonia, and pleural effusions. Examination of the head and neck, including the draining regional lymph node areas in the supraclavicular area, may demonstrate lymphadenopathy, indicating regional lymphatic (N3) spread.

SPUTUM CYTOLOGY

Once the disease is suspected, a simple and effective method of obtaining a positive diagnosis of lung cancer is sputum cytology. The yield from sputum cytology depends on many factors, including the ability of the patient to produce sufficient sputum, the size of the tumor, the proximity of the tumor to major airways and, to a lesser extent, the histologic type of the tumor.

With sputum samples, up to 80% of central tumors can be diagnosed. The yield is much smaller for peripheral tumors, dropping to less than 20% for peripheral tumors smaller than 3.0 cm in diameter. A 3-day collection of early morning sputa, preserved in Saccamano's solution, appears to be the optimal method of assessment. Squamous cell tumors, being more proximal, are more frequently diagnosed by cytology than adenocarcinoma or large cell tumors. Another factor affecting the ability of sputum cytology to diagnose malignancy is the experience and training of the cytopathologist. Viral infections and other acute inflammations can produce cellular changes that are difficult to distinguish from malignancy, especially adenocarcinoma. Frequently, severe dysplasia is misinterpreted as a malignancy, and vice versa.

Squamous cell tumors, being more proximal, are more frequently diagnosed by cytology than adenocarcinoma or large cell tumors. Another factor affecting the ability of sputum cytology to diagnose malignancy is the experience and training of the cytopathologist. Viral infections and other acute inflammations can produce cellular changes that are difficult to distinguish from malignancy, especially adenocarcinoma. Frequently, severe dysplasia is misinterpreted as a malignancy, and vice versa.

With the introduction of CT scanning in the late 1970s, a giant step was taken in the ability to diagnose and stage lung cancer employing noninvasive imaging techniques. CT imaging can confirm abnormalities seen on plain chest radiographs, can often detect early (<1 cm) lesions that cannot be seen on chest radiographs, and has played an important role in staging of lung cancer, especially spread to areas of the mediastinum undetected on plain films. There is general agreement that to be considered “normal,” mediastinal lymph nodes must be smaller than 1 cm in transverse diameter. Any lymph node larger than this suggests lymphadenopathy and should be investigated further by more invasive techniques.

An added advantage of CT scanning is the ability to detect abnormalities below the diaphragm, especially metastases to liver and adrenal glands. For the
investigation of lung cancer, CT scanning should include upper abdominal scanning to the level of the kidneys to include imaging of the liver and adrenal gland.

Abnormalities seen on CT scan, unless associated with unequivocal signs of malignancy, should be confirmed by more invasive cytologic or histologic investigation. 131

Magnetic Resonance Imaging

MRI investigation of pulmonary lesions has been disappointing and has offered no improvement over CT scanning. Exceptions to this rule include investigation of paravertebral tumors, because imaging of the spinal canal without contrast media is possible. Changes in bone marrow of the vertebral suggestiveness of carcinoma can be detected with greater accuracy with MRI. Also, invasion of tissue planes and vascular structures within the mediastinum and at the thoracic inlet can be assessed with greater accuracy using MRI. Routine MRI of all lung cancer is unnecessary and should be reserved for situations in which local tumor invasion of the mediastinum, thoracic inlet, or paravertebral region is questioned on CT scanning. 132,133,134

Radionuclide Scanning

Until the advent of PET scanning, the ability of radionuclide scanning to diagnose and stage lung cancer was limited by its lack of specificity. Nuclide scanning with gallium citrate or cobalt-bromemycin previously was used mainly for detecting unsuspected mediastinal spread once the diagnosis had been made. The rate of incorporation of the radiopharmaceutical by the primary tumor and its metastatic foci was variable, however, and thus has limited its clinical use in both diagnosis and staging. 135,136 Isotope-labeled monoclonal antibodies have also been investigated as a technique for staging and diagnosing lung cancer. Specific monoclonal antibodies directed to lung cancer cells may prove valuable as diagnostic and staging modalities in the future. Routine radionuclide bone scanning to rule out asymptomatic, unsuspected bone metastases in early-stage disease has never been shown to be cost-effective but is still advocated by many practitioners. In clinical stage III disease, before curative therapy is considered, bone scans may be more cost-effective and certainly are of value when bony syndromes are present. 137

Positron Emission Tomography

During the last decade, an exciting new modality, whole-body PET scanning, came into use. This scanning technique, which has yet to be completely investigated, is based on the uptake of a radioactive glucose, fluorodeoxyglucose, in metabolically active cells. In North America and Europe, PET centers are opening almost on a daily basis. It appears to be exceptionally valuable in diagnosing and staging lung cancer and, in the United States, has now been accepted for reimbursement in investigational settings. Virtually all reports demonstrate higher accuracies than CT imaging and bone scanning in identifying occult metastatic disease in the mediastinum and distant sites. 138,139,140 In addition, it appears useful in differentiating benign from malignant lesions when investigating a solitary pulmonary nodule. However, granulomatous inflammation can be metabolically active, whereas bronchoalveolar carcinomas may be metabolically inactive. This limits PET’s usefulness in diagnosing with absolute certainty the soleologic pulmonary nodule.

The amount of activity seen in the tumor—the standard uptake value (SUV)—has been analyzed with regard to ultimate outcome. It does appear that tumors with high SUV numbers have a poor prognosis, which is independent of other prognostic indices, such as stage of disease. The exact level of SUV activity that is independently prognostic has yet to be defined but appears to be somewhere in excess of 7. In addition, the response to therapy (e.g., induction chemotherapy or radiotherapy) as measured by a declining SUV is being investigated with the use of PET. In the future, chemotherapy response rates may be able to be assessed with repeated PET scans; this is being actively investigated. The response to primary chemoradiotherapy may also be assessed using this technique. The exact place of PET scanning in assessing response to therapy, however, has yet to be defined. 141

PERCUTANEOUS FINE-NEEDLE ASPIRATION

Fine-needle aspiration biopsy of pulmonary nodules is an excellent method of obtaining cytologic and histologic material for positive identification of malignancy. This is performed using fluoroscopic or CT-guided techniques. The positive yield in experienced hands can be as high as 95%. An indeterminate biopsy, however, cannot be considered as negative. False-negative examination results are frequent and must be considered indeterminate unless a positive benign diagnosis (e.g., hamartoma, tuberculosis) can be made. 142

Abnormalities identified by imaging scans in bone, liver, or adrenal gland and suggestive of metastatic disease can be confirmed by fine-needle aspiration biopsy using ultrasonographic or CT-guided techniques, and abnormalities identified on physical examination (e.g., large supravacular nodes) are very accessible to fine-needle aspiration. In some centers, confirmation by PET scanning or MRI has been considered accurate enough and has replaced the necessity of biopsy confirmation (e.g., of adrenal tumor).

BRONCHOSCOPY

Although rigid bronchoscopy was used for many years to confirm the diagnosis of lung cancer, the introduction of flexible fiber-optic bronchoscopy more than 20 years ago has revolutionized this approach. The procedure, although invasive, can be performed under local anesthesia with or without sedation and with minimal morbidity and exceptional safety. Using flexible instruments, the proximal tracheobronchial tree can be examined up to the second or third subsegmental division, and cytologic or histologic specimens can be obtained from identified abnormal lesions. The diagnostic yield of fiber-optic bronchoscopy with cytology brushing and biopsy for histology when a visible lesion is identified is higher than 90%. Even with no visible lesion seen, the bronchoseration the area of suspicion can be irrigated and lavaged, yielding cytologic material. With flexible bronchoscopy and image intensification, peripheral lesions can be reached by cytology brushes, needles, or biopsy forceps, and specimens can thus be obtained. This is most effective in lesions larger than 2 cm in diameter.

The increased yield of postbronchoscopy sputum cytology (as compared with routine induction sputum cytology) renders this maneuver valuable as an added diagnostic tool. The bronchoscope is also valuable for staging. The site of the primary tumor in a major airway may affect its stage (T3 vs. T2 vs. T1), and transbronchoscopic needle aspiration through the airway wall, as popularized by Wang, can confirm the presence of malignancy in enlarged mediastinal lymph nodes (N3 vs. N2 vs. N1).143,144 Care must be taken, however, with this latter technique, because false-positive examination results have been reported, and differentiation between resectable N2 and unresectable N2 disease cannot always be determined by needle aspiration alone; a more invasive approach (e.g., mediastinoscopy, thoracoscopy) may be required. 145

MEDIASTINOSCOPY AND MEDIASTINOTOMY

Mediastinoscopy was developed by Carlens approximately 45 years ago to facilitate staging of superior mediastinal lymph nodes (N2 or N3) before consideration of therapy in patients with lung cancer. It remains the most accurate lymph node staging technique to assess superior mediastinal lymph nodes, which are frequently involved in this disease. The procedure is simple, safe, and effective in experienced hands. In two large series, 146,147 the mortality rate was 0%, and the major morbidity rate was less than 1%. In patients suspected of having inoperable disease by virtue of mediastinal involvement as detected by CT or PET scanning, confirmation by mediastinoscopy is indicated. Depending on the philosophy of management of patients with minimal mediastinal involvement, mediastinoscopy is used to a greater or lesser extent by individual practitioners. Mediastinoscopy is extremely valuable for accurate staging of the disease before neoadjuvant (induction) chemotherapy.

In the future, PET scanning may replace this invasive procedure as a method of accurately identifying superior mediastinal involvement. However, prospective studies have suggested that in “negative” PET scans related to the superior mediastinum, approximately 10% of individuals will be found to have microscopic mediastinal nodal involvement. 148 Whether a negative PET scan result is sufficient to allow primary surgery in patients without the addition of mediastinoscopy is yet to be determined. Granulomatous inflammation within the mediastinal lymph nodes will be identified as increased activity on a PET scan. For this reason, “positive” PET imaging in the superior mediastinum must be confirmed histologically as representing metastatic cancer.

Involvement of anterior mediastinal lymph nodes, which occurs frequently in left upper lobe tumors, can be assessed by the extended mediastinoscopy technique, 149 or by video-assisted thoracoscopic biopsy. Because this is the first level of mediastinal lymph nodes involved in disease, many practitioners defer this examination when cervical mediastinoscopy fails to reveal metastatic disease in the superior mediastinum unless these lymph nodes appear involved on imaging studies. Patients without superior mediastinal involvement have a good prognosis after resection, even when
TYPICAL FOLLICLE-LIKE TUMORS

Follicle-like tumors are a group of benign or low-grade malignant tumors that typically develop in the thyroid gland. They are characterized by the presence of glandular structures that resemble normal thyroid follicles. These tumors can be classified based on their histological features and clinical behavior.

CLINICAL MANAGEMENT

The management of follicle-like tumors depends on the histological type, grade, and clinical presentation. Treatment options may include observation, surgical excision, or radioiodine therapy. In some cases, the use of radioactive iodine may be considered to reduce the risk of recurrence or metastasis.

IMMUNOHISTOCHEMISTRY

Immunohistological stains are commonly used to help distinguish follicle-like tumors from other thyroid neoplasms. These stains can reveal specific markers that are characteristic of certain histological types, which can aid in the diagnosis and classification of these tumors.

SUMMARY

Follicle-like tumors are a diverse group of thyroid neoplasms that can be managed effectively with appropriate clinical and imaging tools. Monitoring and treatment strategies should be tailored to the individual patient's needs, based on their histological characteristics and clinical course.

REFERENCES


Table 31.2-6. Univariable Survival Comparison of Three Large Retrospective Datasets

EARLY-STAGE (I, II, AND RESECTABLE STAGE III) DISEASE

The major clinical prognostic determinants for patients with early-stage disease are the size of the tumor and the presence or absence of lymph node spread. These features are well captured in the TNM staging classifications. Additional clinical adverse prognostic factors are age older than 60 years and male gender and performance of a wedge resection instead of lobectomy or pneumonectomy. Histologic subtype does not provide consistent additional prognostic information. Expression of mucin has been shown to be a poor prognostic factor. Mucin decreases tumor cell aggregation and may facilitate formation of metastases. Overall, clinical stage remains the most important prognostic tool. However, newer diagnostic techniques are likely to continue to refine our precision in staging patients. For example, the detection of disseminated tumor cells in lymph nodes or the bone marrow using immunohistochemical analysis has been shown to correlate with a poor prognosis.

ADVANCED-STAGE (UNRESECTABLE STAGE III AND IV) DISEASE

Because advanced-stage lung cancer has few 5-year survivors, TNM staging is not as valuable in assessing prognosis within these groups. Several comprehensive evaluations have searched for pretreatment prognostic factors in patients with advanced-stage NSCLC. Pretreatment stage, performance status, and weight loss are the most important factors. The definitions of weight loss have varied among the reviews. Many trials evaluated small numbers of women. Those that included larger numbers of women generally found them to survive longer than men. Serum lactate dehydrogenase, a predictor of survival in small cell lung cancer and many other malignancies, also appears to be an independent survival variable. The use of chemotherapy has also been shown to be of prognostic importance. Histologic subtype is of no prognostic importance.

Whether any specific metastatic disease site confers a survival advantage or disadvantage remains controversial. Bone and liver metastases have been cited most often as predicting shorter survival. The total number of metastatic sites or total tumor burden has been shown to influence prognosis. In particular, patients with a solitary metastasis have a better prognosis, and an aggressive surgical approach should be considered. As yet, there is no clinically meaningful model combining the various independent factors that can be recommended either to select appropriate therapy or predict outcome for individual patients.

NEW POTENTIAL PROGNOSTIC MARKERS

With the increasing availability of sophisticated molecular testing, a variety of novel potential prognostic factors has emerged. These factors have largely been studied in earlier-stage disease, owing to the ready availability of surgical specimens. Activation of oncogenes (RAS, MYC, C-ERB B-2, and BCL-2) or loss of the tumor suppressor genes (RB, p53, and p16) have frequently been described. Several trials have shown that patients with diploid tumors survive longer than those with aneuploid tumors. Further study is necessary to define the significance of ploidy and that of specific chromosomal alterations within the lung cancer field.

Epidermal Growth Factor Receptors

After the identification of the presence and often increased numbers of EGFRs on lung cancer cells, trials have assessed the impact of EGFR expression on survival. In one trial, patients with operable EGFR-positive tumors survived significantly longer than those with EGFR-negative tumors (median survival, 71 and 28 months, respectively). In a second trial, overexpression of EGFR in primary lung tumors was associated with poor survival. The presence of EGFR on lung cancer cells is a common finding and may be an important therapeutic target in the future.

Blood Group Antigen

Investigators have reported that the expression of blood group antigen A in tumors of patients with blood group types A and AB was associated with longer survival after surgical therapy than was seen in patients with blood types A and AB who had no blood group antigen A expressed on their tumor cells. This finding has been confirmed in some studies, while others have not been able to show this. This is also true for expression of Lewis’ antigen.

Neuroendocrine Markers

After the observation that tumors with neuroendocrine differentiation, such as small cell lung cancer, are responsive to chemotherapy and the fact that many types of NSCLC contain small cell lung cancer elements, several investigators have looked for evidence of neuroendocrine differentiation in NSCLC. They have done this in the hope of identifying a population of NSCLC patients with enhanced responsiveness to chemotherapy and improved survival. Markers of neuroendocrine differentiation include chromogranin, L-dopa decarboxylase, dense core granules, neuron-specific enolase, Leu-7, and chromogranin were more commonly expressed in responding patients. In the same study, responding patients with two or more positive markers survived longer. In another study using a monoclonal antibody to define neuroendocrine differentiation, approximately 30% of tumors were positive, and the presence of biopsy specimens containing more than 50% positively staining cells was associated with shortened survival in a multivariable analysis. Although they remain an intriguing and potentially useful area of investigation, neuroendocrine markers cannot be used to select a specific therapy or to determine response or survival in patients with NSCLC.
Genetic Markers
The intensive study of the role of oncogenes in the pathogenesis of human malignancy has led to an investigation of oncogene activation in lung cancer. In one study, K-ras point mutations occurred in almost one-third of human lung adenocarcinomas, while it is less common in squamous cell cancers. In a follow-up study, the same authors found that the presence of K-ras point mutations can define a subgroup of operable NSCLC patients at high risk for relapse and overall shortened survival. This has largely been confirmed by other studies.

Mutation of the p53 tumor suppressor gene has been frequently investigated. To date, it has no consistent correlation with prognosis. Reduced E-cadherin expression has been associated with unfavorable prognosis in one trial. Reduced expression has been shown to be associated with a poor prognosis. Expression of BCL-2 leads to inhibition of apoptosis. It has been described in approximately 20% of patients and is a favorable prognostic factor.

Angiogenesis is increasingly recognized as an important factor of tumorigenesis. A variety of end points have been evaluated as angiogenic indicators, including microvessel density or immune staining with anti–factor VIII antibodies. Current evidence supports an adverse prognosis correlating with angiogenesis.

OCCULT DISEASE
An occult lung cancer is defined as a tumor in a symptom-free patient without radiographic findings. In most instances, this is detected by finding abnormal cells on screening sputum cytologic examination. On occasion, an occult lung cancer may be identified at bronchoscopy that has been performed for other reasons (e.g., screening patients with other aerodigestive tract abnormalities). These occult tumors are usually found at an early stage either as in situ disease (Tis) or early T1N0 tumors. A truly occult lung cancer, undetected by radiography and asymptomatic, is almost always found at this early stage of disease. An extremely high proportion (>90%) of such tumors are squamous cell and can be totally cured by surgical removal. In many instances, nonsurgical approaches (e.g., laser ablation, hematoporphyrin ablation, or endobronchial brachytherapy (EBBB) may be employed as curative treatment, especially in noninvasive mucosal tumors.

LUNG CANCER SCREENING
In the hope that the screening of high-risk population groups by sputum cytology and chest radiograph would improve the identification of early-stage lung cancer, the National Cancer Institute Cooperative Early Lung Cancer Group was formed more than 20 years ago and developed protocols for screening high-risk people (e.g., male cigarette smokers older than 45 years). More than 30,000 male volunteers at three centers were recruited and followed up. One-half underwent intensive screening with four monthly sputum examinations and an annual chest radiograph, and the other one-half composed a control group. Each center had different methods of following up the control group, but initial chest radiographs were performed by all study groups.

The results of this trial demonstrated that lung cancers identified by screening methods were more frequently early-stage tumors (40% vs. 15%). Patients who developed lung cancer during the screening period had an overall 5-year survival of 35%, as compared with 13% in the general population. Despite this, there was no impact on overall survival of the two groups when all deaths were considered. It was also found that sputum cytology can identify squamous cell carcinomas and that yearly chest radiographs identify with modest accuracy squamous cell carcinoma and adenocarcinomas. Small cell carcinoma is rarely detected at an early stage no matter what the screening technique.

Other mass screening trials using plain chest radiography performed in Europe have also failed to alter the total death rate in screened versus control groups. All trials demonstrated an improved ability to diagnose lung cancer early. Because these screening interventions fail to alter mortality rates, however, mass screening for lung cancer by chest radiography or sputum cytology (or both) cannot be recommended.

Despite the failure of mass chest x-ray screening, most investigators involved in these studies continue to believe that a person at high risk for developing lung cancer would be prudent to undergo annual chest radiography. Sputum cytology may be worthwhile as an initial screen, limiting further sputum cytology follow-up to those patients demonstrating dysplasia.

Chest Radiography
Although there are no specific recommendations from cancer agencies, plain posteroanterior and lateral chest radiographs have been used on a yearly basis in high-risk people in an attempt to provide an earlier diagnosis of lung cancer. Important in this approach is the ability to compare previous radiographs with recent films to detect subtle changes. As yet, routine CT scans of high-risk people have not been performed as a mass screening technique, and the impact of digitized chest radiography has not been assessed.

Computed Tomography Scans
Most recently, two reports of screening using low-dose spiral CT scans have been reported. In a long-term Japanese study, a significant number of very early primary tumors have been identified using this technique, with significantly improved 5-year survival outcome in treated patients. In a more recent U.S. study, the use of low-dose spiral CT scans has confirmed the ability to detect extremely early lung cancers, with a prevalence rate of 30 per 1000 (vs. 3000 to 4000 with plain chest radiographs). These provocative studies have suggested that screening for lung cancer using low-dose, low-cost spiral CT scans is worthwhile in identifying early tumors and it is hoped, in improving the outcome of patients with lung cancer by virtue of earlier detection. Although the exact cost of this type of mass screening program cannot be estimated in relation to finances or the investigation of other abnormalities identified at the time of CT scan (23% of individuals in the American study had other noncalculated benign nodules requiring investigation), this approach is worthy of further study. Whether the discovery of early treatable cancers ultimately affects the overall long-term mortality in a mass screening population will have to be determined prospectively. However, the 5-year survival of screen-detected stage I lung cancer falls from near 70% to less than 20% if left untreated, suggesting a significant benefit for earlier treatment.

Sputum Cytology
The routine use of annual sputum examination for cancer screening is not cost-effective in the detection of early lung cancer. Dysplastic changes identified at sputum cytology, however, should be followed up. Severe dysplasia indicates a significant chance of ultimately developing lung cancer. These patients should be followed up extremely closely. As noted, Tockman et al, have developed a monoclonal antibody that may improve the yearly detection rate of lung cancer using specific monoclonal antibodies.

Bronchoscopy
Bronchoscopy certainly can identify early mucosal changes suggestive of lung cancer. Tis and T1N0 proximal tumors (usually squamous cell) can be identified with relative ease using flexible bronchoscopy. The improved acuity of video equipment will probably further increase this yield. However, many early lesions can be missed. Hematoporphyrins are preferentially taken up by rapidly dividing cells and, by using hematoporphyrin excitation by specific wavelengths (630 or 410 nm) of light, a characteristic fluorescence occurs in tissue containing the hematoporphyrin sensitizer. This technique can be used to detect these occult neoplasms but has the disadvantages of false-positive results (due to fluorescence of cellular atypia or metaplasia), hematoporphyrin light sensitivity, and limited availability. Only two or three centers have pursued this diagnostic approach.

A new approach exploits spectral differences of autofluorescence in dysplastic and malignant cells without using drugs. This technique, called lung imaging fluorescent endoscopy, has been shown to identify early cellular changes and is being investigated for the detection and localization of early lung cancer, especially proximal squamous cell tumors.

MANAGEMENT
The management of occult lung cancer depends on the stage of disease at diagnosis. Because most of these tumors are early but invasive T1N0 carcinomas, many
are treated by surgical excision. Whenever surgery is contraindicated, curative radiotherapy is indicated. With proximal early-stage tumors, the role of brachytherapy alone or to augment the total dose is unknown, but curative treatment can be applied in this fashion.

In patients who have carcinoma in situ, hematoxylinophyrin or neodymium–yttrium aluminum garnet laser destruction of lesions can been used. Hayata et al. found that early lesions should be less than 1 cm in total surface area. Only a complete endobronchial response to such therapy is acceptable. After such a response, local recurrences are rare. Cortese et al. recently reported using photodynamic therapy (PDT) in 21 carefully selected patients with superficial T1N0 lesions, all of which were squamous cell lung cancers. Using PDT, a complete response was identified in 15 of 21 patients at the Mayo Clinic; ultimately, 9 patients were spared an operation, 12 had recurrent disease after treatment, and 6 had complete responses. Recommendations for primary treatment with PDT in minimal occult tumors await further definition. Only those patients who have had complete responses should be maintained on this type of treatment protocol, and they should be closely monitored with follow-up bronchoscopies. Whenever possible, surgical treatment is indicated for invasive T1N0 tumors and for all lesions persisting after nonsurgical (e.g., phototheray, laser destruction, radiotherapy) treatment.

CHEMOPREVENTION

No chemopreventive strategy has been proven effective for NSCLC, either for at-risk people (i.e., smokers or individuals with occupational exposures) or for patients with treated lung cancer who have an increased risk of second primary tumors. No definite link between the dietary intake of carotenoids, vitamins C and E, or selenium and the pathogenesis of lung cancer has yet been established. Chemoprevention trials of carotene, retinol, and the combinations of folic acid plus vitamin B12 and carotene plus retinol in lung cancer have failed to demonstrate a chemopreventive effect. In two studies, an adverse risk was associated with carotene use.

Recent insights into the biology of lung cancer and cellular differentiation suggest several new lines of research in this area. The most relevant to the chemoprevention of lung cancer appears to be the use of derivatives of retinoic acid, particularly 13-cis retinoic acid. This agent has been demonstrated to control leukoploia (a premalignant epithelial lesion) and to prevent second primary cancers in head and neck cancer patients after treatment of their primary tumors. The association of specific chromosomal deletions, inactivation or loss of tumor suppressor genes, and mutation of specific protooncogenes may allow better definition of people at risk for second lung cancers and development of specific interventions for each genetic event. A nationwide trial in the United States is assessing the value of this association. Early unpublished results appear to be negative.

OVERVIEW OF INVASIVE LUNG CANCER MANAGEMENT: TREATMENT MODALITIES

Surgery and radiotherapy have been used independently to obtain local control of the primary tumor and regional lymphatic drainage. Until recently, chemotherapy had been used in an attempt to prolong symptom-free life in patients with metastatic disease. In the last 20 years, however, combined-modality therapies have become much more prevalent and have spurred intensive investigation. All three modalities are now used as primary therapy and, in combination, have been employed to improve disease-free intervals and ultimate survival.

Historically, surgery has provided the best chance of cure in the management of NSCLC when the tumor can be completely resected. Whenever surgery is not an option because of the inability of the patient to tolerate this approach, primary radiotherapy has been offered for patients with limited locoregional disease. Effective chemotherapy in the management of NSCLC is the last modality to be introduced. Although as a single modality chemotherapy rarely provides a total cure in the management of lung cancer, complete responses do occur with locoregional disease and in patients with metastatic disease. Long-term survival occasionally is possible. This section describes these three treatment modalities and, in general terms, their application. The newer forms of systemic therapy (e.g., biologic therapy) also are discussed.

SURGERY

In NSCLC, when the tumor is limited to the hemithorax and can be totally encompassed by excision, surgery provides the best chance for cure (Fig. 31-2-12). In stage I and stage II disease, when the tumor has not extended beyond the bronchopulmonary lymph nodes, a complete excision is almost always possible. Controversy arises in the management of N2 disease. Ipsilateral (N2) mediastinal lymph node involvement, despite being potentially resectable, remains a contentious issue when indications for surgery are discussed. Whenever a complete excision occurs, the patient is afforded a chance of cure. In clinical staging, it is imperative that the surgeon assess whether the tumor and its involved nodes can be completely removed at operation. N2 disease identified preoperatively (clinical staging), either by imaging studies or mediastinoscopy, affords a much poorer prognosis (<10% 5-year survival rate) than occult N2 disease (30% 5-year survival rate) discovered only at the time of surgery.

Except for a few special circumstances, stage III B disease, by virtue of incontrovertible evidence of contralateral lymph node spread (N3) or primary tumor invasion of vital structures (T4), denotes inoperability, with a small likelihood of success after surgical excision. Similarly, lung cancer that has metastasized to distant organs is usually beyond the realm of surgical excision. There has been success, however, in removing the primary tumor as well as a solitary metastatic focus. In selected patients, this affords long-term disease-free control. Surgical approaches are frequently used to palliate symptoms.

Patient Selection

The preoperative assessment of patients considered for surgical treatment of lung cancer includes clinical staging of the disease to assess its resectability, assessment of the cardiopulmonary reserve of the patient to determine whether the intended pulmonary resection is possible, and assessment of the patient with regard to the perioperative risk of the procedure. Traditionally, patients are suitable candidates for pneumonectomy if the predicted forced expiratory volume in 1 second (FEV1) after pneumonectomy is greater than 1.2 L, the patient does not suffer from hypercapnia, and cor pulmonale is not present. Pulmonary function studies best suited to assess these parameters include spirometry, arterial blood gases, diffusion capacity measurements of oxygen uptake with exercise (mVO2) and, when indicated, ventilation-perfusion scans to estimate the proportions of functioning pulmonary tissue required to be excised. Patients undergoing lobectomy or smaller resection require similar postoperative pulmonary function parameters. Prospective analyses, however, have failed to show differences in pulmonary function studies, including FEV1, after lobectomy or smaller resection. The amount of functioning pulmonary tissue removed by lobectomy or smaller resection rarely interferes with ultimate recovery and function and may actually improve pulmonary function, as it does with volume-reduction operations for emphysema.

A more important factor in preoperative assessment is the ability of the patient to tolerate a general anesthetic and the rigors of the early postoperative period. To prevent postoperative cardiopulmonary complications and decrease the chance of other major postoperative problems, care must be taken to determine accurately...
the patient’s cardiopulmonary status before operation. In the hope of ultimately improving the estimate of these risks, m\(\text{VO}_{2}\), cardiac radionuclide studies, and echocardiography have been introduced. The ability of patients to perform the necessary pulmonary toilet (e.g., coughing, deep breathing) after such procedures requires intensive preparative instruction and a period of rehabilitation when necessary. Pulmonary complications increase remarkably when the FEV\(_1\)/FVC ratio is below 75% of predicted, indicating significant airway obstruction. FEV\(_1\)/FVC ratios of less than 50% of predicted lead to significant postoperative morbidity and mortality. Similarly, it appears that an m\(\text{VO}_{2}\) of less than 15 increases morbidity and an m\(\text{VO}_{2}\) of less than 10 leads to significant morbidity and mortality. However, the exact risk for any single patient cannot be estimated. No single test is absolutely predictive. Clinical judgment is extremely important.

Postoperative Care

A major insult to cardiopulmonary reserve reflected by thoracotomy and pulmonary resection demands that patients undergoing such procedures receive assiduous care and monitoring in the postoperative period. This is best served by a 24- to 48-hour period in a monitored setting. With newer forms of pain control (epidural narcotic analgesia, patient-controlled analgesia, intrathoracic analgesia), the potential for less morbidity after pulmonary resection may be realized.

Surgical Procedures

Until 50 years ago, pneumonectomy was considered the surgical excision of choice in managing all lung cancers. Presently, when complete excision can be obtained by lobectomy, thus sparing functioning lung, this is the preferred resection method, with what appears to be an equal opportunity for long-term success. In the last 20 years, there has been a resurgence of interest in smaller resections and lung-conserving operations. Jensik has been the major proponent of segmentectomy for T1–2N0 peripheral tumors. Survival after such a limited resection and the morbidity and mortality of the operation appeared at least equivalent to lobectomy in retrospective analyses. Newer information, however, suggests that locoregional recurrence is increased and survival is decreased when less than a lobectomy is performed. In proximally situated tumors (T3) for which a pneumonectomy may be required for total excision, lung-conserving operations using bronchoplastic procedures to preserve uninvolved lobes (e.g., sleeve lobectomy) have results equivalent to the more extensive pneumonectomy and should be employed when possible. Even when the proximal pulmonary artery is involved, vascular sleeve resections can be used to preserve pulmonary function (Fig. 31.2-13).

With improved surgical and anesthetic technique and perioperative care, the postoperative mortality rate for surgical resections has decreased remarkably during the last 50 years. Today, pneumonectomy can be performed with a mortality rate of less than 6%, lobectomy with less than 3%, and smaller resections with 1% mortality or less. These mortality figures are significantly affected by the age of the patient, stage of the disease, and extent of resection.

The most common complications after resectional surgery are not technical failures of the operation but cardiopulmonary problems, especially supraventricular arrhythmias and respiratory failure. Improved preoperative assessment and postoperative care to identify high-risk patients and to decrease these complications will ultimately lead to lessened operative risks for the patient (Table 31.2-7).

Table 31.2-7. Postoperative Mortality for Surgical Resections

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Mortality Rate</th>
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</thead>
<tbody>
<tr>
<td>Pneumonectomy</td>
<td>6%</td>
</tr>
<tr>
<td>Lobectomy</td>
<td>3%</td>
</tr>
<tr>
<td>Segmentectomy</td>
<td>1%</td>
</tr>
<tr>
<td>Sleeve Lobectomy</td>
<td>5%</td>
</tr>
<tr>
<td>Sleeve Vascular Resection</td>
<td>1%</td>
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<tr>
<td>Vascular Sleeve Resection</td>
<td>1%</td>
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<tr>
<td>Sleeve Vascular Resection</td>
<td>1%</td>
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</table>

RADIOTHERAPY

Radiotherapy is used for the treatment of NSCLC in various ways. In unresectable disease, it is the primary modality for the cure of tumor. In the postoperative setting, it is used as an adjuvant treatment to improve local control. Radiotherapy is also frequently used for the palliation of advanced and metastatic lung cancer.

The vast bulk of radiotherapy for NSCLC is delivered via external-beam radiotherapy, either through a radioactive source, such as cobalt 60, or more commonly via a linear accelerator. Newer techniques, such as three-dimensional conformal radiotherapy (3D-CRT) and intensity-modulated radiotherapy, are especially improved techniques to deliver external-beam radiotherapy more accurately and with fewer side effects. This allows for a higher dose of radiation to be delivered safely. Brachytherapy is another treatment modality that is used for both curative and palliative intent. Alterations in dose fractionation, such as hyperfractionation, are attempts to advantage of the biologic behavior of tumors and normal tissue to optimize repair of radiation damage and limit tumor repolulation.

The maximum tolerated dose of radiotherapy to the thorax has yet to be established. Standard therapy for unresected disease in this country and Europe has consisted of 60 to 65 Gy over approximately 6 weeks. When patients receiving 65 Gy without chemotherapy were carefully evaluated for local tumor control, only 15% were free of disease after treatment. Radiation resistance to the dose levels typically used represents a major factor contributing to the high incidence of local failure. Higher doses appear to be required for improved local control. A phase I–II dose escalation protocol of hyperfractionated radiotherapy established that a dose of 79.2 Gy can be safely delivered. Currently, dose escalation protocols are under way at many institutions to investigate the upper limits of dose that can be tolerated. Doses as high as 102.9 Gy for small tumors and 81 Gy for large tumors have been delivered safely.

External-Beam Radiotherapy
External-beam radiotherapy is generally delivered via high-energy photon beams generated by a linear accelerator. The challenge in delivering radiotherapy is the balancing of toxicity to the lung, spinal cord, esophagus, and other thoracic structures. To avoid an excessive dose of radiation to the lung, treatment is given from opposed anterior and posterior beams. These beams typically include the spinal cord, and the dose that can be delivered this way is limited. Therefore, oblique treatment fields are used to avoid the spinal cord. However, these fields treat more lung and expose the patient to an increased risk of radiation pneumonitis.

When a patient is simulated for radiotherapy, the treatment field encompasses the tumor with enough margin to account for tumor motion, patient movement, and set-up error. The tumor can be demarcated by many methods. The most straightforward is observing the tumor under fluoroscopy and on plain films during simulation. This has the advantage of helping to determine tumor motion. However, this method might lead to underestimation of tumor dimensions because of inadequate imaging technique and disease not discernible on plain films. Therefore, CT images should be used to help to localize tumor. With the advent of CT-based simulation, tumors can be outlined in the axial plane of consecutive images. A representation of the tumor in three dimensions can then be placed on a digitally reconstructed radiograph. Recently, new imaging modalities, such as [18F]fluorodeoxyglucose-PET scanning, have been used to help to define tumor volumes. The treatment field should be verified on the treatment machine prior to the initiation of radiotherapy. Treatment fields should also be checked weekly so that adjustments can be made.

Acute side effects occurring during the course of radiotherapy are organ-specific and related to the fractionation scheme, total dose, and use of sequential or concomitant chemotherapy or radiosensitizers. They typically manifest in the second to third week of treatment. A significant concern of combined therapy is the increased toxicity, which may outweigh the benefit from both modalities.

Delayed acute radiation toxicity can occur 1 to 3 months after completing treatment but has been known to occur as late as 6 months after completion of treatment. One of the most common long-term effects following radiotherapy is the development of chronic myelitis, which may lead to increased myelitis. Jeremic et al. reported to be as high as 60 Gy; in selected cases in which the tumor is paraspinal, it may be appropriate to treat a small portion of the cord to this dose with the maximal spinal cord dose at or below this level. In some cases, depending on the volume of normal organ treated, contribute to acute delayed toxicity for conventional fractionation with radiotherapy. Similarly, the use of concurrent chemotherapy, as well as novel fractionation regimens, can lower the threshold for delayed tissue reactions.

PULMONARY TOXICITY. Animal models have demonstrated increased vascular permeability after thoracic irradiation. Alveolar surfactant levels also increase after thoracic irradiation and, owing to increased vascular permeability, are detectable in the serum. This endothelial injury may lead to an inflammatory response, causing the clinical syndrome of radiation pneumonitis. Elevated serum levels of transforming growth factor-β, a growth factor known to stimulate connective tissue formation, has been demonstrated in patients developing lung toxicity. Radiation-induced clinical pneumonitis represents the most commonly observed delayed acute reaction, usually occurring between 1 and 3 months after completion. Patients with pneumonitis typically present with shortness of breath on exertion, tachypnea, tachycardia, fever, and nonproductive cough. Chest radiography often reveals an infiltrate within the irradiated volume. These symptoms can mimic an upper respiratory infection, which must be ruled out before embarking on specific treatment related to alleviating pneumonitis. Recurrence or spread of tumor must be considered in the differential diagnosis. Although the effects of radiation pneumonitis are usually self-limiting, it is a potentially life-threatening process. The use of corticosteroids (prednisone) in a starting dose of 1 mg/kg/d, followed by a carefully controlled slow taper, usually resolves most clinical symptoms of pneumonitis. Corticosteroids, however, appear to reduce the ability of alveolar macrophages to release tumor necrosis factor in response to infectious agents, which can lead to recurrent respiratory tract infections in patients treated chronically with these drugs.

Enhancement of radiation damage by chemotherapy in terms of acute and late effects appears to be maximum with concurrent treatment, with a tendency for damage to decline as the interval between drug and radiation is increased. Roach et al. analyzed radiotherapy parameters in 24 combined-modality trials completed before 1994, involving more than 1911 patients with both small cell lung cancer and NSCLC, to determine potential risk factors for radiation pneumonitis when radiation is combined with chemotherapy. Multiple fractionation schemes, total doses, and fraction sizes, along with several chemotherapeutic regimens, were used. The overall incidence of pneumonitis was 7.8%. Factors associated with a higher risk included fraction size higher than 2.67 Gy and total dose. Twice-daily radiation, however, appeared to reduce the risk expected if the same total daily dose were given as a single fraction. Based on this analysis, high dose per fraction when combined with chemotherapy should be avoided.

Late radiation injury is related primarily to the dose per fraction and total dose. Most patients who develop clinical pneumonitis eventually become asymptomatic, although nearly all ultimately develop the radiologic evidence of pulmonary fibrosis in the region of the previous pneumonitis. The degree of late pulmonary toxicity and fibrosis is directly proportional to the volume of normal lung irradiated and the total dose delivered, as well as the fraction size. It is not clear whether chemotherapy actually modifies the latency period for the development of late pulmonary reactions or increases the actual incidence. For most patients, pulmonary fibrosis is an expected and unavoidable consequence of high-dose irradiation. For patients presenting with preexisting compromised pulmonary function, however, and for patients who develop severe clinical pneumonitis, a distortion of the pulmonary architecture by fibrosis can have a major impact on the quality of life and functional status.

ESOPHAGEAL TOXICITY. Since the esophagus has a central location, it is exposed to high-dose radiation during the treatment of most NSCLCs and can be a major dose-limiting factor. Radiation may induce acute esophagitis during the course of therapy. Histologic changes occur during the first week of treatment, although clinical symptoms typically begin during the second through fourth weeks of treatment. Esophagitis presents with mild to severe swallowing difficulty requiring diet modification and nonnarcotic or narcotic analgesics, depending on severity. It is caused by an inflammatory response of the esophageal mucosa.

Chemotherapy and radiosensitizers appear to accelerate the onset and severity of symptoms. In a randomized prospective intergroup trial, the rate of grade 3 or worse esophagitis increased from 1.3% to 65% with the addition of concurrent cisplatin and etoposide to 50.4 Gy thoracic radiation. Acute esophagitis generally resolves shortly after the completion of radiotherapy, with few patients progressing to chronic esophagitis. The rare patient with chronic esophagitis may require dilation to relieve stricture formation.

Hyperfractionated treatment has also been shown to increase toxicity. When 60 Gy given via accelerated hyperfractionation was compared to standard fractionation, the grade 3 or worse acute esophagitis toxicity increased from 9% to 35% (P = .0017).

CUTANEOUS TOXICITY. With the use of megavoltage equipment, treatment rarely causes an acute reaction to the skin, such as erythema or moist desquamation. Moist desquamation can occur in the supraventricular region after a course of high-dose radiotherapy, owing to the sloping surface of the chest at the level of the thoracic inlet. The addition of chemotherapy or sensitizer may also enhance the effects of radiotherapy on the skin.

NEUROTOXICITY. A transient myelopathic syndrome (Lhermitte’s syndrome) can occur during the first 6 months after therapy and is manifested by dysesthesias and paresthesias affecting the upper extremities and shoulder girdles on flexion of the neck. It is related to the total radiation dose, dose per fraction, and length of spinal cord irradiated. Lhermitte’s syndrome is self-limiting and does not appear to be related to the development of late radiation myelitis.

The spinal cord can tolerate conventionally fractionated radiotherapy doses in the range of 45 to 50 Gy, and the radiation oncologist should strive to maintain the maximal spinal cord dose at or below this level. In some cases, depending on the volume of spinal cord treated and the dose per fraction, the tolerance has been reported to be as high as 60 Gy; in selected cases in which the tumor is paraspinal, it may be appropriate to treat a small portion of the cord to this dose with the patient’s understanding of potential toxicity.

Neurotoxicity. Myelitis. Jeremic et al. have reported cases of radiation myelitis in 158 patients who lived at least 1 year after receiving hyperfractionated radiotherapy in fraction sizes of 1.2 Gy per day to a total dose of 50.4 Gy. Once it develops, radiation-induced transverse myelitis is irreversible.

CARDIAC TOXICITY. Radiation injury to the heart is usually manifested as pericarditis, although other complications, such as myocardial ischemia and chronic pericardial effusions, can occur. The tolerance for the entire heart is approximately 40 Gy; up to one-third of the heart can tolerate approximately 60 Gy.

Three-Dimensional Conformal Radiotherapy

3D-CRT represents an approach to improve the local outcome of radiotherapy in NSCLC. The major aim of this method is to decrease the risk of underdosing of the tumor. In addition, it avoids normal structures at considerable dose levels of 40 Gy, and the heart can be effectively excluded from the high-radiation-dose regions. This provides a potential for increasing the tumor dose to levels beyond those feasible with conventional radiotherapy, with a concomitant decrease in the normal tissue complication probability. Single-institution and cooperative group studies of
Intraoperative Radiotherapy

Progression and not treatment toxicity. They reported a 7% risk of massive hemoptysis and concluded that all but one case had evidence of tumor progression. They positioned. Treatment lasts only a couple of minutes, owing to the high activity of the source. High-dose-rate intraluminal brachytherapy has largely replaced both monitored intravenous sedation and the application of local anesthesia to the larynx and trachea. The radioactive bronchoscopic guidance is used to localize the tumor and to position a catheter beyond the site of disease. Patients are generally treated under a combination as dyspnea and hemoptysis. This treatment directly introduces a high-activity INTRALUMINAL BRACHYTHERAPY.

Temporary implants use 125I approximately 4 or 5 days after surgery to allow for proper wound healing. It will be applicable only in a small subset of patients with very early, small tumors and must be considered investigational at this time.

Intensity-Modulated Radiotherapy

Intensity-modulated radiotherapy represents a new approach to radiotherapy wherein the beam within the treatment field is dynamically changed during treatment to give more radiotherapy to areas with tumor and less to areas with normal tissue. Its use is being investigated.

Gated Radiotherapy

Motion of the tumor and of the lung itself during the delivery of each treatment appears to affect the outcome of radiotherapy in inoperable NSCLC. Tumors have been shown to move substantially during quiet breathing, causing inaccuracies in treatment delivery. Underdosage of the CTV may result if the tumor target moves outside the treatment volume during the administration of radiotherapy. To compensate for this motion, a large margin is usually used, consequently increasing the amount of normal lung tissue in the high-dose volume and limiting the amount of radiation that can be delivered.

To overcome this, techniques have been developed to keep the tumor still during radiotherapy. Two distinct techniques have been used to reduce the effect of respiratory motion. The first involves confining the radiation delivery to a specific phase in the breathing cycle by gating the linear accelerator while the patient breathes freely. Breathing is monitored with devices that trigger radiation delivery during specific phases of the patient’s respiratory cycle. The use of gated treatments has been evaluated and offers the advantage of allowing patients to breathe freely while the radiation beam is turned on and off. In the second approach, breathing is controlled either voluntarily by the patient or by using an occlusion valve. This technique is less challenging to perform, since it involves no modification to the treatment machine, but it is not suitable for all patients.

Stereotactic Radiotherapy

Stereotactic radiotherapy and radiosurgery have been shown to be effective in treating brain metastases. Stereotactic radiotherapy is a technique by which a high dose of radiation is delivered to a small, well-circumscribed lesion with minimal dose to surrounding structures. This technique has been applied to lung tumors with good local control. It will be applicable only in a small subset of patients with very early, small tumors and must be considered investigational at this time.

Neutron Therapy

Fast neutrons have been examined as a potential modality to improve the results of therapy for NSCLC. The biologic properties of neutrons differ from conventional photon energies, possessing advantages of high-linear-energy transfer. This high-linear-energy transfer can lead to a number of biologic effects, including greater relative biologic effectiveness, reduced oxygen enhancement ratio, less sublethal and potentially lethal damage repair, and less cell cycle specificity than photons.

A randomized trial of 200 patients was performed using modern neutrons to a dose of 20.4 neutron Gy as compared to 66 Gy of standard photons. It showed no difference in overall survival between the two groups. Grade 3 or worse radiation pneumonitis occurred in 11% and 24% of the patients in the photon and neutron groups, respectively. Therefore, unless a specific group of patients who might benefit from neutron therapy can be identified, it is unclear whether this modality is useful for patients with NSCLC.

Brachytherapy

INTRAOPERATIVE INTERSTITIAL BRACHYTHERAPY AND RADIOTHERAPY. Intraoperative interstitial brachytherapy has been applied in the curative and palliative treatment of NSCLC. Implantation of radioactive sources offers an advantage over external irradiation because of the limited penetrability from source to prescription point, resulting in rapid dose fall-off and sparing of surrounding normal tissues.

Indications for implantation include unresectable or incompletely resected tumors found at thoracotomy: hilar tumors adherent to major vasculature with no clearance for safe dissection; attachment of tumors to mediastinal structures, such as the trachea, pericardium, or esophagus; extensive tumor involvement of the chest wall, spine, or paravertebral tissue when a complete resection is not possible; and recurrent or metastatic endobronchial lesions.

For curative techniques, the selection of radioactive sources depends on the tumor location and the amount of gross disease left after surgery. In circumstances in which more than 1 cm of tumor is left behind, a permanent volume implant is usually required. The area to be implanted is determined, and its dimensions are measured. A nomogram is applied to determine the number of radioactive sources (125I or 103Pd) needed and the proper spacing of the needles, which in turn are based on the strength of the sources and the average dimension of the tumor volume. Hollow needles are inserted into the tumor, and radioactive sources are permanently implanted. For close and positive margins or in the presence of a minimal plaque of residual gross disease, either a permanent planar or temporary interstitial implant may be used. For situations requiring permanent placement of radioactive sources, 125I seeds encapsulated in Vicryl or 103Pd seeds can either be directly sutured onto the area at risk or sewn into a premeasured Dexon or Vicryl mesh, which in turn is sutured onto the target area. A similar technique employing 125I embedded in a Gelfoam plaque has been described. Both techniques allow implantation of radioactive seeds in areas that are near vital structures that cannot be directly sutured.

Temporary implants use 192Ir or 125I at either a low- or a high-dose-rate method of delivering radiation using afterloading catheters. Temporary implants have been advocated for tumors invading the chest wall, superior sulcus, mediastinum, and paravertebral regions when a complete resection is not certain. In general, the catheters are spaced 1 cm apart, with a 1-cm margin around the defined target, and exit out the chest wall. The patient is then loaded with radioactive sources (125I or 103Pd) approximately 4 or 5 days after surgery to allow for proper wound healing.

INTRALUMINAL BRACHYTHERAPY. Intraluminal brachytherapy or EBB is generally used as a palliative treatment for obstructive recurrent tumors causing such symptoms as dyspnea and hemoptysis. This treatment directly introduces a high-activity 192Ir source directly into the lumen of the tracheal or bronchial airway. Flexible bronchosscopic guidance is used to localize the tumor and to position a catheter beyond the site of disease. Patients are generally treated under a combination of monitored intravenous sedation and the application of local anesthesia to the larynx and trachea. The radioactive 192Ir source is then introduced into the catheter and positioned. Treatment lasts only a couple of minutes, owing to the high activity of the source. High-dose-rate intraluminal brachytherapy has largely replaced both direct interstitial implantation of 125I seeds into endobronchial tumors and low-dose-rate endobronchial irradiation.

Side effects after intraluminal brachytherapy include massive hemoptysis, fistula formation, chronic mucosal sloughing, and airway edema. Langendijk et al. examined risk factors for massive hemoptysis. The highest complication rate occurred in patients receiving EBB for recurrent tumor (43%) or combination external-beam therapy and EBB (25%). They also found that patients receiving a single fraction of 15 Gy prescribed to 1 cm had a 50% rate of massive hemoptysis, whereas patients receiving 7.5 Gy x 2 or 10 Gy in a single fraction had an 11% rate. Hensequim et al. theorized that most massive hemoptysis is from disease progression and not treatment toxicity. They reported a 5% risk of massive hemoptysis and concluded that all but one case had evidence of tumor progression. They also reported an 8.7% rate of radiation bronchitis. The risk factors for toxicity in their series included palliative intent of treatment and the length of bronchus treated.

Intraoperative Radiotherapy
Experience with the use of intraoperative radiotherapy for NSCLC is limited. This modality does not appear to show a significant benefit over external-beam irradiation alone or in combination with chemotherapy. The technique involves the modification of a linear accelerator through the attachment of an intraoperative cone for electron-beam treatment. Both the optimal dose and threshold tolerance of mediastinal structures are unknown; however, one fraction is generally delivered intraoperatively at a dose of 10 to 20 Gy. The published results are conflicting. With no reported phase III trials, this modality must be considered experimental.

CHEMOTHERAPY

**General Principles**

Chemotherapy for patients with NSCLC has been under investigation for several decades. Conceptually, it has evolved from the administration in the palliative care setting to its integration into combined-modality curative therapy settings in patients with locoregionally advanced disease.

Currently, chemotherapy as a single-treatment modality can be considered standard therapy for most patients with stage IV disease or stage IIIb disease due to pleural effusion or positive scalene lymph nodes. In these settings, prolongation of survival time and amelioration of clinical symptoms are the goals of therapy. It has been conclusively demonstrated in randomized clinical trials that chemotherapy prolongs median survival times as compared with "best supportive care" and also increases quality of life (discussed later in Stage IV Disease).

In patients with locoregionally advanced disease (stage IIIa or IIIB), traditional therapy has consisted of surgery and postoperative radiotherapy (PORT) or radiotherapy alone for patients with unresectable disease. In these patients, chemotherapy is now used as a component of multimodality therapy. Therapy is given with curative intent, and it is hoped that the integration of chemotherapy will lead not only to an increased overall median survival time but to an increase in the percentage of (cured) patients surviving for long periods (discussed later in "Unresectable" Stage IIIa and IIIB Non–Small Cell Lung Cancer).

Strategies in this setting have included classic adjuvant chemotherapy in patients with fully resected disease and induction (or "neoadjuvant") chemotherapy whereby a specified number of chemotherapy cycles are administered prior to definitive local therapy with surgery, radiotherapy, or both. The simultaneous use of chemotherapy and radiotherapy (concomitant chemo-radiotherapy) has also been intensively investigated. In theory, adjuvant and induction chemotherapy are aimed at improving systemic control of occult microscopic metastatic disease. Decreasing the size (downstaging) of the locoregional tumor burden may also be observed with induction chemotherapy. The delay of radiotherapy to allow for administration of induction chemotherapy has been of theoretic concern, since this could lead to the proliferation of clonogenic tumor cells in an unreponsive tumor. Concomitant chemoradiotherapy may also result in systemic antitumor activity. However, this will be realized only if systemically active doses and schedules of the drugs are administered. In clinical practice, the latter has been challenging, since radiation-related toxicities are usually increased in the presence of chemotherapy (i.e., esophagitis and radiation pneumonitis). Therefore, the primary goal of concomitant chemoradiation may be to enhance the antitumor activity of radiation and increase locoregional control (radiation sensitization or enhancement).

It has been conclusively demonstrated that chemotherapy followed by radiotherapy prolongs the median survival time in patients with unresectable stage III disease when compared with radiotherapy alone. 

**Selection of Specific Drugs**

Most patients with NSCLC present with metastatic (stage IV) disease at initial diagnosis. There is no known curative therapy for these patients. The treatment goals are, therefore, broadly defined to maximize survival time and maintain acceptable quality of life. Because metastatic NSCLC is a systemic disease, its therapy is logically based on the use of systemic therapy. Additional local therapy is used to palliate specific sites of disease.

Most traditional drugs have at best moderate single-agent activity in NSCLC. Generally, higher responses were reported, but it remained unclear whether a more pronounced impact on survival was also achieved. One of the earliest chemotherapy regimens was the regimen consisting of cyclophosphamide, doxorubicin (Adriamycin), methotrexate, and procarbazine (CAMP). In a single-institution study, a response rate of 26% was noted.

Combination chemotherapy was investigated in an attempt to increase response rates. Generally, higher responses were reported, but it remained unclear whether a more pronounced impact on survival was also achieved. One of the earliest chemotherapy regimens was the regimen consisting of cyclophosphamide, doxorubicin (Adriamycin), methotrexate, and procarbazine (CAMP). In a single-institution study, a response rate of 26% was noted.

Subsequent clinical trials incorporated cisplatin, which was thought by many investigators to be the most active single agent in NSCLC in the 1980s. Among the most frequently used combinations were the regimens of cisplatin and etoposide, cisplatin and vindesine, or (in Europe) cisplatin and vinblastine or teniposide. Three-drug combinations incorporating ifosfamide, mitomycin C, and leucovorin were also investigated.

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<th>Table 31.2-8</th>
<th>Combination Chemotherapy Regimens for Non–Small Cell Lung Cancer</th>
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Most of these regimens have in common the combination of cisplatin with a vinca alkaloid or etoposide. They were based on the incorporation of drugs with known single-agent activity, unlike earlier combinations, such as CAMP. Phase II studies of these regimens frequently resulted in response rates of 30% to 50%, suggesting higher activity than the first-generation combination regimens. Because cisplatin is logistically difficult to administer and can result in severe toxicity, direct comparisons of cisplatin-based regimens with non–cisplatin-containing combinations were performed. Although some studies reported increased response rates with a cisplatin-containing regimen, there was no consistent increase in survival. Only three studies reported superior survival with cisplatin.

Another question of interest was whether there exists a dose-response curve for cisplatin's activity in NSCLC. One early study suggested an increase in response rate when increasing the cisplatin dose from 60 to 120 mg/m². A second study, however, did not support this observation. The Southwestern Oncology Group (SWOG) initiated a three-arm comparison of cisplatin administered at 100 mg/m² versus 200 mg/m² per cycle versus a third arm of high-dose cisplatin and mitomycin based on promising phase II data for high-dose cisplatin. The response rates for the three arms were 12%, 14%, and 27%, respectively, and median survival times...
were not statistically different at 5 to 7 months. This study discounted the possibility that the cisplatin dose beyond 100 mg/m² results in significantly higher activity. Currently, most clinical trials use doses of 75 or 60 mg/m² every 3 weeks.

The Eastern Cooperative Oncology Group (ECOG) conducted several comparative studies attempting to identify the most active combination in treating NSCLC. In one such study, a first-generation regimen (CAMP) was compared with three cisplatin-containing regimens, including the combination of mitomycin C, vinblastine, and cisplatin (platinum), or MVP. Although the MVP regimen produced the highest numeric response rate at 31%, the median survival time ranged from 4.5 months (for MVP) to 6.5 months and was not significantly different among the four regimens. In another five-arm study, single-agent carboplatin or iproplatin followed by MVP chemotherapy at the time of first progression was compared with first-line MVP and two other cisplatin-based regimens. Patients treated with initial carboplatin had the longest median survival time; first-line MVP again resulted in the highest response rate but in a lower median survival time (23 weeks, versus 32 weeks for initial carboplatin). Carboplatin and cisplatin are now considered to be of equal activity in NSCLC, with single-agent response rates of approximately 10% and a different spectrum of clinical toxicities.

New Drugs

During the decade of the 1990s, several new drugs with single activity in NSCLC were identified. These include the taxanes, paclitaxel, and docetaxel; the antimebolite gemcitabine; the topoisomerase I inhibitor irinotecan; and the vincza alkaloid vinorelbine. The introduction of these agents into clinical practice has generated much enthusiasm, since they are usually tolerated better than cisplatin, have reproducible single-agent activity of 15% to 25%, and, in some cases, have novel intracellular targets. Current standard regimens for stage IV disease and most clinical trials in earlier-stage disease involving chemotherapy are focused on combinations including these drugs and are discussed further in the stage-specific segments.

BIOLOGIC THERAPY

Investigators have evaluated both nonspecific and specific means to stimulate the immune system of patients with NSCLC. Despite this effort and the proven ability to modulate immunologic end points, no immunologic agent or approach has been shown to induce regressions or improve survival in epithelial lung cancer patients. As with all other forms of systemic therapy for this illness, immunotherapy remains an investigational approach. Patients should be treated only as part of formal protocols. In addition, because cytotoxic chemotherapy given as initial treatment for metastatic NSCLC can reliably induce regressions and prolong survival, inclusion of chemotherapeutic drugs in the overall treatment plan should be discussed.

Several trials have tested nonspecific agents to enhance immune response. After observations that patients who survive an empyema after lung cancer surgery appear to have prolonged survival, tested the usefulness of intraoperative bacille Calmette-Guérin (BCG) in stage I NSCLC and found fewer recurrences and deaths in treated patients than in comparable controls. Confirmatory prospective randomized trials have failed to confirm this result and, in fact, demonstrated a decrease in disease-free interval for patients given BCG. Levamisole has also been tested as a nonspecific immunopotentiator in epithelial lung cancer patients, with no evidence of benefit. The combination of BCG and levamisole as adjuvant therapy has been compared to cyclophosphamide, doxorubicin, and cisplatin (CAP) chemotherapy in patients with completely resected stage I and II adenocarcinoma and large cell carcinoma. This trial showed an improvement in both disease-free survival and overall survival among patients randomly assigned to receive CAP chemotherapy. The accumulated data demonstrate that no nonspecific immunostimulating agent tested has been shown to improve symptoms, response, or survival in NSCLC.

Interferones have been tested alone and in combination in patients with epithelial lung cancer. Trials of human leukocyte interferon and recombinant interferon-a and interferon-b have not shown sufficient activity to warrant either use or further study for this indication. The combination of interferon-a and -b given with cisplatin plus etoposide has been compared with the same chemotherapy given alone. No improvement in response or survival and enhanced hematologic toxicity were observed in the combination chemotherapy plus interferon arm of this study. Preclinical data, however, demonstrated additive effects or synergy when interferon was combined with cytotoxic agents, such as fluorouracil or cisplatin, in several tumor types. A therapeutic clinical benefit has not been established. At present, there is no evidence that interferon-a, -b, or -g, given alone or in combination with chemotherapy, can influence the natural history of NSCLC. The use of interferon for this indication remains investigational.

SPECIFICS OF LUNG CANCER MANAGEMENT

LOCALIZED “RESECTABLE” (STAGES I, II, AND IIIA) DISEASE

When disease is localized to the lung or includes only regional draining lymphatic channels, treatment of the primary disease and these regional lymphatics employs a surgical or radiotherapeutic approach. However, despite lack of evidence of distant metastatic disease at initial staging, patients fall most frequently after treatment because of distant recurrences that indicate that despite primary control, micrometastatic disease was probably present at the time of initial treatment. For this reason, even with disease that can be completely resected, combined-modality treatments are being investigated with fervor to eliminate these presumed micrometastatic foci because of distant recurrences that indicate that despite primary control, micrometastatic disease was probably present at the time of initial treatment. For this reason, even with disease that can be completely resected, combined-modality treatments are being investigated with fervor to eliminate these presumed micrometastatic foci at the time of initial therapy.

Primary Surgery

Stage I and II lung cancer denotes disease limited to the hemithorax, with tumor extension no farther than the adjacent resectable structures peripherally (T3) or hilar nodes proximally (N1). In these cases, whenever possible, surgical excision is the treatment of choice.

In most instances, lobectomy is the resection procedure required. When the primary tumor or lymph node involvement extends to the proximal bronchus or proximal pulmonary artery (T3) or cross the major fissure such that a complete resection is only possible by pneumonectomy, this more extensive procedure should be performed. When resectable adjacent structures are involved, an en bloc resection of the involved area together with the pulmonary resection is necessary.

The role of mediastinal lymphadenectomy as part of the surgical procedure when hilar or mediastinal nodes are uninvolved is debated. The proponents of complete mediastinal lymphadenectomy argue that complete removal of mediastinal lymph nodes improves survival. Certainly, this dissection provides the identification of lymph nodes proximally (N1). In these cases, whenever possible, surgical excision is the treatment of choice.

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TABLE 31.2-9. Results of Limited Pulmonary Resection Performed as an Intentional Procedure, Mainly for T1N0 Tumors

In the LCSG trial, there appeared to be no difference in locoregional recurrence rates whether the tumor measured 1, 2, or 3 cm. However, some surgeons do advocate that for very early tumors (1 cm or less) a lesser resection is justified without the need to perform a lobectomy. However, studies have demonstrated that even in these very early tumors, lymphatic permeation may have occurred within that lobe, and the patient would have been better served by a formal lobectomy. The exact role of lesser resections in these very small (often CT-detected) tumors (0.5 to 1 cm) has yet to be defined. This will be important in managing CT-screening-identified subcentimeter nodules.

After surgical resection for stage I and II lung cancer, the 5-year survival rate without recurrence exceeds 50% in stage I and 35% in stage II disease. In completely resected T1N0 tumors, 5-year survival rates exceed 70%. Approximately 25% of patients are tumor-free at death, suggesting that surgical resection in T1N0 lung cancer renders 80% of patients tumor-free.

T3N0 Tumors

Tumors that invade the chest wall, the diaphragm, the mediastinal pleura, or the pericardium or are situated within 2 cm of the carina constitute the designation of T3. At the Japan National Cancer Center, Naruke et al. reported an overall 5-year survival rate of 26% in 327 patients with this stage of disease. At Memorial Sloan-Kettering Cancer Center (MSKCC), 77 patients with completely resected tumor had a 42% 5-year survival rate, but 48 patients with incomplete resections did not survive beyond 2.5 years. From the literature, it appears that approximately 40% of patients with completely resected T3N0 lesions survive at least 5 years.

CHEST WALL INVASION. Involvement of parietal pleura or chest wall muscle or rib constitutes T3 tumors (Table 31.2-10). The deeper the invasion, the worse is the prognosis. In all instances, it is recommended that the tumor be resected en bloc with the involved chest wall, with a minimum of 2 cm of normal chest wall removed in all directions beyond the tumor. When necessary, plastic reconstruction can be used to reconstitute the chest wall. Prognosis is related to the completeness of resection and depth of chest wall invasion, with no patients surviving 5 years after incomplete resection. Whether simple removal of the parietal pleura in tumors only invading this structure is adequate remains a contentious issue. A recent report suggested that with sufficient care and experience, pleurectomy is adequate in selected T3 tumors.

T3N2 Tumors

Tumors that invade the chest wall, the diaphragm, the mediastinal pleura, or the pericardium or are situated within 2 cm of the carina constitute the designation of T3. At the Japan National Cancer Center, Naruke et al. reported an overall 5-year survival rate of 26% in 327 patients with this stage of disease. At Memorial Sloan-Kettering Cancer Center (MSKCC), 77 patients with completely resected tumor had a 42% 5-year survival rate, but 48 patients with incomplete resections did not survive beyond 2.5 years. From the literature, it appears that approximately 40% of patients with completely resected T3N0 lesions survive at least 5 years.

CHEST WALL INVASION. Involvement of parietal pleura or chest wall muscle or rib constitutes T3 tumors (Table 31.2-10). The deeper the invasion, the worse is the prognosis. In all instances, it is recommended that the tumor be resected en bloc with the involved chest wall, with a minimum of 2 cm of normal chest wall removed in all directions beyond the tumor. When necessary, plastic reconstruction can be used to reconstitute the chest wall. Prognosis is related to the completeness of resection and depth of chest wall invasion, with no patients surviving 5 years after incomplete resection. Whether simple removal of the parietal pleura in tumors only invading this structure is adequate remains a contentious issue. A recent report suggested that with sufficient care and experience, pleurectomy is adequate in selected T3 tumors.

TABLE 31.2-10. Results after Surgical Treatment for Non–Small Cell Lung Cancer with Chest Wall Invasion (T3)

SUPERIOR SULCUS TUMORS. Pancoast described a tumor in the apex of the lung invading the first rib, with associated involvement of the brachial plexus and stellate ganglion, creating Pancoast's syndrome (rib erosion, shoulder pain radiating down the arm, Horner's syndrome). Shaw and Paulson were the first to describe a curative resection in this disease. Since that initial report, most surgeons continue to treat a documented superior sulcus tumor with preoperative radiotherapy of 3000 to 4500 cGy, followed by en bloc resection of the involved lung, chest wall and, frequently, the T1 nerve root. Residual disease at the time of resection is treated with PORT or intraoperative brachytherapy, but the results of these R1 or R2 resections are disappointing despite the adjuvant therapy.

The overall survival rate for patients with completely resected tumors is approximately 40% (Table 31.2-11). Adverse prognostic factors include involved mediastinal lymph nodes (stage IIIA) and bony erosion. In a report from MSKCC, lobectomy with en bloc chest wall resection proved far superior to smaller resections in treating this disease, and N2 disease severely affected prognosis.

Usual contraindications to surgery for superior sulcus tumors include a T4 tumor (vertebral body invasion, subclavian artery, or vein invasion) or clinically evident N2 disease. On occasion, palliative resection of such lesions may be required for pain relief. More recently, aggressive curative approaches to remove and replace these adjacent structures have been reported, with some long-term survivors.  

TABLE 31.2-11. Reported Results after Surgical Treatment for Non–Small Cell Lung Cancer with a Superior Sulcus Lesion (T3)

MEDIASTINAL INVASION. Invasion of the mediastinal pleura, pericardium, or mediastinal fat also constitutes T3 disease. In many instances, en bloc resection of the involved mediastinal tissue can accomplish a complete resection. The results of such surgery for this type of invasion are not well-known. At MSKCC, a review
suggested that only approximately 10% of such patients with completely resected disease survive 5 years. From this review of 225 patients with mediastinal invasion, it was apparent that once mediastinal invasion occurs, frequently major structures are involved (T4), or concomitant mediastinal lymph node disease is present (N2 or N3). In such patients, whenever possible, technical resectability should be determined preoperatively. MRI to detect mediastinal invasion value, then CT scanning to detect mediastinal invasion and mediastinoscopy, are indicated before resection of any of these tumors. Of 225 patients analyzed in this series, only 22% had tumors that were resectable, 43% had totally unresectable disease and, in 34%, tumors were incompletely resected. In this report of the results of mediastinal invasion, brachytherapy was used in incomplete resections, with a surprising 22% survival rate in this small subset of patients. A more recent reappraisal of this group of patients confirmed a 30% to 40% 5-year survival rate in patients with completely resected T3N0 disease.

DIAPHRAGMATIC INVASION. Tumors invading the diaphragm frequently spread along the diaphragmatic pleura, and most patients present with a malignant pleural effusion (T4) that usually is unresectable. In the occasional patient, focal diaphragmatic invasion can be completely resected by lobectomy and en bloc resection of the diaphragm, replacing this structure with a synthetic mesh or fabric. In a recent analysis of our material at MSKCC, only seven patients were found with diaphragmatic invasion, and in only two was disease localized enough to be resected. There are no reports of results of such surgery in a series large enough to analyze results, but one would anticipate a result similar to that for T3 tumors elsewhere.

Stage IIIA Disease

T3N1 disease

Stage IIIA disease includes T3N1 tumors. As with any other T status, once lymph nodes are involved, the prognosis is much worse, thus categorizing these patients as IIIA rather than IIB. Even with completely resected tumors, of 32 patients with lymphatic metastases in T3 lesions, only 20% survived 5 years, and few if any survive 5 years when mediastinal nodes are involved.

T1–3N2 DISEASE. The existence of N2 disease remains the most controversial area for primary surgical management of lung cancer. Although potentially resectable, once ipsilateral mediastinal or subcarinal lymph nodes (or both) are involved by tumor, the ultimate prognosis is much worse. When disease is diagnosed preoperatively either by noninvasive or invasive staging techniques, fewer than 10% of all patients treated with primary surgery survive 5 years, no matter the adjuvant therapy.

Selectivity is important before considering surgery for patients with preoperatively identified N2 disease. Adverse prognostic factors include multiple levels of N2 disease, multiple lymph nodes at one level involved with tumor, adenocarcinoma, and extranodal spread of disease. More than 75% of patients with N2 disease present with disease extending beyond one lymph node station.

“Minimal” N2 Disease. Single-station lymph node involvement with microscopic foci of disease not clinically apparent on clinical staging constitutes most of the subset of patients with minimal N2 disease. This early-stage disease is usually discovered at the time of thoracotomy or at pretreatment mediastinoscopy. Five-year survival rates after surgical resection are 10% to 20% and are higher when a complete resection is performed (Table 31.2-12). Incomplete (R1, R2) resection results in a noncurative treatment, with few if any patients surviving beyond 3 years. Patients found to have multiple lymph node stations involved at final pathologic staging also fare poorly.

### TABLE 31.2-12. Results after Surgical Treatment for Non–Small Cell Lung Cancer with N2 Disease

The criteria for resection of minimal N2 disease include no mediastinal involvement seen on CT or PET scan but found to be present at surgery or mediastinoscopy, identifying a single station of lymph nodes involved with only microscopic disease. At the time of surgery, a complete mediastinal lymph node dissection is warranted whenever N2 disease is suspected or known. Proponents of mediastinal lymph node dissection (vs. lymph node sampling) in all patients treated by surgical resection for lung cancer believe that this extended dissection can identify patients with occult N2 disease who might have benefited by complete nodal dissection. One retrospective study suggested a doubling of 5-year survival rates (15.9% vs. 6.7%) when lymph node dissection is carried out in patients with this stage of disease, although this has not been confirmed by other studies.

“Bulky” N2 Disease. Tumors with mediastinal involvement beyond that described as minimal N2 disease constitute the large segment of patients presenting with stage IIIA disease. This more advanced, bulky, or multistation N2 disease usually can be identified preoperatively and is termed clinical N2 disease. It is considered by most surgeons to be inoperable by primary surgery, with few 5-year survivors identified after surgical resection. Induction therapies before surgery using chemotherapy or chemoradiotherapy have been tested in this group. For most of these patients, primary radiotherapy is still considered the standard treatment for local control.

Combined-Modality Approaches (Including Surgery)

SITE OF FAILURE. Recognition of prognostic and surgical factors that predict for specific anatomic failure patterns can allow selection of patients for local, systemic, or combined therapy. After surgical resection, patients with pathologic stage T1–2N0 tumors who have negative resection margins have survival rates in excess of 50%. For these patients, isolated mediastinal or primary site recurrences are unusual, and there is no rationale for the routine use of PORT. Patients with T1N1 tumors have had 5-year local control rates of 12%. The rate of isolated distant failure for T1N1 disease is 33% and provides a clear need for developing effective prophylactic therapy for systemic and central nervous system spread. For T2N1 disease, the isolated local failure rate is 14%, and the distant failure rate is 36%, again demonstrating the need for effective adjuvant systemic therapy. In view of the fact that isolated N1 metastases are rare in these large surgical series, it is reasonable to consider adjuvant local therapy in patients with documented N1 disease when the mediastinal nodes were neither sampled nor dissected because occult N2 disease may be present.

Survival decreases for patients with N2 disease discovered intraoperatively. When no adjuvant therapy is used for these more advanced patients, thoracic recurrence occurs in approximately 20% of patients even if the resection margins are negative, and distant metastases become even more common, suggesting that both failure patterns need to be addressed if survival is to be improved. Although not proven equally effective, increasingly more conservative resections are being performed for early-stage lung cancers. For sleeve lobectomies, isolated local failure rates are more common than distant failures, ranging from 30% to 52%. Isolated local failure rates are particularly high if the procedure is performed to conserve parenchyma in patients with compromised pulmonary function. This high incidence of isolated local failure provides a basis for the selective use of PORT after sleeve lobectomy. Second primary lung cancers occur frequently in all surviving patients at a rate of approximately 1% each year.

ADJUVANT RADIOTHERAPY. Stage I Disease. The results for selected patients managed with surgery alone (T1–2N0) are reasonably good, and in general these patients require no further treatment. Randomized trials of PORT including N0 patients have found no benefit with the addition of adjuvant treatment, and it is not recommended. In fact, some trials have shown a survival disadvantage in patients receiving PORT, presumably from the toxicity of the radiation. The Medical Research Council recently performed a metaanalysis of nine trials of 2128 patients who underwent complete resection and were randomly assigned to either
no treatment or PORT. Doses of PORT varied from 30 to 60 Gy, and most of the trials used cobalt 60. Patients with stage I disease were included in many of the trials. A significantly increased hazard ratio of mortality in stage I patients receiving PORT was reported.

Stage II and Stage III Disease The role of adjuvant radiotherapy for stage II (N1) NSCLC is controversial but has been recommended in the past because the incidence of local failure with surgery alone is high. A locoregional thoracic failure rate of 31% was observed by the Ludwig Lung Cancer Group for patients with completely resected stage II disease. The Medical Research Council metaanalysis reported a trend toward decreased survival in patients receiving PORT with stage II disease.

The LCSG investigated the efficacy of postoperative mediastinal irradiation in completely resected stage II and III squamous cell carcinoma of the lung. This trial randomly assigned 210 patients to receive 50 Gy in 25 fractions after surgery versus observation alone. The locoregional failure rate (as first site of failure) was reduced from 41% to 3% with radiotherapy for all node-positive patients. Despite this improvement, the increase in locoregional control with radiotherapy did not translate into a survival benefit for stage II patients because more than two-thirds of first failures were distant. The LCSG failed to separate patients with N1 and N2 disease but rather combined and analyzed them as a single group. A trend toward improved survival was observed in N2 patients receiving radiotherapy.

The Medical Research Council of the United Kingdom also completed a randomized adjuvant trial in which 308 patients with stage II and III disease were treated with either 40 Gy or no further therapy, although a trend toward improved survival was seen in the T2N2 subgroup. Again, no overall survival benefit was observed. The metaanalysis performed by the Medical Research Council confirmed these results. The Council reported higher local recurrences in 276 patients in the surgery-only arms of the trials. There were fewer local recurrences in patients receiving PORT. In addition, there was a trend toward improved survival in stage III and N2 patients in this arm, although it did not reach significance. PORT has also been advocated for resected NSCLC invading pleura or chest wall without nodal metastases (T3N0). This issue has never been properly examined in prospective fashion, although the LCSG attempted to address this question in a study that was closed owing to poor patient accrual. The survival rate approaches 50% for patients with chest wall tumors undergoing en bloc complete resection (R0), and there would appear to be little gained with additional local treatment. Therefore, the role of PORT remains controversial. It has not been shown to produce a benefit in early-stage disease. It has been shown to improve local control in patients with mediastinal nodal disease but has no proven survival benefit. There is likely a subgroup of patients, such as those with micrometastatic disease, who will have an improved survival from PORT; however, this patient population has yet to be identified.

Positive Margins (R1, R2 Resections) The presence of microscopic disease after curative surgery for early-stage disease at the bronchial resection margin, chest wall, or vascular margin may adversely affect the prognosis of patients. Yet, despite data that suggest that adjuvant radiotherapy reduces local recurrence, the retrospective literature regarding the efficacy of radiotherapy to improve local control is conflicting.

BRACHYTHERAPY. Intraoperative brachytherapy was used as an adjuvant treatment in 23 patients undergoing video-assisted thoracoscopic limited resections (wedge resections) who were unable to tolerate conventional resections. Seeds implanted into a Vicryl mesh were placed thoracoscopically over the tumor bed and resection staple line. A dose of 100 to 120 Gy was delivered. As yet, there have been no local failures in this treatment group.

Adjuvant CHEMOTHERAPY WITH OR WITHOUT RADIOTHERAPY. Given the large number of patients with resectable disease, few randomized studies of adjuvant chemotherapy in NSCLC have been published. Most of these studies used chemotherapy regimens with limited activity.

The LCSG published two large randomized trials using the CAP regimen. The first trial included patients with completely resected stage II or III adenocarcinoma or large cell carcinoma. Patients were randomly assigned to receive either CAP chemotherapy or immunotherapy with intrapleural BCG and levamisole administered for 18 months. In 141 randomly assigned patients, there was a trend for increased time to recurrence and for prolonged overall survival favoring chemotherapy. The survival of the control immunotherapy group was similar to that of earlier patients treated with surgery alone, and the authors attributed the improved survival in the chemotherapy arm to the effects of chemotherapy.

Another study involved patients with incompletely resected disease who were randomly assigned to PORT alone or radiotherapy and six cycles of CAP. Incomplete resection was considered postoperative residual microscopic or macrometastatic disease or disease in the highest resected paratracheal lymph node. One hundred sixty-four patients were analyzed. The chemotherapy group had a significantly longer time to progression (P = .066); median survival was only marginally improved with chemotherapy, and there was no 5-year survival benefit.

Studies in patients with less advanced disease have also been published. The LCSG compared four cycles of CAP to no further therapy in 269 patients with stage I disease. No benefit was identified for chemotherapy, but only 53% of assigned patients completed chemotherapy. A study testing a lower-dose, six-cycle CAP regimen in T1–3N0 disease showed a benefit in time to recurrence and survival; however, an imbalance in the randomization process resulted in the assignment of more patients with advanced disease to the observation arm. A metaanalysis of all trials of adjuvant chemotherapy failed to demonstrate a decided advantage (5%) to this approach.

Since the CAP regimens are no longer considered the most active available regimens in NSCLC, the question of adjuvant chemotherapy in NSCLC remains open. A large intergroup study in the United States is testing the value of four cycles of cisplatin plus etoposide (the first two cycles given with concomitant radiotherapy) versus radiotherapy alone in patients with completely resected N1 or N2 disease. Additional international studies are in progress.

It is possible that recurrence rates in early-stage disease are too low to be effectively influenced by adjuvant chemotherapy. An alternative concept of influencing survival in patients with stage II disease is to focus on different malignancies. A large North American intergroup study randomly assigning patients with stage I disease to postoperative placebo versus cis-retinoic acid chemopreventive therapy has been completed, but the results have yet to be reported. An interesting Japanese study using 1 to 2 years of oral Tegafur in early-stage lung cancer has demonstrated a survival benefit and reduction of second primary tumors in the treated group.

After complete resection of stage I or II lung cancer or microscopic N2 disease, the current standard must be considered surgery alone without adjuvant treatments. Because of the minimal effect of chemotherapy as assessed in the foregoing recent metaanalysis, larger trials of adjuvant chemotherapy are being carried out in North America and Europe. Patients with completely resected disease should be offered inclusion in these randomized trials whenever possible.

INDUCTION RADIOTHERAPY. After the initial studies were published on the use of preoperative irradiation as a component of treatment of NSCLC, many attempts with this induction approach were initiated in the hope of improving both local control and survival of patients with marginally resectable disease. Preliminary acceptance of preoperative irradiation was based on observations of improved resectability as well as on a significant number of complete responses in a surgical specimen after the use of preoperative irradiation. Reports of survival in patients with tumors arising in the superior sulcus after combined preoperative radiotherapy (where no previous survivals occurred) also contributed to the initial enthusiasm of a preoperative radiotherapy-alone approach. Subsequently, a few randomized trials were initiated to answer this question with larger cohorts of patients. The first such major randomized trial was performed by the U.S. Veterans Administration. With a minimum follow-up of 4 years in surviving patients, no increase in survival was noted in the pretreatment group. The overall survival rate was 12.5% in the pretreatment arm, compared with 21% in the surgery-alone arm, although this was not statistically significant.

In 1975, the National Cancer Institute published two separate but integrated multiinstitutional randomized trials addressing the use of preoperative radiotherapy followed by surgery in both operable and inoperable NSCLC without evidence of preoperative radiotherapy advantage.

It is clear from both the nonrandomized and randomized data that preoperative irradiation alone does not improve long-term survival and has no role as a single-induction modality in the management of marginally resectable or unresectable stage IIIA or IIIB disease. The use of radiotherapy as a single preoperative modality is no longer studied consistently, owing to the advent of effective chemotherapeutic agents. Most current trials investigate the use of preoperative concomitant chemoradiotherapy.

Induction Chemotherapy Phase II studies using a variety of chemotherapy regimens have suggested that preoperative chemotherapy could be administered and may be beneficial in locally advanced (N2) disease. Martini et al had demonstrated that otherwise resectable patients with ipsilateral mediastinal lymphadenopathy as the sole site of distant spread can have 3-year survival rates of 43% and 5-year survival rates of 24% if both the primary tumor and ipsilateral mediastinal nodes are completely resected and followed by mediastinal irradiation. However, the same studies revealed that patients with ipsilateral mediastinal lymphadenopathy large enough to be clinically apparent on a plain chest radiograph had only an 18% resectability rate and only an 8% 3-year survival rate. A
program was developed that used preoperative combination chemotherapy with high-dose cisplatin (120 mg/m²), vinca alkaloids, and mitomycin (i.e., MVP) in stage IIIA patients with clinically apparent (palpable mediastinal spread). In a group of 73 patients, the objective major response rate to MVP chemotherapy was 77%, with a 10% complete response rate. Overall, 60% of patients underwent complete resections, and 12% had pathologic complete responses at surgery. The median survival was 19 months for all patients and 37 months for those with complete resections. The 3-year survival rate for the completely resected patients was 44%, a significant improvement over the prior survival rates for this disease. In the 3-year survival rate for clinically evident N2 disease was only 8% (P = 0.001). Two treatment-related deaths occurred. Using the same MVP chemotherapy program before surgery, Burke et al. reported a 69% chemotherapy response rate, a 49% complete response rate, and a median survival of 19 months for all 35 patients studied. Three randomized trials have compared surgery alone to the combined-modality program of induction chemotherapy before surgery. Despite small numbers of patients in each arm, all reported significant differences in both 2-year survival and distant recurrence rates, favoring the induction chemotherapy arm. These survival advantages have been confirmed in 5-year survival update reports. Larger trials have yet been reported, but a recent abstract of a very large phase III clinical trial of all resectable stages except T1N0 has failed to confirm this survival advantage in the N2 disease subset. More recent phase II trials of chemotherapy have been reported in T4 disease and earlier stage tumors. Because of these successful outcomes in most phase III trials of induction chemotherapy in stage III disease, this approach is now being investigated in earlier-stage disease. At least three phase III trials in North America and Europe have been included, involving patients with clinically evident stage I and II disease, excluding T1N0 tumors.

**INDUCTION CHEMOTHERAPY WITH CONCOMITANT RADIOTHERAPY**. Cisplatin-based combination chemotherapy has been combined with concomitant radiotherapy in an effort to increase the resectability and improving locoregional control and survival over radiotherapy alone followed by surgery. Some series also demonstrated a doubling of both local control rates and distant disease-free survival rates, favoring the induction chemotherapy arm. These survival advantages have been confirmed in 5-year survival update reports.

**Selection Criteria**
The selection of patients for definitive management with radiotherapy depends on several factors, the most important of which are extent of disease, performance status, and pulmonary function. Accurate staging is required to establish and exclude patients with distant metastasis from undergoing radical treatment. In addition to distant metastases, malignant pleural and pericardial effusions are an absolute contraindication for surgery. More recently, a significant effort has been put forth in phase I and II trials to optimize the locoregional therapy in a select group of patients with marginally resectable stage IIIA and IIIB disease. The goals of induction therapy are to convert marginally resectable disease, improve locoregional control, and eliminate distant micrometastases.

**Sequential Chemotherapy and Radiotherapy**
Two phase II trials reported results with induction chemotherapy followed by preoperative radiotherapy and surgery for stage III NSCLC. Skarin et al. treated 41 patients with pathologically determined marginally resectable stage IIIA NSCLC. Included within this group were patients with T3N0 disease and patients with N2 mediastinal metastases. Forty-one patients received two cycles of CAP chemotherapy followed by 30 Gy of chest irradiation. A complete resection was accomplished in 36 of 41 patients (88%). The median survival was 32 months, and the 3-year survival rate was 30%. Systemic treatment failed in 18 of 36 patients (50%), and a median survival of 11 months was realized. Using a sequential chemotherapy regimen of vinblastine and cisplatin, Sherman et al. treated 21 patients with this nonresectable regimen followed by 30 Gy of irradiation to the mediastinum. The overall response rate, resection rate, and median survival were similar to those reported by Skarin et al.

**Concurrent Chemotherapy and Radiotherapy**
Several phase II trials have tested the feasibility of combining a variety of induction chemotherapy regimens concurrently with radiotherapy before surgery to maximize induction results through a trimodal strategy. To determine whether surgical resection is a necessary component of a combined-modality approach in the treatment of stage IIIA and IIIB NSCLC, using the SWOG VP-16-platinum regimen, a North American intergroup effort is completing a phase III trial (chemoradiotherapy vs. chemoradiotherapy plus surgery).

**Primary Radiotherapy**
**EXTERNAL-BEAM RADIOTHERAPY**. Selection Criteria The selection of patients for definitive management with radiotherapy depends on several factors, the most important of which are extent of disease, performance status, and pulmonary function. Accurate staging is required to establish and exclude patients with distant metastasis from undergoing radical treatment. In addition to distant metastases, malignant pleural and pericardial effusions are an absolute contraindication for definitive radiotherapy. In some circumstances, however, a small pleural effusion not seen on chest radiography is discovered on staging CT scanning, rendering the decision to proceed with definitive management less clear. Patients with this finding, in the setting of no significant clinical, laboratory, or radiographic findings that suggest distant spread, should be considered for curative treatment.

No specific criteria exist to define the extent of tumor bulk as unsuitable for treatment with curative intent using conventional treatment planning. In general, however, intrathoracic tumors 8 cm or larger are considered relatively prohibitive for high-dose treatment (55 to 70 Gy) due to excessive pulmonary toxicity. Patients with such large tumors with significant recurrence rates, favoring the induction chemotherapy arm. These survival advantages have been confirmed in 5-year survival reports.
For patients with clinical stage I and II NSCLC that otherwise is technically resectable but in whom surgery is prohibitive secondary to severe medical contraindications, as well as for patients who refuse surgery or have clinical but minimal N2 disease, primary radiotherapy alone offers a reasonable alternative approach and potential for locoregional control and cure. Although surgery has resulted in the highest reported survival rates in stage I and II disease, no modern randomized studies have compared surgery to radiation in a comparable group of patients. The observed differences in results between surgery and radiation are due in part to selection bias because, in many instances, patients referred for radiation have worse performance status, are less rigorously staged, and have poor pulmonary function combined with comorbid illnesses. In addition, most surgical series report results after pathologic staging. Surgical series reveal that approximately 25% to 50% of clinical stage I patients are up-staged (see Fig. 31.2-8). The rate of occult N1 or N2 disease is as high as 56% if the patient has a positive preoperative bronchoscopy. Therefore, it is important to evaluate cause-specific survival as an end point in these studies, since many patients die of intercurrent disease. In addition, many historical series reporting results with radiation alone used inferior equipment and treatment planning by today’s standards and delivered inadequate doses.

More modern series have examined the issues of dose and dose escalation in relation to tumor size, local control, and survival for stage I and II disease. The evidence suggests that radical radiotherapy is an effective treatment primarily for tumors smaller than 3 cm (T1) when treated to doses of 65 Gy or higher. This treatment has a greater probability of complete response rates, local control, and disease-free survival almost comparable to some surgical series. Complete response and local control of larger tumors, however, appear less likely with standard radiation fraction schedules and doses, despite availability of modern equipment and CT-based planning.

The need effectively to treat the mediastinum in patients with no evidence of nodal spread has been challenged. The inclusion of large volumes of lung within a radiation port, especially for peripheral T1 and T2 tumors, to prevent regional failure must be balanced against the potential for increased toxicity. The rationale for treating the local tumor volume alone appears justified when the patient's outcome is not subject to negative impact if the regional lymph nodes are not included. The evidence appears to support the use of smaller target volumes to deliver higher doses without compromise of the regional outcome. The regional failure rate is typically less than 10% in reported series where elective nodal areas were not treated. In one series, most patients did receive elective nodal irradiation but still had a failure rate approaching 10%, which suggests that a typical elective dose of 40 Gy is not enough to control occult disease. Selection for this approach would be improved by pretreatment invasive mediastinal staging.

The issue of split-course versus continuous-course radiation has also been examined for stage I and II NSCLC with mixed results and has generally been discouraged when treating with curative intent. Split-course radiotherapy is a reasonable alternative for elderly patients or patients living at great distances in whom a protracted course of treatment is impractical. It is also potentially more cost-effective.

**Results**

One of the earliest studies demonstrating the curability of medically inoperable lung cancer with radiation alone was reported by Hilton and Smart in the early 1940s and 1950s. Thirty-eight patients with stage I or II NSCLC were treated with curative intent. Doses of 50 to 55 Gy were prescribed for squamous cell histology, delivered to the primary site only, and doses of 40 to 45 Gy were prescribed for undifferentiated cancers, delivered to the primary site and mediastinum. Despite inadequate doses, frequent treatment breaks to allow recovery for acute reactions, orthovoltage equipment, unsatisfactory staging, and a mix of histologies, the 2-year and 5-year survival rates were 47% and 17%, respectively.

In 1963, Morrison et al. reported the results of the only randomized trial comparing surgery with radiation for stage I and II NSCLC. Although the outcome for surgery was superior to that for radiotherapy alone, the trial was severely flawed. This study of patients randomly assigned to radiation alone suffered from small patient numbers, the patients received low radiation doses in the range of 45 Gy, and the study included small cell histology (approximately 30%). Additionally, almost 30% of patients undergoing surgery received adjuvant PORT.

Historical series reporting results with primary radiotherapy alone are the victims of selection bias. Many of the same medical contraindications that prohibit surgery, such as age, performance status, severe intercurrent medical illness, and poor pulmonary function, are known to be significant prognostic factors for survival. Patients referred for radiotherapy are more likely to be elderly and to be at greater risk for death from intercurrent diseases. Patients receiving radiotherapy alone generally have also undergone less extensive staging (clinical versus pathologic) than those in surgical series reporting pathologic versus clinical outcome. Some patients discovered on mediastinoscopy to harbor N2 disease may be excluded or separated from outcome analyses in surgical series. Sandler et al. demonstrated the importance of rigorous clinical staging in selecting true stage I NSCLC for primary radiotherapy. In their series of 77 patients with clinical stage I NSCLC treated with primary radiotherapy, treatment in only 2 of 12 patients who underwent “excellent” staging evaluation failed locoregionally at 3 years, in contrast to that in 22 of 24 (87%) and in 30 of 41 (79%) with locoregional failure for “good” or “other” staging, respectively. With the advent of noninvasive assessment of nodal regions through CT and PET, some of this selection bias might diminish.

Tumor size is a prognostic factor in almost every retrospective series reported. For example, Krol et al. found that tumors smaller than 4 cm had a 35% overall survival at 3 years and tumors larger than 4 cm had a 13% 3-year survival. There has also been some evidence that higher doses (>65 Gy) lead to improved survival. Jeremic et al. and Morita et al. have reported treating patients with some of the highest doses seen in the literature, 69.6 Gy and 65 Gy, respectively, and report favorable overall survival. These two factors, tumor size and dose, are interrelated, since a very large tumor, technically T2, is often difficult to treat to high doses secondary to pulmonary toxicity. Squamous cell histology has been shown to be a positive prognostic factor, as has younger age.

**TABLE 31.2-13. Results for Patients Treated with Radiation Therapy Alone for Early-Stage Non–Small Cell Lung Cancer**

**PRIMARY BRACHYTHERAPY.** Hilaris and Martini described the use of brachytherapy at MSKCC for medically inoperable NSCLC in the setting of a tumor that was determined to be unresectable intraoperatively. Permanent or temporary implantation was used as a local conformal boost or as primary treatment alone. These authors reported the results of 55 patients with medically unresectable stage I and II NSCLC. Most (44 of 55) patients underwent biopsy only. The remainder underwent subtotal resection. After surgery, 24 patients received additional external-beam irradiation (median dose, 40 Gy). An actuarial 5-year overall survival of 32% was observed, with a local control at 5 years of 65%. Broken down into stages, the local control rates for T1NO, T2NO, and T1–2N0–1 disease were 100%, 70%, and 70%, respectively. The addition of external-beam irradiation is probably not needed. The best radiotherapy results are still inferior to most surgical series, although there are many confounding factors to account for a portion of this difference. It is hoped that with improved staging and dose delivery, the results with primary radiotherapy will improve.
imaging.

Perol et al. examined the use of high-dose-rate EBB for early-stage NSCLC limited to the endobronchus that was smaller than 1 cm and not visible on CT scan. Nineteen patients were treated with 7 Gy per fraction every week for 3 to 5 weeks. The 2-year overall survival and local control rates were 58% and 75%, respectively.

Tredaniel et al. reported the results of 29 patients with endoluminal localized tumor treated definitively with EBB after loading sources prescribed to a depth of 1 cm from the source center. Complete macroscopic regression was seen in 21 of 25 evaluable patients, with histologically complete responses in 18 of 25. At 23-month follow-up, the median survival had not been reached.

**"UNRESECTABLE" STAGE IIIA AND IIIB NON–SMALL CELL LUNG CANCER**

Whether stage IIIA or IIIB disease is considered unresectable depends, to a large degree, on the experience and attitudes of physicians treating the patient. What one surgeon considers unresectable, another with an aggressive surgical attitude may deem completely resectable. Despite this, when stage IIIA disease is extremely bulky and enlarged lymph nodes surround vital structures in the mediastinum, it is unlikely that any prior surgery or surgical approach will allow a complete resection or significant cure. In centers with more aggressive attitudes, these “unresectable” tumors have become eligible for combined-modality programs that include surgery. Despite this, the standard treatment for locoregional unresectable disease does not include surgery.

Patients with unresectable stage IIIA or IIIB NSCLC have traditionally been treated with radiotherapy alone. Since all known macroscopic disease is confined to the chest, therapy is in theory given with curative intent. However, only 5% to 10% of patients survived beyond 5 years. This was frequently owing to distant disease progression (outside the radiation field), which occurs in up to 70% of patients and reflects the presence of systemic micrometastases at the time of initial therapy. Therapy in a large proportion of patients also progresses within the irradiated volume, reflecting the inability of radiotherapy to eliminate all macroscopic disease. Efforts to increase cure rates have, therefore, attempted to increase both locoregional and systemic control. In practice, induction chemotherapy or concomitant chemoradiotherapy (or both) has been most frequently studied to achieve these goals.

**Aggressive Surgery**

Stage IIIB disease encompasses patients with a T4 or an N3 lesion, both of which are usually considered unresectable disease. Radiotherapy, chemoradiotherapy, or a combination of both remains the standard treatment for these patients. In general, they are not referred for surgical treatment. Nevertheless, in a large retrospective study, patients with surgically resected stage IIIB disease had an overall 5-year survival rate of 6%. There is a danger of clinically overstaging a tumor as T4 and denying a patient with completely resectable T1–3 disease the opportunity of a curative resection. T4 disease in highly selected patients can be completely resected, and long-term survival can be achieved in some of these patients. In this group of patients as well, combined-modality therapy (including surgery) is being investigated (discussed in Induction Chemoradiotherapy).

**T4 TUMORS.** T4 tumors include those invading mediastinal structures (the carina and trachea, the heart and great vessels, the esophagus or vertebral body) as well as the presence of a malignant pleural effusion. Naruke et al. reported a 5-year survival of 8% in 104 selected patients after resection of such a T4 lesion.

**Carinal Invasion.** Although primary lung cancer invading the carina is generally considered unresectable, pneumonectomy with tracheal sleeve resection and direct reanastomosis of the trachea to the contralateral main stem bronchus can be accomplished, with reported 5-year survival rates approaching 20%. In most series reported, patients were highly selected, with most long-term survivors having T4N0 tumors.

Anastomotic dehiscence with bronchial fistula formation and postoperative pulmonary insufficiency are major postoperative problems and are the main cause of the high operative mortality rate, which ranges from 11% to 27%. Only highly selected patients without N2 disease should be offered such a resection. For this reason, prior to resection of such a tumor, mediastinoscopy should be considered mandatory. In some patients, “extended” sleeve lobectomies (resecting the carina) can be used to preserve pulmonary function.

**Invasion of Superior Vena Cava.** Involvement of the superior vena cava has been treated occasionally by en bloc resection and graft replacement. Long-term survivors reported in the literature are limited to case reports. In a retrospective analysis of 18 patients with superior vena cava invasion at MSKCC, there were no 5-year survivors after resection. Preoperative distinction of superior vena cava invasion by the tumor (T4) or by its involved mediastinal lymph nodes (N2) can be difficult. Reported series include only few cases, and the significance of this finding cannot be assessed. It appears likely, however, that only T4 and not N2 lesions can occasionally be cured with such a radical resection.

**Invasion of Myocardium, Aorta, Esophagus, and Vertebral Body.** Surgical resection resulting in complete excision of a primary tumor with other mediastinal organ invasion is usually not possible. Palliative incomplete resections have not demonstrated survival or palliation benefit. In the series from MSKCC, although not all patients underwent resection of the primary tumor or part of the invaded organ, there were no 5-year survivors among 19 patients with aorta involvement and 3 patients with atrial invasion, but 1 patient of 7 (14%) with esophageal invasion lived beyond 5 years. Despite these results, a tumor with limited invasion of the atrial wall can occasionally be completely resected with the hope of an occasional cure.

**En bloc resection of the lung with part of the involved aorta, esophagus, or vertebral body, not uncommon in the treatment of superior sulcus tumors, may result in long-term survival for selected patients. PORT may be of benefit in these situations to augment local control. An analysis from Japanese investigators suggested that long-term survival is limited to patients with minimal atrial or aortic adventitial involvement in tumors invading great vessels.**

**Pleural Effusion.** Approximately 5% to 10% of patients with lung cancer present with a nonmalignant pleural effusion, a result of atelectasis, obstructive pneumonitis, lymphatic or venous obstruction, or pulmonary embolus. Despite being nonmalignant, an effusion evident on prior chest radiograph has a poor prognosis, with a 5-year survival. Investigators at the Mayo Clinic demonstrated that even cytologically negative pleural effusions evident on chest radiographs were predictive of surgical unresectability in 95% of these patients. However, they concluded that in patients with cytologically negative pleural effusions, unresectability must be documented surgically. On the other hand, Naruke et al. reported a 40% 5-year survival rate in 112 patients with nonmalignant effusion, identical to the 5-year survival rate in 1298 patients without effusion.

Even with malignant pleural effusions, occasional 5-year survivals have been documented when all disease has been eradicated. In general, however, malignant pleural effusions, cytologically proven, indicate incurable disease by a surgical approach and are usually treated initially with primary chemotherapy. However, one should never consider a pleural effusion malignant without cytologic or histologic proof. A “bloody” pleural effusion may be due to a traumatic thoracenostesis or concomitant pulmonary infarction and not indicate T4 disease.

**N3 DISEASE.** The role of surgery in preoperatively identified N3 disease previously considered totally inoperable has now been reexamined in phase II trials. Hata et al. have investigated the use of a two-field lymphadenectomy, including both mediastinal exenteration and supraclavicular node dissection for this group of patients. The exact role of postoperative therapies combined with this has not been discussed. The results of such treatment still await long-term reporting. Also, the induction therapies, especially chemoradiation, have been investigated by the SWOG group and others. It does appear that with very intensive induction therapies, some patients survive long term. It does not appear, however, that these survivals are improved by the addition of surgery. In fact, in many phase II trials, no attempt was made to remove the involved N3 lymph nodes. Surgery was directed toward removal of the primary tumor and N2 nodes.

**Pleural Infusion.**
Adjuvant and Neoadjuvant Therapies

After complete resection in patients proven to have T4 or N3 disease, radiotherapy has been usually recommended as adjuvant treatment because of the high incidence of locoregional failure after aggressive surgery for this advanced tumor. Because of the paucity of patients reported to have undergone this treatment, the exact role of adjuvant radiotherapy cannot be assessed. It is in this subset of tumors that neoadjuvant therapies have been investigated in many phase II trials. It does appear that clinically staged T4 tumors (especially T4N0 disease) do reasonably well after this combined-modality approach. In one such study, patients with clinically evident T4 tumors, including superior vena caval syndrome, tracheal involvement, and posterior mediastinal invasion, were treated with MVP chemotherapy followed by surgery. Sixty-three percent of patients underwent a complete resection, and overall survival at 4 years was 19.5%. Despite these encouraging results, in most instances T4 and N3 tumors cannot be resected completely and are usually considered for combined-modality therapy, using radiotherapy as the primary control mechanism.

RADIOTHERAPY. The 2-year survival rate for patients with unresectable locally advanced NSCLC receiving supportive care alone is approximately 4%. Historical series examining the ability of thoracic radiotherapy to have an impact on the natural history of locally advanced NSCLC demonstrated mixed results. Higgins and Shields reported the results of a randomized trial by the Veterans Administration in which male patients with a variety of histologic subtypes of lung cancer, including small cell lung cancer, were prospectively randomly assigned to receive supportive care only or external-beam radiotherapy. Two hundred forty-six patients were treated with platin, and 208 males patients were treated to doses of 40 to 50 Gy. The results of the trial were reported with 1-year minimum follow-up. Most patients had performance status of less than 70. In addition, the radiotherapy was inadequate by modern standards, both in terms of the dose delivered (40 to 50 Gy) and the equipment used (orthovoltage). Radiotherapy alone provided a modest but significant improvement in survival at 1 year, as compared with that in patients who received supportive care only (22% vs. 16%, respectively). Other earlier trials of thoracic radiotherapy for unresectable NSCLC despite inadequate doses also showed a modest but significant improvement in 2-year survival rates in the range of 9% to 18%.

 Cox et al. analyzed the patterns of failure in locally advanced unresectable NSCLC treated with radiotherapy alone and found that the median survival was increased from 6 to 12 months when the primary tumor was controlled. However, they found that 75% of patients with squamous cell cancer died of complications secondary to intransit or parietal tumor progression, as compared with approximately 40% of patients with either large cell cancer or acinar cell carcinoma. In contrast, Berry et al. using similar doses of radiotherapy, could find no improvement in survival with the use of thoracic irradiation as compared with chemotherapy alone. A retrospective study from British Columbia that controlled for tumor stage and other prognostic factors reported improved survival of 79 days in patients receiving high-dose palliative radiotherapy and survival of more than a year in patients receiving radical radiotherapy.

In a multinstitutional cooperative trial, Johnson et al. reported the results of 319 patients with locally advanced unresectable NSCLC without evidence of distant metastases who were randomly assigned prospectively to one of three arms: chemotherapy alone with vindesine, 3 mg/m2 weekly; standard thoracic irradiation to a dose of 60 Gy in 6 weeks; or combined vindesine and thoracic radiotherapy. Although the overall response rate was superior in the radiotherapy arms (radiotherapy alone, 38%; vindesine plus radiotherapy, 37%), there was no difference in survival in the vindesine-alone arm (16%) and in the radiotherapy arm (65%); both median survival and overall survival were also comparable in all three arms. This study has been criticized, however, for the large number of patients in the vindesine-alone arm who received radiotherapy and for the number of patients involved, which was inadequate to detect a difference in survival. A randomized trial of low dose thoracic radiotherapy compared to cisplatin and etoposide alone reported a higher response in the radiotherapy arm but similar overall survival.

Although it seems clear that thoracic radiotherapy does offer a survival advantage to patients with disease limited to the thorax, the poor results of these earlier studies led the RTOG to investigate methods of improving outcome with radiation alone by initially concentrating on dose intensification with conventional fractionation schedules, more recently, using altered fractionation. In addition, they have attempted to identify appropriate selection criteria and prognostic factors for the various approaches and apply the use of innovative treatment planning and technology.

Standard External-Beam Radiotherapy. The earliest trial by the RTOG for unresectable NSCLC focused on dose intensification by attempting to establish the optimal schedule of standard fractionated radiation alone. Protocol 73-01 was limited to 379 patients with either medically inoperable stage I or II or unresectable stage III NSCLC of various histologies. Patients in this trial were randomly selected for one of four dose-escalating arms, including 40-Gy split-course, or 40-Gy, 50-Gy, or 60-Gy continuous-course thoracic irradiation delivered in 4, 5, or 6 weeks with a daily fraction size of 2 Gy. Analysis of patterns of failure and survival showed a higher complete response rate (24%) and 3-year survival rate (15%) with 60-Gy continuous-course radiotherapy, in comparison with lower doses of continuous- and split-course irradiation (40 to 50 Gy). The failure rate within the irradiated volume was 53% to 58% for 40 Gy, 49% for 50 Gy, and 35% for 60 Gy. This improvement in local control was still appreciated near 5 years later. The median time to any failure increased from 8 to 19 months as dose was increased from 40 to 60 Gy. Overall, patient who achieved a complete tumor response also experienced improved survival, as compared with partial responders or patients with stable disease. The 3-year survival rate in complete responders was 23%, as compared with 10% in partial responders and 15% in patients with stable disease.

By escalating the total dose from 40 to 60 Gy, this trial established a significant dose-response relation between local control and short-term survival. Despite the primary local control and survival advantages in patients experiencing a complete response and in patients receiving a dose of 60 Gy, the overall median survival for patients receiving 40 Gy was 9.6 months, as compared with 10.1 months for patients receiving 50 to 60 Gy. In addition, the 5-year survival rate for all patients in this trial was approximately 6%, with no significant differences among the four arms.

Brachytherapy and External-Beam Radiotherapy. Huber et al. randomly assigned 108 patients to either conventional radiotherapy (60 Gy) alone or an EBB boost of 4.8 Gy before and after conventional radiotherapy. There was a trend toward improved local control in patients receiving brachytherapy, although it failed to reach significance. There was no difference in overall survival. Criticisms of the trial include that the majority of patient treatment significantly deviated from the protocol. However, it does suggest that EBRT might play a role in the treatment of primary disease.

A pilot study examined the use of Gelfoam radioactive plaques in addition to postoperative external-beam radiation in patients who have had an R1 or R2 resection of stage III NSCLC. In 12 patients, there was a local control rate of 82% and overall survival of 45%. Whether this is an improvement from standard PORT for these patients remains to be examined in further studies.

Three-Dimensional Conformal Radiotherapy. In a dose-escalation protocol using 3-D CRT at the University of Michigan, patients were treated with doses ranges from 69.3 to 102.9 Gy. The researchers have reported a single case of acute grade 3 pneumonitis and five cases of acute grade 2 pneumonitis. Recently, patients with advanced disease have been receiving neoadjuvant chemotherapy in addition to radiotherapy. The median survival in patients with stage III or recurrent disease was 16 months, and 2-year overall survival was 36%.

Graham et al. reported the results of 3-D CRT from Washington University. They have treated patients to a dose of 60 to 74 Gy. Elective nodal irradiation was given to all except those patients with poor pulmonary function. These investigators report a 2-year survival rate of 53% with this technique. The University of Chicago reported a 2-year local control and a survival rate of 23% and 37%, respectively, in patients treated with doses ranging from 60 to 70 Gy. The MSKCC reported a 2-year local control, disease-free survival, and overall survival rates of 36%, 11%, and 22%, respectively, in a group of patients with advanced-stage disease.

Elective Nodal Irradiation. Standard radiotherapy typically involves a dose of 40 Gy to the entire mediastinum, supraclavicular fossa, and ipsilateral hilum, even if there is no evidence of disease in these areas (e.g., T4N0 tumors). It has been shown that this elective treatment can significantly add to the morbidity of radiation. Many centers have made the decision to eliminate elective nodal irradiation in an effort to increase the dose to the tumor. When RTOG trials were reviewed to estimate the clinical impact of omitting nodal irradiation, it was found that when the ipsilateral hilum and mediastinum were incorrectly treated, there was an increased risk of progression. The MSKCC reported an elective nodal failure rate of 8% and a local failure rate of 65%, which suggests that until regions of known disease can be effectively treated, there is probably no advantage to treat the entire mediastinum and supraclavicular region electively when T4N0 tumors are being treated. Invasive staging or PET scanning may improve decision making.

Altered Fractionation Radiotherapy. Altered fractionation implies any deviation from standard fractionation of 1.8 to 2 Gy delivered once daily, 5 days weekly for 6 to 7 weeks. Several forms of altered fractionation, such as continuous hyperfractionated accelerated radiotherapy (CHART), or variations of these have been investigated. The basic goal of altered fractionation strategies is to deliver higher total doses of radiation to improve the local outcome without increasing late normal tissue toxicity. Altered fractionation schemes exploit the significant differences in the capacity of late-responding and early-responding tissues to repair
radiation cellular damage.

Hyperfractionation Hyperfractionated radiotherapy employs more than 1 fraction per day, using fraction sizes that are smaller than those used with standard fractionation (1.1 to 1.5 Gy per fraction versus 1.8 to 2 Gy per fraction). Thus, hyperfractionation uses multiple small fractions per day to deliver a higher total daily dose and final total dose to improve tumor cell kill without increasing late toxicity and accepting increased but recoverable acute toxicity. 

The RTOG initiated a phase I and II trial to evaluate 1.2-Gy twice-daily fractionation for locally advanced unresectable disease. Eight hundred eighty-four patients were randomly picked to receive doses of 60.0, 64.8, and 69.6 Gy, using 1.2 Gy twice daily with a minimum of a 4-hour interfraction interval. After reasonable time had elapsed to evaluate both acute and late effects, which were considered tolerable, patients were further assigned to one of the two lowest dose arms. In a favorable subgroup of patients, the 69.6-Gy dose results appeared significantly better (P = .002) than results with standard fractionation in comparable patients from an earlier RTOG study and the other arms of the trial. No increased toxicity was seen in the higher-dose arms to account for the decreased survival as compared to the 69.6-Gy arm. Based on these results, the RTOG began a phase III trial comparing 69.6 Gy given via hyperfractionation and 60 Gy given via standard fractionation of thirty-2-Gy fractions. The third arm of the trial replicated the study arm of CALGB protocol 8433: induction chemotherapy with cisplatin and vinblastine followed by 60 Gy of irradiation. The 5-year survivals for standard fractionation, hyperfractionated radiotherapy, and induction chemotherapy plus radiation were 4%, 5%, and 8%, respectively. Since survival in the chemotherapy-plus-radiation arm was significantly higher. As yet, there is no clear survival advantage that can be demonstrated for hyperfractionation as compared to standard radiotherapy. However, many trials continue to use this hyperfractionation regimen of 69.6 Gy. Further studies are needed to find the maximum tolerable dose of radiation with either hyperfractionation or standard fractionation and compare it to 60 Gy.

Accelerated Radiotherapy RTOG trial 84-07 examined the role of an accelerated concomitant boost of radiotherapy. Patients received 45 Gy over 5 weeks to the primary tumor and mediastinal lymph nodes. Two to three times a week, a concomitant boost of 1.8 Gy would be delivered only to the primary tumor and involved lymph nodes. A dose of 25.2 cGy via concomitant boost (70.2 Gy) was found to be tolerable. Two-year survival was 21% for the higher-dose patients. Another RTOG phase II trial (83-12) demonstrated a 2-year survival rate of 25% and a 3-year survival rate of 16%.

Continuous Radiotherapy CHART employs many radiobiologic principles in an effort to improve the therapeutic ratio. CHART delivers 54 Gy in three daily doses of 1.5 Gy over 12 continuous days, including weekends. With CHART, treatment is given every day to counteract rapidly proliferating cells. Hyperfractionation with many smaller doses of radiation may reduce late-tissue toxicity. Accelerating the treatment time from 6 weeks to 2 weeks also may counteract tumor repopulation.

CHART was first examined in a small prospective phase II trial. Some degree of esophageal toxicity was present in all patients. Ten percent of patients developed acute radiation pneumonitis. Two-year survival was 34%.

A phase III randomized study was performed in 13 centers in the United Kingdom. Patients were assigned to either standard radiation of 60 Gy in 30 daily doses of 2 Gy over 6 weeks or CHART. Approximately one-half the patients had stage III disease, the remainder had early-stage disease or unknown staging. No other therapeutic modalities were used. Two-year survival significantly increased from 20% to 29% in the CHART arm. In addition, local control significantly improved from 15% to 23%. Severe esophagitis toxicity also increased from 3% to 19%, and acute radiation pneumonitis was 19% in the conventional group and 10% in the CHART arm. However, late pulmonary toxicity and fibrosis requiring treatment at 2 years was present in 16% of living patients who received CHART as compared to 4% receiving conventional radiotherapy. The investigators concluded that this regimen was tolerable, with the main toxicity being esophagitis and moist desquamation of the skin. Median survival of 13 months was similar to combined-modality approaches. A North Central Cancer Treatment Group Trial evaluated standard radiotherapy (60 Gy in 30 daily fractions of 2 Gy over 6 weeks) to an accelerated hyperfractionated approach (60 Gy in 40 fractions of 1.5 Gy twice daily over 4 weeks). A third arm included the accelerated hyperfractionated approach with concomitant cisplatin and etoposide. The two radiation-alone arms were not significantly different, although there was a trend toward improved local control and overall survival when the two hyperfractionated arms were combined.

Hypofractionated Radiotherapy The reality for many physicians treating unresectable NSCLC is that in many patients, favorable patient parameters are not present. In these patients with unresectable stage III tumors, the results with either radiotherapy alone or combined-modality treatment are poor, and the chance for cure is rare. Studies have examined the use of hypofractionated radiotherapy for unresectable stage III disease and compared the results to those for standard fractionation to 60 Gy in RTOG trials. Depending on one's philosophy, the use of hypofractionated radiotherapy may simply be a palliative approach, or it may be a curative approach with low expectation, based on known results with radiotherapy alone. A study revealed that patients with stage III disease treated with 40-Gy split-course irradiation had better local control rates but higher locoregional failure rates than those receiving 24-Gy in 1.5-Gy fractions over 16 weekly fractions. This was a disease treated with 40 Gy at 1, 2, and 5 years were 47%, 22%, and 7%, respectively. For stage IIIIB disease, the radiation scheme did not correlate with survival and relapse rates. Survival rates at 1, 2, and 5 years were 30%, 9%, and 2%, respectively. The hypofractionated regimen schemes were extremely well tolerated, and no severe complications were observed. Although the data for both schedules of treatment appear comparable, split-course irradiation cannot be routinely recommended based on the available literature for locally advanced NSCLC.

Radiosensitizers Schaeke-Koning et al. demonstrated a survival advantage when weekly or daily cisplatin was added to thoracic radiotherapy. Three-year overall survival improved from 2% to 16% with the addition of daily cisplatin. The benefit was due to increased local control with cisplatin. It is not clear whether cisplatin actually enhances the effect of radiation or whether it is independently cytotoxic, with its effectiveness more dependent on dosing and dose level. Other studies have shown no benefit from the addition of concomitant chemotherapy with thoracic radiation.

A CALGB-ECOG study examined induction chemotherapy with cisplatin and vinblastine followed by 60 Gy radiotherapy with or without radiosensitization with carboplatin, 100 mg/m2. This study differs from those referenced here because it used cytotoxic chemotherapeutic drug for induction in both arms and, therefore, was solely testing the value of radiosensitization. There was no difference in overall survival, failure-free survival, or response between the two arms. There was a higher local control in the carboplatin arms, but this did not have an impact on survival.

Radiation Protectors The radioprotectant amifostine is a sulfhydryl compound the metabolites of which scavange free radicals that are generated in tissues exposed to radiation. A phase II clinical trial using amifostine with sequential chemotherapy and standard radiation (60 Gy) demonstrated no episodes of grade 3 or worse esophagitis or pneumonitis. There was no evidence of tumor protection, either. Amifostine might allow for the use of higher doses of chemotherapy and radiation with acceptable toxicity. RTOG protocol 96-01 is addressing this issue.

Prophylactic Cranial Irradiation for Locally Advanced Non–Small Cell Lung Cancer

The hypothesis that prophylactic cranial irradiation (PCI) can improve survival is based on the assumption that isolated brain failures occur commonly and lead to death, thus they can be effectively prevented by tolerable doses of radiation. PCI has recently been shown on metaanalysis to improve survival in patients with small cell lung cancer. However, isolated brain failures in NSCLC are not common, and it is not possible to predict the patients at risk. Consequently, it is unlikely that survival would be improved to a detectable degree if effective prophylaxis were delivered to the entire population of patients with resected disease. Of 1532 patients treated surgically in prospective trials of the LCSG, only 6.8% (104 of 1532) had first recurrences in the brain. However, 71% of the patients in this series had T1–2N0 tumors. Patients with locally advanced disease treated with thoracic irradiation on the RTOG protocols had an initial brain failure rate of 7% for squamous histology, 19% for adenocarcinoma, and 13% for large cell carcinoma. Even for adenocarcinoma, brain is a less common site of initial failure than are bone (24%) and opposite lung (21%).
Four randomized trials of PCI added to chest irradiation (with or without chemotherapy) have been reported for patients with locally advanced NSCLC and have not demonstrated improved survival, although treatment did reduce the rate of development of brain metastasis. 469,470,471,472 Thus, until systemic treatment and local therapy are sufficient to render the brain as the main site of clinical failure, PCI cannot be recommended for any stage of NSCLC, and its use remains investigational.

The use of PCI after combined-modality therapy that includes surgery has not been sufficiently investigated. However, a recent report involved 75 patients who had stage IIIA or IIIB NSCLC treated by induction therapy and who were treated with PCI (30 Gy over 3 weeks). In this phase II trial, PCI was started after the end of the final chemotherapy cycle and prior to surgery. In those patients who had partial or complete responses to the induction chemotherapy, there were no relapses in the brain as the first site. Further study is warranted, since brain is the most common site of first relapse in most induction therapy reports. 272

**Combined-Modality Treatments, Including Radiotherapy**

**SEQUENTIAL CHEMOTHERAPY AND RADIOTHERAPY (INDUCTION OR NEOADJUVANT CHEMOTHERAPY).** The use of induction chemotherapy is based on several theoretic considerations. 272,266,270 It has been suggested that the early use of chemotherapy lowers the systemic tumor burden and prevents the growth of microscopic systemic disease, while bulky locoregional macroscopic disease is decreased and addressed more easily by subsequent surgery, radiotherapy, or both.

Several large randomized studies of induction chemotherapy in unresectable NSCLC have been published (Table 31.2-15). Generally, studies using more intensive chemotherapeutic regimens and entering larger study cohorts have favored the use of chemotherapy. Metaanalyses of chemotherapy in this setting also suggest a significant therapeutic benefit but are compromised by the limitations of this technique, reflecting the poor design or execution of many of the randomized trials. 472,474

<table>
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<th>TABLE 31.2-14. Selected Randomized Trials Testing Induction Chemotherapy in Locally Advanced Non–Small Cell Lung Cancer Treated by Radiotherapy</th>
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In assessing the role of chemotherapy for unresectable stage III disease, it appears beneficial to concentrate on specific well-designed and -conducted trials. In 1984, the CALGB initiated a randomized study comparing standard radiotherapy to two cycles of induction chemotherapy with cisplatin plus vinblastine followed by radiotherapy. 271,469 Eligible patients had stage III unresectable NSCLC; eligibility was restricted to allow for only 5% weight loss before study entry and a performance status of 0 or 1. Patients with supravacular lymph node involvement or cytologically positive pleural effusion were also excluded. Thus, eligible patients were selected to be in a generally favorable state of health and to be treated with curative intent. This study was closed after an interim analysis, with only 155 eligible patients entered, when a survival difference became apparent. The median survival favored chemotherapy (14 vs. 10 months; P = .006). Thus, the addition of 1 month of chemotherapy to radiation resulted in a 4-month prolongation of life. More interestingly, the chemotherapy also resulted in a doubling of long-term survivors. On both study arms, few patients were noted to have recurrences after 2 years of follow-up. Seventeen percent of patients were alive at 5 years' follow-up on the chemotherapy arm, as compared with 7% of patients receiving standard radiotherapy alone.

A confirmatory three-arm intergroup study was subsequently organized. 272,467 In this study, the two study arms of the CALGB trial were repeated; a third arm was added to test the hypothesis that intensified radiotherapy as a single modality might also result in increased survival rates. Eligibility criteria were identical to those spelled out in the CALGB study. This study largely confirms the results of the CALGB study: median survival times for radiotherapy alone, hyperfractionated radiotherapy, and induction chemotherapy were 11, 12, and 14 months, respectively. This difference again favored the addition of chemotherapy to radiotherapy. The use of hyperfractionated radiotherapy alone resulted in no significant benefit. Long-term survival data from this study suggest that 3-year survival rates are similar for induction chemotherapy and hyperfractionated radiotherapy (and superior to standard fractionation radiotherapy).

Given the systemic activity of chemotherapy, it might be expected that the increased survival rate observed with induction chemotherapy would be due to increased systemic control. However, not all studies have included an analysis of the pattern of failure. A European study tested three cycles of induction chemotherapy with vindesine, lomustine, cisplatin, and cyclophosphamide in patients with squamous cell and large cell lung carcinoma and showed a small survival benefit favoring chemotherapy. Increased systemic control due to chemotherapy was also shown in the intergroup trial, while there was no effect on intrathoracic control. 272,467,469

In summary, induction chemotherapy has been shown in large randomized studies to increase survival rates of patients with unresectable stage III NSCLC. This appears to be due to increased systemic disease control and is, therefore, compatible with the observations of activity for chemotherapy in patients with stage IV disease and the theoretic models supporting induction chemotherapy. Induction chemotherapy is a current standard therapy for these patients.

**CONCOMITANT CHEMORADIOThERapy.** The simultaneous use of chemotherapy and radiotherapy has also been widely investigated (Table 31.2-15). This approach is based on considerations similar to those for sequential chemoradiotherapy in that chemotherapy may cover systemic disease, while radiotherapy can treat locoregional disease. The concomitant approach provides the additional theoretic benefit of increasing locoregional control through a direct interaction of the two modalities, which is not the case when the two modalities are administered in sequence. 272,273 Clinically, the administration of intensive concomitant chemoradiotherapy is complicated by increased toxicities. This includes esophagitis, a risk of radiation pneumonitis, and increased myelosuppression because the thoracic bone marrow is exposed to the radiation.

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<tr>
<th>TABLE 31.2-15. Randomized Trials of Concomitant Chemoradiotherapy with Single-Agent Cisplatin or Carboplatin in Locally Advanced Non–Small Cell Lung Cancer</th>
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As a result, the chemotherapy frequently has been given at suboptimal doses as single-agent chemotherapy instead of combination chemotherapy, or the radiotherapy schedule has been interrupted to allow for recovery of normal tissues. It is known that prolongation of a course of radiotherapy decreases its...
single-modality efficacy. Several single-drug chemoradiotherapeutic trials have been published (see Table 31.2-15). In particular, cisplatin as a single agent has been tested in several randomized clinical trials. A study of weekly cisplatin (15 mg/m²/week) plus radiotherapy to 50.4 Gy found no survival benefit. Similarly, studies of radiotherapy with low daily doses of cisplatin or cisplatin given every 3 weeks showed no survival benefit. Only one study showed improved local control and survival for daily cisplatin added to radiotherapy; however, the patients on the control arm received proracted radiotherapy. Thus, concomitant chemoradiation using single-agent cisplatin or other drugs has largely failed to improve the survival rates of patients with locoregionally advanced NSCLC, although it may provide a locoregional sensitization effect. This appears to be due to the lack of systemic activity of low-dose single-agent therapy; thus, the predominant site of failure in these patients (distant disease) is inadequately addressed.

Several studies testing combination chemotherapy with concomitant radiotherapy or using hyperfractionated radiotherapy have also been published. These studies largely have been performed in the phase I and II settings. Results uniformly indicate increased toxicity. Some studies, however, have also suggested therapeutic benefit and encouraging survival data. The SWOG has published two phase II trials using cisplatin and etoposide with concurrent radiotherapy. In the first such trial, concomitant chemoradiotherapy to 45 Gy was administered in the preoperative setting. The response rate to this regimen prior to surgery was 59%, and 71% of patients were able to undergo surgical resection. This study forms the basis for the large current intergroup trial evaluating concomitant chemoradiotherapy plus chemoradiotherapy boost versus surgical resection in patients with marginally resectable stage IIIA NSCLC. The 3-year survival rate was 26%. In a second study, the SWOG evaluated this chemoradiotherapy regimen in patients with unresectable disease. Here patients received two cycles of cisplatin-etoposide with concurrent radiotherapy to 61 Gy followed by an additional two cycles of chemotherapy in the “adjuvant” setting. For 50 patients, the median survival time was 13 months, and 2- and 3-year survival rates were 33% and 26%, respectively. The SWOG has evaluated a similar regimen of carboplatin, etoposide, and concurrent radiotherapy in patients with poor prognostic features. Pilot data in this group of patients indicated similar median and 2-year survival times, indicating the feasibility of chemoradiotherapy for a suboptimal patient population.

Definitive testing of combination chemoradiotherapy with concurrent radiotherapy in the phase III setting has been limited. A three-arm study investigated the combination of carboplatin and etoposide at two dose levels added to hyperfractionated radiotherapy (1.2 Gy twice daily; total dose, 64.8 Gy). Carboplatin, 100 mg/m² on days 1 and 2, and etoposide, 100 mg/m² on days 1 to 3, of each week of radiotherapy resulted in a significant increase in median survival as compared with hyperfractionated radiotherapy alone (median survival, 8 vs. 18 months). A similar comparison of twice-daily radiotherapy to 69.6 Gy with or without daily intravenous carboplatin (50 mg) and etoposide (50 mg) showed a significant increase in median survival time (22 vs. 14 months) and 4-year survival rates (23% vs. 9%). These studies support the addition of chemotherapy to radiotherapy but do not clarify whether twice-daily radiotherapy is superior to single daily fractions. Intensified radiotherapy schedules are mainly supported by the British CHART study. Since both induction chemotherapy and concomitant chemoradiotherapy prolong survival, it can be asked which of the two approaches is superior. Induction chemotherapy has, indeed, been directly compared with concomitant chemoradiotherapy using the cisplatin-plus-vinblastine regimen in a randomized study by the RTOG. Based on previous pilot studies, patients with stage III NSCLC were randomly chosen to receive induction chemotherapy with cisplatin plus vinblastine (standard), or the same drugs given concomitantly during radiotherapy, or cisplatin with orally administered etoposide and concomitant hyperfractionated radiotherapy. Results from this trial are expected in the near future.

A similar study has been reported by Japanese investigators. Furuse et al. compared the administration of the MVP regimen as induction chemotherapy to its administration with concurrent radiotherapy. Median survival times were 16 versus 13 months, favoring the concurrent administration of chemoradiotherapy. A pattern-of-failure analysis indicated a higher relapse in the brain for patients treated with concurrent chemoradiotherapy, with the possibility of higher intrathoracic control (Table 31.2-16).

**TABLE 31.2-16.** A Randomized Phase III Study of Concurrent versus Sequential Radiotherapy with MVP in Stage III Non–Small Cell Lung Cancer

**INDUCTION AND CONCOMITANT CHEMORADIATION.** An alternative strategy to a direct comparison of induction versus concomitant combined-modality therapy is the administration of both. This strategy is supported by the suggestion that induction chemotherapy and concomitant chemoradiotherapy may exert their favorable influence on survival by different mechanisms. In particular, induction chemotherapy appears to improve systemic disease control, while concomitant chemoradiotherapy leads to higher locoregional control. This hypothesis has been evaluated in several studies. The CALGB compared administration of cisplatin and vinblastine followed by radiotherapy with administration of the same induction chemotherapeutic regimen followed by radiotherapy with weekly doses of concomitant carboplatin. This study showed a median survival time of 13 months on both arms but suggested increased locoregional control for patients receiving carboplatin. This study adds to the evidence that single-agent radiation sensitization with a platinating agent is of clinical benefit. More recently, similar investigations have focused on the integration of novel chemotherapeutic single agents into the setting. Preclinical and early clinical data support a role as radiation enhancers for the taxanes, gemcitabine, vinorelbine, and topoisomerase I inhibitors. Additional trials have evaluated the administration of paclitaxel with or without carboplatin on a weekly schedule with concurrent chest radiotherapy. Phase II trials indicate high response and promising 1- and 2-year survival rates with this approach. Pilot studies using paclitaxel are summarized in Table 31.2-17. A three-arm study by the CALGB evaluating three novel agents (gemcitabine, paclitaxel, or vinorelbine in combination with cisplatin) in the induction and concomitant setting is under way. The radiation dose in this trial is 66 Gy.

**TABLE 31.2-17.** Selected Phase II Trials of Weekly Paclitaxel-Based Chemotherapy with Concurrent Radiotherapy in Patients with Stage III Unresectable Non–Small Cell Lung Cancer
To evaluate further the role of induction chemotherapy within the context of concomitant chemoradiotherapy, the CALGB is conducting a randomized trial comparing concomitant chemoradiotherapy with carboplatin, paclitaxel, and concurrent radiotherapy versus two cycles of induction chemotherapy with carboplatin and paclitaxel followed by the same concomitant chemoradiotherapeutic regimen. This trial will evaluate whether induction chemotherapy is of benefit in patients receiving concomitant chemoradiotherapy.

Additional trials are expanding on observations with accelerated radiotherapy. The aforementioned British trial has indicated that administration of accelerated radiotherapy is superior to standard radiotherapy as a single-treatment modality. Because accelerated radiotherapy will have an impact on locoregional control only, its administration after induction chemotherapy is being evaluated in a randomized Eastern Oncology Cooperative Group Trial.

In reviewing these studies of combined-modality therapy for unresectable NSCLC, it is clear that induction chemotherapy has led to a significant increase in survival rates; concomitant chemoradiotherapy can also achieve this. The existing data support that patients can be treated with induction chemotherapy or concomitant therapy outside of a clinical trial (as a standard therapy); however, the impact of these strategies in survival is small, and participation in clinical trials is strongly encouraged.

**STAGE IV DISEASE**

In most instances, stage IV (M1) disease is treated with primary chemotherapy. The goals of therapy are the palliation of symptoms and prolongation of survival time. On occasion, however, when a solitary site of metastasis occurs (e.g., brain), both the primary tumor and the solitary metastatic site can be treated with curative intent either by a surgical or radiotherapeutic approach.

**Prolongation of Survival by Chemotherapy**

In the 1970s and 1980s, combination chemotherapy, usually cisplatin-based, was demonstrated to result in reproducible response rates of approximately 20% to 30%. Although these studies suggested activity of chemotherapy in stage IV NSCLC, they left unanswered what constituted the optimal chemotherapeutic regimen for NSCLC. Furthermore, because overall median survival times were short at 6 to 8 months and few patients survived beyond 1 year, the general value of chemotherapy in the routine management of patients with stage IV NSCLC was questioned.

Some investigators hypothesized that the survival benefits that patients derived from chemotherapy were not sufficient to offset the toxicities and economic costs. A number of randomized studies were initiated to compare directly best supportive care versus chemotherapy plus best supportive care. The first such study was reported by Cormier et al. and supported the use of chemotherapy. However, like most subsequent studies listed in Table 31.2-18, it included insufficient patient numbers to allow for definitive conclusions. The subsequent Canadian study remains the most frequently cited study in this category. Of interest, it demonstrated not only increased survival time with chemotherapy but acceptable treatment costs.

Additional studies confirmed the finding of a statistically significant increase in median survival for chemotherapy-treated patients compared with those receiving best supportive care only, and all studies suggested at least a statistical trend for improved outcome favoring chemotherapy.

**Quality of Life**

With the limited survival benefit for patients, quality of life (QOL) has been considered as another relevant end point of chemotherapeutic trials in stage IV NSCLC. Validated questionnaires have been developed to assess QOL accurately. The earlier randomized trials comparing chemotherapy gave indirect evidence that chemotherapy can improve QOL. The reason that chemotherapy reduced health care costs in the Canadian study was that patients receiving chemotherapy had a lower incidence of disease-related complications, leading to fewer hospital admissions.

Economic analyses support the use of combined-modality and palliative combination-chemotherapy approaches.

More recently, improved QOL has been prospectively evaluated as an independent variable. Disease-related symptoms will improve after chemotherapy, sometimes even in the absence of a measurable tumor response. QOL scores improved with chemotherapy, whereas they declined over the first 6 weeks with best supportive care. In one study, symptomatic improvement was 70%, whereas the objective response rate was only 35%. Improved survival and QOL were also
TABLE 31.2-21. Comparison of Various Combination Chemotherapy Regimens


Paclitaxel also showed encouraging single-agent activity (see Table 31.2-20). The ECOG performed a three-arm randomized study comparing a regimen of cisplatin plus etoposide with cisplatin plus paclitaxel with a regimen of paclitaxel given either at a low or high dose with granulocyte colony-stimulating factor support. The paclitaxel-plus-cisplatin arms were superior to the etoposide-plus-cisplatin regimen, with no evidence of an increased response rate with a higher paclitaxel dose. This study evaluated paclitaxel as a 24-hour infusion. Shorter infusion duration (3 hours) has been used in most other studies. A European trial showed cisplatin and paclitaxel to result in median survival (10 months) similar to that of cisplatin and teniposide while being better tolerated. Of note, median survival times in both of these studies were better in both arms than historic controls. Other randomized trials confirm the activity of cisplatin or carboplatin-paclitaxel regimens and the favorable toxicity profile of the latter combination (Table 31.2-22).
Encouraging data also exist for docetaxel, gemcitabine, and irinotecan. All three have reproducible single-agent activity and have been investigated in combination with a platinating agent. Gemcitabine has been evaluated in randomized phase II and III trials. Equivalence of single-agent gemcitabine with the (more toxic) combination of cisplatin and etoposide was suggested in two small studies. The combination of gemcitabine and cisplatin showed a significant improvement in median survival (7.6 vs. 9.1 months) versus single-agent cisplatin. A smaller European trial compared cisplatin and gemcitabine with cisplatin and etoposide and suggested a favorable impact on median survival. Tarapazamine, a bioreductive alkylating agent, has been shown to increase the cytotoxicity of cisplatin and prolong survival after therapy with that combination.

Docetaxel has been shown to have activity as second-line therapy in patients with cisplatin-refractory disease. This is encouraging because second-line activity has rarely been observed with other drugs. Second-line activity has also been described for gemcitabine.

Currently, investigators are focused on comparing some of the recent regimens with one another. A comparison of cisplatin and vinorelbine with carboplatin and paclitaxel has been presented. Identical median survival times of 8 months suggested equivalence of antitumor activity, while the toxicity spectrum of the regimens predictably differed (more nausea and vomiting and myelosuppression with cisplatin, more neurotoxicity with carboplatin). The ECOG is comparing carboplatin-paclitaxel with gemcitabine-cisplatin, docetaxel-cisplatin, and cisplatin-paclitaxel. This is an important study, since it will establish the relative activity and toxicity of several novel cisplatin-based regimens versus the combination of paclitaxel and carboplatin. The CALGB is comparing single-agent paclitaxel therapy with the combination of paclitaxel-carboplatin. Evaluating response, survival, economic, and QOL endpoints, this study will establish whether a benefit exists for this “doublet” over single-agent paclitaxel. Similarly, three drug regimens using novel drugs are being evaluated. Additional trials are evaluating the weekly administration of paclitaxel, non-platinum-containing two-drug regimens, three-drug regimens, and other new cytotoxic agents. Of current interest in particular are “cytostatic” molecules inhibiting specific cellular or extracellular targets, including inhibitors of farnesyl transferase, matrix metalloproteinase, or antiangiogenic agents.

In summary, chemotherapy for stage IV NSCLC has been shown to prolong survival as compared with best supportive care. The use of chemotherapy can be supported by cost and QOL analyses. Its administration to the elderly has been shown to be of benefit. Based on recent evidence, current standard regimens are the doublets of cisplatin in combination with either vinorelbine, paclitaxel, or gemcitabine or the combination of paclitaxel and carboplatin. In selected cases, administration of second-line chemotherapy should be considered.

**Current Clinical Approaches to Stage IV Non–Small Cell Lung Cancer**

In the 1990s, most patients with newly diagnosed stage IV NSCLC should undergo treatment with at least one chemotherapeutic regimen. Based on available data from randomized trials, treatment should consist of the combination of cisplatin and vinorelbine, cisplatin and gemcitabine or, alternatively, cisplatin or carboplatin and paclitaxel. Generally, chemotherapy should be restricted to patients with a performance status of 0 to 2. Because it is that group of patients in which most phase II and positive phase III studies have been conducted. Available evidence suggests that patients with a performance status of 2 will have, at best, a minor prolongation in survival time by chemotherapy but may experience significant relief of disease-related symptoms. Single-agent therapy in elderly patients should be considered. Patients should understand that the treatment goals are not cure but prolongation of life and palliation of symptoms; additional palliative measures, such as pain relief, radiotherapy, and surgery, should be applied as most beneficial for symptom relief.

In patients with stable or responding disease, the treatment duration has traditionally been six cycles of chemotherapy. Historically, this is largely based on the cumulative toxicity observed with cisplatin, which frequently limits to six or less the total number of cycles. The optimal duration of chemotherapy is undergoing evaluation in randomized trials. It is possible that newer regimens, particularly those not containing cisplatin, might be tolerated (and active) for more than six cycles. In patients with stable or responding disease, it might, therefore, make sense to continue therapy beyond six cycles. The optimal duration of chemotherapy is undergoing evaluation in randomized trials.

Patients who progress on or after first-line chemotherapy but continue to have a good performance status may be offered second-line chemotherapy. Few drugs have undergone formal testing in this setting. Docetaxel has been most extensively evaluated. In phase II studies, the use of docetaxel in patients not previously exposed to another taxane resulted in a response rate of approximately 10%. Two randomized trials have been presented. A Canadian trial compared second-line best supportive care with docetaxel (at 75 or 100 mg/m²). Improvement in survival (7 vs. 5 months) and improved QOL supported the use of docetaxel at the lower dose. In a second study, docetaxel (at two dose levels of 75 or 100 mg/m²) was compared with vinorelbine or ifosfamide. Median survival times were similar, while 1-year survival was highest at the lower-dose docetaxel arm. QOL analysis also favored docetaxel therapy. Gemcitabine has also had second-line antitumor activity in phase II trials. There is little published information to support the use of other drugs as second-line therapy.

Because novel and more effective or less toxic therapies are still much needed in treating NSCLC, it should be recommended to offer investigational therapies of new drugs or novel combinations of drugs to such patients in prospective phase I and II studies whenever possible. Such an approach holds promise for the intermediate and long-term identification of more active therapies. The empiric use of sequential chemotherapy regimens as second-, third-, or fourth-line therapy cannot be supported using current data. Given the lack of drugs with established activity as second-line therapy, using investigational drugs will not compromise a patient’s chance of obtaining benefit from therapy.

**Solitary Metastases**

**METASTASIS (M1) TO LUNG.** To differentiate between a second primary lung cancer and a metastasis in synchronous lung lesions or among local recurrence, a new primary lung cancer, and a pulmonary metastasis from a previous resected lung cancer in metachronous lung lesions can be difficult. A second or recurrent lung primary is considered a metastasis if the histology is identified to the primary tumor and occurs in the opposite lung or a noncontiguous area of the ipsilateral lung.

Deslauriers et al. found that the presence of satellite nodules discovered at surgery, clearly separated from the primary tumor but with identical histologic characteristics, is a poor prognostic factor. In patients with satellite nodules from all stages of lung cancer, 5-year survival was 21.6%, as compared with 44% if no nodules were present. The mechanism of tumor spread in the lung is not well known, but metastases may develop as a result of a blood-borne or airborne spread from a primary bronchogenic carcinoma. The new TNM staging system fails to classify these synchronous lung lesions specifically.

The same criteria used in selecting patients for surgical resection of a pulmonary metastasis from a primary lung cancer should be used in patients with metastatic lung cancer to the lung from other primary tumors. If a solitary synchronous lesion is discovered in a different lobe from the primary tumor, both lesions should be resected whenever possible.

**METASTASIS (M1) TO BRAIN.** Brain metastases constitute more than 25% of all observed recurrences in patients with resected NSCLC and are seen with greater frequency at autopsy. In a review by the LCSG, the brain was the sole site of first recurrence in only 6.4% of patients with completely resected NSCLC but accounted for approximately 20% of all recurrences. Nearly one-half of the patients seen with brain metastases have solitary lesions on CT scan. When these lesions are symptomatic, the median survival without therapy is limited to 1 month. Corticosteroids and whole brain irradiation can offer effective palliation of symptoms but only modestly increase survival up to 6 months.

A synchronous or metachronous solitary brain metastasis can be treated, whenever possible, by surgical resection, with 5-year survival rates of 10% to 20% (Table 31.2). Surgical excision of a brain metastasis, no matter the primary site (approximately 75% from NSCLC), followed by radiation has been shown to be superior to whole brain radiotherapy alone in prolonging median survival (9.2 vs. 3.4 months), in preventing local recurrence, and in providing a better QOL.
A resurgence of interest in the use of high-dose 3D-CRT or stereotactic radiosurgery in managing solitary brain metastases has followed early results suggesting equivalence to a surgical approach. 157

**METASTASIS (M1) TO THE ADRENAL GLAND.** Adrenal metastases from bronchogenic carcinoma are found in approximately one-third of patients at autopsy. Routine preoperative upper abdominal CT scanning may reveal an adrenal mass in approximately 10% of patients. 158

A few case reports of adenectomy for solitary adrenal metastasis are available, and long-term survival after combined excision of the primary lung tumor and its metastatic lesion has been reported. 159-163 The ultimate role of such an approach has yet to be defined.

**METASTASIS (M1) TO LIVER, BONE, OR SKIN.** No reports of long-term survival have been made after combined surgical excision of a primary lung cancer with a synchronous solitary liver, bone, or skin metastasis. It is rare that these lesions are truly solitary metastatic foci. However, patients with solitary metastatic sites fare reasonably well after complete surgical excision.

**Palliation**

In view of the poor survival rate of patients with locally advanced NSCLC and patients with metastatic disease, effective palliation is an important objective. Carroll et al. 164 followed up 134 inoperable patients and reported that 64% needed immediate local palliation and that, of those with no thoracic symptoms at presentation, one-half required subsequent local treatment. Thus, a watch-and-wait policy is appropriate for only a minority of patients, and it is critical that they be followed up carefully to prevent the development of serious local complications of the disease that may be less easily palliated. It is important to intervene before superior vena cava obstruction, obstructive pneumonia, or lobar collapse develops. The latter two conditions produce a radiographic picture in which tumor and other processes are not easily distinguishable, and large radiation fields may be necessary for effective control.

**Radiotherapy**

**LOCAL DISEASE. External-Beam Irradiation** Numerous trials have been conducted in which the palliative benefit of radiotherapy has been documented. 165-168,174,179,183,189

Various regimens produce a high rate of palliation that often is sustained for a significant proportion of a patient’s survival. The randomized trials suggest that certain symptoms, such as hemoptysis and pain, are more effectively palliated, while dyspnea and poor performance status appear to be more refractory. Investigators in Italy used either 5.5 Gy or 8.8 Gy once a week for a total dose of 44 Gy and reported that 80% of 45 patients experienced an average improvement of 20 points on the Karnofsky performance score. 169,170

The RTOG trial showed that even regimens with larger fraction sizes had a low (8%) incidence of severe complications. An early Medical Research Council trial showed no difference in survival or toxicity between 17 Gy given in two fractions 1 week apart and more conventional palliative fractionation (30 Gy in ten fractions or 27 Gy in six fractions). 181 A follow-up study, however, demonstrated an increase in median survival from 7 months to 9 months when 17 Gy in 2 fractions was compared to 36 to 39 Gy in 12 to 13 fractions. 182 Palliation was quicker and more durable in the hypofractionated arm, however.

A significant number of patients, however, suffer recurrence of symptoms. Few data report on the result of re-treatment with radiation. Jackson and Ball 183 re-treated 22 patients whose disease recurred after radical irradiation and delivered between 20 and 30 Gy in 2-Gy fractions. Symptomatic improvement occurred in 52%, and median survival was 5.4 months.

Superior vena cava syndrome is characterized by venous distention, facial edema, headache, tachypnea, cyanosis, and plethora. 184 It is caused by the obstruction of the superior vena cava by compression, invasion, or thrombosis. Approximately 80% of cases are caused by bronchiogenic cancer, most frequently small cell lung cancer, but non–small cell histologies are also very common. Although some have questioned whether emergent radiation treatment is necessary, 185 others report symptomatic relief with palliative radiotherapy in 80% of patients. 186 High dose per fraction (300 cGy or greater) appears to incite faster relief. 187

**Intraluminal Brachytherapy** Intraluminal brachytherapy or EBB is an excellent palliative treatment for symptoms of hemoptysis, obstruction, and dyspnea. It has been shown to work best in tumors that are endoluminal or submucosal. 188 Direct permanent implantation of iridium seeds into endobronchial tumors was developed at MSKCC in the 1990s. Relief of symptoms was achieved in approximately 60% of cases, but there was significant morbidity due to perforation of the airway, hemorrhage, and ventilatory arrest. 189 Subsequent workers avoided direct implantation into tissues and used temporary intraluminal placement of cobalt 60 or iridium 190 to deliver one or more large fractions over a few days. 191 High-dose-rate fractionated intraluminal therapy was developed to avoid such prolonged treatment times, which were uncomfortable for the patient and required hospitalization with attendant expense and radiation risk to personnel. In a sequential comparison of low- and high-dose rate endobronchial radiation, there was no difference in palliative effect or toxicity. 192 In a population of patients receiving prior radiation, this approach yielded symptomatic improvement in 75% of patients, and there were a few long-term survivors. 193 Similar data were reported by Macha et al., 194 who obtained a response in 75% (44 of 56) of patients receiving 7.5 Gy from the source in four treatments. Radiologic improvement occurred in 88% (22 of 25) of patients with collapse or atelectasis, and improvements in FEV1 and vital capacity were well documented. Delclos et al. 195 reported an 84% response rate in 81 previously treated patients. The median response duration was 4.5 months. Burt et al. 196 gave 15 to 20 Gy at 1 cm in one fraction of high-dose-rate endoluminal brachytherapy and reported relief of hemoptysis in 86% (24 of 28), dyspnea in 64% (21 of 33), and cough in 50% (9 of 18). Unlike in other series, these authors did not use laser therapy before radiation. Laser treatment provides immediate relief of symptoms, facilitates catheter placement beyond the obstruction, and may increase response rates and duration. Seagren and Harrell 197 reported significantly improved response rates among a population of 36 patients who received laser treatment versus 14 who did not.

The optimum brachytherapy fractionation schedule has yet to be determined. Single large fractions have been associated with a large risk of massive hemoptysis. 198 Huber et al. 199 compared two fractionation schedules of high-dose-rate EBB: 3.8 Gy in four fractions and 7.2 Gy in two fractions. There was no difference in overall survival or complications between the two groups, although there was a trend toward improved survival with the large fraction size. Therefore, doses in the range of 5 to 7.5 Gy prescribed to 1 cm should be considered safe for high-dose-rate endobronchial radiation. EBB has also been given concurrently with chemotherapy safely. 200

**Distant Metastases**

NSCLC metastasizes to a variety of organs. For asymptomatic metastatic disease remote from critical locations, the usual approach is expectant management or chemotherapy. Isolated symptomatic lesions, such as bone metastases and spinal cord compression (even if asymptomatic), are managed with palliative courses of radiation (e.g., 30 Gy in ten fractions).

Brain metastases are particularly common in NSCLC and can be debilitating. The standard therapy for multiple brain metastases in NSCLC is whole brain irradiation.
The RTOG studied a variety of dose and fractionation schemes for 1994 patients with brain metastases arising from several primary sites, including lung (approximately one-half of patients). The schedules used were 20 Gy in 1 week, 30 Gy in 2 weeks, 30 Gy in 3 weeks, 40 Gy in 3 weeks, and 40 Gy in 4 weeks. The shorter schedules tended to give more rapid relief of neurologic symptoms, but otherwise the schedules had comparable palliative effects (50% overall), duration of improvement (9 to 13 weeks), and median survival (15 to 18 weeks).

Surgical resection combined with postoperative resection has been advocated for single metastases. At MSKCC, 104 patients with NSCLC were treated with surgery and radiation. Median survival was 16 months for the combined resection arm and 4 months for the radiation-alone arm. The patients were chosen on the principle of tumors for which local control was desired or more aggressively managed primary tumors. Mandell et al. and Patchell et al. assigned 43 patients with resectable solitary brain metastases (82% NSCLC primary tumors) to receive radiation alone or combined resection and radiation to the entire brain. Median survival (40 weeks vs. 15 weeks) and duration of functional independence (38 weeks vs. 5 weeks) were significantly better in the combined group. The magnitude of the difference combined surgically in the trial prompted an increased acceptance of resection and postoperative irradiation for solitary brain metastases from NSCLC. A subsequent study from Patchell et al. examined the role of whole brain radiotherapy in patients who underwent surgical resection. They found that whole brain radiotherapy decreased the rate of neurologic death but did not have an effect on overall survival. Stereotactic radiosurgery for solitary brain metastases appears promising as a substitute for surgery.

**Surgery**

Even when surgery cannot lead to cure, this approach may be used to afford best palliation of symptoms. Such surgical intervention may include bronchoscopic removal or ablation of tumor to relieve endobronchial obstruction or hemoptysis, pleurectomy relief of symptomatic malignant pleural effusions, pericardiectomy for malignant pericardial effusions, endobronchial or endoesophageal stents for relief of obstruction, and (occasionally) surgical resection of primary lung cancer and lung parenchyma for relief of septic complications or massive hemoptysis. On very rare occasions, en bloc resection, albeit incomplete, may be excellent palliation for painful invasion of bony structures, such as vertebrae or ribs.

**Relief of Endobronchial Obstruction**

Bronchoscopic removal of endobronchial tumor is an efficient way of relieving endobronchial obstruction. Simple mechanical debridement with the use of the bronchoscope is often sufficient. Coagulative techniques, such as CO2 laser or neodymium-yttrium aluminum garnet laser, electrocautery, and cryotherapy have been used in conjunction with mechanical debridement. There has been an increase in interest in the use of photocoagulation employing hematoporphyrins and argon beam excitation as a method of relieving endobronchial obstructions. All the techniques can be effective. Massive hemoptysis due to endobronchial tumor is rare but can cause a life-threatening radiation arm. The judicious use of coagulative techniques is required. In most instances, endobronchial debridement and coagulation are best carried out by rigid bronchoscopy. Frequently, endobronchial stents are employed for long-term palliation.

Hemoptysis Frequently, hemoptysis can plague the patient with stage IV lung cancer. As with bronchial obstruction, bronchoscopy is often the treatment of choice to control bleeding and sometimes devastating complications. When uncontrolled bleeding is anticipated, a rigid bronchoscopy should be performed. If significant bleeding is present, a rigid bronchoscopy can be performed under direct vision. The bronchial tree is observed for areas of active bleeding, which can be electrocoagulated with the use of the bipolar electrocautery or cryocautery. The bronchoscope can be passed into the involved airway to facilitate electrocautery and cryotherapy. Tissue can be suctioned to control bleeding and to facilitate coagulative therapy. Coagulative techniques can be used to control bleeding. These include electrocoagulation, cryotherapy, and laser photocoagulation using argon or carbon dioxide laser.


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Section 31.3
Small Cell Lung Cancer

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Epidemiology and Etiology

Small cell lung cancer (SCLC) is the histologic diagnosis in approximately 18% of the more than 171,000 patients diagnosed with lung cancer annually in the United States. Across the world, the proportion of lung cancers that are of the small cell histology tends to be between 10% and 20% in male subjects and 10% and 30% in women. The predominant risk factor for lung cancer is tobacco exposure, which is the cause for up to 90% of cases diagnosed. Among the major histologic subtypes of lung cancer, the association between the extent of tobacco exposure and risk is particularly strong for squamous cell and SCLC. Thus, the incidence of SCLC has paralleled trends in cigarette smoking after a 20- to 50-year lag period. In the twentieth century, manufactured cigarettes first became popular among men, then among women, and successive generations began smoking at progressively earlier ages. Per capita consumption in the United States increased from approximately 54 cigarettes per adult in 1900, to a peak of 4345 cigarettes per adult in 1963. Between 1963 and 1995, the number of adult men who were active smokers declined from 52% to 27%. For women, smoking prevalence declined from 28% to 23% in this time period. However, smoking prevalence for the adult population has changed little from 1993 to 1997, and during the 1990s there have been increasing trends in tobacco smoking among adolescents, particularly girls. In 1997, the prevalence of current cigarette smoking was 36.4% among U.S. secondary school students.

Exposure to other environmental respiratory carcinogens, such as asbestos, benzene, coal tar, and other industrial chemicals may interact with tobacco smoke to increase risk. The presence of underlying lung disease and diet have also been implicated. The risk associated with household exposure to radon gas remains controversial. Pedigree studies and specific metabolic phenotypes have identified familial clusters and populations at increased risk for lung cancer, which is not surprising because several nonrandom genetic defects are associated with this disease. Germ line mutations of genes such as p53 are not likely to contribute to susceptibility to lung cancer. Rather, genetic polymorphisms in genes involved in the activation and metabolism of the procarcinogens in tobacco smoke probably contribute to risk.

These trends in smoking prevalence have important implications for the current and future population demographics of SCLC. Over the next few decades, the incidence of lung cancer should continue to decline in the United States, and as the birth cohorts most heavily exposed to tobacco age, the median age at diagnosis for SCLC will also grow older. Among men, the incidence rates for lung cancer peaked in 1984 and have been declining at a rate of approximately 1.4% per year, with the largest declines noted in the incidence of small cell and squamous cell cancers. Among women, the peak incidence appeared to be in 1994. However, if the increase in popularity of cigarette smoking among adolescents does not change, the declining incidence of lung cancer can be predicted to reverse. Furthermore, female subjects appear to be more susceptible to tobacco smoke carcinogens than male subjects, and racial differences in susceptibility may also exist. These factors, along with the changing demographics of the smoking population, will define the patient population who develops SCLC in future generations.

Pathology

A diagnosis of SCLC is based primarily on light microscopy. In 1981, the World Health Organization proposed a histologic classification that gained wide acceptance. In this classification, SCLC was divided into three subtypes that consist of oat cell, intermediate cell type, and combined oat cell (SCLC combined with squamous or adenocarcinoma). It soon became clear that the morphologic features used to distinguish oat cell from the intermediate cell histology were imprecise, and that even when strict criteria were used, pure SCLC, whether it was classified as oat cell or intermediate cell, behaved identically. Consequently, the International Association for the Study of Lung Cancer proposed a revised classification in 1988 that recognized pure small cell cancer and two less common variants: mixed small cell and large cell carcinoma and combined small cell carcinoma. This classification schema is what is typically used today.

SCLC is composed of neoplastic cells that are typically arranged in clusters, sheets, or trabeculae separated by a delicate fibrovascular stroma. The tumor typically arises in the central airways and initially infiltrates the submucosa, gradually obstructing the lumen by extrinsic or endobronchial spread. The cells are generally 1.5 to 3.0 mm in diameter. Hematoxyphilic encrustation of vessel walls is common. Mitotic rates are high, and necrosis of individual tumor cells within cell clusters is common. Crush artifact, resulting in smearing of nuclear chromatin and loss of mitotic figures, is common.

In the mixed small cell and large cell variant, there is a subset of cells that resembles large cell carcinoma. These cells may be larger than, or equivalent in size to, the more typical small cell component. These cells are distinguished by the presence of prominent, frequent nucleoli and a nuclear chromatin pattern that is more coarsely granular or clumped. There are variable amounts of cytoplasm present. The other subtype recognized in the International Association for the Study of Lung Cancer classification is combined SCLC. In this tumor, small cell carcinoma typically coexists with squamous carcinoma, although adenocarcinoma or one of the less common non–small cell histologies may be present.

In most series, the frequency of the small cell and large cell variant is between 3% and 6%, and for combined SCLC it is 1% to 3%. There is less concordance among pathologists on the diagnosis of the mixed cell variant than there is for pure SCLC. Furthermore, the ability to identify a mixed population is influenced by the size of the biopsied material, with examination of a lymph node more likely to result in identification of a mixed cellular population than a typical...
bronchial biopsy. It remains unclear whether the presence of a mixed cell or a combined histology confers a different prognosis or response to treatment than pure small cell carcinoma. For the mixed small cell subtype, there are series that have identified survival that is inferior to, superior to, or comparable with pure SCLC. There is little information regarding the outcome of patients with combined SCLC. A review of 429 patients treated at Vanderbilt University for SCLC identified nine (2%) with combined small cell and non–small cell histologies. Two of these patients were long-term survivors, and both underwent surgical resection in addition to chemotherapy. Thus, surgery may play a role in the management of combined SCLC, and the presence of non–small cell elements, although uncommon, must be considered in patients who might potentially benefit from resection of residual non-SCLC when the initial diagnosis is based on the limited material available by needle or bronchoscopic sampling.

Although the diagnosis of small cell carcinoma rests primarily on morphologic assessment, immunocytochemistry plays a role, and electron microscopy is of occasional value in difficult cases. Virtually all SCLCs are immunoreactive for keratin and epithelial membrane antigen, so that if a tumor does not stain for these markers, other diagnoses should be considered. One or more markers of neuroendocrine differentiation, such as chromogranin, neuron-specific enolase, Leu-7, and synaptophysin, can be detected in approximately 75% of SCLC. The presence of these markers, however, is not mandatory for the diagnosis and does not distinguish small cell from non-SCLC, as 10% to 20% of non-SCLC exhibit neuroendocrine differentiation. By electron microscopy, the cells are closely apposed, with a high nuclear to cytoplasmic ratio. Chromatin is finely clumped but uniformly dispersed within the nucleus. Few organelles and only occasional uniformly small dense core granules are located in the cytoplasm. The presence of large granules should raise the diagnosis of a carcinoid tumor.

The major diagnostic considerations for a small cell carcinoma are non-SCLC, other small round cell tumors, and a lymphomatous proliferation. Small cell carcinoma composed of larger tumor cells may be difficult to differentiate from a poorly differentiated non-SCLC, particularly if neuroendocrine features are present. Reserve cells are progenitors for bronchial epithelial cells and proliferate in response to chronic irritation of the airways. Features that distinguish reserve cells from small cell carcinoma include retention of cell boundaries within a cell cluster, a lack of the extreme nuclear molding found in small cell carcinoma, and an absence of granularity of the chromatin.

CLINICAL PRESENTATION

In general, the clinical presentation of SCLC is similar to the other histologies of bronchogenic carcinoma. Few patients are asymptomatic at diagnosis. In screening studies, only 4% to 12% of the lung cancers detected as a solitary pulmonary nodule are small cell carcinoma. The initial complaints usually reflect the local presence of a tumor. Cough is the most common symptom. Recent acceleration of cough or accompanying hemoptysis increases the likelihood that an underlying cancer is present. Dyspnea and chest pain are reported in 30% to 40% of patients at diagnosis. Because SCLC typically develops in the central airways, hemoptysis, pneumonia, wheezing, or hoarseness due to vocal cord paralysis may be present. Superior vena caval obstruction is present at diagnosis in 10% of patients with SCLC. Chest imaging typically shows hilar and mediastinal invasion and regional adenopathy. One-third of patients have some degree of atelectasis present. A peripheral location or chest wall involvement by the tumor is uncommon. For example, no more than 2% of SCLC present as a superior sulcus tumor.

Most patients with SCLC have clinically detectable metastases at diagnosis (Table 31.3-1). Bone involvement is usually characterized by osteolytic lesions, often in the absence of bone pain, or elevations in the serum calcium or alkaline phosphatase. However, marked osteoblastic activity is present in a minority of patients. Hepatic and adrenal lesions are typically asymptomatic. Elevations of the serum lactate dehydrogenase (LDH), alkaline phosphatase, or hepatic transaminases are present in the majority of patients in whom liver metastases are identified. In contrast, radiographically confirmed brain metastases are symptomatic in more than 90% of cases. Endovascular metastases (tumor emboli) or lymphangitic spread can be among the underlying causes of dyspnea. Constitutional symptoms, including weight loss, anorexia, and fatigue, are common and correlate with the presence of extensive-stage disease.

TABLE 31.3-1. Sites of Involvement of Small Cell Lung Cancer at Diagnosis and Autopsy

The spectrum of paraneoplasia associated with SCLC differs to some degree from the syndromes observed with non-SCLC. Small cell carcinoma is the histology in only 5% of patients with lung cancer diagnosed with hypertrophic pulmonary osteoarthropathy. Humorally mediated hypercalcemia is rare. On the other hand, the vast majority of lung cancer patients who develop the syndrome of inappropriate antidiuretic hormone, Cushings syndrome, or neurologic paraneoplasia have SCLC. SCLC accounts for approximately 75% of the tumors associated with the syndrome of inappropriate antidiuretic hormone. Although serum concentrations of antidiuretic hormone are elevated in the majority of patients with SCLC, only approximately 10% of patients fulfill the criteria for syndrome of inappropriate antidiuretic hormone, and symptoms are present in no more than 5%. In some cases, ectopic production of atrial natriuretic factor contributes to the disorder in syndrome homeostasis. Similarly, increased serum levels of adrenocorticotropic hormone can be detected in up to 50% of patients with lung cancer, but only 5% of patients with SCLC develop Cushings syndrome. In approximately one-half of these cases, it is present at diagnosis. Some of the cutaneous manifestations of Cushing's syndrome may not be prominent, perhaps because of the rapid growth and clinical course of SCLC. A few studies have demonstrated that a low serum sodium level is an adverse prognostic factor, and patients with Cushings syndrome have a limited survival.

Neurologic paraneoplastic syndromes include sensory, sensorimotor, and autoimmune neuropathies and encephalomyelitis. These syndromes are thought to occur through autoimmune mechanisms, and antinuclear antibodies that bind both to SCLC and neuronal tissues have been identified. Symptoms may precede the diagnosis by many months and are often the presenting complaint. They may also be the initial sign of relapse from remission. In contrast to the endocrine syndromes, the clinical manifestations of these syndromes are usually not responsive to hormone therapy. Subacute peripheral neuropathy is the most frequent neurologic syndrome. The Lambert-Eaton syndrome is characterized by proximal muscle weakness that improves with continued use and hyporeflexia and dysautonomia. Characteristic electromyographic findings confirm the diagnosis. The cause is related to autoantibody impairment of acetylcholine release from the cholinergic nerve terminals. Rare neurologic entities include cerebellar ataxia, retinal degeneration, intestinal dystonia, limbic encephalomyelitis, and necrotizing myelopathy.

STAGING EVALUATION AND PROGNOSTIC FACTORS

The goal of staging is to establish the prognosis, identify patients with disease confined to the chest who are appropriate for combined modality therapy, and assess whether a lung cancer patient will be at increased risk of mortality if treated with an aggressive chemotherapy program. Surgery plays a minor role in the management of this disease, and less than 10% of patients might be considered candidates for thoracotomy. As a result, the revised TNM system for staging lung cancer is not widely employed. Rather, a simpler system, introduced by the Veterans' Administration Lung Study Group (VALSG) is generally used. In the VALSG system, limited stage is defined as disease confined to one hemithorax that can be encompassed in a tolerable radiation field. These patients are currently treated with a combined modality approach. In all other settings, patients are considered to have extensive-stage disease. At presentation, after appropriate staging procedures are performed, 60% to 70% of patients with SCLC have extensive disease and 30% to 40% have limited-stage disease.

In the VALSG staging system, the appropriate classification of selected sites remains controversial. These sites include an ipsilateral pleural effusion, supraclavicular lymphadenopathy (ipsilateral or contralateral), or contralateral mediastinal lymphadenopathy. Several large series have failed to identify a difference in survival between patients with an isolated ipsilateral pleural effusion compared with other patients with limited SCLC, and many groups have included patients with
ipsilateral pleural effusions within their definition of limited-stage disease. However, only 2% to 7% of all patients with otherwise limited SCLC have an isolated pleural effusion, so that small differences in outcome associated with this clinical factor might be missed. In an analysis of two large cooperative group databases, which included in toto more than 4000 patients, the survival of patients with an isolated effusion was similar to patients with one site of extensive disease. In one of these analyses, an isolated effusion conferred a poorer survival compared with other patients classified as having limited disease, which was of borderline significance ($P = 0.051$). In clinical practice, small effusions, usually detected by computed tomography (CT) scan, are sometimes difficult to evaluate. It is assumed that these lesions are malignant, unless there is a transudate, nonmalignant, and cytologically negative on repeat examination. Several clinical judgment in individual cases should be applied for selection of these patients for combined modality therapy until this issue is addressed in a prospective trial.

Although most randomized trials evaluating the role of combined modality therapy in limited-stage SCLC have excluded patients with an ipsilateral pleural effusion, this group usually included patients with ipsilateral, and sometimes contralateral, supraventricular lymph node metastases. The presence of supraventricular lymphadenopathy is commonly associated with extensive disease, but when encountered in patients with otherwise limited disease (5% of cases), carries a trend toward poorer survival. Contralateral mediastinal involvement is also usually classified as limited-stage disease. However, two randomized studies that evaluated the use of the more aggressive, twice daily, radiation regimen, excluded patients with contralateral hilar disease, presumably to reduce the volume of irradiated field and their risk for lobar or cycle failure. If this form of more intensive radiotherapy becomes a standard of care, the potential prognostic significance of the extent of mediastinal nodal involvement will need to be reexamined. Patients with limited-stage disease who present with superior vena cava syndrome have a similar prognosis to other patients with limited-stage disease and have been included in randomized studies investigating the role of combined modality therapy.

Several series have identified a more favorable outcome for patients with “very limited” disease, that is a tumor confined to the lung without evidence of spread to the mediastinum. Retrospective analysis of the University of Toronto database demonstrated that patients without evidence of mediastinal metastases by CT scan or mediastinoscopy who were treated with chemotherapy and radiation had a median survival of almost 16 months and a projected survival at 5 years of 18%. This was significantly better than other patients with limited disease who had more extensive tumor burden. Patients who undergo surgical resection and have an absence of mediastinal metastases have an especially favorable outcome. Survival in this select group is between 50% and 60%. Among the patients with extensive disease, a number of studies have shown that the number of metastatic sites is an important parameter.

OTHER PROGNOSTIC FACTORS

In addition to disease extent based on Valsalva stage, multivariate analyses suggest that performance status and the serum LDH are the most reproducible prognostic factors. Performance status reflects both the underlying extent of the disease and partially dictates tolerance for the intensity of treatment. Although patients with a lower performance status are at a higher risk for treatment-related complications, they may still benefit from a combined modality approach.

An elevated LDH is seen in 33% to 57% of all patients with SCLC, and up to 85% of patients with extensive-stage disease. Biochemical parameters, such as an elevation of the LDH and neuron-specific enolase, are strong predictors of poor outcome in SCLC. Male gender is an adverse prognostic factor in some, but not all series. Older age has been an independent adverse prognostic factor in limited disease in some series, but not in others. Older age often results in a compromised dose intensity, usually due to treatment delays.

Molecular studies have identified several specific lesions involved in the pathogenesis of SCLC, and the prognostic import of the gain or loss of function of these critical genes and gene products is now being evaluated clinically. Drug sensitivity testing in vitro may be useful to guide selection of a chemotherapy regimen, but with current methodologies it is feasible in only a minority of patients and is labor intensive.

ASSESSMENT OF RISK

In many respects, treatment for SCLC is as demanding as a thoracotomy and pulmonary resection. In some large cooperative group trials, treatment-related mortality has exceeded 10%. Accordingly, a careful assessment of a patient’s ability to undergo aggressive therapy, particularly if concurrent chemotherapy and radiation are planned, is warranted. Several retrospective analyses have attempted to identify patients at increased risk for a treatment-related mortality. An analysis of 382 patients treated in a single institution identified age older than 50 years, Karnofsky performance status less than or equal to 50, treatment with a regimen containing three drugs or more, and a prior hypoplastic or aplastic episode as risk factors for chemotherapy-related death. In this study, older patients with a poor performance status had a 22-fold greater risk of death than patients without those risk factors. In another study involving 610 patients, each one of the 71 fatalities that occurred during the first cycle of VP-16-based chemotherapy was matched to the next patient enrolled on the trial. Patients dying early were more likely to have a poor performance status, clinical hepatomegaly, a low serum albumin, and elevations of the blood urea nitrogen and serum alkaline phosphatase. The Copenhagen Lung Cancer Group compared 937 patients treated in its two most recent studies with 819 patients treated in early clinical studies. The mortality during the first cycle of chemotherapy in the recent studies was threefold higher (12.6% vs. 4.2%) compared with the earlier trials. An algorithm was developed to identify high-risk patients that included age, performance status, and serum LDH. Patients were defined as high risk if they had a poor performance status (Eastern Cooperative Oncology Group [ECOG]) 3 or 4, or if they were 65 years old or older and had a serum LDH that was more than twice the upper normal level. Based on this algorithm, 21% of the 937 patients would be considered at high risk. In this high-risk group, the median survival time was 133 days, and the 2-year survival was 4.5%. Mortality during the first cycle of chemotherapy in this group was 33%, and among patients treated without chemotherapy the frequency was 41%. Of note, more than one-half of these early deaths occurred in older patients with an elevated LDH who had a preserved performance status. For these high-risk patients, therefore, less intensive chemotherapy would be appropriate, and careful monitoring and support during treatment is mandatory.

STAGING PROCEDURES

Autopsy and clinical studies have shown that SCLC commonly disseminates to soft tissue and multiple viscera. The head and neck are frequent sites of involvement will need to be reexamined. Patients with limited-stage disease who present with superior vena cava syndrome have a similar prognosis to other patients with limited-stage disease and have been included in randomized studies investigating the role of combined modality therapy. Drug sensitivity testing in vitro may be useful to guide selection of a chemotherapy regimen, but with current methodologies it is feasible in only a minority of patients and is labor intensive.

CT scanning detects intraabdominal lesions in approximately 35% of patients with SCLC at presentation. By the use of chest and abdominal CT, locally advanced or distant disease is diagnosed in 94% to 96% of patients. CT has an accuracy of 85% in detecting liver metastases in SCLC overall, and that increases in patients with abnormalities in liver function test results. Involvement of the adrenal glands by metastatic tumor is almost always clinically silent. Clinical studies have implicated the adrenals as the only metastatic site in SCLC in 8% to 11% of patients at presentation; however, the majority of these cases were not biopsy proven. In autopsy series, adrenal metastases are seen in 35% to 65% of patients with SCLC. The accuracy of noninvasive imaging in differentiating between adenomas and adrenal metastases in patients with lung cancer has been substantial, although newer magnetic resonance imaging (MRI) techniques, such as chemical shift imaging, may improve the accuracy of MRI in differentiating adenomas from metastatic deposits.

Brain metastases are found in 10% of SCLC patients at the time of diagnosis. The cumulative risk for brain metastases increases with survival. Multiple lesions

Older age has been an independent adverse prognostic factor in limited disease in some series, but not in others. Older age often results in a compromised dose intensity, usually due to treatment delays.

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Brain metastases are found in 10% of SCLC patients at the time of diagnosis. The cumulative risk for brain metastases increases with survival. Multiple lesions
are usually found in autopsy in patients with CNS involvement. Leptomeningeal involvement is extremely rare at presentation, but may develop antemortem in 2% to 13% of patients. The majority of these patients have simultaneous brain metastases. The usefulness of a pretreatment brain scan in asymptomatic patients is controversial. Although the yield of brain CT in patients with neurologic abnormalities is high (42% to 88%), it is only 3% to 8% in asymptomatic patients with SCLC. In a patient in whom metastatic disease has been demonstrated by another test or who is not a potential candidate for thoracic irradiation for other reasons, imaging the brain is probably not a mandatory component of the initial staging evaluation. If asymptomatic brain metastases are present, chemotherapy may be adequate treatment, and the early detection and treatment of asymptomatic brain metastases with radiation therapy has not been shown to significantly improve patient outcome, partly due to the effect of systemic failure on survival. If brain metastases are the single site of distant disease, the prognosis may not be significantly altered because the median survival compared with patients with limited disease has been comparable in some series, although not in others. A CT of the brain is needed in patients considered for prophylactic cranial irradiation, as the presence of clinically occult metastases would affect treatment planning.

Up to 40% of patients with SCLC have a positive radionuclide bone scan at diagnosis; in fewer than 10% of cases this is the only site of metastatic disease. Bone involvement shown by bone scan is frequently detected in asymptomatic patients with SCLC and correlates with an elevated alkaline phosphatase level and bone marrow positivity. Further diagnostic evaluation with a plain radiograph and in some cases with a bone CT scan or MRI may be required to investigate areas of equivocal findings that could be due to osteoarthritis or trauma. In assessing response, repeat bone scanning is helpful but not sufficiently reliable. In some cases, patients demonstrate a more intense uptake of metastatic lesions on bone scan, which reflects bone regeneration and is a sign of response to therapy.

The bone marrow is involved in 15% to 30% of patients with SCLC at presentation, but is uncommonly the only site of metastatic disease. As a result, routine bone marrow examinations rarely modify staging. The yield of bone marrow biopsy can be increased by in vitro semisolid cultures of bone marrow aspirates or immunostaining with anti-SCLC monoclonal antibodies, which are positive in 10% and 15% to 66% of histologically negative bone marrow, respectively. However, the clinical significance of bone marrow involvement demonstrated by these methods has not yet been determined. A leukoerythroblastic picture on the peripheral blood, which is present in 8% to 15% of cases at presentation, is highly specific for extensive bone marrow infiltration by SCLC. Severe thrombocytopenia, with a platelet count of less than 50 x 10^9/L, and an elevated LDH are also suggestive of bone marrow metastases. Bone marrow involvement usually coincides with bone and liver metastases, but not with CNS involvement. At least one-half of the patients with a positive bone marrow result have bone metastases detected by bone scan. In patients with a normal bone scan, normal LDH, and no evidence of thrombocytopenia or peripheral blood leukoerythroblasticosis, the yield of bone marrow biopsy is extremely low, and it can be omitted.

MRI allows for the noninvasive evaluation of large volumes of bone marrow and is a sensitive method for detecting bone marrow involvement by SCLC. Bone marrow positivity by MRI has been reported in 30% to 60% of patients with SCLC and identifies marrow involvement missed in the initial biopsy in 3% to 19% of patients. Circulating malignant cells detected by reverse transcriptase polymerase chain reaction for cytokeratin can be found in the peripheral blood of 27% of SCLC patients. The significance of this finding should be investigated.

PET scan has emerged as a promising imaging modality in lung cancer. Most commonly, a radiolabeled glucose analogue, glucosel-2-deoxy-g-glucose, has been used to demonstrate differences in the metabolism of normal and neoplastic cells. The potential role of PET scan in assessing a solitary lung nodule and mediastinal involvement by tumor has been demonstrated in multiple studies and has also proven valuable in the detection of unexpected extrathoracic disease. Thus, as PET continues to technically improve and become more widely available, it may assume an important role in the staging of SCLC.

Technetium-labeled monoclonal antibody imaging has been evaluated as a staging method in SCLC. The accuracy of this imaging modality in staging patients with SCLC is approximately 90%. However, it has limited value in detecting liver metastases or lesions smaller than 2 cm. The presence of somatostatin receptors in SCLC, a neuroendocrine neoplasm, has made possible the use of radiolabeled somatostatin analogues for the imaging of patients with SCLC. Somatostatin receptor imaging is accurate in detecting the primary lesion and mediastinal lymphadenopathy in SCLC, but has not shown sufficient sensitivity (50% or less) in detecting sites of metastatic disease.

**TREATMENT**

Early efforts at the management of SCLC with surgery were characterized by incomplete staging both before and during thoracotomy. Nevertheless, in the 1960s some studies reported 5-year or longer survival in more than 10% of the patients. These results, however, were overshadowed by two studies in the 1970s that provided philosophical justification for not using a surgical approach in this disease. The British Medical Research Council published a 144-patient trial that demonstrated the modest superiority of radiotherapy as primary treatment for operable SCLC. Shortly thereafter, an American study compared the survival of 146 operable but nonresected patients with 41 resected patients and found no differences.

<table>
<thead>
<tr>
<th>Group</th>
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<th>Mean Survival (yr)</th>
<th>Survival Rate</th>
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<td>57</td>
</tr>
<tr>
<td>Radiation</td>
<td>71</td>
<td>3.9</td>
<td>30</td>
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*One patient evaluated with surgery + radiotherapy.
*Significantly survival difference (P < 0.05) in favor of radiotherapy.

**TABLE 31.3-2.** Survival in Patients with Operable Small Cell Lung Cancer Randomized to Surgery or Radiotherapy

The inadequate results with surgery or radiation alone, even in carefully selected patients, highlighted the need for systemic treatment in SCLC, and the primary role of chemotherapy in the management of this disease is now well established. In a study conducted in the late 1960s testing various alkylating agents, cyclophosphamide was shown to double survival compared with supportive care in patients with extensive disease, and shortly thereafter a combination of cyclophosphamide with radiation was shown to improve survival compared with radiation alone in patients with limited disease. An extensive evaluation of the drugs then available demonstrated that anthracyclines and vinca alkaloids, along with certain alkylating drugs, produced single-agent response rates of up to 50%. The antimetabolites appeared to be less active, with response rates reported of 20% to 30%. In the 1980s the epipodophyllotoxins (VP-16 and VM-26) and the platinum analogues were introduced, and their activity ranged from 40% to 60% in previously untreated patients. During the 1990s, two new classes of chemotherapeutic agents, the taxanes and the camptothecins, entered clinical practice and are establishing a role in the management of this disease.

**DEFINITIONS OF ACTIVE CHEMOTHERAPY AND STRATEGIES FOR EVALUATING NEW AGENTS**

As agents such as cyclophosphamide and doxorubicin became established in the management of this disease, it became clear in the evaluation of new drugs that exposure to prior chemotherapy and response to this therapy were at least as important as other known prognostic factors in predicting response to the new agent. For example, the epipodophyllotoxins produce response rates of 40% to 90% in untreated patients, but in relapsed patients the response rate to VP-16 and VM-26 were 5% to 12% and 20%, respectively. Based on retrospective analysis of the activity of effective chemotherapy drugs in different populations, response rates greater than or equal to 10% in patients with refractory disease, greater than or equal to 20% in patients in sensitive relapse (typically defined as response to initial therapy and a treatment-free interval of longer than 3 months before disease progression), and greater than or equal to 30% in patients with previously untreated extensive disease have been proposed as the appropriate targets to declare a new chemotherapy drug active. Because of the biologic aggressiveness of SCLC, the patient population that should be selected to test new drugs remains controversial. Clinical trials that enroll patients with refractory disease, for example, pose the least risk that outcome might be compromised if the new agent turns out to be inactive. However, substantially more patients would
need to be evaluated to establish a response rate of greater than or equal to 10% than would be necessary to establish a response rate of greater than or equal to 30% in previously untreated patients. This means that a much larger number of patients would be exposed to the toxicity of a new drug before it is rejected. Thus, the initial testing of new drugs in patients with sensitive relapse has been proposed as a reasonable compromise, although evaluation in previously untreated patients may be reasonable for new drugs of particular promise.

STANDARD CHEMOTHERAPY AGENTS AND ANALOGUES OF STANDARD AGENTS

A number of chemotherapy drugs fulfill the criteria for activity outlined in the previous section. Several of these drugs, such as nitrogen mustard, methotrexate, altretamine, and camptothecin, are seldom used today. In the 1990s, five drugs, or analogues of these five drugs, have been used in the management of SCLC (Table 31.3-3). Current treatment recommendations are based on the experience with these agents.

**Table 31.3-3. Active Agents in Small Cell Lung Cancer**

The activity of VP-16 is dependent on the schedule of administration. In randomized trials, bolus administration for 3 or 5 consecutive days repeated every 3 to 4 weeks is superior to one dose by bolus or 24-hour infusion every 3 weeks. Two studies that included a pharmacokinetic analysis suggested that the duration of exposure to a threshold concentration of VP-16 was an important determinant of efficacy and toxicity. The availability of an oral formulation has led to the development of more prolonged schedules. As a single agent, prolonged oral regimens of VP-16 were tested in previously treated patients and appeared to have activity comparable with the standard 3- to 5-day bolus schedule. When included in multidrug regimens, the schedule dependence of activity has not been demonstrated. In a randomized trial comparing cisplatin plus VP-16 given as an intravenous bolus for 3 consecutive days to cisplatin plus VP-16 given as a 21-day oral regimen, there was greater hematologic toxicity with no improvement in response or survival in patients receiving the prolonged oral regimen. Continuous infusion of VP-16 for 72 hours was not superior to a 3-day bolus in combination with cisplatin.

Cisplatin has been evaluated as a single agent, particularly in patients who have had previous treatment, and response rates from these studies approximate 15%. Carboplatin produces a comparable response rate in previously treated patients, and in newly diagnosed patients a 60% response rate has been observed. Ifosfamide is an analogue of cyclosophamide that appears to be at least as active as cyclophosphamide in the treatment of SCLC. In newly diagnosed patients, response rates of 50% to 65% have been reported. Teniposide is an analogue of VP-16 and, in a randomized trial in newly diagnosed patients with extensive disease, produced a response rate of 43%, compared with a response rate of 49% for ifosfamide and 56% for the standard cyclophosphamide, doxorubicin, and vincristine (CAV) regimen. At the dose tested, hematologic toxicity and life-threatening complications were much more common in the patients treated with CAV. In other phase II studies, the response rate of teniposide has ranged from 38% to 90%, and in one, 5 of 30 patients experienced a toxic death, underlying the importance of patient selection in determining response and toxicity.

As a single agent, epirubicin has been shown to produce a response rate of approximately 50% in previously untreated patients with extensive disease.

NEWER CHEMOTHERAPY AGENTS

The taxanes bind microtubules and promote microtubular assembly. This interferes with tubulin depolymerization, resulting in a disruption of cell division. In an ECOG study, paclitaxel at a dose of 250 mg/m² infused over 24 hours produced a response rate of 34%. The North Central Cancer Treatment Group used a similar schedule with the addition of granulocyte colony-stimulating factor (G-CSF) support and reported a response rate of 53% with a reduction in the grade IV leukopenia to 14%. Docetaxel at a dose of 100 mg/m² has been reported to produce a response rate of 25% in untreated patients and at a dose of 60 mg/m² a response rate of 13.5% in previously treated patients.

Camptothecin is a plant alkaloid that has the unique mechanism of action of interacting with topoisomerase I, a nuclear enzyme that plays a key role in DNA metabolism. Schiller et al. treated 48 chemotherapy-naive patients with extensive-stage SCLC with intravenous topotecan at 2 mg/m² for 5 days, repeated every 3 weeks. Most patients received G-CSF support. The regimen was active, with a response rate of 40%, 1-year survival of 39%, and median survival of 10 months. In patients progressing or relapsing shortly after completing chemotherapy, the response rate was 6% to 11%. Pooled data from three multicenter studies showed a response rate of 18% in 168 patients in sensitive relapse (>3-month interval from previous chemotherapy treatment); the median survival was 30 weeks, and the 1-year survival was 21%. A randomized trial comparing topotecan with CAV in patients with sensitive relapse demonstrated comparable response rates and survival for the two regimens. Topotecan is also available in an oral formulation, and this preparation appears to be at least as active as the intravenous drug.

Gemcitabine, a pyrimidine antimetabolite, produced responses in 7 of 26 (27%) previously untreated patients with extensive disease and 12 of 19 (63%) patients resistant to cisplatin and VP-16. Preliminary results in another study enrolling patients with resistant disease identified three brief remissions in 12 evaluable patients, which together with the demonstrated activity of gemcitabine in previously treated non-SCLC suggests that the mechanism of drug resistance may differ between gemcitabine and other agents used to treat lung cancer.

Vindesine (Vindesine) is a new vinca alkaloid that in previously treated patients has produced a response rate of 12% to 16%. The activity in newly diagnosed patients with extensive disease was 20%. Because vindesine is well tolerated in an elderly population, it may be a useful component of palliative combination regimens. In combination with carboplatin, for example, it produced a response rate of 74% (32 of 43 patients) and a median survival of 37 weeks in patients with extensive disease.

COMBINATION CHEMOTHERAPY

After the activity of cyclophosphamide was established in SCLC, multidrug combinations were developed and tested (Table 31.3-4). Randomized trials of these early combinations demonstrated superior activity to single-agent cyclophosphamide. The combination of cyclophosphamide, doxorubicin, and dacarbazine produced a higher response rate and survival when compared with an equally toxic dose of single-agent cyclophosphamide. Hansen et al. demonstrated that the addition of vincristine to the combination of cyclophosphamide, doxorubicin, and CCNU improved survival compared with the three-drug combination, highlighting the usefulness of this relatively nonmyelotoxic agent in combination therapy.

Livingston et al. developed the CAV combination, and this became a standard.
With the identification of VP-16 as an important new agent, several modifications of the CAV regimen that included VP-16 were tested. In extensive disease, a slight improvement in survival was noted when VP-16 replaced either doxorubicin or vincristine, although greater myelosuppression was evident in the cyclophosphamide, doxorubicin, VP-16 (CAVE) arm in the latter trial. Hong et al. compared intensive CV (with the dose of cyclophosphamide increased from 1000 to 2000 mg/m²) with and without VP-16, and reported that patients treated with CV had a shorter survival and experienced more myelosuppression than patients treated on the other two arms. Substitution of VP-16 for methotrexate in the tomustine, cyclophosphamide, vincristine, and methotrexate regimen also improved survival. Administration of the VP-16 beginning on day 3 produced better survival but more myelosuppression than beginning the VP-16 on day 14 of the cycle, perhaps because this schedule provided greater dose density, or perhaps because it delivered the VP-16 at a point at which more tumor cells were in cell cycle and therefore more susceptible to the drug.

Five randomized trials have evaluated the addition of VP-16 (CAVE) to the CAV regimen. In three studies, the doses of CAV were equivalent in each arm. Not surprisingly, in these studies the addition of VP-16 resulted in increased hematologic toxicity. Although a better response rate was evident in the arm containing VP-16 in at least some patient subsets in each of these studies, there was an improvement in response duration (of 3 months) and survival (of 6 weeks, P = .03) in only one study. In the last study, Jeit et al. compared CAVE with CAV in 231 patients with limited disease. Despite a reduction in the dose of cyclophosphamide by 33%, there was still greater myelosuppression in the CAVE arm. There was a small improvement in median and 2-year survival with CAVE, which was not statistically significant. Two randomized studies intensified components of this regimen: In one the cyclophosphamide was increased from 1000 to 1200 mg/m² and the dose of doxorubicin increased from 40 to 75 mg/m² in the CAVE arm compared with the CAV arm. The regimens produced equivalent myelotoxicity, response rates, and survival. These results were comparable with the outcomes with less intensive CAV regimens in extensive disease.

The VP-16 and cisplatin (EP) regimen was tested in SCLC because this combination produced synergistic activity in preclinical systems and was established as an active regimen in other diseases. Evans et al. reported response rates of 55% in patients previously treated with CAV and 86% in newly diagnosed patients. Fox et al. reported that two cycles of consolidation with EP added to patients who were responding to six cycles of CAV had a longer survival than patients randomized to CAV only. Prospective studies comparing these two regimens showed comparable response and survival, with a significant reduction in toxicity with EP. There was less myelosuppression with EP, and if given with radiation, patients experienced less esophagitis and interstitial pneumonitis. Consequently, EP became an alternative to CAV as the frontline regimen for SCLC.

Carboplatin can be substituted for cisplatin with no loss of activity and improved tolerance. In combination with VP-16, Bishop et al. reported a response rate of 77% and 58% for limited and extensive disease, respectively. Moreover, randomized trials of multagent regimens in which the two platinum analogues were compared suggested that they were at least equivalent. The Hellenic Cooperative Oncology Group randomized 147 patients to receive VP-16, 100 mg/m², days 1 to 3, and cisplatin, 100 mg/m², or carboplatin, 300 mg/m², along with concurrent radiation. Response and survival were similar in the two arms, although the toxicity, particularly nausea, vomiting, nephrotoxicity, and neurotoxicity, were significantly lower in the patients who received carboplatin. Myelosuppression was also less in the carboplatin arm, but this was not statistically significant. In another large randomized trial, induction with teniposide, vincristine, and either carboplatin or cisplatin produced equivalent activity and toxicity.

Ifosfamide produces less myelosuppression than cyclophosphamide and has significant single-agent activity. Ifosfamide has been substituted for cyclophosphamide in the CAV regimen. Combinations of ifosfamide with cisplatin and etoposide have also been tested. The three-drug regimen VP-16, ifosfamide, and cisplatin, initially tested in refractory germ cell tumors, has also been evaluated. In patients with SCLC, a population that is older and has more comorbid illness than patients with germ cell tumors, a 20% reduction in dose intensity was necessary to avoid excessive myelosuppression. In a randomized trial comparing VP-16, ifosfamide, and cisplatin with EP, one study, which enrolled only patients with extensive disease, identified a significant, although small, difference in both median survival (9.0 vs. 7.3 months) and 2-year survival rates (13% vs. 5%). Myelosuppression was more severe in the arm treated with ifosfamide. Carboplatin has been substituted for cisplatin in regimens that also include ifosfamide, doxorubicin, and VP-16 (ICE), and in single-arm studies impressive response rates and cumulative myelosuppression have been reported. Other three-drug regimens that incorporate these agents, such as ifosfamide, doxorubicin, and VP-16, have been tested but have not been demonstrated to be superior to either EP or CAV.

Several studies are in progress evaluating camptothecin (topotecan or irinotecan)-based regimens in SCLC. In combination with platinum agents, response rates are between 17% and 29% in previously treated patients and 73% and 84% in newly diagnosed patients. Preliminary results of a multicenter randomized trial in Japan found that the combination of irinotecan and cisplatin produced superior survival than the standard VP-16 and cisplatin regimen in patients with extensive stage disease. Combinations of camptothecins with other agents in SCLC are also being evaluated, and many have shown significant activity, albeit with substantial associated myelosuppression. Three-drug regimens, such as paclitaxel, cisplatin, and topotecan, are also being developed.

DURATION OF CHEMOTHERAPY

Through the 1970s, sensitive tumors were often treated with chemotherapy for periods that might extend up to 2 years. This meant that most patients with SCLC received uninterrupted chemotherapy until disease progression or death. In 1984, Feld et al. reported that six cycles of CAV and thoracic irradiation produced survival comparable with the results of a previous treatment program that provided 12 months of maintenance therapy. Subsequently, a large number of randomized trials examined whether maintenance chemotherapy prolonged survival. A few studies have suggested that prolonged treatment programs improve survival, at least in certain patient subsets. The CALGB randomized 258 patients to one of four chemotherapy regimens, and 57 patients in complete remission underwent a second randomization to maintenance therapy or observation. Among the 46 patients with limited disease who proceeded to the second randomization, the median survival was improved with maintenance chemotherapy (16.8 vs. 6.8 months). However, the induction regimens utilized in this study might be considered inferior to currently used treatments. The Medical Research Council randomized 265 patients who had responded to six cycles of induction chemotherapy to an additional six cycles of maintenance or observation. Overall, there was no difference in survival between patients treated with 12 or 18 cycles of chemotherapy, though for patients in complete remission at the time of second randomization, a subset analysis suggested that maintenance may provide a survival benefit. In a second British study, patients treated with six cycles of CAV were randomized to six additional cycles of the same chemotherapy or observation. Most of the patients treated in this study were in complete or near complete remission. For the patients with extensive disease, the median survival was improved by approximately 4 months with maintenance treatment. An additional trial, organized by the Eastern Cooperative Oncology Group (ECOG), randomized patients to CAV alternating with another three drug combination or CAV alone. After six to eight cycles of induction, patients in complete remission underwent a second randomization to maintenance treatment or observation. Patients assigned to CAV and maintenance treatment had a longer progression-free survival and overall survival (P = .09) than patients who received only CAV with no maintenance. For the patients who received the six-drug regimen, those who were given no maintenance survived longer than those who received maintenance treatment. In contrast, four other studies that randomized patients to five or six cycles of chemotherapy or a total of 12 cycles of chemotherapy found no difference in outcome. Among these studies, only one trial evaluated maintenance therapy in complete responders, one study included both complete and partial

**TABLE 31.3-4. Commonly Used Chemotherapy Regimens**
responders. In summary, these studies do not exclude the possibility that there is a subset of patients, perhaps those with particularly chemotherapy-sensitive disease treated with moderately intensive chemotherapy, who may derive a benefit from a maintenance program beyond five to eight cycles of standard chemotherapy. In unselected patients, however, treatment programs that extend beyond six cycles of chemotherapy have not demonstrated an advantage in survival and may be associated with inferior quality of life.

A number of additional studies have evaluated whether four cycles of chemotherapy are adequate. Spiro et al. designed a study that included a double randomization at diagnosis. Patients received four or eight cycles of CEV and on relapse received additional chemotherapy or supportive care. Of the four treatment arms, patients who received four cycles of chemotherapy and only supportive care at relapse had a significantly inferior median survival of 30 weeks. Thus, in this study four cycles of treatment were adequate if chemotherapy was offered to patients appropriate for additional therapy at relapse. Two additional studies also evaluated four cycles of induction with longer treatment programs. Both studies found survival with the longer treatment program to be similar to the shorter program. The Medical Research Council randomized a total of 458 patients to treatment with VP-16, cyclophosphamide, methotrexate, and vincristine (ECMV) for three cycles, ECMV for six cycles, or VP-16 and ifosfamide for six cycles. The median survival for patients treated for only three cycles was approximately 1 month shorter than for patients who received one of the regimens given for six cycles. Although this difference was not statistically significant, the study was not sufficiently powered to exclude a small advantage with longer treatment programs. Among the more symptomatic patients, palliation of symptoms was slightly better for those treated with the ifosfamide and VP-16 combination, but the differences between the three arms were small.

In summary, four to six cycles of induction chemotherapy appear to be optimal in the management of both limited and extensive SCLC. Maintenance chemotherapy beyond induction is of unproven value but may play a role in selected patients, depending on the sensitivity of their disease to chemotherapy and the induction regimen they received. Treatment at relapse should be considered if clinically appropriate.

GENERAL APPROACH TO PATIENTS WITH LIMITED DISEASE

An overview of the management of patients with limited disease is shown in Figure 31.3-1. An occasional patient has stage I disease by noninvasive staging; if this patient is a candidate for thoracotomy, a mediastinoscopy should be considered to ensure that mediastinal nodal metastases are not present before thoracotomy is attempted. Adjunct chemotherapy is indicated in patients whose disease is resected. Other patients with limited disease should be carefully evaluated to determine their capacity to undergo combined modality therapy. Most patients who are not candidates for a clinical protocol should receive four to six cycles of chemotherapy and radiation to the chest. In limited disease, the CAV regimen produces an overall response rate of 80% to 90%, a complete remission rate of 50% to 60%, a median survival time of 12 to 16 months, and a 3-year disease-free survival of 10% to 15%. The VP-16 and cisplatin regimen appears to be at least as active as CAV and is associated with less toxicity if given with concurrent radiation.

Intrathoracic SCLC appears optimally treated with 150 cGy twice a day to a total dose of 4500 cGy in 3 weeks. At least 4 (and preferably 6) hours between treatments are allowed. Customized blocks are used to limit exposure to normal tissues throughout the entire 3-week period. Initial portals are delivered anteriorly and posteriorly each day, switching to a posterior obliqued field to limit direct spinal cord dose to approximately 3600 Gy. Occasionally, a patient's pulmonary function is insufficient for these treatments are allowed. Customized blocks are used to limit exposure to normal tissues throughout the entire 3-week period. Initial portals are delivered anteriorly and posteriorly each day, switching to a posterior obliqued field to limit direct spinal cord dose to approximately 3600 Gy. Occasionally, a patient's pulmonary function is so marginal that a conscious decision is made not to shift to oblique fields because of fear of expanding total treatment volume and thereby increasing the risk of radiation pneumonitis in high-risk patients. In this setting, it becomes imperative to use a spinal cord block that is suboptimal from the standpoint of tumor control but essential from the standpoint of minimizing the risk of myelopathy. Conformal planning may help in this dilemma, but one must acknowledge that our quantitative knowledge of partial organ tolerance is presently negligible.

Some authors have advocated radiation doses up to 6000 cGy for SCLC. In conjunction with mitotane chemotherapy, the routine need for such doses appears doubtful because of the impressive responsiveness of this neoplasm to both chemotherapy and radiation.

The sequencing of radiation and chemotherapy remains controversial and is more fully discussed later in this chapter (see Sequencing of Radiation with Chemotherapy). Concurrent rather than sequential administration of chemotherapy and radiation has produced superior survival in some but not all studies. Concurrent therapy can produce more toxicity than sequential chemotherapy and radiation, and because there is a broad range among individual patients in their capacity to tolerate aggressive therapy, a challenge in designing a treatment program is to satisfy the need to deliver optimal treatment without exposing patients to unacceptable toxicity. After induction therapy, most centers recommend prophylactic cranial irradiation to patients if they have achieved a complete or near complete remission. Some patients with significant adverse prognostic factors may be best served with treatment programs that attenuate the dose and duration of the standard regimens. At the time of disease progression, treatment with an alternative chemotherapy regimen (or even the initial induction regimen if there was an especially long initial remission) should be considered.

ROLE OF RADIOTHERAPY IN LIMITED DISEASE

The systemic nature of SCLC, even when it appears to be localized after careful staging procedures, precludes complete reliance on any local form of treatment. Most patients with limited-stage disease who were treated with chest irradiation alone rapidly developed distant metastases, emphasizing the need for primary systemic treatment. After combination chemotherapy began to be used in the management of SCLC in the 1970s, the response rate and improved survival that resulted led to speculation that chest irradiation added toxicities while contributing little or no therapeutic advantage in patients treated with chemotherapy. However, this neoplasm is also the most responsive of all cell types of lung cancer to thoracic radiotherapy, with objective tumor regression occurring in more than 90% of patients, and the primary tumor is the site of progression in up to 80% of relapsing limited-stage patients treated with chemotherapy alone. Thus, it would seem to be logical to combine chemotherapy and chest irradiation in these patients.

Retrospective reviews of numerous nonrandomized studies using chemotherapy with or without chest irradiation for limited-stage disease revealed the following facts: (1) A lower rate of chest relapse was seen with combined modality therapy, although the frequency of local recurrence still approached 33%; (2) hospitalization time was increased, and organ complications were increased with combined modality treatment, and (3) although median survivals were similar, the 2-year disease-free survival appeared superior for combined modality therapy compared with that achieved with chemotherapy alone.

Retrospective data, however, suffer from many deficiencies. Because chemotherapy alone is less toxic than combined modality therapy, there may have been a consistent bias against giving combined modality therapy to poor-risk patients. If the administration of radiotherapy is delayed for several chemotherapy cycles, patients who develop early progression are generally excluded from receiving radiation. An analysis of local relapse may sometimes be misleading because the definition of what constitutes a relapse may be heterogeneous. Variations in dose and schedule of the radiation and specific chemotherapy programs used further complicate comparison of relapse rates from different series. Less effective chemotherapy combined with effective radiation reduces the site of first failure in the chest because distant metastases are more prone to develop, whereas more effective chemotherapy combined with less effective radiation yields the opposite result. All
these factors make it difficult to assess the value of adding chest irradiation to combination chemotherapy when reviewing uncontrolled data.

**Sequencing of Radiation with Chemotherapy**

The problem of how to integrate chemotherapy and radiation therapy remains far from standardized. Concurrent therapy is defined as combined modality treatment in which chemotherapy and radiation therapy are administered throughout the same time period. In alternating therapy, radiation therapy is administered on days during which no chemotherapy is given, followed by a chemotherapy cycle, and the process is repeated for several iterations of interdigititation. Sequential therapy is defined as the administration of chemotherapy and radiotherapy separately in time, with one modality being given last after completion of the other, often associated with a delay for the second modality to allow the patient an adequate recovery from the initial treatment modality. Several randomized studies reported borderline or significantly improved survival using combined modality treatment. Two of these used concurrent radiotherapy §. One, alternating radiotherapy §, and two, sequential radiation §. The magnitude of survival benefit was modest, ranging from 1 to 4 months in improvement in median survival and increases in the 2-year survival from 7% to 17%. The two studies with the longest follow-up demonstrated less advantage beyond 5 years for patients given radiotherapy, partially because of second primary lung cancers. Of the studies not demonstrating improved survival without chest irradiation, two used sequential radiation therapy and one a concurrent regimen in which chemotherapy was given concurrently with irradiation. The negative trial conducted exclusively in patients in complete remission from chemotherapy was initiated because of earlier uncontrolled data suggesting marked improvement in disease-free survival when radiation was given to complete responders at the completion of drug administration. The randomized trial showed a lack of survival benefit from consolidation therapy when irradiation was given after chemotherapy was completed. Combined modality therapy also increased the complete response rate in most of trials and also significantly reduced chest recurrence rates.

A 1992 metaanalysis evaluated randomized trials in which more than 2100 limited-stage small cell lung cancer patients were randomized to receive either concurrent chemotherapy plus thoracic irradiation or chemotherapy alone. Patients given combined modality therapy had a 14% reduction in death rate, and an absolute 5.4% improvement in 3-year survival compared with those receiving chemotherapy alone. Both differences were highly significant in this metaanalysis. This study reinforces the results of individual studies that demonstrated modest but statistically significant improvement in survival after combined modality treatment. A second and independent metaanalysis reached similar conclusions.  

Whether the variations in the temporal relationships of the radiation therapy and chemotherapy components of combined modality treatment influence the antitumor effects is by no means resolved. Concurrent and alternating combined modality programs that do not incorporate planned delays in chemotherapy for radiotherapy administration may possess superior efficacy. Among the randomized trials, three of four concurrent or alternating programs yielded improved survival, whereas one of three sequential programs produced only marginally significant improvement favoring radiation. However, indirect comparisons from the metaanalysis do not document significant survival advantages for any of the three methods of combining chemotherapy with irradiation.  

The dose of thoracic irradiation needed to control local regional SCLC was initially thought to be reduced when chemotherapy was given with irradiation. Because improved drug treatment yielded better control of distant metastases, however, a high frequency of local failures with lower dose schedules such as 3000 cGy in 2 weeks became apparent. Retrospective data in patients given combined modality therapy suggested that doses higher than 5000 cGy were needed for optimal prevention of local regional failure, and one randomized trial demonstrated superior local tumor control with 3750 cGy compared with 2500 cGy. Many authorities recommend higher doses in the range of 4500 to 5000 cGy or more for optimal local control. Furthermore, simply because a radiotherapy program reduces local recurrences does not mean that it is optimal. 

Randomized trials have yielded conflicting results on whether concurrent irradiation is best given early or late in the chemotherapy program. One study by the Cancer and Acute Leukemia Group B found better results with delayed irradiation perhaps because a greater percentage of projected chemotherapy doses were actually administered. The National Cancer Institute of Canada trial came to the opposite conclusion. Indirect comparisons from the metaanalysis could not resolve this issue.  

Minimizing the toxicity of combined modality approach without compromising therapeutic efficacy is worthy of further research. The addition of chest irradiation has increased myelosuppressive, pulmonary, and esophageal complications of treatment, particularly with concurrent regimens. In the National Cancer Institute (U.S.) trial of 26% of combined modality patients developed severe pulmonary toxicity requiring hospitalization within a median of 2 months from the beginning of treatment compared with only 4% of patients given chemotherapy alone; moreover, five combined modality patients in complete remission died of this complication. In patients who responded completely, pulmonary function test results improved in patients given chemotherapy alone, but did not do so in patients receiving combined modality therapy. The Finnish Institute from Denmark, which also used concurrent chemotherapy and irradiation, reported 7% death from pulmonary and pericardial complications in complete responders. This frequency of cardiopulmonary complications among patients given combined modality treatment is clearly higher than what is seen in patients who are given chemotherapy alone.

One study analyzed the frequency of radiation pneumonitis in lung cancer patients treated with chemotherapy and chest irradiation. Almost 80% of the patients in this series had SCLC. In a multivariate analysis, the only factors that significantly correlated with the increased frequency of radiation-related pulmonary injury were individual fraction sizes of more than 2.50 Gy/fraction, twice daily fractionation as opposed to once-a-day fractions, and the total cumulative dose. Somewhat surprisingly, there were no significant differences among concurrent, alternating, and sequential combined modality treatments. Several trials reported high rates of esophagitis (with occasional strictures) and weight loss in patients given combined modality therapy. Not all concurrent combined modality programs report excessive pulmonary toxicity, suggesting that the selection of drugs combined with irradiation is influential in inducing some of these complications. Platinum and etoposide may be an especially suitable regimen for concurrent treatment in small cell carcinoma of the lung. Two successive trials of sequential combined modality treatment produced 4-year survival rates of approximately 10% in the Southwest Oncology Group; a subsequent trial in which a platinum-etoposide combination was given concurrently with chest irradiation beginning on the first day of therapy resulted in 30% 4-year survival, and severe pulmonary toxicity was seen only in one patient.

Although used less often, alternating regimens interdigitating chemotherapy and irradiation appear to have reduced pulmonary toxicity while maintaining the therapeutic advantage of adding radiation therapy. In one retrospective study, irradiating only the postchemotherapy tumor volume after several chemotherapy cycles did not appear to increase marginal recurrences and was also associated with a low frequency of radiation injury.

**Hyperfractionated Radiation**

Delivering chest irradiation in multiple daily fractions was theorized on experimental grounds to reduce long-term pulmonary toxicity while still maintaining antitumor efficacy. SCLC would appear to be an ideal neoplasm for twice-a-day treatment in that it has a high growth fraction, short cell-cycle time, and small to absent shoulder on the in vitro cell survival curve. Pilot studies in the late 1980s combining etoposide and platinum plus twice-a-day chest irradiation were promising, with median survivals greater than 2 years and in most series low rates of associated pneumonitis. An intergroup study randomized 417 patients with limited-stage SCLC to a program that included cisplatin and etoposide for four cycles and radiation therapy beginning on day 1 of the first cycle. The cumulative dose was 4500 rad in both arms, with one arm receiving the radiation in 180-Gy fractions daily and the other arm receiving 150-Gy fractions on a twice-a-day basis. The daily fractionation scheme required 5 weeks to reach the cumulative dose, whereas the twice-a-day schedule required only 3 weeks. The target volume included the primary tumor plus bilateral mediastinal nodes and the ipsilateral hilum and the supraclavicular nodes when involved. Margins of 1.0 to 1.5 cm were included and cone-downs were prohibited. Local failure was reduced from 52% with the daily schedule to 36% with the twice-a-day schedule (P = .06). Patients who failed in both local and distant sites had a frequency of 32% at the twice-a-day approach (P = .01). More important, although statistically significant differences in survival were not seen at 24 months, the curves deviated so that at 5 years the survival was only 16% with once-a-day treatment, as opposed to 26% with the twice-a-day schedule (P = .04). Overall morbidity was not significantly different between the two arms, although there was a higher frequency of grade III esophagitis with twice-a-day treatment.

It should be reemphasized that selecting patients for combined modality treatment requires an excellent performance status. Combined modality therapy is a complex undertaking requiring close coordination between both medical and radiation oncologists. Because not all combined modality programs have been shown to increase survival but usually do increase toxicities, chest irradiation need not be considered for all patients, especially those who have impaired pulmonary function or poor performance status. Investigational programs that do not include chest irradiation remain entirely appropriate for many patients because the greater antitumor efficacy of combined modality treatment appears to be at least partially offset by enhanced toxicity. If the results of chemotherapy improve so that most patients have
eradication of systemic but not of local disease, then chest radiation therapy could have a survival effect of even greater significance. At present, however, distant metastases remain the predominant cause of failure, and most patients with limited disease who are irradiated still die of their SCLC. Thus, improving systemic treatment currently has a much greater potential for achieving survival gains than does increasing the efficiency of local regional therapy.

**Prophylactic Cranial Irradiation**

Brain metastases are detected in approximately 10% to 15% of SCLC patients at the time of presentation and are subsequently diagnosed during life in another 20% to 25%, with an increasing likelihood of development seen with lengthening survival. In the absence of radiation therapy to the CNS, actuarial analysis reveals a probability of brain metastases ranging from 50% to 80% in terms of those patients who survive 2 years. At postmortem examination, they are found in up to 65% of patients. Because these metastases are somewhat less frequent than the sole site of clinical relapse from complete remissions and are frequently clinically disabling, prophylactic cranial irradiation has been recommended by many but not all since the mid-1980s to curtail their development. The rationale is essentially an extrapolation from original strategies used in acute lymphocytic leukemia of childhood.

A review of 667 patients entered on several prospective randomized trials assessed the benefit of prophylactic cranial irradiation given at or within a few months of diagnosis in patients who were initially free of CNS involvement. When these trials were considered together, doses of prophylactic cranial irradiation ranging from 2000 to 4000 cGy reduced the frequency of clinically detectable brain metastases from 24% to 6%. In most of these trials, a significant reduction of intracranial tumor spread was observed. However, no significant effect of prophylactic cranial irradiation on survival was observed in any of those studies. Retrospective analyses suggestively, both so-called retrospective, overall survival was not significantly improved.

The important observation was that there were no obvious differences in the neuropsychological function between the two groups, but only 33 patients underwent a failure was 19% in patients given prophylactic cranial irradiation and 45% in those who did not receive prophylactic cranial irradiation. Corresponding figures for total survival were 62% and 40%, respectively. The benefit of prophylactic cranial irradiation should be administered only in standard fractions of 200 cGy after completion of chemotherapy.

The neuropsychological and imaging abnormalities may or may not be due to prophylactic cranial irradiation. Chemotherapy, possible paraneoplastic syndromes, and the effects of chronic cigarette and alcohol abuse are some of the factors that may be important contributors. In one study that evaluated cognitive function in patients before and after chemoradiation but before any prophylactic cranial irradiation, deficits were discovered in verbal memory, frontal lobe function, and motor coordination within both groups of patients. Administration of methotrexate, procarbazine, and lomustine has decreased since the 1980s; these particular agents have been incriminated in neuropsychological dysfunction. One of the studies in the metaanalysis included almost 300 patients who were randomized to receive prophylactic cranial irradiation after having achieved a complete response. The primary end point was overall survival, and the analysis was based on intent to treat. Prophylactic cranial irradiation was administered in the metaanalysis was not able to assess the effect of prophylactic cranial irradiation on cognitive function, because most of the studies included did not include a baseline assessment. Two studies assessed baseline neuropsychological function before treatment and demonstrated that many patients appear to have abnormalities of cognitive function as initial manifestations of their cancer, even when brain metastases were not detected and before any treatment.

Some investigators have proposed forgoing the prophylactic cranial irradiation in favor of therapeutic brain irradiation when metastases are detected. This policy assumes that cranial irradiation can effectively control symptoms from overt brain metastases for a substantial fraction of the patient's remaining life. Because the duration of survival is short in most patients who develop brain metastases during the course of their therapy, this assumption is not unreasonable. However, other physicians have questioned the durability of palliation after radiotherapy for overt metastases as well as the difficulty of achieving long-term control in the unusual patient who does survive for a long time.

Another factor that produces considerable controversy in recommending prophylactic cranial irradiation to patients who achieve a complete response is the significant risk of toxicity associated with it. Because the 5-year survival appears to have improved, it is evident that some patients have neurologic and intellectual impairment as well as abnormalities on CT scan that may be related to prophylactic cranial irradiation. In one study, both CT scan and CNS abnormalities were significantly more frequent in patients who had received prophylactic cranial irradiation or therapeutic brain irradiation than in those who had not. These findings were more pronounced because complete responders are at greater risk for possible complications. Many deficiencies on neuropsychological testing have been unsuspected on casual examination, but a few patients have obvious major impairments. CT scan abnormalities continue to worsen for several years after treatment has ended, although the abnormalities may eventually stabilize. Neurologic abnormalities were most prominent in one series of patients who were given prophylactic cranial irradiation concurrently with high-dose chemotherapy or individual radiation fractions of 400 cGy. Some authorities suggest that prophylactic cranial irradiation should be administered only in standard fractions of 200 cGy after completion of chemotherapy.

The neuropathological and imaging abnormalities may or may not be due to prophylactic cranial irradiation. Chemotherapy, possible paraneoplastic syndromes, and the effects of chronic cigarette and alcohol abuse are some of the factors that may be important contributors. In one study that evaluated cognitive function in patients before and after chemoradiation but before any prophylactic cranial irradiation, deficits were discovered in verbal memory, frontal lobe function, and motor coordination within both groups of patients. Administration of methotrexate, procarbazine, and lomustine has decreased since the 1980s; these particular agents have been incriminated in neuropsychological dysfunction. One of the studies in the metaanalysis included almost 300 patients who were randomized to receive prophylactic cranial irradiation after having achieved a complete response to initial treatment. Twenty percent of these patients had extensive-stage disease, virtually all of whom are ultimately expected to relapse and die. The mean time between the initiation of treatment and the randomization was 5 months. The actuarial likelihood of isolated brain metastasis as the first site of treatment failure was 19% in patients given prophylactic cranial irradiation and 45% in those who did not receive prophylactic cranial irradiation. Corresponding figures for total brain metastases were 60% and 77%, respectively. The benefit of prophylactic cranial irradiation was significant. The important observation was that there were no obvious differences in the neuropsychological function between the two groups, but only 33 patients underwent a complete reassessment at 18 months. Inasmuch as neuropsychological abnormalities possibly due to prophylactic cranial irradiation progress over time, these data are insufficient to exclude radiation-associated cognitive damage, but they are nonetheless relevant.

It is important to understand that prophylactic cranial irradiation as opposed to therapeutic irradiation should not require a dose that approaches tissue tolerance. Higher doses may be more successful at eliminating brain metastases but there appears to be prophylactic benefit with relatively modest doses of 24 to 25 Gy. If prophylactic cranial irradiation is administered at a time when no chemotherapeutic agents are being administered, radiation-induced permeability alterations that allow more chemotherapy agent into brain parenchyma should be obviated. Our guidelines for prophylactic cranial irradiation, after thorough discussion with the patient of the potential risks and benefits, are (1) prophylactic cranial irradiation is typically not recommended until at least 2 weeks after completion of all chemotherapy and only to complete responders after induction therapy; and (2) radiotherapy fractions of 200 to 300 cGy are given over 2 to 3 weeks to a total dose of 2400 to 3000 cGy.

**Large-Field Irradiation Therapy**

Pilot studies have examined the role of hemibody and total body radiation in radiosensitive tumor. Hemibody irradiation is an active agent in SCLC and can induce some complete clinical responses in patients who achieve complete response after combination chemotherapy. The initial treatment is usually given to the upper hemibody where the bulk of tumor is located; in some studies treatment of the lower hemibody was administered after hematologic recovery occurred after the upper hemibody dose. A controlled German trial confirmed that chemotherapy produced markedly better survival than hemibody irradiation in patients with extensive disease. As an adjunct to combination chemotherapy in both limited and extensive disease, hemibody irradiation yielded substantial toxicity in several pilot studies without any obvious benefit in tumor response or survival. There is also no evidence that low doses of total body irradiation are of benefit as an adjuvant to chest irradiation in limited-stage or chemotherapy in extensive-stage disease. In a large randomized trial in patients with limited disease given chemotherapy and chest irradiation, additional hemibody radiation therapy to the upper abdominal sites of potential relapse produced no improvement in response duration or survival. Currently, wide-field irradiation has no proven role in the management of this disease.

**ROLE OF SURGERY IN LIMITED DISEASE**

Surgery is reserved for selected patients. In contrast to the majority of patients with limited disease, careful TNM staging is important in those patients being considered for surgical resection. The first hint that proper surgery would lead to less bias in the interpretation of surgical results came from the subset of SCLC...
patients described by Higgins et al.\(^7\) in their report of the management of the solitary pulmonary nodule. In a 10-year follow-up of 15 small cell patients with solitary nodules (1% of total cases), 11 who would be presently classified as having stage I tumors had a 5-year survival of 36%. Rejuvenation of interest in surgical resection for this cancer, however, received its greatest support from the recognition that newly available chemotherapeutic agents could possibly provide effective adjunctive therapy. Meyer\(^7\) reported that of ten pathologically staged stage I and II patients resected and given chemotherapy for at least a year, 80% remained well at 30 months. Of greater significance, however, were the carefully designed trials conducted by the Veterans Administration Surgical Oncology Group.\(^3\) Of 148 small cell carcinoma patients entered on four trials, 132 who survived a potentially curative resection were randomized to receive either preoperative adjunctive chemotherapy or surgery alone. A 23% overall 5-year survival was recorded, with survival patterns that were more favorable in less advanced stages: T1 to T2N0, 28% to 60%; T1 to T2N1, 9% to 31%; and T3 or N2, 3.6%. Although survival was marginally better with the addition of postoperative chemotherapy, it was clear that the small group of patients with localized disease after sophisticated surgical staging techniques could enjoy much better survival with surgical resection alone than was previously appreciated.

Several factors have strengthened the rationale for incorporating surgical therapy into the total package of treatment for selected SCLC patients. Despite the high response rate to present chemotherapy regimens, the rate of relapse in the thorax can approach 75% in the absence of properly administered radiotherapy. A gradual shift toward identification of more localized potentially resectable subgroups of limited disease patients with clinical staging occurred, encouraged both by the use of invasive procedures, including Wang needle biopsy, mediastinoscopy, and mediastinoscopy, and the recognition that the new international staging system for lung cancer\(^2\) can provide a common language for discussing these issues.

Theoretical justifications for combining surgery with other therapies for SCLC have been enumerated by Meyer.\(^2\)

1. Since local relapse is a problem, could surgical removal offer a better chance for disease control?
2. Surgery, unlike radiotherapy, would not limit the possibility of chemotherapy that could be delivered.
3. By rendering the patient free of disease in the chest without affecting bone marrow reserves, surgery could possibly make the chemotherapy more effective.
4. Complete surgical staging could identify patients at higher risk of recurrence. Numerous uncontrolled reports, although not definitive, have provided considerable insight into whether these theoretical considerations are valid.

One of the chief theoretical justifications for adding surgery to the initial regimen for SCLC is the possibility of influencing relapse in the tumor bed or mediastinum. In patients who have had surgery at diagnosis, local recurrences are infrequent,\(^5\) but they do occur because patients with stage I or II disease are overrepresented in this group. Patients who have been pretreated with chemotherapy more often have had clinical stage IIIA disease, and their local relapse rate is higher, in the range of 18% to 28%.\(^5\) These local relapse rates still appear considerably less than in patients given chemotherapy with or without radiation therapy with no surgical intervention. Patients given initial chemotherapy who have a negative biopsy of the primary tumor site at the time of surgery and therefore do not have resection performed have a high frequency of local recurrence.\(^5\) No cancer is present in the resected specimen in 10% to 20% of cases resected for CT,\(^5\) with this particular patient subset enjoying a better prognosis.

Only a modest quantity of data exists on how often surgical resection at the diagnosis of SCLC is possible. Prospective studies of the feasibility of initial thoracotomy by their nature cannot include cases discovered only at thoracotomy to have small cell carcinoma. A review of the literature\(^2\) suggests that as many as 16% of patients with SCLC are operative candidates, but this is likely to be an unrealistically high estimate because those patients who are evaluated by a thoracic surgeon constitute a highly selected group.

There does not seem to be a marked increase in mortality in patients who have operative removal of small cell carcinoma. In the few studies that describe operative risks after chemotherapy and radiotherapy, the mortality varies between 0% and 10%, with many studies reporting no operative mortality or increased morbidity compared with expected outcomes in patients undergoing pulmonary resection for other indications. The extent of resection, pneumonectomy or lobectomy, has generally been dictated by the intraoperative findings rather than the original extent of the tumor in patients given preoperative chemotherapy.

**Surgery Followed by Chemotherapy**

The initial exceedingly poor long-term survival rates with surgery of SCLC were obtained in patients with clinical stages I through III, who for the most part underwent only minimal staging procedures by current standards. Only when results are categorized by tumor stages can the potential curative effects of surgery alone be demonstrated. One report, for example, documents 5-year survival of 35% in stage I and 23% in stage II patients.\(^2\) The only randomized trials of surgery compared with surgery with postoperative chemotherapy were begun approximately 20 years ago and used inferior drug regimens by today's standards.\(^5\) Nonetheless, they did in the aggregate reveal a survival advantage from chemotherapy (Table 31.3-5). Suffice it to say that in the 1990s thoracic oncologists never recommend surgery as sole treatment for SCLC.

<table>
<thead>
<tr>
<th>Adjunct Therapy</th>
<th>Patient</th>
<th>2 (Tumor/Node/Par)</th>
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<tbody>
<tr>
<td>Chemotherapy</td>
<td>26</td>
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<td>Mastes</td>
<td>61</td>
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<td>(Due Jun 30th)</td>
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**TABLE 31.3-5.** Pooled Results from Randomized Surgical Adjutant Studies in Smal Cell Lung Cancer

Statements regarding the efficacy of combined modality approaches for SCLC that include surgical resection can be evaluated only when stratified by the temporal relation among the different modalities. There have been a number of programs of initial surgery followed by systemic chemotherapy after surgery; patients with multiple stages of tumor are included.\(^5\) In general, modern combination chemotherapy programs, usually including cyclophosphamide, doxorubicin, vincristine, or etoposide, have been used. Survival experience is quite heterogeneous, ranging from 5-year survival of 9% in earlier studies to as high as 83% in more recent studies.

Both nodal status and primary tumor or T status have significant effects on the survival of patients whose SCLC is resected. These prognostic factors were addressed directly in a few studies. Angetelli et al.\(^2\) and Shepherd et al.\(^3\) reported increased survival of node-negative compared with N1 and N2 patients after surgical resection and postoperative chemotherapeutic, while Macchiarini et al.\(^7\) found a decrease in 5-year survival with increasing T category in surgically resected patients without nodal metastases. Retrospective reviews published by Rea et al.\(^2\) and Lucchi et al.\(^2\) have reinforced the importance of surgical staging in evaluating the outcomes for surgery and SCLC. Rea et al. reported that of 51 stage I and II SCLC patients resected and given chemotherapy after resection had 5-year survival rates of 52.2% (stage I) and 30% (stage II). In the review by Lucchi et al.,\(^2\) stage I or II resected SCLC patients having postoperative chemotherapy had 5-year survival rates of 47% and 14.8%, respectively. Stage III patients from this series having surgery followed by adjuvant therapy had a 5-year survival of 14.4%. In general, 5-year survival is rare in patients given postoperative chemotherapy after mediastinal node disease has been documented at initial surgical resection,\(^2\) although this observation is not universal.

The largest experience as a cooperative group trial examining the role of surgery followed by adjuvant therapy in SCLC was conducted by the International Society of Chemotherapy Lung Cancer Study Group.\(^2\) Four-year survival rates for completely resected, pathologically staged SCLC patients with N0 (n = 59), N1 (n = 58), and N2 (n = 36) who received postoperative chemotherapy were 69%, 36%, and 33%, respectively. Based on these studies, most authorities believe that any survival benefits of initial surgical resection will likely be confined to patients with pathologic stage I and II disease, and conventional wisdom currently holds that surgical resection at
diagnosis in patients with N2 disease is considered experimental.

Because most available data on outcome of patients who receive surgery and postoperative chemotherapy is uncontrolled, one can only observe that the survival of such patients is clearly better than the survival of patients with limited disease who receive chemotherapy alone and better than the reported outcome of all but a few series of patients, most of them more recent, given chemotherapy and chest irradiation. An extremely important point concerning initial surgical resection that remains unresolved is whether the superior outcome of more localized (i.e., stages I and II) disease in patients who undergo complete resection before initiation of chemotherapy is attributable to the resection itself or to an inherently better prognosis in patients with a tumor burden small enough to permit resection.

Because a controlled trial to address this question cannot be done because of the impossibility of randomizing patients whose small cell carcinoma is diagnosed only at the time of thoracotomy to undergo or not undergo surgical extirpation of their cancers, institutional data on patients with similar tumor burden after clinical staging who do and who do not proceed to thoracotomy may be relevant. In Denmark, survival of clinically operable patients is similar whether an operation with the intent of completing resecting the tumor is performed, although both these groups live much longer than other limited-stage patients. At the University of Toronto, a similar analysis, evaluating only patients without evidence of mediastinal metastases on chest radiography or mediastinoscopy, produced similar conclusions. At present, one can only conclude that early-stage patients may benefit from surgical resection. Certainly, if a resectable SCLC is documented for the first time at thoracotomy, we recommend the surgeon proceed with the operation if mediastinal node metastases are absent. In patients with a proven pathologic diagnosis, thoracotomy for tumors in clinical stage I disease should be considered only after complete staging procedures, including mediastinoscopy or mediastinotomy, reveal no evidence of tumor spread.

The whole question of the SCLC presenting as a solitary pulmonary nodule is somewhat controversial at this time. In a retrospective review of 408 small cell carcinoma patients, Quoix et al. found that solitary pulmonary nodule cases have a median survival of 24 months. The improved prognosis could be explained by a number of factors, not the least of which is simply early diagnosis (lead time bias). Another possibility is that the solitary nodule may represent a fundamentally different category of SCLC or not be small lung cancer at all. Warren et al. reevaluated 50 cases of surgically resected SCLC. Thirty-four were pathologically confirmed to be SCLC, and stage I cases had a surprisingly low 9% 2-year survival. Twelve cases, however, were reclassified as well-differentiated neuroendocrine carcinoma, and 2-year survival of these stage I patients was 75%. The significance of these findings is presently unclear.

**Chemotherapy Followed by Surgery**

Surgical resection in SCLC might theoretically be more effective if performed after initial chemotherapy rather than at the time of diagnosis. Chemotherapy could be given in an immediate attempt to eradicate occult distant metastatic disease, the major cause of treatment failure. Only patients who respond to the chemotherapy (i.e., those most likely to benefit) would undergo thoracotomy. Comprehensive initial preoperative staging procedures could be avoided, or at least be less rigorous, because chemotherapy would be the first treatment. Finally, after response to chemotherapy, a larger fraction of patients might be surgical candidates.

There has been a steady increase since 1984 in the fraction of cases reported to be resectable after chemotherapy response. Moreover, there is more uniformity in presurgical staging procedures, including mediastinoscopy, used to identify patients who might benefit from postchemotherapy surgery. As shown in Table 31.3-6, resection rates in some series can exceed 50%, with estimated 5-year survivals in resected patients of 35% to 65%. Factors that prevent thoracotomy include poor response to chemotherapy, poor pulmonary function or other medical problems, and patient refusal. The selection criteria for potential surgical candidates often exclude those with such adverse prognostic factors as suprACLavicular adenopathy, superior vena cava syndrome, bulky mediastinal involvement, and pleural effusions.

**TABLE 31.3-6. Survival Data with Chemotherapy Followed by Surgical Resection**

The approach of chemotherapy followed by surgery has led to higher survival rates compared with chemotherapy (often with chest irradiation) in patients with stage I disease, with median survival not yet reached in patients from the Toronto study. Stage II and III patients had median survivals of 69 and 52 weeks, respectively, and significant differences in survival were noted in all resected patients compared with 19 eligible patients who did not receive surgery after the chemotherapy. The median survival of stage II and III patients was no different, however, than in otherwise eligible patients not receiving thoracotomy (51 weeks). The best results, not surprisingly, are found in patients with no malignant cells in the surgical specimen. Some authors report absence of long-term survival in patients with initial mediastinal node involvement who undergo postchemotherapy resection.

Whether surgery is best performed before or after chemotherapy in patients known to have stage I disease is considered operable at diagnosis is not known. Survival of patients followed by chemotherapy and with chemotherapy followed by surgery was quite similar in the Toronto study. The more fundamental question, whether postchemotherapy surgery improves survival, also cannot be regarded as settled, although in one institution survival of limited-stage patients who were considered eligible or ineligible for eventual surgical resection should they respond to chemotherapy was similar. A Lung Cancer Study Group trial in which 217 patients who responded to chemotherapy (66% of those beginning chemotherapy) were randomized to undergo or not undergo thoracotomy for attempted surgical resection has matured. This study did not reveal survival differences, and the median survival and 2-year survival were 12 months and 20%, respectively, for both arms. The results of this study, however, are difficult to interpret because only 42% of the registered patients were randomized, 10% did not receive protocol-specified therapy, and the response rate of 65% was low compared with modern response rates with SCLC regimens. This point is emphasized when one considers a more recent pilot study from Japan. Treatment in this pilot study consisted of induction chemotherapy with cisplatin, doxorubicin, vincristine, and etoposide. In stage I patients, most of the surgical resections in the 28% who received postchemotherapy surgery were for stage I and II disease and 43% for stage IIIA disease. The majority of patients in the Lung Cancer Study Group (LCSG) study were stage III (N2, T3, or both) tumors, and, notwithstanding the previously mentioned data from Japan, the role of surgery in N2 disease is of debate not only in SCLC but in non-SCLC. A trial of similar design that concentrates on patients with early-stage SCLC disease could potentially sort out the role of surgery after induction therapy for SCLC, but as so few patients (less than 10%) fall into this category, it is unlikely that this trial can ever be performed.

**GENERAL APPROACH TO PATIENTS WITH EXTENSIVE DISEASE**

For more than 90% of patients, extensive SCLC is a fatal disease within 2 years of diagnosis. Nevertheless, compared with supportive care, chemotherapy offers substantial benefit by improving both the quality and survival of patients with this limited window. Treatment with current chemotherapy produces an overall response rate of 60% to 80%, and the median survival time is 7 to 12 months. Once distant metastases have been identified during staging, further radiographic staging studies are necessary only if dictated by a clinical protocol or as necessary to evaluate a symptomatic complaint. Combination chemotherapy is superior to any single agent tested thus far, including oral VP-16. Treatment should be administered for a total of four to six cycles. Because many of these patients have poor functional status and other adverse prognostic factors, less aggressive chemotherapy programs are acceptable and may provide comparable palliation with less toxicity. Because relapse invariably occurs, enrollment on an investigational study evaluating new targets designed to impair tumor growth is warranted if available. When disease progression does occur, additional chemotherapy should be offered to most patients with a good functional status.
ROLE OF CHEST IRRADIATION IN EXTENSIVE DISEASE

Retrospective reviews of the literature demonstrate that the addition of chest irradiation plus chemotherapy for patients who have extensive-stage SCLC may reduce the frequency of progressive disease in the thorax, but the overall response rates, median survival, and 2-year disease-free survival figures remain unchanged. Because extensive disease patients generally achieve complete response rates of only 20% to 25% with current chemotherapy regimens and frequently relapse in distant metastatic sites, it is logical that an additional localized form of treatment would have minimal effect on survival. Successive large studies by the Southwest Oncology Group also confirm that although thoracic radiotherapy can substantially reduce the frequency of initial relapse at the primary tumor site, there is no apparent effect on survival.

There have been several clinical trials that randomize patients with extensive disease to chemotherapy alone or in combination with irradiation to the chest disease as well as to some or all sites of overt distant metastases. With one more recent exception, no worthwhile advantages in survival have been seen with the addition of radiotherapy for patients with extensive disease. At present, except as part of a clinical trial, there is no indication for chest irradiation in extensive SCLC other than symptomatic palliation.

ROLE OF CHEMOTHERAPY AND RADIATION THERAPY TO THE NEURAXIS

The therapeutic management of overt disease in the CNS with radiation therapy is discussed in detail in Chapter 43.3. For overt metastatic lesions within the CNS, doses of 300 rad daily to doses of 3000 to 3600 Gy typically are used. Overt intracranial metastases appear to be more difficult to sterilize than intrathoracic disease. If there are one or two clinically documented intracranial lesions only, a boost to 5000 cGy may be considered if the patient has an excellent performance status. Stereotactic treatment can also be used.

Chemotherapy is also an alternative option for brain metastases, perhaps because the blood–brain barrier is disrupted in the setting of macroscopic metastatic disease. Small series of patients in whom brain metastases were present at diagnosis have been treated with standard chemotherapy regimens without radiation, and the majority have demonstrated both clinical and radiographic improvement. Chemotherapy has also been used at the time of relapse, and response rates of 33% to 43% have been reported in previously treated patients, the response to chemotherapy in the brain appears to be comparable with the response rates in other organs, and it is not dissimilar from the activity of irradiation, which in one series produced a partial response rate of 50%, and the median survival was 4.7 months in a series of 22 patients. Thus, while brain irradiation remains the standard for patients who have not been previously irradiated, chemotherapy is a reasonable option for patients who develop recurrent disease after prior brain radiation, particularly if active systemic disease is also present.

STRAATEGIES TO OPTIMIZE CHEMOTHERAPY RESPONSE

A number of strategies have been investigated in an attempt to improve treatment outcome using the currently available drugs. These approaches include increasing the number of active agents used in the treatment program, often by the use of cyclic alternation between two combination regimens, increasing the dose intensity, often with the support of hematopoietic growth factors or blood progenitor cells, and weekly chemotherapy regimens, which increase the dose intensity by shortening the interval between treatment rather than increasing the dose.

ALTERNATING CYCLIC COMBINATION CHEMOTHERAPY

The recognition of clonal heterogeneity within a tumor and the inability to develop treatment regimens that included more than four drugs due to overlapping toxicity led to an interest in alternating chemotherapy combinations. The somatic mutation model developed by Goldie and Coldman provided a theoretical underpinning to this approach, and this model predicted that the best probability of cure was achieved by the earliest possible introduction and most rapid alternation of all active agents. As two equally effective non–cross-resistant regimens were available, the model predicted that alternating between regimens every other cycle would be more effective than alternating after every three cycles or giving one regimen continuously for five cycles before switching to the second regimen.

A large number of clinical trials have been conducted attempting to evaluate alternating multidrug combinations, particularly in extensive disease. The EP regimen was initially tested in patients who had progressed after cyclophosphamide-based chemotherapy, suggesting that these drug combinations were non–cross-resistant. The National Cancer Institute conducted a study in which patients were randomized to CAV or CAV alternating with EP. Chemotherapy was given for a total of six cycles. Both the response rate (65% vs. 47%), progression-free survival, and median survival time (9.6 vs. 8.0 months) favored the patients who had received alternating therapy. The results could be explained by the inclusion of a more active regimen (EP) within the alternating arm, an advantage due to greater drug diversity with five effective drugs rather than three, or as support of the Goldie and Coldman concept. Roth et al. subsequently evaluated 437 patients with extensive disease in a randomized trial comparing EP for four cycles, CAV for six cycles, or CAV alternating with EP for a total of six cycles. Although there was a slight improvement in progression-free survival (P = .052) there was no significant difference in response rate or overall survival between the treatment arms. Nonresponders to CAV crossed over to EP, while twice as likely to respond to second-line therapy as nonresponders to EP who crossed over to CAV, although these differences were not statistically significant (28% vs. 14% for induction responders who relapsed, and 15% vs. 8% for patients with primary resistance, respectively). An assumption of the Goldie and Coldman hypothesis is that the alternating regimens are non–cross-resistant, which is not the case with the CAV and EP combinations as demonstrated by the modest activity when nonresponding patients are crossed over from one of these regimens to the other. The European Organization for Research and Treatment of Cancer developed a regimen consisting of vincristine, ifosfamide, mesna, and carboplatin (VIMP) that, in a randomized phase II study, appeared to be as active as CDE. As important, patients who were progressing on, or were within 3 months of stopping either CDE or VIMP, had a greater than 50% likelihood of responding to the alternate combination, indicating that a significant degree of non–cross-resistance existed between these combinations. In a randomized trial, patients with extensive disease were treated with CDE or CDE alternating with VIMP. The study was closed after 143 patients had been registered and demonstrated no significant differences in survival. Although it did not reach its planned accrual, it still had sufficient power to have detected a 2-month increase in median survival time with alternating therapy, had it existed. These studies, therefore, do not support the superiority of an alternating chemotherapy combination in patients with extensive disease.

Alternating non–cross-resistant chemotherapy has also been investigated in patients with limited disease. The National Cancer Institute of Canada randomized 300 patients with limited disease to either CAV for three cycles followed by EP for three cycles, or CAV alternating with EP for a total of six cycles. No differences were noted in response rates, time to treatment failure, or survival. A Japanese study compared CAV to EP with alternating CAV and EP. Patients with limited disease received four cycles of chemotherapy followed by thoracic irradiation. Patients with extensive disease who responded to chemotherapy continued treatment for 1 year. A total of 288 patients were enrolled. No differences in survival based on treatment were noted in the patients with extensive disease. In patients with limited disease, there was improved survival, even after adjusting for other prognostic factors with the alternating regimen compared with CAV (P = .008) or EP (P = .002). In contrast, Urban et al. reported inferior survival with an alternating seven-drug regimen compared with a four-drug regimen, although the seven-drug combination was less intensive based on the magnitude of myelosuppression. These results suggest that an equally intensive alternating regimen is a reasonable alternative.
alternative for patients with limited disease, although the survival advantage noted in the Japanese trial has not been confirmed by another study.

Additional studies have evaluated alternating chemotherapy introduced after achieving a response to an induction regimen. For example, Wolf et al. randomized 321 patients, 135 of whom had limited disease, to treatment with ifosfamide and VP-16, to response plateau followed by CAV, or ifosfamide and VP-16 alternating with CA. A total of six cycles of chemotherapy were delivered in each arm. No difference in outcome was noted based on treatment arm in either limited or extensive disease. Other studies have compared alternating regimens that were designed based on the suggestion of \textit{in vitro} synergy or have compared an alternating multidrug combination with a different standard regimen. For example, a German multicenter trial demonstrated that an alternating eight-drug regimen was slightly superior to CAV. In sum, these studies may be viewed as suggesting a modest advantage for regimens that introduce a greater diversity of active drugs into treatment rather than a test of the Goldie-Coldman hypothesis.

### DOSE INTENSIFICATION

In experimental models, numerous chemotherapy drugs display log-linear or near linear dose-response curves. Increasing the dose of chemotherapy delivered has been demonstrated to improve survival in a number of clinical settings. In SCLC, several approaches to increase dose intensity have been evaluated. These include dose intensification without or with hematopoietic growth factor support, dose intensification with marrow or peripheral blood stem cell support, and compression of the time in which chemotherapy is delivered using a weekly schedule.

Hrynuk and Bush developed a methodology that expresses dose intensity as the drug dose administered per meter squared per week. Limitations of this method include the assumption that all drugs and schedules of administration are therapeutically equivalent. Nevertheless, this method has been used to demonstrate a positive correlation between dose intensity and treatment outcome in advanced breast cancer and ovarian cancer. In SCLC, a retrospective multivariate analysis of 131 patients suggested that modest increases in the dose intensity of cisplatin and cyclophosphamide in a four-drug regimen produced better survival. In contrast, analysis of 80 clinical trials using this methodology found limited and conflicting correlations between dose intensity, response rates, and median survival.

Several randomized trials have attempted to determine whether a modest increase in dose intensity improves survival in this disease. A small trial comparing different doses of a regimen consisting of cyclophosphamide (500 vs. 1000 mg/m²), lomustine (50 vs. 100 mg/m²), and methotrexate (50 vs. 100 mg/m²), survival was inferior in the lower dose arm. Preliminary findings of a cooperative group study in which the dose of cyclophosphamide was increased from 700 to 1500 mg/m² in a regimen that also included lomustine and methotrexate also demonstrated improved survival in the patients treated with the more intensive regimen. These early studies confirm that the use of lower than standard doses of drugs can compromise survival in chemotherapy-sensitive disease.

More recently, several investigators evaluated whether increasing the dose of drugs beyond the dose used in current regimens improves survival. Most of these studies were conducted in patients with extensive disease and used an alternating multidrug combination with a different standard regimen. The delivered dose intensity was 34% greater on the every-2-week schedule, and both the complete remission rate and the incidence of febrile neutropenia were reduced. In a small trial comparing different doses of a regimen consisting of cyclophosphamide (500 vs. 1000 mg/m²), lomustine (50 vs. 100 mg/m²), and methotrexate (50 vs. 100 mg/m²), survival was inferior in the lower dose arm.

A review by Nichols et al., however, concluded that the incidence of febrile neutropenia after conventional chemotherapy for SCLC was approximately 18%. The differences in the reported rates of febrile neutropenia between studies was related both to the chemotherapy regimen used and also to the diligence with which fever was sought and with how febrile neutropenia was defined. Two analyses that compared the use of G-CSF as secondary prophylaxis (G-CSF administered with all subsequent courses of chemotherapy if febrile neutropenia occurred on the previous cycle) suggested that this approach was more costly than a strategy of reducing the dose of the chemotherapy by 25%.

<table>
<thead>
<tr>
<th>TABLE 31.3-7. Randomized Trials Evaluating Dose Intensity in Small Cell Lung Cancer</th>
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<tr>
<td>A number of other studies have evaluated whether shortening the interval between chemotherapy cycles improves survival. In patients with extensive disease, delivering CAVE on days 1 and 8 of the first few courses of chemotherapy did not appear promising. A multicenter study randomized 300 patients to six cycles of vincristine, ifosfamide, carboplatin, and VP-16 delivered every 4 weeks or every 3 weeks. Most of the patients included in the study had limited disease. In the group receiving chemotherapy every 3 weeks, the delivered dose intensity was increased by 26% over the entire treatment program compared with the group treated every 4 weeks. Both the median survival (443 vs. 351 days) and the 2-year survival rate (33% vs. 18%) were better in the intensified arm (( P = .0014 )), even after adjustment in a multivariate analysis. Another multicenter study also explored the importance of the interval between treatment cycles by randomizing 403 patients. Survival in patients with limited disease, to cyclophosphamide, doxorubicin, and VP-16 delivered on an every-3-week schedule or on an every-2-week schedule. Patients treated every 2 weeks received G-CSF support. The delivered dose intensity was 34% greater on the every-2-week schedule, and both the complete remission rate and the overall survival were better in this group. Improved survival was observed in both patients with limited and extensive-stage disease treated every 2 weeks. These studies suggest that for some standard regimens, compression of the treatment cycle, if this can be accomplished without a significant increase in toxicity, may be an effective means to improve survival.</td>
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<tr>
<td><strong>Hematopoietic Growth Factors</strong></td>
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<td>G-CSF and granulocyte-monocyte colony-stimulating factor (GM-CSF) are members of a group of glycoproteins that stimulate the production and maturation of hematopoietic progenitor cells and regulate the function of mature blood cells. Two randomized, placebo-controlled trials demonstrated that the use of G-CSF as an adjunct to CAE chemotherapy significantly reduced the duration of neutropenia, incidence of febrile neutropenia, and the use of hospital resources. A decision analysis based on the results of one of these trials concluded that the routine use of G-CSF led to a net decrease in the total cost per treatment cycle based on billed charges, but was associated with an increased cost based on actual provider costs or payments by the U.S. Medicare system. Moreover, this analysis was extrapolated from the rate of hospitalization due to febrile neutropenia during the first cycle of chemotherapy, which in this study was 55% in the placebo arm and 26% in the group treated with G-CSF. A decision analysis suggested that from an economic perspective a rate of hospitalization greater than or equal to 40% was necessary to justify the routine inclusion of G-CSF into a chemotherapy regimen. These conclusions are consistent with the 1996 guidelines of the American Society of Clinical Oncology, which recommended primary prophylaxis (G-CSF administration concomitant with the first chemotherapy cycle) only when the expected incidence of febrile neutropenia exceeded 40%. A review by Nichols et al. however, concluded that the incidence of febrile neutropenia after conventional chemotherapy for SCLC was approximately 18%. The differences in the reported rates of febrile neutropenia between studies were related both to the chemotherapy regimen used and also to the diligence with which fever was sought and with how febrile neutropenia was defined. Two analyses that compared the use of G-CSF as secondary prophylaxis (G-CSF administered with all subsequent courses of chemotherapy if febrile neutropenia occurred on the previous cycle) suggested that this approach was more costly than a strategy of reducing the dose of the chemotherapy by 25%.</td>
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Maintaining the dose of chemotherapy with growth factor support, rather than reducing or delaying the dose because of hematologic toxicity, would be appropriate if this translated into improved treatment efficacy. Results of studies designed to determine whether hematopoietic growth factors can increase the delivered dose intensity have been mixed. A study that randomized a total of 65 patients to vinristine, ifosfamide, carboplatin, and VP-16 demonstrated that the use of G-CSF as an adjunct significantly improved the delivered dose intensity, although there was no difference in the incidence of febrile neutropenia or the days of hospitalization. In this study, there was no difference in median survival between the arms, although there was a suggestion that long-term survival may be improved with the intensified dose delivery. A subsequent larger trial randomized patients to treatment with this regimen at fixed treatment intervals of every 3 or 4 weeks. In a second randomization, patients were given GM-CSF or placebo following each chemotherapy cycle. Survival was improved for patients treated every 3 weeks compared with those treated every 4 weeks. However, GM-CSF did not reduce the incidence or the duration of febrile neutropenia, nor was there any difference in survival between the patients who received GM-CSF or placebo. With the use of G-CSF, treatment with standard doses of doxorubicin, cyclophosphamide, and VP-16 are feasible every 2 weeks. A randomized trial comparing doxorubicin, cyclophosphamide, and VP-16 given every 2 weeks with G-CSF or every 3 weeks without the growth factor identified improved survival with the every-2-week schedule. Treatment with intravenous antibiotics was similar in the two arms. Although the intensified group did require more transfusions of red cells and platelets, overall quality of life measured by a symptom scale was comparable between the groups.

Two studies evaluated G-CSF as an adjunct to weekly chemotherapy programs. In one trial, G-CSF did not increase the delivered dose intensity, whereas in the other study both dose intensity and survival were improved in the arm that included G-CSF support. A subsequent trial, however, compared this latter regimen with a standard chemotherapy regimen that was given every 4 weeks and found no survival advantage with the intensified program. An attempt to use G-CSF to increase the dose of three myelotoxic drugs in a four-drug regimen by 50% was not feasible and resulted in increased marrow toxicity and a reduction in cumulative drug dose received, and inferior survival. Inclusion of GM-CSF in a combined modality program that consisted of EP plus concurrent radiation in patients with limited disease demonstrated that although the neutrophil nadirs were increased in the arm receiving GM-CSF, these patients developed more episodes of febrile neutropenia requiring intravenous antibiotics and hospitalization. Serious thrombocytopenia and blood transfusions were also increased in the group receiving GM-CSF.

These data suggest that the inclusion of a hematopoietic growth factor within a chemotherapy regimen may permit a modest escalation in the dose intensity of some regimens, but not others. Whether this dose intensity is clinically meaningful is a separate issue, and broad generalizations are difficult. For example, although it appears that administration of doxorubicin, cyclophosphamide, and VP-16 every 2 weeks rather than every 3 weeks improves survival for patients with favorable prognostic features, a program delivering chemotherapy every week was not better than EP alternating with CAV every 3 weeks in patients with extensive disease. In this latter example, multiple variables (drug doses, drug diversity, patient tolerance) differed between the treatment arms and may have contributed to the lack of survival advantage within this subset. Additionally, it is clear that patients who have not been exposed to prior chemotherapy are different from patients who have received prior chemotherapy. Another issue that has not been addressed is whether patients who are at high risk of toxicity due to age or other adverse prognostic factors, and patients who have developed febrile neutropenia on a previous treatment cycle, are better managed by reducing the dose of standard chemotherapy drugs or by adding a myeloid growth factor so that standard regimens can be given at full dose. Thus, dose, treatment interval, drug diversity, and patient selection are all parameters that define clinical outcome. Meaningful improvements in disease control beyond that produced by the programs outlined in Table 31.3-2 using the currently available cytototoxic chemotherapy drugs may still be possible, and this remains an appropriate area of study.

**Marrow and Peripheral Blood Stem Cell Transplantation**

Dose intensification with high-dose chemotherapy, supported by stem cells collected from the peripheral blood or bone marrow, has provided a survival advantage to select groups of patients with hematologic malignancies. In contrast, reviews of the efficacy of high-dose therapy in adult solid tumors have concluded that no role for this approach has been established, even in the diseases most sensitive to chemotherapy and radiation. However, the efficacy of high-dose therapy in SCLC has been evaluated in a relatively limited number of patients with other diseases, such as breast cancer. Many of the earliest studies in SCLC enrolled patients with relapsed or chemotherapy-resistant disease. Although response rates were higher than would be anticipated with additional standard doses of chemotherapy, response durations were brief (ranging from 2 to 8 months) and the median survival was often less than 4 months.

Some subsequent studies evaluated high-dose therapy as an early component of treatment in newly diagnosed patients. With this strategy, patients received little or no induction chemotherapy before the high-dose regimen. It was hoped that by avoiding exposure to multiple cycles of conventional chemotherapy the risk of developing drug resistance in the tumor could be reduced. Response durations and survival, however, were comparable with that achieved with standard chemotherapy.

A more commonly applied approach has been to use high-dose therapy as late intensification after standard treatment. Theoretic support for this strategy is provided by the mathematical model proposed by Norton and Simon, which predicts that as the tumor volume is reduced relative resistance to chemotherapy develops. These studies differ in the number of cycles and type of regimen used for induction, the extent of tumor response required before high-dose consolidation, the composition of the high-dose regimen, and whether radiation, surgery, or both were included as part of the treatment program.

The only reported phase III trial administered five cycles of induction therapy and then randomized patients who achieved a good response to consolidation with dose-intensive VP-16, ifosfamide, carboplatin, and etoposide with bone marrow support, or one additional cycle of conventional doses of these same drugs. A total of 101 patients were randomized, which included 13 patients who initially had incomplete response. The dose intensity of VP-16 was increased in the group receiving GM-CSF, and the median relapse-free survival (P = .002) was superior in the high-dose arm. Although the median survival time was improved (68 vs. 55 weeks), this was not statistically significant (P = .13), and long-term survival was achieved in only 2 of the 23 patients treated with the high-dose regimen. A criticism of this study has been that thoracic irradiation was not included as part of the treatment plan, and in most patients the site of initial relapse was confined to the chest. Accordingly, many groups that have not performed randomized controlled trials have used a multimodality approach. For example, the Southwest Oncology Group treated 58 patients with limited disease with induction chemotherapy and radiation followed by consolidation with high-dose cyclophosphamide and autologous marrow support. Only 21 patients received the consolidation but nine achieved long-term disease-free remissions, and the median survival of the patients receiving consolidation was 27 months.

At the Dana Farber Cancer Institute, patients responding to conventional chemotherapy have been treated with high doses of carbamustine, cyclophosphamide, and cisplatin along with stem cell or marrow support followed by thoracic and prophylactic cranial irradiation. The initial report described 19 patients, and this has been updated to include 36 patients. With the period of observation after completion of the high-dose therapy ranging from 21 months to 9 years, 52% of these patients with limited disease have remained in remission. Inclusion of GM-CSF in a combined modality program that consisted of EP plus concurrent radiation in patients with limited disease demonstrated that although the neutrophil nadirs were increased in the arm receiving GM-CSF, these patients developed more episodes of febrile neutropenia requiring intravenous antibiotics and hospitalization. Serious thrombocytopenia and blood transfusions were also increased in the group receiving GM-CSF.

In one trial, G-CSF did not increase the delivered dose intensity, whereas in the other study both dose intensity and survival were improved in the arm that included G-CSF support. A subsequent trial, however, compared this latter regimen with a standard chemotherapy regimen that was given every 4 weeks and found no survival advantage with the intensified program. An attempt to use G-CSF to increase the dose of three myelotoxic drugs in a four-drug regimen by 50% was not feasible and resulted in increased marrow toxicity and a reduction in cumulative drug dose received, and inferior survival. Inclusion of GM-CSF in a combined modality program that consisted of EP plus concurrent radiation in patients with limited disease demonstrated that although the neutrophil nadirs were increased in the arm receiving GM-CSF, these patients developed more episodes of febrile neutropenia requiring intravenous antibiotics and hospitalization. Serious thrombocytopenia and blood transfusions were also increased in the group receiving GM-CSF.
CHEMOTHERAPY-INDUCED REMISSION BY ROUTINE HISTOLOGIC EXAMINATION. Several randomized studies are evaluating the role of high-dose consolidation in SCLC and should help define whether this approach, as currently practiced, is of value in this disease.

WEEKLY DOSE-INTENSIVE CHEMOTHERAPY REGIMENS

Dose intensity is defined both by the dose and the time interval required to deliver the dose. Therefore, shortening the time interval between chemotherapy cycles is an alternative to increasing the dose as a means of achieving greater dose intensity. Some groups have developed weekly regimens that use six or seven drugs. For example, the Southwest Oncology Group developed a six-drug program that included doxorubicin, cyclophosphamide, methotrexate and leucovorin, vincristine, VP-16, and cisplatin. Among the 48 patients with extensive disease, the complete response rate was 38% and the median survival time was 11.9 months. Four of the five patients with non-small cell lung cancer in which the most significant difference between the two different cycles was an increase in the inclusion of VP-16. A simplified dose of methotrexate (30 mg/m² instead of 200 mg/m²), and a shorter treatment interval (12 weeks instead of 16 weeks). In this study, the complete response rate for patients with extensive disease was 9.7%, and the median survival for this group was 7 months. These differences highlighted the importance of patient selection in the result outcome and the necessity for randomized trials to evaluate new treatment approaches in SCLC.

Three weekly programs have been tested in randomized institutional settings. A multidrug combination developed by Sculler et al., which included seven drugs, was compared with standard treatment of CAV. The planned duration of treatment was 18 weeks in both arms. A total of 215 patients were enrolled that included 120 patients with extensive disease and 95 patients with limited disease. Overall, there was no difference in median survival (49 vs. 43 weeks) or in 2-year survival rates between the treatment arms with the outcome defined as freedom from disease. A second randomized trial evaluated a regimen consisting of VP alternating on a weekly basis with ifosfamide plus doxorubicin. This was compared with a standard chemotherapy regimen consisting of alternating 3-week cycles of CAV and VP.Patients who achieved at least a partial response to chemotherapy received thoracic irradiation, and some patients also received prophylactic cranial irradiation. Included in this study were 438 patients, the majority of whom had limited disease. No differences in either median or 2-year survival rates were evident. In both of these randomized studies, myelosuppression was a dominant side effect, and the actual dose intensity delivered was a lower percentage of the planned dose in the weekly treatment arms. However, treatment-related mortality was low, and no worse, with weekly treatment than with standard therapy. A more intensive weekly program that included cisplatin, vincristine, doxorubicin, and VP-16 (CODE) delivered higher doses of chemotherapy by infusing myelo suppressive and relatively nonmyelo suppressive drugs on alternate weeks and by using an aggressive supportive regimen consisting of corticosteroids, gastroprotective agents, and prophylactic antibiotics. In the initial report, 19 of 48 (40%) patients with extensive disease attained a complete remission, and the 2-year survival was 26%. In a small randomized trial that Japanese received CAV every 3 weeks for a total of 8 cycles or to an as-needed treatment program. When CODE was used to treat patients with extensive disease, they subsequently compared CODE plus G-CSF with a standard regimen consisting of alternate 3-week cycles of CAV and VP. There were 220 patients with extensive disease enrolled in this study. Both the overall response rate and the complete remission rate (15%) were similar in the two treatment arms. The median survival time (11.6 vs. 10.9 months) and 2-year survival rates (11.7% vs. 8.5%) were also comparable. The incidence of neutropenic fever was significantly higher, and there were four toxic deaths in the weekly treatment arm. In North America, a randomized intergroup study compared CODE with alternating CAV and VP over 18 weeks. A total of 219 patients with extensive disease with a good performance status were enrolled. Although the response rate was improved (87% vs. 70%) with the weekly program, the response duration and median survival were equivalent between the two treatment arms. Moreover, febrile neutropenia was more common in the patients treated with CODE, and there were more toxic deaths (8.2% vs. 1.0%) compared with the standard treatment arm. In aggregate, these studies demonstrate that weekly chemotherapy programs offer no advantage to standard treatment given every 3 weeks, and if given at the maximum tolerated dose, weekly chemotherapy is significantly more toxic than standard therapy.

MANAGEMENT OF SMALL CELL LUNG CANCER IN THE ELDERLY AND INFIRM

At diagnosis, 25% to 40% of patients with SCLC are 70 years old or older. Compared with younger patients, the elderly have a poorer performance status and more comorbidity. They are at higher risk for complications from intensive treatment. As a result, many physicians treat elderly patients less aggressively. In one retrospective review management for 20 of 123 (16%) elderly patients consisted only of radiation therapy, and another 23 patients (19%) received only supportive care. Another review of the management of 312 patients diagnosed between 1985 and 1991 showed that in the management of the elderly, 33% of the patients received only supportive care, and in the subset of patients with limited disease only 43% received both chemotherapy and radiation. In contrast, in patients between the ages of 60 and 69 less than 10% of the patients received supportive care and 65% of the patients with limited disease received combined modality therapy. When chemotherapy is given to elderly patients, it is usually given at attenuated doses and often for fewer cycles. In one study, the median white blood cell count was 2800/µL and the nadir platelet count was 198,000/µL. Patients who are treated with chemotherapy derive a survival benefit despite attenuation of both the dose and duration of treatment, and in some series the response and survival for the elderly have been comparable with younger patients.

Few elderly patients have been included in clinical trials, and those who have been enrolled are among a minority with less comorbidity and better functional status. As a result, extrapolation of the published data for standard therapies to the general population of elderly patients may be inaccurate. Consequently, several chemotherapy programs have been developed for the elderly and for patients for whom participation in standard therapy protocols that aim to optimize palliation with acceptable risks. One approach has been to use monotherapy with the epipodophyllotoxin. VP-16 can be given orally, making it particularly attractive in the palliative setting. In a study of 35 elderly patients, one-third of whom had poor performance status, a 5-day course of oral VP-16 every 4 weeks produced a response rate of 71% and survival comparable with the arms with complete response in a younger population. The Medical Research Council designed a trial comparing oral VP-16, 50 mg twice daily for 10 days, with standard combination chemotherapy consisting of either VP-16 and vincristine or CAV. In each arm, chemotherapy was repeated every 3 weeks for a total of four cycles. The median age enrolled in this study was 67 years, and 38% of the patients had a performance status equal to 3 to 4. The study was prematurely stopped after an interim analysis that showed inferior survival in the patients treated with VP-16 monotherapy. Hematologic toxicity was also worse with oral VP-16, and there were 17 deaths during the first month of treatment in this arm compared with fewer deaths on the standard arm.

An alternative approach for providing palliative chemotherapy in Britain was the delivery of chemotherapy as needed to palliate patients, rather than at fixed 3- or 4-week intervals. A total of 300 patients entered the trial. There were randomized to receive CAV every 3 weeks for a total of eight cycles or to an as-needed treatment program. In this arm, patients were evaluated at 3-week intervals after the first treatment cycle and were retreated only if they were symptomatic or had evidence of tumor growth while not receiving treatment. Patients randomized to receive chemotherapy as needed had a median interval between cycles of 42 days and received only 50% as much total chemotherapy as the patients treated on the fixed schedule. Although the median survival times were equivalent, better symptomatic control was achieved with the fixed interval treatment.

Another investigation of less intensive therapy compared the ECMV regimen with VP-16. Three cycles were planned for each arm because a prior study comparing three and six cycles of ECMV showed equivalent survival. A total of 310 patients with extensive disease or limited disease and poor performance status were randomized. A response rate and survival were comparable between the two arms. There were twice as many early fatalities (death during the first treatment cycle) in patients receiving the four-drug ECMV regimen (37 vs. 18). Nevertheless, ECMV produced better palliation of symptoms than did VP-16. Another study compared a regimen of VP alternating with CAV every 3 weeks at standard doses with VP alternating with CAV every 10 to 11 days at 50% of the standard dose. Response and survival were comparable with both schedules, and toxicity was not reduced with the more frequent administration of lower doses.

Several other less intensive regimens have been designed for high-risk and elderly patients that use lower doses of chemotherapy than are used in standard regimens and report reasonable response rates and survival with less toxicity. In a study of 75 elderly patients with reasonably good performance status and limited disease, two cycles of carboplatin and prolonged oral VP-16 were given with concurrent hyperfractionated radiation, and a median survival time of 16 months was observed. In another study, limited disease until the onset of treatment. Murphy et al. administered one cycle of CAV followed by one cycle of VP-16 and cisplatin along with 20 to 30 Gy of concurrent thoracic irradiation. The complete remission rate was 51%, and 28% of the patients were alive and disease-free at 2 years. This same group of investigators have also reported a series of 66 patients who were alive and died with a median survival of 15 months and a 5-year survival of 13% were observed. Several other less intensive regimens have been designed for high-risk and elderly patients that use lower doses of chemotherapy than are used in standard regimens and report reasonable response rates and survival with less toxicity. In one study, the median white blood cell count was 2800/µL and the nadir platelet count was 198,000/µL. Patients who are treated with chemotherapy derive a survival benefit despite attenuation of both the dose and duration of treatment, and in some series the response and survival for the elderly have been comparable with younger patients.
performance status of 3 who were treated with a four-drug regimen consisting of attenuated doses of cisplatin, doxorubicin, vincristine, and VP-16 for a total of four cycles. Concurrent thoracic irradiation was given to patients with limited disease and selected patients with extensive disease. The delivered total dose was 80% of the intended dose. Survival at 2 years was 38% and 18% for patients with limited and extensive disease, respectively. Hospitalization was necessary for 42% of patients receiving combined modality treatment and for 15% of the patients treated with chemotherapy alone. There was just one septic death. Comparison of these single-institution phase II trials with the outcomes observed in controlled cooperative group studies is difficult. Nevertheless, it highlights the importance of developing chemotherapy programs of sufficient intensity to achieve optimal palliation, with manageable toxicity, in elderly and high-risk patients.

**BILOGIC RESPONSE MODIFIERS AND OTHER TREATMENTS**

Although cytotoxic therapy is effective in reducing the disease burden in SCLC, it is rarely curative. The immune response to SCLC appears to be modest, as evidenced by a lack of association with tumor-infiltrating lymphocytes in tumor biopsies. Efforts to augment the immune response have included treatment with nonspecific immunomodulators, therapy with interferons and interleukin-2, and active immunization with antiidiotypic antibodies. Studies that have evaluated bacille Calmette-Guérin, the methanol-extracted residue of bacille Calmette-Guérin, or thymosin fraction V, a soluble product of calf thymus thought to reconstitute immune function, have failed to demonstrate a beneficial effect on response rate, response duration, or survival. The expression of major histocompatibility complex antigens is reduced in SCLC, which may play a role in this tumor’s ability to escape immune surveillance. Interferon-α and Interferon-γ have been shown to increase the expression of major histocompatibility complex antigens on SCLC cells both in vitro and in vivo. Small studies in newly diagnosed patients, however, treated with either interferon-α or interferon-γ showed a total absence of activity. Because immune augmentation may be most effective in patients with low-disease burden, larger studies have evaluated interferons as maintenance treatment in patients responding to chemotherapy. Matton et al. conducted a study in which patients responding to induction chemotherapy were randomized to a maintenance chemotherapy, natural interferon-α, or observation. Although there were no differences overall, a subset analysis showed improved survival for patients with limited disease who received interferon. Another study that administered interferon-α both along with the induction chemotherapy and as a maintenance reported a higher complete response rate and improved median survival. Due to poor accrual, however, the study was stopped prematurely and only 77 patients were evaluable. Two other randomized trials, one in which interferon-α was included both as part of the induction and maintenance regimen, and a second, cooperative group trial in which interferon-α maintenance was evaluated in patients with limited disease who had responded to induction chemotherapy, showed no survival advantage. Interferon-γ maintenance therapy in patients with complete or near complete remissions has also been evaluated in two randomized trials. Although the dose and schedule selected from one trial was confirmed to be biologically active as demonstrated by a significant increase in the expression of HLA-DR and Fc receptors on monocytes, neither study produced an effect on survival. In addition to the typical influenza-like side effects and myelosuppression, a few of the studies in lung cancer have suggested that the interferons may enhance radiation-induced lung injury, and there was at least one case of fatal pneumonitis.

High-dose interleukin-2 has also been evaluated in a group of patients with extensive disease who experienced less than a complete remission to induction chemotherapy. The overall response rate was 21%, but the toxicity was severe, and treatment was discontinued in 11 of 24 patients because of life-threatening side effects. These studies indicate that at the present time treatment with cytokine therapy has not established a role in the management of this disease.

SCLC displays a variety of markers of neuroendocrine differentiation that could serve as targets for biologic agents. Neuronal adhesion molecule is one such target to which an immunotoxin, consisting of a murine monoclonal antibody linked to a modified ricin molecule, has been developed. In a dose-escalation trial, 1 of 21 patients had a partial response that lasted 3 months. In an alternate strategy, a monoclonal antibody directed against gastrin-releasing peptide was developed with the intent of interrupting this autocrine growth loop. Of 12 evaluable patients, 3 had a complete remission that lasted 6 months. The patients treated with these two biologic agents all had disease resistant to chemotherapy. The activity noted is encouraging for further clinical development.

The variable region of an antibody mirrors its antigen. Therefore, a second antibody raised against this variable region structurally mimics the original antigen. Tumors produce urokinase-like enzymes that may participate in the degradation of the extracellular matrix. Initial studies evaluating the addition of warfarin to the chemotherapy regimen improved survival yielded mixed results. In a randomized trial involving a total of 50 patients, the addition of warfarin significantly improved both progression-free and overall survival. In a larger cooperative group study, patients receiving coumadin with chemotherapy had a higher response rate (P = .012) and a 6-week improvement in median progression-free and overall survival, although the difference for the latter two endpoints was not statistically significant. The addition of 1 g/d of aspirin, a dose sufficient to inhibit platelet aggregation, failed to demonstrate a benefit. A subsequent trial by the same group of investigators demonstrated that the subcutaneous administration of unfractionated heparin at therapeutic doses given during the first 5 weeks of chemotherapy resulted in a higher complete remission rate and improved survival.

**TREATMENT AT RELAPSE**

The majority of patients with SCLC relapse within a year of initial therapy, and many are candidates for second-line treatment. Factors that predict the likelihood of response to subsequent chemotherapy include the interval between completion of induction and relapse, the extent of tumor regression achieved with the induction regimen, and the composition of the induction program. For example, the activity of teniposide in previously treated patients was 53% if the chemotherapy-free interval was greater than 2.6 months, compared with 12% if the treatment-free interval was shorter. As a consequence, sensitive relapse is often, and somewhat arbitrarily, defined as a chemotherapy-free interval of greater than or equal to 3 months. In patients in sensitive relapse, response rates to second-line therapy often exceed 50%, and any chemotherapy regimen active in SCLC appears to be effective, including the drug regimen that was initially used for induction. Only For patients who relapse early, both the regimen used for second-line and the induction regimen may be important in determining the likelihood of a secondary response. For example, in patients treated with CAV as the induction regimen, second-line treatment EP produces a response rate of approximately 35%. Only Table 31.3-8. Activity of Combination Chemotherapy Regimens at Relapse

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Response Rate</th>
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<tbody>
<tr>
<td>CAV</td>
<td>35%</td>
</tr>
<tr>
<td>VP+16</td>
<td>50%</td>
</tr>
<tr>
<td>EP</td>
<td>30%</td>
</tr>
</tbody>
</table>

For patients who relapse early, both the regimen used for second-line and the induction regimen may be important in determining the likelihood of a secondary response. For example, in patients treated with CAV as the induction regimen, second-line treatment EP produces a response rate of approximately 35%. Only
approximately one-half as many patients (15%) who experience early relapse after EP induction respond to CAV as a second-line therapy. 251 In some of the randomized trials that have compared CAV with EP, patients not responding to initial therapy (primarily refractory) and crossed over to the alternative regimen were more likely to respond to EP than to CAV, although in this more resistant group of patients the response rates to second-line treatment overall were lower and were 15% to 23% for EP and approximately 8% for CAV. 251,252,253 Drugs that have been reported to be active as second-line agents include carboplatin, ifosfamide, and paclitaxel (Taxol), although the reported response rates have been variable, reflecting the small, heterogeneous populations tested. For example, carboplatin in combination with ifosfamide or paclitaxel has been reported to be active in more than 50% of the patients relapsing after induction with CDE. 254,255 In contrast, in another study zero of ten patients resistant to cisplatin, doxorubicin, and VP-16 responded to carboplatin, ifosfamide, and vincristine. 254 Furthermore, the survival from the start of second-line therapy is rarely more than 4 to 6 months. More dose-intensive therapy with a weekly regimen has been reported to produce a 30% 1-year survival rate in patients with good performance status in sensitive relapse. 256 These studies indicate that for patients with a reasonable performance status second-line therapy with a moderately intensive drug regimen is appropriate. The likelihood of a secondary response may be better in patients who have not previously been treated with a platinum agent. 257 Symptomatic sites of disease can frequently be managed with radiation.

SURGICAL MANAGEMENT OF PERSISTENT OR RECURRENT LOCAL DISEASE

Histologically mixed disease is a not an uncommon occurrence when SCLC is resected after chemotherapy. Non–small cell lung and mixed small and non–small cell elements occur in 5% to 35% of specimens. 258,259,291,292 Whether these pathologic findings may be attributable to selection by chemotherapy of non–small cell elements present in the original tumor, histologic changes induced by chemotherapy, the presence of a second lung cancer, or incorrect initial diagnosis is not resolved. Nevertheless, surgery may prove therapeutically efficacious if the only residual cancer is non–small cell in type. Because of the frequency of mixed histologies at the time of resection after chemotherapy, the Toronto group reported a retrospective analysis of salvage surgery in limited SCLC. 293 Twenty-eight patients underwent thoracotomy after lack of response to induction chemotherapy or relapse after initial response. A resection rate of 92% was possible in this selected group, and ten patients (36%) had mixed elements histologically. Projected 5-year survival was 23%. We believe it is important to verify these findings in other patients who are prospectively identified by specific selection criteria before recommending such an approach.

TREATMENT OUTCOME AND LONG-TERM SURVIVAL

Although current therapy has a significant effect on the natural history of this disease, the number of patients cured remains frustratingly small (Table 31.3-9). Patients are at greatest risk of dying during the first 24 months after diagnosis; this risk declines between years 2 and 3 and is further reduced beyond the third year. In the Surveillance, Epidemiology, and End Results database, overall survival at 2, 3, and 5 years was 11.6%, 7.1%, and 4.6%, respectively. 235 In an analysis of 2196 patients treated on clinical trials in Britain, the hazard fell by a factor of 10 after 3 years but was still approximately seven times that of the general population. 323 Excessive mortality in long-term survivors is due both to late relapse with SCLC and to the development of second primary tumors. Late relapse occurs in approximately 10% of patients who are free of disease at 5 years. 224 Second primary tumors pose an even greater risk than relapse in long-term survivors. Overall, the relative risk of a second primary tumor in survivors beyond 2 years is increased by 3.5-fold. 325 Most of these second primary tumors are non–SCLC or other malignancies of the upper aerodigestive tract, indicating that field canerization due to tobacco exposure has occurred. 325,471 The risk of a second primary tumor increases significantly over time, and continued smoking after the initial diagnosis of SCLC, radiation to the chest, and treatment with alkylating agents magnifies this risk. 224 For example, the risk of a second lung cancer in patients who continue to smoke was approximately fourfold more than those who stopped before the diagnosis of SCLC and twofold greater in patients who received chest irradiation compared with nonirradiated patients. The cumulative risk of a second lung cancer was 32% at 12 years and continued to increase beyond that time point. Consequently, patients successfully treated for SCLC constitute an extraordinarily high-risk group and deserve close medical follow-up. This population would be appropriate for studies evaluating new screening technologies, such as spiral CT scanning, and are candidates for chemoprevention trials.

Long-term survivors are also at increased risk for noncancer-related morbidity. In a French study of patients surviving beyond 30 months, treatment-related sequelae included neurologic impairment in 13% of the patients, pulmonary fibrosis in 18%, and cardiac disorders in 10%. 352 Return to work was possible in 40% of these patients and was not influenced by the presence of late treatment-related complications. In a Danish analysis of patients surviving 5 years or longer, there was a sixfold increase rate of death from nonneoplastic causes, particularly cardiovascular and pulmonary diseases. 259 Few patients with extensive disease attain long-term survival. At 2 years after diagnosis no more than 5% of these patients remain alive, and the survival rate at 5 years is only 1%. 272,273 Although the effect of combination chemotherapy on survival is unambiguous, it is not clear whether any of the agents, treatment schedules, or supportive measures introduced since 1980 have improved survival compared with the therapies available in the 1970s. Analysis of 21 phase III trials conducted in North America between 1972 and 1990 showed an improvement in median survival time from 7 months to 8.9 months when studies initiated in the first decade were compared with studies initiated in the second. 281 In contrast, an analysis of 1111 consecutive patients treated in clinical trials in Scandinavia between 1973 and 1992 demonstrated no improvement in survival over those two decades. 273 In this series, severe myelosuppression and febrile neutropenia was significantly more common in patients treated between 1981 and 1992, suggesting that more intensive therapies in a relatively unsselective population increase toxicity without improving survival. This study highlights one of the great challenges in the management of SCLC. There is significant heterogeneity among patients in their capacity to tolerate aggressive therapy, and optimal management requires therapy that is tailored to the tolerance of the individual patient.

EXTRAPULMONARY SMALL CELL CARCINOMA

Extrapulmonary small cell anaplastic carcinoma is a clinicopathologic entity distinct from SCLC. It is estimated that approximately 1000 cases are diagnosed in the United States annually. 282 On routine histopathologic examination, pulmonary and extrapulmonary small cell carcinomas are indistinguishable. Mixed tumors, which include a variety of cell types, may occur more frequently, and deletions of chromosome 3p may be less common with extrapulmonary tumors. 284 Primary small cell carcinomas have been identified in virtually every organ site. The most common sites include the esophagus and other gastrointestinal organs, the head and neck region, cervix, and bladder. There appears to be a sex predilection based on the primary site: Most of the small cell carcinomas of the head and neck region, esophagus, and bladder are found in male subjects. With the exception of primary tumors arising in the cervix in which a younger age group is affected, the majority of patients are middle-aged or older.

A history of tobacco use is common, particularly in tumors that occur in the head and neck region and the esophagus, but there is not as strong an association with smoking as there is with pulmonary small cell carcinoma. Paraneoplastic syndromes due to the ectopic production of adrenocorticotropic and antidiuretic hormones also occur with extrapolmonary small cell cancer, and there is at least one case report in which humorally mediated hypercalcemia was identified. 285 By definition, patients with extrapolmonary small cell cancers must have a normal CT scan of the chest and preferably a normal bronchoscopic examination.

### TABLE 31.3-9. Effect of Treatment on Survival in Small Cell Lung Cancer According to Extent of Disease

| Extent of Disease | Survival Rate
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Localized</td>
<td>53%</td>
</tr>
<tr>
<td>Regional</td>
<td>26%</td>
</tr>
<tr>
<td>Distant</td>
<td>14%</td>
</tr>
<tr>
<td>Overall</td>
<td>18%</td>
</tr>
</tbody>
</table>

Long-term survivors are at increased risk for noncancer-related morbidity. In a French study of patients surviving beyond 30 months, treatment-related sequelae included neurologic impairment in 13% of the patients, pulmonary fibrosis in 18%, and cardiac disorders in 10%. Return to work was possible in 40% of these patients and was not influenced by the presence of late treatment-related complications. In a Danish analysis of patients surviving 5 years or longer, there was a sixfold increase rate of death from nonneoplastic causes, particularly cardiovascular and pulmonary diseases.

Few patients with extensive disease attain long-term survival. At 2 years after diagnosis no more than 5% of these patients remain alive, and the survival rate at 5 years is only 1%. Although the effect of combination chemotherapy on survival is unambiguous, it is not clear whether any of the agents, treatment schedules, or supportive measures introduced since 1980 have improved survival compared with the therapies available in the 1970s. Analysis of 21 phase III trials conducted in North America between 1972 and 1990 showed an improvement in median survival time from 7 months to 8.9 months when studies initiated in the first decade were compared with studies initiated in the second. In contrast, an analysis of 1111 consecutive patients treated in clinical trials in Scandinavia between 1973 and 1992 demonstrated no improvement in survival over those two decades. In this series, severe myelosuppression and febrile neutropenia was significantly more common in patients treated between 1981 and 1992, suggesting that more intensive therapies in a relatively unsselective population increase toxicity without improving survival. This study highlights one of the great challenges in the management of SCLC. There is significant heterogeneity among patients in their capacity to tolerate aggressive therapy, and optimal management requires therapy that is tailored to the tolerance of the individual patient.
Merkel-cell carcinoma is a distinct entity that is primarily found in the skin and can be distinguished by certain immunochemical characteristics. Extrapulmonary small cell carcinomas can disseminate widely, and the recommended staging studies are similar for pulmonary small cell carcinoma. A two-stage system is generally used. Limited disease is defined as tumor confined to the organ of origin and the local regional nodes that are encompassable within a radiation portal. Tumors that have spread beyond one radiation portal are defined as extensive. In contrast to SCLC, most patients in whom a primary site is identified have limited disease. In a series of 1,521 patients with SCLC, 76% of the tumors were from the right lung and 24% from the left. However, SCLC is not unique to the lung. There are several reports of patients with limited disease who were not managed, with local therapies alone, particularly surgical resection, to achieve a long-term progression-free survival. Surprisingly, small cell cancers of unknown primary site have been successfully managed by local therapy, suggesting that SCLC in the latter two settings may be more similar to limited disease SCLC than to extensive disease SCLC. In contrast, the site of origin of extensive disease tumors is often the lung, and the majority of patients present with results of complete surgical resection. Patients with stage I small cell carcinoma of the cervix have been managed successfully by radical hysterectomy, but if the regional lymph nodes are involved local therapy alone is almost never curative. Although some patients with small-volume disease confined to the organ of origin can be cured with surgery alone, the risk of relapse remains high even in this most favorable subset, and in most patients adjuvant chemotherapy should be strongly considered. For patients with regional or locoregional disease, combinations of chemotherapy and radiation is a reasonable alternative to surgery. Overall, the prognosis for small cell carcinoma is poor. In the Mayo Clinic series, 3- and 5-year survivals were 38% and 13%, respectively.

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CHAPTER 32
Neoplasms of the Mediastinum

ROBERT B. CAMERON
PATRICK J. LOEHRER
CHARLES R. THOMAS, JR.

Introduction
Anatomy
Incidence and Pathology
Diagnostic Considerations
Symptoms and Signs
Radiographic Imaging Studies
Serology and Chemistry
Invasion, Diagnoses, Type
Thymic Neoplasms
Thymic Anatomy and Physiology
Thymoma
Thymic Carcinoma
Thymic Carcinoid
Thymolipoma

Germ Cell Tumors
Etiology
Classification
Incidence and Clinical Presentation
Diagnosis
Immunostaining
Nonseminomatous Germ Cell Tumors
Seminoma
Nonseminomatous Germ Cell Tumors
Malignant Schwannoma
Tumors of Sympathetic Ganglia
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Diagnosis
Management
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Chapter References

INTRODUCTION

Tumors involving the mediastinum may be primary or secondary in nature. Primary neoplasms can originate from any mediastinal organ or tissue but most commonly arise from thymic, neurogenic, lymphatic, germinal, and mesenchymal tissues. All primary mediastinal neoplasms, except those of thymic origin, also occur elsewhere in the body and are discussed in other chapters. Secondary (metastatic) mediastinal tumors are more common than primary neoplasms and most frequently represent lymphomatous involvement from primary tumors of the lung or infradiaphragmatic organs, such as pancreatic, gastroesophageal, and testicular cancer. This chapter provides an overview of primary mediastinal neoplasms. Specific tumors are covered in detail, including thymic, primary mediastinal germ cell, mesenchymal, cardiac, and neurogenic tumors. Esophageal cancer and lymphomas are covered elsewhere, in Chapter 33.2 (Cancer of the Esophagus) and Chapter 45.1, Chapter 45.2, Chapter 45.3, Chapter 45.4, Chapter 45.5, and Chapter 45.6 (Lymphomas).

ANATOMY

The mediastinum occupies the central portion of the thoracic cavity. It is bounded by the pleural cavities laterally, by the thoracic inlet superiorly, by the diaphragm inferiorly, by the sternum anteriorly, and by the chest wall posteriorly. The mediastinum can be divided into three clinically relevant compartments: anterior, middle, and posterior. The anterior mediastinum lies posterior to the sternum and anterior to the pericardium and great vessels, extending from the thoracic inlet to the diaphragm. The middle mediastinum is defined as the space occupied by the heart, pericardium, proximal great vessels, and central airways. The posterior mediastinum is bounded by the heart and great vessels anteriorly, the thoracic inlet superiorly, the diaphragm inferiorly, and the chest wall of the back posteriorly, and it includes the paravertebral gutters. Table 32-1 lists the major anatomic structures within each of the compartments. A thorough understanding of each area’s contents helps define the diagnostic possibilities. Other divisions have been proposed, dividing the mediastinum into three or four compartments. Heitzman even proposed seven anatomic regions. Although the exact scheme that should be used is still debated, these other schemes have limited clinical utility.

FIGURE 32-1. Mediastinal compartments.
TABLE 32-1. Anatomic Structures within the Mediastinum

INCIDENCE AND PATHOLOGY

Mediastinal neoplasms are uncommon tumors that can occur at any age but are most common in the third through the fifth decades of life. Table 32-2 reviews the classification of mediastinal neoplasms. The incidence of primary mediastinal tumors was documented in a review of 1900 patients (Table 32-3). Additionally, 439 patients (18% of all mediastinal masses) were found to have cystic lesions. The distribution of primary mediastinal neoplasms is shown in Table 32-4. Thymic neoplasms predominate in the anterior mediastinum, followed in frequency by lymphomas, germ cell tumors, and carcinoma. Bronchial, enteric, and pericardial cysts are the most common masses in the middle mediastinum, followed by lymphomas, mesenchymal tumors, and carcinoma. In the posterior mediastinum, neurogenic tumors and esophageal cancers are most common, followed by enteric cysts, mesenchymal tumors, and endocrine neoplasms.

Table 32-2. Classification of Mediastinal Tumors

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Adults (%)</th>
<th>Children (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurogenic</td>
<td>25.5</td>
<td>5.9</td>
</tr>
<tr>
<td>Thymoma</td>
<td>20.5</td>
<td>4.9</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>15.5</td>
<td>3.5</td>
</tr>
<tr>
<td>Germ cell</td>
<td>11.5</td>
<td>3.2</td>
</tr>
<tr>
<td>Bronchogenic</td>
<td>7.5</td>
<td>2.9</td>
</tr>
<tr>
<td>Mesenchymal</td>
<td>7.5</td>
<td>2.9</td>
</tr>
<tr>
<td>Primary carcino</td>
<td>5.2</td>
<td>1.5</td>
</tr>
</tbody>
</table>

Table 32-3. Relative Frequency of Primary Mediastinal Tumors

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Adults (%)</th>
<th>Children (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thymoma</td>
<td>28</td>
<td>14</td>
</tr>
<tr>
<td>Neurogenic</td>
<td>11</td>
<td>7.5</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>6.5</td>
<td>5.5</td>
</tr>
<tr>
<td>Germ cell</td>
<td>4.5</td>
<td>3.5</td>
</tr>
<tr>
<td>Bronchogenic</td>
<td>3.5</td>
<td>2.5</td>
</tr>
<tr>
<td>Mesenchymal</td>
<td>3.5</td>
<td>2.5</td>
</tr>
</tbody>
</table>

Table 32-4. Distribution of Primary Mediastinal Masses by Anatomic Location

The incidence of mediastinal tumors in each anatomic compartment also varies with age. In adults, 54% of mediastinal neoplasms occur in the anterior, 20% in the middle, and 24% in the posterior mediastinum. In pediatric populations, 43%, 18%, and 40% of neoplasms occur in the anterior, middle, and posterior mediastinum, respectively. A higher incidence of thymic tumors and lymphomas in adults and neurogenic tumors in children account for these differences. Azarow compared mediastinal masses in 195 adult and 62 pediatric patients (Table 32-5). Cysts were not included but accounted for 16% to 18% of adult and 24% of pediatric mediastinal masses. Therefore, age as well as location establishes the probable diagnosis.

Table 32-5. Relative Frequency of Primary Mediastinal Tumors in Adults and Children

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Adults (%)</th>
<th>Children (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thymic</td>
<td>31</td>
<td>18</td>
</tr>
<tr>
<td>Neurogenic</td>
<td>14</td>
<td>7</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>15</td>
<td>9.5</td>
</tr>
<tr>
<td>Germ cell</td>
<td>11</td>
<td>7</td>
</tr>
<tr>
<td>Bronchogenic</td>
<td>4.5</td>
<td>4.5</td>
</tr>
<tr>
<td>Mesenchymal</td>
<td>4.5</td>
<td>4.5</td>
</tr>
</tbody>
</table>

DIAGNOSTIC CONSIDERATIONS

A meticulous history and physical examination, along with a variety of imaging, serologic, and invasive tests (Table 32-6), often can confirm the suspected diagnosis.
With improved imaging, biopsy, and pathologic techniques, the majority of patients no longer require open surgical biopsy before planning definitive therapy.

### TABLE 32-6. Diagnostic Evaluation of Mediastinal Masses

#### SYMPTOMS AND SIGNS

Approximately 40% of mediastinal masses are asymptomatic and discovered incidentally on a routine chest radiograph. The remaining 60% of cases have symptoms related to compression or direct invasion of surrounding mediastinal structures or to paraneoplastic syndromes. Asymptomatic patients are more likely to have benign lesions, whereas symptomatic patients more often harbor malignancies. Davis found that 85% of patients with a malignancy were symptomatic, but only 46% of patients with benign neoplasms had identifiable complaints. Symptoms and signs of mediastinal neoplasms are shown in Table 32-7. The most commonly described symptoms are chest pain, cough, and dyspnea. Superior vena cava syndrome, Horner's syndrome, hoarseness, and neurologic deficits more commonly occur with malignancies. Systemic syndromes associated with mediastinal neoplasms are shown in Table 32-8 and Table 32-9.

### TABLE 32-7. Symptoms and Signs of Mediastinal Masses

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest pain</td>
<td>Sensory or motor disturbances in the upper extremities and/or neuropathic pain</td>
</tr>
<tr>
<td>Cough</td>
<td>Productive or dry, depending on pathophysiologic state</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>Difficulty with inspiration and shortness of breath</td>
</tr>
<tr>
<td>Anorexia</td>
<td>Lack of appetite, weight loss, and appetite suppression</td>
</tr>
<tr>
<td>Hoarseness</td>
<td>Hoarseness and/or vocal cord swelling</td>
</tr>
<tr>
<td>Soreness</td>
<td>Sensation of pain in the anterior chest wall</td>
</tr>
<tr>
<td>Headache</td>
<td>Severe or moderate, may be accompanied by nausea and vomiting</td>
</tr>
<tr>
<td>Neurologic deficit</td>
<td>Loss of motor, sensory, or autonomic function</td>
</tr>
</tbody>
</table>

### TABLE 32-8. Systemic Syndromes Associated with Mediastinal Neoplasms

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superior vena cava syndrome</td>
<td>Obstruction of the superior vena cava resulting in partial or complete obstruction of the venous return to the heart</td>
</tr>
<tr>
<td>Horner's syndrome</td>
<td>Constrictions of the oculomotor nerve resulting in ptosis and miosis</td>
</tr>
<tr>
<td>Hoarseness</td>
<td>Paralysis or weakness of the vocal cord resulting in hoarseness</td>
</tr>
<tr>
<td>Neurologic deficit</td>
<td>Loss of motor, sensory, or autonomic function</td>
</tr>
</tbody>
</table>

### RADIOGRAPHIC IMAGING STUDIES

Radiographic imaging studies initially localize mediastinal neoplasms. The posteroanterior and lateral chest radiographs define the location, size, density, and calcification of a mass, limiting the diagnostic possibilities. After these results, an intravenous contrast-enhanced computed tomography (CT) scan can further assess the nature (cystic vs. solid) of the lesion and detect fat and calcium. The relationship to surrounding structures and blood vessels also can be determined.

Magnetic resonance imaging (MRI) is used less frequently than CT. Its advantages include multiplanar imaging and absence of ionizing radiation. MRI scans are superior to CT in defining vascular involvement and in distinguishing recurrent tumor from radiation fibrosis. However, patient claustrophobia, time, and expense limit the use of MRI scanning. Other imaging modalities that may be useful include transsthoracic sonography and transesophageal echocardiography.

The utility of positron emission tomography in the evaluation of mediastinal masses is yet to be determined, but it may help clarify the nature of such masses and the presence of necrosis in residual mediastinal tissue after therapy.

### SEROLOGY AND CHEMISTRY

Some mediastinal neoplasms release substances into the serum that can be measured by specific radioimmunoassays. These substances may be used to confirm a diagnosis, evaluate response to therapy, and monitor for tumor recurrence. alpha-Fetoprotein (AFP), human chorionic gonadotropin-b (h-HCG), and lactate dehydrogenase are elaborated by some germ cell tumors and should be obtained in male patients with anterior mediastinal masses. Also, adrenocorticotropic hormone, thyroid hormone, and parathyromone may help differentiate certain mediastinal tumors (see Table 32-9).
INVASIVE DIAGNOSTIC TESTS

The determination of the histologic diagnosis of mediastinal masses often is essential for implementation of appropriate treatment. Previously, most patients underwent surgical procedures to establish the diagnosis of mediastinal neoplasms; however, improvements in less invasive diagnostic and immunohistochemical techniques and in electron microscopy have greatly improved the ability to differentiate the cell types in mediastinal neoplasms. CT-guided percutaneous needle biopsy, using either fine-needle aspiration techniques and cytologic assessment or larger-core needle biopsy and histologic evaluation, now are standard in the initial evaluation of most mediastinal masses. Although fine-needle specimens are usually adequate to distinguish carcinomatous lesions, core biopsies are recommended to distinguish most other mediastinal neoplasms, especially lymphoma and thymoma.

Most series report diagnostic yields for percutaneous needle biopsy of 72% to 100%, and, most recently, that figure is in excess of 90%. Complications include simple pneumothorax (25%), pneumothorax requiring chest tube placement (5%), and hemoptysis (7% to 15%).

Surgical procedures are still occasionally required in the diagnosis of mediastinal tumors. Mediastinoscopy is a relatively simple procedure, accomplished under general anesthesia. It provides access to the middle and a limited portion of the upper posterior mediastinum and has a diagnostic accuracy of more than 90%. Anterior parasternal mediastinotomy (Chamberlain’s operation) yields access to the anterior and lateral anterior mediastinum and is performed under general anesthesia but is minimally invasive and provides a diagnostic accuracy of nearly 100% in most areas of the mediastinum. Thoracoscopy should be reserved, however, for biopsies that cannot be obtained with mediastinoscopy or parasternal mediastinotomy. Thoracoscopy is almost never necessary for diagnosis and should be reserved for rare circumstances.

THYMIC NEOPLASMS

The thymus is an incompletely understood lymphatic organ functioning in T-lymphocyte maturation. It is composed of an epithelial stroma and lymphocytes. Although lymphomas, carcinoid tumors, and germ cell tumors all may arise within the thymus, only thymomas, thymic carcinomas, and thymolipomas arise from true thymic elements. Epithelial thymic neoplasms have been classified into three proposed categories: (1) thymomas, well-differentiated neoplasms; (2) atypical thymomas, moderately differentiated neoplasms; and (3) thymic carcinomas, poorly differentiated neoplasms. This classification is based on features of glandular differentiation; however, further validation of this system is needed.

THYMIC ANATOMY AND PHYSIOLOGY

The thymus develops from a paired epithelial anlage in the ventral portion of the third pharyngeal pouch. It is closely associated with the developing parathyroid glands. The stroma of the thymus consists of epithelial cells, which are likely derived from both ectodermal and endodermal components. During weeks 7 and 8 of development, the thymus elongates and descends caudally and ventromedially into the anterior mediastinum. By week 12, a separate cortex and medulla become evident, and mesenchymal septae develop perivascular spaces that contain blood vessels. Lymphoid cells arrive from the liver and bone marrow during week 9 and are separated from the perivascular space by a flat layer of epithelial cells that create the blood–thymus barrier. Maturation and differentiation occurs in this antigen-free environment. By the fourth fetal month, lymphocytes circulate to peripheral lymphoid tissue.

Six subtypes of epithelial cells have been identified in mature thymus. Four exist primarily in the cortical region and two in the medullary region. Type 6 cells form Hassall’s corpuscles that are characteristic of thymus. These cells have an ectodermal origin and are displaced into the thymic medulla, where they hypertrophy and form tonofilaments, finally appearing as concentric cells without nuclei.

At maturity, the thymus gland is an irregular, lobulated organ. It attains its greatest relative weight at birth, but its absolute weight increases to 30 to 40 g by puberty. During adulthood, it slowly involutes and is replaced by adipose tissue. Ectopic thymic tissue has been found to be widely distributed throughout the mediastinum and neck, particularly the aortopulmonary window and retrocardiac area, and often is indistinguishable from mediastinal fat. This ectopic tissue is the likely explanation for thymomas outside the anterior mediastinum and possibly for failure of thymectomy in some cases to improve myasthenia gravis.

THYMOMA

Thymic neoplasms, mostly thymomas, constitute 30% of anterior mediastinal masses in adults. Thymomas are less common in children, accounting for only 15% of anterior mediastinal masses. Thymomas exhibit no gender predilection and occur most often in the fifth and sixth decades of life. Nearly one-half of these tumors are asymptomatic and are discovered only on routine radiographs. In symptomatic patients, 40% have myasthenia gravis (diplopia, ptosis, dysphagia, fatigue, etc.), whereas others complain of chest pain and symptoms of hemorrhage or compression of mediastinal structures.

Pathology and Classification

Ninety percent of thymomas occur in the anterior mediastinum, and the remainder are located in the neck or other areas of the mediastinum. Grossly, they are lobulated, firm, tan-pink to gray tumors that often contain cystic spaces, calcification, or hemorrhage. They may be encapsulated, adherent to surrounding structures, or frankly invasive. Microscopically, thymomas arise from thymic epithelial cells, although lymphocytes may predominate histologically. True thymomas contain cytologically bland cells and should be distinguished from thymic carcinomas, which have malignant cytologic characteristics. Confusion exists because of previous “benign” or “malignant” designations. Currently, the terms noninvasive and invasive are used. Noninvasive thymomas have an intact capsule, are movable, and are easily resected, although they can be adherent to adjacent organs. In contrast, invasive thymomas involve surrounding structures and can be difficult to remove without en bloc resection of adjacent structures. Despite this difficulty, their cytologic appearance remains benign. Metastatic disease does occur and is most commonly seen as pleural implants and pulmonary nodules. Metastases to extrathoracic sites are rare.

In 1985, Marino and Muller-Hermelink proposed a histologic classification system determined by the thymic site of origin—that is, tumors arising from epithelial cells of the cortex are termed cortical thymomas, those arising from the medullary areas are called medullary thymomas, and those with features of both are termed mixed thymomas. Spindle-shaped cells predominate in the medullary area and likely correspond to spindle cell thymomas of the traditional classification system. Likewise, the cortex contains predominantly round to oval epithelial cells; thus, cortical thymomas probably correspond to the traditional epithelial thymoma. The Muller-Hermelink classification was later revised and further divided into medullary, mixed, predominantly cortical, and cortical thymomas. Well-differentiated and high-grade thymic carcinoma were also described. Medullary and mixed thymomas were considered benign with no risk of recurrence, even with capsular invasion. Predominantly cortical and cortical thymomas exhibited intermediate invasiveness and a low but definite risk of late relapse, regardless of their invasiveness. Well-differentiated thymic carcinomas were always invasive, with a high risk of relapse and death. Some support this revision, claiming that it better correlates pathology with prognosis. Others believe that it has no distinct clinicopathologic advantage over the traditional system. This issue has been re-examined and the World Health Organization Committee on the Classification of Thymic Tumors adopted a new classification system for thymic neoplasms.
based on cytologic similarities between certain normal thymic epithelial cells and neoplastic cells, which is of prognostic significance (Table 32-10).

59

TABLE 32-10. World Health Organization Staging System for Thymic Epithelial Tumors

In 1981, Masaoka et al.60 developed a staging system based on the previous work of Bergh et al.61 The four stages are shown in Table 32-11. The Masaoka stage II classification assesses both microscopic invasion (occult in 28%) and gross tumor adherence as determined by surgical findings.59,62,63 Staging was found to correlate with prognosis, with 5-year survival rates 96% for stage I, 86% for stage II, 69% for stage III, and 50% for stage IV.64 The Groupe d'Etudes des Tumeurs Thymiques (GETT) staging system is surgery-based and demonstrates 90% concordance with the Masaoka system (Table 32-12).63,64

TABLE 32-11. Thymoma Staging System of Masaoka

TABLE 32-12. Thymoma Staging System of Groupe d'Etudes des Tumeurs Thymiques

Associated Systemic Syndromes

A wide variety of systemic disorders are associated with 71% of thymomas.59 The symptoms of these associated disorders often lead to the original discovery of the mediastinal tumor. Autoimmune diseases (systemic lupus erythematosus, polymyositis, myocarditis, Sjögren's syndrome, ulcerative colitis, Hashimoto's thyroiditis, rheumatoid arthritis, sarcoidosis, and scleroderma) and endocrine disorders (hyperthyroidism, hyperparathyroidism, Addison's disease, and panhypopituitarism) are most common.65

Blood disorders, such as red cell aplasia, hypogammaglobulinemia, T-cell deficiency syndrome, erythrocytosis, pancytopenia, megakaryocytopenia, T-cell lymphocytosis, and pancytopenia, have also been noted.66 Other than myasthenia, neuromuscular syndromes include myotonic dystrophy, myasthenia gravis, and Eaton-Lambert syndrome.67 Miscellaneous diseases include hypertrophic osteoarthropathy, nephrotic syndrome, minimal change nephropathy, pemphigus, and chronic mucocutaneous candidiasis.68 Nearly 15% of patients with thymoma develop a second malignancy, such as Kaposi's sarcoma, chemodectoma, multiple myeloma, acute leukemia, and various carcinomas (e.g., lung, colon).69

MYASTHENIA GRAVIS. Myasthenia gravis is the most common autoimmune disorder, occurring in 30% to 50% of patients with thymomas. Younger women and older men usually are affected, with a female to male ratio of 2:1. Myasthenia is a disorder of neuromuscular transmission. Symptoms begin insidiously and result from the production of antibodies to the postsynaptic nicotinic acetylcholine receptor at the myoneural junction. Ocular symptoms are the most frequent initial complaint, eventually progressing to generalized weakness in 80%. The role of the thymus in myasthenia remains unclear, but autoimmunization of T lymphocytes to acetylcholine receptor proteins or an unknown action of thymic hormones remain possibilities.52,67

Pathologic changes in the thymus are noted in approximately 70% of patients with myasthenia gravis. Lymphoid hyperplasia, characterized by the proliferation of germinal centers in the medullary and cortical areas, is most commonly seen. Thymomas are identified in only about 15% of patients with myasthenia.

The treatment of myasthenia gravis involves the use of anticholinesterase-mimetic agents [i.e., pyridostigmine bromide (Mestinon)]. In severe cases, plasmapheresis may be required to remove high antibody titers. Thymectomy has become an increasingly accepted procedure in the treatment of myasthenia, although the indications, timing, and surgical approach remain controversial.54 Some improvement in myasthenic symptoms almost always occurs after thymectomy, but complete remission rates vary from 7% to 63%.54 Patients with myasthenia gravis and thymomas do not respond as well to thymectomy as those without thymomas. Overall survival for myasthenia patients also is lower for patients with thymomas, but no differences were noted based on the extent of invasion present.55

RED CELL APLASIA. Pure red cell aplasia is considered an autoimmune disorder and is found in approximately 5% of patients with thymomas. Of patients with red cell aplasia, 30% to 50% have associated thymomas.66 Ninety-six percent of the patients affected are older than 40 years of age. Examination of the bone marrow reveals an absence of erythroid precursors and, in 30%, an associated decrease in platelet and leukocyte numbers. Thymectomy has produced remission in 38% of
patients. Octreotide and prednisone were effective in one patient with recurrent disease. HYPOGAMMAGLOBULINEMIA. Hypogammaglobulinemia is seen in 5% to 10% of patients with thymoma, and 10% of patients with hypogammaglobulinemia have been shown to have thymoma. Defects in both cellular and humoral immunity have been described, and many patients also have red cell hypoplasia. Thymectomy has not proven beneficial in this disorder.

**Treatment**

Thymomas are slow-growing neoplasms that should be considered potentially malignant. Surgery, radiation, and chemotherapy all may play a role in their management.

**SURGERY.** Complete surgical resection is the mainstay of therapy for thymomas and is the most important predictor of long-term survival. Although median sternotomy with a vertical or submammary incision is most commonly used, bilateral anterolateral thoracotomies with transverse sternotomy, or "skin-shell procedure," is preferred with advanced or laterally displaced tumors. Video-assisted thoracoscopic surgery has also been reported, but long-term results remain unknown. Because of concern about tumor seeding, biopsy procedures are not routinely performed. During surgery, a careful assessment of areas of possible invasion and adherence should be made by the surgeon, who is the best judge of tumor invasiveness. Extended total thymectomy, including all tissue anterior to the pericardium from the diaphragm to the neck and laterally from phrenic nerve to phrenic nerve, is recommended in all cases. Complete surgical resection is associated with improved 5-year survival rates. Rates of complete resection are 71% and with biopsy is only 26%. Survival after complete tumor resection has been similar in patients with noninvasive and invasive thymomas in several studies. Patients with myasthenia gravis and thymoma were studied by Cruccu et al., who reported a 78% 10-year survival rate and a 3% recurrence rate with 4.8% (1.7% since 1980) operative mortality after extended thymectomy. Aggressive resection, including lung, phrenic nerve, pericardium, pleural implants, and pulmonary metastases, is occasionally helpful.

The role of debulking or subtotal resection in stage III and IV disease remains controversial. Several studies have documented 5-year survival rates from 60% to 75% after subtotal resection and 24% to 40% after biopsy alone.

**RADIATION THERAPY.** Radiation therapy is radioresponsive tumors, and, consequently, radiotherapy has been used to treat all tumor stages as well as recurrent disease.

In stage I thymomas, adjuvant radiotherapy has been administered but has not improved on the excellent results with surgery alone (more than 80% 10-year survival rate). In stage II and III invasive disease, adjuvant radiation can decrease recurrence rates after complete surgical resection from 28% to 5%, and in addition, Pollack et al. reported an increase in 5-year disease-free survival for stage II to IIIa from 18% to 62% with the addition of adjuvant radiation. Others have documented similar results.

**COMBINED MODALITY APPROACHES.** The use of neoadjuvant chemotherapy as part of a multimodality approach to stage III and IV thymoma was reviewed by Tomiak and Evans. Combined modality approaches are increasingly being used in stage III and IV disease. Several studies have documented the high 7-year survival rate of 4.3 years in a small study of 16 patients with advanced thymoma treated with cisplatin and etoposide.

The addition of ifosfamide to cisplatin and etoposide has had a lower than anticipated response rate (approximately 32%) in patients with thymoma and thymic carcinoma.

**CHEMOTHERAPY.** Chemotherapy has been used in increasing frequency in the treatment of invasive thymomas. Both single-agent and combination therapy have demonstrated activity in the adjuvant and neoadjuvant settings. Doxorubicin, cisplatin, ifosfamide, corticosteroids, and cyclophosphamide all have been used as single-agent therapy. The most active agents are cisplatin, ifosfamide, and corticosteroids; however, only cisplatin and ifosfamide have undergone phase II trials. The combination of cisplatin, doxorubicin, and ifosfamide has produced complete responses lasting up to 30 months, but lower doses (50 mg/m²) have associated response rates of only 11%. Ifosfamide (with mesna) at a single dose of 7.5 g/m² or as a continuous infusion of 1.5 g/m²/d for 5 days every 3 weeks has resulted in 50% complete and 57% overall response rates. Duration of complete remission ranged from 6 to 6 months. Varying regimens of corticosteroids have shown effectiveness in the treatment of all histologic subtypes of thymoma (with and without myasthenia), with a 77% overall response rate in limited numbers of patients. Corticosteroids also have been effective for patients unsuccessful with chemotherapy; however, the actual impact may only be on the lymphocytic and not the malignant epithelial component of the tumor.

Combination chemotherapy regimens have shown higher response rates and have been used in both adjuvant and neoadjuvant settings in the treatment of advanced invasive, metastatic, and recurrent thymoma. Cisplatin-containing regimens appear to be the most active. Fornasier et al. reported a 43% complete and 91.8% overall response rate with a median survival of 15 months in 37 previously untreated patients with stage III or IV invasive thymoma treated with monthly (median, 5 months) cisplatin, 50 mg/m² on day 1; doxorubicin, 40 mg/m² on day 1; vincristine, 0.6 mg/m² on day 3; and cyclophosphamide, 700 mg/m² on day 4. Leher et al. documented 100% complete and 50% overall response rates with a median survival of 37 months in 29 patients with metastatic or locally progressive recurrent thymoma treated with cisplatin, 50 mg/m², doxorubicin, 50 mg/m², and cyclophosphamide, 500 mg/m², given every 3 weeks for a maximum of 8 cycles after radiotherapy. Park et al. retrospectively described 35% complete and 64% overall response rates with a median survival of 67 months in responding and 17 months in nonresponding patients in 17 patients with invasive stage II and IV thymoma initially treated after relapse with cyclophosphamide, doxorubicin, and cisplatin, with or without prednisone. The European Organization for Research and Treatment of Cancer noted 31% complete and 56% overall response rates with a median survival of 4.3 years in a small study of 16 patients with advanced thymoma treated with cisplatin and etoposide. The addition of ifosfamide to cisplatin and etoposide had a lower than anticipated response rate (approximately 32%) in patients with thymoma and thymic carcinoma.

**COMBINED MODALITY APPROACHES.** The use of neoadjuvant chemotherapy as part of a multimodality approach to stage III and IV thymoma was reviewed by Tomiak and Evans. Six combined reports document 31% complete and 89% overall response rates in 61 total patients treated with a variety of neoadjuvant chemotherapy regimens (80% cisplatin-based). Twenty-two patients (36%) underwent surgery, with 11 (18%) achieving a complete resection (all treated with cisplatin). Nineteen patients were treated with radiotherapy, but only five patients had disease-free survivals exceeding 5 years. Rea et al. reported 43% complete and 100% overall response rates with median and 3-year survival rates of 66 months and 70%, respectively, in 16 stage III and IVa patients treated initially with cisplatin, doxorubicin, vincristine, and cyclophosphamide, followed by surgery. At surgery, 69% were completely resected and the other 31% received postoperative radiation. Macchiarini et al. reported similar findings. Twenty-five percent complete and 92% overall response rates with a remarkable 83% 7-year disease-free survival rate were reported in 12 patients at the M. D. Anderson Cancer Center who received cisplatin, doxorubicin, cyclophosphamide, and prednisone induction chemotherapy followed by surgical resection (80% complete) and adjuvant radiotherapy for locally advanced (unresectable) thymoma. The degree of chemotherapy-induced tumor necrosis correlated with Ki-67 expression.

A multinstitutional prospective trial demonstrated a 22% complete and 70% overall response rate with a median survival of 93 months and a Kaplan-Meier 5-year failure-free survival rate of 54.3% in 23 patients with stage III (22/23) unresectable thymoma (GETT stage IIIaIIIb) stage IV (1/23) thymoma, and thymic carcinoma.
Thymic carcinoma is a rare aggressive thymic neoplasm that has a poor prognosis. Like thymoma, it is an epithelial tumor, but cytologically it exhibits malignant features. Extensive local invasion and distant metastases are common. Approximately 150 cases have been reported. Suster and Rosai reported the largest single series, involving 60 patients ranging in age from 10 to 76 years and with a slight male predominance. Nearly 50% had symptoms of cough, chest pain, or superior vena cava syndrome. Myasthenia and other thymoma-associated syndromes are rare.

The histologic classification of thymic carcinoma was proposed by Levine and Rosai and revised by Suster and Rosai. The tumors are classified broadly as low or high grade. Low-grade tumors include squamous cell carcinoma, mucoepidermoid carcinoma, and basaloïd carcinoma. High-grade neoplasms include lymphoepithelioma-like carcinoma and small cell, undifferentiated sarcomatoid, and clear cell carcinomas. The classification of thymic carcinoma has prognostic significance, with low-grade tumors following a favorable clinical course (median survival rates of 25 years to more than 6.6 years) because of a low incidence of local recurrence and metastasis, and high-grade malignancies exhibiting an aggressive clinical course (median survival of only 11.3 to 15.0 months).

Although the Masaoka thymoma staging system and a proposed tumor-node-metastasis classification system have been used in staging thymic carcinoma, their utility is unproven. The histologic grade remains the best prognostic indicator.

The optimal treatment of thymic carcinoma remains undefined, but currently a multimodality approach, including surgical resection, postoperative radiation, and chemotherapy, is recommended. Initial surgical resection followed by radiation has been used in most studies. Complete resection should be attempted, but usually is not possible. One analysis noted a 9.5-month median survival after resection and postoperative electron beam radiation therapy, with a trend toward improved survival in other studies. Chemotherapy with cisplatin-based regimens similar to those used with thymomas have produced variable responses in small numbers of patients. Combinations of doxorubicin, cyclophosphamide, and vincristine have also been used with responses, but none of these regimens has been established as standard treatment. Use of neoadjuvant chemotherapy has been reported in a small number of patients.

The prognosis of thymic carcinoma is poor because of early metastatic involvement of pleura; lung; mediastinal, cervical, and axillary lymph nodes; bone; and liver. The overall survival rate at 5 years is approximately 35%. Improved survival has been correlated with encapsulated tumors, lobular growth pattern, low mitotic activity, and low histologic grade.

Thymic carcinoid tumors are rare, with fewer than 125 reported cases. They occur predominantly in males and originate from normal thymic Kulchitsky's cells, which are part of the amine precursor uptake and decarboxylation (APUD) group. Most have the ability to manufacture peptides, amines, kinins, and prostaglandins. They are aggressive tumors that invade locally and commonly metastasize to regional lymph nodes. Metastases occur in 70% of patients within 8 years of initial diagnosis.

The gross appearance of thymic carcinoids is similar to that of thymomas, but they are rarely encapsulated. Microscopically, the tumors exhibit a ribbon-like growth pattern with rosette formation in a fibrovascular stroma. The cells are small, round, or oval with eosinophilic cytoplasm and uniformly round nuclei.

Immunohistochemical studies reveal argyrophilic cells that stain with cytokeratin and neuronal-specific enolase. Electron microscopy reveals the presence of secretory granules. Thymic carcinoids, like other foregut carcinoids, are associated with Cushing's syndrome, multiple endocrine neoplasia and, rarely, the carcinoid syndrome.

The diagnosis of thymic carcinoid often requires open surgical biopsy. Complete surgical resection is recommended, although recurrence is common. The effectiveness of adjuvant therapy is unknown, but most reports advocate adjuvant radiotherapy for incompletely resected tumors. Chemotherapy rarely has been used in cases of metastatic or recurrent disease.

Although a 5-year survival rate of 60% has been reported with complete surgical resection, local recurrences are common and distant metastases occur in approximately 30% of patients. The long-term prognosis is generally poor.

Thymolipomas are rare benign neoplasms composed of mature adipose and thymic tissue, and they account for 1% to 5% of thymic neoplasms. These tumors are also known as lipothyromas, mediastinal lipomas with thymic remnants, and thymolipomatous hamartomas. In a review of 27 patients, Rosado-de-Christenson et al. noted an equal gender distribution and a mean age of 27 years. Approximately 50% of patients presented with symptoms of vague chest pain, dyspnea, and tachypnea. Others have reported, in adults only, an association with myasthenia gravis, red cell aplasia, hypogammaglobulinemia, lichen planus, and Graves' disease.

Thymolipomas are soft, lobulated, encapsulated tumors that originate in the anterior mediastinum. They often attain a large size before becoming symptomatic. They frequently contain to the shape of the cardiac and mediastinal structures and are found in the anterior inferior mediastinum “draped along the diaphragm” and connected to the thymus by a small pedicle. Microscopically, the tumors are composed of thymic tissue, often with calcified Hassall's corpuscles, and more than 50% adipose tissue. Histologically, thymolipomas do not appear malignant, and malignant transformation does not occur.

Germ cell tumors are found along the body's midline from the cranium (pineal gland) to the presacral area. This line corresponds to the embryologic urogenital ridge. It is presumed that these tumors arise from malignant transformation of germ cells that have abnormally migrated during embryonic development. Mediastinal germ cell neoplasms account for only 2% to 5% of all germinal tumors, but they constitute 50% to 70% of all extragonadal tumors.

Classification is based on the histologic type and grade of the tumor, the extent of local invasion, and the presence of metastases. The tumors are classified as follows:

- Low-grade tumors: These are well-differentiated tumors with a low proliferation rate and a low tendency to metastasize.
- High-grade tumors: These are poorly differentiated tumors with a high proliferation rate and a high tendency to metastasize.
- Malignant tumors: These are tumors that have metastasized to other parts of the body.

The prognosis of germ cell tumors is influenced by the histologic type and grade of the tumor, the extent of local invasion, and the presence of metastases. Low-grade tumors have a favorable prognosis, with a 5-year survival rate of 90%. High-grade tumors have a poor prognosis, with a 5-year survival rate of only 10%.
Mediastinal germ cell tumors are broadly classified as benign or malignant. Benign tumors include mature teratomas and mature teratomas with an immature component of less than 50%. Malignant germ cell tumors are divided into seminomas (dyserninomas) and nonseminomatous tumors. Nonseminomatous tumors include embryonal carcinomas, choriocarcinomas, yolk sac tumors, and immature teratomas. Seminomas may exist in a pure form, but any elevation of AFP indicates the presence of an element of a nonseminomatous tumor. In addition, mediastinal germ cell tumors have a propensity to develop a component of non-germ cell malignancy (e.g., rhadomyosarcoma or adenocarcinoma, permeative neuroectodermal tumor), which can become the predominant histology.

INCIDENCE AND CLINICAL PRESENTATION

In adults, benign germ cell tumors have no gender predilection, but 90% of malignant germ cell tumors occur in men. In the pediatric population, both benign and malignant extragonadal germ cell tumors occur with equal gender distribution. Mediastinal germ cell tumors are most commonly diagnosed in the third decade of life, but patients as old as 60 years of age have been reported. The incidence of these neoplasms is equal in all races. Many patients with benign tumors, including 50% of teratomas, are asymptomatic; however, 90% to 100% of patients with malignant tumors have symptoms of chest pain, dyspnea, cough, fever, or other findings related to compression or invasion of surrounding mediastinal structures.

DIAGNOSIS

Mediastinal germ cell tumors are most often detected on the basis of standard chest radiographs. More than 95% of the chest films are abnormal, with almost all masses noted in the anterior mediastinum. Three percent to 8% of tumors arise within the posterior mediastinum. Chest CT scans demonstrate the extent of disease, relationship to surrounding structures, and presence of cystic areas and calcification within the tumor. Abdominal imaging should be performed to assess for possible liver metastases. Careful examination of the testicles, including a testicular ultrasound, should always be performed, an isolated tumor mass in the anterior mediastinum without retroperitoneal involvement is not consistent with a testicular primary tumor. It is not necessary to perform blind orchietomy or testicular biopsy in patients with normal physical examinations and unremarkable ultrasound findings.

Determination of serum tumor markers is important in the diagnosis and follow-up of mediastinal germ cell tumors. Immunoassays for b-HCG and AFP should be obtained in all patients possessing mediastinal masses suspicious for germ cell tumors. Elevations of b-HCG and AFP confirm a malignant component to the tumor. AFP or b-HCG, or both, are elevated in 80% to 85% of nonseminomatous germ cell tumors, with AFP being detected in 60% to 80% of these tumors and b-HCG in 30% to 50%. Patients with benign teratomas have normal markers, and patients with pure seminoma may have low levels of b-HCG, but AFP is not detected.

TERATOMAS

Benign teratomas are the most common mediastinal germ cell tumor, accounting for 70% of the mediastinal germ cell tumors in children and 60% of those in adults. They can be seen in any age group but most commonly occur in adults from 20 to 40 years of age. There is no gender predilection.

Teratomas may be solid or cystic in appearance and are often referred to as dermoid cysts if unicellular. Teratomas contain elements from all three germ cell layers, with a predominance of the ectodermal component in most tumors, including skin, hair, sweat glands, sebaceous glands, and teeth. Mesoderm is represented by fat, smooth muscle, bone, and cartilage. Respiratory and intestinal epithelium are often seen as the endodermal component. The majority of mediastinal teratomas are composed of mature ectodermal, mesodermal, and endodermal elements and exhibit a benign course. Immature teratomas phenotypically may appear as a malignancy derived from these ectodermal, mesodermal, and endodermal elements. These latter tumors behave aggressively and generally are not responsive to systemic therapy.

Treatment of “benign” mediastinal teratoma includes complete surgical resection, which results in excellent long-term cure rates. Radiotherapy and chemotherapy play no role in the management of this tumor. The tumor may be adherent to surrounding structures, necessitating resection of pericardium, pleura, or lung. Complete resection of teratomas should be the goal of treatment. Resection of mature teratomas has been shown to result in prolonged survival with little chance of recurrence.

Seminomas grow slowly and metastasize later than their nonseminomatous counterparts, and they may have reached a large size by the time of diagnosis. Symptoms are usually related to compression or even invasion of surrounding mediastinal structures. Twenty percent to 30% of mediastinal seminomas are asymptomatic when discovered, but metastases are present in 60% to 70% of patients. Pulmonary and other intrathoracic metastases are most commonly seen. Extrathoracic metastases usually involve bone.

The treatment of mediastinal seminoma has evolved since the early 1970s. Definitive conclusions regarding treatment are difficult, because several potentially curative treatment modalities exist. Seminomas are extremely radiosensitive tumors, and for many years, high-dose mediastinal radiation has been used as initial therapy, resulting in long-term survival rates of 60% to 80%. A review of recommendations for radiation therapy treatment in extragonadal seminoma was reported by Hainsworth and Greco. Doses of 20 to 40 Gy have been reported to be curative, but most reports note a significant local recurrence rate with doses of less than 45 Gy. Radiation portals should include a shaped mediastinal field and both supracavicular areas.

Mediastinal seminoma often presents as bulky, extensive, and locally invasive disease, requiring large radiotherapy portals. These portals result in excessive irradiation of surrounding normal lung, heart, and other mediastinal structures. Additionally, for 20% to 40% of patients in whom local control is achieved, treatment can be expected to fail at distant sites.

Chemotherapy was previously used only in advanced gonadal seminoma, but encouraging results and the above-mentioned problems with radiotherapy have led to broadened indications; chemotherapy is now being used as initial therapy in many patients with bulky tumors. Pure mediastinal seminoma falls into the intermediate-risk category of the new International Staging System for Germ Cell Tumors. Even patients with visceral metastases fall into this intermediate category and, as such, have a prognosis with cisplatin-based combination chemotherapy exceeding 75% for 5-year survival. Standard systemic therapy consists of cisplatin-based combination chemotherapy. Leman and coworkers reported that 12 of 13 patients treated experienced complete remission, with two recurrences after treatment. Cisplatin-based combination chemotherapy achieved a complete response in three of five patients treated by Giaccione. A collective review of 52 patients was undertaken by Hainsworth and Greco. Fourteen patients had received prior radiation therapy, but all underwent chemotherapy with cisplatin and various combinations of cyclophosphamide, vinblastine, bleomycin, or etoposide. Complete responses to treatment were noted in 85% of patients, and 83% were long-term disease-free survivors. Although chemotherapy appears to be a superior modality in these small series, radiotherapy is less toxic, and the high salvage rate with chemotherapy after radiotherapy failure makes selection difficult. Therefore, the recommended treatment is either supradiaphragmatic radiation or 4 cycles of cisplatin-based combination chemotherapy.

The management of patients with residual radiographic abnormalities after chemotherapy is controversial. Studies have shown that the residual mass is a dense scirrhus reaction in 85% to 90% of patients, and the presence of viable seminoma is rare. Others have shown a 25% incidence of residual viable seminoma in these patients treated with chemotherapy followed by resection of residual masses larger than 3 cm. Close observation without surgery is recommended for residual masses after chemotherapy unless the mass enlarges.

All patients with mediastinal seminoma should be treated with curative intent. Isolated mediastinal seminoma without evidence of metastatic disease is most often...
MANAGED WITH RADIODERMOLYTHETE ALONE, WITH AN EXCELLENT PROGNOSIS AND LONG-TERM SURVIVAL. LOCALLY ADVANCED AND BULKY DISEASE MAY BE TREATED INITIAL WITH CISPLATIN-BASED COMBINATION CHEMOTHERAPY, USUALLY 4 CYCLES OF CISPLATIN AND ETOPOSIDE, WITH RADIOTHERAPY, AND FOLLOWED BY SALVAGE CHEMOTHERAPY (VINBLISTINE, IFOSFAMIDE, AND CISPLATIN) IN THE EVENT OF RECURRENCE. PATIENTS WITH DISTANT METASTASES SHOULD UNDERGO CISPLATIN-BASED COMBINATION CHEMOTHERAPY AS INITIAL TREATMENT.

NONSEMINOMATOUS GERM CELL TUMORS

Nonseminomatous germ cell tumors include chorionicarcinoma, embryonal carcinoma, teratoma, and endodermal sinus (yolk sac) tumors. They may occur in pure form, but in approximately one-third of cases, multiple cell types are present. Other malignant components, including adenocarcinomas, squamous cell carcinomas, and sarcomas, may be present or even represent the predominant tissue type, as usually occurs in immature teratomas. Nearly 85% of nonseminomatous germ cell tumors occur in men, with a mean age of 29 years. Karyotypic analyses have been performed on a number of these patients, and the 47,XXY pattern of Klinefelter’s syndrome has been found in up to 20% of patients. Mediastinal nonseminomatous germ cell tumors are most commonly found in the anterior mediastinum and appear grossly as lobulated masses with a thin capsule. They are frequently invasive at the time of diagnosis, with almost 90% of patients exhibiting symptoms. They appear on CT scans as large inhomogeneous masses containing areas of hemorrhage and necrosis. Elevated levels of hCG are seen in 30% to 50% of patients, and AFP is detected in 60% to 80%.

These tumors carry a poorer prognosis than purely extragonadal seminoma or their gonadal nonseminomatous counterparts, and all patients with primary mediastinal nonseminomatous germ cell tumors fall into the poor risk category of the new International Germ Cell Consensus Classification. Eighty-five percent to 95% of patients have obvious distant metastases at the time of diagnosis. Common metastatic sites include lung, pleura, lymph nodes, liver, and, less commonly, bone.

A number of non–germ cell malignant processes have been found in association with nonseminomatous germ cell tumors. One of the most interesting is that found in association with acute megakaryocytic leukemia. Other hematologic malignancies, such as acute myeloid leukemia, acute nonlymphocytic leukemia, erythroleukemia, myelodysplastic syndrome, malignant histiocytosis, and thrombocytosis, have all been reported. These malignancies may antedate the discovery of the germ cell tumor of the mediastinum. Solid tumors, such as embryonal rhabdomyosarcoma, small cell undifferentiated carcinoma, neuroblastoma, and adenocarcinoma have been described and occur more frequently in primary mediastinal tumors compared to gonadal germ cell neoplasms.

The diagnosis of nonseminomatous germ cell tumors can often be made without tissue biopsy. In many centers, the presence of an anterior mediastinal mass in a young male with elevated serum tumor markers (AFP and b-HCG) is adequate to initiate treatment. If a tissue diagnosis is deemed necessary, fine-needle guided aspiration with cytologic staining for tumor markers may be used for confirmation. An anterior mediastinotomy provides the best exposure for open biopsy if necessary.

Treatment of nonseminomatous germ cell tumors incorporates cisplatin-based chemotherapy, which has markedly improved the prognosis in these patients. In the past, long-term survival after treatment of nonseminomatous germ cell tumors was very rare; however, complete remission is common in more than 50% of patients. Treatment is initiated with cisplatin-containing combination chemotherapy, which often includes etoposide and bleomycin. Treatment should be administered every 3 weeks for 4 courses; patients should then be reappeared with serum tumor markers and CT scans of the chest and abdomen. In a collective review of 158 patients undergoing a variety of combination chemotherapeutic regimens for the initial treatment of nonseminomatous germ cell tumors, complete responses were noted in 54% of patients, and 42% were long-term disease-free survivors.

Patients with negative tumor markers and no radiographic evidence of residual disease after initial chemotherapy require no further treatment. Persistent elevation of serum tumor markers, particularly if they begin to rise again, usually requires salvage chemotherapy. Patients with normal serum tumor markers but radiographic evidence of residual masses after induction chemotherapy should undergo surgical resection 4 to 6 weeks after completion of chemotherapy. Complete resection should be attempted, because debulking procedures provide no benefit. Patients found to have residual viable germ cell tumor undergo 2 additional cycles of chemotherapy. Patients with immature teratoma or non–germ cell malignancies can simply be observed after complete resection. Nichols reports complete remissions in 18 of 31 patients using this regimen, and other series report complete remission rates of 50% to 70%, with long-term survival rates approaching 50%.

Equivalent results are obtained in all histologic subtypes. The treatment of recurrent disease is difficult, because patients with relapsing mediastinal nonseminomatous germ cell tumors do extraordinarily poorly with salvage therapy, such as vinblastine, ifosfamide, and cisplatin, optimal therapy has not been determined. Standard salvage chemotherapy has not proven beneficial, and few patients achieve durable remissions. High-dose chemotherapy with stem cell rescue is effective in only a few selected patients. Most patients are candidates for experimental phase I trials.

MENenchymal TUMORS

Mesenchymal tumors of the mediastinum, or soft tissue tumors, originate from the connective tissue elements of the mediastinum. Smooth and striated muscle, lymphatic tissue, fat, and vascular tissue all give rise to a variety of neoplasms, which may be benign or malignant. Most of these tumors also occur in other parts of the body and are discussed in detail elsewhere on soft tissue sarcomas.

Mesenchymal tumors account for approximately 6% of primary mediastinal neoplasms. They are less common in the mediastinum than in other locations. Approximately 55% are malignant, and there is no gender predilection. In general, treatment of malignant mesenchymal tumors involves combination therapy, including surgical resection, radiation therapy, and chemotherapy. Benign tumors should be completely excised, after which little chance of recurrence remains.

Lipomas are the most common mesenchymal tumor of the mediastinum, representing 2% of all mediastinal neoplasms. Benign lipomas are most often located in the anterior mediastinum. They may grow to large size without symptoms. Treatment is complete resection, and although local recurrence is possible, it is unusual. Malignant liposarcoma is more commonly found in the posterior mediastinum.

Fibromas are encapsulated asymptomatic tumors that may grow to a very large size. Fibrosarcomas often are symptomatic malignancies associated with hypoglycemia. Fibromas are cured with complete surgical excision, but fibrosarcomas are usually unreactable and respond poorly to radiation and chemotherapy. Leiomyomas, leiomyosarcomas, rhabdomyomas, rhabdomyosarcomas, synovial cell sarcomas, mesotheliomas, and xanthogranulomas also occasionally occur in the mediastinum.

Vascular tumors of the mediastinum include hemangiomas, hemangiendotheliomas, and benign and malignant hemangiopericytomas. Ten percent to 30% of all vascular tumors are malignant. Medialalin hemangiomas represent 0.5% of all mediastinal neoplasms but are the most common vascular tumor. They may be cavernous or capillary and are often associated with hemangiomas in other areas of the body. Sixty percent occur in the anterior mediastinum, and 25% occur posteriorly. Diagnosis is best accomplished by CT scan or MRI, in which phleboliths may be seen in 30% of these tumors. Angiography is important in identifying and embolizing major feeding vessels before surgery. Total excision is considered the treatment of choice; however, large, incompletely resected hemangiomas usually do not recur.

Lymphangiomas, also known as cystic hygromas, often extend into the anterior mediastinum from the cervical area. Seventeen percent of the are located exclusively in the mediastinum. They tend to enlarge as patients grow, particularly during puberty. Treatment involves surgical resection, but this is often difficult because of adherence to surrounding structures. Response to radiation is variable. Other lymphatic soft tissue tumors include lymphangiosarcoma and lymphanghiopericytoma.

NEUROGENIC TUMORS

Thoracic neurogenic tumors occur most commonly in the posterior mediastinum but occasionally are found in the anterior mediastinum and elsewhere. They comprise 19% and 30% of all mediastinal tumors and 75% of posterior mediastinal tumors. They originate from peripheral nerves (nerves of the brachial plexus and intercostal nerves), autonomic sympathetic ganglia and, rarely, from the vagus nerve.
Whereas neurogenic tumors in infants and children are frequently malignant and often present with metastatic disease, in adults the majority of these tumors are benign. They occur without gender predilection at any age but are more likely in young adults. Often asymptomatic, they are solitary (except in neurofibromatosis) and found on a routine chest x-ray. Benign tumors can attain a considerable size. They frequently arise in the paravertebral sulcus from the posterior roots of the spinal nerves at the zone of transition between the central and peripheral myelin. They also may arise on the posterior portion of the spinal nerve root in the spinal canal and grow through the intervertebral foramen into the paravertebral area, giving rise to the appearance of a dumbbell- or hourglass-shaped tumor. These tumors must be recognized to plan an appropriate operation in conjunction with a neurosurgeon. Depending on their size and location, lesions may cause spinal cord compression, pain, paresthesias, Horner's syndrome, and muscle atrophy. Superior vena cava syndrome, dyspnea, cough, and bony erosions, which wrongly suggest a malignant process, also have been described.

NEURILEMOMA (SCHWANNOMA)

Neurilemmoma (schwanna) is the most common tumor in the paravertebral sulcus. Arising from the intercostal nerve sheath, the tumor is encapsulated, white or yellowish pink in color, with calcifications and cystic degeneration. Histologically, it is composed of uniform slender fusiform cells with elongated, twisted nuclei that have a tendency to align in a regimented or palisaded appearance. The tumor may contain large blood vessels and may be a source of considerable blood loss during surgical removal. Schwannomas may be further differentiated into melanotic, adenomatous, or psammomatous tumors (Fig. 32-2).

FIGURE 32-2. Schwannoma in the paravertebral area in the apex of the left chest.

NEUROFIBROMA

Neurofibromas are most often benign and asymptomatic. However, they can have an intradural as well as an extradural component and may cause symptoms of cord compression. They are not encapsulated and may have a plexiform appearance. Microscopically, neurofibromas have a heterogeneous cell population, but Schwann cell differentiation is not always present. Neurogenic tumors can be differentiated from leiomyomas, meningiomas, and fibrous histiocytomas by the immunohistochemical identification of S-100 protein. Solitary neurofibromas are cured by surgical excision.

Neurofibromas can occur as multiple lesions in von Recklinghausen's disease. Neurofibromatosis is inherited as an autosomal dominant trait affecting both genders equally; however, approximately one-half of the cases are sporadic. The clinical features vary and include hyperpigmented café au lait skin spots, skin and perineural invasion, mature cartilage, bone, striated muscle, squamous differentiation, and mucin-secreting glands also may be seen. Histologically, they are composed of spindle cells with comma-shaped, irregular nuclei. Neural and perineural invasion, mature cartilage, bone, striated muscle, squamous differentiation, and mucin-secreting glands also may be seen. Clinically, these tumors are aggressive, locally invasive, and highly metastatic. They often recur after resection, leading to a 75% 5-year survival rate. Patients with neurofibromatosis and a malignant nerve sheath tumor have a 15% to 30% 5-year survival rate. Combination chemotherapy is recommended in stage III and IV disease (Fig. 32-3).

FIGURE 32-3. A: Malignant neurofibroma, initially considered to be nonresectable, in a 34-year-old man. B: The tumor was resected after a combination of chemotherapy and radiation therapy.

TUMORS OF SYMPATHETIC GANGLIA

Mediastinal ganglieneuromas are found in the posterior mediastinum along the sympathetic chain in children older than 4 years and in adults in the third and fourth decades of life. Occasionally, a neuroblastoma may mature into a benign ganglioneuroma. The tumor usually is asymptomatic, but sometimes presents with Horner's syndrome and, rarely, with diarrhea caused by production of vasoactive intestinal polypeptide. Ganglioneuromas have a smooth contour and contain areas of...
stippled calcification. They may resemble other benign neurogenic tumors, causing rib erosions. Microscopically, spindle cell proliferation is seen that appears identical to that in a neurofibroma, except that ganglioneuromas exhibit the presence of large ganglion cells. Ganglioneuromas are benign tumors, although regional lymph nodes may contain islands of tumor cells attributed to matured neuroblasts. They require complete excision.

NEUROBLASTOMAS

Although neuroblastomas can be found in any location in which embryonic neuroblasts migrated from the neural crest, they usually originate in the adrenal glands and along nerve plexuses. In the chest, they occur along the sympathetic trunk in the paravertebral sulcus. This tumor is the most common malignancy of early childhood, occurring most commonly in the first 2 years of life. Patients with mediastinal neuroblastomas usually are symptomatic and frequently have metastatic disease. Symptoms are related to local compression (Horner's syndrome and heterochromia of the iris) or to systemic release of vasoactive peptides, such as catecholamines, vanillylmandelic acid, homovanillic acid, and 3-methoxy-4-hydroxy phenylglycol. Encephalopathy, myasthenia, and Cushing's syndrome may be present. Radiographically, a mass is seen in the posterior mediastinum with stippled calcifications, skeletal erosion, and occasional extension into the spinal canal.

Pathology reveals lobulated gray or red tumors with hemorrhagic areas. Microscopically, small cells with scant cytoplasm and polygonal nuclei exhibit various degrees of differentiation. Intra- and extracellular epithelial and neurosecretory granules and extracellular material seen on electron microscopy distinguish neuroblastoma from other childhood tumors, such as lymphoma, Ewing's sarcoma, and rhabdomyosarcoma.

Neuroblastomas are highly aggressive tumors. Survival depends on the age of the patient, the stage of disease, the location of the tumor, and histologic differentiation. The prognosis is better in patients younger than 1 year of age and in patients with limited, well-differentiated tumors. Neuroblastomas may regress spontaneously or undergo maturation into ganglioneuromas. Ganglioneuroblastomas have a better prognosis than neuroblastomas. The staging system for neuroblastoma shown in Table 32-13 was developed to help guide therapy. Treatment for stage I and II disease is simple surgical resection, although adjuvant postoperative radiotherapy is recommended for stage II tumors. For stage III and IV, a combination of chemotherapy and radiation is advised.

**TABLE 32-13. Staging System for Neuroblastoma**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Tumor limited to site of origin.</td>
</tr>
<tr>
<td>II</td>
<td>Tumor extends beyond site of origin, in one or both adrenal glands.</td>
</tr>
<tr>
<td>III</td>
<td>Tumor extends to the hemithorax.</td>
</tr>
<tr>
<td>IV</td>
<td>Metastases present beyond regional lymph nodes.</td>
</tr>
</tbody>
</table>

**GRANULAR CELL TUMOR**

Granular cell tumors (granular cell myoblastomas) are considered benign. They are found in the posterior mediastinum and are derived from Schwann cells. They are soft, gray, and poorly circumscribed tumors consisting of uniform polygonal cells either in nests or strands with eosinophilic granular cytoplasm and a stroma of fibrous connective tissue. Resection is always curative.

**DIAGNOSIS**

Although posterior mediastinal neoplasms are predominately neurogenic, other tumors also must be considered in the differential diagnosis. Goiters, esophageal leiomyomas, solitary fibrous tumors, and bronchial/esophageal duplication cysts all have been reported. Once identified, the nature of these lesions, their relationship to other structures, and the presence of distant metastases can be determined by CT scans. MRI scans can define vascular involvement and provide multplanar views that are valuable in assessing tumor extension into paravertebral foramina. An iodine 131 nuclear scan may be helpful if a goiter is suspected. Histologic diagnosis is not necessary before surgery. However, if surgical resection is not contemplated, a definitive diagnosis is required for further treatment planning. This diagnosis generally requires a generous biopsy obtained by an open surgical procedure or a CT-guided core-needle biopsy.

**MANAGEMENT**

If no contraindication is present, present, resection of all neurogenic tumors is advised. Neurogenic tumors grow and can cause life-threatening symptoms, depending on their size and location. Therefore, observation of neurogenic tumors may be justified only with a stable, asymptomatic, benign tumor in an otherwise poor surgical candidate. The standard approach uses a posterolateral thoracotomy incision, removing the tumor with normal tissue margins. More recently, thorascopic resection of small- to moderate-size tumors has been reported. In dumbbell tumors, the intraspinal component should be removed first. The mortality rate for surgical resection is less than 1%. Complications include Horner's syndrome and chylothorax. Surgery on tumors with spinal canal involvement may be complicated by direct spinal cord trauma, ischemia from spinal artery injury and, rarely, an epidural hematoma with spinal cord compression.

**PRIMARY CARDIAC MALIGNANCIES**

The vast majority of tumors involving the heart and pericardium are metastatic. In addition, most primary cardiac tumors are benign myxomas, 75% to 80% of which arise from the left atrium. Other benign primary cardiac neoplasms include rhabdomyoma, fibroma, lipoma, hemangioma, teratoma, and fibroelastoma. Primary malignant cardiac tumors make up one-fourth of all primary cardiac neoplasms and most commonly originate from the atria. Most are some variant of sarcoma, including angiosarcoma, rhabdomyosarcoma, leiomyosarcoma, fibrosarcoma, lymphoma, malignant fibrous histiocytoma, and mesothelioma of the pericardium. Pheochromocytomas also occur as primary cardiac neoplasms. A high index of suspicion is imperative in establishing a diagnosis, because the presenting symptoms often mimic other nonneoplastic cardiac pathology. Whole body gallium scans, echocardiography, CT, and MRI all may serve to localize a primary cardiac neoplasm. Up to 80% of primary cardiac malignancies present with systemic metastases and have clinical evidence of right heart failure, and many develop tamponade. Surgical resection is required for cure; however, negative margins usually are not possible.

Chemotherapy and external-beam radiation can be administered after surgery, although a report of 15 cases treated at the Institut Gustave-Roussy does not support the routine use of adjuvant chemotherapy for primary cardiac sarcomas. There has been a report of a patient receiving neoadjuvant (induction) chemotherapy, which resulted in a response and subsequent surgical resection.

New surgical techniques, including orthotopic and autotransplantation, may be beneficial in carefully selected patients. With the advent of “gating” technology and sophisticated treatment planning, more accurate targeting with electron beam radiation therapy may be possible, similar to stereotactic radiosurgery of the brain. At times, a pericardial window may be required to palliate symptoms of pericardial tamponade. Currently, long-term survival is rare.

**CHAPTER REFERENCES**


SECTION 33.1
Molecular Biology of Gastrointestinal Cancers

ERIC R. FEARNON

INTRODUCTION

The specific etiologic factors and pathogenetic mechanisms underlying the development of cancers of the gastrointestinal tract appear to be complex and heterogeneous. Although likely etiologic factors include environmental and dietary exposures, defining specific agents that influence cancer risk remains a major challenge. Only limited progress has been made in treatment of patients with advanced gastrointestinal cancer. In light of the obstacles that hinder our ability to more effectively prevent and treat gastrointestinal cancers, it is important to recognize that increasingly significant advances have been made in the gastrointestinal cancer field. Arguably, some of the most encouraging advances have been successes in defining the specific genetic defects that underlie inherited forms of gastrointestinal cancer and in gaining new insights into the constellation of molecular alterations present in sporadic tumors. For most gastrointestinal tumor types, the prevalence and nature of mutations in several distinct oncogenes and tumor suppressor genes have been defined. The conversion of cellular protooncogenes into oncogenic variant alleles (gene copies) can result from specific point mutations or rearrangements that alter gene structure and function or from chromosomal rearrangements or gene amplifications that disrupt regulated expression of the protooncogene. Tumor suppressor gene inactivation can result from localized mutations, complete loss of the gene, or by epigenetic alterations that interfere with gene expression. At present, only somatic (arising in nongerm cells during the patient's lifetime) mutations in protooncogenes have been detected in gastrointestinal cancers. Similarly, the vast majority of tumor suppressor gene mutations are also somatic. Nevertheless, germline (constitutional) mutations in tumor suppressor genes do underlie cancer predisposition in several hereditary gastrointestinal cancer syndromes.

It is not possible to present in this chapter an exhaustive summary detailing the molecular alterations present in each gastrointestinal cancer type. Rather, the focus is on molecular defects in colorectal carcinoma. The basis for this focus is several-fold. Colorectal cancer is the most common gastrointestinal cancer type in the United States and several other regions of the world. Understanding of colorectal cancer molecular biology is generally more advanced than that of other gastrointestinal cancer types, although significant progress has been made on the molecular front in esophageal, gastric, pancreatic, and hepatocellular cancer. Some of the frequent genetic alterations in colorectal carcinomas are also common in other gastrointestinal cancers. Furthermore, study of the multiple genetic alterations that accumulate during the adenoma-carcinoma sequence in the colon has nicely illustrated the means by which multiple genetic alterations underlie tumor initiation and progression in other organ sites. Although the focus of this chapter is on colorectal cancer, selected advances in the molecular biology of pancreatic and esophageal cancer also are highlighted. The main objectives of this chapter are to review the following: (1) the genetic basis of two inherited forms of colorectal cancer; (2) some of the frequent molecular and cellular abnormalities in colorectal tumors; (3) common molecular abnormalities in pancreatic and esophageal cancer; and (4) the potential clinical utility of genetic alterations in early detection and clinical management of gastrointestinal cancer.

COLORECTAL CANCER AS A MODEL SYSTEM

In 2000, approximately 140,000 U.S. residents will be diagnosed with colorectal cancer, and roughly 55,000 will die from the disease. 1 Males and females have a nearly equal likelihood of being diagnosed, and the cumulative lifetime risk of colorectal cancer in the United States is 6%, with an average age of 66 years at diagnosis. Individuals with a family history of colorectal cancer in a first-degree relative, but who otherwise lack clinical features or a family history consistent with a highly penetrant colorectal cancer syndrome, are at increased risk of colorectal cancer. The relationship of these presumptive precursors to one another and to the villous regeneration seen in UC patients as well as the relative risk associated with inflammatory bowel disease, a diet high in fat and animal proteins, and a sedentary lifestyle. 2 Many other exposures, including excess alcohol consumption, smoking, aspirin and nonsteroidal antiinflammatory agent use, and specific dietary components (e.g., micronutrients such as calcium and selenium), have been extensively studied for their effects on colorectal cancer risk. 22-24 However, these exposures remain uncertain risk factors. The reality is that the main dietary and environmental factors that contribute to most colorectal cancers are poorly defined, and perhaps 75% of all incident colorectal cancers arise in people with no well-defined risk factor. On the other hand, many colorectal cancers may be preventable, and improved adoption and implementation of current screening recommendations might save up to 30,000 lives per year. 25

THE ADENOMA-CARCINOMA SEQUENCE IN THE COLON

A variety of benign gastrointestinal tumors have been identified, but a generic term for a localized lesion projecting above the surrounding mucosa is polyp. Most colorectal polyps, particularly small polyps, are of hyperplastic type, and most data indicate hyperplastic polyps are not a precursor to cancer. The adenomatous polyp, or adenoma, is generally thought to be the important precursor lesion to cancer. Adenomas arise from glandular epithelium, and their common features are the dysplastic morphology and abnormal differentiation of the epithelial cells in the lesion. The prevalence of adenomas in the United States is approximately 25% by age 50 years and perhaps 50% by age 70. 26 The notion that most colorectal carcinomas arise from an adenomatous precursor lesion is well supported. First, longitudinal studies have shown a high risk of colorectal cancer development in individuals whose adenomas are not removed, 27 and polypectomy decreases colorectal cancer risk. 28 Second, focal of carcinoma can often be detected in adenomatous polyps, and residual regions of adenomatous glands are often noted in carcinoma specimens. 29-30 Third, individuals affected by syndromes that strongly predispose to the development of adenomas, such as FAP (discussed later in Familial Adenomatous Polyposis and the APC Gene), invariably develop colorectal carcinomas by the third to fifth decades of life if their colons are not removed. 31 Nevertheless, only a fraction of adenomas progress to cancer, and progression probably occurs over a period measured in years to decades. Adenomas larger than 1 cm in size are estimated to have a 15% chance of progressing to carcinoma over a 10-year period. 32

Besides adenomatous polyp development, another clinical situation associated with markedly increased colorectal carcinoma risk is ulcerative colitis (UC). Patients with longstanding and severe UC have a 20-fold or greater increase in colorectal cancer risk compared to the general population. 33 It is generally thought that carcinomas arise in UC patients as a result of chronic cycles of mucosal injury and subsequent regrowth, a situation that may bear some similarity to processes underlying the development of some esophageal, gastric, and pancreatic cancers. Possible cancer precursors in patients with UC include dysplasia and flat adenoma plaques. The relationship of these presumptive precursors to one another and to the villous regeneration seen in UC patients as well as the relative risks of progression of the lesion types is less well defined than the adenoma-carcinoma sequence.

INHERITED COLORECTAL CANCER SYNDROMES

Highly penetrant, inherited predisposition syndromes are estimated to account for only approximately 5% of colorectal cancers. 34 Hereditary syndromes predisposing to colorectal cancer include FAP and HNPCC. Other rare syndromes also associated with an increased, but less clearly defined, risk of colorectal or other
gastrointestinal cancers include Peutz-Jeghers syndrome, Cowden disease, and juvenile polyposis syndrome. The genes responsible for these inherited syndromes have been identified (Table 33.1-1). Consistent with the Knudson two-hit model for tumor suppressor genes, in all cases, inactivating mutations in both alleles are present in the cancers that arise in affected individuals. However, these other cancer predisposition syndromes are rarer than FAP and HNPCC, and with the exception of the DPC4 (deleted in pancreatic cancer locus 4) gene, defects in other familial gastrointestinal cancer genes do not appear to contribute to sporadic cases of colorectal cancer. For these reasons, the discussion here focuses on FAP and HNPCC.

## Familial Adenomatous Polyposis and the Adenomatous Polyposis Coli Gene

FAP is an autosomal dominant syndrome affecting approximately 1 in 8000 individuals and accounting for approximately 0.5% of all colorectal cancers. Hundreds to thousands of adenomas arise in the colon and rectum of affected individuals by the third to fourth decades of life, and the lifetime incidence of colorectal cancer in untreated FAP patients approaches 100%. Several variants of FAP have been described, including Gardner's syndrome, in which affected individuals may manifest extensive polyposis, epidermoid cysts, desmoid tumors, and osteomas; and Turcot's syndrome, in which polyposis and brain tumors can be seen. Families with attenuated forms of FAP (termed attenuated adenomatous polyposis col) also have been described in which some affected individuals have only 10 to 20 adenomas by 50 years of age. The gene that, when mutant, underlies FAP, Gardner's syndrome, and other variants is the adenomatous polyposis coli (APC) tumor suppressor gene on chromosome 5q.

APC is a large gene encoding a protein of 2843 amino acids, and its last exon is remarkable because it contains a 6579-base-pair open reading frame. Although a fraction of germline mutations in FAP patients extinguish APC gene expression, more than 95% of the known mutations lead to premature truncation of APC protein synthesis. The mutations are located predominantly in the 5' half of the gene, and two “hot spots” at codons 1061 and 1309 account for approximately 35% of the germline mutations identified. Some phenotypic variation among those with FAP appears to be because of the specific mutant APC allele present. In spite of the genotype-phenotype associations noted, however, patients with identical APC mutations can display distinct clinical features. For instance, some patients with germline mutations between APC codons 1403 and 1576 manifest Gardner's syndrome features, whereas others with the identical mutation do not. Similarly, despite the fact FAP patients have a greatly increased risk of medulloblastoma and an elevated risk of hepatoblastoma and thyroid cancers, only a subset of individuals within any one kindred manifests these tumors.

![FIGURE 33.1-1. Schematic representation of adenomatous polyposis coli (APC) protein functional domains with respect to germline and somatic mutations. A putative domain involved in homo-oligomerization (α-dimerization) of APC is located at the amino-terminus. Also noted are a series of repeats of unknown function with similarity to the Drosophila armadillo protein; sequences known to mediate binding to β-catenin and axin and regulate β-catenin's abundance and localization; a basic domain in the carboxy terminal third of the protein that appears to facilitate complexing with microtubules (MT), and sequences near the carboxy terminus of APC that interact with the EB1 protein and the human homologue of the Drosophila disc large (hDlg) protein. Germline mutations in the APC gene (predominantly chain-terminating) are dispersed throughout the 5' half of the sequence, with two apparent 'hot spots' at codons 1061 and 1309 account for approximately 35% of the germline mutations identified.](image)

### Somatic Adenomatous Polyposis Coli Mutations in Sporadic Tumors

Notwithstanding the APC gene's critical role in FAP, the gene has an even more prominent role in sporadic colorectal tumors. Roughly 80% of sporadic colorectal adenomas and carcinomas have somatic mutations inactivating APC. The nature and distribution of APC somatic mutations are similar to the germline mutations in FAP patients (see Fig. 33.1-1), with nearly all somatic mutations leading to premature truncation of the APC protein. The data suggest somatic APC mutations are an early and likely rate-limiting event in adenoma development. First, APC mutations have essentially the same frequency in small adenomas as advanced adenomas and carcinomas; in contrast to other somatically mutated genes in colorectal tumors, such as K-ras and p53. Second, somatic APC mutations are found in the earliest lesions analyzed, including microscopic adenomas composed of only a few dysplastic glands. As predicted by the Knudson model, both APC alleles appear to be inactivated in most colorectal adenomas and all colorectal carcinomas. APC somatic mutations are infrequent in tumor types other than colorectal carcinomas, with the possible exception of ampullary carcinomas and desmoid tumors.

### Adenomatous Polyposis Coli Protein Function

The APC protein has been suggested to regulate cell-cell adhesion, cell migration, or possibly apoptosis. Presently, perhaps the best-characterized function of the APC protein is regulation of β-catenin. B-catenin, an abundant cellular protein, was first identified because of its role in linking the cytoplasmic domain of the E-cadherin cell-cell adhesion molecule to the cortical actin cytoskeleton, via b-catenin's binding to a-catenin. The truncated (mutant) forms of the APC protein present in most colorectal carcinomas lack sequences crucial for binding b-catenin and other cellular proteins (see Fig. 33.1-1). A model has been developed to explain the significance of APC's interaction with b-catenin and these other proteins (Fig. 33.1-2). The model indicates that, in collaboration with the glycogen synthase kinase-3 (GSK3) and axin proteins, APC regulates β-catenin’s abundance in the cytoplasm and nucleus. In 75% to 80% of colorectal cancers, APC is mutated and unable to regulate b-catenin (see Fig. 33.1-2B). As a result, b-catenin accumulates in the cytoplasm and nucleus, and complexes with transcription factors of the Tcf (T-cell factor) family, such as Tcf-4. On binding to Tcf proteins, b-catenin functions as a transcription co-activator, activating expression of Tcf-regulated genes. The identities and functions of Tcf-regulated target genes are not yet well understood, although they may include powerful stimulators of cell growth and proliferation (e.g., the c-MYC and cyclin D1 genes) and extracellular proteases [e.g., matrix metalloprotease 7 (MMP-7)] that might facilitate invasion and metastasis. Further

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**TABLE 33.1-1. Genetics of Inherited Colorectal Tumor Syndromes**

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Genes</th>
<th>Inheritance</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>FAP</td>
<td>APC</td>
<td>Autosomal</td>
<td>Polyp size, risk of cancer</td>
</tr>
<tr>
<td>Gardner's</td>
<td>APC</td>
<td>Autosomal</td>
<td>Polyp size, risk of cancer</td>
</tr>
<tr>
<td>HNPCC</td>
<td>APC</td>
<td>Autosomal</td>
<td>Polyp size, risk of cancer</td>
</tr>
</tbody>
</table>

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**Livingstone, 2000:77, with permission.**

Pastel support for the notion that gene activation by the TGFbeta-catenin complex is critical in colorectal tumorigenesis includes the fact that, in a subset of the 20% of colorectal cancers lacking APC mutations, somatic mutations in b-catenin have been found. These mutations are present in the phosphorylation consensus sequences near b-catenin's amino-terminus, and they appear to render mutant b-catenin proteins resistant to regulation by the APC/GSK3/axin complex. Consequently, b-catenin accumulates and activates Tcf-regulated genes (see Fig. 33.1-2).

**FIGURE 33.1-2.** A model indicating the function of the adenomatous polyposis coli (APC) axin, and glycogen synthase kinase 3b (GSK3b) proteins in the regulation of b-catenin (b-cat) in normal cells, and the consequence of APC or b-cat defects in cancer cells. b-cat is an abundant cellular protein, and much of it is often bound to the cytoplasmic domain of the E-cadherin (E-cad) cell-cell adhesion protein. In normal cells, the proteins GSK3b, APC, and axin function to promote degradation of free cytosolic b-cat, probably as a result of phosphorylation of the N-terminal sequences of b-cat by GSK3b. GSK3b activity and b-cat degradation are inhibited by activation of the wingless (WNT) pathway, as a result of the action of the Frizzled receptor and disheveled (Dsh) signaling protein. B: Mutation of APC in colorectal and other cancer cells results in accumulation of b-cat, binding to Tcf-4, and transcriptional activation of Tcf-4 target genes, such as c-Myc, cyclin D1, MMP-7, and PPAR0 (see text). C: Point mutations and small deletions in b-cat in cancer cells inhibit phosphorylation and degradation of b-cat by GSK3b and APC, with resultant activation of c-Myc and other Tcf-4 target genes. (Modified from Fearon ER. Human cancer syndromes: clues to the origin and nature of cancer. Science 1997;278:1043, with permission.)

**Variant Adenomatous Polyposis Coli Alleles and Familial Aggregations of Colorectal Cancer**

In the majority of colorectal cancer patients, no definitive hereditary component can be identified. These cases are, therefore, labeled “sporadic.” Nonetheless, some of these apparently sporadic cases may well have some hereditary component. The identification of genes that confer weak predisposition to colorectal cancer has been underway and will continue to be a difficult issue for the colorectal cancer field. One study has, however, provided fascinating insights into familial forms of colorectal cancer that do not manifest as highly penetrant cancer syndromes. The study was initiated because of the identification of eight colorectal adenomas in a 39-year-old patient with a family history of colorectal cancer. The diagnosis of HNPCC was excluded by molecular analyses (the genetics of HNPCC is discussed in the section Hereditary Nonpolyposis Colorectal Cancer). Diagnosis of FAP was unlikely based on clinical findings. Nonetheless, detailed studies of the patient's APC alleles were carried out. No germine APC mutation of the type predicted to truncate the APC protein was identified. However, a sequence change at codon 1307 was found, resulting in a substitution of isynse (K) for isoleucine (I). Thus, the allele was referred to as the APC1307 allele. The resultant amino acid change was not predicted to alter APC protein function. However, at the DNA sequence level, the variant allele had an extended mononucleotide tract in the coding region of (A), instead of (AATATAAA).

Further studies revealed that the 1307 allele was present only in individuals of Ashkenazi Jewish origin and that those who carried the 1307 allele had a twofold increase in their lifetime risk of colorectal cancer. Moreover, the localized somatic APC mutations in colorectal cancers arising in individuals carrying the 1307 allele were near always small insertions or deletions in or adjacent to the (A) mononucleotide repeat tract. The somatic mutations created framemfrts that lead to truncated APC proteins. Therefore, the 1307 allele appears to be a novel cancer predisposition allele that does not exert its effects by directly altering APC function. Rather, the 1307 allele contains a DNA sequence tract that is a more frequent target for somatic mutation in colonic epithelial cells than the normal APC sequence. Future studies may establish that subtle or unconventional mutations in APC or other genes also contribute to gastrointestinal cancer predisposition by similar mechanisms.

**HEREDITARY NONPOLYPOSIS COLORECTAL CANCER**

HNPCC was first described by Warnth in 1913. Roughly half a century later, Lynch and others described kindreds with autosomal dominant patterns of colorectal and other cancers that are associated with an excessive risk of polypsis. Before identification of the specific inherited mutations that underlie HNPCC, clinical criteria useful for ascertaining families most likely to be affected by HNPCC were outlined. These criteria, termed the Amsterdam [or International Collaborative Group (ICG)] criteria, as are as follows: (1) FAP must be excluded; (2) at least three affected relatives must have historically verified colorectal cancer, and at least two of the affected must be first-degree relatives; (3) the affected individuals must be from at least two successive generations; and (4) at least one of the affected individuals must have developed colorectal cancer before age 50 years. Although the ICG criteria do not identify all individuals who are ultimately found to have HNPCC, these criteria have proven useful for focusing attention on families most likely to have HNPCC. Based on the criteria, HNPCC cases are estimated to account for 2% for 4% of all colorectal cancer cases. Of note, other cancers often seen in families with HNPCC, including endometrial, ovarian, gastric, and hepatobiliary and uranitary tract cancers, are not included in the ICG criteria.

**Mutations in DNA Mismatch Repair Genes in Hereditary Nonpolyposis Colorectal Cancer**

Unlike FAP, in which the intestinal polyposis phenotype usually permits diagnosis of patients by their late teenage years or early 20s, no distinct clinical features are seen in asymptomatic carriers of HNPCC defects. As such, definitively ascertaining the phenotypic status of an individual in an HNPCC kindred who has not yet developed cancer is nearly impossible, thus rendering genetic linkage analyses for mapping predisposition genes very challenging. The initial genetic studies of HNPCC were successful in excluding a role for variant APC alleles in cancer predisposition in HNPCC, as well as excluding APC from several of the genes known to be somatically mutated in sporadic colorectal cancers. A subsequent search of the entire genome for linkage to HNPCC was undertaken using microsatellite sequence markers. Microsatellites are short, repetitive DNA sequence tracts, scattered throughout the genome, and many microsatellite tracts show polymorphic length variation among normal individuals. One such search for linkage in several HNPCC kindreds was successful in mapping a cancer predisposition gene to chromosome 2p. In other HNPCC families, a predisposition gene was localized to chromosome 3p. In yet other families with HNPCC, no evidence for linkage to either chromosome 2p or 3p was found. These findings clearly established that HNPCC was a genetically heterogeneous disease.

In an attempt to establish the potential relevance of the Knudson two-hit model for HNPCC genes, investigators sought to demonstrate that loss of the wild-type APC or b-cat gene on chromosome 3p, the gene on chromosome 2q, the APC gene on chromosome 3p, one allele was found to be mutated in the germline of some HNPCC patients. However, a sequence change at codon 1307 was identified. Moreover, the localized somatic APC mutations in colorectal cancers arising in individuals carrying the 1307 allele were near always small insertions or deletions in or adjacent to the (A) mononucleotide repeat tract. The somatic mutations created framemfrts that lead to truncated APC proteins. Therefore, the 1307 allele appears to be a novel cancer predisposition allele that does not exert its effects by directly altering APC function. Rather, the 1307 allele contains a DNA sequence tract that is a more frequent target for somatic mutation in colonic epithelial cells than the normal APC sequence. Future studies may establish that subtle or unconventional mutations in APC or other genes also contribute to gastrointestinal cancer predisposition by similar mechanisms.
Together, germline mutations in the MSH2 and MLH1 genes account for more than 60% of the known mutations present in HNPCC patients (Table 33.1-2).

![FIGURE 33.1-3. Mismatch repair pathway in human cells. A,B: During DNA replication, DNA mismatches may arise, such as from strand slippage (shown) or misincorporation of bases (not shown). C: The mismatch is recognized by MutS homologues, perhaps most often MSH2 and GTBP/MSH6, although another MutS homologue, MSH3, may substitute for GTBP/MSH6 in some cases. D,E: MutL homologues, such as MLH1 and PMS2, are recruited to the complex, and the mismatch is repaired through the action of a number of proteins, including an exonuclease, helicase, DNA polymerase, and ligase. (Modified from ref. 34, with permission.)](Image)

TABLE 33.1-2. Germline Mismatch Repair Gene Mutations in Hereditary Nonpolyposis Colorectal Cancer (HNPCC)

<table>
<thead>
<tr>
<th>Gene</th>
<th>Function</th>
<th>Implicated in Colon Cancer</th>
<th>Implicated in Endometrial Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>APC</td>
<td>Tumor suppressor</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>MLH1</td>
<td>Tumor suppressor</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>MSH2</td>
<td>MutS homologue</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>MSH6</td>
<td>MutS homologue</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>GTBP</td>
<td>MutS homologue</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

The prevalence of germline mutations in the DNA mismatch repair genes in colorectal cancer patients not meeting the ICG criteria for HNPCC remains uncertain, although some preliminary findings have emerged. A study of 509 consecutive patients in a Finnish tumor registry found that the MI/RER+ phenotype was present in cancers from 12% of patients. Ten of the 63 patients with MI/RER+ cancers (16%, or roughly 2% of total patients) had a detectable germline mutation in MLH1 or MSH2. Patients with an identifiable germline mutation had either a first-degree relative with endometrial or colorectal cancer, were younger than 50 years, or had a previous colorectal or endometrial cancer. Another study of patients from the Netherlands and Norway found that 26% of the 184 families with clustering of colorectal cancer studied had germline mutations in the MSH2 or MLH1 genes. Similar to the Finnish study, germline MSH2 or MLH1 mutations were more likely to be found in individuals from families meeting the ICG criteria, individuals whose cancers arose at a particularly young age, or individuals whose families manifested both colorectal and endometrial cancer.

Mechanisms and Mutation Targets in Cancers with Defective Mismatch Repair

In normal cells of a patient with HNPCC, DNA repair is not usually impaired, because the cells have a wild-type copy of the gene. During tumorigenesis, however, and perhaps even at an early stage in that process, the wild-type allele of the gene that is mutant in all of the patient's constitutional cells is inactivated by a somatic mutation. Then, affected cells manifest a mutator phenotype and accumulate mutations in a much more rapid fashion. HNPCC appears, therefore, to be a disease with more rapid tumor progression from a benign, initiated clone to frank malignancy. In HNPCC patients, the transition from a small adenoma to carcinoma has been estimated to take only 3 to 5 years, instead of the 20 to 40 years believed required for development of most sporadic carcinomas.

Germline mutations in the known mismatch repair genes have only been detected in 2% to 4% of colorectal cancer patients. However, approximately 15% of all colorectal cancers manifest the MI/RER+ phenotype, implying that germline or somatic mutations in mismatch repair pathway genes may present in a substantial fraction of colorectal cancers, regardless of the patient's family history. Only a fraction of the 15% of apparently sporadic colorectal cancers with the MI/RER phenotype develop as the result of a germline mutation in a known mismatch repair gene, such as MSH2 or MLH1. Similarly, somatic mutations in MSH2, MLH1, or other mismatch repair gene pathways are present in only a small fraction of the apparently sporadic cancers with the MI/RER+ phenotype. Although germline or somatic mutation of known mismatch repair genes are infrequent, inactivation of the MLH1 gene via epigenetic changes, such as DNA hypermethylation of the MLH1 promoter, appears to be a causal factor in the majority of “sporadic” colorectal cancer cases with the MI/RER+ phenotype.

The vast majority of the mutations arising in cells with the MI/RER+ phenotype are likely to have either no effect on cell growth or detrimental effects. Such mutations do not promote the clonal outgrowth and evolution characteristic of colorectal tumor progression. A subset of mutations do, however, activate oncogenes, such as K-ras, or inactivate tumor suppressor genes, such as APC and p53.

Oncogene and Tumor Suppressor Gene Mutations in Colorectal Tumor Progression

Somatic mutations in the APC gene appear to be an early and, perhaps, rate-limiting event in the development of upwards of 75% to 80% of colorectal adenomas and carcinomas. Presumably, mutations in other tumor suppressor genes and oncogenes play an important role in tumor progression. Some of the genes believed critical in colorectal tumor progression are discussed in this chapter and summarized in Table 33.1-3. Another important point already noted is that roughly 15% of colorectal carcinomas display the MI/RER+ phenotype. Although the MI/RER+ cancers have a very elevated rate of localized mutations (e.g., point mutations and small deletions and insertions), they are generally near diploid, with few chromosome losses or gains. In contrast to MI/RER+ cancers, upwards of 85% of colorectal carcinomas display frequent chromosome losses and gains. Defects in genes that regulate formation of the mitotic spindle and proper alignment and segregation of chromosomes at mitosis may underlie the chromosome instability phenotype, although few of the specific defects likely to underlie the chromosome instability phenotype in cancer have been defined.
**K-RAS AND OTHER ONCOGENE DEFECTS**

The RAS genes encode small guanosine triphosphatases with critical roles in signal transduction downstream of growth factor receptors, such as that for epidermal growth factor. K-RAS is the most frequently mutated of the three RAS genes, with K-RAS mutations found in approximately 50% of colorectal adenomas larger than 1 cm in size and a similar fraction of carcinomas. The majority of H-RAS mutations are at codon 12, but codon 13 is mutated in 15% to 20% of cases, and codon 61 is infrequently affected. N-RAS mutations are infrequent, and no R-RAS mutations have been reported in colorectal tumors. In adenomatous polyps, K-RAS mutations have been associated with features predictive of subsequent progression to cancer—increased size and more severe dysplasia. Although K-RAS mutations also have been seen in some colonic lesions with very reduced or no malignant potential (e.g., hyperplastic polyps and aberrant crypt foci lacking dysplasia), Notwithstanding these latter observations, inactivation of mutant K-RAS activity in advanced colorectal cancer cells abrogates the tumorigenic growth properties of colorectal carcinoma cells. Hence, RAS gene mutations in colorectal tumors have a role not only in promoting growth of small adenomas to larger and more clinically significant lesions, but also in maintenance of the fully neoplastic phenotype in advanced carcinomas.

Somatic mutations in other protooncogenes, including amplifications of the MYC, MYB, cyclin D1, and HER-2/NEU genes, have been found in only a small percentage of colorectal cancers (see Table 33.1-3). Gain of function mutations in the b-catenin gene are present in 2% to 8% of colorectal cancers and appear to render the mutant b-catenin protein resistant to regulation by the APC protein. Like APC mutations, b-catenin mutations appear to be an early event in adenoma formation. Finally, some oncogene mutations may vary in their frequency in colorectal carcinomas, depending on whether the tumor has the MI/RER+ phenotype. For example, although K-RAS mutations have a roughly similar prevalence in MI/RER+ carcinomas compared with cases with chromosome instability, b-catenin mutations appear to be more common in MI/RER- cases.

**THE P53 GENE**

Allelic loss or LOH is believed to be a common mechanism for tumor suppressor gene inactivation in the roughly 85% of colorectal carcinomas that manifest the chromosome instability phenotype. Although allelic loss of chromosome 17p is an infrequent event in adenomas, 17p allelic losses can be detected in nearly 70% to 75% of colorectal carcinomas. Wild-type p53 alleles are presumed to be targeted for inactivation by 17p LOH, because the remaining p53 allele is mutated in the majority of colorectal tumors with 17p LOH, most often at codons 175, 245, 248, 273, or 282. Only a small subset of carcinomas lacking 17p LOH have p53 mutations, and most adenomas lack 17p LOH and p53 mutation. Hence, mutation and LOH of p53 appear to arise most frequently during the transition from adenoma to carcinoma. The biologic selection for p53 inactivation at this point in tumor development is not well understood. However, based on our understanding of the functions of p53 in cell-cycle check points at the G1/S and G2/M boundaries and in apoptosis, the selection for p53 inactivation may reflect the fact that several distinct stresses on tumor cells activate apoptotic pathways in cells with wild-type p53 function. Such stresses may include DNA strand breakage, hypoxia, and reduced access to glucose or other nutrients. Loss of p53 function at the critical juncture between adenoma and carcinoma may facilitate continued growth and the acquisition of invasive properties in the face of stresses that might otherwise severely limit tumor cell growth in the colon and rectum.

**CHROMOSOME 18 LOSS OF HETEROZYGOSITY**

Chromosome 18q LOH is seen in approximately 60% to 70% of primary colorectal cancers and, rarely, in adenomas, with the exception of large villous adenomas that contain a focus of carcinoma. The prevalence of 18q LOH rises to nearly 90% to 100% in liver metastases from colorectal primary tumors. The findings suggest a role for inactivation of a chromosome 18q tumor suppressor gene(s) in the later stages of tumor progression and metastasis. Several studies have reported that patients whose primary colorectal cancers have 18q LOH have an increased likelihood of distant metastasis and death from their disease, independent of stage and perhaps other clinical and histopathologic features. In colorectal carcinomas, a common region of LOH includes bands 18q12.3 to 18q21.3, and the DCC (deleted in colorectal cancer) gene at 18q21.2 has been suggested to be a candidate tumor suppressor gene. In some studies, loss of DCC transcripts and protein has been noted in more than 50% of colorectal cancers, although the specific mechanisms accounting for DCC inactivation are not well understood. Few specific mutations in the DCC gene have been identified, perhaps in part because the DCC gene spans more than 1.35 million base pairs. DCC encodes a transmembrane protein that functions in transducing signals from netrin chemoattractant and cell guidance factors. Some findings indicate that, in the absence of netrin, the DCC protein may induce apoptosis in epithelial cells, perhaps reconciling why there might be selection for genetic or epigenetic inactivation of DCC in colorectal carcinomas.

Although DCC remains a candidate tumor suppressor gene in colorectal cancer and other tumors, a well-established tumor suppressor gene, termed DPC4/SMAD4 (also known as), is also present in the 18q21 region. As is discussed later (see the section Gene Defects in Pancreatic Carcinoma), DPC4 is mutated in 50% to 55% of pancreatic carcinomas. Furthermore, germline DPC4 mutations have been seen in a subset of patients affected by juvenile polyposis syndrome. Those with juvenile polyposis syndrome develop benign hamartomatous polyps in the intestinal tract, and they also have an increased risk of colorectal and gastric cancer. Nevertheless, DPC4 is mutated in only approximately 10% to 15% of colorectal carcinomas and much less frequently in other gastrointestinal tumors, such as gastric and esophageal carcinomas. The DPC4-related SMAD2 gene is also located in the region of 18q commonly affected by LOH in colorectal carcinomas. A major role for SMAD2 in colorectal cancer has been exuded, because SMAD2 is inactivated in less than 5% of colon carcinomas and SMAD2 alterations are rare or absent in other gastrointestinal carcinomas. Based on the frequencies of mutations in DPC4 and SMAD2, neither gene appears to be the primary tumor suppressor gene targeted for inactivation by 18q LOH in colorectal cancer. Nonetheless, inactivation of either of the two genes likely to have an important role in the tumor process, because each gene encodes a protein that functions to transduce TGF-β growth regulatory signals, and TGF-β has significant growth inhibitory effects on colonic epithelial cells. Whether DCC inactivation is associated with 18q LOH in the majority of colorectal carcinomas or whether additional novel tumor suppressor genes are present in the 18q12.3-q21.3 region remains to be determined.

**GENE DEFECTS IN PANCREATIC CARCINOMA**

Ductal epithelial cells in the pancreas comprise less than 5% of the total cell mass in the organ, yet they are the origin of the most common form of pancreatic carcinoma. The natural history of the progression from normal epithelium to carcinoma in the pancreas is less well understood than in the colon. However, it appears that a flat hyperplastic lesion in which the epithelium changes from its normal cuboidal pattern to columnar may be an early precursor. Papillary hyperplasia, in which the mucosa becomes more crowded and folded, arguably represents the next recognizable stage. Papillary hyperplasia can be associated with varying degrees of cellular and nuclear atypia (i.e., dysplasia), and the most advanced is sometimes referred to as carcinoma in situ. Bona fide carcinoma is marked by invasion through the duct wall. A major difficulty hindering early molecular analyses of pancreatic carcinoma was the fact that pancreatic carcinoma cells engender a strong host desmoplastic and inflammatory response, and the neoplastic cells only constitute a fraction of the total cells in the cancer specimen. Generation and study of pancreatic carcinoma specimens implanted into the flank of immunocompromised mice (i.e., xenografts) have proven crucial in defining specific genetic alterations in oncogenes and tumor suppressor genes in pancreatic carcinoma, because all human DNA isolated from the xenografts is derived from neoplastic cells.
A number of distinct tumor suppressor gene defects are seen in pancreatic carcinomas, although three tumor suppressor genes stand out because of their frequent inactivation—namely, the p16\(^{INK4a}\), p53, and DPC4 genes (see Table 33.1-4). Whereas mutations in the pRb/cyclin D1-cdk4/p16\(^{INK4a}\) pathway are uncommon in colorectal carcinoma, mutations inactivating the p16\(^{INK4a}\) gene are found in roughly 85% of pancreatic carcinomas. A subset of pancreatic carcinomas may epigenetically inactivate p16\(^{INK4a}\), perhaps as a result of hypermethylation of p16\(^{INK4a}\) promoter sequences. In another small fraction of cases, rather than p16\(^{INK4a}\) inactivation, the RB1 tumor suppressor gene is inactivated, presumably with similar net consequences to p16\(^{INK4a}\) inactivation, because the Rb protein is functionally inactive when the p16\(^{INK4a}\) protein is lacking in a cell (i.e., the cyclin D and cdk-4 proteins constitutively phosphorylate pRb in this setting). Mutations in the p53 gene are found in 50% to 75% of pancreatic carcinomas. Similar to the situation in colorectal carcinomas, the vast majority of the p53 mutations are missense mutations accompanied by loss of the wild-type p53 allele. Some alterations inactivating the p14\(^{ARF}\) gene, particularly homozygous deletions, also lead to loss of the p14\(^{ARF}\) protein, an alternative protein product synthesized in part from sequences shared with those encoding the p16\(^{INK4a}\) protein. Because p14\(^{ARF}\) inactivation appears to lead to functional inactivation of the p53 protein, the actual frequency of pancreatic carcinomas with p53 inactivation may be higher than the percentage of cases with demonstrable p53 sequence alterations. As noted earlier in the section Chromosome 18q Loss of Heterozygosity, DPC4 mutations are found in approximately 50% to 55% of pancreatic carcinomas. Among other potential effects, the mutations presumably render the cells resistant to the negative growth regulatory effects of TGF-β. Finally, in addition to the frequent alterations of p16\(^{INK4a}\), p53, and DPC4, several other tumor suppressor gene defects are found in a fraction of pancreatic carcinomas, such as BRCA2 inactivation (see Table 33.1-4). Consistent with the view that BRCA2 defects have an important role in a subset of pancreatic cancers, in addition to the very elevated risk of breast cancer in those carrying a germline BRCA2 mutation, the lifetime risk of pancreatic carcinoma for BRCA2 mutation carriers appears to be increased by three- to fivefold relative to the general population.

### GENE DEFECTS IN ESOPHAGEAL ADENOCARCINOMA

Esophageal cancers are readily distinguished into squamous and adenocarcinoma types on the basis of their histopathologic appearance. Clear differences exist in the pathogenesis of the two types, as well as differences in their epidemiology and incidence in many patients. Not unexpectedly (i.e., loss of heterozygosity), such as those involving chromosomes 5q, 9p, 13q, 17p, and 18q appear to arise in a diploid, proliferating cell population (2N).

#### TABLE 33.1-4. Summary of Selected Tumor Suppressor Gene Defects

<table>
<thead>
<tr>
<th>Gene</th>
<th>Frequency of Defect</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>p16(^{INK4a})</td>
<td>85%</td>
<td>11q22</td>
</tr>
<tr>
<td>p53</td>
<td>50% to 75%</td>
<td>17p13-q21</td>
</tr>
<tr>
<td>DPC4</td>
<td>50%</td>
<td>18q11-12</td>
</tr>
</tbody>
</table>

Flow cytometry analyses indicate aneuploid cell populations are absent in normal esophageal mucosa from patients with gastroesophageal reflux and no NE. Aneuploidy is rare in metastasis and low-grade dysplasia. However, aneuploidy is present in biopsy specimens from approximately two-thirds of patients with high-grade dysplasia and nearly 100% of cancers. The flow cytometry studies also have demonstrated clonal heterogeneity in DNA content among the neoplastic cell populations present in distinct dysplastic areas of a single patient with BE, suggesting that a large area of the esophagus is neoplastically transformed and multifocal progression ensues.

Various oncogene defects have been found in esophageal adenocarcinomas, most notably the amplification of several distinct protooncogenes, including the HER-2/NEU/ErbB2 gene in 22% of cases, the c-myc and GATA-4 genes in 14%, the epidermal growth factor receptor (EGFR) gene in 13%, and the K-RAS gene in 10%. Among the tumor suppressor genes frequently inactivated by genetic and epigenetic alterations in esophageal carcinomas are the p53 and p16\(^{INK4a}\) genes. Missense mutations in one p53 allele coupled with LOH of chromosome 17p and the remaining p53 allele are found in nearly 100% of esophageal adenocarcinomas. p53 mutations and 17p LOH are frequent in high-grade dysplastic regions of premalignant BE. Inactivation of p16\(^{INK4a}\) by mutational and epigenetic (e.g., promoter hypermethylation) mechanisms is frequent not only in high-grade dysplasias, but also in low-grade and nondysplastic BE specimens. Hence, p16\(^{INK4a}\) inactivation frequently precedes p53 inactivation in esophageal tumor progression. Nevertheless, as indicated in Figure 33.1-4, there appear to be multiple genetic routes to cancer in BE. Of some note, although several of the chromosome regions frequently affected by LOH in colorectal and pancreatic carcinomas are also frequently affected by LOH in esophageal adenocarcinoma, including chromosomes 5q and 18q, the APC and DPC4 tumor suppressor genes appear to be infrequently, if ever, mutated in esophageal adenocarcinoma. Further work will be needed to define the tumor suppressor genes on chromosomes 5q and 18q that are inactivated in esophageal adenocarcinoma.

**Figure 33.1-4.** Multiple genetic routes to esophageal adenocarcinoma in the setting of Barrett's esophagus (BE). The clonal progression of cell populations as they progress from the metaplasia (M) seen in BE is illustrated schematically. The figure is not intended to be comprehensive, as there are multiple pathways to cancer. Nevertheless, some general patterns appear to be consistent in studies of p53 and p16\(^{INK4a}\) (CDK4/2A) genes. In some cases, tetraploidy (4N) may precede aneuploidy (An).
Progression to cancer (Ca) is shown as an end point, although additional chromosome changes and mutations may contribute to further progression of the cancer. (Modified from ref. 148, with permission.)

POTENTIAL CLINICAL APPLICATIONS OF MOLECULAR ADVANCES

Advances in the understanding of the inherited and somatic genetic alterations in gastrointestinal cancers have made possible several clinical applications that should improve the diagnosis and care of patients and families affected by these cancers. Although many future clinical applications can be envisioned, only a few potential applications in the colorectal cancer area are described here.

RISK ASSESSMENT

Presymptomatic diagnosis of FAP or HNPCC may be of significant value to members of families with these syndromes. The ability to identify germline mutations in the APC gene in more than 80% of families with FAP and Gardner's syndrome provides the basis for genetic counseling of at-risk families. Individuals from polyposis kindreds are at increased risk to develop colorectal cancer if they have inherited frequent colorectal neoplasms in their adolescent and early adult years. In turn, individuals who have inherited a mutant allele can be closely monitored by colonoscopy and offered surgical intervention at an appropriate time. Perhaps in the not too distant future, effective chemopreventive regimens may delay the onset or perhaps even prevent entirely the development of adenomas and carcinomas. The nonsteroidal antiinflammatory agent sulindac can cause regression of polyps in FAP patients, but sulindac's efficacy is limited in part by its side effects. Encouraging results with selective inhibitors of cyclooxygenase-2 (COX-2) in a mouse polyposis model imply that COX-2 inhibitors may be more useful in prevention than sulindac. Furthermore, because sulindac inhibits colorectal cancer growth via both COX-2-depended and COX-2-independent mechanisms and the COX-2–independent pathway involves the APC-regulated transcription factor PPARα, a strategy of using both COX-2–selective inhibitors and novel PPARα antagonists may be most efficacious in preventing adenoma formation or progression.

Novel mutation detection strategies, such as “chip-based” approaches, will hopefully supersede present laborious methods for detecting mutations in patients with FAP and HNPCC. Nevertheless, although rapid and robust mutation detection strategies will be a significant advance, other problems must be conquered. For instance, although the vast majority of germline APC mutations in FAP patients and many of the germline MSH2, MLH1, PMS1, and PMS2 mutations in HNPCC patients are clearly inactivating (e.g., nonsense, frameshift), a subset of the mutations are missense substitutions. Distinguishing cancer-predisposing missense mutations from benign polymorphic variants is a troublesome issue at present. The development of in vitro assays that accurately predict the functional activity of wild type and mutant alleles in vivo is critical, particularly if large-scale screening for HNPCC mutations in asymptomatic patients is envisioned. Some progress toward this important goal has been achieved. After detection of novel variant alleles that contribute to modestly increased risk of colorectal cancer, akin to the effects of the I1307K APC allele in Ashkenazi Jews, recombinant DNA-based approaches may be used in a more general fashion in the future to estimate an individual's risk of colorectal cancer. The technical and theoretical difficulties of identifying variant alleles that have only subtle effects on colorectal cancer risk are substantial. Moreover, because many uncertainties exist regarding the optimal clinical management of such lower risk patients, as well as legal and ethical issues surrounding presymptomatic genetic testing even in high-risk patients, many challenges lie ahead.

EARLY DETECTION

The results of clinical trials indicate that colonoscopic removal of larger adenomas and early colorectal carcinomas reduces colorectal cancer incidence and most likely decreases mortality. Because of the reduced specificity and sensitivity of current noninvasive tests, such as fecal occult blood testing, the development of highly specific and sensitive tests for early detection of colorectal cancer is an important goal. If inexpensive and reliable molecular diagnostic tests of stool specimens could be developed, such tests might serve an adjunctive role along with more invasive and expensive methods for detection, such as colonoscopy. Preliminary and screening molecular tests that use as controls normal colorectal DNA, the intent of the molecular stool tests would be to identify mutated oncogene or tumor suppressor gene DNA sequences, with such mutant DNA sequences presumably derived from adenoma or carcinoma cells shed into the stool. Preliminary findings from studies of DNA isolated from stool samples of patients known to have carcinomas or advanced adenomas indicate stool-biased tests for mutant oncoproteins and tumor suppressor genes may have utility. The early findings indicate that if a K-RAS gene mutation is present in the primary tumor and the tumor is of sufficient size, mutant K-RAS gene sequences can usually be detected in the DNA of cells shed into the stool. The sensitivity and specificity of present methods for identifying RAS gene mutations in the stool of normal individuals and patients with various types of colorectal tumors have not been fully determined, nor have the preliminary results been confirmed in much larger cohorts. Nonetheless, the early results are encouraging, because approximately 50% of colorectal cancers and adenomas larger than 1 cm in size contain a mutant K-RAS allele.

A possible concern with using K-RAS mutations for early detection of colorectal adenomas and carcinomas is that RAS mutations are not entirely specific to premalignant and malignant lesions of the colon and rectum. K-RAS mutations are frequent in nondysplastic aberrant crypt foci and hyperplastic polypos, and neither has a clear relationship to adenoma or carcinoma development. K-RAS mutations may also be found in stool samples from some patients with pancreatic cancer and pancreatic ductal hyperplasia. Presumably, because the pancreatic duct drains cells from these lesions into the gastrointestinal tract and both lesions have frequent K-RAS mutations. Nonetheless, a K-RAS mutation test for early detection of colorectal tumors may prove useful because aberrant crypt foci, hyperplastic polyps, and, perhaps, even some benign lesions may harbor K-RAS mutations. K-RAS mutations do not offer an efficient stool-based test for colorectal adenomas and carcinomas, similar molecular approaches may be used to identify localized mutations in other oncogenes and tumor suppressor genes, particularly those mutations that are intimately linked to malignant potential in colonic epithelium (e.g., APC and p53 mutations).

PROGNOSTIC MARKERS AND PATIENT STRATIFICATION FOR THERAPY

In addition to presymptomatic diagnosis (risk assessment) and early detection of tumors, several studies indicate characterization of the specific genetic alterations present in a patient can provide increased prognostic information. For instance, the demonstration that chromosome 18q LOH and loss of DCC expression in primary colorectal cancer specimens may predict poor outcome in both stage II (lymph node metastases absent) and stage III (lymph node metastases present) patients. Molecular analyses of lymph node from patients who do not appear to have metastatic disease on the basis of histologic examination may also be very useful for detecting micrometastases and refining the staging of patients. For instance, carcinoembryonic antigen (CEA) expression may be found in lymph nodes of roughly one-half of stage II patients and that the presence of CEA expression in the lymph node predicts poor survival. Presumably because CEA expression results from occult micrometastases. Molecular studies of lymph nodes for mutant oncoproteins or tumor suppressor genes may also prove helpful in refining staging and prognosis.

In the future, if differences are noted in the response rates between patients whose tumors have differing constellation of genetic alterations, it may be particularly useful to define the specific mutations in a patient's tumor, so that a patient might receive the particular chemotherapeutic regimen with greatest efficacy on tumors of that genotype. Similarly, analysis of gene expression patterns may also be of clear benefit in predicting response. Finally, some of the oncoprotein and tumor suppressor alterations in colorectal tumors may provide specific targets for novel chemotherapeutic agents. Some of these agents might antagonize or act selectively on the mutated oncogene products or the growth pathways in which they function. Other agents might act to counter loss of tumor suppressor function in affected cells.

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SECTION 33.2
Cancer of the Esophagus

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Treatment

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Adjuvant Therapy

Endoscopic Palliation Techniques

Treatment Recommendations and Future Directions

EPIDEMIOLOGY

Esophageal cancer represents the third most common gastrointestinal malignancy and ranks among the ten most common cancers worldwide. The incidence of esophageal cancer varies considerably relative to geographic location; high incidence areas have been identified within the Caspian littoral region of northern Iran, Southern republics of the former Soviet Union, and northern China where the incidence exceeds 100 in 100,000 individuals. The incidence of esophageal cancer ranges from 10 to 50 in 100,000 in Sri Lanka, India, South Africa, France, and Switzerland. This disease is less common (average incidence less than 10 in 100,000) in most areas within Japan, Great Britain, Europe, and Canada.1 Squamous cell carcinomas account for the vast majority of neoplasms observed in these regions.

In the United States, esophageal cancers are relatively uncommon (average incidence less than 5 in 100,000); however, U.S. mortality data from 1990 to 1994 have revealed a steady increase in age-adjusted mortality in male as well as female subjects due to this malignancy.2 Within the United States, the incidence of esophageal cancer varies with location, with a high frequency of esophageal squamous cell carcinomas being noted in coastal regions in South Carolina and metropolitan areas including New York City, Detroit, Washington, DC, and Los Angeles, where the incidence approximates 30 in 100,000 individuals.3 Squamous cell carcinomas predominate in these high incidence areas within the United States.

In the recent past, the incidence of esophageal adenocarcinomas has risen dramatically, whereas the incidence of squamous cell carcinomas has remained relatively steady in the United States.4 Before 1980, adenocarcinomas constituted approximately 15% of esophageal malignancies; however, by 1994, nearly 60% of all esophageal malignancies were adenocarcinomas.5 Rates of adenocarcinoma are highest in white men. The incidence of esophageal carcinoma in women is much lower, although the incidence of adenocarcinomas is also increasing in women. Similar trends have been noted in western European countries.67 The rising incidence of esophageal adenocarcinoma cannot be attributed solely to the increased incidence of carcinomas of the cardia, which now account for approximately one-half of gastric cancers in American men.8 Although the precise etiology of these neoplasms has not been elucidated, considerable data indicate that esophageal adenocarcinomas result from chronic gastroesophageal reflux often in the context of hiatal hernia.9

Although cultural as well as dietary practices contribute to esophageal cancers in high incidence areas in Asia, South Africa, South America, and the Middle East, tobacco and ethanol exposure are believed to be the primary risk factors associated with esophageal squamous cell carcinomas in the United States and western Europe.10-12 Tobacco and ethanol consumption have been identified as individual risk factors for this malignancy, and their effects are multiplicative.14 A five- to tenfold increase in esophageal squamous cell cancers has been noted in smokers relative to nonsmokers, and the risk of esophageal carcinoma correlates with extent of tobacco exposure.15 16 Tobacco abuse may also contribute to the pathogenesis of esophageal adenocarcinomas, although to a much lesser extent; a multicenter study by Gammon et al.17 18 as well as additional clinical studies have indicated that the risk of esophageal adenocarcinoma is approximately twofold higher in smokers compared with nonsmokers.17 18 Interestingly, whereas the risk of esophageal squamous cell cancer decreases significantly following cessation of tobacco abuse, little change is noted in esophageal adenocarcinoma risk following smoking cessation.18 These data suggest that tobacco-related carcinogens may be influencing different stages of malignant transformation associated with squamous cell cancers relative to adenocarcinomas. Chemicals in tobacco are known to induce p53 mutations,17 and these mutations appear to be extremely early events during multistep esophageal adenocarcinogenesis.19 The timing of p53 mutations during squamous cell carcinogenesis has not been defined; however, these mutations appear to be relatively late events during pulmonary carcinogenesis.20

Alcohol abuse has been associated with increased risk of esophageal squamous cell cancers, and risk increases with amount of alcohol consumed.21-24 Alcohol interacts in a multiplicative manner with tobacco, with nearly a 100-fold increase in the risk of esophageal malignancy observed in individuals with heavy tobacco and ethanol exposure.22 Specific beverages have been implicated in the pathogenesis of squamous cell cancers in Europe, South Africa, South America, and the United States; however, in all likelihood, ethanol is the major component related to the pathogenesis of these cancers.23 Ethanol consumption appears to have a less significant role in the pathogenesis of esophageal adenocarcinomas.24-26

Data indicate that obesity may be related to risk of esophageal cancer, particularly adenocarcinomas.27 In general, the risk of esophageal squamous cell cancers decreases, whereas risk of adenocarcinoma increases with enlarging body mass. Esophageal squamous cell cancers have been associated with nutritional deficiencies; a low intake of fruits and vegetables may increase the esophageal cancer risk twofold.28-30 Deficiencies in β-carotene, vitamin E, and selenium may also increase the risk of squamous cell cancer in underdeveloped areas. Dietary practices including drinking of extremely hot beverages or ingestion of fermented vegetables may contribute to increased cancer risk in Asia and South America23 however, the role of dietary practices in the pathogenesis of esophageal cancers in the United States is unclear. Although several environmental carcinogens, including asbestos, perichloroethylene, and combustion products, may contribute to the pathogenesis of esophageal squamous cell cancers,22 23 no occupational risk factors have been associated with esophageal adenocarcinomas.

ANATOMY

The esophagus commences at the cricopharyngeus muscle at the level of the cricoid cartilage and extends 5 to 6 cm in the cervical region to enter the thoracic inlet (Fig. 33.2-1). The intrathoracic esophagus extends an additional 20 to 25 cm to the gastroesophageal junction. Typically, many radiologists and surgeons divide the
esophagus into thirds whereby the upper third extends from the cricopharyngeus to the superior portion of the aortic arch, the middle third extends from the aortic arch to the inferior pulmonary veins, and the distal third extends from the level of the inferior pulmonary veins to the gastroesophageal junction.

FIGURE 33.2-1. General anatomy of the esophagus with major landmarks identified. GE, gastroesophageal.

The blood supply to the esophagus is segmental, with vessels extending into the esophagus to form a submucosal vascular plexus (Fig. 33.2-2). The cervical esophagus is supplied primarily by the superior and inferior thyroid arteries, whereas the thoracic esophagus is supplied by esophageal arteries arising directly from the aorta near the level of the carina; the distal esophagus and gastric cardia are supplied primarily by the left gastric artery. Venous drainage from the esophagus is into the azygous and hemiazygous veins as well as intercostal veins that ultimately drain into the azygous system (Fig. 33.2-3).

FIGURE 33.2-2. Blood supply of the esophagus.

FIGURE 33.2-3. Venous drainage of the esophagus.

The esophagus contains abundant mucosal and submucosal lymphatics that communicate with lymphatic channels in the muscular layers to drain either directly through the esophageal wall to adjacent lymph nodes or to the thoracic duct (Fig. 33.2-4). Lesions in the upper third of the esophagus tend to drain initially to internal jugular, cervical, and supraclavicular nodes; in contrast, middle third lesions drain initially to paratracheal, hilar, subcarinal, paraesophageal, and pericardial nodal regions. Distal third tumors tend to drain to nodes along the lesser curvature, left gastric artery, and celiac axis. However, because the pattern of lymphatic drainage is primarily longitudinal rather than segmental, extensive regional dissemination of cancer cells may occur irrespective of the location of the primary tumor. Celiac nodal metastases have been observed in 10% of patients with upper third carcinomas, and nearly 45% of individuals with middle third lesions; approximately 30% patients with middle or lower third carcinomas have metastatic disease in deep cervical lymph nodes at presentation.

FIGURE 33.2-4. Major lymphatic drainage areas of the esophagus.

HISTOLOGY

The overwhelming majority of esophageal malignancies may be classified as either squamous cell carcinomas or adenocarcinomas. Squamous cell carcinomas account for approximately 40% of esophageal malignancies diagnosed in the United States and the vast majority of cancers arising in high-incidence areas throughout the world. Approximately 60% of these neoplasms are located in the middle third of the esophagus, whereas 30% and 10% arise in the distal third or proximal third of the intrathoracic esophagus, respectively. Typically, these tumors are moderately well differentiated and often are associated with contiguous or
noncontiguous carcinoma in situ, as well as widespread submucosal lymphatic dissemination. 72,73

Adenocarcinomas frequently arise in the context of Barrett's esophagus; as such, these tumors tend to be localized in the distal third of the esophagus and may be fungating or stenotic in appearance. 74,75 Many of these tumors are well-differentiated adenocarcinomas, and the vast majority are associated with intraepithelial neoplasia. 76,77 No significant survival differences have been noted in adenocarcinoma patients compared with similarly staged individuals with squamous cell cancers. 78

Several rare forms of the esophagus have been described, including squamous cell carcinoma with sarcomatous features, as well as adenoid cystic, and mucoclepidemoid carcinomas. 79,80,81,82 These neoplasms are indistinguishable clinically and prognostically from the more common types of esophageal carcinomas.

Small cell carcinomas account for approximately 1% of esophageal malignancies and arise from argyrophilic cells in the basal layer of the squamous epithelium. 83-85 These neoplasms are usually located in the middle or lower third of the esophagus and may be associated with ectopic production of a variety of hormones including parathormone, secretin, granulocyte colony-stimulating factor, and gastrin-releasing peptide; individuals with these cancers often present with systemic disease. 86,87 Although small cell carcinomas frequently respond to radiation and chemotherapy, patients with these neoplasms typically succumb to widespread distant metastases. 88,89

Leiomyosarcoma is the most common mesenchymal tumor affecting the esophagus, accounting for less than 1% of all esophageal malignancies. 90,91 These neoplasms usually arise as lower third tumors and typically present as bulky masses with significant hemorrhage and necrosis. 92,93 Malignant lymphoma and Hodgkin's disease rarely involve the esophagus; esophageal involvement typically is secondary to extension from other sites, although primary malignant lymphoma of the esophagus has occasionally been reported. 94,95 Patients with acquired immunodeficiency syndrome may exhibit Kaposi's sarcoma involving the esophagus. 96,97 Malignant melanoma involving the esophagus is exceedingly rare and presents as a bulky polypoid intraesophageal tumor of varying color depending on melanin production. 98,99 The prognosis is extremely poor for these patients despite aggressive therapy.

PREDISPOSING CONDITIONS

TYLOSIS

Tylosis (local nopedipomolytic palmpolantar keratoderma) is a rare disease inherited in an autosomal dominant manner that is characterized by hyperkeratosis of the palms and soles and esophageal papillomatosis. Patients with this condition exhibit abnormal maturation of squamous cells and inflammation within the esophagus and have extremely high risk of developing esophageal cancer. 80,81 The tylosis esophageal cancer (TOC) gene has been mapped to 17q25 by linkage analysis of pedigrees associated with high risk of esophageal cancer development. 51 In addition to being mutated in tylosis, the TOC gene is frequently deleted in sporadic human esophageal cancers. 52,53 Wada et al. 54 used 20 microsatellite markers focusing on the TOC locus to investigate loss of heterozygosity in 58 sporadic esophageal squamous cell carcinomas. Loss of heterozygosity was observed in 37 of 52 (71%) informative cases, 80% (33 of 37) of which involved the TOC locus. Envoiplakin, encoding a protein component of desmosomes that is expressed in esophageal keratinocytes, has been mapped to the TOC region. 55; however, no tylosis-specific mutations involving this gene have been observed. 56 Further studies are required to define the tumor suppressor gene(s) mapping to 17q25 that are inactivated in tylosis-associated as well as sporadic esophageal carcinomas.

PLUMMER-VINSON/PATERNER-KELLY SYNDROME

Plummer-Vinson/Paterson-Kelly syndrome is characterized by iron-deficiency anemia, glossitis, ketosis, brittle fingernails, splenomegaly, and esophageal webs. Approximately 10% of individuals with Plummer-Vinson/Paterson-Kelly syndrome develop hypopharyngeal or esophageal epidermoid carcinomas. The mechanisms by which these tumors arise have not been fully defined, although nutritional deficiencies as well as chronic mucosal irritation from retained food particles at the level of the webs may contribute to the pathogenesis of these neoplasms. 82

CAUSTIC INJURY

Squamous cell carcinomas may arise in lye strictures, often developing 40 to 50 years following caustic injury. 2 The majority of these cancers are located in the middle third of the esophagus. The pathogenesis of these neoplasms may be similar to that implicated in esophageal cancers arising in patients with Plummer-Vinson syndrome. These cancers are often diagnosed late due to the fact that chronic dysphagia and pain due to the stricture obscures symptoms of esophageal cancer.

ACHALASIA

Achalasia is an idiopathic esophageal motility disorder characterized by increased basal pressure in the lower esophageal sphincter, incomplete relaxation of this sphincter following deglutition, and aperistalsis of the body of the esophagus. A 16- to 30-fold increase in esophageal cancer risk has been noted in achalasia patients. 56 In a retrospective analysis, Aggestrup et al. 57 observed the development of esophageal carcinomas in 10 of 147 patients undergoing esophagomyotomy for achalasia. These neoplasms typically are squamous cell carcinomas, believed to result from prolonged irritation from retained foods at the air–fluid interface in the megasphagus, and arise an average of 17 years following onset of achalasia symptoms. The insidious nature of carcinomas arising in the context of chronic dysphagia and pain attributable to megaesophagus contributes to their late diagnosis in achalasia patients. 58

HELICOBACTER PYLORI INFECTION

Helicobacter infection has been associated with gastritis and peptic ulcer disease. Several studies suggest that the extent of Helicobacter gastritis may correlate inversely with diminished gastrointestinal reflux and esophageal cancer. 59,60 Sharma et al. 61 observed no evidence of Helicobacter pylori in specialized intestinal metaplasia in 209 esophageal biopsies from 58 patients with columnar-lined epithelium. In another study, El-Serag et al. 62 evaluated the database of the Department of Veterans Affairs and noted that Helicobacter pylori infection and atrophic gastritis were associated with diminished acid output and increased risk of gastric carcinoma, but diminished risk of esophageal carcinoma. These data have been confirmed by Chow et al., 63 who also noted an inverse relationship between Helicobacter infection and risk of gastroesophageal adenocarcinoma. Thus, available data indicate that Helicobacter has little, if any, role in the pathogenesis of esophageal cancer.

HUMAN Papillomavirus infection

Several studies suggest that human papillomavirus (HPV) may contribute to the pathogenesis of esophageal squamous cell cancers in high-incidence areas in Asia and South Africa. 65 This oncogenic virus, which has been associated with cervical and oropharyngeal cancers, 66 encodes two proteins (E6 and E7) that sequester the Rb and p53 tumor suppressor gene products. Using polymerase chain reaction techniques, de Villiers et al. 67 detected HPV DNA sequences in 17% of esophageal squamous cell cancers from China. In an additional study using similar techniques, Lavergne and de Villiers et al. 68 identified a broad spectrum of HPV in approximately one-third of esophageal cancer specimens obtained from patients with high-incidence areas in China and South Africa. Shigabagi et al. 69 detected HPV sequences in 15 of 72 (21%) esophageal cancer specimens obtained from Japanese patients. In contrast, HPV sequences have not been observed in cancers arising in low-incidence areas. Poljack et al. 70 observed no evidence of HPV in 121 formalin-fixed, paraffin-embedded esophageal cancer specimens obtained from patients in Slovenia. Similarly, Rugge et al. 71 detected no HPV in 18 carcinomas arising in Italian patients. Turner et al. 72 observed no evidence of HPV in 51 formalin-fixed, paraffin-embedded esophageal cancer specimens obtained from patients in North America. In a large population-based control study, Lagergren et al. 73 compared 121 esophageal squamous cell cancers and 173 adenocarcinoma patients with 302 population-based controls in Sweden. These authors observed no association between HPV infection and risk of esophageal cancer in this low-incidence area. Collectively, these data suggest that HPV may contribute to the pathogenesis of esophageal squamous cancers in high-incidence regions; however, this oncogenic virus appears to have little, if any, role in the pathogenesis of esophageal malignancies arising in low-incidence areas.
PRIOR AERODIGESTIVE TRACT MALIGNANCY

Carcinomas of the aerodigestive tract arise as the consequence of multistep processes in cancerization fields. Patients with upper aerodigestive tract cancers develop second primary cancers at a rate of approximately 4% per year. Nearly 10% of secondary neoplasms arising in patients with prior histories of oropharyngeal carcinoma arise in the esophagus. Levis et al. observed that approximately 10% of second primary cancers in patients with prior histories of lung carcinoma arose in the esophagus. The increased risk of second primary tobacco-related carcinomas warrants close surveillance of patients with histories of aerodigestive tract malignancy.

BARRETT'S ESOPHAGUS

Barrett's esophagus is characterized by the presence of columnar epithelium lining 3 or more cm of the distal tubular esophagus in the presence or absence of hiatal hernia. Short segment Barrett's esophagus is defined as intestinal metaplasia involving less than 3 cm of the distal esophagus at the region of the lower esophageal sphincter. The prevalence of Barrett's esophagus ranges between 0.45% and 2.2% among all patients undergoing upper gastrointestinal endoscopy, increasing to 10% to 20% in patients undergoing endoscopy for symptomatic gastroesophageal reflux disease, and 30% to 50% in patients with peptic strictures. Barrett's esophagus is twice as prevalent in men compared with women, and increases with age, reaching a plateau in the seventh to ninth decade of life; this disease is infrequently observed in nonwhites. In all likelihood, the prevalence of Barrett's esophagus exceeds that which has been previously reported given the fact that most individuals with this disease are asymptomatic.

Although a congenital etiology has been proposed, considerable data indicate that Barrett's esophagus is primarily an acquired condition resulting from gastroesophageal reflux. The vast majority of patients diagnosed with Barrett's esophagus have significant gastroesophageal reflux, and Barrett's metaplasia has been observed following esophagogastrectomy or Heller's myotomy presumably as the result of gastroesophageal reflux in the absence of a competent lower esophageal sphincter. Three types of columnar metaplasia have been identified in Barrett's esophagus. The fundic type mucosa is characterized by the presence of chief and parietal cells in addition to surface mucus-secreting cells containing neutral mucus; juncional type epithelium resembling that of gastric cardia is composed primarily of mucus-secreting cells. Specialized or intestinal type epithelia resemble that of the small bowel, appearing as a villiform surface comprised of mucus-secreting cells as well as goblet cells staining positively for acid-fast mucins. Specialized epithelium is distinctive for Barrett's esophagus, being present in virtually all cases, and is the type most commonly associated with malignant degeneration.

Barrett's esophagus has been associated with a 30- to 40-fold increase in the risk of adenocarcinoma, the incidence of which increased at a rate of 10% per year during the 1980s. Currently, esophageal adenocarcinomas account for as much as 60% of all esophageal cancers diagnosed in the United States, and nearly 65% of esophageal adenocarcinomas have evidence of metaphasic columnar epithelia adjacent to them. Presumably, many other esophageal adenocarcinomas have arisen in and replaced short segment Barrett's esophagus before clinical presentation.

Although presumed to arise as the result of malignant transformation in specialized epithelia, the prevalence of adenocarcinoma in Barrett's esophagus has not been conclusively defined; however, estimates range between 0% and 64%. Sharma et al. identified 20 individuals with high-grade dysplasias (nearly one-half of whom would be expected to have invasive carcinomas) out of 177 patients with short segment Barrett's esophagus. Hriott et al. prospectively examined the prevalence of adenocarcinoma of the esophagus and gastroesophageal junction in patients with specialized intestinal metaplasia involving long segment Barrett's esophagus, short segment Barrett's esophagus, or esophagogastroduodenoscopy. Of 833 patients studied by esophagogastroduodenoscopy, the overall prevalence of specialized intestinal metaplasia was 13.2% (1.6% long segment Barrett's esophagus, 6.0% short segment Barrett's esophagus, and 5.6% esophageogastic junction). Dysplasia or cancer was noted in 31% of long segment Barrett's esophagus, 10% of short segment Barrett's esophagus, and 6.4% of esophagogastic junction–specialized intestinal metaplasia patients. Although the prevalence of short segment Barrett's esophagus or esophaagogastic junction–specialized intestinal metaplasia was approximately 3.5-fold higher than that of long segment Barrett's esophagus, the prevalence of dysplasia in long segment Barrett's esophagus was two to four times higher than that observed in the two other conditions.

Additional studies have been performed to ascertain the incidence of adenocarcinoma in Barrett's esophagus. Cameron et al. followed 104 patients with Barrett's esophagus for an average of 8.5 years, only two of whom developed carcinoma, for an incidence of 1 in 141 patient-years. In an additional study, Spechler et al. observed the development in carcinoma in 2 of 105 patients followed for an average of 3.3 years. In a prospective study, Robertson et al. observed one case of cancer in Barrett's esophagus in 56 patient-years. In a retrospective study, Katz et al. reported on 102 patients with Barrett's esophagus undergoing surveillance over a 24-year period; during 563 patient-years, three patients developed adenocarcinoma a minimum of 4 years after diagnosis; 23 additional patients progressed to low-grade dysplasia (19) or high-grade dysplasia (4) during the study period. In a large prospective analysis, O'Connor et al. evaluated 136 patients enrolled in an endoscopic surveillance program at the Cleveland Clinic. The average duration of follow-up was 4.2 years, with a total of 570 patient-years. Thirty patients (22%) had short segment Barrett's esophagus. Two patients developed adenocarcinoma (incidence, 1 in 285 patient-years), and four patients progressed to high-grade dysplasia.

Flow cytometry techniques may enhance the efficiency and optimize expense of screening surveillance programs in patients with Barrett's esophagus, which already appear to identify cancers at earlier stages compared with those detected outside the context of screening programs. Flow cytometric abnormalities in this condition. Fennerty et al. reported on 102 patients with Barrett's esophagus undergoing surveillance over a 24-year period; during 563 patient-years, three patients developed adenocarcinoma a minimum of 4 years after diagnosis; 23 additional patients progressed to low-grade dysplasia (19) or high-grade dysplasia (4) during the study period. In a large prospective analysis, O'Connor et al. evaluated 136 patients enrolled in an endoscopic surveillance program at the Cleveland Clinic. The average duration of follow-up was 4.2 years, with a total of 570 patient-years. Thirty patients (22%) had short segment Barrett's esophagus. Two patients developed adenocarcinoma (incidence, 1 in 285 patient-years), and four patients progressed to high-grade dysplasia. Low-grade dysplasias developed in an additional 24 patients. In another prospective study, Weston et al. reported that the incidence of high-grade dysplasia or adenocarcinoma in Barrett's esophagus was 1 per 72 patient-years.

Although esophageal adenocarcinomas are frequently preceded by histologically defined stages of metaplasia and progressively severe dysplasia in Barrett's esophagus, the risk of progression to malignancy cannot be predicted by histologic parameters due to significant discordance between histologic, cytogenetic, and flow cytometric abnormalities in this condition. Fennerly et al. analyzed 86 patients with Barrett's esophagus and noted that 23 of 73 patients without dysplasia, and 4 of 13 patients with low-grade dysplasia had aneuploidy or increased G$_n$/S fraction evaluated by flow cytometry. Widespread cellular proliferation and aneuploidy occur relatively early in Barrett's esophagus, and progression to malignancy is associated with three well-defined cell-cycle events: (1) mobilization of G$_n$ cells into G$_0$; (2) loss of G$_0$/S regulation and increased S-phase fraction; and (3) accumulation of cells in G$_1$/M, frequently with significant aneuploidy. Evidence of genomic instability has been observed in metaphasic epithelia as well as histologically normal tissues adjacent to Barrett's esophagus, indicating that the histologic alterations underestimate the severity of genetic events during progression to malignancy in Barrett's epithelia. Reid et al. prospectively evaluated 62 patients with Barrett's esophagus and observed that 9 of 13 patients with abnormal flow cytometry, including two with Barrett's metaplasia, five with low-grade dysplasia, and two with high-grade dysplasias, progressed to either high-grade dysplasia or invasive carcinoma; none of 49 patients with normal flow cytometry progressed to malignancy during the 34-month study. Interestingly, five patients with low-grade dysplasia who had normal flow cytometry parameters reverted to Barrett's metaplasia during the study. Collectively, these data indicate that histologic changes do not accurately reflect the severity of genomic instability in Barrett's esophagus. Further, 15% to 20% of patients with Barrett's esophagus have columnar-lined epithelia exhibiting aberrant cell-cycle regulation; 70% of these individuals progress to malignancy within a 3-year period. Although the incidence of adenocarcinoma in patients with Barrett's esophagus may be relatively low, use of flow cytometry techniques may help to identify those patients who are at high risk for the development of esophageal cancer.

Flow cytometry techniques may enhance the efficiency and optimize expense of screening surveillance programs in patients with Barrett's esophagus, which already appear to identify cancers at earlier stages compared with those detected outside the context of screening programs. However, surveillance protocols may have limited effect on the incidence of advanced esophageal carcinomas. Bytzer et al. evaluated the incidence of esophageal adenocarcinoma in Denmark over a 20-year period and ascertained the proportion of patients with a prior diagnosis of Barrett's esophagus. A history of diagnosis of reflux was present in 21% of patients, and 23% of individuals had undergone previous endoscopy for reflux or dyspepsia. Interestingly, only 1.3% of 524 esophageal cancer patients had a prior diagnosis of Barrett's esophagus. In essence, greater than 98% of patients would not have entered endoscopic surveillance programs. Collectively, these data indicate that endoscopic surveillance may be beneficial in patients with Barrett's esophagus, but the vast majority of esophageal cancer patients have no antecedent symptoms that might enable early detection. Clearly, additional factors other than gastroesophageal reflux contribute to malignant transformation in Barrett's esophagus.

MOLECULAR BIOLOGY

Flow cytometric and molecular analyses of dysplastic squamous and Barrett's epithelia have revealed that esophageal cancers arise via widespread clonal outgrowth of cells exhibiting aberrant cell-cycle regulation. In general, genomic instability precedes the appearance of histologic abnormalities in esophageal mucosa and the extent of cell-cycle derangements influences progression to malignancy in this setting. Many of the oncogene and tumor suppressor gene mutations frequently observed in esophageal cancers and their precursor lesions perturb cell-cycle regulation by disrupting the G$_0$ restriction point. Table...
A reciprocal relationship between retinoblastoma (Rb), cyclin D, and p16 expression has been observed in esophageal cancers similar to what has been reported for other solid tumors. In general, esophageal cancers that lack Rb expression tend to have normal cyclin D1 and p16 expression, whereas cancers that retain Rb expression typically exhibit overexpression of cyclin D1, p16 inactivation, or both. In the majority of esophageal cancers, restriction point control is circumvented via overexpression of cyclin D1, and inactivation of p16, often in the context of p53 mutations.

The epidermal growth factor receptor (EGFR) is a 170-kD tyrosine kinase receptor that is overexpressed in approximately 30% and 70% of esophageal adenocarcinomas and squamous cell cancers, respectively. Approximately 40% of these tumors also express transforming growth factor-a, which binds to EGFR and stimulates proliferation via autocrine mechanisms. Several studies suggest that overexpression of EGFR may have prognostic significance in esophageal cancer patients. Ikakura et al. reported that EGFR immunoreactivity correlated significantly with diminished survival of patients undergoing esophagectomy for squamous cell cancer. Iihara et al. noted that expression of transforming growth factor-a, EGFR, or both correlated with reduced survival in patients with node-positive esophageal squamous cell carcinomas. More recently in studies involving a total of 223 patients, Kitagawa et al. and Shimada and coworkers observed that EGFR overexpression significantly enhanced predilection for lymph node metastases, hematogenous recurrence, and diminished survival in patients undergoing potentially curative esophagectomies.

The erbB2 gene product is a 185-kD receptor molecule with intrinsic tyrosine kinase activity, which also regulates expression and function of a variety of other receptors including EGFR; in addition, p185 modulates expression of matrix metalloproteases and vascular endothelial growth factor by cancer cells. Overexpression of erbB2 correlates with in vitro drug resistance, and abrogation of p185 expression enhances chemosensitivity in cancer cells. The prognostic significance of erbB2 overexpression in esophageal cancers is unclear. Polkowski et al. observed overexpression of erbB2 in approximately 25% of adenocarcinomas of the distal esophagus and gastroesophageal junction. Interestingly, 10 of 30 stage III to IV tumors overexpressed erbB2 in contrast to 0 of 11 stage I to II cancers; however, subsequent regression analysis revealed that erbB2 expression was not independent of clinical stage in determining patient survival. Furthermore, Wang and colleagues observed no significant correlation between erbB2 expression and long-term survival in 117 patients undergoing potentially curative resections for esophageal squamous cell carcinoma. In contrast, Brien et al. observed that erbB2 amplification independently correlated with diminished survival in patients with Barrett's adenocarcinomas.

Together with its kinase partners, cdk4 and cdk6, cyclin D1 directly regulates phosphorylation of the Rb protein at the restriction point, thereby facilitating G1/S transit; abrogation of cyclin D1 expression inhibits the proliferation and tumorigenicity of cancer cells. Approximately 40% to 60% of esophageal carcinomas and 30% of premalignant esophageal lesions exhibit overexpression of cyclin D1 resulting directly from amplification of the cyclin D1 protooncogene, or indirectly from mutations involving upstream growth factor receptors such as EGFR and p185. Several studies suggest that cyclin D1 overexpression may be prognostically relevant in esophageal cancers. Shimada et al. observed that cyclin D1 overexpression correlated with hematogenous recurrence and diminished survival in esophagectomy patients. In an additional study, Roncalli et al. detected amplification of cyclin D1 in 17 of 55 of esophageal carcinomas, noting that overexpression of cyclin D1 correlated significantly with lymph node metastases, advanced tumor stage, and reduced overall survival in esophageal cancer patients.

Cyogenetic and molecular analyses have revealed nonrandom patterns of allelic loss in esophageal cancers and their precursor lesions indicative of selective pressure to specifically inactivate tumor suppressor genes in these regions during multistep esophageal carcinogenesis. Deletions involving 3p have been detected in 60% to 100% of esophageal cancers as well as a significant percentage of specimens derived from Barrett's esophagus. Although the tumor suppressor genes that are silenced by 3p mutations have not been identified conclusively, one major target appears to be the fragile histidine triad (FHIT) gene, which modulates cell-cycle progression and apoptosis. Point mutations as well as promoter hypermethylation contribute to aberrant expression of FHIT in 50% to 90% of esophageal carcinomas, and the majority of Barrett's metaplasia specimens examined to date. Although FHIT mutations correlate with increased tobacco exposure and diminished survival in lung cancer patients, the prognostic significance of these mutations in esophageal cancers has not been defined as yet.

The retinoblastoma (Rb) gene, located on 13q14, encodes a 105-kD nuclear phosphoprotein that governs the G1/S restriction point via complex interactions with a variety of cyclin-dependent kinases, transcription factors, and viral oncoproteins. Rb is a critical mediator of cell-cycle arrest after DNA damage. Mutations resulting in the loss of Rb protein expression have been observed in 20% to 60% of esophageal cancers and their precursor lesions. RB mutations tend to occur more frequently in tumors that also exhibit mutations involving p53 and appear to correlate with advanced disease, nodal metastases, and diminished survival in esophageal cancer patients.

The p16 tumor suppressor gene product encoded on 9p21 inhibits the activity of cdk4 and cdk6, thereby preventing cyclin D–dependent phosphorylation of the Rb protein at the restriction point. Restoration of p16 expression by gene therapy techniques results in profound cell-cycle arrest in esophageal cancer cells. Allelic deletions or point mutations inactivate p16 in approximately 20% of esophageal cancers, and allelic loss involving 9p21 precedes the onset of aneuploidy in Barrett's esophagus. Promoter hypermethylation silences p16 in an additional 30% to 50% of esophageal cancers and adenocarcinomas. Although not extensively studied, loss of p16 expression appears to correlate with overexpression of cyclin D1 and diminished survival in esophageal cancer patients.

The p14ARF gene product is encoded by an alternate reading frame in the p16 locus and functions to stabilize p53 by preventing its interaction with MDM2. ARF is critical for initiating p53-mediated apoptosis in response to activated protooncogenes, but appears dispensable for p53-mediated response to genotoxic stress. Inactivation of ARF occurs by allelic deletion as well as methylation mechanisms that may simultaneously inactivate p16. Xu et al. performed a comprehensive analysis of the mechanisms responsible for silencing of p16 and p14ARF in 40 esophageal cancers. Promoter hypermethylation involving ARF and p16 was observed in 15% and 40% of specimens, respectively. Nearly all of the methylations involving ARF also silenced p16; in contrast, most of the p16 methylations were exclusive. Homozygous deletions involving ARF or p16 were seen in 33% and 18% of specimens, respectively. These data suggest that p14ARF is a primary target for homozygous deletion, whereas p16 appears to be silenced by hypermethylation in esophageal cancers. The prognostic significance of p14ARF mutations in established esophageal cancers has not been defined.

The p53 gene product regulates cell-cycle progression, DNA repair, apoptosis, and neovascularization in normal and malignant tissues via highly complex DNA and protein interactions. As previously mentioned, oncogene activation is mediated to p53 via p14ARF; however, genotoxic stress resulting from DNA damage as well as telomeric shortening directly induces p53 expression. In response to aberrant growth signals, p53 mediates either cell-cycle arrest in part via induction of p21 or apoptosis by a variety of transcription-dependent, as well as transcription-independent, mechanisms. p53 may influence the metastatic potential of tumor cells by inhibiting expression of vascular endothelial growth factor. Additional studies have shown that restoration of p53 expression by gene therapy techniques

| TABLE 33.2-1. Oncogene and Tumor Suppressor Gene Mutations in Esophageal Cancers and Their Precursor Lesions that Disrupt the G1 Restriction Point |
|-----------------|-----------------|-----------------|
| Oncogene        | Tumor Suppressor |
| EGFR            | p53             |
| erbB2           | p16             |
| Cyclin D1       | p14/ARF         |
| TGF-α1          | alphavirus      |
results in cell-cycle arrest and apoptosis as well as enhanced sensitivity to chemotherapy and ionizing radiation in esophageal cancer cells.\textsuperscript{186,190}

Fifty percent to 80% of esophageal cancers exhibit p53 mutations, most of which occur in evolutionarily conserved residues within the sequence-specific DNA binding domain.\textsuperscript{188,194} p53 mutations precede the development of aneuploidy in Barrett's esophagus,\textsuperscript{192} and the frequency of these mutations increases dramatically during histologic progression to malignancy in this condition.\textsuperscript{195,196} Several studies suggest that p53 mutations correlate with Rb mutations in esophageal cancers, as well as disease-free and overall survival in patients with these neoplasms.\textsuperscript{195,197,198}

Malignant transformation not only depends on the inactivation of growth constraints mediated by the Rb and p53 tumor suppressor pathways, but equally important requires activation of telomerase, a ribonucleoprotein that adds hexanucleic DNA repeats to chromosomal ends to prevent loss of telomere length during DNA replication.\textsuperscript{187,190} Abrupt expression of telomerase has been observed in the vast majority of esophageal cancers examined to date.\textsuperscript{199} Koyanagi et al.\textsuperscript{200} detected telomerase expression in 100% of 57 esophageal squamous cell cancers compared with less than 10% of normal tissue samples. In addition, Morales et al.\textsuperscript{202} observed high-level telomerase expression in 100% of adenocarcinomas and high-grade Barrett's dysplasias; in contrast, only weak or moderate expression was seen in metaplasia or low-grade dysplasia samples. Similar findings have been noted by Lord et al.\textsuperscript{203} who observed high-level telomerase expression in all stages of Barrett's esophagus, the level of which appeared to increase during histologic progression to cancer. Interestingly, telomerase reverse transcriptase expression in histologically normal esophageal squamous epithelia in cancer patients was significantly higher than that observed in esophageal biopsies obtained from noncancer patients. Although the clinical relevance of telomerase activity in cancer patients has not been defined, the fact that telomere length may correlate with chemosensitivity in esophageal cancer cells and that inhibition of telomerase activity induces death in cultured cancer cells\textsuperscript{204} strongly suggest that telomerase expression may significantly influence the clinical course of esophageal carcinomas.

CLINICAL PRESENTATION

Because it lacks a serosal coat, the esophagus is able to distend and accommodate considerable intraluminal tumor growth before deglutition is affected; as such, 50% of esophageal cancer patients have locally advanced unresectable disease or distant metastases at presentation. Dysphagia and weight loss are the initial symptoms in approximately 90% of patients presenting with esophageal cancer. Approximately 75% of the esophageal circumference must be involved with tumor before dysphagia is experienced; hence, although many patients relate a vague discomfort with swallowing for several months, dysphagia to solid foods may progress rapidly to total obstruction from circumferential tumor growth. Approximately 20% of patients experience odynophagia (painful swallowing). Although the vast majority of esophageal cancer patients present with weight loss, cachexia is seen in less than 10% of these individuals. Additional presenting symptoms may include dull retrosternal pain resulting from invasion of mediastinal structures, cough, or hoarseness due to paratracheal nodal or recurrent laryngeal nerve involvement. Infrequently, patients may present with pneumonia secondary to tracheoesophageal fistula or exanguinating hemorrhage due to erosion of the esophageal neoplasm into the aorta.

DIAGNOSIS

Esophageal cancer should be suspected in any patient complaining of dysphagia and weight loss. A thorough history should be ascertained, focusing on preexisting conditions, as well as tobacco and ethanol abuse, which are known to be associated with increased esophageal cancer risk. Aspiration cytology should be performed on palpable cervical lymph nodes to rule out extrathoracic metastases. Chest radiography and barium swallow should be performed; the barium swallow provides an inexpensive and important initial assessment of the extent of the disease within the esophagus and should include the entire esophagus as well as stomach and duodenum; double-contrast studies are preferable because they provide more precise evaluation of mucosal patterns and allow detection of small lesions that may be missed on single-contrast examination. Computed tomography (CT) of the chest and upper abdomen should be obtained to evaluate the extent of disease within the chest and rule out visceral metastases in the abdomen.

Patients who are suspected to have a primary esophageal carcinoma on the basis of history, physical examination, or radiographic studies should undergo esophagoscopy to establish tissue diagnosis and define the extent of the esophageal lesion. At the time of endoscopy, attention should focus on the identification of the neoplasm in relation to cricopharyngeus, the squamocolumnar junction, and the diaphragmatic hiatus; in addition the presence or absence of satellite lesions, Barrett's esophagus, and esophagitis should be noted. Biopsies and brushings should be obtained from suspicious lesions; the combined diagnostic accuracy of these two procedures exceeds 90%.\textsuperscript{205} Vital stains including toluidine blue or Lugol's iodine may be useful to guide endoscopic biopsies in situations in which lesions are equivocal. Frequently, strictures are encountered that require dilatation to allow passage of the endoscope and provide temporary relief of dysphagia. Occasionally, the esophagus is so stricutured it cannot be safely dilated; in these situations, multiple biopsies in four quadrants should be obtained, and the patients treated as if they have esophageal carcinoma irrespective of biopsy results. Bronchoscopy should always be performed in patients with potentially resectable upper and middle third esophageal carcinomas to rule out recurrent laryngeal nerve involvement and to identify and biopsy suspicious areas within the membranous trachea to rule out impending esophagorespiratory fistula.

Once a tissue diagnosis of esophageal cancer has been established, additional studies should be obtained to accurately stage the disease according to American Joint Committee on Cancer criteria (outlined in Table 33.2-2 and Table 33.2-3) in order to ascertain prognosis and optimize treatment. Tumor length and the degree of obstruction appear to have less effect than the extent of wall penetration and lymph node metastases in determining survival of esophageal cancer patients. Current noninvasive imaging modalities are imperfect regarding evaluation of local regional disease and detection of distant metastases in these individuals.\textsuperscript{206} Conventional CT scans detect the primary tumor in 75% to 80% of cases; however, sensitivity for local regional nodal disease is only 50% to 70%.\textsuperscript{207,208} Specific finding of lymph node metastases may influence survival and it is essential to evaluate both the thoracic and abdominal compartment in patients with these neoplasms.

Clinical and endoscopic features of esophageal cancer have not been defined, the fact that the clinical presentation may correlate with chemosensitivity in esophageal cancer cells and that inhibition of telomerase activity induces death in cultured cancer cells\textsuperscript{204} strongly suggest that telomerase expression may significantly influence the clinical course of esophageal carcinomas.

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<th>Table 33.2-2. Tumor, Node, Metastasis (TNM) System for Esophageal Cancer</th>
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<td>Stage</td>
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| Table 33.2-3. Tumor Stages for Esophageal Cancer |
Endoscopic ultrasonography (EUS) has been advocated as a means to enhance the accuracy of staging of esophageal cancers. Several studies indicate that in experienced hands, EUS accurately assesses wall involvement in 50% to 90% of tumors and mediastinal lymph node status in 67% to 100% of patients with localized esophageal cancers. Reid et al., as well as Catalano and colleagues, reported that EUS may be a valuable noninvasive means to detect celiac nodal metastases in esophageal cancer patients (sensitivity, 70% to 80%, and specificity, 88% to 98%). However, the accuracy of EUS is highly dependent on the expertise of the ultrasonographer; an incomplete or erroneous assessment of lymph node metastases, invasion of adjacent organs, and poor staging of early carcinomas have been reported. Furthermore, EUS has limited value in staging patients with high-grade obstruction or assessing response to induction therapy in esophageal cancer patients.

Operative mortality. Overall 5-year survival was 21%. Patients with stage I disease had a 47.5% 5-year survival compared with patients with stage III disease whose survival was better for T1 and T2 tumors (63% 5-year survival). Vigneswaran et al. and colleagues resections for carcinoma, and the survival rates are quite consistent with those reported by other surgeons who practice a similar approach (survival advantage for patients with adenocarcinoma (24% vs. 17%). This study by the University of Michigan group represents the largest experience with transhiatal resection of esophageal cancer and the survival rates are comparable with those reported by other surgeons who practice a similar approach (survival advantage for patients with adenocarcinoma (24% vs. 17%). This study by the University of Michigan group represents the largest experience with transhiatal esophagectomy for cancer of the intrathoracic esophagus and cardia treated with transhiatal esophagectomy; adenocarcinoma was present in 69% of these individuals, whereas 28% had epidermoid cancer. Hospital mortality was 4.5% and morbidity was 27%. Major complications included anastomotic leaks (13%), recurrent laryngeal nerve injury (7%), wound infection (3%), pulmonary complications (2%), bleeding (1%), and chylothorax (1%). More than 90% of patients were discharged within 21 days of hospitalization. Overall survivals at 2, 3, and 5 years were 47%, 34%, and 23%, respectively. Five-year survival was 59% for stage I patients and 22% for patients at stage IA. Patients with stage III disease had 2- and 5-year survival rates of 32% and 10%, respectively. There was an overall statistically significant survival advantage for patients with adenocarcinoma (24% vs. 17%). This study by the University of Michigan group represents the largest experience with transhiatal resections for carcinoma, and the survival rates are quite consistent with those reported by other surgeons who practice a similar approach. (Table 33.2-4: the debate focuses primarily on the need for and the extent of lymph node dissection during esophagectomy for cancer. The following discussion summarizes the current status of surgery, chemotherapy, radiation therapy, and combined modality treatment protocols.

**TREATMENT**

The treatment of choice for patients with esophageal cancer is Esophagectomy remains the standard of care; however, its role has been challenged due to the generally poor outcomes following surgical resection alone in patients who typically have locally advanced disease. A survey of community care practice patterns between 1988 and 1993 revealed an increase in the use of chemoradiation therapy to enhance the survival of patients with esophageal cancer. Currently, in many institutions, primary resection is deferred in favor of combined modality therapy with or without adjuvant esophagectomy. The routine use of combined modality therapy is more widely accepted than the use of surgery alone to evaluate esophageal cancer patients. Several studies indicate that in experienced hands, EUS accurately assesses wall involvement in 50% to 90% of tumors and mediastinal lymph node status in 67% to 100% of patients with localized esophageal cancers. Reid et al., as well as Catalano and colleagues, reported that EUS may be a valuable noninvasive means to detect celiac nodal metastases in esophageal cancer patients (sensitivity, 70% to 80%, and specificity, 88% to 98%). However, the accuracy of EUS is highly dependent on the expertise of the ultrasonographer; an incomplete or erroneous assessment of lymph node metastases, invasion of adjacent organs, and poor staging of early carcinomas have been reported. Furthermore, EUS has limited value in staging patients with high-grade obstruction or assessing response to induction therapy in esophageal cancer patients.

**SURGICAL RESECTION**

**Transhiatal Esophagectomy**

Transhiatal esophagectomy entails extirpation of the intrathoracic esophagus through the esophageal hiatus of the diaphragm without the need for a thoracotomy incision. An upper abdominal incision and a low-neck incision are required to isolate the esophagus at either end. The organ is next carefully stripped from its mediastinal attachments and removed. The prepared esophageal substitute, usually a greater curvature gastric tube, is advanced across the esophageal bed in the posterior mediastinum, and gastrointestinal continuity is restored by an end-to-side esophagogastronomy in the neck. No attempt is made to perform a systematic lymph node dissection apart from the few parahiatal nodes removed with the specimen. Occasionally, sampling of readily accessible celiac and periesophageal nodes is performed.

Transhiatal esophagectomy is one of the more commonly used techniques for esophagectomy in North America and Europe. Orringer et al. reported on 800 patients with cancer of the intrathoracic esophagus and cardia treated with transhiatal esophagectomy; adenocarcinoma was present in 69% of these individuals, whereas 28% had epidermoid cancer. Hospital mortality was 4.5% and morbidity was 27%. Major complications included anastomotic leaks (13%), recurrent laryngeal nerve injury (7%), wound infection (3%), pulmonary complications (2%), bleeding (1%), and chylothorax (1%). More than 90% of patients were discharged within 21 days of hospitalization. Overall survivals at 2, 3, and 5 years were 47%, 34%, and 23%, respectively. Five-year survival was 59% for stage I patients and 22% for patients with stage IA. Patients with stage III disease had 2- and 5-year survival rates of 32% and 10%, respectively. There was an overall statistically significant survival advantage for patients with adenocarcinoma (24% vs. 17%). This study by the University of Michigan group represents the largest experience with transhiatal resection for carcinoma, and the survival rates are quite consistent with those reported by other surgeons who practice a similar approach. (Table 33.2-4: The debate focuses primarily on the need for and the extent of lymph node dissection during esophagectomy for cancer. The following discussion summarizes the current status of surgery, chemotherapy, radiation therapy, and combined modality treatment protocols.)

**TABLE 33.2-4. Types of Esophageal Resection**

<table>
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<th>Type of Resection</th>
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<td><strong>Transhiatal Esophagectomy</strong></td>
<td>Extirpation of the intrathoracic esophagus through the esophageal hiatus of the diaphragm without the need for a thoracotomy incision. An upper abdominal incision and a low-neck incision are required to isolate the esophagus at either end. The organ is next carefully stripped from its mediastinal attachments and removed. The prepared esophageal substitute, usually a greater curvature gastric tube, is advanced across the esophageal bed in the posterior mediastinum, and gastrointestinal continuity is restored by an end-to-side esophagogastronomy in the neck. No attempt is made to perform a systematic lymph node dissection apart from the few parahiatal nodes removed with the specimen. Occasionally, sampling of readily accessible celiac and periesophageal nodes is performed.</td>
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**Note:** The accuracy of EUS is highly dependent on the expertise of the ultrasonographer; an incomplete or erroneous assessment of lymph node metastases, invasion of adjacent organs, and poor staging of early carcinomas have been reported. Furthermore, EUS has limited value in staging patients with high-grade obstruction or assessing response to induction therapy in esophageal cancer patients.
5-year survival was 5.8%. Patients with adenocarcinoma had a 5-year survival of 27%, whereas none of those with squamous cell cancer were alive at 5 years.

### Table 33.2-5. Transhiatal Esophagectomy for Esophageal Cancer

Only two studies have reported local recurrence rates following transhiatal esophagectomy. One of these studies reported a 35% local recurrence rate following resection alone in a four-arm randomized trial comparing resection with preoperative chemoradiotherapy. A significant reduction in the local recurrence rate without improvement in overall survival was noted in the combined modality arm. Local recurrence as a component of treatment failure was observed in 39% of patients in the surgery alone arm versus 19% of those receiving combined modality treatment. In a prospective study using serial CT scans, Barbier et al. also detected local recurrence in 39% of 50 esophageal cancer patients following transhiatal resection.

In summary, transhiatal esophagectomy can usually be performed with an operative mortality of 5% or less in the hands of experienced esophageal surgeons. Five-year survival rates are generally in the 20% to 25% range. Survival for patients with stage I tumors is in the 60% to 70% range, whereas patients with stage III disease have a 5% to 10% 5-year survival. Finally, the procedure is associated with failure to control or eradicate local disease in nearly 40% of patients.

### Standard Transthoracic Esophagectomy

Transthoracic esophagectomy is probably the most widely performed operation for cancer of the esophagus worldwide. The procedure can be carried out through a right or left thoracotomy incision depending on the preference of the surgeon and the location of the tumor within the esophagus. Generally, a right thoracotomy is required for adequate exposure of tumors in the middle or upper third that are anatomically intimately related to the membranous trachea or the arch of the aorta. Tumors located at the gastroesophageal junction or in the lower third of the esophagus can be usually approached through a right thoracotomy incision. A left sixth interspace incision provides excellent exposure of the lower mediastinum, and a semicircular diaphragmatic incision performed 1 inch from the costal arch allows access to the upper abdomen. The esophagus is mobilized from its mediastinal bed along with adjoining periesophageal as well as lesser curvature lymph nodes; no radical mediastinal or upper abdominal lymphadenectomy is performed. Gastrointestinal reconstruction is subsequently achieved by preparation of the esophageal substitute (usually stomach) and advancing it to the neck for a cervical anastomosis. Patients operated on through a right thoracotomy require a laparotomy to prepare the gastric tube and pass it across the posterior mediastinum or retrosternal space for a cervical anastomosis. In patients operated on through a left thoracotomy, the esophagus is mobilized along its course in the supra aortic posterior mediastinum well into the neck. The prepared gastric tube is then passed underneath the aortic arch and attached to the esophageal stump. Following reattachment of the diaphragm and closure of the thoracotomy, a small left cervical incision is performed to retrieve the esophagus and the gastric tube. A cervical incision is then performed and the previously mobilized esophagus and gastric tube are easily delivered to the neck for a cervical anastomosis.

Ellis reported his experience with more than 500 esophageal cancer patients who underwent standard transthoracic esophagectomy. One-third of the patients had squamous cell cancers, whereas the remaining two-thirds had adenocarcinomas of the esophagus or gastroesophageal junction. Hospital mortality was 3.3%. Complications occurred in 34% of patients and resulted in a prolonged hospital stay in 21% of individuals. Overall 5-year survival including operative mortality and noncancer-related deaths was 24.7%. Patients who had a complete (R0) resection had a 5-year survival of 29%, whereas no patients with either residual microscopic (R1) or macroscopic disease (R2) survived 5 years. There was no significant effect of cell type on survival. Five-year survival was 79% for patients with stage I disease, 38% for those with stage II A, and 27% for those with stage II B. Patients with stage III disease had 3- and 5-year survival rates of 20% and 13.7%, respectively.

Some of the more pertinent surgical series pertaining to standard transthoracic esophagectomy that have been reported within the last decade from North America and Europe are listed in Table 33.2-6. Resectability rates have ranged from 60% to 90%, and hospital mortality has ranged from 3.2% to 23%. Five-year survival rates have varied between 9% and 24%. The variability in rates of resectability, hospital mortality, and 5-year survival may have been related to differences in patient selection, surgical expertise, and the retrospective nature of most of these studies. More instructive to review are the survival results achieved by the surgical arms of randomized trials comparing various preoperative regimens to surgical resection alone. The most recent of these trials was the North American Intergroup trial that compared chemotherapy followed by surgery with surgery alone. There were 467 eligible patients of whom 227 underwent primary surgical resection, the majority through a transthoracic approach. One hundred six patients had squamous cell cancer (47%) and 121 had adenocarcinoma (53%). Hospital mortality was 6%. Major complications occurred in 26% of patients. Overall survival at 1, 2, and 3 years were 60%, 37%, and 26%, respectively. Actuarial 5-year survival was 20%. There was no difference in outcome between patients with adenocarcinoma and those with epidermoid cancer. In a separate trial performed by Walsh et al., 113 patients were randomized to receive either surgery alone or chemoradiation followed by transthoracic esophagectomy. Hospital mortality in the control arm was 2%, and the 3-year survival was 6%. Bossert et al. performed a randomized trial comparing transthoracic esophagectomy alone with radiotherapy followed by esophagectomy. Three- and 5-year survival rates in the surgery alone arm were 38% and 22%, respectively. Finally, Law et al. reported on 147 patients with squamous cell carcinoma randomized to either chemotherapy followed by esophagectomy or esophagectomy alone. There were 73 patients in the control arm, and nearly all underwent resection by a transthoracic approach. Hospital mortality was 8.7%. Survival rates at 2 and 5 years were 31% and 10%, respectively.

### Table 33.2-6. Transthoracic Esophagectomy for Esophageal Cancer

Local recurrences following standard transthoracic resections have been reported in 30% to 60% of patients. Most of the data regarding local recurrences have been obtained from surgical control arms of various randomized trials. Giloux et al. reported the incidence of local recurrence in a study comparing surgical resection alone with preoperative radiotherapy. Local recurrences were observed in 67% of patients in the surgery alone arm compared with 47% of individuals in the experimental arm. Similarly Nygaard et al. reported a 35% local recurrence rate following resection alone in a four-arm randomized trial comparing resection with preoperative chemotherapy, preoperative radiotherapy, and preoperative chemoradiation. In the Intergroup trial comparing esophagectomy alone with chemotherapy followed by esophagectomy, the local recurrence rate in the control arm was 31% among 135 patients who received a complete (R0) resection. An additional 68
patients had R1 or R2 resections. The overall local failure rate (persistent or recurrent disease) in all 227 patients in the control arm was 21%. In the previously randomized trial reported by Law et al., 21% of patients developed local recurrence, while an additional 10% had both local and distant recurrences; thus local recurrence was a component of treatment failure in 31% of patients in this study.

**Comparison of Transhiatal and Transthoracic Esophagectomy**

Several retrospective studies have shown little difference in the operative mortality and morbidity between transhiatal and transthoracic esophagectomy with limited lymph node dissection. Rindani et al. reviewed the results from 44 series published between 1986 and 1996. Thirty-three articles described results of 2875 patients who underwent transhiatal resection, whereas 29 articles reported results of transthoracic resections in 2868 patients. Transhiatal resection was 6.3% after transhiatal and 9.5% after transthoracic esophagectomy. Major pulmonary and cardiovascular morbidity was similar in both groups. Transhiatal esophagectomy was associated with a higher incidence of anastomotic leaks (16% vs. 10%), anastomotic strictures (28% vs. 16%), and recurrent laryngeal nerve injury (11% vs. 5%). Overall 5-year survival was 24% after transhiatal esophagectomy and 26% following transthoracic resection.

Two randomized trials have compared transhiatal resection with transthoracic resections. Chu et al. reported on 39 patients with carcinoma of the lower third of the esophagus who were prospectively randomized to receive either a transhiatal (n = 25) or a transthoracic resection (n = 19). There were no significant differences between the groups in terms of blood loss, postoperative ventilatory requirements, cardiopulmonary complication rates, and median hospital stay. Median survival was 16.0 months following transhiatal esophagectomy and 17.0 months following transthoracic resection. Forty-nine patients were randomized to receive either a transhiatal (n = 32) or transthoracic esophagectomy. There were no differences between the two groups with respect to hospital mortality, morbidity, incidence of pulmonary complications, or long-term survival.

In summary, survival rates achieved with the surgical transhiatal esophagectomy are comparable with those reported for standard transthoracic resection. However, radical lymph node dissections have not been performed in any of the aforementioned series; hence the survival results reflect the effect of the surgical incision rather than the extent of lymphadenectomy.

**En Bloc Esophagectomy**

The deep location of the esophagus within the narrow confines of the mediastinum and the lack of a well-defined mesentery have generally precluded the application of en bloc resection to patients with esophageal carcinoma. In 1963, Logan described results pertaining to 250 patients who underwent en bloc resection for cancer of the cardia, noting a 16% 5-year survival. Although that survival rate was remarkable at the time, the 21% operative mortality limited a wider adoption of the procedure. Skinner introduced the technique in 1969, which was later modified and applied to cancer of the thoracic esophagus. The basic principle of the operation is extirpation of the tumor-bearing esophagus within a wide envelope of adjoining tissues that include both pleural surfaces laterally and the pericardium anteriorly. The surgical specimen is composed of the esophagus, the aorta, and the thoracic duct throughout its mediastinal course, are resected en bloc with the specimen. This posterior mediastinectomy necessarily results in a complete mediastinal node dissection from the tracheal bifurcation to the esophageal hiatus. Additionally, an upper abdominal lymphadenectomy is performed including the common hepatic, celiac, left gastric, lesser curvature, paraaortic, and retroperitoneal nodes. The purpose of this extended resection is to maximize locoregional control of the primary tumor; local recurrence rates following en bloc resection are reported to be less than 10%. This is a strikingly low local failure rate compared with those observed following transhiatal or standard transthoracic resections, or chemonabothiation delivered with curative intent.

Critics have argued that the en bloc procedure is associated with a high operative mortality and morbidity without an apparent survival advantage. In fact, in the earliest report by Skinner, 25% of 25 patients with cancer of the cardia treated by en bloc resection was 11%, and the 5-year survival was only 18%. However, in more recent series, hospital mortality has ranged between 2% and 7%, and several investigators have reported survival rates exceeding those achievable by standard resection. Lerut et al. reported their experience with 129 patients who had an R0 resection for cancer of the thoracic esophagus. Approximately two-thirds of patients had squamous cell cancer, and one-third had adenocarcinoma of the esophagus. Resection was accomplished by the en bloc technique, with a hospital mortality of 7.5%. Survival was significantly better following en bloc resection compared with standard resection (48% vs. 41%; P = .002). Interestingly, multivariate analysis showed that the survival advantage after en bloc resection was apparent only in patients with nodal metastasis (P = .005). Furthermore, patients with stage III tumors had a 5-year survival of 22% after en bloc resection, compared with 13% after standard resection (P = .05). Hagen et al. reported similar results in a smaller group of patients with adenocarcinoma of the distal esophagus and gastroesophageal junction. En bloc resection was performed in 30 patients, and transthoracic resection was done in 16 patients. Overall survival was significantly better after en bloc resection (41% vs. 14%; P < .001). A survival advantage was observed in patients with early lesions (T1 and T2) in whom the 5-year survival was 75% versus 21% in favor of en bloc resection. Similarly, patients with transmural (T3) tumors and five or fewer positive nodes had a significantly better survival after en bloc resection (27% vs. 9%).

An important criticism of most of these studies is the failure to clearly define the criteria used to stratify patients to receive one procedure versus another. For example, in the study by Hagen et al., patients receiving transhiatal esophagectomies were significantly older or more debilitated than those undergoing en bloc resections. Preferential inclusion of early-stage patients into the en bloc groups may have biased survival outcomes. Arguably some early-stage patients undergoing en bloc resections might have had similarly favorable outcomes following a more limited procedure.

Altorki et al. reported on 155 patients who underwent resection for carcinoma of the esophagus between 1988 and 1998. During the first 4 years of the study, standard transthoracic resections were performed in nearly all patients; thereafter en bloc resections were carried out preferentially in nearly all patients. The overall hospital mortality for 80 patients with cancer of the cardia treated by en bloc resection was 11%, and the 5-year survival was only 18%. However, in more recent series, hospital mortality has ranged between 2% and 7%, and several investigators have reported survival rates exceeding those achievable by standard resection. Results, suggesting that the extended procedure may improve the accuracy of staging in esophageal cancer patients. Conceivably, some node-negative patients were understaged during standard resections, resulting in apparently worse survival relative to similarly staged patients who had undergone en bloc resections. Survival was also significantly better after en bloc resection in patients with nodal metastases (33% vs. 13%; P = .002). Five-year survival was significantly higher in patients with stage III disease treated by en bloc resection (34% vs. 11%; P = .007). This survival advantage was noted despite an analysis of variance showing no difference between the groups in terms of age, gender, performance status, tumor size, cell type, or number of positive nodes per patient. The 5-year survival rate (11%) in stage III patients undergoing standard resection in this series is similar to those reported in other series following similarly limited resections, suggesting no obvious selection bias in favor of en bloc resection. The survival advantage conferred by en bloc esophagectomy in patients with stage III disease confirms previous observations by Lerut et al. Furthermore, the 7.8% (8 of 108) local recurrence rate observed following en bloc esophagectomy in Altorki's trial is dramatically less than those observed following transhiatal or standard transthoracic resections.

**Three-Field lymphadenectomy**

Three-field lymph node dissection for carcinoma of the esophagus has been practiced by Japanese surgeons since the early 1980s. This effort was initially prompted by studies showing that the cervical lymph nodes were the site of tumor recurrence in 30% to 40% of patients in whom a curative resection had been performed. The extended procedure included dissection of the cervical, mediastinal, and upper abdominal nodes in patients with carcinoma of the thoracic and abdominal esophagus. In 1991, Isozo et al. reported the results of a nationwide study on three-field dissections performed at 35 institutions throughout Japan. Nearly 1600 patients underwent esophagectomy with three-field lymph node dissection, whereas 2800 underwent two-field dissection. The following observations were made:

- Approximately one-third of patients had previously unsuspected metastases in cervical lymph nodes. The prevalence of cervical nodal metastases was highest in patients with T4 or N3 tumors (40%), but even patients with lower third cancers had a 20% probability of metastatic carcinoma involving the cervical lymph nodes.
- The frequency of nodal metastases increased with depth of tumor penetration through the esophageal wall. Patients with intramucosal carcinoma had a 30% probability of nodal metastases, while invasion into the submucosa, muscularis propria, or adventitia signaled a 50%, 60%, and 80% probability of nodal disease, respectively. Interestingly, a statistically higher prevalence of nodal metastases was observed after three-field intramucosal lymph node dissection in patients with T1 and T2 tumors, but not in those with more advanced disease.
- The cervical lymph nodes most frequently involved with metastatic carcinoma were the nodal chains along the recurrent nerves, as well as the deep cervical nodes along the posterior aspect of the internal jugular vein. Supraventricular nodal disease was infrequent and was associated with a distinctly poor outcome.

Collectively, these observations indicate that a large number of patients will be inaccurately staged after en bloc resection with isolated mediastinal and abdominal lymphadenectomy. Approximately one-third of patients will have their tumor, node, metastasis (TNM) stage upstaged as a result of the extended procedure. Although
most surgeons readily concede that extended lymphadenectomy improves tumor staging, many question its effect on the survival of patients with locally advanced esophageal cancer. However, Japanese surgeons have provided a compelling argument for a positive effect of three-field lymph node dissection on survival in these individuals. Akayama et al. reported their experience with 717 patients in whom an R0 resection was performed using either a two-field (n = 393) or three-field technique (n = 324). Five-year survival in node-negative patients was 84% after the three-field procedure compared with 55% after two-field lymphadenectomy (P = .004). Furthermore, in patients with node-positive disease, the 5-year survival was 28% for patients receiving two-field dissections (P = .008), indicating that the improved survival rates observed in patients receiving extended lymphadenectomies were not simply due to stage migration. Similar results have been reported by a number of Japanese surgeons. Most studies have reported 5-year survival rates of 25% to 30% in patients with positive cervical lymph nodes. These impressive data suggest that the recurrent laryngeal nodes should be considered a regional (N1) rather than a distant (M1) site of disease for tumors of the intrathoracic and abdominal esophagus. Indeed, lymphoscintigraphy studies using radiolabeled colloid injected into the midthoracic esophagus have routinely demonstrated tracer uptake within the upper mediastinal and cervical nodes as well as the left gastric lymph nodes.

In spite of the intriguing results reported by Japanese surgeons, most European and North American oncologists have viewed three-field dissection with skepticism. There are several reasons that might explain the lack of enthusiasm for the procedure:

- There is a prevailing concept among western surgeons that patients with carcinoma of the esophagus have systemic disease at the time of presentation. Cure following resection has often been considered a chance phenomenon dependent more on the biologic behavior of the tumor than on the surgical strategy pursued.
- Three-field lymph node dissection has been associated with a definite, albeit a statistically insignificant, increase in hospital morbidity. Foremost among the potential complications is injury to one or both recurrent nerves, reported in up to 70% of patients, some of whom have required tracheostomy and prolonged mechanical ventilation. Furthermore, at least one study examined the quality of life following esophagectomy with three-field lymph node dissection with particular emphasis on the effect of vocal cord paralysis. Twenty percent of patients reported severe hoarseness, restricted food intake, and reduced exercise tolerance up to 60 months postoperatively.
- Nearly all of the Japanese randomized retrospective studies comparing surgical therapies delivered over two decades. Two randomized studies have been reported. Nashira et al. randomized 62 patients with squamous cell carcinoma of the esophagus to receive a two-field or three-field lymph node dissection. Hospital deaths occurred in 3% after two-field dissection and in 7% after three-field lymphadenectomy. There were no differences between the two groups in 5-year survival or recurrence rates. In another trial, Kato et al. randomized 150 patients to receive transtracheal esophagectomy with either two-field or three-field lymph node dissection. Hospital mortality and morbidity were comparable in both groups; a significantly higher 5-year survival was observed in patients who underwent a three-field dissection (48% vs. 33%).

Altorki et al. reported the only experience with this procedure in North America. Esophagectomy with a three-field node dissection was performed in 34 patients, 10 of whom had adenocarcinomatous. Hospital mortality and morbidity were 2.3% and 35%, respectively. Recurrent nerve injury occurred in 6% of patients. An average of 60 nodes were resected per patient; 70% of these individuals had nodal metastases, most of which were within the lesser gastric curve, parahiatal, and recurrent laryngeal nodes. Cervical nodal metastases were present in 30% of patients regardless of cell type or location of the primary tumor within the esophagus. With a median follow-up of 42 months, 3-year and 5-year survival was 46%. Node-negative patients had a 77% 5-year survival, whereas those with nodal metastases had a 5-year survival of 33%. Three of the ten patients with metastases involving cervical or recurrent laryngeal nodes were disease free a minimum of 3 years after operation. Local recurrence was observed in two patients.

Lerut et al. reported the only European experience with esophagectomy and three-field lymph node dissection. Thirty-eight patients underwent the procedure with no hospital mortality. Overall survival rates at 3 and 5 years were 45% and 37%, respectively. Patients with nodal metastases had a 27% 5-year survival; individuals with cervical node disease had a 20% 5-year survival. The patterns of nodal metastases observed by Altorki and Lerut are similar to those reported by Japanese investigators and appear independent of tumor histology. The potential survival advantage offered by three-field dissection in esophageal cancer patients (particularly those with adenocarcinoma) is encouraging given the limited efficacy of chemotherapy and radiation in these individuals.

CHEMOTHERAPY

Five-year survival rates for esophageal cancer patients resected at most major centers in the United States range from 15% to 20%. Although radical esophagectomy may salvage some patients with locally advanced carcinomas, the vast majority of individuals succumb to their disease, suggesting that most patients have occult metastases at presentation. Studies of patterns of recurrence, and data from autopsy series confirm the potential for tumor spread to all organs. These data have provided the rationale for using systemic therapy in conjunction with surgery, radiation, or both in patients with apparently localized disease or as the primary treatment for patients with clinically evident disseminated disease.

Until fairly recently, standard criteria of treatment response required a bidimensional lesion that could be serially measured. For the esophageal cancer patient with metastatic disease, treatment response can be reliably assessed using pulmonary, soft tissue, and liver nodules as indicators. CT, magnetic resonance imaging, and positron emission tomography (PET) scans may be performed to confirm a clinical complete response; however, biopsy is subject to sampling error and is not a reliable indicator of complete histologic resolution of disease. A variety of single agents and combination regimens have been evaluated in patients with recurrent or metastatic carcinoma of the esophagus. These patients often have a high tumor burden and poor performance status with little prospect for prolongation of survival. Phase II clinical trials in this population have identified drugs with activity and they have been integrated into combined modality regimens for the treatment of earlier stage disease.

The accumulated experience with chemotherapy to date is almost entirely in patients with squamous cell histology. Due to the rising incidence of adenocarcinoma of the esophagus, gastroesophageal junction, and cardia in the United States, patients with this histology now make up two-thirds of referrals for chemotherapy. Only recently have trials with new agents and combined modality regimens included both histologies.

Chemotherapy for Palliation of Recurrent and Metastatic Disease

SINGLE AGENTS. Studies of single agents are summarized in Table 33.2-7. The cumulative response rate for any one drug is low (on the order of 15% to 30%), and there is no indication of survival benefit. Symptomatic improvement, if reported, is brief. Response data for many of the older drugs have come from broad phase I and II trials conducted in the early 1970s, which included small numbers of esophageal cancer patients. Bleomycin, 5-fluorouracil (5-FU), mitomycin, and cisplatin (CDDP) have been used most often because of their single-agent activities and their additive or synergistic effects with radiation. Because of the potential for pulmonary toxicity, bleomycin is no longer included in combination regimens, having been replaced by 5-FU. Similarly, mitomycin is less often used because of its toxicity profile, which includes hemolytic-uremic syndrome and cumulative myelosuppression.

<table>
<thead>
<tr>
<th>TABLE 33.2-7. Trials of Single Agents with Activity in Carcinoma of the Esophagus</th>
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<tr>
<td><strong>Drug</strong></td>
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<tr>
<td>5-Fluorouracil (5-FU)</td>
</tr>
<tr>
<td>Mitomycin</td>
</tr>
<tr>
<td>Cisplatin (CDDP)</td>
</tr>
<tr>
<td>Bleomycin</td>
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5-FU has remained an important drug for the treatment of gastrointestinal malignancies. One study using a protracted infusion schedule for 6 weeks in patients with newly diagnosed esophageal cancer reported an 85% response rate that contrasts with an Eastern Cooperative Oncology Group trial in which a 15% response rate was observed in previously treated patients given intermittent bolus 5-FU.

There are seven trials pertaining to cisplatin as a single agent in esophageal cancer patients. Two of which used doses ranging from 50 to 120 mg/m² every 3 to 4 weeks. The cumulative response rate in patients with metastatic or recurrent disease was 21%. Administration of the drug as a single bolus dose once every 3 weeks or in a divided dose over 5 days every 3 weeks appeared to be equally efficacious. Employing a more dose-intense schedule of cisplatin (120 mg/m² on day 1 and 15). Miller et al. observed a 73% response rate in 15 patients before surgery. Although no complete responses were observed, these data suggest that sensitivity to chemotherapy is greater in the newly diagnosed patient.

A randomized phase II trial of cisplatin alone and cisplatin in combination with 5-FU in 92 patients with metastatic squamous cell carcinoma of the esophagus was reported by the European Organization for Research and Treatment of Cancer (EORTC). An 18% response rate was observed in 45 patients receiving single-agent cisplatin at a dose of 100 mg/m² every 3 weeks. Although the response rate in the combination therapy arm was 36%, survival was similar for both groups. No studies of single-agent cisplatin have been performed in patients with adenocarcinoma of the esophagus.

Two investigational agents have demonstrated moderate activity in squamous cell carcinoma of the esophagus. These are the vincristine vindesine and the polyamine synthesis inhibitor mitoguazone (methyl-GAG). Responders included patients previously treated with cisplatin-based combination chemotherapy.

Vinorelbine, a semisynthetic vinca alkaloid that inhibits microtubule assembly, has been approved for use in lung cancer. It has less neurotoxicity compared with vincristine and vinblastine; neutropenia is dose limiting. The EORTC reported a 20% response rate in chemotherapy-naive patients with metastatic squamous cell carcinoma of the esophagus. In a subsequent trial, vinorelbine was combined with cisplatin in 57 patients with metastatic squamous cell cancer resulting in a 32% response rate and 6-month median duration of response. Vinorelbine has not been evaluated in patients with adenocarcinoma of the esophagus.

The taxane paclitaxel is the first entirely new compound to be tested in both adenocarcinoma and squamous cell carcinoma of the esophagus. Paclitaxel promotes the stabilization of microtubules and is a cycle-specific agent affecting cells in the G2/M phase. Paclitaxel also enhances radiation effects that may be both concentration and schedule dependent. The only trial of single-agent paclitaxel in esophageal cancer used the maximum tolerable dose of 250 mg/m², derived from initial phase I trials using a 24-hour infusion schedule. A 34% response rate was observed in 33 patients with adenocarcinoma, and a 28% response rate was noted in 18 patients with squamous cell carcinoma of the esophagus. The overall response rate was 32%. All patients had good performance status, were chemotherapy-naive, and had distant metastases. The dose-limiting toxicity of paclitaxel is myelosuppression, primarily neutropenia. There are no completed studies using either shorter or longer infusion schedules such as 1, 3, and 96 hours.

Drugs that have been adequately tested in squamous cell cancer of the esophagus and have response rates of less than 5% are the methotrexate analogues, dichloromethotrexate and trimetrexate, etoposide, cisplatin, mitoguazone, and vindesine. Carboplatin has been studied in both adenocarcinoma and squamous cell carcinoma patients using a fixed dose schedule of 300 to 400 mg/m² in individuals with normal renal function. In contrast to the activity observed in phase II evaluations of cisplatin, responses were observed in only 3 of 59 chemotherapy-naive patients who received carboplatin.

Therefore, substitution of carboplatin for cisplatin is not recommended when treating patients with either adenocarcinomas or squamous cell carcinomas of the esophagus.

Combination Chemotherapy

Only in more recent years have combination regimens been evaluated in patients with adenocarcinoma. Older trials (before the mid-1990s) and those from Europe have almost exclusively been limited to patients with squamous cell carcinomas. Because esophageal cancer is a relatively uncommon malignancy, many studies have included patients treated preoperatively as well as those with recurrent or metastatic disease, and some have also included patients with locally advanced, unresectable neoplasms. In addition to the variation in patient populations, more recent trials have often limited eligibility to patients with no prior chemotherapy and performance status of 0 or 1. Thus, it is difficult to compare treatment efficacies reported from these phase II trials.

The results of platinum-based combination chemotherapy regimens are detailed in Table 33.2-8. Most series have had small numbers of patients and therefore 95% confidence intervals have been large. Nearly all responses have been partial, with only an occasional clinical complete response. Duration of response has been variable but on average has ranged from 3 to 6 months.

**Table 33.2-8.** Selected Combination Chemotherapy for Recurrent and Metastatic Carcinoma of the Esophagus

<table>
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<tr>
<th>Drug Combination</th>
<th>Response Rate</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Cisplatin</td>
<td>20%</td>
<td>Median duration of response is 6 months.</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>34%</td>
<td>Dose-limiting toxicity is myelosuppression, primarily neutropenia.</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>28%</td>
<td>Only studied in patients with normal renal function.</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>32%</td>
<td>Not recommended when treating patients with either adenocarcinomas or squamous cell carcinomas of the esophagus.</td>
</tr>
</tbody>
</table>

Trials in the 1980s testing three-drug regimens such as cisplatin, bleomycin, and vindesine and cisplatin, mitoguazone, and vindesine or vinblastine yielded response rates of 30% to 40% in epidermoid cancer patients. Toxicity was primarily moderate myelosuppression. Bleomycin and mitoguazone were replaced by 5-FU, which has synergistic activity with cisplatin.

The two-drug combination of cisplatin (100 mg/m² day 1) and 5-FU (1000 mg/m²/day continuous infusion for 96 to 120 hours) is the regimen most commonly used to treat patients with either squamous cell or adenocarcinoma histology. A 35% response rate has been observed in patients with metastatic, recurrent, or locally advanced, incurable squamous cell cancer of the esophagus. Higher response rates (in the 40% to 60% range) have been reported from trials administering two to three cycles of cisplatin and 5-FU as neoadjuvant therapy before surgery. The difference in response rates may be related to better performance status, nutrition, and smaller volume disease in the surgical candidates. Attempts to substitute carboplatin for cisplatin have been unsuccessful; in a phase II trial of carboplatin and vinblastine, investigators from Memorial Sloan-Kettering Cancer Center observed no responses in 16 patients even though 11 with advanced, inoperable cancers were previously untreated, and 15 had Karnofsky performance scores of 70% or better.

Three trials using interferon-α as a biomodulator of 5-FU suggested possible benefit. Preclinical data had indicated synergistic cytolytic activity when interferon was combined with 5-FU, possibly due to interferon-mediated stimulation of thymidine phosphorylase, which increases the conversion of 5-FU to its active metabolite, fluorodeoxyuridylate. Ilson and associates treated 26 incurable esophageal cancer patients with interferon-α (3 million U subcutaneously daily), cisplatin (100 mg/m² day 1), and continuous infusion 5-FU (750 mg/m²/day for 5 days) recycled every 28 days; the complete and partial response rates were 50%, and the duration of response ranged from 11 to 74 weeks. Treatment responses were observed in 8 of 11 with squamous cell carcinoma (73%; 95% confidence interval, 47% to 99%) and 5 of 15 adenocarcinoma patients (33%; 95% confidence interval, 9% to 57%). The combination of 13-cis retinoic acid and interferon-α, however,
had no activity. 335 Despite the lack of single-agent activity for etoposide, the Rotterdam Esophageal Cancer Study Group 336 reported a 48% response rate in patients with unresectable or metastatic squamous cell carcinoma. This experience using cisplatin (80 mg/m² day 1) and etoposide (100 mg/m² intravenously on days 1 to 2 and 200 mg/m² orally on days 3 to 5 every 4 weeks) served as the basis for a phase III evaluation of this regimen in the preoperative setting. 337

Combination regimens including paclitaxel have been evaluated in esophageal cancer patients. In three phase II trials of paclitaxel and cisplatin, response rates ranged from 44% to 52%; activity was comparable in both histologic types. 338–340 Ilson and associates 338 evaluated paclitaxel administered by 24-hour infusion in doses of 200 to 250 mg/m² with growth factor support combined with cisplatin (75 mg/m²). Toxicity (primarily myelosuppression) was severe, leading to one or more hospitalizations in 50% of patients and five treatment-related deaths; as such, this particular regimen cannot be recommended. Van der Gaast and associates from Rotterdam reported two separate trials. 339,340 The first evaluated escalating doses of 3-hour infusion paclitaxel (100 to 200 mg/m²) combined with a fixed dose of cisplatin (60 mg/m²) administered every 2 weeks. 339 A 52% response rate was observed in 59 patients. Doses of paclitaxel above 180 mg/m² caused dose-limiting neurotoxicity. The second trial evaluated a weekly regimen of cisplatin (70 mg/m²) and 3-hour paclitaxel infusion. 340 A preliminary report indicated that the maximum tolerable dose of paclitaxel was 100 mg/m²/week, and that the response rate in 22 adenocarcinoma patients was 50%. The antitumor activity reported for these three regimens was comparable, but toxicities varied considerably.

The three-drug combination of paclitaxel, 175 mg/m² (3-hour infusion), combined with cisplatin (20 mg/m²/24h × 5) and 5-FU (1000 mg/m²/24h continuous infusion × 120 hours) was evaluated in 60 patients at four centers. 341 A 48% response rate was reported (56% in patients with squamous cell cancers and 46% in adenocarcinoma patients); significantly more complete responses were observed in patients with squamous cell carcinomas. Toxicity was severe, resulting in hospitalizations for 48% of patients, primarily for severe stomatitis, fever, and neutropenia. The addition of paclitaxel to the established cisplatin and 5-FU regimen did not raise the response rate sufficiently to warrant further evaluation in a larger comparative trial.

It is clear that the optimal dose and scheduling of paclitaxel in combination with other active drugs remains to be determined. In general, shorter infusion schedules of paclitaxel result in less myelotoxicity, but more neurotoxicity when this taxane is combined with cisplatin. The regimen of paclitaxel and carboplatin has not been tested in esophageal cancer. However, because of the lack of activity of carboplatin as a single agent or in combination with other agents used to treat esophageal cancer, it should not be substituted for cisplatin until appropriate clinical trials have been performed.

A new regimen under evaluation in esophageal cancer patients is the combination of irinotecan and cisplatin administered in low dose on a weekly schedule. 342 In vitro studies have demonstrated sequence-dependent synergy for cisplatin followed by irinotecan, which prevents removal of cisplatin-induced DNA-interstrand cross-links. Two trials have yielded encouraging results with a regimen of cisplatin (30 mg/m²) followed by irinotecan (65 mg/m²) administered weekly for 4 weeks, repeated every 6 weeks. 336,339 Ilson and associates 339 observed a 57% response rate in 35 patients [12 of 23 (52% response) in adenocarcinoma patients and 8 of 12 (66% response) in patients with squamous cell cancers]; median duration of response was 4.2 months. 339 Dysphagia and global quality of life were improved in the majority of patients. Ajani and associates 336 observed a 51% response rate using the same regimen in 25 adenocarcinoma patients, but recommended reduction of the irinotecan dose to 50 mg/m² in previously treated patients. Toxicity in both studies consisted of myelosuppression and diarrhea in a minority of patients. Diarrhea was ameliorated with prophylactic use of antiarrheal agents, dose reduction, or both.

In summary, more recent trials of combination regimens that include paclitaxel or irinotecan appear to have higher response rates than previous regimens; however, duration of response remains brief for esophageal cancer patients, and some trials have been reported only in preliminary abstract form and consist of small numbers of evaluable patients. In addition, the toxicities associated with many of these phase II single-institution experiences have been excessive.

Further follow-up of early reports and additional patient trials using the most promising regimens are needed. Based on the available data, the standard regimen of cisplatin and infusional 5-FU remains the recommended first-line treatment for patients with recurrent or metastatic disease of either histology. No specific paclitaxel-based regimen has yet emerged as more efficacious and less toxic than cisplatin/5-FU; however, alternative dosing schedules are currently under investigation.

Preoperative Chemotherapy

Nearly three-fourths of patients in the West present with locally advanced (stages IIb and III) disease, and the poor survival rates achieved with surgery alone have provided the impetus for the evaluation of preoperative chemotherapy in resectable esophageal cancer patients.

The potential benefits of induction chemotherapy include downstaging the disease to facilitate surgical resection, improvement in local control, and eradication of micrometastatic disease. Esophagectomy following induction therapy enables comprehensive pathologic assessment of treatment response, which may be important in selecting patients for postoperative adjuvant therapy. The disadvantages of preoperative chemotherapy include the potential selection of drug-resistant clones and micrometastatic disease. Esophagectomy following induction therapy enables comprehensive pathologic assessment of treatment response, which may be important in selecting patients for postoperative adjuvant therapy. The disadvantages of preoperative chemotherapy include the potential selection of drug-resistant clones and micrometastatic disease.

Trials evaluating chemotherapy followed by surgery in esophageal cancer patients have been underway since the late 1970s. Stimulated by the promising results of cisplatin-based induction chemotherapy trials in patients with locally advanced oropharyngeal cancers, phase II trials using similar regimens were conducted in esophageal cancer patients in parallel with studies evaluating concurrent chemoradiation followed by surgery or chemoradiation as definitive therapy. Encouraging results with cisplatin and bleomycin, 343 with or without the addition of a vinca alkaloid 336, 337 or mitoguazone, 338 and later with cisplatin and 5-FU, 339,340,342–344 led to randomized trials initiated in the 1980s. For squamous histology, the response rate to cisplatin (100 mg/m² day 1) and 5-FU (1000 mg/m² for 96 or 120 hours) every 3 weeks ranged between 42% and 66%, with 0% to 10% pathologic complete response rates; curative resection rates ranged from 40% to 80%, and median survival rates ranged from 18 to 28 months. 339,340,341,342,343 In these trials, two or three cycles of chemotherapy were administered before resection. A barium esophagogram and CT scans were used to initially stage patients and to assess response to induction therapy.

Five randomized trials evaluating preoperative chemotherapy in esophageal cancer patients are summarized in Table 33.2-9. 344–346,348,349,350 Four of the trials enrolled only patients with squamous cell carcinoma. 344–346,348 The Scandinavian trial reported by Nygaard et al. 344 involved randomization to one of four treatment arms: surgery alone, radiotherapy followed by surgery, two courses of induction cisplatin and bleomycin followed by surgery, and all three modalities in sequence. No improvement in survival was noted in patients in the two treatment arms that included chemotherapy in this study.

**TABLE 33.2-9.** Randomized Trials of Preoperative Chemotherapy

In a study performed at the National Cancer Institute, Roth et al. 344 compared the combination of cisplatin, bleomycin, and vindesine for three courses followed by surgery, with surgery alone in 39 esophageal cancer patients. Six months of postoperative adjuvant cisplatin and vindesine were planned for patients in the
prooperative chemotheraphy arm. A 47% major response rate including one pathologic complete response was documented using barium esophagogram and CT scans. Resectability rates were similar in the two groups, but a higher percentage of patients in the prooperative chemotheraphy group had negative margins. Responders to chemotheraphy had significantly longer survival than nonresponders (median, 20 vs. 6.2 months; \( P = .008 \)). However, 3-year survival rates in the two treatment groups were not significantly different. All recurrences included distant metastases; the local recurrenc rate was low (6.9%). Weight loss of greater than 10% was associated with poor survival in a multivariate analysis of potential prognostic variables.

A multicenter trial from Germany reported by Schlag et al. compared prooperative cisplatin and 5-FU (three cycles) and surgery with surgery alone. The trial was stopped early after only 46 patients were enrolled because of a substantial increase in operative morbidity and mortality in the chemotheraphy group. Response to chemotheraphy was documented with serial CT scans, barium esophagogram, and endoscopy before treatment and before surgery. A 41% major response rate was observed, including pathologic complete response in two patients. There was no difference in median survival in the overall comparison; however, responders to prooperative chemotheraphy survived longer than nonresponders (13 vs. 5 months).

The small numbers of patients enrolled in these three trials and the lack of prospective randomized controlled data in patients with adencarcinoma of the esophagus led the U.S. Gastrointestinal Intergroup to mount a multicenter trial. Trial 0113 registered 467 patients with resectable disease to receive either three cycles of cisplatin and 5-FU followed by surgery and then two cycles of the same chemotheraphy as adjuvant treatment for those who had a curative resection, or immediate surgery in contrast to other trials, barium esophagogram was the only test required to assess clinical response to prooperative chemotheraphy. Thus, it is not surprising that only a 19% response rate was reported. Survival and patterns of failure were the major study end points. No differences were observed between the surgery control arm and the prooperative chemotheraphy 5-FU arm in terms of curative resection rate (59% vs. 62%), treatment mortality (6% vs. 7%), overall median survival (16.1 vs. 14.9 months), or 5-year survival (26% vs. 23%). Furthermore, the median survival of patients who had a curative resection was the same in both treatment groups (27.4 vs. 28.0 months). The patterns of failure were also similar between the two groups (local recurrence 31% vs. 32%, and distant recurrence 50% vs. 41% in the surgery alone versus chemosurgery arms, respectively). Tumor histology did not influence response to treatment. As reported in the Roth trial, pretreatment weight loss was a significant predictor of poor outcome in this study.

The failure of the large, well-controlled Intergroup 0113 trial to show benefit from the addition of cisplatin and 5-FU to surgery suggests either that this strategy does not work as had been theorized or that the induction chemotheraphy agents and surgical techniques have not been optimized. Hence, the efficacy of any prooperative chemotheraphy regimen in the treatment of resectable esophageal cancer patients remains unresolved; as such, induction chemotheraphy should not be routinely considered for these individuals unless administered in the context of well-designed, prospective, randomized clinical trials.

Kok and associates reported preliminary results of a trial involving patients with squamous cell cancers. This study, which represents the only positive randomized trial in the literature, differed from the other trials reviewed previously in that patients in the prooperative chemotheraphy arm were evaluated for response after two courses; nonresponders went on to surgery, whereas responding patients received three more courses of chemotheraphy before surgery. The regimen consisted of cisplatin (80 mg/m\(^2\) day 1) and etoposide (100 mg/m\(^2\) intravenously on days 1 to 2 and 200 mg/m\(^2\) orally on days 3 to 5). At a median follow-up for surviving patients of 15 months, the median survival of prooperative chemotheraphy patients was significantly longer than those randomized to immediate surgery (18.5 vs. 11.0 months; \( P = .002 \)). These data raise the question of possible benefit from more intensive therapy than delivered in other trials and also demonstrate the potential relevance of identifying patients with chemosensitive tumors. A final report with further follow-up is awaited.

In conclusion, although a survival advantage has been demonstrated for definitive chemoradiation compared with radiotherapy alone, four of five randomized trials of chemotheraphy followed by surgery versus surgery alone have shown no benefit from this sequence of treatments. As such, more recent trials have focused on the evaluation of prooperative concurrent chemotheraphy regimens that may have a greater likelihood of achieving histologic complete response and improving long-term survival in esophageal cancer patients.

**Postoperative Adjuvant Chemotheraphy**

Widespread dissemination of disease is the primary cause of death in esophageal cancer patients. As such, considerable efforts are underway to identify novel chemotheraphy agents and to intensify exposure to agents with documented activity in this disease. Administering chemotheraphy after surgery to patients who have already received chemotheraphy or chemoradiation preoperatively has not been easily achieved in phase II and phase III trials. Only 36% of patients who were candidates for adjuvant cisplatin and 5-FU in Intergroup trial 0113 received the two planned courses.

Adjuvant chemotheraphy in patients who have had surgery alone as their primary curative treatment is more feasible from the standpoint of patient tolerance, but it remains unclear whether current agents confer a survival advantage. The Japanese Oncology Group has studied this question in three separate randomized trials. One study compared prooperative radiotherapy (50 Gy) to prooperative adjuvant chemotheraphy (two courses of cisplatin and vindesine) in 258 patients following curative resection. No differences were observed in survival (44% vs. 42% at 5 years), time to recurrence, or site of recurrence. Because these results could be interpreted as showing an equivalent beneficial effect from adjuvant chemotheraphy and adjuvant radiotherapy, a second trial of surgery alone compared with surgery followed by two courses of adjuvant cisplatin and vindesine was conducted. A total of 205 resected patients were randomized after surgery; 98 patients were assigned to surgery alone, 58 patients to surgery followed by two courses of adjuvant chemotheraphy, and 49 patients to surgery followed by three courses of chemotherapy. Resectability rates were similar in the two groups, but a higher percentage of patients in the preoperative chemotherapy arm. A 47% major response rate including one pathologic complete response was documented using barium esophagogram and CT scans. Tumor histology did not influence response to treatment. As reported in the Roth trial, pretreatment weight loss was a significant predictor of poor outcome in this study.

More recently, these investigators have reported preliminary results of a third trial. The study design was the same as that previously described, except that the chemotheraphy was changed to cisplatin and 5-FU for two courses after curative resection. A total of 242 patients were randomized with stratification for N0 status. At a median follow-up of 40.4 months, the estimated 5-year disease-free survival rate was 46% for the control group and 58% for chemotherapy patients (\( P = .05 \)); survival rates were 77% versus 82% in node-negative patients (\( P = .3 \)), and 35% versus 53% in node-positive patients (\( P = .06 \)) in the control and adjuvant arms, respectively. Overall survival rates were 51% for controls and 61% for chemotherapy patients (\( P = .3 \)). These data suggest that adjuvant chemotheraphy may decrease the high recurrence rate in this neutrophilic cancer, but it is unlikely that these results have a major effect on micrometastatic disease; thus, it is not surprising that more significant differences in survival did not emerge from this trial. However, the improvement in disease-free survival that approached statistical significance is intriguing, and further evaluation of adjuvant chemotheraphy in both histologic types of esophageal cancer should be performed.

The Eastern Cooperative Oncology Group is currently conducting a phase II trial (EB296) evaluating adjuvant cisplatin and paclitaxel for four courses in patients with resected, node-positive adencarcinomas of the esophagus, gastrolesophageal junction, and cardia. A comparison with matched controls from a contemporary surgical series is planned.

The role of prooperative adjuvant chemotheraphy or chemoradiation is currently undefined. There are no clear data indicating that administration of prooperative chemotheraphy will prolong survival, particularly for patients who have undergone a curative resection and have negative nodes. However, patients who have positive margins of resection should be considered for postoperative chemoradiation. Those who have had R0 resections but have nodal metastases (stages IIIB and III) should be enrolled in clinical trials evaluating adjuvant treatments.

**RADIATION THERAPY**

Considerable controversy exists as to the ideal therapeutic approach for esophageal cancer. This controversy is not limited to squamous cell cancers, where the Patterns of Care study examined 61 academic and nonacademic radiation oncology practices to determine practice patterns in the United States from 1992 to 1994. During that time period, treatment approaches varied considerably. Among combined modality therapy in 44%, radiation alone in 20%, prooperative combined modality therapy in 13%, postoperative combined modality therapy in 8%, postoperative radiation in 4%, and preoperative radiation in 1%. Various oncology groups have published treatment guidelines, none of which have a clear consensus at present. In fact, there is still no consensus at present.

Because the effect of histology has not been adequately assessed, it is reasonable to treat both squamous cell cancers and adencarcinomas in a similar manner.

**Primary Therapy**

Primary therapy of esophageal cancer is either surgical or nonsurgical. Although the overall results of these approaches are similar, the patient populations selected for treatment with each modality are usually different, resulting in a potential selection bias against nonsurgical therapy. Patients with poor prognostic features, including those with comorbid conditions, or unresectable or metastatic disease, are more commonly selected for treatment with nonsurgical therapy. Furthermore,
surgical series report results based on pathologically staged patients, whereas nonsurgical series express results pertaining to clinically staged individuals. Pathologic staging has the advantage of excluding some patients with metastatic disease. In addition, because some nonsurgical patients are treated with palliative rather than curative intent, the intensity of chemotherapy and the doses and techniques of radiation therapy may be suboptimal.

**Nonsurgical Therapy**

**RADIATION THERAPY ALONE.** Many series have reported results of external-beam radiation therapy alone; most include patients with unfavorable features such as clinical T4 disease and positive lymph nodes (Table 33.2-10). For example, in the series by De-Ren, 184 of the 676 patients had stage IV disease. Overall, the 5-year survival rate for patients treated with conventional doses of radiation therapy alone is 0% to 10%.

The use of radiation therapy as a potentially curative modality requires doses of at least 50 Gy at 1.8 to 2.0 Gy per fraction. Furthermore, given the large size of many unresectable esophageal cancers, doses of 60 Gy or greater are probably required. Shi and colleagues reported a 33% 5-year survival rate with the use of late-course accelerated fractionation to a total dose of 68.4 Gy. However, in the radiation therapy alone arm of the Radiation Therapy Oncology Group (RTOG) 85-01 trial in which patients received 64 Gy at 2 Gy/d with modern techniques, all patients were dead of disease within 3 years.

**Combined Modality Therapy**

**CONVENTIONAL APPROACHES.** A number of single-arm, nonrandomized trials have been conducted to evaluate the efficacy of combined modality therapy alone in esophageal cancer patients. The series reported by Coia and associates is the only one in which patients with early-stage malignancies (clinical stages I and II) were analyzed separately from those with more advanced disease. Patients received 5-FU and mitomycin C concurrently with 60 Gy. The local failure rate was 25%, the 5-year actuarial local relapse-free survival was 70%, and the 5-year actuarial survival was 30% in early-stage patients.

The Southwest Oncology Group 9060 trial reported by Poplin et al. included 32 patients who received 5-FU and cisplatin concurrently with 50 Gy, followed by two cycles of 5-FU and cisplatin. Since the choice of further management (observation, radiation, chemotherapy, and surgery) was based on the tumor response, this study cannot be considered a pure combined modality therapy trial. Although the median survival was 20 months, the authors concluded that the complexity and toxicity of this treatment regimen precluded its further use.

Six randomized trials have been performed comparing radiation therapy alone with combined modality therapy (Table 33.2-11). Five of the six trials used suboptimal doses of radiation, and three used inadequate doses of systemic chemotherapy. For example, in the series from Araujo and colleagues, patients received only one cycle of 5-FU, mitomycin C, and bleomycin. The EORTC trial used subcutaneous methotrexate. In the Scandinavian trial reported by Nygaard and associates, patients received low doses of chemotherapy (cisplatin, 20 mg/m², and bleomycin, 10 mg/m², for a maximum of two cycles).

**TABLE 33.2-10. Selected Series of Radiation Therapy Alone for Esophageal Cancer**

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Stage</th>
<th>Dose (Gy)</th>
<th>Concurrent Chemotherapy</th>
<th>Survival Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>De-Ren</td>
<td>184</td>
<td>IV</td>
<td>67.4</td>
<td>5-FU</td>
<td>33%</td>
</tr>
<tr>
<td>Coia</td>
<td></td>
<td></td>
<td>60</td>
<td>5-FU and mitomycin C</td>
<td>70%</td>
</tr>
<tr>
<td>Poplin</td>
<td>32</td>
<td></td>
<td>50</td>
<td>5-FU and cisplatin</td>
<td>20%</td>
</tr>
<tr>
<td>Araujo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nygaard</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**TABLE 33.2-11. Randomized Trials of Radiation Therapy versus Combined Modality Therapy for Esophageal Cancer**

In the Eastern Cooperative Oncology Group Esophageal Cancer Trial-1282 trial, patients who received combined modality treatment had a significantly increased median survival compared with those receiving radiation alone (15 vs. 9 months; \( P = .04 \)), but had no improvement in 5-year survival (9% vs. 7%). However, this was not a pure nonsurgical trial since approximately 50% of patients in each arm underwent resection after 40 Gy. Furthermore, the decision to proceed with surgery was left to the discretion of the individual investigator. The operative mortality was 17%. Lastly, the Pretoria trial reported by Slabber et al. was limited to a total of 70 patients with T3 squamous cell cancers and used a low-dose (40 Gy) split-course radiation schedule.

The only trial that was designed to deliver adequate doses of systemic chemotherapy with concurrent radiation therapy was the RTOG 85-01 trial reported by Henskovic et al. This Intergroup trial primarily included patients with squamous cell carcinoma. Patients received four cycles of 5-FU (1000 mg/m²/24 hours × 4 days) and cisplatin (75 mg/m² on day 1). Radiation therapy (50 Gy at 2 Gy/d) was given concurrently with day 1 of chemotherapy. Curiously, cycles 3 and 4 of chemotherapy were delivered every 3 weeks (weeks 8 and 11) rather than every 4 weeks (weeks 9 and 13). This intensification may explain, in part, why only 50% of the patients finished all four cycles of the chemotherapy. The control arm was radiation therapy alone, at a higher dose (64 Gy) than that delivered in the combined modality treatment arm.
The phase II Intergroup trial 0122 (Eastern Cooperative Oncology Group PE289/RTOG 90-12) was designed to evaluate the addition of induction chemotherapy to combined modality therapy for esophageal cancer. Another approach to dose intensification of combined modality therapy is to increase the radiation dose above 60 Gy. This can be achieved through the use of brachytherapy, which allows the escalation of the dose to the primary tumor while protecting the surrounding dose-limiting structures such as the lung, heart, and spinal cord. Brachytherapy involves the use of a radioactive source that is placed intraluminally via endoscope or a nasogastric tube. Brachytherapy has been used both as primary therapy (usually as a limited dose treatment) and as an adjuvant therapy in combination with external-beam radiation.

In summary, neoadjuvant chemotherapy, as delivered in the previously mentioned trials, does not appear to improve the results of combined modality therapy. New approaches, such as intensification of combined modality therapy, including escalation of the radiation dose, have been pursued in an attempt to improve these results.

**INTENSIFICATION OF COMBINED MODALITY THERAPY.** The phase II Intergroup trial 0122 (Eastern Cooperative Oncology Group PE289/RTOG 90-12) was designed to intensify the RTOG 85-01 combined modality arm. The development of the neoadjuvant chemotherapy approach used in Intergroup 0122 was based, in part, on the results of a randomized trial of preoperative radiation therapy (55 Gy) versus no preoperative chemotherapy (5-FU, cisplatin, vindesine) from Memorial Sloan-Kettering Cancer Center. This trial revealed that the resectability (65% vs. 58%), objective response (64% vs. 55%), and local failure (15% vs. 6%) rates with either preoperative radiation therapy or preoperative chemotherapy were similar. Both the chemotherapy and radiation therapy in Intergroup 0122 were intensified as follows: (1) the 5-FU continuous infusion (1000 mg/m²/24 hours) was increased from 4 days to 5 days; (2) the total number of cycles of chemotherapy was increased from four to five cycles; (3) three cycles of full-dose neoadjuvant 5-FU and cisplatin were delivered before the start of combined modality therapy; and (4) the radiation dose was increased from 50.0 to 64.8 Gy.

The final results of the Intergroup trial 0122 have been reported. For the 38 eligible patients, the primary tumor response rates were 47% complete and 8% partial; 3% had stable disease. The first site of clinical failure was local in 39% of patients and distant in 24% of individuals. For the total patient group, there were six deaths during treatment of which 9% (4 of 45) were treatment related. The median survival was 20 months and the 5-year actuarial survival was 20%. Therefore, this intensive neoadjuvant approach did not appear to offer a benefit compared with conventional doses and techniques of combined modality therapy. However, the higher radiation dose (64.8 Gy) was tolerable and is being further tested in Intergroup trial 0123, which is the replacement trial for RTOG 85-01 (Fig. 33.2-6).

A limited number of phase II trials have tested the use of induction chemotherapy before radiation therapy or combined modality therapy. Valerdi et al. reported the results of 40 patients with clinical stage II and III squamous cell cancers who received two cycles of neoadjuvant cisplatin, vindesine, and bleomycin (days 1 and 29) followed by 60 Gy. In contrast with Intergroup 0122, no chemotherapy was delivered with the radiation therapy. The pathologic complete response rate was 53%. With a median follow-up of 78 months, the local failure rate was 62%, median survival was 11 months, and the 5-year actuarial survival was 15%. These results are similar to those obtained with the RTOG 85-01 combined modality arm, with the exception of the higher treatment-related death rate of 5%.

Using a five-drug neoadjuvant regimen, Roca and colleagues treated 55 patients (54 with squamous cell) with bolus cisplatin, 5-FU, leucovorin, bleomycin, and mitomycin C for 15 days followed by 60 Gy plus concurrent 5-FU, leucovorin, and cisplatin. No maintenance chemotherapy was delivered. All anatomic sites within the esophagus were acceptable, and 53% of patients had clinical stage III disease. Although the treatment-related mortality was only 4% and the 3-year survival was 35%, the local failure rate was 42%, which was similar to the 45% reported in the RTOG 85-01 combined modality therapy arm.

In summary, neoadjuvant chemotherapy, as delivered in the previously mentioned trials, does not appear to improve the results of combined modality therapy. New trials using paclitaxel (Taxol)-based induction chemotherapy are in progress.

**INTENSIFICATION OF THE RADIATION DOSE.** Another approach to dose intensification of combined modality therapy involves increasing the radiation dose above 60 Gy. There are two methods by which to increase the radiation dose to the esophagus: brachytherapy and external-beam radiation.

**Brachytherapy.** Intraluminal brachytherapy allows the escalation of the dose to the primary tumor while protecting the surrounding dose-limiting structures such as the lung, heart, and spinal cord. A radioactive source is placed intraluminally via endoscope or a nasogastric tube. Brachytherapy has been used both as primary therapy (usually as a substitute for surgery) and as an adjuvant therapy in combination with external-beam radiation.
In addition to increasing the total dose, radiation can be intensified by accelerated fractionation or hyperfractionation. Selected series using these approaches have revealed that it was unlikely that the high-dose arm would achieve a superior survival compared with the standard-dose arm.

4 of chemotherapy every 4 weeks rather than every 3 weeks. The Intergroup 0123 opened in late 1994 and was closed to accrual in 1999 when an interim analysis showed a 50 Gy; (3) not beginning cycle 3 of 5-FU and cisplatin until 4 weeks following the completion of radiation therapy rather than 3 weeks; and (4) delivering cycles 3 and 4 of chemotherapy as well as boost following external-beam radiation therapy or combined modality therapy. It can be delivered by high dose-rate or low dose-rate. Although there are technical and radiobiologic differences between the two dose rates, there are no clear therapeutic advantages.

As a single therapy, brachytherapy is used as a palliative modality and results in a local control rate of 25% to 35% and a median survival of approximately 5 months. There were no significant differences in local control or survival with high dose-rate brachytherapy compared with external-beam radiation. Jager et al. treated 88 patients with 15 Gy, and 67% had improvement of dysphagia at 4 to 6 weeks and 47% had complete restoration of swallowing.

A major limitation of brachytherapy is the effective treatment distance. The primary isotope is $^{192}$Ir, which is usually prescribed to treat to a distance of 1 cm from the source. Therefore, any portion of the tumor that is greater than 1 cm from the source receives a suboptimal radiation dose. This limitation has been confirmed by pathologic analysis of treated specimens.

More encouraging results have been reported from series combining brachytherapy with external-beam or combined modality therapy; however, it is not clear if this advantage is due to the therapy or a selection bias in favor of patients treated in the curative setting as opposed to those treated for palliation only. In a phase II trial reported by Calais et al., a total of 53 patients with clinically unresectable adenocarcinoma or squamous cell carcinoma of the esophagus received 60 Gy plus three cycles of concurrent 5-FU, cisplatin, and mitomycin C followed by high-dose-rate intraluminal brachytherapy (5 Gy/week × 2). With a median follow-up of 39 months, the 3-year and 5-year actuarial survivals were 27% and 18%, respectively. Severe late toxicity occurred in 11%. One patient died of treatment-related toxicity. Two patients (4%) developed a fistula; however, both were due to tumor progression. Swallowing function was reported as good in 76%. The local failure rate was 43% (23 of 53).

Other trials of brachytherapy following external-beam radiation or combined modality therapy have reported less favorable results. Schraube and associates treated 54 patients with 60-Gy external-beam radiation followed by a 14-Gy brachytherapy boost, observing a median survival of 8 months and a 2-year overall survival of 10%. Major toxicity was seen in 15%. Using a similar treatment regimen in 35 patients with squamous cell carcinomas, Akagi et al. reported a 26% local failure rate, a 5-year survival of 35%, and a 26% incidence of late complications. Moni et al. reported a 62% local failure rate and 2-year survival of 27% in 21 patients with primary, nonmetastatic disease. However, for the total group of 47 patients there was a 36% grade III+ complication rate including a 17% incidence of fistula.

The trial by Yorozu et al. was limited to a more favorable subset of patients with clinical T1 to T2 disease. A total of 125 patients received 40- to 60-Gy external-beam radiation followed by a 8- to 24-Gy high dose-rate brachytherapy boost. With a median follow-up of 3.1 years, the 5-year survival was 26% and local failure was 44%. Esophageal ulcers were seen in 41% and were fatal in 6% of patients.

In the RTOG 92-07 trial, 75 patients with squamous cell cancers (92%) or adenocarcinomas (8%) of the thoracic esophagus received the RTOG 85-01 combined modality regimen (5-FU, cisplatin × 4 with concurrent 50 Gy) followed by a boost during cycle 3 of chemotherapy with either low dose-rate (19 patients) or high dose-rate (56 patients) intraluminal brachytherapy. The choice of the dose rate was at the discretion of the investigator. Due to low accrual, the low dose-rate option was discontinued and the analysis was limited to patients who received the high dose-rate treatment. High dose-rate brachytherapy was delivered in weekly fractions of 5 Gy during weeks 8, 9, and 10. Following the development of several fistulas, the fraction delivered at week 10 was discontinued. Although the complete response rate was 73%, with a median follow-up of only 11 months, local failure as the first site of failure occurred in 27% of patients. Acute toxicity included grade 3/4 toxicity in 36% of patients.

Other trials of brachytherapy following external-beam radiation or combined modality therapy have reported less favorable results. Schraube and associates treated 54 patients with 60-Gy external-beam radiation followed by a 14-Gy brachytherapy boost, observing a median survival of 8 months and a 2-year overall survival of 10%. Major toxicity was seen in 15%. Using a similar treatment regimen in 35 patients with squamous cell carcinomas, Akagi et al. reported a 26% local failure rate, a 5-year survival of 35%, and a 26% incidence of late complications. Moni et al. reported a 62% local failure rate and 2-year survival of 27% in 21 patients with primary, nonmetastatic disease. However, for the total group of 47 patients there was a 36% grade III+ complication rate including a 17% incidence of fistula.

In summary, in the palliative setting, intraluminal brachytherapy is an effective modality for decreasing symptoms such as dysphagia and bleeding. In patients treated in the curative setting, the addition of brachytherapy does not appear to improve results compared with radiation therapy or combined modality therapy alone. Therefore, the benefit of adding intraluminal brachytherapy to radiation or combined modality therapy remains unclear.

**External-Beam Therapy**

There are limited data examining the tolerance of external-beam doses of greater than or equal to 60 Gy when delivered concurrently with chemotherapy. In a separate toxicity analysis from Coia and associates, the results of 90 patients with clinical stages I to IV squamous and adenocarcinomas of the esophagus were reported; the incidence of grade III toxicity was 22%, and grade IV toxicity was 6%. There were no treatment-related deaths.

Calais et al. reported the results of 53 patients with clinically unresectable disease who received 5-FU, cisplatin, and mitomycin C plus 65 Gy. The full dose of radiation could be delivered in 96% of patients. The incidence of World Health Organization grade III+ toxicity was 30%, and the overall 2-year survival was 42%. It should be noted that the chemotherapy in this trial was not delivered at doses adequate to treat systemic disease.

On the encouraging side, almost all patients in both the Intergroup 0122 and the Calais trials (96% and 94%, respectively) who started radiation therapy were able to complete the full dose (64.8 to 65.0 Gy). Therefore, this higher dose of radiation was considered tolerable and was used in the experimental arm of the Intergroup esophageal trial 0123 (RTOG 94-05). Intergroup 0123 is the follow-up trial to RTOG 85-01. In this trial, patients with either squamous cell or adenocarcinomas who are selected for a nonsurgical approach are randomized to a slightly modified RTOG 85-01 combined modality regimen with 50.4 Gy versus the same chemotherapy with 64.8 Gy (see Fig. 33.2-6).

The modifications to the original RTOG 85-01 combined modality therapy arm include (1) using 1.8 Gy fractions to 50.4 Gy rather than 2 Gy fractions to 50 Gy; (2) treating with 5-cm proximal and distal margins for 50.4 Gy rather than treating the whole esophagus for the first 30 Gy followed by a cone-down with 5-cm margins to 50 Gy; (3) not beginning cycle 3 of 5-FU and cisplatin until 4 weeks following the completion of radiation therapy rather than 3 weeks; and (4) delivering cycles 3 and 4 of chemotherapy every 4 weeks rather than every 3 weeks. The Intergroup 0123 opened in late 1994 and was closed to accrual in 1999 when an interim analysis revealed that it was unlikely that the high-dose arm would achieve a superior survival compared with the standard-dose arm.

In addition to increasing the total dose, radiation can be intensified by accelerated fractionation or hyperfractionation. Selected series using these approaches are summarized in Table 33.2-12. Although these approaches are reasonable, most series report an increase in acute toxicity without any clear therapeutic benefit. These regimens remain investigational.

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**Table 33.2-12. Selected Series of High-Dose Accelerated Fractionation/Hyperfractionated Combined Modality Therapy**

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Dysphagia is a common problem in patients with esophageal cancer. Not only is it the most frequently presenting symptom, but it can remain a problem up to the time of the patient's death. Many of the series that have examined palliation are retrospective, and most do not use objective criteria to define and assess this symptom. Some have not reported the number of patients presenting with dysphagia or the percentage who were palliated until the time of death. Furthermore, few series have carefully examined other variables that may have influenced results such as histology, stage, and location of the primary tumor.

As seen in Table 33.2-13, a limited number of series have examined the palliative effects of radiation alone or combined modality therapy. Overall, external-beam radiation therapy alone palliates dysphagia in approximately 70% to 80% of patients.

### Table 33.2-13. Palliation of Dysphagia with External-Beam Radiation Therapy with or without Chemotherapy

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dysphagia Palliation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiation alone</td>
<td>70% to 80%</td>
</tr>
<tr>
<td>Radiation combined with chemotherapy</td>
<td>75% to 85%</td>
</tr>
<tr>
<td>External-beam radiation with or without chemotherapy</td>
<td>80% to 90%</td>
</tr>
</tbody>
</table>

The most comprehensive and carefully performed analysis of swallowing function in patients receiving combined modality therapy is from Coia et al. Using a swallowing score modified from O'Rourke et al., Coia et al. analyzed 102 patients treated with three 5-FU-based combined modality regimens. Before the start of therapy, patients had some degree of dysphagia. Within 2 weeks following the start of treatment, 45% had improvement in dysphagia and by the completion of the 6-week therapy, 83% had improvement. Overall, 88% had an improvement in dysphagia. The median time to maximum improvement was 4 weeks (range, 1 to 21 weeks), and all but two patients were able to swallow at least soft or solid foods at the time of maximum symptomatic improvement.

Variables such as treatment intent, histology, and tumor location were examined. All of the 25 patients treated with curative intent who survived more than 1 year were able to eat soft or solid foods following treatment. The benign stricture rate (defined as a stricture in the absence of recurrent disease) was 12%. Ninety-one percent of patients treated in the noncurative setting had an initial improvement in swallowing, and 67% were palliated until death. Histology and stage had no effect on the rate of palliation; however, patients with distal third lesions had significant improvement in dysphagia compared with individuals with upper or middle third tumors (95% vs. 79%; P < 0.05).

Intraluminal brachytherapy achieves palliation of dysphagia in 40% to 90% of patients. Because it is usually prescribed to 1 cm from the source, it may not sufficiently treat gross disease. There is a selection bias against brachytherapy since it is commonly used for patients who have either failed to respond to external-beam radiation or who are medically unfit to travel for daily outpatient treatment. Even accounting for these selection biases, given its limited effective range, brachytherapy has not proven to be as successful as external-beam radiation in treating the entire tumor volume.

In summary, external-beam radiation therapy, either alone or in combination with chemotherapy, palliates dysphagia in approximately 80% of patients, one-half of whom are palliated until death. If a patient requires rapid palliation (within a few days), alternative approaches such as laser or stent are recommended, since external-beam radiation with or without chemotherapy requires at least 2 weeks to obtain palliation. However, palliation achieved by external-beam therapy is more durable than that obtained by other palliative modalities since it treats the problem (the gross tumor mass), not just the symptom. If external-beam radiation is not possible, then brachytherapy should be considered.

### Acute and Long-Term Toxicity of Radiation Therapy

The toxicity of radiation therapy is a function of total dose and technique of administration, as well as chemotherapy exposure. There are limited toxicity data in patients who received conventional doses of radiation therapy. Essentially all patients experience lethargy and esophagitis commencing 2 to 3 weeks after the start of radiation; these symptoms begin to resolve 1 week after the completion of therapy.

The most carefully documented acute radiation-related toxicity data are from the control arm of RTOG 85-01 in which patients received radiation therapy alone to a dose of 64 Gy. The incidence of acute grade III toxicity was 25%, and grade IV toxicity was 3%; the incidence of long-term grade III+ toxicity was 23% and grade IV+ was 2%.

As with surgery, radiation therapy can produce esophageal strictures. The total incidence of stricture (benign plus malignant) in patients receiving radiation therapy alone or radiation combined with chemotherapy is 20% to 40% in modern studies, and up to 60% in historical series; nearly one-half of these strictures are malignant since they are associated with local recurrence. The incidence of stricture is lower in series in which careful radiation techniques were used. For example, Coia et al. noted that the incidence of benign stricture was 12% in a subset of 25 patients who were locally controlled and survived at least 1 year.

One series examined the functional results in patients who developed benign or malignant strictures. Eighty patients received 45 to 56 GY and 53% received some form of chemotherapy. Of the 24 patients (30%) who developed a benign stricture, 71% were able to tolerate a full or soft diet and required dilation with a median interval between dilations of 5 months. Therefore, even in the subset of patients who develop a benign stricture, dilation is effective in the majority of patients. In contrast, in the 28% of patients who developed a malignant stricture, dilation was unsuccessful and esophageal intubation was required.

The high incidence of fistulae reported in the RTOG 92-07 trial of combined modality therapy plus intraluminal brachytherapy (18% actuarial, 14% crude) has not been seen in series using radiation therapy or combined modality therapy without intraluminal brachytherapy. The incidence of other long-term grade III+ toxicities such as pneumonitis or pericarditis is 5%. If appropriate radiation doses and techniques are used, spinal cord myelitis should not occur.

### Treatment-Related Deaths

The issue of treatment-related deaths in patients receiving combined modality therapy is complex. Although the incidence was only 2% in RTOG 85-01, subsequent trials have reported a higher treatment-related mortality (i.e., 9% in Intergroup 0122 and 8% in RTOG 92-07). This mortality is lower than the 10% to 15% incidence reported in the historical surgical series, although only slightly higher than the 6% reported in the surgical control arm of Intergroup 0113. It is interesting to note that as the mortality with surgery has decreased, there has been a corresponding increase in the treatment-related mortality reported in the nonoperative trials. As previously discussed, this may be related, in part, to selection bias against patients treated with the nonoperative approach. Only a randomized trial of surgical versus nonsurgical therapy can address this issue.

### Comparison of Definitive chemoradiation and Surgery

Appropriate randomized trials comparing chemoradiation and surgery have not been performed. However, it is an important issue for the practicing oncologist and for...
the establishment of standards of care. The positive results of RTOG 85-01, demonstrating a 27% 5-year survival rate for patients treated with definitive chemoradiation compared with no survivors after treatment with radiotherapy alone, are a major advance. Without a doubt, this treatment option has influenced the selection of patients for surgical management because it provides an alternative for restoring swallowing function in patients with locally advanced disease for whom resection would likely be palliative.

For patients with earlier stage disease that appears resectable, definitive chemoradiotherapy may also be appropriate treatment; however, prospective trials comparing this approach with surgery, stratified for histology and stage have yet to be performed. Nonetheless, contemporary series suggest that the nonsurgical approach offers a survival rate that is the same or better than that achievable with surgery alone in most medical centers. For example, the median and 5-year survival rates in the surgical control arm of Intergroup 0113 trial were 16 months and 20%, respectively, and in the surgical control arm of the Dutch trial by Kok et al., the median survival rate was 11 months. The incidence of local recurrence (local failure plus local persistence of disease) as the first site of failure was 45% in RTOG 85-01 and 39% in Intergroup 0122. Although local recurrence as the first site of failure in Intergroup 0113 was 31%, this analysis was limited to patients who underwent a complete resection with negative margins (R0 resection). Since an additional 30% of patients had residual local disease, if one was to score these patients as having local persistent disease (as was done in the RTOG 85-01 analysis), the comparable local failure rate with surgery alone was 30% + 31% = 61%. The treatment-related mortality was also similar (2% in RTOG 85-01 and 6% in Intergroup 0113).

In summary, the local failure, survival, and treatment-related mortality of definitive chemoradiation as administered in RTOG 85-01 and those observed following surgery alone appear comparable. Despite these observations, it is clear that both approaches have limited success; as such trials combining all three modalities (surgery plus preoperative chemotheraphy and radiotherapy) have been initiated.

TREATMENT IN THE SETTING OF A TRACHEOESOPHAGEAL FISTULA

The presence of a malignant tracheoesophageal fistula is an unfavorable prognostic feature; however, occasionally patients may survive for a prolonged period of time. Historically, radiation therapy was believed to be contraindicated due to concerns of exacerbating the fistula as the tumor responded. There have been several reports that challenge these views. In a Mayo Clinic series, ten patients with malignant tracheoesophageal fistula received 30 to 66 Gy external-beam radiation, with a median survival of 5 months. None of these patients experienced an enlarged or more debilitating fistula following radiation. Arlington and Bohorquez described a patient who developed a fistula while receiving external-beam radiation to a total dose of 56.5 Gy, which healed 2 months following the completion of radiation.

Although the experience is limited, data suggest that radiation may not necessarily increase the severity of a malignant tracheoesophageal fistula, and it can be administered safely. Due to the poor prognosis of this group of patients, it is unclear if it improves outcome particularly in individuals who may also be palliated by stents.

ADJUVANT THERAPY

Adjuvant Radiation Therapy without Chemotherapy

The rationale of adjuvant radiation therapy is based on the patterns of failure following potentially curative surgery in patients with clinically resectable disease. Unfortunately, few surgical series report these data. The incidence of local failure in the surgical control arms from the preoperative radiation therapy randomized trials from Mei et al. and Gignoux et al. was 12% and 67%, respectively. The local failure rate in the surgical control arm from the postoperative radiation therapy randomized trial from Teniere et al. was 35% for patients with negative local regional lymph nodes and 38% for patients with positive local regional lymph nodes. The surgical control arm of Intergroup 0113 provides a modern, more relevant baseline for the results of surgery alone. As previously discussed there was a 31% local failure in patients with a R0 resection and a total local failure rate (including the additional 30% of patients with persistent disease) of 61%. Although the majority of patients with esophageal cancer succumb to distant metastases, the incidence of local failure following transthoracic or standard thoracoscopic resection is high enough to warrant the evaluation of adjuvant radiation therapy.

Preoperative Radiation Therapy

Six randomized trials of preoperative radiation therapy for patients with clinically resectable disease are summarized in Table 33.2-14. The series performed by Launois et al., Gignoux et al., and Nygaard et al. were limited to patients with squamous cell carcinoma. Patients with both squamous cell carcinoma and adenocarcinoma were included in the series by Arnot et al.; the histologies of the esophageal cancers treated in the series by Huang et al. and Mei et al. were not indicated.

| Table 33.2-14. Randomized Trials of Preoperative Radiation Therapy for Esophageal Cancer |

Overall, preoperative radiation therapy did not increase resectability, and only two series reported local failure rates. Although Mei and colleagues reported no difference in local failure, Gignoux et al. observed a significant decrease in local failure in patients who received preoperative radiation therapy compared with those treated by surgery alone (46% vs. 67%, respectively).

Two trials have reported an improvement in survival in patients receiving preoperative radiation therapy, although the significance of these observations is debatable. In a previously described four-arm randomized trial, Nygaard et al. observed that the 48 patients who received preoperative radiation therapy without chemotherapy had a 20% 3-year survival compared with 5% survival in control patients; however, this did not reach statistical significance. Huang et al. also reported improved survival in surgical patients treated with preoperative radiation therapy relative to surgical controls (46% vs. 25%, respectively); however, formal statistical analysis was not performed. Furthermore, metaanalysis from the Oesophageal Cancer Collaborative Group showed no clear evidence of a survival advantage for preoperative radiation therapy.

The aforementioned randomized preoperative radiation therapy trials used suboptimal designs. Conventional radiation therapy doses were not delivered, and some trials used split-course radiation. Furthermore, none of the trials allowed an adequate interval between completion of radiation therapy and surgery (in general, a 4- to 6-week interval is recommended). Consequently, radiation-related morbidity cannot be appropriately assessed in these trials. The only study that allows analysis of the effect of radiation techniques is a randomized trial from France involving patients with squamous cell carcinomas who received combined modality therapy using continuous or split-course radiation. The 95 patients who received continuous-course therapy had a significantly higher local control rate (57% vs. 29%), 2-year event-free survival rate (33% vs. 23%), and a borderline significant 2-year survival rate (37% vs. 23%) relative to patients treated with split-course radiation. Because it is less effective than continuous-course, split-course radiation is not recommended.
In summary, since only two of the six series have reported local failure rates, it is difficult to draw firm conclusions regarding the influence of preoperative radiation therapy on local control. Two series have reported an improvement in survival; one in which half of the patients also received chemotherapy, and in the other a statistical analysis was not performed. Four of the six series have reported no advantage in overall survival. Nonrandomized trials performed by Yadava et al. and Sugimachi and associates have also shown no survival benefit. Based on the available, albeit limited, randomized trials, preoperative radiation therapy does not appear to significantly enhance local control or improve survival in esophageal cancer patients.

**Postoperative Radiation Therapy**

Several nonrandomized reports of postoperative radiation therapy have suggested that postoperative radiation therapy may be beneficial in esophagectomized patients. Yamamoto and associates reported a 94% 2-year local control rate in node-negative patients. In patients who underwent a three-field dissection, Hosokawa and associates added intraoperative radiation followed by 45 Gy postoperatively; the 5-year survival was 34%. In patients who received the highest dose of intraoperative radiation (25 Gy), 22% developed fatal tracheal ulceration. No treatment-related deaths were seen with doses less than 20 Gy.

There have been only two randomized trials limited to patients treated in the adjuvant setting (Table 33.2-15). Teniere and colleagues reported the results of 221 patients with squamous cell carcinoma randomized to surgery alone versus surgery plus postoperative radiation therapy (45 to 55 Gy at 1.8 Gy per fraction). With a minimum follow-up of 3 years, postoperative radiation therapy had no significant effect on survival. In the series by Fok et al., patients with squamous cell or adenocarcinomas receiving either curative or palliative resections were evaluated; although the total dose of radiation therapy was conventional, the dose per fraction (3.5 Gy per fraction) was unconventional. No significant decrease in local failure, distant failure, or improvement in median survival was achieved by use of postoperative radiation therapy.

**TABLE 33.2-15. Randomized Trials of Postoperative Radiation Therapy for Esophageal Cancer**

For reasons that are unclear, postoperative radiation therapy has been recommended for patients with positive local regional lymph nodes. Although the data from Teniere et al. support the use of postoperative radiation therapy for decreasing local failure, the benefit was limited to patients with negative lymph nodes in whom postoperative radiation therapy decreased local failure from 35% to 10%. Postoperative radiation therapy had no significant effect in patients with positive nodes.

In summary, although limited data suggest that adjuvant postoperative radiation therapy may decrease local failure in node-negative patients, it appears to have no effect on overall survival. The only role for postoperative radiation therapy is for patients with positive margins. Based on the postoperative results from combined modality therapy trials such as RTOG 85-01, patients selected to receive postoperative radiation therapy should also be considered for systemic chemotherapy.

**Preoperative Combined Modality Therapy**

Given the limited success of single-modality treatment using radiation therapy or surgery for the primary management of esophageal cancer and the absence of survival improvement when radiotherapy is used in the adjuvant setting (preoperatively or postoperatively), efforts have focused on the use of systemic chemotherapy before surgery or in conjunction with preoperative radiation therapy. As previously discussed, the rationale to use chemotherapy before surgery includes the reduction of local and micrometastatic tumor deposits and downstaging the primary tumor by enhanced delivery of cytotoxic agents via intact microvasculature. Furthermore, many of the active agents in esophageal cancer (i.e., 5-FU, cisplatin, mitomycin C, paclitaxel) are known to enhance radiosensitization in cancer cells. Conceivably, chemotherapy in conjunction with radiotherapy may prevent dissemination of tumor cells during surgery, thus decreasing the rate of distant metastases in patients receiving potentially curative resections.

Combined modality therapy has been used both in the preoperative setting as well as in primary, nonsurgical management of unresectable lesions. In the preoperative trials, patients have had clinically resectable disease, whereas in the nonsurgical trials patients typically have had unresectable neoplasms or have been deemed inoperable on the basis of additional comorbid conditions. Some of the preoperative combined modality regimens have employed accelerated courses of radiation (either twice a day or large fraction sizes [greater than 2 Gy]) plus a short, but intensive course of systemic chemotherapy. Others have used more conventional fractionation (1.8 to 2.0 Gy/d) and moderate total doses of radiation (40 to 50 Gy). In contrast, the nonsurgical combined modality regimens have commonly used conventional fractionation and moderate to high doses of radiation (50.0 to 64.8 Gy) plus longer, but less intensive chemotherapy regimens. Some of these regimens have included neoadjuvant chemotherapy before starting the combined modality therapy. The differences in patient populations and study designs preclude meaningful comparisons of these trials.

**Nonrandomized Trials**

In general, the nonrandomized series of preoperative combined modality therapy have used two treatment strategies. Patients have either undergone a planned operation (Table 33.2-16), or for a variety of reasons, were selected for an operation (Table 33.2-17). The results of these two approaches must be analyzed separately since selection factors for surgery may have influenced outcomes. This discussion focuses on series that have been limited to patients with clinically resectable neoplasms, thus excluding those with metastatic disease. Most of the trials have used 5-FU and cisplatin-based chemotherapy, although several more recent trials have used Taxol- or docetaxel (Taxotere)-based regimens. Posner and colleagues added interferon to the regimen, and Nesbitt et al. administered neoadjuvant Taxol before the start of preoperative combined modality therapy.

**TABLE 33.2-16. Selected Nonrandomized Trials of Planned Preoperative Combined Modality Therapy for Esophageal Cancer**
The results of selected phase II series in which patients have undergone preoperative combined modality therapy followed by a planned operation are summarized in Table 33.2-18. Leichman and colleagues from Wayne State University reported the results of 21 patients with squamous cell carcinomas. Patients received 30 Gy and 2 cycles of concurrent 5-FU and cisplatin. Individuals with residual tumor at surgery received an additional 20 Gy postoperatively. Pathologic complete response rate was 37%, and the median survival was 18 months in the 19 patients who underwent an operation; a 27% operative mortality was observed. Forty-eight percent of patients required hyperalimentation during preoperative therapy. This pilot trial was expanded to a Southwest Oncology Group trial (8037) for patients with squamous cell carcinoma. Of 113 patients evaluated in this trial, only 71 underwent an operation. The pathologic complete response rate was 16%, and the operative mortality was 11%. Despite a 3-year actuarial survival rate of 16%, all patients were dead of disease within 4 years.

Since these initial reports, a variety of treatment approaches have been examined. In most studies, pathologic complete response rates were approximately 25%. Intensive combined modality regimens using hyperfractionated radiation have been evaluated by Urba et al. and Forastiere and colleagues from the University of Michigan, as well as Shahab and colleagues from Ellis Fischel Cancer Center, and Adelstein et al. Some of these regimens achieved higher pathologic complete response and survival rates, usually with corresponding increases in acute toxicity. For example, Rault et al. reported a 56% complete pathologic response rate and a 52% 3-year survival rate, but a 63% incidence of grade III+ acute toxicity. In the series by Adelstein et al., patients received preoperative accelerated fractionation (1.5 Gy twice a day to 45 Gy) plus 5-FU and cisplatin. The 27% complete response and 44% 3-year survival rates observed in this trial were comparable with those reported in other series using conventional fractionation; however, the 18% surgical mortality was higher.

In addition to the different treatment schedules, variable surgical techniques have been used in these trials. For instance, investigators from the University of Michigan performed transhiatal resections exclusively, whereas others preferentially did hierv-Lewis procedures. Transhiatal esophagectomy is thought to be a more conservative operation relative to the hierv-Lewis procedure, although as previously discussed, both operations appear to be inferior to en bloc esophagectomy in terms of achieving local control and improving survival in esophageal cancer patients.

More conventional doses of chemotherapy and radiation therapy techniques have been advocated by Stahl et al., Jones and colleagues, Forastiere et al., and Bates and associates. In addition, these investigators have sought to determine if preoperative endoscopy with biopsy can accurately assess response to treatment, and whether achievement of pathologic complete response following chemoradiation improves overall survival. Bates et al. reported a 65% 3-year survival rate in patients who achieved a pathologic complete response, compared with a 25% survival rate in those who did not. Forastiere and associates reported 2-year survival rates of 78% for pathologic complete responders compared with 46% for those having residual tumor in the resected esophagus (P = .008). In a previous trial with long-term follow-up, these investigators observed 5-year survival rates of 60% and 32% for pathologic complete responders and those with residual disease following induction therapy, respectively. These nonrandomized data suggest that with aggressive induction chemoradiation therapy, patients who are downstaged to pathologic-negative status may have a survival advantage. In addition, the fact that long-term survival was observed in 25% to 30% of patients with residual tumor in the resected specimen suggests that surgery was an important component of the multimodality regimens. Bates et al. noted a 41% false-negative rate with preoperative endoscopy and biopsy, indicating that this technique cannot reliably determine the need for further therapy. Furthermore, Jones and colleagues reported that CT scan had a sensitivity of 65%, specificity of 33%, a positive predictive value of 58%, and a negative predictive value of 41% in evaluating pathologic response following preoperative combined modality therapy in esophageal cancer patients. EUS may have similar limitations, although FDG PET may prove to be a useful noninvasive means to assess response to induction therapy. Thus, at present, no methods short of surgical resection accurately determine which patients have achieved pathologic complete response following induction chemoradiation therapy.

In some trials, patients have been selected for surgery based on their overall medical status and response to preoperative therapy (see Table 33.2-17). Gill and colleagues evaluated the role of surgery following combined modality therapy consisting of two cycles of 5-FU and cisplatin and radiation therapy. The study was biased in that only patients with more favorable prognoses were selected for surgery. Although the differences were not statistically significant, the local failure and distant failure rates were higher in the patients who underwent surgery compared with those who did not. Using a similar approach of limiting surgery to those patients who responded to preoperative therapy and delivering higher radiation doses to nonresponders, Kavanagh and associates reported that patients who underwent surgery had a lower local failure rate (24% vs. 44%); however, there were no differences in distant failure or median survival. The 1992 to 1994 Patterns of Care survey study reported a significant improvement in survival of patients selected to received preoperative combined modality therapy compared with combined modality therapy alone.

**Randomized Trials**

There have been three randomized trials comparing preoperative combined modality therapy with surgery alone in patients with clinically resectable disease (Table 33.2-18). The series from Le Prise et al. is not included since patients received sequential rather than concurrent chemotherapy plus radiation.

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**TABLE 33.2-17.** Selected Nonrandomized Series of Preoperative Combined Modality Therapy Plus Surgery for Esophageal Cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Patients</th>
<th>分期</th>
<th>Response</th>
<th>Survival</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leichman et al.</td>
<td>Phase II</td>
<td>21 patients</td>
<td>Squamous</td>
<td>37%</td>
<td>18 months</td>
<td>63%</td>
</tr>
<tr>
<td>Forastiere et al.</td>
<td>Randomized</td>
<td>100 patients</td>
<td>Adenocarcinoma</td>
<td>41%</td>
<td>2 years</td>
<td>78%</td>
</tr>
</tbody>
</table>

**TABLE 33.2-18.** Randomized Trials of Preoperative Combined Modality Therapy for Esophageal Cancer

Urba and associates from the University of Michigan randomized 100 patients (75% with adenocarcinoma) to preoperative cisplatin (20 mg/m² days 1 to 5 and 17 to 21), plus two cycles of concurrent 5-FU and cisplatin. Individuals with residual tumor at surgery received an additional 20 Gy postoperatively. Pathologic complete response rate was 37%, and the median survival was 18 months in the 19 living patients who underwent an operation; a 27% operative mortality was observed.
In a series from Dublin, Walsh et al. reported a significant survival benefit with preoperative combined modality therapy. In this trial, 113 patients with adenocarcinoma of the midesophagus or distal esophagus (including the cardio) were randomized to two cycles (weeks 1 and 6) of 5-FU (15 mg/kg/24 hours 1 to 5), cisplatin (75 mg/m² day 7), plus concurrent preoperative radiation therapy (2.67 cGy/d to 40 Gy) versus surgery alone. Resection was performed 8 weeks following the start of chemotherapy, and a variety of operations were allowed. Combined modality therapy was well tolerated. The incidence of acute grade III+ toxicity was 15%. The operative mortality was 9% in the multimodality treatment arm compared with 4% in surgery control arm. With a median follow-up in surviving patients of 18 months, a significant improvement in both median survival (16 vs. 11 months; \( P = .01 \)) and 3-year survival (32% vs. 6%; \( P = .01 \)) was observed in patients receiving preoperative therapy compared with those treated with surgery alone. A major criticism of this trial is the high operative mortality (9%) and the low 3-year survival rate (6%) in the surgical control arm. In the Intergroup 0113 (RTOG 89-11) trial the operative mortality and 3-year survival rates were 6% and 25%, respectively, in the surgical control arm.

The third randomized trial of preoperative combined modality therapy was reported by Bosset et al. from the EORTC. A total of 282 patients with clinically resectable (stages I and II) squamous cell carcinomas were randomized to preoperative combined modality therapy versus surgery alone. The preoperative regimen included 3.7 Gy × 5 followed by a 2-week rest and another 3.7 Gy × 5. Chemotherapy was limited to cisplatin, 80 mg/m², 0 to 2 days before starting radiation therapy. With a median follow-up of 66 months, patients who received preoperative combined modality therapy had a significantly greater 3-year disease-free survival (40% vs. 28%) and local disease-free survival (relative risk, 0.6), yet had no improvement in median survival (19 months) or overall 3-year survival (36%) compared with patients treated with surgery alone. However, this combined modality therapy regimen was unconventional in design; not only was the radiation split course and delivered with unusually high doses per fraction, but the doses of chemotherapy were not adequate for systemic therapy.

Although two of the three randomized trials demonstrated a survival advantage, they are limited by small numbers of patients and short follow-up, hence their results should be interpreted with caution. To help clarify this controversy, the Intergroup has developed a randomized trial of preoperative combined modality therapy (Cancer and Leukemia Group B C9781), which is the follow-up trial to Intergroup 0113. The preoperative regimen is based on the combined modality arm from RTOG 85-01 and uses conventional 5-FU, cisplatin, and 50.4 Gy; the control arm is surgery alone since preoperative chemotherapy was not beneficial in Intergroup 0113.

Paclitaxel-based regimens have activity in patients with advanced esophageal cancer, and preoperative combined modality regimens using paclitaxel have achieved encouraging results. However, an increase in acute radiation esophagitis has been seen in initial reports. Safran et al. reported a 9% incidence of radiation esophagitis in patients receiving 3-hour paclitaxel infusion. More protracted infusions appear to be better tolerated; in an ongoing phase I dose escalation trial using 96-hour paclitaxel infusion plus cisplatin and 5040 cGy (reported in abstract form by Kelsen and associates), no patients experienced grade III+ esophagitis at the 80 mg/m² dose level of paclitaxel. As with combined modality regimens in other gastrointestinal cancers, development of ideal regimens and schedules remains an active area of clinical investigation.

In summary, the efficacy of preoperative combined modality treatment for resectable esophageal cancer patients remains unclear. Although an apparent benefit has been seen in phase II trials that have used intensive regimens, significant toxicities have been observed. Whereas two of the three randomized trials revealed a survival advantage for combined modality treatment, in the study by Urba et al. this advantage reached significance only by multivariate analysis, and the trial by Walsh et al. had an unusually low survival rate in the surgical control arm. Both trials had relatively small numbers of patients and limited follow-up. Further maturation of these randomized trials, together with results of the Intergroup Trial Cancer and Leukemia Group B C9781, may allow more definitive conclusions regarding the role of preoperative combined modality therapy. In the interim, preoperative combined modality therapy remains an investigational approach, results of which should be compared with the best results achievable by surgery alone in patients who have been optimally staged.

Due to selection bias, it is difficult to determine what is the best treatment for esophageal cancer. The standard of care is either surgery alone or primary combined modality therapy. The results of these two approaches appear similar, although no direct comparative trials have been performed.

**Radiation Field Design and Treatment Techniques**

Similar to the expert surgical skills required for a successful esophagectomy, radiation field design for esophageal cancer requires careful techniques. There are a number of sensitive organs that, depending on the location of the primary tumor, will be in the radiation field. These include but are not limited to skin, spinal cord, lung, heart, intestine, stomach, kidney, and liver. Minimizing radiation to these structures while delivering an adequate dose to the primary tumor and local regional lymph nodes requires patient immobilization and CT-based treatment planning for organ identification, lung correction, and development of dose-volume histograms.

Although CT can identify adjacent organs and structures, it may be limited in defining the extent of the primary tumor. To assess the consistency of target-volume delineation, Tai and colleagues sent sample cases with CT scans to 48 radiation oncologists throughout Canada and asked them to fill out questionnaires regarding treatment techniques as well as outline the boost target volumes. There was substantial inconsistency in defining the planning target volume, both in the transverse and longitudinal dimensions. Therefore, in addition to a CT scan, barium swallow should be obtained at the time of radiation therapy simulation. The integration of other imaging modalities in radiation treatment planning such as esophageal ultrasound, PET scan, and magnetic resonance imaging are under active investigation.

At present, the standard radiation dose for patients selected for curative nonoperative combined modality therapy approach is 50.4 Gy at 1.8 Gy per fraction. The radiation field should include the primary tumor with 5-cm superior and inferior margins and 2-cm lateral margins. The primary local regional lymph nodes should receive the same dose. For cervical (proximal) primary tumors (defined as at or proximal to the carina), the treatment volume includes the bilateral supraclavicular nodes, and for distal gastroesophageal primaries the celiac axis nodes should be included. An example of a four-field technique for a distal esophageal cancer is seen in Figure 33.2-7.

**FIGURE 33.2-7.** An example of a four-field technique for the treatment of a distal esophageal cancer.

For cervical primaries, patients are placed supine. Various field designs are possible and their choice depends on the geometry of the primary tumor in relation to the spinal cord. The spinal cord dose should be limited to 45 Gy. Field designs include a three-field technique (two anterior obliques and a posterior) or more commonly anteroposterior and posteroanterior to 39.6 to 41.4 cGy, followed by a left or right opposed oblique pair with photons plus an electron boost to the contralateral supraclavicular area, both to a total dose of 50.4 Gy. For midesophageal primary tumors patients are placed prone to help exclude the spinal cord from the radiation field and receive four fields (anteroposterior and posteroanterior and opposed laterals). For distal primaries patients are treated supine using the same four-field technique. Care should be taken to exclude as much of the normal stomach as possible, especially if the patient is receiving radiation therapy preoperatively.

CT-based three-dimensional treatment planning should be performed and all fields treated each day. Dose-volume histograms help guide the radiation oncologist in choosing the radiation plan that minimizes the loss of normal organ function.

A variety of radiation treatment regimens may be used in the palliative setting. Since the goal is rapid amelioration of symptoms, the most common approach is to treat...
Tumor Markers and Predictors of Response to Combined Modality Therapy

It would be helpful to predict tumors that have a higher likelihood of responding to radiation or combined modality therapy. In 38 patients with squamous cell carcinoma who received combined modality therapy with or without surgery, Sarbia et al. observed that tumors without p53 expression and those with weak Bcl-XL expression had a higher response to chemotherapy (56% and 53%, respectively) than tumors positive for p53 or those having high-level Bcl-XL expression (30% and 32%, respectively; \( P = 0.0378 \)). Following preoperative combined modality therapy, patients with p53-negative tumors had significantly better mean survivals compared with those whose tumors expressed p53 (31 vs. 11 months; \( P = 0.0378 \)). There was no significant effect of the expression of apoptosis-regulating genes. Using multivariate analysis, Pomp et al. found that overexpression of p53 correlated with diminished survival in 69 patients with squamous or adenocarcinomas treated with radiation alone. In another study, Merchant et al. found a correlation between decreasing phospholipid expression and increasing T stage and grade.

ENDOLUMINAL PALLIATION TECHNIQUES

As previously discussed, surgery remains the standard of care for patients with resectable neoplasms; however, many esophageal cancer patients are inoperable due to locally advanced or distant metastatic disease. Although chemotherapy and radiation therapy are typically used to palliate unresectable disease, many individuals require additional measures to relieve dysphagia and pain. Esophageal dilation frequently can alleviate esophageal obstruction secondary to malignancy; however, results usually are temporary, and patients require repeated treatments. Lundell et al. reported their experience with esophageal dilation in 41 esophageal patients. Although complications were observed in less than 5% of these individuals, dysphagia recurred in all patients, and most dilations had to be repeated every 4 weeks.

Whereas in a strict sense surgery for locally advanced esophageal cancer can be considered palliative in nature, resection of esophageal carcinomas in the context of known distant metastases or the treatment of unresectable obstructing neoplasms using surgical bypass procedures presently cannot be advocated in light of data demonstrating safe and effective palliation by endoluminal stents, laser, or photodynamic therapy (PDT) techniques. Orringer et al. reported results of bypass procedures in 37 patients with unresectable esophageal carcinomas, noting an operative mortality of 24%, an anastomotic leak rate of 19%, and effective palliation in only 25% of individuals. The average survival of patients leaving the hospital following esophageal bypass procedure was less than 6 months. In additional studies, Mannel et al. evaluated 124 patients undergoing esophageal bypass for unresectable disease. Although 82% of patients experienced complete and durable palliation, hospital mortality was approximately 11%, and in these individuals was only 5 months. Hitting et al. compared results of 26 patients undergoing surgical bypass, 45 patients undergoing laser palliation, and 215 patients tended to experience more sustained palliation, survival rates were comparable in both patient groups. In a more recent study, Segalin et al. reported an operative mortality of 20% and median survival of 6 months for 49 patients undergoing esophageal resection for advanced metastatic disease. In contrast, 30-day mortality was 10%, and median survival was 4 months for 254 patients treated with intubation procedures. Laser therapy was performed in 50 patients with no operative mortality and a median survival of 4 months.

Although previous studies employing intubation techniques have reported high morbidity and mortality, current data indicate that expandable stents placed by endoscopic methods afford cost-effective and durable palliation in esophageal cancer patients. Rajman et al. evaluated 101 patients with malignant dysphagia, 83 of whom had esophageal stenting secondary to esophageal cancer, and 13 of whom had digestive tract fistulas. The majority of strictures were in the distal third of the esophagus and most were secondary to esophageal tumors. The mean length of stricture was approximately 7 cm. Initial stent placement was successful in 100 patients, and the vast majority experienced significant improvement in their dysphagia. Life-threatening complications were noted in approximately 8%; there were no procedure-related deaths. All digestive tract fistula stent failures were successfully controlled by endoscopic stents. Ninety-nine patients died of their disease within a mean follow-up of 201 days. In an additional series, Cwikl et al. reported long-term results of 100 patients with malignant dysphagia treated with self-expanding Nitinol stents. Esophageal strictures were due to squamous cell carcinoma in 43 patients, adenocarcinoma in 18, anastomotic recurrence in 14, or extrinsic compression from mediastinal tumors in 14 individuals. One hundred six stents were placed in 100 patients. Complications included incomplete expansion due to stent twisting (four patients), stent migration (four patients), tumor ingrowth (17 patients), food impaction (five patients), fracture of stent wires (two patients), benign stricture (two patients), and tumor bleeding (four patients). Forty-seven patients experienced transient chest pain following deployment of the stent. Esophageal perforations were observed in five patients, three of whom were successfully treated with additional stent placement. Ninety-seven patients experienced significant reduction in dysphagia; at the time of their deaths, 42 patients had no dysphagia, 39 had grade 1 dysphagia, 16 had grade 2 dysphagia, and 3 experienced grade 3 dysphagia.

Cantore et al. compared results of 25 patients undergoing esophageal bypass with 30 patients treated with autoexpandable esophageal stents. Dysphagia was not relieved in 24% of surgical patients, and hospitalization for these patients ranged from 18 to 50 days; the hospital mortality was 24%. Survival in these patients was only 5.4 months. Treatment of 50 individuals with 30 expandable esophageal stents, noting an expanded mortality of 24%, an anastomotic leak rate of 19%, and effective palliation in only 25% of individuals. The average survival of patients leaving the hospital following esophageal bypass procedure was less than 6 months. In additional studies, Mannel et al. evaluated 124 patients undergoing esophageal bypass for unresectable disease. Although 82% of patients experienced complete and durable palliation, hospital mortality was approximately 11%, and in these individuals was only 5 months. Hitting et al. compared results of 26 patients undergoing surgical bypass, 45 patients undergoing laser palliation, and 215 patients tended to experience more sustained palliation, survival rates were comparable in both patient groups. In a more recent study, Segalin et al. reported an operative mortality of 20% and median survival of 6 months for 49 patients undergoing esophageal resection for advanced metastatic disease. In contrast, 30-day mortality was 10%, and median survival was 4 months for 254 patients treated with intubation procedures. Laser therapy was performed in 50 patients with no operative mortality and a median survival of 4 months.

Although less commonly used, PDT has been advocated as an additional means to palliate obstructing esophageal carcinomas. Loh et al. reported results of a randomized multicenter trial evaluating PDT versus neodymium:yttrium-aluminum-garnet (Nd:YAG) laser treatment for palliation of dysphagia secondary to esophageal carcinomas. Two hundred thirty-six patients were evaluated, of whom 218 patients underwent treatment; 110 individuals received PDT, and 108 patients were treated with YAG laser. Significant improvement in dysphagia was noted in all patients without obvious differences between groups. Objective tumor responses were observed in 15 patients. PDT was improved with concomitant laser/pump therapy in 17 patients following treatment of esophageal perforations. Fourteen individuals treated with laser techniques. These results suggest that PDT and Nd:YAG laser are equally efficacious with regard to palliation of dysphagia, and that PDT may be associated with a relatively lower risk of acute perforations.

Maier et al. reviewed their experience with 119 cases of unresectable esophageal cancers treated with endoluminal palliation techniques. Twenty-one patients required dilatation and Nd:YAG laser obliteration before therapy; 44 patients received PDT followed by brachytherapy; 25 of these individuals also received external-beam radiation therapy. Seventy-five patients refused PDT and were treated with high-dose brachytherapy, 17 of whom also received external-beam radiation therapy. PDT was more successful than brachytherapy in relieving stenosis; significant relief of dysphagia was observed. The mean number of PDT treatments was four (range, one to seven); because of concerns regarding stricture formation and perforations, PDT was not repeated within 3 months. Major complications were noted in 9.2% of patients. Four esophageal perforations occurred that were treated by esophageal exclusion and mediastinal drainage techniques. Four esophageal stenosis/stricture were observed, all of which were treated with endoluminal stents. Mean overall survival was 7.7 months; a statistically significant difference in survival was observed for patients receiving PDT and external-beam therapy compared with those receiving brachytherapy alone.

Thus, current data indicate that endoluminal stents, laser, or PDT can efficiently palliate obstructing esophageal cancers with far less morbidity and mortality than surgical bypass techniques. Relative contraindications to esophageal stenting include complete obstruction not allowing guidewire placement, noncurvilinear tumors not enabling stabilization of the stent, endoluminal dilation above the stenosis, or high cervical esophageal lesions. Although laser and PDT require more expertise, these modalities may either be used initially to palliate obstructing esophageal lesions or as an adjunct to treat tumor ingrowth, which occurs in 20% to 30% of stent patients. Endoluminal stenting, Nd:YAG laser, and PDT should be viewed as complementary modalities for palliation of unresectable, obstructing esophageal carcinomas.

TREATMENT RECOMMENDATIONS AND FUTURE DIRECTIONS

Although individuals occasionally are diagnosed early due to participation in screening protocols, the vast majority of patients with esophageal cancer present with either locally advanced (stages III or IV) or inoperable metastatic disease. Esophagectomy remains the standard of care for patients who can tolerate resection. Available data from well-designed prospective randomized trials do not support the routine use of induction chemotherapy in resectable patients. Furthermore, there are no convincing data that justify the routine use of chemotherapy following esophagectomy. Radiation therapy has no proven benefit as the sole modality in the induction setting, and current data indicate a potential benefit of this treatment modality in patients with positive(functional margins, but not in completely resected individuals irrespective of nodal status. Limited data suggest that combined chemoradiation therapy may be beneficial in the induction setting in resectable patients, particularly in individuals achieving pathologic complete responses; surgery remains an important component of these aggressive protocols since no other modality exists. Induction chemotherapy appears to enhance local control following surgery, however. Although not well-designed, prospective randomized trials is required before multimodality treatment can be considered the standard of care for individuals with resectable cancers. Data from Altorki et al., Lerut and colleagues, and Akkaya and coworkers indicate that en bloc esophagectomy, particularly with three-field lymphadenectomy, enhances the accuracy of staging and appears to improve local control and overall survival in esophageal cancer patients. If confirmed by other expert esophageal cancer surgeons, these results should be considered the standard against which all other treatments are compared. Patients with unresectable cancers should be...
Flavopiridol is a synthetic flavone that inhibits several cyclin-dependent kinases (including cdk4 and cdk6), diminishes cyclin D1 and Bcl-2 expression, and induces cell-cycle arrest and apoptosis in a variety of cancer cells. Additional studies have demonstrated that pretreatment of esophageal cancer cells with flavopiridol markedly enhances their sensitivity to paclitaxel, in part, by synchronizing them in G0/G1. In addition to being a novel agent for the treatment of esophageal cancers, flavopiridol may be a potential chemoprevention agent since it effectively targets those mitotic events (i.e., cyclin D overexpression, as well as p16 and p16 inactivation) that are known to occur early during multistage esophageal carcinogenesis.

Approximately 50% of esophageal cancers exhibit loss of p16 expression due to promoter hypermethylation. Additional studies have demonstrated that sequential DAC and depsipeptide treatment enhances NY-ESO-1 expression in esophageal cancer cells and enables their recognition by HLA-restricted cytolytic T cells specific for this cancer testis antigen. Clinical trials designed to evaluate the ability of DAC and depsipeptide to mediate target gene induction and apoptosis in esophageal carcinomas and augment antitumor immunity in patients with these malignancies are underway in the Surgery Branch, National Cancer Institute. Evaluation of these agents, as well as other novel compounds targeting p53 mutations and transforming expression in cancer cells, may ultimately enable evolution of more precise and efficacious treatment regimens for highly lethal esophageal neoplasms.

CHAPTER REFERENCES


Adenocarcinoma of the stomach has been the leading cause of cancer death worldwide through most of the twentieth century. It now ranks second only to lung cancer with an estimated 755,500 new cases diagnosed annually worldwide. The incidence of this disease has gradually decreased in many parts of the world, principally because of changes in diet, food preparation, and other environmental factors. The decline in incidence has been dramatic in the United States, where this disease ranks fourteenth as a cause of cancer deaths. It is estimated that 21,900 new cases are diagnosed annually, with approximately 13,500 deaths per year. With the exception of just a few countries in the world, the prognosis for this disease remains poor. The overall 5-year survival rate in the United States and most of the Western world ranges from 5% to 15%. The explanations for these poor results are multifactorial. The lack of defined risk factors and specific symptomatology, treatment is surgical resection of all gross and microscopic disease. Even after a "curative'' gastrectomy, disease recurs in both regional and distant sites in at least 80% of patients. Efforts to improve these poor results have focused on developing effective pre- and postoperative systemic and regional adjuvant therapies. It is generally accepted that patients with chemoresponsive tumors are more likely to have a survival advantage. Consequently, a greater emphasis is being placed on predicting chemoresponsiveness in gastric cancer. This chapter details the current thinking regarding the origins, treatment, and prevention of this universal health problem.
became intermediate between the countries of origin and adoption. These studies suggest that environmental exposure in early life is essential in determining risk but that other environmental or cultural factors may be continually influencing the predisposition to cancer.

In the United States, stomach cancer occurs at a higher incidence in men than in women (ratio of approximately 2:1). It is more frequent in black men than in white men (1.5:1). Starting at the fourth decade, the incidence of stomach cancer increases with advancing age and has a peak incidence in the seventh decade in men and a slightly later peak incidence in women. The mortality rate for stomach cancer has decreased from 31.5 per 100,000 for white men in 1935 to 7.8 per 100,000 for all U.S. men in 1983. However, this decline in mortality simply reflects the decrease in the incidence of the disease, and relative 5-year survival rates have not changed considerably.

One of the most striking epidemiologic observations has been the increasing incidence of adenocarcinomas involving the proximal stomach and distal esophagus. In 1991, Blot and colleagues reviewing the National Cancer Institute's Surveillance, Epidemiology, and End Results database, reported that, during the period 1976 to 1987, a shift to proximal gastric lesions was noted. The annual increase in proximal gastric lesions was 4.3% for white men, 4.1% for white women, 3.6% for black men, and 5.6% for black women. This annual rate of increase on a percentage basis is greater than that of lung cancer or melanoma. The incidence of adenocarcinoma elsewhere in the stomach was approximately the same or slightly lower. By 1984 to 1987, cancers of the cardia made up 47% of all gastric cancers in white women. European investigators have reported similar data. This trend is worrisome, because proximal gastric cancers are thought to have a poorer prognosis, stage for stage, compared with distal cancers. The etiologic basis for this rising trend is being aggressively pursued. Increasing prevalence of obesity in the United States may be one factor contributing to this trend. Elevated body mass index and caloric consumption have been associated with adenocarcinoma of the distal esophagus and gastric cardia. Gastroesophageal reflux disease may be another risk factor. A population-based, case-control study performed in Sweden found that, for persons with recurrent symptoms of reflux, as compared to those without such symptoms, the odds ratio was 7.7 (95% confidence interval, 5.3 to 11.4) for esophageal adenocarcinoma and 2.0 (95% CI, 1.4 to 2.9) for adenocarcinoma of the gastric cardia. Others have found tobacco use to be associated with these tumors at these sites. Gammon et al. observed an increased odds ratio of 2.4 (95% CI, 1.7 to 3.4) for cigarette smokers. Conversely, aspirin and nonsteroidal antiinflammatory drug use has been associated with a lower risk of esophageal and cardia cancers, implicating inflammation in the etiology of this disease.

ETIOLOGY AND PATHOGENESIS

It is generally accepted that the carcinogenic process leading to the intestinal-type cancers takes many years to develop into invasive adenocarcinoma. Many studies have investigated the role of diet in association with the development of stomach cancer, concluding that the consumption of raw (uncooked) vegetables, fruit, citrus fruit, and high fiber are inversely related to stomach cancer risk. Dietary factors that may be associated with an increased risk of stomach cancer are listed in Table 33.3-1. Antioxidants, which can prevent the conversion of nitrates to nitrosamine, appear to be protective. Diets rich in vitamins A and C and micronutrients such as selenium, zinc, copper, iron, and manganese may lower the risk of gastric carcinoma.

The incidence of cancers affecting the gastric body and antrum is inversely related to socioeconomic status, which probably reflects a number of social, occupational, or cultural factors. A higher incidence has been associated with the practice of smoking or salting meat and fish and a low incidence with the use of refrigeration and better food preparation. The use of well water, which may contain high concentrations of nitrates or Helicobacter pylori, has been shown to be a risk factor for gastric cancer. Smoking has been reported to increase the relative risk, whereas no consistent data have supported that alcohol consumption affects the incidence of stomach cancer.

Correa and colleagues have proposed a model for the pathogenesis of intestinal-type gastric cancer. Normal mucosa, either through environmental or other factors, becomes atrophied in association with impaired gastric acid secretion and an increased gastric pH. Subsequent bacterial colonization results in further mucosal injury directly or via the production of nitrites or N-nitroso compounds from dietary nitrites. In laboratory animals, the ability of chronically administered oral N-nitroso compounds to produce intestinal metaplasia and subsequent carcinoma has been well described. In humans, this mechanism is supported by the observation of a high prevalence of chronic atrophic gastritis and intestinal metaplasia in populations with a high incidence of gastric cancer and the association of gastric cancer with pernicious anemia.

The Epstein-Barr virus genome has been identified in human gastric cancers with lymphoepithelioid features. This is an uncommon finding that has been associated with tumors of younger patients (younger than 35 years), tumors located in the cardia, or in stump carcinomas. The frequency in Japan is estimated to be approximately three times that of North America.

The data in support of radiation exposure increasing the risk of gastric cancer come from the Japanese atomic bomb reports. An initial analysis of patients irradiated for peptic ulcer disease followed through 1962 showed no significant tumor increase. A subsequent study of 2049 irradiated patients and 763 medically managed patients was undertaken in 1984 to estimate the risk of cancer due to gastric irradiation. A relative risk of 3.7 was found for stomach cancer.

The occurrence of gastric carcinoma clustered in families suggests the existence of a genetic susceptibility to cancer of the stomach. Estimates of familial clustering of gastric cancer range from 1% to 15% of all gastric cancers. The most celebrated example of the genetic predisposition toward stomach cancer is illustrated in the Bonaparte family: Napoleon, his father, and his grandfather all died of gastric carcinoma. Gastric cancer occurs with increased frequency in family members diagnosed with hereditary nonpolyposis colorectal cancer and Li-Fraumeni syndrome. In 1998, Guilford et al. identified an E-cadherin germline mutation present in the Bonaparte family: Napoleon, his father, and his grandfather all died of gastric carcinoma. Gastric cancer occurs with increased frequency in family members diagnosed with hereditary nonpolyposis colorectal cancer and Li-Fraumeni syndrome. In 1998, Guilford et al. identified an E-cadherin germline mutation present in the Bonaparte family: Napoleon, his father, and his grandfather all died of gastric carcinoma.

Prior Gastric surgery and GASTRIC CANCER

In 1922, Balfour made the original observation that an association existed between the development of gastric cancer and previous partial gastrectomy for benign disease. A gastric stump cancer arises in the gastric remnant no less than 5 years after partial gastrectomy to distinguish a de novo gastric stump cancer from a locally recurrent tumor that was not recognized at the original operation. Two metaanalyses have been published that indicate an increased risk of gastric stump cancer in patients with partial gastrectomy. The increased risk is observed only after a latency period of at least 15 years, is increased in patients operated on for gastric but not for duodenal ulcer, and is slightly higher in women than in men. The type of reconstruction does not appear to influence the relative risk of developing gastric stump cancer. Baas et al. compared 26 stump carcinomas with 24 conventional stomach cancers and found that DNA in situ hybridization for Epstein-Barr virus was positive in nine stump carcinomas versus two carcinomas in the nonoperated stomach, suggesting etiologic differences between stump carcinoma and
cancers arising in the intact stomach.

Because histamine-2 receptor antagonists suppress gastric acid secretion, it has been suggested that chronic use of these agents may predispose the gastric epithelium toward malignant degeneration. However, the only increased risk of stomach cancer in histamine-2 receptor antagonist users has been restricted to patients who had started treatment within 5 years before the diagnosis of stomach cancer. This suggests that there may have been a misdiagnosis in some patients rather than a causal role for the drug.

**Helicobacter pylori and Gastric Cancer**

In 1982, Marshall and Warren first isolated *H pylori* from biopsies of gastric epithelium. The role for *H pylori* in initiating mucosal injury and the subsequent development of chronic atrophic gastritis is well known. In patients who had undergone resection for intestinal-type gastric cancer, the presence of *H pylori* has been identified in noncancerous tissue in almost 90% of patients, compared with 32% with the diffuse form of gastric cancer. Several studies have reported a significant association between *H pylori* infection and gastric cancer, particularly for tumors in the distal stomach. The risk of developing gastric cancer correlated with increasing *H pylori* immunoglobulin G antibody was higher when the time interval between the diagnosis of *H pylori* infection and gastric cancer was more than 10 years. Personnet and colleagues found a particularly strong association between *H pylori* infection and stomach cancer in women and blacks. The intestinal and diffuse types of gastric adenocarcinoma, as well as gastric lymphoma, were associated with *H pylori* infection. However, others have found a significantly higher incidence of *H pylori* infection in patients with intestinal but not diffuse-type gastric cancer. Although *H pylori* has been classified as a class I carcinogen, the incidence of *H pylori* infection in matched controls in these studies was between 51% and 76%, indicating that most people with *H pylori* infection do not develop stomach cancer and that other contributing factors are important in its pathogenesis. It has been shown that *H pylori* isolates that process the cagA gene are more virulent in nature and produce significant amounts of gastritis and epithelial injury. Patients with cagA *H pylori* infection have a slightly higher risk of developing stomach cancer than those with cagA-negative strains. Further research may define whether characteristics of certain subtypes of *H pylori* or unique characteristics of its host promote malignant transformation. At the present time, antibiotic therapy in *H pylori*-positive patients should be reserved for those with proven ulcer disease or nonulcer dyspepsia in whom other measures have been unsuccessful.

**ANATOMIC CONSIDERATIONS**

The stomach begins at the gastroesophageal junction and ends at the pylorus (Fig. 33.3-1). Above it lie the diaphragm and left lobe of the liver; before it is the abdominal wall, and below it are the transverse colon, mesocolon, and greater omentum. Behind and to the sides are the spleen, pancreas, left adrenal gland, left kidney, and splenic flexure of the colon. Cancers arising from the proximal greater curvature may directly involve the splenic hilum and tail of pancreas, whereas more distal tumors may invade the transverse colon. Proximal cancers may extend into the diaphragm, spleen, or the left lateral segment of the liver.

**FIGURE 33.3-1.** Blood supply to the stomach and anatomic relationships of the stomach with other adjacent organs likely to be involved by direct extension of a large gastric malignancy.

The blood supply to the stomach is extensive and is based on vessels arising from the celiac axis (see Fig. 33.3-1). The right gastric artery, arising from the hepatic artery, and the left gastric artery, arising from the celiac axis directly, course along the lesser curvature. Along the greater curvature are the right gastroepiploic artery, which originates from the gastroduodenal artery at the inferior border of the proximal duodenum, and the left gastroepiploic artery, branching from the splenic artery laterally. The short gastric arteries (vasa brevia) arise directly from the splenic artery and make a relatively small contribution to the blood supply to the proximal portion of the stomach. The preservation of any of these vessels in the course of a subtotal gastrectomy for carcinoma is not necessary (nor possible if the operation is performed correctly), and the most proximal few centimeters of remaining stomach are well supplied by collateral flow from the lower segmental esophageal arcade. The rich submucosal blood supply of the stomach is an important factor in its ability to heal rapidly and produce a low incidence of anastomotic disruption.

The venous supply of the stomach tends to parallel the arterial system. The venous efflux ultimately passes the portal venous system and is reflected in the fact that the liver is a primary site for distant metastatic spread.

The lymphatic drainage of the stomach is extensive, and distinct anatomic groups of perigastric lymph nodes have been defined according to their relationship to the stomach and its blood supply. There are six perigastric lymph node groups: along the greater curvature are the subpyloric and gastroepiploic nodes, and along the lesser curvature are the suprapyloric and the lesser curvature lymph nodes. Proximally are found the right and left pericardial nodes. The second echelon (extraperigastric) nodes include the common hepatic, left gastric, splenic hilum, and splenic artery lymphatics, which drain into the celiac and periaortic lymphatics. Proximally are the lower esophageal lymph nodes; extensive spread of gastric cancer along the intrathoracic lymph channels may be manifested clinically by a proximal tumors may invade the transverse colon. Proximal cancers may extend into the diaphragm, spleen, or the left lateral segment of the liver.

**PATHOLOGY AND TUMOR BIOLOGY**

Approximately 95% of all malignant gastric neoplasms are adenocarcinomas, and in general, the term gastric cancer refers to adenocarcinoma of the stomach. Other malignant tumors are very rare and include squamous cell carcinoma, adenoacanthoma, carcinoid tumors, and leiomyosarcoma. Although no normal lymphoid tissue is found in the gastric mucosa, the stomach is the most common site for lymphomas of the gastrointestinal tract. The increased awareness of association between *H pylori*-associated lymphoid tissue lymphomas and *H pylori* may explain, in part, the rise in incidence. The differentiation between adenocarcinoma and lymphoma can sometimes be difficult but is essential because staging, treatment, and prognosis are different for each disease.

**HISTOPATHOLOGY**

Several staging schemas have been proposed based on the morphologic features of gastric tumors. The Borrmann classification divides gastric cancer into five types depending on macroscopic appearance. Type I represents polyoid or fungating cancers, type II encompasses ulcerating lesions surrounded by elevated borders, type III represents ulcerating lesions infiltrating the gastric wall, type IV are diffusely infiltrating tumors, and type V are unclassifiable cancers. The gross morphologic appearance of gastric cancer and the degree of histologic differentiation are not independent prognostic variables. Ming has proposed a histomorphologic staging system that divides gastric cancer into either a prognostically favorable expansive type or a poor prognosis infiltrating type. Based on an analysis of 171 gastric cancers, the expansive-type tumors were uniformly polyoid or superficial on gross appearance, whereas the infiltrative tumors were almost always diffuse. Grossly ulcerated cancers were equally divided between the expanding or infiltrative forms. Broder's classification of gastric cancer grades tumors histologically from 1 (well differentiated) to 4 (anaplastic). Bearzi and Rancail have correlated the degree of histologic differentiation with the gross appearance of 41 primary gastric cancers seen on endoscopy. Ninety percent of protruding or superficial cancers were well differentiated (Broder's grade 1), whereas almost one-half of all ulcerated cancers were poorly differentiated or diffusely infiltrating (Broder's grades 3 and 4).
The most widely used classification of gastric cancer is by Laurén.\textsuperscript{5} It divides gastric cancers into either intestinal or diffuse forms. This classification scheme, based on tumor histology, effectively characterizes two varieties of gastric adenocarcinomas that manifest distinctively different pathology, epidemiology, and etiologies. The intestinal variety represents a differentiated cancer with a tendency to form glands. In contrast, the diffuse form exhibits very little cell cohesion and has a predilection for extensive submucosal spread and early metastases. Although the diffuse-type cancers are generally associated with a worse outcome than the intestinal type, this finding is not independent of tumor, node, metastasis (TNM) stage.

** PATTERNS OF SPREAD**

Carcinomas of the stomach can spread by local extension to involve adjacent structures and can develop lymphatic metastases, peritoneal metastases, and distant metastases. These extensions can occur by the local invasive properties of the tumor, lymphatic spread, or hematogenous dissemination. The initial growth of the tumor occurs by penetration into the gastric wall, extension through the wall, and involvement of an increasing percentage of the stomach. The two modes of local extension that can have a major therapeutic impact are tumor penetration through the gastric serosa, where the risk of tumor invasion of adjacent structures or peritoneal spread is increased, and involvement of lymphatics. Zinner\textsuperscript{22} has evaluated the spread in the gastric wall and has found a wide variation in its extent. Tumor spread is often through the intramural lymphatics or in the subserosal layers. Local extension can also occur into the esophagus or the duodenum. Duodenal extension is principally through the muscular layer by direct infiltration and through the subserosal lymphatics, but is not generally of great extent. Extension into the esophagus occurs primarily through the submucosal lymphatics.

Local extension does not occur solely by radial intramural spread but also by deep invasion through the wall to involve adjacent structures. Extension can occur through the gastric serosa to involve omentum, spleen, adrenal gland, diaphragm, liver, pancreas, or colon. Data from several large older series indicated that 60% to 90% of patients had primary tumors penetrating the serosa or invading adjacent organs and that at least 50% had lymphatic metastases.\textsuperscript{23,24} Of the 1577 primary gastric cancer cases admitted to Memorial Sloan-Kettering Cancer Center between July 1, 1985, and June 30, 1998, 60% of the 1221 resected cases had evidence of serosal penetration, and 68% had positive nodes. Lymph node metastases were found in 18% of pT1 lesions after R0 resection in 941 patients. This rate increased significantly to 60% in pT2 lesions. The highest incidence of lymphatic metastasis was seen in tumors diffusely involving the entire stomach. Tumors located at the gastroesophageal junction also had a high incidence relative to other sites. The pattern of nodal metastases also varies depending on the location of the primary site (Table 33.3-2), with the left gastric artery nodes being consistently at increased risk for nodal metastases regardless of tumor location.

Gastric cancer recurs in multiple sites, both locoregionally and systemically.\textsuperscript{25} The literature reveals disagreements over failure patterns (Table 33.3-4). These disagreements are likely related to the patient cohorts accepted for evaluation, the time at which failure was determined, and the method of determination of failure patterns. In two older autopsy series, the rate of locoregional failure (defined as tumor in perigastric tissues (e.g., in the retroperitoneal “gastric bed,” perigastric lymph nodes, gastric remnant]) after potentially curative resection was 40% to 80%.\textsuperscript{23,26} Many patients had multiple sites of local failure. Shiu and coworkers\textsuperscript{27} found a 23% local recurrence rate in 169 patients treated for carcinoma of the body of the stomach.

**TABLE 33.3-2. Pattern of Nodal Metastases from Gastric Cancer**

<table>
<thead>
<tr>
<th>Primary Site</th>
<th>Nodal Site</th>
<th>Other Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esophageal</td>
<td>Left gastric artery</td>
<td>Nonspecific</td>
</tr>
<tr>
<td>Liver</td>
<td>Common hepatic</td>
<td>Nonspecific</td>
</tr>
<tr>
<td>Stomach</td>
<td>Splenic</td>
<td>Nonspecific</td>
</tr>
<tr>
<td>Pancreas</td>
<td>Hypogastric</td>
<td>Nonspecific</td>
</tr>
</tbody>
</table>

**TABLE 33.3-3. Site of Metastases at Autopsy or Operation**

<table>
<thead>
<tr>
<th>Site of Metastases</th>
<th>Primary Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>Esophagus</td>
</tr>
<tr>
<td>Stomach</td>
<td>Pancreas</td>
</tr>
<tr>
<td>Splenic</td>
<td>Hypogastric</td>
</tr>
</tbody>
</table>

**TABLE 33.3-4. Failure Patterns in Gastric Cancer Patients**

Gunderson and Sosin\textsuperscript{28} reanalyzed the reoperation series performed by Wangensteen at the University of Minnesota, where patients had a second-look laparotomy after resection of the primary tumor. This type of analysis is valuable because it can demonstrate the early (and perhaps most treatable) modes of failure rather than simply showing diffuse metastatic disease at autopsy. Sixty-nine percent of patients had evidence of a locoregional recurrence, and 42% of patients had peritoneal seeding. Most of the local failures were located in the gastric bed (81%), although recurrences also occurred in the anastomosis or stump (39%) or in the regional lymph nodes (63%). A trial from the British Stomach Cancer Group found an incidence of local failure in patients treated with surgery alone to be 37 of 69 (54%).\textsuperscript{29} A series evaluating local failure patterns reported by Landry and coworkers\textsuperscript{30} showed a total locoregional failure rate of 38%, with most of the local recurrences in the gastric bed, the anastomosis, or the gastric stump. The incidence of local failure increased when the primary disease extended through the gastric wall or when lymph nodes were involved at the initial surgery. Liver metastases occurred in 30% of patients and peritoneal seeding in 23%. Extraperitoneal failure was relatively rare and
Some newer series suggest a higher incidence of peritoneal seeding as a failure pattern. Wisbeck et al. evaluated autopsy and clinical records of 85 patients who died of gastric cancer. Sixteen patients had a resection with curative intent; 15 of these developed a locoregional recurrence, eight developed peritoneal seeding, and seven developed lung metastases. Of the entire cohort, 40 of 85 (47%) developed peritoneal seeding. Arai and colleagues treated 25 patients with preoperative chemotherapy. At the time of surgery, eight had peritoneal carcinomatosis, and it developed subsequently in an additional five patients. Because imaging studies were not done routinely postoperatively, they could not accurately determine the risk of locoregional failure. These data suggest that increased attention to methods of controlling local and regional disease as well as systemic disease is needed to improve long-term results.

CLINICAL PRESENTATION

SIGNS AND SYMPTOMS

Most patients with gastric cancer are diagnosed with advanced-stage disease, and this is reflected in the vague, nonspecific symptoms that characterize the disease. Patients may have a combination of signs and symptoms, such as weight loss, anorexia, fatigue, or epigastric discomfort, none of which unequivocally indicates gastric cancer. The clinical significance of weight loss in gastric cancer should not be underestimated. Dewys and colleagues showed that, in 179 patients with advanced, nonmeasurable gastric cancer, more than 80% of patients had a greater than 10% decrease in body weight. Patients with weight loss had a significantly shorter survival than those without weight loss.

In some patients, symptoms may suggest the presence of a lesion in specific locations. A history of dysphagia may indicate the presence of a tumor in the cardia with extension through the gastroesophageal junction. A complaint of early satiety is actually a very infrequent symptom of gastric cancer, but is indicative of a diffusely infiltrative tumor that has resulted in loss of distensibility of the gastric wall. Persistent vomiting is consistent with an antral carcinoma obstructing the pylorus. Significant gastrointestinal bleeding is uncommon with gastric cancer; however, hematemesis does occur in approximately 10% to 15% of patients. However, many patients are diagnosed after the development of ascites, jaundice, or a palpable mass, indicating extensive and incurable disease.

Because the transverse colon is held in close proximity to the stomach by the gastrocolic ligament, it is a potential site of malignant fistula and large bowel obstruction from a gastric primary. Diffuse peritoneal spread of disease frequently produces other sites of intestinal obstruction. A large ovarian mass (Krukenberg’s tumor) or a large peritoneal implant in the pelvis (Blumer’s shelf), which can produce symptoms of rectal obstruction, may be felt on pelvic or rectal examination. Nodular metastases in the subcutaneous tissue around the umbilicus or in peripheral lymph node areas reflect the disease, which can be established with minimal morbidity.

SCREENING

Mass screening programs for gastric cancer have been most successful in high-risk areas, especially in Japan. A variety of screening tests have been studied in Japanese patients, with a sensitivity and specificity of approximately 90%. They frequently include the use of double-contrast barium radiographs or upper endoscopy. The yield in screened populations has been substantial; in some Japanese studies, up to 40% of newly diagnosed patients have early gastric cancer, and up to 60% of patients actively participating in routine mass screening programs have the disease. This is clinically important because, as discussed below in Pathologic Staging and Prognosis, early gastric cancer has a very high cure rate when treated surgically. However, the fact that gastric cancer remains the number one cause of death in Japan may reflect the limitations of a mass screening program when the entire population at risk is not effectively screened. Newer studies have verified that a low serum pepsinogen I/II ratio can be used to better select patients at increased risk for atrophic gastritis and gastric cancer.

PRETREATMENT STAGING

TUMOR MARKERS

Carcinoembryonic antigen (CEA) is elevated in approximately one-third of primary gastric cancer patients. The sensitivity of CEA is low, but when elevated, the level does generally correlate with stage. Combining CEA with other markers, such as the sialylated Lewis antigens CA19-9 or CA50, can increase the sensitivity over CEA alone. A large study evaluated the prognostic significance of serum levels of CEA (n = 237), a-fetoprotein (n = 164), human chorionic gonadotropin-b (b-HCG) (n = 165), CA19-9 (n = 64), and CA125 (n = 104), as well as tissue staining for C-erb B-2 (n = 160) and b-HCG (n = 160). In a multivariate analysis, only serum b-HCG 4 IU/L (hazard ratio, 1.7; 95% CI, 2.8 to 1.1) and CA125 350 U/mL (hazard ratio, 2.2; 95% CI, 4.2 to 1.2) had prognostic significance. Elevated serum b-HCG and CA125 in gastric cancer before chemotherapy may reflect not just tumor burden but aggressive biology, however, these findings must be compared to other known preoperative markers of stage, such as endoscopic ultrasonography (EUS) T and N stage.

ENDOSCOPY

Upper endoscopy is used routinely for the initial diagnosis and staging of gastric adenocarcinoma and should be performed in any patient with localized disease for which surgical treatment is anticipated. Numerous reports have demonstrated diagnostic accuracy of more than 95% for advanced disease. The size, location, and morphology of the tumor, including the proximal and distal extent of spread, as well as other mucosal abnormalities, should be carefully evaluated. Decreased distensibility of the stomach, abnormal peristaltic activity, or abnormal pyloric function may indicate extensive submucosal infiltration or extramural extension of tumor into the vagi. The likelihood of a positive yield on biopsy is greater than 95% when six to ten tissue samples are obtained. Detecting the faint mucosal irregularities usually associated with early gastritis-like carcinomas can be enhanced by endoscopic dye spraying with vital dyes, such as 0.1% indigocarmine. This technique has been used extensively in Japan with good success.

EUS has been used extensively to stage the depth of invasion and regional lymph node extent in potentially operable gastric cancer. EUS uses a high-frequency (7.5 to 12 MHz) transducer at the end of the scope and allows highly accurate staging of the depth of invasion of the primary tumor (T stage) and is more accurate than a computed tomographic (CT) scan for staging T and N status. Although it appears more useful than a CT scan for detecting perigastric lymph node metastases, the overall accuracy of EUS for assessing all regional nodes is less satisfactory. Because CT may identify metastases to distant nodes and sites, such as the liver, ovaries, and peritoneum, CT and EUS are best used as complementary tests. EUS has become an invaluable tool to assess which early gastric cancers are candidates for endoscopic resection, a curative treatment in properly selected patients (see Treatment of Local Disease, below).

COMPUTED TOMOGRAPHY

Once gastric cancer is suspected, a barium study or flexible upper endoscopy with biopsy is performed. After the diagnosis is established, staging procedures involve careful physical examination, routine blood screening tests, and abdominal and chest CT scanning. Barium contrast studies have limited accuracy for determining resectability, but by using double-contrast techniques, a positive diagnosis of lesions between 5 and 10 mm can be made in 75% of patients. CT of the chest, abdomen, and pelvis is useful for assessing the lateral extension of the tumor and presence of systemic metastases. However, up to 50% of patients have more extensive disease at laparotomy than was predicted by preoperative CT. With newer triphasic spiral CT scanning methods, greater emphasis has been placed on identifying low-volume disease and predicting the T stage. Takao et al. reported an accuracy for spiral CT of 82% for staging T status in advanced gastric cancer and 15% in early gastric cancer by obtaining images with the stomach filled with water. Few Western centers routinely apply these techniques, and without them the accuracy of T staging is generally poor.

POSITRON EMISSION TOMOGRAPHY

Whole body [18F]fluorodeoxyglucose (FDG) positron emission tomography (PET) is being applied increasingly in the evaluation of gastrointestinal malignancies. The positron-emitting [18F]fluorodeoxyglucose (FDG) is rapidly taken up by the tumor cells, which expresses high-fluoro-2-deoxyglucose transporters, and is transported into cells by either type I or II hexose transporters. Once in the cell, the fluorine-18 is phosphorylated into FDG-6-phosphate, which in most tumor tissues is not metabolized further. The preferential accumulation of positron-emitting FDG by tumor cells has been used successfully to image human tumors. Several studies have documented improved efficacy of detecting recurrent colorectal and hepatic (primary and metastatic) tumor sites, with a sensitivity ranging from 92% to 100% and an accuracy of 90% to 96%. Results from a study in esophageal cancer demonstrated that PET could detect 20% of metastases missed by CT. Little information regarding the use of FDG-PET in the management of
gastric cancer is available. In a pilot study begun here at Memorial Sloan-Kettering Cancer Center, we set out to assess the feasibility of FDG-PET imaging in gastric cancer patients. Fifteen studies were performed on 14 gastric cancer patients with various stages of disease. One hundred forty-five lesions were imaged with concurrent histologic confirmation. The preliminary results show FDG-PET to have a sensitivity of 60%, specificity of 100%, and an overall accuracy of 94% in identifying gastric cancer. The most consistent finding has been uptake in the primary tumor, indicating a possible role in treatment response assessment as well as for staging.

LAPAROSCOPY

The introduction of fiberoptic, video-assisted laparoscopy in the early 1980s added a means of direct and immediate assessment of the abdominal cavity without the morbidity of a laparotomy. Comparative studies of CT and laparoscopy have consistently shown laparoscopy to provide additional information that was not seen by preoperative CT imaging. In a study of 103 consecutively staged gastric cancer patients, laparoscopy had an accuracy of 94% when compared to what was found at laparotomy. Disease missed by CT was mostly peritoneal metastases. The rate of detecting occult M1 disease by this method ranges from 13% to 37%. Patients without clinically significant bleeding or obstruction that are found to have occult metastatic disease are incurable and may benefit from participation in new treatment protocols. Use of induction chemotherapy and selective resection of responding patients is an attractive alternative to immediate resection. Contrary to previously held dogma, most stage IV patients rarely develop significant symptoms from the primary tumor before death. None of the 24 patients with metastatic disease discovered at laparoscopy who were followed until death required subsequent laparotomy for complications of the primary tumor. Because CT may identify metastases to distant sites (liver, adrenal glands, and ovaries), thus avoiding an operation, CT, EUS, and laparoscopy are all considered complementary tests.

The development of laparoscopic ultrasonicographic probes has added a third dimension to the laparoscopic examination. Ultrasound is used to identify gastric cancer, although more invasive than EUS, is superior in identifying unsuspected metastases to liver and lymph nodes. Considering the low morbidity and significantly shorter hospital stay, laparoscopy, whenever feasible, should eliminate the need for patients undergoing laparotomy without resection.

PATHOLOGIC STAGING AND PROGNOSIS

As with other neoplasms, the uniform and accurate staging of gastric cancer is essential to meaningfully predict prognosis and assess response to treatment. The R classification indicates the amount of residual disease left after tumor resection. R0 indicates no gross or microscopic residual disease; R1 indicates microscopic residual disease, and R2 signifies gross residual disease. This is an obvious but most important prognostic factor, but it was not always indicated in the past, making interpretation of survival results difficult.

The International Union Against Cancer (UICC) and American Joint Committee on Cancer (AJCC) TNM classification for stomach cancer is shown in Table 33.3-5. The depth of tumor invasion (Fig. 33.3-2) determines T stage. The relationship between T stage and survival is well defined (Fig. 33.3-3). The General Rules for Gastric Cancer Study in Surgery and Pathology was published in English in 1995 by the Japanese Research Society for Gastric Cancer. The definition of the primary tumor stage based on the depth of invasion and the presence and extent of serosal invasion is shown in Table 33.3-6. T stage is further divided into mucosa (m), submucosa (sm), and muscularis propria (pm). The subserosa (ss) and S1 tumors have been reclassified to further stratify the degree and type of serosal invasion. INFa is a subserosal tumor with expansive growth, INFb is a subserosal tumor with intermediate-type growth, and INFg is a subserosal tumor with infiltrating growth. S2 and S3 are now defined as either se (cancer cells exposed to the peritoneal cavity), si (cancer cells infiltrating neighboring tissue), or sei (the coexistence of se and si). Survival results based on T stage are fairly consistent among Japan, Europe, and the United States (see Table 33.3-6).

<table>
<thead>
<tr>
<th>T Stage</th>
<th>Definition</th>
<th>American Joint Committee on Cancer Staging of Gastric Cancer, 1997</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tis</td>
<td>in situ</td>
<td>(From the Memorial Sloan-Kettering Cancer Center Department of Surgery Prospective Gastric Cancer Database.)</td>
</tr>
<tr>
<td>T1</td>
<td>mucosa</td>
<td>(From the Memorial Sloan-Kettering Cancer Center Department of Surgery Prospective Gastric Cancer Database.)</td>
</tr>
<tr>
<td>T2</td>
<td>submucosa</td>
<td>(From the Memorial Sloan-Kettering Cancer Center Department of Surgery Prospective Gastric Cancer Database.)</td>
</tr>
<tr>
<td>T3</td>
<td>muscularis propria</td>
<td>(From the Memorial Sloan-Kettering Cancer Center Department of Surgery Prospective Gastric Cancer Database.)</td>
</tr>
<tr>
<td>T4</td>
<td>subserosa</td>
<td>(From the Memorial Sloan-Kettering Cancer Center Department of Surgery Prospective Gastric Cancer Database.)</td>
</tr>
</tbody>
</table>

FIGURE 33.3-2. Definition of American Joint Committee on Cancer/International Union Against Cancer T stage based on depth of penetration of the gastric wall.
The AJCC/UICC N stage was changed in 1997 to reflect the number of involved lymph nodes. Tumors with one to six involved nodes are classified as pN1; 7 to 15 involved nodes are pN2, and more than 15 involved nodes is N3. Survival decreases dramatically as the number of metastatic lymph nodes increase. The N stage survival rate based on the number of nodes involved is shown in Figure 33.3-4 for 941 R0 gastric cancer patients treated at Memorial Sloan-Kettering Cancer Center. The previous classification was based on the localization of lymph node metastases. An analysis of 477 R0 resected node-positive cases from the German Gastric Cancer Study compared survival using both staging systems. This new 1997 AJCC further separated the survival of patients categorized by the old N definition (Fig. 33.3-5). Survival was significantly changed in the old N2 group by applying the new N stage classification. Differences between the two staging systems were not as great for N1 patients. Within the groups with one to six, 7 to 15, and more than 15 involved nodes, the location of metastatic lymph nodes did not significantly alter the prognosis. The new classification can now be applied in surgical trials with fewer methodologic problems, and it seems more reproducible provided that a minimum of at least 15 lymph nodes are examined. Several studies have assessed quantitative involvement of lymph nodes and survival after resection for gastric cancer and found that survival with up to three to four metastatic lymph nodes is better than with more extensive lymph node involvement. Once nodal metastases are found, Japanese survival statistics are better than those seen in Western patients (Table 33.3-7). Possible explanations for this observation include a potential difference in the biology of the tumor between the two patient populations or that the Japanese are removing and analyzing more lymph nodes, resulting in stage migration. The new AJCC/UICC requirement that a minimum of 15 nodes be removed and analyzed may minimize these differences.

FIGURE 33.3-4. Kaplan-Meier curves of disease-specific survival according to the 1997 American Joint Committee on Cancer N stage. N0 (no positive nodes; n = 355) A; N1 (one to six positive nodes; n = 354) B; N2 (7 to 15 positive nodes; n = 164) C; N3 (>15 positive nodes; n = 60) D. (From the Memorial Sloan-Kettering Cancer Center Department of Surgery Prospective Gastric Cancer Database.)

FIGURE 33.3-5. This graph demonstrates the range in 5-year survival rates according to the 1997 American Joint Committee on Cancer/International Union Against Cancer N stage within two groups of patients classified by the 1992 N1 and N2 staging. Inm, lymph node metastases. (Data modified from ref. 122.)

Under the current staging system, the presence of more than 15 perigastric lymph node metastases is classified as N3 disease, which is staged as M1. The Japanese staging system extensively classifies 18 lymph node regions into four N categories depending on their relationship to the primary tumor as well as anatomic location. The careful and complete prosection of the operative specimen may often be performed by the attending surgeon or designated surgical resident. Involvement with N1 and N2 lymph node groups represent regional disease, which is encompassed by the D2 lymphadenectomy, whereas N3 and N4 lymph nodes are considered distant metastases. In addition, the presence and extent of intraabdominal metastases to the peritoneum and liver are categorized (Table 33.3-8).
incidence of lymph node metastases in gastric cancer and that the rate of skip metastases was less than 1%. In this study, as well as in others, who underwent curative (D2) resection for gastric cancer, Sowa and coworkers outcomes of patients operated on in different periods were compared, and it is possible that other factors could have influenced survival. In a series of 486 patients with 454 patients undergoing extensive regional lymph node dissection (ELD) for gastric carcinoma. The therapeutic effect of ELD was greatest in patients with 166 patients undergoing total gastrectomy with curative intent for tumors with positive serosal invasion when a D2 lymphadenectomy was performed compared with 62 metastases (N3–4), or diffusely infiltrating carcinomas (linitis plastica). Takeda and coworkers compared to the first. However, radical (D2) resection did not improve survival for patients with extranodal disease, such as peritoneal metastases, distant lymph node with respect to stage, depth of tumor invasion, presence of serosal invasion, and N1 or N2 nodal metastases, improved survival was noted in the most recent period 1966, 1969 to 1973, and 1971 to 1985. The 30-day operative mortality rate declined from 3.8% in the first period to 1.0% in the latest. When patients were compared although not a formal component of stage grouping, the histopathologic grade and type and, when available, the peritoneal lavage cytology status should be recorded. The presence of free peritoneal cancer cells has been shown by a number of investigators to be an M1 equivalent. These include well-differentiated, superficial type IIla or IIIC lesions that are generally smaller than 3 cm in diameter and located in an easily manipulated area. Tumors invading the submucosa are at increased risk for metastasizing to lymph nodes and are not appropriate for endoscopic resection. Takekoshi et al. reported a series of 308 endoscopic resections for early cancer. Forty-four patients had residual or recurrent lesions after endoscopic mucosal resection. All recurrences were resected, and no patients died of gastric cancer. In experienced hands, endoscopic mucosal resection is a suitable alternative to gastrectomy for favorable early gastric cancer.

SURGERY

The only potentially curative treatment for localized gastric cancer is complete surgical resection. The principles that guide operative management are based on the Halstedian belief that gastric cancer progresses from mucosa to submucosa where it then invades into lymphatics. From there, lymph node involvement occurs but before the disease reaches the systemic circulation. Clearly this is an oversimplified view of tumor progression; however, support for this theory comes from the strong correlation between depth of invasion and the extent and number of lymph node metastases. Others have argued that epithelial cancers can metastasize directly into the systemic circulation, thus bypassing lymph nodes. Molecular factors, which govern invasion and metastases, differ from one tumor to the next, such that even some early gastric cancers do recur and are fatal after curative surgery. In general, the success of an R0 resection is directly dependent on stage as determined by the TNM system. It is well accepted that surgery carries a high cure rate for stage IA and IB cancers and much poorer results for stages IIA and IIB. Disagreement exists among surgeons with respect to the appropriate extent of resection, because improved outcome has not been conclusively linked with more radical surgery. Current areas of discussion include the potential therapeutic benefit from extended lymphadenectomy, the routine use of total versus subtotal gastrectomy for tumors of the body or antrum, and prophylactic splenectomy.

Extended Lymphadenectomy

The Japanese Research Society for Gastric Cancer proposed a standardized D2 resection for patients undergoing curative gastrectomy. As radical surgery for gastric cancer has become uniformly accepted in Japan, the operative mortality rate for D2 resection has declined and 5-year survival after curative resection has improved. Many large retrospective reports from Japan, other Asian countries, and specialty centers in the West advocate a D2 lymphadenectomy for patients with resectable gastric cancer. Maruyama and colleagues have reported results from more than 20,000 cases from a nationwide registry in Japan for three periods: 1963 to 1966, 1969 to 1973, and 1971 to 1985. The 30-day operative mortality rate declined from 3.8% in the first period to 1.0% in the latest. When patients were compared with respect to stage, depth of tumor invasion, presence of serosal invasion, and N1 or N2 nodal metastases, improved survival was noted in the most recent period compared to the first. However, radical (D2) resection did not improve survival for patients with extranodal disease, such as peritoneal metastases, distant lymph node metastases (N3–4), or diffusely infiltrating carcinomas (linitis plastica). Takeda and coworkers also have reported that 5-year survival improved from 21% to 46% in 166 patients undergoing total gastrectomy with curative intent for tumors with positive serosal invasion when a D2 lymphadenectomy was performed compared with 62 patients in whom no systematic lymphadenectomy was performed. Kodama and colleagues have compared survival in 254 patients undergoing simple resection with 454 patients undergoing extended regional lymph node dissection (ELD) for gastric carcinoma. The therapeutic effect of ELD was greatest in patients with serosal invasion (T3) or with positive lymph node metastases; patients with T1, T2, T4, or N0 disease did not show a benefit from ELD. In all of these studies, outcomes of patients operated on in different periods were compared, and it is possible that other factors could have influenced survival. In a series of 486 patients who underwent curative (D2) resection for gastric cancer, Sowa and coworkers demonstrated that tumor size and depth of penetration were directly related to the incidence of lymph node metastases in gastric cancer and that the rate of skip metastases was less than 1%. In this study, as well as in others, T1–2 lesions had metastases limited to perigastric lymph nodes in 15% to 40% of patients, suggesting that, in cases of less-advanced cancers, a systematic lymphadenectomy may be
Reports have also come from the United States and Europe that are mostly retrospective series advocating D2 lymphadenectomy for gastric cancer. Keller and colleagues, reporting for the German Stomach Cancer TNM Study Group, recommended systematic lymphadenectomy for resectable gastric cancer because occult lymph node metastases were pathologically identified two to three times more frequently than when no systematic lymphadenectomy was performed. Roder et al. reported the results of the German Gastric Cancer Study, in which the treatment of 1998 patients was prospectively recorded and assessed in a systematic, uniform manner. They demonstrated a survival advantage after D2 lymphadenectomy for stage II and IIIA tumors. The issue of stage migration was dismissed on the basis that both the standard and extended lymph node dissection groups had far more than the recommended 15 lymph nodes examined. In a retrospective analysis of 210 patients, Shiul et al. found that, if their lymphadenectomy encompassed one echelon of pathologically uninvolved nodes beyond the level of nodal metastases, survival was significantly improved over those with a less extensive lymphadenectomy (69% vs. 25%, respectively). Irwin and Bridger have reported a similar 60% 5-year survival rate in 22 patients undergoing curative D1 resection, but all 22 had pathologically negative nodes (T1–3,N0).

Because of the technical difficulty of an extended lymphadenectomy, some authors have addressed the possibility of using selective lymph node dissection in gastric cancer with macroscopically suspicious nodes. In one series, however, the mean size of metastatic lymph nodes in 370 patients undergoing D2 gastrectomy was 7 mm, and others have reported that surgeons could correctly diagnose metastatic involvement by intraoperative macroscopic examination in only 20% of patients. Noguchi and colleagues have reported that, although a direct correlation exists between lymph node size and the frequency of metastases, 30% of all metastases to lymph nodes occur in nodes smaller than 3 mm in size. Therefore, it is unlikely that selective lymphadenectomy based on gross appearance of lymph nodes is feasible or appropriate.

The need for and extent of lymphadenectomy necessary for patients with early gastric cancer, defined as primary tumors limited to the mucosa or submucosa, is controversial. Risk factors for lymph node metastases have been identified for intramucosal tumors in early gastric cancer. Some have advocated selective lymphadenectomy, particularly if other favorable factors exist, such as a primary tumor of small size (less than 1.5 cm), protruded-type tumor (Bormann type I), and tumors confined to the mucosa. Hochwald et al. analyzed 165 early gastric cancers for clinical and pathologic factors associated with a low incidence of lymph node metastases. Tumor size (relative risk [RR], 4.8; 95% CI, 4.0 to 5.5), depth of invasion (RR, 3.4; 95% CI, 2.9 to 4.0), and the presence of venous invasion (RR, 3.3; 95% CI, 2.8 to 3.8) were all independently associated with having positive nodes. However, of the 47 tumors smaller than 4.5 cm in size and limited to the mucosa only, 4% had lymph node metastases. Kurhara et al. found that when submucosal carcinomas were classified into three categories according to depth of invasion by dividing the submucosal (sm) layer into three equal parts—sm1, sm2, and sm3—the incidence of lymph node metastasis increased from 2% to 12% and 20%, respectively. With the availability of EUS and mucosal strip biopsy techniques such as endoscopic mucosal resection, informed decisions can be made regarding the risk of lymph node metastases and need for lymphadenectomy. The approach to early gastric cancer is evolving into one of selective management. The favorable long-term results of endoscopic mucosal resection suggest that lymphadenectomy is not needed in properly selected cases.

For advanced cancers, considerable debate continues as to whether the routine use of an extensive en bloc resection of second-echelon lymph nodes (D2 resection) is superior to a more limited lymphadenectomy of the perigastric lymph nodes (D1 resection). Four prospective randomized trials have now been completed on this subject. Dent et al. reported the first prospective randomized trial of D1 versus D2 gastrectomy from Cape Town, South Africa (Table 33.3-9). At surgery, only 43 patients of 403 explored were randomized to receive either D2 or D1 gastrectomy. They found no difference in 5-year survival rates. Patients undergoing D2 resection had a significantly longer operating time, greater transfusion requirement, and longer hospital stay. A second single-institution, prospective, randomized trial comparing the standard lymphadenectomy (D1) to D3 total gastrectomy (lymphadenectomy of celiac axis, and porta hepatis) in 55 patients with antral cancer was reported from Hong Kong. The length of hospitalization and morbidity was significantly increased in the D3 group. Median survival was significantly shorter than for D1 resection patients. In Japan and in specialty centers in the West, however, where extended D2 resection is performed routinely, operative mortality is minimal and does not appear to be related to the extent of lymphadenectomy. Given the small sample sizes, these trials lacked the statistical power needed for meaningful interpretation of survival results.

In 1989, two major randomized trials were conducted to further address the D2 controversy. In the United Kingdom, the Medical Research Council (MRC) conducted a trial that accrued 737 patients, with 400 patients randomized into two equal arms at the time of laparotomy. Postoperative morbidity was significantly greater in the D2 group (46% vs. 28%; P < 0.001). Hospital mortality was an alarming 13% for the D2 group and 6% for D1 (P < 0.04; 95% CI for D2, 4% to 11%). The excess morbidity and mortality seen in the D2 group was associated with the routine use of distal pancreatectomy and splenectomy, which proponents of the D2 lymphadenectomy would point out is not required for adequate lymph node clearance. In a follow-up publication, Cuschieri et al. reported that the 5-year survival rates were 35% for D1 resection and 33% for D2 resection (difference, −2%; 95% CI, −12% to 8%). Both overall and recurrence-free survival were the same. The authors concluded that their findings indicated that the classic Japanese D2 lymphadenectomy offered no survival advantage over the D1. The question of whether D2 resection without pancreatcospplenectomy is better than standard D1 resection could not be dismissed by the results of this trial.

The Dutch Gastric Cancer Group conducted a subsequent larger and rigorously monitored trial. In this study, 996 patients were entered and 711 were randomized (380 in the D1 group and 331 in the D2 group). In an effort to assure quality control, all operations were monitored. Initially, this oversight was done by a Japanese surgeon who trained a group of Dutch surgeons who, in turn, acted as supervisors during surgery at any one of the 80 participating centers. A number of observations were made from this trial. Despite the extraordinary efforts made to ensure quality control of the two types of lymph node dissection, both noncompliance (not removing all lymph node stations) and contamination (removing more than was indicated) occurred, thus blurring the distinction between the two operations. The percentages of patients given a positive D1 lymphadenectomy in the D2 group (43% vs. 25%, P < .004), and these patients required a longer hospitalization. Pancreatcospplenectomy also was performed en passant in the D2 group as part of the classic operation.

In summary, the D2 operation is a systematic approach toward the removal of high-risk perigastric lymph nodes. Most retrospective single-center reports indicate that the routine use of extended lymphadenectomy for gastric cancer can be performed safely. Four prospective randomized trials have not shown a survival advantage for the D2 lymph node dissection and do not support the routine use of extended D2 gastrectomy. A modified D2 operation avoiding pancreatcospplenectomy will provide superior staging information and may avoid the added morbidity and mortality associated with the additional organ resection. The advanced stage of disease at surgery in most patients remains the key determinant of survival. If there is a survival benefit from the D2 lymphadenectomy, it is limited to those with few lymph node metastases.

### Table 33.3-9: Prospective Randomized Trial Comparing D1 versus D2–3 Resection for Potentially Curable Gastric Carcinoma

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Design</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRC</td>
<td>UK</td>
<td>Randomized</td>
<td>Increased morbidity and mortality in D2 group, no survival advantage</td>
</tr>
<tr>
<td>UK</td>
<td>Randomized</td>
<td>35% 5-year survival for D1 vs. 33% for D2</td>
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<tr>
<td>Japan</td>
<td>Randomized</td>
<td>Similar 60% 5-year survival rate in 22 patients undergoing curative D1 resection, but all 22 had pathologically negative nodes (T1–3,N0)</td>
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</table>

Total versus Subtotal Gastrectomy

Ideally, the extent of gastric resection should provide the optimal cancer procedure with the minimal attendant morbidity. The rationale for the routine use of total gastrectomy is presumably based on the appreciation that extensive intramural extension of tumor may be present and that simultaneous multiple gastric cancers have been reported. Although older retrospective data do suggest that survival is improved with total gastrectomy compared with subtotal gastrectomy, current evidence does not support this finding. Three prospective randomized trials have addressed this question for the treatment of distal gastric cancers. A French cooperative prospectively randomized trial of total gastrectomy versus subtotal gastrectomy has reported data on postoperative morbidity, mortality, and
5-year survival. One hundred sixty-nine patients with adenocarcinoma of the antrum who were operated on with curative intent were included for analysis. 147 The groups were well matched for the usual prognostic variables. The overall complication rate and postoperative mortality rate was 32% and 1.3% for total gastrectomy and 34% and 3.2% for subtotal gastrectomy, respectively. No difference was found in cumulative 5-year survival between groups. The second single institution prospective randomized trial, as reported above in the Extended Lymphadenectomy section, compared subtotal gastrectomy and D1 lymphadenectomy with total gastrectomy and D3 lymphadenectomy in 55 patients with antral cancers from Hong Kong. 148 No survival advantage was found after the more extensive resection. Bocelli et al. 149 reported the 5-year survival rates from a multicenter randomized Italian trial conducted by the Italian Gastrointestinal Tumor Study Group. The median follow-up was 72 months after subtotal gastrectomy (range, 2 to 125 months) and 75 months after total gastrectomy (range, 7 to 113 months). The 5-year survival rate was 65.3% after subtotal gastrectomy and 62.4% after total gastrectomy for gastric cancer. The data support the use of subtotal gastrectomy for the treatment of advanced distal tumors, provided a 5-cm gross negative margin can be achieved.

Other series have reported an operative mortality after total gastrectomy, ranging from 4% to 18%, and that anastomotic leak is responsible for up to 50% of these operative deaths. 150-152 Others have argued that the functional results after total gastrectomy may be slightly worse than with distal subtotal gastrectomy. 153,154 Moreover, the ability to completely dissect paracardial lymph nodes is not related to the extent of gastric resection. 155 Therefore, although routinely used by many, there is not considered the initial option in patients in whom a 5-cm gross proximal margin can be obtained with a subtotal resection.

Carcinomas arising in the proximal one-third of the stomach have a worse prognosis than distal gastric lesions. 156 Total gastrectomy has traditionally been the procedure of choice for proximal tumors. Review of the prospective gastric database at Memorial Sloan-Kettering Cancer Center from July 1985 to August 1995 identified 391 patients with proximal gastric cancers. Ninety-eight of these patients underwent either a total or proximal gastric resection exclusively through an abdominal approach. Patients undergoing esophagogastrectomy were excluded. Patients were matched for clinical and pathologic factors. The length of hospital stay was the same for patients undergoing resection for proximal gastrectomy (16.5 days; range, 8 to 55 days) and for total gastrectomy (18 days; range, 8 to 48). Postoperative morbidity for proximal gastrectomy (6.0%) and total gastrectomy (3.0%) were not significantly different. The overall 5-year survival rate for proximal gastric cancer was 43% and was 41% for total gastrectomy. Total and proximal gastric resection have similar time to first recurrence, and the pattern of recurrence was the same. As was found for distal tumors, the extent of resection for proximal gastric cancer does not affect long-term outcome.

The functional sequelae and postoperative mortality of proximal gastric resection are considered to be worse than for total gastrectomy. In a series of 89 patients reported by Buh and associates, 156 who were treated with total gastrectomy, distal gastric resection, or proximal gastric resection, the latter group had a higher incidence of dumping, heartburn, and reduced appetite. In addition, quality of life and capacity to work were reduced in patients with proximal gastric resection. The Norwegian Stomach Cancer Trial has prospectively studied the incidence of postoperative complications and mortality in more than 1000 consecutive patients undergoing surgery for gastric cancer. 157 The postoperative mortality rate in more than 760 patients undergoing resection was 8.4% and was highest in patients undergoing proximal resection (16%) compared to total gastrectomy (8%). Subtotal gastrectomy (10%), or distal resection (7%). Factors significantly related to the incidence of postoperative complications included advancing age, male gender, no antibiotic prophylaxis, and splenectomy. Similar to the postoperative mortality, the complication rate was highest for proximal resections (52%), followed by total gastrectomy (38%), subtotal resection (28%), and distal resection (19%). Therefore, for proximal lesions, it appears that total gastrectomy using a variety of reconstructive options may provide better functional results, but this observation has not been tested in a prospective randomized fashion. 158 There appear to be fewer complications and a lower operative mortality after total gastrectomy for the treatment of proximal gastric cancers.

Prophylactic Splenectomy

Several authors have critically evaluated the value of routine splenectomy during gastric resection for tumors not adjacent to or invading the spleen. 159-161,162,163 and 164 In a multivariate analysis of more than 250 patients who underwent total gastrectomy with curative intent, no correlation was found between splenectomy and survival. 165 The Norwegian Stomach Cancer Trial has demonstrated a higher complication rate with the use of splenectomy in their prospective trial (42% vs. 27%). 166,167 In Sasaki’s analysis of potential risk factors in patients from the Dutch multicenter randomized study of D1 versus D2 lymphadenectomy, splenectomy was the most important risk factor for developing a complication (RR, 2.13; 95% CI, 1.44 to 3.16). 168 The consensus from the literature is that prophylactic splenectomy increases morbidity and mortality without an apparent survival benefit. 169,170,171,172 and 173

TECHNIQUE OF OPERATION

Beginning with laparoscopy allows for careful intraoperative staging of disease. Inspection for the presence of ascites; hepatic metastases; peritoneal seeding; disease in the pelvis, such as a “drop” metastasis; or ovarian involvement should be performed. Once distant metastases have been ruled out depending on the location of the lesion, a bilateral subcostal incision or a midline abdominal incision can be used to gain adequate exposure to the upper abdomen. The stomach should be inspected to assess the location and extent of tumor. The size and location of the primary tumor dictates the extent of gastric resection. A D2 lymphadenectomy sparing the spleen and pancreas can be done safely and provides an excellent specimen for surgical and pathologic staging, but this procedure should only be performed by or with an experienced surgeon.

The D2 subtotal gastrectomy commences with mobilization of the greater omentum from the transverse colon. After the omentum is mobilized, the anterior peritoneal leaf of the transverse mesocolon is incised along the lower border of the colon, and a plane is developed down to the head of the pancreas. The infrapyloric lymph nodes are dissected, and the origin of the right gastroepiploic artery and vein are ligated. With a combination of blunt and sharp dissection, the plane of dissection continues on to the anterior surface of the pancreas, extending to the level of the common hepatic and splenic arteries. This maneuver can be tedious, but theoretically it provides additional protection against serosal spread of tumor to the local peritoneal surface.

The right gastric artery is ligated. At this point, the duodenum is divided distal to the pylorus. The stomach and omentum are then reflected cephalad. The gastrecthepatic ligament is divided close to the liver up to the gastroesophageal junction. Dissection is then continued on the hepatic artery toward the celiac axis. Once near the celiac axis, the lymph node-bearing tissue is dissected until the left gastric artery is visualized and can be divided at its origin. The proximal peritoneal attachments of the stomach and distal esophagus can then be incised, and the proximal extent of resection is chosen.

For tumors of the mid- and proximal stomach, dissection of the lymph nodes along the splenic artery and splenic hilum is important. This technique is not indicated for antral tumors, given the low rate of splenic hilar nodal metastases seen with these tumors. The stomach is then divided 5 cm proximal to the tumor, which dictates the extent of gastric resection. Despite the fact that the entire blood supply of the stomach has been interrupted, a cuff of proximal stomach invariably shows good vascularization from the feeding distal esophageal arcade. When feasible, most surgeons prefer to anastomose jejunum to stomach versus esophagus because of the technical ease and excellent healing. Reconstruction using a variety of techniques has been described and is a matter of personal choice (Fig. 33.3-7).

FIGURE 33.3-7. Variations in types of reconstruction after total or subtotal gastrectomy include (left to right) the Roux-en-Y, Braun, and Lawrence techniques.

ADJUVANT THERAPY
As already mentioned, the prognosis for patients with gastric cancer is, to a large extent, dependent on the stage of the disease at the time of diagnosis. Patients with early-stage gastric cancer (Tis, T1N0M0; or shallow penetrating T2N0M0) have a good to excellent prognosis, with cure rates exceeding 70% to 80% after operation alone. Although surgery, however, patients with locally advanced cancers without nodal metastases (T3N0 gastric cancers) have an at least 50% chance of dying within 5 years; lymph node metastases have an even more ominous prognosis. Although 80% to 90% of American patients fall in the high-risk group, preoperative identification of patients at low risk for recurrence is difficult. Newer preoperative staging techniques, such as laparoscopy, have been demonstrated to be highly sensitive and specific in identifying patients with intraabdominal metastatic tumor, particularly in the peritoneal cavity. However, these techniques still have a relatively low sensitivity for separating deeply penetrating T2 from T3 tumors, as well as a low sensitivity for identifying metastatic lymphadenopathy. Therefore, for patients who have more than early-stage gastric cancer (deeply penetrating T2 or T3 tumors and patients with lymph node metastasis), the use of systemic therapy early in the treatment plan is rational in a disease in which a high propensity is seen for systemic failure with or without local recurrence. Neoadjuvant chemotherapy (also known as preoperative or primary chemotherapy) is an attractive concept in diseases such as gastric cancer for which complete resection of the primary tumor is often difficult or impossible, and because systemic dissemination at the time of diagnosis is common. A more traditional approach to adjuvant therapy is the use of postoperative treatment.

**POSTOPERATIVE TREATMENT**

Table 33.3-10 summarizes the results of a number of prospective randomized trials of postoperative chemotherapy in gastric cancer. These studies date back to the 1960s. Two early trials from the Veterans Administration Surgical Oncology Group investigated the use of thiotepa or 5-fluorodeoxyuridine (FUDR) after surgical resection. Both were negative. A series of trials have involved the use of mitomycin (see Mitomycin-Containing Regimens) and doxorubicin-containing combination chemotherapy adjuvant regimens have been reported (see Anthracycline-Containing Regimens). The uses of several doxorubicin-containing combination chemotherapy adjuvant regimens have been reported (see Anthracycline-Containing Regimens). Table 33.3-10 summarizes the results of a number of prospective randomized trials of postoperative chemotherapy in gastric cancer. These studies date back to the 1960s. Two early trials from the Veterans Administration Surgical Oncology Group investigated the use of thiotepa or 5-fluorodeoxyuridine (FUDR) after surgical resection. Both were negative.

### TABLE 33.3-10. Intravenous Adjuvant Therapy for Gastric Cancer: Selected Phase III Trials

**Nitrosourea-Containing Regimens**

Four studies have used a combination of 5-fluorouracil (5-FU) and the nitrosourea methyl chloroethylcyclohexylnitrosourea (CCNU) as adjuvant therapy after gastric resection. It should be noted that, in advanced disease, 5-FU and methyl CCNU had only modest effectiveness, and this combination was an inferior arm in a randomized trial in patients with advanced disease (see Nitrosourea-Containing Regimens). The Gastrointestinal Tumor Study Group randomly assigned patients to either no additional treatment or to 18 months (originally 2 years) of methyl CCNU and 5-FU. At a final analysis, the survival curves reached statistical significance in favor of the chemotherapy arm. However, an identical study using 5-FU and methyl CCNU performed during the same period by the Eastern Cooperative Oncology Group using the same dose and schedule and including a group of 180 patients (89 controls, 91 treated) demonstrated no difference in disease-free or overall survival rate (median survival, 32.7 and 36.6 months; 2-year survival rate, 57% for both groups) (see Table 33.3-10). A third study by the Veterans Administration Surgical Oncology Group using the same agents on a different schedule was also negative.

Estrada and colleagues studied the use of 12 to 18 months of methyl CCNU, 5-FU, and doxorubicin or observation in a small group of 66 evaluable patients after resection. At 5 years, no difference was noted in disease-free survival (29% treated vs. 34% observed) or overall survival (29% vs. 37%). Two treatment-related deaths were reported. Most current adjuvant or neoadjuvant studies do not include a nitrosourea.

**Mitomycin-Containing Regimens**

A series of trials have involved the use of mitomycin (see Mitomycin-Containing Regimens). One Spanish trial investigated the use of high-dose mitomycin C alone after surgical resection. In this study, only 33 patients received chemotherapy; 37 patients were in a control group. A striking difference in survival was noted (seven relapses in the treatment arm, 23 in the control arm; P = .001). The chemotherapy dose schedule was mitomycin C, 20 mg/m² once every 6 weeks for four doses. An update continues to show a significant survival advantage for the mitomycin-treated group. However, this study has not been confirmed by other mitomycin-containing trials.

In a larger study, evaluable patients were randomized after gastrectomy to receive (within 7 days of surgery) mitomycin C, 10 mg/m² monthly for six doses, plus oral uracil and fluorouracil (UF) or to expectant observation. With a median follow-up of 3.1 years, no difference was noted in disease-free or overall survival between treatment and control groups (median survival for patients receiving chemotherapy, 2.3 years; for observation, 2.6 years). This study does not confirm the role of mitomycin C in the adjuvant setting. However, although the total dose was similar (80 mg/m² vs. 60 mg/m²), the dose intensity was different. Allum and coworkers reported the results of a three-arm randomized trial comparing postoperative 5-FU and mitomycin C with or without cyclophosphamide, 5-FU, vincristine, and methotrexate induction compared with surgery only. The study allowed entrance up to 12 weeks after surgery. The surgery-only group received saline every 3 weeks; 140 patients received 5-FU and mitomycin C plus a 5-day induction course of cyclophosphamide, 5-FU, vincristine, and methotrexate; 141 patients received 5-FU and mitomycin C alone. Therapy was continued for 2 years. With a median follow-up of 100 months, the median survival was 15.5 months; no significant difference was noted between the treated or control groups.

Japanese studies involving mitomycin also have been reported. Nakajima et al. treated a group of 243 patients who received either mitomycin C, 5-FU, plus uracil and fluorouracil (UFT) or to expectant observation. With a median follow-up of 3.1 years, no difference was noted in disease-free or overall survival between treatment and control groups (median survival for patients receiving chemotherapy, 2.3 years; for observation, 2.6 years). This study does not confirm the role of mitomycin C in the adjuvant setting. However, although the total dose was similar (80 mg/m² vs. 60 mg/m²), the dose intensity was different. Allum and coworkers reported the results of a three-arm randomized trial comparing postoperative 5-FU and mitomycin C with or without cyclophosphamide, 5-FU, vincristine, and methotrexate induction compared with surgery only. The study allowed entrance up to 12 weeks after surgery. The surgery-only group received saline every 3 weeks; 140 patients received 5-FU and mitomycin C plus a 5-day induction course of cyclophosphamide, 5-FU, vincristine, and methotrexate; 141 patients received 5-FU and mitomycin C alone. Therapy was continued for 2 years. With a median follow-up of 100 months, the median survival was 15.5 months; no significant difference was noted between the treated or control groups.

A preliminary report in patients with advanced gastric cancer has compared a cisplatin, epirubicin, and FU combination to a combination of mitomycin, epirubicin, and FU. Although the initial report indicated an advantage to the mitomycin-containing arm, at the presentation itself no advantage was reported. Most current adjuvant or neoadjuvant studies do not include mitomycin.

**Anthracycline-Containing Regimens**

The uses of several doxorubicin-containing combination chemotherapy adjuvant regimens have been reported (see Anthracycline-Containing Regimens). Coombes and colleagues.
studied 215 patients with curatively resected gastric cancer who were randomized to receive FU, doxorubicin (Adriamycin), and mitomycin (FAM) or no postoperative therapy. Two hundred eighty-one patients were evaluable for analysis. Chemotherapy could be started as late as 6 weeks from surgery. Twenty-six percent of patients in the control arm had N2 disease versus 18% in the treated group, but this difference was not statistically significant. With a median follow-up of 68 months, 56% of patients in the treated arm and 51% of those in the control arm had a recurrence in disease. No significant difference was reported in disease-free survival or overall survival (FAM: 45.7%; control: 35.4%). A number of subgroup analyses were performed, the most positive of which was that there was an effect for patients with T3 or T4 tumors who had positive lymph nodes (P = .07 in favor of the FAM group). This, however, was an unplanned subgroup analysis. Three FAM patients died from suspected treatment-related complications. In a second FAM study, the Southwest Oncology Group also failed to note an improvement in survival for the treated group. Both groups of investigators concluded that chemotherapy, including FAM, when given in the adjuvant setting, should be used only in an investigational setting.

Krook and colleagues used a different doxorubicin-containing combination in the adjuvant setting. After curative resection, 125 evaluable patients were randomized to either observation alone or to three cycles of 5-FU, 250 mg/m²/d, for 5 days plus doxorubicin, 40 mg/m², on day 1. Treatment began between 4 and 6 weeks after resection. No differences were noted in overall survival between the two groups (median survival of observation group, 31 months; treatment group, 36 months). The 5-year survival rate was almost identical (33% vs. 32%). Two treatment-related deaths, both related to sepsis during leukopenia, were reported.

The FU, doxorubicin (Adriamycin), and methotrexate (FAMTX) regimen has been extensively studied in patients with advanced metastatic disease, and in randomized trials it was superior to regimens such as FAM. There is one randomized trial from the Netherlands comparing neoadjuvant FAMTX to surgery alone. Five patients who were eligible and evaluable patients were entered: 27 were randomized to receive FAMTX before surgery and 29 to undergo surgery only. In the FAMTX plus surgery treatment group, 15 patients (56%) had curative resections versus 18 of 29 (62%) in the surgery-only arm. Forty-four percent of treated patients could not complete the planned four courses of FAMTX due to disease progression or toxicity. Response evaluation after chemotherapy was possible in 25 patients: two complete responses, six partial responses. The difference in curative resectability rate was 6.5% (95% confidence interval ~32% to +19%) in favor of surgery only. The authors concluded that more active regimens than FAMTX will be required for future randomized trials.

Neri et al. used a regimen containing epirubicin, FU, and leucovorin for patients with stage III disease. Chemotherapy was given for 7 months. Fifty-five patients were followed expectantly, and 48 received chemotherapy. The median survival rate for patients receiving therapy (20.4 months) was superior to those undergoing observation (13.6 months; P = .01). At an average of 36 months of follow-up, 25% of patients receiving adjuvant therapy were alive compared to 13% of those who were followed expectantly. Although these results are encouraging, they are at odds with the study by Krook et al. in a similar number of patients. Use of this regimen should still be considered experimental, and it requires a larger confirmatory trial.

Tsavaris et al. performed a small randomized trial in which epirubicin was substituted for doxorubicin to create the FU, epirubicin, and mitomycin (FEM) regimen. Eighty-four patients were randomized to receive three cycles of FEM or no treatment. Recurrence or death occurred in 64% of patients receiving FEM versus 81% of the control group, however, this difference was not statistically significant.

Cisplatin-Containing Regimens

Although cisplatin-containing combinations have undergone extensive studies in patients with advanced metastatic disease, as discussed below (see Palliative Treatment of Gastric Cancer), currently no randomized trials are available in which patients with curative resections of gastric cancer were postoperatively and randomly assigned to receive or not receive a cisplatin-based regimen.

METAANALYSIS OF ADJUVANT CHEMOTHERAPY TRIALS

Earle and Maroun presented the preliminary results of a metaanalysis involving 12 trials performed in Western countries. It was not clear that individual patient data was obtained. In this analysis, the crude odds ratio for death for patients receiving adjuvant therapy was 0.81 (0.67 to 0.98) with a relative risk of 0.94 (0.88 to 1.01). These authors concluded that the survival benefit from these trials in patients undergoing curative resections was small. In an earlier analysis, Hermans et al. reviewed 11 trials reported since 1980. In these studies, surgery was followed by postoperative chemotherapy or by observation alone. A total of 2096 patients were studied. The odds ratio was 0.86 (0.78 to 1.08), which was not statistically significantly superior to observation alone. In a later brief report by the same authors, two additional trials were added to this database that indicated a slight benefit to postoperative adjuvant therapy.

In both cases, the metaanalysis performed involved a variety of chemotherapy regimens, most of which had FU in common. They were a review of the literature, rather than a pooled analysis of individual patient data. Furthermore, the number of patients involved is relatively small in comparison to the metaanalysis in breast cancer, for example. Gastric cancer outcomes to date suggest a modest benefit for older chemotherapeutic regimens. Almost all of these trials are seriously handicapped by their statistical design: With a small number of patients accrued, only very large differences could be expected to show a statistical benefit. Particularly as newer, potentially more effective chemotherapy regimens are developed, a high priority should be placed on designing trials that have adequate numbers of patients who are carefully staged so that the trials have appropriate power to allow an assessment of benefit.

INTRAPERITONEAL CHEMOTHERAPY

The rationale for the use of intraperitoneal therapy after resection of primary gastric cancer is based on the high risk of peritoneal metastasis as a component of first failure. Autopsy series and second-look laparotomy series have reported that up to 50% of patients have clinically evident peritoneal carcinomatosis as a site (sometimes the only site) of failure. The pharmokinetic rationale for intraperitoneal therapy has been well described. Drug concentrations within the peritoneal cavity are severalfold to one to two logs higher than concentrations that can be achieved after oral or intravenous treatment. Clinical support for the use of intraperitoneal therapy has come from other tumors. For example, a decrease of all sites of failure in patients receiving adjuvant colon cancer treatment using intravenous FU plus oral levamisole was reported; the only exception was peritoneal recurrence. In ovarian cancer, a large randomized trial demonstrated a small but statistical and clinically significant survival advantage for women receiving a portion of their therapy intraperitoneally. Thus, as is the case for many abdominal malignancies, a strong rationale exists for maximizing the effectiveness of currently available antineoplastic agents by using intraperitoneal treatment as a portion of the adjuvant therapy.

During the 1990s, an increasing number of reports have summarized data on the use of immediate postoperative intraperitoneal chemotherapy for patients with gastric cancer. Interpretation of this data is hampered, however, by the retrospective nature of some of these trials. In addition, most prospective studies are pilot or phase II, involving small numbers of patients and testing feasibility. Last, even the small number of phase III trials reported to date are severely underpowered, making definitive conclusions regarding the use of intraperitoneal therapy, at this point, impossible. Table 33.3-11 lists selected reports involving intraperitoneal chemotherapy given as adjuvant treatment in the postoperative setting. Although the database is limited, several themes are clear. The technique most commonly used is to administer intraperitoneal treatment (with or without hyperthermia) at the end of resection of all gross disease. Intraperitoneal chemotherapy is delivered in the operating room or recovery room or, at the latest, within several days of resection. In the latter case, this involves placement of an intraperitoneal catheter with therapy started soon after operation and given for repeated courses. No randomized comparative studies of the two techniques are available. The theoretical advantage of immediate intraoperative treatment is better distribution, whereas the theoretical advantage of intraperitoneal therapy via an implanted catheter is the ability to give repeated courses. Both techniques also have been used with established peritoneal carcinomatosis, but it is even harder to draw conclusions regarding this patient population. A fluorinated pyrimidine (FU or FUDR) or mitomycin C is usually part of the treatment plan.
Several centers in the United States and Europe are currently evaluating the feasibility of CHPP for patients with peritoneal carcinomatosis. Hamazoe and colleagues\(^1\) did have a significantly better 5-year survival rate compared with historically matched controls. In patients who underwent major gastric resection, the incidence of an primarily from centers in Japan\(^2\). Several multiarm studies have evaluated the efficacy of prophylactic or therapeutic CHPP administered immediately after resection for gastric cancer reported\(^3\).

CHPP takes advantage of the favorable pharmacokinetics that can be achieved with intraperitoneal chemotherapy\(^4\). Continuous hyperthermic peritoneal perfusion (CHPP) for the treatment or prophylaxis of peritoneal carcinomatosis usually is administered during exploratory laparotomy. Therapy began 2 to 4 weeks after surgery. This study also allowed entrance of patients with documented peritoneal metastasis so that patients (most with stage IIIA or IIIB tumors) received intraperitoneal cisplatin, 25 mg/m\(^2\), and systemic FU in high-risk patients having undergone potentially curative resections with gastric cancer. Thirty-five patients were without evidence of recurrent disease at a mean follow-up of 24 months, 51% of patients remained alive and free of disease. Toxicity was acceptable. An unusual side effect of sclerosing encapsulating peritonitis was noted in 15% of patients. Further investigation revealed that solutions containing FU had a pH of greater than 8.5. The authors speculated that this resulted in hydrolysis of cisplatin to a reactive alkylating species. To avoid further sclerosing encapsulating peritonitis, the authors subsequently avoided mixing cisplatin and FU.

In preclinical studies, Archer and Grey\(^5\) used a rat model to demonstrate that intraperitoneal chemotherapy is capable of treating both peritoneal and liver micrometastasis. In a second study, Murthy and coworkers\(^6\) demonstrated in a mouse model that the frequency of tumor formation at sites of surgical trauma in the peritoneum ranged from 28% to 82%, depending on the type of incisions made in the peritoneal cavity, as opposed to a 33% rate of peritoneal tumors in nonoperated mice. Data from several animal models indicate that the risks of peritoneal implantation and intraabdominal tumor spread immediately after laparotomy are high\(^7\). Clinically, a randomized trial in colon cancer by Sugarbak and colleagues\(^8\) demonstrated a marked decrease in peritoneal metastasis with intraperitoneal chemotherapy when compared with intravenous treatment, but showed no change in survival.

During the late 1980s and early 1990s, one of the most extensively used intraperitoneal agents in gastric cancer was mitomycin C. As is the case for all intraperitoneal therapy in gastric cancer, however, the small number patients involved hamper interpretation of this data. The initial promising study of Hajiwara and colleagues\(^9\) indicated a marked improvement in survival for patients randomized to intraperitoneal therapy compared to those receiving no postoperative treatment. Mitomycin was adsorbed to a carbon-containing solution and infused immediately after the end of the operative procedure. In this study, 24 patients received treatment with mitomycin and 25 were observed after operation. A highly significant difference in favor of the intraperitoneally treated group was found (2-year survival, 68.6% vs. 26.9%, the difference was maintained at 3 years). This study sparked a number of reports, some of which are included in Table 33.3-11. Retrospective reviews using higher-dose mitomycin with or without activated charcoal raised concerns regarding toxicity, with some studies indicating a high risk of intrabdominal toxicity leading to an increase in perioperative mortality. To more definitively test the hypothesis that intraperitoneal mitomycin offered benefit, Rosen and colleagues\(^10\) reported their results using a similar technique. Ninety-one patients were randomly assigned to resection followed by observation or resection followed by carbon-adsorbed mitomycin C, 50 mg, given intraperitoneally. The study was stopped prematurely when an interim analysis revealed a marked increase in postoperative complications (25% vs. 16%) and an increased perioperative mortality (11% for patients receiving intraperitoneal therapy vs. 2% for the control arm). No survival advantage was noted at the time of the interim analysis, and the trial was closed. This randomized trial, plus the phase II and prospective data, indicate that intraperitoneal mitomycin C, particularly in higher dosages of 25 to 50 mg, given with or without activated charcoal and with or without hyperthermia may be associated with a marked increase in toxicity with only questionable improvement in survival.

Regimens that do not contain mitomycin C also have been studied. These primarily involve the use of fluorinated pyrimidines (either FU or fluorouridine), usually given with leucovorin or other agents (e.g., cisplatin) or both. Mitomycin in lower doses also has been used with FU. Phase II studies performed in the United States at single institutions by Crookes et al.\(^11\) and Alik et al.\(^12\) indicated that postoperative intraperitoneal therapy using fluorinated pyrimidines could be given with safety, however, unusual toxicity has occasionally been noted. Alik and colleagues\(^13\) from Memorial Sloan-Kettering Cancer Center reported the results of a phase II study involving intraperitoneal cisplatin and FU plus systemic FU in high-risk patients having undergone potentially curative resections with gastric cancer. Thirty-five patients (most with stage IIIA or IIIB tumors) received intraperitoneal cisplatin, 25 mg/m\(^2\), on days 1 to 4 and FU, 750 mg/m\(^2\), as a single dose. Each drug was given daily for 4 days in a row for up to five cycles on a once a month basis. FU systemically as a continuous 24-hour infusion was given simultaneously. With a median follow-up of 24 months, 51% of patients remained alive and free of disease. Toxicity was acceptable. An unusual side effect of sclerosing encapsulating peritonitis was noted in 15% of patients. Further investigation revealed that solutions containing FU had a pH of greater than 8.5. The authors speculated that this resulted in hydrolysis of cisplatin to a reactive alkylating species. To avoid further sclerosing encapsulating peritonitis, the authors subsequently avoided mixing cisplatin and FU together before administration. No further episodes of sclerosing encapsulating peritonitis were seen. In a further update of this trial with a minimum follow-up of 42 months, 40% of patients remain alive and free of disease.

Yu et al.\(^14\) reported the results of a randomized trial in which 248 patients were randomly assigned to receive intraperitoneal therapy or to observation. Patients receiving intraperitoneal chemotherapy were given mitomycin C on postoperative day 1 and FU on postoperative days 2 to 5. The study included patients with all stages of gastric cancer, and in the case of other mitomycin-containing regimens, and mortality were higher in the experimental arm (postoperative mortality). The therapeutic agent administered into the perfusate was usually mitomycin C (10 mg/mL). Steady-state concentrations of mitomycin C were approximately tenfold higher in the perfusate compared with serum. With the significant hyperthermia, a mild increase in hepatic transaminases was noted after treatment. However, the studies did confirm that CHPP could be safely administered after a major extirpative procedure.

Continuous hyperthermic peritoneal perfusion (CHPP) for the treatment or prophylaxis of peritoneal carcinomatosis usually is administered during exploratory laparotomy after a primary tumor resection in patients who have established carcinomatosis or who are considered at high risk for developing peritoneal disease. CHPP takes advantage of the favorable pharmacokinetics that can be achieved with intraperitoneal chemotherapy and the established synergistic cytotoxicity of hyperthermia and chemotherapy.\(^15\)

Most of the initial clinical experiences came from Japanese investigators who administered CHPP to patients in whom peritoneal seeding was identified at the time of gastric resection for cancer.\(^12\).\(^16\)\(^17\)\(^18\) The therapeutic agent administered into the perfusate was usually mitomycin C (10 mg/mL). Steady-state concentrations of mitomycin C were approximately tenfold higher in the perfusate compared with serum. With the significant hyperthermia, a mild increase in hepatic transaminases was noted after treatment. However, the studies did confirm that CHPP could be safely administered after a major extirpative procedure.

Fujimoto and coworkers\(^19\) and Gilly and colleagues\(^20\) reported that malignant ascites could be palliated effectively with CHPP. Fujimoto's group reported that five of six patients with malignant ascites secondary to recurrent gastrointestinal cancer had resolution of the ascites after undergoing tumor resection and CHPP; all five patients were without evidence of recurrent disease at a mean follow-up of 12.8 ± 5 months. Gilly's group reported that nine of ten patients had no evidence of recurrent ascites on ultrasound obtained 2 months after CHPP. Fujimura and colleagues\(^21\) treated 31 patients with peritoneal carcinomatosis secondary to recurrent gastric cancer with cisplatin and mitomycin C administered via CHPP. In 12 of 31 patients who underwent a second-look operation, four had a complete response and one had a partial response to treatment. However, it is important to appreciate that CHPP is only effective in treating small-volume peritoneal disease. Yonemura and coworkers\(^22\) introduced CHPP with 30 mg mitomycin C and 300 mg cisplatin as prophylactic treatment for peritoneal recurrence after curative resection of 79 advanced gastric cancers. Survival was compared to that of 81 patients treated during the same period. Prolonged survival was reported in the subgroup of patients with tumors that penetrated the serosa. No increase in morbidity or mortality was reported between the two groups.

Several multimodal studies have evaluated the efficacy of prophylactic or therapeutic CHPP administered immediately after resection for gastric cancer reported primarily from centers in Japan\(^23\)\(^24\)\(^25\)\(^26\)\(^27\)\(^28\)\(^29\)\(^30\). In a report by Koga and coworkers\(^31\), a subset of 47 patients who had histopathologic evidence of serosal invasion, the 3-year survival rate in the CHPP-treated group was better than in the control group, but not significantly. In the same study, a larger CHPP-treated cohort did have a significantly better 5-year survival rate compared with historically matched controls. In patients who underwent major gastric resection, the incidence of an abdominal leak and length of postoperative hospital stay were lower in the CHPP-treated group. Fujimoto and colleagues\(^32\) reported that overall survival was significantly longer in patients treated with CHPP; in the subgroup analysis, the beneficial effect was observed in patients with and without documented peritoneal seeding. Peritoneal disease was the major contributing cause of death in patients who did not receive CHPP. In a three-armed randomized trial reported by Fujimura and colleagues\(^33\), the efficacy of CHPP was compared with continuous normothermic peritoneal perfusion and surgery alone in patients with gastric cancer and serosal invasion undergoing resection with curative intent. In the two perfusion groups, survival was significantly better compared with the group receiving surgery alone. Hamazoe and colleagues\(^34\) reported that survival was slightly better in 42 patients treated prophylactically with CHPP compared with 40 untreated control patients. Several centers in the United States and Europe are currently evaluating the feasibility of CHPP for patients with peritoneal carcinomatosis.\(^35\)\(^36\)\(^37\)\(^38\)\(^39\)\(^40\)\(^41\)\(^42\)\(^43\)\(^44\)\(^45\)\(^46\)\(^47\)\(^48\)\(^49\)\(^50\)\(^51\)\(^52\)\(^53\)\(^54\)
In summary, intraperitoneal chemotherapy given with curative intent is a rational strategy to pursue until such time as more highly effective systemic agents can be developed. Future studies will probably require intergroup or international trials to accrue adequate numbers of patients in a timely fashion.

**IMMUNOCHEMOTHERAPY**

Japanese and Korean investigators have performed a number of trials investigating the use of immunomodulatory agents as adjuvant treatment after curative resection of gastric cancer. Many of these trials involved using a protein-bound polysaccharide (PSK) alone or combined with chemotherapy after gastrectomy. PSK is a polysaccharide extracted from *Coriolis versicolor*, whose mechanism of action is not fully understood. The control arm in most of these studies, however, also received chemotherapy. Nakazato and coworkers\(^{[2]}\) reported the results of a study involving\(^{[2]}\) patients who were randomly assigned to receive mitomycin plus FU (given by mouth) or the same chemotherapy plus PSK. The experimental arm received treatment with PSK for 36 months after surgery. As part of the eligibility process, patients had to have a positive purified protein derivative (PPD) test. Both groups received ten cycles of chemotherapy. With a minimum follow-up of 5 years, a significant survival advantage was seen for the PSK group; 70.7% of the PSK group versus 59.4% of the standard treatment group were alive and disease-free at 5 years. Ochiai and colleagues\(^{[3]}\) compared chemotherapy versus chemoinmunotherapy after resection. The immunotherapy used was a *Nocardia rubra* cell wall preparation. No surgery-only control group was established; both groups received mitomycin, FU, and cytosine arabinoside chemotherapy. In this study, therapy was started perioperatively: Patients received mitomycin during surgery and on day 1, and then began weekly mitomycin, FU, and cytosine arabinoside. The chemoinmunotherapy group had 90 patients, and the chemotherapy immunotherapy group had 97 patients. No difference in survival for patients having curative resections was seen. A subgroup of 71 patients did not undergo a curative resection and were analyzed separately. A survival advantage for those receiving chemoinmunotherapy was seen.

In other trials, Japanese investigators have studied the use of chemoinmunotherapy plus immunomodulating agents after potentially curative resection. In one trial, chemotherapy with mitomycin, FU, and cytosine arabinoside plus OK432 (a *Streptococcus pyogenes* preparation) was given to 74 patients, whereas a control group of 64 patients underwent surgery alone.\(^{[2]}\) Of the group receiving postoperative treatment, 44.6% were alive at 5 years compared to 23.4% of those randomized to surgery only. In a follow-up three-arm trial, patients were randomized to receive chemoinmunotherapy with OK432 plus chemotherapy with mitomycin and FU. A second group received chemotherapy alone, whereas the third arm was a control arm of observation after surgery. At 5 years, 45.3% of the chemoinmunotherapy group were alive compared to 29.8% of the chemotherapy group and 24.4% of the surgery group. Kim and colleagues\(^{[3]}\) performed a similar trial using FAM chemotherapy with or without OK-432. Fifty patients received chemotherapy alone, and 49 patients received chemoinmunotherapy plus OK-432. These authors reported a significant improvement in survival for chemoinmunotherapy versus chemotherapy alone (62% vs. 52%, \(P = .04\)).

In summary, data from Japanese and Korean investigators suggest that immunotherapy may improve outcome for patients undergoing potentially curative resection. The number of patients in any given trial is small, however, and the power of the observation therefore relatively weak. Large-scale confirmatory trials are necessary before accepting immunotherapy as a standard of care.

**RANITIDINE**

Preliminary data had suggested that ranitidine or cimetidine might be useful in preventing recurrence of resected gastric cancer. Primrose et al.\(^{[4]}\) performed a double-blind placebo-controlled trial of ranitidine, 150 mg twice daily, versus placebo taken for up to 5 years. No other adjuvant therapy was allowed. Patients with resectable gross disease, including those with stage IV tumors, were allowed entrance into this trial. The study, as is the case with other adjuvant trials, has only a small number of patients (41 in one arm and 46 in the other). No difference was seen in overall outcome, although a trend to benefit in stage IV patients was noted. In a second trial with a similar design using cimetidine, a similar lack of benefit was noted. Thus, to date, therapy using histamine-2 blockers has not shown benefit in preventing recurrence in patients with resected gastric tumors.

**TAMOXIFEN**

Using a hormonal approach, Harrison and colleagues\(^{[5]}\) treated 100 patients in a randomized trial with tamoxifen as a single agent. This study allowed entrance of patients who had residual gross disease, and thus the study was not evaluating truly adjuvant chemotherapy. Slightly more than one-half (55.8%) of tumors were estrogen receptor–positive. Tamoxifen had no effect on survival outcome; in fact, the control group did slightly better than the treated group.

**NEOADJUVANT CHEMOTHERAPY**

A strong rationale exists for the use of neoadjuvant chemotherapy before attempted resection in high-risk gastric cancer patients. For patients with locally advanced gastric cancers, performing a potentially curative resection (R0) is difficult; the risk of distant failure, even with resection, is high. Locally advanced gastric cancers usually are defined as those with potentially resectable T3 or T4 tumors without distant metastases. Because assessment of lymph node involvement is difficult with the preoperative staging techniques currently available, T2 lesions, particularly those with suspicious lymph nodes, also are frequently included in these studies. Many pilot and formal phase II trials have been reported, either in abstract or full form during the last 3 to 5 years. Results from selected trials are shown in Table 33.3-13. Almost all of these trials have involved the use of systemic chemotherapeutic regimens, which have demonstrated moderate response rates in patients with metastatic measurable gastric cancer. However, assessing response in patients with localized tumors is difficult. The overall accuracy of repeat endoscopy after induction chemotherapy has been poor.\(^{[6]}\) Reports indicate that even CT scans performed carefully after induction chemotherapy have a low overall sensitivity and accuracy, primarily because their negative predictive value is so limited.\(^{[6]}\) Kelsen et al.\(^{[6]}\) and others have investigated the use of EUS and CT scans in predicting pathologic stage in patients undergoing induction chemotherapy. In these trials, preoperative EUS stage before and after neoadjuvant chemotherapy was compared to pathologic T, N, and M stage. Postchemotherapy EUS was inaccurate in separating T2 from T3 tumors and in assessing lymph node status.\(^{[6]}\) Therefore, data from phase II trials indicating down-staging should be interpreted with caution.
TABLE 33.3-13. Neoadjuvant Therapy for Locally Advanced Gastric Cancer: Selected Phase II and Phase III Trials

Another technique for predicting outcome early in the treatment course involves the use of PET scanning. A decrease in F-18 fluoro-2-deoxyglucose uptake has been proposed as an early marker for objective regression in patients receiving systemic chemotherapy for locally advanced or metastatic disease. Although preliminary studies with PET in gastric cancer have now been reported, definitive, large-scale trials correlating survival outcome with change in PET scan are still awaited.

Although assessing the degree of tumor regression is difficult, phase II studies of neoadjuvant chemotherapy have demonstrated that such treatment can be given with acceptable toxicity and with no apparent increase in operative morbidity or mortality. Several phase II pilot studies have been reported using this approach (see Table 33-3-13). Ajani and colleagues performed a single-arm phase II trial involving 48 patients who had gastric cancers that were potentially operable. Etoposide, doxorubicin, and cisplatin chemotherapy was given for three courses before operation followed by two planned postoperative courses. Eighty-five percent of patients underwent operation, and 77% had potentially curative resections. Toxicity, primarily due to neutropenia, was substantial but generally manageable. One chemotherapy-related death was reported. In a second study, Ajani and colleagues used a similar regimen of cisplatin, FU, and etoposide for two preoperative and three postoperative courses. One patient underwent reoperation, and 72% had potentially curative resections. The most common site for recurrent disease was peritoneal carcinomatosis either found at surgery or developing subsequently. Lowy et al. summarized the long-term results of these and a third sequential phase II trial. A total of 83 patients were treated. All the studies involved the use of cisplatin-based therapy. Seventy-three percent of patients underwent R0 resections. Although response to therapy can be difficult to interpret, 4% of patients had pathologic complete responses. Response to chemotherapy as assessed clinically was thought to be an independent predictor of survival.

Leichman and colleagues reported the initial results of a trial in which 38 patients with resectable gastric tumors received two cycles of a preoperative chemotherapy regimen involving 5-FU, 200 mg/m^2, given over 3 weeks with weekly intravenous leucovorin, 20 mg/m^2, and monthly cisplatin, 100 mg/m^2. Postoperative intraperitoneal therapy involved FU, 3,000 mg total dose, daily for 3 days plus cisplatin, 200 mg/m^2, with intravenous sodium thiosulfate. Ninety-two percent of patients underwent laparotomy; 87% of patients had resection. Postoperative intraperitoneal therapy was possible in 68% of study patients. One treatment-related death was reported. Premedication was performed with DOPE delayed until the day of surgery. The postoperative chemotherapy regimen involved FU, 200 mg/m^2, and intravenous sodium thiosulfate. Ninety-two patients underwent laparotomy; 87% of patients had resection. Postoperative intraperitoneal therapy was possible in 68% of study patients. One treatment-related death was reported. Premedication was performed with DOPE delayed until the day of surgery.

In a follow-up study, the same group of investigators treated a group of 35 patients with preoperative cisplatin and FU chemotherapy for two cycles followed by postoperative intraperitoneal fluorouracil plus leucovorin. All patients underwent pretreatment laparoscopy and EUS, and all had T3 or lymph node–positive tumors. Preoperative toxicity was tolerable, without any increase in operative morbidity or mortality. The R0 resection rate was 82%, and the estimated median survival was 22.5 months. Fink and colleagues treated a group of 49 patients with preoperative cisplatin, FU, and leucovorin (PLF). The R0 resection rate was 76%. Median duration of survival for all patients was 36 months, and at a median follow-up of 28 months, the median survival for the R0-resected patients had not been reached.

Alexander and coworkers treated 22 patients with locally advanced gastric cancer with three cycles of 5-FU, leucovorin, and interferon followed by resection and three cycles of postoperative consolidation chemotherapy. The response rate to neoadjuvant therapy was 38%, and 18 patients (82%) underwent resection with curative intent. Endoscopic tumor biopsies were obtained in 13 patients before and during cycle two of neoadjuvant chemotherapy, and thymidine synthase (TS) levels were quantitated by Western blot. Pretreatment TS levels in tumor were significantly higher in responders versus nonresponders. After exposure to 5-FU, levels of free TS were increased in malignant tumors. Pretreatment TS levels were significantly higher in responders versus nonresponders. After exposure to 5-FU, levels of free TS were increased in malignant tumors. Pretreatment TS levels were significantly higher in responders versus nonresponders. After exposure to 5-FU, levels of free TS were increased in malignant tumors. Pretreatment TS levels were significantly higher in responders versus nonresponders. After exposure to 5-FU, levels of free TS were increased in malignant tumors. Pretreatment TS levels were significantly higher in responders versus nonresponders. After exposure to 5-FU, levels of free TS were increased in malignant tumors.

In summary, neoadjuvant approaches involving preoperative chemotherapy with or without postoperative intraperitoneal treatment are now under way in the United States and in Europe. To date, the data indicate no increase in operative morbidity or mortality. Because evaluating the primary tumor is difficult, down-staging can only be estimated. The approach, although promising, requires definitive randomized phase III trials before firm conclusions regarding the value of this technique are established.

ADJUVANT RADIATION AND CHEMORADIATION THERAPY

Few studies have evaluated radiation therapy alone (with no concomitant chemotherapy) as an adjuvant to surgical resection of gastric cancer. Most of the studies that have evaluated radiation therapy as an adjuvant have used concomitant 5-FU chemotherapy.

Some of the earliest data on radiation therapy of gastric cancer come from the Mayo Clinic, where studies were performed in the 1960s on the use of radiation therapy alone for gastric cancer and for other gastrointestinal malignancies. Although these reports were based on patients with locally advanced tumors, they laid the groundwork for the present adjuvant studies. Children and colleagues reviewed a study of patients with advanced gastric cancer who were randomized to either radiation therapy alone to a dose of approximately 4000 cGy or radiation therapy combined with 5-FU as a radiation sensitizer (bolus 5-FU for 3 days, 15 mg/kg/d). This study showed a significant improvement in survival with the combination of 5-FU and radiation compared with radiation alone. Because the dose of 5-FU was extremely low, most people have interpreted these data as showing an advantage to 5-FU as a radiation sensitizer. This observation also is consistent with the data that have been obtained in other gastrointestinal sites, such as rectal and pancreatic cancer, for which 5-FU has improved survival when combined with radiation therapy. The British Stomach Cancer Group study randomized patients to postoperative radiation therapy; postoperative chemotherapy with FAM; or surgery alone. At 5-year follow-up, no
significant difference was seen among any of the three arms, but the local recurrence rate was decreased by the use of radiation therapy (54% with surgery alone vs. 32% with radiation therapy, P < 0.01). Two studies used chemotherapy plus concurrent radiation. In one study, however, incompletely resected patients were included. Dent and colleagues treated 142 patients who were randomly assigned to no additional therapy or to 2000 cGy given in eight treatments over 10 days plus FU, 12.5 mg/kg, daily for 4 days immediately before the beginning of radiation. A second cycle was given on day 28. Patients in “division one” had no residual gross disease but may have had incomplete resection. The control group had 31 patients, and the chemotherapy/radiation group had 35 patients. No difference in survival between the two groups was reported. Moertel and coworkers from the Mayo Clinic have reported the results of a randomized trial of radiation therapy (3750 cGy in 24 fractions) plus 5-FU (15 mg/kg x 3) versus surgery alone for poor prognosis patients, including those with scirrhous carcinomas, metastases to regional lymph nodes, invasion of adjacent structures, or tumors originating in the caudina. Eighty percent of patients had positive nodal disease, and approximately 25% had invasion of adjacent structures. The treated patients had a 5-year survival rate of 20% versus a 4% 5-year survival rate in the surgery-only controls. However, the issue is confused by the fact that ten patients who were randomized to adjuvant treatment refused therapy. In this small cohort of patients, the 5-year survival rate was 30%. Locoregional recurrence was 60% in the surgery alone arm compared with 50% in the combination arm. The survival results in these studies are also similar to those reported in randomized series, such as that by Slot and colleagues, in which 57 patients with poor prognostic factors received postoperative radiation therapy to a dose of 30 to 50 Gy combined with 5-FU. The 5-year survival rate was 26%, with 16 patients having a locoregional recurrence as their first sign of relapse.

Although there have been other evaluations of chemotherapy with radiation therapy, no advantage has been shown to date with any drug regimen besides 5-FU when combined with chemotherapy. The data suggest that, for patients with nodal positivity, serosal involvement, or close or positive surgical resection margins, postoperative radiation therapy may be of value. This approach has been used in the United States in a national intergroup trial (INT 116) evaluating two cycles of chemotherapy with 5-FU and leucovorin followed by radiation therapy to a dose of 4500 cGy with concurrent chemotherapy. Intergroup 116 involved a total of 556 evaluable patients, 275 of whom were followed expectantly after operation, and 281 who were randomly assigned to receive postoperative chemoradiation therapy. All patients had undergone an R0 resection. The type of lymphadenectomy was not mandated by the study protocol. Postoperative chemoradiation therapy involved the use of FU and leucovorin chemotherapy and 45 Gy of external-beam radiation therapy. One cycle using the Mayo Clinic regimen of FU, 425 mg/m², and leucovorin, 20 mg/M², for 5 consecutive days was followed by concurrent chemoradiation. Doses were decreased during radiation to FU, 400 mg/M², and leucovorin, 20 mg/M², daily for 4 days during week 1 of irradiation, and for 3 days at the end of radiation. One month after the completion of radiation, additional chemotherapy using FU, 425 mg/M², and leucovorin, 20 mg/M², daily for 5 days was given for two additional cycles. This data has been presented in abstract form. The two arms were well balanced for important prognostic indicators. Eighty-five percent of patients had lymph node metastases. With close attention to detail, especially to radiation therapy treatment planning, toxicity was tolerable, although three (1%) toxic deaths on the experimental arm were reported. Postoperative adjuvant chemoradiation therapy resulted in a significant improvement in both disease-free and overall 3-year survival rates. The median survival was improved from 26 months for the surgery-only cohort to 40 months for those receiving chemoradiation. Three-year survival rate was 41% for surgery only and 52% for postoperative chemoradiation (P = 0.33, hazard ratio, 1.28) (J. McDonald, personal communication). If the final report confirms these initial data, postoperative chemoradiation using FU and leucovorin will become the standard of care for resected R0 patients able to tolerate such treatment.

To try to increase the total radiation dose that can safely be delivered, newer radiation approaches have been tried. An approach that has been investigated at a few centers is intraoperative electron-beam radiation therapy. In this technique, pioneered by Abe and Takahashi, patients receive a single dose of high-energy electrons delivered to the tumor bed at the time of gastrectomy. Because most of the radiosensitive normal structures can be moved from the radiation beam, the risk of producing significant bowel complications is reduced. In a nonrandomized trial, Abe has demonstrated an improved 5-year survival rate in patients with locally advanced disease (usually because of posterior infiltration) who were treated with intraoperative radiation therapy (20%). A small randomized trial of a similar approach at the National Cancer Institute did not demonstrate any significant survival advantage, although it did demonstrate an improvement in local control compared with surgery alone. A number of phase II trials have been performed that demonstrate the feasibility of this approach in a large number of centers, but these trials do not allow any conclusions regarding efficacy. Comparison of the results of the two arms of this randomized trial with the Mayo Clinic regimen used in the American trial suggests that using the Mayo Clinic regimen may have added significant benefit to the chemoradiation therapy. To date, the Mayo Clinic regimen is the only one with acceptable toxicity and no adverse effects to date. The use of this regimen is recommended for patients with localized disease, and further studies are required to determine its efficacy in patients with more advanced disease.

In general, the presence of normal tissues close to the tumor mass limits the radiation dose that can be delivered safely. The spinal cord, kidneys, small bowel, and liver are all in close proximity and cannot be entirely avoided. In addition, the stomach itself is a radiation-sensitive tissue, and high doses (more than 5000 cGy) to a functional stomach produce a significant incidence of ulceration and bleeding. When irradiating the upper abdomen, a number of acute side effects from therapy may occur, including nausea, weight loss, and fatigue. With properly planned radiation fields, the nausea is not generally severe, but given the prolonged course of radiation, if careful attention is not given to the patient's nutritional status, the therapy can end up producing more harm than good. Usually, a combination of antiemetics, multiple small feedings, and nutritional supplements are sufficient to control the side effects of treatment, but on occasion, feeding tubes are useful. If patients cannot maintain their weight before the initiation of radiation therapy, they usually have difficulty with the therapy. The other acute side effects are relatively minor and easily managed. The possible late side effects that must be considered include damage to spinal cord, liver, kidney, and stomach.

Late liver and renal failure or radiation-induced spinal cord transaction are all possible complications from excess irradiation, but if proper attention is paid to these structures during treatment planning, a clinical problem should rarely develop. The tolerance dose of the stomach itself is on the order of 5000 cGy, so those doses above this level have a real risk of producing gastric ulceration. It is common for at least one kidney to be required in the radiation field to a high dose (more than 3000 cGy), which produces a very high chance of significant renal injury, usually to the left kidney. Studies have demonstrated that, for a patient with baseline renal function that is within normal range, treating one kidney to high dose has a very low likelihood of producing renal injury that adversely affects the patient's quality of life. The compensatory hypertrophy of the unirradiated kidney results in adequate renal function, and the risk of renovascular hypertension is very low. If the equivalent of one kidney can be eliminated from the radiation field and the patient is left with a normal kidney, the compensatory hypertrophy is relatively normal or absent. However, if the radiation treatment planning is done adequately in regard to the kidneys. Standard radiation tolerance doses should be observed for the other normal tissues mentioned previously.

If radiation therapy is being used as an adjuvant or with curative intent, the patterns of spread of the tumor must be considered in planning the radiation field. In contrast to many other tumor sites, a standard radiation field is often inappropriate in treatment of gastric cancer because the spread patterns relate to the site of origin and the extension that is found on preoperative imaging studies and at surgery. The lymphatic pattern of spread has already been discussed, and this pattern greatly influences the radiation fields that are appropriate. Although one usually wishes to encompass much of the stomach (or the gastric bed), for tumors that originate in the cardia, it is not necessary to irradiate the entire cardia of the stomach and to extend the radiation field to encompass the lower esophagus, but it is necessary to treat the periduodenal lymph nodes. Similarly, for tumors originating in the caudina, it is essential that the field extend up into the esophagus and that there is full coverage of the bed of the gastric cardia and fundus, but one can safely avoid irradiating the periduodenal nodes. Often, a local failure from gastric cancer occurs from posterior extension of the primary tumor onto the pancreas and into other retroperitoneal tissues. Therefore, full coverage

### TABLE 33.3-14. Gastric Cancer: Surgery Alone versus Surgery and Intraoperative Radiation Therapy (IORT), Japan

<table>
<thead>
<tr>
<th>Technique of Radiation Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SURGERY</strong></td>
</tr>
<tr>
<td><strong>TUMOR</strong></td>
</tr>
<tr>
<td><strong>Surgery</strong></td>
</tr>
<tr>
<td><strong>R0</strong></td>
</tr>
<tr>
<td><strong>R1</strong></td>
</tr>
<tr>
<td><strong>R2</strong></td>
</tr>
<tr>
<td><strong>R3</strong></td>
</tr>
<tr>
<td><strong>(no distant metastases)</strong></td>
</tr>
</tbody>
</table>

**Notes:** 1. R0 = no residual disease, 2. FU = fluorouracil, 3. IORT = intraoperative radiation therapy.
of these areas of posterior invasion is essential. An example of a typical radiation field is shown in Figure 33.3-8. The radiation fields are primarily anteroposterior fields, although lateral and oblique fields can be very useful for the final boost. If lateral fields are used for a substantial portion of the large-field treatment, then care must be taken to avoid treating large segments of the liver to doses higher than 2000 or 2500 cGy.

The total radiation dose to be used is determined primarily by the tolerance of the normal tissues mentioned above. Generally, a dose of 4500 cGy given at 180 cGy/d has a minimal chance of producing significant late complications. At doses higher than 5000 cGy, the risk of late complications increases, and doses greater than this should be limited to very small volumes. As mentioned above, the data strongly suggest that the combination of 5-FU and radiation is more effective than radiation alone. Although the optimal method of drug administration is not known, it is appropriate to use, as a minimum, 3 days of bolus 5-FU during the first and last week of radiation therapy.

PALLIATIVE TREATMENT OF GASTRIC CANCER

Since the late 1970s, many chemotherapeutic agents have been studied in gastric cancer. Although reports of very high response rates with some of the newer combination chemotherapy regimens have been published, the median survival of patients with advanced cancer continues to be dismal.

SINGLE-AGENT CHEMOTHERAPY

The objective response rates reported for single agents in patients with gastric cancer are shown in Table 33.3-15. FU is the most extensively studied single agent in this disease, with an overall objective response rate of 21%. The two most commonly used schedules for administering 5-FU as a single agent are daily intravenous injections for 5 consecutive days, repeated every 4 to 5 weeks, and weekly intravenous injections. Both schedules have similar response rates and toxicity profiles. The major side effects of 5-FU are mucositis, diarrhea, myelosuppression, and (using a continuous infusion) the hand-foot syndrome. 5-FU has been a common element in most combination chemotherapy regimens for gastric cancer.

<table>
<thead>
<tr>
<th>Chemotherapeutic Agents</th>
<th>Response Rate</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxorubicin (Adriamycin)</td>
<td>17%</td>
<td>Central nervous system, bone marrow suppression, nausea, vomiting</td>
</tr>
<tr>
<td>Mitomycin C</td>
<td>19%</td>
<td>Myelosuppression, diarrhea, gastrointestinal distress</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>19%</td>
<td>Nephrotoxicity, neurotoxicity</td>
</tr>
<tr>
<td>Drifluoromethylornithine</td>
<td>20%</td>
<td>Myelosuppression, mucositis</td>
</tr>
<tr>
<td>Etoposide</td>
<td>25%</td>
<td>Myelosuppression, nausea, vomiting</td>
</tr>
<tr>
<td>Mitomycin C</td>
<td>23%</td>
<td>Myelosuppression, diarrhea</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>25%</td>
<td>Nephrotoxicity, neurotoxicity</td>
</tr>
<tr>
<td>Vinblastine</td>
<td>25%</td>
<td>Myelosuppression, peripheral neuropathy</td>
</tr>
<tr>
<td>Bleomycin</td>
<td>26%</td>
<td>Pulmonary toxicity, myelosuppression</td>
</tr>
<tr>
<td>Mitomycin C</td>
<td>27%</td>
<td>Myelosuppression, diarrhea</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>30%</td>
<td>Myelosuppression, neuropathy</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>30%</td>
<td>Myelosuppression, peripheral neuropathy</td>
</tr>
<tr>
<td>Topotecan</td>
<td>30%</td>
<td>Neutropenia, myelosuppression</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>30%</td>
<td>Myelosuppression, diarrhea</td>
</tr>
<tr>
<td>Irinotecan</td>
<td>30%</td>
<td>Myelosuppression, diarrhea</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>35%</td>
<td>Nephrotoxicity, neurotoxicity</td>
</tr>
<tr>
<td>5-Fluorouracil</td>
<td>49%</td>
<td>Myelosuppression, mucositis</td>
</tr>
</tbody>
</table>

Currently, several new agents have been identified as having substantial activity in advanced gastric cancer. As shown in Table 33.3-15, the taxanes paclitaxel and docetaxel have both undergone phase II trials. For paclitaxel, both 3-hour and 24-hour infusions given every 3 weeks have been studied. Overall, approximately 20% of patients have had major objective regressions, primarily partial remissions. It is unclear as to whether a substantial difference exists between the two schedules. Response also has been seen in patients who have received prior chemotherapy. Similar data exists for docetaxel. The overall response rate is approximately 20% to 25%, with most studies having used an every 3-week dosing schedule. The two taxanes have not yet been compared in prospective randomized studies. Irinotecan, a new agent in the treatment of patients with colorectal cancer, also has single-agent activity in gastric cancer. Responses have been reported in both previously treated and untreated patients.

Both of these new classes of agents have now been used in multidrug combinations as described in the following sections. In addition to the identification of the taxanes and irinotecan, interest is increasing in oral fluorinated pyrimidine therapy. In this case, although the agents being studied are not of a new class but rather are FU prodrugs, ease of administration and the mimicking of chronic infusional therapy is of interest. UFT has been the most well-studied oral fluorinated pyrimidine. Responses in 20% to 30% of patients have been reported. Fewer data are available for S1, although in one study, an unusually high response rate of 49% was reported. Also shown in Table 33.3-15 are newer agents studied since 1996 that have not demonstrated antineoplastic activity.

COMBINATION CHEMOTHERAPY

Numerous attempts have been made to develop more effective combination chemotherapy regimens using known active drugs; some trials also have included other agents that did not have substantiated activity. Both phase II and prospective randomized phase III trials have been reported (Table 33.3-16 and Table 33.3-17). In general, results from multicenter phase III trials have had lower response rates than single-institution phase II studies for the same drug regimen. Several combination chemotherapy regimens have shown response rates in the range of 30% to 50%, usually in phase II studies.
and cisplatin-containing combinations have been reported to have higher response rates and, in some trials, a survival advantage.

In a review of Japanese studies, Ogawa reported a cumulative response rate of 36% in 356 patients with a combination of 5-FU, mitomycin C, and cytarabine. The mean survival was reported as 16 to 20 months. In a randomized trial of 5-FU alone versus 5-FU, mitomycin, and cytarabine, however, Coccioni and colleagues found no statistical difference among the response rate, duration of response, or median survival in the two arms.

In a phase III trial, the North Central Cancer Treatment Group compared single-agent 5-FU to 5-FU plus doxorubicin and to FAM (see Table 33.3-17). The primary end point of this study was survival. The median survival of all patients was 29 weeks. The investigators also did not notice any significant differences in the palliative effect among these three treatment regimens.

Cisplatin-Based Chemotherapy

Although many phase II studies have been performed during the 1990s involving a variety of cisplatin-containing and non–cisplatin-containing combinations, only a few phase III randomized studies have been reported. Most of these trials involve relatively small numbers of patients, so that the ability to make definitive statements of superiority of one treatment over the other is limited.

To assess the individual contribution of cisplatin, methyl CCNU, and triazinate in combination with 5-FU and doxorubicin, the Gastrointestinal Tumor Study Group performed a prospective randomized trial comparing FAP, FAME (FU, doxorubicin (Adriamycin), and methyl CCNU), and FAT (5-FU, doxorubicin (Adriamycin), triazinate). The primary end point was survival. Of 249 patients studied, 38% had measurable disease and were evaluable for response. The response rates for FAP, FAME, and FAT were 19%, 15%, and 20%, respectively. Median survival rates were 31 weeks (FAP), 24 weeks (FAME), and 30 weeks (FAT). Severe toxicity was seen in 69% of patients treated with FAP, 62% on FAME, and 42% on FAT.

Cunningham and coworkers substituted epirubicin, an analogue of doxorubicin that, in preclinical studies, has less cardiac toxicity with equivalent tumor activity to doxorubicin, for doxorubicin in the ECF regimen in one report. Ten of 14 evaluable patients (71%) achieved an objective response. In a second trial involving 52 evaluable patients, the response rate was 37%, with a 17% complete remission rate. Median durations of survival were not reported. The Italian Oncology Group for clinical research performed a randomized phase III trial comparing the FAM regimen to a cisplatin, epirubicin, leucovorin, and FU (PELF) regimen. Nonhematologic toxicity was significantly more frequent with PELF compared with FAM, including two treatment-related deaths. PELF had a significantly higher response rate (43%) than did FAM (15%). The median duration of survival was not significantly different. Waters et al. reported the long-term results of a randomized trial in which ECF was compared to the FAMTX combination. This is one of the largest phase III trials in advanced gastric cancer reported.

In phase II studies led by Cunningham and colleagues, ECF had a high response rate with acceptable toxicity. FAMTX had been shown in earlier trials to be superior to FAM, which was one of the standards of the early 1980s. In the randomized MRC study, 126 patients received ECF and 130 patients received FAMTX. The overall response rate for ECF was significantly higher than that of FAMTX (46% vs. 21%). Median survival was also longer for ECF (8.7 vs. 6.1 months). In the update, long-term survival was presented. At 2 years, 14% of patients receiving ECF were alive versus 5% of FAMTX patients. In an earlier trial, Kim and colleagues compared FU and cisplatin to the FAM regimen. This smaller trial had 54 to 57 patients per arm. The response rate to the cisplatin-containing combination was 51%, significantly better than the 25% to 26% for the non–cisplatin-containing arms. The median duration of survival of 8.5 months was almost identical to the median duration of survival for ECF.

Barone and colleagues compared a cisplatin, epirubicin, and etoposide combination to FU plus leucovorin. In this small study, 32 patients received cisplatin-containing therapy and 33 received FU plus leucovorin. Response rates were similar (22% vs. 18%, respectively), as was median survival. The 2-year survival rate was 14% for patients receiving cisplatin, epirubicin, and etoposide compared to 3% of those receiving 5-FU plus leucovorin. The Turkish Oncology Group compared two cisplatin-containing combinations: etoposide, epirubicin, cisplatin versus FU, epirubicin, and cisplatin. 20% of patients responded to the etoposide, epirubicin, and cisplatin regimen versus 15% to FU, epirubicin, and cisplatin. Median survival rates were short (6 vs. 5 months). Thus, to date, epirubicin- and cisplatin-containing combinations have been reported to have higher response rates and, in some trials, a survival advantage.
Cisplatin -Etopoide Variants

Because of evidence that etoposide and cisplatin may be synergistic and that the combination of the two may be helpful in overcoming multidrug resistance, these drugs have been combined in many tumors. Two phase II trials of etoposide and cisplatin in advanced gastric cancer (including gastroesophageal junction adenocarcinoma) showed 75% response rates. 2A Three response rates were 22% for the cisplatin alone, 47% for the etoposide alone, and 75% for the combination. A fourth trial in patients with metastatic gastric cancer showed a 50% response rate for the combination. 2B A particularly impressive feature of these responses was that all patients improved during the drug. Cisplatin at a dose of 60 mg/m² was given on days 1 and 29 and every 6 weeks thereafter, with etoposide given at a dose of 100 mg/m² on days 3, 5, 7, and 31, 33, and 35. Toxicity was generally tolerable. In the second trial, Elliott and coworkers 2A saw 13 responses in 46 evaluable patients. Etoposide was given at a dose of 130 mg/m² x 3 plus cisplatin, 45 mg/m² x 3, on days 2 and 3. Both drugs were given by continuous intravenous infusion, and the cycles were repeated every 4 weeks. Most patients experienced severe toxicity. The median duration of response was 4 months.

Preussner and colleagues 2B used the combination of etoposide, doxorubicin, and cisplatin (EAP) and reported a 64% response rate in 67 patients, with a complete remission rate of 21%. Including patients with locoregional tumor treated in a separate trial, Wilke and colleagues 2A treated 145 patients with EAP, resulting in a cumulative response rate of 57%. Analyzing responders versus non-responders, it was found that patients with locoregional tumors had a complete response rate of 83%, with a 29% complete remission rate, as opposed to those with metastatic disease who had a response rate of 49% with a complete remission rate of 8%. Similarly, the median survival time for patients with locally advanced disease was 17 months in comparison with 8.5 months for those with metastatic disease. In four subsequent phase II trials of EAP involving 173 evaluable patients, a cumulative response rate of 53% and a complete remission rate of 6% has been seen. 2C 2D However, in each of the subsequent trials after the initial study reported by Preussner, a treatment-related death rate of 10% to 14% with EAP was noted.

In part because EAP caused severe toxicity in older patients, Wilke and colleagues 2A devised a combination chemotherapy regimen of etoposide, leucovorin, and FU (ELF) for patients older than 65 years with advanced gastric cancer. The rationale for this combination was that EAP and FU are active agents in gastric cancer that are well tolerated and have no cumulative toxicity, the dose limiting toxicity being overlapping myelosuppression; etoposide and FU are synergistic and are not cross-resistant; and leucovorin enhances the cytotoxicity of FU in other tumors. Fifty-one patients older than 65 years of age or with cardiac disease were treated. The overall response rate was 53%, including 12% complete remissions. The response rate in patients with locally advanced disease was 70% compared with 49% in patients with distant metastases. The median duration of response was 9.5 months. Twenty percent of patients experienced grade 3 or 4 myelosuppression; however, nonhematologic toxicity was generally mild. The authors recommended ELF as a suitable regimen for high-risk patients (advanced age or cardiac risk factors).

Fluorouracil, Doxorubicin (Adriamycin), and Methotrexate

The concept of biochemical modulation of 5-FU involves the use of agents designed to increase the pool of phosphoribosylpyrophosphate in tumor cells, resulting in increased 5-FU ribonucleotide metabolites, thereby increasing the effectiveness of 5-FU-directed tumor kill. This approach led Klein 2A to study sequential high-dose methotrexate followed by 5-FU in combination with Adriamycin (FAMTX) (the FAMTX regimen) in advanced gastric cancer. The interval between methotrexate and 5-FU is 1 hour in the original FAMTX regimen. Klein reported a response rate of 59% in 100 evaluable patients, with a complete remission rate of 12% and a treatment-related mortality rate of 3%. In a review of his experience, Klein noted a 6% long-term (more than 5 years) survival rate for patients receiving FAMTX.

Kelsen and colleagues 2D reported the results of a randomized trial comparing EAP to FAMTX in advanced gastric cancer. The response rates were similar. Three patients (10%) had complete remissions in the FAMTX arm; no complete remissions were seen with EAP. Although no significant differences were reported in the response rate, EAP was significantly more toxic than FAMTX for neutropenia, anemia, and thrombocytopenia. Most important, four treatment-related deaths (13%) were noted on the EAP arm as opposed to none on the FAMTX arm (P = 0.04). In view of the significant toxicity difference, the study was closed. The median durations of survival of all patients was similar (FAMTX, 7 months; EAP, 6 months). The authors concluded that FAMTX was at least as active as EAP but was significantly less toxic.

The European Organization for Research and Treatment of Cancer published the results of a multicenter prospective randomized trial comparing FAMTX with FAM. 2A (see Table 13.3). The response rate of 41% for FAMTX was significantly superior to the 9% response rate for FAM (P < 0.001). Five complete responders were reported in the FAMTX arm compared with none on the FAM regimen. Survival among FAMTX patients was also superior (42 weeks compared with 29 weeks for FAM; P = 0.004). The toxic death rate of the two combinations was similar (FAMTX, 4%; FAM, 3%). At 1 year, 41% of FAMTX versus 22% of FAM patients were alive. Nonhematologic toxicity was noted in 9% of the patients on the FAMTX arm. Seven treatment-related deaths occurred in patients on FAM than on the FAMTX regimen. As noted previously, in a randomized trial performed by Cunningham and colleagues, 2D ECF was superior to FAMTX in terms of response rate, quality of life, and survival.

The European Organization for Research and Treatment of Cancer has performed a randomized trial of FAMTX versus ELP versus cisplatin and 5-FU. In a preliminary result of this study, 274 eligible patients were randomized. 2D No significant difference was found in severe toxicity (World Health Organization scale 3 or 4+) between the three arms. The response rates in the subgroups of patients with measurable disease in the preliminary report also showed no significant difference. Median survival was 7 to 8 months. The analysis was preliminary because not all patients had been fully assessed. 2D

In summary, as is the case for adjuvant trials, few adequately powered, large-scale phase III studies have been performed comparing one regimen with another. From the point of view of median survival, little substantial difference exists between one regimen and another, particularly in those in which both arms include cisplatin. However, it is of note that 2-year survival success rates of 10% to 15% have been reported in several series reporting longer-term data, indicating that at least some patients have an initial palliative benefit. Although some investigators have proposed that one regimen be considered the standard of care, as yet no convincing data shows that one cisplatin and FU-containing combination is markedly better than another.

The identification of several new classes of agents with substantial single-agent activity (the taxanes and irinotecan) and new modalities of treatment (including newer approaches, such as immunotherapy, angiogenesis blockade, monoclonal antibody chemotherapy combinations, and manipulation of molecular biologic targets) should be vigorously pursued. Their inclusion in multidrug combinations may lead to further improvements in palliation, and eventually to cure, when these agents are used in the multimodality setting. Several large-scale randomized trials are currently underway for comparison, for example, docetaxel and cisplatin-containing treatment to "standard" cisplatin and FU or, alternatively, irinotecan and cisplatin-containing therapy to cisplatin and FU.

PREDICTING RESPONSE

The development of techniques that will allow physicians to choose those individual chemotherapeutic agents that are most likely to work in the individual patient is a high priority. It is particularly important because currently available cytotoxic chemotherapy for gastric cancer has only modest to moderate effectiveness, with the possible exception of the combination of etoposide, doxorubicin, and cisplatin (EAP) and its variants, which have substantial palliative benefit. Although some investigators have proposed that one regimen be considered the standard of care, as yet no convincing data shows that one cisplatin and FU-containing combination is markedly better than another.

Several new techniques for molecular analysis are being studied to allow individualization of therapy. These include immunohistochemical stains for expression of the molecular marker of interest (such as TS) or use of reverse transcriptase-polymerase chain reaction technology to measure relative gene expression. In gastric cancer, a substantial amount of data involves the use of relative gene expression of messenger RNA. For example, in trials from the University of Southern California and Memorial Sloan-Kettering Cancer Center, studies have been performed in patients with locally advanced but not metastatic gastric cancer. Although response has been used in the outcome analysis in several of these trials, it should be recognized that response assessment in locoregional gastric cancer can be difficult; subsequent trials will use 2-year survival, which has been recommended by the Southwest Oncology Group and the EORTC. 2B Medger et al. from the same group reported an analysis of a sub-group of patients receiving neo-adjuvant cisplatin and FU chemotherapy followed by resection and intraperitoneal FU chemotherapy. Response and survival were correlated with molecular markers in 38 evaluable patients. Those with low levels of relative TS and ERCC1 (excision repair cross complementing gene; a marker for cisplatin sensitivity) had a significantly longer median and long-term survival than did patients with high levels of expression. Fata and colleagues 2B evaluated the predictive value of TS, thymidylate phosphorylase, thymidine deoxyribonuclease, and ERCC1 in inoperable gastric cancer patients undergoing dehyung surgery, without pre- or postoperative chemotherapy. This study addressed the question as to whether levels of expression of a molecular marker were independent predictors of outcome, or whether levels of gene expression were only important in the context of chemotherapy. In a preliminary assessment, patients with low relative gene expression of TS, TP, or ERCC1 did not have an improved outcome (either disease-free or overall survival). They noted that surgery-treated patients with high TS gene expression, a marker that would predict resistance to chemotherapy, had a better survival compared to patients with low TS. This finding was persistent even in a multivariable analysis adjusting for stage.
Conversely, patients receiving cisplatin and FU preoperative chemotherapy with low TS were more likely to have better outcome. Several other groups also have investigated the use of similar molecular markers. Boku and colleagues used immunohistochemistry to measure TS, p53, vascular endothelial growth factor, and glutathione S-transferase. Thirty-nine patients in this study had unressectable disease and received cisplatin plus FU. Patients with immunohistochemistry negative for TS (indicating low expression) had a higher response rate and survived longer than patients with positive stains, as did those negative for p53, BCL2, and glutathione S-transferase. Conversely, patients with vascular endothelial growth factor–positive tumors had a higher response rate. A multivariant analysis indicated that a combination of favorable molecular phenotypes had a greater impact on survival than did performance status or other clinical parameters.

Resistance to chemotherapy has been reported by many investigators to be associated with mutations of the p53 oncogene. Several such studies have been performed in gastric cancer. Cascini and colleagues performed immunohistochemistry on pretreatment endoscopic biopsies in 30 patients with locally advanced but not metastatic disease. As is the case in other studies in this group of patients, assessing response can be difficult. With this caveat, 16 of 30 patients had high levels of p53 expression by immunohistochemistry. Ten of 12 responding patients had p53-negative tumors. These authors concluded that mutation of p53 oncogene confers resistance to chemotherapy. On the other hand, Ikeguchi et al. found no relationship between p53 status and intraperitoneal chemotherapy, nor did Yeh and colleagues. A definitive study in which adequate numbers of patients with advanced gastric cancer receive the same chemotherapy irrespective of their molecular marker profile and are followed prospectively has not yet been performed. Such studies have been proposed for other tumors (such as colorectal cancer). The identification of molecular markers measured by immunohistochemistry, by reverse transcriptase-polymerase chain reaction, or by other techniques that could predict outcome would be a substantial improvement in directing therapy.

CHEMOTHERAPY VERSUS BEST SUPPORTIVE CARE

During the late 1980s and early 1990s, considerable debate occurred over whether chemotherapy for patients with advanced gastric cancer had any advantages over best supportive care. This issue is of importance, not only in addressing the options for standard care treatment for patients with advanced disease, but in the implication that effective systemic therapy given in the palliative setting may lead to an increase in cure rate for patients with localized, high-risk, potentially curable tumors. Four randomized trials have been reported in which patients were assigned to either chemotherapy and best supportive care or best supportive care alone. In all of these trials, the option for the initiation of chemotherapy at the time of symptomatic or objective progression was at the discretion of the treating physician. Although these studies have relatively small numbers of patients (recognizing the difficulty of performing such studies and that, in several cases, the study was stopped when benefit was seen in the chemotherapy-receiving arm), the data are fairly consistent. Patients randomized to receive best supportive care alone, even when allowed to receive chemotherapy at a later date, have a median survival of 3 to 5 months. Patients randomized to immediate chemotherapy had a median survival of 9 to 11 months. More impressive is the 1- and 2-year survival when reported. As shown in Table 33.3-18, the 1-year survival rate is 35% to 40% for patients receiving chemotherapy versus approximately 10% for those randomized to best supportive care. The 2-year survival rate is 6% to 10% for patients receiving chemotherapy versus 0% of patients with initial observation. These data strongly support the conclusion similar to that of other malignancies, such as colorectal and breast cancer, that systemic chemotherapy has a real although modest effect on survival in patients with advanced disease. Furthermore, the results support the use of systemic cytotoxic chemotherapy as part of multimodality therapy in patients with less-advanced but high-risk cancers. None of the regimens used in the best supportive care trials included cisplatin nor, of course, the more recently identified active agents paclitaxel, docetaxel, and irinotecan. As already discussed, however, reports on longer-term follow-up of randomized chemotherapy trials also show 5% to 15% of patients living for longer than 2 years.

SURGERY FOR PALLIATION

Because the survival for patients with advanced gastric cancer is so poor, any proposed operation should have a good chance of providing sustained symptomatic relief while minimizing the attendant morbidity and need for prolonged hospitalization. Eltckom and Gleyzeet have reviewed the results of palliative resection versus intestinal bypass. Gastrojejunostomy in 75 patients with advanced gastric cancer. The most frequent symptoms for which patients underwent operation included pain, hemorrhage, nausea, dysphagia, or obstruction. Operative mortality was 25% for gastrojejunostomy, 20% for palliative partial or subtotal gastrectomy, and 27% for total or proximal palliative gastrectomy. The most common and often fatal complication was anastomotic leak. After gastrojejunostomy, 80% of patients had relief of symptoms for a mean of 5.9 months compared with palliative resection, which provided relief of symptoms in 60% of patients for a mean of 16.4 months. Although the duration of palliation was significantly longer after resection (P < .01), the selection criteria for resection versus bypass were not controlled, and some bias against performing a palliative resection in high-risk patients with more advanced disease may have occurred. Meijer and colleagues have also reported a retrospective analysis of 51 patients undergoing either palliative intestinal bypass or resection. In 20 of 26 patients (77%) undergoing resection, palliation was considered moderate to good with a mean survival of 9.5 months. After gastroenterostomy, some palliation was noted in 8 of 25 patients (30%), and survival was 4.2 months. Butler and colleagues have presented the results of total gastrectomy for palliation in 27 patients with advanced gastric cancer. Operative mortality was only 4%, whereas morbidity occurred in 48% of patients. Median survival was 15 months, with a survival rate of 38% at 2 years. This substantial survival rate at 2 years reflects the fact that, although all patients were symptomatic before surgery, only one-half had stage IV disease. Patients with limited plasctica present a very difficult therapeutic challenge. Resection may provide palliation of symptoms; however, survival after total gastrectomy is exceedingly poor, ranging from 3 months to 1 year.

Bozzetti and colleagues have reviewed the outcomes of 246 patients with advanced gastric cancer who underwent simple exploratory laparotomy alone, gastrointestinal bypass, or palliative resection at the National Cancer Institute of Milan. When survival was compared in patients with similar type and extent of disease, a consistent trend was seen for improved median survival with palliative resection in patients with local spread (4.4 vs 8 months) and distant spread of disease (3 vs 8 months). Biddle et al. has reported similar results in 45 patients undergoing palliative resection at the M. D. Anderson Cancer Center for advanced gastric cancer. Operative mortality for resection was 22%. In 21 patients who had undergone a palliative bypass procedure, survival was significantly shorter than for those undergoing resection (P < .01).

In select patients with symptomatic advanced gastric cancer, resection of the primary disease appears to provide symptomatic relief with acceptable morbidity and mortality, even in the presence of macroscopic residual disease. The criteria for deciding which patients may benefit from palliative operation have not been established, and the data available represent retrospective analyses of patients selected for operation. The choice of procedure in these studies may have been influenced by differences in opinion regarding the value of palliative surgery in patients with such a grave prognosis.

RADIATION FOR PALLIATION

To date, no studies have evaluated the use of radiation therapy in patients with locally recurrent or metastatic carcinoma of the stomach. Its use is likely to be limited to palliation of symptoms, such as bleeding or controlling pain secondary to local tumor infiltration. Although minimal data are available, radiation therapy seems to be fairly effective (from anecdotal experience) in controlling bleeding, as is true in other sites. This can often be accomplished at relatively low radiation doses. Pain from local tumor invasion can also be palliated, although the doses required are higher (4000 cGy). On rare occasions, a case may arise of a patient with a focal local recurrence without metastases who would be amenable to relatively high-dose radiation therapy to try to prolong survival or in whom radiation therapy would be given as an adjuvant to surgical resection. At present, however, no data support such an approach.


A series of reports have validated the epidemiologic association between chronic pancreatitis and pancreatic cancer, increased frequency in patients with long-standing diabetes, whose diabetes was diagnosed after 40 years of age. Cancer and that this risk persisted for more than a decade. Pancreatic cancer is supported by a cohort study showing that, after an initial hospitalization for diabetes, patients had an increased risk of developing pancreatic cancer and that this risk persisted for more than a decade. Diabetes mellitus has been implicated as both an early manifestation of pancreatic carcinoma and an increased risk of pancreatic cancer, and may facilitate the study of chemopreventive strategies.

Data regarding the effect of coffee consumption and excessive alcohol consumption appear to be conflicting. For each of these factors, a few studies have suggested a positive relationship with an increased risk of pancreatic cancer, whereas other studies have failed to consistently demonstrate such an association.

In Japan, the incidence of pancreatic cancer increased sharply from 1.8 per 100,000 in 1960 to 5.3 per 100,000 in 1985. Application of molecular epidemiologic techniques that are being developed for lung cancer may provide greater specificity in linking tobacco smoke with the development of pancreatic cancer and may facilitate the study of chemopreventive strategies.

In the United States, the incidence of pancreatic cancer steadily increased for several decades but has leveled off since the late 1970s, with 28,300 new cases (2% of all cancer diagnoses) estimated in the year 2000. Epidemiologic studies evaluating this trend suggest that the decreased incidence is due to a steady decline in the rate for white men, which peaked during the period of 1970 to 1974. By contrast, rates for white women, African American men, and African American women have not fallen and may have increased slightly. In Japan, the incidence of pancreatic cancer increased sharply from 1.8 per 100,000 in 1960 to 5.3 per 100,000 in 1985.

Overall, pancreatic cancer incidence and mortality statistics are similar for the United States and Western Europe. Between 1989 and 1991, mortality rates for pancreatic cancer in the United States were 10 per 100,000 for men and 6.7 per 100,000 for women. Although the overall mortality rates in industrialized societies appear similar, geographically and ethnically dissimilar populations show considerable differences in mortality rates from pancreatic cancer. In Europe, for the time period of 1985 to 1989, mortality rates ranged from 3.3 per 100,000 in Spain to 10.3 per 100,000 in Hungary and Czechoslovakia. Spain, Portugal, and Greece recorded an extremely low mortality rate of 3 per 100,000 among men.

The reasons for these regional differences and the changing incidence of pancreatic cancer remain obscure, but they might possibly be related to the trend of a declining smoking rate.

Etiologic Factors

Investigations have identified a number of factors that may contribute to the pathogenesis of pancreatic cancer. Current estimates suggest that approximately 30% of pancreatic cancer cases are due to cigarette smoking. Studies that have explored the dose-response relationship have shown that the risk of pancreatic cancer increases as the amount and duration of smoking increase and that long-term smoking cessation (more than 10 years) reduces risk by approximately 30% relative to current smokers. Application of molecular epidemiologic techniques that are being developed for lung cancer may provide greater specificity in linking tobacco smoke with the development of pancreatic cancer and may facilitate the study of chemopreventive strategies.

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Diabetes mellitus has been long associated with pancreatic cancer; however, not all studies have supported such a relationship. The precise mechanism has yet to be defined. Diabetes mellitus has been implicated as both an early manifestation of pancreatic carcinoma and a predisposing factor. It is known that pancreatic cancer can induce peripheral insulin resistance, and the argument that long-standing diabetes mellitus is also a risk factor for pancreatic cancer is supported by a cohort study showing that, after an initial hospitalization for diabetes, patients had an increased risk of developing pancreatic cancer and that this risk persisted for more than a decade. However, the increased risk was limited to patients with non-insulin-dependent diabetes or patients whose diabetes was diagnosed after 40 years of age. Metaanalysis of studies published between 1975 and 1994 showed that pancreatic cancer occurred with increased frequency in patients with long-standing diabetes. The mechanisms underlying the association between pancreatic cancer and diabetes are obscure; however, the diabetic state seems to enhance the growth of pancreatic cancer in animal models.

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## INTRODUCTION

Cancer of the exocrine pancreas continues to be a major unsolved health problem, with approximately 28,200 deaths per year in the United States and 50,000 deaths per year in Europe (excluding the former USSR). In the United States in the year 2000, pancreatic cancer is expected to be the fourth leading cause of cancer-related death for both men and women and to be responsible for close to 5% of all cancer-related deaths. Because of difficulties in diagnosis, the aggressiveness of pancreatic cancers, and the lack of effective systemic therapies, generally fewer than 5% of patients with adenocarcinoma of the pancreas survive 5 years after diagnosis. Thus, incidence rates and mortality rates are virtually identical.

## EPIDEMIOLOGY

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The reasons for these regional differences and the changing incidence of pancreatic cancer remain obscure, but they might possibly be related to the trend of a declining smoking rate.

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hereditary and nonhereditary chronic pancreatitis and pancreatic cancer. Pathologic examination of lesions along the pancreatic duct has revealed a spectrum of mucous cell hyperplasias (papillary and nonpapillary hyperplastic lesions and atypical hyperplastic lesions currently termed pancreatic intraepithelial neoplasia) in patients with chronic pancreatitis and patients with pancreatic cancer. The identification of mutations in the K-ras oncogene, a mutation found almost universally in established pancreatic cancers, in regions of mucous cell hyperplasia in patients with chronic pancreatitis provided the first molecular link between chronic inflammation and the initiation of multistep pancreatic carcinogenesis. Calculation of a general estimate of population-attributable risk has suggested that chronic pancreatitis may explain as many as 5% of pancreatic cancer cases.

The emergence of the importance of inherited genetic syndromes in gastrointestinal tract neoplasia has led to closer investigation of the potential role for heritable factors in pancreatic cancer. Considerable progress in our understanding of familial pancreatic cancer has been made since the late 1990s. Currently, it is estimated that as many as 5% to 8% of pancreatic cancer cases are associated with a familial predisposition. Several hereditary disorders predispose persons to both endocrine and exocrine pancreatic cancer. These include the multiple endocrine neoplasia type 1 syndrome, hereditary pancreatitis, hereditary nonpolyposis colon cancer/Lynch syndrome II, von Hippel-Lindau syndrome, ataxia-telangiectasia, and the familial atypical multiple mole melanoma syndrome. In addition, case reports and formal epidemiologic studies have suggested the possibility of familial aggregations of pancreatic cancer outside the context of these rare familial syndromes.

Through the establishment of large familial pancreatic cancer registries, progress has been made in understanding the specific genetic alterations responsible for the familial aggregation of pancreatic cancer in some families. Genetic testing of kindreds with increased rates of pancreatic cancer has revealed germline mutations in genes known to be important in pancreatic carcinogenesis: p16, BRCA2, and STK11/LKB1 but not Smad4. Evaluation of approximately 30 extended families with presumed familial pancreatic cancer has suggested that transmission is consistent with an autosomal dominant pattern and that even second-degree relatives of patients from these families are at increased risk. Interestingly, unlike for other familial gastrointestinal cancers (e.g., colon cancer in familial polyposis coli), the age at onset, tumor histopathology, and overall survival for patients with familial pancreatic cancer are often the same as those for patients with sporadic cancers.

Presently, the management and genetic counseling documented to be at increased risk of pancreatic cancer is extremely controversial. Options range from close observation to aggressive surgical intervention, the optimal surveillance and surgical strategies have yet to be defined. However, continued study of patients with familial pancreatic cancer and their families is expected to provide insight into the critical molecular genetic abnormalities leading to familial pancreatic cancer. These genetic abnormalities may then provide new perspectives on the process of pancreatic carcinogenesis for patients with sporadic pancreatic cancer and provide opportunities for early detection and chemoprevention.

**PATHOLOGY AND MOLECULAR PATHOGENESIS**

**CELLULAR PATHOLOGY**

The normal pancreatic architecture is characterized of a secretory gland: A background of acinar cells accounts for approximately 80% of the cell number and volume of the gland; 1% to 2% is clusters of islet cells; 10% to 15% is single-layered, cuboidal ductal cells; and a sparse interlacing network of blood vessels, lymphatics, nerves, and collagenous stroma is present. This architecture is markedly altered in carcinoma, in which the predominant histologic feature is a dense collagenous stroma with atrophic acini, remarkably preserved islet cell clusters, and a slight to moderate increase in the number of ducts, both of normal appearance and cancerous. The diagnosis of ductal adenocarcinoma rests on the identification of mitoses; nuclear and cellular pleomorphism; discontinuity of ductal epithelium; and evidence of perineural, vascular, or lymphatic invasion.

Ninety-five percent of malignant neoplasms of pancreatic origin arise from the exocrine portion of the gland and have light-microscopic features consistent with those of adenocarcinomas. Much more infrequent are tumors arising from the islets of Langerhans’ (endocrine) cells of the pancreas. Primary nonpancreatic tumors of the pancreas (e.g., lymphomas or sarcomas) are extremely rare. A current view of the histologic classification of exocrine pancreatic neoplasms is presented in Table 33.4-1.

**TABLE 33.4-1.** Histologic Classification of Epithelial Tumors of the Exocrine Pancreas

Extensive “preneoplastic” lesions have been demonstrated in the pancreatic ducts adjacent to frankly invasive cancers with a higher frequency than was seen in a matched control population without pancreatic cancer. Furthermore, clinical studies have documented progression of lesions from mild dysplasia to high-grade dysplasia and from high-grade dysplasia to infiltrating ductal adenocarcinoma. Finally, the identification of mutated K-ras, a genetic change found in the majority of patients with invasive pancreatic cancer, in papillary and dysplastic papillary ductal lesions has provided further evidence that these hyperproliferative states are the precursors of infiltrative ductal carcinoma. Current evidence supports the general hypothesis that progression of the ductal lesions is characterized by the accumulation of additional genetic and biochemical changes. For example, papillary ductal lesions can be shown to harbor mutations in genes that are typically altered in invasive pancreatic carcinoma, including P16 and P53. Activated telomerases can also be found. Interestingly, other malignancies that can masquerade as pancreatic cancer, such as carcinoma of the ampulla of vater, only infrequently contain a mutated K-ras oncogene. At present, however, accurate identification of high-risk patient subsets who are destined to develop invasive cancer and thus are candidates for intervention is not possible.

**ONCOGENES AND TUMOR SUPPRESSOR GENES**

Studies using archival human pancreatic tumor tissue and human pancreatic cancer cell lines have identified a number of characteristic genetic abnormalities associated with pancreatic cancer. As described previously, these studies have revealed specific point mutations at codon 12 of the K-ras oncogene in 75% to 90% of pancreatic adenocarcinoma specimens. The ras protein is an important signal-transduction mediator for receptor protein tyrosine kinases. Signaling is initiated by the recruitment of guanine nucleotide exchange proteins that promote hydrolysis of guanosine triphosphate (GTP) to guanosine diphosphate (GDP). Ras bound to GTP is maintained in an active configuration that triggers other enzymatic second messengers, such as theraf, phosphatidylinositol, and protein kinase C pathways, which leads to nuclear signals resulting in cellular division and proliferation. The mutated ras oncogene is not able to convert GTP to inactive GDP, resulting in a constitutively active ras protein product, unregulated cellular proliferation signals, and susceptibility to transformation. The K-ras mutation in pancreatic carcinogenesis is proposed to be an early event in pancreatic tumor progression.

Data suggest that up-regulation of vascular endothelial growth factor (VEGF) occurs as a result of the activation of mutations of the ras oncogene. VEGF is an endothelial cell–specific mitogen that promotes angiogenesis in solid tumors. Angiogenesis is essential for tumors to grow larger than 1 mm, and angiogenesis must occur for metastasis formation and growth. Overexpression of VEGF has been demonstrated in several tumors, and VEGF messenger RNA has been shown to be overexpressed in a Syrian hamster pancreatic cancer cell line. Therefore, ras mutations may contribute to pancreatic carcinogenesis not only by promoting tumor cell proliferation but also by indirectly stimulating tumor angiogenesis. The available data also suggest that ras and oncogenes mediate their effects on gene
expression partly by activating the transcription factors AP-1 and Rel/NF-κB. These transcription factors have been shown to up-regulate a number of genes whose protein products play important roles in tumor invasion, angiogenesis, and metastasis and are relevant to pancreatic cancer carcinogenesis. Other proangiogenic factors, such as interleukin-8, are also up-regulated by AP-1 and NF-κB. In addition, the tumor suppressor genes p53 and p16 have been shown to regulate the expression of VEGF. Numerous agents that inhibit angiogenesis are currently undergoing testing in phase I and II clinical trials in patients with various types of cancer in the United States.

Additional genetic alterations in human pancreatic cancer have been described, many by Kern and colleagues at Johns Hopkins University. Their studies have been facilitated by xenograft enrichment of human tumors obtained at the time of surgical resection. Pieces of the fresh human tumors are implanted subcutaneously in athymic nude mice, and the resulting tumors are harvested when they have grown to 1 cm in diameter. This allows the neoplastic cells to expand while preventing similar expansion of contaminating stromal cells. Subsequent molecular studies can then be performed on a population of pure tumor cells. Using this technology, three chromosomal loci with homozygous deletions have been identified in pancreatic ductal carcinomas. They are appropriately termed DPC (deleted in pancreatic cancer) 1/2, 3, and 4. DPC1/2 is located on chromosome 13q12 (the region of the BRCA2 gene). DPC3 (p16/MTS-1) on chromosome 9q21, and DPC4 on chromosome 18q21.1. The most recently discovered tumor suppressor gene, is an important component of the transforming growth factor-β signaling pathway that normally down-regulates the growth of epithelial cells, stimulates differentiation, and promotes apoptosis.

Loss of this important growth regulatory pathway contributes to unregulated cell growth. DPC4 was found to be homozygously deleted in 30% of pancreatic carcinomas and inactivated through loss of heterozygosity and intragenic mutation in another 20% of the cases studied.

The p16 protein belongs to a class of cyclin-dependent kinase (CDK)–inhibitory proteins (including p21/WAF1/Cip1) and inhibits the cyclin D1/CDK-4 complex that normally acts to phosphorylate the retinoblastoma (Rb) protein. Inactivation of p16 leads to hyperphosphorylation of Rb, loss of cell-cycle control, and unregulated cell growth. Allelic deletions involving p16 have been found in 85% of human pancreatic tumor xenografts. The second p16 allele is inactivated by three mechanisms: point mutations in 40% of cases, deletion of the second allele in 40%, and promoter silencing through hypermethylation of the p16 promoter in 15%. Interestingly, p16 mutations also have been detected in 30% to 50% of melanoma-prone kindreds. A report of 19 families with a history of melanoma in at least two first-degree relatives found pancreatic cancer only in families with germline p16 mutations. Patients with malignant melanoma in the cancer registries of the Surveillance, Epidemiology, and End Results program were followed to determine the incidence of pancreatic cancer in this cohort. Nearly twice as many pancreatic cancers as expected were found in patients diagnosed with malignant melanoma before age 50, and the pancreatic cancer incidence was more than twice that expected in female melanoma patients younger than 50 years.

The tumor suppressor gene p53 is critical to normal cellular function, and its amino acid sequence is highly conserved among many species. After DNA damage, p53 protein levels increase because of posttranslational changes in protein stability. The normal p53 response to DNA damage leads to both cell-cycle arrest and apoptosis. The p53 gene is the most commonly mutated gene in human cancer. Seventy percent of pancreatic adenocarcinomas have loss of p53 function. Inactivation of p53 function occurs through loss of one p53 allele and mutational inactivation of the other. Mutations in the p53 sequence are more frequently seen in poorly differentiated tumors, and patients whose tumors have a p53 intragenic frameshift deletion experience a significantly reduced disease-free survival (compared to those with other mutations or wild-type p53). However, this type of relationship has not been documented in all studies.

Based on the frequency with which mutations in K-ras, p53, and p16 are found, a model of pancreatic carcinogenesis has been suggested whereby the malignant clone evolves from cells driven by a dominant oncogene (K-ras) with subsequent deregulation of cell growth precipitated by abnormal cell-cycle control resulting from mutations in p53, p16, or both.

Exactly how the increasingly complex molecular alterations described thus far in human pancreatic cancer interact during pancreatic carcinogenesis is still unclear. However, in vitro studies designed to correct these alterations may lead to novel treatment strategies and improve our understanding of the relative roles of these changes in pancreatic cancer biology.

CLINICAL SIGNS AND SYMPTOMS

The lack of obvious clinical signs and symptoms delays diagnosis in most patients with pancreatic cancer. Jaundice, due to extrahepatic biliary obstruction, is present in approximately 50% of patients at diagnosis and is associated with a less advanced stage of disease than are other signs or symptoms. Small tumors of the pancreatic head may obstruct the intrapancreatic portion of the bile duct and cause the patient to seek medical attention when the tumor is still localized and potentially resectable. In the absence of extrahepatic biliary obstruction, few patients present with potentially resectable disease.

The pain typical of locally advanced pancreatic cancer is a dull, fairly constant pain of visceral origin localized to the region of the middle and upper back. The pain is due to tumor invasion of the celiac and mesenteric plexus. Vague, intermittent epigastric pain occurs in some patients; its etiology is less clear. Fatigue, weight loss, and anorexia are common, even in the absence of mechanical gastric outlet obstruction. Pancreatic exocrine insufficiency due to obstruction of the pancreatic duct may result in malabsorption and steatorrhea. Although malabsorption and mild changes in stool frequency are common, diarrhea occurs infrequently.

Glucose intolerance is present in the majority of patients with pancreatic cancer. Although the exact mechanism of hyperglycemia remains unclear, both altered b-cell function and impaired tissue insulin sensitivity are present. The importance of islet cell function to the development of exocrine cancer is suggested by the work of Bell and Stayer, who demonstrated that pretreatment of hamsters with streptozocin and the resulting destruction of islet cells prevented the induction of pancreatic cancer in these animals by the carcinogen N-nitrosobis-(2-oxopropyl) amine. This work was substantiated by studies in Chinese hamsters, which demonstrated that only genetically diabetic animals did not develop cancers in response to this carcinogen.

In the absence of jaundice, patient complaints are nonspecific, as are clinical signs on physical examination. However, important staging information with direct implications for therapy can be obtained from the physical examination. This information includes performance status, cardiopulmonary function, and the presence or absence of left supravclavicular adenopathy and ascites.

NATURAL HISTORY AND PATTERNS OF TREATMENT FAILURE

Rational anticancer therapy for solid malignancies is based on accurate knowledge of the natural history and patterns of treatment failure for each tumor type. Pancreatic cancer spreads early to regional lymph nodes, and subclinical liver metastases are present in the majority of patients at the time of diagnosis, even when findings from imaging studies are normal. Patient survival depends on the extent of disease and performance status at diagnosis.

The extent of disease is best categorized as resectable, locally advanced, or metastatic. Patients who undergo surgical resection for localized nonmetastatic adenocarcinoma of the pancreatic head have a long-term survival rate of approximately 20% and a median survival of 13 to 20 months (Table 33.4-3). As is discussed later (see Treatment of Potentially Resectable Disease), survival is clearly maximized by combining surgery with either preoperative or postoperative 5-fluorouracil (5-FU)-based chemotherapy and radiation therapy (chemoradiation). However, disease recurrence after a potentially curative pancreaticoduodenectomy remains common, as illustrated in Table 33.4-3. Local recurrence occurs in up to 86% of patients who undergo surgery alone; local-regional tumor control is maximized with combined-modality therapy in the form of chemoradiation and surgery. With improved local-regional disease control, liver metastases become the dominant form of tumor recurrence and occur in 25% to 53% of patients after potentially curative combined-modality treatment.
Patients with locally advanced, nonmetastatic disease have a median survival of 6 to 10 months. A survival advantage has been demonstrated for patients with locally advanced disease treated with 5-FU–based chemoradiation compared to no treatment or radiation therapy alone. Knowledge of the prognosis and patterns of treatment failure associated with adenocarcinoma of the pancreas leads to the following basic treatment principles: (1) The treatment must not be worse than the disease. The low cure rate and modest median survival after pancreatectomy mandate that treatment-related morbidity be low and treatment-related death be rare. (2) Improvements in patient survival and quality of life will result from the development of innovative treatment strategies directed at the known sites of tumor recurrence. To date, the data have clearly demonstrated that, as local-regional treatment has become more effective, the dominant site of failure has shifted to hepatic metastases. Therefore, future improvements in survival duration will result either from effective systemic or regional therapy directed at subclinical liver metastases or from strategies for screening and early diagnosis directed at increasing the number of patients eligible for potentially curative surgery. Future improvements in the quality of patient survival will result from the application of innovative multimodality therapy to carefully selected (staged) patients and the avoidance of unnecessary patient morbidity due to the inappropriate use of surgery, radiation, and chemotherapy in poorly selected (advanced disease) patients.

CLINICAL AND PATHOLOGIC (SURGICAL) STAGING

A standardized system for the clinical and pathologic staging of pancreatic cancer does not currently exist in the United States. The system of the American Joint Committee on Cancer in cooperation with the TNM Committee of the International Union Against Cancer appears in Table 33.4-4. However, this TNM (tumor, node, metastasis) staging system provides only one system for both clinical (radiographic) and pathologic staging. Pathologic staging can be applied only to patients who undergo pancreatectomy; in all other patients, only clinical staging, based on radiographic examinations, can be done. Without surgery, the histologic status of regional lymph nodes cannot be determined. In addition, treatment and prognosis are based on whether the tumor is potentially resectable, locally advanced, or metastatic, definitions that may not directly correlate with TNM status. For example, both potentially resectable and locally advanced tumors may be categorized as T4; isolated involvement of the superior mesenteric vein (SMV) would be considered T4 disease but does not preclude resection in the absence of arterial encasement.

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<tr>
<td>IV</td>
<td>Any tumor, any size. Evidence of arterial encasement or invasion of the celiac axis or SMA.</td>
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Tumors of the pancreas are unlike other solid tumors of the gastrointestinal tract in that accurate diagnosis, clinical staging, and pathologic evaluation of resected specimens require extensive interaction and cooperation among physicians of different specialties. Accurate clinical staging requires high-quality computed tomography (CT) to accurately define the relationship of the tumor to the celiac axis and superior mesenteric vessels. The use of standardized, objective radiologic criteria for preoperative tumor staging allows physicians to develop detailed treatment plans for their patients, avoid unnecessary laparotomy in patients with locally advanced or metastatic disease, and improve rates of resectability at laparotomy. Therefore, a system for clinical staging like the one illustrated in Table 33.4-5 is useful to practicing medical oncologists, surgeons, and radiation oncologists.

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If the primary tumor cannot be resected completely, surgery (pancreaticoduodenectomy) for pancreatic resection. 

RESECTABILITY SHOULD BE DETERMINED PREOPERATIVELY. Accurate preoperative assessment of resectability increases resectability rates and minimizes positive-margin resections. A common misconception in pancreatic tumor surgery is that resectability is determined best at laparotomy. In fact, however, resectability is most accurately determined preoperatively by imaging studies, not at the time of "exploratory" laparotomy. 

At the time of surgical exploration for pancreatic head cancer, a Kocher maneuver (mobilization of the pancreatic head and duodenum from their retroperitoneal attachments) is the first procedure performed to assess the relationship of the tumor to the SMA by palpation. However, the presumed accuracy of this determination of resectability should be determined preoperatively.

At the University of Texas M. D. Anderson Cancer Center, the surgeon and pathologist evaluate each specimen first by frozen-section examination of the common bile duct transection margin and the pancreatic transection margin. The retroperitoneal margin, defined as the soft tissue margin directly adjacent to the proximal 3 to 4 cm of the superior mesenteric artery (SMA), is evaluated by permanent-section examination. This can be done either by taking a 2- to 3-mm full-face (en face) section of the margin or by inking the margin and sectioning the tumor perpendicular to the margin. The retroperitoneal margin must be evaluated or accurately inked at the time of tumor resection by the pathologist and surgeon; identification of the retroperitoneal margin is not possible later. A positive bile duct or pancreatic transection margin is treated with re-resection; however, this is not possible in the retroperitoneum, where the aorta and SMA origin limit the extent of surgical resection.

Samples of multiple areas of each tumor, including the interface between the tumor and adjacent uninvolved tissue, are submitted for paraffin-embedded histologic examination (five to ten blocks). Sections 4-μm thick are cut and stained with hematoxylin and eosin. Final pathologic evaluation of permanent sections includes a description of tumor histology and differentiation; gross and microscopic evaluation of the tissue of origin (pancreas, bile duct, ampulla of Vater, or duodenum); and assessments of maximum transverse tumor diameter, lymph node status, and the presence or absence of perineural, lymphatic, and vascular invasion. When segmental resection of the SMV is required, the area of presumed tumor invasion of the vein wall is serially sectioned and examined in an attempt to discriminate benign fibrous attachment from direct tumor invasion. In patients who received preoperative chemoradiation, the grade of treatment effect is assessed on permanent sections using the grading schema developed by Cleary and reported by Evans et al. 

The cell method for subclassing of regional lymph nodes in pancreaticoduodenectomy specimens is based on the work of Cubilla et al. The soft fibrofatty tissue containing regional lymph nodes is divided into six regions as outlined on an anatomic pathology dissection board. If lymph nodes are not identified, fat or other potentially neoplastic tissue is submitted for microscopic examination. Staley and colleagues have demonstrated that the number of lymph nodes identified in the surgical specimen is inversely related to the increased incidence of recurrent disease. 

When the surgical specimen is resected, the superiority of treatment is assessed by the use of a standardized system of specimen analysis. The dissection board used at our institution provides a simple means of improving lymph node identification and documenting the location of histologically confirmed lymph node metastases. The Japanese staging system involves extremely detailed analysis of margins and lymph node groups but is not a practical system for widespread application. As the use of multimodality treatment strategies for pancreatic cancer becomes more common, it will be even more important to standardize pathologic assessment of tumor specimens.

Maintaining an active pancreatic tumor banking program is critical to the ongoing success of translational research programs. Only through the coordinated efforts of such interdisciplinary programs will new treatments advance from the laboratory to clinical practice. Pathologists should routinely bank tumors for collaborative research efforts. At the M. D. Anderson Cancer Center, small sections of normal pancreas (when possible) and tumor are collected immediately for RNA extraction, and additional samples are snap frozen in liquid nitrogen and stored at −80°C. A representative section of tumor and normal tissue is routinely fixed in 70% ethyl alcohol for paraffin block processing, and a hematoxylin and eosin–stained slide is made.

PRETREATMENT DIAGNOSTIC STUDIES

TUMORS OF THE PANCREATIC HEAD AND PERIAMPULLARY REGION

Few anatomic regions in the human body cause greater confusion and controversy regarding appropriate diagnostic evaluation and treatment than does the peripancreatic region. The reasons for this are unclear because of the differential diagnosis of extrahepatic biliary obstruction (of the pancreas, bile duct, ampulla of Vater, or duodenum), a benign stricture (usually due to pancreatitis), and choledocholithiasis. Benign tumors of the periampullary region are resected with positive margins (morbidity rate of 20% to 30%, a mean hospital stay of 1 to 2 weeks, and a median survival after surgery of only 6 months. Remaining patients are found to have unsuspected liver or peritoneal metastases or local tumor extension to the mesenteric vessels. LAPAROTOMY SHOULD BE THERAPEUTIC, NOT DIAGNOSTIC. The fact is largely responsible for the variability in diagnostic and treatment recommendations: Typically, surgeons favor surgery, gastroenterologists favor endoscopically placed stents, and radiologists favor transhepatic stents.

General Principles

The recommended diagnostic evaluation for a patient with extrahepatic biliary obstruction and presumed cancer of the head of the pancreas is based on the following three principles.

LAPAROTOMY SHOULD BE THERAPEUTIC, NOT DIAGNOSTIC. If the primary tumor cannot be resected completely, surgery (pancreaticoduodenectomy) for pancreatic cancer offers no survival advantage. However, only 30% to 50% of patients who undergo operation with curative intent have their tumors successfully removed; the remaining patients are found to have unsuspected liver or peritoneal metastases or local tumor extension to the mesenteric vessels. Therefore, the majority of patients who undergo surgical exploration for presumed cancer of the pancreatic head receive no survival benefit; however, the laparotomy results in a perioperative mortality rate of 20% to 30%, a mean hospital stay of 1 to 2 weeks, and a median survival after surgery of only 6 months. Furthermore, in patients whose tumors are resected with positive margins (Table 33.4-6), the survival duration is less than 1 year and is no different from the survival duration achieved with palliative chemotherapy and irradiation in patients who have locally advanced, unresectable disease. Therefore, in contrast to the case for selected patients with colorectal or gastric cancer, no data support palliative (positive-margin) resection for adenocarcinoma of the pancreas.

The recommended diagnostic evaluation for a patient with extrahepatic biliary obstruction and presumed cancer of the head of the pancreas is based on the following three principles.
In patients with locally advanced or metastatic pancreatic cancer, operation for palliation is rarely undertaken. Innovations in stent construction and the development of the expandable metallic stent have demonstrated its accuracy and safety. Commonly in patients with localized, potentially resectable disease because of the growing popularity of neoadjuvant therapy. Reports of EUS-guided FNA of the pancreas have demonstrated its accuracy and safety. False-positive results should be anticipated when biopsy material is interpreted by an experienced cytopathologist. If a low-density mass is not seen on CT scans, the study should be repeated.

Palliative Laparotomy Should be Avoided When Possible.

In patients with locally advanced or metastatic pancreatic cancer, operation for palliation is rarely needed. Multiple studies have compared operative biliary decompression and endoscopic stent placement in patients with jaundice due to malignant obstruction of the intrapancreatic portion of the common bile duct. The higher initial morbidity and mortality rates and longer hospital stay associated with operative biliary bypass are countered by the higher frequency of hospital readmission for stent occlusion and cholangitis with endoscopic stent placement. Physicians typically advocate either surgery or endoscopic stenting; however, a selective approach based on the patient’s extent of disease and performance status is more appropriate. Patients with liver metastases or ascites have a median survival of less than 6 months, making endoscopic stent placement an obvious choice. Patients with locally advanced disease treated with chemoradiation have a median survival of 10 to 12 months, with 20% surviving 2 years. Patients with a superior performance status at diagnosis often survive longer; yet, it is difficult in most patients to predict, at diagnosis, the tempo of disease progression. Clearly, one would like to avoid operation (with its morbidity and often lengthy recovery period) in patients with rapidly progressive disease. Similarly, it would like to have a durable means of biliary decompression in patients who are expected to survive longer than 6 to 9 months. Therefore, in patients with locally advanced nonmetastatic disease, it is reasonable to proceed with endoscopic stent placement and reserve operative biliary bypass for patients who survive long enough to experience stent occlusion. As is discussed later (see the section Palliative Methods of Biliary and Gastric Decompression), innovations in stent construction and the development of the expandable 10-mm balloon-expandable stent have improved patency rates and resulted in more widespread application of stenting. Data from Raikar and colleagues at the Mayo Clinic have demonstrated that endoscopic stenting for unresectable pancreatic cancer provides an equivalent duration of survival with a reduced cost and shorter hospital stay than operative biliary decompression, despite the need for subsequent stent exchanges.

Computed Tomography and Endoscopic Retrograde Cholangiopancreatography

Improved CT technology has resulted in CT being the study of choice to determine the extent of disease and resectability status in patients with pancreatic cancer. Image resolution has improved considerably with the use of dynamic scanning, whereby intravenous contrast material is delivered by an automatic injector. The development of helical or spiral scanning has improved scan speed through continuous rotation of the x-ray tube around the gantry. This allows the entire pancreas to be imaged during the bolus phase of contrast enhancement. In addition, scan data can be processed to display images in three-dimensional and multplanar formats. Helical CT performed with contrast enhancement and a thin-section technique can accurately assess the relationship of the low-density tumor to the celiac axis, SMA, and portal vein. However, design of the scan protocol and interpretation of scans must be done by experienced radiologists who understand the clinical importance of accurate staging and assessment of resectability in patients with pancreatic cancer. A completed CT scan report should contain the following information necessary to determine resectability: (1) the presence or absence of extrapancreatic metastatic disease, (2) the location of the SMV and SMPV confluence and their relationship to the tumor, and (3) the relationship of the tumor to the celiac axis and SMA. If such information is not apparent from review of the scans or the report, the study should be repeated.

Our diagnostic schema, based on high-quality CT, appears in Figure 33.4-1. A patient is deemed to have locally advanced, unresectable disease when clear evidence on the CT scans shows encasement of the SMA or celiac axis or occlusion of the SMV. The accuracy of CT in predicting unresectability is well established; current technology has eliminated the use of laparotomy to assess local tumor resectability. If a low-density mass is not seen on CT scans, patients with extrahepatic biliary obstruction undergo diagnostic and therapeutic endoscopic retrograde cholangiopancreatography (ERCP). A malignant obstruction of the intrapancreatic portion of the common bile duct is characterized by the double-duct sign, proximal obstruction of both the common bile and pancreatic ducts, which can often be accurately differentiated from cholecystolithiasis and the long, smooth tapering bile duct stricture seen with chronic pancreatitis. To prevent cholangitis in patients who undergo diagnostic ERCP in the setting of extrahepatic biliary obstruction, endoscopic stents are routinely placed. Endoscopic stent placement also is done in patients with elevated bilirubin levels who are enrolled in preoperative chemoradiation protocols.

Endoscopic Ultrasonography and the Role for Pancreatic Biopsy

Accurate staging and biliary decompression are achieved with CT and ERCP in the majority of patients. Endoscopic ultrasonography (EUS)-guided fine-needle aspiration (FNA) has greatly simplified tissue acquisition in patients with localized, nonmetastatic pancreatic cancer. Angiography is performed selectively and is largely limited to patients who have undergone a previous biliary bypass involving the common bile duct to define hepatic arterial anatomy before metastases or pancreaticoduodenectomy. Laparoscopic cystogastrostomy should be considered before opening the abdomen in patients with potentially resectable disease. CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography.
not occur. However, false-negative results may be common, resulting in negative predictive values as low as 40%. In a patient who presents with extrapancreatic biliary obstruction, has a malignant-appearing stricture of the intrapancreatic portion of the common bile duct, and has no history of recurrent pancreatitis or alcohol abuse, the absence of a mass on CT or EUS should not exclude the possibility of a carcinoma of the pancreas or bile duct. Similarly, negative results of EUS-guided FNA should not be interpreted as definitive evidence that a malignancy does not exist. The results of EUS, with or without FNA, should be considered in the context of the clinical situation and as a complement to CT and ERCP findings.

Although pretreatment pancreatic biopsy is frequently used, physicians should be cautioned about the use of intraoperative pancreatic biopsy. In patients with resectable disease, there is no indication for routine intraoperative biopsy, and as stated, the use of preoperative EUS-guided FNA should be limited to those patients undergoing preoperative chemoradiation in whom cytologic confirmation of malignancy is needed. In contrast to the minimal risk of FNA, a risk of peritoneal dissemination of tumor cells resulting from surgical manipulation and intraoperative large-needle biopsy is supported by data from Staley et al. Having undergone a previous laparotomy with tumor biopsy before definitive pancreatectoduodenectomy was the only factor associated with an increased risk of local-regional tumor recurrence in their study. Furthermore, intraoperative pancreatic biopsy is associated with significant complications, such as pancreatitis, pancreatic fistula, and hemorrage. Nevertheless, because of the perceived risk of tumor dissemination, 237 Nevertheless pancreatic FNA (a common concern when CT-guided FNA was popular), patients with presumed periampullary or pancreatic neoplasms are often brought to the operating room for planned intraoperative diagnostic biopsy before extirpative surgery. If the frozen-section findings are negative, many surgeons do not proceed with tumor resection because of concerns about performing such an extensive procedure, and many surgeons believe that an accurate or intraoperative pancreatic biopsy is unnecessary, because a negative biopsy in the appropriate clinical setting is likely due to sampling error and therefore should not influence the decision to proceed with pancreatectoduodenectomy. In the absence of cholecodocholithiasis found at ERCP or a history of pancreatitis, obstruction of the intrapancreatic portion of the common bile duct is almost always secondary to malignancy. If the decision to perform pancreatectoduodenectomy is based on high-quality images obtained at ERCP and on an accurate clinical history, it is extremely unlikely that pancreatectoduodenectomy will be performed for benign disease. Furthermore, if the preoperative FNA result is benign or nondiagnostic, it is a mistake to assume that the patient does not have cancer or that a tissue diagnosis can be obtained at surgery before complete tumor resection. The diagnosis of a malignant obstruction of the intrapancreatic portion of the common bile duct should be accurately established by high-quality images obtained by CT, ERCP, and EUS, unnecessary and preventable patient morbidity occurs when laparotomy, pancreatectoduodenectomy, or both are used as diagnostic studies because of the physician's failure to obtain state-of-the-art pretreatment imaging.

Laparoscopy and Angiography

During the 1990s, laparoscopy has been used in patients with radiologic evidence of localized disease to detect extrapancreatic tumor not seen on CT scans, thereby allowing laparotomy to be limited to patients with localized disease. Studies by Cuscheri and Warshaw et al. have demonstrated the value of laparoscopy in detecting liver and peritoneal metastases not seen on CT scans. This favorable initial experience with laparoscopy in the identification of subclinical metastatic disease has led to a policy of routine laparoscopy in the staging of pancreatic adenocarcinoma in many centers. However, it is important to remember that 70% of patients with pancreatic cancer present with locally advanced or metastatic disease; if laparoscopy is done early in the diagnostic sequence, it will have a very high yield of positive findings. If laparoscopy is performed after high-quality contrast-contrast-enhanced CT, the yield will likely be much lower. For example, Contol and colleagues evaluated 115 patients with periampullary tumors thought to be resectable based on CT. All patients underwent careful laparoscopic examination, including inspection of the lesser sac and biopsy of celiac, portal, or perigastric lymph nodes. Unresectable disease was found at laparoscopy in 41 (38%) of 108 evaluable patients. Sixty-one (91%) of the 67 patients with presumed resectable tumors underwent resection. Although the authors did not describe the specific CT scanning protocol used to evaluate their patients, the low radiologic resectability rate in comparison to that achievable with high-quality CT suggests that optimal preoperative imaging was not used in all patients before laparoscopy.

Contrast-enhanced helical CT allows accurate assessment of vital tumor-vessel relationships, remains the study of choice for detecting intrapancrealhuy liver metastases, and is less invasive and therefore less costly than laparoscopy (which still requires general anesthesia in most centers). CT remains the initial study of choice for determining whether a patient has potentially resectable, locally advanced, or metastatic disease; such clinical staging is critical for accurate treatment planning. Laparoscopy may prevent unnecessary laparotomy in approximately 10% of patients with presumed localized, potentially resectable pancreatic cancer. Laparoscopy before laparotomy (during a single anesthesia induction) is a reasonable approach in patients with biopsy-proven or suspected potentially resectable pancreatic cancer in whom a decision has been made to proceed with pancreatectoduodenectomy. However, data are not available to support the cost-effectiveness of laparoscopy's routine use as a staging procedure under a separate anesthesia induction before treatment planning. Furthermore, laparoscopy should not be used to compensate for inadequate CT imaging.

Contrast-enhanced helical CT also has reduced the role of preoperative angiography. Angiography does not provide the detail that is needed to determine the anatomic relationship between the tumor and the SMA that is provided by high-quality contrast-enhanced CT. Angiography allows contrast enhancement of the tumor and subsequent use of selective angiography to evaluate vascular anatomy. Furthermore, the use of angiography to reoperative cases, in which identification of aberrant hepatic arterial anatomy may prevent intravenous administration during portal dissection when there is extensive scarring from a previous biliary procedure. Having a previously placed biliary stent in place may also prevent inadvertent hepatic artery injury during portal dissection. However, if the patient has undergone previous abdominal surgery, the absence of a mass on CT or EUS should not exclude the possibility of a carcinoma of the pancreas or bile duct. Similarly, negative results of EUS-guided FNA should not be interpreted as definitive evidence that a malignancy does not exist. The results of EUS, with or without FNA, should be considered in the context of the clinical situation and as a complement to CT and ERCP findings.

TUMORS OF THE PANCREATIC BODY AND TAIL

Because adenocarcinomas of the pancreatic body and tail do not cause obstruction of the intrapancreatic portion of the common bile duct, early diagnosis is rare; virtually all patients have locally advanced or metastatic disease at the time of diagnosis. CT provides an excellent assessment of the relationship of the tumor to the celiac axis and the SMA origin. Arterial encasement is present in the majority of patients, except for the anecdotal patient who presents with upper gastrointestinal symptoms related to malignancy. If the decision to perform pancreaticoduodenectomy is based on high-quality images obtained at ERCP and on an accurate clinical history, it is extremely unlikely that pancreatectoduodenectomy will be performed for benign disease. Furthermore, if the preoperative FNA result is benign or nondiagnostic, it is a mistake to assume that the patient does not have cancer or that a tissue diagnosis can be obtained at surgery before complete tumor resection. The diagnosis of a malignant obstruction of the intrapancreatic portion of the common bile duct should be accurately established by high-quality images obtained by CT, ERCP, and EUS, unnecessary and preventable patient morbidity occurs when laparotomy, pancreatectoduodenectomy, or both are used as diagnostic studies because of the physician's failure to obtain state-of-the-art pretreatment imaging.

Other, more encouraging reports suggest that CT-occult extrapancreatic disease is uncommon, being found in only 4% to 15% of patients with tumors considered resectable after high-quality CT. In a study by Rumstadt and colleagues from the University of Heidelberg, 398 patients with pancreatic or periampullary cancer treated between 1990 and 1995 were evaluated preoperatively with high-quality CT, ERCP, and angiography. On the basis of this imaging evaluation, 194 patients were considered to have a high probability of resectability based on the absence of involvement into adjacent tissue or distant metastases. Of these 194 patients, 172 (89%) underwent successful pancreatectoduodenectomy. Only 9% (5 of 194) of the patients thought to have resectable tumors were found to have occult metastatic disease at laparotomy. The authors concluded that only this small group of patients would have benefited from laparoscopy.

Contrast-enhanced helical CT allows accurate assessment of vital tumor-vessel relationships, remains the study of choice for detecting intrapancrealhuy liver metastases, and is less invasive and therefore less costly than laparoscopy (which still requires general anesthesia in most centers). CT remains the initial study of choice for determining whether a patient has potentially resectable, locally advanced, or metastatic disease; such clinical staging is critical for accurate treatment planning. Laparoscopy may prevent unnecessary laparotomy in approximately 10% of patients with presumed localized, potentially resectable pancreatic cancer. Laparoscopy before laparotomy (during a single anesthesia induction) is a reasonable approach in patients with biopsy-proven or suspected potentially resectable pancreatic cancer in whom a decision has been made to proceed with pancreatectoduodenectomy. However, data are not available to support the cost-effectiveness of laparoscopy's routine use as a staging procedure under a separate anesthesia induction before treatment planning. Furthermore, laparoscopy should not be used to compensate for inadequate CT imaging.

TREATMENT OF POTENTIALLY RESECTABLE DISEASE

PREOPERATIVE AND POSTOPERATIVE CHEMORADIATION

EBRT and concomitant 5-FU chemotherapy (chemoradiation) were shown in several studies to prolong survival in patients with locally advanced adenocarcinoma of the pancreas. Those data were the foundation for a prospective randomized study of adjuvant chemoradiation (500 mg/m² of 5-FU for 6 days and 40 Gy of radiation) after pancreatectoduodenectomy conducted by the Gastrointestinal Tumor Study Group (GITSG); that trial also demonstrated a survival advantage from multimodality therapy compared with resection alone (20 vs. 11 months). However, owing to a prolonged recruitment, 5 (24%) of the 21 patients in the adjuvant chemoradiation arm could not begin chemoradiation until more than 10 weeks after pancreatectoduodenectomy, despite the fact that the only patients likely to be considered for protocol entry were those who recovered rapidly from surgery and had a good performance status. Similar findings have been reported from the European Organization for Research and Treatment of Cancer (EORTC). In 1987, the EORTC initiated trial 40891 comparing adjuvant 5-FU-based chemoradiation with surgery alone. Between 1987 and 1995, 218 patients were randomly assigned to either chemoradiation (40 Gy in a split course and 5-FU given as a continuous infusion at a dose of 25 mg/kg/d during EBRT) or no further treatment after pancreatectoduodenectomy for adenocarcinoma of the pancreas or periampullary region. Patients were recruited from 29 centers in Europe, one in France, and three in the Netherlands. Analysis was performed on 207 of the patients, 114 (55%) of whom had pancreatic cancer. Eleven patients were deemed ineligible for analysis because of extensive local disease with incomplete resection. The median survival duration was 24.5 months for those who received adjuvant therapy and 19 months for those who received surgery alone (P = .2; for
patients with pancreatic cancer, the median survival was 17.1 months for those who received adjuvant therapy compared with 12.6 months for those who received surgery alone (P = .099). Concerns over trial design, methodology, and data interpretation include the following:

1. The precise anatomic (pathologic) distinction between pancreatic and periampullary adenocarcinoma was not defined, and the high proportion of periampullary (nonpancreatic) tumors is unexplained.
2. Patients were considered for enrollment in this trial after recovery from pancreaticoduodenectomy; despite this selection bias, 21 (20%) of 104 evaluable patients randomized to receive chemoradiation did not receive intended therapy owing to patient refusal, medical comorbidities, or rapid tumor progression.
3. No assessment of the retroperitoneal margin of resection was performed, and therefore no mechanism to assess the completeness of surgical resection was available. Furthermore, although the method of follow-up was not defined (raising the concern that sites of recurrent disease were underestimated), tumor recurrence in the pancreatic bed was a site of first progression in 20% of patients. This finding, combined with the short survival in the observation arm (12 months for patients with pancreatic adenocarcinoma), suggests that many patients underwent incomplete resection.
4. Although the survival differences for the subset of patients with pancreatic cancer were not significant (P = .099), the wide confidence interval (relative risk, 0.7; 95% confidence interval, 0.5–1.1) does not exclude the possibility of a clinically meaningful improvement in survival in the chemoradiation arm that was not apparent because of the small sample size.

Despite these concerns, the authors concluded that postoperative adjuvant chemoradiation should not be considered standard therapy after pancreaticoduodenectomy for cancer. 220

Two additional trials of postoperative adjuvant therapy after pancreaticoduodenectomy are ongoing: the European Study Group of Pancreatic Cancer (ESPAC)-1 trial and the Radiation Therapy Oncology Group (RTOG) trial. The ESPAC-1 trial is a four-arm study incorporating a stratified factorial design to compare adjuvant chemoradiotherapy (40 Gy in a split course and 5-FU), adjuvant chemotherapy (5-FU and folinic acid), chemoradiation followed by chemotherapy, and observation alone after pancreaticoduodenectomy for pancreatic and periampullary carcinomas. 225-227 More than 40 centers in nine countries are participating in this study, which began accrual in 1994. In July 1998, the RTOG activated the first American phase III cooperative group study of postoperative adjuvant therapy for resected pancreatic adenocarcinoma since the GITSG trial. 225 Patients are randomized to receive either gemcitabine or 5-FU to be given before and after 5-FU–based chemoradiation.

Despite the selection bias involved in the enrollment of patients into postoperative adjuvant therapy studies, prospective and retrospective data suggest an improved survival duration with the addition of postoperative adjuvant chemoradiation after pancreaticoduodenectomy (Table 33.4-7). 133, 139, 151-153, 167, 170-172, 176 The most compelling data reported of late come from Yeo and colleagues 170 at Johns Hopkins University, who reviewed all patients who underwent pancreaticoduodenectomy for adenocarcinoma of the pancreatic head during a 4-year period. One hundred twenty patients received adjuvant chemoradiation, and 53 underwent pancreaticoduodenectomy alone. The median survival for those who received adjuvant therapy was 19.5 months, compared with 13.5 months for the group who received surgery alone.

TABLE 33.4-7. Chemoradiation Studies in Patients with Resectable Pancreatic Cancer

A survival advantage was also demonstrated for patients treated with adjuvant combination chemotherapy (5-FU, doxorubicin, and mitomycin C) after pancreatectomy. 144 The median survival was 23 months in the 30 patients randomized to receive adjuvant therapy, compared to 11 months in the 31 patients treated with surgery alone. Forty-six additional patients were ineligible after surgery, thus increasing the difficulty in performing multiinstitutional protocol-based research involving as complex a surgical procedure as pancreaticoduodenectomy. The toxicity of the surgery and chemoradiotherapy was significant; only 24 of 30 patients received chemotherapy, and only 13 of those received all six planned courses of chemotherapy. 183 A previous pilot study of adjuvant 5-FU, doxorubicin, and mitomycin C using a different schedule of administration found similar toxicity and therefore questioned the use of adjuvant combination chemotherapy, even of moderate toxicity, after pancreatectomy. 145

The risk of delaying or not receiving postoperative adjuvant therapy. 137, 145-147, 149 combined with small published experiences of successful pancreatic resection after EBRT. 145, 214, 215, 218-220 prompted many institutions to initiate studies in which chemoradiation was given preoperatively. 145, 214, 220 Results of these and other studies have suggested specific advantages of preoperative versus postoperative chemoradiation, including the following considerations. 145, 149 (1) Because chemoradiation and radiation are given first, delayed postoperative recovery has no effect on the delivery of multimodality therapy 149-150; (2) pancreatic/jejunal anastomotic leaks, the most common major complication after pancreaticoduodenectomy, are decreased in patients who receive preoperative chemoradiation 149; (3) the high frequency of positive-marginal resections that have been reported supports the concern that the retroperitoneal margin of excision, even when negative, may be only a few millimeters—surgery alone is thus inadequate local therapy for most patients 149; and (4) patients with disseminated disease evidence on restaging studies after chemoradiation are not subjected to laparotomy. 149

In patients who receive chemoradiation before planned pancreaticoduodenectomy, repeat staging CT after chemoradiation reveals liver metastases in approximately 25%. 139, 149 If these patients had undergone pancreaticoduodenectomy at the time of diagnosis, it is probable that the liver metastases would have already been present clinically; these patients would therefore have undergone a major surgical procedure only to have liver metastases found soon after surgery. In the M. D. Anderson Cancer Center trials, patients who were found to have disease progression at the time of restaging had a median survival of only 7 months. 149 The avoidance of a lengthy recovery period and the potential morbidity of pancreaticoduodenectomy in patients with such a short expected survival duration represents a distinct advantage of preoperative over postoperative chemoradiation. Furthermore, when delivering multimodality therapy for any disease, it is beneficial, when possible, to deliver the most toxic therapy last, thereby avoiding morbidity in patients who experience rapid disease progression not amenable to currently available therapies.

The survival advantage for the combination of chemoradiation and surgery compared with surgery alone (see Table 33.4-7) likely results from improved local-regional tumor control. Because of the poor rates of response to 5-FU–based systemic therapy in patients with measurable metastatic disease, it is unlikely that 5-FU–based chemoradiation regimens significantly impact the development of distant metastatic disease. Data from the M. D. Anderson Cancer Center support this belief. 139, 149, 150-152 Thirty-eight patients were enrolled on 39 consecutive patients who underwent pancreaticoduodenectomy and inoperative electron-beam radiation therapy (IOERT; 10 Gy) for adenocarcinoma of the pancreatic head after preoperative infusional 5-FU (300 mg/m² 7/d, 5 days per week) and EBRT (50.4 Gy). Thirty-eight patients were evaluated for analysis of patterns of treatment failure; one perioperative death occurred. Overall, 38 recurrences were found in 29 patients; eight recurrences (21%) were local-regional (pancreatic bed, peritoneal cavity, or both), and 30 (79%) were distant (lung, liver, bone). The liver was the most frequent site of tumor recurrence, and liver metastases were a component of treatment failure in 53% of patients (69% of all patients who had recurrences). Fourteen patients (37% of all patients; 48% of patients who had recurrences) had liver metastases as their only site of recurrence. Isolated local or peritoneal recurrences were documented in only four patients (11%). In contrast, previous reports of pancreaticoduodenectomy alone for adenocarcinoma of the pancreas documented local recurrence in 50% to 80% of patients. 139, 149 The improvement in local-regional control with preoperative chemoradiation was seen despite the fact that 14 of 38 evaluable patients had undergone laparotomy with tumor manipulation and biopsy before referral for chemoradiation and reoperation. If these 14 patients are excluded, only two patients (8%) experienced local or peritoneal recurrence as any component of treatment failure. However, the chemoradiation program was associated with gastrointestinal toxic effects (nausea, vomiting, and dehydration) that required hospital admission in one-third of patients. 149 In addition, the multicenter Eastern Cooperative Oncology
Group trial documented the need for hospital admission in 51% of patients during or within 4 weeks of completing chemoradiation. These findings led to a change in the delivery of radiation therapy and 5-FU at the M. D. Anderson Cancer Center. A rapid-fractionation program of chemoradiation was designed to test the gastrointestinal toxicity seen with standard-fractionation chemoradiation (5.5 weeks) while attempting to maintain the excellent local tumor control achieved with multimodality therapy. In a study of the revised regimen, rapid-fractionation chemoradiation was delivered over 2 weeks with 18-MeV photons using a four-field technique at a total dose of 30 Gy (3 Gy per fraction for ten fractions, 5 days per week). 5-FU was given concurrently by continuous infusion at a dosage of 300 mg/m^2d, 5 days per week. Restaging with chest radiography and abdominal CT was performed 4 weeks after completion of chemoradiation in preparation for pancreaticoduodenectomy. Thirty-five patients received this treatment; 27 were taken to surgery, and 20 (74%) underwent successful pancreaticoduodenectomy. Local tumor control and patient survival were equal to the results reported above with standard-fractionation (5.5 weeks) chemoradiation: Local-regional recurrence developed in only 2 (10%) of the 20 patients who underwent resection, and the median survival for all 20 patients was 25 months.

Because of the large percentage of patients who develop distant metastatic disease, predominantly in the liver, the improved local-regional tumor control achieved with combined-modality therapy (chemoradiation and surgery) translates into only a small improvement in median survival. Therefore, more effective systemic agents are needed to both maximize radiation sensitization and treat microscopic extraanatomic metastatic disease. One such potential agent is gemcitabine (Z-deoxy-2’-Z-difluorocytidine; Gemzar), a deoxycytidine analogue capable of inhibiting DNA replication and repair. After a phase I study, gemcitabine was evaluated in a multicenter trial of 44 patients with advanced pancreatic cancer. Although only five objective responses were documented, the investigators noted frequent subjective symptomatic benefits, often in the absence of an objective tumor response. Toxicity appeared to be minor and included myelosuppression, particularly thrombocytopenia, as well as a flu-like syndrome and mild hemolytic-uremic syndrome. Based on these observations, gemcitabine was compared to 5-FU in previously untreated patients with advanced pancreatic cancer. Patients treated with gemcitabine had a median survival of 6.65 months, compared to 4.41 months (p = .0025) in those treated with 5-FU. Twenty-four percent of patients treated with gemcitabine were alive at 9 months, compared to 6% of patients treated with 5-FU. In addition, more clinically meaningful effects on disease-related symptoms (pain control, performance status, and weight gain) were seen with gemcitabine (24% of patients) than with 5-FU (6% of patients). Similar systemic effects and demonstrable disease responses were documented in patients who were treated with gemcitabine after experiencing disease progression while receiving 5-FU.

Gemcitabine is also a potent radiation sensitizer of human pancreatic cancer cells in vitro, supporting studies examining its use in vivo. Laboratory studies suggest that the inhibitory effect of gemcitabine on DNA synthesis (when combined with irradiation) is prolonged in tumor compared to normal tissues. This may provide a window of opportunity for the combination of gemcitabine and EBRT when delivered in a fractionated schedule. Such data provide the basis for the ongoing phase I studies of this drug-radiation combination in patients with locally advanced pancreatic cancer; gemcitabine (combined with EBRT) is being given in escalating doses weekly as a single agent, in combination with 5-FU, or in combination with cisplatin, at a fixed dose with escalating doses of EBRT, and as a twice-weekly infusion with either standard-fractionation or split-course EBRT. Wolff and colleagues from the M. D. Anderson Cancer Center have reported a phase I study of rapid-fractionation EBRT (30 Gy over 2 weeks, 3 Gy per fraction) and concomitant weekly gemcitabine in patients with locally advanced adenocarcinoma of the pancreatic head. Gemcitabine was given during the first 2 weeks of irradiation and continued weekly to complete a 7-week course of systemic therapy. The maximum tolerated dose of gemcitabine using this treatment schedule was 350 mg/m^2week. Dose-limiting toxicities included fatigue, anorexia, nausea, vomiting, and dehydration; febrile neutropenia occurred in only one patient. Future studies of gemcitabine-based chemoradiation will likely incorporate a fixed dose-rate schedule of administration because current data suggest an improved response rate with such a schedule.

The results with gemcitabine for locally advanced and metastatic pancreatic cancer suggest that gemcitabine may be useful in patients with potentially resectable disease. Hoffman and colleagues have reported a phase I study of preoperative standard-fractionation EBRT (50.4 Gy) and escalating weekly doses of gemcitabine (300 mg/m^2, 400 mg/m^2, 500 mg/m^2) for potentially resectable pancreatic cancer. Eight (53%) of 15 patients required hospitalization after chemoradiation. Pancreaticoduodenectomy was completed in eight patients; so far, the histologic response to the preoperative therapy appears to be superior to that with prior chemoradiation combinations. No experience with adjuvant gemcitabine-based chemoradiation after pancreaticoduodenectomy has been published; acute and late toxic effects of this drug-radiation combination may be more significant than when it is used in the preoperative setting. The evolution of multimodality therapy for patients with potentially resectable pancreatic cancer appears in Figure 33.4-2. Future regimens will likely emphasize neoadjuvant therapy and capitalize on our expanding understanding of the molecular basis of metastasis, allowing conventional chemoradiation and surgery to be combined with systemic or regional delivery of novel agents that inhibit essential steps in tumor cell growth.

![Figure 33.4-2](https://example.com/fig3342.png)

**FIGURE 33.4-2.** The evolution of multimodality neoadjuvant (preoperative) therapy for patients with potentially resectable adenocarcinoma of the pancreatic head. Current treatment schemas combine 5-fluorouracil (5-FU) chemoradiation (ChemoXRT) and pancreaticoduodenectomy. Short-course rapid-fractionation chemoradiation avoids the gastrointestinal toxicity of standard-fractionation chemoradiation and reduces overall treatment time. Future treatment schemas (currently being studied in the protocol setting) emphasize the importance of improving local and systemic disease control with more potent radiation-sensitizing agents and novel systemic therapies. n, restaging evaluation; ChemoXRT #1, 50.4 Gy, 1.8 Gy per fraction: 5-FU 300 mg/m^2d, M–F; ChemoXRT #2, 30 Gy, 3.0 Gy per fraction: 5-FU 300 mg/m^2d, M–F; ChemoXRT #3, 30 Gy, 3.0 Gy per fraction: with improved radiation-sensitizing agents (gemcitabine). aSystemic agents: novel systemic agents, such as inhibitors of angiogenesis, farnesyl-protein transferase, epidermal growth factor, and so forth.

**PANCREATICODUODENECTOMY**

**Background**

Current surgical treatment is based on the procedure of pancreaticoduodenectomy as described in 1935 by Whipple et al. Their two-stage pancreaticoduodenectomy consisted of bile duct diversion and gastrojejunostomy during a first operation and, after the patient recovered (approximately 3 weeks later), resection of the duodenum and pancreatic head. By 1941, the world experience totaled 41 cases, and the perioperative mortality rate was 30%. Before 1940, the pancreatic remnant was not reanastomosed to the small bowel, and the high mortality rate was largely due to pancreatic fistula from the oversewn pancreatic remnant. In 1941, Whipple modified his technique to include a pancreaticojejunostomy, with the entire procedure done in one operation. In 1946, Waugh and Clagett from the Mayo Clinic described their modification of the one-stage procedure to its current form. The goals of surgical therapy outlined by Waugh and Clagett have not changed since that date: (1) there should be reasonable opportunity for cure, (2) the risk of death should not outweigh the prospects for cure, and (3) the patient should be left in as normal a condition as possible.

**Surgical Mortality Rates**

Advances in operative technique, anesthesia, and critical care have resulted in a 30-day in-hospital mortality rate of less than 2% for pancreaticoduodenectomy when performed at major referral centers by experienced surgeons. At such centers, mortality rates remain less than 2% despite the use of multimodality therapy, the frequent need for complex vascular resection and reconstruction, and the referral of many patients after an initial unsuccessful attempt at tumor resection. Mortality rates from other institutions, including university centers and the Department of Veterans Affairs hospitals, have been reported in the range from 7.8% to more than 10%. Data from New York State have demonstrated that hospitals performing fewer than nine pancreatic resections per year have an unacceptably high perioperative mortality rate of 12%. Data from Maryland and Ontario, Canada, also have demonstrated that increased patient volume is...
associated with lower surgery-related mortality. The most compelling data on the relationship of hospital volume to perioperative mortality and long-term survival after pancreaticoduodenectomy come from the Center for the Evaluative Clinical Sciences at Dartmouth Medical School. Birkmeyer et al. studied 7229 Medicare patients older than 65 years of age who underwent pancreaticoduodenectomy at 1772 hospitals between 1992 and 1995. The study population was divided into quartiles according to hospital volume, with high-volume centers defined as those that performed five or more pancreaticoduodenectomies per year. Forty-high-volume hospitals (2%) performed 1541 (21%) of the 7229 pancreaticoduodenectomies. In-hospital mortality was 11% overall, 4% in high-volume hospitals, and 10% to 15% in medium-volume (two to five pancreaticoduodenectomies per year) and very low-volume (fewer than one pancreaticoduodenectomy per year) hospitals. These data suggest a linear relationship between surgical volume and outcome. Birkmeyer and colleagues suggested that more than 100 deaths per year could potentially be prevented by the referral of pancreatic cancer patients to high-volume hospitals. Furthermore, in an analysis of survival duration, after exclusion of perioperative deaths and adjustment for case mix, patients who underwent surgery at high-volume hospitals were less likely to experience late mortality. The authors concluded that patients considering pancreaticoduodenectomy at low-volume hospitals should be given the option of referral to a high-volume center.

Patient outcome is optimized and costs minimized by the referral of patients requiring major pancreatic resections for malignant disease to centers with active multidisciplinary treatment programs. However, because surgical resection benefits only patients who undergo a complete resection, it is essential that surgery be done only on patients with localized, potentially resectable pancreatic cancer. In the absence of significant innovations in systemic therapy, the only potential for major improvements in the quality of life of patients with pancreatic cancer lies in our ability to limit surgery-related morbidity to those patients most likely to benefit from surgical intervention (i.e., to avoid laparotomy in patients with unresectable disease). Therein lies the importance of determining resectability using strict CT criteria (see Pretreatment Diagnostic Studies, earlier in this chapter).

**Technique**

Pancreaticoduodenectomy as currently performed in the United States incorporates selected aspects of the traditional Whipple procedure and emphasizes the importance of removing all soft tissue to the right of the SMA. The surgical resection is divided into six clearly defined steps, the most important of which is step 6, during which the pancreas is divided and the specimen is removed from the SMPV confluence and the right lateral border of the SMA. This is performed by completely mobilizing the SMV and portal vein medially, the uncinate process is then dissected off of the SMV and its posteriorly located first jejunal branch. Only after full mediastinal mobilization of the SMV can one identify the SMA (lateral to the SMV). The pancreatic head and all soft tissue to the right of the SMA are then removed with direct ligation of the inferior pancreaticoduodenal artery or arteries.

The high incidence of local recurrence after standard pancreaticoduodenectomy (see Table 33.4-3) mandates that close attention be paid to the retroperitoneal margin. The retroperitoneal margin is the soft tissue margin along the right lateral border of the proximal SMA. This margin contains the lateral portion of the mesenteric neural plexus that surrounds the artery. Importantly, perineural invasion involving the mesenteric plexus at the SMA origin and tumor cell infiltration of lymphatic vessels and connective tissue may extend beyond the confines of the palpable tumor in the pancreatic head and result in a microscopically positive retroperitoneal margin even when all gross disease is completely resected. A more extensive retroperitoneal dissection to the right of the SMA is not associated with greater operative morbidity and is necessary to obtain a negative retroperitoneal margin. This important margin of resection is often confused with the soft tissue posterior to the pancreatic head and duodenum and anterior to the inferior vena cava (posterior pancreaticoduodenal region). Direct invasion of the inferior vena cava is uncommon, and removal of all tissue anterior to this vessel is easily accomplished. As is true for other solid tumors, adequate local-regional control of pancreatic cancer requires negative margins of excision, and the margin of greatest importance at the time of pancreaticoduodenectomy is the soft tissue margin along the proximal SMA (retroperitoneal margin). In addition, clear identification of the SMA avoids the potential for iatrogenic injury.

Segmental resection of the SMPV confluence is performed when the tumor is inseparable from the lateral wall of the SMV or portal vein. Although an occasional patient may have such a small area of venous involvement that a saphenous vein patch is an obvious choice, the majority of patients with involvement of the SMPV confluence require segmental venous resection. The technical feasibility of portal vein resection was first reported by Fortner in his large series of type I regional pancreatectomies that included routine portal vein resection. More recently, surgeons have reported the safety of pancreatectomy with en bloc resection of the SMPV confluence. Fuhrman and colleagues have demonstrated that invasion of the SMV or portal vein is not associated with histopathologic variables (margin and lymph node positivity) that suggest a poor prognosis. Their data imply that venous involvement is a function of tumor location rather than an indicator of aggressive tumor biology. Additional data from the M. D. Anderson Cancer Center have confirmed that patient survival is not affected by the need for venous resection at the time of pancreaticoduodenectomy. In contrast to previous reports on venous resection, the preferred technique for resection of the SMPV confluence at M. D. Anderson involves preservation of the splenic vein–portal vein junction and use of an internal jugular vein interposition graft placed between the SMV and portal vein. It is important to emphasize the distinction between regional pancreatectomy and pancreaticoduodenectomy with segmental resection of the SMV or SMPV confluence. Venous resection is not an attempt to improve en bloc lymphatic and soft tissue clearance, as is performed in regional pancreatectomy. It is unlikely that a local-regional resections (to the left of the SMA and celiac axis) in poorly selected patients with advanced disease will impact survival.

Venous resection should be performed only in carefully selected patients who have tumor adherence to the SMV or SMPV confluence but no evidence of tumor extension to the SMA or celiac axis. The rationale for venous resection and the anatomic difference between tumor invasion of venous and arterial structures have been reviewed. Because the need for venous resection is unexpected in many patients and is discovered only after gastric and pancreatic transection, when nonresectional procedures are no longer an option, surgeons who perform pancreatectomies should be familiar with standard vascular techniques for resection and reconstruction of the SMPV confluence.

**PYLORUS PRESERVATION**

Preservation of the antipyloroduodenal segment in combination with pancreaticoduodenectomy (Fig. 33.4-3) was first described by Traverso and Longmire in 1978. Since then, increasing numbers of pancreatic surgeons have used this modification of the procedure, particularly for patients with benign disease or small periampullary lesions. Proponents of the technique argue that preservation of the antipyloric pump mechanism results in improved long-term upper gastrointestinal tract function with associated satiety nutritional sequelae. Physiologic studies suggest that pylorus preservation decreases intestinal transit time, lessens diarrhea (steatorrhea), normalizes glucose metabolism, and improves postoperative weight gain. Detractors of pylorus-preserving pancreaticoduodenectomy counter that the reported improvements in gastrointestinal tract function and nutrition are small, if any, and that they come at the expense of an increased incidence of delayed gastric emptying during the early postoperative period. Clinically significant long-term gastrointestinal dysfunction occurs in very few patients after standard pancreaticoduodenectomy with distal gastric resection. Additionally, leaving the distal stomach and duodenum may compromise margins of excision, prevent adequate peripyloric lymphadenectomy, and negatively impact patient survival. Published data to date involve retrospective comparisons that have yielded mixed results. Most investigators would agree that pylorus preservation should not be performed in patients with bulky tumors of the pancreatic head or with duodenal tumors involving the first or second portions of the duodenum.

![FIGURE 33.4-3. Illustration of the completed reconstruction after pylorus-preserving pancreaticoduodenectomy.](image)
cancer. The resection or retention of the pylorus is of much less significance than the proper selection of patients for pancreaticoduodenectomy and the status of the retroperitoneal margin after tumor resection. For example, three reports advocating pylorus preservation for malignant pancreatic and periampullary cancers reported positive resection margins in 25%, 29%, and 37% of patients. In the presence of a positive margin of resection, patients do not survive long enough to receive a potential nutritional benefit (if one exists) from pylorus preservation.

ADJUVANT INTRAOPERATIVE ELECTRON-BEAM RADIATION THERAPY

Despite the use of postoperative adjuvant EBRT and 5-FU, the incidence of disease recurrence in the tumor bed has been reported to be as high as 50%. This rate of local recurrence is due to the high incidence of residual macroscopic or microscopic disease at the resection margins and in the retroperitoneal soft tissues after pancreatectoduodenectomy and to the inability of 40 to 50 Gy of EBRT to control this level of tumor burden. IOERT, which delivers a single large dose of radiation to the tumor bed at the time of surgery, has been used alone and in combination with postoperative EBRT to improve local control. With IOERT, the total radiation dose delivered to a tumor or tumor bed can be increased over the dose that can be given by EBRT because sensitive normal tissues are displaced from the radiation field during the surgical procedure. Furthermore, this single intraoperative dose is believed to be biologically equivalent to an external-beam radiation dose at least two to three times greater given by means of conventional fractionation.

The data on the efficacy of pancreatic resection with IOERT alone or in combination with preoperative or postoperative EBRT are limited to retrospective or prospective single-institution studies and one small randomized trial. The only reported prospective, randomized, controlled clinical trial of IOERT for resectable pancreatic cancer was performed at the U.S. National Cancer Institute beginning in 1980. Twenty-four patients who underwent resection for pancreatic adenocarcinoma were randomized to receive IOERT (20 Gy) to the bed of the resected pancreas or observation. Patients in the IOERT group who had extrapancreatic tumor extension also received postoperative EBRT (45 to 55 Gy). Most patients had locally advanced disease that would be considered unresectable by conventional criteria. Patients underwent extensive extirpative surgery to remove all gross evidence of the primary tumor; the procedures frequently required vascular and adjacent organ resections, and this extent of surgical therapy resulted in considerable morbidity. The overall perioperative mortality rate was 27%, and the morbidity rate was 71%; the mortality and morbidity did not differ significantly between the IOERT and observation groups. The median survival of patients who received IOERT was 18 months, compared to 12 months for the observation group. Local recurrences occurred in all 12 patients (100%) in the observation group but in only 4 (33%) of 12 patients who received IOERT. One patient who received IOERT remained disease-free more than 15 years after therapy. Because of the small patient numbers, statistically significant survival differences were not reached between the IOERT and control groups.

More recently, investigators from the M. D. Anderson Cancer Center studied a regimen that included preoperative chemoradiation and IOERT. Patients with potentially resectable pancreatic cancer received preoperative EBRT (50.4 Gy in 28 fractions or 30 Gy in ten fractions) and concomitant protracted-infusion 5-FU (300 mg/m²/d) followed by pancreatectoduodenectomy and IOERT (10 to 20 Gy) to the resection bed. Based on this group's experience, it appears that IOERT can be delivered with minimal morbidity after preoperative chemoradiation and pancreatectoduodenectomy. The median survival duration in their most recent study was 25 months. Disease recurrence occurred in 70% of patients at a median follow-up of 37 months; 86% of recurrences were distant, and only 14% were local-regional. The results of these studies show that IOERT may be combined safely with pancreaticoduodenectomy and contemporary chemoradiation protocols. Although local control appears improved by IOERT, marked improvements in survival have not been demonstrated. At present, IOERT should be limited to investigative protocols.

RECONSTRUCTION

After pancreatectoduodenectomy with or without IOERT, gastrointestinal reconstruction is performed in a counterclockwise direction (Fig. 33.4-4). The transected jejunum is brought through a small incision in the transverse mesocolon to the right or left of the middle colic vessels, and a two-layer, end-to-side, duct-to-mucosa anastomosis is performed over a small Silastic stent (if the pancreatic duct is not dilated). A two-layer anastomosis that ligates the cut end of the pancreas into the jejunal loop can be performed if the pancreatic duct is not suitable for a duct-to-mucosa anastomosis. However, we prefer a duct-to-mucosa anastomosis. A single-layer biliary anastomosis is then completed, followed by an antecolic, end-to-side gastrojejunostomy constructed in two layers. Gastrostomy and feeding jejunostomy tubes are placed using the Witzel technique, and two closed-suction drains are placed.

Gastrointestinal reconstruction after pancreatectoduodenectomy is associated with two recognized complications: leak at the pancreaticojejunosotmy and delayed gastric emptying. Anastomotic leak from the biliary and gastric anastomoses should be very uncommon. Initial techniques for gastrointestinal reconstruction after resection of the pancreaticoduodenectomy involved simple closure of the pancreatic stump. Because of a high rate of pancreatic fistula formation, surgeons quickly switched to implantation of the pancreatic remnant into the jejunum. A more recent alternative is implantation of the pancreatic remnant into the posterior wall of the stomach. Regardless of the technique used, results appear dependent on the experience of the surgeon. With greater experience, the incidence of complications decreases.

Delayed gastric emptying is common after standard pancreatectoduodenectomy and may be more frequent with pylorus preservation. The cause is multifactorial but largely related to denervation of the upper gastrointestinal tract during resection of the pancreatic head and attached soft tissues and nerves to the right of the SMA. Symptoms of nausea, vomiting, and postprandial fullness resolve in 4 to 12 weeks in virtually all patients. The routine placement of gastrostomy and jejunostomy tubes at the time of surgery avoids needless patient morbidity due to temporary gastric emptying dysfunction. Patients can be discharged while receiving enteral feeding (via the jejunostomy tube) and allowed to advance their oral diet as tolerated. In addition, such tube placement prevents the expense and potential complications associated with intravenous hyperalimentation in patients who require prolonged hospitalization because of perioperative or postoperative complications. Poor gastric emptying in the absence of other concomitant intraabdominal pathologic conditions should not be the cause of prolonged hospitalization.

TREATMENT DECISIONS: POTENTIALLY RESECTABLE DISEASE

The use of contrast-enhanced helical CT allows accurate assessment of local tumor resectability. High-quality CT with objective CT criteria for resectability has replaced exploratory laparotomy as a means of assessing resectability. Pancreatectoduodenectomy should be considered only in patients with a good performance status (Karnofsky scale, 70% or higher) and as part of a multimodality treatment program that includes either preoperative or postoperative chemoradiation. The modest survival rates seen with current treatments (see Table 33.4-2) argue strongly for enrollment of all patients into clinical trials of new combinations of surgery, chemoradiation, and newly developed systemic agents. Published perioperative mortality rates support the referral of patients with potentially resectable disease to centers that are experienced with the operative management of pancreatic cancer and that perform at least nine major pancreatic resections per year.

PALLIATIVE METHODS OF BILIARY AND GASTRIC DECOMPRESSION

Debate over the best method of biliary decompression (surgical bypass or endoscopic stent) in patients with terminal pancreatic cancer stimulated a series of
Prospective randomized trials. These studies demonstrated that both methods are effective in relieving jaundice. Stenting is associated with lower initial morbidity and mortality rates and shorter hospital stays than operative bypass, but stent occlusion often results in the need for readmission to the hospital. Surgical biliary bypass provides a durable means of biliary decompression, but with greater initial morbidity. It is reasonable to assume that surgical complications are higher in patients with advanced disease and a poor performance status. In contrast, stent occlusion is more likely in patients with locally advanced or low-volume metastatic disease as they survive long enough to experience this complication. Logic argues strongly for a selective approach to biliary decompression based on an accurate assessment of performance status and tumor burden.

Patients with unresectable pancreatic cancer due to locally advanced or metastatic disease have a median survival of 6 months; however, this duration of survival can be quite variable, ranging from 3 to 14 months depending on performance status and extent of disease. Laparotomy in this patient group is associated with a mortality rate of 20%, a 30-day mortality rate of 20%, and a 90-day mortality rate of 30%. Patients who survive 2 to 4 weeks after laparotomy have an additional 2 to 4 weeks, the patient with unresectable disease has invested 10% to 20% of overall survival time in achieving biliary drainage. Therefore, the incentive for the development of a less invasive method of biliary decompression is obvious. Technological advances in stent construction have now made endoscopic stent placement the procedure of choice in patients with advanced pancreatic cancer. In patients with metastatic disease, whose survival duration is rarely longer than 6 to 9 months, biliary obstruction should be managed with outpatient endobiliary stent placement; this avoids the morbidity, hospital stay, and prolonged recovery period associated with operative biliary bypass. Stent occlusion is minimized with the use of large-caliber polyethylene stents (10.0 or 11.5 Fr.) without side holes; these stents reduce sludge and improve patency compared with smaller stents. Expandable 10-mm metal stents further decrease bacterial colonization and biofilm formation, resulting in improved patency compared with polyethylene stents; however, that improved patency comes at a higher initial cost.

Patients with locally advanced, nonmetastatic pancreatic cancer have a median survival of 10 to 14 months (with current chemotherapy and chemoradiation regimens); endoscopic biliary decompression (even with an expandable metal stent) is associated with an increased incidence of stent occlusion as survival duration increases. Currently consensus has not reached on how to manage an obstructed bile duct in patients with locally advanced, unresectable, nonmetastatic pancreatic cancer who have a good performance status. The desire to avoid palliative surgery (biliary bypass) that provides no antitumor therapy is balanced by the need for durable biliary decompression without the risk of recurrent cholangitis secondary to stent occlusion. This controversy is best illustrated by two publications from the same institution: one supports endobiliary stenting, whereas the other supports operative bypass.

We use a selective approach to biliary decompression. Outpatient endoscopic stenting is performed in all patients who are not candidates for pancreaticoduodenectomy. In patients with a life expectancy of 3 to 5 months (i.e., those with poor performance status or liver or peritoneal metastases), an 11.5-Fr, polyethylene stent is placed. In patients with a life expectancy of 6 to 12 months (i.e., those with locally advanced, nonmetastatic disease), a self-expanding metal stent is preferred. However, patients who develop symptomatic obstruction or migration or who by clinical criteria seem to do poorly with endoscopic biliary bypass are quickly referred for operative biliary bypass. A multidisciplinary approach to these patients is critical—the medical oncologist, gastroenterologist, and surgeon must communicate and avoid overly dogmatic approaches to palliative care.

Operative biliary bypass is routinely performed in patients who are brought to the operating room for planned pancreaticoduodenectomy and are found to have locally advanced or extrapancreatic metastatic disease. In such patients, a biliary-enteric bypass is performed. Previous studies have demonstrated no difference in outcome between cholecystojejunostomy and choledochojejunostomy. However, the gallbladder should not be used for biliary decompression in the setting of acute or chronic cholecystitis or biliary tract tumors. In patients with chronic cholecystitis, operative cholecystectomy and decompression is performed with a segment of jejunal tube graft. In patients with biliary tract tumors, the gallbladder and a portion of the common bile duct are transported through the umbilicus to the operating table, and resection of the tube graft is performed. In patients with advanced or extrapancreatic metastatic disease, a biliary-enteric bypass is performed. Previous studies have demonstrated no difference in outcome between cholecystojejunostomy and choledochojejunostomy; these two nonrandomized studies do not support the practice of routine prophylactic gastric bypass.

In patients with unresectable disease, laparoscopic cholecystojejunostomy represents another alternative for biliary decompression. We use this technique in patients with locally advanced, nonmetastatic disease in whom attempted endoscopic stenting has been unsuccessful. Tumors of the uncinate process or the inferior aspect of the pancreatic head that extend to the root of the mesentery often deform the ampulla of Vater, making endoscopic cannulation difficult. Laparoscopic cholecystojejunostomy is an attractive option in these patients. Because laparoscopically assisted cholecystojejunostomy depends on a patent cystic duct–common bile duct junction, it is important not to consider this form of biliary decompression in patients with large tumors that extend cephalad to the porta hepatitis.

Patients with symptomatic jaundice and ascites present a unique technical challenge. A subset of these patients have had such advanced disease (and poor performance status) that pain control and hospice care are all that is indicated. For the occasional patient who presents with jaundice and the rapid onset of ascites and requires palliative treatment, we prefer endoscopic stent placement followed by early peritoneovenous shunting if an initial attempt at diuretic therapy is unsuccessful. If endoscopic stenting is not technically possible, laparoscopic cholecystojejunostomy is a reasonable alternative in the absence of high-volume carcinomatosis.

Transhepatic biliary drainage with an internal-external catheter is not advised in patients with ascites because the ascitic fluid leaks around the catheter at the skin entrance site. In patients with malignant ascites, the surgeon should avoid using transabdominal catheters and making large abdominal incisions because of the risk of ascitic leak.

The subject of prophylactic gastrojejunostomy is not as relevant to the current surgical management of patients with pancreatic cancer as it was before the 1990s. Accurate preoperative imaging has increased resectability rates so that fewer patients are found to have unresectable disease at surgery. Advocates of prophylactic gastrojejunostomy state that the procedure can be performed safely, is not associated with postoperative delayed gastric emptying, and prevents subsequent gastric outlet obstruction in 10% to 20% of patients. Detractors argue that concomitant gastric bypass at the time of therapeutic biliary bypass significantly increases operative morbidity, that the incidence of subsequent gastric outlet obstruction (in patients who receive only a biliary bypass) is much less than 10%, and that, if clinically evident gastric outlet obstruction occurs, it is usually a manifestation of end-stage disease. However, some investigators have shown that prophylactic gastrojejunostomy in patients undergoing pancreaticoduodenectomy and even in patients with unresectable disease, and not have intraoperative evidence of impending gastric outlet obstruction (such patients were excluded from analysis) at the time of laparotomy were randomly assigned to receive either a prophylactic gastrojejunostomy or no further surgery. Subsequent gastric outlet obstruction developed in 8 (19%) of the 43 patients who did not receive a gastric bypass, compared to 0 of 44 patients who received a gastrojejunostomy. Postoperative delayed gastric emptying occurred in 2% of patients in both groups, and the mean survival duration (8.3 months) was identical in both groups. Furthermore, no perioperative deaths occurred, and the mean hospital stay was approximately 8 days; again, no difference was noted between groups. The authors concluded that a retrocolic gastrojejunostomy should be performed routinely when a patient with pancreatic or periampullary cancer is found at operation to have unresectable disease. It appears that high-volume referral centers can perform palliative surgical biliary and gastric bypass procedures with low morbidity and mortality; however, these results may not be easily translated to low-volume centers with less experience. For example, a review of patients at 74 Department of Veterans Affairs hospitals from 1987 to 1991 concluded that prophylactic gastric bypass should be performed in patients with locally advanced, nonmetastatic pancreatic cancer, but the 30-day operative mortality rate (15% to 20%) was unacceptably high for palliative surgery in patients with such a short anticipated survival.

In contrast to the data from Johns Hopkins University, Espat et al. from Memorial Sloan-Kettering Cancer Center reported a low incidence of gastric outlet obstruction in patients with advanced pancreatic cancer. These investigators reported the longitudinal follow-up of 155 patients with pancreatic adenocarcinoma who were found to have unresectable or advanced disease or who were managed by laparoscopic surgery for presumed localized disease by CT. The median survival was 6.2 months for those with metastatic disease and 7.8 months for those with locally advanced disease; these survival durations support the authors' contentions that the patients did not have high-volume metastatic disease at the time of laparoscopy. At a median follow-up of 26 months (of patients who died of disease), only 3% (2 of 69) of patients had undergone a subsequent open surgical procedure. Gastrojejunostomy for symptomatic gastric outlet obstruction was performed in 2 of these three patients. Two additional patients underwent elective gastric bypass (one was performed laparoscopically) at the time of biliary bypass. One additional patient required a percutaneous gastrostomy tube for poor gastric emptying during the terminal phase of his disease. Raiker et al. from the Mayo Clinic also reported a low incidence of subsequent gastric outlet obstruction in patients with unresectable pancreatic cancer who had endoscopic biliary decompression. In their study, only 1 (3%) of 34 patients treated with endoscopic biliary decompression required surgical bypass for gastric outlet obstruction. These two nonrandomized studies do not support the practice of routine prophylactic gastric bypass.

The apparent differences in the incidence of gastric outlet obstruction in the above studies are not readily explained. In general, we do not perform prophylactic stenting in patients with pancreatic cancer. If a patient is found to have unresectable disease during surgery for planned pancreaticoduodenectomy, we consider gastrojejunostomy when chronic symptoms or anatomic findings suggest impending obstruction. However, in patients with locally advanced or limited metastatic disease with good performance status, the Johns Hopkins data (based on a prospective randomized trial) would support the creation of a retrocolic gastrojejunostomy whenever deemed necessary.
TREATMENT OF LOCALLY ADVANCED DISEASE

Approximately 40% of the 28,600 patients diagnosed with ductal adenocarcinoma of the pancreas in 1999 presented with unresectable but nonmetastatic disease. Because these patients' tumors are unresectable by a Whipple procedure or total pancreatectomy owing to invasion of the portal or mesenteric vessels and they have no clinically demonstrable metastases, radiotherapeutic approaches frequently have been used. These approaches have included EBRT, with and without 5-FU chemotherapy; IOERT; and, more recently, EBRT with new chemotherapeutic (radiosensitizing) agents.

EXTERNAL-BEAM IRRADIATION WITH OR WITHOUT 5-FLUOROURACIL

In all except one study, conventional EBRT combined with 5-FU chemotherapy has been shown to improve survival in patients with locally advanced unresectable pancreatic cancer compared to irradiation alone or chemotherapy alone (Table 33.4-8). The most favorable median survival duration and 2-year survival rate for EBRT plus 5-FU were approximately 10 months and 12%, respectively. When interpreting the GITSG trials of this combination, it is important to remember that all patients were entered in the GITSG studies after laparotomy, at which time the disease was deemed unresectable by the operating surgeon. The significant morbidity reported with palliative pancreatic surgery suggests that only patients with a high performance status could have recovered rapidly enough to be eligible for these studies. Thus, although surgical staging provided a more uniform study population, it also introduced significant selection bias: Only rapidly recovering patients were considered for treatment. Comparison of future findings to these data must take into account this selection bias.

Because of the limited tolerance of normal tissue in the upper abdomen (liver, kidney, spinal cord, and bowel) to EBRT, total doses of only 45 to 54 Gy, in 25 to 30 fractions, have usually been given. For an unresectable lesion, this dose of radiation is inadequate, as demonstrated by the high rates of tumor progression and poor survival seen in both prospective and retrospective studies. For example, the Mayo Clinic reported a local failure rate of 72% for 122 patients with unresectable pancreatic cancer treated with an EBRT dose of 40 to 60 Gy.

Because surgical resection of the primary tumor remains the only potentially curative treatment for pancreatic cancer, preoperative irradiation has been studied to assess its ability to convert locally unresectable pancreatic cancer to resectable disease (Table 33.4-9). In a study from the New England Deaconess Hospital, 16 patients with locally advanced unresectable pancreatic cancer were treated with 45 Gy of EBRT and infusional 5-FU to enhance resectability. Of these 16 patients, only two (13%) were able to undergo resection. Similarly, investigators from Duke University reported that only 2 (8%) of 25 patients with locally advanced pancreatic cancer treated with 45 Gy of EBRT and 5-FU (with or without cisplatin or mitomycin C) subsequently underwent complete resection with negative margins. These and other studies (see Table 33.4-9) indicate that it is unlikely that neoadjuvant chemoradiation can convert unresectable lesions to resectable ones and thereby increase the number of patients potentially cured with combined-modality therapy. It is important to remember that as one loosens the definition of a locally advanced pancreatic cancer, results appear more optimistic. If, however, one maintains a strict (CT) definition of locally advanced pancreatic cancer that includes only arterial involvement (low-density tumor inseparable from the SMA or celiac axis on contrast-enhanced CT) or SMV or SMPV confluence occlusion, successful down-staging to allow complete surgical resection will be rare with currently available chemotherapy or chemoradiation techniques.

INTRAOPERATIVE ELECTRON-BEAM RADIATION THERAPY

To enhance the local-regional tumor control achieved by conventional EBRT and chemotherapy, specialized radiation therapy techniques that increase the dose of radiation to the desired tumor volume have been used in an attempt to improve local tumor control without increasing normal tissue morbidity. These include iodine 125 implants or intraoperative electrons as a boost dose in combination with EBRT and chemotherapy. A lower incidence of local failure in most series and improved median survival in some have been reported with these techniques when compared with conventional EBRT (Table 33.4-10), but it is uncertain whether the differences are due to superior treatment or to case selection.
In the Massachusetts General Hospital and Mayo Clinic studies combining EBRT and IOERT for locally advanced pancreatic cancer, local tumor control was improved; however, the median survival was only approximately 12 months, and the 2-year survival rate remained approximately 20%. Most patients developed liver metastases, peritoneal seeding, or both. Although slight gains in survival may be achieved by improving local tumor control, the high incidence of distant metastases precludes significant improvements in long-term survival duration with IOERT.

NEW AGENTS COMBINED WITH RADIATION THERAPY

Because of the high incidence of hepatic and peritoneal metastases and the poor results with standard chemotherapy, current and future research efforts include evaluation of EBRT with new radiosensitizing agents (paclitaxel and gemcitabine). Interest in these agents is based on both their systemic cytotoxic effects and their radiosensitizing properties. In radiologic models, paclitaxel results in enhanced radiosensitization through tumor reoxygenation after apoptotic clearance of paclitaxel-damaged cells. In a phase I trial at Brown University evaluating paclitaxel and 50 Gy of EBRT for patients with unresectable pancreatic and gastric cancers, the maximum tolerated dose of weekly paclitaxel with conventional irradiation was 50 mg/m². The response rate was 31% among 13 evaluable pancreatic cancer patients. In the Brown University phase II study, which administered 50 Gy of EBRT with 50 mg/m²/week of paclitaxel, 6 (33%) of 18 evaluable pancreatic cancer patients had a partial response; stable disease has been observed in seven patients (39%); only one patient (6%) has had local tumor progression after completion of treatment; and four (22%) have developed distant metastases. These data have led to the initiation of an RTOG phase II study evaluating paclitaxel with EBRT for patients with unresectable pancreatic cancer.

Gemcitabine also has been the focus of an investigation in patients with advanced pancreatic cancer. Burris and colleagues randomized 160 previously untreated patients with advanced and metastatic pancreatic cancer to receive either gemcitabine or 5-FU. Patients who received gemcitabine had a statistically improved median survival, 1-year survival rate, and clinical benefit compared to patients who received 5-FU. In radiobiologic models, gemcitabine also has been observed to be a potent radiosensitizer, likely because it depletes intracellular deoxyxynucleoside triphosphates. At present, numerous investigators are pursuing phase I and II studies combining EBRT with gemcitabine. Investigators from Wake Forest University and the University of North Carolina have reported the results of a phase I trial of twice-weekly gemcitabine and 50.4 Gy of concurrent upper abdominal EBRT in 19 patients with unresectable pancreatic cancer. In this study, the maximum tolerated dose of gemcitabine was 40 mg/m². At this dose level, gemcitabine was well tolerated. Of eight patients with a minimum follow-up of 12 months, three remain alive, and one of the three has no evidence of disease progression. On the basis of these data, a phase II Cancer and Leukemia Group B study of EBRT and twice-weekly gemcitabine is currently accruing patients with locally advanced pancreatic cancer. At the Massachusetts General Hospital, Dana-Farber Cancer Institute, and Brigham and Women's Hospital, a phase I/II study (unpublished) is under way examining preoperative EBRT (50.4 Gy) to the pancreas with continuous-infusion 5-FU and weekly gemcitabine for locally advanced pancreatic cancer. If no evidence of distant metastases is found at the time of restaging after completion of chemoradiation, patients proceed to laparotomy and IOERT to the primary tumor.

RADIATION THERAPY TECHNIQUES

For patients undergoing surgery, clips should be placed to mark the extent of the lesion for postoperative EBRT. Used sparingly (e.g., a single small vascular clip placed in each location to mark superior, inferior, lateral, and medial margins), small clips produce only minimal interference on CT scans. Titanium clips produce less CT interference but sometimes cannot be located on lateral simulation x-ray films because of their lesser density. During simulation and treatment, the patient should be supine. An initial set of anteroposterior and cross-table lateral x-ray films is obtained after injection of renal contrast medium to identify operative clips and renal position relative to the field center. Additional films can be obtained with contrast medium in the stomach and duodenal loop.

Radiation therapy for locally advanced cancer generally involves multiple-field, fractionated, external-beam techniques with high-energy photons to deliver 45 to 54 Gy in 1.8-Gy fractions to unresected or residual tumor (as defined by CT and clips) and to at-risk nodal areas. For lesions in the head of the pancreas, major at-risk lymph node groups include the pancreaticoduodenal, porta hepatis, celiac, and suprapancreatic nodes. The suprapancreatic lymph node group is included with the body of the pancreas in the radiation field to encompass a 3- to 5-cm margin beyond gross disease; however, more than two-thirds of the left kidney is excluded from the anteroposterior-posteroanterior field because at least 50% of the right kidney needs to be included in this field to treat the entire pancreatic head and duodenum. The entire duodenal loop with a margin of grossly uninvolved tissue is included because pancreatic head lesions may invade the medial wall of the duodenum and place the entire circumference at risk.

For pancreatic body or tail lesions, at least 50% of the left kidney may need to be included in the radiation field to achieve adequate margins and to include lymph node groups at risk (i.e., lateral suprapancreatic and splenic hilum nodes). Because inclusion of the entire duodenal loop is not indicated with body or tail lesions, at least two-thirds of the right kidney can be preserved; with tailored blocks, it is usually possible to do this and still cover the pancreaticoduodenal and porta hepatitis nodes adequately.

For pancreatic head lesions, the superior field extent is at the middle or upper portion of the T11 vertebral body to achieve adequate margins along the celiac vessels (T12-L1). The superior field extent is occasionally more superior for pancreatic body lesions to obtain an adequate margin around the primary tumor.

For the lateral fields, the anterior field margin is 1.5 to 2.0 cm beyond gross disease. The posterior margin is at least 1.5 cm behind the anterior portion of the vertebral body to allow adequate margins around paraaortic nodes, which are at risk for posterior tumor extension of head or body lesions. The dose to the lateral fields is usually limited to 18 to 20 Gy because a moderate volume of kidney or liver may be in the fields.

After resection, anteroposterior-posteroanterior and lateral fields are designed on the basis of preresection CT tumor volumes, operative clip placement, and postoperative CT lymph node volumes. The only border that can be reduced is the anterior border of the lateral fields, because the primary tumor has been resected. This border is determined by vascular or nodal boundaries (porta hepatitis, superior mesenteric, and celiac arteries) as demonstrated on CT.

Three-dimensional conformal therapy is currently being investigated in patients with pancreatic cancer. Figure 33.4-5 illustrates a multifield technique and composite isodose distribution for a patient with an unresectable pancreatic head cancer. Preliminary studies indicate that five or six conformal fields can be designed to improve dose-volume characteristics over those achieved with conventional four-field treatment designs, but the posterior wall of the stomach and the medial wall of the duodenum cannot be excluded from the high-dose volume.

### TABLE 33.4-10. External-Beam and Intraoperative Radiation Therapy for Locally Advanced Unresectable Pancreatic Cancer

<table>
<thead>
<tr>
<th>Field</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>Anterior</td>
<td>Includes the entire duodenal loop with a margin of grossly uninvolved tissue.</td>
</tr>
<tr>
<td>Posterior</td>
<td>Includes the entire pancreas in the radiation field for a 3- to 5-cm margin beyond gross disease.</td>
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### FIGURE 33.4-5. A multifield radiation technique (A) and composite isodose distributions (B) for a patient with an unresectable adenocarcinoma of the pancreatic head.
TREATMENT DECISIONS: LOCALLY ADVANCED, NONMETASTATIC DISEASE

Patients with clear evidence of encasement of the celiac axis or SMA or occlusion of the SMPV confluence on contrast-enhanced helical CT do not require laparotomy to confirm that the tumor is unresectable; cytologic confirmation of malignancy can be achieved with EUS- or CT-guided FNA. This fundamental advance in the pretreatment diagnosis of pancreatic tumors can improve the quality of patient survival and reduce health care costs by avoiding the morbidity and prolonged recovery associated with palliative pancreatic cancer surgery. Published data have suggested an increased survival duration for patients treated with chemoradiation, but this benefit is limited largely to patients with higher performance status. In selected patients, aggressive treatment programs consisting of EBRT and chemotherapy may result in a median survival of approximately 12 months and a 2-year survival rate of 20%, although long-term survivors are rare. A program of chemoradiation is justified in fully ambulatory patients with locally advanced disease who have minimal symptoms. Systemic therapy with gemcitabine also represents a reasonable alternative in these patients. For patients with poor performance status, chemoradiation is probably not indicated. Current pharmacologic and interventional techniques for pain control, including percutaneous injection of alcohol into the celiac plexus, have proven highly successful in patients with pancreatic cancer. Furthermore, adequate pain control improves performance status and quality of life, which may translate into increased length of life. The limited therapeutic options available for patients with locally advanced disease and the modest impact of current treatments on survival rates provide the rationale for the entry of these patients into trials examining novel systemic agents.

TREATMENT OF METASTATIC AND RECURRENT DISEASE

The early emergence of metastatic disease in patients with exocrine pancreatic cancer suggests that systemic therapy (chemotherapy) should play a major role in the management of this disease. However, only marginal success has been achieved in identifying effective systemic therapies for pancreatic cancer. Most studies of single-agent or combination chemotherapy in patients with advanced adenocarcinoma of the pancreas have documented low response rates and little reproducible impact on patient survival or quality of life. Response rates as high as 15% to 30% occasionally seen in pilot studies of novel agents or combinations have generally been difficult to reproduce in larger trials, suggesting that patient selection often accounts for apparent differences between study results. The inherent difficulty in accurately applying bidimensional measurements to local pancreatic masses and the problem of interobserver variations in the measurement of metastatic disease may also contribute to the poor reproducibility of clinical trial findings in patients with locally advanced or metastatic pancreatic cancer.

Because of the large volume of published material on this disease, we have chosen to present the results of important new studies and approaches to therapy; comprehensive reviews of the results of chemotherapy for pancreatic cancer are available, and a previous edition of this text provides a comprehensive review of past chemotherapy trials.

SINGLE-AGENT CHEMOTHERAPY

The thymidylate synthase inhibitor 5-FU remains the most extensively evaluated chemotherapeutic agent for pancreatic cancer. In 212 cases collected from the literature in the pre-CT era, the response rate to 5-FU was 28%. However, despite numerous trials, the optimal dose and schedule of 5-FU have not been clearly defined. Two of the most commonly used schedules are continuous infusion of 1000 mg/m² for 5 days or bolus infusion of 400 to 500 mg/m² for 5 days. A highly potent and specific thymidylate synthase inhibitor, Tomudex, has been evaluated in patients with advanced pancreatic cancer. However, despite its potent inhibition of thymidylate synthase and other biochemical advantages over 5-FU, clinical trial results have been disappointing, with only 2 of 42 patients achieving an objective response. Additional regimens based on protracted infusions of 5-FU continue to be explored but have not demonstrated any major effect on the outcome of the disease. The new oral 5-FU prodrugs (capecitabine, uracil-tegafur, and S-1) have not yet been comprehensively tested in pancreatic cancer, but given the limited impact of intravenous 5-FU on this disease, expectations for these agents are low.

Most of the cytotoxic chemotherapeutic agents studied during the 1990s have demonstrated little objective evidence of significant activity against advanced pancreatic cancer. Table 33.4-11 In a subsequent clinical trial, Rouger and coworkers at the Institut Gustave-Roussy reported five objective responses (29%) in 17 patients with hepatic metastases. However, toxic effects were substantial and included grade 3 or 4 neutropenia in all patients and severe edema in 13%. In three patients, the edema was so severe that therapy had to be discontinued. Three confirmatory phase II trials failed to confirm the initial response findings. Similarly, paclitaxel, even when administered using an aggressive schedule with granulocyte colony-stimulating factor, had only minimal efficacy against advanced pancreatic cancer. Novel analogues of the topoisomerase I inhibitor camptothecin have also undergone evaluation in patients with advanced pancreatic cancer. Topotecan, administered once daily for 5 days or using a 21-day continuous infusion schedule, was ineffective. Irinotecan (CPT-11) was evaluated in 34 patients by the EORTC Early Clinical Trials group. Irinotecan was administered intravenously over 30 minutes at a dose of 350 mg/m² every 3 weeks; objective partial responses were documented in only three patients, with a median survival for the entire group of 5 months.

Gemcitabine is a deoxycytidine analogue with structural and metabolic similarities to cytarabine. As a prodruk, gemcitabine must be phosphorylated to its active metabolites gemcitabine diphosphate and gemcitabine triphosphate (dFdCTP). In both preclinical and clinical testing, gemcitabine demonstrated activity in solid tumors greater than that of cytarabine. These observations can be potentially explained by the following properties of gemcitabine: (1) It is three to four times more lipophilic than cytarabine, resulting in greater membrane permeability and cellular uptake; (2) it has higher affinity for deoxycytidine kinase, and (3) the intracellular retention of dFdCTP is long. In the initial multicenter trial, objective responses to gemcitabine were documented in only 5 (11%) of 44 patients with advanced pancreatic cancer, but the investigators noted frequent subjective symptomatic benefits, often in the absence of an objective tumor response. Based on these observations, two subsequent trials of gemcitabine in patients with advanced pancreatic cancer have been completed. In one randomized trial, gemcitabine was compared to 5-FU in previously untreated patients. Patients treated with gemcitabine had a median survival of 5.65 months, compared to 4.41 months (P = .0025) in those treated with 5-FU. Twenty-four percent of patients treated with gemcitabine were alive at 9 months, compared to 6% of patients treated with 5-FU. In addition, more clinically meaningful effects on disease-related symptoms (pain control, performance status, weight gain) were seen with gemcitabine (23.8% of patients) than with 5-FU (4.8% of patients). Similar systemic effects and demonstrable disease responses were documented in patients who were treated with gemcitabine after experiencing disease progression while receiving 5-FU. These results have helped gemcitabine to become the accepted first-line therapy for patients with advanced pancreatic cancer.
advanced pancreatic adenocarcinoma in the United States, although this approach is not necessarily shared worldwide. 354

During the early phase II trials of weekly gemcitabine in chemotherapy-naive patients, it became clear that much higher doses could be safely administered (using 30-minute bolus infusions) than were tolerated in patients who had received multiple prior chemotherapies. However, previous cellular pharmacologic studies of this agent suggested that simply increasing the dose administered over 30 minutes may not increase cytotoxicity or improve gemcitabine's therapeutic index. During the early clinical experience in patients with solid tumors, dFdCTP levels were measured in peripheral blood mononuclear cells and showed that the rate of gemcitabine phosphorylation, like that of cytarabine, was subject to saturation kinetics. 323,334 The concentration of dFdCTP in the circulating mononuclear cells increased in proportion to the gemcitabine dose between 35 and 250 mg/m², but further increments in cellular dFdCTP were not observed at higher doses (350 to 1000 mg/m²); instead, the plasma gemcitabine concentrations rose to more than 20 nmol/L, suggesting saturation of gemcitabine 5'-phosphatase accumulation. The rate of dFdCTP accumulation and the peak cellular concentration were highest at a dose rate of 350 mg/m² per 30 minutes (approximately 10 mg/min/m²), during which steady-state gemcitabine levels of 15 to 20 nmol/L were achieved in plasma. 323 Similar results were found in a pilot trial of gemcitabine in leukemia patients in which dFdCTP levels were measured in circulating malignant cells. 323 A more comprehensive phase I trial in leukemia patients showed that a gemcitabine dose rate of 10 mg/min/m² achieved a mean steady-state gemcitabine level of 26.5 nmol/L and was sufficient to maximize the rate of dFdCTP accumulation in circulating leukemic cells.

The most commonly applied approach to dose intensification in phase II studies of gemcitabine was to maintain the weekly schedule and increase the dose administered over 30 minutes. 355 However, because the plasma levels of gemcitabine achieved using this approach are well above 20 nmol/L, this strategy is not likely to increase intracellular levels of the active metabolite dFdCTP or improve efficacy. The pharmacodynamic relationships documented through the studies just described suggest that increasing the infusion time while holding the dose rate constant increases intracellular levels of the active metabolite gemcitabine diphosphate and dFdCTP and thus achieves the goal of dose intensification. To establish the feasibility of this approach, a phase I study 356,357 of gemcitabine was conducted in patients with advanced solid tumors whereby dose escalation was achieved by increasing the duration of the weekly gemcitabine infusions while maintaining the dose rate at 10 mg/min/m². A subsequent randomized phase II trial 358 in patients with metastatic pancreatic cancer suggested that short infusions (10 mg/min/m²) of gemcitabine may be more effective than the standard 30-minute bolus technique.

Given gemcitabine's manageable toxicity profile and favorable intracellular pharmacology, gemcitabine-based combinations are also under active evaluation. 333,340 Early trials have combined gemcitabine with 5-FU, 341 capcitabine, 342 docetaxel, 343 344,345 paclitaxel, 346 epirubicin, 347 and marnnastat. 348

**TABLE 33.4-12. Gemcitabine-Based Combination Chemotherapy Trials in Patients with Advanced Pancreatic Cancer**

Despite the encouraging results with gemcitabine and gemcitabine-based combinations, the median survival for patients with metastatic disease continues to be less than 6 months, with very few patients achieving long-term disease stabilization. Although two trials have supported the superiority of chemotherapy over supportive care, 337,338 some of the effects attributed to chemotherapy may not be substantially different from what can be achieved with aggressive supportive care alone. The study of novel chemotherapeutic agents based on the evolving understanding of the pathobiology of pancreatic cancer must continue.

**MODULATION OF 5-FLUOROURACIL**

Interest remains in the possibility of increasing the activity and therapeutic index of 5-FU by use of biochemical modulators. N-((Phosphonoacetyl)-L-aspartate disodium (PALA) depletes uridine nucleotide pools by inhibiting aspartate transcarboxamylase, favoring incorporation of 5-FU nucleotide metabolites into RNA and thereby potentiating the antitumor activity of 5-FU. Administering methotrexate before PALA and 5-FU results in increased formation of fluorouridine monophosphate. A study by Morrell et al. 349 using a weekly schedule of PALA at a dose of 250 mg/m² followed 24 hours later by a 24-hour continuous infusion of 5-FU (2600 mg/m²) in patients with advanced pancreatic cancer was associated with severe toxicity, including one death, and only one response. A similar study demonstrated less toxicity but also no benefit from the use of PALA plus 5-FU compared with 5-FU alone. 350 The addition of methotrexate or 6-methylmercaptopurine riboside also provided no benefit over 5-FU alone. 351,352

Regimens that rely on the modulation of 5-FU and prolong inhibition of thymidylate synthase have demonstrated efficacy against colon cancer but have shown little activity against pancreatic cancer. Prospective clinical trials in patients with advanced pancreatic cancer have evaluated high-dose leucovorin (500 mg/m²), administered daily or as a continuous infusion for 6 days, in combination with 5-FU. 353,354 The daily dose of 5-FU ranged from 375 mg/m² to 600 mg/m². Objective response rates averaged less than 10%, and toxicity was often significant. The substitution of 5-methyltetrahydrofolate for leucovorin also failed to demonstrate clinical meaningful biochemical modulation of 5-FU. 355 Thus, despite some evidence to the contrary, 356,357 the current consensus is that the addition of leucovorin to 5-FU provides no therapeutic advantage over single-agent 5-FU in advanced pancreatic cancer.

Another potential modulator of 5-FU is interferon-a, with or without leucovorin. 358,359,360 Schellhammer et al. 361 combined 5-FU (20 mg/kg on day 3) with interferon-a (10 × 10⁶ U/d for 3 days) and leucovorin (200 mg on day 3). The observed response rate (4 of 32) and median duration of survival (5.5 months) were no different than with 5-FU alone. Gattan et al. 362 used three potential biomodulators—cisplatin, leucovorin, and methotrexate—in an effort to enhance the cytotoxicity of 5-FU. Six regimens were seen in 24 patients with advanced pancreatic cancer, but no survival occurred in more than one-half of the study population. Thus, the results from clinical trials to date have not demonstrated any reproducible benefit of 5-FU modulation in patients with pancreatic cancer.

**HORMONAL THERAPY**

Johnson and Corbishley 363 were the first to note that pancreatic tumors contain sex steroid hormone receptors, stimulating interest in a hormonal approach to the management of pancreatic cancer. This interest continues as investigators refine their understanding of the hormonally controlled signal transduction pathways that control cellular proliferation. 358,359,364 Early research in this area demonstrated that serum testosterone concentrations were lower in both men and women with pancreatic cancer than in patients with other cancers or healthy controls. 365,366,367 Laboratory evidence that exocrine pancreatic cancers are sensitive to gastrointestinal hormones, sex steroids, and growth factors led to the use of hormonal manipulation in patients with pancreatic cancer. 358,359,365,367 Cyproterone acetate, an androgen, inhibited the growth of human pancreatic xenografts in nude mice, 365 and a luteinizing hormone—releasing hormone (LHRH) analogue, D-trypt-6-LHRH, induced regression of nitrosamine-induced pancreatic cancers in hamsters. 368 When this analogue was combined with RC-160, an experimental somatostatin analogue, the same growth inhibition was observed. 369 Another somatostatin analogue, SMS-201-995, also demonstrated in vivo inhibition of human adenocarcinoma cell lines. 370 These laboratory observations stimulated clinical trials evaluating LHRH agonists, growth factor inhibitors (octreotide), 371,372 and tamoxifen, and more recently, futamamide 373 in patients with advanced pancreatic cancer. Consistent with the cytostatic effect of hormonal therapy, objective responses were not seen; median survival duration ranged from 3 to 8 months. 374,375,376,377,378,379,380,381,382,383,384,385,386,387 The potential cytostatic effects of tamoxifen continue to be studied in the laboratory. 388

Several uncontrolled clinical studies have suggested improved survival in patients with pancreatic cancer treated with tamoxifen, 389,390,391 yet other studies have not
confirm this observation. A case-control study involving 80 patients did suggest a survival advantage for patients treated with tamoxifen. However, in a prospective, randomized, double-blind trial, pancreatic cancer patients receiving tamoxifen had a median survival of 115 days compared to 122 days for the placebo-treated patients; 8% of patients were alive at 1 year in both groups. A small trial reported by Crown et al. using CT to evaluate tumor response also demonstrated no benefit with tamoxifen. Studies with ocreotide, steroids, and LHRH agonists, as well as combinations of these agents, have not shown an increase in survival for patients with pancreatic cancer. Likewise, a pilot study of MK329, a cholecystokinin antagonist, in 18 patients with pancreatic cancer demonstrated no antitumor activity. Nevertheless, despite the lack of a clear effect of currently available hormonal therapies on exocrine pancreatic carcinoma, research in this area continues.

COMBINATION CHEMOTHERAPY

In general, combination chemotherapy has not been a successful approach to the management of pancreatic cancer. However, the results of prior studies of combination chemotherapy are presented here for historical purposes.

5-Fluorouracil, Doxorubicin (Adriamycin), and Mitomycin C Regimen

The combination of 5-FU, doxorubicin (Adriamycin), and mitomycin C (FAM) for metastatic pancreatic adenocarcinoma was first described by Smith et al. in 1980, based on previous work demonstrating a 13% partial response rate with doxorubicin in previously untreated patients. Twenty-seven of 39 patients had measurable disease; ten (37%) of these achieved a partial response. These ten patients had a median survival of 12 months, compared with 3.5 months in nonresponders. Biltan et al. reported similar results. An earlier report of streptozotocin, mitomycin C, and 5-FU (SMF) for advanced pancreatic cancer suggested a response rate of 43%, although many patients experienced severe gastrointestinal and renal toxicity. Therefore, several cooperative groups compared FAM and SMF. The Cancer and Leukemia Group B studied 184 patients and found response rates of 14% for FAM and 4% for SMF (not significantly different), both of which were much lower than suggested by previous reports. Comparison of FAM to two schedules of SMF, FAM to 5-FU alone, and to 5-FU and doxorubicin confirmed these low response rates. More recently, FAM was combined with aminoglutethimide without benefit. Despite these negative trials, a randomized study of a modified FAM regimen compared to no treatment demonstrated an improved median survival for FAM-treated patients. However, this was a small study involving only 44 patients, and the pancreatic cancer was pathologically confirmed in only 31. Based on the results to date, the use of FAM chemotherapy in the management of advanced pancreatic cancer cannot be recommended.

Mallinson Regimen

In 1980, Mallinson et al. first reported on a regimen of induction therapy with 5-FU, cyclophosphamide, methotrexate, and vincristine followed by maintenance treatment with 5-FU and mitomycin C for advanced pancreatic cancer. A median survival of 44 weeks was reported for patients who received therapy, compared with 9 weeks for patients offered only supportive care. However, a phase III trial comparing the Mallinson regimen to 5-FU alone and to 5-FU, doxorubicin, and cisplatin was unable to confirm these results; the median survival was only 4.5 months in patients who received the Mallinson regimen.

Cisplatin-Containing Regimens

After a trial that showed significant activity of cisplatin administered at a dose of 100 mg/m² every 4 weeks, cisplatin was combined with continuous-infusion 5-FU. However, response rates have been seen with low-dose schedules, and toxic effects have been seen in a high percentage of patients. Somewhat better results have been observed with higher doses of cisplatin (100 mg/m²) combined with 5-FU (1000 mg/m²/iv) administered by continuous infusion. In a study of 40 pancreatic cancer patients, 13 of whom were previously treated and 36 of whom had metastatic disease, one complete and nine partial responses (response rate, 26.5%) were documented; the median survival rate was 7 months. This high-dose regimen was associated with one treatment-related death and the occurrence of grade 4 granulocytopenia in 27% of patients. The most recent report of cisplatin and 5-FU comes from Japan. These investigators used a lower dose of both agents (5-FU, 500 mg/m²/iv; cisplatin, 80 mg/m²) based on phase I studies in their country. In 37 previously untreated patients with pancreatic adenocarcinoma, the response rate was only 8%.

Other Combinations

A combination regimen of 5-FU, leucovorin, mitomycin C, and dipyridamole produced 12 responses in 16 patients with locally advanced pancreatic cancer. Five of these were objective complete responses documented by CT and tumor marker measurements. At the time of this report, median survival had not yet been reached but was projected to be greater than 1 year. Five patients had received EBRT, but this was not believed to have affected overall survival. In a subsequent report from the same group, this regimen achieved an overall response rate of 39% in patients with locally advanced pancreatic cancer, with six patients achieving sufficient improvement in their tumor status on CT scans to justify surgical exploration.

Based on laboratory data suggesting synergy of this drug combination, Dougherty et al. reported on a phase III study of cisplatin, high-dose cytarabine, and caffeine (CAC) in 26 patients with advanced pancreatic cancer. A partial response was documented in 7 of 18 evaluable patients. This finding prompted a phase III study by Kelsen et al. comparing CAC to SMF. Eighty-two patients were randomized, and 90% were evaluable; objective responses were seen in two patients who received CAC and four patients who received SMF.

The question of the benefit gained by multagent chemotherapy compared with single-agent therapy also has been examined. The Southwest Oncology Group performed a series of phase II trials comparing single-agent chemotherapy with combination chemotherapy (5-FU, doxorubicin, mitomycin C, and streptozocin). The single agents studied included mitoguazone, dihydroyxanthracenedione, and diaziquone. Eighty-two patients received single-agent therapy, and 71 received combination chemotherapy; the median survival durations were 3.4 and 4.8 months, respectively, indicating no significant benefit from combination chemotherapy.

In sum, these results confirm the ineffectiveness of conventional combination chemotherapy and support clinical studies evaluating novel single agents in previously untreated patients with advanced pancreatic cancer.

REGIONAL CHEMOTHERAPY

The high incidence of liver metastases and local tumor recurrence in the pancreatic bed has prompted investigation of regional chemotherapy. Regional approaches to chemotherapy for pancreatic cancer have included infusion of the SMA or celiac axis, combined intraarterial and SMV infusion, and isolated perfusion with extracorporeal chemofiltration. One report includes a phase II study from the Puget Sound Oncology Consortium of combined intraarterial cisplatin, intravenous infusional 5-FU, and EBRT in 16 patients with locally advanced pancreatic adenocarcinoma. No treatment-related deaths occurred, five patients achieved a minor response, and the median survival was 9 months. The authors thus concluded that this regimen was not superior to more standard chemoradiation regimens.

Maurer et al. treated 12 patients with locally advanced, recurrent, or metastatic pancreatic cancer with intraarterial chemotherapy (mitoxantrone, folinic acid, 5-FU, and cisplatin). Only one patient achieved a partial response, and the median survival was 6 months. However, an improvement in tumor-related pain was achieved in 9 of 11 evaluable patients.

Researchers at Tulane University combined intraarterial chemotherapy (mitomycin C, 5-FU, and mitoxantrone) with hemofiltration. They reported two complete responses and ten partial responses in 32 patients with advanced pancreatic cancer. Although these results demonstrate the feasibility of the regional chemotherapy approach to pancreatic cancer, future pilot studies aimed at achieving local control of disease in the pancreas or at decreasing the growth or development of liver metastases will require more sophisticated therapeutic agents to achieve meaningful antitumor effects.

Regional chemotherapy infusion may be more applicable to patients who have undergone pancreatectoduodenectomy and in whom liver metastases are the dominant site of disease recurrence. Ishikawa and colleagues treated 21 patients with continuous-infusion 5-FU (125 mg/d) delivered through the hepatic artery and portal vein for the first 4 to 5 weeks after pancreatectoduodenectomy. No chemotherapy-related complications were reported; one patient died of surgery-related complications. Survival in the 20 evaluable patients was superior to that of historical controls, and liver metastases were the cause of death in only 8% of patients at 3
years of follow-up. Updated results from Ishikawa et al. with 27 patients who received postoperative adjuvant intraarterial and portal venous 5-FU demonstrated a 5-year survival rate of 39%; this high survival rate was thought to be secondary to a marked decrease in hepatic metastases. Reported experiences from both Lygidakis and Stringaris (intraarterial immunochemotherapy) and Beger et al. (intraarterial chemotherapy) support the potential benefit of adjuvant intraarterial therapy after pancreaticoduodenectomy. These results come from highly talented and very experienced physicians; similar results will be difficult to produce outside of specialty centers because of the complexity of the treatment delivery. However, the concept of postoperative, adjuvant, liver-directed regional therapy will likely receive greater attention because of improved local tumor control with contemporary forms of chemoradiation and surgery.

NEW APPROACHES TO SYSTEMIC DISEASE

Despite advances in the understanding of the molecular biology of pancreatic cancer, the systemic treatment of metastatic disease remains unsatisfactory. Chemotherapy and the administration of biologically active molecules, such as tumor necrosis factor, interferons, have not resulted in significant improvements in response rates or patient survival. The study of novel chemotherapeutic agents based on the evolving understanding of the molecular biology of pancreatic cancer must receive the highest priority.

A number of general areas of clinical investigation may yield favorable results. These include interruption or modulation of known growth factors and signal transduction pathways involved with cell growth, invasion, and angiogenesis. Some of the systemic agents undergoing clinical investigation are described in this section, with an emphasis on therapies that are intended to inhibit specific signals required for cell growth and metastasis.

**Farnesyl Transferase Inhibition**

Because the ras oncogene is mutated and thereby constitutively activated in the majority of pancreatic cancers, inhibition of ras signaling has been postulated as a possible target for therapy. A particularly attractive approach under active development is the inhibition of ras protein function through interruption of essential posttranslational processing (farnesylation) necessary to localize ras proteins to the cytoplasmic side of the plasma membrane. This effort involved the discovery and synthesis of specific small molecules that inhibit the protein farnesyl transferase. Oral and intravenous. The functional consequence of this inhibitory effect is that the ras oncoprotein cannot localize to the cell membrane and is rendered inactive. A number of these small molecules are under investigation and include drugs that are administered orally and intravenously. Phase I and II trials of these agents are under way.  

Other approaches are also under investigation. The monoterpenic limonene and its more potent metabolite perillyl alcohol decrease farnesylated ras levels, probably through a different mechanism than lovastatin (which acts via hepatic hydroxymethylglutaryl coenzyme A reductase inhibition, thereby lowering plasma levels of farnesyl pyrophosphate). Orally administered perillyl alcohol demonstrated significant in vivo activity against pancreatic cancer in a Syrian golden hamster model. A phase I clinical trial of orally administered perillyl alcohol has been reported. Perillyl alcohol also holds promise as a potential chemopreventive agent for pancreatic cancer.

**Somatostatin Analogues**

Overexpression of the somatostatin receptor occurs in both ductal adenocarcinomas and neuroendocrine tumors. Physiologically, somatostatin is an antihypertensive hormone that inhibits the trophic effects of cholecystokinin and other factors. Binding the somatostatin receptor with the octapeptide somatostatin analogue octreotide has been demonstrated to inhibit cell growth in vitro. Initial animal studies were encouraging, but early clinical trials have proved disappointing. Two large multicenter phase III clinical trials have been conducted comparing a long-acting octreotide analogue with a placebo in the treatment of advanced pancreatic cancer. In one trial, patients received either a placebo or a long-acting octreotide analogue (SMS-201-995 5-FU LAR; octreotide pamote LAR) alone. No objective responses were observed, and the median survival times for patients receiving the octreotide analogue or the placebo were equivalent (16 weeks). In the other trial, all patients received 5-FU infusions with either an octreotide analogue (SMS-201-995 5-FU LAR) or a placebo. The addition of the octreotide analogue to 5-FU provided no advantage in terms of objective response or survival.

A novel variation of this approach used an octapeptide analogue of somatostatin containing methotrexate attached to the a-amino group of D-phenylalanine in position 1 of the octapeptide. Subsequent experiments with this agent against the MIA PaCa-2 human pancreatic cancer cell line in nude mice demonstrated significant inhibition of tumor growth. Further preclinical trials investigating the efficacy of such an approach continue.

Another strategy being explored is binding somatostatin analogues, such as octreotide, with radioisotopes, specifically yttrium 90, to selectively deliver therapeutic doses of radiation.

**Receptor Tyrosine Kinase Inhibition**

**TRASTUZUMAB (HERCEPTEX).** Binding the HER2/neu oncoprotein with specific antibodies leads to growth-inhibitory signaling and promotes apoptosis. Trastuzumab (Herceptin) is a humanized monoclonal antibody developed in mice that specifically binds the HER-2 receptor. Preclinical studies have shown that Herceptin leads to growth inhibition in cell lines that overexpress HER2/neu. Clinical trials in patients with metastatic breast cancer whose tumors overexpress HER2/neu have demonstrated that Herceptin has activity as a single agent, with objective response rates of 11% to 26%. Preclinical studies also have suggested synergy between Herceptin and cytotoxic agents. In a clinical trial, response rates and survival were both improved in women receiving Herceptin and chemotherapy compared to chemotherapy alone for metastatic breast cancer (all patients had tumors that overexpressed HER2/neu). Side effects were generally mild, but it should be noted that, when Herceptin was delivered in combination with an anthracycline, class III or IV heart failure (by New York Heart Association criteria) was observed in 19% of patients, compared to only 3% of patients receiving anthracycline-based chemotherapy without herceptin.

In pancreatic cancer, 30% to 40% of human tumors overexpress HER2/neu; however, the role of Herceptin has not yet been defined. A phase II trial is now under way to assess the combination of Herceptin and gemcitabine in patients with advanced pancreatic cancer.

**EPIDERMAL GROWTH FACTOR RECEPTOR MONOCLONAL ANTIBODY (C225).** Antibodies to the epidermal growth factor receptor have been shown to compete with the growth stimulatory ligands for binding to this receptor. Binding with specific antibodies leads to growth inhibition and in some cases to apoptosis. A humanized monoclonal antibody to epidermal growth factor receptor (C225) has demonstrated potent competitive binding to the receptor, leading to growth inhibition. In vitro studies suggest an additive effect of C225 with cytotoxic agents. Data from laboratories at the M. D. Anderson Cancer Center suggest a synergistic interaction in animal models of metastasis when gemcitabine and C225 are combined. The exact mechanisms of this synergy are being investigated, including effects on growth inhibition, apoptotic cell death, and angiogenesis. Clinical trials are under way with C225 in head and neck cancer patients; a clinical trial studying the toxicity and efficacy of gemcitabine combined with C225 is planned for patients with advanced pancreatic cancer.

**Matrix Metalloproteinase Inhibitors**

Matrix metalloproteinase inhibitors (MMPIs) occur as both endogenous factors that tightly regulate the activity of proteases in the extracellular milieu and as exogenous synthetic molecules. The two primary endogenous inhibitors are tissue metalloproteinase inhibitors 1 and 2. Both are fairly large proteins (28 kD and 21 kD, respectively) and unlikely to be clinically relevant because of their poor pharmacologic properties.

A number of synthetic MMPIs have been developed, including batimastat, marimastat, and BAY 12-9566. Batimastat is an orally bioavailable agent that has been studied clinically in patients with advanced prostate cancer, colorectal cancer, ovarian cancer, and pancreatic cancer. Interestingly, the dose-limiting toxicity is often musculoskeletal pain with arthralgias and myalgias. BAY 12-9566 is another orally bioavailable MMPI. Both batimastat and BAY 12-9566 are under investigation in multicenter phase III trials. In one randomized trial, batimastat is being compared with gemcitabine as a treatment for advanced pancreatic cancer; the results from this trial will be available soon. Marimastat is also being investigated in a randomized, double-blind, placebo-controlled trial designed to evaluate whether this agent can delay or prevent the onset of metastatic disease after pancreaticoduodenectomy in patients undergoing surgery with curative intent. In yet another clinical trial, patients with advanced pancreatic cancer are being randomized to receive gemcitabine with marimastat or gemcitabine alone; the primary end point of this trial is survival (data unpublished).
Antiangiogenic Agents

Tumor vascularity is an important requirement for tumor growth beyond a few millimeters, and it is now accepted that specific endogenous angiogenic factors exist that allow for endothelial cell growth and migration into tumor nodules. One such factor is VEGF, which is up-regulated in pancreatic cancer. Strategies have been developed to inhibit the effects of VEGF, including monoclonal antibodies and siRNA. In addition, a specific inhibitor to the receptor tyrosine kinase for VEGF has been discovered (SU5416). Phase I and early phase II clinical trials of SU5416 are currently under way.

Another antiangiogenic agent being studied is TNP-470, an analogue of fumagillin. Fumagillin is derived from the fungus Aspergillus fumigatus and is found to inhibit angiogenesis in an in vitro angiogenesis model. Pharmacokinetic studies of TNP-470 have demonstrated that it has a half-life of only 1 hour, suggesting that prolonged or frequent infusions of the agent may be required for activity. Nevertheless, as a single agent, TNP-470 produced a complete response in one patient with metastatic cervical cancer, with other study subjects achieving disease stabilization.

Two other antiangiogenic molecules that have been isolated from tumor-bearing animals are angiostatin, which is a peptide fragment of plasminogen, and endostatin, a fragment from collagen XVIII. Both angiostatin and endostatin have shown significant antitumor activity in animal models, and angiostatin has induced tumor dormancy in mice. Endostatin entered clinical trials in the latter part of 1999.

Gene Therapy

Given the large number of somatic mutations in pancreatic cancer, gene therapy represents a potentially powerful approach to this disease. Generally, gene therapy for pancreatic cancer includes approaches designed to replace the function of inactivated tumor suppressor genes such as p53, p16, and SMAD4/DPC4. Correcting loss of functional cellular changes is more challenging than inhibiting overexpressed proteins or a mutated oncogene. However, in vitro reintroduction of genetic information into cells has been shown to be an effective way to alter cellular growth, induce apoptosis, and sensitize pancreatic cancer cells to chemotherapy and radiation. Other approaches use genetic strategies to inhibit dominant oncogene function. The high frequency with which K-ras is altered in exocrine pancreatic cancer and its central function in signal transduction suggest that inhibiting production of the K-ras protein could lead to significant growth-inhibitory effects. This strategy has been used successfully in lung adenocarcinoma cells using retroviral constructs coding for K-ras antisense RNA. In addition, evolving ribozyme technologies offer the possibility of improved inhibition compared with traditional antisense approaches. A particularly interesting gene-therapy approach uses an oncolytic adenovirus that is genetically modified to replicate only in p53-deficient cells. Direct injection of this oncolytic virus has been shown to be feasible. The challenge in gene therapy for pancreatic cancer may be to deliver treatments that are capable of targeting both the local and metastatic components of this neoplasm.

DISEASE DEFINITIONS: METASTATIC DISEASE

The complex pathophysiological abnormalities accompanying metastatic pancreatic cancer often make specific treatment decisions extremely difficult. Many patients present to the medical oncologist or surgeon with profound debilitation, severe pain, and extensive metastatic disease. For these patients, chemotherapy is unlikely to result in significant improvements in quality of life or survival, and the toxic effects of chemotherapy may create additional complications. Management with supportive care or nontoxic hormonal approaches may be the optimal strategies for these patients.

For patients with metastatic pancreatic cancer who present with a good performance status, systemic chemotherapy is appropriate. In view of the limited impact of the currently available agents on survival, continued enrollment of patients in phase II trials of new agents or combinations is essential. In the absence of access to a phase II trial, treatment with gemcitabine appears to be the standard in the United States. However, it must be recognized that the primary impact of gemcitabine is on continued enrollment of patients in phase II trials of new agents or combinations is essential. In the absence of access to a phase II trial, treatment with gemcitabine appears to be the standard in the United States. However, it must be recognized that the primary impact of gemcitabine is on survival, continued enrollment of patients in phase II trials of new agents or combinations is essential.


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INTRODUCTION

Primary hepatobiliary malignancies are the most common of solid-organ cancers, and include hepatocellular carcinomas (HCCs), cholangiocarcinomas, and gallbladder cancers. As a group, these tumors represent both major diagnostic and therapeutic challenges. Though surgery can be potentially curative for these tumors, until recently, most cases of hepatobiliary cancers were discovered at a stage far too advanced for complete excision. These tumors also are highly resistant to chemotherapy, limiting options for palliative treatment. However, the last two decades have seen great advances in the diagnosis of and therapy for these tumors. Advances in imaging have allowed for earlier detection and more accurate staging of disease. The safety of surgical therapy has improved and, as a consequence of increased understanding of the biology of these diseases, favorable short- and long-term results are increasingly achieved by extensive but rational resection. Palliative measures such as radiotherapy and ablative therapy have extended the limits of tumor eradication and treatment. In this chapter, a discussion of the current therapy for these hepatobiliary tumors will be presented, emphasizing the recent major advances as well as the most important areas of ongoing and future studies.

HEPATOCELLULAR CARCINOMA

HCC is the most common solid-organ tumor worldwide, being responsible for more than 1 million deaths annually. The difficulties in treating HCC and the high mortality associated with it are attributable to a number of factors. First, this cancer usually is associated with cirrhosis, which is not only a cause of morbidity but also limits treatment options for the cancer. Second, HCC is usually asymptomatic at early stages and has a great propensity for intravascular or intrabiliary extension, even when the primary tumor is small. As a result, the carcinoma is usually at an advanced stage when discovered. This tumor is, therefore, usually beyond curative therapy at presentation and, indeed, often beyond any useful therapy.

EPIDEMIOLOGY AND ETIOLOGY

At least 1 million new cases of HCC occur yearly. The incidence of HCC increases with age and is four to eight times more common in men than in women. This cancer is clearly associated with chronic liver injury and, therefore, geographic distribution of HCC closely mirrors that of viral hepatitis (Table 33.5-1). Countries with a high incidence of hepatitis B virus (HBV) infection—namely Taiwan, Korea, Thailand, Hong Kong, Singapore, Malaysia, China, and countries of tropical Africa—have the highest incidence of HCC. Areas in which hepatitis C virus (HCV) infections are endemic, such as Japan and Italy, also experience an increased rate of HCC. In low-incidence areas such as Australia, North America, and Europe, HCC occurs in only 1 to 3 per 100,000 population. In high-incidence areas, HCC also occurs in younger individuals as compared to its occurrence in low incidence areas. In Mozambique, one of the areas of highest incidence of HCC, 50% of patients with the tumor are younger than 30 years. In fact, the incidence of HCC among men aged 25 to 34 years is more than 500-fold that of the same age group in Western countries.

This etiologic association between HBV infection and HCC is well established. In a landmark study examining HBV infection and HCC, Beasley et al. followed 22,707 male subjects in Taiwan, 15.2% of whom were HBV chronic carriers, as exhibited by detection of hepatitis B surface antigen (HBsAg) in the serum. Of the 116 cases of HCC that occurred during a mean follow-up period of 7 years, 113 occurred in patients positive for HBsAg. This study demonstrated that HCC was related not
simply to a history of HBV infection but to the chronic carrier states and that the relative risk of developing HCC was 200-fold greater in individuals with evidence of HBV infection than in noninfected individuals. Epidemiologic evidence has also clearly linked HCV infection with HCC. Antibodies to HCV have been found in as many as 78% of patients with HCC in Japan, Italy, and Spain, and in 36% in the United States. In contrast to HBV-associated HCC, however, HCC rarely occurs in HCV carriers before the development of cirrhosis. In addition, the incidence of HCC in cirrhotic carriers of HCV is estimated to be as high as 5% per year, as compared to 0.5% per year for HBV carriers.

Chemical carcinogens also have been linked to primary liver cancers. Chemicals such as nitrates, hydrocarbons, solvents, organochlorine pesticides, primary metals, and polychlorinated biphenyls have been implicated in the development of HCC. Colloidal thorium dioxide (Thorotrast), which emits high level a, b, and g radiation and was used as an angiographic agent in the 1930s, has been linked to angiosarcoma, cholangiocarcinoma, and HCC.

Of all the chemicals linked to development of HCC, the most important is ethanol. Alcohol abuse has been linked to the development of not only HCC but also carcinomas in the larynx, mouth, and esophagus. Ethanol is thought to produce HCC through development of hepatic cirrhosis or as a co carcinogen with other agents such as HBV, HCV, hepatotoxins, and tobacco. Rather than through direct effect on the hepatocytes.

Aflatoxins produced by the fungi Aspergillus flavus and Aspergillus parasiticus have also been linked to HCC. These are fungi that grow on grains, peanuts, and other food products and are the most common cause of food spoilage in the Tropics. These fungi produce aflatoxins designated as B1, B2, G1, and G2. Aflatoxin B1 is the most hepatotoxic, and chronic exposure to these mycotoxins leads to development of HCC.

Some congenital conditions also lead to development of HCC. Genetic diseases such as hemochromatosis, Wilson's disease, hereditary tyrosinemia, type I glycogen storage disease, hepatic porphyria of both intermittent and cutanea tarda types, familial polyposis coli, ataxia telangiectasia, familial cholestatic cirrhosis, biliary atresia, congenital hepatic fibrosis, neurofibromatosis, situs inversus, fetal alcohol syndrome, a-amylase deficiency, and the Budd-Chiari syndrome have all been linked to a higher incidence of HCC. Ultimately, though, the unifying etiology of HCC may be chronic injury and inflammation.

**PATHOLOGIC FEATURES**

HCC has been graded as well differentiated, moderately well differentiated, and poorly differentiated. The well-differentiated variety may be difficult to distinguish from a regenerating nodule on fine-needle biopsy. No firm correlation of grade to prognosis has been established. HCC can be classified generally into three different growth patterns, and these growth patterns have a much greater influence than does histologic grade on resectability and, therefore, greater influence on long-term outcomes. The hanging type of tumor is attached to the normal liver by a small vascular stalk, even if the tumor is large. This type is easily excised with little loss in functional parenchyma. The pushing type generally is well demarcated and often encapsulated by a fibrous capsule. This type of tumor displaces normal vascular structures rather than infiltrates and invades the major vessels. It is often resectable, even when tumor bulk is substantial. Finally, the infiltrative variety has a very indistinct tumor-liver interface and tends to exhibit a much greater degree of vascular infiltration and invasion, even when the tumor is small. Excising the infiltrative variety often is complicated by positive margins. The practical nature of this gross pathologic classification is reinforced by the distinctive radiologic appearance of these three different growth patterns on imaging.

The most important pathologic issue is the distinct appearance and clinical behavior of the fibrolamellar variant of HCC. The contrast in clinical behavior is summarized in Table 33.5-2. On gross and radiologic inspection, fibrolamellar HCC is generally well demarcated and often encapsulated, with a central fibrotic area. It is a variant that generally occurs in young patients who lack underlying cirrhosis. a-Fetoprotein (AFP), which is commonly elevated in the usual case of HCC, is not elevated in fibrolamellar HCC. Other serum markers that often are elevated in fibrolamellar HCC include neurotensin and vitamin B12 binding protein. The fibrolamellar variant of HCC is associated with a prolonged survival as compared with typical HCC, likely owing to the well-demarcated nature of the tumor and the greater range in treatment options for patients without underlying cirrhosis.

**TABLE 33.5-2.** Comparison of Standard Hepatocellular Carcinoma with the Fibrolamellar Variant

HCC can also appear with mixed or combined features of HCC and cholangiocarcinoma. The two components of this tumor may be separate, adjacent to each other, or intimately mixed. Bilary differentiation in HCC is associated with a poor prognosis, because such tumors are more rapidly growing and less vascular and, therefore, are more resistant to embolic therapy. In the clear-cell variant of HCC, the cells have an abundant, pale, finely granular or vacuolated cytoplasm as a result of abundant glycogen, fat, or water. The prognostic importance of finding the clear-cell variant has been debated, but this subtype may be associated with a better prognosis.

**CLINICAL PRESENTATION**

Even though it is generally a slow-growing tumor, the majority of HCCs present at an advanced stage, when most are beyond curative treatment. Because the liver is relatively hidden behind the right costal cartilages, tumors must reach substantial size before they are palpable. Furthermore, the large functional reserve of the liver masks any small impairment produced by local parenchymal disturbances. Therefore, small tumors are most often asymptomatic and are usually discovered during screening programs or incidentally during imaging performed for other abdominal conditions.

Most cases of HCC are detected only when tumors are large, at a stage when local symptoms are common. Patients usually complain of a dull, right upper quadrant ache, sometimes referred to the shoulder. Hepatomegaly is a frequent accompanying finding. The liver edge is hard and irregular, due both to tumor and the usual accompanying cirrhosis. A vascular bruit can be heard in approximately 25% of cases. General symptoms of malignancy, including anorexia, nausea, lethargy, and weight loss, are common. The most common clinical presentation is the triad of right upper quadrant pain, mass, and weight loss. Central necrosis of large tumors can also lead to fever, and HCC can present as pyrexia of unknown origin. For most patients, the presentation of HCC will also be the first presentation of the underlying cirrhosis. In one study, although 90% of patients were eventually found to have cirrhosis, fewer than 10% were thought, at first evaluation for HCC, to have chronic liver disease on the basis of history and clinical examination.

Hepatic decompensation is another common presentation of HCC, with patients seeking medical attention owing to typical symptoms of liver failure such as ascites, jaundice, or encephalopathy. This decompensation of liver function is most often attributable to bulk replacement of functional parenchyma in a patient with previously compensated cirrhosis. HCC has a great propensity for vascular invasion and intravascular growth. Therefore, hepatic failure may also be due to portal vein occlusion secondary to intravascular tumor thrombus. A much rarer cause of liver failure is Budd-Chiari syndrome, resulting from direct invasion and occlusion of the hepatic vein and inferior vena cava by tumor and tumor thrombus.

Gastrointestinal bleeding often complicates the clinical course of patients with HCC and, in 10% of patients, is the presenting finding. In approximately one-half of these cases, bleeding is from esophageal varices, which can result from portal hypertension due to cirrhosis alone or with an added contribution of intraportal
thrombus. Patients with gastrointestinal bleeding from esophageal varices have an extraordinarily poor prognosis, with a median survival measurable in weeks. 34 The particularly poor prognosis of variceal bleeding complicating HCC is due to the common finding of intraportal thrombus, which further increases the portal pressure and makes control of bleeding varices more difficult. In fact, in one study, nearly one-fourth of patients with HCC died from massive variceal hemorrhage. 35 Gastrointestinal bleeding can occur from other causes as well, such as benign peptic ulcer or direct invasion of the gastrointestinal tract by tumor. 36

The most dramatic presentation of HCC is tumor rupture, which is the initial presentation in 2% to 5% of patients with HCC. 37,40,41,42,43 Patients present with acute abdominal pain and swelling and are found to have, in addition to swelling, guarding, rebound tenderness, and ileus. Patients also commonly have signs of hemodynamic instability or overt hypovolemic shock. Diagnosis is confirmed by findings of either tumor mass or peritoneal blood through imaging, laparotomy, or paracentesis. 39,40,42

Jaundice as a presenting symptom of HCC occurs in up to one-half of all patients. The most common cause of the jaundice is hepatic parenchymal insufficiency, 35,40 and 37 On rare occasions (<10% of jaundiced patients), jaundice associated with HCC results from biliary obstruction. 35,43,44,45,46,47 The biliary obstruction can occur from intraluminal tumor, from hemobilia, or from extraluminal bile duct obstruction. In the clinical evaluation of jaundice in a patient with HCC, it is enormously important to distinguish hepatocellular failure from obstruction. The former usually indicates that the patient is beyond any therapeutic benefit, whereas the latter can be treated, often with good palliation and even potential cure. 39,40,45,46

Rarely (<5% of cases), HCC can present with paraneoplastic syndromes owing to hormonal or immune effects of the tumors. 37 The most important of these syndromes are hypoglycemia, erythrocytosis, hypercalcemia, and hypercholesterolemia. Porphyria cutanea tarda, viritilization and feminization syndromes, carcinoid syndrome, hypertrophic osteoarthropathy, hyperthyroidism, and osteoporosis can also occur. 39,40,45,46

**DIAGNOSTIC INVESTIGATIONS**

For patients suspected of suffering from HCC, the aims of diagnostic investigations are (1) verification of diagnosis, (2) determination of extent of disease, (3) determination of functional liver reserve, and (4) assessment of biologic determinants that affect long-term prognosis.

**Verification of Diagnosis**

Diagnosis of HCC can usually be positively established noninvasively by a combination of history, physical assessment, imaging, and blood tests. There is little diagnostic doubt in a patient with a liver mass consistent with an HCC visible on computed tomography (CT) or magnetic resonance imaging (MRI) and a serum AFP of more than 500 ng/dL. This combination is diagnostic, and treatment can be instituted without tissue diagnosis. The presence of cirrhosis or hepatitis infection, as documented by presence of HBsAg or HCV virus in the blood, is further confirmation.

In the patient with a space-occupying lesion on ultrasonography (US) or CT and a nondiagnostic AFP level, the role of a percutaneous needle biopsy often is debated. There is no doubt that needle biopsy is diagnostic for HCC. However, complications are also not infrequent. Hemorrhage or tumor rupture can occur. Furthermore, there is also a small but finite risk of tumor spillage and seeding of the needle by biopsy tract. 35 In cases of potentially resectable HCC, where the diagnostic certainty is high, we would proceed to surgical exploration without tumor biopsy. Indeed, in this clinical scenario, the histologic appearance of the nonneoplastic liver may have a greater impact on surgical planning. If advanced cirrhosis will preclude safe resection, we often perform a biopsy the portion of the liver that does not contain tumor, for histologic evaluation.

In patients with a nondiagnostic AFP level who are not surgical candidates and, therefore, are not candidates for curative therapy, tumor biopsy is performed if the patients are candidates for palliative therapy. In that case, fine-needle aspiration for cytologic evaluation is usually performed in preference to core-needle biopsy for histology, as comparative studies indicate that smear cytology yielded a much higher percentage of correct diagnoses as compared to microhistology (86% vs. 66%). 40 Patients who are not candidates for palliative therapy do not need a definitive diagnosis, and biopsy is discouraged.

**Determination of Extent of Disease**

The two issues to be resolved by the extent-of-disease evaluation are whether the disease is isolated to the liver and whether distribution of tumor in the liver is amenable to surgical excision. The most common sites of metastases of HCC include lung, peritoneum, adrenal gland, and bone. Hence, chest radiography is mandatory. Cross-sectional imaging, such as CT or MRI, of the abdomen should be scrutinized for peritoneal and adrenal sites of disease. Many centers consider bone scans mandatory prior to liver resection. Certainly, in patients with pain attributable to bony metastases, a bone scan should be performed. A finding of extraparenchymal disease changes the prognosis of the patients greatly, as such a finding precludes the possibility of hepatectomy as curative therapy.

The extent of liver involvement usually is determined by CT scanning. This diagnostic imaging modality is widely available and relatively inexpensive. In interpreting angiograms, most importantly for the patient with HCC, the number and distribution imaging modality must be determined, as well as the degree of vascular invasion. In this regard, triple-phase (non–contrast-enhanced, arterial phase, and portal phase) CT images should be obtained. HCCs are generally highly vascular tumors, and tumors on images with contrast enhancement may become isodense with the surrounding liver. Tumors sometimes are visible only during the non–contrast-enhanced phase. Because HCC has a great propensity for vascular invasion and extension, tumor thrombus in the portal vein, hepatic vein, or vena cava is not unusual. Scans should therefore be scrutinized for evidence of such invasion, as therapy and prognosis can be altered significantly by such findings. If such invasion is suspected but not proven by CT, Doppler US or MRI is indicated.

At some centers, hepatic angiography is standard. 53 Some have even advocated routine use of iodized oil (Lipiodol) injected angiographically to delineate hepatic extent of disease further. 54 This lipid is preferentially retained in HCC because of the particle size. These angiographic methods are highly sensitive for the presence of tumor. Nonetheless, with current helical CT or MRI, there is only minor incremental yield. We rely on angiography only when we suspect small tumors not visible by conventional cross-sectional imaging, such as for a patient with small amounts of disease seen on CT who has a very high AFP level.

**Assessment of the Patient's General Condition and Hepatic Functional Reserve**

In the evaluation of patients for possible hepatectomy, cardiopulmonary assessment should be conducted as for any major procedure. Patients older than 65 years or with a history or symptoms consistent with cardiopulmonary disease should be referred for formal medical preoperative evaluation.

Assessment of baseline liver function and assessment of complications of cirrhosis are paramount in the process of determining the optimal treatment option for each patient. Recovery from liver resection is reliant on the capacity of the liver to regenerate. The cirrhotic liver often has a reduced capacity for regeneration. In addition, cirrhosis and portal hypertension often are associated with derangements in hepatic production of coagulation factors and with thrombocytopenia, which explains the increased risk of liver failure and bleeding after resection for HCC. Indeed, the complication rate after ablative therapies is increased proportionate to the degree of liver dysfunction. 49 Consequently, many clinical and laboratory methods have been devised for determining the level of risk for various therapies.

**SERUM LIVER FUNCTION TESTS AND CLINICAL ASSESSMENT.** Various liver function tests, alone or in combination, have been touted as useful for predicting risks of liver resection and other treatments for HCC. Various single serum measures of liver function have been suggested as useful predictors of perioperative outcome, including serum bilirubin 2 and serum alanine aminotransferase. 2 A doubling of bilirubin has been suggested as a contraindication for liver resection. 2 Other investigators have deemed a platelet count of fewer than 50,000 or a prolonged prothrombin time (>4 seconds over control) as a relative contraindication for hepatic resection. 2 Most investigators, however, have not relied on a single parameter but rather have used a combination of clinical and biochemical parameters to gauge safety of hepatectomy and other treatments. In this regard, the most clinically useful system is the Pugh-Child's classification, which is a point-scoring system for evaluation of liver function based on the levels of serum bilirubin, coagulation profile, serum albumin, presence or absence of ascites and encephalopathy, and nutritional status (Table 33.5-1). 2,2 Functionally well-compensated cirrhosis is classified as Pugh-Child's classification grade A; decompensated cirrhosis is grade B; and decompensated cirrhosis is grade C. Generally, partial hepatectomy is offered only to patients who are Pugh-Child's grade A and to the most favorable grade B patients. 2 In general, Pugh-Child's grade C patients are offered only supportive care, as even nonsurgical ablative methods, such as embolization, are associated with procedure-related mortality in one-third of patients. 2
DYNAMIC TESTS. Many sophisticated dynamic measures of liver function have also been used in attempts to quantitate hepatic function. Investigators have attempted to use elimination of certain dyes that are exclusively cleared by the liver, such as bromsulfophthalein or indocyanine green, as measures of hepatic function. Galactose clearance or $^{14}$Caminopyrine clearance has also been used to evaluate the specific metabolic capacity of the liver. Of these, the most commonly used evaluative modalities in clinical practice are indocyanine green retention at 15 minutes and the $^{14}$Caminopyrine breath test, though controversy still exists concerning their usefulness. We do not use these tests on a routine basis in our care of the patient with HCC but have found the clinical Pugh-Child's classification sufficiently discriminatory for selecting patients for therapies.

PORTAL PRESSURES AND BLOOD FLOW. Another relatively simple test that may be predictive of perioperative outcome is the hepatic venous wedge pressure. By passing a venous catheter through the vena cava into the hepatic vein, the hepatic venous pressure can be directly ascertained. By balloon occlusion of the hepatic vein, the hepatic venous wedge pressure, which is a reflection of the portal pressure, can be determined. These measurements have been touted as useful in segregating Pugh-Child's grade B patients who may have favorable results from resection from those likely to experience major complications.

POTENTIALLY CURATIVE TREATMENTS

Therapies for HCC can be separated into resection, ablation, radiotherapy, systemic chemotherapy or immunotherapy, and supportive care. Resectional therapy represents the only potentially curative option.

Partial Hepatectomy

Partial hepatectomy represents the most common procedure for treatment of HCC performed with curative intent. The liver is normally a very resilient organ with remarkable regenerative capacity. In a noncirrhotic liver, routine recovery can be expected even after resection of more than two-thirds of the functional parenchyma in the United States, nearly one-half the patients with HCC will have no associated cirrhosis. For patients with no cirrhosis, operative mortality at most major centers is generally less than 5%, and very extensive procedures are justified by the low risk and the potential for long-term survival and cure. For a patient without cirrhosis, partial hepatectomy is a relatively safe procedure and is the treatment of choice for eradication of HCC.

Worldwide, however, most cases of HCC are associated with cirrhosis, which greatly increases the risk for partial hepatectomy (see Table 33.5-5). This increase in risk is due in part to intraoperative factors. These patients will usually have rigid and hard parenchyma and established varices that are difficult to manipulate and are prone to bleeding. In addition, such patients will have thrombocytopenia and coagulation defects that further exacerbate the risk of hemorrhage. Postoperatively, the liver may not regenerate, resulting in liver failure. Furthermore, postoperative exaggeration of portal hypertension may lead to ascites and variceal bleeds. It is understandable, therefore, that resection is associated with increased morbidity and mortality in these patients. Even for a cirrhotic patient with well-compensated liver function, we are reluctant to remove more than 20% to 25% of the functional parenchyma. Until recently, even at centers with a low mortality for partial hepatectomy in the noncirrhotic population, partial hepatectomy for patients with cirrhosis was associated with a 10% mortality or higher (see Table 33.5-5). This nihilistic view adopted by some for this disease, as well as the interest in treating this disease by total hepatectomy and liver transplantation. Nevertheless, even now, cirrhotic patients who survive the operation have a 5-year survival of approximately 30% (Table 33.5-6). Over the last decade, a number of series have demonstrated increasing safety of partial hepatectomy in cirrhotic patients (see Table 33.5-5). The mortality at most major centers treating HCC has been reduced to the 5% level, owing to improvements in patient selection, perioperative support, and surgical technique.
Patient selection for surgery depends first and foremost on hepatic function. As discussed earlier, in Serum Liver Function Tests and Clinical Assessment, the most commonly used clinical selection criteria for patient's fitness for surgery relies on the Pugh-Child's score. Few surgeons are willing to perform hepatic resection for patients with a Pugh-Child's grade C liver status. Most surgeons will consider resection only for patients with Pugh-Child's grade A liver functional reserve and the best Pugh-Child's grade B patients.

The major changes in operative conduct that have improved perioperative outcome include a willingness to use inflow occlusion during resection and a willingness to accept nonanatomic resection. Temporary occlusion of the hepatic artery and portal vein during liver resection by clamping the gastrophatic ligament has been a useful technique for reducing blood loss during hepatectomy for patients with no cirrhosis. In the past, surgeons have been reluctant to use such inflow occlusion, called the Pringle maneuver, in cirrhotic patients because of fears that cirrhotic parenchyma will not tolerate the transient ischemia. Recent studies have indicated that the reluctance to use this technique was largely unfounded and that cirrhotic liver can tolerate a Pringle maneuver for more than 30 minutes. The most important change in operative technique, however, is a willingness to use limited, nonanatomic resections. For patients with no cirrhosis, most major centers adhere to the anatomic boundaries of the various segments during liver resection for cancer. Lobectomies, sectorectomies, and segmentectomies are preferred over wedge and other nonanatomic resections because limited resections are more likely to result in a positive microscopic margin. In the cirrhotic liver, however, a smaller resection margin is acceptable if it will reduce the chance of postoperative liver failure. The smallest resection that will remove all gross tumor is generally used at most centers.

As safety of resections has improved, reports of increasingly large experiences in the treatment of HCC provide long-term results that allow for analysis of prognostic factors that influence long-term outcome. Many factors that previously were thought to be contraindications to surgical resection have not been substantiated by data. It is still desirable to remove multiple lesions if possible, and preoperative portal vein embolization for multiple deposits can allow safer hepatectomies. 51-55 Five-year survival in patients resected of multiple tumors is expected to be between 24% and 28%. Presentation with intrahepatic tumor and obstructive jaundice also does not preclude long-term survival after surgical resection. Therefore, distinguishing biliary obstruction from hepatic insufficiency as the cause for jaundice is very important in a patient who presents with HCC and jaundice. Finally, synchronous direct invasion of adjacent organs such as the diaphragm by HCC is not an absolute contraindication to resectional surgery.

One group that has a particularly poor prognosis is patients with major intravascular extension of tumor. Even though tumor thrombus can be treated with liver resection and thrombus extraction, the risk of disseminated disease is extremely high in these patients. If the tumor thrombus involves the vena cava or main portal vein, liver resections accompanied by venous tumor thrombectomies are unlikely to result in long-term survival.

Neoadjuvant Treatment of Tumors

Many groups have attempted to treat HCC with local or systemic therapies prior to attempts at surgical resection. The rationale for such neoadjuvant therapies is that large primary tumors may be sufficiently reduced in bulk to make resection safer and that local and systemic microscopic disease may be reduced or eradicated, thereby improving long-term outcome. In this regard, methods that have been employed to achieve these goals include transarterial chemoembolization, combined chemotherapy [doxorubicin (Adriamycin) and 5-fluorouracil (5-FU)] and radiotherapy (2100 cGy), hepatic artery infusion of chemotherapy agents, radioimmunotherapy, fractionated regional radiotherapy, and transarterial 90Y microspheres.

Another form of preoperative treatment is immunomobilization. Neoadjuvant transarterial immunoembolization (TIE) was tested with OK-432, a Streptococcus preparation. In a comparison of 22 patients who underwent TIE versus transarterial embolization (TAE) alone, the 1- and 2-year disease-free survival rates after resection were 85% and 85% for TIE and 62% and 56% for TAE, respectively. Lygidakis and Tsiliakos randomized 91 patients with HCC to resection alone or to resection with neoadjuvant chemoembolization and immunotherapy. Of 20 patients, 2 had preoperative complete necrosis of tumor as a consequence of preoperative therapy. Overall, survival was 18 months for resection alone and 36 months for the group receiving chemoembolization.

Promising data have recently emerged from studies of neoadjuvant use of systemic chemoimmunotherapy consisting of cisplatin, 5-FU, Adriamycin, and interferon-α(IFN-α). In a regimen modified from that initially suggested by Patt et al., Leung et al. were able to produce objective response in tumors believed not to be resectable and converted one-fourth of these tumors to resectability. Whether preoperative use of this regimen by Leung et al. would help to select the patients most favorably treated with resection and whether continuing such chemotherapy as adjuvant therapy after resection will improve long-term outcome awaits prospective studies. Overall, though, each of these studies consisted of only a few patients and, though such neoadjuvant therapy seems promising, a definitive role for any of these treatments in a neoadjuvant setting has not been unequivocally demonstrated.

An alternative neoadjuvant approach that attempts to improve outcome of resections involves embolization of the portal vein nourishing the side of the liver to be removed. Compensatory preoperative hypertrophy of the side of the liver not involved by the tumor will ensue and potentially allows a safer hepatic resection. Whether such theoretic advantage is sustained by clinical data awaits prospective randomized trials.

Adjuvant Therapy

Though up to one-third of patients can expect to remain disease-free long after hepatectomy for HCC, the majority will experience recurrence, indicating the presence of residual microscopic disease at the time of liver resection. This explains the keen interest in developing adjuvant therapy directed at microscopic residual disease.

In a study from China, 61 patients with resected HCC were randomized to no further therapy or postoperative hepatic infusion of Lipiodol and cisplatin with systemic epirubicin. The treated group seemed to have a higher extrahepatic recurrence and a worse outcome. Another study of 57 patients with resected HCC randomized to hepatic arterial infusion and systemic epirubicin versus no further treatment again demonstrated no difference in overall and disease-free survival.

Though transarterial chemoembolization is used extensively for the treatment of unresectable disease, randomized studies have not supported the use of this modality in the adjuvant setting. In fact, in three different studies, survival has been worse for those treated with chemoembolization after resection. To date, no study has demonstrated that any systemic chemotherapy or immunotherapy improves survival after hepatectomy for HCC.

Two positive randomized trials of adjuvant therapy after resection for HCC have been reported. The first involves the use of the retinoid derivative polyprenoic acid, which had been shown to inhibit hepatocarcinogenesis in rodents. In a study randomizing patients, after curative resection or PEI for HCC, to receiving either polyprenoic acid or placebo, significantly higher numbers of patients receiving placebo developed additional HCC. Currently, polyprenoic acid is not available in the United States, but these data encourage further study of this and other retinoid derivatives in adjuvant treatment for HCC and in chemoprevention for patients at high risk for developing HCC.

The other positive adjuvant study involved the use of radioembolization employing transarterial delivery of 131I-labeled Lipiodol. This compound has demonstrated positive results...
significant activity against small HCCs, but problems with dosimetry have limited its use for patients with bulky unresectable disease. In a prospective, randomized study, Lau et al. compared 21 patients who received 50 mCi of transarterial 131I-Lipiodol within 6 weeks of liver resection for HCC with 22 patients receiving no adjuvant therapy. The 3-year survival rates for the treated group and the control group were 85% and 46%, respectively. These results await multicenter studies to confirm with bigger numbers not only the long-term cancer results but also the feasibility of using such radioembolization methods in diverse centers.

Total Hepatectomy and Liver Transplantation

From a theoretic standpoint, total hepatectomy and liver transplantation is the most attractive treatment for HCC. This treatment allows for removal of the liver cancer with the widest margin possible. It also allows for resection of disease in the portal venous system as well as parenchyma that may be predisposed to formation of second primary tumors. A number of studies have attempted to define the biologic parameters predicting good long-term outcome after liver transplantation. The best results are seen in patients with fibrolamellar histology and in patients with small incidental tumors found unexpectedly within the explanted liver. Characteristics associated with poor long-term outcome include advanced stage, the presence of a margin involved by tumor, large tumors, multiple tumors, microscopic or macroscopic vascular invasion, and bilobar disease. Patients with tumors smaller than 5 cm have a mean survival of 55 months, whereas those with tumors larger than 5 cm have a mean survival of only 24 months. Therefore, most transplantation centers will not consider patients with tumors larger than 5 cm for transplantation. Currently, at most centers, only patients with fewer than three tumors, all smaller than 5 cm, and with no main portal vein or vena caval involvement are considered for liver transplantation.

In clinical practice, however, biology of the cancer is not the most important determinant of the usefulness of transplantation. Liver transplantation is associated with substantial morbidity and mortality (Table 33.5-7). Series from the 1980s and early 1990s often report mortality rates as high as 10% to 20%. Though some recent series have reported much-improved perioperative mortality (see Table 33.5-7), the morbidity is still substantial. In patients with liver dysfunction in either the Pugh-Child's grade B or C categories, however, total hepatectomy with liver transplantation represents the only potentially curative option.

The greatest obstacle is the limited availability of livers for transplantation. Even in the United States, where active public campaigns have resulted in comparatively high rates of organ donations for transplantation, only 3000 to 4000 livers are available each year. This would explain the limited numbers of livers used in transplantation for treatment of liver cancers. Only approximately 100 transplantations are performed each year for this indication (Fig. 33.5-1). In countries in the Far East, where organ donation goes against social and religious beliefs, the shortage of donated organs is even greater. Living-related liver transplants offer a potential source of organs for such use. However, the morbidity associated with donation of a lobe of liver is substantial, and mortality is not only a theoretic but a documented actual complication. For patients with cancer, the likelihood of recurrence brings into question the ethics of endangering a donor's life.

In addition, the costs of liver transplantation are substantial. Certainly, it is much more cost-effective to use available livers for the treatment of benign diseases. In many parts of the world, however, the high costs completely rule out transplantation for any indication. Because of these obstacles, liver transplantation is not likely to make an important impact on the worldwide treatment of cancer in the near future.

Comparing results of partial hepatectomy with results of liver transplantation for HCC has been difficult, primarily because patients with very distinct clinical characteristics are usually selected for each treatment. Patients selected for partial hepatectomy generally have good liver function and may have enormous tumors. Patients selected for transplantation almost always have small tumors but may have advanced liver failure. In the past, the reported 1-, 3-, and 5-year survival rates of liver transplantation for HCC were 40% to 82%, 16% to 71%, and 19.6% to 36%, respectively, rates that were highly comparable to those achieved with partial hepatectomy (see Table 33.5-7). These results indicated not so much that these two techniques were equivalent as that the right patients were being selected for each treatment.

Recently, two series of studies have encouraged a renewed comparison of these two treatment options. In a series from the transplantation literature, operative mortality appears to have been dramatically reduced to a current low of less than 5%. With such low operative mortality, Mazzaferro et al. are reporting 3-year survival after transplantation of 85% for small HCC. This has fueled enthusiasm for liver transplantation in this clinical setting. At the same time, a number of articles examining partial hepatectomy for HCC have been published that include sufficient data in the subset of patients with small tumors to allow comparison. It appears that partial hepatectomy for patients with small tumors also results in very favorable outcomes. For a patient with a tumor that is less than 5 cm in diameter, the 5-year survival can be expected to be 45% to 57%. In fact, disease-free survival can be expected in 44% of patients (Fig. 33.5-9). These results are comparable to the best results for liver transplantation. Therefore, given the organ shortage and costs of liver transplantation, partial hepatectomy should still be regarded as the curative treatment of choice. For patients with cirrhosis or with Pugh-Child's grade A cirrhosis, partial hepatectomy should be considered first. Total hepatectomy with transplantation may be necessary in this group if removal of tumor requires extensive resection of nonneoplastic liver. For patients with severe liver dysfunction, total hepatectomy and transplantation is a better option and may be the only viable option.

### Table 33.5-7. Results of Liver Transplantation for Hepatocellular Carcinoma

<table>
<thead>
<tr>
<th>Year</th>
<th>No. of Patients</th>
<th>1-Year Survival</th>
<th>3-Year Survival</th>
<th>5-Year Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>1985</td>
<td>100</td>
<td>45%</td>
<td>36%</td>
<td>28%</td>
</tr>
<tr>
<td>1986</td>
<td>120</td>
<td>47%</td>
<td>39%</td>
<td>31%</td>
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<tr>
<td>1987</td>
<td>140</td>
<td>50%</td>
<td>42%</td>
<td>34%</td>
</tr>
<tr>
<td>1988</td>
<td>160</td>
<td>53%</td>
<td>45%</td>
<td>37%</td>
</tr>
<tr>
<td>1989</td>
<td>180</td>
<td>55%</td>
<td>47%</td>
<td>39%</td>
</tr>
<tr>
<td>1990</td>
<td>200</td>
<td>58%</td>
<td>50%</td>
<td>42%</td>
</tr>
</tbody>
</table>

### FIGURE 33.5-1. Number of liver transplantations performed each year in the United States for cancer. Use of liver transplantation for this indication is greatly limited by the shortage of organs. (Data from UNOS.)

In a series from the transplantation literature, operative mortality appears to have been dramatically reduced to a current low of less than 5%. With such low operative mortality, Mazzaferro et al. are reporting 3-year survival after transplantation of 85% for small HCC. This has fueled enthusiasm for liver transplantation in this clinical setting. At the same time, a number of articles examining partial hepatectomy for HCC have been published that include sufficient data in the subset of patients with small tumors to allow comparison. It appears that partial hepatectomy for patients with small tumors also results in very favorable outcomes. For a patient with a tumor that is less than 5 cm in diameter, the 5-year survival can be expected to be 45% to 57%. In fact, disease-free survival can be expected in 44% of patients (Fig. 33.5-9). These results are comparable to the best results for liver transplantation. Therefore, given the organ shortage and costs of liver transplantation, partial hepatectomy should still be regarded as the curative treatment of choice. For patients with cirrhosis or with Pugh-Child's grade A cirrhosis, partial hepatectomy should be considered first. Total hepatectomy with transplantation may be necessary in this group if removal of tumor requires extensive resection of nonneoplastic liver. For patients with severe liver dysfunction, total hepatectomy and transplantation is a better option and may be the only viable option.
Because the incidence of recurrence of HCC after liver transplantation is high, many investigators have attempted to improve long-term results by use of adjuvant therapies. Cherqui et al. 142 used an adjuvant regimen combining neoadjuvant chemoembolization and radiotherapy with posttransplantation chemotherapy. Stone et al. 143 used a regimen of aggressive neoadjuvant, intraoperative, and postoperative chemotherapy. Farmer et al. 144 used an adjuvant chemotherapeutic regimen combining 5-FU, cisplatin, and doxorubicin. These are all small studies based on a sound understanding of HCC and represent promising approaches. All use neoadjuvant therapy because patients often spend a considerable amount of time awaiting availability of a liver for transplantation. However, given the small number of transplantations performed yearly for HCC, the role, timing, and regimens to be used are far from decided.

PALLIATIVE TREATMENT MODALITIES

Most patients presenting with HCC will have disease that is not treatable by partial heptectomy. Even if the disease is confined to the liver, the likelihood of treatment with total heptectomy and transplantation is low for reasons outlined in the preceding section. 145 Total Hepatectomy and Liver Transplantation. Nevertheless, if the disease is confined completely or largely to the liver, local tumor ablative therapies can be performed and result in good local control of disease. The ablative methods with the longest track record include ethanol injection, embolization, and cryotherapy. These will be discussed with specific emphasis on technical limitations, morbidity, and their likely role in patient clinical management. Other more investigative modalities, such as radiotherapy, radiofrequency ablation, and laser heat ablation, also are discussed.

Systemic Therapies

When a patient has widely disseminated disease, only systemic therapies make sense. However, the results of chemotherapeutic therapy or other systemic therapies for HCC have been dismal.

SYSTEMIC CHEMOTHERAPY. Numerous chemotherapeutic regimens have been tested for use against HCC (Table 33.5-8). HCC is, however, highly resistant to chemotherapy, owing to multiple factors: Tissue analysis has revealed that HCC harbors high levels of dehydropyrimidine dehydrogenase (DPD), and it is known that cells high in DPD are generally resistant to 5-FU. 146 In addition, HCC exhibits overexpression of the MDR1 (multidrug resistance) gene 147,148 and the gene product P glycoprotein. 149 This would explain the modest effects of 5-FU on HCC. In an Eastern Cooperative Oncology Group (ECOG) study of eniluracil (a DPD inhibitor) and 5-FU, 5 of 35 patients with HCC developed stable disease but no responses.

**TABLE 33.5-8. Systemic Chemotherapy for Hepatocellular Carcinoma**

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>Response Rate</th>
<th>Median Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxorubicin</td>
<td>20%</td>
<td>4 months</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>10%</td>
<td>6 months</td>
</tr>
<tr>
<td>5-Fluorouracil</td>
<td>5%</td>
<td>3 months</td>
</tr>
</tbody>
</table>

Doxorubicin is the most popular drug studied, though published data from 13 studies indicate that administration of this drug either alone or in combinations results in less than a 20% response and a median survival of less than 4 months. 145,146 Response to either single agent or multiagent systemic chemotherapy occurs in only 10% to 20% of patients (see Table 33.5-8). Furthermore, even the objective responses are short-lasting. In a systemic review 145 and metaanalysis 147 of the published randomized studies on HCC, neither doxorubicin nor any chemotherapeutic agent used singly or in combination has been shown to have any survival benefit for HCC patients. It is generally acknowledged that systemic chemotherapy has minimal impact on survival of patients with this disease. At our institution, systemic chemotherapy is offered mostly in the context of clinical trials. Moreover, most patients with unresectable disease are jaundiced or have a poor performance status because of extensive liver disease, making use of chemotherapeutic drugs virtually impossible.

HEPATIC ARTERIAL INFUSION. Because the results with systemic chemotherapy are far from optimal, regional delivery of chemotherapy has been attempted. Such regional approaches rely on the dual nutrient blood supply of the liver, portal vein, and hepatic artery. Hepatic tumors, however, derive their blood supply mainly from the hepatic artery. 147,148 Infusion of chemotherapy directly into the hepatic artery may allow increased effective dose at the tumor with fewer systemic side effects.

Hepatic arterial infusion (HAI) chemotherapy can be accomplished through a percutaneously placed angiographic catheter, through an implantable arterial port inserted at open operation and connected to an external infusion pump, or using self-contained subcutaneous infusion pumps implanted at surgery. Drugs with high liver extraction rates and short plasma half-lives are particularly well suited for HAI chemotherapy. 147,148 The fluoropyrimidines [5-FU and 5-fluorodeoxyuridine (5-FUDR)], cisplatin, doxorubicin, and 4'-epidoxorubicin are chemotherapeutic agents that have been tested in this mode of delivery.

Most data for treatment of HCC by HAI chemotherapy are gleaned from various phase II clinical trials 145,148,149. Intraarterial doxorubicin seems to be more active than intravenous treatment. 145,148 The highest response rates have been obtained with the drug FUDR. This drug has a high hepatic extraction ratio and short serum half-life, making it ideal for regional therapy. Warren et al. 150 reported a response rate of 60% in 15 patients. Aliq et al. 150 reported a 50% response rate in ten patients using an HAI regimen of mitomycin C, FUDR, and subcutaneous IFN. Makela and Kairaluoma 151 reported a 48% response rate with HAI mitomycin, with a median survival of 14 months. HAI of cisplatin has produced responses between 20% and 40%. In a small study comparing HAI of doxorubicin with systemic administration of doxorubicin, the response rate was greatly increased with HAI. 153

![Figure 33.5-2](image-url) Survival (solid line) and disease-free survival (dotted line) after resection of (A) small (<5 cm) or (B) large (>10 cm) hepatocellular carcinoma. Results of resection for these small tumors are highly favorable and comparable to liver transplantation. (From ref. 84, with permission.)
Though these results are encouraging, this route of chemotherapy is unlikely to make a great impact on the treatment of HCC. Significant toxicity, including cholangitis and bone marrow suppression, can still be encountered. Furthermore, the studies with the most encouraging results used surgically implanted infusion pumps or ports. Most patients with unresectable disease are not in sufficiently fit condition for surgery and pump implantation, as any operation in patients with underlying cirrhosis of the liver carries significant morbidity.

**SYSTEMIC IMMUNOTHERAPY.** Most studies of immunotherapy for HCC have involved the use of IFN-a or IFN-b. In a randomized controlled trial, high-dose IFN-a (18 to 50 mIU/m² three times weekly) was found to be superior to doxorubicin in inducing more tumor regression (10% partial response), less toxicity, and fewer fatalities. The same group also compared high-dose IFN-a (50 mIU/m² three times weekly) to supportive treatment and found better survival and tumor regression for the patients treated with IFN. However, the median survival was only 14.5 weeks for patients so treated. In another study comparing IFN-b with the chemotherapeutic agent menogaril, a slightly longer 1-year but shorter 2-year survival was found for the patients treated with IFN-b. These modest results certainly do not support the use of IFN as a single agent. Furthermore, all these studies used relatively high doses of IFN, and therefore toxicities requiring dose reduction were not uncommon.

Most current studies of immunotherapies, therefore, involve use of lower doses of IFN in combination with chemotherapeutic agents. The most promising combination is a regimen of cisplatin, doxorubicin, 5-FU, and IFN-a. Using this combination, Leung and Lau achieved a partial response rate of 26% in 50 patients with unresectable HCC. Six of these patients experienced sufficient regression of tumor to allow subsequent surgical resection. Two of these six patients had a complete response as confirmed by pathologic analysis. This regimen incites significant toxicity, as demonstrated by a 4% treatment-related mortality. Future randomized multicenter trials must be performed to define completely the clinical role for this regimen.

**SYSTEMIC HORMONAL THERAPY.** HCC has long been observed to be more common in men. Subsequently, it was noted that these tumors also express receptors for estrogens and androgens. Therefore, hormonal manipulation has been the basis of a number of trials directed at HCC. Of the antiestrogen compounds, tamoxifen has undergone the most extensive testing. This drug inhibits growth of HCC in vitro. The mechanisms of action against HCC, however, may not be related to its antiestrogen effects. Hepatocellular tumors express a high level of the MDR gene product P-glycoprotein. Tamoxifen is a potential MDR-reversing agent. Overall, results of clinical trials using tamoxifen have been mixed. Three small, randomized studies comparing tamoxifen to no treatment or placebo showed that tamoxifen significantly prolonged survival. Another recent randomized study of 469 patients with HCC showed no difference in survival in patients receiving tamoxifen or no tamoxifen. Tamoxifen is not believed to be clinically useful as a single agent.

A number of trials have also attempted to combine tamoxifen with other therapeutic agents. There were encouraging results in phase II trials. In 33 patients with HCC who were receiving tamoxifen and etoposide (VP-16), 8 (24%) had a partial response, with a median survival of 8 months in the responders. Combining epirubicin and VP-16 produced a 36% response rate in 36 patients. However, a randomized study of 59 patients with inoperable HCC showed no difference in response rates or survival between patients who received doxorubicin and those who received doxorubicin plus tamoxifen. Further larger-scale randomized trials are required to define tamoxifen’s exact role in the management of HCC in combination with chemotherapeutic agents.

Antiangiogenic treatment has also been attempted using agents such as ketoconazole and cyproterone acetate. The experience is, however, still too preliminary to permit firm conclusions. Overall, hormonal manipulation in the treatment of HCC has a good theoretic basis but has not yet been upheld by clinical data.

**Ablative Therapies**

**PERCUTANEOUS ETHANOL INJECTION.** Percutaneous ethanol injection (PEI) was first advocated by Sugita in 1983 for ablation of liver tumors. Tumor cells are killed by a combination of cellular dehydration, coagulative necrosis, and vascular thrombosis. Direct injections can be easily performed during open surgery or laparoscopy or percutaneously using ultrasound guidance. This ablative procedure is most often performed percutaneously and is very effective and safe for treating small HCCs. Ethanol injections are usually very well tolerated by patients, side effects being primarily pain, fever, and a transient rise in liver enzymes. Though other side effects, including bleeding, tumor rupture, needle tract tumor implantation, and death, can occur, these are uncommon complications. HCC is well suited for such injections because the tumors are most often soft and lie in a hard, cirrhotic liver. The injected alcohol tends to diffuse well within the soft tumors for good coverage of the cancerous tissues.

Because of technical limitations, only tumors smaller than 3 cm are generally treatable by PEI. In addition, most clinicians are unwilling to treat more than three tumors by this method. Tumors at the dome of the liver are difficult to treat because of overlying lung and the risk of pneumothorax. Patients with ascites are poor candidates for such injections, as the risk of bleeding is higher in these patients because the abdominal wall is not directly against the liver and cannot act to tamponade the sites of injection.

When tumors are within the limits for injection, results are very good. Nonrandomized studies have demonstrated a 3-year survival rate of 55% to 77% after PEI. In one large phase II trial that included 210 patients, the 5-year survival was found to be 33%. These treatments are unlikely to be curative, however. Patients should be followed up closely by imaging, and repeated treatments should be given when appropriate.

In a nonrandomized case study comparing liver resection (n = 33) with PEI (n = 30) in the treatment of small (>4-cm) HCCs, the recurrence rate was higher with PEI, but 1- and 4-year survival rates were similar for both treatment modalities. A large study involving 120 patients showed no benefit of tamoxifen over placebo in terms of tumor progression or survival. Another recent randomized study of 469 patients with HCC showed no difference in survival in patients receiving tamoxifen or no tamoxifen. Tamoxifen is not believed to be clinically useful as a single agent.

**TABLE 33.5-9. Hepatic Arterial Chemotherapy for Hepatocellular Carcinoma and Other Hepatobiliary Tumors**

<table>
<thead>
<tr>
<th>Study</th>
<th>No.</th>
<th>Treatment</th>
<th>Remaining tumor</th>
<th>1-year survival</th>
<th>5-year survival</th>
</tr>
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Tumor ablation can also be accomplished by injection of other agents. Agents so tested have included acetic acid, hot saline, glass microspheres containing 90Y, and various chemotherapeutic drugs. Partial and complete destruction of tumors has been documented with each of these. However, an advantage of any of these agents over ethanol has not been demonstrated to date. Ethanol is so well tolerated and the procedure so simple, particularly as compared to injections of radioactive isotopes, that until results from future comparative trials demonstrate a better alternative, PEI remains the treatment of choice for small, locally limited HCC.

**CRYOSURGERY.** Repeated freezing and thawing of tissues also produces tissue destruction. Recent technologic advancements have allowed for design and mass marketing of vacuum-sealed probes that are cooled by liquid nitrogen or argon. These probes can be introduced into tumors, and freezing can be performed under...
ultrasound guidance until the ice ball is more than 2 cm beyond the tumor margin. The tumor then is thawed and frozen again to produce effective cryoablation. The major advantage of this method over ethanol injection is the relatively larger size of tumor that can be treated effectively by cryoablation. Using probes of a diameter of 2 to 3 mm, a 5- to 6-cm ice ball can be produced. By placing multiple probes in proximity to one another, ice balls of up to 10 cm can be produced.

The major disadvantage is the need for general anesthesia and laparoscopy or laparotomy. Furthermore, not only is freezing of tumors near major vascular channels difficult because of the risks of bleeding, but complete freezing is virtually impossible because warm blood circulates in the vessels.

A number of series have been published that clearly demonstrate the safety of such an ablative approach in experienced hands. Recently, as smaller and smaller cryoprobes have become available, some investigators have also attempted to perform the cryoablation percutaneously. Whether this will represent an advance is not yet known. Certainly, comparative studies of cryoablative versus nonsurgical ablative methods such as ethanol injection or embolization are needed.

In our practice, we are prepared to perform cryoablative therapy whenever an operation is performed to attempt resection. If a tumor is found to be unreatsectable at the time of surgery, and the patient has already incurred the risks of anesthesia and laparotomy, we will proceed with cryoablative therapy. In contrast, hepatic parenchyma derives most of its nutrients from the portal vein, and complete occlusion of the hepatic artery does not render the liver ischemic. In contrast, hepatic tumors derive most of their nutrients from the hepatic artery. To induce ischemia and death of unresectable tumors, surgical hepatic arterial ligation was at one time the treatment of choice but has largely been abandoned for two main reasons. First, long-term clinical efficacy is poor, probably owing to the rapid development of collateral vessels after ligation of the main vessels. Second, in patients with cirrhosis and portal hypertension, a high percentage of nutrient blood supplying functional noncancerous parenchyma is derived from the hepatic artery. Ligation of the main hepatic artery therefore was associated with a high procedure-related mortality, as high as 13%. Hence, this procedure has largely been abandoned as a treatment mode for HCC in the cirrhotic patient.

Hepatic arterial embolization. The liver has a dual nutrient blood supply consisting of the hepatic artery and the portal vein. Under normal conditions, the hepatic parenchyma derives most of its nutrients from the portal vein, and complete occlusion of the hepatic artery does not render the liver ischemic. In contrast, hepatic tumors derive most of their nutrients from the hepatic artery. To induce ischemia and death of unresectable tumors, surgical hepatic arterial ligation was at one time the treatment of choice but has largely been abandoned for two main reasons. First, long-term clinical efficacy is poor, probably owing to the rapid development of collateral vessels after ligation of the main vessels. Second, in patients with cirrhosis and portal hypertension, a high percentage of nutrient blood supplying functional noncancerous parenchyma is derived from the hepatic artery. Ligation of the main hepatic artery therefore was associated with a high procedure-related mortality, as high as 13%. Hence, this procedure has largely been abandoned as a treatment mode for HCC in the cirrhotic patient.

Percutaneous selective TAE is a much safer method for treating liver tumors when vascular interruption is desired and has largely replaced surgical arterial ligation. In this method, a catheter is introduced through a percutaneous femoral approach and is threaded under fluoroscopic guidance to the hepatic artery. The branch feeding each tumor can then be cannulated selectively and occluded with degradable or nondegradable particles, coils, or oils. Such selective embolization maintains patency of the main hepatic arteries, thus sparing normal functional liver parenchyma. In addition, it allows repeated treatments through the same arteries. Possible adverse effects include pain, fever, nausea, and transient increase in liver enzymes. Hepatic insufficiency and infected necrotic tumor are rare complications but may be a cause of treatment-related mortality. The risk of complications is clearly related to the degree of hepatic dysfunction. Treatment-related mortality is as high as 30% in patients with Pugh-Child's grade C hepatic function. Therefore, embolization generally is performed only for patients with Pugh-Child's grade A or B liver function. In addition, patients with portal vein occlusion tolerate arterial interruption very poorly, and presence of tumor thrombus in the main portal vein is considered a relative contraindication to embolization.

There is no doubt that such embolization produces effective response in approximately one-half the patients (Table 33.5-10). For patients with painful, unresectable tumors, embolization is effective therapy. It can also be life-saving therapy for patients with ruptured HCC. Documenting the benefits of embolization in other settings has been more difficult. Randomized studies comparing TAE to chemotherapy or to supportive care have been unable to document an improvement in survival. However, most studies are plagued by difficulties and flaws, including small sample size. More important, in these studies has usually involved embolization of the main hepatic arteries rather than the safer and more effective selective embolization performed at major centers.

| Table 33.5-10. Embolization and Chemoembolization for Hepatocellular Carcinoma |

To improve the efficacy of embolization, investigators have attempted to soak the embolization particles, such as Gelfoam, with chemotherapeutic agents prior to delivery by chemoembolization. In two randomized studies of chemoembolization versus embolization alone, however, there were no differences in survival.

In other attempts to improve the results of TAE, investigators have used Lipiodol or ethiodized oil (Ethiodol). Each of these agents is a lymphangiogram dye derived from poppy seed oil that selectively wedges within HCC when administered via the hepatic artery. Embolization of tumors using these oils was originally developed to enhance visualization of HCC. It then was discovered that these oils can be used to deliver and concentrate chemotherapeutic agents at sites of tumor. By mixing hydrophilic drugs with Lipiodol, an emulsion is produced that can be administered intraarterially to produce Lipiodol chemoembolization. Phase I and II studies and small phase III studies have demonstrated a significant tumor response rate after such treatment. Treatment with doxorubicin and Lipiodol produced responses in 10 of 18 patients with small HCCs (<4 cm) and in 5 of 49 patients with large tumors. Yoshikawa et al. randomized 19 patients to receive Lipiodol-epirubicin and compared them with 17 patients who received epirubicin alone through the hepatic artery. Lipiodol-epirubicin gave a higher tumor response rate as compared with epirubicin alone (42% vs. 12%, respectively).

Larger, randomized trials have been unable to substantiate a survival benefit for such Lipiodol chemoembolizations, however. Madden et al. randomized 136 HCC patients to receive intraarterial Lipiodol-epirubicin versus supportive care and found no survival benefit. Instead, there was an increased morbidity for the treatment arm. A randomized study comparing treatment using Lipiodol plus Adriamycin to Lipiodol alone showed a trend toward a better response at 1 and 2 years with the combination of Lipiodol and Adriamycin, but the difference was not statistically significant.

A further modification of this same theme involved the intraarterial administration of hydrophilic drugs mixed with Lipiodol in an emulsion, followed by temporary or
permanent occlusion of the hepatic artery by embolization using a Gelfoam pellet, Avonol particles, or starch particles. Okuda et al. treated 52 patients with HCC using HAI 5-FU plus cisplatin followed by particle embolization and Lipiodol injections. They reported a response rate of 71% and a 5-year survival of 46%. In another study comparing particle embolization with epirubicin and Lipiodol versus chemotherapy alone in 38 patients, the 1- and 2-year survivals were 73 and 35 versus 43 and 0 in the two groups, respectively. A randomized study comparing intraarterial Lipiodol-cisplatin and Gelfoam embolization to supportive care showed no improvement in survival among the treated group, though this is likely attributable to the high incidence of liver failure in the treated patients. Another randomized study comparing treatment with Lipiodol-cisplatin plus Gelfoam embolization to Lipiodol and Gelfoam in patients with HCC showed a worse outcome in the group using cisplatin. The case for chemoembolization with or without Lipiodol administration is, therefore, far from proven. Because of the small size of individual studies, metaanalyses of the published randomized studies have been performed but have failed to show any clear benefit of transarterial chemoembolization over no treatment.

Particle embolization clearly produces responses in the majority of tumors. At times, the response can be very dramatic, resulting in impressive relief of symptoms. Hence, these treatments may be useful in a patient with ruptured tumors or tumors that are symptomatic in pain or paraneoplastic syndromes. In addition, it is our bias (though not yet supported by randomized trials) that, for the subset of patients with good liver function, tumors of less than 10 cm in diameter, less than 50% liver replacement by tumors, and no portal vein thrombus, selective embolization may be beneficial. It is in this favorable subset of patients that future clinical trials should be directed, examining the utility of embolization. We believe that current data do not support the use of chemoembolization or Lipiodol mixtures but rather indicate that these complex mixtures may merely add cost and complications without improving efficacy. At present, we prefer to use simple particle embolization for treatment of symptomatic or favorable tumors. It is likely that effective palliative therapy will be a combination of local therapy by embolization and an as-yet-undefined systemic treatment.

Radiotherapy

Initial attempts to use whole liver irradiation in the treatment of primary hepatobiliary cancer were unsuccessful. For instance, in the series by El-Domeiri et al. and Phillips and Murikami, only 1 of 31 patients with unresectable disease who underwent radiation survived more than 1 year. The most important reason for this lack of success is the low tolerance of the liver to whole organ radiation. Instead, the irradiation tolerance of the whole liver in patients with primary HCC may tend to be lower than in those with metastatic cancer to the liver, as many patients with primary disease have some degree of underlying cirrhosis.

Attempts have been made to increase the effectiveness of whole liver irradiation in the treatment of patients with unresectable hepatoma by the addition of intravenous chemotherapy and/or doxorubicin and 5FU as a radiosensitizer. The benefit of adding 131I antifolin monoclonal antibody therapy to doxorubicin and 5FU for patients who had received initial treatment with doxorubicin plus 5FU and whole liver irradiation (21 Gy in seven fractions) was a reduction in the time to progression and an increase in median overall survival (67). RTOG 88-23 measured the benefit of combining antibody with hepatic artery cisplatin for patients who had received induction treatment with whole liver irradiation (21 Gy in seven fractions) and intraarterial cisplatin. The conclusions from these and other studies are that 131I antifolin increased toxicity without benefit and that hepatic arterial cisplatin may be superior to either intravenous or hepatic arterial doxorubicin and 5FU when combined with irradiation. The finding that hepatic arterial cisplatin and radiation can produce an objective response rate of 43% and a median survival of 7.5 months in a relatively large group of patients suggests that these combinations have some activity.

In contrast to the relative ineffectiveness of whole liver irradiation (when used alone), focal liver irradiation can produce regression of primary hepatobiliary cancers (Fig. 33.5-3). At least four techniques have been assessed: 90Y microspheres, 131I-labeled ethiodized oil, and external-beam radiotherapy with either protons or photons. In 90Y therapy, 90Y oxide is incorporated into a stable glass matrix. When bombarded with neutrons, 90Y is converted to 90Sm. In this process, the beta emitter emits a half-life of 64.5 hours and average electron energy of 2.23 MeV, which produces an electron range of approximately 2.5 cm. The microspheres have been infused into the hepatic artery as a form of regional therapy for well-vascularized tumors, producing objective response rates ranging from 0% to 26% (89,90,91,232,233) (for review, see Ho et al. (235)). Note that 90Y doses (50 to 150 Gy) cannot be compared directly to the more familiar external-beam doses, as the former are calculated by assuming full decay with all radiation homogeneously deposited in the liver. More important, low dose-rate irradiation (<0.2 Gy/min) delivered by 90Y has far less effect than the same physical dose delivered by standard external-beam treatment (>2 Gy/min). A better understanding of the dosimetry of this technique as well as of the technical factors (such as pulmonary shunting, which can lead to radiation pneumonitis, or variant arterial supply to the stomach, which can produce gastric ulcers) is required before the application of microspheres can become routine. 131I microspheres are not available for clinical use in the United States currently.

Another method of delivering focal liver irradiation involves hepatic arterial administration of 131I ethiodized oil. Ethiodized oil has been used extensively for chemoembolization for HCC (discussed earlier in the section Hepatic Arterial Embolization); in this approach it is formulated with radioactive iodine in an attempt to deliver localized irradiation using the beta (electron) component of the 131I emissions. Randomized trials led by French investigators compared 131I-labeled ethiodized oil to chemoembolization and 131I-labeled ethiodized oil to supportive care for patients with portal vein thrombosis. In the former study, 129 patients were randomized to receive either 50 mCi of 131I-labeled ethiodized oil or chemoembolization with cisplatin (70 mg). There was no difference in overall survival between the two groups (median survival, approximately 40 weeks), but the toxicity of the ethiodized oil arm was significantly less. In the latter study, 27 patients were randomized to receive either 60 mCi of 131I-labeled ethiodized oil or control treatment (such as tamoxifen). The ethiodized oil group showed a statistically significantly greater median survival (approximately 6 months as compared to 2 months). Although these findings suggest that 131I-labeled ethiodized oil has activity in HCC, this small study does not permit a firm conclusion to be drawn. Furthermore, as is the case for 90Y, little is known about the tumor and normal tissue dosimetry. 131I-labeled ethiodized oil is not available for use in the United States currently.

FIGURE 33.5-3. Treatment of hepatocellular carcinoma (HCC) by conformal radiation. The large HCC in the right lobe of the liver (A) has had a dramatic response (B) to such treatment.

Traditional external-beam photon techniques, either alone or in combination with chemoembolization, have produced objective responses in patients with unresectable HCC. However, standard photon techniques often require the treatment of large volumes of normal liver. In contrast, three-dimensional conformal radiotherapy (3D-CRT) planning using beams not confined to the axial plane can substantially reduce irradiation of normal liver. Phase I and II trials for patients using 3D conformal external-beam irradiation combined with hepatic arterial FUHDR have demonstrated that high-dose focal irradiation can produce a 60% response rate (see Fig. 33.5-3). Recent results support the hypothesis that the dose delivered is an important prognostic factor in both local control and survival for patients with primary hepatobiliary cancers. In this study, dose is prescribed (to a maximum of 90 Gy) according to the fraction of normal liver that is spared, based on a normal tissue complication probability (NTCP) model. Patients who can receive more than 70 Gy have a median survival in excess of 17 months, which approaches that achieved by surgical resection. In a multivariate analysis, dose is a prognostic factor independent of tumor size.

Although 3D techniques permit parts of the liver to be treated with doses of radiation far higher than the entire liver can tolerate, it is possible that both higher doses and larger volumes than have been used in the current studies could be used safely. A first step in defining these limits is to develop an NTCP model to describe the dependence of liver tolerance on the combination of dose and volume. A number of theoretic models (all of which require knowledge of the 3D dose distribution) have been proposed to estimate the volume dependence of normal tissue tolerance. Initial investigations have suggested that it will be possible to derive a quantitative model to predict radiation-induced liver disease. More recently, an NTCP model with parameters calculated from patient data has been used
prospectively to prescribe a dose that would subject each patient to a predetermined complication risk. Twenty-one patients have completed treatment on such a protocol. The mean dose delivered was 56.6 ± 2.3 Gy (range: 40.5 to 81 Gy). One of 21 patients developed radiation-induced liver disease. The observed complication rate of 4.8% (95% confidence interval, 0% to 23.8%) did not differ significantly from the predicted 8.6% NTCP (based on dose delivered). These results suggest that an NTCP model can be used prospectively to deliver safely far higher doses of radiation to patients with intrahepatic cancer than were possible using previous approaches. The widespread adoption of 3D conformal planning systems should permit these concepts to be tested in multiinstitutional trials.

Another method of delivering highly conformal radiation is with protons. Investigators at the Proton Medical Research Center in Japan have demonstrated response rates similar to those just reported using 3D-CRT. Interestingly, high-dose focal irradiation using either photons or protons can produce hypotrophy in the nonirradiated liver, resembling the effect of partial hepatectomy.

In summary, whole liver irradiation alone has little efficacy in the treatment of HCC. The addition of hepatic arterial cisplatin may increase the efficacy somewhat. High-dose focal irradiation, especially using external-beam photons or protons, can produce objective responses in the majority of patients, although the relative merit of these techniques as compared to other nonsurgical approaches described in this chapter has not been assessed in randomized trials.

SCREENING FOR HEPATOCELULAR CARCINOMA

Patients found to have small (<5-cm) HCC have a much better prognosis than do those presenting with larger tumors. The size of a tumor is a significant risk factor for intrahepatic and extrahepatic spread. The frequency of intrahepatic metastases rose by almost one-third between HCCs smaller and larger than 5 cm (60% to 90%), and the rate of portal vein tumor thrombosis almost doubled (40% to 75%). Many more treatment options are also available for patients with small tumors. Tumors smaller than 3 cm can be treated by PEI, RFA, resection, or transplantation, whereas tumors smaller than 5 cm can be treated by cryoablation, resection, or transplantation. Hence, smaller tumors are not only biologically more favorable but are technically more easily treated. Because symptomatic tumors are usually large, widely disseminated, and beyond therapeutic option, the rationale for screening patients at risk for HCC is clear.

Whole population screening, even in areas where HBV is endemic, is almost certainly not a financially viable option. In epidemiologic studies, it is apparent that the incidence of HCC in HB Ag-positive patients is approximately 0.5% annually. Therefore, the yield for screening programs is low. Hepatitis occurs mainly in developing countries, where the cost of any population screening program will also be too prohibitive.

In the presence of HCV, however, the risk of HCC in a patient with established cirrhosis is estimated to be as high as 5% per year. Also, HCV occurs more often in industrialized nations. Hence, it is much more justifiable and likely that screening programs will be developed for detection of HCC in patients with cirrhosis due to HCV infection.

As a clinician striving to deliver optimal care for individual patients, screening high-risk patients for HCC is justifiable. Patients with established cirrhosis or chronic HCV infection are clearly important candidates for screening. Patients with chronic HBV infection should also be considered for screening. Furthermore, only patients with Pugh-Child’s grade A or B liver functional status should be screened, as patients with Pugh-Child’s grade C disease will generally be too sick for therapeutic interventions and early detection of HCC will only cause anxiety and detrimentally affect the patient’s likelihood for liver transplantation. Screening protocols are largely based on the biases of each major center. Some have advocated frequent testing, including ultrasound examination every 3 months and serum AFP testing once every 2 months. Because HCC is slow-growing, however, with a documented median doubling time of 4 to 5 months for small HCCs, we advocate AFP and liver function tests every 3 months and liver imaging every 6 months.

OTHER PRIMARY TUMORS OF THE LIVER

HEPATOBLASTOMA

Hepatoblastoma affects approximately 1 in 100,000 children and is the most common primary malignant liver tumor in children. It is usually diagnosed before the age of 3 years, with a 2:1 male predominance. Patients usually present with abdominal swelling and elevated serum AFP (>75% of patients). CT scans will reveal a vascular mass that often (50%) is speckled with calcifications. The Children’s Cancer Study Group staging system is shown in Table 33.5-11. Overall long-term survival varies between 15% and 37%, and prognosis is associated with unresectable tumors and tumors demonstrating anaploidy and anaplastic characteristics.

<table>
<thead>
<tr>
<th>Group</th>
<th>Description of tumor, or patient, as a whole.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>Complete resection of tumor, with or without adjuvant therapy.</td>
</tr>
<tr>
<td>Group II</td>
<td>Partially resectable tumor, or patient.</td>
</tr>
<tr>
<td>Group III</td>
<td>Nonresectable tumor, but resectable metastases.</td>
</tr>
<tr>
<td>Group IV</td>
<td>Nonresectable tumor, or patient.</td>
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</tbody>
</table>

Complete resection is possible in 50% to 65% of children with hepatoblastoma and is associated with cure rates between 30% and 70%. Unlike adult primary liver tumors, chemotherapy may produce response in a significant number of patients with hepatoblastomas. Preoperative chemotherapy has been used with some success in converting unresectable tumors to resectable lesions. Adjuvant chemotherapy has also been used after resection of hepatoblastoma. Evans et al. reported that 20% of 24 patients with hepatoblastomas were relapse-free 8 to 42 months after surgical resection coupled with adjuvant vincristine, doxorubicin, 5-FU, and cyclophosphamide.

Radiotherapy has been used in the treatment of unresectable hepatoblastomas, but its utility is far from proven. Orthotopic liver transplantation should be considered in children with unresectable hepatoblastoma if the tumor does not become resectable after preoperative chemotherapy. Penn reported on 18 patients undergoing liver transplantation for unresectable hepatoblastoma. Though tumors recurred in six patients, five have survived disease-free for more than 2 years, with actuarial survival rates of approximately 50%.

ANGIO SARCOMA

Angiosarcomas are malignant mesenchymal tumors of the liver that are also referred to as hemangiosarcomas. Only approximately 25 cases occur in the United States each year. Peak incidence is in the sixth and seventh decades, with a predominance in men (85%). Abdominal pain, abdominal swelling (usually due to liver enlargement), liver failure, nausea, anorexia, vomiting, and jaundice are seen. These malignant tumors have been associated with exposure to thorotrast, arsenic, or vinyl chloride.

Angiosarcomas are aggressive neoplasms. Partial hepatectomy can result in long-term survival, but most patients present with advanced tumors that cannot be treated by excision. Distant metastases are found at initial presentation in one-half of patients. Most patients die within 6 months of diagnosis. Even with surgical excision, few patients survive more than 1 to 3 years after complete resection because of metastatic disease. Results of radiotherapy and chemotherapy or both have been disappointing. The results of orthotopic liver transplantation for treatment of angiosarcoma have also been poor. Penn et al. reported development of tumor...
recurrences in 9 of 14 transplant patients with tumors classified as either angiosarcomas or epithelioid tissue sarcomas. The 2-year survival rate was 15%, and no patient survived more than 28 months postoperatively.

The liver can occasionally be the primary site for rhabdomyosarcoma, though this is more common in children than in adults. Hepatic metastases from a gastrointestinal or urologic primary tumor must be ruled out before the diagnosis of primary leiomyosarcoma of the liver can be made. Surgical resection is the treatment of choice for these primary hepatic sarcomas. Unresectable disease carries an unfavorable prognosis.

Undifferentiated sarcomas of the liver are very rare and usually occur in children between the ages of 6 and 15 years. Most undifferentiated sarcomas of the liver are found at an advanced stage, when surgical resection is not possible. The patient with such a tumor rapidly succumbs to the sarcoma, as such tumors usually are not responsive to radiotherapy or chemotherapy.

**EPITHELIOID HEMANGIOENDOTHELIOMA**

Epithelioid hemangioendothelioma is another malignant soft tissue tumor of endothelial cell origin. Factor VII staining differentiates hemangioendothelioma from other nonvascular tumors. Infantile hemangioendothelioma, which is benign, is unlikely; the adult variety is malignant and highly aggressive. Average age at presentation is 50 years, and the usual presenting signs and symptoms consist generally of nonspecific complaints, including pain, and an abdominal mass. In contrast to angiosarcoma, there is a female predominance (63% of patients).

Weiss and Enzinger recommended radical surgery, if possible. However, these tumors are almost always diffuse and multifocal and, therefore, are unlikely to be cured by partial hepatectomy. If hemangioendothelioma is suspected, a percutaneous biopsy is performed for diagnosis. Frozen-section analysis is not usually helpful at open surgery because special stains are required for diagnosis of this tumor. Patients with hemangioendotheliomas should be considered for total hepatectomy and liver transplantation. Penn reported a series of 21 patients who underwent orthotopic liver transplantation for treatment of epithelioid hemangioendotheliomas; 7 of 21 patients experienced tumor recurrence. The actuarial survival rate was 82% at 2 years and 43% at 5 years.

**CHOLANGIOCARCINOMA**

Cancers of the bile ducts are rare tumors, with only approximately 4000 cases presenting in the United States annually. Because of the proximity of the bile duct to the liver, the pancreas, and major vascular structures, surgical excision of these tumors usually requires a major hepatic or pancreatic resection or both. Major vascular reconstructions may also be necessary. The technical demands of such resections and the lack of effective alternative therapies for cholangiocarcinomas explain the nihilistic attitude that generally surrounds this disease. Advances in imaging over the last two decades now allow for earlier diagnosis of bile duct cancer and better surgical planning. Recent improvements in operative technique have substantially improved the outlook of patients presenting with this cancer.

**EPIDEMIOLOGY AND ETIOLOGY**

Cholangiocarcinoma is an uncommon cancer, with an incidence of 1 to 2 cases per 100,000 population in the United States and constituting approximately 2% of all reported cancers. It is a disease of the elderly, with the majority of such lesions occurring in patients older than 65 years and the peak incidence occurring in the eighth decade of life. Untreated, bile duct cancers are rapidly fatal diseases, and the majority of patients will die within 6 months to a year of diagnosis. Death usually results from liver failure or biliary sepsis.

Long-term survival is highly dependent on the effectiveness of surgical therapy. Indeed, it has been shown that tumor location within the biliary tree has no impact on survival, provided that complete resection is achieved. Nonetheless, it is more likely that distal bile duct cancer will be resected with curative intent, which explains the relatively more favorable prognosis of distal tumors.

A number of conditions are associated with an increased incidence of cholangiocarcinomas, including PSC, choledochal cysts or Caroli's disease, and pyogenic cholangiohepatitis and other hepatic infections. In addition, environmental agents may influence the incidence of cholangiocarcinomas.

**Primary Sclerosing Cholangitis**

In Western nations, the disease most often associated with development of cholangiocarcinoma is primary sclerosing cholangitis (PSC). This is an autoimmune disease characterized by inflammation of the periductal tissues and, at advanced stages, is characterized by multifocal strictures of the intrahepatic and extrahepatic bile ducts. The majority (70% to 80%) of patients with PSC also have associated inflammatory bowel disease in the form of ulcerative colitis. In a longitudinal study of patients with PSC, 8% of patients developed clinically apparent cholangiocarcinoma over a 5-year period. This explains the high incidence (30% to 40%) of occult cholangiocarcinoma found in autopsy or explant specimens from patients with PSC.

Cholangiocarcinomas presenting in patients with PSC are often multifocal and not amenable to treatment by partial hepatectomy. Liver transplantation is often the only treatment possible for these patients, not only because of multifocal cancer but also because of the baseline hepatic insufficiency from the underlying inflammatory disease.

**Choledochal Cysts or Caroli’s Disease**

The increased risk of cholangiocarcinoma in patients with congenital cystic disease of the biliary tree is well recognized. The reason for the malignant transformation is thought to be related to chronic inflammation and bacterial contamination within the cystic areas. Early excision of the choledochal cyst significantly reduces the risk of cancer. Fifteen to twenty percent of adult patients with unexcised choledochal cysts or cysts previously treated with bypass will be found to have a cholangiocarcinoma.

**Pyogenic Cholangiohepatitis and Other Hepatic Infections**

In the Orient, chronic infections of the liver can predispose to development of cholangiocarcinoma. Pyogenic cholangiohepatitis or Oriental cholangiohepatitis results from chronic portal bacteremia and portal phlebitis, which gives rise to intrahepatic pigment stone formation. This hepatolithiasis leads to recurrent episodes of cholangitis and stricture formation. Those patients who do not succumb to sepsis will have approximately a 10% chance of developing cholangiocarcinoma. In Southeast Asia, biliary parasites (Clonorchis sinensis, Opisthorchis viverrini) are also associated with an increased risk of cholangiocarcinoma. In areas where these parasites are endemic, the incidence of cholangiocarcinoma is as high as 87 per 100,000.

**Influence of Environmental Agents**

Several radionuclides and chemical carcinogens, including thorium, radon, nitrosamines, dioxin, and asbestos, have also been implicated in the development of cholangiocarcinomas.

**PATHOLOGY AND CLASSIFICATION**

Cholangiocarcinoma can arise anywhere within the biliary tree. Approximately 10% of cholangiocarcinoma cases arise within the intrahepatic bile ducts. These usually present as hepatic masses that are thought at first to be HCCs or metastatic tumor of unknown origin. The intrahepatic variety is more common and can occur along the entire length of the bile duct from the confluence of the hepatic ducts to the ampulla. Some have classified these extrahepatic tumors into proximal ( hilar), middle, and distal bile duct tumors. Those tumors distal to the cystic duct usually require pancreatotomy for treatment. Fewer than 10% of patients will present with multifocal or diffuse involvement of the biliary tree.

Cholangiocarcinomas are characterized by early invasion of adjacent organs. Nodal metastases are also common and occur in up to one-third of cases. In
Cholangiocarcinomas can be separated into three distinct macroscopic subtypes: sclerosing, nodular, and papillary. Most are sclerosing tumors, which are very firm and are seen as annular thickening of the bile duct, often with diffuse infiltration and fibrosis of the periductal tissues. Nodular tumors are firm tumors that project into the lumen of the duct. Frequently, features of both sclerosing and nodular tumors are found, and the tumor is described as nodular-sclerosing. Papillary tumors are soft and friable and often demonstrate little transmural invasion. These tumors have a more favorable prognosis than do the others, and are more common in the distal bile duct, and account for approximately 10% of all cholangiocarcinomas.

The overwhelming majority (>90%) of cholangiocarcinomas are adenocarcinomas, often well differentiated and mucin-producing. Rarely, malignant obstruction of the bile duct may be due to other cell types, such as carcinoid tumors, arising primarily in the biliary tree or to tumors metastatic to the biliary tree.

**DISTAL BILE DUCT CANCERS**

Distal bile duct cancers are rare cancers that usually are reported as part of a series of periampullary tumors or as a series describing all bile duct cancers. Distal bile duct tumors represent approximately 20% to 30% of all cholangiocarcinomas or 5% to 10% of all periampullary tumors. Approximately 2000 new cases of distal bile duct cancer are diagnosed in the United States each year. They are almost always adenocarcinomas. The papillary variety is also more common in this location than in other parts of the bile duct.

**Clinical Presentation and Diagnosis**

On the practical level, patients with distal bile duct cancers usually present with jaundice and a mass at the head of the pancreas. Except in the case of the papillary variety of this cancer, patients are brought to the operating room with the diagnosis of periampullary cancer, and it is in the final pathologic analysis that the anatomic site of origin of the tumor becomes clear. The importance of distinguishing distal bile duct cancer from the other periampullary tumors is in the prognostic implications, as distal bile duct cancer has a much more favorable outcome than does the more common adenocarcinoma of the pancreas.

Jaundice is the presenting symptom in up to 90% of patients with distal bile duct cancer. Abdominal pain, weight loss, fever, or pruritus are also common symptoms, though these occur in one-third of cases or fewer. If the patient reports that the jaundice is intermittent, a papillary bile duct cancer should be suspected. Most often, however, the symptoms and signs will be indistinguishable from adenocarcinoma of the pancreatic head or other periampullary malignancies.

US will demonstrate a dilated extrahepatic and intrahepatic biliary tree. Cross-sectional imaging by CT scanning will usually then demonstrate a mass in the region of the head of the pancreas. Endoscopic retrograde cholangiopancreatography (ERCP) may be diagnostic if it demonstrates an obstruction in the bile duct that does not involve the pancreatic duct. Most often, however, ERCP will demonstrate distal biliary obstruction without diagnostic information on the cell origin of the malignancy. In fact, we tend not to perform ERCP if the patient is a surgical candidate, preferring to operate on the patient without direct biliary manipulation, as this decreases the risk of biliary sepsis.

If surgical resection is planned, a preoperative tissue diagnosis of cancer is not necessary and often is not possible. Endoscopic brush biopsy has a low sensitivity, making a negative result virtually useless. Performing a percutaneous needle biopsy is difficult because of the small size of these tumors. Therefore, preoperative diagnosis is usually based on clinical impression. In patients with a stricture of the distal bile duct and a clinical presentation consistent with cholangiocarcinoma, cross-sectional imaging studies are scrutinized for signs of unresectable cancer. In this regard, a contrast-enhanced helical CT scan with overlapping 5-mm sections through the area of the pancreas is the most useful. This test allows for evaluation for vascular involvement or metastatic disease. Magnetic resonance cholangiopancreatography (MRCP) may also be used for evaluation of these periampullary tumors.

If the tumor is judged unresectable by radiologic criteria, it is usually of sufficient size for diagnosis by percutaneous needle biopsy. Biliary obstruction then can also be treated by endoscopic stenting or, if necessary, through percutaneous transhepatic stenting to avoid surgery.

**Treatment Options**

Complete resection is the only effective and potentially curative therapy for cancers of the lower bile duct. In comparison to pancreatic cancer, distal bile duct cancer is more often amenable to resection and patients less often have microscopic disease at the resection margin and less frequently demonstrate spread of tumor to adjacent lymph nodes. Completeness of resection, presence of lymphatic metastases and tumor differentiation are the prognostic factors that most strongly influence long-term outcome. In a series of 200 patients with distal bile duct cancer, 76% had lymph node metastases, and 38% had poorly differentiated tumors.

The results of resection for distal bile duct cancer as compared to the other periampullary tumors are demonstrated in Figure 33.5-4. The results are similar to those for duodenal cancer, more favorable than those for adenocarcinoma of the pancreas, and less favorable than those for neuroendocrine or ampullary tumors. Five-year survival rates of up to 40% have been reported after complete resection. It has long been assumed that survival after resection of distal bile duct tumors is more favorable than after resection of hilar cholangiocarcinomas, but this commonly held belief has been refuted by data. Though it is true that resectability rates are higher for distal bile duct cancers and the likelihood of achieving a negative margin during resection is greater, the survival rates of the various bile duct tumors, if adjusted for stage and completeness of resection, appear to be comparable.

**FIGURE 33.5-4.** Survival for patients with various peripancreatic tumors.
TABLE 33.5-12. Survival after Resection of Distal Cholangiocarcinoma

Because of the rarity of distal cholangiocarcinoma, no prospective data are available to guide the use of adjuvant therapy after resection. 335 We tend not to use adjuvant therapy if resection margins are clear of tumor, though many other practitioners use regimens of chemoradiation originally developed for adenocarcinoma of the pancreas.

In patients with nonresectable cancers, palliation for biliary obstruction can be achieved with a surgical bypass or biliary endoprostheses. Endoprosthesis for distal biliary obstruction are usually placed endoscopically and provide more durable palliation than does an endoprosthesis placed for hilar obstruction. 337 Surgical bypasses also provide excellent relief of jaundice and can be achieved with an acceptably low morbidity and mortality. In our practice, patients found to have unresectable disease at laparotomy are subjected to surgical bypasses, as they will already have incurred the risk of anesthesia and laparotomy. Furthermore, patients expected to survive longer than 6 months are also considered for surgical bypass. 338 All other patients are treated with biliary endoprostheses.

Chemotherapy or radiotherapy or both have offered generally poor results as palliative treatment for unresectable cases. Survival beyond 1 year is uncommon in patients subjected to palliative therapies. 339,340,341,342

PROXIMAL OR HILAR CHOLANGIOCARCINOMA

Proximal or hilar cholangiocarcinomas were first described by Altemeier 343 in 1957 and subsequently by Klatskin 344 in 1965. Of the hepatobiliary tumors, these cholangiocarcinomas represent the greatest diagnostic and therapeutic challenge because of the vast number of vital structures that can be involved by even a small hilar cholangiocarcinoma. Proximal or hilar cholangiocarcinomas require the most extensive of liver resections and vascular reconstruction for extirpation.

Clinical Presentation and Diagnosis

CLINICAL FINDINGS. Most patients with cholangiocarcinomas come to medical attention because of jaundice or abnormal liver function tests. Other associated symptoms are non-specific. Abdominal pain or discomfort, anorexia, weight loss, and pruritus are the most common symptoms but are seen in only approximately one-third of patients. Fever usually is seen only after biliary manipulation. 337,345-347,348 In some patients, pruritus precedes jaundice by some weeks, and this symptom should prompt an evaluation, especially if associated with abnormal liver function tests. Intermittent jaundice may be seen with papillary tumors and is usually due to intermittent detachment of pieces of friable tumors from the right or left hepatic duct that pass into and occlude the common hepatic duct. The serum bilirubin level is usually greater than 10 mg/dL and averages 18 mg/dL, whereas bilirubin levels of 2 to 4 mg/dL are the norm in patients with obstruction from choledocholithiasis. 335 Malignancy should be strongly suspected in patients with deep, painless jaundice who present with no fever or other signs of infection.

On physical examination, jaundice is usually obvious. Patients with proximal biliary obstruction is usually associated with a decompensated and nonpalpable gallbladder. Thus, a palpable gallbladder would suggest a more distal obstruction or gallbladder cancer. Signs of portal hypertension are rare but would be an ominous indication of advanced vascular involvement or the alternative diagnosis of cirrhosis and HCC.

Medical history and family history should be scrutinized for conditions such as PSC or Oriental cholangiohepatitis that may predispose to cholangiocarcinoma. Many tumors express carcinoembryonic antigen (CEA) and the carbohydrate antigen CA 19-9. The diagnostic value of these serum markers is, however, debated. 335 It has been suggested that CEA levels in hepatic bile may help to distinguish between benign and malignant strictures in patients with premalignant conditions. 338 Diagnosis of cholangiocarcinoma is usually made radiologically.

RADIOGRAPHIC EVALUATION. Radiologic imaging is central to the diagnosis and treatment planning for patients with cholangiocarcinomas. The importance of imaging studies results from the difficulties in obtaining a positive tissue diagnosis by biopsy, particularly when the tumors are small and in the potentially curable stages. Relying on the results of percutaneous needle biopsy or biliary brush cytology is dangerous, as the results of these tests are often misleading and one may miss the opportunity to resect an early cancer. 349,350 Therefore, the preoperative and, often, operative diagnoses are based mainly on the history and radiologic appearance of the tumors.

The differential diagnosis must include gallbladder carcinoma, Mirizzi syndrome, idiopathic benign focal stenosis (malignant masquerade), or sclerosing cholangitis. Unless there is a large intraluminal mass in the gallbladder, distinguishing gallbladder carcinoma from hilar cholangiocarcinoma can be difficult. Mirizzi syndrome is caused by a large gallstone impacted in the neck of the gallbladder, resulting in biliary obstruction from periductal inflammation. 351,352,353 Benign focal strictures (malignant masquerade) can also occur at the hepatic duct confluence but are uncommon. 338,354,355 Beyond diagnosis, the radiologic evaluation is aimed at determining resectability, as surgical resection is the most effective and only potentially curative therapy. Imaging may locate occult distant metastases and thereby spare patients from nontherapeutic surgery. In defining the degree of invasion of adjacent organs and vascular anatomy, imaging is also essential for planning the surgical procedure and directing major vascular reconstructions when necessary.

Most patients will present to the surgeon having already been subjected to a sonogram and CT. US is usually the first investigation performed because it is noninvasive, readily available, and provides important diagnostic information regarding the jaundiced patient. Generally, intrahepatic biliary dilatation will be seen without evidence of extrahepatic bile duct abnormality and without evidence of stones. In experienced hands, the tumor will often be clearly defined by US, as will information important for planning of surgery such as delineation of the biliary extent of disease, vascular involvement, presence of lymph node metastases in the porta hepatis, and presence of noncontiguous liver metastases. US not only may demonstrate the level of biliary ductal obstruction but can also provide information regarding tumor extension within the bile duct and in the periductal tissues. 356,357 in centers specializing in treatment of cholangiocarcinomas, a good Doppler US may indeed provide diagnostic information equivalent to that provided by a combination of angiography and CT and is highly accurate in predicting resectability. 357,360 However, US is more operator-dependent than is most cross-sectional imaging. Therefore, in most circumstances, other cross-sectional imaging is necessary.

Most patients will present to a tertiary care center having already been imaged by CT. CT remains an important study for evaluating patients and is less dependent than US on the skills of the operator. Important information regarding level of biliary obstruction, vascular involvement, and presence of nodal or noncontiguous metastases can be assessed. One of the most important findings to be gleaned from a CT scan, however, is the presence of hepatic lobar atrophy, which is usually indicative of portal venous occlusion. 358

In years past, most patients also were subjected to direct angiography and cholangiography. Angiography allows for determination of arterial or portal venous vascular encasement. Cholangiography demonstrates the location of the tumor and the biliary extent of disease. Recently, however, MRCP has emerged as a noninvasive substitute for direct cholangiography. 361,362,363 MRCP not only may identify the tumor and the level of biliary obstruction but also may reveal obstructed and isolated ducts not appreciated at endoscopic or percutaneous study. Magnetic resonance angiography (MRA) or CT angiography has become a substitute for direct angiography. Today, the need to perform invasive tests is moot. When direct cholangiography is needed, percutaneous transhepatic cholangiography (PTC) is preferred over ERCP because it is more likely to provide the details of the intrahepatic biliary tree necessary for surgical planning.

For patients presenting with proximal cholangiocarcinomas, a Doppler US, helical CT, and chest radiograph may suffice as preoperative radiologic evaluation. In patients in whom further delineation of biliary or vascular involvement may be necessary, MRCP and MRA are the next tests of choice. This noninvasive approach prevents biliary instrumentation and bacteriuria and the associated increased perioperative morbidity. 364,365 When necessary, direct cholangiography or angiography is used.

Staging

The most commonly used staging systems are the modified Bismuth-Corlette and the American Joint Committee on Cancer (AJCC) TNM (tumor, node, metastasis) staging system. The former classifies patients based on the extent of biliary duct involvement by tumor, 338 whereas the latter is based largely on pathologic criteria
The only curative option is complete surgical excision of the cholangiocarcinoma. Until the last decade, such surgical resections were rarely accomplished, because complete excision usually requires a major liver resection, biliary resection and reconstruction and, often, a major vascular resection and reconstruction. As advances in diagnostic imaging have been made, earlier detection of cholangiocarcinoma and improved operative planning are possible. As surgical techniques have evolved to make major hepatectomies routine, increasing numbers of resections have been accomplished. The results generated over the last decades has firmly established resection as safe and effective treatment and have helped to define patient selection and operative conduct.

**RESECTION.** It has become clear over the last three decades that curative treatment of tumors involving the upper third of the bile duct very much depends on aggressive surgical excision. Until as recently as one decade ago, surgical treatment of hilar cholangiocarcinomas was associated with a mortality as high as 30%. Before the 1990s, most surgical series were small, operative mortalities were high, and only a handful of 5-year survivors were reported. That this entire disease was regarded with pessimism was understandable. It is not surprising, therefore, that until recently, the surgical therapy for proximal biliary malignancies consisted mainly of biliary-enteric bypass as palliation for jaundice and cholangitis. Results reported over the last decade, however, have indicated a major improvement in safety of these operations such that resections of hilar tumors can be accomplished (even when liver atrophy, that may be more applicable than the other systems, given modern surgical therapies) In the era of effective surgical therapy for cholangiocarcinomas, this staging system is a better predictor of resectability and outcome than is the AJCC classification.

The goals of surgical management for cholangiocarcinomas are eradication of tumor and establishment of adequate biliary drainage. For tumors of the hepatic ducts and the biliary confluence, symptoms often appear late in the course of disease when the lesion has already involved adjacent structures, including the portal vein or adjacent hepatic parenchyma. Complete resection, therefore, usually requires not only biliary resection but also major liver resection and, often, major vascular and biliary reconstruction.

Discussion of the fine details of resections for hilar cholangiocarcinomas is beyond the scope of this chapter. The reader is referred to standard texts of surgical techniques for detailed technical discussions.

Laparoscopic evaluation should be considered before a formal laparotomy is performed. Metastatic disease is common in patients with hilar cholangiocarcinoma. One-half or more of the patients will have metastatic disease found at surgery. Recent studies suggest that staging laparoscopy combined with laparoscopic US may be useful in hepatobiliary malignancies to find such metastatic disease and thereby prevent unnecessary laparotomies.

We recently proposed a staging system, using preoperative imaging and taking into account the extent of biliary ductal involvement, vascular involvement, and lobar atrophy, that may be more applicable than the other systems, given modern surgical therapies. In the era of effective surgical therapy for cholangiocarcinomas, this staging system is a better predictor of resectability and outcome than is the AJCC classification.

**TABLE 33.5-13.** American Joint Committee on Cancer TNM Staging System for Proximal (Hilar) Cholangiocarcinoma and Cancer of the Extrahepatic Bile Ducts

**TABLE 33.5-14.** Proposed Staging System for Proximal (Hilar) Cholangiocarcinoma in the Era of Effective Surgical Therapy

**Treatment with Curative Intent**

**TABLE 33.5-15.** Results of Resection for Proximal (Hilar) Cholangiocarcinoma after 1990
The factors most influential in predicting recurrence are a margin-positive resection, node-positive tumor, and vascular involvement by tumor. Of these, the only factor over which the surgeon can routinely have influence is the surgical margin. There is now substantial evidence that partial hepatectomy is usually required to achieve a surgical margin clear of tumor. Bile duct excision and partial hepatectomy, often with en bloc caudate lobectomy, are frequently necessary to achieve negative margins. Indeed, several recent studies show a parallel between the number of patients undergoing partial hepatectomy and the number of patients with negative margins (Fig. 33.5-6A). Furthermore, there is a direct correlation between negative margins and long-term survival (see Fig. 33.5-6B). Clearance of tumor is essential for potential cure.

In the era when surgeons were unwilling to perform major liver resections to clear tumor, only the smallest of hilar cholangiocarcinomas could be resected. Given that extensive liver resections are now routine at many major centers, extensive unilobar disease is commonly resected with curative intent. In a recent study, of the 30 patients subjected to resections of cholangiocarcinoma, including 25 (83%) with negative histologic margins, 15 patients had tumor involvement of secondary biliary radicals, 11 had unilobar lobar liver atrophy, and 8 had encasement or occlusion of a major portal vein branch. In the past, these findings would have been considered technically inoperable.

The entire extrathepatic bile duct should be removed, as this assists in resection of the lymphatic tissues in the porta hepatis. Lymphatic metastases are common, and a complete portal lymphadenectomy is essential. Biliary continuity is then reestablished using a jejunal reconstruction. Portal vein invasion by tumor does not rule out resection, long-term survival, or potential cure, provided that the portal vein involvement is unilobar and on the side of the dominant biliary involvement. Bilateral portal venous involvement or unilobar invasion contralateral to extensive biliary invasion usually denotes unresectable disease and, consequently, poor prognosis.

Recent results of resection have shown great improvement over previous results. Median survival is longer than 24 months. Five-year survival is accomplished in nearly 30% of patients (see Table 33.5-15). Such long-term survival can be achieved with an acceptable operative mortality. For those surviving the operative procedure, surgical resection provides not only improved survival but also improved quality of survival.

ADJUVANT THERAPY. To date, no chemotherapy regimen has consistently shown activity in cholangiocarcinoma. Although chemotherapy based on 5-FU often is offered to patients with nonresectable disease, the likelihood of response is less than 10% (see later in Chemotherapy and Immunotherapy). There is certainly no proven role for adjuvant chemotherapy in the treatment of cholangiocarcinoma.

In two separate reports from Johns Hopkins, no benefit of adjuvant external-beam and intraluminal radiotherapy was demonstrated. In contrast, Kamada et al. suggested that radiation may improve survival in patients with histologically positive hepatic duct margins. Additionally, in a small series of patients (five with hilar cholangiocarcinoma) from Louisville, resectability was reportedly greater in patients given neoadjuvant radiotherapy prior to exploration. In a series of 23 patients with cholangiocarcinoma, Ureño et al. used a chemotherapy regimen for adjuvant therapy, consisting of postoperative irradiation, 5-FU, leucovorin, and IFN. The 5-year survival was 53%. These results certainly encourage further study of radiotherapy with or without chemosensitization in the adjuvant treatment of
cholangiocarcinoma. Given the small size of the studies and lack of randomized trials, the utility of radiotherapy, and particularly ILB, is far from proven. In our practice, adjuvant therapy is generally used only if there is a positive margin or in the setting of metastases to lymph nodes. Other patients are not offered adjuvant therapy.

LIVER TRANSPLANTATION. Orthotopic liver transplantation has been attempted for unresectable hilar tumors. Klempauer et al. reported 4 long-term survivors of 32 patients submitted to transplantation for hilar cholangiocarcinoma. Comparable results were reported by Iwatsuki et al. These results do not justify the use of precious organs when many patients with benign disease are dying awaiting liver transplantation. Therefore, most centers do not currently perform liver transplantation for cholangiocarcinoma.

Palliative Treatments

Patients with hilar cholangiocarcinoma most often die from liver failure due to tumor progression or from sepsis due to biliary infection. If resection is not feasible, then palliative treatment must be directed first and foremost at preventing or relieving biliary infection. Secondarily, palliative antitumor treatments such as radiotherapy or chemotherapy should be considered, though neither of these modalities has been clearly proven to prolong survival significantly.

BILIARY DRAINAGE. The important concept in the prevention of biliary sepsis is the understanding that jaundice alone is not necessarily an indication for biliary decompression. Unlike biliary obstruction in the lower bile duct, where a single stent usually effectively relieves the biliary obstruction, biliary obstruction near the hilus is much more difficult to relieve. Even with a small tumor, a single stent likely will drain only one-half of the liver. When the tumors are large and involve second- or third-order bile ducts, many stents may be required to provide effective biliary decompression; it is also possible that effective biliary decompression cannot be achieved in such cases. Biliary manipulation of any kind may therefore introduce bacteria into the biliary tree and cause sepsis that may not subsequently be fixable.

Good indication for biliary drainage must exist before attempts are made. Our current indications for biliary decompression in inoperable patients are intractable pruritus, cholangitis, the need for access for intraarterial radiotherapy, or the need for drainage for administration of chemotherapeutic agents. When none of these indications exists, the patient is probably better served by avoiding biliary manipulation. Supportive care alone is probably the best approach, particularly for elderly patients with significant comorbid conditions.

Unfortunately, most patients present to a tertiary care center already having undergone manipulation of the biliary tree. Most of these patients, therefore, have bacteriuria and, possibly, overt sepsis, and drainage of the biliary tree is an essential part of the therapy to prevent immediate life-threatening complications.

Biliary drainage can be accomplished nonsurgically or surgically. Nonsurgical drainage is preferred if the patient has significant comorbid conditions or if the tumor as evaluated by preoperative imaging is clearly not resectable for cure. Though biliary decompression can theoretically be accomplished either by percutaneous transhepatic puncture or by endoscopic stent placement, hilar tumors are notoriously difficult to traverse with the endoscopic technique. Moreover, the failure rate and incidence of subsequent cholangitis are high. Thus, most patients with unresectable hilar tumors are not candidates for endoscopic biliary drainage. Percutaneous transhepatic biliary drainage and subsequent placement of a self-expandable metallic endoprosthesis (Wallstent, Boston Scientific, Boston, MA) is the palliative procedure of choice for these patients. However, as mentioned, satisfactory results are more difficult to achieve in patients with hilar tumors than in those with distal biliary obstruction.

Frequently, hilar tumors isolate the liver into multiple obstructed biliary units, and two or more stents must be placed for adequate drainage. Portal venous involvement and consequent hepatic lobar atrophy may also complicate drainage procedures, as drainage through an atrophic lobe usually does not relieve jaundice. Furthermore, a stent placed for a hilar obstruction is associated with a substantially higher rate of occlusion than that placed in the distal duct. Therefore, most patients will require multiple manipulations of their stents placed for hilar obstruction. These difficulties also explain the high periprocedural mortality in this patient population: 14% at 30 days.

Biliary enteric bypass is a surgical alternative to percutaneous placement of an endobiliary prosthesis. Certainly, patients whose tumors are found to be unresectable at operation should be considered for such bypasses, because they will have already incurred the morbidity of laparotomy. Patients with small, unresectable, but well-localized disease are particularly good candidates for biliary enteric bypass, as this allows access to the biliary tree for ILB. Typically, segment III bypass is used. Relief of jaundice will be achieved if at least one-third of the functioning hepatic parenchyma is adequately drained. Additional percutaneous stenting to reestablish biliary continuity of the two sides of the liver is required if the bypass is to an atrophic or small lobe or if infection has occurred in the contralateral lobe of liver. In our recent report of 55 consecutive bypasses in patients with malignant hilar obstruction, segment III bypass yielded a 1-year bypass patency of 80%, and there were no perioperative deaths.

CHEMOTHERAPY AND IMMUNOTHERAPY. Many different chemotherapeutic regimens have been investigated in small uncontrolled studies, with generally poor results (Table 33.5-17). A study by the European Organization for Research and Treatment of Cancer studying mitomycin C on patients with gallbladder and biliary carcinomas showed a response rate of 10% (3 of 30). The group also compared oral 5-FU to 5-FU with either streptozotocin or MeCCNU in patients with gallbladder or biliary duct cancer and demonstrated a similarly low response rate of 9%, with no differences in the types of drugs used. Some of the newer drugs have also not demonstrated significant efficacy as single-agent therapy. Paclitaxel demonstrated no activity in 15 patients with biliary carcinoma, and a phase II study of docetaxel likewise demonstrated no activity.

TABLE 33.5-17. Results of Chemotherapy for Biliary Tract Tumors (Cholangiocarcinomas or Gallbladder Cancers)

<table>
<thead>
<tr>
<th>Chemotherapy Regimen</th>
<th>Number of Patients</th>
<th>Response Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-FU</td>
<td>30</td>
<td>10%</td>
</tr>
<tr>
<td>5-FU and IFN</td>
<td>20</td>
<td>9%</td>
</tr>
<tr>
<td>5-FU and cisplatin</td>
<td>15</td>
<td>33%</td>
</tr>
<tr>
<td>5-FU and doxorubicin</td>
<td>10</td>
<td>31%</td>
</tr>
</tbody>
</table>

Combinations of various chemotherapeutic agents have been tested, with mixed and conflicting results. Patt et al. used 5-FU and IFN as combined therapy for patients with cholangiocarcinoma. Of 32 patients, 11 (34%) had a partial response, with a median time to disease progression of 9.5 months and a median survival of 12 months. However, another phase II study analyzing the effect of 5-FU combined with IFN-α2a and paclitaxel failed to show any benefit. In one study combining 5-FU, mitomycin, and doxorubicin, 31% of patients responded, whereas in another trial, there were no responses among 18 patients. The combination of 5-FU, cisplatin, and epirubicin produced a 33% response rate in 15 patients with biliary tract carcinoma in an Italian study, and 5-FU, leucovorin, and carboplatin produced a 21% response rate among 14 patients. Rougier et al. using continuous-infusion 5-FU and cisplatin, produced a 33% response rate in 18 patients. Gemcitabine and 5-FU plus gemcitabine have also been tested and, in one study involving 14 patients, 42% responded. At present, either 5-FU and cisplatin or 5-FU and gemcitabine must be considered the regimens of greatest promise in the palliative treatment of unresectable cholangiocarcinoma. We tend to use the latter combination because of its lower toxicity as compared to the former.

The blood supply to the biliary tree is derived primarily from the hepatic artery. Therefore, attempts have been directed at delivering chemotherapeutic treatment via hepatic arterial infusion to patients with cholangiocarcinoma. In one study of 11 patients (4 with cholangiocarcinomas and 7 with gallbladder cancers), hepatic infusion of 5-FU and mitomycin produced 7 responses but a median duration of response of only 3 months and a median survival of 12.5 months. Reed et al. reported seven significant regressions in nine patients with biliary carcinoma treated with intraarterial FUDR. This approach is far from proven and, at present, operative intervention to implant an arterial infusion pump for delivery of regional chemotherapy should be performed only in the investigational setting.
Tamoxifen is a potential MDR-reversing agent and has been shown to inhibit human cholangiocarcinoma cell lines.420 No clinical data exist, however, to indicate whether this may be a reasonable therapeutic modality for patients with unresectable cholangiocarcinomas.

**PALLiative RADIOTHERAPy.** External-beam irradiation with or without IBL has also been used for palliation of patients with unresectable perihilar bile duct cancer. External-beam irradiation is usually delivered to a dose of 5000 to 6000 cGy. IBL most often uses an isodose volume of 2000 cGy delivered percutaneously. Several authors have demonstrated the feasibility of radiotherapy in small, nonrandomized trials.293-341,401,402,403,404 However, to date, no study has clearly demonstrated efficacy for this modality. In a group of 12 patients treated with a combination of endoluminal and external-beam radiotherapy, the median survival was 15 months. Though episodes of cholangitis and intermittent jaundice were relatively common, the incidence of serious complications was low, and there were no treatment-related deaths. Cameron et al.343 reported improved survival in irradiated patients as compared to a group of patients who were operated on but not irradiated; however, the median survival in both groups was less than 1 year. Others have reported no benefit of radiotherapy in this setting and question its routine use, given the increased incidence of complications and the greater time spent in hospital.425 Certainly, radiotherapy has not been shown to produce improved survival as compared with biliary decompression in randomized, controlled trials. Though anecdotal reports of long-term survivors after external-beam radiotherapy show that some individuals may benefit from such treatment, such potential benefit must be weighed against the possible complications, such as duodenal or bile duct stenosis and duodenitis.

Evidence in the literature supports using fluoropyrimidines as radiosensitizers, and chemoradiotherapy is used as standard therapy for a number of other tumor types. For bile duct cancers in particular, however, evidence supporting the use of chemoradiotherapy is sparse. In a study conducted by the Eastern Cooperative Oncology Group, 16 patients with pancreatic carcinoma and 9 with bile duct cancers were treated with a combination of FU (2000 mg/m²) and concurrent radiotherapy (59.4 Gy). The entire group had a median survival time of 11.9 months. Unfortunately, 15 of the 25 patients had clinical or radiographic evidence of progression of disease at the site of the primary tumor, which was in the radiotherapy port. Moreover, median survival for the patients with locally advanced, unresectable disease that was treated with radiotherapy with or without systemic chemotherapy tends to be less than 1 year.401,402,403,404 Our current practice is to use combined intestinal irradiation and external-beam irradiation in patients with very limited, locally unresectable disease, when there are no indications of distant spread. Multicenter, randomized trials are in order for this subpopulation. Radiotherapy is clearly inappropriate in patients with widespread disease.

**PERIPHERAL CHOLANGIOCARCINOMA**

Peri- or intrahepatic cholangiocarcinoma is another rare disease, accounting for 1000 to 2000 cases per year in the United States.416 Clinical presentation is similar to that for HCC, with the most common symptoms being right upper quadrant pain, epigastric pain, and weight loss.417 Jaundice occurs in only 24% of patients with hilar cholangiocarcinoma as compared with 71% of patients with hilar or Klatskin tumors.418 Because the tumor is usually asymptomatic in its early stages, most patients have advanced disease at presentation. On cross-sectional imaging by CT or MRI, the peripheral cholangiocarcinoma usually is confused with HCC or metastatic tumor from an unknown primary source. Unlike HCC, AFP levels will be normal. A search for alternative primary cancers that may have produced a liver metastases will not be fruitful. A solitary lesion not associated with the gallbladder in a patient with no cirrhosis and no other primary cancer and with a normal serum AFP should raise suspicion of a peripheral cholangiocarcinoma. However, intrahepatic metastases and tumor growth along the biliary tract frequently occur. When multiple tumors are found, it is even more difficult to distinguish these tumors from metastatic disease originating from a distant site.

Lymph node involvement is more common with peripheral cholangiocarcinoma than with hilar bile duct tumors. In a series of 65 peripheral and 27 hilar cholangiocarcinomas, Nakajima et al.426 found lymph node involvement in 86% of peripheral tumors as compared with 33% of hilar tumors. Intrahepatic and systemic metastases were found in 68% and 71%, respectively. The TNM staging of intrahepatic or peripheral cholangiocarcinoma is the same as that for HCC.

Conventional surgical resection, when possible, is the treatment of choice. In a series of 42 patients with peripheral cholangiocarcinoma, Altaye et al.425 reported that survival was indistinguishable from that of 70 patients with hilar cholangiocarcinomas. The median survival was 12 months, and no patient survived more than 42 months. Others have reported more favorable results. Chen et al.427,428 reported on 20 patients with peripheral cholangiocarcinoma undergoing surgery over a 10-year period who had a median survival of 21 months. Four patients lived more than 3 years, and one patient was alive 5 years after resection. Our own report of 32 cases of resected peripheral cholangiocarcinoma, median survival was 59 months, with an actuarial 5-year survival of 42%. Vascular invasion and intrahepatic satellite lesions were predictors of worse survival (P < .05).429

The few data available concerning results of liver transplantation for this disease have not been encouraging. Penn430 reported a 17% actuarial 5-year survival rate for 109 intrahepatic and extrahepatic cholangiocarcinoma patients who received liver transplants at various centers throughout the world. In this series also, there was no significant difference between the recurrence rates of hilar and peripheral tumors.

Data for chemotherapy or radiotherapy in treating this disease is even more sketchy. Stillwagon et al.431 reported a 5% complete response and 46% partial response for the treatment of peripheral cholangiocarcinoma with a regimen of initial whole liver irradiation to 2100 cGy in seven fractions and doxorubicin, cisplatin, and 131I anti-CEA antibody.432 Although the median survival was 14 months from diagnosis and 10 months from treatment, no patient survived more than 2 years from the start of therapy.

**TUMORS OF THE GALLBLADDER**

Alfred Blalock recommended in 1924 that “...in malignancy of the gallbladder when a diagnosis can be made without exploration, no operation should be performed, inasmuch as it only shortens the patient’s life.”433 This nihilistic view of gallbladder cancer is understandable because this rapidly growing tumor has a propensity for early dissemination by direct invasion of liver, by lymphatic spread, by hematogenous spread, and by production of peritoneal “drop” metastases. In addition, because of the proximity of the liver and major vasculature, extensive hepatic resections often are required to eradicate local disease. Until recently, therefore, most cases in which patients were cured of gallbladder cancer occurred “accidentally” when early-stage disease was completely excised by simple cholecystectomy for suspected stone disease. With improving safety of liver resections and biliary reconstructions, major resections are increasingly performed for gallbladder cancer and have demonstrated a curative potential even for advanced disease. Given that gallbladder cancer treated by any method other than complete excision is associated with a median survival of less than 6 months, surgery, when possible, is standard treatment.  

**EPIDEMIOLoGy AND ETIOLOGY**

Gallbladder cancer is a relatively rare disease in the United States, with an incidence of approximately 1.2 cases per 100,000 population per year.424 Even though this would make gallbladder cancer the most common biliary tract malignancy in this country and the fifth most common gastrointestinal malignancy, only 2000 to 3000 cases occur in the United States annually. Certain geographic regions and racial or ethnic groups demonstrate a much higher incidence, which can be 25 times higher than the national figure.427 The highest incidences are reported in Chileans, northeastern Europeans, Israelis, American Indians, and Americans of Mexican origin. In fact, gallbladder cancer is the main cause of death from cancer among women in Chile.428 Within the United States and the United Kingdom, urban areas show higher incidences than rural regions.425,426 This cancer affects women two to six times more often than it does men.431 The incidence steadily increases with age, reaching its maximum in the seventh decade of life.428

The epidemiology of gallbladder cancer is similar to the epidemiology of gallbladder stones.432 Though there is still no general agreement as to whether this represents cause and effect or common risk factors, Seventy-five to ninety-eight percent of all patients with carcinoma of the gallbladder have cholelithiasis.431 Gallbladder cancer is usually associated with cholesterol-type gallstones. Other risk factors include the presence of an anomalous pancreaticobiliary duct junction,425 chronic typhoid infection,425 and inflammatory bowel disease.425 Calcification of the gallbladder (porcelain gallbladder), signifying long-standing inflammation, is associated with gallbladder cancer in 10% to 25% of cases.428 These conditions suggest that chronic inflammation may play an important role in the development of gallbladder cancer. Though reports of families clusters of gallbladder cancer exist in the literature,433 congenital predisposition is not believed to play a major role in the development of this cancer.

Exposure to a number of chemicals has been suggested to play a role in carcinogenesis in the gallbladder, including methyldopa,434 oral contraceptives,435 isoniazid,435 and chloroform used in the rubber industry.436 None of these associations have been definitively proven, however. It may be that chronic inflammatory acts as a promoter for some other carcinogenic exposure. This is suggested by the studies of Kowalewski and Todd,437 in which carcinoma of the gallbladder was induced in 68% of hamsters in whom cholesterol pellets were inserted into the gallbladder and the carcinogen dimethyltritosamine was administered, as compared to only 6%
PATHOLOGIC FEATURES

In general, gallbladder cancers can be categorized by growth pattern into infiltrative, nodular, papillary, or combined forms. Most common are the infiltrative and combined nodular-infiltrative forms. The infiltrative tumors cause thickening and induration of the gallbladder wall, sometimes extending to involve the entire gallbladder. These infiltrative tumors often are difficult to distinguish from a chronically inflamed but benign gallbladder. Because the spread of tumor is often along the subserosal plane, which, incidentally, is the plane of dissection during cholecystectomy for gallstone disease, it is not uncommon for tumor to go unrecognized and for tumor to be disseminated by cholecystectomy.

Nodular types of gallbladder cancer are more distinctive and can show early invasion through the gallbladder wall into the liver or neighboring structures. Despite this invasiveness, nodular disease may be easier to control surgically than the infiltrative form, wherein the margins are less defined.

Papillary carcinomas exhibit a polypoid appearance. This variety has a much better prognosis than the other types owing to its relatively low invasiveness. A papillary tumor may be sufficiently large to fill the entire lumen of the gallbladder and still show minimal invasion of the gallbladder wall. Most gallbladder cancers (90%) are of epithelial cell origin and can be separated histologically into adenocarcinoma, squamous, adenosquamous, and oat cell subtypes. Most are adenocarcinomas. Rarely, tumors can be of mesenchymal cell origin and result in embryonal rhabdomyosarcoma, leiomyosarcoma, malignant fibrous histiocytoma, angiosarcoma, and Kaposi's sarcoma. Even more rarely, carcinosarcoma, carcinoid, lymphoma, and melanoma can occur at this site. In addition, the gallbladder can be involved with metastatic cancers. While classification is academically interesting, the only primary histologic type having clear prognostic significance is the papillary adenocarcinoma, for which the outlook is comparatively favorable. Grading of tumors is also performed and may have prognostic significance. However, it is extent of dissemination and resectability that has the greatest influence on outcome.

PATTERN OF SPREAD AND STAGING

Gallbladder cancer generally disseminates by all four routes of tumor spread: direct adjacent organ invasion, lymphatic spread, hematogenous spread, and peritoneal drop metastases. The gallbladder is attached to the undersurface of the liver along segments IVb and V. The organ has a thin wall, a narrow lamina propria, and only a single muscle layer. Direct invasion of the liver is therefore common. In addition, the infundibulum and the cystic duct abut the common bile duct and are in proximity of the major vasculature of the porta hepatis. Tumors of the infundibulum or the cystic duct may occlude the hepatic arteries, portal veins, and bile ducts, making tumor unresectable at an early stage or dictating an extensive resection and vascular reconstruction. Whereas tumors of the fundus may be resected by a limited liver resection, tumors of the infundibulum must often require a major liver resection for extirpation.

Once gallbladder cancer penetrates the thin muscle layer, it has access to major lymphatic and vascular channels. Lymph node metastases and hematogenous metastases are therefore common. An autopsy study revealed a 94% incidence of lymphatic metastasis and 65% incidence of hematogenous dissemination. In general, lymphatic spread of tumor occurs around the bile duct and involves cystic and percholedochal nodes first and subsequently descends to portal and caval nodes. Further spread will lead tumor to nodes in the retropancreatic, interaortocaval, and superior mesenteric artery lymph nodes. Therefore, it is essential that full mobilization of the duodenum and head of the pancreas be performed for full evaluation of the extent of lymphatic spread of disease. Though autopsy studies demonstrate as high a rate of distant metastases as 32% in lung and 5% in brain, such spread is clinically apparent only late in the disease. Metastases to the lung is rare, however, in the absence of advanced locoregional disease.

Gallbladder cancer has a great propensity for peritoneal spread and for seeding incisions and laparoscopic port sites. At postmortem examination, Perpetuo et al. reported that 60% of gallbladder cancer patients had peritoneal spread. This reflects a predilection for transserosal tumor both to the shed and to implant and grow. In addition, a large proportion of patients present after previous cholecystectomy for presumed gallstone disease, when violation of tumor is likely.

Multiple staging systems have been advocated for the classification of gallbladder cancer. The most popular systems are listed in Table 33.5-18. Most useful are the modified Nevin system and the AJCC–Union Internationale Contre le Cancer TNM staging system. The Japanese Biliary Surgical Society system is included because of the extensive literature on gallbladder cancer originating in Japan. Understanding the Japanese system is essential for interpreting this literature.

TABLE 33.5-18. Summary of Most Commonly Used Staging Systems for Gallbladder Cancer

Nevin et al. originally classified patients into five stages, based primarily on the thickness of invasion, and combined patients with direct liver extension or distant metastases into stage V. This staging system was later modified by Donohue et al. such that tumors with contiguous liver invasion were reclassified as stage 3 and noncontiguous liver involvement as stage 5. Stage 4 continued to include lymph node metastasis. The disadvantage of this system is that it does not differentiate between tumors that invade through muscle without invading the liver and tumors with minimal (<2 cm) or extensive (>2 cm) invasion of the liver, factors that seem to have significant prognostic significance.

In the TNM staging system, T1 tumors are those involving only the mucosa or muscle layer. T2 tumors involve perimuscular connective tissue. T3 tumors extend beyond the serosa but involve less than 2 cm of liver. T4 tumors invade beyond 2 cm of liver. T1 or T2 tumors with no lymph node metastases are stage I and II, respectively. T3 of N1 (perihilar) nodal involvement is classified as stage III. T4 tumors with no lymph node or distant metastasis constitute stage IVA, while distant nodal or other metastases are classified as stage IVB. We agree with Donohue et al. that direct liver invasion is less ominous than nodal metastases, which in turn are less ominous than distant metastases. Included in Table 33.5-18 is a proposed revision of the TNM staging system that we believe more closely segregates patients according to biologic features of the disease.

CLINICAL PRESENTATION

Distinguishing the clinical presentation of gallbladder cancer from gallstone disease is usually difficult. Pain is the most common symptom, occurring in 60% to 95% of cases. Symptoms are often mistaken for biliary colic or chronic cholecystitis. Jaundice occurs in one-fourth to one-half of patients and usually denotes far-advanced disease or an infundibular tumor. Gallbladder cancer can also cause obstructive jaundice by direct invasion of the common hepatic duct or by compression and involvement of the common hepatic duct by percholedochal lymph nodes. A high correlation between Mirizzi syndrome and gallbladder cancer exists. Anorexia, weight loss, and anemia are other nonspecific symptoms that often accompany this cancer. Obstruction of the cystic duct or the neck of the gallbladder may lead to hydrops of the gallbladder, which manifests as a mass in the right upper quadrant. A firm, fixed mass, however, would be an ominous sign and usually denotes extensive local invasion. In a review from Thorbjarnarson and Glenn, the presence of a right upper quadrant mass in association with gallbladder cancer reflected unresectability in 23 of 25 patients.

Laboratory examination usually reveals nonspecific liver function abnormalities. Increased alkaline phosphatase or bilirubin levels are found commonly in cases of
advanced tumors. CEA and CA 19-9 are tumor markers that may be useful in the diagnosis and treatment of this cancer. A CEA level greater than 4 ng/mL is 93% specific for the diagnosis of gallbladder cancer, as compared to controls undergoing cholecystectomy or upper abdominal surgery for benign conditions, though it is only 50% sensitive. Serum CA 19-9 levels greater than 20 units/mL have a 79.4% sensitivity and 79.2% specificity. These markers may be useful when radiologic imaging is ambiguous or indeterminate.

RADIOLOGIC EVALUATION

Before the routine use of CT and US, the preoperative diagnosis rate for gallbladder carcinoma was generally less than 10%, which, in part, explains the dismal outcomes of surgical therapy in the era prior to sophisticated cross-sectional imaging, as many patients with incurable disease were subjected to exploration. With the routine use of CT scanning and real-time US in the 1980s, preoperative diagnosis was achieved in 75% to 88% of patients. Beyond diagnosis, the goals of imaging also include accurate staging. The goal of imaging is to determine extent of liver invasion, invasion of other adjacent organs, vascular involvement, extent of biliary involvement, presence of nodal metastases, and presence of peritoneal metastases.

Because the majority of patients will present with symptoms suggestive of biliary colic or chronic cholecystitis, the diagnostic workup will usually begin with abdominal US. Discontinuous gallbladder mucosa, echogenic mucosa, submucosal echolocuency, or a mass greater than 1 cm should arouse suspicion of gallbladder cancer. The finding most convincing of a gallbladder malignancy is an inhomogeneous mass replacing all or part of the gallbladder. The index of suspicion should be high for elderly patients, patients with atypical symptoms, and patients with suspicious laboratory findings such as anemia, hypoalbuminemia, and abnormal liver function tests. US can also delineate the degree of biliary involvement and can define the presence of arterial or portal venous involvement by tumor. In experienced hands, US will provide diagnostic information equivalent to that provided by much more expensive cross-sectional imaging.

CT scanning is usually the next imaging examination performed because of its wide availability, low cost, low risk, and high yield. On CT, gallbladder cancer can appear as a mass almost filling the gallbladder lumen in 42% of cases, a polyoid mass in 26%, and diffuse wall thickening in 6% of gallbladder cancer patients. CT is better than US in demonstrating liver atrophy, which usually is indicative of ipsilateral portal vein involvement by tumor. CT is also better at detecting lymphadenopathy, particularly for retropancreatic nodal disease, which would rule out the potential for cure, though only 38% of pathologically positive nodes were identified preoperatively by CT scan.

In years past, jaundice or radiologic signs of biliary obstruction would lead to direct cholangiography via ERC or PTC. Indeed, direct cholangiography may provide a diagnosis. A long stricture at the mid-common bile duct is more likely to be a gallbladder cancer than any other malignancy. Direct cholangiography also allows brush sampling of the area of tumor invasion for diagnosis by cytology. Such cholangiography, however, carries the risk of introducing bacteria into an obstructed biliary tree and may cause infection and sepsis. In addition, the presence of a biliary catheter or stent may produce sufficient inflammation to obscure margins between tumor and normal ductal epithelium. This may, in turn, compromise surgical resection.

Angiography was another common test for assessing vascular invasion when the mass encroached on the porta hepatis, but this invasive method of examination carries finite risks. Cholangiography and angiography remain important tests in certain settings, but Doppler US, magnetic resonance cholangiography, and MRA have largely replaced these invasive procedures in the majority of cases.

Magnetic resonance procedures have long been accepted as invaluable for characterizing hepatic tumors. Such procedures may also identify and characterize lymph node metastases with greater precision than other cross-sectional imaging techniques. With recent advances in hardware and software, the extent of biliary involvement can now be determined through MRCP. MRA allows for assessment of vascular invasion to determine resectability and can demonstrate anomalous anatomic findings to assist in surgical planning.

If a patient presents with a clinical picture and ultrasound scans suspicious for gallbladder cancer, a CT scan of the abdomen and a chest radiograph usually are obtained. Findings of pulmonary metastases, peritoneal metastases, vascular or biliary involvement not amenable to reconstruction, contiguous liver metastases, or distant nodal disease indicate unresectability. Tissue confirmation of diagnosis can be obtained by needle biopsy, and the patient can be sent for alternative therapy.

Barring signs of unresectability, medically fit and nonjaundiced patients may proceed directly to surgical exploration. For those with jaundice or equivocal CT findings, MRCP represents the next least invasive test that may have utility. In patients with medical contraindications to immediate surgery, particularly those with renal insufficiency or sepsis, a PTC should be performed to delineate extent of biliary involvement and to treat the jaundice. At times, arteriography is still needed to demonstrate clearly unresectable vascular involvement. On rare occasions, the gallbladder cancer can erode into the transverse colon and produce a colonic fistula as a source of sepsis. In patients in whom this condition is suspected, a colonoscopy should be performed and full bowel preparation should be undertaken prior to surgical exploration.

ROLE FOR NEEDLE BIOPSY

Generally, needle biopsy is contraindicated if a patient is thought to have a resectable gallbladder cancer. This cancer has a great propensity to spread in needle tracts, a laparoscopic port site, surgical wounds, and the peritoneal cavity. Therefore, needle biopsy is not indicated if surgical exploration is otherwise appropriate. However, if radiologic studies demonstrate an unresectable tumor, percutaneous fine-needle aspiration cytology is highly accurate and may avoid an unnecessary laparotomy in many patients. If the tumor is clearly unresectable and the patient is jaundiced, direct cholangiography allows for placement of stents to relieve jaundice and allows diagnosis to be established by bile cytology or brush biopsy. Yield can be expected in 50% to 75% of cases, and the false-positive rate is less than 1%.

TREATMENT

Surgical Management

Much controversy exists as to the extent of surgery required for treatment of gallbladder cancer. Recommendations have ranged from simple cholecystectomy to ultraaggressive resections consisting of combined major liver resection and pancreaticoduodenectomy. This controversy exists because, until recently, the operations required for complete resection of cancer were associated with prohibitive morbidity and mortality. The majority of patients undergoing treatment for gallbladder cancer are in their seventh or eighth decade of life and may be at increased risk for radical surgery as a consequence of concomitant medical problems. The major morbidity after resection for gallbladder cancer has ranged from 5% to 54% and mortality from 0% to 21% (Table 33.5-19). In a multistitutional review of 1686 gallbladder cancer resections from Japan, a comparison of morbidity by procedure was made. The mortality rates were 2.9%, 2.3%, and 17.9%, respectively. The morbidity and mortality rates of major liver resections have decreased in recent reports, even in the aged population. Most recent series report a mortality rate of 5% or less even with extensive liver resections. With these improvements in perioperative outcome, radical resections are increasingly accepted.

Table 33.5-19

<table>
<thead>
<tr>
<th>Level of Operation</th>
<th>Morbidity Rate</th>
<th>Mortality Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple cholecystectomy</td>
<td>5%</td>
<td>0%</td>
</tr>
<tr>
<td>Combined major liver resection and pancreaticoduodenectomy</td>
<td>54%</td>
<td>21%</td>
</tr>
</tbody>
</table>
TABLE 33.5-19. Morbidity and Mortality of Resection for Gallbladder Cancer

Controversy concerning the extent of resection is also based on the dismal results of treatment in decades past. Until the last decade, the results of treatment for gallbladder cancer in general, including surgical treatment, were dismal. Piehler and Crichton reviewed 5836 cases in the world’s literature from 1960 to 1978. The overall 5-year survival rate was consistently less than 5%, with a median survival of 5 to 6 months. Even for the 25% who were treated by resections with curative intent, only 16.5% survived 5 years. In fact, the only long-term survivors were among the group in which the tumor was small enough not to be recognized at the time of cholecystectomy. Perpetuo et al. reviewed a 36-year experience with gallbladder cancer from the M. D. Anderson Cancer Center and reported a 5-year survival rate of less than 5% and median survival of 5.2 months. Cubertafond et al. recently reported the results of a French Surgical Association survey of 724 carcinomas of the gallbladder. These investigators reported a median survival of 3 months, a 5-year survival rate of 5%, and a 1-year survival rate of 14%. They observed no differences among the various surgical procedures adopted and concluded that no progress had been made in the treatment of gallbladder cancer. A review of gallbladder cancer from Australia revealed a 12% 5-year survival rate, with all survivors having stage I or II disease. The median survival for patients with stage III or IV disease was only 46 days. These miserable results sowed the seeds of nihilism that surrounded this disease in the past.

Over the last decade, many reports have demonstrated the utility of aggressive therapy. As a result, a more reasoned approach based on the biology of the disease is now advocated. The following recommendations are based on the goal of complete resection of tumor. To achieve this goal, surgery must remove the cancerous gallbladder, remove any adjacent organ invaded by tumor, remove involved lymph glands, and provide biliary continuuity if resection of the bile duct is necessary. Surgical strategy is best directed by the suspected T stage of disease.

T1 DISEASE. Patients with T1 stage tumor (tumor confined within the mucosa or muscular layers of the gallbladder) most often present after the gallbladder has already been removed by simple cholecystectomy for presumed gallstone disease. Ample literature reports that patients with T1 tumors may be cured by simple cholecystectomy alone. The 5-year survival rate is expected to be 85% to 100% (Table 33.5-20). Therefore, when patients present after simple cholecystectomy, the pathologic findings are reviewed to ensure that margins are negative. Particular attention is paid to the cystic duct margin. If all margins are negative, no other therapy is undertaken. If the cystic duct margin is positive, patients should be subjected to a common bile duct excision and biliary reconstruction.

Alternatively, the early-stage tumor may be discovered radiographically by a vigilant radiologist. If a T1 cancerous lesion is suspected, an open simple cholecystectomy should be performed and the diagnosis and stage confirmed immediately by frozen-section pathology. If a benign lesion or a T1 tumor is confirmed, simple cholecystectomy is all that is necessary. If deeper invasion is found, further resection according to stage should be performed, as outlined next.

T2 DISEASE. T2 tumors remain subserosal but have invaded through the muscular layer. It would at first seem logical that a simple cholecystectomy may be adequate for T2 tumors. However, there are two good reasons for performing more extensive resection. First, the plane that is generally taken between the liver and gallbladder is subserosal and may violate T2 tumors along the liver interphase. In the review by Yamaguchi and Tsuneyoshi, 25 patients had tumor extending into the subserosal layer and 11 of these had positive microscopic margins after simple cholecystectomy. Second, T2 tumors are associated with a high incidence of regional nodal metastases (Table 33.5-21). Therefore, the most reasonable primary operation for T2 gallbladder cancer is the radical cholecystectomy that was first advocated by Thorbjarnarson and Glenn. This includes a wedge resection of the gallbladder bed and regional lymphadenectomy of the hepatoduodenal ligament. Except for the thinnest of patients, total nodal clearance in the porta hepatis is difficult without removal of the common bile duct. In addition, adequate lymph node dissection of the porta hepatis has a good chance of devascularizing the common bile duct, and subsequent benign structure is a possible late consequence. For both reasons, we prefer to remove the common bile duct as part of the clearance of lymphatic tissue in this region. A hepaticojejunostomy using a Roux-en-Y loop of jejunum is the preferred method of reestablishing biliary continuity.

A large number of patients will present for definitive therapy after simple cholecystectomy. Good evidence supports a repeat exploration for a more definitive resection. Data from many series have demonstrated that simple cholecystectomy results in 30% to 40% 5-year survival, while radical cholecystectomy or a more extensive liver resection results in a 5-year survival of 80% to 90% (Table 33.5-22). This could be explained by the possibility of residual tumor in the gallbladder bed or the 30% to 50% chance of regional lymph node involvement in cases of T2 gallbladder cancer. In an article by Shirai et al., the 5-year survival rate after radical re-resection for stage II tumors was 90%, as compared to 40% 5-year survival for simple cholecystectomy alone. In a study comparing 20 patients treated by radical re-resection for T2 tumors with 18 patients treated by simple cholecystectomy, de Arexabala demonstrated a 50% improved 5-year survival rate for the more aggressive approach (70% vs. 20%).

TABLE 33.5-20. Survival after Resection of Stage I Gallbladder Cancers

<table>
<thead>
<tr>
<th>Stage</th>
<th>No. of Cases</th>
<th>Pathological Nodal Metastases (%)</th>
<th>Radical Hepaticojejunostomy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>9</td>
<td>12 (44)</td>
<td>8</td>
</tr>
<tr>
<td>T2</td>
<td>18</td>
<td>18 (90)</td>
<td>9</td>
</tr>
</tbody>
</table>

TABLE 33.5-21. Incidence of Nodal and Peritoneal Metastases from Gallbladder Cancer According to T Stage of Disease
TABLE 33.5-23. Survival after Resection of Stage II (T2) Gallbladder Cancers

T3 AND T4 CANCERS. The greatest controversy in surgical management of gallbladder cancer lies in the treatment of advanced tumors. The debate centers on whether radical surgery is ever justified for such advanced disease, given the perceived poor long-term prognosis. The literature from the last decade has provided much support for an aggressive approach by confirming a possibility for long-term survival after resection of locally advanced disease. Onoyama et al. recently reported a 63.6% 5-year survival for patients with Japanese Biliary Surgical Society stage II disease and a 44.4% 5-year survival for stage III disease after extended cholecystectomy (these stages combined represent AJCC stage III). Similarly, Nakamura et al. reported 13 radical resections for tumors of Nevin's stage V, with 54% alive at 1 year and 15% (two patients) alive for longer than 7 years. Similar results were recently reported from the Memorial Sloan-Kettering Cancer Center, where a 67% 5-year survival was achieved for patients with completely resected stage III disease and a 33% 5-year survival was noted for patients with completely resected stage IV tumors. It is clear from these results that an aggressive approach to locally advanced disease is justified.

TABLE 33.5-24. Survival after Resection of Stage III and IV Gallbladder Cancers

POSITIVE RETROPERITONEAL NODES. Metastases to cystic, portal, and portacaval lymph nodes may be curable by regional lymphadenectomy. Onoyama et al. reported a 5-year survival rate of 60% for patients having metastatic disease to N1 nodes. Shirai et al. reported a 45% 5-year survival for patients with positive regional nodes, documenting nine patients surviving for more than 5 years after radical resection. Such findings support radical lymphadenectomy for gallbladder cancer.

Some researchers have advocated even more radical lymphadenectomies. The next nodal area for extension of tumor includes the retropancreatic and aortocaval nodes, which explains the recommendation of some investigators to perform a pancreaticoduodenectomy for patients with suspicious retropancreatic nodes. It is assumed that nodal clearance is improved with pancreaticoduodenectomy. One multicenter series of 150 hepatopancreatoduodenectomies for gallbladder cancer reported a 54% morbidity and 15.3% mortality rate. Most other series report higher mortality rates. Such high morbidity and mortality of combined hepatectomy and pancreaticoduodenectomy is not justified by the long-term outcome. Long-term survival is extremely rare, even after such radical resection, when N2 nodes contain metastatic disease.

RE-RESECTION AFTER LAPAROSCOPIC Cholecystectomy. A significant number of gallbladder cancers will present for definitive therapy after prior cholecystectomy. This is particularly common for early-stage tumors, which account for most cancers diagnosed at pathologic analysis. For patients treated initially with open cholecystectomy, data clearly indicate that a radical re-resection is justified for tumors with a depth of penetration equal to or greater than T2. As would be expected, however, prognosis for patients subjected to two operations is less favorable than for patients treated with a single procedure. Gall et al. reported a median survival of 42 months for patients undergoing a curative resection at the first operation as compared to 13 months for those requiring two operations.

Laparoscopic cholecystectomy has given birth to an entirely new clinical entity since 1989—namely, laparoscopically discovered gallbladder cancer. To date, few data have addressed the utility of radical re-resection after gallbladder cancer has been discovered laparoscopically. We recently reported a series of 42 gallbladder cancers discovered at laparoscopy. One patient with T1 gallbladder cancer was advised that his laparoscopic cholecystectomy was a definitive procedure, and no additional therapy was undertaken. All other patients underwent extent-of-disease evaluation and re-resection as appropriate. Of the 41 patients with T2, T3, or T4 disease, 5 were not offered further surgery because disease was determinate on imaging to be unresectable. The remaining 36 patients were subjected to surgical exploration, which revealed that an additional 17 patients had unresectable disease. The survival of the 19 re-resected patients was significantly different from that of the patients whose disease was found to be unresectable. Only 3 of these 19 patients subjected to re-resection have died, and the median survival has not been reached, whereas 14 of the 17 patients whose disease was deemed unresectable have died, with a median survival of 4 months. These data would indicate that such reexploration and re-resection are justified and useful.

Gallbladder cancer has a great potential for peritoneal dissemination. This propensity for abdominal seeding is further enhanced by laparoscopic exploration. Data indicate that the incidence of peritoneal metastases is higher now than that reported in the prelaparoscopy age. During reexploration, therefore, care must be taken to perform a full abdominal inspection to rule out peritoneal disease.

Special consideration should also be extended for the laparoscopic port sites: A number of studies have demonstrated the propensity of tumor to recur in the laparoscopic port sites. It has become our standard practice to excise laparoscopic port sites at reexploration. Whether such excision of port sites is useful will be proven only by future follow-up, but it is known that the procedure adds little morbidity.

Chemotherapy, Radiotherapy, and Adjuvant Therapy

In general, chemotherapy and radiotherapy have offered poor results in the treatment of gallbladder cancer. A European Organization for Research and Treatment of Cancer cooperative study examined bolus mitomycin C in advanced gallbladder and biliary tree carcinoma, with no significant activity identified. Other regimens based on 5-FU, Adriamycin, or nitrosoureas alone and in combination for gallbladder cancer result in only minimal responses. In a study that treated 30 patients with advanced gallbladder carcinoma with 5-FU, leucovorin, and hydroxyurea, 9 had a partial response. However, the median duration of response was only 6.5 months, and the median survival was only 8 months. Regional therapy has recently been examined using intraarterial mitomycin C for gallbladder cancer. A 48% overall response rate and a prolongation of median survival from 5 months to 14 months as compared to historic controls was reported. However, a regional approach is rarely indicated, since the major reasons for unresectability usually are disseminated disease and extensive involvement of the porta hepatitis.

The results for radiotherapy have also been poor, because the mode of spread of gallbladder cancer does not lend itself well to radiotherapy. Although Houry et al. suggest that radiotherapy may increase survival after no resection or palliative resection of gallbladder carcinoma, the suggested benefit is small, with a median
survival of only 6 to 8 months. However, because it does appear to be well tolerated, radiotherapy with or without chemosensitization is the most common palliative modality used.

Because of the rarity of this disease in general and the rarity of completely resected gallbladder cancers, it is not surprising that there are no prospective, randomized studies examining the utility of adjuvant therapy. Nonetheless, as part of many retrospective studies, the issue of adjuvant therapy has been addressed. Chao and Greager compared 15 patients who received some form of chemotherapy or radiotherapy (or both) after resection for gallbladder cancer to 7 patients who did not receive any adjuvant therapy and found no significant difference in outcome. Oswalt and Cruz reported a median survival of 20 weeks in 13 patients treated with adjuvant chemotherapy, as compared to 8 weeks in patients treated with surgery alone. Morrow et al. from the University of Minnesota reported a median survival of 4.5 months for those receiving adjuvant chemotherapy or radiotherapy versus 3 months for those treated with surgery alone. With such small sample sizes and the generally dismal results in these series, it is difficult to draw firm conclusions from these data.

Definitive data for adjuvant radiotherapy also are lacking, but the existing data are a bit more encouraging than are those for chemotherapy. Todori et al. examined intraoperative radiotherapy after complete resection for stage IV gallbladder cancer and reported a 10% 3-year survival for patients receiving intraoperative radiotherapy versus 0% for surgery alone. Hanna and Rider reviewed results for 51 patients with gallbladder cancer and found survival to be significantly longer in patients receiving postoperative radiotherapy as compared with those who underwent only surgery. In another retrospective study, the median survival of patients receiving postoperative irradiation was 63 months, as compared with 29 months for patients undergoing surgery alone. Though the data are encouraging, firm support for such adjuvant therapy awaits confirmation by prospective trials. Nevertheless, given the high incidence of local recurrence of gallbladder carcinoma and the low morbidity of radiotherapy, it is unreaonable to recommend some form of radiotherapy, particularly for patients with advanced-stage disease.

**Other Palliative Management**

Palliative management for gallbladder cancer usually is directed at relief of jaundice, treatment of sepsis, and palliation for pain and bowel obstruction. Decisions on palliative treatment should take into account the short survival of patients with nonresectable gallbladder cancer. The median survival for patients presenting with unresectable disease is generally 2 to 4 months, with a 1-year survival rate of less than 5%. All palliative treatments should, therefore, be kept as simple as possible, given the aggressive nature of this disease. For jaundiced patients, for example, procedures to achieve relief of jaundice should be attempted only if patients are symptomatic (itching or experiencing biliary sepsis) or require a normal bilirubin level for chemotherapy. This is because any attempt to relieve the jaundice can result in introduction of bacteria into the biliary tree, which subsequently becomes a source of biliary sepsis. If the patient is experiencing pruritus or biliary sepsis, percutaneous drainage of the biliary tree is preferred. Surgical bypass often is difficult because of advanced disease in the porta hepatis. Even though a segment III bypass is possible, and can be performed at the time of laparotomy for attempted resection, it is unreasonable to perform exploratory surgery on patients with the sole goal of achieving biliary bypass. Kapoor et al. report a 12% 30-day mortality rate for segment III bypasses. In addition, subjecting a patient with an anticipated 4-month survival to a palliative procedure that requires a 1- to 2-month recovery period is unwise. In the event of a preoperative diagnosis of advanced, unresectable gallbladder cancer in the jaundiced patient, a noninvasive diagnostic approach to biliary drainage is justified. This disease is rapidly progressive, and so it is preferable to avoid the morbidity and recovery time of a laparotomy and surgical bypass.

**GALLBLADDER POLYPS**

A section on gallbladder cancer must include a discussion of gallbladder polyps, as polyps are found in up to 5% of patients in the general population. The majority of polyps are benign and can be classified as epithelial tumors (adenoma), mesenchymal tumors (fibroma, lipoma, hemangioma), or pseudotumors (cholesterol polyps, inflammatory polyps, and adenomyoma). Most polyps are cholesterol polyps, which histologically are submucoval deposits of lipid-laden macrophages. Of the various types of polyps, the only type believed to be precancerous is the adenoma.

Distinguishing benign from malignant or premalignant lesions is essential in the patient presenting with a polyp. US is the most practical test for evaluating polypoid lesions of the gallbladder and has a sensitivity of 90.1% and a specificity of 93.9% in making the diagnosis. In general, malignant lesions were significantly more likely to be found in patients older than 50 years and more likely to be present as a solitary lesion, to be sessile in character, and to measure greater than 1.0 cm in diameter. Conversely, cholesterol polyps, which account for more than 90% of benign lesions, are more likely to occur as multiple lesions (more than three), to small, and to retain an intact mucosa. Because of the poor prognosis of gallbladder cancer and the low morbidity of a cholecystectomy, most investigators recommend open cholecystectomy for any solitary polyp greater than 1.0 cm. Some investigators have advocated an even more aggressive approach. Shinkai et al. recommend cholecystectomy for patients with fewer than three polyps, regardless of size.

**Figure 33.5-6 is our recommended algorithm for the treatment of gallbladder polyps. It is based on the recommendations of Boulton and Adams and on the findings in longitudinal follow-up studies in which small (<1-cm) gallbladder polyps were followed by imaging, demonstrating a low rate of subsequent diagnosis of cancer. For symptomatic polyps, cholecystectomy should be performed. For patients with gallbladder polyps and other conditions that warrant cholecystectomy (e.g., cholelithiasis), cholecystectomy should be performed. Likewise, for patients with characteristics suspicious for cancer—namely, a lesion larger than 1 cm, fewer than three lesions, and eroded mucosa—cholecystectomy should be performed. Other patients should be followed by US every 6 months, and any suspicious findings should prompt cholecystectomy.**

**FIGURE 33.5-6. Algorithm for treatment of gallbladder polyps. (Modified from ref. 49B.)**

**CHAPTER REFERENCES**


Patients with adult celiac disease (nontropical sprue), particularly those who are unresponsive to dietary gluten withdrawal, are also at significantly increased risk for exceedingly difficult appearance of dysplasia.

Patients with chronic Crohn's disease are at increased risk for the development of small bowel carcinoma.

A number of small bowel lesions are thought to predispose patients to the development of small bowel malignancy. The adenoma-carcinoma sequence has been well established.

PREMALIGNANT LESIONS

5.0) and an increased risk of small bowel carcinoma after colorectal carcinoma (relative risk, 7.1 to 9.0).

In a review of the Surveillance, Epidemiology, and End Results program registries from 1973 to 1982, Weiss and Yang looked at the incidence of second cancers among 2581 cases of small bowel malignancy from a Surveillance, Epidemiology, and End Results Table. The incidence of sarcoma levels off after the seventh decade.

The first small bowel tumor, a perforated duodenal carcinoma, was described by Hamberger in 1746. The first small bowel leiomyoma was described by Foerster in 1858, and the first small bowel leiomyosarcoma was described by Wesener in 1883. An early review of malignant small bowel tumors was published by Leichtenstein in 1876, and Heurtaux published a review of benign small bowel tumors in 1899. Many of the earlier reviews were weighted heavily by the autopsy incidence of tumors. Most of the current information we have about the presentation, diagnosis, management, and outcome of bowel tumors is derived either from small single-center series or larger collective reviews.

INCIDENCE

Small bowel tumors, both benign and malignant, are exceedingly unusual. It has been estimated that small bowel tumors constitute fewer than 10% of all gastrointestinal tumors, although the incidence varies significantly depending on whether autopsy data are included. Approximately 64% of all small bowel tumors are malignant. These account for 0.1% to 0.3% of all malignancies. Some 2100 to 2400 new cases of small bowel malignancies occur each year in the United States, approximately 0.4 to 1 case per 100,000 population, with a slight male predominance. Fewer than 1000 deaths are due to primary malignant small bowel tumors annually in the United States, which is approximately 0.5 deaths per 100,000 population. By contrast, approximately 36% of small bowel tumors are benign, with roughly equal gender incidence.

In a review of the Surveillance, Epidemiology, and End Results program registries from 1973 to 1982, Weiss and Yang showed the incidence of malignant small bowel tumors to be low in patients younger than 30 years of age, with a steady increase in incidence with age for adenocarcinoma, carcinoid, and lymphoma. The incidence of sarcoma levels off after the seventh decade.

ETIOLOGY

CHARACTERISTICS OF THE SMALL BOWEL

The small bowel constitutes approximately 75% of the length of the gastrointestinal tract and provides 90% of the absorptive surface. Despite this predominance in length and surface area, however, it appears to be resistant to the development of malignancy. Small bowel malignancies account for only 1% to 3% of all gastrointestinal malignancies, and they are estimated at 36 to 60 times less frequent than malignancies of the colon. A number of hypotheses have been formulated to explain this finding. Transit through the small bowel is relatively rapid compared with the colon, resulting in less contact of the mucosa with potential carcinogens. Any potential carcinogens would be diluted by the large volume of secretions, which create liquid small bowel contents. This liquid in turn may be less mechanically irritating to the small bowel mucosa than solid stool would be to the colonic mucosa. The small bowel contains a small, metabolically inactive bacterial population, one that may not be capable of transforming potential procarcinogens to their active component. The contribution of the alkaline pH to the resistance of small bowel neoplasms is unknown. The proximal small bowel contains a number of microsomal enzyme systems known to detoxify carcinogens, particularly benzoazene hydroxylase. Finally, high numbers of lymphocytes and B cells secrete immunoglobulin A in the distal ileum, which may contribute to a local immunosurveillance system that prevents the development of malignancies. Evidence in support of this supposition is derived from immunocompromised patients, either those with acquired immunodeficiency syndrome or those on chronic immunosuppression, who seem more prone to the development of malignancies, both lymphoma and Kaposis sarcoma, in the distal small bowel.

The small intestine does appear to be susceptible to carcinogens. It is of interest that, as is shown later, adenocarcinomas in the small intestine occur proximally, in much the same distribution as azoxymethane-induced adenocarcinoma in rats. This distribution of small bowel adenocarcinomas also correlates with the length of contact of the small bowel mucosa with pancreaticobiliary secretions, implicating bile as a possible carcinogen. Diversion of the bile in animals has been shown to decrease the incidence of experimentally induced small bowel malignancy.

Chow and colleagues looked at risk factors in 430 patients with small bowel cancer, who they compared with 921 case-control patients dying of other causes. They found that weekly or more frequent consumption of red meat and monthly or more frequent consumption of salt-cured smoked foods was associated with a two- to threefold increase in risk. Tobacco use and alcohol consumption were not associated with increased risk of small bowel cancer in the study. Lowenthal and Sonn showed an excellent correlation between dietary fat intake and the incidence of small bowel carcinoma in various countries around the world. Poland showed that the incidence of methylazoxymethanol acetate-induced intestinal carcinoma in rats could be markedly reduced by dietary restriction, further implicating oral intake as a possible promoter of intestinal malignancy.

Other factors that predispose patients to development of large bowel adenocarcinoma may also play a role in the development of small bowel adenocarcinoma. Neugut and Santos looked at the incidence of second cancers among 2581 cases of small bowel malignancy from a Surveillance, Epidemiology, and End Results program cohort collected from 1973 to 1988. They found an increased probability of subsequent colorectal carcinoma after small bowel carcinoma (relative risk, 3.6 to 5.0) and an increased risk of small bowel carcinoma after colorectal carcinoma (relative risk, 7.1 to 9.0).

PREMALIGNANT LESIONS

A number of small bowel lesions are thought to predispose patients to the development of small bowel malignancy. The adenoma-carcinoma sequence has been well described. Perzin and Bridge observed that 25% of primary small bowel carcinomas demonstrated adenomatous epithelium in the same lesion. This finding has particular significance in patients with familial adenomatous polyposis, in whom polyps of the upper gastrointestinal tract are being recognized with increasing frequency.

Patients with chronic Crohn's disease are at increased risk for the development of small bowel carcinoma. These patients usually exhibit malignancy by the appearance of dysplasia. However, distinguishing clinically between distal small bowel malignancy and Crohn's disease without histologic confirmation can be exceedingly difficult.

Patients with adult celiac disease (nontropical sprue), particularly those who are unresponsive to dietary gluten withdrawal, are also at significantly increased risk for...
development of small bowel malignancy, particularly lymphoma, although adenocarcinomas also have been reported. 54,55,56 and 57

Patients with Peutz-Jeghers syndrome have been reported to develop primary carcinoma of the gastrointestinal tract. 58,59 and 60 The primary polyp of Peutz-Jeghers is a hamartoma, and the in situ transformation of a hamartomatous polyp to adenocarcinoma has not been clearly demonstrated. Because these patients often have an adenomatous component in their primarily hyperplastic and hamartomatous polyps, the development of malignancy more likely represents malignant evolution of that adenomatous component rather than transformation of the other hamartomatous elements. 58,59

Patients with von Recklinghausen’s neurofibromatosis also have been reported to have gastrointestinal involvement, both benign and malignant. 55,56 and 57 Although most of these small bowel tumors are benign neurofibromas and leiomyomas, malignant tumors of nerve tissue origin have been reported. 55 Case reports of a proximal small bowel adenocarcinoma and carcinoid tumor occurring in association with neurofibromatosis have also appeared. 55,58

ANATOMY

Grossly, the small bowel extends from the pylorus to the iliacsacral valve. It is estimated to measure 625 cm in length but may vary from 300 to 850 cm. 58 The duodenum, measuring approximately 25 cm, forms a C loop; the first portion extends 5 cm horizontally from the pylorus before turning inferiorly into the second portion. The second, or descending, portion of the duodenum is approximately 10 cm long, just anterior to the hilus of the right kidney. Typically, the ampulla of Vater, through which pancreaticobiliary secretions pass into the small bowel, is found midway down the descending second portion of the duodenum medially. The third portion of the duodenum travels transversely in close relationship to the uncinate process of the pancreas, anterior to the ureter, inferior vena cava, vertebral column, and aorta. This leads to the fourth portion of the duodenum, which measures approximately 2.5 cm in diameter, ascends to join with the proximal jejunum, and is suspended on the right cross of the diaphragm by the ligament of Treitz at the level of the second lumbar vertebra.

The jejunum, comprising the proximal 250 cm of the small bowel distal to the duodenum, and the ileum, the remaining 350 cm of small bowel, are supported on a fan-shaped mesentery that measures approximately 15 cm in length. More distally, this mesentery becomes progressively longer, with arterial blood supply, venous and lymphatic drainage, and small bowel innervation traversing between its two leaves. Grossly, the duodenum tends to be the largest in diameter and the ileum the smallest.

The arterial blood supply for the duodenum is derived from the gastroduodenal branch of the hepatic artery as well as the inferior pancreaticoduodenal branch of the superior mesenteric artery. The blood supply for the remaining small bowel is derived from intestinal branches of this superior mesenteric artery. Venous return from the entire small intestine is into the portal vein. Lymphatic drainage of the duodenum is to peripancreatic nodes. The remainder of the small bowel drains into the abdominal lymph nodes through channels that parallel the course of the mesenteric blood vessels. Autonomic innervation of the small bowel is by means of the celiac and superior mesenteric plexus. Sensory fibers are responsive to distention but not to other painful stimuli.

Microscopically, the intestine is a hollow muscular tube composed of four layers: serosa, muscularis, submucosa, and mucosa. The muscular layer consists of an outer longitudinal layer and an inner circular layer. Immediately beneath the mucosa is the lamina propria. The absorptive surface of the intestine is increased manifold by the presence of dense glandular villi covered by an epithelium of mucus-secreting goblet cells and absorptive cells, secretory Paneth’s cells, and rare argentaffin cells. Mucus-secreting Brunner’s glands are found in the duodenum but not in the distal small bowel. The myenteric plexus of Auerbach is located between the two muscular layers of the intestine. Meissner’s plexus is located in the small bowel submucosa. Lymphatic tissue is found in the lamina propria of the submucosa; this tissue increases as one progresses distally, becoming quite abundant in the distal ileum, where it is seen as Peyer’s patches.

PATHOLOGY

More than 35 histologic variants of small bowel neoplasms have been described. For practical purposes, they can be subdivided as benign and malignant and further classified according to their cell of origin (Table 33.6-1). Thirty-six percent of all small bowel tumors are benign.

A number of authors have commented on the inordinately high incidence of second primary malignant tumors in patients with primary small bowel malignancy. 55 The reason for this high incidence is not clear, although many have linked it to a defect in the individual patient’s immune surveillance system. The clinical implications of these observations are clear. Any patient who has had a primary small bowel malignancy should be watched closely for the development of a second malignant tumor.

PRESENTATION

Although no specific symptom complex is diagnostic of small bowel tumors, either benign or malignant, a few generalizations can be made. Presentation depends on the location of the tumor and its growth pattern. Malignant lesions are more often symptomatic than are benign lesions, and for a shorter duration. 55,56,57,58 and 59 Furthermore, in large part because of the nonspecific nature of the symptoms, the delay between the onset of symptoms and the final diagnosis is often significant, averaging 6 to 8 months. 60,61,62 and 63 The average age at presentation of patients with small bowel tumors is the seventh decade and is slightly younger for patients with malignant tumors than for patients with benign tumors. 55,56

Although fewer than 50% of patients with benign small bowel tumors develop symptoms, 55 more than 90% of patients with malignant tumors of the small bowel have symptoms before diagnosis. 55,64,65 These symptoms can be subdivided into four general categories: mass, obstruction, bleeding, and perforation.

In patients with benign tumors, pain from obstruction is the most common symptom, occurring in 42% to 70% of cases. Bleeding, usually chronic, is seen in 20% to 53% of patients. 55,64,66 The most common cause of adult intussusception is a benign small bowel tumor. A palpable mass or perforation is rare.

In patients with malignant tumors, the most common symptoms are pain (not always associated with obstruction) in 32% to 86% and weight loss in 32% to 67% of cases. 55,64,67,68,69 Bleeding occurs somewhat less frequently than in patients with benign small bowel tumors. 55 Perforation, usually localized, is seen in roughly 10% of patients, usually those with lymphomas or sarcomas. A mass that may represent dilated bowel proximal to an obstructing tumor is palpable in fewer than 25% of patients with malignant small bowel tumors.

DIAGNOSIS

The diagnosis of small bowel tumors is rarely made preoperatively. In fact, the diagnosis of small bowel malignancy is frequently delayed, not necessarily because of delay in presentation to the physician. Maglinte and colleagues, 55 in a review of 77 patients with small bowel malignancy, reported the average delay between onset...
of symptoms and presentation to the physician as 1 month, whereas the average interval from seeing the physician to final diagnosis was 7.8 months.

With the exception of an elevated 5-hydroxyindole acetic acid level in the presence of carcinoid syndrome, all the presenting signs and symptoms of small bowel tumors are nonspecific. Laboratory examination may reveal a mild anemia in the presence of chronic blood loss. Hyperbilirubinemia may be seen in the presence of periampullary duodenal tumors. Mild to moderate elevations of liver function tests may be seen in the presence of hepatic metastases, occasionally associated with an elevation in carcinoembryonic antigen.

Radiologic studies may be more suggestive of the diagnosis. Plain abdominal films that reveal signs of partial or complete bowel obstruction in the absence of prior laparotomy are suggestive of primary small bowel neoplasm, although nonspecific as to the diagnosis. Upper gastrointestinal series with small bowel follow-through is abnormal in 53% to 83% of patients and delineates small bowel tumor in 30% to 44% of patients. A number of investigators have suggested that this diagnostic accuracy can be improved to in excess of 80% using enteroclysis, with particular attention to the distensibility of the small bowel. Barium enema can be useful in the diagnosis of small bowel disease, particularly lymphoma, in which thickening of the distal ileum can be seen on reflu xing contrast material into the distal small bowel. This finding, however, is nonspecific and can be identical to the appearance of regional ileitis. Hyams and associates suggested that a rectal biopsy revealing granulomatous disease can reliably distinguish between inflammatory and neoplastic changes in the terminal ileum.

Computed tomography (CT) is thought to be somewhat more accurate in detecting small bowel tumors. In a review of 35 patients with small bowel tumors, Laurent and colleagues found the CT scan to be abnormal in 97%, predicting tumor in 80%. CT was predictive of the tumor histology 69% of the time and of the tumor stage in 81% of patients. Of 18 malignant tumors, the CT predicted extravascular invasion and liver metastases correctly 75% of the time; CT was accurate in predicting regional lymph node status only 25% of the time. Laurent and colleagues described characteristic CT findings for the following:

- Adenocarcinoma: partially obstructing concentric narrowing in the proximal small bowel, best detected with tumors more than 3 cm in diameter
- Lymphoma: thickened distal small bowel, best seen with tumors larger than 2 cm
- Leiomyosarcoma: eccentric tumor of the mid- or distal small bowel, with malignancy suggested by the presence of necrosis, ulceration, and size greater than 5 cm
- Carcinoid: homogeneous mesenteric mass, often associated with stranding of the mesentery
- Lipoma: small homogeneous fat density; small bowel or mesenteric nodule

Dudiak and coworkers in a review of 63 patients with small bowel tumors, found that CT was able to detect a tumor in 73% of patients and to correctly predict the diagnosis in 43%. Radiologic criteria similar to those of Laurent and associates were described. Other investigators have focused on small bowel thickness as measured by CT scanning to predict enteric disease. However, although small bowel wall thickness is predictive of disease, it is not predictive of malignancy.

Angiography is rarely helpful in the diagnosis of small bowel tumors. Angiograms may be distinctly abnormal in vascular smooth muscle tumors of the small bowel and may help to define the source of occult but active upper gastrointestinal bleeding in patients with a small bowel hemangioma. Alldi and colleagues reported angiography as being helpful in patients with small bowel arteriovenous malformations, identifying lesions in nine patients after negative laparotomy. In addition, angiography may on occasion demonstrate occlusion of the peripheral branches of the mesenteric circulation that is responsible for a syndrome of mesenteric ischemia seen occasionally in the carcinoid syndrome.

Nuclear medicine scans using technetium-labeled red blood cells may be helpful, again to delineate an occult source of chronic gastrointestinal blood loss in the presence of a normal colonic and upper gastrointestinal endoscopy. It can be difficult to localize the site of bleeding with this test, however, and Oliver and coworkers suggested that if technetium-labeled red blood cell scanning is used, the sensitivity of the examination improves if more frequent images are obtained.

With more sophisticated instrumentation, endoscopy is being more frequently used in the investigation of small bowel disease. Clearly, upper gastrointestinal endoscopy with total duodenoscopy is the mainstay for detection, diagnosis and, occasionally, treatment of more proximal neoplasms. Interest has been renewed in peroral enteroscopy. With new instrumentation, and some experience, total small bowel enteroscopy can be achieved. Enteroscopy can be helpful in diagnosing both focal lesions and more diffuse lesions, such as Mediterranean lymphoma. It may be most useful in localizing the source of occult nongastric, noncolonic gastrointestinal bleeding. Lida and associates described the use of intraoperative enteroscopy to increase the detection of polyps in familial adenomatous polyposis syndrome. In addition, intraoperative enteroscopy with trans–illumination of the bowel wall has been useful in patients with identified arteriovenous malformations that cannot be otherwise localized at the time of operation.

Colonoscopy with retrograde ileoscopy has been described as useful in the diagnosis of primary lymphoma of the ileum. In experienced hands, the small bowel can be visualized by retrograde ileoscopy in up to 30% of patients.

MANAGEMENT

BENIGN TUMORS OF THE SMALL BOWEL

The distribution of benign small bowel tumors by diagnosis and anatomic location is shown in Table 33.6-2. Most common are leiomyomas, followed by adenomas, lipomas, vascular lesions, and fibrous lesions.

### TABLE 33.6-2. Distribution of Benign Tumors of the Small Bowel by Site in 13 Series

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leiomyomas</td>
<td>80%</td>
</tr>
<tr>
<td>Adenomas</td>
<td>10%</td>
</tr>
<tr>
<td>Lipomas</td>
<td>5%</td>
</tr>
<tr>
<td>Vascular lesions</td>
<td>2%</td>
</tr>
<tr>
<td>Fibrous lesions</td>
<td>1%</td>
</tr>
<tr>
<td>Others</td>
<td>3%</td>
</tr>
</tbody>
</table>

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**Leiomyomas**

Leiomyomas of the small bowel account for 20% to 40% of all benign small bowel tumors and are the most common small bowel tumor according to a review by Wilson and associates. These tumors may grow within or outside the bowel lumen, and the growth pattern determines the presenting symptoms. Perforation is unusual. It can be difficult to distinguish benign from malignant smooth muscle tumors of the gastrointestinal tract intraoperatively, even with histologic evaluation by frozen section. According to the comprehensive review by Skandalakis and Gray, malignancy in lesions less than 4 cm in diameter is distinctly unusual. Histologic criteria of malignancy include necrosis, nuclear pleomorphism, and frequent mitotic activity. Surgical management of small bowel leiomyomas includes adequate...
Although villous adenomas of the duodenum are unusual, the duodenum is the most common small bowel location for these lesions. Their most common presenting sign is obstructive jaundice, and diagnosis is straightforward with upper gastrointestinal endoscopy. Most lesions are located in the second portion of the duodenum, usually on the medial wall, surrounding the ampulla of Vater. They are being increasingly recognized as a component of the familial adenomatous polyposis syndrome. A number of reports of villous tumors of the duodenum have appeared since the late 1980s. These tumors have a high propensity for malignant degeneration, averaging 45%. Risk factors associated with malignancy include size greater than 5 cm, age over 50 years, and more distally situated polyps. This propensity toward malignant degeneration, together with their location around the ampulla of Vater, combine to make management decisions difficult. Although a number of experts have advocated local excision for benign lesions, one cannot always be certain of the benign nature of a tumor before complete histologic examination. Furthermore, local recurrence rates of 17% to 75% have been reported after local excision of these tumors. Occasionally with malignant degeneration. Certainly, close ongoing endoscopic surveillance is mandatory after local excision of these lesions. Survival after complete excision is excellent in patients with both benign villous adenomas and carcinoma in situ. Patients with invasive carcinoma fare comparably to those with periampullary adenocarcinoma.

Small bowel adenomas. Adenomas in the remainder of the small intestine are distinctly unusual. These tend to be distributed more proximally, and case reports of malignant degeneration have appeared. These should be managed with segmental resection.

Peutz-Jeghers hamartomas. Peutz-Jeghers hamartomas are always multifocal and occur primarily in the small intestine. Symptoms of low-grade obstruction with chronic recurrent intussusception usually become apparent in the second decade of life and frequently warrant repeated surgical intervention. Appropriate surgical management of these tumors includes enterotomy and polypectomy. If bowel resection is required, an absolute minimum length of bowel should be sacrificed, because this is a chronic problem, and frequent reoperation can be anticipated. It is important to verify the status of both the stomach and colon before management decisions difficult. Although a number of experts have advocated local excision for benign lesions, one cannot always be certain of the benign nature of a tumor before complete histologic examination. Furthermore, local recurrence rates of 17% to 75% have been reported after local excision of these tumors. Occasionally with malignant degeneration. Certainly, close ongoing endoscopic surveillance is mandatory after local excision of these lesions. Survival after complete excision is excellent in patients with both benign villous adenomas and carcinoma in situ. Patients with invasive carcinoma fare comparably to those with periampullary adenocarcinoma.

**Other Benign Lesions**

Angiomas of the small bowel are less common and may be multifocal. They are usually discrete and well circumscribed, presenting most often as occult gastrointestinal bleeding. Management consists of segmental resection of the small bowel.

Lipomas of the small intestine are distinctly unusual. Patients usually present with symptoms of abdominal pain consistent with partial bowel obstruction. The difficulty in managing these lesions is that they may involve the small bowel diffusely. Surgical management involves resection of the symptomatic segment of bowel.

Brunner's gland hamartomas are extremely rare, with fewer than 100 reports in the world literature. Symptoms at presentation depend on the size of the tumor and range from a lack of symptoms to chronic upper gastrointestinal bleeding and duodenal or biliary obstruction. Because these are submucosal tumors, preoperative diagnosis is rarely possible. Treatment involves either endoscopic removal of pedunculated lesions or surgical resection of larger lesions.

Upper digestive tract involvement has been estimated to occur in 2% to 25% of patients with systemic neurofibromatosis (von Recklinghausen's disease). This range may well represent an underestimate, because much of the involvement is asymptomatic and detected only on postmortem examination. Typically, the involvement is characterized by submucosal neurofibromas, originating in the submucosal nerve plexus. Duodenal paragangliomas have been reported to occur in association with von Recklinghausen's disease. Although these lesions are generally considered benign, Inai and colleagues reported a case of duodenal paraganglioma with regional lymph node metastases.

Inflammatory polyps may occur at any point within the small bowel, from the duodenum through the ileum, and occasionally are reported in association with preexisting Crohn's disease. These are uniformly benign lesions arising from the submucosa, are usually solitary, and present with symptoms of obstruction. Management consists of polypectomy or segmental small bowel resection.

**MALIGNANT TUMORS OF THE SMALL BOWEL**

The distribution of malignant small bowel tumors by anatomic location and diagnosis is shown in Table 33.6-3.

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Duodenum</th>
<th>Jejunum</th>
<th>Ileum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenocarcinoma</td>
<td>0%</td>
<td>6%</td>
<td>94%</td>
</tr>
<tr>
<td>Gastric</td>
<td>9%</td>
<td>8%</td>
<td>83%</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>9%</td>
<td>0%</td>
<td>90%</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>6%</td>
<td>5%</td>
<td>93%</td>
</tr>
<tr>
<td>Sex anomalies</td>
<td>76%</td>
<td>24%</td>
<td>60%</td>
</tr>
</tbody>
</table>

**Adenocarcinoma**

Adenocarcinomas constitute 25% of all small bowel tumors and 39% of all malignant small bowel tumors. These tumors are distributed proximally in the small bowel, with nearly 80% located in the duodenum or jejunum. For purposes of analyzing mode of presentation, diagnosis, management, and outcome, these tumors can be separated into two categories: those of the duodenum and those of the jejunum and ileum.

Duodenum. Approximately 45% of all adenocarcinomas of the small bowel arise within the duodenum. In general, approximately 15% of these are in the first portion of the duodenum, 40% are in the second portion of the duodenum, and 45% are in the distal duodenum. A distribution pattern that parallels the relative lengths of each portion. The median age of these patients is 60 years. Symptoms relate primarily to the size and site of the tumor. The most common symptom is upper abdominal pain related to partial duodenal obstruction. Anemia with Hemoccult-positive stools is frequent, although frank upper gastrointestinal hemorrhage is unusual.

**Table 33.6-3. Distribution of Malignant Tumors of the Small Bowel by Site in 27 Series**

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Duodenum</th>
<th>Jejunum</th>
<th>Ileum</th>
</tr>
</thead>
<tbody>
<tr>
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<td>93%</td>
</tr>
<tr>
<td>Sex anomalies</td>
<td>76%</td>
<td>24%</td>
<td>60%</td>
</tr>
</tbody>
</table>
Diagnosis is usually suspected from an upper gastrointestinal series. Hypotonic duodenography may improve the accuracy of this test. Histologic confirmation can be obtained preoperatively in most patients by upper gastrointestinal endoscopy with total duodenoscopy.

As can be seen from Table 33.6-4, most patients who present with duodenal carcinoma undergo exploration; in these patients, resectability rates tend to be high. In general, patients with tumors of the first and second portions of the duodenum require pancreatoduodenectomy; patients with tumors of the third and fourth portions of the duodenum often can undergo complete resection with segmental duodenectomy and primary anastomosis. Because 22% to 71% of patients with duodenal adenocarcinoma have positive nodes at presentation and a finite 5-year survival rate is seen in the presence of regional nodal involvement; curative resection of duodenal carcinomas should always include a systemic regional lymphadenectomy regardless of the primary tumor location.

### Table 33.6-4. Duodenal Adenocarcinoma

A number of authors have commented on the steady decrease in operative mortality after pancreatoduodenectomy; this procedure can now be performed with an operative mortality rate of less than 5%. Outcome in duodenal carcinoma patients is determined by resectability, lymph node involvement and, in some series, histologic grade. No clear-cut evidence has established that pancreatoduodenectomy results in superior survival to that with segmental resection when the latter is technically feasible.

The role of postoperative adjuvant therapy has not been clearly defined in this group of patients. In patients with advanced unresectable disease, it may be that palliative radiation therapy can be of some benefit in controlling chronic blood loss. Because these tumors clinically appear to behave more like gastric cancer than pancreatic cancer, participation in an investigational chemotherapy program with a 5-fluorouracil (5-FU)-based regimen may be warranted.

### JEJUNUM AND ILEUM

Tumors of the jejunum and ileum account for the remaining 55% of small bowel adenocarcinoma. As can be seen in Table 33.6-5, much of the information about these tumors is derived from small series collected over a number of years. The report by Adler and associates is a collected series based on several large tumor registries. In general, most reports are from institutions that see fewer than one patient with small bowel adenocarcinoma per year.

### Table 33.6-5. Survival of Patients with Adenocarcinoma of the Small Intestine

These patients present with signs or symptoms of obstruction in 50% to 74%, or occult gastrointestinal bleeding in 33% to 64%. Although adenocarcinoma of the small bowel may be suspected based on a small bowel follow-through series or CT scan, neither examination is specific, and the diagnosis is frequently not made until laparotomy.

At the time of operation, 77% to 100% of distal small bowel adenocarcinomas are resectable, although regional lymph node metastases are frequent. The principles of surgical resection include attainment of negative surgical margins and wide resection of the corresponding mesentery of the involved segment of small bowel.

Survival in these patients is generally poor, with most series reporting only 20% to 30% of patients alive at 5 years (see Table 33.6-5). Prognostic factors in these patients include depth of tumor penetration and the presence of nodal or systemic metastases. Histologic grade of the tumor also has been shown to be predictive of outcome. Radiation therapy is difficult in these patients given the mobile nature of the small bowel mesentery and the inability to localize the target field. Because these tumors are rare, any meaningful comment on the impact of chemotherapy in their management is difficult. Jigyasu and associates reported one partial response in 14 patients treated with 5-FU–based combination chemotherapy accrued over 30 years.

### Carcinoid Tumors

Carcinoid tumors represent 29% of all small bowel malignancies and 19% of all small bowel tumors; they are second only to adenocarcinoma in frequency. The small bowel is the second most common site of carcinoid tumors after the appendix. Ninety percent of all small bowel carcinoids arise in the ileum. These tumors are often silent, with many series including otherwise asymptomatic tumors discovered incidentally, either at laparotomy or autopsy. When present, the most common presenting symptom is vague, nonspecific abdominal pain. This pain may be due to a number of causes. Frequently, an intense desmoplastic fibrous reaction occurs around the primary tumor, with shortening of the small bowel mesentery, which is thought to be induced in some way by the biochemical products of the tumor. This reaction induces foreshortening of the mesentery with kinking of the bowel and either ileus or partial bowel obstruction. Partial bowel obstruction may also occur from the tumor itself, although this appears less often. In addition, a syndrome of chronic mesenteric ischemia has been described in these patients, associated with a mesenteric angiopathy described as elastic vascular sclerosis. On angiography, this condition is manifest by occlusion of the peripheral small vessels of the mesenteric arcade.

Although only 10% to 17% of patients with small bowel carcinoid present with carcinoid syndrome, up to 67% develop features of the syndrome at some point during the course of the disease. Symptoms include flushing of the head, neck, and upper chest in 84% to 94% of patients and a watery secretory diarrhea in 70% to 86% of patients; both symptoms are present in 58% of patients. Right-sided valvular heart disease is present in 37% to 50% of patients, and bronchial asthma is manifest in 17% to 23% of patients. These symptoms are often prompted by emotion, alcohol intake, or the ingestion of tyramine-containing foods, such as blue cheese or chocolate. Virtually all patients with evidence of carcinoid syndrome have bulky liver metastases and elevated urinary 5-hydroxyindole.
Lymphoma

Lymphoma may involve the gastrointestinal tract either primarily or as a manifestation of extensively disseminated systemic disease. Primary small bowel lymphoma constitutes 1% to 4% of all gastrointestinal malignancies and, in a review of series, 15% of all small bowel malignancies (see Table 33.6-3). The gastrointestinal tract is the most frequent site of extranodal lymphoma, the stomach being the most frequent site, followed by the small bowel and colon, respectively. Within the small bowel, the incidence of lymphoma increases as one progresses distally, the most frequent site being the ileum. The incidence parallels the relative amount of lymphatic tissue in the wall of the small bowel at these locations.

The incidence of primary intestinal lymphoma in the United States nearly doubled in the period from 1985 to 1990. Factors implicated in this increase include the increasing number of immunocompromised patients (acquired immunodeficiency syndrome patients, transplantation recipients) and the increasing number of immigrants from Third World countries. For the diagnosis of primary small bowel lymphoma, one must satisfy the criteria specified by Dawson and coworkers: (1) There must be no peripheral or mediastinal lymphadenopathy, (2) the peripheral blood smear must display a normal white blood cell count and differential, and (3) tumor involvement must be predominantly in the gastrointestinal tract.

Most authors think that there should be no evidence of liver or spleen involvement. Antecedent conditions reported to be associated with the development of primary small bowel lymphoma include nontropical sprue and Crohn's disease.

Patients with gastrointestinal lymphoma have been traditionally staged using a modification of the Ann Arbor staging system. Because this was not a staging system originally designed for lymphomas of the gastrointestinal tract, Blackledge and colleagues described a staging system to incorporate the prognostic significance of perforation. Another clinically relevant modification of the Ann Arbor staging system, by Mussoff and Schmidt-Vollmer, recognizes the prognostic significance of regional (stage II, E), as opposed to extraregional (stage II, E), lymph node involvement.

**TABLE 33.6-6. Staging Systems for Small Bowel Lymphoma**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Ann Arbor staging system</td>
</tr>
<tr>
<td>IIA</td>
<td>Stage II, extranodal involvement</td>
</tr>
<tr>
<td>IIB</td>
<td>Stage II, extranodal involvement</td>
</tr>
<tr>
<td>III</td>
<td>Stage III, extranodal involvement</td>
</tr>
<tr>
<td>IV</td>
<td>Stage IV, extranodal involvement</td>
</tr>
<tr>
<td>E</td>
<td>Stage E, extranodal involvement</td>
</tr>
</tbody>
</table>

Five clinically distinct subtypes of primary small intestinal lymphoma have been described: the adult Western type; the pediatric type; the immunoproliferative small intestinal disease, or Mediterranean, type; enteropathy-associated T-cell lymphoma; and Hodgkin's lymphoma. The most common lymphoma of the small intestine, the Western type, occurs primarily in adults at a median age of 54 to 61 years and has a distinct male predominance. These lesions are usually focal and are found in the distal small bowel. The most common presenting symptom is abdominal pain related to partial bowel obstruction. The most common physical finding is a mass. Anemia occurs in approximately 20% of these patients, and approximately 10% of patients present with perforation.

The diagnosis of Western-type lymphoma is often made only at laparotomy. Radiologic findings suggestive of this diagnosis include a diffuse segment of thickened distal small bowel on follow-through examination. This finding can often be even better demonstrated by CT scan. However, radiologically, the diagnosis is easily
confused with other segmental disease of the distal small intestine, such as Crohn’s disease. 179

Several systems have been described to classify the pathology of small bowel lymphomas. Using the Rappaport system, approximately 60% of non-Hodgkin’s lymphomas are diffuse histiocytic (40% diffuse large cell and 20% immunoblastic), 25% are lymphocytic, and the remainder are of mixed type. The more recently described Kiel system uses both morphology and cell surface markers to classify lymphomas. Although histologic staging systems remain in evolution, the grade of the lymphoma remains most predictive of outcome. Most small bowel lymphomas are intermediate or high grade. 158,114,177

Management of these patients usually entails surgical exploration with resection of the affected segment of small bowel together with its subjacent mesentery. Fifty percent to 78% of patients who present with this type of lymphoma undergo complete surgical resection. 158,170,171

The role of adjuvant therapy in patients who undergo complete resection is debated. Most authors agree that any patient with evidence of incompletely resected disease or regional nodal metastases can benefit from systemic chemotherapy. 178 Some believe that adjuvant chemotherapy is warranted after complete resection of all high-grade lymphomas, even if they are stage I. 168,182 Auger and Allan 183 reported on 16 patients undergoing complete surgical resection of intestinal lymphomas. The median survival in patients who underwent complete resection with chemotherapy was 34 months, compared with 14 months in patients who underwent complete surgical resection without adjuvant chemotherapy. 171 These 16 patients were not broken down by the presence or absence of nodal metastases, and as such, the issue of adjuvant chemotherapy remains unresolved in patients with lymphoma localized to the bowel.

Adjuvant radiation therapy had been advocated by some investigators, 183,184 although the permanent long-term side effects of abdominal radiation therapy, together with the efficacy of contemporary combination chemotherapy, make this option less attractive. 171

Most of the larger more recent series report 5-year survival rates in excess of 50% with aggressive multimodality therapy. Prognostic factors include tumor grade, stage at presentation, complete response to therapy, complete resectability, histologic subtype, and the use of multimodality therapy. 159,163,170,171,172,178,179 Patients with B-cell lymphomas tend to have better median survival than those with T-cell lymphomas. 159 In contrast to the indolent course of patients with carcinoid tumors, most deaths in patients with small bowel lymphoma occur within 2 years of diagnosis. 158,163,173

The second major type of lymphoma is childhood lymphoma. This disease typically occurs in patients younger than 15 years of age and presents with symptoms of pain and physical findings of a mass in the right lower quadrant, often with associated intussusception. Histologically, nearly one-half of these lymphomas resemble a Burkitt’s-type lymphoma. 184 These patients often require resection before systemic therapy, because perforation while on treatment is not uncommon. The prognosis for these children is improving in the era of combined-modality therapy, with a survival rate of 76% reported by Fleming and colleagues 185; all deaths in this series occurred within 10 months of diagnosis. Outcome depends on stage at presentation and resectability. 159,168,185

A third clinically distinct type of intestinal lymphoma is immunoproliferative small intestinal disease, or Mediterranean lymphoma. This is the most common lymphoma encountered in Middle Eastern and African populations, occurring with equal gender predilection in young adults, with a median age of 30. 159,168,185 Typically, these patients present with the triad of pain, malabsorption (manifest by weight loss and diarrhea), and nail clubbing. 159 Approximately 50% of these patients present with a mass. Mediterranean lymphoma generally involves the entire small bowel and is manifested histologically by villous atrophy and an intense lymphoplasmacytoid infiltrate in the lamina propria of the small bowel. As such, diagnosis can often be made by peroral jejunal biopsy. Surgery is reserved for cases in which the diagnosis is unclear or for complications such as obstruction or perforation. Grossly, the bowel appears to be involved by a diffuse thickening with some nodularity. Lymph nodes are involved in 85% of patients. As a biologic curiosity, approximately 30% of patients with Mediterranean lymphoma have free a heavy-chain protein in their serum and jejunal fluid. This finding, however, is neither specific nor diagnostic in this disease.

Treatment of patients with Mediterranean lymphoma consists primarily of systemic chemotherapy, although reports of whole abdominal radiation therapy have appeared. 159 The use of tetracycline in the management of this lymphoma supports the role of an infectious etiology. 186,187 Prognosis is variable, with Al-Bahrani and associates 188 reporting a 23% 5-year survival rate; El Saghir and colleagues 189 reported an overall 5-year survival rate of 58% after aggressive therapy.

Enteropathy-associated T-cell lymphoma is an unusual variant of intestinal lymphoma, most often seen in the Middle East and often associated with an antecedent history of malabsorption or frank celiac disease. The malignancy is believed to derive from unrestrained proliferation of T-cell clones from the reactive T-cell population in the enteropathic bowel. 190 It is usually disseminated at presentation and is often associated with significant malnutrition. Prognosis is generally poor despite multiagent chemotherapy. 191

Primary Hodgkin’s lymphoma of the small bowel is extremely unusual, accounting for fewer than 3% of all small bowel lymphomas. 158,172 In many cases, this diagnosis may represent impingement of mesenteric lymphadenopathy on the small bowel rather than primary visceral involvement. 158 Management consists of diagnostic and palliative surgery followed by definitive systemic chemotherapy.

**Sarcoma**

Sarcomas of the small intestine are extremely unusual, constituting only approximately 9% of all small bowel tumors and 14% of all small bowel malignancies (see Table 33.6-2). Most are of smooth muscle origin (leiomyosarcomas and leiomyoblastomas), although case reports of other histologies have appeared. More recent reports have grouped these tumors under the category of gastrointestinal stromal tumors, from which another variant, gastrointestinal autonomic nerve tumors, can be distinguished based on immunohistochemistry and electron microscopy. 192,193 From a clinical and prognostic viewpoint, however, these tumors can be discussed together.

Sarcomas of the small intestine can present with a number of symptoms, depending on their growth pattern. Endoenteric lesions can present as either bleeding or obstruction. Exenteric lesions can present as an abdominal mass or perforation before any sense of obstruction is evident. Although the diagnosis may be suggested by upper gastrointestinal series with small bowel follow-through or enteroclysis, with or without abdominal CT scan, it is rarely made with certainty preoperatively. These tumors also tend to be highly vascular, with a plethora of tumor vessels seen with arteriography. Intraoperatively, these tumors have a variety of appearances, but they are usually appreciated as firm, encapsulated masses that arise in relation to the bowel. It is difficult both clinically and by frozen-section examination to distinguish a small leiomyosarcoma from its benign counterpart, the leiomyoma.

The principles of surgical management include wide resection of the primary tumor, including any adjacent structures that may be invaded. Duodenal tumors often require pancreateoduodenectomy if the medial wall of the second portion of the duodenum is involved. Smaller leiomyosarcomas of the duodenum may be treated with wedge or sleeve resection. For sarcomas of the jejunum and ileum, the involved segment of intestine is resected together with its supporting mesentery. Deliberate or extended lymphadenectomy is unnecessary, because these tumors involve regional lymph nodes in fewer than 15% of cases. 159

The overall 5-year survival rate for patients with small bowel sarcoma is approximately 20% and depends on tumor size, histologic grade, local invasiveness, and resectability. 181,182,182,182,183,184,185,186,187,188,189,190,191,192,193,194,195,196,197,198,199,200 in a review of patients at Memorial Sloan-Kettering Cancer Center, all of nine patients with high-grade sarcomas of the small bowel had experienced recurrences, whereas none of four patients with low-grade sarcomas had recurrences. 201

Peritoneal and liver metastases are the most common causes of treatment failure. No evidence suggests that adjuvant chemotherapy or radiation therapy after complete resection diminishes the risk of subsequent recurrence.

Standard treatment of symptomatic metastatic disease usually involves doxorubicin-based combination chemotherapy, with or without high-dose ifosfamide. Although response rates of up to 40% have been reported with these regimens, no convincing impact on the survival of patients with advanced metastatic gastrointestinal sarcoma has been demonstrated.

**Metastatic Disease**

The small bowel is not infrequently involved by metastatic disease. The most common tumor metastasizing to the gastrointestinal tract is melanoma, with 60% of patients who die of melanoma having autopsy evidence of metastatic disease involving the gastrointestinal tract. 202 Other extraabdominal tumors known to
SECTION 33.7
Cancer of the Colon

INTRODUCTION

Colorectal cancer represents a major public health problem, especially in developed countries. As such, it has attracted the efforts of researchers from a wide variety of disciplines, including epidemiologists, molecular biologists, nutritionists, gastroenterologists, prevention experts, surgeons, radiation therapists, nurses, medical oncologists, and outcomes researchers. This chapter section and Chapter 33.8 present some of the exciting information that has been generated about this common malignancy.

ANATOMY
GROSS ANATOMY

The large bowel is divided into the colon and the rectum. Segments of both may be intraperitoneal or extraperitoneal. The treatment and pattern of recurrence of colon and rectal cancer are affected by the location of the tumor in these organs and its relationship to the peritoneal cavity and surrounding structures. Treatment failures in large bowel tumors involving extraperitoneal segments often occur because of a locoregional recurrence. This is especially true of rectal cancers, which usually have no serosal covering and are surrounded by fat, bone, nerves, blood vessels, and viscera within the confines of the pelvis. The colon has segments that are largely intraperitoneal, and the relationship of certain aspects of the colon to the retroperitoneum and its structures are important factors in tumor spread. The cecum, transverse colon, and sigmoid loop are the intraperitoneal portions of the colon. The ascending colon, descending colon, splenic and hepatic flexures, and beginning and end of the sigmoid colon have their posterior surface in the retroperitoneum.

The large bowel is immediately recognized by its large diameter, haustra, and presence of appendices epiploicae and tenia coli. The tenia consist of condensations of longitudinal muscle fibers starting near the base of the appendix and continuing throughout the abdominal colon to form a continuous longitudinal muscle coat in the upper rectum. Haustra are outpouchings of bowel wall separated by folds that give a classic appearance on radiography or barium enema.

The first part of the colon is the cecum, with the appendix lying at the lower pole. The ascending colon lies on the right aspect of the retroperitoneum and extends up to the hepatic flexure. The hepatic flexure lies near the gallbladder fossa and porta hepatis and overlies the lower portion of the right kidney and the duodenum. The transverse colon is variable in its length. The splenic flexure lies just beneath the left diaphragm and abuts the hilum of the spleen and tail of the pancreas. The descending colon lies along the left retroperitoneum and terminates in the sigmoid colon. The descending colon is of variable length. The sigmoid colon is the narrowest portion of the large bowel, and it terminates at its junction with the upper rectum just below the sacral promontory.

VASCULAR SUPPLY

In general, the artery and vein supplying and draining each segment of the colon accompany each other in the mesocolon. The mesocolon contains vessels, lymph nodes, nerves, and lymphatic trunks. The marginal artery and vein form an arcade along the mesocolic side of the colon. The presence of collateral circulation allows performance of mesenteric resection to the level of the principal nodes found at the origin of the major vessels supplying segments of the colon.

The superior mesenteric artery (SMA) and the inferior mesenteric artery (IMA) contribute to the arterial supply of the colon (Fig. 33.7-1). Shortly after its origin, the SMA divides into the middle colic artery and the trunk of the SMA. The middle colic artery immediately forms two to three large arcades in the transverse mesocolon. The SMA ileocolic arterial branches then extend from the SMA. The right colic artery arises as a separate branch from the SMA in 10.7% of cases. The ileocolic artery gives off a right colic artery to the upper ascending colon and forms an anastomosis with branches from the middle colic artery. The ileal branch of the ileocolic artery gives off branches to the distal small bowel and cecum, whereas the colic branch supplies the ascending colon. An anastomosis occurs between the distal SMA and the ileal branch of the ileocolic artery at the junction of the terminal ileum and cecum.

The arterial supply to the left side of the colon comes from the IMA, which arises from the aorta. The IMA gives off the left colic artery. It also gives off three to four sigmoidal arteries. The anastomosis between the vessels of the middle colic artery and those of the left colic artery occurs at the splenic flexure. This vessel parallels the course of the colon between the middle colic artery and the branches of the IMA. This is critical in surgical reconstruction of the left colon and rectum.

The venous drainage of the colon parallels that of the arterial supply. The drainage of the superior and inferior mesenteric veins is to the portal vein. This enhances the production of liver metastases. The venous drainage of the lower rectum is also into the vena cava and, therefore, rectal cancers are more likely to produce isolated pulmonary metastases than are cancers at other large bowel sites.

LYMPHATIC DRAINAGE

Curative surgical resection and staging of large bowel cancer requires resection of the lymph nodes that drain the primary tumor site. The relationship between the blood vessels supplying the affected segment of colon and the draining lymphatics determines the extent of bowel resection to be done.

Lymphatic drainage of the large bowel follows its arterial supply in the mesocolon (Fig. 33.7-2). Invasive carcinoma of the large bowel is identified by spread beyond the muscularis mucosa into the submucosa, where it gains access to lymphatic channels through open junctions formed by the destruction of lymphatic endothelial cells. The efferent lymphatic channels pass from the submucosa to the intramuscular and subserosal plexus of the bowel to the first tier of lymph nodes lying adjacent to the large intestine and known as epicolic nodes. Paracolic nodes lie on the marginal vessels along the mesenteric side of the colon and are frequently involved in metastases. Intermediate nodes are located along the major arterial branches of the SMA and IMA in the mesocolon. The principal nodes are found around the origin of these vessels from the aorta, and they drain into retroperitoneal nodes.

FIGURE 33.7-1. Anatomic segments and vascular supply to the colon and rectum. a, artery; Inf, inferior; Int, internal; L, left; mes, mesenteric; R, right; Sup, superior; v, vein. (From Jones T, Shepard WC. A manual of surgical anatomy. Philadelphia: WB Saunders, 1945, with permission.)

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FIGURE 33.7-2. For tumors that lie between two pedicles, lymphatic flow may drain in either or both directions. From a study of cleared specimens, it was possible to determine the preferential route by the location of lymphatic metastases. The numbers signify the percentage of metastasizing carcinomas in the indicated locations that have demonstrated positive nodes along a given vascular route. For example, node-positive tumors lying between the ileocolic and right colic arcades metastasize along the ileocolic pedicle in 100% of cases and along the right colon in 12% of cases. (From Hertzer FP, Slanetz CA. Patterns and significance of lymphatic spread from cancer of the colon and rectum. In: Weiss L, Gilbert HA, Ballon SC, eds. Lymphatic system metastasis. Boston: GK Hall, 1980:283, with permission.)
EPIDEMIOLOGY

Colorectal cancers rank third in frequency in men and second in women. Male incidence rates, adjusted for age and race, appear greater than female rates for both proximal and distal cancers (odds ratio (OR) 1.32 for proximal cancers and 1.68 for distal cancers, respectively). The mortality rate is similar in men and women, the ratio being 1.05:1.0. Colorectal cancer is the fourth leading cause of cancer mortality because it has a better prognosis than more common cancers. A 5-year survival rate of 61% is reported by the U.S. Surveillance, Epidemiology, and End Results program, as compared with a 5-year survival rate of 41% to 42% in European and Indian registries. Slightly lower survival rates of 32% and 38% are reported in China and developing countries, respectively. The lowest estimated survival rate (30%) is in Eastern Europe.

The incidence of colorectal cancer is higher in developed countries than in developing countries. Fewer than one-third of these cancers occur in developing countries. The incidence rates vary tenfold. The lifetime risk of developing colorectal cancer in developed countries appears to be 4.6% in men and 3.2% in women. Incidence rates are relatively low in Africa and Asia, except in Japan, which now has an incidence rate similar to that in Europe. Sharp increases in incidence have been seen in Eastern Europe and Japan. The geographic differences in colorectal cancer incidence appear to be attributable to differences in exposures that are essentially dietary and environmentally imposed on a background of genetically determined susceptibility. Immigration from a low-incidence to a high-incidence environment will increase a person's risk. This has been most evident among immigrants to the United States from Japan.

Decreases in the incidence of colon and rectal cancers in the United States began in the mid-1980s and continue today. African American men have the highest incidence rates of colon and rectal cancer among U.S. racial and ethnic groups. Differences in subsite distribution between African Americans and whites have been noted. African Americans have the highest mortality rates for colon and rectal cancer among ethnic and racial groups. Studies have postulated that these differences are not due to biologic aggressiveness of the tumors but rather to access to care. U.S. colorectal cancer mortality and incidence rates continue to decline, with age-adjusted rates dropping to 16.8 and 42.7 per 100,000 population, respectively, in 1996. An analysis of data from population studies that included the National Cancer Institute’s Surveillance, Epidemiology, and End Results program reports that changes in the use of endoscopic polypectomy, dietary factors, energy intake, physical activity, serum cholesterol, cigarette smoking, and obesity contributed to this fall in incidence after 1986.

Recent epidemiologic studies have suggested that the anatomic distribution of colorectal cancer may have undergone a distal to proximal shift over several decades. The U.S. National Cancer Database has reported that cecal and ascending colon tumors increased in incidence from 33.9% to 36.1%, tumors of the transverse colon increased from 15.8% to 17.2%, and tumors of the sigmoid colon decreased from 36.0% to 33.4%. These changes occurred between 1986 and 1992. Reports suggest that the apparent distal to proximal shift may be a result of preventive measures and improved diagnostic techniques used in developed, high-incidence countries but that these have not had an impact in less developed nations. In an analysis of improvements in survival over time by anatomic subsites of colon cancer, it was found that 5-year survival rates improved significantly for patients with left colon and transverse colon cancers, owing to advances in treatment and diagnostic techniques, whereas survival rates from right colon cancer did not improve.

ETIOLOGY

The essential element of the etiology of colorectal cancer is a process of genetic change in the epithelial cells of the colonic mucosa. These changes are discussed more fully in the Chapter 33.1 that address the molecular biology of this disease.

Epidemiologic factors have provided initial evidence about the specific factors that initiate the process of carcinogenesis in the large bowel mucosa. Chief among the factors that can initiate colorectal cancer development are a predisposition to mutagen effects, fecal mutagens, meat intake, bile acids, altered vitamin and mineral intake, and fecal pH.

PREDISPOSITION TO MUTAGEN EFFECTS

There is an interaction between mutagen exposure and genetic constitution. Metabolic pathways may be altered by polymorphisms in genes responsible for detoxifying DNA damage. Protection from the effects of mutagen-induced DNA damage is achieved by a range of detoxification enzymes. Examples are reduced glutathione S-transferase (GSH transferase), DT-diaphorase, and N-acetyltransferase.

Differences among individuals can account for susceptibility to mutagens from the diet. An example is a polymorphism in N-acetyltransferase, an enzyme that catalyzes the formation of mutagenic products from heterocyclic amines, which can play a role in colorectal cancer development. Heterocyclic amines are substances formed in cooked meats. Differences in N-acetyltransferase activity classify individuals as slow or fast acetylators. Risk for colorectal cancer development increases with the level of red meat consumption in fast acetylators but not in slow acetylators.

Individuals with risk factors for colorectal cancer have significantly lower levels of GSH transferase activity in their blood lymphocytes. Strategies to enhance the expression of detoxifying enzymes are available.

FECAL MUTAGENS

Mutagenic compounds such as fecapentaenes, 3-ketosteroids, and heterocyclic amines in the stool may be produced by the interaction of digestion and food products. These compounds produce reactive molecules that may form bulky adducts to DNA. One of the chief influences of diet is the production of fecal mutagens by certain diets. Changes in the fecal microflora indicate that changes in diet may alter mutagenic activity by altering extracellular superoxide formation. For instance, a change in a lactovegetarian diet to a diet with increased fiber intake caused a dilution of mitogenic activity within the stool. Other factors may moderate the effects of fecal mutagens. Intake of antioxidants reduces the mutagenicity of compounds in the stool. Changes in intestinal transit time owing to fiber intake affects the exposure of the mucosa to mutagens.

In addition to mutagenic compounds such as fecapentaenes, the presence of other products of digestion such as 3-ketosteroids, which are products of cholesterol metabolism, may act as tumor promoters or initiators.

MEAT INTAKE

Armstrong and Doll (1975) described the high correlation of meat intake and mortality from colorectal cancer. Among the risk factors are the intake of red meats and the compounds that result from cooking meats at high temperatures. In a study of meat preparation, it was observed that the association between red meat and colorectal cancer could be due to heterocyclic amines present in cooked meat. This mechanism has been implicated in the high incidence of colorectal cancer in New Zealand. The method of red meat preparation and frequency of intake can be correlated with the prevalence of distal colorectal adenomas. Subjects who ate fried, red meat more than once per week had an OR of 2.2 for distal colorectal adenomas, as compared with those who ate lightly browned red meat one time or less per week. In Western countries, fried meat is the main source of exposure to heterocyclic amines. Nurses who consumed the highest ratio of red meat to white meat had a higher relative risk (RR) of colon cancer (OR 2.49, P<.001).

BILE ACIDS

Normal bile acids that are related to the digestion of fat can induce intestinal mucosal hyperproliferation, which acts as a marker for neoplasia risk. The presence of bile acids correlates with fat consumption, which is a known risk factor for colorectal cancer. Bile acids have been shown to activate AP-1, a transcription factor associated with the promotion of neoplastic transformation in colonic cells. They are also able to induce apoptosis, and variations in the epithelial apoptotic response to bile acids may correlate with risk. Cholecystectomy can result in high levels of bile acids in the cecum and ascending colon and appears to increase the
frequency of right-sided carcinoma. In a retrospective study of colorectal cancer patients, it was found that levels of the secondary bile acid deoxycholic acid were higher than normal and that the ratio between deoxycholic acid and cholic acid may be an indicator of risk.

**VITAMIN AND MINERAL INTAKE**

Calcium can alter colonic mucosal proliferation by binding fatty acids and bile acids in the stool, resulting in insoluble complexes that are less likely to affect the mucosa. It can also decrease proliferation of the mucosa directly. These effects of calcium may be site-specific within the colon. In a large study of U.S. health professionals, the risk reduction from high calcium intake appeared modest after adjusting for confounding variables. Two case-control studies suggest that any protective effect of calcium may occur only at low levels of fat intake. The National Polyp Prevention Trial indicated that supplemental calcium intake reduced adenoma formation by 19%. A similar effect has been seen in patients with hereditary nonpolyposis colon cancer (HNPPC) syndrome.

In case-control studies, the use of multivitamins has been shown to reduce the risk of adenoma formation in high-risk patients. In an update of the Nurses’ Health Study, Giovannucci et al. found a reduced risk of colon cancer [OR, 0.25; confidence interval (CI), 0.13 to 0.51] after 15 years of use of folate-containing multivitamins. The contribution of dietary folate appeared to be modest.

That folate is a potentially protective agent has been demonstrated also by other studies. Experimental tumor studies have shown that folate depletion increases the risk of tumor formation and that it also reduces methyl group availability for DNA methylation. Individuals with different forms of the 5,10-methylenetetrahydrofolate reductase gene may demonstrate different risks for colorectal cancer, which may account for differences in the effectiveness of folate supplementation on colorectal cancer risk. Administration of a folate agent may interact with alcohol consumption as a risk factor because demands for folate are raised by alcohol consumption. Low folate intake has been implicated in increased colorectal cancer risk, especially when combined with alcohol and a low-protein diet.

Populations with increased vitamin D intake have been noted to be at reduced risk for colon carcinoma. The effects of dihydroxyvitamin D$_3$, on differentiation are mediated through protein kinase C and its activation by dihydroxyvitamin D$_2$. Total vitamin D intake was inversely related to colorectal cancer incidence in the Nurses’ Health Study (RR, 0.33; CI, 0.16 to 0.70).

A reduced risk of colon cancer is associated with the use of vitamin C. Antioxidants such as vitamin E have been given in conjunction with vitamins C and A in studies indicating some protection against colorectal cancer risks. There is a weak association between high iron exposure and colorectal polyps (OR, 1.5; CI, 1.0 to 2.3). Low levels of selenium correlated with the presence of adenomas, whereas increased levels were associated with reduced risk of adenomas (OR, 0.58; CI, 0.31 to 1.08). Intervention trials have found a beneficial effect of selenium supplementation.

**FECAL PH**

Another aspect of the interaction between the intestinal milieu and the genome of the intestinal mucosa is the fact that alkaline environments in the stool support higher concentrations of free bile acids and other potential carcinogens. This pH may affect the solubility of bile acid and carcinogens and make them more damaging to the DNA of the intestinal mucosal cells. Epidemiologic studies show that higher rates of colon carcinoma are found in subjects with a higher stool pH.

**PRIMARY PREVENTION**

Primary prevention of colorectal carcinoma is defined as the identification and eradication of etiologic factors responsible for this disease. Dietary factors, energy intake, nonsteroidal antiinflammatory drug (NSAID) use, and such lifestyle factors as hormone use in women, tobacco and alcohol use, parity, and exercise, will be discussed. These issues are addressed extensively in Chapter 22, Chapter 23.1, Chapter 23.2, Chapter 23.3, Chapter 23.4, Chapter 23.5, Chapter 23.6, and Chapter 23.7.

**DIETARY FACTORS**

**Fiber**

The term fiber refers to a diverse group of complex carbohydrates. Numerous epidemiologic studies suggest that fiber exerts a protective effect, whereas other epidemiologic studies report no protective activity of fiber in relation to colorectal cancer. High fiber intake may be associated with other dietary habits that also decrease cancer risk.

Certain types of fiber appear to be more effective than others in reducing the risk of carcinogenesis. Cellulose and bran are specific examples of fibers that have demonstrated increased effectiveness. In an epidemiologic study of 16,448 health professionals, a trend toward a reduced risk of distal colorectal adenomas from fruit fiber ingestion but not from cereals or vegetables was seen. When data from this study were adjusted for incidents of poly development, the risk reduction associated with soluble fiber intake was stronger (RR, 0.27; CI, 0.11 to 0.66). Fiber may not reduce rectal cancer risk as much as it reduces colon cancer risk. Intervention trials involving fiber are appealing because of fiber's ready availability and low cost. However, the effect of fiber may not be independent of meat intake. A recent long-term analysis of this issue failed to demonstrate a significant reduction in risk for colorectal cancer or adenomas (OR, 0.95; CI, 0.73 to 1.25) attributable to dietary fiber.

** Dietary Fat**

Epidemiologic data suggest a direct relationship between total fat intake and increased cancer risk in the colon and rectum, and migrant studies show that changes toward a low-fat, low-fiber Western diet result in a rise in colorectal cancer incidence. Type of dietary fat may be important in the risk for colorectal cancer, as studies appear to link animal fat and red meat to colon cancer risk but do not support an association between colon cancer and vegetable fat. However, fish oils may have protective effects. Elevated levels of serum triglycerides have been associated with a higher risk of adenomatous polyps (OR, 1.5). Interestingly, lower cholesterol levels have been demonstrated in patients in whom colorectal cancer is diagnosed.

**ALCOHOL AND TOBACCO INTAKE**

Daily alcohol intake has been associated with a twofold increase in colon carcinoma. A more moderate risk is likely when a number of studies are considered. Genetic polymorphisms in metabolic pathways may modify this risk. In addition, current and past smoking habits are independent factors that increase risk. Among Japanese men and women, it was found that long-term smoking conveyed a 1.6 to 4.54 RR for adenoma formation.

**HORMONE REPLACEMENT IN WOMEN**

In a review of 59,002 postmenopausal participants in the Nurses’ Health Study, self-reported data were used to study the relationship between postmenopausal hormone therapy and colorectal carcinomas and adenomas. Current use of postmenopausal hormones was associated with decreased risk of colorectal cancer (RR, 0.65; CI, 0.50 to 0.83). The protective effect of hormonal replacement disappeared within 5 years after hormone use was discontinued. Similar protective effects were noted in a Minnesota study. In the Nurses’ Health Study, oral contraceptive use has been implicated in reducing the risk of colorectal cancer development by 40% (OR, 0.60; CI, 0.40 to 0.89). A higher parity was found to increase risk in those women with a family history of colorectal cancer.

**ENERGY INTAKE, PHYSICAL ACTIVITY, AND OBESITY**

Multiple studies have correlated factors such as energy intake, physical activity, and other lifestyle factors with colorectal cancer risk. In animal models, restricted energy intake has reduced the development of colon tumors. The interaction between obesity and reduced physical activity was demonstrated by an alteration in
intestinal prostaglandin activity, which can correlate with colon cancer risk. The Nurses’ Health Study showed an inverse relationship between physical activity and adenomas. In this same study, obesity was associated with an increased risk. A similar protective effect from physical activity in men was noted in a population-based cohort study conducted in Norway. Excessive weight and abdominal obesity were found to be risk indicators in men and women. An exploration of the relationship among obesity, energy intake, and insulin as a growth factor indicated an increased risk of colorectal cancer in the face of a high fasting glucose level, high insulin levels, and obesity. Epidemiologic studies in the United States and Italy have shown a similar association between diabetes mellitus and colorectal cancer risk. Nonsteroidal antiinflammatory drugs (NSAIDs) are effective in reducing risk in a variety of colorectal polyps and adenomas. There is evidence that the use of aspirin or other NSAIDs reduces the incidence of colorectal cancer. However, in a large aspirin intervention trial involving more than 22,000 U.S. male physicians, a secondary analysis did not confirm a reduced incidence of colorectal cancer. Several studies have shown that the use of aspirin is associated with decreased colorectal cancer risk. The use of aspirin has been associated with a reduced risk of colorectal cancer. The Nurses’ Health Study showed an inverse relationship between physical activity and adenomas. In this same study, obesity was associated with an increased risk. A similar protective effect from physical activity in men was noted in a population-based cohort study conducted in Norway.

**NONSTEROIDAL ANTIINFLAMMATORY DRUGS**

Experimental, epidemiologic, and intervention trials address the role of aspirin and NSAIDs in colorectal cancer biology. Human and experimental animal colon tumors contain increased amounts of prostaglandin E2, and this compound is thought to participate in colon cancer carcinogenesis. Formation of prostaglandins requires the action of cyclooxygenase (COX), which exists in two isoforms. COX-2 appears to be responsible for increased prostaglandin E2 in response to growth factors in human and animal colonic tumors. COX-2 inhibition, therefore, may play a role in colon cancer prevention.

Aspirin, a relatively nonselective COX-2 inhibitor, has been associated with lower-than-expected rates of colorectal adenomas and carcinomas in epidemiologic studies. However, in a large aspirin intervention trial involving more than 22,000 U.S. male physicians, a secondary analysis did not confirm a reduced incidence of colorectal cancer.

In a Wisconsin study, regular NSAID use conferred a lower risk of a colorectal cancer diagnosis than did nonuse (OR, 0.65; CI, 0.40 to 1.03). Importantly, the risk reduction was greater for those using nonaspirin compounds (OR, 0.43; 95% CI, 0.20 to 0.89) as compared with users of aspirin compounds (OR, 0.79; CI, 0.46 to 1.36). The NSAID sulindac has been studied in the setting of familial adenomatous polyposis (FAP), where it achieved a 56% reduction in polyps. The long-term use of nonselective COX inhibitors can be associated with increased toxicity. Use of more selective COX-2 inhibitors may be beneficial in preventing toxicity with long-term use while maintaining the agents’ preventive effects.

**SECONDARY PREVENTION**

Secondary prevention focuses on the identification of high-risk populations and interventions that can prevent the development of colorectal carcinoma. It involves identifying those persons at increased risk of death from colorectal cancer owing to the presence of premalignant lesions or early cancers. Examples of secondary prevention strategies are screening for adenomas, treatment of adenomatous polyps by endoscopic polypectomy, or excision of the large bowel in FAP. High-risk states can be identified by an individual’s age, genetic makeup, and predisposing diseases such as previous cancer or inflammatory bowel disease. In addition, prevention strategies are screening for adenomas, treatment of adenomatous polyps by endoscopic polypectomy, or excision of the large bowel in FAP. FAP syndromes are a group of syndromes characterized by the early onset of multiple polyps and a virtually 100% risk of colorectal cancer development. FAP represents but a small percentage of the overall number of colorectal cancer cases. Its importance as a model for sporadic colorectal cancer development far outweighs its importance as a problem in public health. It affects from 1 in 8000 to 1 in 10,000 persons. These syndromes have autosomal dominant inheritance with high but variable penetrance. The phenotype may vary by mutation site. Synchronous cancers are common in FAP patients.

There is an association between FAP and perianpillary, thyroid, and specific cancers or nonneoplastic growth such as osteomas, sebaceous cysts, and gastric fundic gland polyps. It is important to realize that 10% to 20% of the cases are de novo mutations with no apparent family history. After the colorectal cancer risk has

**TABLE 33.7-1. Risk Factors for Colorectal Cancer**

**CLINICAL RISK FACTOR: AGE**

Age is the most relevant factor affecting colorectal cancer risk in most general populations. The peak onset of colorectal cancer in the United States is at age 65 years. People older than 40 years are the largest increased-risk group. Fewer than 10% of cancers of the colorectum occur in people younger than 40 years. The increase in incidence occurs into the eighth decade of life, when a decline begins. The most common risk factor for polyp development is age greater than 50 years.

**FIGURE 33.7-3. Cumulative incidence of colorectal cancer by age in the general population (open circle), hereditary nonpolyposis colon cancer population (open square), and familial adenomatous polyposis population (closed circle).**

**GENETIC RISK FACTORS**

**FAMILIAL POLYPOSIS SYNDROMES**

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A subset of polyposis patients have Gardner's syndrome, which is characterized by colonic adenomatous polyposis associated with the presence of mesenteric or abdominal wall desmoid tumors, lipomas, and fibromas. The presence of a mesenteric desmoid tumor is a cause of great morbidity in these patients. Other diseases included under the category of polyposis syndromes are Turcot's syndrome and Oldfield's syndrome. Hamilton has described the presence of two germline defects in Turcot's syndrome that are seen with both polyposis and HNPCC syndromes. There can often be considerable overlap between these adenomatous polyposis syndromes, and they are best characterized on the basis of their common genetic abnormality in the adenomatosis polyposis coli (APC) gene.

The basic genetic defect in FAP is a mutation in the APC gene. The genetic locus for the APC gene has been identified at 5q21. The most common abnormality is an alteration in the genetic sequence resulting in the generation of a stop codon, which in turn results in the production of a truncated nonfunctional protein. This is the basis for a commonly used screening procedure in which the truncated protein is synthesized in vitro and is identified. Since the introduction of genetic testing into the medical armamentarium, it is important that patients have access to appropriate genetic counseling and proper interpretation of test results.

HEREDITARY NONPOLYPOSISS COLON CANCER

The HNPCC syndrome is inherited as an autosomal dominant trait with high penetrance. Its phenotypic features are early-onset colorectal cancer (mean age, 46 years), multiple (synchronous or metachronous) colorectal cancers (35%), and colorectal cancers usually (but not always) located in the proximal colon. There is an associated early onset of adenocarcinoma of the colon, ovary, pancreas, breast, bile duct, endometrium, stomach, genitourinary tract, and small bowel. In addition, sebaceous gland adenomas and carcinomas are seen in the Muir-Torre syndrome, a variant of HNPCC. A high rate of colorectal cancer is seen in first-degree relatives of patients with HNPCC. Approximately 1% to 6% of colorectal cancers fit the criteria for HNPCC.

The phenomenon of microsatellite instability is present in the tumor of patients (90%) with HNPCC and in 12% to 15% of sporadic colorectal cancer cases. The genes responsible for this are hMSH2, hMLH1, PMS1, PMS2, and hMSH6. Germline mutations in these genetic loci produce the DNA mismatch repair phenomenon, causing the development of colorectal cancer in patients with HNPCC. Though the results of genetic testing depend on criteria used for instituting testing, the overall mutation detection rate appears to be greater than 50% in suspected cases. HNPCC cancers are more likely to be signet-ring cancers and poorly differentiated, with extensive inflammatory infiltrates. There may be a more rapid time course for the development of cancers in this syndrome.

The Amsterdam criteria, developed in 1991, are helpful in identifying and categorizing patients with a familial history of colorectal cancer. The initial Amsterdam criteria—Criteria I—require that at least three relatives have colorectal cancer. In addition, one of the three relatives must be a first-degree relative of the other two; the colorectal cancer must involve at least two successive generations; at least one family member who developed colorectal cancer must be younger than 50 years; and FAP must be excluded. These criteria may underestimate the true incidence of HNPCC as pedigrees analysis is uninformative for some families. Because the initial Amsterdam criteria were unspecific and to define criteria for HNPCC recognition strictly, families with more subtle histories or extracolonic cancers may be missed. Therefore, newer criteria were established to address these concerns.

### Table 33.7-2. Amsterdam II Criteria

| Amsterdam Criteria II (Table 33.7-2) include consideration of extracolonic tumors and eliminate the requirement that one of the index cancers be a colorectal cancer. The HNPCC cancers accepted are colorectal, endometrial, small bowel, urethral, or renal pelvic. This less exclusionary set of criteria will reduce the number of families in which colorectal cancer is suspected but fail to receive genetic counseling and mutation analysis. Counseling is critical for appropriate management. Aaltonen et al. examined the feasibility of screening for HNPCC mutations in patients with colorectal carcinoma. They prospectively screened tumor specimens from patients with colorectal adenocarcinomas for microsatellite instability. DNA from the normal tissues of patients with tumors demonstrating replication errors was screened for germline mutations in the mismatched repair genes MLH1 and MSH2. Sixteen percent of patients with replication errors had detectable germline mutations. All the patients in whom germline mutations were detected had a family history of colorectal cancer or were younger than 50 years. In patients with replication errors, further testing should be carried out for germline mutations in known DNA mismatch repair genes. Because successful strategies for identifying patients suspected of harboring HNPCC have been terminated, the Bethesda guidelines for testing colorectal tumors for microsatellite instability have been developed (Table 33.7-2). These guidelines are expected to apply to 15% to 20% of colorectal cancer patients in the United States. |

| 1. Individuals with cancer in families that meet the Amsterdam Criteria I |
| 2. Individuals with colorectal cancer in addition to one or more extracolonic cancers (colon cancer is required) |
| 3. Individuals with colorectal cancer in addition to at least one extracolonic cancer ( satisfactory family history) |
| 4. Individuals with colorectal cancer in addition to extracolonic cancer diagnosed age ≤50 |
| 5. Individuals with colorectal cancer in addition to extracolonic cancer diagnosed age ≤50 |
| 6. Individuals with colorectal cancer in addition to extracolonic cancer diagnosed age ≤50 |

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| TABLE 33.7-3. Bethesda Guidelines for Testing Colorectal Tumors for Microsatellite Instability |

INHERITED COLORECTAL CANCER IN ASHKENAZI JEWS

Israeli Jews of European birth have the highest colorectal cancer incidence of any Israeli ethnic group. There are reports of a missense mutation (I 1307 K) in the APC gene.
gene found in 6% of unselected Ashkenazi Jews and 28% of this population who have a family history of colorectal cancer. Colorectal cancer is found in 13% of those with polyps. This condition lacks the florid polyposis seen in FAP. These polymorphisms of the APC gene create a hypermutable region of the APC gene that causes a predisposition to colorectal cancer. There do not appear to be any differences in clinical presentation or family history between carriers of the mutation and noncarriers, so genetic testing in this population may be required to identify high-risk individuals for screening. This mutation appears to be unique to Ashkenazi Jews.

ATTENUATED FAMILIAL ADENOMATOUS POLYPOSIS SYNDROME

Attenuated FAP syndrome is characterized by the development of flat adenomas that are precursor lesions to carcinoma. Genetic linkage studies identify abnormalities on chromosome 5Q, and this may be a variant of FAP, with the mutation being more proximal or distal in the gene than common mutations with classic FAP. In patients with attenuated FAP syndrome, disease onset is later than usual for FAP, neoplasms appear in the proximal colon, and oligopolyposis is present. Because these characteristics commonly are associated with HNPCC, making the clinical diagnosis is difficult.

Peutz-Jeghers Syndrome

Peutz-Jeghers syndrome is an autosomal dominant inherited condition in which hamartomatous polyps can occur throughout the gastrointestinal (GI) tract. The polyps are nonneoplastic and have a characteristic branching muscular framework. Melanin pigmentation surrounding the lips is associated with this syndrome. There is an estimated frequency of associated GI cancers throughout life, their polyps should be managed symptomatically. Prophylactic colectomy is not recommended. Germ-line mutations in a chromosome 19 gene have been found in Peutz-Jeghers syndrome families.

Juvenile Polyposis

In juvenile polyposis, multiple hamartomatous polyps occur in the colorectum, although they may also be found in the small bowel and stomach. Jass et al. defined this syndrome as the presence of more than five juvenile polyps, which differs from the solitary juvenile polyposis seen in children. These investigators found colorectal cancer in 18 of 80 cases. Neoplasia can occur in the index polyps or in a separate adenoma. Colonoscopic control of polyps appears appropriate, whereas colectomy may be used for large numbers of polyps, symptomatic polyps, or cancer.

A subset of patients with juvenile polyposis has been identified to carry germline mutations in the risk of colorectal cancer has been estimated at 38%. There is a 21% risk of upper GI cancers.

FAMILY HISTORY OF COLON CARCINOMA OR POLYPS

Even among populations that do not exhibit any of the well-characterized familial cancer syndromes, there is an increased risk among those who have first-degree relatives with colorectal cancer. This group accounts for most of the increased risk population (15% to 20% of patients). An autosomal dominant mode of inheritance has been suggested. Depending on the age at onset of the cancer and the number of relatives involved, lifetime risk can increase from 1.8 to 6-fold. It appears that the age-adjusted risk for those with one affected first-degree relative is approximately 1.7 (CI, 1.34 to 2.19). For those with two or more affected first-degree relatives, the risk is 2.75 (CI, 1.34 to 5.63). The age at onset of the colorectal cancer in the affected relative is an important factor: Risk can be increased 5.37-fold (CI, 1.98 to 14.6) in those who have an affected first-degree relative whose colorectal cancer occurred at less than 45 years of age. When the age at onset is 60 years or older, there is little increased risk, beyond that of having an affected first-degree relative. People with first-degree relatives having colorectal cancer have an 8% risk of developing large adenomas, and colonoscopy appears to be the most appropriate screening technique for these lesions.

In the review of data from participants in the National Polyp Study who had a newly diagnosed adenomatous polyp, information was gathered on the history of colorectal cancer in their parents and siblings. The RR of colorectal cancer was 1.78 for parents and siblings of patients with adenomas as compared with controls. The RR for colorectal cancer in siblings of patients in whom adenomas were diagnosed before 60 years of age was 2.59 (CI, 1.46 to 4.58). When this group was compared with the siblings of patients 60 years of age or older at the time of diagnosis of colorectal cancer, the RR was 1.24. Synchronous cancers are seen in 10% to 20% of cases.

Genetic alterations associated with inflammatory bowel disease suggest that there are accumulated genetic defects similar to those of sporadic carcinomas. The pattern of progressive genetic abnormalities has been confirmed by analysis of p53 abnormalities found in both active colitis and dysplasia. The RR for patients with proctitis alone is 1.7 (CI, 4.8 to 7.0), patients with left-sided colitis have an RR of 2.8 (CI, 1.6 to 4.4), and a 14.8-fold RR (the highest risk of colorectal cancer) is seen in those suffering from pancolitis (CI, 11.4 to 18.9). The mean age at onset of cancer has been found to be 48 years. The value of assessment of cancer risk based totally on the presence of dysplasia has been questioned. Ulcerative colitis patients operated on for colorectal cancer may not have a preoperative diagnosis of dysplasia. Other researchers have found that screening for high-grade dysplasia is a useful marker of the risk of coexisting cancer mandating colectomy.

GRANULOMATOUS COLITIS

Crohn's disease can affect the ileocecal area or may be limited to portions of the colon. In the absence of colonic involvement, there is no increased risk of colorectal cancer. The RR for ileocolic involvement was 3.2 and, for colonic involvement, was 5.6. The RR for those with associated GI cancer of 2% to 3% although these patients may develop dysplasia, metachronous adenocarcinomas are less likely to carry a risk of carcinoma as compared with villosus polyps. In general, approximately half of the polyps larger than 2 cm will harbor a carcinoma. The greater the number of adenomas, the more likely it is that a cancer will develop. If these multiple polyps harbor...
advanced characteristics, the incidence of colon cancer development increases six-fold (OR, 6.6; CI, 3.3 to 11.8). In studies of patients with colon polyps identified on flexible sigmoidoscopy, it was found that at complete colonoscopy, 20% had advanced lesions such as adenomas greater than 1 cm with a villous component, severe dysplasia, or invasive cancer. The risk of proximal colonic neoplasia was increased with sessile lesions in the distal colon. In a multicenter, prospective study of colonoscopic findings in patients with proximal colonic cancer, 116 patients were found to have cancer proximal to the splenic flexure, and 34% had neoplasia distal to the splenic flexure. Most average-risk patients with proximal colonic cancer will have normal results on flexible sigmoidoscopy.

After the removal of rectal or sigmoid polyps with villous or tubulovillous histology or size greater than 1 cm, the rate of colon cancer incidence was increased threefold over the general population (OR, 3.6; CI, 2.4 to 5.0). The cumulative incidence of colon cancer appears to be approximately 4% at 5 years and 14% at 10 years in patients with an untreated rectosigmoid polyp. Sixty-six percent of these cancers are in the index polyp, and 34% are at other sites. These findings help to demonstrate the effectiveness of polypectomy in preventing colon cancer.

**PELVIC IRRADIATION**

The data implicating irradiation as a cause of colorectal cancer are controversial. Such reports imply that patients are followed up for extremely long periods, because the interval between pelvic irradiation and the onset of a radiation therapy–induced GI tract malignancy appears to be 15 to 28 years. The radiation doses and techniques may have an impact on the overall incidence of GI tract cancers induced by pelvic radiation therapy. Second cancers are increased in patients with previous malignancies. The risk of colorectal cancer in this population is small and should not alter plans for curative treatment for pelvic malignancies.

**NONCANCER SURGERY**

Some studies suggest that cholecystectomy increases the incidence of colorectal cancer. The etiology for the relationship between cholecystectomy and colorectal carcinoma is controversial. In a study conducted in the United Kingdom, a metaanalysis of 35 studies was conducted. The OR for a positive association between cholecystectomy and colorectal cancer was found to be only 1.11 (95% CI, 1.02 to 1.21). For women, the OR was 1.14 (95% CI, 1.01 to 1.26) and, for right-sided cancer, the ratio was 1.86 (95% CI, 1.31 to 2.65). It appears that the cumulative lifetime risk for colorectal cancer was quite small. Data from case-control studies have shown an increased risk for proximal colon cancers after cholecystectomy. However, there was no indication that there was an increased risk for distal colorectal cancer. The risk of colorectal cancer after cholecystectomy cannot be separated from the presence of cholelithiasis as a possible marker for dietary changes that affect colorectal cancer risk. The risks associated with ureterosigmoidostomy may be related to the presence of mutagens within the stool or urine. An additional factor is that patients subjected to such operations may have confounding factors such as previous pelvic irradiation.

**SCREENING**

Screening involves testing asymptomatic individuals to assess the likelihood that they may have colorectal cancer or precursors. For a screening technique to be practical, it must be a risk-based approach to the assessment of asymptomatic patients. Colorectal cancer lends itself to screening because of the long period between the development of early mucosal abnormalities and the development of invasive carcinoma. Adenomatous polyps are the well-described precursor lesions of invasive colorectal cancer and can be effectively managed by endoscopic intervention. In the general population, the risk of development of a colorectal adenoma is approximately 15%, and it is estimated that 2% to 5% of these sporadic polyps will develop into an invasive carcinoma.

Screening tests are available that detect early curable disease and are well-established aspects of medical practice. The screening techniques do not involve excessive risk. The benefits of early diagnosis are improvements in treatment effectiveness and survival.

**SCREENING OF HIGH-RISK GROUPS**

**Familial Adenomatous Polyposis**

Once an average-risk person reaches the fourth decade of life, his or her risk of developing colorectal cancer increases almost 100%. Screening is not an effective management tool. On establishment of a diagnosis of FAP, patients should be considered for colectomy to reduce the risk of colorectal cancer development. In cases in which there is a remaining rectal stump that has been cleared of polyps, the patient should undergo annual screening to assess for polyp development and the need for proctectomy or fulguration of polyps. The usual recommendation is to start annual screening for FAP during early adolescence. If no polyps are found after age 24, the cumulative lifetime risk for colorectal cancer was 70% to 90%.

**Hereditary Nonpolyposis Colon Cancer**

Patients affected by HNPCC have cancers that develop from adenomatous polyps that are commonly proximal to the splenic flexure. The risk of colorectal cancer in HNPCC patients begins to increase by age 20 and is very high by age 45. The risk for colorectal cancer by age 60 is estimated to be 57% to 80%. Colorectal cancer is the most common cause of mortality. The cumulative lifetime risk for colorectal cancer was 88%. The risk of metachronous colorectal cancer was estimated at 45% in those not undergoing a prophylactic total colectomy. The cumulative lifetime risk for colorectal cancer was 98%. The risk of metachronous colorectal cancer was estimated at 45% in those not undergoing a prophylactic total colectomy. The cumulative lifetime risk for colorectal cancer was 98%. The risk of metachronous colorectal cancer was estimated at 45% in those not undergoing a prophylactic total colectomy. Endoscopic surveillance would reduce lifetime risk by 52%. Mortality from endoscopic surveillance was estimated to be approximately 0.02%. These investigators found a life expectancy benefit of 2.1 years associated with prophylactic colectomy as compared with surveillance. However, when estimates of health-related quality of life were incorporated into the analysis, surveillance became the preferred cancer prevention mode.

In a study using data from the International Collaborative Group on HNPCC, rectal cancers were found to have developed in 11% of patients at a median of 158 months from the time of their abdominal colectomy. Adenomas were found to have developed in the rectal mucosa in five of eight of the patients who developed rectal carcinoma and hence were deemed a marker of risk. The risk of developing rectal cancer was estimated to be 3% for every 3 years after abdominal colectomy for the first 12 years. The authors recommended endoscopic surveillance of the rectum after abdominal colectomy. Lin et al. (1998) estimated that rectal cancer was more common in MSH2 kindreds.

**Family History of Colorectal Cancer or Adenomatous Polyps**

Hereditary Nonpolyposis Colon Cancer

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SPECIALTY ORGANIZATIONS RECOMMEND THAT PEOPLE WITH FIRST-DEGREE RELATIVES WHO HAVE HAD COLORECTAL CANCER OR ADENOMATOUS POLyps SHOULD BE SCREENED ON A SCHEDULE SIMILAR TO THAT FOR AVERAGE-RISK PERSONS BUT BEGINNING AT AGE 40 INSTEAD OF 50. INDIVIDUALS WHO HAVE A RELATIVE WITH AN EARLY-ONSET DISEASE SHOULD BEGIN SURVEILLANCE 3 TO 10 YEARS PRIOR TO THE AGE OF ONSET IN THE INDEX INDIVIDUAL. OWING TO THE OVERLAP BETWEEN PATIENTS WHO HAVE BEEN AFFECTED BY A HNPCC MUTATION AND ANOTHER GENETICALLY UNDEFINED FAMILIAL COLONIC CANCER RISK, IT IS PRUDENT TO CONSIDER COMPLETE EXAMINATION OF THE COLON IN THESE PATIENTS AS OPPOSED TO FLEXIBLE SIGMOIDOSCOPY.

PERSONAL HISTORY OF COLORECTAL CANCER OR ADENOMATOUS POLyps

Patients who have had a previous colorectal cancer are at increased risk for polyph formation and development of second primary cancers. It is recommended that patients in whom a colorectal cancer has been resected undergo complete examination of the colon within 1 year after resection. This surveillance scheme is similar to that recommended for patients with a previous polypectomy. If the results of this examination are otherwise normal, then the patient can undergo evaluation in 3 years, with subsequent examinations dependent on the findings at that initial examination. Any subsequent cancers often are preceded by polyps, in the same adenoma-to-carcinoma sequence seen in sporadic colorectal cancer. Because of the effectiveness of polypectomy, the follow-up procedure should be colonoscopy.

Patients who have undergone previous removal of an adenomatous polyp should undergo colonoscopy during follow-up. The rate of metachronous adenoma formation is 20% over 3 years. The Polyph Prevention Study did not demonstrate any increase in risk of developing advanced polyps when subsequent screening was deferred for 3 years. No direct evidence supports a recommendation for the cessation of screening.

INFLAMMATORY BOWEL DISEASE

Because the rate of colorectal cancer development in patients with inflammatory bowel disease is related to dysplasia and duration and extent of disease, surveillance colonoscopy is an important consideration in the management of these patients. Colonoscopic surveillance should begin annually after 8 years of disease in patients with pancolitis or after 15 years of disease in those with colitis involving the left side of the colon. Random biopsy should be performed to detect dysplasia, which is a marker for the presence of colorectal cancer. However, there is no direct evidence that this practice is more effective than colectomy performed on the basis of extent and duration of disease.

SCREENING OF AVERAGE-RISK GROUPS: THE GENERAL POPULATION

Subjects who are healthy and have an average risk of colon cancer represent the largest population appropriate for screening. There is a relatively high risk of colorectal cancer in the United States, and the screening can be targeted to older individuals in whom colorectal cancer is much more common. For average-risk groups, the screening techniques consist primarily of digital rectal examination, fecal occult blood testing, and endoscopic examination. It is hoped that less invasive but sensitive tests such as virtual colonoscopy may be useful in screening in the future.

Any discussion of screening techniques must be analyzed in the context of the effectiveness and cost of such programs for asymptomatic individuals. These considerations and evolving clinical practice have generated recommendations that asymptomatic patients with no family history of colorectal cancer begin screening at 50 years of age with digital rectal examination and fecal occult blood assessment annually and flexible sigmoidoscopy every 5 years. Alternative approaches may be total colonoscopy every 10 years or a double-contrast barium enema every 5 to 10 years.

DIGITAL RECTAL EXAMINATION

The digital rectal examination is part of the routine physical examination. Approximately 5% to 10% of colorectal cancers may be palpable.

FECAL OCCULT BLOOD TESTING

Fecal occult blood testing relies on the presence of blood in the stool to indicate a neoplastic lesion in the large bowel. Testing for the presence of fecal occult blood using guaiac-impregnated paper slides is a relatively low-cost examination that is based on the ability of heme to catalyze a reaction involving the oxidation of guaiac in the presence of hydrogen peroxide, which produces a blue stain.

Other techniques rely on the detection of hemoglobin by its conversion to porphyrin or the detection of human hemoglobin by immunochromatic approaches.

The advantages of this test are ease, low cost, and low risk to the patient. The use of this test has been criticized, however, for its relatively low ability to predict the presence or absence of disease, leading to missed lesions (owing to poor sensitivity) and unnecessary invasive workups in patients without colorectal neoplasia.

Nonetheless, studies have demonstrated a decline in mortality from colorectal cancer in patients screened annually with fecal occult blood testing as compared with control groups. This improvement is attributable to the fact that cancers detected by fecal occult blood testing were at an earlier stage of disease at diagnosis, resulting in a decrease in the proportion of patients who had metastatic disease at the time of cancer discovery. These findings support the use of this method of cancer screening.

Not all rectal cancers bleed and not all blood in the GI tract is due to cancer. Some cancers may bleed intermittently. False negative fecal occult blood test results have been reported in 20% to 30% of patients with known colorectal cancers. The ability to detect polyps in the colon and rectum by testing for fecal occult blood is even less successful. Yearly testing for fecal occult blood has been recommended, because randomized trials show that yearly testing is more effective than testing every 2 years.

Fecal occult blood testing provides only a suspicion of colorectal cancer or polyps. The consequences of a positive test are that the patient requires a complete colon examination, usually in the form of a barium enema and sigmoidoscopy or colonoscopy. The costs and effectiveness of fecal occult blood testing as a screening modality must be evaluated in the context of these additional tests resulting from a positive examination. Elements of an ordinary diet, including red meat and certain vegetables that may have peroxidase activity, can cause false-positive reactions in guaiac-based tests. The use of salicylates and vitamin C can cause either false-positive or false-negative examinations, respectively. Because of these factors, the best results for fecal occult blood testing in screening for colorectal cancer are from studies that use rehydrated tests on two samples from each of three consecutive stools in individuals who were adhering to a restricted diet and who were abstaining from foods and drugs that could alter test results. Fecal occult blood testing is limited by the fact that the testing is aimed mainly at detecting cancer, owing to the low incidence of bleeding in small adenomatous polyps. An additional drawback of such testing is that the false-positive rate commits large groups of patients to undergoing the cost and inconvenience of testing with colonoscopy or barium enema when no colorectal pathologic process is present.

In a randomized trial of 46,551 asymptomatic people between the ages of 50 and 80 years, fecal occult blood testing was studied. Patients were evaluated with colonoscopy after fecal occult blood tests proved positive. The 13-year cumulative mortality rate per 1000 from colorectal cancer was 5.88% in the annually screened group, 8.33% in the biannually screened group, and 8.83% in the control group. A randomized, controlled trial was performed in England with patients aged 45 to 74 years who were offered either fecal occult blood testing every 2 years or routine medical management. Again, colonoscopy was used to evaluate positive tests, which resulted in a 15% reduction in mortality in the screened group. Some practitioners have expressed concern that the improvement in mortality seen in these studies could be related to chance for colonoscopy and its effects.

FLEXIBLE SIGMOIDOSCOPY

Flexible sigmoidoscopy can be used to evaluate the region from the anal verge to approximately 60 cm of the distal large intestine. This can allow detection of up to one-half to two-thirds of colorectal adenomas and cancers. Because distal adenomas and cancers are an indicator of more proximal neoplasia, a patient with findings of neoplastic polyph on flexible sigmoidoscopy should undergo complete colonic examination.

Flexible sigmoidoscopy screening programs can be expected to detect neoplasms in the distal colon and rectum in up to 8% of asymptomatic persons older than 40 years. Reductions in sigmoid and rectal cancer risk with rigid proctosigmoidoscopy of 70% were seen in a case-control study. It has been proposed that once-only sigmoidoscopy would be a cost-effective method of screening and subsequently assigning patients to low- or high-risk groups. Its use is a recommended...
The diagnosis of colorectal cancer can be made either by the workup of a symptomatic patient or by discovery of cancer by screening in an asymptomatic patient. Most Americans are not currently screened for colorectal cancer. In a survey of the general population, it was found that only approximately 17.3% of people aged 50 years or older had undergone fecal occult blood testing in the previous year and that only 9.4% had undergone sigmoidoscopy in the previous 3 years. The majority of patients will be found to have colorectal cancer on investigation of symptoms or signs.

Patients who present with symptoms are not appropriate candidates for a screening examination (i.e., less than a total colonic examination). Those in whom symptoms are compatible with the diagnosis of colorectal cancer, such as those with rectal bleeding, iron-deficiency anemia, obstruction, or alteration in bowel habits, should undergo total colonic examination. Colonoscopy will allow biopsy of colonic masses as well as removal of polyps; however, a mass in the colon should not be managed conservatively, even in the case of an equivocal biopsy. Those individuals with obstructive tumors should undergo examination of the whole colon as soon as is practical after management of the obstructing tumor.

A wide variety of abdominal symptoms and signs are consistent with colorectal cancer. These include rectal bleeding, discovery of occult blood in the stool, abdominal pain, change in bowel habits, nausea, vomiting, distention, weight loss, fatigue, and anemia. Rectal bleeding is more commonly associated with rectal cancer than colon cancer. Because it can be such an obvious symptom, patients who develop rectal bleeding come to medical attention sooner than those who do not have obvious rectal bleeding. Patients who present with rectal bleeding must not be managed for hemorrhoids without workup, even though many more patients will have benign causes for rectal bleeding as compared to the number who will have rectal carcinoma.

Abdominal pain in colorectal cancer may be caused by partial obstruction, which is commonly a cramping type of pain. A more diffuse type of abdominal pain may occur with the development of perforations, leading to signs of generalized peritonitis. Other pain syndromes that may be present in colorectal carcinoma can develop from involvement of the pelvic floor by rectal cancer—caused tenesmus. Locally advanced rectal cancer may be associated with involvement of the sciatic nerve or obturator nerve, producing a neuropathic pain syndrome.

Partial or complete obstruction may occur in 2% to 16% of newly diagnosed cases of rectal cancer. The presence of obstruction has been found to reduce the 5-year survival rate to 31%, as compared with 72% for patients without obstruction.

Malignancy of the colon can result in a free perforation with peritonitis or a contained perforation and fistula formation. Approximately half of perforations caused by colorectal cancer are into the free abdominal cavity. Contained perforation with involvement of adjacent organs is most commonly seen in oecal or sigmoid carcinomas. Either type of carcinoma may involve loops of small bowel, bladder, abdominal wall, or the retroperitoneum. When there is such involvement in the setting of a sigmoid colon carcinoma, the condition may mimic diverticulitis. Diagnosis in these circumstances can be difficult. It is justifiable to pursue surgery in such patients to clarify the diagnosis as well as to treat. Radiologic signs indicating diverticulitis include the presence or absence of intramural fistulas and the degree of mucosal abnormality. Tumor perforation can occur either at the site of a primary tumor or in the cecum when it is dilated because of obstruction. Perforation is a bad prognostic factor, not only because it heralds an increased risk of cancer spread but also because of the mortality associated with peritonitis.

In the 10% to 15% of patients who present with metastatic disease, signs and symptoms are usually present. Pain in the right upper quadrant, especially when accompanied by palpable hepatomegaly or a mass, often will indicate the presence of liver metastases. This finding should prompt investigation with imaging as well as endoscopy. Fever without an overt cause may also be a manifestation of metastatic disease. Patients with diffuse liver involvement or carcinomatosis may manifest ascites with signs of abdominal distention or symptoms of early satiety or bowel obstruction. Development of umbilical nodules may occur as a sign of inoperable disease. In patients with advanced colorectal cancer, supraclavicular adenopathy may be present. Inguinal adenopathy may develop in patients with an advanced low rectal carcinoma.

PATHOLOGIC FEATURES

Gross Appearance

Size alone is not a reliable predictor of outcome from colorectal cancer because of the predominance of biologic behavior in predicting outcome. A 1-cm, clinically detectable colorectal neoplasm may contain 30 or more successive generations of malignant cells prior to detection. Colorectal cancers can be exophytic or fungating, or tumors may be ulcerated. In general, ulcerated tumors predominate. Annular tumors produce obstructive symptoms and have the classic appearance of an apple-core lesion on barium enema. Tumors of the right colon often are fungating masses that grow into the lumen and for which the symptom is occult bleeding as opposed to obstruction; they often present with a palpable mass. Left-sided tumors tend to be more annular and cause obstructive symptoms.

Residual adenomas can often be found in addition to invasive cancer. Assessment of the colon specimen for synchronous lesions is important. In 3% to 5% of primary colorectal cancers, a synchronous carcinoma will be found. The number and type of neoplastic lesions, polyps, or invasive carcinomas in a colorectal specimen are important in identifying associated inherited colorectal cancer syndromes.

Histologic Types

Adenocarcinoma represents 90% to 95% of all colorectal tumors. Tumors can be further classified by grade and histologic subtypes (Table 33.7-4).

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Description</th>
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<tbody>
<tr>
<td>Tubular adenocarcinoma</td>
<td></td>
</tr>
<tr>
<td>Signet-ring adenocarcinoma</td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma with signet-ring features</td>
<td></td>
</tr>
<tr>
<td>Squamous carcinoma</td>
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<tr>
<td>Small cell carcinoma</td>
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<td>Carcinoid</td>
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<td>Neuroendocrine carcinoma</td>
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**TABLE 33.7-4.** World Health Organization Classification of Malignant Primary Tumors of the Large Intestine: Histopathologic Variants of Colorectal Carcinoma

The vast majority of colorectal cancers are moderately differentiated, gland-forming adenocarcinomas. Less common variants are classified on the basis of the predominance of an unusual pattern as compared with the usual adenocarcinoma of the colon. Mucinous or colloid carcinomas exhibit the majority of tumor in mucin pools, which are often of low cellularity. Signet-ring tumors display a large amount of intracellular mucus pushing the nucleus to the side of the cell. These often are associated with diffuse intramural spread beyond the obvious mucosal lesion. In poorly differentiated cancers, features of neuroendocrine differentiation may appear.

Approximately 4% to 17% of carcinoid tumors appear in the rectum, and 2% to 7% are found in the colon. They often present as submucosal masses with normal colonic mucosa overlying lesions. Sarcomas may account for 0.1% to 0.3% of all colorectal malignancies. These are chiefly leiomyosarcomas.

**DEGREE OF DIFFERENTIATION.** 
Broders (1925) designated four grades of differentiation based on the percentage of differentiated tumor cells found in the overall tumor...
The degree of differentiation for colonic adenocarcinoma commonly refers to the degree to which there are well-formed glands. There is a spectrum of histopathologic findings used to assess differentiation in typical cancers of the colon and rectum. Glands may range from large and dilated to small and compact. Gross pathologic evaluation of lymph nodes in colorectal cancer specimens is unreliable. Large nodes may show only lymphoid hyperplasia, whereas smaller nodes may harbor micrometastases detectable only by histologic examination, immunohistochemistry, or molecular techniques. This factor is important in understanding the inaccuracy of imaging techniques that typically rely on the size of lymph nodes as criteria for determining nodal involvement with tumor.

The number of lymph nodes found directly influences the accuracy and frequency of findings of Dukes' grade C cases. By using more intensive methods of lymph node assessment such as fat clearance, fewer false-negative lymph node stagings occur.

Goldstein et al. showed an increase in the percentage of patients with at least one lymph node metastasis when 12 to 20 lymph nodes were recovered from each specimen, as compared with specimens in which fewer lymph nodes were found. Wong et al. found, in a sample of patients statistically similar to a sample in the National Cancer Database Report, that examination of at least 14 T2 or T3 carcinoma colorectal cancer specimens was required to stage patients accurately.

Molecular Detection of Micrometastases

Owing to the effective use of adjuvant therapies for node-positive colorectal cancer, there is a theoretic advantage to the use of a more intensive method of detecting cancer cells in the lymph nodes of resected specimens. This improved detection is necessary of the approximately 20% rate of distant metastases in patients with resected stage II colon cancer who could theoretically benefit from systemic adjuvant chemotherapy. An increase in the detection of micrometastases has been demonstrated with fat-clearing techniques, serial sectioning, and immunohistochemistry, detection of epithelial antigens, and molecular screening with polymerase chain reaction–based (PCR-based) methods to detect tumor-specific RNA. The detection of micrometastases in regional lymph nodes by PCR technique has been demonstrated to have prognostic value in stage II colon carcinoma. Though the potential for the use of these techniques is great, currently gross pathology and histopathology are the mainstays of pathologic staging of colorectal carcinoma.

SPREAD OF COLORECTAL CANCER

The capability of a tumor to invade and metastasize is not only the most visible hallmark of cancer but also the leading cause of death in cancer patients. Colorectal cancers can spread locally or distantly via the lymphatic and venous systems. In addition to unregulated tumor growth, imbalances in regulation of cell proliferation and differentiation are responsible for these events to occur. We owe much of our current knowledge in this area to the pioneering work of Dukes et al. in the early 1930s involving careful analyses of rectal cancer cases. Although Dukes' work helped to explain the natural history of colorectal cancer and this information remains largely current, it hypothesized a very rigid pattern of spread. Dukes believed that lymph node invasion and distant metastasis could occur only after the tumor had extended through the bowel wall. Gross assessment of local extent can be misleading in some cases due to desmoplastic response, the effect of neoadjuvant therapies, or infection surrounding tumor perforation. Locally recurrent tumors are characterized by the predominance of the tumor mass in or around the bowel wall or an anastomotic site rather than in the mucosa itself.

Lymph Node Pathology

The inclusion of lymphoid nodules and germinal centers at the periphery of infiltrating carcinomas is termed a Crohn's-like lymphoid reaction. This is sometimes considered to be associated with HNPCC or with a high incidence of microsatellite instability. Many of these adjunctive characteristics of the histopathologic assessment of a tumor are subject to considerable intraobserver and interobserver variability in reporting.

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Dukes' (1932) grading system was based on cytotologic characteristics as well as glandular formation and nuclear polymorphism. The system ranges from stage A through stage D, the latter stage being the most poorly differentiated, with only occasional gland formation and markedly pleomorphic cells marked by a high incidence of mitoses. Jass et al. (1986) provided a system of classifying differentiation based on histologic type, overall differentiation, nuclear polarity, tubal configuration, pattern of growth, lymphocytic infiltration, and amount of desmoplastic reaction. Other aspects of the histopathologic evaluation of a colorectal tumor include assessments for vascular or lymphatic invasion. Extramural venous invasion is considered an indicator of worsening prognosis. Invasion of perineural spaces can be identified.

The degree of fibrosis present in tumors will vary widely. The pattern of infiltration at the edge of tumors can be pushing, expansive, or infiltrative. The host inflammatory response at the periphery of tumors can be composed of lymphocytes, neutrophils, mast cells, and macrophages. Angiogenesis may be noted at a tumor's periphery.

Invasion into the submucosa is the hallmark of the development of the potential for metastatic spread and is the key histopathologic characteristic of colorectal cancer. It is best assessed by histopathologic assessment. In colon carcinoma, the mesentry and serosal surfaces are at greatest risk for violation by tumor penetration. In rectal cancer, perirectal fat and adjacent organs are most commonly involved by direct invasion through the bowel wall. Gross assessment of local extent can be misleading in some cases due to desmoplastic response, the effect of neoadjuvant therapies, or infection surrounding tumor perforation. Locally recurrent tumors are characterized by the predominance of the tumor mass in or around the bowel wall or an anastomotic site rather than in the mucosa itself.

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and Wilkie (1933) found them in 6 of 51 specimens, Gabriel et al. (1935) in 1 of 62, and Grinnell (1939) in 4 of 118 specimens.

A second exception to the usual mode of lymphatic spread is seen when the lymphatics are blocked by tumor. When this occurs, the natural interconnection of lymphatic channels allows lymph nodes at a great distance from the relevant chain to be affected. Lymphatic obstructions are responsible for the retrograde extension of tumor spread. In a review of 913 specimens from patients with colorectal cancer, Grinnell (1966) found 34 (3.7%) to have this type of spread. In colon carcinoma, the lymphatic flow follows the major arteries, with three levels of lymph nodes: pericolic, intermediate, and principal. Tumors located between more than one major vessel may metastasize in any direction.

Dukes divided 985 rectal cancers into four different categories depending on the tumor grade. Stage A tumors were very well differentiated, whereas stage D tumors were anaplastic. There was a close correlation between the tumor grade and the incidence of local spread, lymph node involvement, and venous spread. The same correlation between tumor grade and lymphatic involvement has been demonstrated by other researchers.

With the advent of advanced staging techniques such as sentinel node biopsy and molecular analysis of lymph nodes, the existence of discontinuous or skip metastases needs to be taken into consideration when planning changes in current surgical techniques.

HEMATOGENOUS SPREAD

Despite our continuous efforts toward early detection, approximately 10% to 15% of colorectal cancer patients have evidence of distant metastasis at the time of the initial diagnosis. The liver is by far the most commonly involved organ. The colon is drained by the portal venous system. The rectum is drained by two different systems: The superior hemorrhoidal veins enter the portal system to the liver, whereas the middle and inferior hemorrhoidal veins drain to the inferior vena cava and spread to the lungs via the systemic circulation. This dual venous drainage system has important implications in the pattern of hematogenous spread. Brown and Warren retrospectively analyzed the results of 70 autopsies in patients with rectal cancer. They identified 23 patients (33%) with metastasis to the liver only and 6 patients (9%) with metastasis to the lung only. Metastasis to other sites without liver or lung involvement were rare, seen in only three patients (4%). The patients with lung metastasis only were found to have liver primary lesions. Diones (1965) described rectal cancer patients with upper rectal lesions and lung metastasis only. However, because metastasis was determined in routine clinical examinations, liver metastasis may have been missed in those patients.

Brown and Warren reported that 14% of the patients they analyzed had vertebral involvement. In his larger series, Diones (1965) described 6% of the patients with spread to the pelvis and lumbosacral spine. Even though some (or even most) of those lesions were the result of direct extension or were present in patients with widespread metastases, at least some patients have isolated metastases to the spine. Although the vertebral venous plexus is a high-pressure system, it may open during special circumstances, such as defecation. This would allow tumor cells to invade vertebral bones and the central nervous system using communications between the portal system and the paravertebral veins.

IMPLANTATION

Implantation refers to the capability of cancer cells to deposit and grow on another surface after being released from the primary tumor. Most normal human cells, regardless of their origin, are in constant contact with an extracellular matrix and cannot survive for long when away from it, undergoing apoptosis or cell-cycle arrest. However, cancer cells have been known to be able to survive without interaction with an extracellular matrix. The ability of cancer cells to detach from the primary tumor and either to penetrate into the circulation or to implant in a different surface away from their original extracellular matrix is most likely related to changes in the cell adhesion molecules.

Implantation may occur when cancer cells are shed intraluminally, from the serosal surface, and by surgical manipulation. Umpleby and Williamson (1967) determined the viability of tumor cells shed into the intestinal lumen in 49 patients. Viable exfoliated tumor cells were demonstrated in 52 of 74 specimens collected (70%). The number of viable tumor cells recovered from the distal resection specimen by Auter and Cohan was inversely related to the distance of the tumor from that margin, confirming earlier observations made by McGrew et al. (1954). Zeng et al. prospectively screened the serosa overlying the primary tumor mass in 65 patients who underwent surgery for colon cancer. Malignant cells were present in the cytologic analysis of 23% of all patients and 26% of those with tumors invading through the muscularis propria but not through serosa. After reviewing clinical, reoperation, and autopsy series, Brodsky and Cohen determined the incidence of peritoneal seeding followed by peritoneal failure to be fairly frequent among patients who experience recurrence of colorectal cancer. The risk of colorectal cancer spread caused by surgical manipulation is well recognized, and the improvement of surgical technique has been a way of preventing recurrences since the early decades of the twentieth century.

STAGING AND PROGNOSTIC FEATURES

The most reliable prognostic factor identified to date in colorectal cancer is the staging of disease at the time that treatment is initiated. The staging of colorectal cancer has been an evolving field since the beginning of the twentieth century, with multiple authors attempting to develop a reliable and reproducible system. The first widely used system was introduced by Dukes in the 1930s and, like the majority of staging systems developed to date, relied on information obtained during surgery. Imaging techniques used preoperatively have not been successful in reliably staging colorectal cancer. Both conventional computed tomography (CT) scanning and conventional magnetic resonance imaging have an unacceptably low accuracy for identifying the early stages of primary colorectal cancers. The low staging accuracy of these imaging techniques is related to the fact that no current method can assess the depth of tumor infiltration within the bowel wall, and both have difficulty in diagnosing lymph node involvement. For colorectal cancer patients evaluated with CT scans or magnetic resonance imaging, the overall accuracy of primary tumor staging is approximately 70%, with sensitivity for lymph node detection of only approximately 45%. The sensitivity for positive lymph nodes is higher for rectal tumors. The development of new imaging techniques such as positron emission tomography (PET) and endoscopic ultrasonography may enhance the usefulness of imaging in stage determination for colorectal cancer. These imaging techniques would be especially important in rectal cancer, wherein preoperative treatment with chemotherapy and radiation therapy is a viable therapeutic option.

Besides the pathologic staging determined by depth of penetration through the bowel wall and involvement of lymph nodes, distant organs, or both, several other potential independent factors for survival have been identified. The number of factors reported to have an impact on the overall survival of patients with colorectal cancer continues to grow, but the prognostic value of few of these factors has been confirmed in larger trials. The presence of obstruction or perforation, vascular or lymphatic invasion (or both), perineural invasion, peritumoral lymphocytic invasion, the character of invasive margin and tumor type, presence and number of mast cells, age and gender, tumor grade, DNA content, increased mitosis and low Bcl-2 expression, low apoptosis rate, vascular endothelial growth factor (VEGF) levels, and allelic loss of chromosome 18q are among the growing number of prognostic factors used in the analysis of colorectal cancer. The rapidly evolving field of molecular biology holds the promise of accurate staging and, it is hoped, individualized prognosis and treatment tailoring in the not-so-distant future.

DUKES' CLASSIFICATION

At the beginning of the twentieth century, surgery became routine for the treatment of colorectal cancers, including those arising in the colon and rectum. Almost immediately, the need arose for a staging system that allowed for comparisons among different surgical experiences and for determination of prognosis. A number of authors have tackled this challenge, with varying results. Based partially on earlier experiences, Dukes developed the first practical system in the early 1930s. The initial Dukes' system was directed to rectal cancers and was remarkable for its simplicity and ability to give adequate prognostic information. The tumors were classified from A to C, with stage A indicating penetration restricted to the bowel wall, stage B indicating penetration through the bowel wall, and stage C indicating lymph node involvement. Over the years, several authors have attempted to make improvements on the initial work by Dukes, and the system has been extended to include both colon and rectal cancers. Dukes himself made a few changes in his system, first dividing stage C into C1 (local lymph nodes involved) and C2 (lymph nodes at the point of ligature involved) and later adding a fourth stage for distant metastasis, which was denoted as stage D by subsequent authors.

Kirklin et al. (1949) divided Dukes' stage A into more restricted stage A (mucosa and submucosa involvement only) and a new B1, which involved the muscularis propria (but not penetration through it). The old stage B became B2. One problem seen with the earlier version of the Dukes’ system was its inability to separate the different subtypes of colorectal cancer. In 1954, Ajani and his colleagues introduced the TNM system, which included T for tumor (tumor size), N for node (presence of metastasis), and M for metastasis. This system was further refined in 1988 by the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC), and is still in use today.

Brown et al. (1941) described Dukes’ stage A into a more restricted stage A (mucosa and submucosa involvement only) and a new B1, which involved the muscularis propria (but not penetration through it). The old stage B became B2. One problem seen with the earlier version of the Dukes’ system was its inability to separate the different subtypes of colorectal cancer. In 1954, Ajani and his colleagues introduced the TNM system, which included T for tumor (tumor size), N for node (presence of metastasis), and M for metastasis. This system was further refined in 1988 by the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC), and is still in use today.
One of the problems not addressed by any of the commonly used variations of the Dukes’ system is its inability to classify patients further based on the extent of their lymph node involvement. After the initial revision by Gabriel and Dukes in 1935 in which the location of the affected lymph nodes was considered, the issue was left unaddressed. The ideal number of lymph nodes that should be evaluated before the specimen can be considered negative for lymph node involvement remains controversial. It is well-known that up to 70% of affected lymph nodes in colorectal cancer are less than 5 mm in diameter, making them easy to overlook. In 1994, Hernanz et al. analyzed 193 specimens and suggested that at least six nodes had to be identified before the specimen could be called negative. Wong et al. recently readdressed the same question and, after analyzing 196 cases, concluded that at least 14 nodes should be evaluated in each specimen. The advent of improved pathologic techniques and sensitive methods such as PCR may have an impact on the number of positive lymph nodes detected. However, the prognostic value of these positive lymph nodes, which otherwise would not be detected, is still undetermined.

The National Surgical Adjuvant Breast and Bowel Program (NSABP) carried out an analysis of the prognostic variables in 844 patients with Dukes’ stage C lesions. The level of positive nodes provided little information over and above that provided by the two most important prognostic factors, depth of tumor penetration and the number of positive nodes. The subset of patients with one to four positive nodes fared remarkably better than did patients with larger numbers of involved nodes, and the number of positive nodes appeared to be the single most important prognostic factor. The newer classifications of colorectal cancer have incorporated the number of involved lymph nodes as an important prognostic factor.

The size of the primary tumor in colorectal cancer, contrary to most solid tumors, does not seem to influence prognosis. A review of 391 patients treated surgically at the University of Texas M. D. Anderson Cancer Center from 1965 to 1975 demonstrated that the mean diameter of Dukes’ stage B2 tumors was actually greater than the mean diameter of stage C2 tumors (P<.001) and D tumors (P<.05). The size of the primary tumor showed no relationship to 5-year adjusted survival. These results were confirmed by the NSABP experience.

Even though the modified Dukes’ staging still is commonly used worldwide, the number of applied variations makes correlation of different studies less than ideal. Therefore, use of the TNM staging has been encouraged. This system is compatible with and is gradually replacing the Dukes’ system.

**THE JASS SYSTEM**

The traditional Dukes system was primarily anatomic; the influence of the tumor grade and other pathologic features remained largely ignored. After analyzing 447 patients treated surgically for rectal cancer, Jass et al. (1986) were able to assess a number of histopathologic factors using the Cox regression model. The important variables included lymphocytic infiltration, tubule configuration, and pattern of growth. Subsequently, the authors compared the grade-related parameters with the established stage-related parameters. The best prognostic model included the number of affected lymph nodes, the presence of lymphocytic infiltration, and extent of spread through the bowel wall. The model was tested on a second data set comprising 331 patients, and similar results were derived. The authors concluded that their classification was simple to use and was superior to staging by the method of Dukes. The NSABP compared the Jass classification with the traditional Dukes system and validated its results. However, the criteria used in the Jass prognostic system for colorectal cancer have been found to be less than optimal in routine practice and are not readily reproducible.

Others have also questioned the superiority of the Jass system over the conventional Dukes’ system. In a retrospective study of 312 colorectal carcinomas, Deans et al. found the Dukes classification to be of greater prognostic value and more reproducible than the components of Jass’s classification. The simplicity and reproducibility of the new TNM staging system has discouraged further use of the Jass system by the major clinical groups.

**TUMOR, NODE, METASTASIS (TNM) CLASSIFICATION**

Despite its initial shortcomings, the TNM classification is the preferred system for colorectal cancer patients (Table 33.7-5). Starting in the late 1970s, both the American Joint Committee on Cancer (AJCC) and the Union Internationale Contre le Cancer (UICC) made attempts to unify the staging system for colorectal cancer with a simple classification similar to the TNM system used for most solid tumors. However, the initial TNM classifications were complicated and failed to provide adequate prognostic information for the different stages. The survival for patients with stage II disease was the same as or worse than that for patients with stage III cancer. Even though the modified Dukes’ staging still is commonly used worldwide, the number of applied variations makes correlation of different studies less than ideal. Therefore, use of the TNM staging has been encouraged. This system is compatible with and is gradually replacing the Dukes’ system.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Tumor (T)</th>
<th>Lymph Node (N)</th>
<th>Metastasis (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>T&lt;2</td>
<td>N&lt;2</td>
<td>M&lt;1</td>
</tr>
<tr>
<td>I</td>
<td>T2-4</td>
<td>N0</td>
<td>M&lt;1</td>
</tr>
<tr>
<td>II</td>
<td>T3-4</td>
<td>N0-1</td>
<td>M&lt;1</td>
</tr>
<tr>
<td>III</td>
<td>T4</td>
<td>N2-3</td>
<td>M&lt;1</td>
</tr>
<tr>
<td>IV</td>
<td>Any T</td>
<td>Any N</td>
<td>Any M</td>
</tr>
</tbody>
</table>

**TABLE 33.7-5. Tumor, Node, Metastasis Stage Grouping**

Eventually, the AJCC and the UICC unified their TNM systems, creating a simpler system with greater prognostic value. The 1988 and 1994 revised systems included the number of affected lymph nodes as an important variable, and the newest system was found to have greater prognostic accuracy. The rules for classification of colorectal cancer are relatively simple. Colorectal cancers are commonly staged after surgical exploration and pathologic evaluation of the resected specimen. Tumors invading the stalk of polyps are classified according to the same definitions adopted for colorectal cancers. Carcinoma in situ (CIS) includes cancers confined to the glandular basement membrane or lamina propria. T1 tumors invade the submucosa, T2 tumors invade the muscularis propria, and T3 tumors invade through the muscularis propria into the subserosa or into nonperitonealized pericolic or perirectal tissue. T4 tumors invade other organs or structures or perforate the visceral peritoneum. Tumors invading other colorectal segments by way of the serosa (i.e., carcinoma of the cecum invading the sigmoid) are classified as T4. Recurrent tumors at the site of surgery are assigned to the proximal segment of the anastomosis.

The new TNM classification calls for at least 12 lymph nodes to be analyzed. N0 denotes that all nodes are negative. N1 includes tumors with metastasis in one to three regional lymph nodes. N2 indicates metastasis in four or more regional lymph nodes. Metastatic nodules or foci found in the pericolic, perirectal, or adjacent mesentery without evidence of residual lymph node tissue are equivalent to regional node metastasis. Involvement of the external iliac or common iliac lymph nodes is classified as metastatic disease (M1). The concept of distant metastasis is virtually self-explanatory.

The TNM system also classifies a tumor based on its histologic grade, including four levels from well-differentiated to undifferentiated, and should not be used for sarcomas, lymphomas, and carcinoids arising in the colorectum. Additional independent prognostic factors worthy of attention include the histologic type, carcinoembryonic antigen (CEA) level, and vascular invasion. The authors strongly recommend that the TNM staging system be used routinely (Table 33.7-6).
Cancers characterized by erosion are believed to manifest earlier than those characterized by invasion. Therefore, tumors.

Carcinoma of the colon that is complicated by obstruction or perforation has been recognized as having a poorer prognosis. Bowel perforation was a poor prognostic factor only for disease-free survival.

A review of the Massachusetts General Hospital records compared patients presenting with obstruction or perforation with a control group undergoing curative resection. The actuarial 5-year survival rate seen in patients presenting with obstruction was 31%, in contrast to 59% in control patients. For patients with localized bowel obstruction strongly influenced the prognostic outcome. The effect of bowel obstruction was more pronounced when the obstruction was located in the right colon. The larger-sized tumor needed to block the ascending colon completely might allow a longer time for these tumors to grow and spread when compared with tumors located in the descending colon. The available data support the notion that patients in whom colorectal cancer is diagnosed prior to the expected rapid growth of this segment of society.

Although the risk of colon cancer is similar in men and women, women frequently have the perception that colorectal cancer is a male disease and so they underestimate their true risk. Parity appears to exert its predominant effect on risk of cancer of the right colon. The use of oral contraceptives has also been linked to a decrease in risk of colon and rectal cancer. However, some investigators have recently questioned the true effect of reproductive events or oral contraceptives. Interestingly, partly could have no effect on the absolute risk of colorectal cancer but appears to have led to a decrease in proximal and an increase in distal colon cancer. Increasingly, the use of estrogen replacement therapy in postmenopausal women has been linked with a decrease in risk of subsequent colorectal cancer. The confirmation of this finding would have far-reaching implications in public health.

The duration of symptoms has not been conclusively proven as a prognostic factor. Contrary to what could be expected, several large studies have failed to demonstrate a direct relation between the duration of symptoms prior to diagnosis and pathologic stage at the time of surgery for colorectal cancer. Patients in whom disease is diagnosed and treated prior to the development of any symptoms do tend to have early-stage colorectal cancer and improved survival. However, patients with a short symptomatic history of colon cancer do not have a better prognosis than patients with a long history. Cancers detected by routine screening are less likely to have spread to lymph nodes or adjacent organs and, consequently, are less likely to be symptomatic. Beachs and Sanfelippo (1971) reported that the 5-year survival for symptomatic colorectal cancer patients was 48%, as compared with 71% for asymptomatic patients, confirming that patients who present with symptoms from their tumors are more likely to have advanced disease and less likely to have a favorable outcome.

The prognosis for elderly patients with colorectal cancer is less well studied. Patients older than 80 years submitted for curative surgery have similar operative mortality when compared with patients in their fifties to seventies. Patients with cancer in 17 countries in Europe on whom colorectal cancer was diagnosed between 1978 and 1989 showed a possible decreased survival rate with increasing age.

Additional data on the prognosis for very elderly patients affected by colorectal cancer is greatly needed in view of the expected rapid growth of this segment of society.

AGE. Although colorectal cancer is a disease that occurs predominantly in older adults, it also affects a significant number of younger patients. Starting with the 1958 article by Hoerner, several investigators have reported more aggressive tumor behavior and a worse overall survival rate for patients with colorectal cancer whose disease was diagnosed before the patient had reached the age of 40. Several explanations for this finding have been explored, including the notion that younger patients are more prone to delayed diagnoses. They seem to have a higher frequency of high-grade tumors, and their disease is more commonly diagnosed at an advanced stage. Recio and Bussey (1965) noted an increased percentage of mucinous tumors in younger patients. In their study, high-grade tumors accounted for 53% of all tumors in the young group and only 20% in the older group. The most common histologic pattern in young patients is an aggressive, mucin-producing adenocarcinoma, particularly in patients younger than 20 years old. When comparing patients with colorectal cancer who were younger than 40 years with older patients, Behbehani et al. (1985) found both a higher incidence of poorly differentiated tumors (21% vs. 9%, respectively) and a more advanced stage at presentation in the young patients. The survival rate for young patients was 23% versus 61%, respectively, for the general population. Stage III patients had a survival rate of 56% in the general population, as compared with 34% in young adults. Data compiled by the Commission on Cancer Data from the National Cancer Database from hospital cancer registries across the United States showed that the very elderly tended to present with an earlier stage of disease than younger patients. Others have supported the notion that young patients tend to present with more advanced disease, reflecting a more aggressive tumor or a delay in diagnosis; however, most analyses have failed to show a significant difference in prognosis when stage-adjusted survival is analyzed.

The prognosis for elderly patients with colorectal cancer is less well studied. Patients older than 80 years submitted for curative surgery have similar operative mortality when compared with patients in their fifties to seventies. Patients with cancer in 17 countries in Europe on whom colorectal cancer was diagnosed between 1978 and 1989 showed a possible decreased survival rate with increasing age. Additional data on the prognosis for very elderly patients affected by colorectal cancer is greatly needed in view of the expected rapid growth of this segment of society.

GENDER. Several older analyses have shown a survival advantage for women (as compared to men) with colorectal cancer. Among known associations with reduced colorectal cancer risk, women appear to ingest more dietary fiber, to benefit more from physical activity and body mass, and to consume less alcohol. Hormonal characteristics may also affect a woman’s risk of developing colorectal cancer. However, others have failed to demonstrate a significant difference in prognosis based on gender alone.

An inverse association has been detected between the number of pregnancies and the risk of colon cancer. Parity appears to exert its predominant effect on risk of cancer of the right colon. The use of oral contraceptives has also been linked to a lower risk of colon and rectal cancer. However, some investigators have recently questioned the true effect of reproductive events or oral contraceptives. Interestingly, partly could have no effect on the absolute risk of colorectal cancer but appears to have led to a decrease in proximal and an increase in distal colon cancer. Increasingly, the use of estrogen replacement therapy in postmenopausal women has been linked with a decrease in risk of subsequent colorectal cancer. The confirmation of this finding would have far-reaching implications in public health.

Although the risk of colon cancer is similar in men and women, women frequently have the perception that colorectal cancer is a male disease and so they underestimate their true risk. Partially in consequence, women are less likely than men to undergo screening studies. This represents a true public health problem.

SYMPTOMS. As the natural history of colorectal cancer becomes better understood, we are compelled to believe that the length of time required for the development and growth of colorectal cancer allows a window of opportunity for early detection and an increase in cures for colorectal cancer. Indeed, screening efforts have been proven to reduce mortality from colorectal cancer. Cancers detected by routine screening are less likely to have spread to lymph nodes or adjacent organs and, consequently, are less likely to be symptomatic. Beahrs and Sanfelippo (1971) reported that the 5-year survival for symptomatic colorectal cancer patients was 48%, as compared with 71% for asymptomatic patients, confirming that patients who present with symptoms from their tumors are more likely to have advanced disease and less likely to have a favorable outcome.

OBSTRUCTION AND PERFORATION. Carcinoma of the colon that is complicated by obstruction or perforation has been recognized as having a poorer prognosis. Patients with colorectal cancer were entered into randomized clinical trials of the NSABP showed that the presence of bowel obstruction strongly influenced the prognostic outcome. The effect of bowel obstruction was more pronounced when the obstruction was located in the right colon. The larger-sized tumor needed to block the ascending colon completely might allow a longer time for these tumors to grow and spread when compared with tumors located in the descending colon.

A review of the Massachusetts General Hospital records compared patients presenting with obstruction or perforation with a control group undergoing curative resection. The actuarial 5-year survival rate seen in patients presenting with obstruction was 31%, in contrast to 59% in control patients. For patients with localized perforation, the 5-year actuarial survival rate was 44%.

According to a study involving 709 patients who underwent resection for colorectal carcinoma, stage was the strongest prognostic variable. However, obstruction had an independent effect in the same multivariate analysis. The Gastrointestinal Tumor Study Group (GITSG) multivariate analysis concluded that obstruction was an important indicator of prognosis, independent of Duke’s stage. Bowel perforation was a poor prognostic factor only for disease-free survival.

HEMORRHAGE OR RECTAL BLEEDING. Cancers characterized by erosion are believed to manifest earlier than those characterized by invasion. Therefore, tumors presenting with bleeding are thought to be found earlier and to be associated with a better prognosis. This belief has not been confirmed in other studies. In the GITSG multivariate analysis, the presence of melena or rectal bleeding showed a trend as a prognostic factor for prolonged survival but failed to reach statistical significance (P = .08). Chapuis et al. (1985) demonstrated by univariate analysis in a large study conducted in Australia that the presence of rectal bleeding predicted
longer survival; however, the significance of this symptom disappeared on multivariate analysis.

**PRIMARY TUMOR LOCATION.** Multiple analyses have shown that cancers arising at or below the peritoneal reflection (rectosigmoid and rectum) have a worse 5-year survival rate than those arising above the reflection. With regard to colon primary tumors, different authors have reached different conclusions. Some, including Wolmark et al. (1967, 1983) in a large retrospective review of data from the NSABP, reported that lesions in the right side carry a worse prognosis. Poorer prognosis for patients with disease in the left colon has been reported. Several investigators report no difference based on the location of the primary tumor. The large GITSG colon cancer experience showed that tumor location (left, right, and rectosigmoid or sigmoid) was of low prognostic value.

**PRIMARY TUMOR SIZE.** In contrast to most solid tumors, the size of the primary tumor is not considered in the staging of colorectal cancer, reflecting the unusual nature of these cancers. Even though some authors have shown improved survival with smaller tumors, most studies have failed to demonstrate a significant prognostic value for the size of the primary tumor at the time of diagnosis. Data collected by the NSABP also underscore the lack of a relation between tumor size and lymph node metastasis. Indeed, an M. D. Anderson Cancer Center review demonstrated that patients with Dukes B2 tumors frequently had larger primary lesions than did patients with Dukes stage C and D tumors.

**PRIMARY TUMOR CONFIGURATION.** When compared with ulcerating tumors, exophytic tumors tend to penetrate the bowel wall less frequently (24% vs. 39%, respectively) and have less frequent nodal metastases and fewer hematogenous metastases (23% vs. 31%, respectively). Analysis of a GITSG colon adjuvant study revealed that the presence of an exophytic lesion had a beneficial effect on survival when compared with ulcerating lesions.

**BLOOD TRANSFUSION.** Considerable controversy has surrounded the association of perioperative blood transfusions and the recurrence rate of colorectal cancer. Some investigators have reported worse disease-free survival in patients who require transfusions. The reason for this outcome would be a transfusion-related form of immunosuppression. However, when differences in confounding background variables are accounted for, the significance of transfusion seems less evident, and several authors believe it to have no direct relation to prognosis. By multivariate analysis in a prospective study, no negative influence of transfusion on survival could be detected.

A retrospective analysis evaluating 1051 patients treated with curative surgery for stage II or III colorectal adenocarcinoma at the Mayo Clinic demonstrated that the use of blood components probably had no impact on disease recurrence, and the documented adverse impact of transfusions is more likely due to other variables or to the underlying illness necessitating the transfusion. This was confirmed in a study in which patients were randomized to receive, when needed, perioperative transfusions with either autologous or allogeneic blood. There were no differences in disease-free survival between the two groups. Disease-free and cause-specific survivals were increased in the group that did not receive any transfusions, as opposed to those who received the transfusions, suggesting that the conditions that necessitate transfusion may be more important than the transfusion itself.

**Pathologic Features**

**VASCULAR ENDOTHELIAL GROWTH FACTOR.** VEGF is an important factor in the angiogenic process. Several studies have demonstrated a correlation between the expression of VEGF and vessel count in the tumor specimen, and a combination of vessel count and expression of VEGF may be useful for predicting distant recurrence in patients with node-negative colon cancer. VEGF is being evaluated as a possible prognostic marker and also is currently an important new target for novel therapeutic agents in the treatment of cancer.

**LYMPH NODE MICROMETASTASIS.** Lymph node status has long been recognized as one of the best prognostic markers in patients with colorectal cancer. To minimize false-negative results, a minimum number of lymph nodes should be evaluated, though there is no clear consensus on the ideal number. The TNM classification calls for at least 12 nodes to be examined, whereas a recent review suggested that 14 nodes may be a better target. New techniques directed at increasing the number of lymph nodes available for analysis are being developed, including new staining procedures and sentinel lymph node mapping. Unfortunately, despite all efforts, a significant number of patients with grossly negative lymph nodes eventually experience disease recurrence, and many of those patients who experience recurrence are believed to have had microscopic involvement of their lymph nodes.

Determining the actual lymph node status of patients who received potentially curative surgery would be a valuable tool in the treatment of colorectal cancer. This is especially true for those patients with stage II disease in whom the need for adjuvant therapy remains an intensely debated topic. Several different techniques are being explored, including immunohistochemistry, radioimmunologically guided surgery, and histochemical detection of micrometastatic deposits in bone marrow aspirates. An area of intensive research is the use of reverse transcriptase–PCR (RT-PCR) targeting different primers in blood, bone marrow, and lymph nodes. Primers used thus far with varying degrees of success have included matrilysin (matrix metalloproteinase 7), cytokeratin, and galectin cyclic C. Additionally, some reports have focused on the expression of vascular endothelial growth factor (VEGF) in malignant cells and VEGF isoforms in tumor vessels. VEGF is being evaluated as a possible prognostic marker and is currently an important new target for novel therapeutic agents in the treatment of cancer.

**RADIAL (LATERAL) MARGINS.** Whether the proximal and distal margins are involved in colorectal cancer has traditionally been emphasized in pathologic reports. However, the fact that penetration of the primary tumor carries significant prognostic value should be carefully considered. Quietre et al. reported an 85% incidence of metastasis in patients with colorectal cancer with radial margins versus only 3% in patients with completely negative margins. Some reports have focused on the importance of positive lateral margins in patients with negative proximal and distal margins. A recent review of 325 patients who underwent curative surgery for rectal cancer demonstrated 29% local recurrence for patients with positive radial margins versus 8% local recurrence for those with negative radial margins.</p>
In contrast to blood vessel invasion, the presence of lymphatic vessel involvement has been almost uniformly reported as a poor prognosticator for survival. In a series of 352 patients with colorectal cancer, Secco et al. identified 39 cases (11%). The same incidence had been reported previously. Mucinous carcinomas seem to have a predilection for the rectum and the sigmoid colon. Several series have indicated that the prognosis for mucinous carcinoma is intermediate between that for signet-ring carcinoma and the prognosis for regular adenocarcinoma. Some authors have argued that the worse outcome for these patients is due to the more advanced stage at presentation.

Recent reports showing a reduced incidence of the K-ras mutation in patients with signet-ring and poorly differentiated carcinomas in relation to ordinary colorectal carcinoma suggest that these types of carcinomas may have a different genetic background than well- or moderately differentiated colorectal carcinomas. Mucinous carcinomas seem to exhibit less apoptotic activity than does regular colorectal cancer (19% vs. 51%, respectively, \( P = .01 \)).

**CELL-CYCLE PARAMETERS AND PLOIDY.** Aneuploidy is an abnormal balance of chromosomes, and recent evidence seems to indicate that it may cause genetic instability, leading to the karyotypic and phenotypic heterogeneity commonly seen in cancer cells. Even though the results of DNA analysis of colorectal adenocarcinomas varies greatly depending on study methodology, aneuploidy is commonly observed in colorectal cancer cells, especially in advanced stages. In a series of 51 cases analyzed by Sacconetti et al., normal mucosa adjacent to aneuploid tumors showed only a 7% incidence of aneuploidy, whereas the mucosa adjacent to diploid cancers demonstrated only diploid characteristics.

Due to the controversies, there is enough evidence to suggest that a greater proportion of the higher-stage tumors are aneuploid and that aneuploid tumors tend to have a higher growth rate and poorer survival than diploid tumors. When various prognostic factors are analyzed, aneuploid tumors are associated with factors that are indicative of a poor prognosis. The prognostic value of the tumor's ploidy is especially important in stage II patients. In a small study by Nori et al. (1995), the DNA content of colon cancers in 20 stage II patients with evidence of disease relapse was measured and compared with 20 stage II patients in whom there was no evidence of relapse. Aneuploidy occurred in 80% (80%) with recurrence, as compared to only 8 patients (40%) in the control group. Aneuploidy was associated with significantly higher tumor recurrence rate (\( P = .024 \)) and a shorter overall survival (\( P = .002 \)). These results are consistent with an earlier North Central Cancer Treatment Group (NCCCTG) analysis of 694 patients with stage II or III colorectal cancer enrolled in some of their adjuvant trials. Patients with diploid tumors had a higher survival rate than did those with aneuploid tumors (\( P < .001 \)). The proliferation index (the sum of the percentage of cells in G1 phase plus those in G2/M phase) was also a strong prognostic factor (\( P = .001 \)). When the ploidy and proliferation data were combined, the patients in the favorable group had a 5-year survival rate of 74%, as compared with 54% for the unfavorable group (\( P < .001 \)). Despite some negative reports, the most series and multivariate analyses have confirmed that the DNA content is an important independent prognostic factor for survival in colorectal cancer.

**BLOOD VESSEL INVASION.** Vascular invasion can be divided into blood vessel and lymphatic invasion. Blood vessel invasion generally refers to venous invasion, as arterioles and venules are rarely involved. Involvement refers to the involvement of vessels located within the bowel wall, whereas extramural invasion refers to the involvement of vessels located outside the bowel wall. The incidence of blood vessel invasion in colorectal cancer varies from as low as 17% to as high as 81%, depending on the series reported and on whether special elastic tissue stains were used. The prognostic value of the presence of blood vessel invasion for overall survival remains controversial. Whereas some researchers have found it to be an independent prognostic factor, others have not been able to confirm this finding.

Minsky et al. (1988) have evaluated the prognostic value of blood vessel invasion independently in colon and in rectal cancers. Analysis of 294 patients who had curative surgery for colon cancer showed that blood vessel involvement resulted in a significant decrease in the 5-year actuarial survival rate. However, when examined by proportional hazards analysis, blood vessel invasion was not an independent prognostic variable. The same group retrospectively reviewed 168 patients who had curative surgery for rectal cancer. A significant decrease in 5-year actuarial survival was seen in patients with extramural blood vessel involvement as compared with patients who had tumors with intramural or no blood vessel involvement. When the intramural and extramural types of involvement were compared, no significant impact was noted on the patterns of failure or survival.

Krasna et al. and Inoue et al. have used elastic tissue stains and evaluated the prognostic value of blood vessel invasion independently from lymphatic vessel involvement. In the first series, metastases were seen in 60% of patients with vascular invasion as opposed to 17% of those with no vascular invasion (\( P = .0001 \)). Survival in these patients was 29.7% and 62.2%, respectively (\( P < .003 \)). In the second series, a higher incidence of vascular invasion was seen in patients who died of cancer within 2 years of surgery. These differences were not evident with the use of routine hematoxylin and eosin staining.

**LYMPHATIC VESSEL INVASION.** In contrast to blood vessel invasion, the presence of lymphatic vessel involvement has been almost uniformly reported as a poor prognosticator for survival. In a series of 204 patients with colorectal carcinomas, Minsky et al. reported 73% incidence of metastasis in patients with perineural invasion, as compared with 27% in those without such invasion (\( P < .01 \)). The 5-year survival rate also was statistically lower for the patients with lymphatic vessel invasion. Proportional hazards analysis confirmed that lymphatic vessel invasion is an independent prognostic factor for survival. Other authors have reached a similar conclusion in their own reviews, suggesting that the presence of lymphatic vessel invasion should be considered a useful prognostic factor for survival in colorectal cancer.

**PERINEURAL INVASION.** The ability of colorectal cancers to invade perineural spaces as far as 10 cm from the primary tumor was first reported in 1943 by Seefeld and Bargen. This was also the first work in which the presence of perineural invasion was demonstrated to be associated with increased disease recurrences and worse 5-year survival. This conclusion has been confirmed by others. Krasna et al. reported a 73% incidence of metastasis in patients with perineural invasion, as compared with 27% in those without such invasion (\( P = .01 \)).

In patients with lymphatic vessel invasion, the incidence of positive lymph nodes was 59% as opposed to 25% for the control group (\( P = .0004 \)). The 5-year survival rate also was statistically lower for the patients with lymphatic vessel invasion. Proportional hazards analysis confirmed that lymphatic vessel invasion is an independent prognostic factor for survival.

Other authors have reached a similar conclusion in their own reviews, suggesting that the presence of lymphatic vessel invasion should be considered a useful prognostic factor for survival in colorectal cancer.

**CARCINOMEOBRYONIC ANTIGEN.** Since it was first described in 1965, CEA has become the most reliable tumor marker for use in the detection of colorectal cancer. It is recommended as a monitoring tool for patients who have been treated with curative intent. Further, it is a poor prognostic factor for cancer recurrence in patients in whom perineural invasion has been demonstrated preoperatively and who failed to normalize after a potentially curative operation. The prognostic potential of the preoperative CEA level remains unclear, and even the value above which the CEA is considered significantly elevated has varied from as low as 2.5 ng/dL to as high as 10 ng/mL, depending on the series reported.

Since the 1970s, several authors have presented evidence indicating that CEA is an independent prognostic factor. In one of the largest reports, Harrison et al. reviewed 572 patients who underwent curative resection for node-negative colon cancer at the Memorial Sloan-Kettering Cancer Center. The preoperative CEA level and the stage of disease predicted survival by both univariate and multivariate analysis.

However, Chapman et al. reported that, although the 5-year survival rate for patients with an elevated CEA was 39% as compared with 57% for patients with a normal CEA level (\( P = .001 \)), the proportion of patients with an elevated CEA level increased with more advanced stage tumor and a poorly differentiated tumor grade. Once controls were in place for the variable of stage, CEA was not a predictor of survival. This study confirmed the work by other authors that failed to demonstrate a significant independent prognostic value for preoperative CEA level. An elevated CEA level may be a reflection of a more advanced colorectal carcinoma.

**IMMUNE RESPONSE TO THE PRIMARY TUMOR.** Careful pathologic evaluation of the primary tumor site has demonstrated that a significant number of tumors exhibit evidence of local infiltration and that this reaction is a positive prognostic factor. Jass et al. demonstrated that the presence of lymphocytic infiltration was a very important independent prognostic factor in colorectal cancer. This finding led to the development of the Jass staging system. By univariate analysis, the presence of lymphocytic infiltration has been demonstrated to have prognostic significance in colon cancer. Secco et al. have demonstrated that the presence of lymphocytic infiltration has been demonstrated to be of prognostic value for local failure in rectal cancer. NSABP protocol R-01 showed that survival was significantly decreased with increasing numbers of eosinophils and mast cells present at the tumor border. Recent work by Diederichsen et al. using flow cytometry to study the phenotype of tumor-infiltrating lymphocytes in 41 cases of colorectal cancer showed that expression of class II human leukocyte antigen (HLA) did not correlate with any lymphocyte surface markers. Because tumor-infiltrating lymphocytes are “turned off” rather than stimulated when tumor cells express HLA class II but not CD80, the lack of correlations...
DELETIONS IN COLORECTAL CANCER. Allelic deletions involving chromosome 18q occur in more than 70% of colorectal cancers. In colorectal cancer, the DCC gene was cloned from a region of chromosome 18q, and whereas the DCC gene was expressed in most normal tissues, including colonic mucosa, its expression was greatly reduced or absent in most colorectal carcinomas tested. The mechanism of action of DCC is unknown. It may function as a tumor suppressor gene by inducing apoptosis.\(^\text{[32]}\) Experimentally, DCC induces apoptosis in the absence of ligand binding and blocks apoptosis when engaged by netrin-1. It is a caspase substrate, and mutation of the site at which caspase 3 cleaves DCC suppresses the proapoptotic effect of DCC completely.\(^\text{[33]}\)

In a series of 118 patients who had undergone curative surgery for stage II or III colon cancer, those patients whose tumor exhibited no evidence of chromosome 18q allelic loss showed a better disease-free and overall survival than did those whose tumor demonstrated 18q allelic loss. When patients were stratified by tumor stage, a significant survival advantage for patients whose tumor had no allelic loss on chromosome 18q was observed in stage II and in stage III disease. In particular, patients with stage II disease whose tumor had no chromosome 18q allelic loss demonstrated an excellent clinical outcome, with a 5-year disease-free survival rate of 98%. In contrast, the 5-year disease-free survival rate of patients with stage II disease and chromosome 18q allelic loss was only 54%. In a multivariate analysis, the status of chromosome 18q was a significant independent prognostic factor for both disease-free and overall survival.\(^\text{[34]}\) Several investigators have shown that not only deletion of and lowered messenger RNA expression of the DCC gene but also marked reduction of DCC protein occurred in colon cancer tissues.\(^\text{[35]}\) In addition, colon cancer patients with liver metastases expressed significantly lower levels of DCC as compared to patients without such metastases.

Additional Tumor Biologic Features

ONCOGENES AND MOLECULAR MARKERS. Oncogenes and molecular markers are discussed extensively in Chapter 33.1. However, the study of molecular markers has extremely advanced our understanding of the development and treatment of colorectal cancer. Molecular markers have the potential to revolutionize the way such cancers are treated. Some of the areas of intensive research currently are thymidylate synthase,\(^\text{[36]}\) dihydropyrimidine dehydrogenase (DPD),\(^\text{[37]}\) and the presence of microsatellite instability.\(^\text{[38]}\)

\(\text{p53} \) gene

The \(\text{p53} \) gene located on chromosome 17p is a well-known tumor suppressor gene. Attallah et al.\(^\text{[39]}\) reported no significant difference in \(\text{p53} \) overexpression between patients with stage II and stage III colorectal cancer; however, flow cytometric analysis revealed a slightly higher incidence of DNA aneuploidy in 75% of \(\text{p53} \)-positive cases as compared with 64.3% \(\text{p53} \) positivity in diploid tumors.

The abnormal \(\text{p53} \) appears to be a late phenomenon in colorectal carcinogenesis. This mutation may allow the growing tumor with multiple genetic alterations to evade cell-cycle arrest and apoptosis.\(^\text{[40]}\) In a retrospective review of 141 patients with resected stage II and stage III colon carcinoma, the presence of a \(\text{p53} \) mutation was the single most important risk factor associated with poorer survival in patients with either stage of disease (stage II, \(P = .02 \)); stage III, \(P = .006 \)).\(^\text{[41]}\) A \(\text{p53} \) mutation increased the risk of death by 2.82 times in patients with stage II disease and by 2.39 times in patients with stage III colon carcinoma.\(^\text{[42]}\)

The Southwest Oncology Group (SWOG) assessed the prognostic value of \(\text{p53} \) in 66 stage II and 163 stage III colon cancer patients in adjuvant intergroup trial 0035.\(^\text{[43]}\) \(\text{p53} \) expression was found in 63% of cancers and was associated with favorable survival in stage III but not stage II disease. Seven-year survival with stage III disease was 56% with \(\text{p53} \) expression versus 43% with no \(\text{p53} \) expression (\(P = .012 \)).\(^\text{[44]}\) The true independent prognostic value of \(\text{p53} \) remains to be defined.

IMMUNOLOGY AND MARKERS. The most frequently used marker tumor in colorectal cancer continues to be CEA, though several other markers have been evaluated in this disease. For example, many investigators have demonstrated that the blood group antigens ABH and Lewis, which are normally expressed only in the proximal colon, can be reexpressed in distal colon cancers. Also, an antigen that is incompatible with the individual's blood type can be expressed.\(^\text{[45]}\) Similar alterations occur in adenomatous polyps, but with reduced frequency. ABH antigens are not commonly expressed in hyperplastic polyps but are seen in neoplastic polyps.\(^\text{[46]}\)

CA 19-9 is a carbohydrate cell surface antigen, a sialylated lacto-N-fucopentose related to the Lewis blood group substance. CA 19-9 does not appear to be as sensitive as CEA but does have some value as a prognostic factor, especially if combined with CEA.\(^\text{[47]}\) However, currently available data do not justify the routine use of CA 19-9 in colorectal cancer outside of an investigational trial. Several other antigens have been defined with the use of monoclonal antibodies, but their use remains restricted and has not been adopted in clinical practice because these antibodies seem to add little to the currently available markers.

ADDITIONAL FACTORS. A comprehensive review of every prognostic factor studied in colorectal cancer is beyond the scope of this chapter. Extensive review of such factors as the amount of collagen type IV present in the tumor matrix,\(^\text{[48]}\) the presence of reactive lymph nodes, and the morphometric measurements of the tumor cell (nuclear morphology) have yielded conflicting results.\(^\text{[49]}\) Other factors as proliferating cell nuclear antigen expression,\(^\text{[50]}\) sucrase isomaltase,\(^\text{[51]}\) helix pomatia agglutinin,\(^\text{[52]}\) microacinar growth pattern,\(^\text{[53]}\) autocrine motility factor,\(^\text{[54]}\) ornithine decarboxylase,\(^\text{[55]}\) fibroactin, and tumor-associated glycoprotein DF3 have shown some prognostic value, but the true value of many of these factors continues to be explored in colorectal cancer.

TREATMENT OF PRECANCEROUS CONDITIONS

NEOPLASTIC POLYPS (ADENOMAS)

Adenomas are the most common neoplasms in the large bowel. They are classified into three types—tubular, tubulovillous, and villous—according to their histologic appearance. Tubular adenomas account for 75% of polyps found, tubulovillous adenomas account for 15% of all neoplastic polyps, and villous adenomas account for 10%. The malignancy rate of tubular adenomas is 5%, but it rises to 40% in villous adenomas. The malignancy rate for tubulovillous adenomas is 22%, suggesting that these tumors behave more like villous than like tubular adenomas. The entire colon must be examined if a histologically proven adenoma has been removed from the colon or is found on endoscopic biopsy.\(^\text{[56]}\) Endoscopic removal of polyps should be performed to confirm the diagnosis of a benign or malignant polyo. Polyps with a stalk can be removed by endoscopic snare polypectomy. Sessile lesions can be removed in a piecemeal fashion; however, there is an increased risk of complications, and judgment must be used to assess this risk and the practicality of attempting piecemeal removal of tumors, especially in the relatively thin-walled abdominal colon.

The National Polyp Study demonstrated a synchronous polyp detection rate of 29% to 35% at colonoscopic follow-up for patients in whom an adenomatous polyp has been demonstrated.\(^\text{[57]}\) This detection rate depends on the number of interventions and the time intervals from the last colonoscopy. Approximately 15% of patients will have evidence of small adenomas after the colon is considered cleared of polyps at colonoscopy.

Further management and timing of surveillance depends on the characteristics of the adenomas removed initially, as well as on their number and the clinical status of the patient. Follow-up of adenomas containing in situ carcinoma or severe dysplasia that have been completely removed is the same as that for benign adenomas: routine follow-up colonoscopy at 3-year intervals once the colon is cleared.\(^\text{[58]}\) Individuals in whom the colon is not cleared of all polyps will require an earlier examination. In addition, patients having multiple adenomas are at a higher risk for oversight of synchronous adenomas and, therefore, these patients should be examined at 1 year. A large sessile adenoma that cannot be removed endoscopically will often require surgery.

Large villous adenomas (i.e., >2 cm in diameter) have a malignant potential that is significantly greater than that for other adenomatous polyps. Even small villous adenomas have a greater malignant potential than do adenomatous polyps of the same size. They are sessile, in most cases, and grossly appear velvety owing to frond-like glands. Villous adenomas require complete excision for histologic examination. Random biopsies of villous adenomas are unreliable and only contribute to difficulties in management. If such adenomas can be palpated in the rectum, they are more likely to be benign if they are soft. However, excision is still required.

Surgical resection should be performed. This is due to the high risk of recurrence, complications from endoscopic polypectomy, and presence of invasive cancer. When located in the rectum, such lesions can often be treated by local excision. Submucosal techniques of transanal excision or the Kraseke approach, which are used for large lesions that otherwise cannot be approached by transanal excision, are appropriate in the complete excision of rectal villous adenomas.\(^\text{[59]}\)

Circumferential villous adenomas of the lower rectum can be removed in three to four longitudinal strips and have subsequent mucosal advancement. Alternatively, low anterior resection or proctectomy with colonic Anastomosis can be used to manage large circumferential villous adenomas of the lower rectum. Laser ablation of the lesion has the disadvantage of destroying tissue before pathologic examination is carried out. Nonetheless, this may be reasonable when an operative approach is prohibited.
MANAGEMENT OF FAMILIAL ADENOMATOUS POLYPOSIS

Because the risk of development of colorectal carcinoma in patients with FAP is virtually 100% when the colon and rectum are left intact, resection is the only therapeutic intervention known to alter the natural history of this disease. \[22\] Owing to the high rate of development of carcinomas before the age of 40, this surgical intervention usually is performed relatively early in life (15 to 20 years of age). Surgery should not be delayed once the diagnosis is established. \[22\] Surgical procedures in these patients range from total abdominal colectomy and ileorectal anastomosis to total proctocolectomy with ileoanostoma. \[22\] Total proctocolectomy and end ileostomy are rarely used for these patients except in the presence of a failed ileoanal reservoir, in patients older than 50 years, in the face of poor medical condition, or in patients with poor sphincter tone. An alternative to end ileostomy in these patients may be the use of a Kock pouch to act as a continent ileostomy.

Removal of the entire abdominal colon with a small bowel anastomosis performed to the upper rectum is the procedure selected for many patients with polyposis. It carries a relatively low mortality rate and low morbidity rate. \[22\] Advantages to this procedure include the avoidance of a stoma, relatively normal bowel habits, and avoidance of bladder and sexual dysfunction. \[22\] Selection of this procedure requires that the surgeon be able to remove or fulgurate any rectal polyps and necessitates continued endoscopic surveillance of the rectum. Risk of subsequent carcinoma in the rectal stump increases with age, the presence of malignancy in the original colectomy specimen, the length of the rectal stump, and the number of rectal polyps present preoperatively (Fig. 33.7-4). \[22\] Patients with a rectal stump greater than 10-15 cm long appear to be at greater risk of rectal cancer. \[22\] In a review of 11 member registries from the leads Castle Polyposis Group, the cumulative incidence of rectal carcinoma was found to be 13% at 25 years.

Total proctocolectomy with ileoanostoma is commonly used in patients who are unable to accept the risk of subsequent rectal carcinoma, those with extensive rectal polyps, or those who develop large numbers of rectal polyps after ileorectal anastomosis. The advantages of this procedure are virtual elimination of rectal cancer risk and avoidance of a permanent stoma. Total proctocolectomy with ileoanal anastomosis does carry a higher complication rate than does abdominal colectomy. Mortality rates vary from 10% to 24. \[22\] Stool frequency varies from three to six bowel movements per day, with occasional nocturnal stooling; however, quality of life is similar to that of patients with ileorectal anastomosis. \[22\] Continent and bowel habits improve with time, and most patients are free of antidiarrheal agents by 1 year after surgery. Satisfaction for patients undergoing total proctocolectomy and ileoanostoma can be quite high. This operation can be performed in selected patients with FAP and coexistent cancer without compromising oncologic or functional outcomes. \[22\] It also can be performed after a previous ileorectal anastomosis.

Vasen et al. \[1996\] and Wu et al. \[2010\] have described a correlation between specific sites of mutations within the APC gene and the subsequent development of rectal carcinoma after ileorectal anastomosis. Vasen's group noted that the risk of secondary surgery for cancer or polyps is higher in patients with a mutation after codon 1250 (RR, 2.7; P < 0.05). Wu's group \[2010\] reported that APC gene mutations at codons 1309 and 1328 were associated with severe polyposis and should be treated with total proctocolectomy. The utility of this technique in selecting patients for the appropriate surgical procedure requires further investigation. \[22\] A thorough discussion between patient and physician, taking into account the patient's medical characteristics, history, and wishes, will help in the decision making about management techniques for FAP. \[22\] Referral to an established registry will lower the stage of disease at which cancer is diagnosed in relatives of the proband and thereby will improve survival.

Colorectal carcinoma is but one component of the overall syndrome of FAP. Additional tumors of the GI tract (e.g., perianampullary cancer) as well as thyroid, brain, or hepatic tumors can complicate this disease. \[22\] A difficult problem that occurs in approximately 3.5% to 38.0% of patients with FAP is desmoid tumor. Specific mutations can be associated with desmoid disease. \[22\] These tumors frequently occur in the mesentry of the small bowel and extend into the retroperitoneum. Mesenteric desmoid tumors often are unresectable because of involvement of the superior mesenteric vessels. Even if resected, there is a very high recurrence rate and a very high surgical morbidity rate. \[22\] Because of the poor results of surgical resection of mesenteric desmoid tumors, a variety of medical treatments, as well as radiation therapy, have been described. \[22\] In an FAP patient who has been protected from colorectal cancer by surgery, upper GI tract tumors and desmoids become more frequent causes of mortality. \[22\]

ULCERATIVE COLITIS

The process of screening and selection of patients for surgery based on biopsy-proven, high-grade dysplasia of the colon in patients with ulcerative colitis was presented earlier, in Screening. As described, patients can be observed, with surgery performed only for those with high cancer risk or invasive carcinoma. This discussion of the indications for surgery related to the risk of colorectal cancer is not relevant to the indications for surgery related to complications of inflammatory bowel disease itself.

Commonly, the timing of colectomy is related to findings of dysplasia on random biopsy of the colon. Some studies have emphasized the development of cancer in patients with ulcerative colitis in whom dysplastic changes were seen in the colon on biopsy. Such findings have generated screening strategies based on the presence of dysplasia. \[22\] The disadvantages to this approach are the need for life-long screening even in the presence of quiescent disease and the requirement that experienced pathologists perform the evaluation for dysplasia. \[22\] The appeal of this technique is that it can provide indications for resection of the large bowel before the presence of a colorectal carcinoma becomes obvious by symptoms or gross appearance.

Duration of disease is another factor in timing surgery. Identifying neoplastic lesions at colonoscopy can be difficult because of the marked distortion of the mucosa and the flat appearance of many cancers associated with ulcerative colitis. The presence of a mass is an indication for surgery even in the absence of a biopsy specimen that exhibits dysplasia or cancer.

The options for a patient who has indications for surgery due to cancer risk in ulcerative colitis include total proctocolectomy with end ileostomy, total proctocolectomy with Kock pouch, total abdominal colectomy with ileorectal anastomosis, and total proctocolectomy with ileal anastomosis. \[22\] Each of these procedures has advantages and disadvantages that should be considered in light of each patient's individual circumstances. Total proctocolectomy with end ileostomy is most suitable for elderly patients, those with impaired sphincter function, and those in whom an ileoanal pouch is technically impossible or has failed. It is a single-stage procedure with a lower rate of complications than the alternative procedures. Total abdominal colectomy with ileorectal anastomosis is a relatively simple procedure that avoids any of the risks of proctectomy and the need for ileostomy. However, it does appear to carry the risks of recurrence of symptoms in the retained rectum as well as a small risk of carcinoma in the retained rectal segment. It should not be used in patients with preexisting large bowel cancer or rectal dysplasia, because of an approximately 70% risk of subsequent development of rectal carcinoma or dysplasia. Close endoscopic follow-up is required for any patient with a retained rectum who undergoes ileorectal anastomosis for chronic ulcerative colitis. Rectal cancer risk has been estimated to be 0% to 22%. \[22\]

In selected cases, restorative proctocolectomy can be performed for patients with cancer in the setting of ulcerative colitis. \[22\] Multicentricity is seen in 25% of such
patients. A complication with this procedure can be pouchitis, which occurs in 7% to 42% of patients. Pouch failure occurs in a small number of patients because of either technical difficulties at the time of surgery or pelvic sepsis. Problems of early age at onset of colorectal cancer, multiple neoplasms, and need for surveillance are similar to those encountered by patients with Crohn's disease.

HEREDITARY NONPOLYPOSIS COLON CANCER

The development of molecular genetic techniques to establish a presymptomatic diagnosis of HNPCC and the increasing clinical recognition of families with this syndrome have made the consideration of prophylactic colectomy realistic. Total abdominal colectomy appears to be appropriate, even though there is still a small but cumulative risk of rectal carcinoma development in patients with HNPCC who have undergone abdominal colectomy. Because the majority of such patients will be adequately treated by an abdominal colectomy, it could be considered as prophylactic management of their colorectal cancer risk. It is appropriate to perform total abdominal colectomy at the time of operation for colorectal cancer or endoscopically untreated colorectal polyps in patients with HNPCC, because of the high risk of synchronous and metachronous colorectal cancer.

Experience with this operation for FAP demonstrates that abdominal colectomy has low complication rates and good functional outcomes that are acceptable for such a prophylactic procedure. Some have recommended that patients with proven germline mutations be given the option of prophylactic abdominal colectomy. The Cancer Genetics Consortium, however, has not found adequate evidence to make a recommendation for prophylactic abdominal colectomy in patients with HNPCC.

MANAGEMENT OF POTENTIALLY CURABLE COLON CANCER

PRETREATMENT EVALUATION

After colorectal carcinoma has been diagnosed, the pretreatment assessment is conducted to determine the most appropriate form of treatment. Whereas surgical management is required for most patients with a diagnosis of colon carcinoma, the appropriateness of a surgical resection will be determined by the extent of disease and comorbidities. Even in cases of metastatic colorectal carcinoma, surgery may be required for palliation. Some authors have recently documented an ability to manage colon cancer patients nonoperatively in the presence of metastatic disease without significant complications from bleeding, perforation, or obstruction.

A well-conducted history and physical examination will provide a great deal of information about the patient's extent of disease and suitability for treatment. Specific aspects of the history taking should focus on a personal history of cancer or polyps and family history of colorectal cancer or polyps. Physical examination will reveal the patient's general suitability for anesthesia and extent of disease. Supraceliac adenopathy can indicate advanced disease. The abdominal examination can reveal distention due to ascites or obstruction. An abdominal mass may be palpated to reveal the location of the tumor. Extensive hepatomegaly will produce a mass or tenderness in the right upper quadrant. Rectal examination can reveal presence of a mass outside the rectum, caused by peritoneal metastases, and may detect synchronous lesions in patients with colon cancer.

Laboratory examinations should evaluate for the presence of anemia or hepatic dysfunction. Both of which can be consequences of the patient's underlying carcinoma or comorbid conditions. The CEA level will be most useful in terms of subsequent assessment for disease recurrence if the initial CEA is elevated.

Complete colonic examination will not only allow a biopsy of the index lesion but will also provide information about the exact location of the lesion. Additionally, it will provide information on the presence or absence of synchronous colon cancers, which are present in 1.5% to 7.6% of cases. In addition, significant synchronous polyps can occur in 25% to 40% of patients. The colon should be endoscopically cleared of these lesions. If polyps cannot be removed endoscopically, they should be included in the planned resection.

Chest radiography may reveal the presence of metastases or preexisting severe pulmonary disease that might contraindicate laparotomy. CT scanning is used to reveal clinically inapparent liver metastases or the extent of local spread of a colon carcinoma. Intraoperative ultrasonography is another useful technique that will be more sensitive in the detection of liver metastases.

SURGICAL MANAGEMENT OF CARCINOMA OF THE COLON

Radical resection with curative intent is appropriate for 80% to 90% of patients with colon carcinoma. The surgical principles of elective colonic resection include the appropriate use of outpatient bowel preparation to reduce the fecal and bacterial load of the colon. This, along with the use of parenteral antibiotics and appropriate anastomotic techniques, will reduce the risk of postoperative sepsis and morbidity. In patients with partially obstructing lesions, modification of the bowel preparation or the use of hydration along with the bowel preparation may be required preoperatively. It is important to use prophylaxis for deep venous thrombosis to reduce the subsequent risks of deep venous thrombosis and pulmonary embolism. Measures such as early ambulation and the use of intermittent compression devices and consideration of the use of low-dose heparin or low-molecular-weight heparin in the perioperative period reduce the incidence of venous thrombosis.

Surgical management must include the assessment of liver metastases. Although this is commonly accomplished by palpation and inspection, intraoperative ultrasonography of the liver has increased the rate of detection of small metastases. The Doppler perfusion index has also been found to predict liver failure, because occult disease alters liver blood flow. However, liver metastases still occur in 13% to 21% of patients who have negative results on intraoperative ultrasonography.

Extent of Resection

The extent of colonic resection is determined by the blood vessels that must be divided to remove the lymphatic drainage of the tumor-bearing portion of the colon with tumor-free margins. This is the primary treatment approach in patients with colon carcinoma. Segmental resections without extensive mesenteric resection sometimes are performed in palliative situations. Resection of intermediate and principal nodes requires ligation and division of the main vascular trunks to the affected colon segment. Tumor-free margins usually are accomplished by resection of at least 5 cm of normal bowel proximal and distal to the tumor. However, in very aggressive tumors with lymphatic submucosal spread, this may be inadequate. In general, spread beyond the gross limits of the tumor of more than 1.2 cm occurs only in rare cases.

FIGURE 33.7-5: A. Surgical resection for a cecal or ascending colon cancer. B. Surgical resection for a cancer at the hepatic flexure. C. Surgical resection for a descending colon cancer. D. Preferred surgical procedure for cancer of the middle and proximal sigmoid colon. In poor-risk patients, the inferior mesenteric artery and the left colic artery may be preserved. E. Surgical resection for cancer of the rectosigmoid. F. A more radical surgical resection for cancer of the rectosigmoid. (Modified from Enker WE, Surgical treatment of large bowel cancer. In: Enker WE, Cancer of the colon and rectum. Chicago: Year Book, 1978:73)
artery, and right branches of the middle colic artery usually are divided, and resection of the distal 10 cm of ileum is carried out along with resection of the cecum, ascending colon, and proximal transverse colon. If the main branch of the middle colic artery is taken near the origin from the superior mesenteric vessels, the bowel resection is extended to the distal third of the transverse colon to ensure that there is viable bowel for anastomosis. Uncontrolled data exist to demonstrate improvement in outcomes from extending this resection.

For tumors of the left colon, which includes the descending and upper sigmoid colon, the IMV is ligated near its origin at the aorta, and the splenic flexure of the colon is anastomosed to the upper rectum. In more limited resections for tumors in the left half of the transverse colon and splenic flexure, the resection may be limited to the ascending and descending left colic arteries and left branch of the middle colic artery. Anastomosis then is constructed between the proximal transverse colon and proximal sigmoid colon. Tumors of the distal sigmoid colon are usually resected along with the IMV near its origin at the aorta and the vessels that supply the sigmoid colon. The anastomosis is created between the area of the splenic flexure and the upper rectum. Growths between the hepatic flexure and splenic flexure may require a transverse colectomy or an extended right colectomy. The aim of transverse colectomy is removal of the transverse colon, the attached greater omentum, and the lymphatics lying in the drainage of the middle colic artery. For all these procedures, anastomosis may be created by either hand-sewn techniques or the use of stapling devices, with a low rate of anastomotic leak.

### Extent of Lymph Node Resection

Some patients with node-positive colon carcinoma may be cured by surgical resection alone. Therefore, adequate lymphadenectomy is critical. In addition to its therapeutic benefits of preventing local progression and subsequent development of symptoms due to mesenteric recurrence, lymphadenectomy is critical in the staging of patients with colon carcinoma. In colon cancer, recovery of lymph nodes is the parameter used for adjuvant therapy recommendations in the United States. Controversy exists over the curative efficacy of extensive lymphadenectomy in patients with colon carcinoma. Excellent results have been obtained with wide mesenteric resection, whereas other studies have found patients with principle node involvement to be incurable. In a recent update regarding this issue, Stallen and Grimm reviewed 2409 cases of curative resections. They found that specific groups of patients benefited from high ligation of the vascular pedicle. These were patients with transmural node-negative tumors and those with limited nodal spread. Those in whom the highest nodes were involved did not appear to benefit.

### Contiguous Organ Involveement

For tumors that are adjacent to adjacent organs, adhesions should not be divided. In one-half of cases, the adherence may be caused by invasion of these adjacent organs by a transmural bulky colon carcinoma. Separation of sites of adherence can disrupt the tumor, increase recurrence, and reduce survival rates. The organs commonly involved with transverse colon tumors are the stomach and omentum. Tumors of the splenic flexure may involve the spleen, tail of pancreas, left kidney, or distal rectosigmoid colon or cecum. Tumors anywhere in the colon may involve the abdominal wall or may have adherent loops of small intestine. Occasionally, tumors of the cecum or sigmoid may involve the bladder at its dome or, in female patients, the uterus. Adjacent organ involvement should be resected in continuity with the colon and primary tumor. Radical resection may still be curative in 20% to 50% of patients, even if adjacent tissues are invaded by malignant infiltration.

### No-Touch Technique

Manipulation of a tumor-bearing colon during mobilization has been shown to release tumor cells into the circulation. This fact provides a theoretic basis for using a no-touch technique consisting of early vascular ligation prior to mobilization, to prevent subsequent development of distant metastases due to seeding. Molecular techniques have enhanced the ability to detect cancer cells released into the circulation during operative manipulation. A prospective, randomized trial by Wiggers et al. showed that in patients who underwent preliminary ligation of vessels, liver metastases appeared later than in patients who did not undergo this procedure. However, no overall survival benefit was demonstrated. The small benefit seen in this study occurred only in the subset of patients with sigmoid colon cancer and histologic evidence of venous recurrence.

### Laparoscopic Colectomy

Laparoscopic techniques have become widely used in the management of benign and malignant colorectal conditions. These techniques are able to be carried out safely and successfully, especially in the hands of an experienced laparoscopic surgeon. Even assessment of the liver is carried out by laparoscopic intraoperative ultrasonography. With laparoscopic colectomies, there is a theoretic advantages of a shortened hospital stay and a more rapid recovery. The shortened stay associated with laparoscopic colectomy, attributable to early postoperative feeding, has also translated to a change in the management of colon resection patients who are treated by open techniques.

The overall complications of laparoscopic colorectal surgery are comparable to those of open resection in a large randomized trial of laparoscopic and open colectomy in the United States. However, the intraperitoneal complications with laparoscopic surgery may be somewhat different from those seen with open surgery and include contamination injury to the bowel, peritonitis, and development of an enterocutaneous fistula at the port site. The risk of an anastomotic leak from a colonic anastomosis in a laparoscopically assisted procedure is similar to the leak rate seen after open resection and anastomosis.

### Prophylactic Oophorectomy

Ovarian metastases and colorectal cancer can occur at the time of presentation in 2% to 8% of patients and as a subsequent site of metastases in 1% to 7% of curatively resected patients. Survival from ovarian metastases is poor in both settings, being 9% with synchronous metastases and 20% with metachronous metastases. Ovarian metastases are always accompanied by additional metastases, most of which are unseetable. Isolated ovarian metastases should be resected.

Prophylactic removal of the ovaries at the time of colorectal cancer resection has been considered in order to reduce the risks of poor survival from metachronous metastases. This will be pertinent for only the 1% to 7% of women who develop metachronous metastases, of whom only 6% to 20% will have disease confined to the ovaries. Ultimately, this applies to approximately 1% to 4% of women undergoing curative resection for colorectal cancer. Disadvantages of prophylactic resection of the ovaries can be an increase in operative morbidity, infertility, and induced menopause in premenopausal women. The effects of oophorectomy on cardiovascular risk and bone density are important considerations in the quality of life of long-term survivors. A policy of prophylactic oophorectomy in patients with colorectal cancer at the Mayo Clinic, no incidence of gross or microscopic ovarian metastases was found in 77 patients randomized to oophorectomy. No differences were seen in overall survival, whether or not patients were randomized to oophorectomy. A trend was
noted toward an improved recurrence-free survival with prophylactic oophorectomy. No selection criteria based on tumor size, grade, or other characteristics exist at this time.\textsuperscript{229}

In clinical practice, isolated synchronous ovarian metastases should be resected by oophorectomy. In premenopausal women, there is no substantial proof of benefit of this procedure, though the potential for harm by prophylactic oophorectomy does exist. In postmenopausal women, prophylactic oophorectomy can be considered after careful explanation to the patient of the risks and potential benefits.

Oncologic Results of Surgical Management

For patients undergoing curative resection for colon cancer, overall survival rates vary between 55% and 75%, with most recurrences seen in the first 2 years of follow-up. Survival after curative resection is markedly affected by the presence of nodal metastases. For node-negative patients, survival with surgery alone varies between 75% and 90%. Even in these cancers, such factors as depth of penetration, contiguous organ involvement, lymphatic and vascular invasion, differentiation, and perineural invasion, as well as molecular and cellular characteristics, will affect survival.\textsuperscript{230}

Important issues in surgically resected apparently node-negative colon cancer are the methods of lymph node evaluation and the detection of occult metastatic disease. Standardizing node evaluation and using immunohistochemical techniques can identify occult nodal metastases in up to 26% of those whose nodes test negatively by routine techniques.\textsuperscript{231} In addition, radioimmunologically guided surgical evaluation of apparently node-negative patients after resection is highly predictive of occult metastatic disease causing recurrence.\textsuperscript{232} However, convincing data on survival improvement based on these techniques are lacking. Some have even questioned the relevance of occult micrometastatic disease in patients who have undergone curative resection.\textsuperscript{233} In a group of surgically resected patients with micrometastases in resected nodes and original Dukes’ stage A or B colorectal cancer, survival time was 48 months, which mimicked the survival time for patients without micrometastases.

Among patients with node-positive cancers, survival can be affected by the number of positive nodes. Patients with one positive node may have survival rates in the 69% to 75% range, whereas 5-year survival for those with four or more positive nodes or metastases along a named vascular trunk will be in the 27% to 40% range.\textsuperscript{234} Overall, survival rates for patients with node-positive cancers appear to be approximately 40% to 50%. The analysis by Cohen et al. (1991) of node-positive colon cancer patients treated with one operation alone showed a significant difference in survival for patients having one to three positive nodes (66% 5 year survival) and those with four or more positive nodes (37% 5-year survival).

Patterns of Recurrence

Locoregional failure in colon cancer occurs in adjacent soft tissues, regional and retroperitoneal nodes, and the peritoneum. The major pattern of recurrence in colon cancer is disseminated disease with liver metastasis in two-thirds of patients in whom treatment fails. Few patients will have isolated recurrence. There is a 6% rate of anastomotic recurrence.\textsuperscript{235} As mentioned, the abdominal colon consists of portions that are intraperitoneal (e.g., the cecum, transverse colon, and sigmoid colon) and portions that are less mobile and lie against the retroperitoneum (e.g., the ascending and descending colon and hepatic and splenic flexures). The portions lying against the retroperitoneum are at higher risk for minimal marginal margins at the time of surgical resection and therefore are at higher risk for local recurrence. Gunderson demonstrated that local failure increased in these areas of immobility and with extension of tumor through the bowel. In patients with transmural node-negative disease, areas of mobile bowel had a 13% local failure rate, whereas areas of immobile bowel had a 29% local failure rate. Local recurrence rates were even higher when there was gross extension into pericolic fat. Retroperitoneal nodal failures can be seen in up to two-thirds of patients in whom resection of transmural tumors fails. Patients with node-positive disease exhibit locoregional failure more commonly than do those with negative nodes.

In lesions that occur in areas of the bowel covered by serosa, extension through the bowel wall will increase the risk for peritoneal spread. In the autopsy series reported from the University of Washington, treatment failure manifested as peritoneal seeding in 36% of patients who died from colon cancer. This is chiefly a component of multiple sites of recurrence. In a series of 533 patients studied at the Massachusetts General Hospital, peritoneal failure rates varied from 0% to 4% for stage A and B lesions, whereas for stage C lesions, rates of peritoneal failure ranged from 14% to 16%.

SPECIFIC MANAGEMENT PROBLEMS

Synchronous Cancer

Synchronous cancers are relatively uncommon, having an incidence of 3.4%, as described by Finan et al.\textsuperscript{236} In addition to the presence of another malignancy, there can be up to a 30% to 40% incidence of synchronous neoplastic polyps in the colon of a patient with a large bowel carcinoma.\textsuperscript{237} These facts emphasize the need for complete colonic examination at the time of diagnosis of a colon carcinoma.

Most synchronous neoplastic polyps can be removed at the time of preoperative colonoscopy. If this cannot be accomplished owing to obstructing lesions or an emergency operation for perforation, the index lesion should be addressed at the time of surgery and subsequent complete colonscopic examination should be carried out in the early postoperative period.\textsuperscript{238} If the synchronous lesions are in the same colonic segment, they can be included in the resection, which should maintain the principles of wide anatomic resection and lymphadenectomy.

When lesions are in widely disparate parts of the colon and cannot otherwise be cleared by endoscopic polypectomy, then consideration should be given to either two segmental resections or subtotal colectomy. Partial colectomies will require subsequent intensive colonic surveillance. However, they may be the most appropriate alternative for an elderly patient. Subtotal colectomy may be the treatment of choice for a younger patient with synchronous lesions.\textsuperscript{239} Passman et al.\textsuperscript{240} conducted an 18-year, multistitutional database study of 4878 patients with colon cancer. They found a 3.3% incidence of synchronous tumors. They also found that patients with synchronous colon cancers have the same survival rate as patients with solitary colon tumors when the highest stage of the synchronous tumor is considered.\textsuperscript{241}

Obstructing Cancers

Intestinal obstruction is the most common emergency presentation of colorectal carcinoma.\textsuperscript{242} Poor prognosis is associated with this presentation, even when analyzed stage for stage, with an overall survival of 31% at 5 years. Patients who present with this problem are frequently elderly or in poor condition because of dehydration, and operative mortality can approach 28%.\textsuperscript{243} Operative approaches in such patients have included a three-stage operation with an initial diverting colostomy followed by resection and then colostomy closure. An alternative approach is the use of a two-stage Hartmann procedure in which the resection is performed and an end colostomy is created while the distal colon is closed. The second operation then reestablishes continuity.

Staged resection is most useful in elderly persons with multiple comorbidities.\textsuperscript{244} As techniques of preoperative resuscitation and perioperative care have advanced, further alternatives for obstructing lesions distal to the splenic flexure have been studied. The first is subtotal colectomy, the second is an extended right colectomy to include the obstructing lesion without colonic decompression, and the third is the use of a terminal ileostomy.\textsuperscript{245} The results of these three operations are similar in terms of survival, but marked differences are present in terms of the length of hospitalization. Nuyens et al.\textsuperscript{246} reported on a series of 103 patients with obstructing left-sided colon carcinomas undergoing an extended right colectomy without colonic decompression or a segmental left colectomy with intraoperative lavage. They found that both procedures had an acceptably low anastomotic leak rate and mortality. Poon et al.\textsuperscript{247} studied emergency primary resection and anastomosis with intraoperative colonic lavage for left-sided obstruction. Hospital mortality rate was 5% to 9%. The anastomotic leak rate with this approach was 4%.

The alternative approach of subtotal colectomy with ileorectal anastomosis has been compared with intraoperative lavage in primary colonic anastomosis in a randomized trial.\textsuperscript{248} This trial showed no difference in mortality or morbidity rates. However, patients with subtotal colectomy had a higher postoperative frequency of bowel movements.\textsuperscript{249}

Patients with right-sided obstructing lesions should undergo a radical right hemicolectomy with primary anastomosis.

Perforating Cancers

Perforation of the colon due to carcinoma can occur either at the site of the tumor itself (in approximately 65% to 82% of patients with perforation) or in the
bowel proximal to an obstructing tumor (in 18% to 35% of patients). Many of these patients will have local or regionally advanced disease at the time of the discovery of perforation, and approximately one-third of these patients will have metastatic disease at the time of laparotomy. Overall 5-year survival for patients with localized perforation is approximately 44%. This complication occurs in 2% to 8% of all patients with colorectal cancer. These patients can present with diffuse peritonitis and require emergency management. Some contained perforations will extend into adjacent bowel loops or viscera and therefore cause a fistula that should be resected on bloc with the tumor at the time of resection.

The presence of a perforation or fistula will increase cancer recurrence rates. Local recurrence rates of 23% have been reported by Carraro et al. in a study of 83 patients with large bowel perforation and colorectal cancer. This compares with figures of 28% to 44% reported in the literature. Peritoneal seeding is a particularly common failure in patients with perforated colorectal cancers, with carcinomatosis rates of 17% to 18%.

### Malignant Polyps

The management of neoplastic polyps that are benign has already been addressed. In this section, we will consider the management of a malignant polyp in which the invasive component has perforated the muscularis mucosae and therefore has the potential for metastatic spread. The rationale for colon resection for a malignant polyp post endoscopic removal is minimization of the risk of residual carcinoma at the site of the polypectomy, the risk of metastatic spread to regional lymph nodes, and the risk of disease dissemination.

The risks and benefits of resection must be weighed against the patient's potential for morbidity and mortality from either the cancer or a surgical resection. The risks of mortality from elective colorectal surgery are approximately 1% to 2%. However, in a given individual, age and the presence or absence of comorbidity will dictate surgical mortality.

Malignant colorectal polyps may be pedunculated or sessile. Endoscopic removal will be more successful in managing malignant pedunculated polyps. Critical factors in determining the need for surgery after colonoscopic removal of a malignant polyp are the differentiation features of the carcinoma (well or moderately differentiated), the presence of vascular or lymphatic invasion, the presence of a clear polyp resection margin, and assessment that the polyp has been completely removed. Most commonly, the issue dictating surgical resection will be an inadequate or questionable margin.

Haggitt et al. (1985) have described various levels of invasion of carcinoma into pedunculated polyps (Fig. 33.7-6). They noted that, in a pedunculated polyp, an invasive component in the head of the polyp may be a substantial distance from the submucosa and therefore may be resected endoscopically with a significant margin. In a sessile polyp, the invasive component has early access to the submucosa and therefore has an earlier opportunity for dissemination. Sessile polyps will have a higher incidence of lymph node metastases than pedunculated polyps with invasive cancer. When the invasive cancer is limited to the head of a pedunculated polyp, lymph node metastasis rates appear to be approximately 3%, in contrast to 10% to 25% for sessile polyps (Table 33.7-7). The incremental improvement related to extensive surgery in patients with cancers limited to the head of the polyp is low. Patients with favorable risk criteria and a cancer limited to the head of a pedunculated polyp will be treated best by colonoscopic polypectomy alone. Sessile polyps are best treated by surgical resection, though some investigators have disputed this.

![Figure 33.7-6](image)

**FIGURE 33.7-6.** Levels of invasion in a pedunculated adenoma (A) and a sessile adenoma (B). The stippled areas represent zones of carcinoma. Any invasion below the muscularis mucosae in a sessile lesion represents level 4 invasion (submucosa). In contrast, invasive carcinoma in a pedunculated adenoma must traverse a considerable distance before it reaches the submucosa of the underlying bowel wall. However, any cancer that penetrates the muscularis mucosae is at risk for dissemination.

| TABLE 33.7-7 | Cancer in Polyps: Risk of Lymph Node Metastases |

After colonoscopic removal of the malignant polyp, it is important to document carefully the site of polypectomy in the event that surgical resection is warranted. We commonly perform this procedure using endoscopically placed clips, which are both palpable and evident on abdominal radiographs. Follow-up colonoscopy is generally performed 3 to 6 months after removal of a malignant polyp, to assess the polypectomy site for any residual mass. Presence of a mass is an indication for further endoscopic evaluation, which may then be followed by surgical resection if the mass is not endoscopically resectable. Adenoma recurrence rates vary from 15% to 30% over a 10-year period. The risk of lymph node metastases depends on the extent of invasion and the presence of lymphatic or vascular invasion. Sessile polyps have a higher incidence of lymph node metastases than pedunculated polyps with invasive cancer.

Whitlow et al. studied a group of 59 patients who underwent treatment for malignant colonic polyps. Sixty-three percent of the patients were managed with polypectomy and surveillance. The remainder underwent colectomy. The most common indications for colectomy were Haggitt level 3 or 4 invasion, inadequate margins, patient preference, or poor differentiation, in that order. Residual disease was found in 3 of the 22 patients undergoing colectomy. Importantly, there were no cancer-related deaths in either treatment group. None of the patients in Whitlow's group had evidence of lymph node involvement at the time of colectomy.

Netzer et al. studied the outcomes in 32 patients with endoscopically removed low-risk malignant polyps versus the outcomes of 38 patients with high-risk polyps. High-risk malignant polyps were defined as having an incomplete polypectomy, a margin that was not clearly cancer-free, lymphatic or vascular invasion, or grade 3 carcinoma. In this series, 73% of the patients had pedunculated malignant polyps and, of these, 8.5% had adverse outcomes. Of the 27% of patients with sessile malignant polyps, 58% had had adverse outcomes defined as residual disease at colectomy or cancer recurrence during the follow-up period. Large sessile lesions in the colon often require surgical resection as the safest approach. Biopsy and observation alone is usually not the best approach, unless operative morbidity is expected to be excessive.

**ADJUVANT THERAPIES**
Local Adjuvant Radiation Therapy in Colon Cancer

Although the overall incidence of local failure is relatively low in colon cancer, data suggest that, on the basis of anatomic location and selected pathologic features, certain subsets of patients have a higher incidence of local failure. However, there is not uniform agreement as to how to define these subsets. For example, Gunderson et al. (1985) divided the colon into two regions. The “anatomically immobile” (or mainly retroperitoneal) region included the ascending colon, hepatic flexure, splenic flexure, and descending colon. The “anatomically mobile” (or mainly intraperitoneal) region included the cecum and transverse colon. The highest incidence of local failure occurred in the cecum (30%), whereas the other intraperitoneal sites, the transverse colon, had one of the lowest rates of local failure (13%).

In contrast, Minsky et al. (1988) reported a general trend of increased local failure with more distal colon sites. Patients with cecal cancer had a significantly lower incidence of local failure (3%), as compared to those with cancer of the transverse colon (15%) or descending colon (25%). These data do not support the notion that bowel mobility is predictive of local failure.

In the series by Willett et al. (1984), the colon was divided into two groups. Group 1 included the cecum and ascending, midsigmoid, transverse, and descending colon. Group 2 included the high and low sigmoid colon, the splenic flexure, and the hepatic flexure. In stage T1–2N0M0 disease, there was a higher incidence of local failure in group 1 tumors (16% to 24%) as compared with group 2 tumors (0% to 11%). Overall, there is no consistency as to which anatomic site or sites have the highest local failure rates. This inconsistency may reflect the differences in methods used to detect failure (reoperation versus clinical or radiographic methods) and to determine failure (cumulative vs. first failure) rather than the true natural history of the disease.

Locoregional Radiation Therapy. Although all the series are retrospective, the most comprehensive series examining the role of locoregional radiation therapy in colon cancer is the study by Willett et al. at the Massachusetts General Hospital (Table 33.7-9). After potentially curative surgery for stages T3–4N0–2M0 colon cancer, 203 patients received postoperative adjuvant radiation therapy. Eligibility included patients with the following stages of disease: T4N0–2M0 tumors regardless of anatomic site, T3N1–2M0 tumors excluding midsigmoid and transverse colon, and selected high-risk T3N0M0 tumors with close margins. Patients received 45 Gy to the primary tumor bed with a 5-cm margin and inclusive of the primary draining lymph nodes. This was followed by a shrinking-field technique to 50.4 to 55.0 Gy depending on the volume of small bowel that could be excluded from the high-dose field. Of the 203 patients, 173 were treated in the adjuvant setting and 30 after a subtotal resection. Sixty-three received bolus 5-fluorouracil (5-FU) with a variety of doses and schedules.

The results were compared with a historical control group of 395 patients who underwent surgery only. Three patient groups appeared to benefit from postoperative radiation therapy. There was a significant improvement in local control and disease-free survival for patients with stage T4N0M0 or T4N1–2M0 disease. Also, patients with stage T4N0 disease with a perforation or fistula had improved local control and disease-free survival. Finally, radiation therapy salvaged some patients with residual disease after subtotal resection, resulting in a 37% 5-year disease-free survival. There was no benefit in local control or disease-free survival in patients with stage T3N0M0 or T3N1–2M0 disease.

For the total patient group, the incidence of grade 3+ acute bowel toxicity was 8%. The incidence was lower in the patients who received radiation therapy plus chemotherapy (4% vs. 16%, respectively). Grade 3+ long-term bowel toxicity was 4.5%. Therefore, with careful treatment techniques, the acute and long-term bowel toxicities of postoperative locoregional radiation therapy (with or without chemotherapy) for colon cancer are comparable with those reported for rectal cancer.

Other reports of adjuvant locoregional radiation therapy are limited by small numbers of patients and short follow-up. Most have been limited to colonic cancers.

Based on the retrospective data from the Massachusetts General Hospital, a randomized phase III intergroup trial coordinated by the Mayo Clinic and NCCITG (INT 0130) was developed. Patients with T4 or selected T3N1–2 colon tumors were randomized to 12 cycles of bolus 5-FU plus levamisole with or without locoregional radiation therapy (45.0 to 50.4 Gy in 25 to 28 fractions) beginning with cycle two of chemotherapy. The trial was closed early due to poor accrual, with only 222 of the anticipated 400 patients randomized, leaving 189 eligible patients. Grade 3+ toxicity was modestly higher in the combined-modality therapy arm (43% vs. 35%). With a median follow-up of 35 months, there was no significant difference in survival between the two arms. The patterns of failure data have not been reported.

In a phase I trial of 21 patients (4 with colon cancers) who received upper abdominal radiation plus continuous-infusion 5-FU at 150 mg/m² Martenson et al. reported a 40% grade 3+ toxicity rate. In contrast, the recommended dose of continuous-infusion 5-FU plus concurrent radiation for patients with rectal cancer who receive adjuvant therapy is 225 mg/m². These data suggest that the dose of continuous-infusion 5-FU needs to be attenuated in patients receiving...
combined-modality therapy for upper abdominal malignancies. This is most likely related to the larger radiation field.

In summary, the retrospective data from the Massachusetts General Hospital suggest that there are subsets of colon cancer patients with high local failure rates in whom the addition of postoperative locoregional radiation therapy may improve local control and disease-free survival. The randomized INT 0130 trial did not show a survival advantage with combined-modality therapy versus chemotherapy alone. It must be emphasized, however, that the INT 0130 trial was closed prior to meeting its accrual goals and has not yet reported local control results. Although postoperative locoregional radiation therapy in colon cancer remains investigational, two clinical situations exist in which its use is reasonable: in a patient with close or positive resection margins and in a patient who has undergone a resection of a T4 colon cancer adherent to pelvic structures. These cancers (most commonly sigmoid or cecal primary lesions) have local failure rates similar to rectal cancers, and it is reasonable to treat them as such with adjuvant combined-modality therapy, including six cycles of 5-FU–based chemotherapy plus concurrent pelvic radiation.

**WHOLE ABDOMEN RADIATION THERAPY.** The use of whole abdomen radiation therapy is limited by dose considerations. To treat the volume at risk with a potentially curative dose of radiation required for microscopic disease, the whole abdomen would need to receive 45 Gy. Although limited portions of the abdomen can tolerate this dose, the tolerance of the whole abdomen with conventional fractionation is 30 Gy. Based on the high incidence of abdominal failure in some colon cancers, a number of phase II adjuvant trials were designed to examine the efficacy of whole abdomen radiation therapy. In Table 33.7-10, the results are encouraging, but further follow-up is needed. Currently, whole abdomen radiation therapy remains investigational.

**TABLE 33.7-10.** Whole Abdomen Adjuvant Radiation Therapy for Colon Cancer

In general, patients received 20 to 30 Gy to the whole abdomen with or without a boost to the primary tumor bed. In three of the series, 5-FU was delivered with a variety of doses and schedules. The combined results revealed an in-field (abdominal) failure rate of 12% to 50%. Significant toxicity varied from 5% to 38%. Although the initial phase II results appeared promising, three of the series have never been updated.

The most encouraging data have been reported by Fabian et al. from the SWOG 8572 study. In this phase II adjuvant pilot trial, 41 patients with T3N1–2M0 disease received whole abdomen radiation therapy plus continuous-infusion 5-FU (200 mg/m²/24 h) followed by 9 monthly cycles of maintenance continuous-infusion 5-FU (1000 mg/m²/24 h × 4 days). Due to unacceptable toxicity in the first six patients, the protocol was modified such that the 5-FU was started on day 1 and radiation began concurrently on day 8 and a 1-week treatment break from both the 5-FU and radiation was required at day 42. The tumor bed boost (1.6 Gy × 10 days) was delivered first, followed by whole abdomen radiation therapy (1 Gy/d × 30 days) for a total dose of 30 Gy to the whole abdomen and 46 Gy to the tumor bed. With a median follow-up of 5 years, the 5-year disease-free and overall survival rates were 58% and 67%, respectively. Limiting the analysis to the 20 patients with more than four positive nodes, the 5-year disease-free and overall survival rates were 55% and 74%, respectively. For the total patient group, the patterns of failure included local failure (12%), liver failure (22%), and peritoneal and other abdominal failure (15%). In contrast with other whole abdomen radiation therapy trials, toxicity during the combined-modality segment was tolerable (17%, grade 3; 7%, grade 4). The toxicity during the maintenance chemotherapy was also acceptable (25%, grade 3; 3%, grade 4). These results are encouraging, but further follow-up is needed. Currently, whole abdomen radiation therapy remains investigational.

**Adjunct Systemic Therapy for Colon Cancer**

**SINGLE-AGENT STUDIES.** The fact that a substantial number of patients treated surgically with curative intent eventually die of metastatic disease was understood early. Once the natural history of the disease became better defined, subsets of patients with a higher risk of recurrence could be identified. The next logical step was the development of adjuvant treatments attempting to improve the long-term disease-free and overall survival rates. The first trials were conducted in the 1950s, and a partial summary of these first-generation studies is provided in Table 33.7-11. The chemotherapeutic agents available were restricted to thiopeta, fluorouridine (FUDR), and 5-FU, and they were commonly used with suboptimal intensity.

**TABLE 33.7-11.** First-Generation Randomized Trials of Adjuvant Therapy for Large Bowel Cancer

Even though these early trials are generally considered negative because no dramatic benefit could be elicited, some studies with the fluoropyrimidines did demonstrate a 5% to 10% benefit in 5-year survival. The results were intriguing enough to justify continuous efforts with novel agents and combinations of the available agents in the same setting.

**INITIAL COMBINATION CHEMOTHERAPY STUDIES.** The combinations explored in the 1970s included chemotherapy and, occasionally, nonspecific immunotherapy with bacille Calmette-Guérin (BCG), BCG variations, and levamisole. These drugs are well represented in six large studies published in peer-reviewed journals and are summarized in Table 33.7-12. Methyl-CCNU plus 5-FU (MF) and MF plus vincristine (Oncovin; MOF) were commonly used, because at that time, they were believed to be more active in advanced disease than 5-FU alone. With more than 3700 patients entered in these six trials, a trend favoring the chemotherapy-treated groups was noted. However, the only trials to achieve statistical significance were NSABP C-01 and NCCTG 78-48-52.
Levamisole. Levamisole is a synthetic, orally active agent with antihelmintic and immunomodulatory properties. The observation that levamisole enhances the immune response of mice vaccinated against Brucella bacteria led to its investigation in cancer. The drug is well absorbed from the GI tract after oral administration and is extensively metabolized by the liver.

Levamisole was initially evaluated in the treatment of advanced colorectal cancer in combination with 5-FU. More than 400 patients were enrolled in three randomized trials evaluating the addition of levamisole to 5-FU chemotherapy. The results were disappointing, with no improvement in response rate, time to progression, or survival in favor of the levamisole-treated groups.

Since 1974, levamisole has been investigated as a single agent in the adjuvant treatment of colorectal cancer. Despite the good results seen initially, two large, prospective, randomized, placebo-controlled trials reported subsequently have failed to demonstrate a significant benefit for levamisole administered as a single agent. Eventually, levamisole was combined with 5-FU in the adjuvant setting. Small trials comparing 5-FU-based chemotherapy with or without levamisole did not demonstrate a benefit for the levamisole-treated group. In a larger trial, after curative surgery for colorectal cancer, 141 patients were randomized to receive a 6-month course of 5-FU with or without levamisole or supportive treatment only. After 5 years of follow-up, a significant survival advantage was detected in the patients receiving levamisole as compared with patients treated with 5-FU alone.

The true turning point in the adjuvant treatment of colorectal cancer came with the results of two well-known randomized trials (Table 33.7-13). In one, conducted by the NCCTG and the Mayo Clinic, 401 eligible patients with Dukes stage B and C colorectal cancer after curative surgery were randomized to receive no further treatment, levamisole alone, or 5-FU plus levamisole. Levamisole plus 5-FU (P = .003) and, to a lesser extent, levamisole alone (P = .05) reduced cancer recurrence in comparison with no adjuvant therapy. Whereas both treatment regimens were associated with overall improvements in survival, these improvements reached borderline significance only for patients with stage C disease treated with levamisole plus 5-FU (P = .03). These promising results led to a large national intergroup confirmatory trial involving the NCCTG, the Eastern Cooperative Oncology Group, and SWOG, which changed dramatically the way oncologists approached and treated colon cancer.

Twelve hundred and ninety-six patients with Dukes stage B2 or C resected colon cancer were randomly assigned to observation or to treatment for 1 year with levamisole combined with 5-FU or with levamisole alone. Therapy with levamisole plus 5-FU reduced the risk of cancer recurrence among patients with stage C disease by 41% (P < .0001) after a median follow-up of 3 years. The overall death rate was reduced by 33% (P = .006). Treatment with levamisole alone had no detectable effect. The results in patients with stage B2 disease were equivocal, and no treatment recommendation could be made.

In 1995, Moertel et al. updated the results of this trial. With the 929 patients with stage C disease followed for a median of 6.5 years, 5-FU plus levamisole reduced the recurrence rate by 40% (P < .0001) and the death rate by 33% (P = .007). Levamisole alone reduced the recurrence rate by only 2% and the death rate by only 6%.

### TABLE 33.7-12. Second-Generation Colon Cancer Adjuvant Trials

The NSABP C-01 study randomly assigned 1166 patients with Dukes stage B and C colon carcinoma to receive chemotherapy or immunotherapy or to be observed only. When compared with the control group, the patients treated with MOF had statistically superior disease-free survival (P = .02) and overall survival (P = .05). At 5-year follow-up, the group treated with MOF had an 8% survival improvement over the control group. There was no significant difference between the BCG and control groups (P = .40). This was the first randomized trial to demonstrate a benefit in disease-free and overall survival for patients treated with chemotherapy. The toxicity of the MOF regimen is significant, and five patients in the NSABP C-01 trial developed acute leukemia or myelodysplasia. This particular toxicity was evaluated by Boice et al., who found 19 cases of leukemia or myelodysplasia among 2067 patients treated with regimens containing MF, with an estimated risk of 2.3 cases per 1000 patients per year.

### TABLE 33.7-13. Adjuvant Studies of Levamisole plus 5-Fluorouracil

Toxic effects of levamisole alone were infrequent, usually consisting of mild nausea with occasional metallic taste, fatigue, dermatitis, or leukopenia, and those of levamisole plus 5-FU were essentially the same as those of 5-FU alone, including nausea, vomiting, stomatitis, diarrhea, dermatitis, and leukopenia. The cost-effectiveness of this treatment for a typical patient has been calculated as a very reasonable $2094 per year of life saved. Prospective, randomized, placebo-controlled trials reported subsequently have failed to demonstrate a significant benefit for levamisole administered as a single agent. A comparison of these two groups indicated a disease-free survival advantage for patients treated with 5-FU plus leucovorin (P = .0004). The 3-year disease-free survival rate for patients in this group was 73%, as compared with 64% for patients receiving MOF. The overall survival at 3 years was 84% for those randomized to receive 5-FU plus leucovorin and 77% for the MOF-treated cohort (P = .003). Patients treated with postoperative 5-FU plus leucovorin had a 30% reduction in the risk of developing a treatment failure and a 32% reduction in mortality risk as compared with similar patients treated with MOF.

**Combinations of 5-Fluorouracil and Leucovorin.** The relative success of combinations of 5-FU with leucovorin in the treatment of advanced colorectal cancer led several investigators to explore this combination in the adjuvant setting. Combinations of 5-FU and leucovorin were tested against different control groups (Table 33.7-14). The NSABP C-03 randomized 1081 patients with Dukes stage B and C colon cancer to receive either MOF or 5-FU plus leucovorin. A comparison of these two groups indicated a disease-free survival advantage for patients treated with 5-FU plus leucovorin (P = .0004). The 3-year disease-free survival rate for patients in this group was 73%, as compared with 64% for patients receiving MOF. The overall survival at 3 years was 84% for those randomized to receive 5-FU plus leucovorin and 77% for the MOF-treated cohort (P = .003). Patients treated with postoperative 5-FU plus leucovorin had a 30% reduction in the risk of developing a treatment failure and a 32% reduction in mortality risk as compared with similar patients treated with MOF.
In the International Multicentre Pooled Analyses of Colon Cancer Trials (IMPACT), three randomized trials conducted to investigate the efficacy of 5-FU and high-dose leucovorin after surgery for stage II and III colon cancer were pooled for combined analysis. All included trials used the same treatment regimen: 5-FU, 370 to 400 mg/m²/d, plus leucovorin, 200 mg/m²/d, 5 days every 28 days for six cycles. A pooled analysis of the results was performed, including 1493 eligible patients with resected stage II and III carcinoma of the colon. 5-FU plus leucovorin significantly reduced mortality by 22% and adverse events by 35%, increasing 3-year event-free survival from 62% to 71% and overall survival from 78% to 83%.

In an Italian study reported by Francini et al., 239 patients with surgically resected Dukes stage B2 or C colon cancer were randomly assigned to chemotherapy with 5-FU and leucovorin or to observation alone. In stage B2, no significant difference between the adjuvant arm and the observation arm was noted. In stage C, adjuvant chemotherapy produced an advantage over observation in terms of a reduction in cancer recurrence rate, with a 3-year disease-free survival of 81% versus 64% and an improvement in overall survival (P = .0025).

An intergroup study was planned to compare 5-FU plus leucovorin to control only, but the study was closed prematurely in September 1989 after 309 patients had been enrolled, when reports of the positive results of 5-FU plus levamisole adjuvant therapy precluded randomization to an untreated control group. Patients were randomized to observation or 5-FU plus low-dose leucovorin daily for 5 days every 28 days for six cycles. Preliminary results released after a median follow-up of 3.5 years showed a significant advantage in recurrences in favor of the 5-FU plus leucovorin group (P = .001).

5-Fluorouracil plus Levamisole versus 5-Fluorouracil plus Leucovorin. Both 5-FU plus levamisole and 5-FU plus leucovorin regimens have been found to be successful in prolonging disease-free and overall survival. The similar results obtained with the use of either levamisole or leucovorin as 5-FU modulators made necessary a direct comparison between the two modalities (Table 33.7-15). When these two regimens were directly compared in randomized clinical trials, it appeared that a small disease-free survival and overall survival advantage had emerged in favor of 5-FU plus leucovorin.

The intergroup study INT 0089 was the largest trial to address this question. Starting in 1989, 3759 patients with stage II (20%) and stage III (80%) colon cancer were randomly assigned to receive 5-FU plus low-dose leucovorin, 5-FU plus high-dose leucovorin, or 5-FU plus both levamisole and leucovorin for 6 to 7 months, or 5-FU plus levamisole for 12 months. The results are summarized in Table 33.7-16. The leucovorin-containing arms demonstrated a trend toward better results than the 5-FU plus levamisole only arm. Additionally, the toxicity profile was different among the regimens. Patients in the 5-FU plus low-dose leucovorin or the 5-FU plus levamisole arms experienced a greater incidence of stomatitis and neutropenia, whereas patients in the 5-FU plus high-dose leucovorin arm had a greater incidence of diarrhea. The addition of levamisole to 5-FU plus leucovorin did increase toxicity, with no significant increase in disease-free or overall survival.

The NSABP C-04 study, also summarized in Table 33.7-16, compared 5-FU plus levamisole to 5-FU plus high-dose leucovorin and to a combination of the three agents. A total of 2152 patients with Dukes B (41%) or Dukes C (59%) colon cancer were randomized into one of the three treatment arms. At 5 years, there was an advantage for the leucovorin-containing arms, with 69% of the patients treated with 5-FU plus levamisole alive as compared to 74% of the patients receiving 5-FU plus leucovorin and 72% of those receiving 5-FU, leucovorin, and levamisole.

The NCCTG joined with the National Cancer Institute of Canada to examine the effectiveness of a regimen of 5-FU plus levamisole plus leucovorin as adjuvant therapy for patients with high-risk colon cancer and evaluated 6 months versus 12 months of chemotherapy in the same setting. A total of 891 eligible patients with stage II or III colon cancer were randomly assigned to receive adjuvant chemotherapy with 5-FU and leucovorin combined with levamisole or a standard regimen of 5-FU plus levamisole. Patients also were randomly assigned to receive either 12 months or 6 months of chemotherapy. After a median follow-up of 5.1 years, there was no significant improvement in patient survival when chemotherapy was given for 12 months as compared with 6 months. When chemotherapy was given for 6 months, standard 5-FU plus levamisole was associated with inferior patient survival (P = .01). These data suggest that a 6-month regimen of 5-FU plus levamisole...
were detected in survival or disease-free survival for the 80 eligible patients. However, there was a significant improvement in survival (treated by resection alone or resection plus a vaccine made with irradiated autologous tumor cells plus BCG. After 6.5 years, no statistically significant differences in survival were observed between the treatment and control groups.

The use of vaccines has been explored extensively as well. Hoover and Hanna reported in a randomized trial that vaccination with irradiated autologous tumor cells plus BCG led to an improvement in survival compared to the control group.

The combination of traditional chemotherapy with immunotherapeutic agents is an interesting field of research. At least one combination was proven effective in a large, randomized trial. In fact, until recently the combination of 5-FU plus levamisole was considered the standard adjuvant treatment for stage III colorectal cancer. For example, in a randomized trial comparing 5-FU plus levamisole versus a combination of 5-FU, leucovorin, and irinotecan, the results of those trials are eagerly awaited.

In 1975, a randomized trial of adjuvant portal vein infusion with 5-FU at 1 g/d and heparin at 5000 U/ld for 7 days was initiated in patients undergoing surgery for Dukes stage A, B, and C colorectal cancer. A total of 117 patients received the infusion, and 127 were enrolled in the control arm. There were fewer liver metastases in the perfusion group, and a statistically important overall survival improvement was noted in Dukes’ stage B and C patients. Several other trials have followed the same basic design.

The Swiss Group for Clinical Cancer Research investigated the efficacy of a perioperative intraportal cytotoxic regimen in a randomized trial of 533 patients with operable colorectal carcinoma. Patients were randomly assigned to either a single course of portal infusion with mitomycin (one dose of 10 mg/m^2) plus 5-FU (500 mg/m^2 every 24 hours for 7 days) starting immediately after surgery or to no adjuvant treatment. Five hundred and five patients were evaluated. At a median follow-up of 8 years, adjuvant therapy reduced the risk of recurrence by 21% and the risk of death by 25%. The benefit obtained with a single course of adjuvant chemotherapy via the portal vein for patients with operable colorectal carcinoma might be due to the systemic effects of the portal chemotherapy.

Between March 1984 and July 1988, in the largest randomized trial to date, the NSABP explored the use of chemotherapy and heparin administered by portal vein infusion versus no further treatment. A total of 1158 patients with Dukes’ stage A, B, and C carcinoma of the colon were entered into the NSABP C-02 protocol. Therapy began on the day of operation and consisted of 5-FU, 600 mg/m^2 with 5000 U/ld by constant infusion for 7 successive days. Randomization was assigned postoperatively, and 23% of patients were later found to be ineligible, primarily because of metastatic disease. A comparison at 4 years involving 901 eligible patients distributed between the two groups indicated both an improvement in disease-free survival, from 64% to 74% (P = .02), and a borderline improvement in overall survival, from 73% to 81% (P = .07) in favor of the chemotherapy-treated group. When compared with the treated group, patients who received no further treatment had a 2.6 times the risk of developing a treatment failure and 1.25 times the likelihood of dying after 4 years. However, the incidence of hepatic metastasis was not significantly altered, and the benefits observed could potentially be explained by the systemic effect of the chemotherapy.

A large metaanalysis has been conducted to assess the effects on recurrence and survival of administering 5-FU-based chemotherapy by portal infusion after colorectal cancer surgery. Data from ten trials involving approximately 4000 patients were available for analysis. The final result showed that portal infusion of 5-FU for approximately 1 week after surgery in patients with colorectal cancer may produce a small absolute improvement in 5-year survival. This result is somewhat disappointing, and it is possible that the reason for the survival benefit is the systemic exposure to chemotherapy. The use of portal vein infusion cannot be considered routine in the adjuvant treatment of colorectal cancer.

The use of hepatic arterial infusion in the adjuvant setting has been controversial. However, recent data published by the Memorial Sloan-Kettering Cancer Center group demonstrated that patients who had liver resections did benefit from the addition of hepatic arterial infusion to their adjuvant regimen. Further studies are necessary to confirm this.

The combination of traditional chemotherapy with immunotherapeutic agents is an interesting field of research. At least one combination was proven effective in a large, randomized trial. In fact, until recently the combination of 5-FU plus levamisole was considered the standard adjuvant treatment for stage III colorectal cancer. Preliminary and early clinical data have suggested that interferon-α2 (INF-α2) enhances the efficacy of 5-FU therapy in colorectal cancer. In an attempt to improve on the results obtained with the use of 5-FU and leucovorin in the adjuvant setting, the NSABP C-05 protocol evaluated the addition of recombinant IFN to 5-FU plus levamisole in a randomized trial including 2176 patients with Dukes stage B or C colon cancer. The results showed no statistically significant difference in disease-free survival or overall survival at 4 years of follow-up. Toxicity was more pronounced in the combination of 5-FU, leucovorin, and irinotecan. The results of those trials are eagerly awaited.

The use of vaccines has been explored extensively as well. Hoover and Hanna randomized 98 colorectal patients with Dukes stage B2 and C disease into groups treated by resection alone or resection plus a vaccine made with irradiated autologous tumor cells plus BCG. After 6.5 years, no statistically significant differences were detected in survival or disease-free survival for the 80 eligible patients. However, there was a significant improvement in survival (P = .02) and disease-free survival (P = .039) in the colon cancer group, although no benefits were seen in patients with rectal cancer. The potential negative impact of the radiation therapy in the immune system of the rectal cancer patients has been postulated as a reason for this difference.

The Eastern Cooperative Oncology Group conducted a larger trial that enrolled a total of 412 patients with Dukes’ stage B2 and C colon cancer and randomized them to observation or to vaccination with autologous irradiated tumor cells in combination with BCG and with irradiated tumor cells alone. When the results were
Patients with primary colorectal cancer who have metastatic disease at presentation the primary tumor should always be resected. Survivals were on the order of 14 to 16 months in this group of patients with asymptomatic intact primary tumors.

Patients with synchronous primary colon tumors should have appropriate resections unless their medical condition does not allow it. Whereas palliative surgery in colorectal cancer patients with synchronous metastases is a reasonable method to control perforation, hemorrhage, and bleeding, it can carry substantial morbidity and mortality. In a series presented by Liu et al., patients with colon cancer underwent resection as palliation. As compared with standard operative mortality for elective colon resection, 3% of patients in this group had an operable mortality of 10%, whereas in those in whom more than 50% of the liver was replaced, mortality was significantly higher.

Follow-up is carried out to find potentially curable recurrences, to palliate symptomatic recurrences, and to identify and resolve treatment-related problems. The biology of colorectal cancer works both for and against the effectiveness of follow-up after the curative resection of colorectal cancer. Solitary liver and lung metastases can be resected and result in long-term survivals in a significant number of patients. Local recurrences of rectal cancer can also be resected with curative intent. Detection of these recurrences can be worthwhile in terms of survival. However, the reality is that most recurrences will represent the outgrowth of multiple occult metastatic sites that were unresponsive to initial surgery and adjuvant therapy. These are unlikely to respond to subsequent therapy, and so they prevent any survival advantage that might have resulted from earlier therapies. Most colorectal cancers that recur or metastasize are biologically determined to be incurable.

Critical factors in carrying out and designing follow-up protocols for colorectal cancer patients are the cost-effectiveness of such follow-up and the effects of follow-up on survival. An important study was carried out by Schoemaker et al. in a university hospital setting in South Australia. These researchers conducted a randomized controlled trial with 5-year follow-up in patients who had undergone curative resections for colorectal cancer. Patients were followed by either an intensive follow-up regimen or a standard follow-up regimen. The study group encompassed Dukes stage A, B, and C cancer patients. Standard follow-up consisted of history and physical examination, blood counts, and liver function tests that were carried out every 3 months for 2 years and every 6 months thereafter. The intensive follow-up consisted of the standard follow-up plus annual chest radiography, CT of the liver, and colonoscopy. The results of this study demonstrated no difference in the survival rate at 5 years between patients who received intensive follow-up and those who received standard follow-up.

In a prospective, randomized study of follow-up after radical surgery for colorectal cancer, Kjæstensen et al. made similar findings. The differences between the randomized groups in this study were based on the frequency of follow-up. The intensively followed group had examinations at 6 and 12 months after treatment, whereas the other group had examinations at 5 and 10 years. It was found that recurrences were detected with the same frequency in both groups, but the diagnosis of recurrence was made earlier in the intensively followed group. There was no overall improvement in survival by the intensive follow-up regimen.

The pattern of recurrence of rectal cancer as opposed to colon cancer is an important factor in evaluating the role of follow-up strategies. The role of follow-up in detection and management of local recurrences of colorectal cancer was studied by Pietra et al. Patients were randomly assigned to either a conventional follow-up or to an intensive follow-up after resection of primary colorectal carcinoma. In the intensively followed group, local recurrence of rectal carcinoma was more frequently detected. More than 90% of these recurrences in the intensively followed group were detected at scheduled visits. Again, local recurrences were detected earlier in the intensively followed group, and curative re-resection was more frequently carried out in this group. In this study, patients in the intensive follow-up group had an improved 5-year survival, mainly due to the re-resection of local recurrences of rectal carcinoma. The usefulness of CEA determination in detecting luminal recurrences of colorectal cancer was also supported, because it initiated workup for recurrence in asymptomatic patients who were most likely to undergo a curative reoperation.

Other studies have disputed the value of CEA in the follow-up of patients with colorectal carcinoma, on the basis of a lack of detectable increase in survival. In a study of second-look operations for recurrent colorectal cancer initiated by an elevation of CEA level, it was found that nearly half of the colorectal cancer patients who developed recurrence underwent second-look operations and that approximately half of these patients underwent resection. As determined by modern imaging techniques, 1 patient in 72 who underwent exploration for recurrence had no detectable disease at the second-look operation. The group who underwent resection at a stage II or III resection had a 5-year survival rate of 41%. It appears that when modern imaging techniques are used to evaluate an elevated CEA level, patients can be more appropriately selected for surgery.
examination every 3 months, along with CEA determination, chest radiography, and colonoscopy every 6 months in year 1, physical examination and CEA level determination every 6 months in years 2 through 5, and colonoscopy every 1 to 2 years during this period. Costs were estimated on the basis of Medicare reimbursement guidelines. It was found that of the 421 patients in whom recurrent disease was found, 96 underwent surgical resection with curative intent. CEA level determination was the most cost-effective way to identify patients with recurrence that could be surgically treated. CEA monitoring is controversial but has been adopted for routine surveillance by national groups in the United States. 

Rosen, conducted a metaanalysis evaluating two and three comparative cohort studies showing more than 2000 patients. The analysis looked at the outcomes of curative resection rates, survival after re-resection, length of survival after recurrence, and cumulative 5-year survival in these patients. Fourteen single-cohort studies were also included in the analysis, and a study of these additional patients supported the findings of the metaanalysis. The metaanalysis indicated that the cumulative 5-year survival rate was 1.16 times higher in the intensively followed group ( \( P = .005 \)). Furthermore, 2.5 times more curative resections were performed for patients undergoing intensive follow-up, and those in the intensive follow-up group had a higher survival rate than did those followed less intensively.

**EXTENT OF DISEASE WORKUP AFTER RECURRENCE**

Certain groups of patients with proven or suspected recurrence may benefit from a more extensive workup to identify occult metastatic disease. Examples of this situation are patients with potentially resectable hepatic metastases or patients with locally recurrent rectal cancer. Another group that may benefit are those patients with a rising CEA level in which the source has not been identified on conventional evaluation with physical examination, endoscopy, chest radiography, and CT scan. Two such tests are 18-fluorodeoxyglucose PET and scanning after the injection of radiolabeled antibodies that bind to CEA.

Studies of patients with recurrent or metastatic colorectal cancer have demonstrated high sensitivity (91% to 93%) and specificity (98% to 100%) of these tests in identifying sites of recurrence. In patients with solitary hepatic metastases on conventional imaging, PET found additional inoperable disease in 11%. PET was able to identify additional unsuspected sites of tumor in 21% of patients. Overall, approximately 20% to 30% of patients with a potentially resectable recurrence have been found by PET to have additional disease. The positive predictive value of elevated CEA determinations in patients with an equivocal or negative conventional workup was 89%. This group of patients appeared to benefit most from the additional information provided by PET. It appears, however, that PET will be limited in detecting certain variances due to small size or the presence of necrotic low metabolically acting tumors.

The use of injectable radiolabeled antibodies demonstrated the presence of occult metastatic sites in many patients believed to have a localized primary lesion or recurrent disease. This technique appears to be especially adept at identifying microscopic disease in celiac or extraperitoneal nodes that usually are not evaluated by traditional surgical exploration. When imaging techniques were used to identify antibody uptake, there was a significant increase over the use of CT alone in the ability to detect unresectability.

**CHEMOTHERAPY FOR METASTATIC COLORECTAL CANCER**

Metastatic colorectal cancer is a resistant disease, and the dismal 5-year survival reflects this difficulty extremely well. Both MDR1 and GSH S-transferase gene expression are thought to be increased in colon cancer cells. However, this belief has not been confirmed universally. The human mdr1P glycoprotein is overexpressed in multidrug resistant tumor cells and is believed to play a role in the elimination of certain cytotoxic drugs used in the chemotherapy of colorectal cancer. GSH S-transferases are thought to impart resistance to different chemotherapeutic agents, especially alkylating agents. The mean GSH S-transferase level is significantly increased in colon cancer as compared with the level in adjacent normal tissue. The paucity of chemotherapeutic agents with activity in colorectal cancer reflects the intrinsic resistance demonstrated in those cells.

**5-FLOUROURACIL**

Since its introduction by Heidelberger et al. (1957) in 1957, 5-FU has become firmly established as the most important antineoplastic drug in the treatment of colorectal cancer. Trials demonstrated that 5-FU's bioavailability when administered orally is erratic, with less than 75% of a dose reaching the systemic circulation and marked variability in plasma levels observed among patients. This pharmacologic observation led to the development of 5-FU as an intravenous agent. The variability in oral absorption might be associated with varying levels of DPD, the first catabolic enzyme in 5-FU metabolism in the GI tract. 5-FU has been used in a variety of schedules, and determining the best dose, method, and duration of its administration has been the object of intense investigation.

The overall response rate for single-agent 5-FU has been reported to be as high as 30% but, realistically, it is closer to 20%. Median survival for patients responding to 5-FU treatment is believed to be in the 12- to 18-month range. Accumulated clinical evidence suggests that the use of protracted intravenous infusion of 5-FU may be superior and better tolerated than intravenous bolus dosing and that modulation of 5-FU may yield higher response rates.

**Continuous Infusion**

Lokich et al. demonstrated clearly the feasibility of a continuous infusion of 5-FU as a treatment for colorectal cancer. When administered for protracted periods, the major toxicity of 5-FU is mucositis. Additionally, hand-foot syndrome is seen in approximately 5% to 25% of patients. The lack of significant hematologic toxicity makes continuous-infusion regimens very attractive. The results from larger randomized trials are encouraging. Despite a response rate and overall survival that are statistically equivalent to those of bolus regimens, as shown in the SWOG experience, the single-agent infusion regimens demonstrated a favorable toxicity profile and a trend toward longer survival. A metaanalysis involving 1219 patients treated in six randomized trials confirmed the superiority of continuous infusion 5-FU over bolus regimens regarding response rates and toxicity. Even though the overall survival was superior for the continuous-infusion group, the medians were very similar. The need for a central venous catheter, with its inherent problems (e.g., infection, thrombus, and slippage) and for a portable pump and the cost and inconvenience for the patients are the major problems associated with continuous-infusion regimens. However, they are acceptable alternatives in the treatment of colorectal cancer patients.

**Biochemical Modulation of 5-Fluorouracil**

The relatively disappointing results of single-agent 5-FU led many investigators to explore the use of agents that could modulate its activity. One approach to improve the activity of 5-FU has been the addition of biochemical modulators to 5-FU regimens. Several modulators have been studied, among them leucovorin, methotrexate, trimetrexate, and IFN-a. Of these biochemical modulators, leucovorin is without doubt the most successful. This agent, also known as folinic acid, is a tetrahydrofolic acid derivative that can enhance the therapeutic and toxic effects of fluoropyrimidines such as 5-FU. The reduction in DNA synthesis by 5-FU involves the formation of a complex ofFdUMP, thymidylate synthetase (TS), and a cofactor designated 5’10 methylene tetrahydrofolate (Me-THP). The enzyme TS is essential to DNA synthesis because it is the only source of thymidylate in the cell, convertingdUMP to dTMP. If the enzyme becomes trapped in a complex withFdUMP and Me-THP, it is no longer able to convert dUMP to dTMP, and DNA synthesis is reduced. DNA synthesis is not completely inhibited because there is turnover of theFdUMP/TS/Me-THP complex, freeing up the TS to convert dUMP to dTMP, although in reduced quantities. Leucovorin enhances the inhibition of DNA synthesis by stabilizing theFdUMP/TS/Me-THP complex.

In a metaanalysis of nine randomized trials of advanced colorectal cancer comparing 5-FU alone with 5-FU plus leucovorin, significant improvement in response rate was seen in patients receiving 5-FU and leucovorin as compared with those receiving 5-FU alone. This improvement in response did not result in a significant survival advantage in most studies. However, Poon et al. were able to demonstrate a statistically significant survival advantage for the combination of 5-FU with leucovorin over 5-FU alone or in combination with methotrexate. The leucovorin dose and schedule required for optimal modulation of 5-FU has not been clearly defined. Doses ranging from 20 to 500 mg/m² of leucovorin have been administered on daily or weekly schedules.

In an attempt to determine the best regimen of 5-FU, the SWOG randomly allocated 626 patients to receive one of seven regimens: (1) 5-FU alone, (2) 5-FU with low-dose leucovorin, (3) 5-FU with high-dose leucovorin, (4) 5-FU by continuous infusion, (5) 5-FU by continuous infusion plus weekly leucovorin, (6) 5-FU by 24-hour infusion, and (7) 5-FU by 24-hour infusion plus PALA. There was no statistical difference in the response rates, which ranged between 15% and 29%, with a median survival for the entire group of 14 months. Despite the statistically equivalent efficacy, the single-agent infusion regimens demonstrated encouraging results, with a favorable toxicity profile trend toward longer survival.
A metaanalysis involving 1219 patients treated in six randomized trials confirmed the superiority of continuous-infusion 5-FU over bolus regimens in terms of response rates and toxicity. Even though the overall survival was superior for the continuous-infusion group, the medians were very similar.  

A bimonthly regimen combining bolus with 24-hour infusion of 5-FU plus high-dose leucovorin has been extensively examined in France. A study comparing bimonthly with monthly 5-FU plus leucovorin noted a higher response and more favorable toxicity profile for the bimonthly schedule but no statistically significant improvement in overall survival.  

**INTERFERON.** The combination of IFN-α and 5-FU has demonstrated synergistic cytotoxicity against human colon cancer cell lines in preclinical studies. The exact mechanism of action of IFN when combined with 5-FU is unknown. The principal advantage of adding IFN is to potentiate 5-FU-induced DNA strand breaks. The addition of IFN also seemed to increase the 5-FU exposure by decreasing its clearance.  

Waddell et al. initially reported a response rate of 63% for the combination of 5-FU and IFN. Based on this promising result, multiple trials were conducted using IFN as a 5-FU modulator, showing response rates in the range of 25% to 40%. The toxic effects were significant and included leukopenia, mucositis, diarrhea, fever, chills, myalgia, and neurotoxicity. A group of researchers at the Royal Marsden Hospital randomized patients to receive 5-FU, 750 mg/m² by continuous infusion for 5 consecutive days, followed by weekly bolus 5-FU, 750 mg/m² either with or without IFN (10 MU subcutaneously three times weekly). Objective response was observed in 10% of the patients who received 5-FU plus IFN and in 30% of those who received 5-FU only. Patients who received IFN did experience significantly more toxicity. The NSABP C-05 protocol compared 5-FU plus leucovorin with the same combination plus IFN. With 2176 patients evaluated, there was no statistically significant difference in either disease-free survival or overall survival. Toxic effects were observed in 61.8% of patients in the 5-FU plus leucovorin group and in 72.1% of patients in the IFN group. These results indicate that the use of IFN as a 5-FU modulator added to the toxicity of the regimen without affecting efficacy. This regimen has been largely abandoned and should not be used outside an investigational trial.  

**TRIMETREXATE.** Trimetrexate, a dihydrofolate reductase inhibitor, potentiates the cytotoxicity of 5-FU. Phase II studies demonstrated objective responses with trimetrexate plus 5-FU and leucovorin in patients previously treated with and without 5-FU. However, severe diarrhea and hypersensitivity were observed with this combination regimen. Blanke et al. reported the results of a phase II study combining trimetrexate, 5-FU, and leucovorin in patients with advanced colorectal cancer. Thirty-eight patients received trimetrexate, 110 mg/m² on day 1, leucovorin, 200 mg/m² on day 2, and 5-FU, 500 mg/m² on day 2 immediately after leucovorin. Oral leucovorin, 15 mg, was given every 6 hours for seven doses. This regimen was repeated weekly for six courses every 4 weeks. Two patients achieved a complete response, and the overall response rate was 50%. Diarrhea was the most common toxicity. A phase II trial involving patients with previously treated colorectal cancer disclosed a disappointing 4% overall response rate. A randomized phase III trial comparing 5-FU plus leucovorin against a combination of 5-FU, leucovorin, and trimetrexate has completed accrual. Final results have not been reported.  

**ORAL FLUOROPYRIMIDINES**  
Oral fluoropyrimidines are thought to provide prolonged exposure to 5-FU with lower peak concentrations than those observed with bolus schedules of intravenous 5-FU. This may reduce the occurrence of toxic effects associated with a high plasma concentration of 5-FU, such as neutropenia and stomatitis. 5-FU has been studied in several different dosing schedules, and clinical trials suggest the importance of constant exposure to 5-FU. The toxicity profile of 5-FU is schedule-dependent and, whereas bolus schedules produce mainly neutropenia, protracted infusions produce mainly stomatitis and hand-foot syndrome. Additionally, cancer patients seem to prefer the convenience of oral instead of intravenous medications, as long as the efficacy remains at least equal for both modalities.  

In the last decade, several oral agents have been introduced for the treatment of colorectal cancer in the Western world (Table 33.7–18). The erratic bioavailability of oral 5-FU caused by the varying GI levels of DPD, the primary catabolic enzyme of 5-FU, was overcome by the development of 5-FU prodrugs that are well absorbed enterally and then are enzymatically converted to 5-FU or by the coadministration of DPD inactivators.  

**TABLE 33.7–18.** Summary of Recent Randomized Trials Comparing Intravenous 5-FU/LV versus Oral Fluorinated Pyrimidines for the Treatment of Advanced Colorectal Cancer  

**Uracil, 5-Fluourouracil, and Tegafur**  
Tegafur is a prodrug of 5-FU originally studied in the United States as an intravenous medication. The agent was believed to be too toxic, and so its development as an intravenous medication was discontinued. In the early 1980s, tegafur was tested as an oral medication at the M. D. Anderson Cancer Center, and it was shown to have antitumor activity when administered this way. At the same time, Japanese investigators began to study and use tegafur as an oral medication. Uracil, a competitive inhibitor of DPD, was later combined with tegafur to provide sustained levels of 5-FU. The combination of uracil, 5-FU, and tegafur is known as UFT. The previously demonstrated activity and favorable toxicity profile of UFT led to its development as an oral alternative to intravenous 5-FU for the treatment of solid tumors, especially colorectal cancer.  

Two large, multinational phase III trials comparing the oral regimen of UFT plus leucovorin to intravenous 5-FU and leucovorin as the initial treatment for patients with metastatic colorectal cancer have been reported. In the first trial, 816 patients were randomly allocated to intravenous 5-FU plus leucovorin or to oral UFT and leucovorin. UFT was taken at a dose of 300 mg/m² in three divided doses for 28 days followed by 1 week of rest. Oral leucovorin was administered at 90 mg/d, with the UFT administered at the same frequency daily. The intravenous 5-FU and leucovorin were administered for 5 consecutive days, with cycles repeated every 28 days. The study demonstrated statistical equivalence of 12.4 months for the UFT plus leucovorin arm and 13.4 months for the intravenous arm. No statistical difference was seen for the two treatment arms regarding response (12% for UFT plus leucovorin and 15% for intravenous 5-FU plus leucovorin). Severe neutropenia and stomatitis were less common in the oral regimen.  

The second trial compared time to progression between patients receiving an intravenous 5-FU plus leucovorin regimen or UFT plus leucovorin. Three hundred and eighty patients were randomized to two treatment groups that were identical to those described in the first study except that the intravenous 5-FU plus leucovorin was repeated every 35 days. The treatment arms were equivalent in terms of time to progression, with a median of 3.4 months in the UFT plus leucovorin group and 3.3 months in the intravenous 5-FU plus leucovorin group. The median survival times were 12.2 and 11.9 months, respectively.  

**Capcitabine**  
Capcitabine, a fluoropyrimidine carbamate, was developed as an oral alternative to intravenous 5-FU. Capcitabine is absorbed through the intestinal mucosa as an intact molecule, not being affected by the thymidine phosphorylase present in the intestines. It then is metabolized in the liver by carboxylesterase to
5'-deoxy-5-fluorouridine (5'DFCR), which is converted by cytidine deaminase to 5'DFUR mainly in the liver and tumor tissues. Finally, 5'DFUR is metabolized by thymidine phosphorylase to 5-FU at the tumor site. Preclinical studies demonstrated capecitabine's activity in 5-FU-sensitive and -resistant cell lines. Colorectal cancers, like many other solid tumors, tend to have high levels of thymidine phosphorylase, which is known for its angiogenic properties.

In phase I trials, diarrhea, vomiting, and hand-foot syndrome (palmar-plantar erythrodysesthesia) were dose-limiting toxic effects. A large multinational, randomized, open-label phase II trial evaluated three schedules of capecitabine (i.e., continuous, intermittent, and intermittent with leucovorin) in metastatic colorectal cancer. The response rates for the three groups ranged from 21% to 24%. The median time to disease progression ranged from 127 to 230 days, with the best time to disease progression seen in patients treated in the intermittent capecitabine arm, without leucovorin. The addition of leucovorin seemed to increase the incidence of toxic effects, without improving therapeutic activity.

Results of two phase III trials comparing capecitabine, 2500 mg/m²/d for 2 weeks every 3 weeks, to bolus 5-FU, 425 mg/m²/d, plus leucovorin, 20 mg/m²/d, daily for 5 days every 4 weeks, as first-line treatment for metastatic colorectal cancer, were recently reported at the 1999 American Society of Clinical Oncologists’ meeting. The first trial enrolled 602 patients, and the second trial enrolled 605 patients. Both trials demonstrated a higher response rate with capecitabine as compared with bolus 5-FU plus leucovorin. Taking into account all randomized patients using intention-to-treat analysis, investigator response rates were 26.6% versus 17.9% (95% CI, 1.9% to 15.1%) in the first trial and 24.8% versus 15.5% (95% CI, 2.8% to 15.5%) in the second trial. The median survival duration was 54 versus 57.1 weeks (P = .2363), respectively. The toxicity profile of capecitabine was favorable, with fewer treatment-related serious adverse events and hospitalizations in the capecitabine arm as compared with the 5-FU plus leucovorin arm. The most common adverse events with capecitabine were palmar-plantar erythrodysesthesia (hand-foot syndrome) and diarrhea.

**Eniluracil**

Eniluracil, also known as 776C85 and ethynyluracil, is a potent irreversible inactivator of DPD, the first enzyme in the degradative pathway of 5-FU. When it is used in combination with an oral formulation of 5-FU, eniluracil makes the absorption and bioavailability of 5-FU more reliable, and the 5-FU bioavailability and half-life are increased.

Phase I trials have demonstrated that a dose ranging from 10 to 40 mg/d of eniluracil inactivates DPD maximally. The concentration of 5-FU obtained with a 28-day oral dosing regimen of this agent plus eniluracil is similar to steady-state concentrations from protracted intravenous infusions of 5-FU. Main toxic effects included fatigue and diarrhea. Nausea, vomiting, mucositis, pain, dehydration, and constipation were relatively uncommon.

Based on these results, a phase II trial of 5-FU, 1.0 mg/m²/d, plus eniluracil, 10 mg/m², orally twice daily for 28 days followed by a 7-day rest period was conducted in patients with previously untreated colorectal cancer. However, after approximately one-third of the patients had been treated, the doses of both agents were increased because of the unexpectedly low toxicity observed. The doses were increased to 5-FU, 1.15 mg/m², and eniluracil, 11.5 mg/m², twice daily for 28 days. The objective response rate was 29%. This dose and schedule is currently being used in two pivotal trials comparing this oral combination with intravenous 5-FU plus leucovorin and with a protracted intravenous schedule of 5-FU in metastatic colorectal cancer patients.

**IRINOTECAN**

Camptothecin is an agent derived from the Chinese ornamental tree Camptotheca acuminate. Its clinical development began in the United States in the late 1960s but was eventually halted due to excessive toxicity. In the late 1980s, irinotecan, also known as CPT-11, an analogue of camptothecin, was developed in Japan. Pivotal phase II studies of irinotecan in advanced colorectal carcinoma were conducted in the United States, including patients who had received prior chemotherapy with 5-FU and had progressed while on treatment within the last 6 months. The dose of irinotecan ranged from 100 to 150 mg/m² given weekly for 4 weeks, followed by 2 weeks of rest. The overall response rate ranged from 12.5% to 23%. Grade 3 and 4 toxicities were noted in 30% of patients, with a 20% hospitalization rate for diarrhea.

In phase I trials, diarrhea, vomiting, and hand-foot syndrome (palmar-plantar erythrodysesthesia) were dose-limiting toxic effects. After a median follow-up of 13 months, the overall survival was significantly better in the irinotecan group (P = .0001), with a 36.2% 1-year survival rate in the irinotecan group versus 13.8% in the supportive-care group. In a quality-of-life analysis, all significant differences except diarrhea favored the irinotecan group.

![FIGURE 33.7-7. Probability of survival of the 279 patients enrolled in a trial of irinotecan versus supportive care for metastatic colorectal cancer refractory to 5-fluorouracil. (From ref. 479, with permission.)](image1)

![FIGURE 33.7-8. Survival curve in patients on irinotecan or infused 5-fluorouracil for advanced colorectal cancer refractory to first-line 5-fluorouracil. (From ref. 485, with permission.)](image2)

Rougerie et al. reported the results of the second trial, in which 267 patients with advanced colorectal cancer in whom 5-FU therapy had failed received either second-line fluorouracil by continuous infusion or irinotecan, 300 to 350 mg/m² infused once every 3 weeks. Patients treated with irinotecan lived longer than patients receiving second-line infusional 5-FU (P = .035). Median survival duration was 10.8 months in the irinotecan group and 8.5 months in the 5-FU group (Fig. 33.7-8).
A randomized phase III trial compared the combinations of irinotecan plus 5-FU and leucovorin with 5-FU plus leucovorin and single-agent irinotecan as first-line treatment of patients with advanced colorectal cancer (Table 33.7-19). Approximately 220 patients were enrolled in each of the three treatment groups. Objective responses were noted in 51% of patients receiving the three-drug combination, 29% of patients receiving 5-FU with leucovorin, and 30% of patients receiving single-agent irinotecan ($P<.001$). The median time to treatment failure for each of the three treatment groups was 5.4, 3.9, and 3.2 months, respectively. The median survival duration, however, did not achieve a statistical difference, with a median survival of 14.4 months for the triple combination, 12.6 months for 5-FU plus leucovorin, and 12.0 months for the group receiving irinotecan ($P=.173$). A new analysis is planned when the data mature further.

### TABLE 33.7-19. Summary of Recent Randomized Trials Comparing 5-FU/LV versus Irinotecan or Oxaliplatin for the Treatment of Advanced Colorectal Cancer

A second phase III trial, conducted primarily in Europe, examined the role of irinotecan plus 5-FU and leucovorin in the first-line setting. This trial randomized 387 patients to receive either of two commonly used 5-FU plus leucovorin regimens with or without irinotecan. Response rates were significantly improved with the use of irinotecan (49% vs. 23%). Additionally, the median survival was statistically superior for the group receiving irinotecan with the 5-FU plus leucovorin (16.8 vs. 14 months). The combination of irinotecan with 5-FU and leucovorin is being investigated against other promising combinations and against standard 5-FU plus leucovorin in a large intergroup trial in the United States.

### OXALIPLATIN

Oxaliplatin is a novel diamino-cyclohexane platinum agent that acts mainly by causing interstrand and intrastrand cross-links in DNA. It has been investigated as a single agent in colorectal cancer both in previously treated and untreated patients. In chemotherapy-naive patients with advanced colorectal cancer, two phase II trials assessed the activity of oxaliplatin, 130 mg/m², given over 2 hours every 3 weeks. Response rates ranged from 20% to 24%, with a median response duration of 6 to 7 months and a median progression-free survival of approximately 4 months. Peripheral neuropathy and laryngopharyngeal dysesthesia were the main toxicities reported in previously treated patients, the overall response rate was considerably lower (10%), and the median survival duration was 8.5 months.

Preclinical models demonstrated synergy between oxaliplatin and 5-FU, and this was subsequently confirmed in clinical trials. A phase II trial involving 90 patients with advanced colorectal cancer evaluated the combination of chronomodulated 5-FU, 700 mg/m²/day, leucovorin, 300 mg/m²/day, and oxaliplatin, 25 mg/m²/day, given for 4 days every 2 weeks. The response rate was 50%, and the median survival duration was 15 months.

The potential benefits of oxaliplatin when added to 5-FU and leucovorin as first-line therapy for patients with advanced colorectal cancer were subsequently evaluated in phase III randomized trials (see Table 33.7-19). A study with 200 patients compared chronomodulated 5-FU plus leucovorin administered every 3 weeks with or without oxaliplatin at 125 mg/m² given over 6 hours on day 1. The overall response rates were 53% versus 16% ($P<.001$) for the combinations with and without oxaliplatin, respectively. However, the overall survival duration was equivalent in both arms (19.4 vs. 17.6 months, respectively). This survival equivalence was attributed to crossover and surgery after chemotherapy.

A second study reported by De Gramont et al. randomized 420 patients to receive 5-FU plus leucovorin on days 1 and 14 of a 28-day schedule with or without oxaliplatin, 85 mg/m². The response rates in the first 200 patients were 57% versus 26% in patients treated with and without oxaliplatin, respectively. The corresponding median progression-free survival duration for the treatment groups was 39.6 versus 27.8 weeks. Once more, however, no significant impact on overall survival has been demonstrated ($P=.12$).

As second-line therapy, oxaliplatin in combination with 5-FU and leucovorin has also shown promising results. In one trial, 46 patients with 5-FU-refractory colorectal cancer were treated with oxaliplatin administered as a 2-hour infusion on day 1, followed by leucovorin on days 1 and 2, and 5-FU as a 24-hour infusion for 2 consecutive days. Treatment was repeated every 2 weeks. The overall response rate was 46%, and median survival duration was 17 months. Limiting toxicities were neutropenia and peripheral neuropathy. A second trial involving the addition of oxaliplatin, 85 mg/m² every 2 weeks, to the same 5-FU plus leucovorin regimen under which patients had progressed produced an overall response rate of 20%, a median response duration of 37 weeks, and a median survival duration of 57 weeks.

The combination of oxaliplatin and irinotecan in patients with 5-FU-refractory colorectal cancer was recently reported. The overall response rate among the 34 treated patients was 44%, with stable disease in another 35% and a median time to progression of 7.5 months.

### RALTITREXED

Raltitrexed is transported into cells by the reduced folate carrier, metabolized to a polyglutamate species, and retained intracellularly, resulting in prolonged TS inhibition. It is the first of the specific TS inhibitors to have undergone extensive clinical evaluation, and it is currently approved for treatment of colorectal cancer by regulatory agencies in Europe, Canada, Australia, and South America.

The efficacy of raltitrexed as monotherapy for patients with advanced colorectal cancer was evaluated in three phase III clinical trials. Two international trials, one with 439 patients and the other with 495 patients, compared intravenous bolus raltitrexed, 3 mg/m² repeated every 3 weeks, to daily intravenous bolus 5-FU, 425 mg/m²/day, plus leucovorin, 20 mg/m²/day for 5 days (Mayo regimen), or to 5-FU, 400 mg/m²/day, plus leucovorin, 200 mg/m²/day (Machover regimen) repeated every 4 weeks. The third trial was conducted in the United States and compared two raltitrexed dosages (3 mg/m² and 4 mg/m² every 3 weeks) with the Mayo regimen. However, because of the unacceptable toxicities seen with the 4 mg/m² dose, subsequent analyses were based on a two-treatment comparison with 427 patients. All three trials produced similar response rates ranging from 14% to 19% for the raltitrexed group and from 15% to 18% for the 5-FU plus leucovorin group. In all three trials, survival duration ranged from 10 to 12 months. The study conducted in the United States showed a significant difference in survival duration (9.7 vs. 12.7 months; $P=.01$) between the two treatment groups, favoring the 5-FU with leucovorin group. The main advantage of raltitrexed is its easy schedule, allowing a single intravenous treatment every 3 weeks.

Several studies have been conducted using hepatic arterial infusion in patients with advanced colorectal cancer with liver metastasis. Response rates have been consistently superior for the arms using hepatic arterial infusion; however, a convincing survival advantage has never been shown (Table 33.7-20). The use of hepatic arterial infusion for treatment of advanced colorectal cancer still must be considered investigational.
SUMMARY

After four decades, 5-FU remains the mainstay of treatment for colorectal cancer. However, the advent of newer agents has introduced new options for the treatment of this disease. Ongoing trials are determining which agent, or combination of agents, should be considered the gold standard in treatment of advanced colorectal cancer. The increased response rates and prolonged progression-free survival seen with the combinations of 5-FU, leucovorin, and either irinotecan or oxaliplatin are very exciting and warrant their consideration as front-line therapy. The use of agents that are able to maintain the same efficacy as older regimens with improved convenience and less toxicity may have a positive impact in the quality of life of patients as well. However, an improvement in survival will be needed for the establishment of a clear new standard. For now, whenever possible, patients should be encouraged to participate in well-designed clinical trials involving new regimens, because despite the impressive advances seen in the last few years, advanced colorectal cancer remains a highly lethal disease.

MISCELLANEOUS COLORECTAL TUMORS

CARCINOIDs

Carcinoid tumors of the GI tract, although characteristically indolent, are also quite heterogeneous with respect both to histologic and endocrine features and to clinical presentation and behavior. Because they are relatively uncommon, most reports do not have a significant number of patients for a detailed analysis. For decades, a series including 2837 cases published in 1975 remained the largest available reference. Modlin and Sandor recently evaluated an impressive 8305 cases. The most frequent sites for carcinoids were the GI tract (74% of cases) and the bronchopulmonary system (25% of cases). Within the GI tract, 29% of cases occurred in the small bowel, 19% in the appendix, and 13% in the rectum. The highest incidence rates were seen among African American men (2.12 per 100,000 per year).

The clinical presentation is usually indistinguishable from that of colorectal adenocarcinoma, and most patients are asymptomatic at the time of diagnosis in 45% of the patients and that the overall 5-year survival rate of all carcinoid tumors, regardless of site, is 50%. The 5-year survival rate for carcinoid tumors of the GI tract varied markedly. It was considerably lower for pancreatic (34%), colonic (41%), and small intestinal tumors (55%) and better for appendiceal (86%), bronchopulmonary (76.6%), and rectal carcinoids (72.2%). These improved 5-year survival rates were associated with a lower incidence of invasive growth or metastatic spread. A search for additional tumors is generally advised, because multiple carcinoids and second neoplasms are not uncommon.

Most carcinoid tumors are clinically silent, and the diagnosis is not made before surgery. Surgical treatment depends on the localization and size of the tumor. Small bowel carcinoid tumors metastasize in 20% to 30% of the cases if the tumor is smaller than 1 cm. Therefore, the primary tumor should always be resected widely, including the regional lymph nodes. Carcinoid tumors of the appendix measuring less than 1 cm usually do not metastasize. For such patients, an appendectomy is the treatment of choice. For tumors larger than 2 cm, a right hemicolectomy should be performed. If the tumor is between 1 and 2 cm, surgical treatment depends on the presence of positive lymph nodes, extension of the tumor into the mesoappendix or subserosal lymphatic invasion, and age of the patient. Carcinoid tumors of the colon and rectum measuring less than 2 cm rarely metastasize. Surgical treatment for patients with such small tumors is local excision, whereas for patients with tumors larger than 2 cm, wide resection is advocated.

SARCOMAS

Rarely, tumors may arise directly from the stromal and smooth muscle elements in the colon or rectum. These tumors are known as smooth muscle tumors or stromal tumors of the colon and rectum. These mesodermal tumors are essentially leiomyosarcomas. The true incidence of leiomyosarcomas in the colon and rectum is unknown. Only small numbers of patients have been reported to date, all in small series.

The most common anatomic location of leiomyosarcoma is the stomach (47%), followed by small intestine (24%), rectum (11%), colon (7%), duodenum (5%), and esophagus (5%). Symptoms and physical findings are nonspecific, with pain, palpable masses, and melena being the most common. Patients frequently present with GI bleeding and significant anemia. The only therapy with accepted value is surgery with wide margins. Chemotherapy is of unproven value as an adjuvant and as treatment for this type of tumor. The tumor grade is an important prognostic factor. In patients resected with curative intent who have low-grade lesions, disease-free survival at 8 years exceeds 80%, as compared with a mean disease-free interval of only 18 months for patients with high-grade lesions.

Other authors have confirmed that the stage of the tumors and the presence of high-grade features are the main independent factors that affect survival. DNA ploidy is not an independent prognostic factor for survival in patients with leiomyosarcomas. Recurrences are noted at regional and distant sites. The prognosis for patients with leiomyosarcoma is guarded, and almost two-thirds of the patients die within 1 year. The use of adjuvant radiation therapy in patients with resected leiomyosarcomas of the rectum may improve local control and allow for sphincter preservation. It is unlikely that large randomized trials for the treatment of colorectal leiomyosarcomas will ever be conducted owing to the rarity of this disease. Patients with advanced cases should be encouraged to participate in trials designed for GI leiomyosarcomas in general.

LYMPHOMA

Colorectal lymphomas account for fewer than 1% of all colorectal cancers but account for 15% of all GI lymphomas. Most cases involve the cecum and the rectum. Virtually all colorectal lymphomas are non-Hodgkin's type, including both B- and T-cell types of low-, intermediate-, and high-grade histologies. Immunohistochemical studies usually show a preponderance of B-cell phenotype. Colorectal non-Hodgkin's lymphoma is a disease that affects both the pediatric and adult population and, although pediatric patients have an excellent prognosis, long-term survival can be expected in only approximately 50% of adult patients.

The diagnosis of colorectal lymphoma must be confirmed histologically and by the absence of evidence of primary lymphoma elsewhere by imaging studies or clinical examination (i.e., evidence of splenomegaly, or palpable lymphadenopathy). In addition, both the peripheral smear and the bone marrow must be determined to be normal. Colorectal lymphomas usually present with a mass, symptoms of obstruction, or signs of bleeding. The clinical presentation is usually indistinguishable from that of colorectal adenocarcinoma, and most patients are asymptomatic at the time of diagnosis.

Patients with colon lymphoma often are treated initially with surgery. The lack of well-designed trials makes any recommendation extremely difficult. The use of combined-modality treatment, including surgery and chemotherapy, seems to yield superior results. Several authors have recommended the use of radiation therapy, especially in cases involving low-grade lymphomas, bulky disease, positive lymph nodes, or incomplete resection. The true role of radiation therapy in colon lymphomas is still uncertain.

Radiation therapy is more attractive in cases involving the rectum. However, patients treated with radiation therapy alone have a very poor long-term survival. Whenever possible, combined-modality surgery and radiation therapy should be considered. The use of chemotherapy in earlier disease stages is controversial but should be considered for patients with advanced-stage disease or more aggressive histologic types. Because of the rarity of this cancer, patients should be encouraged to be treated in larger centers where there is experience in the management of lymphomas.
EXTRACTION RESULTS: extrapolational small cell carcinomas \vspace{2pt} small cell carcinosomas are very uncommon, accounting for fewer than 1000 cases annually. Histologically, small cell carcinosomas arising from different organs are indistinguishable, and a lung primary should also always be ruled out. Fewer than 100 cases have been reported since 1961, the most frequent site being the rectum, followed by the cecum and sigmoid.

The presentation is similar to that of adenocarcinomas and includes weight loss, bleeding, abdominal pain, and change in bowel habits. Metastasis is common, affecting 85% of the patients at the time of diagnosis. The liver is the organ most frequently involved by metastasis, but almost any organ may be affected. Patients with brain metastases can be treated aggressively with a multidisciplinary approach, including local therapy with surgery or radiation therapy (both) and chemotherapy. Patients with advanced disease should receive chemotherapy. The chemotherapy should be based on accepted treatment regimens used in the treatment of small cell lung carcinomas.

CHAPTER REFERENCES


SECTION 33.8
Cancer of the Rectum

JOHN M. SKIBBER
PAULO M. HOFF
BRUCE D. MINSKY

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Lymphatic Drainage
Bowel Function
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Site-Specific Treatment Options
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Subtotal Resection and Postoperative Radiation Therapy
Preoperative Radiation Therapy Following Surgery
External-Beam Radiation Therapy Alone
Postoperative Radiation Therapy and Chemotherapy
Intraoperative Radiation Therapy Alone for Gross Residual Disease
Investigational Radiation Therapy Approaches
Neutron Beam Radiation Therapy
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Surgery for Locally Recurrent Rectal Cancer
Location of Recurrence
Evaluation of the Patient with Locally Recurrent Rectal Cancer
Imaging Patients with Local Recurrence
Surgery for Recurrence
Chapter References

INTRODUCTION
Many overlapping issues in the management, biology, pathology, and staging of colon and rectal cancer are discussed in Chapter 33.7. Issues of sphincter preservation, locoregional recurrence, and the application of multidisciplinary management in rectal cancer are the focus of this chapter.
ANATOMY

The rectum is usually divided into three portions (Fig. 33.8-1). The lower rectum is the area 3 to 6 cm from the anal verge. The midrectum is 6 to 10 cm, and the upper rectum extends approximately 10 to 15 cm, from the anal verge. The rectum usually reaches its upper limit at approximately 12 cm from the anal verge. Externally, its upper extent can be identified where the tenia spread to form a longitudinal coat of muscle. The upper third of the rectum is surrounded by peritoneum on its anterior and lateral surfaces. At the rectovesical or rectoureteral pouch, the rectum becomes completely extraperitoneal. The rectum follows the curve of the sacrum in its lower two-thirds. It enters the anal canal at the level of the levator ani. The anorectal ring is at the level of the puborectalis sling portion of the levator muscles. The location of a rectal tumor is usually indicated by the distance between the anal verge, dentate line, or anorectal ring and the lower edge of the tumor. These points of reference are all different. Also, these measurements differ depending on the use of a rigid or flexible endoscope.

FIGURE 33.8-1. Division of the rectum into upper, middle, and lower thirds.

LYMPHATIC DRAINAGE

The majority of the lymphatic drainage of the rectum passes upward along the superior hemorrhoidal artery toward the inferior mesenteric artery. Perirectal nodes above the midrectum drain along the superior hemorrhoidal artery. Below 7 to 8 centimeters from the anal verge, they drain laterally along the middle hemorrhoidal artery and the iliac nodes and the obturator fossa. Hypogastric and iliac node drainage is along the aorta. Lymphatics are common in the rectovaginal septum in women, which is analogous to the Denovilliers’ fascia in men.

BOWEL FUNCTION

Mechanisms of fecal continence include both sphincter control and creation of the neorectal angle where the rectum sweeps anteriorly and then enters the anal canal. The floor of the pelvis is formed by the levator ani muscles, which separate the pelvis from the perineum and ischiorectal fossa. The urethra, vagina, and anus pass through the levators.

Surgical procedures for rectal carcinoma can have marked impact on rectal function. The degree of this alteration depends on the extent of rectal resection. Other factors affecting bowel function include postoperative radiation therapy or pelvic sepsis. These may reduce the compliance of the newly constructed rectal reservoir. Although overall sphincter function usually is maintained after sphincter-preserving surgery and adjuvant therapy, subtle changes in function can be observed that reduce discrimination between gas, liquid, or formed stool.

AUTONOMIC NERVES

An understanding of the autonomic nerve supply to pelvic organs is critical in preservation of sexual and bladder function after rectal cancer surgery. The sympathetic trunks converge over the sacral promontory to form the hypogastric plexus. These trunks run underneath the pelvic peritoneum laterally to the sidewall or the pelvis. These trunks are lateral to the mesorectum. The fibers from these nerves follow arteries supplying the pelvic viscera. Parasympathetic fibers to the pelvic viscera emerge from the second, third, and fourth sacral nerve roots overlying the piriformis muscle. The parasympathetic fibers proceed laterally as the nervi erigentes to join the sympathetic fibers at the site of the pelvic plexus that is just lateral and somewhat anterior to the tips of the seminal vesicle in men. Sharp section of the mesorectum preserves these structures.

DIAGNOSIS

Compared to more proximal colon cancers, tumors arising in the rectosigmoid area are much more prone to present with symptoms. Although all colorectal cancers have a high rate of occult blood in the stool, the rectal cancers are associated with a higher incidence of anemia, left colon and rectal cancers have a higher incidence of gross bleeding. Cheung and colleagues evaluated prospectively 337 patients presenting with frank rectal bleeding. After making a clinical diagnosis, flexible sigmoidoscopy followed by barium enema was performed. Excluding seven digitally palpable rectal cancers, 30 cancers (9.5%), 34 polyps (10%), 7 cases of proctitis (2%), and 25 cases of bleeding diverticula (7%) were detected. The authors concluded that patients with frank rectal bleeding should be screened routinely for left colon cancer irrespective of the clinical diagnosis. This recommendation highlights the fact that hemorrhoids should be considered a diagnosis of exclusion. Patients should have a total colon examination by either a combination of flexible sigmoidoscopy and barium enema, or by a colonoscopy. Barium enema may miss a distal cancer and should not be used alone.

Changes in the bowel habits are a common presenting feature for rectal cancers. Although the incidence of bowel obstruction appears to be lower for the rectal lesions, compromise of the rectal reservoir by tumor makes symptoms common. Unexplained constipation, frequently alternating with diarrhea, and changes in the caliber of stools are classic presenting symptoms for rectal cancer and should be promptly investigated. The entire colon should be carefully evaluated, with particular attention to the rectosigmoid area.

Another common symptom from rectal cancer is tenesmus. This sensation results from the circumferential growth and transmural penetration by the primary tumor. It is characterized by a sensation of urgency and inadequate emptying of the rectum. Even though some degree of tenesmus may be seen with less extensive tumors located distally in the rectum, it is usually a sign of advanced disease. Additional symptoms include rectal invasion and pain seen with tumors that have invaded the prostate or bladder that have destroyed the high sacral nerve roots, causing urinary symptoms. Tumors invading posteriorly may cause buttock or perineal pain. These symptoms imply a locally advanced tumor and poor overall prognosis.

Besides the obvious benefits from early diagnosis of colorectal cancer, appropriate staging in rectal cancer is of particular importance. Increased emphasis has been placed on conservative surgical techniques as an alternative to radical surgery for selected patients. The goals of conservative management are to select patients with low risk for nodal metastases and achieve local tumor control while preserving anal sphincter function. Patient selection is critical to obtain results comparable to patients treated with radical surgery. Alternatively, interest has been increasing in the use of neoadjuvant combinations of chemotherapy and radiotherapy in the treatment of more advanced rectal cancers.

RADIOLOGIC EVALUATION

Computed Tomography

The intravenous pyelography that was obtained preoperatively in the past has fallen out of favor and has been replaced by the use of other imaging techniques, such as the computed tomographic (CT) scan. Although conventional CT scanners and experienced radiologists are now widely available, this test remains of limited value in the staging of rectal cancer. It is very useful to evaluate the presence of distant metastasis, to evaluate gross invasion of adjacent organs, and as a follow-up tool.
However, it still lacks sufficient accuracy to be used for preoperative staging as a single test.

Netri and colleagues (1985) preoperatively evaluated 78 patients with rectal adenocarcinoma with digital rectal examination, proctoscopy, double-contrast barium enema, pelvic CT scan, liver ultrasound, and chest x-ray. Data obtained by each diagnostic procedure were compared with the pathologic data. CT scan had an accuracy of 100% for detecting infiltration of the muscularis of the rectum. However, it was less accurate in identifying extrarectal tumor invasion, with an accuracy of 72%. In the evaluation of lymph node involvement, accuracy was 77%, specificity was 74%, and sensitivity was 80%. Liver metastases were detected with 94% accuracy, 97% specificity, and 50% sensitivity. Similarly, Zheng and colleagues (1984) assessed the extent of local spread in 85 patients with rectal carcinoma. In 37 patients with carcinoma of the rectum who were scanned before surgery, good correlation was found between the extent of local invasion assessed by scanning and by postoperative histologic assessment. Scanning was not a reliable method for assessing regional lymph node involvement.

Hundt and colleagues evaluated the use of a subsecond spiral-CT scanner using two contrast medium phases in staging of 37 patients with proven colorectal cancer (14 patients with rectal primaries). The results were compared with the findings of pathologic examination after surgery. The spiral CT had a sensitivity of 97% in the arterial phase and 89% in the venous phase in detecting the carcinoma. The staging results were in accordance with the pathology in 30 of 37 cases (81%) during the arterial phase and in 24 of 37 cases (65%) in the venous phase. Lymph nodes were detected in 27 of 32 patients (84%) during the venous phase. The correct classification of the N stage was possible in 23 of 34 cases (68%). The authors concluded that the arterial phase is superior compared with the venous phase for local tumor staging, and the venous phase is used for lymph node assessment. These results are not dramatically better than the ones previously reported with conventional CT. The role of conventional CT is in assessing patients with colorectal tumors is well established. However, the low accuracy of CT for identifying early stages of primary colorectal cancers prevents its routine use for preoperative clinical staging.

**Magnetic Resonance Imaging**

Magnetic resonance imaging (MRI) remains a relatively expensive imaging method and is not as widely used as CT scanning. However, it has been extensively studied in the diagnosis and staging of rectal cancer. Kusunoki and colleagues (1994) used MRI to evaluate preoperatively the local extension of rectal cancer in 33 patients. The sensitivity rate was 84.2% and the specificity rate was 92.9%. In a series including 61 patients, MRI was reported to have an accuracy of 79% for extent of local involvement, but only 56% for extent of lymph node involvement. These results were inferior to the ones obtained with the use of ultrasound in the same population.

MRI using an endorectal coil allows for an excellent anatomic detail of the three rectal wall layers and a very high spatial resolution. Regular MRI has been compared with endorectal MRI and with endorectal ultrasound (EUS) for preoperative staging of rectal carcinoma. In a small series, the results of the preoperative staging were correlated with the histopathologic findings in 15 patients. MRI correctly staged 10 of 15 patients. Without the endorectal surface coil, only three of six were correct, and with the endorectal surface coil, seven of nine were correct. The authors of this study suggested that endorectal coil MRI use may lead to better staging results with MRI techniques and that the results with endorectal MRI could equal those of EUS for staging small tumors in the rectal wall. Another study evaluated 23 patients with rectal carcinoma using endorectal MRI. The diagnostic accuracy in the evaluation of tumor extent and nodal involvement as compared to surgical pathology was 78.2% and 78.9%, respectively. The major problem was a tendency to overstage parietal infiltration and lymph node involvement.

Although not widely used in the initial staging of rectal cancer, MRI has gained respect for its results in the evaluation of local recurrences. In a small study comparing the relative values of MRI versus CT in diagnosing local recurrence for rectosigmoid cancer, MRI showed superior sensitivity, specificity, and accuracy to CT and better definition of the extent of tumor. At the time of the initial imaging, ten patients had recurrent tumor and four of the remaining eight patients later demonstrated local recurrence. The authors suggested that MRI could equal those of EUS for staging small tumors in the rectal wall. Another study evaluated 23 patients with rectal carcinoma using endorectal MRI. The diagnostic accuracy in the evaluation of tumor extent and nodal involvement as compared to surgical pathology was 78.2% and 78.9%, respectively. The major problem was a tendency to overstage parietal infiltration and lymph node involvement.

ENDORECTAL ULTRASOUND

The interest in developing endoscopic ultrasound as an accurate imaging technique for rectal cancer is not recent. In rectal cancer, the depth of tumor infiltration and metastatic involvement of lymph nodes are important prognostic factors, and EUS of the rectum combines the advantages of both endoscopy and sonography, providing information not available from other imaging diagnostic techniques (Fig. 33.8). Early animal models using dogs demonstrated its superiority against conventional CT scans, and its potential in predicting pathologic stage. The superiority of EUS against CT scan has been confirmed in studies involving human patients, and it has become the preferred method of preoperative local tumor staging. Hildebrandt and Feifel (1985) even proposed an ultrasonic staging system, which corresponded to the standard pathologic staging systems (e.g., T1 for ultrasound T stage, uN for ultrasound N stage).

**FIGURE 33.8-2. Layers of the rectal wall on endorectal ultrasound.**

Detry and colleagues suggested that a low percentage of affected lymph nodes were detected by EUS and that lymph node size was the most reliable parameter to determine tumor involvement. The group at the University Hospital of Wurzburg examined the value of EUS in the preoperative staging of 160 potentially locally resectable tumors. The sensitivity for adenomas and T1 tumors was 81% and the specificity was 98%. For T2 tumors, the sensitivity was only 41% and the specificity, 92%. The majority of T2 tumors were overstaged. The overall staging accuracy for all tumors was 77.5%. The accuracy for lymph node staging was 83%. The authors concluded that adenomas and T1 tumors could be assessed with a high degree of accuracy using EUS. However, T2 carcinomas tended to be overstaged. Similarly, Benini and colleagues (1996) found that EUS after adjuvant therapy for rectal cancer is of a lesser predictive value, chiefly because of overstaging. However, a more recent report by Massari and colleagues that included 85 patients affected by rectal carcinoma showed an overall accuracy in staging depth of infiltration of 91%. Overstaging occurred in only 4% of patients, whereas understaging occurred in 5%. The overall accuracy in staging lymph node involvement was 76%, sensitivity was 69.8%, specificity was 84.4%, positive predictive value was 85.7%, and negative predictive value was 67.5%. The authors concluded that EUS is a safe and accurate diagnostic method for staging both tumor invasion and lymph node metastatic involvement, and for selecting an appropriate surgical strategy in patients affected by rectal cancer.

It is interesting to note that the accuracy of EUS is improving in more recent series, indicating that experience and new knowledge may have an impact on the staging inaccuracies resulting from over- or underestimation of tumor depth and misinterpretation of lymph node involvement. Technical pitfalls in EUS of the rectal wall include difficulty locating the lesion, improper balloon inflation, improper imaging plane, shadowing artifacts due to air or stool, reverberation artifacts, refraction artifacts, and inappropriate transducer setting. Sources of error in tumor staging with EUS include interpretation differences, operator bias, tumor stenosis, peritumoral inflammation, postbiopsy and postsurgical changes, postirradiation changes, hemorrhage, and pedunculated or villous tumors. Saifer and colleagues suggested that the rectal anatomy affects staging accuracy of EUS in the lower rectum because the structure of the ampullar recti renders the examination more difficult and that the endosonographic layers are less well defined at this level. The same study did not show a predictive value for the tumor position with respect to rectal circumference. The presence of peritumoral tissue reaction (PTR) is a common cause of overstaging. Maier and colleagues evaluated the preoperative EUS results in 40 consecutive patients with biopsy-proven rectal cancer and compared them with histopathologic reports on the specimens. Twenty-eight (70%) of 40 rectal
cancers were staged correctly with EUS. PTR was responsible for the misinterpretation in six of seven overstaged cases. In a second part of the study, another 40 patients were prospectively evaluated with EUS. The thickest part of the PTR was measured, and results were compared with the histopathologic findings. Thirty-eight (95%) of 40 cancers were staged correctly, and the presence or absence of PTR was described in 39 cases (98%). A statistically significant positive correlation was noted between histopathologic classification of PTR and its thickness measured with EUS \( (P = .0001) \).

Despite the increased use of preoperative radiotherapy alone or in combination with chemotherapy for the treatment of stages II and III rectal cancers, our ability to assess local eradication of rectal cancer after radiation therapy remains poor. Conventional imaging and clinical examination techniques are unable to safely predict which patients do not require surgical excision after curative radiation therapy for rectal cancer. The postradiation preoperative staging results of 25 patients with rectal cancer who were found to have stage T0N0 lesions after surgery were examined. All 25 patients were staged by digital rectal examination. In addition, 13 patients were assessed using CT, six by EUS, and one by MRI. Radiologic assessment and physical examination overstaged most irradiated lesions. No technique could reliably distinguish between postradiation fibrosis and residual cancer.

### CLINICAL STAGING SYSTEM

The same pathologic staging systems extensively described in Chapter 33.7 are used for rectal tumors. However, the pathologic staging systems cannot be used for making preoperative treatment decisions. Furthermore, patients treated with local modalities, such as transanal resection, do not have a lymph node pathologic evaluation. A reliable and reproducible clinical staging system would be very useful.

Several authors have proposed innovative ways of clinically staging rectal cancer patients. Abrams (1980), for example, evaluated the gross and microscopic pathologic features of 167 rectal cancers. He demonstrated that 63% of nonulcerated tumors were limited to the bowel wall versus only 28% of the ulcerated tumors. It has been noted that the size of an ulcerated tumor significantly affects its ability to be resected. Tumors with mucosal ulceration should be classified as T3 tumors, with an additional margin of tissue for adequate oncologic resection below the tumor. Tumors that have penetrated the muscularis propria are classified as T4 tumors. The thickness of the tumor in the bowel wall may be evaluated with EUS. The same pathologic staging systems extensively described in Chapter 33.7 are used for rectal tumors. However, the pathologic staging systems cannot be used for making preoperative treatment decisions. Furthermore, patients treated with local modalities, such as transanal resection, do not have a lymph node pathologic evaluation. A reliable and reproducible clinical staging system would be very useful.

At the University of Texas M. D. Anderson Cancer Center, preoperative treatment of rectal cancers with chemotherapy and radiotherapy has become common. Patients are routinely staged by physical examination, proctoscopy, and conventional imaging studies (i.e., chest x-ray, CT scans of abdomen and pelvis). The degree of rectal wall involvement and the presence of involved lymph nodes are determined by EUS. Based on the results of these studies, patients are clinically classified according to a “clinical” TNM stage. The main problem with this approach is the risk of overstaging, especially if the EUS is done by inexperienced physicians, because this imaging modality is highly operator-dependent. The same pathologic staging systems extensively described in Chapter 33.7 are used for rectal tumors. However, the pathologic staging systems cannot be used for making preoperative treatment decisions. Furthermore, patients treated with local modalities, such as transanal resection, do not have a lymph node pathologic evaluation. A reliable and reproducible clinical staging system would be very useful.

### TREATMENT OF RESECTABLE RECTAL CANCER

Goals in the treatment of rectal carcinoma are local control of disease and cure, with maintenance of an acceptable quality of life. The biology of a particular patient's tumor is the most important factor in overall outcome. Adequate surgical removal of the tumor is the major treatment factor affecting local control and cure. The principles of the surgical management of rectal cancer are: (1) removal of the primary tumor with adequate margins of normal tissue, (2) treatment of the draining lymphatics, and (3) restoration of function. Appropriate adjuvant therapies can enhance local control, reduce systemic recurrence, and increase organ preservation.

Clinical staging by history, physical examination, proctoscopy, and imaging is appropriate for establishing resectability and proper sequencing of adjunctive therapies. The management of rectal cancer is best planned by clinical staging that takes into account the extent and location of the primary tumor, its locoregional spread, and presence or absence of metastatic sites. The same pathologic staging systems extensively described in Chapter 33.7 are used for rectal tumors. However, the pathologic staging systems cannot be used for making preoperative treatment decisions. Furthermore, patients treated with local modalities, such as transanal resection, do not have a lymph node pathologic evaluation. A reliable and reproducible clinical staging system would be very useful.

In patients with low rectal cancer, abdominoperineal resection (APR) has been the standard of management. However, APR requires a permanent colostomy, which adversely affects the patient's quality of life. The majority of patients with rectal cancer do not require a permanent colostomy for curative therapy. Curative excisions can extend from endoscopic removal of malignant polyps to local excision, radical resection, or multivisceral resections.

### SITE-SPECIFIC TREATMENT OPTIONS

For purposes of surgical management, the rectum is usually divided into thirds. The middle and lower thirds are extraperitoneal, whereas the upper third may be covered by its anterior or lateral surfaces by peritoneum. The selection of an appropriate surgical technique takes into account not only the extent and location of the tumor, but also the biologic characteristics of the tumor and the patient's overall condition (Table 33.8.1).

#### TABLE 33.8.1. Surgical Procedures for Rectal Cancer

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Description</th>
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<tbody>
<tr>
<td>Upper Third</td>
<td>Recurrence patterns and cure rates for tumors in the upper third of the rectum are similar to those for the colon. Advanced tumors in this location may involve the retroperitoneal structures (i.e., ureters, bladder, muscle) or major vessels. The lowermost edge of these tumors is usually 10 to 12 cm from the anal verge. Extirpation of these tumors should include resection of the bowel segment containing the tumor along with the mesorectum to approximately 5 cm below the lower edge of the tumor (Lopez-Kostner, 1998)]. It is usually inappropriate to attempt local excision techniques in this area because of the relationship between the upper rectum and peritoneal cavity and because of the poor exposure due to the distance from the anal verge.</td>
</tr>
<tr>
<td>Middle Third</td>
<td>The appropriate procedure for radical resection of most rectal carcinomas is a low anterior resection (LAR). This procedure encompasses the sigmoid colon, a segment of the rectum containing the tumor with a margin of tissue below the tumor, and the mesorectum. Reconstruction is performed between the left colon and the rectal stump. Most tumors in the middle rectum are not amenable to local excision because of the proximal extension of the tumor. APR does not reduce local recurrence rates compared to appropriate sphincter-preservation surgery for patients with midrectal tumors.</td>
</tr>
<tr>
<td>Lower Third</td>
<td>Cancers in the distal rectum can require APR for adequate radial and distal margins. The entire mesorectum is included in this resection. Management of these tumors has been most clearly affected by multidisciplinary treatment strategies that allow for adequate oncologic resection and preservation of the anal canal. Important techniques have been proctectomy and coloanal anastomosis (CAA), as well as local excision. Both of these treatments are commonly combined with...</td>
</tr>
</tbody>
</table>
The use of staples has evolved to make an anastomosis easier when there is a short rectal stump deep within the pelvis. The double-staple technique of Knight and Griffin is most commonly used to restore intestinal continuity after resections in which a short rectal stump remains (Griffin, 1990). Alternative forms of local therapy for low rectal cancers include transanal endoscopic microsurgery (TEM), endocavitary radiation, fulguration, and laser ablation.

**SURGICAL ISSUES IN RESECTABLE RECTAL CANCER**

This section discusses the major issues that are common to surgical procedures for rectal cancer.

### Mucosal Margins

Attaining tumor-free margins at the edges of a rectal cancer resection specimen is the hallmark of curative surgical therapy. The purpose of obtaining such a margin is to prevent local failure and effect cure.

Spread beyond the lower edge of a rectal cancer may occur by submucosal spread in intramural lymphatics. Fewer than 5% of rectal cancers show distal mucosal spread beyond the edge of the tumor, and only 2.5% have histologic evidence of spread beyond 2 cm. These tumors commonly show aggressive biologic characteristics. Margins may need to be increased in locally aggressive tumors, such as those showing poor differentiation or vascular and lymphatic invasion. In these cases, the spread may be discontinuous. It does not appear that a mural mucosal margin of 5 cm is necessary to prevent local recurrence. Even margins of 1 cm have been demonstrated to provide adequate protection from local recurrence in the absence of aggressive histologic features. Distal margins of more than 2 cm do not reduce the risk of anastomotic recurrence.

The impact of neoadjuvant therapies on the suitability of margins is unclear at this time. However, some have proposed that distal margins may be reduced in the face of preoperative chemoradiation. These concepts have allowed for an increase in sphincter-preserving procedures without detracting from local control and survival. However, clinical response at the primary site can be misleading. Many patients have residual microscopic disease within the bowel wall, despite a complete response at the mucosal surface. Complete excision of the primary site with margins of normal tissue is recommended.

The difference between margins reported in the literature and margins in situ at surgery can be significant. This fact is due to contraction of the specimen after its excision and the stretching of the rectal wall. Therefore, generous gross margins can be required to assure adequate resection. A microscopically involved margin is unacceptable for a curative resection and will not be salvaged by radiation and chemotherapy. The need for negative mural margins also applies to local excision specimens for which a 1-cm margin of grossly normal bowel wall around the tumor is recommended for satisfactory resection.

### Proximal Lymph Node Dissection

The lymphatic spread of rectal cancer is upward as well as lateral and distal. The proximal extent of the mesorectum and the rectosigmoid mesentery should be included in the resection. Node dissection at the base of the inferior mesenteric artery does not enhance survival compared with lymph node excision just distal to the origin of the left colon. This is particularly true for low rectal cancers in which positive nodes between the left colic origin and the inferior mesenteric artery origin are found in fewer than 6% of resectable cases. For low rectal resections or CAA, however, ligation of the inferior mesenteric artery just above its origin at the aorta is required to eliminate tension on the anastomosis. Retroperitoneal adenopathy above the level of the inferior mesenteric artery is frequently a harbinger of occult systemic spread that is not amenable to cure by surgery alone.

### Total Mesorectal Excision

The mesentery of the rectum contains its blood supply and lymphatics in a bilobed fat packet situated immediately posterior and lateral to the thick-walled rectum. Both are contained in the visceral layer of the endopelvic fascia. The majority of resectable primary rectal tumors and involved lymph nodes in rectal cancer specimens are found within this structure. Nodes are involved in T1 cancers in 5.7% of cases; T2 tumors have positive nodes in 19.6%, and T3 and T4 cancers have positive nodes in 65% and 78% of cases, respectively. Involvement of the radial or circumferential margin correlates with subsequent local recurrence and poor survival.

Resection of the mesorectum should extend farther distally than the acceptable margin for rectal wall transection (Fig. 33.8-3). Because the mesorectum tapers as it proceeds distally, it is totally excised for most middle and lower rectal cancers. More proximal rectal tumors can be treated by a mesorectal excision extending 5 cm beyond the lower tumor edge. Total mesorectal excision has been associated with a high rate of anastomotic leak when used for upper rectal tumors.

**FIGURE 33.8-3.** Total mesorectal excision.

The work of Quirke and others (1986) has dramatically demonstrated the importance of lateral tumor spread in the local recurrence of resected rectal cancers (Table 33.8-2). Among patients with local recurrence, tumor involvement at the circumferential margins of resection has been found in 85% of cases. Because of difficulty in obtaining adequate exposure in the low pelvis and the surrounding structures, circumferential margins around rectal cancer can be highly variable and minimal. Surgical experience and surgical technique have demonstrated their key role in the prevention of local recurrence by controlled sharp dissection done with attention to these margins. The mechanism for involvement of the circumferential margins can be direct spread, mesenteric implants, vascular or lymphatic invasion, or cancer-bearing lymph nodes. Up to 23% of patients can have mesorectal tumor implants aside from discrete nodes. Tumor involvement of the circumferential margins of resection is frequently due to spread in the mesorectum distal to the tumor that can be violated by blunt dissection. It has been implied that a positive circumferential margin after mesorectal excision is a prognostic factor for distant metastases also.

| Constant Character 
<table>
<thead>
<tr>
<th>Spineal</th>
<th>Distal</th>
<th>Involvement of</th>
<th>Radial Margin</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td>Negative</td>
<td>8 (19%)</td>
<td>2 (9%)</td>
</tr>
<tr>
<td>1</td>
<td>Positive</td>
<td>3 (12%)</td>
<td>2 (8%)</td>
</tr>
</tbody>
</table>

TABLE 33.8-2. Distal Mesorectal Spread in Producing an Involved Radial Margin

Circumferential clearance of rectal tumors by total mesorectal excision has become the accepted surgical procedure for the management of most rectal cancer. Total mesorectal excision by full mobilization of the rectum along anatomic planes has been demonstrated to be effective in the surgical management of rectal cancer. 2-46 Dissection is carried out along areolar planes that allow for hemostasis, identification of important nerves, and prevention of violation of the visceral fascia investing the mesorectum. 46 This type of surgical resection for rectal cancer produces a negative surgical margin in more than 90% of resectable rectal cancers and reduces the possibility of local recurrence.

Lateral Pelvic Lymph Node Dissection

Lymphatic drainage of the rectum not only flows proximally along the inferior mesenteric vessels, but also follows the middle rectal vessels to the lateral pelvic sidewall and into internal iliac nodes. These nodes may be a source of recurrence. The incidence varies from 1% to 7% in resectable cases. Wide pelvic lymphadenectomy including lateral pelvic lymph nodes has been proposed for the treatment of rectal cancer. Although there is little doubt that the presence of metastases in such lymph nodes is a significant negative prognostic factor, no evidence supports a therapeutic benefit of the routine addition of extensive lymphadenectomy to standard locoregional procedures. 2-46 Gross disease can be resected when this procedure would provide a negative margin of resection. 2-46 The morbidity of this procedure is significant, with the majority of patients developing urinary dysfunction and impotence.

RADICAL SURGICAL TREATMENT OPTIONS

Patients with stage II and III rectal cancer (60% to 80% of patients with rectal cancer) have tumors that are large and biologically aggressive. They are at higher risk of local and systemic recurrence after treatment. Accordingly, strategies have been developed to address these issues through locoregional resection and multimodality therapy. However, adequate surgical resection and technique are the most critical treatment factors determining patient outcome.

The surgical management of stage II and III tumors is based on several issues: (1) the importance of the lateral spread of rectal cancer in local tumor recurrence; (2) the need for total mesorectal excision to minimize pelvic recurrence; (3) restoration of function by CAA after resection of low rectal cancers; and (4) optimization of bowel function and quality of life after low rectal anastomosis. Oncologic results of radical resection and patterns of failure are discussed later in this chapter.

Selection of Radical Excision Procedures

The surgical procedure chosen for radical excision is determined largely by tumor location. Three different operative procedures can be performed, all with adherence to the principles of total mesorectal excision: LAR, APR, and total proctectomy with CAA. For rectal cancer patients, a major component of quality of life is sphincter preservation. This is simple to accomplish in middle and upper rectal cancers where LAR achieves adequate removal of the tumor and surrounding lymphatics and end-to-end anastomosis. In patients with low rectal cancers that do not involve the levators or sphincters, the anus may still be spared by proctectomy and CAA. 2-46 Preoperative chemoradiation may facilitate this. However, patients with levator or sphincter involvement are best managed by APR and permanent colostomy.

Abdominoperineal Resection

Preoperative planning of the stoma site and counseling about the consequences of a colostomy are critical to a successful outcome. Proper selection of a site must be planned preoperatively with attention to body habitus. APR involves a combined transabdominal and perineal approach to complete resection of the rectum, mesorectum, levator muscles, and anus, with formation of a permanent colostomy. The rectum and mesorectum are mobilized via an abdominal approach down to the levator muscles. A perineal approach is then used to widely resect the levator complex and anus along with an appropriate margin of perianal skin. A permanent end colostomy is done. As sphincter preservation (LAR and proctectomy plus CAA) has advanced, the overall proportion of rectal cancer patients undergoing APR has decreased. 2-46 However, APR remains the only surgical option for some patients with rectal cancer, specifically in those patients with sphincter complex involvement or levator muscle involvement.

Low Anterior Resection

LAR involves the transabdominal resection of a portion of the rectum as well as the mesorectum. After complete mobilization of the rectum en bloc with the mesorectum, the rectum is divided at least 2 cm below the distal edge of the tumor (see Fig. 33.8-3). Although the length of mesorectal excision will exceed this, evidence indicates that total mesorectal excision is not required for upper rectal cancers. Reconstruction of the rectum is then carried out between the completely mobilized left colon and the remaining rectal stump. The use of LAR in midrectal and selected low rectal cancer has increased for two main reasons. First, the double-stapled technique has permitted a simpler and lower anastomosis, with leak rates (clinical or radiographic) similar to or better than with handsewn techniques. Second, although 5 cm was previously felt to be the minimum acceptable distal margin, the acceptance of a 2-cm distal margin has enabled lower tumors to be resected by LAR. 2-46 The timing of sphincter-preserving surgery after preoperative radiation has been demonstrated to influence sphincter preservation. A 6- to 8-week interval increases the sphincter preservation rate from 68% for a 2-week interval to 76%. 2-46

Proctectomy and Coloanal Anastomosis

Although LAR and APR are the traditional methods of locoregional resection in rectal cancer, proctectomy with CAA has emerged as a well-accepted surgical option in carefully selected patients. This procedure spares patients a permanent colostomy while obtaining good functional and cancer-related outcomes. 2-46 A review of 117 patients from the Mayo and Cleveland Clinics provides a perspective on the current utility of proctectomy and CAA in patients with low rectal cancer. 2-46 The patients were treated over a 10-year period (1981 to 1991). The median distance of the tumor from the anal verge was 6 to 7 cm. The technique used required complete mobilization of the rectum to the levators, transanal transection of the rectum, complete mobilization of the left colon, and coloanal anastomosis (Fig. 33.8-4). The authors recommend loop ileostomy. The effectiveness of the procedure in preventing local recurrence was demonstrated by the low local recurrence rate of 7%. Fecal continence was satisfactory in 78%, and overall bowel function appeared to be improved in patients who had a colonic J pouch reservoir created for the CAA. No surgery-related deaths were reported. Early and late complications were related mainly to the anastomosis leaking and healing with a sticture.

FIGURE 33.8-4. Coloanal anastomosis.
the mesorectum. The fully mobilized rectum can be amputated by a transanal technique or by transsection at the upper end of the anal canal with a stapler. The reconstruction consists of delivering the mobilized left colon to the anal canal and performing an anastomosis. A hand-sewn anastomosis can be performed with full-thickness sutures through the colon and internal sphincter. Alternatively, a stapled anastomosis may be done. A diverting stoma is then usually created.

Several groups have reported on patients who have a 6- to 10-cm colon J pouch reservoir constructed with no additional risk or compromise of the anastomosis. The formation of the colon J pouch has been compared to the straight CAA in a randomized clinical trial. Hallbook and colleagues (1996) demonstrated a reduction in the frequency and urgency of bowel movements in the first year after pouch formation. Physiologic measures and short-term outcomes appear to be improved with the pouch. However, these differences may disappear with time. It has been suggested that lower leak rates with a colon J pouch may be obtained because of improved vascular supply to the apex of the pouch and the side-to-end anastomosis. Postoperative problems after CAA are related to rectal capacitance and compliance. These manifest as the problems of urgency and frequency in bowel movements. This gradually improves over the 9 to 10 months after temporary stoma closure. Complete fecal continence usually is achieved in 85% to 100% of patients. In a series from the Mayo Clinic by Drake et al., patients who had a CAA for malignancies had a stool frequency of 2.6 per 24 hours, and only 1 of 19 patients had any incontinence. The Mayo and Cleveland Clinics study is similar to the reports of others in describing proctectomy and CAA for rectal cancer.

**Multivisceral Resection for Locally Advanced Rectal Cancer**

Approximately 6% to 10% of rectal cancers are locally advanced in, and require extensive surgery for, complete tumor extirpation. Pelvic exenteration involving en bloc removal of the rectum, bladder, distal ureters, and other pelvic organs can be required to obtain negative margins of resection. A number of studies have demonstrated 5-year survival rates ranging from 33% to 50% for these selected patients with locally advanced rectal cancer. Despite the ability to achieve long-range survival rates in selected patients, the operation remains a formidable one, with significant morbidity and a mortality up to 6%. Patients who undergo such resections for primary tumors have better survival rates than those with recurrence.

Metterdouss et al. reported a series of 40 patients undergoing pelvic exenteration for rectal carcinoma in which tumor-free margins were obtained. The 5-year overall survival rate was 49%, with a median survival of 56 months. Adjuvant chemoradiation appeared to provide a reduction in risk of recurrence. In the series, five patients experienced local failure. Comparable results have been reported by Lopez and associates (1987). Long-term local control is obtained in approximately 70% of the patients who undergo resection with tumor-free margins. The results of such surgery cannot be separated from the benefits of adjuvant chemoradiation in this high-risk population.

Results from surgical procedures for rectal cancer requiring multivisceral resection have improved. This finding may be related to improvements in perioperative care, patient selection, and surgical techniques. Of major importance in the management of such patients, who are often heavily irradiated, is the use of vascularized tissue flaps to accomplish healing of pelvic and perineal wounds.

**Morbidity and Mortality from Radical Resection**

The major cause of infection in procedures in which reconstruction has been done is anastomotic leak. Anastomotic leaks can occur in 2% to 5% of cases, and they may result in subsequent stricture. The consequences of pelvic sepsis can be a major cause of mortality from resection of rectal cancer. Use of a diverting stoma for a low rectal anastomosis will not prevent anastomotic leak, but it will reduce the clinical manifestations of sepsis, the need for reoperation, and mortality.

Bladder dysfunction can be a complication of extensive pelvic dissection, especially if disruption of autonomic nerve trunks occurs. Sacral parasympathetic nerve injuries result in loss of the awareness of the need to void. Management by intermittent catheterization, medications, or transurethral resection may be required.

Resection of the rectum for carcinoma has been associated with a high rate of erectile dysfunction or retrograde ejaculation in men. This sexual dysfunction is caused by injury to pelvic autonomic nerves and is especially frequent in cases in which extensive lateral dissection has been done. Pelvic dissection to preserve the hypogastric sympathetic nerve trunks arising from the preaortic plexus and the parasympathetic trunks arising from the sacral nerve roots can reduce this morbidity.

It is also important to realize that erectile dysfunction is not uncommon in the age group of individuals who develop sporadic rectal cancer and that factors other than an intact autonomic nervous system can impact on a patient’s sexual function after the diagnosis and management of rectal carcinoma.

With sharp nerve-sparing dissection, impotence has been reduced to a rate of 10% to 28%, or lower, in many series with resection of rectal carcinoma. Creation of a stoma can produce complications requiring reoperation in 15% to 20% of patients. Reconstruction of the rectum avoids a permanent colostomy. However, bowel movements and urgency may be frequent because of the smaller neorectum. The reconstructed rectum usually is composed of a more proximal segment of left colon, which is brought down to a rectal stump of varying lengths. Improving the rectal reservoir function by construction of a colon J pouch improves short-term functional results. Function does improve with time. The use of fiber supplements may enhance this improvement. Epididymal development of bowel movements is also a prominent symptom in patients with a small rectal pouch after reconstruction. Anal sphincter tone and local reflexes regulating sphincter function are generally preserved after resection. Actual sphincter function usually is maintained in the majority of patients. Function is diminished by the presence of postoperative pelvic sepsis or the use of postoperative radiotherapy. Operative mortality for radical resections ranges from 0.6% to 3.0%.

**TREATMENT OF INVASIVE CANCER BY NONRADICAL APPROACHES**

**SELECTION OF PATIENTS**

The criteria used to select patients for local excision are intended to make a negative-margin, full-thickness local excision technically feasible and to ensure a low risk of lymph node metastases (Table 33.8-3). Physical assessment, CT, and EUS are helpful in the preoperative evaluation of these rectal cancer patients. Imaging findings can be used to select patients for local excision procedures by determining the depth of tumor penetration into the rectal wall and the presence of enlarged lymph nodes in the mesorectum. Ninety percent of rectal cancers do not meet the criteria for treatment by local excision alone because of the size or extent of the tumor. Factors that can help identify patients who are at low risk for lymphatic metastases include small tumor size, absence of lymphatic and vascular invasion, well or moderate tumor differentiation ploidy, and absence of clinical or radiologic evidence of enlarged lymph nodes.

<table>
<thead>
<tr>
<th>Tumor &lt; 2 cm in greatest dimension</th>
<th>Limited only to the submucosa or superficial musculature</th>
<th>Favorable pathologic grade</th>
<th>(R)etention of 70% or more of normal muscularis propria</th>
</tr>
</thead>
</table>

**TABLE 33.8-3. Indications for the Local Excision of Rectal Cancer**

The major factor predicting patient survival and perirectal lymph node metastases is the depth of penetration of the primary tumor. Morson (1966) has reported that lymphatic metastases occur with 10% of tumors confined to the submucosa, 12% of tumors invading the muscularis propria, and 39% of tumors extending beyond the bowel wall. A study of T1 and T2 tumors treated by radical resection showed an incidence of lymphatic metastasis of 12% for T1 tumors and 22% for T2 tumors. The incidence of lymphatic metastasis was increased by lymphatic or blood vessel invasion (BVI) and in poorly differentiated tumors. Nelson et al. reported that 29% of...
patients with lesions smaller than 2 cm in diameter had evidence of lymph node metastasis. Thus, selection for local excision based on the classic indications fails to adequately treat a significant number of patients with lymphatic involvement. This makes the addition of adjuvant therapy to local excision a logical choice.

LOCAL EXCISION TECHNIQUES

Full-thickness local excision is effective in the treatment of selected early, low rectal cancers. Local excision is used as curative therapy for patients who have superficial tumors, and it is used as alternative therapy in medically compromised patients and in those who refuse standard therapy. Patient selection is paramount to using these techniques successfully, which requires an understanding of the limitations of the techniques and an appreciation of the biology of T1–2 rectal cancer.

The oncologic results of local treatment with and without adjuvant treatment are described in Adjuvant Radiation Therapy for Resectable Rectal Cancer, later in this chapter.

The choice of technique for local excision is dictated by tumor characteristics and the surgeon’s ability to have adequate exposure and control of the margins of excision. In general, the transanal approach has less morbidity. Posterior approaches can offer the advantage of better exposure for larger lesions. However, posterior approaches entail a higher rate of fistula formation and the potential for tumor seeding of the posterior wound. Whichever method is selected, the surgeon must perform a full-thickness excision with at least 1-cm margins of normal tissue surrounding the tumor. An inadequate margin is a predictor of failure. Piecemeal or submucosal excision is not considered adequate surgical treatment of invasive rectal cancer. Fragmentation of the tumor is associated with an increased incidence of local recurrence. If the lesion cannot be adequately resected by local excision, then a more standard locoregional operative approach should be used. In a curative case, the patient should be counseled to consider local excision as a form of definitive biopsy. This is especially true when transmural penetration or adverse histologic characteristics are found in the local excision specimen. In most instances, these patients should undergo more extensive surgical therapy.

Transanal Excision

Transanal excision is the most common method used for local excision. Size and degree of circumferential involvement predict the potential for a technically successful transanal excision. Both adequate dilatation of the anus and a good light source are essential, and exposure is aided by the use of specialized retractors.

The excision is begun by marking a margin of normal tissue around the lesion, which must be greater than 1 cm. The local excision is performed in a full-thickness manner, meaning that the deep plane of dissection includes the perirectal fat. The defect usually is closed to avoid subsequent scarring. Proper orientation of the specimen is required for pathologic assessment of the margins. Lynch nodes are usually not recovered by this technique.

Posterior Proctotomy

A posterior proctotomy is useful for large posterior lesions and provides better access to more proximal lesions. Otherwise known as a Kraske’s procedure, a posterior longitudinal incision is made just above the anus to the inferior border of the gluteus maximus. The coccyx is removed and the underlyinglevator muscles are divided in a longitudinal fashion in the midline. This permits excellent exposure for mobilization of the rectum and allows for a full-thickness local excision or, alternatively, a sleeve resection. A transspincteric excision (Bevan’s or York-Mason) involves a similar approach as the posterior proctotomy, except the entire anal sphincter is divided posteriorly in the midline. It is critical to identify, mark, and reconstruct each portion of the sphincter complex, but if this is done, minimal functional problems are observed.

Transanal Endoscopic Microsurgery

TEM, in which either submucosal (for adenomas) or full-thickness (for invasive carcinomas) excision is performed through an operating rectoscope, has emerged as an option for the local treatment of rectal cancer. It allows improved exposure compared to the transanal approach and does not carry the risk of fecal fistula or sphincter dysfunction associated with posterior or transspincteric proctotomy. In one series, local recurrence occurred in 2 of 16 (13%) patients with T1 lesions undergoing TEM. The authors of this series believe that TEM alone is not an appropriate treatment for T2 lesions. Further follow-up and experience is required to establish the role for TEM.

Fulguration

Fulguration can be used in highly selected patients to treat lower rectal carcinomas. Chin and Eisenthal have reported good results with rectal coagulation for rectal cancers less than 4 cm in diameter that are well or moderately differentiated and less than 7.5 cm from the anal verge. Eighty-one of 114 patients with low rectal cancers were treated primarily by electrocoagulation with curative intent, and a 65% 5-year survival rate is achieved in highly selected individuals. Stahl et al. reported similar results in 33 patients treated with electrocoagulation. This is carried out through an operating proctoscope. Bipolar coagulating current is used to coagulate the lesion along with a 1-cm margin of normal mucosa. This procedure is followed by debridement of the coagulated tissue, and the process is repeated until no residual tumor is noted. This technique can be carried out through the entire bowel wall for posterior and lateral lesions. Although it is used for anterior lesions, it should be carried out with caution because of the proximity of the rectovaginal septum or prostate. Complications of this procedure can include bleeding, stricture, abscess, or perforation. The overall complication rate is 21%, and a mortality rate of 2.7% was reported.

Endoscopic Laser

Endoscopic laser may be used for palliative purposes in patients with extensive metastases for rectal obstruction or hemorrhage. It may be used as definitive therapy in those who refuse surgery or are a poor surgical risk, as a bridge to neoadjuvant therapy, or to allow bowel preparation. It is most useful for noncircumferential lesions that are less than 7 cm in diameter and have limited invasion. It may be combined with external-beam radiotherapy after successful recalciﬁzation. Highly selected patients with small tumors who undergo complete local destruction of the tumor with subsequent negative biopsies can occasionally be treated definitively. A mean survival of 50 months has been achieved by Brunetaud et al. in a series of patients treated by such techniques. Laser treatment can be combined with photosensitizing agents to achieve more efﬁcient tumor obliteration. This technique of photodynamic therapy is especially useful in patients being managed for obstruction who are otherwise unresectable.

Endocavitary Irradiation

Radiation has been used as a single modality with curative intent for selected early rectal cancers. Most investigators have used intracavitary irradiation alone for early, noninvasive tumors. For more advanced tumors, it is combined with a temporary iridium 192 implant or external-beam radiation, or both. Before delivery, the anus is dilated and a 4-cm proctoscope is introduced. A low-energy x-ray unit is placed through the scope almost against the tumor. Generally, 50-kV x-rays, in doses of 30 Gy per treatment, are given using this “contact” approach. Three or four such treatments over 1 month are required. Bulky tumors may require additional irradiation with an 192Ir implant or external beam to reach the deeper pararectal tissues.

RESULTS OF TREATMENT OF RECTAL CANCER

This section presents the results after potentially curative surgery alone for clinically resectable rectal cancer. Overall, cure rates for cancers in the lower third of the rectum are lower than those for cancers in the upper two-thirds.

ONCOLOGIC RESULTS OF RADICAL SURGICAL RESECTION ALONE

Numerous studies have compared the oncologic results of APR with those of sphincter-preserving procedures (LAR or proctectomy plus CAA). In a randomized clinalongitudinal incision to examine the benefit of adjuvant therapy in rectal cancer, patients who underwent APR had a higher recurrence rate than patients undergoing LAR (P < 0.05). However, this finding was likely reflective of the larger, more advanced tumors seen in the patients undergoing APR. Several other studies involving large numbers of rectal cancer patients have shown no significant differences in local control or survival between patients undergoing APR and those undergoing sphincter preservation.

Survival does not appear to be compromised.

Outstanding surgical results have indicated that total mesorectal excision is the optimal technique for the radical resection of rectal cancer (Table 33.8-4). McAnena et al. have described the long-term outcome of 57 patients treated by this approach. The mean follow-up was 4.8 years. Local recurrences were seen in only 3.5% of
the patients, and the overall 5-year survival rate was 81%. In a report by MacFarlane and coworkers on patients undergoing operation exclusively, 135 patients with Duke’s B and C rectal cancers were treated over a 13-year period with a mean follow-up of 7.5 years. None of these patients received adjuvant radiation or chemotherapy. Despite this fact, only a 5% local recurrence rate was reported.

Table 33.8-4. Local Recurrence Rates after Surgery Alone

Further long-term follow-up of a larger group of patients confirmed these findings, specifically with a 10-year local recurrence rate of 4% and a 10-year disease-free survival rate of 78%. Heald (1986) reported his group’s experience between 1978 and 1997 with 380 patients who underwent curative resection with a 10-year local recurrence rate of 8%. This reduction in local recurrence rate has been reported as the reason for a high survival rate for these patients. This compares favorably with the results from the North Central Cancer Treatment Group (NCCTG) study that forms the basis for current recommendations for adjuvant therapy in the United States in which chemotherapy and radiation were used for high-risk rectal cancers in addition to surgical resection.

In North America, similar results have been obtained with high rates of local recurrence-free survival when a total mesorectal excision is done by meticulous sharp dissection along the pelvic sidewalls. Enker’s report on this subject called for full rectal mobilization along anatomic planes to obtain complete mesorectal excision. In a series of 42 men who underwent sphincter-preserving surgery for low rectal cancer using this technique, only one local recurrence was noted (median follow-up, 20 months). This result was accomplished with preservation of potency in 86.7% of patients. In 156 stage I and II rectal cancer patients treated without adjuvant therapy between 1987 and 1995 at Memorial Sloan-Kettering Cancer Center, local recurrences rates were reduced to 8.3% by using mesorectal excision without radiotherapy. Zaheer (1998) reported the Mayo Clinic experience in 514 patients with surgical resection of stage I, II, and III rectal cancer. Two hundred seventy-two of these patients had stage I disease, and 173 had stage II or III rectal cancer. The local recurrence rate for all stages was 7%, whereas the local recurrence rate for node-negative cancers was 13%.

S URGEON-RELATED OUTCOMES

The frequency of local recurrence varies greatly for individual surgeons, from less than 10% to more than 50%. Norwegian surgeons have removed rectal cancer surgery from routine surgical teaching and concerning total mesorectal excision. They propose that the surgical specimens obtained by such surgeons be audited. Where regionalization of all rectal cancer surgery has occurred, survival appears to have improved and local recurrence rates have dropped to 7% after the addition of total mesorectal excision from historical controls, with a local recurrence rate of 23%.

Several studies have suggested that the surgeon is an important prognostic factor in rectal cancer. In a population-based study of 683 patients, Porter et al. (1998) found a significant local recurrence and survival advantage in patients of both surgeons with colorectal surgery fellowship training and surgeons with a higher caseload. In addition, a greater rate of sphincter preservation for low rectal cancer also was found to be associated with higher case loads. Other studies suggest that hospital volume, hospital type (university vs. community), and surgeon experience improve survival and recurrence outcomes.

ONCOLOGIC RESULTS OF NONRADICAL APPROACHES

The incidence of lymph node metastases in patients with T1 tumors approximate the recurrence rate for T1 cancer treated by local excision alone. Studies describe a 3% to 10% rate of local recurrence after excision alone. Survival rates in patients with T1 rectal carcinomas treated with local excision alone or radical resection are 90% to 100%.

In patients with T2 rectal carcinomas, the risk of lymph node metastasis is 10% to 30%. Recurrence rates may be 17% to 24% in patients with T2 tumors after local excision alone. Survival rates are 78% to 82% with excision alone.

Many studies, mostly retrospective and single institutional studies, examine the results of local excision alone in the management of T1–2 rectal cancer. In a review of all published series with reasonable follow-up describing this approach, Graham et al. found the combined local recurrence rate for T1 lesions was 5% (range, 0% to 12%) and for T2 lesions was 18% (range, 8% to 27%). Lower local recurrence rates in similar patients treated by APR (0% to 10%) have brought into question the use of local excision alone for early rectal cancer.

Table 33.8-5. Patterns of Local Recurrence after Local Excision Alone

Papillon and colleagues (1992) in Lyon, France, pioneered the treatment of selected patients with rectal cancers using endocavitary irradiation. Exophytic, superficial, well to moderately differentiated tumors without colloid histology with a maximum diameter less than 4.5 cm were treated. If the tumor was felt to invade muscle, an interstitial ir implant was added. In 245 patients, the 5-year disease-free survival rate was 76%, and the local failure rate was only 5%. Sischy and associates (1984) have reported similar results. The local failure rate in 94 patients treated with endocavitary irradiation alone was 5%. Hull et al. (1994) reported a 71% disease-free survival rate in 126 patients. With a median follow-up of 55 months, Schild and associates reported 10% local failure and 76% 5-year survival. In 102 patients treated by Maingon et al., the local failure rate was 15% and the 5-year survival was 81%. In 22 patients who were stage T1,N0 by rectal ultrasound, none developed local failure.

Five-year survival rates with local treatment options vary from 50% to 90%, with many deaths secondary to intercurrent disease and not related to cancer. In selected patients, a 10% cancer-related 5-year mortality can be expected with local excision, fulguration, or primary irradiation. For clinically staged T1 and early T2 cancers, our treatment preference is to perform a full-thickness local excision when possible. This allows an assessment of margins and other pathologic features, thereby
providing the best determination of whether any additional therapy is needed.

In an attempt to help select the ideal combination of radiotherapeutic and surgical approaches for sphincter preservation, the Dijon clinical staging system has been proposed. The staging system takes into account the tumor size and depth of penetration of the rectal wall. Briefly, T1A tumors are defined as superficial, exophytic, and smaller than 3 cm; CS T1B tumors have a limited infiltrative component and are smaller than 3 cm; CS T2A tumors are superficial, exophytic, and are 3 to 5 cm in size; CS T2B tumors have a limited infiltrative component and are 3 to 5 cm; and CS T3 tumors are deeply infiltrative or fixed, regardless of size. High-grade and colloid tumors are excluded. The rationale for the different T stages is based on the technical parameters of endocavitary radiation. Tumors smaller than 3 cm are easily covered with the intracavitary cone, whereas tumors 3 cm or larger require overlapping of fields and therefore a higher level of technical expertise. The radiotherapeutic doses and techniques of Papillon (1992) were used.

According to the Dijon guidelines, patients with CS T1A tumors can be adequately treated with endocavitary radiation alone. Stages CS T1B and T2A require the combination of endocavitary radiation and interstitial 192Ir brachytherapy, and CS T2B tumors should receive preoperative external-beam therapy followed by, depending on the tumor response, either surgery or endocavitary radiation.

In an update from Maingon et al. of 151 patients treated with this approach, the incidence of initial local control and ultimate local control by stage was 78% and 87% for T1, 58% and 79% for T2, and 54% and 69% for T3, respectively. For the Dijon stage T1 tumors (treated by endocavitary radiation alone), local failure increased with tumor size (13% for 3 cm or smaller vs. 28% for larger than 3 cm).

**Nonradical Approaches: Advanced Rectal Cancers**

Patients with extensive T2 or transmural (T3) disease are not adequately treated with conservative measures such as local excision, fulguration, cryosurgery, or endocavitary radiation alone. Those selected for radiation therapy alone are usually medically inoperable or have such advanced local disease that resection would compromise a vital structure. In the nonradical setting, a variety of techniques have been used, including various combinations of external-beam, 192Ir interstitial brachytherapy, and endocavitary radiation. Papillon and Berard (1992) have treated 67 patients with T2–3 rectal cancers with pelvic radiation (3 Gy × 10) followed by endocavitary radiation. The 5-year disease free survival rate was 60%. A similar approach was reported by Kodner et al. (1993). Twenty-eight patients with invasive but favorable tumors received 45 Gy followed 6 weeks later by 60 Gy with endocavitary radiation. Favorable tumors were defined as smaller than 3 cm, mobile, well to moderately differentiated, and clinically confined to the rectal wall. No local failures were reported, and the cure rate was 82%. As already discussed, Maingon et al. have recommended the addition of preoperative external-beam radiation or 192Ir brachytherapy for these more advanced tumors.

Although the best results are seen in patients who are able to have surgical resection as a component of their therapy, some patients do not undergo surgery because they are medically inoperable, present with extensive unresectable disease grossly invading bone, have received prior pelvic radiation, or refuse surgery. In general, they have been treated with external-beam radiation with or without chemotherapy. The largest series is from the Princess Margaret Hospital, which reports a 14-month median survival rate and 5% 5-year survival rate in 519 patients. In the subset of patients in whom high doses of radiation are delivered (50 Gy or more), the median survival is 24 months and is 13% at 5 years. Other series report similar results (14% at 3 years and 31% at 2 years); however, they have shorter follow-up and a smaller number of patients. Selected series are seen in Table 33.8-6. In a subset of patients without metastatic disease who received more than 46 Gy, Overgaard and colleagues (1984) reported a 30% 2-year survival rate. A 30% 3-year survival rate was reported by Minsky and associates (1991).

### TABLE 33.8-6. Palliative Radiotherapeutic Options (Nonsurgical)

| Pelvic radiation also provides very effective palliation. In the subset of 84 patients who received more than 45 Gy in the series from the Princess Margaret Hospital, the following presenting symptoms were palliated by 6 to 8 weeks after the completion of radiation: pain (89%), bleeding (79%), neurologic (52%), mass effect (71%), discharge (50%), urologic (22%), and other (42%). In the Thomas Jefferson University series, symptomatic relief was achieved in the following categories: pain (85% complete, 28% partial), bleeding (100% complete), and mass effect (24% complete, 64% partial). The duration of palliation was 8 to 10 months.

Even in elderly patients, pelvic radiation offers effective palliation. Valenti et al. delivered combined modality therapy (38 to 45 Gy plus mitomycin C and continuous infusion 5-fluorouracil (5-FU)) to a group of 17 patients with a median age of 79 (range, 75 to 90). Symptomatic relief was obtained in four of four patients with pelvic pain and five of six patients with rectal bleeding. The 18% incidence of grade 3+ toxicity was similar to that reported for the general population who receive preoperative combined modality therapy.

These data suggest that patients with advanced rectal cancers who are medically inoperable should be treated aggressively with pelvic radiation therapy as a component of their therapy. It offers not only a defined cure rate but a high degree of palliation of symptoms.

### PATTERNS OF RECURRENT AFTER RADICAL SURGERY

Despite radical surgery, local-regional failure occurs frequently in patients with transmural or node-positive rectal cancers. The incidence of treatment failure in the pelvis is directly related to the extent of transmural penetration (microscopic vs. gross) and the additive risks of lymph node metastases. Local failure rates as a function of stage are listed in Table 33.8-7. Wound recurrence is rare (0.6%); however, it is a harbinger of metastatic disease.

### TABLE 33.8-7. Local Failure after Surgery Alone for Resectable Rectal Cancer: Selected Single Institution Series
A major limitation in assessing the true incidence and patterns of failure is the heterogeneity of the series. This is due to variables such as the diagnosis by clinical, surgical, or autopsy criteria; reporting failure as the first site or as total (cumulative) failure; whether local failure includes extrapelvic disease; whether crude or actuarial calculations are used; the technical expertise of the surgeon; and whether patients have received adjuvant therapy. For example, in a series from the Netherlands, 36% of patients received radiation therapy.

Based on a compilation of selected series, the incidence of local failure (as a component of failure) is less than 10% in stage T1–2N0M0; this rate increases to 15% to 35% in stages T3N0M0 and T1N1M0 and is as high as 45% to 65% in stage T3–4N1–2M0. **100** When local failure does occur, it is severely debilitating and salvage has been of limited success. Therefore, decreasing local failure is, by itself, an important end point in the treatment of rectal cancer.

### RADIATION THERAPY ALONE FOR RESECTABLE RECTAL CANCER

In most cases, radiation therapy without surgery is limited to patients who are medically inoperable. This section excludes patients amenable to a local excision and adjuvant radiation therapy.

A variety of techniques have been used, including various combinations of external-beam irradiation, interstitial brachytherapy, and intracavitary irradiation. In a report from Papillon, T1 patients with clinical T2 or T3 rectal cancers received 3 Gy x 10 to the pelvis. Eight weeks later, an additional 25 Gy was delivered by intracavitary irradiation and 20 to 30 Gy by interstitial brachytherapy. The 5-year disease-free survival rate was 65%, and 62% of patients retained normal sphincter function. Although 7% developed anal stenosis, they all healed.

In a report from the Princess Margaret Hospital, 42 patients with early-stage, potentially resectable (T2–3) disease who were either medically inoperable or refused surgery received 50 Gy or more with or without 5-FU and achieved a 5-year survival rate of 21% (see Table 33.8-6). At the Centre Hospitalier Lyon Sud, 29 patients received endocavitary radiation plus 39 Gy of accelerated pelvic radiation with or without brachytherapy. With a median follow-up of 46 months, the local failure rate was 38% and the 5-year survival rate was 68%.

A similar approach was reported by Myerson and coworkers (1989). Thirty patients received 45 Gy followed 6 weeks later by 30 to 90 Gy with intracavitary irradiation. Their tumors were defined as larger than 3 cm, nonmobile, well- or moderately well-differentiated, and clinical stage T2 or pathologic stage T3. Deeply ulcerated or infiltrating tumors were excluded. With a median follow-up of 2 years, the local failure rate was 30%, and the 2-year disease-free survival rate was 42% (55% with salvage). Minor proctitis occurred in 17%.

As recommended for patients with advanced disease, patients with clinically resectable but medically inoperable disease should be treated aggressively with radiation therapy as a component of their therapy.

### ADJUVANT THERAPY AND SPHINCTER-SAVING OPERATIONS AS AN ALTERNATIVE TO ABDOMINOPERINEAL RESECTION

Conservative management (sphincter preservation) has been used in two broad groups of patients with distal rectal cancer as an alternative to APR. The first are early localized tumors. In general, these include small, exophytic, mobile tumors without adverse pathologic factors (i.e., high grade, BVI, lymphatic vessel invasion (LVI), colloid histology, or the penetration of tumor into or through the bowel wall). These selected tumors comprise 3% to 5% of all rectal cancers and are adequately treated with a variety of local therapies alone. The second group of patients includes those tumors that otherwise would be suitable for one of the above local therapies except for (1) invasion of tumor into or through the muscularis propria, (2) positive lymph nodes, or (3) the presence of one or more adverse clinical or pathologic factors. In the context of conservative management, these tumors are considered unfavorable, because local therapy alone is not adequate treatment.

### LOCAL EXCISION AND POSTOPERATIVE RADIATION THERAPY

The standard surgical treatment for resectable, transmural, or node-positive rectal cancer is an LAR or APR. If the pathology confirms that the tumor penetrates through the bowel wall or involves the mesorectal or pelvic lymph nodes, adjuvant combined modality therapy consisting of six cycles of 5-FU–based chemotherapy plus concurrent pelvic radiation therapy is recommended.

Given the morbidity of standard surgery as well as the frequent need for adjuvant therapy, the use of a more conservative approach, such as local excision plus adjuvant therapy (radiation therapy with or without chemotherapy), as primary therapy for selected cases of rectal cancer is appealing. This approach has been successful in other anatomic sites, such as in breast cancer and sarcomas of the extremities. In the rectum, it offers an opportunity for sphincter preservation.

The results of local excision and postoperative radiation therapy depend on a number of factors, such as the type of surgery (full-thickness vs. piecemeal excision), and clinicopathologic factors, such as tumor size, T stage, grade, margins, and LVI. Most series include some patients who have undergone suboptimal surgery, such as a piecemeal excision, or have positive or unassessable margins. Because few of the published series have adequate numbers to perform a meaningful multivariate analysis, it is difficult to determine the influence of these selected clinicopathologic features on one another. Until more complete data are available, a patient should not be excluded from treatment with local excision and radiation therapy based solely on these clinicopathologic features.

Local excision has been performed both before and after radiation therapy. The advantage of performing a local excision before radiation is that pathologic details, such as margins, depth of bowel wall penetration, and histologic features, can be well characterized. Knowledge of these details are useful in the development of selection criteria.

### SELECTION CRITERIA

To determine which tumors have a high enough incidence of local failure or positive mesorectal or pelvic lymph nodes to require adjuvant pelvic radiation, it first must be determined which tumors are adequately treated with local therapy alone. The selection of tumors for local therapy is based on both clinical and pathologic factors. Clinical information such as tumor size, mobility, location, and circumference can be obtained at the time of physical examination. Accurate pathologic information is more difficult to obtain from a biopsy. Of the available local therapies, only a full-thickness local excision provides accurate pathologic information.

### Clinical

A major limitation of the series that examine local excision alone is that the analyses are univariate rather than multivariate. Therefore, clinical and pathologic factors are not examined as independent variables. Furthermore, variation is seen in patient selection, the definition of clinical and pathologic features, and the length of follow-up among the series. Because of these differences, it is difficult to make firm recommendations for the selection of patients for conservative management based solely on clinical criteria. The most reasonable approach is to determine whether a local excision can be performed adequately (i.e., full thickness, nonfragmented, and with negative margins). If so, then the clinical criteria for a local excision have been met.

### Pathologic

Pathologic criteria are more objective. Patients with T1 tumors without adverse pathologic factors have a low enough incidence of local failure (5% to 10%) and positive nodes (less than 10%) that they do not require adjuvant therapy. However, once adverse pathologic factors are present (high grade, BVI, LVI, colloid histology, signet-ring cell), the local failure rate is at least 17% and the incidence of positive mesorectal or pelvic nodes is at least 10% to 15%. Biggers et al. reported the results of 141 patients with T2 rectal cancers who underwent local excision alone at the Mayo Clinic. Blumberg and associates found positive nodes in 10% of T1 and 17% of T2 cancers. In the combined group of 159 patients, the incidence increased with the presence of LVI (14% for LVI vs. 33% for LVI-positive). Even in the 42 patients with the most favorable characteristics (well or moderately differentiated, LVI-negative, T1 cancers), 7% had positive nodes. The 5-year survival rate was 65% and the local failure rate was 27%. Hager and colleagues (1983) performed a local excision on 20 patients with T2 rectal cancers that were otherwise "low risk" (nonmucinous, well to moderately differentiated, no LVI, with negative
The incidence of local failure was still 17%. Other series have reported local failure rates as high as 43% in patients with T2 cancers after either local excision or transanal excision.\textsuperscript{122}

Willett et al.\textsuperscript{123} reported a group of 40 patients who underwent local excision alone at the Massachusetts General Hospital (MGH). In this series, a separate analysis was performed on those patients whose tumors had unfavorable clinical and pathologic factors. Factors including tumor size larger than 3 cm, high grade, T2 stage or higher, vascular invasion (BVI and/or LVI), moderate or marked stromal fibrosis, a fragmented resection, and positive margins were associated with a local failure rate of at least 20% as well as an increase in distant metastasis. Therefore, local therapy alone is inadequate for tumors with these adverse pathologic factors.

An alternative approach to pathologically determine the incidence of positive pararectal lymph nodes is ultrasound-guided biopsy. Milsom and colleagues\textsuperscript{124} from the Cleveland Clinic performed biopsies on 26 patients and reported an accuracy rate of 77%, with a sensitivity of 71%, a specificity of 89%, a positive predictive value of 92%, and a negative predictive value of 62%.

### RESULTS

#### Results Compared with Radical Surgery

Because the pelvic lymph nodes are not pathologically examined at the time of a local excision, it is not possible to accurately compare, stage for stage, the results of this approach with radical surgery.

Although data exist to help predict the incidence of positive pelvic nodes based on the clinical and pathologic features of the primary tumor,\textsuperscript{125-127} an accurate comparison of this approach with standard surgery requires a randomized trial. Most series select patients for adjuvant therapy based on the presence of unfavorable clinical or pathologic features, or both. In the series from the University of Florida,\textsuperscript{128} for example, patients had at least one or more of the following adverse features: equivocal, close, or positive margins; T2–3 disease; perineural invasion; and had undergone a fragmented excision. Likewise in the MGH series,\textsuperscript{129} 38 of the 47 patients had T2 or high-risk T1 cancers (poorly differentiated and/or LVI).

### Survival

As seen in Table 33.8-8, the 5-year actuarial survival in these selected series is approximately 80% (range, 70% to 94%).\textsuperscript{129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139} In most series, patients had T1–3 tumors and underwent a local excision followed 4 to 6 weeks later by 45 to 50 Gy to the pelvis. Some patients received an external-beam or brachytherapy boost. In most series, a limited number of patients received 5-FU. Although not randomized, these survival data appear comparable with the results of radical surgery alone for stage T1–2N0 disease.

#### TABLE 33.8-8. Local Excision plus Postoperative Therapy: Survival, Salvage, and Functional Results: Selected Series

The Intergroup Cancer and Leukemia Group B 8984 trial is the only prospective, multiinstitutional phase II trial. Patients underwent a local excision with careful assessment of negative margins and, depending on T stage, received postoperative combined modality therapy.\textsuperscript{140} A total of 110 eligible patients (all with negative margins) were entered. The 51 patients with T2 disease received postoperative combined modality therapy. With a median follow-up of 48 months, the crude local failure rate was 14%, the 6-year failure-free survival rate was 71%, and overall survival was 85%. This approach is feasible in a multiinstitutional, cooperative group setting.

### Local Failure

When the series are combined, the average crude local failure rate increases with T stage: 5% for T1, 14% for T2, and 22% for T3 (Table 33.8-9). When the series are combined, the crude incidence is 12% and increases with the percentage of T3 cancers included in each series.

#### TABLE 33.8-9. Local Excision plus Postoperative Therapy: Local Recurrence by T Stage: Selected Series

Actuarial analysis is an alternative method of determining the risk of local failure. The actuarial method, which accounts for the different length of follow-up for each patient, offers the most accurate method of risk analysis. As with crude failure, the incidence of actuarial failure increases with increasing T stage. It was 10% in the series of T1–2 cancers from the MGH,\textsuperscript{141} 14% from the University of Florida series in which only 2% of patients had T3 cancers,\textsuperscript{142} and 27% in the Memorial Sloan-Kettering Cancer Center series in which 21% of patients had T3 cancers.\textsuperscript{143}

The impact of positive margins on local failure is unclear. In the Memorial Sloan-Kettering series, for the total patient group, 5-year actuarial local failure was higher in patients with positive versus negative margins (35% vs. 23%).\textsuperscript{129} A similar increase in crude local failure rates was reported in the Vancouver series (40% vs. 6%).\textsuperscript{138} In contrast, no significant differences were reported in the series from Fox Chase Cancer Center\textsuperscript{144} or the MGH.\textsuperscript{129} In the MGH series, this lack of difference may have been related to a higher radiation dose delivered to that subset. Of the six patients with positive margins (none of whom developed local failure), five of the six received doses of more than 60 Gy.
A full-thickness local excision is recommended because patients who undergo a piecemeal excision usually have higher local failure rates. In those patients who do undergo a full-thickness excision, the impact of positive margins is unclear. Most investigators would recommend that negative margins be obtained if technically feasible and a reexcision performed if needed, providing that it does not compromise sphincter function. If this is not possible, doses of more than 50.4 Gy, if the small bowel is excluded from the high-dose field, are probably necessary. In patients who undergo radical surgery for rectal cancer, 80% of local recurrences occur within the first 2 years. In contrast, the Memorial Sloan-Kettering series has reported local failures at 48 months, and the MGH series has reported local failures as late as 64, 72, 86, and 91 months. Furthermore, in the MGH series the median time to local recurrence was 55 months. In a group of 85 patients with more favorable prognostic factors who underwent local excision alone. Therefore, patients who are treated with local excision and postoperative adjuvant therapy require close follow-up beyond 5 years. On a positive note, most local recurrences occur at the anastomotic site and not in pelvic lymph nodes. Of the 18 local failures reported in the MGH series, only one involved the pelvic nodes. None were seen in the series from the University of Pennsylvania and Catholic University. Furthermore, salvage of local failures is possible. With the exception of the University of Florida experience, in which only one of five local failures could be salvaged with an APR, most series report that at least one-half of the patients who undergo a salvage APR can be cured: Beth Israel Deaconess Medical Center reported three cures out of four; University of Pennsylvania, two of three; Memorial Sloan-Kettering Cancer Center, five of eight; Vancouver, three of seven; Catholic University, one of two; Fox Chase, three of four; Intergroup trial, four of seven; and MGH, five of nine. sphincter function was good to excellent in 88% of patients with an intact rectum. In an update of 44 patients with tumors of 3 cm or smaller from the dentate line suitable for a local excision (n = 18); or group III, T3 or >3 cm down-staged with preoperative radiation to <T2 and <3 cm underwent a local excision after 45 to 55 Gy. In a report by Mohiuddin et al., APR. Of the six patients with positive margins, two developed local failure. The 20 patients with local control had "normal" sphincter function. In the University of Pennsylvania and Catholic University series use the previously published Memorial Sloan-Kettering Sphincter Function Scale. They report 94% and 100% good to excellent function, respectively. In a study from the Cleveland Clinic, 22% reported good to excellent function, the University of Pennsylvania reported 92% satisfactory function, and the M. D. Anderson Cancer Center reported that all patients were continent.

Chemotherapy

Limited data are available on the use of chemotherapy in patients who undergo local excision and postoperative radiation therapy. In most series, 5-FU was delivered as a radiosensitizer rather than in the adjuvant setting. In a subgroup analysis, the MGH reported a lower 5-year actuarial local failure rate (4% vs. 19%, P = NS) but at the same time a lower relapse-free survival rate (67% vs. 81%, P = NS) in patients receiving 5-FU-based combined modality therapy versus radiation alone. Because the numbers are limited and the data are not stratified by T stage, the impact of chemotherapy is unclear. However, given the positive impact of chemotherapy on local control and survival in patients with resectable rectal cancer reported in the randomized postoperative rectal adenocarcinoma adjuvant trials, all patients should receive two cycles of 5-FU-based therapy concurrently with radiation. For patients with T2–3 disease in whom the incidence of pelvic lymph nodes is at least 20%, an additional four cycles of adjuvant chemotherapy for a total of six cycles is recommended.

Summary

The data suggest that the approach of local excision and postoperative radiation is a reasonable alternative to radical surgery in selected patients. It should be limited to patients with either T2 tumors, or T1 tumors with adverse pathologic factors (poorly differentiated and/or LVI). Although the local failure rates are approximately double those reported with radical surgery, one-half of the failures can be salvaged with an APR without an apparent detriment to overall survival. Functional results are generally good to excellent. Transmural (T3) tumors have a 25% local failure rate and are treated more effectively with radical surgery and pre- or postoperative therapy. The results of local excision and postoperative radiation therapy are encouraging; however, randomized trials are needed to determine if this approach ultimately has similar local control and survival rates as radical surgery.

PREOPERATIVE RADIATION THERAPY FOLLOWED BY SURGERY

Sphincter preservation is a major goal of preoperative therapy. A number of preoperative treatment approaches have been used, and their selection depends on factors such as tumor histology, size, location, mobility, and anatomic constraints, and the technical expertise of the surgical, radiation, and medical oncologists. An analysis of 1316 patients treated in two previously published Scandinavian trials of intensive short course radiation reveals that down-staging is most pronounced when the interval between the completion of radiation and surgery is at least 10 days. However, none of the randomized trials of intensive short course preoperative radiation address whether the degree of down-staging is adequate to enhance sphincter preservation.

From the viewpoint of sphincter preservation, the advantage of preoperative therapy is to decrease the volume of the primary tumor. When the tumor is located in close proximity to the dentate line, this decrease in tumor volume may allow the surgeon to perform a sphincter-preserving procedure that would not otherwise be possible. However, patients whose tumors directly invade the anal sphincter are unlikely to undergo sphincter preservation, even after a complete response to radiation therapy. In general, when sphincter preservation is the goal of therapy, the use of preoperative therapy should be limited to patients who are not technically able to undergo a local excision because of tumor size or anatomic constraints. For example, if the tumor is close to the anal sphincter, a full-thickness local excision with negative margins may require partial removal of the sphincter, resulting in compromised sphincter function.

Two surgical approaches have been used after preoperative pelvic radiation: local excision and LAR plus CAA. To assist in the choice of the surgical procedure, some investigators have used transrectal ultrasound for restaging after the completion of preoperative therapy. However, most series reveal that posttreatment staging is only of modest accuracy. Williamson and colleagues reported that, in 15 patients who completed preoperative combined modality therapy, 38% were down-staged by transrectal ultrasound. At pathology, T stage was down-staged in 47% and N stage in 88%. Another series found transrectal ultrasound correctly predicted the T and N stage in 62% and 76%, respectively. In another series, the accuracy of transrectal ultrasound was 93% for T stage, but only 61% for N stage. Newer techniques, such as color Doppler flow and intracavitary MRI coils and PET, are being investigated. In a comparative study of 80 patients, the accuracy of predicting T stage and N stage preoperatively was 81% and 84% with transrectal ultrasound, 65% and 57% with CT, and 81% and 63% with an MRI endorectal coil, respectively.

LOCAL EXCISION

The results of 25 patients who received 34.95 Gy at 2.33 Gy per fraction to a partial pelvic field followed in 6 to 8 weeks by a transanalis or transspincteric local excision and a 20- to 25-Gy boost with afterloading was reported by Olmezguine et al. The median tumor size was 4 cm, 80% were exophytic, 72% were well to moderately differentiated, and all were mobile. With a mean follow-up of 41 months, the local failure rate was 20%, and three of the five failures were salvaged with an APR. Of the six patients with positive margins, two developed local failure. The 20 patients with local control had "normal" sphincter function.

In a report by Mohiuddin et al., 48 selected patients who met specific criteria (group I, T3 and medically unsuitable for a LAR (n = 15); group II, <T2 and <3 cm suitable for a local excision (n = 18); or group III, T3 or >3 cm down-staged with preoperative radiation to <T2 and <3 cm) underwent a local excision after 45 to 55 Gy. With a median follow-up of 40 months, the 5-year actuarial survival rate was 84% and the local failure rate was 10%. Local failure by group was 20% for group I, 11% for group II, and 0% for group III. Postoperative wound complications were seen in 10%, and four patients required a subsequent colostomy (three for local failure). Sphincter function was good to excellent in 88% of patients with an intact rectum. In an update of 44 patients with tumors of 3 cm or smaller from the dentate line selected to undergo a local excision after preoperative radiation therapy, the local failure rate was 14% and the 5-year survival rate was 90%.

LOW ANTERIOR RESECTION AND COLORECTAL ANASTOMOSIS
PREOPERATIVE PROSPECTIVE CLINICAL ASSESSMENT

The most accurate method by which to determine if preoperative therapy has contributed to sphincter preservation is to perform a prospective clinical assessment. This requires that the operating surgeon examines the patient before the start of preoperative therapy and declares the type of operation required. It should be noted that this assessment is based on an office examination and may not accurately reflect the assessment when the patient is relaxed under general anesthesia. The only method by which to account for this potential bias is a randomized trial of preoperative versus postoperative therapy. With this randomized design, the accuracy of the assessment could be determined, because one-half of the patients are randomized to undergo surgery before postoperative therapy.

An interval analysis of the first 116 patients enrolled on the National Surgical Adjuvant Breast Project (NSABP) R-03 randomized trial of preoperative versus postoperative combined modality therapy has been reported by Hyams and colleagues (Table 33.8-10). Because one-half of the patients were randomized to undergo surgery before the postoperative therapy, the accuracy of the office assessment to predict the type of operation required could be determined. Of the 57 patients randomized to the postoperative combined modality arm, 26 were declared clinically to require an APR and all 26 patients underwent the procedure. Therefore, the data suggest that the office assessment is an accurate method by which to predict the type of operation required. The incidence of postoperative complications was similar in the preoperative and postoperative arms (33% and 30%, respectively). The results from this report should be considered preliminary, because the trial was still open to accrual at the time of the analysis.

<table>
<thead>
<tr>
<th>TABLE 33.8-10. Results of Preoperative Therapy in Patients Prospectively Declared to Require an Abdominoperineal Resection (APR)</th>
</tr>
</thead>
</table>

SURGICAL ISSUES IN COLOANAL ANASTOMOSIS

Careful surgical techniques must be used when performing a CAA after preoperative therapy. To perform the anastomosis with unirradiated bowel, the splenic flexure must be mobilized. To enhance anastomotic healing, a diverting colostomy should be performed and is closed 2 to 4 months postoperatively. For example, in the R90-01 trial of preoperative radiation therapy, patients received 3 Gy × 13 and were randomized to either a short interval (2 weeks) or a long interval (6 to 8 weeks) between the end of radiation and surgery. Of the total of 144 patients who underwent a sphincter-preserving operation, 57 had a temporary diverting colostomy. The incidence of anastomotic complications requiring surgery was 5% in that group compared with 23% in the 87 patients who did not undergo the temporary diverting colostomy.

TECHNICAL ASPECTS OF PREOPERATIVE RADIATION THERAPY

If the goal of preoperative therapy is sphincter preservation, conventional doses and techniques of radiation are recommended. These include multiple-field techniques to a total dose of 45.0 to 50.4 Gy at 1.8 Gy per fraction. Surgery should be performed 4 to 6 weeks after the completion of radiation. This design allows for recovery from the acute side effects of radiation and enhances tumor down-staging.

Since the publication of the Swedish Rectal Cancer Trial, which revealed a significant improvement in survival with intensive short course preoperative radiation, some physicians have advocated this alternative approach. Typically, the intensive short course includes 25 Gy in five fractions followed by surgery 1 week later. Not only are these treatment programs associated with increased surgical morbidity and mortality, but by virtue of their design, they do not enhance sphincter preservation. Therefore, they should be used with great caution.

CLINICAL EXPERIENCE

A total of seven series have reported results in patients with clinically resectable, invasive rectal cancer (T2–3 or T4 tethered to the vagina) who underwent a prospective clinical assessment before the start of preoperative therapy and were declared to need an APR (see Table 33.8-10). All use conventional radiation techniques and, with the exception of the R90-01 trial which used 3-Gy fractions, the remainder used standard radiation doses (1.8 to 2.0 Gy per fraction). Two of the series are from Memorial Sloan-Kettering Cancer Center. The initial approach to sphincter preservation at Memorial Sloan-Kettering was preoperative radiation therapy alone, and the results of this prospective phase III trial have been reported by Wagman et al. The current approach at Memorial Sloan-Kettering is preoperative combined modality therapy, which has been reported by Gramm and associates. Preoperative radiation therapy (without chemotherapy) was reported by Rouanet et al. from the Montpellier Cancer Institute and by Francois and associates from the Lyon R90-01 trial. The other three trials used combined modality therapy. Hyams and colleagues reported an interval analysis of the ongoing NSABP R-03 phase III randomized trial of preoperative versus postoperative combined modality therapy. The remaining trials were reported by Maghfoo and colleagues from Ellis Fischel Cancer Center and Valentini et al. from the Catholic University in Rome.

Other series have been conducted in which patients receive preoperative radiation therapy followed by sphincter preservation. In the series from Papillon and Gerard from the Centre Leon Berard, patients did not undergo a prospective clinical assessment by their surgeon, and therefore, the impact of preoperative radiation therapy on enhancing sphincter preservation cannot be determined. Thomas Jefferson University has a large experience with preoperative radiation therapy. In tumors located in the distal 2 cm of the rectum, preoperative radiation therapy allowed sphincter preservation in 91% of patients, 88% of whom had “satisfactory” functional results. Because this trial included patients with early (T1) as well as unresectable (T4) disease, the results are not comparable to the other series.

As seen in Table 33.8-10, sphincter-preservation rates were only 23% in the interim analysis of the NSABP R-03 trial and 44% in the R90-01 trial, whereas the other five trials report that approximately 75% of patients are able to undergo sphincter preservation after preoperative therapy. Local failure rates vary from 0% to 17%, and survival rates range from 100% at 2 years to 72% at 5 years. Four series report functional outcome. Wagman et al. and Valentini et al. both use the Memorial Sloan-Kettering Cancer Center Sphincter Function Scale. The R90-01 trial defines normal function as a patient without soiling or requiring pads. The Montpellier series does not define “perfect” function.

One series has reported that the detrimental effect on sphincter function associated with postoperative therapy may not be as problematic with preoperative therapy. The short-term and long-term impact of preoperative radiation therapy on sphincter function has been examined by Birnbaum and colleagues. Patients received conventional doses and techniques of radiation and were assessed objectively by anal manometry with or without transrectal ultrasound. In the 20 patients assessed for short-term results and the ten patients assessed for long-term results, radiation therapy had a “minimal” effect on sphincter function. The results of the R90-01 trial support the advantage of a longer interval (at least 4 weeks) between the completion of radiation and surgery. A total of 201 eligible patients were randomized to either a short interval (2 weeks) or a long interval (6 to 8 weeks). Patients randomized to the long interval had a significantly higher incidence of clinical complete response (pathologic complete response and/or a few residual foci of cells; 26% vs. 10%, respectively; P = .0054), with no increase in operative morbidity.
In summary, five of the seven trials suggest that preoperative therapy allows sphincter preservation in approximately 75% of patients judged clinically to require an APR. The majority have good to excellent functional results. Given the suggestion of decreased acute toxicity and enhanced sphincter preservation with preoperative radiation therapy, three randomized trials of conventional dose preoperative versus postoperative combined modality therapy for clinically resectable, T3 rectal cancer have been developed. Two are from the United States (INT 0147, NSABP R-03) and one from Germany (CAO/ARO/AIO 94). All three use conventional doses and techniques of radiation therapy and concurrent 5-FU-based chemotherapy, and they require a preoperative clinical assessment declaring the type of operation required. However, low accrual resulted in the early closure of the INT 0147 trial and may jeopardize the NSABP R-03 trial as well. The German trial continues to accrue patients and should help provide an answer to the relative effectiveness of preoperative versus postoperative therapy and its ability to enhance sphincter preservation.

TREATMENT RECOMMENDATIONS

For patients with clinically resectable disease, the preoperative approach should be used in situations in which sphincter-preserving surgery is not technically possible at initial presentation. The decision of whether to use preoperative radiation therapy or preoperative combined modality therapy is based on the results of transrectal ultrasound. If a transrectal ultrasound reveals T2 disease, the patient may have pathologic T2N0M0 disease; therefore, the sole reason for the preoperative therapy is to convert the operation from an APR to an LAR plus CAA. In this setting, preoperative radiation therapy alone is recommended. If positive mesorectal or pelvic lymph nodes are identified at the time of surgery, the patient should receive 6 months of adjuvant postoperative 5-FU–based chemotherapy. Two potential disadvantages are associated with this approach. First, the ultrasound may under-stage approximately 10% of patients who have pathologic stage T3 disease. Second, because preoperative radiation down-stages pelvic lymph nodes by approximately 50%, the rate of node-positive disease is unknown, and some node-positive patients may not receive chemotherapy. Obviously, these disadvantages need to be weighed against the risk of overtreating these patients with combined modality therapy.

For patients with transrectal ultrasound stage T3 disease, preoperative combined modality therapy followed by surgery and postoperative 5-FU–based chemotherapy is recommended. This approach is based on extrapolation of the significant improvement in local control and survival in patients with T3 or N1–3 disease who receive adjuvant postoperative combined modality therapy. Whether preoperative combined modality therapy is more effective than preoperative radiation therapy is unknown. An ongoing randomized trial from the European Organization for Research and Treatment of Cancer (EORTC) will address this question.

At the present time, the most common preoperative combined modality therapy regimens include 45.0 to 50.4 Gy of pelvic radiation at 1.8 Gy per fraction plus concurrent bolus 5-FU plus leucovorin or continuous infusion 5-FU. Some have advocated 5-FU plus mitomycin C, which is more commonly used in the treatment of anal cancer. One trial using neoadjuvant 5-FU plus methotrexate followed by continuous infusion 5-FU plus concurrent radiation did not report a benefit compared with conventional 5-FU plus leucovorin. Phase III trials are in progress combining new systemic chemotherapeutic agents, such as nitrosourea (Tomudex), Orzel (oral tegafur, uracil, and 5-fluorouracil plus leucovorin), CPT-11, and oxaliplatin, with preoperative radiation therapy. Whether any of these combinations will be more effective than 5-FU–based therapy remains to be determined.

ADJUVANT RADIATION THERAPY FOR RESECTABLERECTAL CANCER

The rationale of radiation therapy is based on the patterns of failure after potentially curative surgery (see Table 33.8-7). The incidence of local failure as a component of failure is less than 10% in stages T1–2N0M0; the incidence increases to 15% to 35% in stage T3N0M0 and is as high as 45% to 65% in stages T3–4N1–2M0. When local failure does occur, it is severely debilitating and salvage has been of limited success. In 1936, Daland et al. (1936) stated that the morbidity associated with local failure is often devastating, and as many as 68% of patients have one or more pelvic symptoms, including infection, ulceration, obstruction, and intractable pain for 9 to 12 months before death. The same holds true today. Therefore, even though it does not increase survival, the ability of radiation therapy to decrease local failure is, by itself, an important end point.

For unsubstantiated reasons, some consider colorectal adenocarcinomas to be radioresistant. This assumption has been based on the observation that these tumors do not respond as rapidly to radiation as other histologies. The radioresistant theory was disproved in 1965 by Svit et al. (1965), who showed that the rapidity of tumor response to radiation is not an accurate reflection of their curability. Brierey et al. (1995) reported the results of 66 patients with rectal cancer treated with radiation therapy alone. As seen in Figure 33.8-5, of the patients who achieved a complete response to radiation therapy, only 80% had achieved the complete response by 4 months.

FIGURE 33.8-5. Time to a complete response from the start of treatment for 66 patients with inoperable rectal cancer who received radiation therapy alone and achieved a clinical complete response. (From Brierey JD, Cummings BJ, Wong CS, et al. Adenocarcinoma of the rectum treated by radical external radiation therapy. Int J Radiat Oncol Biol Phys 1995;31:255, with permission.)

Some physicians contend that adjuvant therapy is not necessary if patients undergo resection with a total mesorectal excision. In one series, total mesorectal excision, which involves sharp dissection around the integral mesentery of the hindgut, decreased the local recurrence rate to 5%. These data must be interpreted with caution for a number of reasons. First is selection bias. This operation allows the identification and exclusion of patients with more advanced disease as compared with patients treated in the adjuvant trials in which more conventional surgery is performed. Second, some patients with T3 or N1–2 disease received radiation therapy with or without chemotherapy (i.e., 18% in the series by Haas-Kock et al., 28% in the series from Enker and associates, and 58% in the series from Aresta et al.). In a combined analysis of 1411 patients from five international centers, an undisclosed number received adjuvant radiation or combined modality therapy. Third, some series (i.e., Alken et al.) exclude operative deaths. Lastly, total mesorectal excision may also be associated with higher complication rates. In the Basingstoke Hospital experience reported by Carlsen and colleagues, the anastomotic leak rate was 16% in patients who underwent total mesorectal excision (all of whom required hospitalization) compared with a leak rate of 8% in a similar group of patients who underwent conventional surgery (with only 25% requiring hospitalization). Poon and colleagues recommend the creation of a diverting stoma to decrease the high leak rate with total mesorectal excision.

The Dutch CKVO 95-04 trial examines the role of intensive short course preoperative radiation therapy in patients who undergo a total mesorectal excision. Patients are randomized to an intensive short course of radiation (5 Gy × 5) versus surgery alone. Postoperative radiation, which is performed with conventional doses, is reserved for patients in the surgery-only arm who do not undergo a curative resection. Investigator participation is limited to surgeons who have demonstrated proficiency in performing a total mesorectal excision. The trial is open to accrual.

Dahlgberg and colleagues report a 3% local failure rate in patients with resectable rectal cancer with the combination of total mesorectal excision and intensive short course preoperative radiation. Because patients with clinical stage T1–3 disease were included, it is difficult to compare these results with series that are limited to T3 disease.

The use of total mesorectal excision has increased awareness of the importance of surgical technique. Careful surgical techniques are central to the successful management of rectal cancer. However, they should be considered a valuable component of therapy, not competitive with adjuvant therapy. Given the selection bias,
higher complication rates in some series, and the fact that adjuvant therapy is used in some series, the benefits and risks of total mesorectal excision must be more carefully documented. The total mesorectal excision series need to focus on all end points, such as local control, survival, sphincter preservation and function, surgical morbidity and mortality, and quality of life.

Radiation therapy has been used in three major approaches to the adjuvant treatment of resectable rectal cancer. These include postoperative, preoperative, and pre- plus postoperative radiation therapy.

ADJUVANT POSTOPERATIVE RADIATION THERAPY

Most patients in the United States undergo surgery and, if needed, receive postoperative therapy. The primary advantage with this approach is pathologic staging. Despite advances in preoperative imaging techniques, which allow more accurate patient selection, postoperative therapy remains the most common approach. The primary disadvantages include an increased amount of small bowel in the radiation field and a potentially hypoxic postsurgical bed, and if the patient has undergone an APR, the radiation field must be extended to include the perineal scar.

Nonrandomized Trials

Nonrandomized data from the MGH [12] and the M. D. Anderson Cancer Center [12] reveal crude local failure rates of 4% to 31% in patients with stage T3–4N0M0 disease and 8% to 53% in patients with stage T3–4N1–2M0 disease who received 4500 to 5500 cGy (Table 33.8-11). The MGH series is the largest reported experience from a single institution in which careful radiation techniques were used and long follow-up is available. The MGH results were compared with a historical control group of 142 patients who underwent surgery only. Stage for stage, an improvement was seen in both local control and survival in those patients who received postoperative radiation therapy. The MGH results of 261 patients who received postoperative radiation therapy have been updated, providing 5-year actuarial local control data. Actuarial local control by stage include 87% for T3N0M0, 83% for T4N0M0, 76% for T1–2N1–2M0, 77% for T3N1–2M0, and 23% for T4N1–2M0.

In summary, the retrospective data suggest that postoperative radiation therapy decreases local failure. The only randomized trial, which confirms this finding (with borderline significance), is from the NSABP. It should be noted that, of the randomized trials that compare radiation therapy to a surgical control arm, the NSABP is the only trial in which the radiation therapy was delivered with a continuous course, in full doses, and with “modern” techniques.

ADJUVANT PREOPERATIVE THERAPY

Preoperative adjuvant therapy (most commonly radiation therapy combined with systemic chemotherapy) is an alternative to postoperative therapy.

Wiggenraad and associates treated 123 patients with postoperative radiation and correlated results with p53 status as determined by immunohistochemistry. With a median follow-up of 40 months, no significant difference was noted in local failure or survival by p53 status.

Randomized Trials

Five randomized trials have examined the use of adjuvant postoperative radiation therapy alone in stages T3 or N1–2 rectal cancer. [13,14 and 15] None have shown an improvement in overall survival. The series from Odense University is a two-arm trial comparing postoperative radiation therapy with surgery alone. In two of the series, one of the arms included radiation plus chemotherapy [Gastrointestinal Tumor Study Group (GITSG)] [16] or chemotherapy alone (NSABP R-01). In the Mayo Clinic/NCCCTG trial 79-47-51, there was no surgery-only control arm.

Two trials reveal a decrease in local failure: NSABP R-01 (16% vs. 25%, \( P = .06 \)) and the Medical Research Council (21% vs. 34%, \( P = .001 \)). These trials are discussed in length in the section on combined modality therapy of resectable rectal cancer (see Radical Surgery and Adjuvant Postoperative Combined Modality Therapy for Resectable Rectal Cancer, earlier in this chapter). In this section, the discussion is limited to the comparison of the radiation therapy arm compared with the surgical control arm.

As discussed in the section on patterns of failure (see Patterns of Recurrence after Radical Surgery, earlier in this chapter), local failure rates depend on whether they are reported as first or cumulative failure. The randomized trials usually express failure as first site of failure as opposed to the nonrandomized trials, which express failure as cumulative failure. For example, in the Mayo Clinic/NCCCTG trial, the incidence of local failure in node-positive patients was 25% when expressed as first failure compared with 63% when expressed as cumulative failure. More favorable local failure results (local failure as the first site of failure) were reported from the GITSG (18% vs. 25%, \( P = .01 \)) and the NSABP (15%).

In the GITSG series, 58 patients underwent surgery alone and 50 received postoperative radiation therapy (40 to 48 Gy). No significant differences were noted in either local failure or survival between these two arms. Many criticisms have been leveled at the radiation therapy techniques used in the GITSG series. First, 35% of the patients treated with radiation therapy varied from the protocol specifications. Second, the radiation dose was chosen by the individual investigator (patients could receive 40 or 48 Gy). The issue of radiation dose is important, because dose response in radiation therapy follows a sigmoidal distribution. Therefore, a small decrease in dose can result in a large difference in local control. For example, in the Mayo Clinic/NCCCTG trial 79-47-51, patients in the postoperative radiation-alone arm who received 50.4 Gy had a slightly lower local failure rate compared with those who received 45 Gy (18% vs. 24%). Although no difference in overall survival was reported, patients who received adjuvant radiation therapy in the NSABP trial had a borderline significant decrease in local failure compared with surgery alone (15% vs. 25%, \( P = .06 \)).

In the series from Odense University, 494 patients were randomized to postoperative radiation therapy (45 to 50 Gy) versus surgery alone. In patients with stage T2–3N0 disease, no difference was noted in the incidence (6%) or mean time to local failure between the arms. In patients with stage T1–3N1–2 disease, no difference was reported in local failure (6% vs. 9%); however, the mean time to local failure was significantly longer in patients who received radiation therapy compared with the surgical control arm (19 months vs. 6 months, \( P = .01 \)). This series also has raised many criticisms. These include a short median follow-up (3 years) and that 43% of the patients were not randomized, the radiation therapy was split course, 20 patients in the radiation arm received less than 45 Gy, and the incidence of local failure in the surgery control arm was unusually low for node-positive cancers (9%).

The EORTC randomized 172 patients with T3 or N1–2 disease to 46 Gy versus observation. No significant difference was seen in local failure or survival. An increase was noted in chronic diarrhea and cystitis in the radiation arm; however, it must be emphasized that patients were treated with only two fields per day. As discussed in the section on toxicity of pelvic radiation (see Complications of Pelvic Radiation Therapy, later in this chapter), this two-field technique is associated with an increase in radiation associated toxicity.

In summary, the retrospective data suggest that postoperative radiation therapy decreases local failure. The only randomized trial, which confirms this finding (with borderline significance), is from the NSABP. It should be noted that, of the randomized trials that compare radiation therapy to a surgical control arm, the NSABP is the only trial in which the radiation therapy was delivered with a continuous course, in full doses, and with “modern” techniques.

TABLE 33.8-11. Adjuvant Postoperative Radiation Therapy for Resectable Rectal Cancer: Selected Nonrandomized Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patients</th>
<th>Radiation Therapy</th>
<th>Disease Stage</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>MGH</td>
<td>142</td>
<td>No surgery</td>
<td>T3–4N0–2M0</td>
<td>Decreased local failure</td>
</tr>
<tr>
<td>M. D. Anderson Cancer Center</td>
<td>123</td>
<td>Postoperative</td>
<td>T3–4N0–2M0</td>
<td>Decreased local failure</td>
</tr>
<tr>
<td>Mayo Clinic/NCCCTG</td>
<td>122</td>
<td>Postoperative</td>
<td>T3–4N0–2M0</td>
<td>Decreased local failure</td>
</tr>
<tr>
<td>Medical Research Council</td>
<td>216</td>
<td>Postoperative</td>
<td>T3–4N0–2M0</td>
<td>Decreased local failure</td>
</tr>
</tbody>
</table>

Patterns of Recurrence after Radical Surgery

As discussed in the section on patterns of failure, the randomized trials usually express failure as first site of failure as opposed to the nonrandomized trials, which express failure as cumulative failure. For example, in the Mayo Clinic/NCCCTG trial, the incidence of local failure in node-positive patients was 25% when expressed as first failure compared with 63% when expressed as cumulative failure. More favorable local failure results (local failure as the first site of failure) were reported from the GITSG (18% vs. 25%, \( P = .01 \)) and the NSABP (15%).

Complications of Pelvic Radiation Therapy

The EORTC randomized 172 patients with T3 or N1–2 disease to 46 Gy versus observation. No significant difference was seen in local failure or survival. An increase was noted in chronic diarrhea and cystitis in the radiation arm; however, it must be emphasized that patients were treated with only two fields per day. As discussed in the section on toxicity of pelvic radiation, this two-field technique is associated with an increase in radiation associated toxicity.
The primary advantages of preoperative therapy are sphincter preservation and a lower incidence of acute toxicity.

The disadvantage of preoperative radiation therapy is the potential of overtreating patients with either early (pathologic stage T1–2N0) or metastatic disease. With improved imaging techniques, such as EUS, ultrasound-guided pararectal lymph node biopsy, CT, MRI with a phased-array, or an endorectal coil, and PET, the number of patients who are overtreated is decreased. Experienced investigators report the accuracy of EUS in predicting T stage preoperatively as high as 90%.192

Results of Adjuvant Preoperative Therapy

Nonrandomized trials of preoperative radiation therapy with or without chemotherapy have reported decreased local recurrence and, possibly, improved survival.193 Some trials include patients with early-stage or metastatic disease. Because these patients are excluded from the postoperative adjuvant therapy trials, a randomized trial is necessary to accurately compare the results of preoperative and postoperative therapy. The phase III trials in which preoperative radiation or combined modality therapy is used to enhance sphincter preservation have been discussed in the section on sphincter preservation (see Adjuvant Therapy and Sphincter-Saving Operations as an Alternative to Abdominoperineal Resection, earlier in this chapter) and are reviewed in Table 33.5-10.

The only randomized trial comparing preoperative versus postoperative radiation therapy (without chemotherapy) is the Uppsala trial, in which 471 patients were randomized to receive either intensive short course preoperative radiation (25.5 Gy in five fractions) or, for patients with T3 or N1–2 disease, 60 Gy postoperatively.200 A significant decrease was noted in local recurrence with preoperative radiation (13% vs. 22%, \(P = .02\)); however, no difference was found in 5-year survival (42% vs. 38%). Although a significant increase of perineal wound sepsis was seen in the preoperative group (33% vs. 18%, \(P < .01\)), other short- and long-term side effects were decreased. For example, the incidence of small bowel obstruction (5% vs. 11%) and total grade 3+ toxicity (20% vs. 41%) was lower in the preoperative group compared with the postoperative group. The increase in the incidence of perineal wound sepsis in the preoperative arm may have been related to the anticipated radiation techniques and high dose per fraction delivery. It should be emphasized that this increase has not been reported in the series that use conventional radiation doses and block the perineal skin in the lateral fields.

Given the advantage of the addition of concurrent chemotherapy to radiation therapy in the postoperative setting, a variety of preoperative combined modality treatment programs have been developed. Retrospective studies suggest that preoperative combined modality therapy increases pathologic down-staging compared with preoperative radiation therapy192 and is associated with a lower incidence of acute toxicity compared with preoperative combined modality therapy. Most trials of preoperative combined modality therapy primarily include patients with unresectable disease. These are discussed in the section on locally advanced and unresectable rectal cancer (see Treatment of Locally Advanced and Unresectable Rectal Cancer, later in this chapter). Most preoperative combined modality therapy trials for patients with clinically resectable disease have used either bolus or continuous infusion 5-FU–based chemotherapy.

Combining the results of the published series, grade 3+ toxicity during the combined modality segment is 15% to 25%, the pathologic complete response rates are 9% to 29%, and the incidence of local failure is 0% to 10%. The limited data do not allow a valid comparison of the results of bolus versus continuous infusion 5-FU.

Whether preoperative combined modality therapy is more effective than preoperative radiation therapy is being addressed in an ongoing randomized trial from the EORTC. This trial will determine if bolus 5-FU plus leucovorin, either preoperatively or postoperatively, or both, is superior to preoperative radiation therapy alone.

Eleven modern randomized trials of preoperative radiation therapy (without chemotherapy) for resectable rectal cancer are ongoing.197 All use low to moderate doses of radiation. The Second Medical Research Trial, which revealed a significant improvement in local control, distant control, and disease-free survival is excluded from this discussion because patients had fixed or partially fixed disease.

Some of the trials show a decrease in local recurrence, and in five of the trials, this difference reached statistical significance. An analysis of the trials reported before 1988 suggests that a dose-response effect may favor preoperative radiation compared with postoperative radiation.202 Although in some trials a subset analysis has revealed a significant improvement in survival,25 until the Swedish Rectal Cancer Trial263 no one had reported a survival advantage for the total treatment group.

Intensive Short Course Preoperative Radiation

The first randomized trial of preoperative radiation therapy to reveal a significant improvement in survival by intent to treat was the Swedish Rectal Cancer Trial.142 A total of 1,168 patients with clinically resectable rectal cancer were randomized to 25 Gy in five fractions, followed by surgery 1 week later versus surgery alone. With a median follow-up of 75 months, patients randomized to the preoperative arm had an improvement in local failure (12% vs. 27%, \(P < .001\)) and an improvement in disease-free survival (52% vs. 39%, \(P = .001\)). This increase is consistent with other trials of preoperative radiation therapy.202

Although the results are intriguing, these data need to be confirmed by additional studies, because the other ten randomized trials of preoperative radiation therapy have been negative. Even if future trials confirm this survival advantage, other equally important end points in rectal cancer need to be addressed. These include acute toxicity, sphincter preservation and function, and quality of life. Radiation fraction sizes and techniques have a major impact on these end points.

Conventional radiation techniques include the use of multiple fields rather than simple anterior-posterior fields, computerized treatment planning, and customized block techniques. The techniques allow the delivery of high doses of radiation while sparing the surrounding normal tissues, such as the small bowel. The simple anterior-posterior radiation techniques commonly used with the other intensive short course radiation therapy trials, such as the Uppsala trial, are associated with an increase in toxicity.

Although prior trials of intensive short course radiation have revealed a significant increase in mortality,\(^{143}\) these differences were not reported in the Swedish Rectal Cancer Trial. This may have been related to the use of multiplet-field techniques. In the Swedish trial, patients who received radiation with multiple-field techniques had a significant decrease in postoperative mortality compared with those who received treatment with anteroposterior techniques (3% vs. 15%, \(P < .001\)). The postoperative mortality with surgery alone was 12%. However, the incidence of postoperative morbidity for the total group of patients receiving radiation (regardless of the technique) was still significantly higher when compared with the surgery control arm (44% vs. 34%, \(P < .001\)). This increase is consistent with other trials of intensive short course preoperative radiation.202

The absence of an increase in mortality in the Swedish trial may have been related to the fact that 91% of patients received radiation using the more sophisticated multiple-field radiation techniques. In patients who receive conventional doses and techniques of preoperative combined modality therapy, the volume of small bowel in the radiation field may be the dose-limiting organ with radiation therapy.137

It should be noted that even when multiple-field techniques are used, data from the Stockholm I and II trials\(^{137}\) report a significant increase in postoperative mortality when patients receive intensive short course radiation compared with surgery alone (4% vs. 1%). These high complication rates with intensive short course radiation have not been reported in patients who receive conventional doses and techniques of preoperative radiation. In the R90-01 trial,261 patients were treated with multiple-field techniques but with 3-Gy fractions. The anastomotic complication rate was 17%.

Another criticism of the intensive short course preoperative radiation trials is the lack of preoperative staging. Myerson et al.262 treated 83 patients with this approach, and only 20 had transrectal ultrasound staging.

In summary, even with suboptimal radiation techniques, the more recent randomized preoperative trials reveal a significant decrease in local failure. Although the intensity of short course (25 Gy) of preoperative radiation therapy is used in some European countries, it is not favored in North America because (1) it is unlikely that it could be combined with adequate doses of systemic chemotherapy; (2) it is not designed to enhance sphincter preservation; and (3) regardless of the technique, it is still associated with a significant increase in postoperative morbidity.

PREOPERATIVE AND POSTOPERATIVE RADIATION THERAPY
The approach of using both preoperative and postoperative therapy, also known as the sandwich technique, includes a short preoperative course of radiation (5 to 15 Gy), followed by surgery, and in patients with T3N1M0 disease, an additional 40 to 45 Gy postoperatively. This approach was designed to combine the theoretical advantages of low-dose preoperative radiation therapy (decreased tumor seeding) while preserving postoperative radiation therapy for those patients with T3 or N1–2M0 disease. The results of this approach have been reported by a number of investigators.  

The Radiation Therapy Oncology Group (RTOG) presented the results of a randomized trial of 350 patients (87% with rectal cancer) who were randomized to 5 Gy preoperative therapy versus surgery alone (RTOG 81-15). Patients with a pathologic stage T3 or N1–2 disease received a minimum of 45 Gy postoperatively. No chemotherapy was delivered. With a minimum follow-up of 5 years, no differences were found in local failure, distant failure, or overall survival between the arms. A retrospective analysis of 155 patients treated at the Institut Gustave Roussy also revealed no advantage of the sandwich technique compared with preoperative radiation.  

Because the randomized trials of postoperative combined modality therapy reveal a significant improvement in survival, the benefits of preoperative therapy, including down-staging and sphincter preservation, require a standard dose rather than low to intermediate doses of radiation, and because the RTOG randomized trial was negative, the sandwich approach should be abandoned.

SELECTED CONTROVERSIES IN THE ROLE OF PREOPERATIVE THERAPY

PREDICTION OF RESPONSE WITH TUMOR MARKERS

A variety of tumor markers have been identified that may help predict those tumors that will respond favorably to preoperative therapy (Table 33.8-12). Based on the experience that rapidly dividing cells are more sensitive to radiation, Willett et al. analyzed the proliferative index in patients with locally advanced or unresectable disease who received preoperative radiation therapy with or without 5-FU. Tumors with a higher proliferation index had a higher response rate to preoperative therapy and, after radiation, a corresponding reduction was noted in the proliferative index. In a follow-up study, the authors reported that the addition of 5-FU to preoperative radiation decreased three markers of proliferation [mitotic counts, Ki-67, and proliferating cell nuclear antigen (PCNA)] compared with radiation therapy alone.

![Image](72x862 to 272x1004)

**TABLE 33.8-12.** Prognostic Predictors of Response to Preoperative Therapy in Rectal Cancer

Desai and colleagues reported a higher incidence of recurrence but less down-staging in PCNA-positive rectal cancers. By multivariate analysis, Neoptolemos and associates showed that this index did not add to the prognostic value of the Dukes’ staging system. The proliferative index may be useful in predicting the response to preoperative therapy. However, given the conflicting data, additional experience is needed.

In the series reported by Rich of 50 patients treated with preoperative combined modality therapy, tumors with a low spontaneous apoptosis index and positive BCL-2 staining had lower rates of down-staging. In 167 patients treated with preoperative radiation, a significant increase in down-staging in well-differentiated cancers was reported. Using residual tumor cell density rather than stage as a measure, this difference did not reach statistical significance. By univariate analysis, patients with a pathologic complete response had a nonsignificant improvement in survival. Berger and associates found that well-differentiated tumors had a greater degree of down-staging compared with moderately or poorly differentiated tumors.

In conclusion, although some tumor markers may be predictive of response, the decision to use preoperative therapy should not be made solely on their presence or absence. The development of tumor markers to predict response and prognosis remains an active area of investigation.

DOES THE RESPONSE OF THE PRIMARY TUMOR PREDICT OUTCOME?

Most studies suggest that sphincter preservation is increased with a corresponding increase in the response rate of the primary tumor. It is more controversial as to whether the response rate predicts outcome and if the subset of patients who achieve a complete response still require radical surgery.

In an analysis of 88 patients with clinical T3–4 rectal cancers who received preoperative radiation with or without 5-FU plus leucovorin, a decrease was noted in local failure (4% vs. 15%) and a significant increase was noted in 5-year cancer-specific survival (100% vs. 45%, P = .01) in patients who achieved a complete or near-complete response (pathologic stage T0–2N0 disease) compared with those with less of a response (pathologic stage T3–4 or N1–2).  

Ahmad and colleagues reported a 5-year actuarial local control rate of 96% and a 91% survival rate in the subset of 49 of a total of 315 patients with clinical T3–4 disease who achieved a complete response after preoperative radiation.

Two studies have examined whether surgery is still necessary after a complete response, and the reported results have been conflicting. Habr-Gama and colleagues treated 118 patients with clinical T1–3 rectal cancers with preoperative 50.4-Gy radiation plus 5-FU plus leucovorin. Of the 36 patients who achieved a biopsy-proven complete response, 30 did not undergo surgery. With a median follow-up of 36 months, 28 (93%) remained without evidence of disease. In a smaller series from Rossi et al., 16 patients (13 with tethered disease) received similar preoperative treatment. If they achieved a biopsy-proven complete response, they received an additional boost of 20 to 30 Gy with brachytherapy. Of the six patients (38%) who had a complete response, they remained without evidence of disease for a median of only 11 months.

Although the results from Habr-Gama and colleagues are intriguing, radical surgery after preoperative adjuvant therapy remains the standard of care. In the subset of patients who are either medically inoperable or refuse radical surgery, local excision may be an alternative.

RADICAL SURGERY AND ADJUVANT POSTOPERATIVE COMBINED MODALITY THERAPY FOR RESECTABLE RECTAL CANCER

The anatomy and natural history of rectal adenocarcinoma require attention to issues of local and systemic tumor control. Despite many clinical trials, until 1990 there was considerable controversy about whether adjuvant therapy improved the survival rate of patients undergoing surgical resection of their primary tumors. Even a metaanalysis of the worldwide published experience, which demonstrated a statistically significant benefit for adjuvant chemotherapy in rectal cancer patients (38% decrease in the mortality rate), was not completely convincing for many physicians. However, a Consensus Development Conference sponsored by the National Institutes of Health in 1990 concluded that effective adjuvant therapy exists for stages II and III (Modified Astler Coller stages B2 and C or TNM stage T3 or N1–2) rectal cancers. This conclusion was based on the clinical data derived over the preceding 20 years. Especially important were the results of some of the randomized studies summarized in Table 33.8-13. Two of the studies included a surgery-only control group, and four studies used surgery plus postoperative pelvic irradiation as the means for achieving definitive local control.  

![Image](72x862 to 272x1004)
The majority of U.S. patients undergo surgery and, if they have stage T3 or N1–2 disease, receive postoperative adjuvant combined modality therapy. The most compelling advantage to this approach is pathologic staging. Although advances in preoperative imaging techniques allow more accurate patient selection, it still remains the most common approach. The primary disadvantages of the postoperative approach include an increased amount of small bowel in the radiation field and a potentially hypoxic postsurgical bed, and if the patient has undergone an APR, the radiation field must be extended to include the perineal scar.

RESULTS OF POSTOPERATIVE THERAPY

After the publication of the randomized trials from the GITSG and Mayo/NCCTG (79-47-51), which revealed a significant improvement in local control (Mayo/NCCTG) and survival (GITSG and Mayo/NCCTG) with postoperative radiation plus bolus 5-FU plus methyl chloroethylcyclohexylnitrosourea (CCNU; lomustine), the National Cancer Institute Consensus Conference concluded in 1990 that combined modality therapy was the standard postoperative adjuvant treatment for patients with T3 or N1–2 disease. Although radiation therapy decreases local recurrence in one-half of patients, it is the addition of 5-FU–based chemotherapy that further decreases local recurrence to approximately 10% to 12% and is the agent responsible for increasing overall 5-year survival rates by approximately 10% to 15% (from 50% up to 60% to 65%).

With this increase in local control and survival, the addition of chemotherapy comes an increase in acute toxicity. The incidence of grade 3+ toxicity in the combined modality arms of the GITSG and Mayo/NCCTG 79-47-51 trials was 25% to 50%. Furthermore, the percentage of patients finishing six cycles of chemotherapy in those trials was only 65% and 50%, respectively. Miller and colleagues reported that patients who received combined modality therapy versus radiation therapy alone in the Mayo/NCCTG 79-47-51 trial had a higher rate of severe and life-threatening diarrhea, both during radiation (20% vs. 4%, \( P = .001 \)) and at any time during treatment (22% vs. 4%, \( P = .001 \)). As previously discussed, the acute toxicity with preoperative combined modality therapy may be less than in the postoperative setting.

The majority of combined modality therapy regimens include six cycles of 5-FU–based chemotherapy plus concurrent pelvic radiation. Six cycles of chemotherapy are thought to be necessary to treat systemic disease. However, in a randomized trial from Norway, 144 patients were randomized to postoperative radiation plus bolus 5-FU (500 to 750 mg/m² limited to days 1 and 2 of weeks 1, 2, and 3 of radiation) versus surgery alone. Despite the fact that 5-FU was delivered with radiosensitizing doses rather than doses adequate to treat systemic disease, this combined modality therapy regimen significantly decreased local recurrence (12% vs. 30%, \( P = .01 \)) and improved 5-year survival (84% vs. 50%, \( P = .05 \)). Although these results with limited-dose 5-FU are encouraging, additional experience with this approach is needed before modifying the standard recommendation of six cycles of systemic chemotherapy.

Retrospective data suggest that there may be subsets of patients with T3N0 disease who may not require adjuvant therapy and that there may be patients with stage I disease who should be considered for adjuvant therapy. In a review of 117 patients with T3N0 disease, Willett et al. identified a favorable subset of patients with well- or moderately differentiated cancers invading less than 2 mm into the perirectal fat who, after surgery alone, had a 10-year actuarial local failure rate of only 5% compared with 29% in T3N0 patients without those favorable features. In a separate analysis, they identified a subset of patients with stage I disease who have an increased incidence of local failure after an APR. These results must be confirmed in a randomized trial before a change in the standard of care of combined modality therapy can be recommended.

Since the 1990 National Cancer Institute Consensus Conference, the focus of the intergroup postoperative trials has been the identification of the optimal chemotherapeutic agents and their method of administration. In the follow-up trial to the 79-47-51 trial, the Mayo/NCCTG designed a four-arm trial (86-47-51) to determine if methyl CCNU was necessary, as well as to compare the relative effectiveness of 5-FU when delivered as a bolus versus a continuous infusion. Because methyl CCNU did not improve either local control or survival, it is no longer recommended for use in the adjuvant treatment of rectal cancer.

When compared with bolus 5-FU (with or without methyl CCNU), patients who received continuous infusion 5-FU (also known as prolonged venous infusion) had a significant decrease in the overall rate of tumor relapse (37% vs. 47%, \( P = .01 \)), distant metastasis (31% vs. 40%, \( P = .03 \)), as well as an improvement in 4-year survival (70% vs. 60%, \( P = .005 \)). These data suggest that, when 5-FU is used as a single agent with radiation therapy, it is more effective as a continuous infusion compared with a bolus.

Differences were also found in the individual acute toxicities of continuous infusion and bolus 5-FU regimens. For example, during the combined modality segment, patients who received continuous infusion 5-FU had a significant increase in grade 3+ diarrhea (24% vs. 14%, \( P < .01 \)), whereas they had a significant decrease in grade 3+ leukopenia (2% vs. 11%, \( P < .01 \)) compared with bolus 5-FU.

Building on the positive results of continuous infusion 5-FU reported in the Mayo/NCCTG 86-47-51 trial, the replacement postoperative Intergroup trial INT 0114 was designed. The primary end point of this trial is to determine whether a benefit exists to continuous infusion 5-FU throughout the entire chemotherapy course (six cycles) as compared with continuous infusion only during the combined modality segment (two cycles) and bolus 5-FU during the remaining four cycles. The control arm is arm 4 (bolus 5-FU, leucovorin, and levamisole). The trial opened to accrual in 1993 and is actively accruing.

The NSABP R-01 three-arm trial of comparing the postoperative methyl-CCNU, vincristine (Oncovin), and 5-FU (MOF) regimen vs. radiation therapy vs. surgery alone revealed a significant improvement in 5-year disease-free survival (42% vs. 30%, \( P = .006 \)) and overall survival (53% vs. 43%, \( P = .05 \)) with postoperative MOF chemotherapy compared with surgery. The advantage in overall survival of the chemotherapy arm was most evident in males (60% vs. 37%) and in males younger than 65 years of age (44% vs. 26%). In contrast, females who received chemotherapy experienced a lower survival (37% vs. 54%). It should be emphasized that the trial was not stratified by gender. Additional studies revealed that overexpression of thymidylate synthase in the primary tumor was associated with a worse prognosis and that such patients derived the greatest benefit from adjuvant MOF chemotherapy.

As a follow-up to the R-01 trial, the NSABP designed a four-arm trial (R-02) in which patients were randomized, depending on gender, to either MOF with or without radiation or 5-FU plus leucovorin with or without radiation. A preliminary analysis revealed a significant decrease in local failure in the two combined modality therapy arms compared with the two that included chemotherapy alone (7% vs. 11%, \( P = .045 \)). However, this decrease in local failure did not result in an increase in median survival. Other results are pending.

The most recent Intergroup postoperative trial to report results was INT 0114 (see Table 33.8-13). This was a four-arm trial in which all patients received six cycles of postoperative chemotherapy plus concurrent radiation therapy during cycles three and four. The goal of this trial was to determine if combinations of bolus 5-FU–based chemotherapy (5-FU plus low-dose leucovorin vs. 5-FU plus levamisole vs. 5-FU and leucovorin and levamisole) were superior to single-agent 5-FU.

With a median follow-up of 4 years, no significant differences were found between the four arms (5-FU alone, 5-FU plus leucovorin, 5-FU plus levamisole, or 5-FU and leucovorin and levamisole) in terms of local failure (12%, 9%, 13%, 9%, respectively) or 3-year survival (78%, 80%, 79%, 79%, respectively). Although the total incidence of acute grade 3+ toxicity was similar for the four arms (76%, 72%, 70%, 75%, respectively), differences were noted between the regimens. For example, the 5-FU alone arm had a higher incidence of hematologic toxicity, whereas the 5-FU plus levamisole arm had a higher incidence of diarrhea. A subset analysis

TABLE 33.8-13. Stage T3N1–2M0 Rectal Cancer: Selected Completed Adjuvant Trials
Dysuria occurs in 10% to 15% of patients and is usually controlled with phenazopyridine hydrochloride (Pyridium). Skin erythema most commonly occurs in skin folds in the completion of radiation.

renewal system. In the small bowel, loss of the mucosal cells results in malabsorption of various substances, including fat, carbohydrate, protein, and bile salts. The dose rate and fraction size more than of the total dose of radiation. The mechanism is primarily the depletion of actively dividing cells in what is otherwise a stable cell

radiation therapy. These symptoms usually are transient and resolve within a few weeks after the completion of radiation therapy. They appear to be a function of the normally reveals an inflamed, edematous, and friable rectal mucosa consistent with acute radiation proctitis and should be discouraged while patients are receiving chemotherapy. The total incidence of grade 3+ toxicity in the INT 0114 trial of postoperative radiation with 5-FU with or without leucovorin and/or levamisole modulation was 72% to 76%.

Preoperative radiation therapy increases the chance of sphincter preservation. By down-staging the primary tumor, preoperative irradiation allows the surgeon to change the planned operation from an APR to a LAR and CAA.

Higher initial doses of chemotherapy can be delivered with preoperative than with postoperative irradiation. This difference was observed in comparing two phase I trials of combined bolus 5-FU, high-dose leucovorin, and radiation therapy (50.4 Gy) reported from Memorial Sloan-Kettering Cancer Center. Patients with unresectable disease received preoperative radiation therapy and two cycles of concurrent 5-FU plus leucovorin followed by surgery and postoperative 5-FU plus leucovorin. Patients with resectable disease received the same chemotherapy and radiation therapy in the postoperative setting. The dose of radiation and leucovorin remained constant while the 5-FU dose was escalated. The maximal tolerated dose of 5-FU was higher with preoperative versus postoperative therapy.

Based on its toxicity, increased chance of sphincter preservation, and higher chemotherapy doses, preoperative combined modality therapy, if delivered with appropriate doses and techniques, is an attractive approach and is a standard of care for clinical T3 disease. The NSABP R-03 and the German CAO/ARO/AIO '94 randomized trials will help determine the relative effectiveness of preoperative versus postoperative combined modality therapy.

COMPLICATIONS OF PELVIC RADIATION THERAPY

As seen with other cancer therapies, pelvic radiation is associated with acute and long-term toxicity. Complications of pelvic radiation therapy are a function of the volume of the radiation field, overall treatment time, fraction size, radiation energy, total dose, and technique. Large field sizes, a short overall treatment time, large fraction sizes (more than 2 Gy per fraction), orthovoltage or low-energy megavoltage radiation (cobalt 60), doses of more than 50.4 Gy when small bowel is in the high-dose field, the use of a two-field (anteroposterior (AP)/posteroposterior (PA)) technique, treatment of only one field per day, the use of a direct perineal boost field, and the lack of computerized dosimetry all contribute to an increased incidence of radiation complications.

Risk factors unrelated to radiation techniques include patients with pelvic inflammatory disease, hypertension, diabetes mellitus, inflammatory bowel disease, or obesity, and patients who have had prior pelvic surgery or receive concurrent chemotherapy.

Most studies describing the tolerance of patients with inflammatory bowel disease have been limited to case reports. Furthermore, most do not indicate whether the disease is active, requiring antiinflammatory therapy, or if the patient had undergone a total proctocolectomy. This factor is important because the issue of toxicity may be one of the most critical factors in patients with ulcerative colitis who have undergone a total proctocolectomy. The most comprehensive analysis of the tolerance of patients with inflammatory bowel disease was reported by Willett and colleagues. They examined the records of 28 patients (17 colorectal patients and 11 who received concurrent 5-FU) who were treated with 40 Gy or more of pelvic or abdominal radiation therapy. Of the 28 patients, 18 had ulcerative colitis and 10 had Crohn's disease. Overall, 43% of patients had active disease requiring antiinflammatory therapy.

The total incidence of severe toxicity was 46%, which caused 22% of patients to stop radiation and 29% to undergo surgery for complications. Acute toxicity was similar in ulcerative colitis and Crohn's disease; however, late toxicity was limited to patients with ulcerative colitis. In the 18 patients treated with specialized radiation techniques to reduce total dose to or exclude the small and large bowel from the radiation field, the 5-year actuarial incidence of late toxicity was 23% compared with 73% in the 12 patients who were not treated with these specialized techniques (P = .02). Unless the large bowel can be excluded from the radiation field in patients with ulcerative colitis and the large and small bowel is excluded from the radiation field in patients with Crohn's disease, the use of radiation in patients with inflammatory bowel disease is contraindicated.

Radiation complications also are increased in patients with collagen vascular disease. However, a report of six patients with systemic lupus erythematosus who received chest wall radiation for breast cancer or Hodgkin's disease suggests that it is not an absolute contraindication to radiation therapy. Acute (short-term) and long-term complications of pelvic radiation occur with distinct clinical courses and pathologic manifestations. The most frequent serious complication of pelvic radiation is small bowel damage. In animals, transforming growth factor-b and mast cell hyperplasia may be involved in the molecular pathogenesis of radiation enteritis.

ACUTE COMPLICATIONS

Acute complications occur in all patients during treatment and include thrombocytopenia, leukopenia, dysuria, and effects on the small bowel (diarrhea, abdominal cramping, and increased bowel frequency) and large bowel (acute proctitis, tenesmus, bloody or mucous discharge). Proctoscopic examination of the rectal mucosa normally reveals an inflamed, edematous, and friable rectal mucosa consistent with acute radiation proctitis and should be discouraged while patients are receiving radiation therapy. These symptoms usually are transient and resolve within a few weeks after the completion of radiation therapy. They appear to be a function of the dose rate and fraction size more than of the total dose of radiation. The mechanism is primarily the depletion of actively dividing cells in what is otherwise a stable cell renewal system. In the small bowel, loss of the mucosal cells results in malabsorption of various substances, including fat, carbohydrate, protein, and bile salts. The management of bowel-related complications usually involves the use of diphenoxylate, narcotics, or both. The bowel mucosa usually recovers in 1 to 3 months after the completion of radiation.

Dysuria occurs in 10% to 15% of patients and is usually controlled with phenazopyridine hydrochloride (Pyridium). Skin erythema most commonly occurs in skin folds and is treated prophylactically with nonmetallic skin creams. If grade 3+ toxicity develops, a 3-day to 1-week treatment break commonly is required.
Although concurrent chemotheraphy significantly improves the local control rate of radiation therapy, it increases the acute toxicity. The incidence of grade 3+ toxicity with postoperative radiation therapy is approximately 5%, whereas in some reports it is increased to as high as 25% to 50% in patients receiving postoperative combined modality therapy. In the INT 0114 trial of postoperative combined modality therapy using 50.4 Gy plus bolus 5-FU with or without leucovorin and/or levamisole, the total incidence of grade 3+ toxicity was 72% to 76%. An analysis of 204 patients who received the postoperative combined modality therapy arm of the Mayo/NCCOG 79-47-51 trial showed the incidence of acute grade 3+ diarrhea was 22% compared with 4% who received radiation therapy alone (*P* = 001). The acute toxicity of preoperative combined modality therapy appears to be lower than postoperative combined modality therapy.

**LONG-TERM COMPLICATIONS**

Long-term complications occur less frequently but are substantially more serious. The initial symptoms commonly occur 6 to 18 months after completion of radiation. Complications may include persistent diarrhea, increased bowel frequency, proctitis, small bowel obstruction, perineal and scrotal tenderness, delayed perineal wound healing, urinary incontinence, and bladder atrophy and bleeding. Injury to the vascular and supporting stromal tissues of the bowel is the presumed pathophysiology. Schuster et al. found that bile acid malabsorption due to ileal dysfunction was not an inevitable late complication of pelvic radiation, and it is not the major determinant in the pathophysiology of chronic radiation-induced diarrhea.

The most common long-term complications are due to small bowel damage and include enteritis, adhesions, and small bowel obstruction requiring surgical intervention. All the MGH, 165 patients received 45 Gy postoperatively to the pelvis with a boost to the tumor bed to 50.4 Gy. The incidence of long-term mild to moderate complications was 8% [2% proctitis, 2% perineal and scrotal tenderness (resolved), 1% delayed perineal wound healing, 1% small bowel obstruction (resolved), 1% urinary incontinence, and 1% bladder atrophy and bleeding (resolved)]. The incidence of small bowel obstruction requiring surgery was similar in the patients who received radiation (6%) compared to a historical group of patients who were treated with surgery alone (5%).

A retrospective review of 304 patients treated with a median of 50.84 Gy of postoperative pelvic radiation at the Mayo Clinic was presented by Miller et al. The median follow-up was 5.3 years; 65% of patients received chemotheraphy; and the small bowel was excluded after 50.4 Gy. The crude incidence of complications included 4% acute enteritis, 6% chronic enteritis, and 12% chronic proctitis. The actuarial incidence of complications at 5 years included 14% proctitis and 7% enteritis. The mean time from diagnosis to complications was 2.1 years. By multivariate analysis, the two independent factors associated with an increase in complications was increasing age (median age, 67 years vs. 62 years) and radiation dose (median, 54 Gy vs. 50.4 Gy). Other long-term complications, such as pelvic fractures and lumbosacral plexopathy are very rare occurrences and may be caused by factors unrelated to the radiation, such as osteoporosis or disease progression.

Overall, the incidence of small bowel obstruction requiring surgery after postoperative pelvic radiation for rectal cancer is 4% to 12% in most series and as high as 17.5% in earlier series. In patients treated with surgery only, 2% to 15% may develop similar complications. Small bowel-related late complications are directly proportional to the volume of small bowel in the radiation field. Late radiation proctitis, similar to small bowel injury, is related to the treatment volume and dose of radiation.

**SPHINCTER FUNCTION**

Radiation therapy can adversely effect sphincter function; however, most series are retrospective, nonrandomized, nonblinded, retrospective telephone surveys. Furthermore, sphincter function is affected by other factors, such as the type of operation, the functional scale used, and whether patients received conventional radiation techniques as opposed to intensive short course radiation.

Using a retrospective telephone survey, Kollmorgen et al. from the Mayo Clinic assessed the impact of postoperative combined modality therapy delivered with conventional doses and techniques of pelvic radiation and 5-FU-based chemotherapy on bowel function and compared it with a matched group of patients who underwent surgery alone. The 41 patients who received combined modality therapy had a significant increase in the number of bowel movements, clustering of bowel movements, nighttime bowel movements, occasional incontinence, urgency, and, wore pads more often compared with 59 patients who underwent surgery alone. Sphincter function after a CAA was retrospectively assessed by Paty and associates. The 40 patients who received pre- or postoperative radiation therapy, or both (with or without chemotheraphy) after a CAA had increased stool frequency and difficulty with evacuation compared with 41 patients who underwent surgery alone. Unconventional radiation doses and techniques were used in 43% of patients.

In contrast with the previous studies, Birnbaum and colleagues have prospectively examined the short-term and long-term impact of preoperative radiation therapy on sphincter function. Patients received conventional doses and techniques of radiation and were assessed objectively by anal manometry with or without transrectal ultrasound. In the 20 patients assessed for short-term and ten patients assessed for long-term results, radiation therapy had a minimal effect on sphincter function. As one would predict, patients who receive preoperative radiation with intensive short course radiation have inferior function results. Patients who received 5 Gy × 5 in the Swedish Rectal Cancer Trial had a significant increase in bowel frequency, incontinence, urgency, and emptying difficulty. This impaired the patient's social life 30% of the time compared with 10% of the time with surgery alone. In another analysis of patients who received 5.1 Gy per fraction, a significant increase in bowel function was found.

**SEXUAL FUNCTION**

In addition to the previously discussed variables that can effect assessment of sphincter function, series examining sexual function using subjective methods have the additional shortcoming of bias due to the sensitive nature of the questions. Answers to such questions are subjective and may be influenced by the interaction between the patient and interviewer. Age and psychological factors, such as depression and anxiety about the diagnosis of cancer, can further influence the results. Furthermore, it should be emphasized that both the surgery required for an APR and the psychological impact of a permanent colostomy can have an adverse impact on sexual function.

A retrospective analysis of sexual function in men and women by Havenga and associates found that radiation therapy with or without 5-FU had a negative impact after total mesorectal excision for rectal cancer. In a group of 18 males with a median age of 70 who received 52.5 Gy with an unconventional fraction size of 2.63 Gy per fraction for bladder cancer, 56% were able to attain an erection sufficient for intercourse compared with 72% of patients in the 6 months before the start of radiation therapy. Because the patients did not undergo surgery, receive hormonal therapy, or have prostate cancer, this study is a better indication of the impact of radiation therapy alone.

In conclusion, although radiation can adversely effect sphincter and sexual function, the ultimate functional results are a result of a combination of therapies, including radiation, surgery, and chemotheraphy. The risk of dysfunction must be evaluated in the context of the benefit of adjuvant therapy, which includes decreased local failure, improved survival, and, in selected patients, the ability to perform sphincter-preserving surgery as an alternative to an APR.

**MINIMIZING TOXICITY OF RADIATION THERAPY**

**RADIATION TREATMENT TECHNIQUES**

Small bowel–related complications are directly proportional to the volume of small bowel in the radiation field. In patients receiving combined modality therapy, the volume of small bowel in the radiation field limits the ability to escalate the dose of 5-FU. A number of simple radiaothecapeutic techniques are available to decrease radiation-related small bowel toxicity (Table 33.8-14). First, small bowel contrast allows identification of the location of the small bowel. The use of multiple-field techniques (preferably a three-field technique) permits a larger volume of small bowel to be blocked from the pelvis compared with an AP/PA (two-field) technique. In one series, the small bowel obstruction rate in patients with rectal cancer who received pelvic radiation therapy was higher with a single-field (21%) as compared with a multiple-field technique (9%). The small bowel obstruction rate increased to 30% when an extended-field radiation was used.
TABLE 33.8-14. Techniques to Minimize the Acute Toxicity to the Small Bowel from Radiation Therapy

The treatment of all fields each day results in a lower integral dose and more homogeneous dose distribution. A study by Sigmon et al. suggests that patients with endometrial or rectal cancer who receive pelvic radiation by a continuous course as compared with a planned split course have fewer chronic bowel complications. The use of lateral fields for the boost as well as positioning the patient in the prone position further decreases the volume of small bowel in the lateral radiation fields.

The treatment should be designed with the use of computerized radiation dosimetry and be delivered by high-energy linear accelerators, which, by nature of their depth dose characteristics, deliver a higher dose to the tumor volume while sparing the surrounding normal structures. When the perineal scar must be treated, it should be included in the pelvic radiation fields. The use of a separate perineal field is associated with an increased risk of overlap of the radiation fields and should be avoided.

Even in expert hands, daily variations occur in patient positioning for pelvic radiation ranging from 3.4 to 9.0 mm. Using electronic portal imaging, Tinger et al. found that errors exceeding 5 mm or 10 mm are significantly more frequent intertreatment (40% to 51%, and 3% to 23%, respectively) compared with intratreatment (1% to 7%, and 0%, respectively). In national clinical trials, pretreatment quality control review can decrease the error rate in radiation field design.

The advantage to the combination of a multiple-field technique, high-energy photons, and computerized dosimetry is illustrated in Figure 33.8-6. With this combination, a homogenous dose distribution is maintained throughout the target volume such that prescribing to the 98% isodose line covers the volume at risk and gives only 35% to 55% of the dose to the small bowel. In contrast, when the same patient receives 60Co with an AP/PA arrangement, an inhomogeneous dose distribution is provided throughout the target volume such that the dose must be prescribed to the 90% isodose line to cover the volume at risk, thereby giving 110% to 130% of the dose to the small bowel. Furthermore, if computerized treatment planning was not performed and the dose was prescribed to the midplane, parts of the tumor volume would be underdosed by 10%.

After pelvic surgery, the small bowel commonly fills the pelvis. Adhesions can form, resulting in fixed loops of small bowel in the radiation fields. In this situation, despite treatment of the patient in the prone position, the use of multiple-field techniques may be of limited value (Fig. 33.8-7). In contrast, when radiation therapy is delivered preoperatively to a patient who has not undergone prior pelvic surgery, the small bowel is usually mobile. As illustrated in Figure 33.8-8, when no small bowel fixation is present, treatment in the prone position was successful in excluding most of the small bowel from the posteroanterior field and completely from the lateral fields.
Clinical series document the importance of field size and technique in minimizing the toxicity of pelvic radiation. In the series from the M. D. Anderson Cancer Center, 62 patients received postoperative pelvic radiation (40 to 50 Gy plus 6- to 10-Gy boost). Some patients received the radiation by a combination of AP/PA and a boost with opposed laterals or a direct perineal field. In selected patients, the superior border of the field was at L2-3 and the incidence of small bowel obstruction requiring surgery was 17.5%. When the superior border of the field was decreased to L3, the incidence of small bowel obstruction decreased to 10% to 12%. The incidence of small bowel obstruction after surgery alone was 5%.

Various physical maneuvers to exclude the small bowel from the pelvis have been examined. Gallagher et al. determined the volume, distribution, and mobility of small bowel in the pelvis after a variety of maneuvers. Regardless of the prior surgical history, a significant decrease was seen in the average small bowel volume when the patients were treated in the prone position with the combination of abdominal wall compression and bladder distention compared with the supine position. Use of a four-field technique further decreased the volume of small bowel. Treatment in the prone position without abdominal wall compression was not consistently effective in displacing small bowel and, in some patients (most commonly obese), the volume of small bowel increased.

Caspers and Hop (1983) performed a similar study in 50 patients who received pelvic radiation for bladder or prostate cancer. The use of the Trendelenburg or inclined procubitis positions was helpful in excluding small bowel from the pelvic radiation fields, especially for obese patients. Although the prone position was less effective than these inclined positions, it was superior to the supine position.

SMALL BOWEL CONTRAST

Small bowel contrast is essential to determine the position of small bowel during radiation simulation. It should be used routinely in patients receiving curative pelvic radiation therapy. Herbert et al. found that, in patients with endometrial and rectal cancer who had small bowel contrast used at the time of radiation simulation, there was a change in the treatment field as well as a lower incidence of overall and chronic complications. A multivariate analysis revealed that both the use of small bowel contrast and a lower superior border of the treatment field were predictive for decreased radiation toxicity. Visualization of small bowel contributed to an adjustment in the radiation field, resulting in a decrease in the incidence of toxicity.

IMMOBILIZATION MOLDS AND TISSUE EXPANDERS

The effectiveness of custom bowel immobilization molds (belly board) in 30 patients with pelvic malignancies has been analyzed by Shanahan et al. Using a CT-based volumetric analysis, the combination of the prone position and immobilization molds decreased the mean small bowel volume in the radiation field by 66% compared with patients treated with the supine position without the immobilization mold. Fu and colleagues reported that, when patients with pelvic malignancies were treated in the prone position, a belly board reduced the volume of small bowel by 28% to 50%, depending on the type of prior surgery. A similar benefit using dose volume histogram analysis in 12 patients was reported by Das and associates.

Pelvic tissue expanders are also effective in decreasing the volume of small bowel in the radiation field. Herbert and colleagues reported a significant decrease in small bowel volume in 14 patients who had a tissue expander compared with 63 who did not (25 cm³ vs. 239 cm³, P < .0001). The decrease of small bowel volume was associated with a decrease in acute toxicity. Hoffman and colleagues recommended their use when native tissue is not available for small bowel exclusion. To examine the effectiveness of a silicone rubber–molded balloon during pelvis radiation, Sezeur et al. measured stool weight, steatorrhea, and a1-antitrypsine clearance. The tests remained stable, suggesting that the tissue expander was effective throughout the course of radiation.

It must be emphasized that any physical maneuver beyond the use of the prone position may be associated with patient discomfort, thereby leading to increased movement and daily set-up errors. For example, Brierley and associates analyzed the variation of small bowel volume in the pelvis before and during adjuvant pelvic radiation therapy for rectal cancer. They found that the displacement of small bowel from the posterior pelvis by bladder distention was not reliably maintained throughout the treatment course. Therefore, the previously described physical maneuvers and techniques, such as abdominal wall compression and belly boards, may not be beneficial. The use of such techniques should be tailored to the individual patient.

Likewise, uncertainties exist with the use of small bowel contrast. Gallagher et al. reported a 20% average increase in small bowel volume after full doses of pelvic radiation when patients were reexamined after the completion of treatment.

THREE-DIMENSIONAL RADIATION TREATMENT PLANNING

Innovative techniques using three-dimensional treatment planning are being investigated. In a report from the Photon Treatment Planning Collaborative Working Group, it was found that the most important contribution of three-dimensional treatment planning in rectal cancer was the ability to plan and localize the target and normal tissues at all levels of the treatment volume rather than using the traditional method of planning with only a single central transverse slice and simulation films. A slight improvement also was noted when no constraints were placed on the type of plans (i.e., when non-coplanar beams were used). A randomized trial of conformal versus conventional radiation therapy in 266 evaluable patients with pelvic malignancies has been reported by Tall et al. Although a decrease in the volume of normal tissue volumes in the radiation field was seen with conformal versus conventional treatment (889 cm³ vs. 792 cm³), no difference was noted in the level of symptoms or in medication prescribed.

Investigators in Uppsala examined six patients with rectal cancer who underwent both proton and conventional photon treatment planning. By dose-volume histogram analysis, protons offered only a marginal benefit in sparing normal tissues.

RADIATION THERAPY AND SURGERY SEQUENCING

The major disadvantage of delivering radiation therapy in the postoperative setting is the increased incidence of fixed loops of small bowel in the pelvis. The potential merits of the use of preoperative compared with postoperative radiation therapy have been previously discussed. From the issue of toxicity, the primary advantages of preoperative radiation are decreased volume of small bowel in the radiation field and the absence of a perineal scar to be treated.

Some of the randomized trials of preoperative radiation therapy report an increased incidence of complications compared with surgery alone. However, as previously discussed, the radiation therapy in these trials was commonly delivered with inferior techniques, such as AP/PA. The use of large fields and fraction sizes. These techniques all contribute to an increased incidence of radiation complications. For example, in the Stockholm Rectal Cancer Study Group, the radiation therapy was delivered in 5-Gy fractions, the superior border was at L2, the majority of patients received 40 Gy with an AP/PA technique, and surgery was within 7 days of the completion of radiation. In contrast, the nonrandomized trials of preoperative radiation therapy that use higher doses with smaller fraction and field sizes reveal that, when preoperative radiation therapy is delivered with careful radiation techniques, the toxicity is minimized.

SURGICAL TECHNIQUES

Surgical techniques to minimize small bowel injury include reperitonealization of the pelvic floor, construction of an omental pedicle flap, retroversion of the uterus, placement of clips in the high-risk areas to better define the tumor volume, and the use of absorbable mesh, which temporarily removes the small bowel from the pelvis. Rodier and colleagues reported their experience with polyglycolic acid mesh in 60 patients. The mesh was effective in excluding the small bowel from the pelvis in 93% of patients with various pelvic malignancies. It was completely resorbed in 3 to 5 months, and the complication rate related to the mesh was 8%.
Thorn and associates reported a similar approach in 52 patients. They noted a prolonged postoperative ileus (median, 8.5 days), but no other unusual postoperative complications. In 20 patients who underwent placement of mesh, Bilellet et al. reported postoperative complications possibly related to mesh in five patients and a mild postoperative ileus in 17. Because pelvic radiation therapy does not begin until approximately 4 months postoperatively, the mesh may be resorbed by that time.

**DIETARY SUPPLEMENTS AND RADIOPROTECTORS**

The benefit of dietary supplements and radioprotectors is controversial. Five randomized trials have examined the efficacy of various compounds to decrease bowel toxicity. These trials have included such compounds as butyric acid to decrease chronic radiation proctitis, sucralfate enemas to decrease acute radiation proctitis, diazoxide to decrease acute enteral and mesalazine (5-aminosalicylic acid) to decrease acute radiation enteritis. All of these randomized trials have been performed in a randomized trial of 73 patients with pelvic malignancies, the addition of 5-aminosalicylic acid increased rather than decreased acute radiation toxicity. Diarrhea was more frequent in the radiation plus 5-aminosalicylic acid arm compared with radiation alone (91% vs. 74%, $P = .07$).

In a phase II trial using an elemental diet, Craighead and Young reported a decrease in acute enteritis in 17 patients with gynecologic cancer, but only 77% of the patients complied with the diet. McArdle et al. (1986) compared the results of an elemental diet in 24 patients with bladder cancer who received 4 Gy × 5 before cystectomy with a similar historical group of 32 patients who received a regular diet or total parenteral nutrition with the same therapy. A significant decrease was reported in the incidence and severity of diarrhea, nausea and vomiting, abdominal cramps, and the time to the recovery of small bowel function in the patients who received the elemental diet. The mechanism of protection of the mucosa by an elemental diet is unclear. Theories include a reduction of proinflammatory secretory, the removal of abrasive bulk in the chyme, and a decrease in the rate of crypt cell turnover.

In a phase III study of 13 patients with chronic radiation proctitis, oral sodium pentosanpolysulfate resulted in a complete resolution of symptoms in 82% and a partial resolution in 9%. Although patients receiving pelvic radiation have reduced lactose absorption, the available data suggest that lactose-restricted diets do not prevent radiation-induced diarrhea. Stryker and Bartholomew examined 64 patients undergoing pelvic radiation for various malignancies who were randomized to a regular diet, a regular diet including lactase enzyme, or a lactose-restricted diet. No significant differences were found in stool frequency or diphenoxylate usage among the three dietary groups.

Liu et al. performed a randomized trial of pelvic radiation therapy (2.25 Gy per fraction to 45 Gy) with or without the radioprotector WR-2721 in patients with inoperable or unresectable rectal cancer. The incidence of RTOG long-term grade 3+ gastrointestinal, genitourinary, and skin toxicity was 3% in the radiation therapy alone arm compared with 0% in the radiation therapy plus WR-2721 arm. A separate trial by Montana and colleagues (1992) showed no benefit with a topical application of WR-2721 to the rectal mucosa. Based on these data, WR-2721 does not offer radioprotection in patients with rectal cancer who receive pelvic radiation therapy.

Patients with gynecologic malignancies who receive pelvic radiation therapy may have a lower long-term incidence of severe toxicity with increased caffeine consumption. One study suggested that sucralfate may decrease acute and long-term small bowel toxicity in patients receiving pelvic radiation therapy for prostate and bladder cancer.

In summary, all cancer therapies have associated toxicities. It must be emphasized that all patients receiving pelvic radiation therapy have acute treatment-related toxicity, and despite the use of careful treatment techniques, approximately 1% have severe long-term toxicity. These toxicities must be examined in perspective, because the benefits of radiation therapy include significantly decreasing local failure and, in the preparative setting, sphincter preservation. This is all the more reason to pay careful attention to techniques, which help to decrease the acute and long-term toxicities of pelvic radiation.

The exclusion of small bowel from the treatment field is the most important factor in decreasing the toxicity. With the use of careful radiation techniques as well as physical and surgical methods, the toxicity can be reduced to an acceptable level. In patients who have not had prior pelvic surgery, preoperative radiation therapy (when delivered with conventional fractionation and multiple-field techniques) may have less toxicity compared with postoperative combined radiation therapy. The results of the ongoing randomized trials of preoperative versus postoperative combined-modality therapy for resectable rectal cancer (NSABP R-03 and CAO/ARO/AIO 94) will provide a more definitive answer. Unless a contraindication exists, the most simple techniques to decrease radiation toxicity, such as the use of small bowel contrast, multiple-field techniques, high-energy linear accelerators, custom blocks, avoiding a direct perineal boost, and treatment in the prone position, should be part of the standard treatment of patients receiving curative adjuvant radiation therapy.

**TREATMENT OF LOCALLY ADVANCED AND UNRESECTABLE RECTAL CANCER**

A significant improvement in local control and survival can be achieved for patients with primary resectable (T3) rectal cancer with the use of combined modality therapy. It is more difficult to obtain these results for locally advanced or unresectable cancers. For locally advanced or unresectable rectal cancers, collectively defined as T4 disease, no uniform determination of resectability has been established. Depending on the series, T4 disease can vary from a tethered or “marginally resectable” cancer to a fixed cancer with adherence or direct invasion of adjacent organs or vital structures. This definition has prognostic implications, because patients with gross invasion of tumor into vital pelvic structures may be approached in a palliative rather than a curative fashion. The definition of resectability also depends on whether the assessment is made by radiographic criteria, a clinical office examination, examination under anesthesia, or at the time of surgery. For example, tumors thought to be unresectable at the time of clinical or radiographic examination may be found to be more mobile when the patient is relaxed under anesthesia. Prognostic differences also exist between primary and recurrent tumors, and many series do not report the results separately. The heterogeneity of the disease and absence of a uniform definition of resectability may explain some of the variation in results seen among the series.

**TUMORS AMENABLE TO POTENTIALLY CURATIVE RADICAL SURGERY**

Selected patients with primary unresectable disease may be cured with radical surgery, such as a pelvic exenteration. These include tumors invading the prostate, the base of the bladder, or the uterus, where the disease can be resected en bloc with negative margins.

**MULTIVISCEERAL RESECTION FOR LOCALLY ADVANCED RECTAL CANCER**

Approximately 6% to 10% of rectal cancers are locally advanced and require extensive surgery for complete tumor extirpation. Pelvic exenteration involving en bloc removal of the rectum, bladder, distal ureters, and reproductive organs can be required to obtain negative margins of resection. A number of studies have demonstrated 5-year survival rates ranging from 33% to 50% for these selected patients with locally advanced rectal cancer. Despite the ability to achieve long-range survival rates in selected patients, the operation remains a formidable one, with significant morbidity and a mortality of up to 6%. Patients who undergo such resections for primary tumors have better survival rates than those with recurrence.

In a report by Melanissos et al., a series of 40 patients undergoing pelvic exenteration for rectal carcinoma obtained tumor-free margins. The 5-year overall survival rate was 49% with a median survival of 56 months. Adjuvant chemoradiation appeared to provide a reduction in risk of recurrence. In the series, five patients developed local failure. Comparable results have been recorded by Lopez et al. (1987), Kraybill et al. (1988), and Boey et al. (1982). Long-term local control is obtained in approximately 70% of the patients who undergo resection with tumor-free margins. The results of such surgery cannot be separated from the benefits of adjuvant chemoradiation in this high-risk population.

Improved results from surgical procedures for rectal cancer requiring multivisceral resection have occurred in more recent years. This finding may be related to improvements in perioperative care, patient selection, and surgical techniques. Of major importance in the management of such patients, who are often heavily radiated, is the use of vascularized tissue flaps to accomplish healing of pelvic and perineal wounds.

Physical examination, CT scan, MRI, and cystoscopy all play a role in staging patients with locally advanced rectal cancer. Involvement of the sciatic notch indicated by symptoms or scans predicts a situation unlikely to be helped by surgery. With CT or MRI imaging, recurrent pelvic tumor, especially following an APR, is difficult to differentiate from scar. PET may offer a more accurate assessment.

**RADIATION THERAPY**
**Preoperative Pelvic Radiation Therapy**

Because surgery commonly leaves residual disease in the pelvis in patients with locally advanced or unresectable disease, the standard approach has been to use preoperative pelvic radiation therapy. Given the increased complete response and resection rates when 5-FU-based chemotherapy is added to radiation in the preoperative setting, as well as the improvement in local control in the postoperative setting, most patients receive combined modality therapy. The goals of preoperative therapy are to convert an unresectable cancer to a resectable status and decrease the incidence of local failure.

The optimal use of preoperative radiation therapy requires full doses (45 Gy or more) and, to achieve optimal down-staging, a 4- to 6-week delay between the completion of radiation and surgery. This discussion is limited to those series that meet these criteria.

In a seminal report from the MGH of 25 patients with recurrent or primary unresectable cancer, a complete resection with negative margins was possible in 64% of patients after preoperative radiation therapy. Despite negative margins, the incidence of local failure was 38%. The nine patients who were unable to undergo a complete resection were dead of disease within 28 months.

The British Medical Research Council completed a randomized trial of preoperative radiation therapy (40 Gy in 20 fractions) versus surgery alone for 279 patients with clinical T4 primary rectal cancer. Patients who received preoperative radiation had a significant decrease in local failure (36% vs. 48%, \( P = 0.04 \)) and distant failure (35% vs. 48%, \( P = 0.02 \)). An improvement was noted in median survival (31 months vs. 24 months, \( P = NS \), but no difference in survival was reported (32% vs. 28%). The 36% local failure rate after preoperative radiation is consistent with the MGH data and supports the need for additional treatment, such as intraoperative radiation therapy (IORT).

As one would predict, the results of the patients with primary disease are more favorable than those with recurrent disease. In the MGH series, the rate of complete resection with negative margins was 59% for patients with primary cancers compared with 44% of those with recurrent cancers. Limiting the analysis to the most favorable group of patients with primary cancers and negative margins, the 5-year actuarial local failure rate was 29%, and the disease-free survival rate was 60%. Therefore, even in the most favorable group of patients (primary cancer and negative margins), local failure is still almost 30%. At the University of Florida, in the 48% of patients who were able to undergo a complete resection with negative margins, the local failure rate was 55% and the 5-year determinate survival rate was 20%. Tobin et al. reported a local failure rate of 20% and a 5-year survival rate of 60% in 85 patients treated with preoperative radiation. At Memorial Sloan-Kettering Cancer Center, 56% of patients underwent a complete resection with negative margins after preoperative radiation, and the local failure rate was 24%.

Tethered cancers have the most favorable outcome of all T4 cancers. In a separate report from the MGH, the results of 28 patients with tethered rectal cancers treated with preoperative radiation were presented. Tethered disease was defined as the sensation on the examining finger of partial tumor mobility consistent with extensive perirectal spread and adherence but not fixation to unresectable structures. Although a complete resection with negative margins was possible in 93%, the local failure rate was 24%. Tobin et al. report a local failure rate of 14% and 5-year survival rate of 68% in 49 patients with tethered cancers treated with preoperative radiation.

In summary, after full-dose preoperative radiation, most series report that 48% to 64% of patients are converted to a resectable status. However, despite a complete resection and negative margins, the local failure rate varies, depending on the degree of tumor fixation, from 24% to 55%.

**IMPROVING THE RESULTS OF PREOPERATIVE RADIATION THERAPY**

A major limitation of pelvic radiation therapy is that the dose required to achieve an adequate level of local control, in many cases, exceeds the tolerance of the surrounding normal tissues. In an attempt to improve the results of preoperative radiation, a number of approaches have been used. The most promising have included IORT and the addition of systemic chemotherapy.

**Intraoperative Radiation Therapy**

The primary advantage of IORT is that radiation can be delivered at the time of surgery to the site with the highest risk of local failure (the tumor bed) while decreasing the dose to the surrounding normal tissues. IORT can be delivered by two techniques: electron beam and brachytherapy. With the electron-beam technique, the radiation is delivered by a linear accelerator and, with the use of a cone, is directed to the tumor bed. When the IORT is finished, the cone is removed and the surgery is completed.

Brachytherapy is delivered with both low-dose and high-dose techniques. The low-dose method involves implantation of radioactive sources, with either removable Ir-afterloading catheters or iodine 125 or palladium 103 permanent seeds. The permanent seeds can be sutured or implanted directly into the tumor. As an alternative, they can be placed in a Dexon mesh that is then sutured to the tumor bed. Most of the low-dose brachytherapy experience has been in patients with gross residual disease. It also has been used as an alternative to electron-beam IORT in patients with negative margins. High-dose-rate brachytherapy uses a flexible multichannel applicator that conforms to the tumor bed. The applicator is positioned, and an Ir source is programmed to deliver a uniform dose to the area at risk using a similar dose rate to electron-beam IORT.

The results of IORT depend on whether the patient has primary unresectable or recurrent disease and whether the margins of resection are negative or whether microscopic or gross residual disease is present. This discussion is limited to patients who, in general, receive preoperative pelvic radiation with or without 5-FU-based chemotherapy. Most receive 45.0 to 50.4 Gy to the pelvis and 10 to 20 Gy IORT with either electrons or high dose-rate with a flexible applicator. The lower IORT dose is used for patients with negative margins, and the higher doses are used for patients with microscopic or gross residual disease.

**Primary Unresectable Disease**

The largest experience and longest median follow-up in preoperative therapy followed by IORT has been reported from the MGH. As seen in Table 33.8-15, for patients with negative margins, local failure is decreased from 18% without IORT to 11% with IORT. In patients with positive margins, local failure is decreased from 83% without IORT to 43% with IORT if gross residual disease is present and to 32% with IORT if microscopic residual disease is present. For the total patient group (with or without IORT), the 5-year disease-free survival rate was 63% for patients with negative margins and 32% for patients with positive margins. These results underscore the importance of delivering preoperative therapy to help achieve the most complete resection possible. If negative margins cannot be obtained, then microscopic residual is still preferable to gross residual. Series from the Mayo Clinic and Memorial Sloan-Kettering Cancer Center report similar local failure rates in patients with negative margins (7% vs. 8%, respectively). The results of other series from Munich, Heidelberg, and the Beth Israel Deaconess Medical Center are seen in Table 33.8-15.

**Table 33.8-15.** Primary Locally Advanced or Unresectable Rectal Cancer with and without Intraoperative Radiation (IORT): Selected Series
Recurrent Disease

In the setting of recurrent disease, the largest experience with IORT is from the Mayo Clinic. The higher IORT doses were used for patients with residual disease. For patients with negative margins, the crude local failure rate was 6%, which increased to 18% for microscopic and 25% for gross residual disease. The 5-year actuarial local failure rates were 27% for microscopic disease. For the total patient group, overall 5-year survival was 20%. The M. D. Anderson Cancer Center, Memorial Sloan-Kettering Cancer Center, and the French IORT group reported similar local failure rates for the total patient group (36%, 37%, and 31%, respectively). In one series of 25 patients selected to receive IORT, the 5-year survival rate was 21%. In contrast, the results from the MGH were not as favorable. They reported an 89% 5-year actuarial local failure rate for patients with gross residual disease and 70% for the total patient group. The 5-year disease-free survival rate was 21% for patients with negative margins and only 7% for those with positive margins.

Complications of Intraoperative Radiation Therapy

Initial reports of neuropathy, vasculitis, bone necrosis, and ureteral injury in dogs who received IORT have been described. In two series, hyperthermia increased the neurologic complication of IORT. In canines, IORT-induced secondary malignancies are seen in 15%, with most occurring with doses of more than 25 Gy.

As the IORT data have matured, similar morbidity has been reported in humans. The incidence of toxicity depends on whether the patient has primary or recurrent cancer. In the MGH IORT experience, the incidence of complications was higher in those with recurrent disease (10%, soft tissue or sacral injury; 16%, pelvic neuropathy) compared with primary disease (2%, sacral necrosis or ureteral obstruction).

Higher complication rates have been reported from the Mayo Clinic. In patients with primary or recurrent colorectal cancer, the incidence of peripheral neuropathy was 32%. The symptoms of pain, numbness, and tingling resolved in 40% of patients, but only 13% had resolution of weakness. Ureteral obstruction or hydronephrosis were seen in 63% of patients who did not have evidence of ureteral obstruction at presentation. Although no relationship was found between the incidence of complications and the external-beam dose, the incidence of complications increased with the IORT dose.

In contrast to patients who undergo adjuvant therapy for resectable rectal cancers, it is difficult to clearly separate treatment-related complications from disease-related complications in patients with recurrent rectal cancers. Complications such as delayed healing, infection, fistula, and neuropathy may be the result of recurrent tumor, aggressive surgery, radiation, or a combination of these. The 2-year actuarial risk of significant complications in the 42 patients with advanced or recurrent rectal cancer who received IORT as a component of their therapy in the RTOG 85-08 trial was 16%. However, compared with a nonrandomized group who underwent surgery without IORT, no significant increase was found in acute surgical complications in the IORT patients.

In summary, the phase III data suggest that the addition of IORT to preoperative radiation therapy improves local control compared with preoperative radiation therapy alone. The results in the subset of patients with recurrent cancer or residual disease are not optimal. No phase III trials of IORT are in progress.

Preoperative Combined Modality Therapy

The encouraging results seen in patients with resectable rectal cancer who receive adjuvant postoperative combined modality therapy have been described. In two series, hyperthermia increased the neurologic complication of IORT. In canines, IORT-induced secondary malignancies are seen in 15%, with most occurring with doses of more than 25 Gy.

The third advantage is that the start of systemic therapy is not delayed, the metastatic burden is the smallest, and few drug-resistant cells are likely to be present. The fourth advantage is sphincter preservation.

A number of phase III trials of preoperative combined modality therapy for patients with T4 disease have been conducted. Some include patients with T3 disease, thereby making interpretation of the local control and survival results difficult. The majority have used 45.0 to 50.4 Gy plus two cycles of concurrent 5-FU–based chemotherapy, with bolus 5-FU plus leucovorin or continuous infusion 5-FU, followed by surgery and an additional four cycles of postoperative chemotherapy. Some have used methotrexate or interferon. Marsh et al. have combined chronobiologically shaped 5-FU infusion with preoperative radiation therapy, Trials examining the use of newer chemotherapeutic agents, such as raltitrexed (Tomudex), Orzel (oral tegafur, uracil, and 5-fluorouracil plus leucovorin), and CPT-11, and oxaliplatin, with preoperative radiation therapy are in progress.

INTRAOPERATIVE OR POSTOPERATIVE RADIATION THERAPY FOR RESIDUAL DISEASE

For a variety of reasons, some patients with locally advanced or unresectable cancer do not receive preoperative radiation therapy or, despite a preoperative assessment of resectability, are not able to undergo a complete resection. In this setting, does IORT or postoperative pelvic radiation therapy have any benefit? As previously discussed, the interpretation of treatment results is complicated, because many studies combine patients with primary and recurrent cancers as well as...
those with gross and microscopic residual disease. Patients are randomly selected to receive chemotherapy, and some series include patients with metastatic disease. This discussion is limited to those series in which patients have disease limited to the pelvis.

Likewise, for patients who have been unsuccessful with prior pelvic radiation, the options are limited. The standard therapy is usually palliative surgery or systemic chemotherapy. The response rate with chemotherapy may be reduced in a pelvis that has received full-dose radiation. Is there a role for more aggressive treatment?

A variety of radiotherapeutic options for patients who have been unsuccessful with prior pelvic radiation are available and are listed in Table 33.8-17. Although these are investigational approaches in selected patients, they may offer an improvement in local control.

### Table 33.8-17. Failure after External Beam Radiation: Aggressive Surgical and Radiotherapeutic Options

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<th>Option</th>
<th>Description</th>
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| Subtotal resection and postoperative radiation therapy | At the Mayo Clinic, 17 patients with rectal cancer received postoperative radiation therapy (40 to 60 Gy). Six received concurrent 5-FU-based systemic chemotherapy. For the total patient group, local failure was 76% and 5-year actuarial survival was 24%. The seven patients with gross residual disease had higher local failure (86% vs. 70%) and lower survival (14% vs. 30%) compared with the ten patients with microscopic residual disease. No clear dose-response curve emerged, but only one patient received 56 Gy or more. In a separate report from the Mayo Clinic, the results of 106 patients who underwent a palliative (subtotal) resection for locally recurrent rectal cancer were presented. 5-FU was delivered in 48%. In the subset of 34 patients with gross residual disease who received IORT and postoperative therapy, the 3-year survival rate was 44%. However, despite the encouraging survival rate, 40% developed local failure and 60% developed distant failure. Univariate analysis revealed a significant improvement in survival in those patients with microscopic compared with gross residual disease, the use of IORT, a limited number of sites of tumor fixation, and higher performance status. These data suggest that, even in patients with locally recurrent disease, an aggressive approach should be considered.

Other reports have included patients with both rectal and colon cancers as well as patients with both primary and recurrent disease. At the MGH, patients received somewhat higher doses of radiation (60 to 70 Gy) compared with the Mayo Clinic external-beam therapy alone series. Seven patients received electron-beam IORT. For the total group, local failure was 42% and the 5-year disease-free survival rate was 18%. The 23 patients with gross residual disease had a higher local failure rate (57% vs. 30%) and a significant decrease in survival (4% vs. 42%) compared with the 30 patients with microscopic residual disease. The improvement in local control compared with the Mayo Clinic external-beam therapy alone series may have been related to the higher radiation doses. No clear dose-response curve was noted in patients with gross disease, but patients with microscopic residual disease who received less than 60 Gy did have a higher incidence of local failure compared with those who received 60 Gy or more (38% vs. 26%). Another factor that may have an impact on the local failure rate is the volume of gross residual disease. As seen in Table 33.8-15 and Table 33.8-16, this is consistent with the experience from the MGH and the Mayo Clinic IORT series, in which patients with gross residual disease had lower survival and higher local failure rates compared with patients with microscopic residual disease. The dose of radiation needed to treat potential microscopic disease (after a complete resection) is 45.0 to 50.4 Gy, which is within the tolerance of the surrounding normal tissues. However, when microscopic or gross biopsy-proven residual disease is present (after a subtotal resection), the dose of required radiation is higher. Even in situations in which the small bowel can be excluded from the external-beam radiation field, other surrounding normal tissues limit the dose to 60 to 65 Gy, which may be inadequate to control large volumes of gross residual tumor. Therefore, it is not surprising that the results for patients with residual disease who receive postoperative radiation therapy are disappointing. The obvious advantage of preoperative therapy is that it decreases the primary tumor volume, thereby allowing maximum surgery and IORT.

**Reirradiation Followed by Surgery**

In patients with a local recurrence who have received prior pelvic radiation, Lingareddy et al. reported the use of reirradiation in a selected group of 39 patients. They received a median dose of 36 Gy using limited lateral fields plus continuous infusion 5-FU. The whole pelvis was not treated, and the bladder and small bowel were excluded as much as possible from the radiation field. With a median follow-up of 3 years, the 5-year actuarial local failure rate was 55% and survival was 24%. In highly selected patients, retreatment with limited fields may be an option; however, this approach should be considered experimental.

**External-Beam Radiation Therapy Alone**

Patients selected for radiation therapy alone are usually medically inoperable or have very advanced local disease such that resection would compromise a vital structure. This approach has been previously discussed in the section Radiotherapy Alone for Rectal Cancer (see Table 33.8-6).

**Postoperative Radiation Therapy and Chemotherapy**

Two randomized trials of postoperative combined modality therapy versus radiation alone have been conducted in patients with medically inoperable or advanced local disease. In the RTOG trial, 129 patients with residual, primary unresectable, or recurrent rectal cancer were randomized to radiation therapy plus concurrent 5-FU followed by maintenance 5-FU plus methyl CCNU versus radiation therapy alone. Some patients received IORT. No significant difference was reported in the estimated actuarial 2-year survival rate in patients who received combined modality therapy compared with radiation therapy alone (44% vs. 36%). Of the patients with gross residual disease (in either arm), 25% were without evidence of disease, 6% were locally controlled, and 50% died with a component of local failure.

The Eastern Cooperative Oncology Group randomized 30 patients with recurrent, residual, or primary inoperable rectal cancer to postoperative continuous course radiation therapy versus split course radiation therapy plus 5-FU followed by maintenance 5-FU plus methyl CCNU. The median survival in both arms was 17 months. The five patients with primary inoperable cancer (considered gross residual) had the shortest 2-year survival rate (0%), compared with the 16 patients with recurrent disease (25%) or the nine with residual disease (54%).

Therefore, postoperative combined modality therapy, as delivered in these two randomized trials, did not have a significant impact on survival compared with postoperative radiation therapy alone in this subset of patients. Other chemotherapeutic agents and schedules are being investigated.

**Intraoperative Radiation Therapy Alone for Gross Residual Disease**

A subset of patients with recurrent rectal cancer have clinically unresectable gross residual pelvic disease and, because of prior full-dose pelvic radiation therapy, would require an attempt at resection without the benefit of pre- or postoperative radiation therapy, or both. Furthermore, when IORT is not available, this group of
patients is commonly approached in a palliative fashion, because surgery alone cannot control gross residual disease. The results of 36 patients with recurrent rectal cancer who had gross residual disease remaining in the pelvis after biopsy alone or subtotal resection were reported by Minsky et al.27 from the Memorial Sloan-Kettering Cancer Center. With a median follow-up of 24 months, the local failure rate was 44% and the 4-year actuarial survival rate was 25%. The local control rate was dependent on the volume of residual disease. With brachytherapy, the tumor volume is proportional to the volume of the implant. The local failure rate was lower in those patients who underwent subtotal resection compared with a biopsy alone (33% vs. 66%), and in those with an implant volume of less than 40 cm$^3$ compared to 40 cm$^3$ or more (39% vs. 100%). Severe treatment-related complications were seen in 11% of locally controlled patients. The experience with electron-beam IORT in this group of patients is more limited. Calvo et al.26 reported a subgroup of five patients with gross residual or recurrent colorectal cancer who received 10- to 80-Gy electron-beam IORT. All tumors were larger than 4 cm. With a median follow-up of 11 months, the incidence of local failure was 40%. Complications included pelvic abscess (in one patient), pelvic pain (in two), and lower extremity neuropathy (in one). The more recent trial by Martinez-Monge and associates included patients with extrapelvic disease; therefore, it is not discussed. In summary, the limited data suggest that IORT with electrons or brachytherapy does not improve the ultimate survival rate in this group of patients. However, it does offer reasonable local control (56% to 60%) with acceptable morbidity. Because local control, in and of itself, is an important end point in the treatment of rectal cancer, it is appropriate to continue to evaluate IORT as part of an overall aggressive approach in patients with residual disease who are unable to receive pelvic radiation therapy.

**INVESTIGATIONAL RADIATION THERAPY APPROACHES**

A number of investigational radiation therapy approaches have been used in an attempt to enhance the treatment results in patients with both resectable and unresectable rectal cancers and other pelvic malignancies. These include neutron beam radiation, hyperthermia, radiosensitizers, and altered radiation fractionation schemes. Radioprotectors (discussed earlier in *Dietary Supplements and Radioprotectors*) and three-dimensional treatment planning (discussed earlier in *Three-Dimensional Radiation Treatment Planning*) already have been described.

**NEUTRON BEAM RADIATION THERAPY**

The theoretical advantages of neutron beams compared with more conventional radiation include increased sensitivity of hypoxic cells and more advantageous radiation repair and sensitivity characteristics of normal tissues. The results of two randomized trials that have compared neutrons and photons in patients with unresectable and recurrent rectal cancers were reported by Duncan et al.29 A total of 35 patients received neutrons using a variety of techniques and doses. Not only were no significant differences in local control or survival detected, but patients who received neutrons experienced higher acute and long-term grade 3+ skin toxicity. The preferential absorption in fat of neutrons may have contributed to the complications seen in the skin and subcutaneous tissues. Similar severe and fatal complications were reported in a series of 25 patients with advanced rectal cancer treated by Blattmann et al. (1982). Despite the theoretical advantages, little interest has been shown in the treatment of rectal cancer with neutrons.

**HYPERTHERMIA**

Hyperthermia, in conjunction with radiation, has been mostly used as a palliative modality in rectal cancer. Nonrandomized data from Rhomberg et al.17 suggest that razoxane may improve local control and median survival in patients who receive radiation for inoperable recurrent rectal cancer. Other trials of radiosensitizers have not revealed a clear benefit.

**RADIOSENSITIZERS**

Randomized clinical trials in rectal cancer have clearly shown that 5-FU is a radiosensitizer. When combined with adjuvant postoperative radiation therapy, it significantly decreases local failure compared with radiation therapy alone.13 Various mechanisms for 5-FU–mediated radiosensitization have been proposed, but none alone explain all the interactions.14 Nonrandomized data from Rhomberg et al.17 suggest that razoxane may improve local control and median survival in patients who receive radiation for inoperable recurrent rectal cancer. Other trials of radiosensitizers have not revealed a clear benefit.

**ALTERED RADIATION FRACTIONATION SCHEMES**

Various fractionation protocols have evolved with the goal of enhancing tumor cell damage by radiation without increasing normal tissue injury. The repair of subcellular injury, regeneration, cell-cycle redistribution, and reoxygenation are all factors at the cellular level contributing to differences in how various normal tissues and tumors respond to fractionated radiation. The use of hyperfractionation and accelerated fractionation schemes take advantage of some of these factors. The late effects should be the same as or, more likely, less than conventional fractionation schemes. A phase I trial from Lausanne of postoperative accelerated hyperfractionation (1.6 Gy twice a day to 48 Gy) reported acceptable acute toxicity.26 Updated data from this group suggests that twice daily radiation is better tolerated when delivered preoperatively rather than postoperatively.177 Pozzetti et al.26 reported a pathologic complete response rate of 9% in 59 patients with ultrasound stage T2–3 disease who preoperatively received 1.5 Gy twice a day for 45 Gy. This rate was lower than the 14% pathologic complete response rate in 36 patients with ultrasound stage T2–3 disease who received 50.4 Gy with conventional 1.8-Gy fractions at the Memorial Sloan-Kettering Cancer Center.

The major limitation of accelerated hyperfractionation is acute normal tissue toxicity. Because it is unlikely that these altered fractionation schemes can be combined with adequate doses of systemic chemotherapy, Movsas and colleagues have limited the hyperfractionated portion to the boost. In their phase I trial of preoperative combined modality therapy, patients receive conventional pelvic radiation plus continuous infusion 5-FU followed by a boost with escalating doses of hyperfractionated radiation (1.2 Gy twice a day).28 Providing that the small bowel was excluded after 52.3 Gy, the recommended dose level with this approach was 61.8 Gy.

In a randomized trial of patients receiving radiation therapy for pelvic malignancies, three-dimensional conformal radiation therapy decreased the volume of normal tissue at risk, but did not decrease acute toxicity.14 Other techniques, such as neutron beam radiation, hyperthermia, radiosensitizers, radioprotectors, altered radiation fractionation schemes, and proton and three-dimensional treatment planning, are encouraging but remain experimental.

**TREATMENT OF PATIENTS WITH SYNCHRONOUS METASTATIC DISEASE**

A subset of patients present with unresectable pelvic disease and synchronous extrapelvic disease. Because the natural history of these patients is dependent on a variety of factors, such as the volume and site(s) of metastatic disease and, in those with recurrent disease, the disease-free interval, treatment recommendations are individualized and no standard of care has been established. The management of these patients is discussed in greater detail in Chapter 52.3. At Memorial Sloan-Kettering, the general approach is to deliver preoperative combined modality therapy both as a therapeutic measure and to help identify those who may benefit from an aggressive surgical approach. If after the completion of therapy a response has been seen in both the primary and metastatic site(s), then the patient is evaluated, on a case by case basis, for surgery of the primary and metastasis.

**FOLLOW-UP AFTER POTENTIALLY CURATIVE TREATMENT**

Patients should follow up with their primary treatment team after curative treatment for many reasons. An important aspect of this follow-up is management of treatment-related problems and assessment for local-regional recurrences. These may have an impact on quality of life that is not apparent from survival statistics. Dietary modifications, including the use of a fiber supplement, may be necessary for management of bowel function. Antidiarrheal agents frequently are required. This management can occur on an ongoing basis during follow-up, because these symptoms are most profound during the initial year after treatment and tend to abate during the latter part of the follow-up period. In addition, patients who undergo creation of ostomies for their colorectal cancer management benefit from consultation with an enterostomal therapist. Counseling and appropriate referral for the management of sexual or bowel dysfunction can occur during follow-up visits.
TREATMENT OF RECURRENCE

Management of recurrent disease is individualized. The treatment is based on the extent of recurrence as well as the patient’s overall potential for curative therapy and their medical condition. In most patients, recurrent disease is multifocal and treated with systemic chemotherapy. Highly selected patients can be considered for operative therapy. Others with an unresectable recurrence may need palliation. A chief symptom requiring palliation in patients with recurrent rectal carcinoma is obstruction. The use of salvage surgery for recurrence after local excision is presented in Recurrent Disease, earlier in this chapter. The use of surgery for lung metastases or hepatic metastases is discussed in Chapter 52.2 and Chapter 52.3, respectively.

PALLIATION OF OBSTRUCTION DUE TO LOCALLY RECURRENT RECTAL CANCER

In patients with synchronous metastatic disease, the management of rectal obstruction can make use of a number of techniques that can help avoid palliative colostomy. Frequently, patients in this circumstance are markedly debilitated and very poor surgical risks. These circumstances often make the risks of surgical intervention prohibitive, especially in light of the limited potential for survival. Palliative pelvic irradiation is a useful technique in patients who have not undergone previous radiotherapy. Palliative endoscopic placement of self-expanding metallic stents has also been used as an alternative to palliative colostomy. Success rates can be high with stenting. In a majority of patients, this technique results in the successful placement of the stent. Many have no further complications from their obstruction for a period of 1 to 7 months after stent placement. For those in whom stent placement is unsuccessful, palliative colostomy can be performed. Neodymium:yttrium-aluminum garnet laser treatment also can be highly successful in relieving obstruction.

SURGERY FOR LOCALLY RECURRENT RECTAL CANCER

Among patients with failure after curative treatment of rectal carcinoma, between 10% and 30% of recurrences are confined to the pelvis. The absence of metastatic disease is one of the key factors in determining a patient's potential for curative surgical resection for locally recurrent disease. Local recurrences of rectal cancer tend to be highly symptomatic, with pelvic pain, rectal obstruction, bleeding, urinary tract dysfunction, and fistulas.

LOCATION OF RECURRENCE

Localized pelvic recurrences may be classified based on the tumor location within the pelvis. Recurrences can be heterogeneous, and the pattern of extension of local recurrence may be much more extensive than that of the primary rectal cancer. These tend to be in perianastomotic tissues and more frequently involve adjacent organs. Axial recurrences appear centrally in the pelvis. These may include anastomotic recurrences after local or radical surgery. Anteriorly based recurrences in the pelvis chiefly involve the seminal vesicles and prostate in men and the vagina and uterus or bladder in women. Posterior recurrences tend to involve the sacrum, which may extend into the pyriformis muscle, the sciatic notch, and sciatic nerve. Lateral recurrences can involve the soft tissues of the pelvic sidewall and the iliac blood vessels and lymph nodes, as well as the obturator internus muscle and the pyriformis muscles. Recurrences may extend into the bony sidewalls of the pelvis.

EVALUATION OF THE PATIENT WITH LOCALLY RECURRENT RECTAL CANCER

The preoperative workup of a patient with a suspected local rectal cancer recurrence involves assessment of both the presence of extrapelvic metastatic disease and a determination of the extent of the local recurrence. Under certain circumstances, intraoperative exploration may be required to reveal an unresectable recurrence; however, it is best to avoid this procedure because of morbidity without improvement in survival.

When patients present with locally recurrent rectal cancer, they usually are asymptomatic. These symptoms may range from cramping or constipation from bowel obstruction to pelvic or sciatic pain to dysuria and urinary tract dysfunction. Important examinations are pelvic examination in females, digital rectal examination, proctoscopy, and cystoscopy. Examination of the inguinal lymph nodes in patients with a previous low rectal cancer can detect lymph node recurrence.

IMAGING PATIENTS WITH LOCAL RECURRENCE

When presented with a patient having locally recurrent rectal carcinoma, staging of the abdomen and pelvis, either with CT or MRI, and imaging of the pulmonary fields with chest x-ray is required. These tests do an excellent job of identifying patients with visceral metastases; however, peritoneal implants may be missed until surgery is done.

The operative approach is determined by the extent and location of the recurrence. Specific questions can be asked from pelvic imaging studies, such as MRI or CT, that help to determine resectability and the procedure required. These questions pertain to (1) involvement of the sciatic nerve or lumbosacral plexus; (2) extension outside the pelvis through the sciatic notch or levators; and (4) involvement of seminal vesicles or prostate and bladder in men and involvement of vagina, cervix, and bladder in women. Although ELIS can aid in the assessment of local recurrence, it is limited because of the postoperative changes seen around a rectal anastomosis. CT scan identifies distant metastases as well as the extent of pelvic involvement. However, postoperative or postradiation chemotherapy changes may lead to fibrosis, making it indistinguishable from recurrence. CT scanning sensitivity for detecting pelvic recurrences is between 70% and 82%. CT scans can also identify potential sites for fine-needle aspiration biopsies of suspected areas of recurrence. This may be useful in evaluating patients with a recurrence or in planning operative therapy. MRI appears to be especially useful in determining neurologic and sacral involvement and planning for the resections of these structures.

Nuclear imaging has been reported to be useful in the pretreatment evaluation of patients with recurrent colorectal cancer. It can identify sites of occult metastatic disease that would make pursuit of an extensive resection fruitless. Although nuclear imaging studies frequently lack the anatomic definition necessary to enhance the determination of the local extent of disease, their ability to exclude patients with clinically undetectable metastatic disease may be of value. PET is a technique that has been used in conjunction with the glucose analogue [18F]fluorodeoxyglucose to image colorectal cancers. Accuracy in detecting sites of recurrent colorectal cancer has been reported to approach 83% in patients with recurrent colorectal cancer. PET whole body scanning has provided additional information beyond conventional imaging.

SURGERY FOR RECURRENT DISEASE

In patients taken to the operating room for locally recurrent rectal cancer, cystoscopy and bilateral urethral stent placement should be performed to facilitate subsequent evaluation and to allow the operation to proceed with alacrity. Thorough exploration of the abdominal cavity should be carried out to assess for evidence of metastatic disease. Specific sites to be examined are the peritoneal surface, omentum, retroperitoneal lymph nodes, and liver. If metastatic sites are found, then consideration can be given to palliative management, such as colostomy or urologic diversion. Patients with perianastomotic recurrence should undergo resection to achieve negative margins. In most cases, this involves an APR. In perineal recurrences after APR, patients should undergo wide excision. It should be noted, however, that the tumor presenting at the level of the perineal skin is often a small component of the overall pelvic recurrence. Most of these cases require extensive soft tissue reconstruction for adequate closure of the excision site. Recurrences that involve adjacent structures may require pelvic exenteration to achieve negative margins. Multiple organs may be adherent to the site of the recurrence, and these should be resected en bloc to avoid violation of the recurrent tumor. This requires development of planes outside the normal anatomic planes used for resectable lesions. Removal of nodal disease along the internal iliac artery and wide excision of the pelvic floor is required.

In patients with a posterior extension of pelvic recurrence, rectal resection, sacrectomy can be required in combination with the pelvic visceral resection. Where there is limited distal sacral and coccyx involvement, this can be resected en bloc with the pelvic viscera resected through an abdominal and perineal approach. If more extensive sacral involvement is present, the patient can undergo a combined abdominal, perineal, and posterior approach for formal sacrectomy. Vascular ligations of the internal iliac vessels and nodal resection below this level are carried out through the abdominal approach as well as the division of any remaining rectal segment and division of the ureters and construction of an ileal conduit. The patient can then be turned into a prone position for subsequent resection of the perineal soft tissues, laminctomy, and ligation of the dural sac followed by en bloc removal of the pelvic tissues.

Patients with extensive pelvic sidewall involvement can undergo extended lateral resections to include obturator and internal iliac nodes as well as surrounding pelvic soft tissues. Areas of close margins can be treated with IORT or


Anal cancers, while still uncommon tumors, have increased substantially in incidence since the 1980s. As discussed in this chapter, it is possible that this increase in incidence is due to sexual transmission of human papilloma virus (HPV). Thus, in theory at least, anal squamous cell (epidermoid) tumors may represent a preventable disease. For almost two decades, combined modality treatment involving radiation and chemotherapy has resulted in 5-year survival rates of approximately 80% and in sphincter preservation for most patients with squamous cell carcinomas of the anal canal. Surgical resection involving an abdominal perineal resection (APR) is reserved for patients with local failure or progression. This approach has served as a model for other cancers of the successful use of curative nonoperative combined modality therapy.

EPIDEMIOLOGY AND ETIOLOGY

INCIDENCE, AGE, AND GENDER

In the United States, cancers of the anal region account for 1% to 2% of all large bowel cancers and 3.9% of all anorectal carcinomas. The majority of these patients (75% to 80%) have squamous cell carcinomas. Approximately 15% have adenocarcinomas. In 1998, a total of 3300 cases of cancers of the anal region were reported in the United States, including 1400 men and 1900 women. It is estimated that there will be 500 deaths per year.

The U.S. National Cancer Database provided data to examine the epidemiology of patients with anal canal cancer. In this analysis, a total of 2339 cases of anal carcinoma diagnosed in 1988 and 1993 were compared. There was little difference in mean age or in the male to female ratio during the 5-year period. Two-thirds of newly diagnosed patients were women, indicating that both in the United States and in Europe, women are substantially more likely to develop anal canal cancers than are men. Most patients were white. The proportion of patients with squamous cell carcinoma increased slightly, compromising between 75% and 80% of newly diagnosed patients. Seventy-five percent of patients have stage I or II tumors. In this analysis, no comment was made regarding the incidence of disease in homosexual or bisexual men.

HUMAN PAPILLOMA VIRUS INFECTION AND ANAL CANCER

HPV infection is closely correlated with squamous cell carcinoma. Frisch et al. conducted a population-based case-control study in Denmark and Sweden for patients with anal canal cancers. Two control groups (patients with adenocarcinoma of the rectum and healthy persons from the general population) were included. A variety of behavioral factors, such as sexual activity and venereal infection, tobacco consumption, and anal inflammatory lesions, were examined. In this large study involving 417 patients with anal cancer, 534 controls with adenocarcinoma of the rectum, and 554 general population controls, a strong positive correlation was found both in univariate and multivariate analysis for the amount of sexual activity and the risk of anal cancer. An additional association between venereal infection in both men and women was noted. The authors concluded that sexual activity was strongly associated with the development of anal canal cancer and that HPV infection was the presumed etiologic cause.

Anal intraepithelial neoplasia (AIN) is rare in heterosexual men, whereas the incidence is 5% to 30% in human immunodeficiency virus (HIV)–negative homosexual men. Similarly, such changes are rare among HIV-negative women. High-grade anal lesions that almost always contain HPV have been reported, primarily among HIV-positive individuals. It is suspected that, similar to cervical carcinoma in which HPV is strongly associated and may be a necessary factor for development of the disease, high-grade AIN lesions are the immediate precursors to anal cancer.

ANAL CANCER AND ACQUIRED IMMUNODEFICIENCY SYNDROME

An association between acquired immunodeficiency syndrome (AIDS) and an increased risk for anal canal cancer has been noted for some time. Treatment of the HIV-positive patient is discussed later in this chapter (see Treatment of the Human Immunodeficiency Virus–Positive Patient). Melbye et al. linked databases for AIDS and those for cancer in American patients. The relative risk (RR) of anal cancer at the time of or after AIDS diagnosis was 84.1 among homosexual men. The relative risk of anal cancer for up to 5 years before AIDS diagnosis was 13.9. This marked increased risk of anal cancer in patients with AIDS is presumably because of immunodeficiency, perhaps increasing susceptibility to HPV infection. A similar increase in risk has been noted for renal transplant patients undergoing
Although earlier studies suggested that anal-receptive intercourse was directly linked to an increased risk of anal cancer, this finding has not been confirmed in more recent larger scale trials. Particularly in women, most patients did not report sexual activity involving anal intercourse.

Golde et al. reviewed the clinical outcome and cost effectiveness of screening for premalignant (squamous intraepithelial lesions) or malignant anal lesions in homosexual and bisexual HIV-positive men. Their analysis indicated that screening of homosexual and bisexual men who were HIV-positive, no matter what the stage of their HIV status, prolongs quality-adjusted life expectancy.

Anal canal carcinoma has also been associated with condylomata in both the general population and in male homosexuals. Pfister and Fuchs also noted that HPV-16 infection has a strong association with high-grade AIN and a risk of anogenital malignancy. HPV infection alone may be insufficient for malignant transformation, however, as many persons with HPV-positive cytology do not develop either AIN or anal carcinoma.

In women without a history of genital warts, anal cancer was associated with seropositivity for herpes simplex virus type 1 (RR, 4.1) and Chlamydia trachomatis (RR, 2.3). In men without a history of warts, there was an association with gonorrhea (RR, 17.2). Among individuals with AIDS, an increased risk of anal cancer has been found.

MOLECULAR AND CHROMOSOMAL ABNORMALITIES

The E6 oncoprotein of HPV inactivates the growth-controlling p53 suppressor gene product, which may play an important role in the pathogenesis of anal cancer. Overexpression of p53 protein has been studied in patients receiving combined modality therapy. In an analysis involving approximately 20% of patients entered into Radiation Therapy Oncology Group (RTOG) protocol 87-04, in whom 5-fluorouracil (5-FU) plus radiation with or without mitomycin C was given, immunohistochemistry for p53 overexpression was performed. Although there was a trend toward worse outcome (decreased local control and survival) in patients overexpressing p53, this did not reach statistical significance.

Smoking has been shown to be a risk factor for the development of anal cancer. Frisch et al. studied the relationship between anal cancer and smoking in Danish and Swedish patients. A positive correlation for an increased risk of anal cancer in premenopausal women who smoked versus lifelong nonsmokers was noted. Smoking was not statistically significantly related to anal canal cancers in men or postmenopausal women. They suggested that suppression of estrogen may play a role for anal carcinogenesis in premenopausal women. In the case-control study reported by Daling and colleagues, current cigarette smoking was a major risk factor in both sexes (RR, 7.7 in women and 9.4 in men). This is similar to the report by Daniell, who noted that 54% of 13 women with anal cancer were current smokers, compared with only 26% of 202 age-matched patients with colon cancer. In a matched controlled study of 56 women with anal carcinoma, there were strong associations with herpes simplex virus type 1, cigarette smoking, and increasing numbers of sexual partners. In a multivariate analysis, cigarette smoking was an independent variable.

Prior radiation therapy may play a role in the development of anal carcinoma, as may immunosuppression. Immunosuppressed renal transplant patients have a 100-fold increase in anogenital tumors compared with the general population. As noted previously, increasing immunosuppression in HIV-positive patients is correlated with increased risk for anal canal cancer.

Animal studies offer some clues to the genesis of anal tumors. In mice, anal carcinomas may be induced by chemical carcinogens.

ANATOMY

A clear anatomic distinction between the anal canal and the anal margin is needed because of the different natural histories of cancers that arise in these two distinct anatomic areas. Considerable confusion exists when comparing series in the literature because of the use of different definitions of the anal canal and the anal margin. The anatomic components of the anal canal and anal margin are illustrated in Figure 33.9-1.

FIGURE 33.9-1. Anatomy of the anal canal. A tumor in location A is always considered anal canal cancer; in location C, it is anal margin cancer. A tumor in location B has been called canal or margin cancer, depending on institutional preference, but now should be called anal canal cancer by the American Joint Committee on Cancer and the Union Internationale Contra le Cancer definition.
lined by cuboidal epithelium, start just distal to the anorectal ring and extend to the dentate line. The dentate line is defined as the demarcation between the columnar epithelium of the proximal canal and the stratified squamous epithelium of the lower canal and is the site where the anal glands empty. The junction is not an abrupt histologic change but rather a transition zone that extends for 6 to 12 mm and contains columnar, cuboidal, squamous, and transitional epithelia. The stratified squamous epithelium extends from just below the dentate line to the anal verge, which is defined as the junction of the squamous epithelium with the perianal skin, which is a keratinized squamous epithelium containing hair follicles.

Definitions of the proximal and distal extent of the anal canal have varied among authors. A number of authors have defined the distal limit of the anal canal as the dentate line and all tumors below this as anal margin cancers. Some have defined the distal extent of the anal canal to reach to the anal verge. Others refer to anal margin tumors as tumors that arise within 5 cm of the anal verge. The anatomic boundary used for distinguishing anal canal from anal margin tumors alters their incidence. When the anal verge is used as the distal margin of the anal canal, 15% of tumors arise from the anal margin, but this number climbs to 30% when the dentate line is used as the distal limit. To clarify this issue, the American Joint Committee on Cancer (AJCC) and the Union Internationale Contre le Cancer (UICC) have formed a consensus that the anal canal extends from the anorectal ring (dentate line) to the anal verge. This is an important distinction, as these two governing bodies agree that anal margin tumors behave in a similar fashion to skin cancers and therefore are to be classified as skin tumors and treated as such.

The arterial supply to the distal rectum and anal canal is supplied by the superior, middle, and inferior hemorrhoidal arteries, which arise from the inferior mesenteric, hypogastric, and internal pudendal arteries, respectively. Venous drainage follows the inflow patterns. The internal rectal sphincter motor innervation is supplied by sympathetic fibers, whereas the sacral parasympathetics mediate the sensation of distention. The external rectal sphincter is innervated by the inferior hemorrhoidal nerve, which is derived from the internal pudendal nerve. The lower rectal wall is supplied by the pelvic plexus composed of the pelvic sympathetic and parasympathetic nerves. The sensory component of the hair-bearing skin beyond the anal verge is innervated by the inferior hemorrhoidal branches of the internal pudendal nerve.

Squamous tumors may arise from the entire length of the anal canal as well as develop from the anal margin. Basaloid carcinomas, which are a variant of squamous carcinoma, arise from the epithelium just above the dentate line and are commonly referred to as cloacogenic carcinomas. The adenocarcinomas in this region arise from the glands at the dentate line. Small cell carcinomas in this region are of neuroendocrine origin and are rare. Tumors of the anal margin include squamous carcinoma, basal cell carcinoma, Bowen's disease, Paget's disease, verrucous carcinoma, and Kaposi's sarcoma. Malignant melanomas may arise from either location, but more commonly from below the dentate line.

An interesting difference in the presence of HPV DNA between cloacogenic and squamous carcinomas has been found. When studied by in situ hybridization, all 14 cloacogenic carcinomas were HPV-negative, whereas two-thirds of the 21 squamous carcinomas were HPV-positive (mostly for types 16 to 18). In another study, however, there was no difference in the percentage of HPV RNA positivity (approximately 75%) between cloacogenic and squamous carcinomas.

In the anal margin, pathologies other than squamous cell carcinoma include basal cell carcinoma identical with that in skin in other areas, Bowen's disease, and Paget's disease. Patients with Bowen's disease usually present with long-standing perianal pruritus. Raised irregular eczematous-appearing plaques are seen. Biopsy of this intraepithelial neoplasm is diagnostic with large periodic acid–Schiff-negative cells. As with Bowen's disease, patients with perianal Paget's disease frequently present with pruritus, although they may be asymptomatic or, at the other extreme, have a bleeding erythematous or eczematoid plaque. The histologic appearance reveals characteristic periodic acid–Schiff-positive large vacuolated cells. In the absence of an underlying anal canal cancer, the origin of the cells is likely from the apocrine glands. An associated anorectal carcinoma should be excluded. Goldblum and Hart studied immunohistochemical features of specimens from 11 patients with Paget's disease and were able to distinguish two types of perianal Paget's disease. One type has endodermal differentiation with gastrointestinal-type glands containing intraluminal necrosis, signet-ring cells, CK20 positivity, and GC-DFP15 positivity. Such cases are likely to be associated with rectal adenocarcinoma. The other type is a primary cutaneous intraepithelial neoplasm in which the Paget's cells display sweat gland differentiation, GC-DFP15 positivity, and CK20 negativity.

### PRECANCEROUS CHANGES

Precancerous changes have been studied by a number of investigators. In particular, the increasing incidence of anal canal carcinomas among certain populations (e.g., homosexual or bisexual men who are HIV-positive) has led to scrutiny of the role of AIN and dysplasia (see Epidemiology and Etiology, earlier in this chapter).

Fenger and Nielsen studied the incidence of precancerous changes in the anal canal epithelium. Of 306 specimens of the anal transition zone, seven (2.3%) showed squamous cell dysplasia, which was severe in only one. With an average follow-up of 27 months, no case of dysplasia had progressed to carcinoma. In a group of 139 patients with perianal AIN (most with carcinomas of the rectum but some with anal canal tumors), 15 (10.8%) had dysplasia that was thought to be precancerous or to represent carcinoma in situ. Severe dysplasia or carcinoma in situ was seen in 13 of the 16 patients (81%) with squamous cell carcinoma of the anal canal. They concluded that most anal canal tumors arising in the anal transition zone are preceded by multicentric areas of dysplasia.

Palefsky and colleagues studied the incidence of the premalignant condition, AIN, and its relationship to anal HPV infection among homosexual men who were HIV-positive. Infection with multiple subtypes of HPV was seen in 12% of patients; these patients had a markedly increased risk for cytologic abnormalities (RR, 39.0).
In addition, patients who had abnormal cytology were significantly more likely to have lower median T4 counts. They concluded that immunosuppressed male homosexuals may be at significant risk for the development of anal canal neoplasia, related to the presence of HPV.

Surawicz and colleagues found that in 90 homosexual men with an abnormal examination result of the anal canal, 89% had HPV-associated changes. In a prospective study of 37 homosexual men, Palefsky and associates found a substantial increase over time in the percentage of patients with cytologic abnormalities of the anal canal (27% to 65% over an average 17-month period). There was also an increase in the presence of AIN and of identifiable HPV infection.

Flow cytometric analysis of normal epithelium along the anal transition zone and, in smaller groups of patients, of anal canal tumors has been performed in fresh specimens by Fenger and Bichel. A normal diploid population was seen in normal squamous epithelium in the anal transition zone, along with a small hyperdiploid peak, the relevance of which was unclear. Three patients with squamous cell carcinoma of the anal canal were studied. They had a high proliferative index but near diploid peaks. In contrast, Goldman and coworkers found that most anal tumors had an aneuploid pattern. Scott and colleagues studied flow cytometry in 235 patients with resected tumors of the anal canal and perianal skin. In a multivariate analysis, depth of penetration, inguinal node involvement, and DNA ploidy were of independent prognostic significance.

**SQUAMOUS CELL CANCER**

**NATURAL HISTORY**

Anal canal carcinomas often spread by local extension, extending cephalad to involve other organs in the pelvis. Local extension to adjacent structures and into the sphincteric muscles is common on initial presentation. Extension to the vaginal septum was seen in 9 of 76 (12%) women in the Memorial Sloan-Kettering series. Although it is often stated that these tumors can invade the prostate, urethra, bladder, and seminal vesicles in male subjects, in this series the tumors approached these organs but did not invade them.

Hematogenous spread appears to occur more often from tumors that arise at the dentate line or above. This pattern of spread allows tumor cells into the portal system, and liver metastases also involve the lung in 5% to 8% of patients. Hematogenous metastases also involve the lung in 2% to 4% of cases and bone in 2% of cases. Distant metastases occur with equal frequency independent of the histologic cell type involved. Distant metastases rarely, if ever, are seen with anal margin tumors.

Lymphatic spread can occur via the inguinal, pelvic, and mesenteric nodes (see Anatomy, earlier in this chapter). Because routine lymphadenectomy is no longer performed in anal cancers, the data pertaining to lymph node involvement are from historic surgical series. Many interconnections exist between these lymphatic channels, and tumors arising above or below the dentate line may have mesenteric nodal involvement. Of 33 anal canal tumors arising below the dentate line, six had mesenteric nodal involvement in their abdominoperineal specimens, confirming these interconnections.

Inguinal lymph nodes are involved in 15% to 63% of cases of anal canal tumors. In one series, 17 of the 115 patients (15%) had inguinal nodes involved at the time of presentation, similar to the incidence reported in other series. Metachronous inguinal nodes appeared in 24 of 96 patients (25%), with a median time to presentation of 12 months. Pelvic nodes are not as commonly involved, whereas mesenteric nodes are more likely to be involved if the tumors are proximal (50%) compared with distal (14%). Anal margin tumors rarely spread to the mesenteric nodes.

Survival after lymph node dissection with positive nodes at presentation ranged from 0% to 83%. However, modern combined modality therapy has greatly affected this result. Patients who have lymph node dissection for metachronous lesions have a better long-term survival, with rates up to 83%

**DIAGNOSIS**

Although anal cancers are located in one of the most accessible sites of the digestive tract, these tumors are frequently misdiagnosed and a delay in treatment often results. The initial and most common symptom is bleeding, and this occurs in more than one-half of the patients. The bleeding is rarely substantial and is usually attributed to hemorrhoids. Other common symptoms include pain, tenesmus, pruritus, change in bowel habits, abnormal discharge, and, infrequently, inguinal lymphadenopathy. Most of these symptoms are associated with benign conditions of the anus, including fissure, fistula in ano, hemorrhoids, anal pruritus, and anal condyloma, which results in a delay of diagnosis. The diagnosis may be further confounded because benign perianal conditions may coexist in 60% of anal margin tumors and in 6% of anal canal tumors. Patients often treat themselves for extended periods before seeking medical attention. The duration of symptoms varies from 2 weeks to longer than 4 years, with a mean of 6 months.

Proper treatment for these tumors is often delayed due to inappropriate diagnosis at the initial evaluation in up to one-third of patients. It has been generally accepted that the delay in diagnosis has an adverse effect on the outcome, but this has been challenged. The diagnosis may also be made indirectly in tissues examined routinely after minor anorectal procedures. The patients with these incidental tumors have the most favorable outcomes.

Screening of high-risk populations (i.e., HIV-positive homosexual men) may increase the percent of patients diagnosed with earlier stage tumors.

Distant metastases occur with equal frequency independent of the histologic cell type involved. Distant metastases rarely, if ever, are seen with anal margin tumors.

Distant metastases occur with equal frequency independent of the histologic cell type involved. Distant metastases rarely, if ever, are seen with anal margin tumors.

Analyzing the lymph nodes using immunohistochemistry allows for the determination of depth of penetration and involvement of adjacent organs. In women, the vagina may be infiltrated with tumor and, although it is commonly thought in men that the prostate and seminal vesicles are involved, this is not often confirmed pathologically.

Any suspicious lesion in the anal canal should have a biopsy taken, and this can frequently be done in an outpatient procedure. If the patient has pain or spasms precluding this, then an examination under anesthesia is performed. An incisional biopsy is used to make the diagnosis. The lesion should be excised only if it is a small superficial lesion. Inguinal lymphadenopathy should be aspirated to determine tumor involvement to accurately stage the patient. Inguinal lymph node dissection is not warranted due to the associated morbidity, failure to have an effect on outcome, and the adequate control with combined modality therapy (radiation therapy plus concurrent chemotherapy).

An extent of disease workup should include computed tomography of the abdomen and pelvis to evaluate the primary tumor and to detect liver metastases. Chest radiography is performed to determine if pulmonary metastases are present.

**STAGING**

In 1997 the AJCC and UICC developed a common staging system. This current staging system takes into account the fact that anal canal carcinoma is primarily treated by combined modality therapy (or in selected cases by radiation alone). APR is reserved for patients who fail to respond to initial treatment. Thus, the TNM classification for anal canal cancers is primarily clinical. The primary tumor is assessed for size and, for T4 tumors, invasion of local structures such as the vagina, urethra, or bladder. The TNM classification is seen in Table 33-9-2. Nodal status is based on distance from the primary site rather than number of lymph nodes involved. This staging system applies to carcinomas, including cloacogenic carcinomas. Melanomas and sarcomas are not included in this staging system.
PROGNOSTIC FACTORS

The most important prognostic factors in anal cancer are T stage and lymph node status. As seen in Table 33.9-2, these two factors, as well as the presence or absence of metastatic disease, define the stage. The most striking difference in results is seen when comparing T1 and 2 primary cancers (smaller than or equal to 5 cm) versus T3 and 4 primary cancers (larger than 5 cm) (Tables 33.9-3, 33.9-4, and 33.9-5). The local failure rates with T3 to 4 primary cancers are approximately 50% after combined modality therapy. Because prognostic factors such as tumor size and lymph node status may be interrelated, a multivariate analysis is required to determine if they are independent prognostic variables.


<table>
<thead>
<tr>
<th>Stage</th>
<th>T Stage</th>
<th>N Stage</th>
<th>M Stage</th>
<th>Description</th>
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<td>T1</td>
<td>N0</td>
<td>M0</td>
<td>Tumor is limited to the anus (no lymph node involvement)</td>
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<td>N0</td>
<td>M0</td>
<td>Tumor is limited to the anus (no lymph node involvement)</td>
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<td>N0</td>
<td>M0</td>
<td>Tumor is limited to the anus (no lymph node involvement)</td>
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<tr>
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<td>T4</td>
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<td>M0</td>
<td>Tumor is limited to the anus (no lymph node involvement)</td>
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<td>Tumor is limited to the anus (no lymph node involvement)</td>
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TABLE 33.9-3. Mitomycin C–Based Phase II Combined Modality Therapy Trials for Anal Cancer: Selected Series

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TABLE 33.9-4. Cisplatin-Based Phase II Combined Modality Therapy Trials for Anal Cancer: Selected Series

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TABLE 33.9-5. Randomized Trials of Combined Modality Therapy for Anal Cancer

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T Stage: Univariate Analysis

Salmon and colleagues found that size was significantly related to survival in a study in which radiation therapy alone was the primary treatment. In another radiation therapy alone series, size was prognostic for 5-year survival but not for primary tumor control. In a series of 116 patients treated by external-beam and brachytherapy by Peiffert et al., there was an increase in local failure with T stage (T1, 11%; T2, 24%; T3, 45%; and T4, 43%) and a corresponding decrease in 5-year survival (T1, 94%; T2, 76%; T3, 53%; and T4, 19%) (Table 33.9-6). Similar data were reported by Gerard and colleagues. In 95 patients treated with combined modality therapy plus brachytherapy there was an increase in 5-year colostomy-free survival with T1 and T2 tumors versus T3 and T4 tumors (T1, 83% and T2, 89%, vs. T3, 50% and T4, 54%). Doci and associates treated 35 patients with 5-FU, cisplatin, and external-beam radiation and reported a complete response rate of 100% for T1 and T2 cancers versus 60% for T3 cancers (see Table 33.9-4). The Intergroup randomized phase III trial of radiation, 5-FU with or without mitomycin C, reported a significantly higher complete response rate by tumor size (smaller than 5 cm, 93%, vs. larger than or equal to 5 cm, 83%; P = .02) (see Table 33.9-5). Similar findings were reported by univariate analysis in the European Organization for Research and Treatment of Cancer (EORTC) randomized trial of 45 Gy with or without 5-FU/mitomycin C.
TABLE 33.9-6. Brachytherapy as a Component of Treatment for Anal Cancer: Selected Series

In a series from the Princess Margaret Hospital, tumor size did not appear to have a significant effect on local failure, providing the patients received the combination of 5-FU, mitomycin C, and external-beam radiation (smaller than 4 cm, 95% vs. larger than 4 cm, 86%).

N Stage: Univariate Analysis

In contrast to T stage, the effect of positive lymph nodes is less clear. Furthermore, although the 1997 AJCC/UICC staging system differentiates between positive inguinal and pelvic lymph nodes, most series do not report the data separately. It must be emphasized that, unlike rectal cancer, inguinal lymph nodes in anal cancer are considered nodal metastasis rather than distant metastasis, and patients should be treated in a potentially curative fashion. In the historic literature, synchronous metastases to inguinal lymph nodes have been considered an indicator of a poor prognosis. However, the use of combined modality therapy has altered the poor prognosis previously reported with positive inguinal nodes.

In a series by Cummings et al. from the Princess Margaret Hospital (see Table 33.9-3), patients with negative nodes who received combined modality therapy had a higher 5-year cause-specific survival compared with those with positive nodes (81% vs. 57%). The incidence of local failure was only 13% in patients with positive nodes. Doci et al. found no significant difference in the complete response rate after 5-FU, cisplatin, and external-beam radiation in patients with node-positive compared with node-negative cancers (100% vs. 92%). In a separate report of 56 patients who received 5-FU, mitomycin C, and radiation, the eight patients who had node-positive disease all achieved a complete response. By univariate analysis, patients with positive versus negative nodes who received 5-FU, mitomycin C, and radiation (36% vs. 19%; P = .03); however, this difference was not found to be significant by multivariate analysis. In patients treated with 5-FU, cisplatin, and external-beam and brachytherapy, Gerard et al. also reported no significant differences in 5-year colostomy-free and overall survival in patients with node-positive compared with node-negative disease.

The Intergroup randomized phase III trial of radiation and 5-FU, with or without mitomycin C, reported a higher colostomy rate (which is an indirect measurement of local failure) in N1 versus N0 patients (28% vs. 13%). In node-negative patients, and possibly node-positive patients, the addition of mitomycin C decreased the overall colostomy rates. The EORTC randomized trial of 45 Gy with or without 5-FU/mitomycin C also reported that patients with positive nodes experienced significantly higher local failure (P = .03) and lower survival (P = .038) rates compared with node-negative patients. However, there was no difference in prognosis between N1 versus N2 and N3 disease.

Multivariate Analysis

In the series from Allan and associates, factors by univariate analysis associated with a significant increase in local failure included age younger than 66 years, male gender, tumor extent more than one-third circumference, lymph node involvement, overall treatment time 75 days or greater, and the use of external-beam radiation for the boost treatment. By multivariate analysis, however, the only variable for which there was a possible effect was overall treatment time (P = .09). In the EORTC randomized trial of 45 Gy with or without 5-FU/mitomycin C, multivariate analysis identified that positive nodes, skin ulceration, and male gender were independent negative prognostic factors for local control and survival. Goldman and coworkers also reported by multivariate analysis that gender was also important, with women faring better than men. In a multivariate analysis of 242 patients by Schlienger et al., T stage was the only significant prognostic factor, in a further update with 286 patients analyzed by multivariate analysis, tumor size, clinically abnormal lymph nodes, and total irradiation dose influenced prognosis. Constantinou and colleagues (see Table 33.9-3) reviewed 50 patients who received combined modality therapy and found that radiation dose and percent hemoglobin were independent prognostic factors for local control; radiation dose was an independent prognostic factor for disease-free survival; and radiation dose, percent hemoglobin, and T stage were independent prognostic factors for survival.

Other Prognostic Features

Histologic cell type for squamous cancers of the anal canal (squamous vs. cloacogenic) has not been found to be of major prognostic relevance. Cloacogenic carcinomas have been considered to have a slightly better prognosis in some series; however, in 243 patients with resectable anal canal tumors, Papillon and Montebart reported a worse prognosis for patients with nonkeratinizing and basaloid carcinoma than for patients with keratinizing lesions. Small cell carcinomas of the anus are rare and, similar to extrapulmonary small cell cancers in other parts of the body, appear to have a worse prognosis, with a high propensity for systemic dissemination.

Asymptomatic patients have a better prognosis than symptomatic patients, but this may be directly related to the size of the tumor. Location may be of modest prognostic importance, with anal margin tumors having a better outcome than those in the anal canal (see Treatment later in this chapter).

Three studies have examined DNA content (i.e., whether tumors were diploid or nondiploid); two found no prognostic effect of this factor, whereas in one large multivariate analysis, DNA ploidy was an independent prognostic factor in the 184 patients whose tumors were analyzed for DNA. In one study, DNA grade was a significant prognostic factor, with low-grade tumors resulting in a 5-year survival of 75% compared with only 24% for high-grade tumors. Data from the Princess Margaret Hospital suggest the DT-diaphorase mutation is not a strong determinant of treatment outcome in patients who fail combined modality therapy.

Tanum and Holm reported p53 expression in 34% of patients with anal carcinoma. Pretreatment biopsies from 80 patients treated on the combined modality therapy arm of the Intergroup randomized trial were examined by immunohistochemistry for p53 expression. Altar and colleagues reported a significant increase in local failure in 47% of patients with positive versus negative nodes who received 5-FU, mitomycin C, and radiation (36% vs. 19%; P = .03); however, this difference was not found to be significant by multivariate analysis. In patients treated with 5-FU, cisplatin, and external-beam and brachytherapy, Gerard et al. also reported no significant differences in 5-year colostomy-free and overall survival in patients with node-positive compared with node-negative disease.

In a retrospective analysis from the Princess Margaret Hospital, p53 was measured by immunohistochemistry in 49 patients who received combined modality therapy. The incidence of p53 expression was 82%. By univariate analysis, p53 expression of 5% or greater was a poor prognostic factor for 5-year survival (78% vs. 88%; P = .027). However, significant differences were not seen in disease-free or overall survival.

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TREATMENT

Anal Margin

Cancers of the anal margin are uncommon, accounting for approximately 15% of all tumors of the anal region. They account for 15% to 25% of all squamous cell cancers of the anus and, in general, have a different natural history and more favorable prognosis than squamous cell carcinomas of the anal canal. The average age of onset is 60 to 70 years, with a wide range. Most are well to moderately differentiated, with fewer than 10% being poorly differentiated. The 1997 AJCC/UICC staging system defines the anal margin as a cancer arising at the junction of the hair-bearing skin and the mucous membrane of the anal canal. It must be
emphasized that these tumors are staged as skin cancers rather than anal canal cancers. There is confusion in the literature as a variety of other definitions has been used, the most common being an area of skin measuring from 5 cm to as wide as 10 cm centered on the anal orifice. To further confuse the issue, some series do not report results of anal canal and margin separately.

The lymphatic drainage of anal margin cancers is different from anal canal cancers. Cancers of the anal margin drain primarily to the inguinal lymph nodes, whereas cancers of the anal canal drain primarily to the internal iliac and superior hemorrhoidal nodes.

**SURGERY.** Squamous cell carcinoma of the anal margin, as in skin elsewhere, has a favorable prognosis and rarely requires radical surgery. Wide local excision of these lesions is an attractive approach because it can be performed with primary closure and infrequently requires a split-thickness skin graft. The use of a wide local excision implies that an adequate margin of normal tissue (1 cm) can be secured beyond the tumor without anal incontinence. If the tumor encompasses more than one-half of the circumference of the anus, local excision should be abandoned due to poor anal control; combined modality therapy or APR are advocated.

Most authors recommend wide local excision for squamous cell carcinomas of the anal margin, Bowen’s disease, and Paget’s disease. Wide excision results in control of local disease in the majority of patients. Anal margin tumors rarely metastasize to visceral organs or regional lymph nodes, and this represents an important difference between anal margin tumors and anal canal tumors. High-grade intraepithelial carcinomas (AIN III or carcinoma in situ) may be surgically treated. Other options may include laser ablation or combined modality therapy for extensive lesions that would otherwise require an APR.

Local recurrence after primary treatment of anal margin cancers is routinely treated by repeat local excision. APR or combined modality therapy is reserved for patients with extensive disease. Of the 11 local recurrences treated at Memorial Sloan-Kettering, ten had a local excision and one had an APR. Of the nine patients who survived longer than 5 years, two required a second procedure to control disease. In the same study, four patients had an inguinal node recurrence as the only site of failure, and all underwent inguinal lymphadenectomy. Two of these patients were long-term survivors, one died of disease, and one was lost to follow-up. The median survival exceeded 5 years. The authors concluded that few patients die from anal margin tumors.

An APR or combined modality therapy should be performed when anal margin cancers invade into deep muscle or have vascular, lymphatic, or perineural involvement. A number of series have shown no benefit to the routine use of APR for anal margin tumors, but the small number of patients in these studies combined with patient selection bias makes interpretation of these data difficult.

**RADIATION THERAPY.** Squamous cell carcinoma of the anal margin tends to be early or only moderately advanced at the time of diagnosis. Although early cancers of the anal margin are successfully treated by local excision, nonoperative treatment should be considered for some patients. Papillon suggested that radiotherapy should be used for patients with anal margin carcinomas that are considered unresectable or patients who have extensive or recurrent lesions; in addition, patients who are medically inoperable may be able to have radiotherapy.

Early studies of therapy for anal margin cancers used interstitial radium needle implants; however, the high incidence of radionecrosis and the relatively poor geometry suggested that external-beam therapy was better tolerated. Although photons are most the frequent radiation treatment, electron-beam therapy may also be successfully used for early perianal epidermoid carcinomas. Results of radiation therapy for perianal lesions, stage for stage, are similar to results for anal canal lesions, with more extensive lesions requiring more aggressive therapy. Some authors have recommended APR for extensive lesions. Radiation therapy with or without chemotheraphy, however, appears to be an excellent alternative that yields a similar cure rate while offering sphincter preservation.

Selected series reporting the use of primary nonoperative therapy for anal margin cancers are seen in Table 33.9-7. Patients received radiation therapy (external beam with or without brachytherapy) or combined modality therapy. The numbers of patients in each series are small, making it difficult to make definitive conclusions. Combining the series, the overall local control rate is approximately 75% and the 5-year survival is 65% to 70%. In a retrospective analysis from Cummings, loca control with T1 and T2 disease was 100% compared with 60% for patients with T3 disease. Likewise, patients who received combined modality therapy had an 88% local control rate compared with 64% local control in patients who received external-beam radiation alone. Peiffert and associates reported the results of 32 patients who were treated with external-beam radiation, brachytherapy, or both. Patients with node-negative disease had a 100% 5-year survival compared with 40% 5-year survival in patients with node-positive disease.

**TABLE 33.9-7. Treatment of Anal Margin Cancer: Selected Series**

In a retrospective comparison of 54 patients with anal margin cancers with 216 patients with anal canal cancers treated with 40-Gy external-beam radiation plus bleomycin, Friberg et al. reported better results in patients with cancers of the anal margin versus anal canal. There was an improvement in 5-year survival (74% vs. 57%), tumor-specific survival (90% vs. 89%), relapse-free survival (65% vs. 54%), and the incidence of an intact sphincter (91% vs. 58%), respectively.

In summary, squamous cell carcinoma of the anal margin is uncommon, and the literature is limited by small numbers and the lack of a standard anatomic definition. A reasonable approach is to recommend a local excision for smaller tumors (smaller than or equal to 4 cm) that are not in direct contact with the anal verge. If the patient requires an APR due to anatomic constraints or if a local excision would compromise sphincter function, or if the tumor is larger than 4 cm, node positive, or both, then nonoperative treatment is an appropriate alternative. Based on the randomized trials from the EORTC or United Kingdom Coordinating Committee on Cancer Research (UKCCCR) revealing an advantage of combined modality therapy compared with radiation therapy alone in patients with anal canal cancers (EORTC) or anal canal and margin cancers (UKCCCR), combined modality therapy rather than radiation therapy alone is recommended.

**Anal Canal**

**LOCAL EXCISION.** Local treatment of epidermoid tumors of the anal canal is reserved for selected patients with tumors that are smaller than 2 cm in diameter, well-differentiated tumors, or tumors found incidentally at the time of hemorrhoidectomy. Local excision may also be performed for patients who are medically inoperable or who refuse a permanent colostomy.

Of 188 patients with anal canal carcinoma treated at the Mayo Clinic, 19 were treated with local excision. For the 12 patients with tumors confined to the epithelium and subepithelial connective tissues, 11 had tumors smaller than 2 cm in size and one patient had two lesions. Overall survival for these patients was 100%. One of 12 patients had a recurrence, and this patient was without evidence of disease 5 years after an APR. Patients with tumors penetrating into muscle who refused a colostomy had a higher recurrence rate. These patients’ disease often can be salvaged with an APR or combined modality therapy.

Results of local treatment for tumors smaller than 2 cm were not as favorable at Memorial Sloan-Kettering: Only three of eight patients with local excisions had prolonged survival. For more advanced lesions, high local recurrence rates and poor overall survival mitigate against the use of local excision.
COMBINED MODALITY THERAPY

Biopsy. With the advent of combined modality therapy, surgery for the initial diagnosis and staging of anal canal tumors should be limited to a biopsy of the primary tumor and evaluation of the inguinal lymph nodes. For most distal lesions, the biopsy is performed under local anesthesia. A punch or incisional biopsy obtains adequate tissue to make a histologic diagnosis. For patients with more proximal tumors or significant pain and spasm, the biopsy may require general anesthesia. Clinically enlarged lymph nodes should be aspirated. If the cytology is nondiagnostic or demonstrates only benign disease, an open excisional biopsy of one or two lymph nodes should be performed. Under no circumstances should a formal lymph node dissection be performed for the initial evaluation of suspicious nodes.

Therapy. Until the late 1970s, the conventional treatment for anal canal cancer was an APR. The landmark publication that challenged this practice was a report from Nigrò et al. of three patients with squamous cell cancer of the anal canal who, after preoperative 30 Gy plus concurrent 5-FU and mitomycin C, were found to have a pathologic complete response at the time of surgery.

Since that time, increasing evidence from single-arm phase II studies has indicated that initial combined modality therapy (chemotherapy plus concurrent external-beam radiation therapy) yields a high rate of tumor regression (including a complete response rate of approximately 80% to 90%) in most patients with squamous cell cancers of the anal canal. Surgery, most commonly an APR, is reserved for salvage. Even in patients with relatively large (larger than or equal to 5 cm) primary cancers, although the complete response rates are lower (50% to 75%), the majority of patients may be spared a colostomy and has an excellent overall survival.

Given that anal canal tumors are uncommon, and because the results of phase II trials using combined modality therapy are impressive, there has been, until relatively recently, no prospective, controlled randomized trials of combined modality therapy versus radiation alone or surgery alone. Results of two prospective randomized trials from Europe of combined modality therapy versus radiation alone (EORTC and UKCCCR) support the use of combined modality therapy. In the United States, combined modality therapy has been well established, and randomized trials focus on defining the ideal combined modality therapy regimen. For example, the Intergroup trial (RTOG 87-04/ECOG 1289) examined the role of adding mitomycin C to radiation plus 5-FU. It is unlikely that a prospective trial of surgery versus nonoperative therapy (combined modality therapy or radiation alone) will be performed. Combined modality therapy has an acceptable toxicity profile as well as a high disease-free and overall survival and is considered the standard of care for squamous cell carcinoma of the anal canal.

The results of two randomized trials that confirm an advantage for combined modality therapy using 45-Gy external-beam pelvic radiation plus continuous infusion 5-FU and bolus mitomycin C versus radiation alone are seen in Table 33.9-5. The UKCCCR trial randomized a total of 585 patients of whom 51% had T3 disease, 20% had positive nodes, and 23% had anal margin cancers. At 6 weeks after treatment, patients with 50% or greater response had additional radiation, whereas those with less than 50% response had salvage surgery. Although the improvement in 4-year survival with combined modality therapy did not reach statistical significance (65% vs. 58%), the improvement in crude (64% vs. 41%) and 3-year actuarial local control (61% vs. 29%) was significant. The early grade 4+ toxicity was significantly higher (48% vs. 39%); however, the incidence of late toxicity was similar (42% vs. 38%). In the EORTC trial, 110 patients, of whom 76% had T3 disease and 48% had positive nodes, underwent a similar randomization. At 6 weeks after treatment, patients with a partial or complete response had additional radiation, whereas those with less than a partial response had salvage surgery. Patients who received combined modality therapy had a higher complete response rate (80% vs. 54%) and a significantly higher 5-year actuarial local control rate (68% vs. 50%) and colostomy-free survival rate (72% vs. 40%). The overall survival rate was not significantly different (57% vs. 52%). Patients receiving combined modality therapy had a higher incidence of ulceration.

Although neither of the randomized trials revealed a significant advantage in overall survival with combined modality therapy, given the advantage in local control and colostomy-free survival, they helped to establish combined modality therapy as the standard of care in squamous cell cancers of the anal canal.

The Intergroup trial has established that mitomycin C is an important component of combined modality therapy. A total of 291 patients (47% with T3 disease and 17% with positive nodes) were randomized to 45 Gy plus continuous infusion 5-FU with or without mitomycin C. At 6 weeks after the completion of treatment, patients with less than a complete response had an additional 9 Gy to the primary tumor plus concurrent 5-FU and cisplatin. If there was still less than a complete response 6 weeks after the completion of this salvage therapy, an APR was performed. Patients who received mitomycin C had a higher complete response rate (92% vs. 85%) and a significantly lower colostomy rate (9% vs. 22%) and a corresponding significant increase in colostomy-free survival (71% vs. 59%). There was little difference in overall 4-year survival (75% vs. 70%). Early grade 4+ toxicity was significantly increased in the mitomycin C arm (23% vs. 7%). Although overall survival was not significantly increased given the advantage in colostomy-free survival, mitomycin C is considered a necessary component of combined modality therapy.

The combined modality therapy arm using radiation, 5-FU, and mitomycin C from the Intergroup trial is the most common treatment approach in the United States. Details are seen in Table 33.9-5. Patients received continuous course pelvic radiation to a total dose of 45 Gy (30 Gy to the whole pelvis followed by 15 Gy to the true pelvis) and two cycles (weeks 1 and 5) of concurrent continuous infusion 5-FU (1000 mg/m² days 1 through 4) and bolus mitomycin C (10 mg/m² bolus day 1). If 6 weeks following completion of the initial treatment there was persistent disease, patients received 1 week of salvage therapy. Salvage therapy involved one cycle of chemotherapy (continuous infusion 5-FU, 1000 mg/m²/1–4; bolus cisplatin, 100 mg/m² day 2) and concurrent 900 Gy (limited to the primary tumor). If there was residual disease on biopsy 6 weeks after the salvage therapy, then an APR was recommended.

There is considerable controversy as to the need for the first biopsy at 6 weeks after initial treatment. Data from the Princess Margaret Hospital suggest that squamous cell cancers of the anus regress slowly and continue to decrease in size for 3 to 12 months after the completion of combined modality treatment. Based on these data, an increasing number of investigators advocate a more conservative approach and do not recommend a posttreatment biopsy. In the Intergroup trial, of the 25 patients with biopsy residual disease after 45 Gy and 5-FU and mitomycin C who then received salvage therapy with 9 Gy plus 5-FU and cisplatin, 55% achieved a complete response 6 weeks later (a total of 12 weeks after the completion of the initial 45 Gy). It is unclear if the complete response was a result of the salvage therapy or was due to an additional 6 weeks of tumor regression after initial therapy.

At the Princess Margaret Hospital, Memorial Sloan-Kettering, and other centers, if there is residual disease at the 6-week posttreatment evaluation patients do not receive the 1 week of salvage therapy. The patients are examined every 6 weeks, and providing the tumor continues to decrease in size, no salvage therapy is performed. If there is progression of disease or no response at 6 weeks after initial therapy, however, APR is necessary. In addition to careful physical examination, anal ultrasonography may be helpful in following the tumor. In the current Intergroup phase III anal canal cancer protocol (RTOG 98-11) (Fig. 33.9-24), biopsy at 6 weeks after the initial 45 Gy is optional.

**FIGURE 33.9-2.** Intergroup phase III anal canal cancer protocol (RTOG 98-11). CDDP, cisplatinum; 5-FU, 5-fluorouracil; LN + and −, lymph node positive and negative; MMC, mitomycin C.
There are a subset of patients who, for a variety of reasons, undergo an excisional biopsy, such as a hemorrhoidectomory, polypectomy, or local excision, first and then are referred for definitive combined modality therapy. Because the margins may be either negative or at most microscopically positive, is full-dose radiation (45 Gy) necessary? Hu and colleagues treated eight patients after excision biopsy with 30 to 34 Gy plus 5-FU and mitomycin C. With a median follow-up of 81 months, the 5-year actuarial local control rate was 100% and the overall survival was 88%. Although the data are limited, they do suggest that combined modality therapy with 30 Gy plus 5-FU is effective. If given on day 1 or 2 of each cycle. If given, the second chemotherapy cycle usually begins on day 28. In those trials using cisplatin, it is substituted for mitomycin C at a bolus dose of 75 mg/m². The group from Humbolt University in Berlin has added regional hyperthermia to combined modality therapy. However, this approach remains investigational.

Combined modality therapy can be delivered concurrently or sequentially. In the concurrent regimen, radiation therapy and chemotherapy are initiated on the same day. In the sequential regimen, chemotherapy is given before the start of radiation therapy. Since the report from Miller et al. that reported a complete response rate of only 45% with sequential 5-FU, mitomycin C, and 30 Gy, almost all combined modality therapy trials have used concurrent chemoradiotherapy plus radiation. Although concurrent therapy is favored by many because the need for salvage APR appears lower, there are no randomized comparison trials. For certain subgroups of high-risk patients (e.g., large T4 tumors), induction chemotherapy followed by concurrent chemoradiotherapy and radiation to higher doses may prove to be a useful option. It is currently being tested in a single-arm Cancer and Leukemia Group B trial for advanced anal canal tumors. Combined modality therapy trials can be broadly divided into those that use either 5-FU and mitomycin C chemotherapy or, more recently, 5-FU and cisplatin chemotherapy.

Mitomycin C versus Cisplatin. Mitomycin C–based trials are shown in Table 33.9-3. When comparing the results, it is important to consider the percentage of patients with T3 disease, node-negative disease, or both. With the exception of the series by Miller et al., which used sequential chemotherapy, the mean (average) results include a complete response rate of 84% (81% to 87%), a local control rate of 73% (64% to 86%), and a 5-year survival rate of 77% (66% to 92%). These results are comparable with the 5-FU and mitomycin C–containing combined modality arms of the three randomized trials seen in Table 33.9-5. For patients with T1 and T2 disease, the complete response rates are in excess of 90%, with ultimate local control rates after surgical salvage of 80% to 90%. In patients with T3 and T4 disease, approximately 50% of patients require a salvage APR. If they achieve a complete response after the completion of combined modality therapy, then only 25% require a salvage APR.

The RTOG 92-08 trial included 47 patients, 49% with T3 and T4 and 89% with node-positive disease. The RTOG 92-08 pilot trial reported by Meropol et al. was limited to patients with T3 and T4 disease. With induction 5-FU and cisplatin and concurrent 5-FU and cisplatin plus radiation, the complete response rate was 80%, colostomy-free survival was 56%, and crude survival was 78%.

The Intergroup has developed a randomized trial (RTOG 98-11) to compare this approach with conventional 5-FU, mitomycin C, and 45 Gy (see Fig. 33.9-2). The Cancer and Leukemia Group B pilot trial reported by Meropol et al. was limited to patients with T3 and T4 disease. With induction 5-FU and cisplatin and concurrent 5-FU and cisplatin plus radiation, the complete response rate was 80%, colostomy-free survival was 86%, and crude survival was 78%.

Intensification of the Radiation Dose: External Beam. Retrospective data from the Massachusetts General Hospital, M. D. Anderson Hospital, and others suggest improved local control with increased radiation dose. In an attempt to improve local control and survival, two parallel pilot trials of radiation-dose intensification were designed. In both trials, patients received 36 Gy to the pelvis (30.6 to the whole pelvis plus 5.4 Gy to the true pelvis), and, after a 2-week break, received an additional 23.4 Gy to the primary tumor with a 2- to 3-cm margin for a total dose of 59.4 Gy. The main differences between the two trials was the type of chemotherapy. The RTOG 92-08 trial (see Table 33.9-3) used concurrent 5-FU and mitomycin C, whereas the ECOG 4292 trial (see Table 33.9-4) used 5-FU and cisplatin.

The RTOG 92-08 trial included 47 patients, 49% with T3 and T4 and 89% with node-positive disease. With a median follow-up of 21 months, the local failure rate was 19%, 4-year colostomy-free survival was 71%, and overall survival was 73%. Although the incidence of grade 3 to 4 toxicity (26%) was similar to a standard regimen of 45 Gy plus 5-FU and mitomycin C used in RTOG 89-04, the 2-year colostomy rate was higher (30% vs. 7%). The reason for the increase is unclear. The improved control may be related to the higher percentage of patients requiring a treatment break of longer than 2 weeks (96% vs. 12%). The ECOG 4292 trial entered 19 patients and reported a 68% complete response rate 8 weeks after the completion of 59.4 Gy and a 79% grade 3+ toxicity rate. In contrast, Pfieffer et al. and Gerard and colleagues treated patients with the boost given with either external-beam or brachytherapy and reported higher complete response rates (90% and 89%, respectively).

Intensification of the Radiation Dose: Brachytherapy. Brachytherapy is an ideal method by which to deliver conformal radiation for anal cancer while sparing the surrounding normal structures such as small intestine and bladder. Much of the initial experience with brachytherapy in anal cancer was from investigators in England and France who used radium needles. Due to radiation protection concerns and a high anal necrosis rate, afterloading catheters have replaced radium needles. However, it is not clear that it has a lower rate of complications.

Selected series that use brachytherapy as a component of treatment of anal cancer are shown in Table 33.9-4. In most series, patients received 30 to 55 Gy of pelvic radiation with or without 5-FU and mitomycin C or cisplatin followed by a 15- to 25-Gy boost with afterloading catheters. Most use low dose-rate, however, some investigators have advocated high dose-rate. There are biologic differences between low dose- and high dose-rate brachytherapy; however, at the present time there does not appear to be a difference in efficacy.

Combining the series, the mean results include a complete response rate of 83% (73% to 91%), local control rates of 81% (73% to 89%), and a 5-year survival rate of 70% (60% to 84%). The average complete response and local control rates appear similar to those achieved with external-beam–based combined modality therapy. Furthermore, the 5-year survival rates appear lower. Of equal concern is the increased incidence of anal necrosis. Reports of anal necrosis include those of Papillon et al. (2%), Gerard et al. (15%), Peiffert et al. (25%), and Roed et al. (76%). The incidence of severe complications included those of Sandhu et al. (8%), Wagner et al. (9%), and Allah et al. (12%).

A new technique of ultrasound-guided three-dimensional tumor reconstruction and brachytherapy has been reported by Lohrert and colleagues. In patients receiving more than 4 Gy fractions, the incidence of severe complications was 63%; however, none were seen when the dose was limited to less than 4-Gy fractions.

In summary, it is unclear if increasing the radiation dose in patients receiving combined modality therapy improves the results compared with conventional doses of 45 Gy to 50 Gy. Although there are no randomized data, the phase II trials suggest that even in experienced hands, brachytherapy is associated with higher complication rates than external-beam therapy.

The ideal combined modality therapy regimen and the most appropriate radiation dose to use for patients with anal canal tumors limited to the primary site have not yet been defined. At the present time in the United States, combined modality therapy with the RTOG combined modality therapy regimen of continuous-course radiation (45 Gy in 1.8-Gy fractions) plus two cycles of concurrent continuous infusion 5-FU on weeks 1 and 5, plus mitomycin C bolus on days 1 and 29, remains the standard of care. This is the control arm of RTOG 98-11 seen in Figure 33.9-2. For patients with T3 and T4 disease (primary tumors larger than 5 cm) it is reasonable to boost with an additional 5.4 to 9.0 Gy. In RTOG 98-11 the experimental arm uses the same design except it adds two cycles of induction 5-FU and cisplatin as well...
as 5-FU and cisplatinum (CDDP) during the radiation. The posttreatment biopsy at 8 weeks is now optional.

Radical Surgery. With the advent of multimodality therapy for the primary treatment of patients with anal canal tumors, the role of surgery is important mostly from an historic perspective. Because of the high propensity of anal canal tumors to recur locally, a wide perineal resection was initially proposed for treatment. If necessary, gluteal or perineal flaps were raised to cover the residual defect. Some authors advocated the resection of the posterior vaginal wall to obtain clear surgical margins, whereas others thought this to be unnecessary unless the rectovaginal septum was involved. Bilateral inguinal lymph node dissection was performed in patients undergoing radical surgical resection of their primary tumor until it was shown that prophylactic inguinal lymph node dissections were beneficial in only 6% of patients. The high morbidity with little gain led others to quickly condemn the use of this procedure. Combined modality therapy controls more than 90% of inguinal nodal disease. Recurrence develops in up to 40% of patients having an APR for primary treatment of anal canal tumors. The median time to recurrence is 12 to 15 months. Local recurrence is the rule, with the majority in the pelvis and the remainder in the inguinol or pelvic nodes. Distant metastases are less common but can be seen in up to 31% of patients. Greenall and colleagues observed a median survival of 10 months for patients with pelvic recurrence and 7 months with visceral metastases.

Overall survival did not improve dramatically after the advent of radical surgery. Five-year survival rates after APR for primary treatment range from 55% to 71%. Survival was adversely affected by the size of the primary tumor. In patients treated at Memorial Sloan-Kettering Cancer Center, 60% of patients with tumors smaller than 5 cm were alive at 5 years, whereas only 40% of those with tumors larger than 5 cm were alive at 5 years. Miller et al. improved overall survival from 55% in historic controls to 62% for patients treated with a preparative combined modality therapy regimen. Of equal significance was the preservation of anal function in the majority of patients treated with combined modality therapy.

Radiation Therapy Alone. There is a subset of patients who have been treated with radiation therapy alone. Because both the UKCCCR and EORTC randomized trials have shown a significant advantage to the combined modality arm for local control (UKCCCR) and local control and colostomy-free survival (EORTC), combined modality therapy is standard of care. However, external irradiation alone is a reasonable alternative for patients who cannot tolerate chemotherapy due to medical contraindications.

Age alone is not a contraindication to combined modality therapy. Although some elderly patients may not tolerate chemotherapy well, less aggressive treatment in patients older than 65 years old appeared to jeopardize their outcome in a Canadian retrospective study. Studies of combined modality therapy in patients 75 years old or older have been reported from both Valenti and colleagues and Allal et al. Rates of complete response, local control, and acute and long-term toxicity were similar to those reported for the general population. Although some chemotherapy dose attenuation and radiation field modifications may be needed, combined modality therapy in selected patients 75 years old and older should be considered.

Radiation Alone: External Beam. The results of major studies using external-beam radiation alone are seen in Table 33.9-8. The mean results include a local control rate of 74% (61% to 100%) and a 5-year survival rate of 63% (50% to 94%). Although the series of 18 patients from Martenson and Gunderson from the Mayo Clinic had the highest survival and local control rate, they also had a high rate of complications requiring surgery (17%). In most series, local control and survival decrease with increasing T stage. Overall, these results are comparable with those of patients who receive combined modality therapy with 45 Gy plus 5-FU and mitomycin C. However, the mean incidence of complications requiring surgery is 10% (range, 3% to 17%), which probably reflects the high radiation doses that must be delivered to the primary site to control this disease if radiation therapy is the sole treatment modality. Therefore, unless there is a compelling reason to avoid systemic chemotherapy in an individual patient, combined modality therapy should remain the standard of care.

**TABLE 33.9-8. Radiation Therapy Alone: Selected Series**

**Radiation Alone: Brachytherapy with or without External Beam.** Brachytherapy (interstitial radiation) alone has the potential of curing only early lesions that are unlikely to have spread to the lymph nodes. Historically, radium needles have been used, although interstitial implants with 192Ir are most common in modern series. Radium needles have been used for many years at the Christie Hospital in Manchester, England, for early anal cancers. Radium needles were the exclusive treatment modality in 74 patients, 43 with anal canal lesions and 31 with anal margin lesions. Of the 68 evaluable patients with minimum follow-up of 5 years, there were 35 locoregional failures, of which only seven were salvaged by surgery. Local control was achieved in only 64% of tumors smaller than 5 cm in diameter and in only 23% of tumors larger than 5 cm.

Radium needle implantation has also been used extensively by Papillon, but he has abandoned this technique because of painful local reactions and inability to achieve lymph node control because of the small target volume. Early studies with radium needles yielded a severe necrosis rate of approximately 25%.

Several studies with small numbers of patients have been reported in which external-beam radiation is combined with brachytherapy (173Cs, 192Ir, or radium needles). Good local control was achieved, but there was a relatively high rate of complications requiring surgery or leading to death.

The largest experience is from the Centre Leon Berard in which 221 patients with anal carcinoma were treated over a 15-year period with external-beam radiation therapy (45 Gy) followed by a dose of 35 Gy, followed by 2 months later by an additional 15 to 20 Gy with 192Ir implant. The investigators reported only a 3% rate of serious complications and achieved a 65% 5-year disease-free survival and a 79% locoregional control rate. Combined brachytherapy and external irradiation may be useful in treating extensive lesions. Another study from France confirmed a high 5-year survival rate (61%) and good local control (75%), but a 6% rate of complications requiring surgery. The importance of treating the inguinal nodes prophylactically was illustrated in this study. In 28 N0 patients, two had an inguinal recurrence, neither of whom had received inguinal irradiation. Both developed distant metastases and died of disease.

In summary, radiation therapy alone with either external-beam or combined with brachytherapy may yield comparable local control and survival rates with combined modality therapy. However, it is associated with increased complication rates. In contrast to combined modality therapy in which the complications are commonly acute (i.e., diarrhea, hematologic, skin, and nausea), the complications with radiation therapy alone usually involve anal necrosis requiring surgery. As seen in Table 33.9-6, similar toxicity has been reported in patients receiving combined modality therapy plus brachytherapy. Even in experienced hands, brachytherapy is associated with a moderate degree of anal necrosis and should be used with caution.

**RADINATION THERAPY TREATMENT TECHNIQUES**

A comprehensive discussion of techniques to decrease the toxicity of pelvic radiation, such as physical maneuvers, immobilization molds, dietary supplements and
radioprotectors, three-dimensional treatment planning, and other investigational approaches, is presented in Chapter 33.8 and is not discussed here. However, there are some general principles specific to the design and delivery of radiation for anal cancer that are presented in this chapter. Last, a caveat: Technique recommendations should be interpreted with caution. Radiation oncology, as with other medical specialties, is both an art and a science. Therefore, the recommendations made in this chapter should serve as a guide rather than a cookbook.

The design of pelvic radiation therapy fields for anal cancer is based on knowledge of the natural history of the disease and the primary nodal drainage. Because the internal iliac and presacral nodes are posterior in reference to the external iliac nodes, many of the normal structures in the anterior pelvis can be spared with the use of lateral fields. As this approach underdoses the inguinal nodes, they should be supplemented with electrons. Examples of field arrangements are seen in Figure 33.9-3.

FIGURE 33.9-3. Idealized treatment fields for a clinical T2N0M0 squamous cell carcinoma of the anal canal. The inguinal nodes are included in the posterolateral (PA) field and are supplemented with electrons.

PELVIC FIELD

A prone three-field technique (posterior plus opposed laterals) is recommended. This arrangement results in the lowest dose to the anterior structures such as the genitalia and bladder. The underdosed inguinal nodes are then treated concurrently with electrons to bring the dose up to 100% of the prescription dose. An alternative method is to use an anterior/posterior technique. Although this technique treats the pelvic and inguinal nodes in the same field, it results in the highest dose to the anterior pelvic structures and skin, thereby increasing toxicity. An electron boost for the perineum is not recommended as there will be overlap between the electron and photon fields. The portion of the perineum that needs to be treated should be included in the photon fields. The whole pelvis receives 30.6 Gy followed by a 14.4-Gy cone down to the true pelvis for a total dose of 45 Gy.

PRIMARY TUMOR BOOST FIELD FOR COMBINED MODALITY THERAPY SALVAGE AT 6 WEEKS

If the RTOG recommendations for combined modality therapy salvage are followed, then an additional 9 Gy (concurrent with 5-FU and cisplatin) are delivered. Using opposed laterals, the field includes the primary tumor plus a 2- to 3-cm margin in all directions. As an alternative, patients with T3 tumors can receive an additional 5.4 Gy to the primary tumor plus a 2- to 3-cm margin to a total dose of 50.4 Gy, which is delivered immediately after the 45 Gy of pelvic radiation.

MEDIAL AND LATERAL INGUINAL LYMPH NODES

After treatment of the pelvis in the prone position, the patient is treated in the supine position with electrons for inguinal nodes. The medial and lateral inguinal nodes are outlined with a 2-cm margin in all directions. The inguinal nodes are included in the posterior pelvic photon field. They receive only exit dose from this field, usually approximately 30% to 40% of the pelvic field prescription. This is determined from the treatment plan. Because they need to receive a total of 1.8 Gy/d, the remaining dose should be given concurrently with electrons. The depth of the inguinal nodes can be determined from a computed tomographic scan. If this is not available, then a clinical estimate may be used. If the inguinal lymph nodes are positive by biopsy, a four-field technique (anterior/posterior plus opposed laterals) is recommended as the external iliac nodes should be treated. In this setting, inguinal node dose should be 50.4 Gy.

COMPLICATIONS AND CRITICAL NORMAL TISSUES

As seen with other cancer therapies, pelvic radiation is associated with acute and long-term toxicity. Complications of pelvic radiation therapy are a function of the volume of the radiation field, overall treatment time, fraction size, radiation energy, total dose, and technique. Large field sizes, a short overall treatment time, large fraction sizes (greater than 2.0 Gy/d), orthovoltage or low-energy megavoltage radiation (Cobalt 60), doses of greater than 50.4 Gy when there is small bowel in the field, the use of an anterior/posterior technique, treatment of only one field per day, the use of a direct perineal boost field, and the lack of computerized dosimetry all contribute to an increased incidence of radiation complications. Critical normal tissues that should be considered in the treatment of anal canal cancer include bone marrow, rectum, small bowel, bladder, and skin. The acute toxicity is due to a combination of chemotherapy and radiation therapy. Toxicities include leukopenia, thrombocytopenia, proctitis, diarrhea, cystitis, and perineal erythema. It must be emphasized that even when pelvic radiation is delivered with appropriate doses and techniques, almost all patients receiving combined modality therapy for anal cancer develop acute grade 3+ toxicity requiring a treatment break at some point in their treatment courses. Approximately 1% develop long-term severe toxicity.

Unless there is a contraindication, the most simple techniques to decrease radiation toxicity, such as the use of small bowel contrast, multiple field techniques, high-energy linear accelerators, custom blocks, avoiding a direct perineal boost, and treatment in the prone position, should be part of the standard treatment of patients receiving curative pelvic radiation therapy. Any physical maneuver beyond the use of the prone position, such as a belly board, abdominal wall compression, or a full bladder, may be associated with patient discomfort, thereby leading to increased movement and daily setup errors.

Radiation therapy can affect sphincter function. There is an increasing body of literature reporting the effect of radiation therapy on functional results in rectal cancer. However, it is not directly applicable to anal cancer as patients do not undergo pelvic surgery. There are limited reports of functional outcome in the anal cancer literature. One series reports that full function was maintained in 93% of patients, and a second series that used anorectal manometry reported complete continence in 56%. Both series used brachytherapy as a component of therapy. It is hoped that new trials will include a functional analysis.

INGUINAL NODE INVOLVEMENT

When examining the effect of positive lymph nodes on local control and survival, it is important to differentiate the site of nodal disease as well as synchronous versus metachronous nodal disease. Most series do not separate N1 versus N2 versus N3 disease. However, there are data examining synchronous versus metachronous nodal disease.

Early experience from the 1950s from Stearns et al. suggested that patients with grossly positive inguinal lymph nodes synchronous with the primary tumor were incurable. A subsequent report indicated that 2 of 13 patients survived 5 years after an APR followed 6 weeks later by inguinal lymphadenectomy. Older studies also demonstrated a small cure rate for surgical treatment of patients with synchronous unilateral inguinal nodes. There are conflicting reports as to the prognosis of patients with synchronous nodal disease who are treated with combined modality therapy. Compared with node-negative patients, Allal et al. report a higher rate of local failure (N1 to N3, 36%, vs. N0, 19%). Although Cummings and associates from the Princess Margaret Hospital reported a local failure rate of only 13% in node-positive patients, 5-year cause-specific survival was lower (N1 to N3, 57% vs. N0, 81%). By multivariate analysis, the EORTC randomized trial reported that positive nodes were an independent negative prognostic factor for local failure and survival.
In contrast, in the series of combined modality therapy plus brachytherapy from Gerard et al., patients with N1 versus N0 disease had similar 5-year survival rates with progressive residual or recurrent disease. Likewise, complete response rates in the primary tumor are not affected by the presence of nodal disease. Doci and associates report similar rates in patients receiving cisplatin-based therapy (N1 to N3, 92%, vs. N0, 100%) and in a separate series of patients receiving mitomycin C–based therapy, eight of eight patients with N1 to N3 disease achieved a complete response. Overall, external-beam radiation alone can control positive nodes in 65% of patients, and combined modality therapy can achieve nodal control in approximately 90% of patients.

The current treatment recommendations for patients with positive inguinal nodes include biopsy followed by combined modality therapy with a boost of 45.0 to 50.4 Gy to the involved groin. Because the external iliac nodes should be treated in the pelvic radiation field, a four-field technique is recommended. Inguinal node dissection should not be performed as part of the initial therapy; however, it may be done for isolated inguinal recurrence.

The development of unilateral metastatic inguinal lymph nodes does not carry such an ominous prognosis. After therapeutic groin dissection, the 5- to 7-year survival rates exceeded 50% in two series, but it was 0% in a small series reported from the Mayo Clinic. Current strategies in patients with metastatic isolated inguinal node metastases after combined modality therapy include a formal groin dissection followed by chemotheraphy. The use of radiation under these circumstances depends on prior dose and fields.

**RESIDUAL OR RECURRENT CANCER**

**ANAL MARGIN**

Locally recurrent anal margin cancers are more successfully controlled by local excision than are recurrences of anal canal cancer. The largest reported series of recurrent tumors included 16 of 48 patients who, after a local excision, had local recurrences (11), in the inguinal nodes (4), or both (1). There were no visceral failures. The median time to recurrence was 26 months. Ten of the patients with local recurrences underwent repeat local excision, and only one required an APR. Nine of these patients survived longer than 5 years. All patients with inguinal node recurrences had inguinal lymphadenectomies, and two were long-term survivors. Although there is little reported experience with radiation therapy or combined modality therapy for patients with local recurrence after a local excision, it is a reasonable option for patients who would otherwise require an APR.

**ANAL CANAL**

After primary treatment of anal canal tumors with combined modality therapy, patients should be evaluated for response to therapy. This is usually done 4 to 6 weeks after the completion of therapy, but Nigro recommended waiting for 8 weeks and Cummings et al. recommended at least 8 to 12 weeks. Depending on the initial T stage and how soon the biopsy is performed after the completion of combined modality therapy, persistent disease is found in 10% to 25% of patients.

Controversy exists concerning the appropriate definition and management of patients with residual disease after combined modality therapy. Whether one waits 6 or 30 weeks after the completion of therapy, if the tumor continues to decrease in size, it has been hypothesized that the cancer is in the process of responding to the therapy and therefore is not a treatment failure. Selected patients with microscopic foci of tumor may undergo local excision of persistent disease. Therefore, patients who undergo salvage APR or further combined modality therapy within 6 weeks after the completion of initial therapy may be treated unnecessarily. Patients with progressive residual microscopic or gross disease are candidates for either an APR or additional combined modality therapy. There are no randomized trials to suggest which of these two alternatives are superior. APR is the most frequently reported salvage therapy, with 5-year survival rates of 30% to 50%. However, there are also reports of successful long-term salvage with combined modality therapy. Because there is a maximum radiation dose that pelvic structures can safely tolerate, the decision to give additional radiation depends on careful review of the radiation fields and dosimetry.

A retrospective, nonrandomized study of patients from all of the Veterans Administration hospitals suggested that salvage surgery was superior to salvage with chemotherapy either with or without radiation therapy, with a 53% salvage rate with surgery compared with only 19% for the conservative attempts. Nigro and others recommend a second course of combined modality therapy for patients with macroscopic disease, and several have been salvaged with this therapy. If local failure occurs after a second course of combined modality therapy and there is no evidence of extrapelvic disease, then an APR should be done.

In the RTOG randomized study, discussed in the section Combined Modality Therapy, biopsy was performed on most patients after their initial therapy. For those with positive biopsy results, salvage chemotherapy using cisplatin and 5-FU and localized boost radiation were given. Of the 27 patients who received this salvage regimen, 24 underwent biopsy after its completion. Of these, 12 (50%) had a negative biopsy result, and five of these had no further surgery after a minimum of 3 years of follow-up. This indicates that at least some patients can have sphincter-preserving treatment despite failure to achieve a complete remission with first-line therapy.

In a French study, local failure after radiation therapy alone occurred in 50 patients of whom 28 subsequently underwent salvage APR. Local tumor control was obtained in 12 of 26 patients (46%), and the 5-year survival was 56%. Similar local control rates and overall survival were found in 24 patients treated with APR after failure with combined modality therapy at Memorial Sloan-Kettering Cancer Center. Others have not had such good results with salvage APR.

The literature is confusing as investigators have used varying definitions of persistent and recurrent disease. Two series from France used different definitions of persistent versus recurrent disease and reported conflicting results. When persistent disease was defined as a recurrence up to 6 months after combined modality therapy, surgical salvage with APR improved survival. In contrast, when recurrent disease was defined as any recurrence after a clinical complete response, regardless of the disease-free interval, patients with recurrent disease had survival rates superior to those with persistent disease. In this series, of the 27 patients who underwent salvage surgery for local failure after combined modality therapy, only 44% died of disease.

It must be emphasized that patients should be followed closely by digital rectal examination and anoscopy (every 6 to 12 weeks) until a complete clinical response is documented. Any local progression of disease should be defined and treated as early as possible.

**METASTATIC DISEASE**

Because primary combined modality therapy has been so effective, the number of patients with this uncommon malignancy who developed advanced metastatic disease is small. Perhaps as a result, the number of chemotherapeutic agents that have been tested in patients with advanced anal canal cancer is small and the reports are anecdotal.

Single-agent trials of doxorubicin (Adriamycin) and of cisplatin have been reported by several investigators. Fischer and colleagues reported a response to both doxorubicin as a single agent and cisplatin at a dosage of 2 mg/kg in an elderly man with advanced disease. Salem and coworkers studied cisplatin as a single agent in three patients: One achieved a complete response and the other two had partial responses. Earlier trials with 5-FU and vincristine in small groups of patients were ineffective. Bleomycin and vincristine were used by Livingston and colleagues in a single patient, and a partial regression was observed.

Combination chemotherapy with cisplatin and 5-FU in patients with advanced disease has now been reported in small groups of patients. Responses have been reported using both systemic and regional (hepatic-arterial) routes. Of a total of six patients described in three reports, three complete and three partial responses were noted. In a study from France using this combination and involving seven patients with local recurrence alone and 13 patients with metastasis, there were two complete and nine partial responses. In one study, three of eight patients achieved a complete clinical response with cisplatin and fluorouracil, of whom two were 5-year survivors.

A noncisplatin regimen was used by Wilking and colleagues. A total of 15 patients with advanced disease received bleomycin, vincristine, and high-dose methotrexate. Major objective regressions were seen in 3 of 12 patients with measurable tumors, but their duration of response was only 1 to 5 months. Toxicity was severe, with four patients having probable treatment-related deaths. McGill and Quan treated 24 patients using cisplatin, bleomycin, and alkaidox. Six of 21 evaluable patients (29%) responded. Carboplatin has also been reported to have activity in this disease.

Although response rates in patients with metastatic disease are difficult to evaluate in view of the paucity of data, the use of neoadjuvant (induction) therapy has
allowed an assessment of the effectiveness of chemotherapy alone without the confounding variable of concurrent radiation in larger groups of patients. Most more recent regimens involve the use of a platinum compound with 5-FU. Peffert et al. reported the preliminary results of a trial involving induction cisplatin plus 5-FU chemotherapy for tumors followed by combined modality therapy. In a group of 26 evaluable patients, 72% had complete or partial responses from neoadjuvant chemotherapy alone. The regimen used was cisplatin, 80 mg/m² on day 1, followed by a 4-day continuous intravenous infusion of 5-FU at 800 mg/m². Other investigators have reported similar findings.

At the present time, therefore, cisplatin plus 5-FU–containing combinations appear to have a high degree of activity in patients with anal canal tumors whether used in metastatic disease or as part of induction therapy for advanced local regional disease. The high cure rate seen with primary combined modality therapy may slow the identification of newer agents. The use of agents with high degrees of activity in other squamous cell malignancies as part of a neoadjuvant approach may be a strategy to identify newer agents in this disease.

FOLLOW-UP

Close observation of patients after treatment of anal cancer is essential, because patients with local failure are amenable to resection and may be salvaged with long-term survival. The majority of recurrences occur within the first 3 years, and patients should be examined by physical examination and anoscopy every 6 to 12 weeks until a complete response is achieved, then every 3 months for a total of 2 years. Follow-up examinations can then be decreased to every 6 months for the next 3 years and then annually thereafter. The usefulness of computed tomography of the abdomen and pelvis for follow-up is unclear. Transectal ultrasound may be of value. It must be emphasized that because the most common site of failure is at the primary tumor site, there is no substitute for physical examination. In a limited series of 33 patients, Peterson and colleagues reported a 76% sensitivity, 86% specificity, and a 62% positive predictive value of squamous cell carcinoma tumor–associated antigen.

ANORECTAL MELANOMA

Anorectal melanomas are relatively rare, accounting for less than 1% of all anal canal tumors. The patients present with nonspecific complaints, which are often attributed to hemorrhoids conditions, and the correct diagnosis is seldom made accurately at the initial examination. This delay may be responsible for the advanced stage seen in most at diagnosis. The stage (tumor thickness and nodal status) at presentation is the primary determinant of survival, and distant metastasis is common.

Clinical presentation and pathologic features

Anorectal melanomas are slightly more common in women, and the median age at presentation is in the sixth decade. Most patients present with bleeding as the initial complaint, which is often attributed to hemorrhoids. Symptoms are often present for 1 to 3 months before evaluation and also include pain, tenesmus, pruritus, change in bowel habits, and weight loss. An initial error in diagnosis has been reported in up to 80% of patients. The usefulness of computed tomography of the abdomen and pelvis for follow-up is unclear. Transectal ultrasound may be of value. It must be emphasized that because the most common site of failure is at the primary tumor site, there is no substitute for physical examination. In a limited series of 33 patients, Peterson and colleagues reported a 76% sensitivity, 86% specificity, and a 62% positive predictive value of squamous cell carcinoma tumor–associated antigen.

Patterns of spread

Anorectal melanomas spread locally by direct extension upward in the submucosal plane of the rectum, but they seldom invade bladder, vagina, sacrum, or prostate. Regional spread via the lymphatic channels is superiorly to the mesenteric system or laterally to the inguinal system. Inguinal nodes are present in 20% of patients, and mesenteric nodes are involved in up to 65% of patients undergoing radical surgery. Hematogenous spread is found in up to 29% of patients at diagnosis and overall in up to 69% of patients. Distant metastasis is most common in the lungs, liver, and bone.

Treatment and outcome

The classic surgical approach for the treatment of anorectal melanoma was APR with pelvic lymph node dissection and bilateral groin dissection. Because those with inguinal nodes uniformly die of this disease, this part of the procedure is no longer performed. Because of the high systemic failure rate, several authors have questioned the wisdom of radical surgery and have advocated wide local excision for treatment of this disease. In the early reports from Memorial Sloan-Kettering Cancer Center, the only long-term survivors were patients who had undergone an APR with or without lymphadenectomy. Similar results were found at the Mayo Clinic. Siegel and colleagues had two long-term survivors treated with local excision and chemotherapy, and the M. D. Anderson group had one survivor at 5 years who was treated with wide local excision alone. Despite a better local control rate with APR, no series has shown a survival advantage for patients who had an APR compared with patients having wide local excision. However, none of these studies was randomized, thus lending potential bias in favor of local excision, which was usually performed for smaller lesions.

Several factors have been analyzed to determine their effect on outcome. Age and race are the only factors that have consistently been shown not to affect overall survival. Size was not an important factor in the results from the study by Quan et al., but had a direct effect on survival in the study by Goldman and colleagues. Tumor thickness is the most important factor in determining outcome for cutaneous melanomas. Wanebo and colleagues noted three survivors at 5 years; all had tumors less than 2 mm thick, and all were treated with an APR. Of the patients with tumors larger than 2 mm, none lived 5 years, and 85% were dead by 2 years. Another study noted three long-term survivors who had anorectal melanoma discovered incidentally at the time of hemorrhoidectomy. Of the 18 patients with mesenteric lymph node metastases, there was only one long-term survivor. Female gender is associated with a better prognosis.

The inability of several authors to show a survival benefit for APR compared with wide local excision can be entirely attributed to the small numbers of patients involved in the studies, selection bias, and the lack of the scientific method. Any relative advantage of adjuvant immunotherapies, chemotherapy, and radiation therapy is similarly obscured and difficult to interpret. Treatment recommendations must therefore be less than absolute. A histologic margin of at least 3 mm should be obtained if local excision is to be used. In view of probably higher local control rates, APR can still be recommended. However, none of these studies was randomized, thus lending potential bias in favor of local excision, which was usually performed for smaller lesions.

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Adenocarcinoma

Primary adenocarcinoma of the anal canal arising from the anal glands is a rare tumor. Most adenocarcinomas in the canal represent rectal cancer with downward spread. In general, they should be treated like adenocarcinomas of the rectum, including APR, and if T3 disease, node-negative disease, or both exist, six cycles of adjuvant chemotherapy with 5-FU, weekly irinotecan, and/or postoperative concurrent radiation therapy are given. However, the radiation fields should include the inguinal nodes. Basik and colleagues treated ten patients with surgery and reported a median survival of 29 months.

Adenosquamous cancers of the anus are also rare and have an equally poor prognosis. Given the squamous component, it is reasonable to treat these patients with combined 5-FU and mitomycin C and concurrent radiation therapy. If there is residual disease, this would be followed by a salvage APR.

Sarcoma

Leiomysarcomas of the large intestine are unusual neoplasms, accounting for less than 0.1% of all malignancies of the colon and rectum. Few cases of leiomyosarcoma of the anus have been reported. The optimal treatment for this neoplasm is not known. The standard surgical approach is APR. Using a technique well established for management for sarcomas of the extremities, Minsky et al. have treated several patients using local excision and 131I brachytherapy in an attempt to preserve the anal sphincter. This technique may be an alternative to APR in selected patients.

Treatment of the Human Immunodeficiency Virus–Positive Patient
Given the 40- to 80-fold increase of anal cancer in the HIV-positive population compared with the general population, HIV-positive patients have received lower doses of radiation and chemotherapy due to a concern that standard therapy may not be tolerated. With a better understanding of the immunologic deficits seen in HIV-positive patients, more recent reports have recommended therapy based on clinical and immunologic parameters such as a history of prior opportunistic infections and CD4 counts.

Hoffman and associates treated 17 HIV-positive patients with a median of 51.8 Gy plus concurrent 5-FU and mitomycin C. With a median follow-up of 17 months, the nine patients with CD4 counts greater than 200 µL were all without evidence of disease with acceptable toxicity. In contrast, of the eight patients with a CD4 count less than 200 µL, four had grade 4 toxicity for toxicity or local failure. Despite the increase in morbidity, the disease of seven (88%) was locally controlled after salvage surgery. They recommend treating HIV-positive patients with standard doses of combined modality therapy but minimizing the radiation fields in patients with CD4 counts less than 200 µL. Similar results were reported from Peddada et al., who treated eight HIV-positive patients with 30 Gy plus concurrent 5-FU and mitomycin C. The four with a CD4 count less than 200 µL, three of four developed grade 4 toxicities, whereas one of the four with a CD4 count greater than 200 µL had grade 4 toxicity. However, all achieved a complete response. With a median follow-up of 38 months, four are alive without evidence of disease, and of the four who died of HIV-related complications, all had no evidence of anal cancer at the time of death. In another report, four HIV-positive patients without evidence of other HIV-related diseases received combined modality therapy. Only one patient required a treatment break.

Management of the HIV-positive patient is complex and requires careful attention to all aspects of the patient's medical history, coexisting medical conditions, and personal wishes. The limited experience suggests that in patients with a CD4 count greater than 200 µL who do not have signs or symptoms of other HIV-related diseases, aggressive combined modality therapy is appropriate. They should be followed carefully, however, and frequent modifications during therapy will likely be necessary. For those patients with a CD4 count less than 200 µL or who have signs or symptoms of other HIV-related diseases, attenuated doses of radiation, chemotherapy, or both are recommended at the start of treatment.

FUTURE DIRECTIONS

PREVENTION AND EARLY DETECTION

Accumulating evidence has implied HPV as a causative and perhaps necessary factor in the development of squamous cell carcinoma of the anus. Because this is the most common histology, anal cancer may represent a preventable disease as is the case for cervical carcinoma. Both in women and in men (particularly homosexual men), the use of condoms to stem the spread of AIDS, may also affect the development of anal cancer. Early detection and screening in high-risk individuals (such as the use of anal cytology in male homosexuals and immunosuppressed patients) should be encouraged to diagnose the tumor at the earliest possible stage. The use of antiviral agents in patients with HPV infection may be another method for decreasing incidence of this disease. If the tumor is not diagnosed at a stage early enough to allow surgical resection (the majority of cases), new approaches involving combined modality therapy have clearly been demonstrated to offer equivalent or better results when compared with an APR. APR should be reserved for patients failing to respond to combined modality therapy. New efforts aimed at finding better chemotherapeutic regimens for the higher risk (T4 and node-positive) tumors are underway. In addition to the new nononcotypic agents capable of curative treatment without the toxicities of chemoradiation therapy should be explored.

CHAPTER REFERENCES

SECTION 34.1
Molecular Biology of Genitourinary Cancers

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Kidney Cancer: Location of a Renal Carcinoma Gene

Knudson's two-hit model was the model for scientists searching for the clear cell renal carcinoma gene. In accord with Knudson's model, both copies of the gene for the hereditary form of renal carcinoma associated with von Hippel-Lindau disease (VHL), hereditary papillary renal carcinoma (HPRC), and hereditary clear cell renal carcinoma are inactivated in renal carcinomas from VHL patients (germinal inactivation of the VHL gene plus a somatic inactivation of the VHL gene). In sporadic (nonhereditary) clear cell renal carcinoma somatic inactivation of both copies of the VHL gene has been detected in the majority of tumors. In sporadic renal carcinomas, the incidence of renal carcinoma is seen in dialysis patients with acquired cystic disease, in which a rate 30 times higher than normal has been estimated. A family history of this malignancy has been associated with an increased risk of developing of renal carcinoma.

Knudson's two-hit model was the model for scientists searching for the clear cell renal carcinoma gene. In accord with Knudson's model, both copies of the gene for the hereditary form of renal carcinoma associated with von Hippel-Lindau disease (VHL), hereditary papillary renal carcinoma (HPRC), and hereditary clear cell renal carcinoma are inactivated in renal carcinomas from VHL patients (germinal inactivation of the VHL gene plus a somatic inactivation of the VHL gene). In sporadic (nonhereditary) clear cell renal carcinoma somatic inactivation of both copies of the VHL gene has been detected in the majority of tumors. In sporadic renal carcinomas, the incidence of renal carcinoma is seen in dialysis patients with acquired cystic disease, in which a rate 30 times higher than normal has been estimated. A family history of this malignancy has been associated with an increased risk of developing of renal carcinoma.

Like colon cancer, breast cancer, and retinoblastoma, renal carcinoma occurs in both a familial (hereditary) and sporadic (nonhereditary) form. It has been estimated that up to 4% of renal carcinomas may have a hereditary basis. At least four types of hereditary renal carcinoma have been categorized: renal carcinoma associated with von Hippel-Lindau disease (VHL), hereditary papillary renal carcinoma (HPRC), hereditary renal carcinoma associated with Birt-Hogg-Dubé syndrome, and hereditary clear cell renal carcinoma.

VHL disease is a hereditary cancer syndrome with an autosomal dominant inheritance pattern in which affected individuals develop tumors in a number of organs, including the kidney. HPRC is a newly described form of inherited renal carcinoma in which affected individuals develop multifocal, bilateral, early-onset papillary renal carcinoma. Birt-Hogg-Dubé syndrome is a dominantly inherited cancer syndrome in which affected individuals are at risk to develop cutaneous, renal, and other manifestations. The cutaneous manifestation involves filiform comedones; the kidney tumors can be chromophobe renal carcinoma, oncocytoma, or papillary renal carcinoma.

LOCATION OF A RENAL CARCINOMA GENE

The initial studies to provide information with reference to a potential location for a renal carcinoma gene came from the work of Cohen and coworkers, who in 1979 reported a kindred in which affected individuals developed early-onset, bilateral, multifocal clear cell renal carcinoma. In this family, every member who developed renal cancer had a germline abnormality detectable on karyotypic analysis, a balanced translocation from the short arm of chromosome 3 to the long arm of chromosome 6. This led Cohen and coworkers to study this family in more detail.

In the fourth, but less well understood form of inherited renal carcinoma, hereditary clear cell renal carcinoma, patients have a predisposition to develop bilateral, multifocal clear cell renal carcinoma.

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ABNORMALITIES IN SPORADIC CLEAR CELL RENAL CARCINOMA

These mutations in hereditary renal carcinoma led scientists to study nonhereditary renal carcinoma to determine if changes on chromosome 3 were also present in sporadic cases. When Zbar et al. studied tumor tissue from 18 patients with sporadic, nonhereditary renal carcinoma by restriction fragment polymorphism analysis, loss of heterozygosity (LOH) on the short arm of chromosome 3 was detected in tumor tissue from 11 of 11 evaluable patients. LOH was detected in tumor tissue from patients with localized as well as advanced disease, suggesting the presence of a gene involved in the earliest development of this neoplasm. To more precisely define the prevalence of chromosome 3p LOH in sporadic renal carcinoma, as well as the location of a candidate gene for renal carcinoma, Anglard et al. analyzed...
DNA from normal and tumor tissue from 60 patients with various stages of renal carcinoma for losses of alleles at different chromosomal loci. LOH that was independent of tumor stage was detected at one or more of ten loci tested on chromosome 3 in tumor tissue from nearly 90% of patients. LOH was detected in clear cell renal carcinoma but not in papillary renal carcinoma. These findings and those of others showed deletion of a segment of chromosome 3p to be a consistent finding in clear cell renal carcinoma. 

Although these findings pointed to the presence of a renal carcinoma gene on the short arm of chromosome 3, the chromosome 3p area of minimal deletion in the renal tumors was too large to search by conventional cloning strategies available at the time. This then led investigators to initiate studies of the familial form of renal carcinoma associated with VHL disease, with the supposition that the gene for VHL may be involved in the sporadic form of renal carcinoma.

**HEREDITARY RENAL CARCINOMA (VON HIPPEL-LINDAU DISEASE)**

VHL disease is a familial cancer syndrome in which affected individuals develop tumors in a number of organs, including kidney, cerebellum, spine, eyes, pancreas, adrenal glands, inner ear, and epididymis. Patients with VHL disease often develop early-onset, bilateral, multifocal renal carcinoma and multiple renal cysts.

Frequently, renal tumors are found growing inside the renal cysts. The renal carcinoma in VHL patients is uniformly clear cell renal carcinoma. It has been estimated that up to 600 clear cell renal carcinomas and 1100 benign or atypical cysts may be found per kidney in an affected VHL patient. These kidney cancers are sporadic and have been reported to metastasize in up to 40% of untreated patients. The cerebellar and spinal hemangioblastomas are multifocal and marked by extreme vascularity. Although these central nervous system tumors are noninvasive, they can cause significant morbidity. The renal angiomata can be the first clinical manifestation of VHL. These benign, hypervascular renal tumors can be detected as early as 1 year of age. One identified manifestation of VHL is a tumor that develops in the endolympathic sac of the inner ear. These papillary tumors are low-grade malignancies that rarely metastasize but can invade locally. VHL patients can develop islet cell tumors of the pancreas and pancreatic cysts. The islet cell tumors are rarely functional; however, they can be malignant and can spread.

Eighteen percent to 20% of VHL patients develop pheochromocytomas. These tumors can be bilateral or extraadrenal and can be malignant. The epididymal cystadenomas that VHL patients develop are frequently bilateral and are uniformly benign.

**Figure 34.1-2.** Physical (A) and genetic (B) map of the von Hippel-Lindau (VHL) region which was used to identify the VHL gene. cDNAs, complementary DNAs; Cen., centromere; Tel., telomere. (From ref. 39; with permission.)

**Localization of the von Hippel-Lindau Gene to Chromosome 3**

To identify the VHL gene, studies were carried out to perform genetic linkage analysis on chromosome 3p. The VHL gene was initially mapped to a 6- to 8-centimorgan (cm) region of chromosome 3 at 3p25-26. Subsequent multipoint linkage analysis localized the VHL gene to a 4-cM interval at 3p26 between RAF1 and the anonymous marker D3S18. No evidence for genetic heterogeneity was identified. However, early evidence was found for clinical heterogeneity; kindreds with different tumor phenotypes were identified. The VHL gene was found to have characteristics of a tumor suppressor gene. Tory et al. studied VHL renal carcinomas and showed loss of the chromosome 3p, which carried the wild-type allele of the VHL gene. Knudson's model and the finding of frequent LOH in sporadic renal carcinoma suggested that inactivation of both copies of the VHL gene was an early step in renal carcinogenesis.

**Figure 34.1-3.** A: Distribution of von Hippel-Lindau (VHL) gene mutations in clear cell renal carcinoma (lower panel) and in the germline of patients with VHL disease (upper panel). (Adapted from refs. 40 and 44.) B: Clear cell renal carcinoma is characterized by mutation of the VHL gene.

**Identification of the von Hippel-Lindau Gene**

A critical step in identification of the VHL gene was the finding by Yao et al. and Richards et al. of overlapping germline deletions in unrelated VHL kindreds. The detection of these nested germline deletions in the VHL kindreds was crucial for detection of candidate complementary DNAs for the VHL gene. In 1993, Latif et al. reported the identification of the VHL gene. In the initial report, rearrangements of the VHL gene were detected in 28 of 221 VHL kindreds. Eighteen of the rearrangements were due to deletions of the VHL gene, including three nonoverlapping deletions. Intragenic mutations that segregated with the disease were detected in three VHL kindreds. The initial sequence of the VHL complementary DNA revealed a short open reading frame encoding only 284 amino acids, the remainder representing a large 3' untranslated region of the gene. Neither the predicted amino acid nor the nucleotide sequences showed any significant homology to proteins or genes in the databases.

**Genotype and Phenotype Correlations: von Hippel-Lindau Subtype Classification**

In the initial studies, Chen et al. detected mutations in 85 of 114 families (75%). Stolle et al. developed an improved method for detection of germline mutations in the VHL gene and reported detection of germline mutations in the VHL gene in 99% of VHL families tested. Striking correlations were noted between the germline mutations and the clinical phenotype. VHL families are classified as VHL type 1 (families without pheochromocytoma) and VHL type 2 (families with pheochromocytoma). Whereas 56% of the mutations associated with VHL type 1 were insertions or microdeletions, nonsense mutations, or length mutations, 96% of the mutations associated with VHL type 2 were missense mutations. Crosse et al. detected missense VHL gene mutations in 9 of 11 families with pheochromocytoma, and large deletions or mutations predicted to cause a truncated protein in 36 of 53 families without pheochromocytoma. When Zbar et al. analyzed mutations in 473 families from North America, Europe, and Japan, germline mutations were detected in 299 of 473 families (63%) tested. Mutations predicted to produce full length, mutant VHL proteins were detected in 89% of VHL families with pheochromocytoma with mutations detected. A mutation hot spot was identified at a CpG island in codon 167, where 12% of the mutations were found. The codon 167 mutations were associated with a phenotype characterized by few to
no renal carcinomas and frequent pheochromocytomas. Thus, three distinct cancer phenotypes are associated with germline VHL gene mutations: (1) VHL type 1 (VHL without pheochromocytoma), (2) VHL IIA (pheochromocytomas, retinal angiomas, and central nervous system hemangioblastomas), and (3) VHL IIB (VHL IIA plus renal cancers and pancreatic involvement) (Fig. 34.1-4).

**FIGURE 34.1-4.** A. Hereditary papillary renal carcinoma (HPRC) is an autosomal dominant inherited cancer syndrome characterized by the appearance of bilateral, multifocal papillary renal carcinoma. B. The renal tumors are uniformly of papillary histologic pattern. C. The gene for HPRC, c-Met, is located on the long arm of chromosome 7.321 Activating mutations of the c-Met gene are detected in the germline of affected individuals. (From refs. 320 and 74, with permission.)

**VON HIPPEL-LINDAU GENE MUTATIONS: CLEAR CELL RENAL CARCINOMA**

To determine the role of the VHL gene in renal carcinoma, Gnarra et al. analyzed tumors and cell lines from 110 patients with sporadic, nonfamilial renal carcinoma for VHL mutations and LOH. LOH was detected in 98% of the samples, and VHL gene mutations were observed in 57% of clear cell renal carcinomas analyzed. VHL gene mutations were not detected in tumor tissue from patients with papillary renal carcinoma or with lung, breast, ovarian, cervical, prostate, or colon cancers. The somatic VHL mutations differed from the germline mutations in that a higher percentage of somatic mutations clustered in exons 2 than were detected in the germlines. VHL gene mutations were found in early- and late-stage clear cell renal carcinomas, and when multiple samples were tested from the same patient, the identical mutation was found. Shuin et al. detected somatic mutations in 56% of primary renal carcinomas and an 84% LOH of the VHL gene. Whaley et al. detected somatic VHL in renal carcinomas and no mutations in more than 180 sporadic tumors of other types. VHL gene mutations have been identified in clear cell renal carcinomas in Europe, Japan, and North America. VHL gene mutations also have been detected in tumor tissue from patients from the 3:8 translocation family described by Cohen et al. and from tumor tissue from patients with 2:3 translocations, further supporting the conclusion that the VHL gene has an important and specific role in clear cell renal carcinoma.

Silencing of the von Hippel-Lindau Gene by DNA Methylation in Renal Carcinoma

Herman et al. demonstrated that hypermethylation of a normally unmethylated CpG island in the 5′ region of the VHL gene provides another important mechanism for inactivation of the VHL gene in a significant portion of clear cell renal carcinomas. In 5 of 27 (19%) of the renal tumors evaluated, hypermethylation of the VHL gene was found. The VHL gene is expressed normally in both nonneoplastic kidney and in renal carcinomas with inactivating VHL gene mutations. However, as would be predicted as a consequence of methylation of a 5′ CpG island, none of the five renal tumors expressed the VHL gene. When one of the renal carcinoma cell lines with a hypermethylated (and silent) VHL gene was treated with the hypomethylating agent 5-aza-2′deoxycytidine, the VHL transcript was reexpressed, revealing that methylation of the gene was associated with nonexpression. Further studies are needed to determine the prevalence of hypermethylation of the VHL gene in sporadic clear cell renal carcinomas and the potential role of such hypomethylating agents as 5-aza-2′deoxycytidine.

The VHL Gene Has the Characteristics of a Tumor Suppressor Gene

Studies of the genetics of VHL and the VHL gene in sporadic renal cell carcinoma have determined that this kidney cancer gene fits Knudson's two-hit model for a tumor suppressor gene. In tumors from VHL patients and from patients with sporadic renal cell carcinoma, a frequent loss of the nonmutant allele is noted, demonstrating that both copies of the VHL gene are inactivated in these tumors.

CHARACTERISTICS OF THE VON HIPPEL-LINDAU TUMOR SUPPRESSOR GENE PRODUCT

The von Hippel-Lindau Product Is Part of a Multifunctional Complex

When the VHL gene was identified, no significant homology was identified with any known genes. The rat homologue is 88% identical to human VHL; however, it lacks the human protein's NH2-terminal acidic pentamer repeat. Duan et al. determined that the rat and human VHL proteins formed oligomeric complexes with a number of unidentified proteins in cultured mammalian cells. A complex containing proteins of apparent molecular masses of 9 and 16 kD and VHL was the most consistently observed. When certain naturally occurring VHL missense mutations were introduced into the VHL gene in COS-7 cells, complete or partial loss of the p16–p9 complex was observed. When the p16 and p9 proteins were purified and sequenced, they were found to be part of the elongin (SII) complex. Elongin (SII) is a heterotrimer consisting of two regulatory subunits (B and C) and a transcriptionally active subunit (A) that activates transcription elongation by RNA polymerase II. The VHL protein binds specifically and tightly to elongin B and C, and from tumor tissue from patients with 2:3 translocations, further supporting the conclusion that the VHL gene has an important and specific role in clear cell renal carcinoma.

Cul-2 Is a Component of the von Hippel-Lindau Complex

A series of studies have been performed to determine that Cul-2 is a part of the VHL complex. Cul-2 is from a family of proteins called cullins, which are highly homologous to the Saccharomyces cerevisiae protein Cdc53p. Based on the apparent similarity of members of the VHL multiprotein complex with yeast proteins (e.g., elongin C and Cul2 to Skp1 and Cdc53, respectively), a model for the regulation of hypoxia-inducible messenger RNAs (mRNAs) has been developed.

Regulation of Vascular Endothelial Growth Factor Messenger RNA by the von Hippel-Lindau Product

Angiogenesis is a marked feature in the clinical manifestation of VHL and sporadic clear cell renal carcinoma. A number of growth factors have been implicated in angiogenesis, including vascular endothelial growth factor (VEGF). VEGF is markedly elevated in renal carcinomas and in VHL-associated tumors. The VHL gene product has been found to regulate the stability of VEGF mRNA, potentially explaining the increased VEGF levels in these tumors and providing an explanation for the angiogenesis associated with their development. This fact may provide unique opportunities for treatment of patients with these tumors.

Nuclear and Cytoplasmic Localization of the von Hippel-Lindau Gene Product

Duan et al. demonstrated that the VHL protein can be found both in the nucleus and the cytosol of transiently transfected cells. To define the determinants of VHL localization, Lee et al. showed that nuclear transport of VHL is tightly regulated and that it is determined by the density at which the cells are cultured. When the cells in culture are sparse, the VHL protein is found predominantly in the nucleus. When the cells in culture were grown to confluence, the VHL protein is found in the cytoplasm. Deletion mutation analysis revealed that a putative nuclear localization signal is located in the N-terminal region of the VHL gene. This study suggests that VHL nuclear transport is regulated by density of the cells. Understanding this novel physiologic control mechanism could provide unique insights into the role of this multifunctional tumor suppressor gene.
HEREDITARY PAPILLARY RENAL CARCINOMA

Papillary renal cancer is a histologic variant of renal carcinoma that is distinct from clear cell renal carcinoma. Whereas clear cell renal carcinoma is characterized by LOH on the short arm of chromosome 3 and mutation of the chromosome 3p VHL gene, neither chromosome 3 LOH nor VHL gene mutation are detected in tumor tissue from patients with papillary renal carcinoma. HPRC, a distinct form of hereditary renal carcinoma, has been described. HPRC is an autosomal dominant form of inherited renal carcinoma that is characterized by the appearance of bilateral, multifocal papillary renal carcinoma (i.e., HPRC is distinct from VHL disease or other inherited forms of renal carcinoma).

HEREDITARY Papillary Renal Carcinoma Is Characterized by Germline Mutation of the MET Gene

Genetic linkage analysis localized the HPRC gene to a 27-cM interval at chromosome 7q31.1-34. Missense mutations were identified in the tyrosine kinase domain of the MET gene in the germline of affected members of HPRC families. Subsequent studies identified MET mutations in two other large North American HPRC families, confirming that the mutation in the MET protooncogene is the basis for HPRC. Activating mutations of the MET gene have been shown to cause malignant transformation in vitro and in vivo, implicating this gene in both hereditary and sporadic forms of papillary renal carcinoma. These findings support the molecular genetic classification of renal carcinoma between clear cell and papillary renal carcinoma, with clear cell renal carcinoma being characterized by VHL gene mutation. HPRC is characteized by a germline mutation of the Met protooncogene. Understanding of the fundamental genetic basis of these forms of kidney cancer will hopefully lead to better methods for diagnosis, prevention, and therapy of patients with kidney cancer.

PROSTATE CANCER

In 1990, prostate cancer became the most common form of cancer (other than skin cancer) diagnosed in U.S. men, surpassing lung cancer. In 1999, an estimated 200,000 new prostate cancer cases were diagnosed, accounting for more than 35% of all cancers affecting men, and more than 40,000 deaths will result from this disease. Despite these figures, our understanding of the molecular genetics of prostate cancer is still in an embryonic stage. This section provides an overview of the efforts to define and characterize genetic alteration responsible for the initiation and progression of prostate cancer. The first part of this section describes familial prostate cancer and reviews the evidence supporting the existence of a hereditary form of the disease. The second part reviews aspects of somatic alterations found in prostate cancer cells, and the potential role of these genetic changes in the progression of prostate cancer.

MULTISTEP CARCINOGENESIS AND PROSTATE CANCER PROGRESSION

The process of carcinogenesis is complex, requiring a number of steps. In the case of prostate cancer, evidence for this multistep requirement is readily demonstrated in the studies of experimental carcinogenesis in rodents. In the pioneering studies of Thompson et al., expression of a single oncogene (ras) in normal prostate cells of the mouse is insufficient for transformation; the overexpression of a second oncogene (myc) is necessary before transformation becomes a frequent event. Even in the case of two oncogenes, not every cell expressing these becomes transformed, suggesting that further steps are necessary, presumably including inactivation of tumor suppressor genes. Although in clinical specimens of human cancers the requirement for multiple steps is less easily demonstrated, the finding of multiple genetic alterations as a common characteristic of human tumors supports this concept.

Application of the multistep concept to carcinogenesis in the human prostate would suggest that incidental or latent cancers (i.e., clinically undetected prostate cancers found in most aged men dying from non–prostate cancer causes at autopsy) as well as putative precursor lesions (i.e., prostatic intraepithelial neoplasia (PIN)) have undergone only a subset of the steps, “hits,” or mutations necessary for the emergence of the fully malignant phenotype. Furthermore, this hypothesis would suggest that specific and discrete genetic alterations may be associated with different stages and even grades of prostate cancer. Although such a hypothesis is attractive, no definitive proof has been provided to suggest that this is the case, although certain specific mutations (e.g., in the p53 gene) have been shown to be strongly associated with progression of prostate cancer.

What are the molecular events responsible for the progression of prostate cancer, or, in other words, why and how does prostate cancer evolve from an indolent to a life-threatening disease? Is this evolution inevitable, or are some prostate cancers destined never to progress to advanced disease, let alone clinically detectable disease, regardless of the time frame provided? Conversely, are some prostate cancers capable of metastasis very early in their natural history? A critical issue for addressing these questions effectively is to understand the mechanisms of prostate cancer progression in molecular genetic terms, particularly if therapeutic approaches aimed at blocking this progression are to be other than empirically based.

PROSTATE CANCER INITIATION AND PROGRESSION: GENETICS VERSUS ENVIRONMENT

The initiation of prostate cancer (i.e., the formation of a histologically identifiable lesion) appears to be a very frequent event, occurring in one-third of men older than 45 years. Geographically, this rate of histologic cancer incidence is roughly the same worldwide. The number of clinically manifest cases and the mortality rates, however, differ widely among various populations, strongly suggesting important environmental factors in modulating the transition between tumor initiation and prostate cancer progression. This feature of prostate cancer is emphasized by studies demonstrating large increases in prostate cancer incidence in Japanese men (a low-risk population) when they move to the United States.

On the other hand, studies of familial aggregation of this disease have suggested that between 5% and 10% of prostate cancers may be directly attributable to the inherited component. These findings support the hypothesis that specific and discrete genetic alterations may be associated with different stages and even grades of prostate cancer.

HEREDITARY PROSTATE CANCER

Although not widely recognized as having a strong familial component until more recently, evidence demonstrating familial clustering of prostate cancer has been available as early as 1960 from studies of the Utah Mormon population, and multiple subsequent studies have confirmed this observation. Two large studies are of particular interest in answering the question of whether prostate cancer clusters in families. Cannon et al. published a genetic epidemiologic study on prostate cancer in the Utah Mormon population. Notably, prostate cancer showed the fourth strongest degree of familial clustering after lip cancer, skin melanoma, and ovarian cancer. Prostate cancer had a higher familiality than both colon and breast carcinoma, two solid tumors that are well recognized as having a genetic or familial component.

A case-control study of patients treated for prostate cancer at Johns Hopkins University School of Medicine was carried out to assess the extent of familial aggregation in prostate cancer. Extensive prostate cancer pedigrees were obtained for 691 men with prostate cancer and 640 control subjects. A positive family history of prostate cancer was the only consistent risk factor found in this study. Men with a father or brother affected were twice as likely to develop prostate cancer as men with no relatives affected. In addition, a trend of increasing risk was found with increasing number of affected family members, such that men with two or three first-degree relatives affected had a five- and 11-fold increased risk of developing prostate cancer. Cox proportional hazards analysis in the case relatives revealed that risk was particularly increased to relatives of younger probands (younger than 55 years).

These studies suggest a familial clustering in risk to prostate cancer but do not directly address the underlying etiologic mechanism. It is important to note that familial clustering could as easily reflect a shared environmental risk factor as a genetic mechanism. To directly address this question and to test whether a Mendelian form of prostate cancer could explain the observed clustering of this disease, segregation analyses by Gronberg et al. have been carried out. Additional segregation analyses by Grönberg et al. provide further support for the
existence of dominantly acting prostate cancer susceptibility alleles.

These results emphasize that the genetics of prostate cancer are likely similar to those of colon and breast cancer, in which a subset of the disease occurs in persons who inherit defective copies of one of a series of critical, rate-limiting steps required for neoplastic transformation. Just as linkage studies in families with multiple members affected with these diseases were critical to the identification of colon and breast cancer susceptibility genes (e.g., APC, hMSH2, BRCA1, BRCA2), linkage analyses in prostate cancer families are an active area of study. As of 1999, four separate loci suspected of harboring hereditary prostate cancer genes have been reported (Table 34.1-1). Three of these loci are on chromosome 1, and the fourth is on the X chromosome. The finding of multiple distinct loci, along with the high likelihood that multiple additional loci will be identified, emphasizes the extensive and potentially complex genetic heterogeneity that characterizes hereditary prostate cancer. Only when these genes are cloned and characterized will their contributions to the underlying pathogenesis of this disease be assessable.

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TABLE 34.1-1. Prostate Cancer Susceptibility Loci Identified by Linkage Studies

SOMATIC ALTERATIONS IN PROSTATE CANCER

Role of Oncogenes

A number of oncogenes have been examined in prostate cancer tissue and cell lines, primarily at the expression level, including ras, myc, sis, fos, EGFR, and ERBB2 (reviewed by Strollo and Slamann). Expression of each of these genes and, in some cases, overexpression when compared to normal genes has been detected in prostate cancer cells, but at widely varying frequencies. None of these genes have been observed to undergo mutational activation in a majority of prostate cancers, and the mechanisms responsible for their overexpression, when present, remain largely undefined. Of particular interest in this regard is the study by Bubendorf et al., which demonstrated that, whereas gene amplifications of ERBB2 and NMYC were never observed in any stage prostate cancer, the androgen receptor gene, myc, and cyclin D1 were observed to be amplified in 22%, 11%, and 5% of hormone-refractory, metastatic prostate cancers, respectively.

RAS. Several studies provided early evidence of a potentially important role for activated ras genes in prostate cancer, particularly in rodent models. Feeth et al. using DNA transfection experiments, were the first to demonstrate the presence of an activated K-ras gene in a human prostate cancer specimen. Subsequent studies found low frequencies of ras gene mutations in both localized and metastatic prostate cancer (less than 4%). These results, all obtained in Northern American patients, demonstrate that activation of ras oncogenes via point mutation is not a common event in either the initiation or progression of prostatic neoplasia.

In contrast to these studies, other reports examining prostate tissue from Japanese men suggest that ras gene mutations do occur at significant frequencies (approximately 25%) in prostate cancer, both in latent carcinoma and clinically manifest disease. These studies raise the interesting possibility that significant differences may exist in the genetic events associated with prostate cancer in American men compared with Japanese men (wherein the latter have an approximately fivefold lower incidence rate of clinically manifest disease).

Additionally, in this latter study, human papillomavirus DNA was detected in more than 40% of the prostate cancer samples analyzed. The detection of human papillomavirus DNA in prostate cancer from Northern American men is controversial, but the most recent evidence, suggests that this family of viruses is not commonly found in prostate cancer, at least not at levels comparable to those found in cervical cancer, in which a definitive etiologic link has been established.

C-MYC. The c-myc gene has been implicated in prostate cancer since the experimental carcinogenesis studies of Thompson et al. A role for c-myc overexpression as an important aspect of prostate cancer has been suggested by the frequent finding of increased copy number of the portion of 8q containing the c-myc gene in clinical prostate cancer specimens, particularly advanced cases. Sato et al. observed that cases of prostate cancer characterized by fluorescence in situ hybridization (FISH) as having more copies of c-myc than copies of chromosome 8 centromere were highly associated with poor outcomes.

bcl-2: An Inhibitor of Apoptosis

The bcl-2 gene is located on chromosome 18q21. It was identified because of its involvement at the breakpoint of the t(14;18) interchromosomal translocation occurring in human follicular B-cell lymphomas. This translocation results in enhanced expression of the bcl-2 gene. The bcl-2 gene encodes for a membrane-bound 26-kD protein. bcl-2 has been demonstrated to be an oncogene, in that its induced overexpression can lead to malignant transformation. bcl-2 is unique among oncogenes, however, in that its expression does not enhance the rate of cell proliferation, but instead decreases the rate of cell death. The role of bcl-2 in the development and progression of carcinoma of the prostate has been examined by McDonnell et al. Using immunohistochemical (IHC) techniques, bcl-2 is not usually expressed in androgen-dependent prostatic cancer cells, whereas it is expressed in androgen-independent prostatic cancer cells. This observation has been confirmed by Colombet et al. These findings suggest that enhanced expression of bcl-2 protein in carcinomas of the prostate is associated with the transition to androgen independence.

Androgen Receptor

The role of androgen in normal prostate physiology is unquestioned, because these hormones are strictly required for normal development and maintenance of prostate growth and function. However, the role of androgens and androgen receptors (AR) in prostate cancer is much less clear. Studies have generated a great deal of renewed interest in this pathway and its role in the critical progression of prostate cancer to androgen independence. An initial hypothesis that loss of AR gene expression may be important in androgen-independent disease was not supported by several studies that showed continued or even elevated AR gene expression in androgen-independent tumors. Newmark et al. were the first to report a mutated androgen receptor in a clinical specimen of prostate cancer; curiously, it was found in a localized cancer before any hormonal therapy. This and other findings of mutations before hormonal therapy would suggest that mutant AR might provide a growth advantage, even in the presence of normal androgen levels. Kelly et al. and Sartor et al. described a number of patients who experienced a paradoxical response to withdrawal of the antiandrogen, flutamide, in that a number of clinical parameters (e.g., prostate-specific antigen levels, bone pain) improved on cessation of drug treatment. One explanation proposed for this response is that such patients harbor AR gene mutations similar to those found in the prostate cancer cell line LNCaP (Thr to Ala change at codon 868), which alters the ligand specificity of the receptor such that both estrogens and antiandrogens, as well as androgens, act as agonists. The frequency of such mutations in prostate cancer patients is unknown, but a study by Taglini et al. found five of ten samples of hormone-refractory prostate cancer metastatic to bone had mutations of the AR gene, and at least two of these mutations resulted in a shift in hormone specificity of AR. Visakorpi et al. demonstrated that up to 30% of prostate cancer specimens from men unsuccessful with hormonal therapy are characterized by increases in copy number of the X chromosome region (q11-q13) containing the androgen receptor. These results suggest that instead of being insensitive to androgen, such tumors may become supersensitive to androgen by an as yet undetermined mechanism, or perhaps sensitive to a different nonandrogen steroid hormone. Furthermore, a number of studies suggest that via novel interaction with other growth factor or signaling pathways, the requirement for androgen binding to the receptor may be bypassed. Thus, although the precise role of androgen and the androgen receptor is still being defined, it is possible that altered regulation of the pathway plays a fundamental role in prostate cancer progression to androgen-independent disease.
Chromosomal Deletions in Prostate Cancer

Unlike other solid tumors, such as renal cell carcinoma, cytogenetic analyses of prostate cancer specimens have revealed few consistent chromosomal deletions. An early cytogenetic study by Atkin and Baker, however, suggested chromosomes 7q and 10q as the sites of frequent chromosomal losses in prostate cancer. Early studies of allelic loss by Carter et al. and Kunitin et al. confirmed frequent LOH on chromosome 10 and also highlighted portions of chromosomes 16 and 8 as being frequently deleted in clinical specimens of prostate cancer. Deletion mapping studies by Bergerheim et al. suggested that the critical regions resided between pter and the plasminogen activator, tissue type locus at p12-q11.2 on chromosome 8 and q22.1 on chromosome 16. Interestingly, loss of chromosome 8p in prostate cancer had been previously observed in a study by Konig et al., who found cytogenetic evidence of chromosome 8p deletions in a number of prostate cancer xenografts, and suggested a correlation existed between loss of this region and the development of androgen independence.

Of the chromosomal regions analyzed in prostate cancer, the short arm of chromosome 8 has received the most attention, because it appears to be the most frequent site of LOH, occurring in the majority of cases of prostate cancer examined. Two or possibly three distinct regions of LOH occur on this chromosomal arm, with the region 8p21-12 being deleted in the majority of prostate cancer precursor lesions (PIN). Most distally, 8p22 is deleted in most adenocarcinomas. Subregional deletion analysis of chromosome 8p in prostate cancer has been performed using a variety of molecular tools, all of which have confirmed a high frequency of loss in this region, especially, but not exclusively, within chromosomal band 8p22. However, in situ hybridization (ISH) and microsatellite analysis has shown loss of chromosome 8p22-p12 in 80% of prostate cancer lymph node metastases. Microcell transfer of human chromosome 8 into a rat prostate cancer cell line has been reported to suppress metastatic ability. An association of chromosome 8p loss and higher stage has been reported.

Several 8p candidate tumor suppressor genes have been identified, including N33, which is located in a homozgyously deleted region of 8p22. This novel gene is expressed in many normal tissues but not in some cancers, most notably those of the colon. Other candidate genes identified on this chromosomal arm include the putative transcription factor FEZ1 and an androgen-regulated homeobox gene, NXK3.1.

The frequent loss of sequences on chromosome 8p provides a marker to determine the similarity or difference between primary prostate cancers and their metastases. This approach has been used to determine the concordance rates for 8p loss in a series of PIN, primary, and metastatic lesions obtained from the same patient. Cases were observed in which there was complete concordance in that all samples of cancer had retained or lost the same 8p marker, but cases also were noted in which the PIN sample would show loss, but not the primary tumor or the lymph node tumor samples. In addition, some cases showed differences among the multiple primary lesions within the prostate. These data and similar findings demonstrate the complex genetic relationship that exists between primary and metastatic lesions and suggest that the primary prostate cancer that gives rise to a given metastatic deposit is not easily predicted on the basis of morphologic characteristics.

Concomitant with deletion of sequences from the short arm, chromosome 8 is frequently affected by gain of sequences on the long arm. First observed by Southern analysis, a CGH study of lymph node metastases indicated that 85% of such tumors showed evidence of 8q gain, making this the most common numerical alteration observed in this study. Van den Berg et al. reported that gain of 8q sequences in prostate cancer was highly correlated with disease progression. Similarly, in the CGH study of Visakorpi et al., gain of 8q sequences was seen in 88% of tumor recurrences after hormonal therapy, whereas only 6% of primary tumors showed this alteration. An obvious candidate gene that may be the target of these amplification events in prostate cancer is the oncogene c-myc, which is located at 8q24, although most of the amplification events on 8q are large, suggesting that many genes are affected. In this respect, two other 8q genes, PSCA and the p40 subunit of transcription factor 8, are found to be frequently included in the gained regions of chromosome 8 and show increased expression in a subset of prostate cancers.

Comparative Genomic Hybridization Analysis of Prostate Cancer

Visakorpi et al. used CGH to survey the genome of a series of both untreated, localized prostate cancers and tumors from patients unsuccessful on hormonal therapy. This important study found chromosome 8p to be the most frequently deleted, followed by 13q, 6q, 16q, 18q, and 9p. In a series of advanced prostate cancers from men unsuccessful with hormonal therapy, a significant increase was found in deletions of chromosome 5q and gains of chromosomes 7p, 8q, and X, when compared to untreated primary tumor samples. Evidence has been found that the androgen receptor gene may be the target of gene amplification events on this latter chromosome. Thus, these studies confirm previous studies of allelic loss in prostate cancer and, at the same time, expand the chromosomal regions implicated as harboring “prostate cancer genes.”

Specific Gene Alterations in Prostate Cancer

A number of genes have been found to be mutated in prostate cancer, including p53, PTEN, Rb, ras, CDKN2, AR, MX1, and POLB, although the latter two, located on chromosomes 10q25 and 8p11.2, respectively, remain to be confirmed. ras mutations are uncommon (fewer than 5% of cases), as are point mutations of Rb, although loss of one copy of Rb readily occurs. To date, the most consistently observed site of point mutations is the p53 gene, and these mutations are common only in advanced disease. Microsatellite instability is uncommon but detectable in prostate cancer, and the IHPM52 gene has been found to be mutated in a prostate cancer cell line that exhibits this phenotype.

PS3. p53 mutations are uncommon in localized disease but become frequent in deposits of metastatic prostate cancer, particularly those to bone. Other observed heterogeneity of p53 mutations within different tumors in the same gland, and within different regions of the same gland, appears to be a somewhat unique feature of prostate cancer.

Further, LOH and point mutation of p53 do not appear to be tightly coupled in this disease. A large number of studies have examined the prognostic significance of nuclear p53 protein immunostaining in both localized and advanced prostate cancer, and although the results are somewhat disparate, two conclusions can be drawn: (1) p53 staining tends to be very heterogeneous, resulting in problems for scoring and interpretation of staining results and in inconsistencies due to sampling biases; and (2) in general, tumors with positive p53 staining are associated with a worse feature of prostate cancer.

PTEN. A series of studies have examined prostate cancer specimens for alterations in the dual function phosphatase gene PTEN and found that this gene is inactivated by a combination of mechanisms, including hemi- and homozygous deletion, point mutation, and promoter methylation. These changes are observed most commonly in advanced disease, and they may play a role in the acquisition of metastatic potential. However, McMenamin et al. demonstrated that the majority of clinically localized prostate cancers had abnormal PTEN protein expression, with one in five cases being completely negative.

Wu et al. demonstrated that, in prostate cancer cells lines with inactivated PTEN, the AKT/phosphoinositide 3 kinase pathway is constitutively activated due to increased accumulation of the PTEN substrate PIP3. Activation of this pathway results in suppression of apoptosis and increased cell survival. These findings have stimulated extensive interest in these pathways as novel therapeutic targets in advanced prostate cancer.

Rb. The importance of Rb gene inactivation in prostate cancer was initially suggested by the studies of Bookstein et al., who demonstrated the presence of inactivating mutations in the Rb gene in clinical specimens of prostate cancer, as well as the ability of reinduction of a cloned copy of Rb to suppress the tumorigenicity of DU145 prostate cancer cells, which had been used to produce a nonfunctional truncated Rb protein. Combined CGH and LOH studies reveal that one copy of Rb is lost in advanced prostate cancer at rates approaching 80%, although limited sequencing studies suggest that point mutations are present in fewer than 20% of clinical samples. IHC studies of Rb expression demonstrate lack of expression in 10% to 22% of tumors, with a questionable correlation between tumor LOH of Rb and lack of expression. These data, together with LOH events on 13q that do not include Rb, suggest the presence of an additional or alternative
prostate tumor suppressor gene near the RB locus.

CDKN2. Much attention has been focused on the p16/CDKN2 gene, a negative regulator of cell-cycle progression located at chromosome 9p21, since the finding of frequent homozygous deletions in a wide variety of cancer cell lines. A relatively high frequency of homozygous (approximately 20%) and hemizygous losses of CDKN2 have been observed in clinical specimens of prostate cancer. In the latter case, loss events in the vicinity of the CDKN2 gene are more common in metastatic deposits of prostate cancer (43% vs. 20% in primary tumors). In a small but detectable fraction of primary tumors (approximately 15%), the CDKN2 gene shows evidence of inactivation by promoter methylation. Whether all of the loci loss events at 9p21 in prostate cancer are associated with CDKN2 inactivation or whether they reflect inactivation of a neighboring gene (e.g., p15) has not been determined.

P27 (CDKN1B). A number of studies that reduced levels of the cyclin kinase inhibitor p27 are associated with a more aggressive prostate cancer phenotype, although the mechanism of this down-regulation is not clear. Interestingly, Kibel et al. described a homozygous deletion of the p27 gene in a lethal case of prostate cancer, and in a high frequency of LOH of p27 in advanced prostate cancers in general. Thus, it is possible that, in prostate cancer, in addition to increased ubiquitin-mediated p27 protein degradation, which has been demonstrated in colon and other cancers, at least a subset of lesions may inactivate this gene via deletion.

E-CADHERIN AND KAI-1. Genes whose down-regulation has been implicated in prostate cancer progression include the cell adhesion molecule genes E-cadherin and KAI-1, which are located at chromosomes 16q22.1 (a frequent site of LOH) and 11p11.2, respectively. E-cadherin protein levels are frequently reduced in hormone-refractory lesions, and this finding has prognostic significance. Various studies have suggested that the down-regulation of these genes has not been determined, in the case of E-cadherin, gene inactivation via promoter methylation has been found in prostate cancer cell lines and at a low but detectable rate in clinical specimens of prostate cancer. GSTP. Similarly, the gene for the phase II detoxification enzyme glutathione S-transferase p, has also been found to be extensively methylated in the promoter region, in a completely cancer-specific fashion, with concomitant absence of expression. In fact, this methylation event, being found in more than 90% of all prostate cancers and PIN lesions, is the most common genomic alteration yet observed in prostate cancer. The mechanism by which this region becomes specifically methylated in prostate cancer and the basis for its apparent selection in the carcinogenic pathway is unclear at present. Because this enzyme is a key part of an important cellular pathway to prevent damage from a wide range of carcinogens, the inactivation of this activity may result in increased susceptibility of prostate tissue to both tumour initiation and progression resulting from an increased rate of accumulated DNA damage. Indeed, reactivation of this or a similar cellular defense pathway, perhaps by dietary intervention, has been proposed as a treatment strategy aimed at blocking the progression of initiated prostate cancer foci.

BLADDER CANCER

Approximately 90% of malignant tumors arising in the urinary bladder are of epithelial origin, the vast majority being transitional cell carcinomas. Based on morphologic evaluation and natural history, urothelial neoplasms have been classified into two groups having distinct behavior and prognosis: low-grade tumors (always papillary and usually superficial) and high-grade tumors (either papillary or non-papillary, and often involving the submucosa and muscularis). Clinically, superficial bladder tumors (stage Ta) have a very high recurrence rate (75% to 85%), while high-grade tumors, particularly those with an invasive component (stage T1), have a high incidence of progression to muscle-invasive (stage T2) and metastatic disease (stage M1). In addition, new telomeric and locus-specific probes are being used to identify genetic aberrations using nonisotopic detection methods. Poddighe and collaborators used a dual labeling hybridization assay. Gene amplification was associated with protein overexpression and was found only in tumors with aneusomy of chromosome 17, and more frequently in muscle-invasive lesions.

Recent studies in well-characterized cohorts of patients, using tissue microdissection techniques, are required to delineate the potential role of H-RAS mutations in bladder cancer. Further studies in well-characterized cohorts of patients, using tissue microdissection techniques, are required to delineate the potential role of H-RAS mutations in bladder cancer. Because clinical staging and morphologic evaluation determine the therapeutic modality, the pathological assessment of tumor specimens carries significant consequences. However, it is well known that two morphologically similar tumors presenting in any assigned stage may behave in different fashions, a fact that seriously hampers the ability to accurately predict clinical outcome. For these reasons, biologic markers and new detection methods are being developed to monitor and identify recurrence and progression in patients treated for superficial disease. The important issues in patients presenting with muscle-invasive carcinomas include metastatic potential and response to neoadjuvant regimens. The implementation of objective predictive assays will enhance our ability to assess tumor biologic activities and to design effective treatment regimens.

CYTOGENETICS AND INTERPHASE CYTOGENETICS OF BLADDER TUMORS

Cytogenetic studies of bladder cancer cells by karyotyping have revealed a variety of chromosomal abnormalities. Nonrandom chromosomal changes consisting of monosomy of chromosome 9p21 and interstitial deletions of chromosome 13 have been observed. Other common abnormalities include trisomy of chromosome 7, deletions of chromosomes 11p and 3p, and chromosome 1 alterations. However, most of these analyses were performed using small cohorts, lacking clinico-pathologic correlations, and combining superficial and muscle-invasive lesions. In one study, Tyrrkus et al. karyotyped 17 carcinomas in situ of the urinary bladder and found no chromosome 9 alterations, but identified nonrandom chromosomal changes involving chromosomes 1, 5, 8, and 11.

More recent interphase cytogenetic studies have been conducted, mainly using centromeric probes, in a search for numerical alterations in bladder cancer. In addition, new telomeric and locus-specific probes are being used to identify genetic aberrations using nonisotopic detection methods. Poddighe and collaborators reported chromosomal alterations at 1q12, as well as numerical abnormalities of chromosomes 1, 7, 9, 11, and 18. Waldman et al. also reported numerical aberration of chromosomes 7, 9, and 11 in 27 bladder tumors.

FISH has been used to assess erbB-2 (17q21) gene amplification and c-myc (8q24) copy number gains in bladder cancer. Sauter et al. reported amplification of erbB-2 in 10 of 141 bladder tumors using a dual labeling hybridization assay. Gene amplification was associated with protein overexpression and was found only in tumors with an invasive component. A similar approach is being used for the analysis of c-myc gene copies. FISH has been used in three cases, whereas 32 of the remaining 84 tumors showed a low-level c-myc copy number increase. No association was found between low-level copy number increase and protein overexpression. However, strong association was demonstrated between c-myc gene length and tumor grade, stage, and Ki-67 labeling index, consistent with a role of chromosome 8 alterations in bladder cancer progression.

FISH assays also have been used for analyses of specific gene losses. Physical p53 gene deletion (at 17p13) was examined by FISH in 151 bladder tumors. 17p deletion was found to be highly correlated with tumor stage and grade (P < 0.01). FISH has been used more recently to assay bladder irradiation signals. Labeled probes to centromeric sequences for chromosomes 1, 7, 9, 11, 15, and 17 were used on samples from 76 patients monitored for recurrent bladder tumors. Significantly, 24% of patients with history of bladder cancer but no clinical evidence of disease exhibited monosomy of chromosome 9.

ONCOGENES: MOLECULAR AND IMMUNOPATHOLOGY ANALYSES OF BLADDER TUMORS

The first mutation of the RAS family of oncogenes, a point mutation in codon 12 of the H-RAS gene (11p15.1), was identified in the bladder cancer cell line T24 and subsequently identified in bladder cancers. There has been controversy regarding the mutation frequency of RAS genes in bladder tumors. Before the advent of polymerase chain reaction (PCR)-mediated DNA amplification, it was estimated that the rate of point mutations in RAS oncogenes ranged from 10% to 16% of samples analyzed. The predominant alteration identified was codon 12 substitutions of the H-RAS gene, with a few cases presenting K-RAS mutations and no mutations detected affecting N-RAS. However, two reports by Czerniak and colleagues, using a PCR-based method, revealed that approximately 40% of bladder tumors harbor H-RAS codon 12 mutations. Several studies have confirmed this high frequency of H-RAS point mutations. Ooi et al. studied a cohort of 124 patients affected with pTa or pT1 transitional cell carcinomas. The codon 12 G to T substitution was found in nonrecurrent and recurring primary tumors, as well as in initial pTaT1 lesions from patients who had disease progression. More recently, a prospective study by Fitzgerald et al. reported the detection of mutations in exon 1 of the H-RAS gene in urine sediments from 44 of 100 patients presenting with bladder neoplasms. It should be noted that different members of the RAS family are mutated with different frequencies. The frequency of K-RAS mutations in colorectal cancer is approximately 40%, whereas N-RAS mutations are commonly found in hematopoietic neoplasms. Moreover, evidence indicates that mutant RAS alleles are involved in the earlier phases of neoplastic transformation of colorectal carcinomas. Further studies in well-characterized cohorts of patients, using tissue microdissection techniques, are required to delineate the potential role of H-RAS mutations in bladder cancer.

Overexpression and amplification of particular growth factor receptors have been reported in bladder cancer. Neal and coworkers observed increased expression of epidermal growth factor receptors (EGFR) in invasive versus superficial bladder tumors. This group of investigators also reported that overexpression of EGFR was associated with high-grade, high-stage bladder cancer and was an independent prognostic factor. Messing noticed that EGFR was expressed at detectable levels in the basal layer of the normal urothelium, whereas increased expression in basal and suprabasal layers was identified in transitional cell carcinomas. Rao et al. also found increased expression of EGFR in urothelial samples with dysplastic changes, postulating that overexpression of EGFR may be an early event in
bladder carcinogenesis. In a more recent study, Nguyen et al. reported that overexpression of EGFR was not an independent prognostic marker in patients with advanced bladder cancer.

Amplification of the c-erbB-2 gene was found in 1 of 14 bladder tumors in a study by Wood and collaborators. This case also displayed overexpression when analyzed for mRNA and protein levels. In addition, five cases displayed high levels of mRNA with no signs of gene amplification, and only three of these five cases had protein overexpression. Sato et al. observed c-erbB-2 protein (p185) overexpression in 23 of 88 bladder tumors analyzed and found a significant association with overexpression and poor clinical outcome, which is an independent prognostic factor. More recently, Underwood et al. studied c-erbB-2 status in 236 bladder tumors. Sixteen of 89 patients with recurrent disease had evidence of c-erbB-2 amplification; however, gene amplification was not observed in the nonrecurrent tumors. A strong association with disease progression and c-erbB-2 amplification was reported. Nevertheless, protein overexpression could not be linked to disease progression. c-erbB-2 amplification was of predictive value in multivariate analysis for overall bladder cancer death; however, stage and grade remained the most significant independent prognostic parameters.

A cellular protooncogene product, mdm2, has been shown to bind to p53 and act as a negative regulator, inhibiting its transcriptional transactivation activity and targeting p53 for ubiquitin-mediated degradation. The MDM2 gene is located on the long arm of chromosome 12 (12q13-14) and encodes a 90-kD nuclear protein. Lianes et al. undertook a study to determine the frequency and clinical relevance of identifying MDM2 and TP53 alterations in patients affected with bladder neoplasms. These investigators analyzed a cohort of 87 patients and observed that 26 of 87 cases had abnormally high levels of mdm2 protein; however, only one case showed focal amplification. A striking association was noted between mdm2 overexpression and low-stage/low-grade bladder tumors (P < .01). Based on these results, it was concluded that aberrant mdm2 phenotypes are frequent events in bladder cancer and may be involved in tumorigenesis or early tumor progression in urothelial neoplasms. In an independent study, Barbaresci et al. reported mdm2 nuclear overexpression in 5 of 25 bladder tumors analyzed, but this survey lacked clinicopathologic correlations.

TUMOR SUPPRESSOR GENES: MOLECULAR AND IMMUNOPATHOLOGY ANALYSIS OF BLADDER TUMORS

Molecular genetic studies of bladder cancer have identified abnormalities of tumor suppressor genes involved in tumor development and progression. Confirming initial cytogenetic observations, LOH on the short arm of chromosome 11 and 9q allelic losses were reported as frequent events in bladder tumors. It was also observed that 17p LOH was a common event in high-grade bladder cancer.

In an attempt to define the role of molecular and immunopathologic tumor suppressor genes in the pathogenesis and progression of human bladder cancer, a combined molecular genetics and immunopathology approach was undertaken by Presti et al. in a survey of 34 unselected patients, five suspected or known tumor suppressor gene regions (3p21-25, 11p15, 13q14, 17p11-13, and 18q21) were studied. An IHC assay was also used for the analysis of the retinoblastoma gene product (pRB). This study demonstrated that tumor grade correlated with deletions of 3p (P = .004) and 17p (P = .063). Tumor stage was correlated with deletions of 3p (P = .010), 17p (P = .015), and altered pRB expression (P = .054). Vascular invasion correlated only with deletions of 17p (P = .038). This study also revealed that deletions of 17p (TP53 locus) and 18q (DCC gene locus) are common in invasive tumors, whereas deletions of 3p and 1p occur in both superficial and invasive tumors. Dabbiaggi et al. followed this study by analyzing 60 paired normal and bladder tumor tissues using polymorphic DNA markers on 18 different chromosomal arms. Allelic deletions were correlated with clinicopathologic parameters. Distinct genotypic patterns were associated with early and late stages of bladder cancer. Genetic correlation with clinicopathologic data suggested the existence of two different genetic pathways for the evolution of superficial bladder tumors. Briefly, 9q deletions were found in 60% of the informative cases, confirming previous reports. Superficial papillary tumors confined to the mucosa (pTa) and almost all tumors invading the lamina propria (pT1) showed 9q alterations. In contrast, only 10 of 23 muscle-invasive tumors (pT2-4 or pT2+) had 9q deletions. A statistically significant difference was observed when comparing 9q LOH between pT1 versus pT2+ tumors (P = .021). Moreover, 9q deletions were the sole abnormality found in some of the bladder lesions studied, suggesting the presence of a candidate tumor suppressor gene on chromosome 9q important in a subset of superficial bladder tumors. None of the pTa lesions showed 9q alterations; however, three of ten T1 tumors and 8 of 26 T2+ tumors presented with 5q LOH, indicating that 5q deletions may be involved in the transition from papillary superficial (pTa) to early invasive (pT1) tumors. Allelic loss of 17p was detected in 21 of 47 informative cases. Deletions were not identified among pTa lesions, whereas 21 of 38 invasive tumors exhibited 17p LOH. These findings support the involvement of 17p in the progression of bladder cancer. Allelic deletion of 3p was not present in any of the informative pTa neoplasms; however, 18 of 33 invasive tumors had such alterations. A statistically significant association was reported with the various pathologic parameters of poor outcome and 3p LOH. Allelic losses of 11p, 6q, and 18q were frequently detected in the corresponding invasive bladder tumors analyzed. However, statistically significant differences were not observed between these abnormalities and clinical pathologic parameters of poor outcome, suggesting late involvement in bladder cancer progression. Other bona fide and putative suppressor loci analyzed in the Dabbiaggi et al. study showed a lower rate of LOH and lacked association with clinicopathologic parameters.

In a subsequent allelotyping study, Habuchi et al. investigated the role of allelic losses of seven chromosomal arms (1p, 3p, 9q, 10q, 11p, 13q, and 17p) in 49 urothelial cancers. They found 9q LOH as a common event in bladder tumor and, invasive tumors showed higher frequencies of 17p and 19q losses when compared to noninvasive lesions. Deletions of the long arm of chromosome 13, including the RB locus on 13q44, were independently reported by two groups. In one of these studies, Cairns et al. used intragenic RB probes and found 28 of 94 informative cases with LOH at the RB locus, with 26 of these 28 lesions being muscle-invasive tumors.

The relevance of RB alterations in bladder cancer was disclosed in two independent studies. Using a mouse monoclonal antibody (mAB) and IHC in frozen tissue sections of 48 primary bladder tumors, Cordon-Cardo and collaborators found normal levels of RB expression in 34 cases. However, a spectrum of altered patterns of expression, from undetectable pRB levels to heterogeneous expression of pRB, was observed in 14 patients. Thirteen of the 38 patients diagnosed with muscle-invasive tumors were categorized as pRB altered, whereas only one of the ten superficial carcinomas had the altered pRB phenotype. The survival rate was significantly lower in the pRB altered group as compared to those with normal RB expression (P < .001). Similarly, Logothetis et al. found altered pRB expression in locally advanced bladder cancer. Forty-three patients were evaluated using the RB-WL-1 polyclonal antiserum and IHC. These investigators reported altered pRB expression in 37% of the tumor specimens analyzed. A significant decrease in disease-free survival rate was reported for patients with documented abnormal pRB levels. Taken together, these data suggest that altered pRB expression occurred in all grades and stages of bladder cancer but was more commonly associated with muscle-invasive tumors. Moreover, altered patterns of pRB may become an important prognostic variable in patients presenting with invasive bladder cancer.

The clinical implications of detecting TP53 mutations and altered patterns of its encoded product (p53) in bladder tumors has been the focus of a series of investigations. Early studies revealed that TP53 mutations were common events in bladder cancer and associated with tumor stage and grade. Significant overexpression of p53 in RB altered patients compared to those with normal RB expression (P < .001). Similarly, Logothetis et al. found altered pRB expression in locally advanced bladder cancer. Forty-three patients were evaluated using the RB-WL-1 polyclonal antiserum and IHC. These investigators reported altered pRB expression in 37% of the tumor specimens analyzed. A significant decrease in disease-free survival rate was reported for patients with documented abnormal pRB levels. Taken together, these data suggest that altered pRB expression occurred in all grades and stages of bladder cancer but was more commonly associated with muscle-invasive tumors. Moreover, altered patterns of pRB may become an important prognostic variable in patients presenting with invasive bladder cancer.

FIGURE 31.5. Schematic representation of the proposed model of bladder cancer progression as it may relate to the pathologic staging of this cancer.

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approach, they also tested the hypothesis that p53 nuclear overexpression detected by IHC can reliably identify the presence of mutant TP53 products in bladder neoplasms. Nuclear immunoreactivities were observed in 26 of 42 bladder tumors analyzed. Abnormal shifts in mobility were noted in 14 of the 42 cases in distinct exons. A strong association was noted between p53 nuclear overexpression and 17p LOH (P < 0.01), as well as p53 nuclear overexpression and detection of TP53 mutations by SSCP and sequencing (P < 0.01). Using receiver operating curve (ROC) statistical analysis, the accuracy of detecting TP53 mutations by IHC was estimated to be 90.3%. In addition, this study defined as an appropriate cutoff point for IHC 20% tumor cells displaying nuclear immunoreactivities (p53-positive phenotype).

The aim of three analyses was to investigate altered patterns of p53 expression with tumor progression in patients with superficial bladder tumors. Detection of IHC and 20% positive nuclear staining as the cutoff value. However, the primary antibody used was a purified rabbit polyclonal (NCL-CM1, 1:150 dilution). The mean follow-up time was more than 10 years. Nuclear overexpression of p53 was associated with tumor grade and disease progression. In univariate analysis, p53 overexpression predicted poor outcome in the entire group. However, in a multivariate survival analysis, overexpression of p53 had no independent prognostic value over clinical stage and mitotic index. Early et al. determined the relation between nuclear accumulation of p53 and tumor progression in a cohort of 243 patients treated by radical cystectomy using IHC and antibody PA61801. These investigators noticed that detection of nuclear p53 was significantly associated with an increased risk of recurrence (P < 0.001) and decreased overall survival (P < 0.001). Moreover, p53-negative phenotype was an independent predictor of recurrence and survival.

The neadjuvant use of chemotherapy offers the advantages of bladder preservation and early treatment of micrometastases in patients diagnosed with invasive bladder cancer. However, despite the chemosensitivity of invasive urothelial neoplasms, complete pathologic response in the primary lesion occurs in only 20% to 30% of patients. To determine whether aberrant p53 expression has independent significance for response, relapse, and survival in patients with muscle-invasive bladder cancer treated with neoadjuvant M-VAC (methotrexate, vinblastine, Adriamycin (doxorubicin), and cisplatin) chemotherapy, Sarkis et al. evaluated 90 patients who received this regimen with a median follow-up of 5.8 years. Patients whose tumors had p53-negative phenotype (n = 47) had a significantly higher proportion of cancer deaths. Multivariate analysis revealed that p53 overexpression had independent significance for long-term survival (P < 0.001).

As already discussed, loss of genetic material on chromosome 9 is an early abnormality detected in bladder tumors.

The results of this study were consistent with the hypothesis that tumor progression is due to an accumulation of genetic and epigenetic changes that result in deregulation of cell-cycle control, leading to uncontrolled cellular proliferation. The results also suggested that the identification of specific genetic alterations may be useful for the selection of patients who may benefit from targeted therapies. Overall, the study provided important insights into the molecular mechanisms underlying bladder cancer progression and identified potential therapeutic targets.
In the study of the genetic events leading to bladder cancer, the hope is that the understanding of the molecular mechanisms in this malignancy may lead to new strategies for the detection of these cancers. In addition, the role of genetic factors in the development of bladder cancer may provide a potentially more sensitive method for detection of bladder cancer. In one instance, genetic abnormalities could be detected years before the disease was clinically apparent. This has shown that genetic instability is associated with bladder tumors and can occur early in bladder tumorigenesis. In a blinded study in which urine samples from 25 patients with suspicious bladder lesions were analyzed by conventional cytology and genomic instability analysis, microsatellite changes identified in DNA from urine cells were detected in patients who were found to have bladder cancer. This study may provide a new sensitive method for the detection of bladder cancer and may provide improved methods for prediction of clinical course in individual patients.
RENAL CARCINOMA

Each year in the United States, approximately 31,000 cases of kidney and upper urinary tract cancer occur, resulting in more than 11,900 deaths. These tumors account for approximately 3% of adult malignancies and occur in a male-female ratio of 1.5:1. They are more common among urban than rural residents. Although most cases occur in persons aged 50 to 70 years, renal carcinoma has been observed in children as young as 6 months. Between 1975 and 1995, a steady and significant increase in the incidence of renal carcinoma was seen, from 2% to 4% per year, an increase of 43% since 1973.  

Renal carcinoma was first described by Konig in 1826. As early as 1855, Robin concluded that the renal tubular epithelium was the most probable tissue of origin of the cancer, an observation that was confirmed by Waldeyer in 1867. In 1863, Grawitz, noting that the fatty content of the cancer cells was similar to that of adrenal cells, concluded that the tumors arose from adrenal rests within the kidney and introduced the term stroma lipomatodes aberrata renis for these clear cell tumors. The term hypernephroid tumors was introduced in 1984 by Birch-Hirschfeld. Since then the conceptually incorrect term hypernephroma has frequently been applied to renal tumors.  

Renal carcinoma occurs in both a sporadic and a hereditary form. There are four main forms of hereditary renal carcinoma (HRC). The most studied form of HRC is von Hippel-Lindau (VHL) syndrome. VHL syndrome is a hereditary cancer syndrome in which affected individuals are at risk to develop tumors in a number of organs, including the kidney. A recently described form of HRC is hereditary papillary renal carcinoma (HPRC). Another recently described form of hereditary kidney cancer is familial renal oncocytoma (FRO), which has been found to be associated with the cutaneous condition Birt-Hogg-Dubé syndrome. Hereditary clear cell renal carcinoma is a rare condition that is inherited in an autosomal dominant fashion in which patients develop clear cell variant renal carcinoma. In the hereditary syndromes, the kidney cancer is often bilateral and tends to occur in a younger age group. An increased incidence of renal carcinoma has also been observed in patients with autosomal dominant polycystic kidney disease and tuberous sclerosis.  

ETIOLOGY

A number of environmental, hormonal, cellular, and genetic factors have been studied as possible causal factors in the development of renal carcinoma. In studies of risk of renal carcinoma, cigarette smoking has been found to be a definite risk factor. A statistically significant dose response has been observed in both genders for pack-years of cigarette use. It has been estimated that 30% of renal carcinomas in men and 24% in women may be directly due to smoking. Obesity is associated with an increased risk of development of renal carcinoma, particularly in women. Analgesic abuse, which is known to be associated with renal pelvis cancer, is also associated with an increased incidence of kidney cancer. The increased risk for the development of renal carcinoma is observed primarily in patients who abuse phenacetin-containing analgesics and develop analgesic nephropathy.  

Environmental and occupational factors have also been associated with the development of kidney cancer. Brauch et al. demonstrated an association between the development of renal carcinoma and long-term exposure to high levels of the industrial solvent trichloroethylene. There is an increased incidence of renal carcinoma among leather tanners, shoe workers, and workers exposed to asbestos. Exposure to cadmium is associated with an increased incidence of kidney cancer, particularly in men who smoke. An association between gasoline exposure and kidney cancer has been observed in animal studies. Although there is an increased incidence of renal carcinoma reported with exposure to petroleum, tar, and pitch products, studies of oil refinery workers and petroleum products distribution workers do not identify a definite relationship between gasoline exposure and renal cancer. There may be an increased risk of kidney cancer in older workers or in workers exposed to gasoline for prolonged periods.  

An increased incidence (100-fold) of renal carcinoma has been noted in patients with end-stage renal disease who develop acquired cystic disease of the kidneys. Acquired cystic disease is a recently described phenomenon in which patients on long-term dialysis for renal failure develop cysts in their native kidneys. Renal carcinoma has been found in association with the papillary hyperplasia observed in the cyst epithelium of these kidneys. The risk of developing kidney cancer has been estimated to be greater than 30 times higher in dialysis patients with cystic changes in their kidney than in the general population. It is estimated that 35% to 47% of patients on long-term dialysis will develop acquired cystic disease and that nearly 5.8% of the patients with acquired cystic disease will develop renal cancer. Kidney cancer can develop at any time in patients with end-stage renal disease, and it can occur in kidney transplant recipients as well. It can develop in patients with end-stage renal disease who are undergoing either hemodialysis or chronic ambulatory peritoneal dialysis, but it also has been reported to occur in patients with end-stage renal disease who are not being dialyzed. Although many of these cancers are clinically insignificant and are found incidentally at autopsy or after bilateral nephrectomy, some will follow an aggressive course. Careful surveillance of patients with end-stage renal disease with ultrasonography and computed tomography (CT) is recommended.  

HEREDITARY FORMS OF RENAL CARCINOMA

Like breast cancer, colon cancer, and retinoblastoma, renal cancer occurs in both a sporadic (nonhereditary) and a hereditary form. At least four forms of HRC are recommended.
recognized: VHL, HPRC, FRO, and HRC (Table 34.2-1). 224, 225, 226 and 227

VON HIPPEL-LINDAU SYNDROME

The VHL syndrome, which is predicted to occur in 1 in 36,000 live births, is a familial cancer syndrome in which affected individuals have a predisposition to develop tumors in a number of organs, including the kidneys, brain, spine, eyes, adrenal glands, pancreas, inner ear, and epididymis. 222, 225 Forty percent of VHL patients develop multiple, bilateral tumors or cysts in the kidneys. The renal carcinoma acquired by VHL patients is clear cell renal carcinoma. 225 These patients can have hundreds of small clear cell tumors and cysts in their kidneys. The tumors, which tend to occur early in life, can metastasize, and the affected individual may succumb to the malignancy. VHL patients can also develop pheochromocytoma, pancreatic cysts and islet cell tumors, retinal angiomas, central nervous system hemangioblastomas, inner ear tumors (endolymphatic sac tumors), and epididymal cystadenomas (Table 34.2-2).

**TABLE 34.2-1.** Hereditary Forms of Renal Carcinoma

<table>
<thead>
<tr>
<th>Form of Carcinoma</th>
<th>Alteration</th>
<th>Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal carcinoma associated with von Hippel-Lindau disease</td>
<td>VHL</td>
<td>125/125</td>
</tr>
<tr>
<td>Hereditary papillary renal carcinoma</td>
<td>HPRC</td>
<td>9/10</td>
</tr>
<tr>
<td>Hereditary renal carcinoma associated with Retinoblastoma</td>
<td>HRC</td>
<td>12</td>
</tr>
<tr>
<td>Hereditary renal carcinoma (clear cell)</td>
<td>HRC</td>
<td>125/127</td>
</tr>
</tbody>
</table>

**TABLE 34.2-2.** Classification of von Hippel-Lindau (VHL) Syndrome

THE VHL GENE. Identification of the VHL gene by Latif et al. 30 in 1993 was an important step for physicians managing patients with VHL disease. Critical to management of VHL patients is the knowledge of who is affected and who is not. Early identification of at-risk individuals is essential for initiation of early intervention with the potential to prevent of life-threatening complications of the disease, such as metastatic kidney cancer. 2, 8

VHL GERMLINE MUTATION TESTING. Identification of the VHL gene has allowed the detection of germline mutation in nearly 100% of VHL families. 31, 32 The VHL clinical features can be heterogeneous, and manifestations such as kidney cancer occur. In some families, VHL syndrome can be confused with other hereditary cancer syndromes, such as multiple endocrine neoplasia type 2. The availability of germline mutation screening can aid the physician in making the correct diagnosis as well as in performing presymptomatic screening in at-risk individuals. (See Chapter 34.1.)

ROLE OF THE VHL GENE IN CLEAR CELL RENAL CANCER. The VHL gene has been found to be mutated in a high percentage of tumors and cell lines from patients with sporadic (nonhereditary) clear cell renal carcinoma. 33, 34 VHL gene mutations have not been detected in either tumors from patients with papillary renal carcinoma or from the germline of patients with HPRC. This has led to the development of a molecular genetic classification of renal carcinoma of papillary versus clear cell (nonpapillary) renal carcinoma, 35 with clear cell renal carcinoma being characterized by inactivation of the VHL gene. 35 The determination that VHL gene mutations can be detected in formalin-fixed tissue from patients with clear cell renal carcinoma provides a potential method for significantly improving clinicians’ ability to diagnose this disease, by analysis of either tissue blocks or tissue aspirates from patients suspected of having this disease. 35

HEREDITARY PAPILLARY RENAL CARCINOMA

HPRC is a recently described form of HRC. 9, 10 HPRC is an inherited disorder with an autosomal dominant inheritance pattern in which affected individuals develop bilateral, multifocal papillary renal carcinoma (Fig. 34.2-1). These tumors, which are often detected incidentally, can spread in a fashion similar to sporadic renal carcinoma. Abdominal CT is recommended for evaluation of at-risk individuals, as even large papillary renal tumors are frequently undetectable by renal ultrasound evaluation. 9

**FIGURE 34.2-1.** A: Abdominal computed tomography scan of a patient with hereditary papillary renal carcinoma, demonstrating bilateral, multifocal papillary renal carcinoma. 9 B: Hereditary papillary renal carcinoma kindred. The black boxes and circles represent individuals found to have kidney cancer. The circles below these represent the result of germline testing for the c-Met mutation. (From ref. 9, with permission.)

THE HPRC GENE: MET. Genetic linkage studies in HPRC kindreds localized the HPRC gene and led to the identification of the c-Met protooncogene as the gene
Familial Renal Oncocytoma and Birt-Hogg-Dubé Syndrome

A new, recently described form of HRC is FRO. Affected individuals can develop bilateral, multifocal oncocytoma or oncocytic neoplasms in the kidney. Similar renal manifestations have been found to occur in patients with a hereditary cutaneous syndrome, Birt-Hogg-Dubé syndrome (BHD). BHD patients have a dominantly inherited predisposition to develop fibrofolliculomas, benign tumors of the hair follicle that appear predominantly on the face, neck, and upper trunk. Affected BHD individuals are at risk to develop fibrofolliculomas, renal tumors, colon polyps, or tumors, and pulmonary cysts. Individuals in BHD kindreds are at risk to develop renal tumors. The renal tumors that occur in BHD can be clear, papillary, chromophobe, or oncocyotomas and are malignant and can metastasize if not detected and treated. Studies are currently under way to identify the gene for this hereditary cancer syndrome and to develop a test for germline testing of at-risk individuals.

PATHOLOGY

Immunohistologic and ultrastructural analysis has established that the proximal renal tubular epithelium is the true tissue of origin of renal carcinoma. Renal tumors tend to be spherical but may vary widely in size. The average diameter is approximately 7 cm; however, renal tumors can often grow to fill the entire retroperitoneum. Previously, renal lesions 2 cm or less in diameter were considered to be renal adenomas, while lesions 2 cm or more in diameter were considered to be carcinomas. The distinction between benign and malignant tumors is no longer made on the basis of size but on the basis of classic histologic criteria. Although renal carcinoma tends to arise in the cortex of the kidney, it can originate in the interior of the kidney. Often a pseudocapsule is formed around the tumor by compression of surrounding tissue. Hemorrhage and necrosis may be present and, frequently, large areas of sclerosis and fibrosis are found within the tumor. Calcification and single or multiple fluid-filled cysts may be seen within the tumor also. Sporadic renal carcinoma appears in either kidney with equal frequency; it is most often solitary and unilateral.

Renal tumors can be of five main cellular types: clear cell, papillary, chromophobe, oncocytoma, and collecting duct (for review, see Zambrano et al. ). Clear cell carcinomas contain lightly staining cells with vacuolated cytoplasm containing cholesterol-like substances, neutral lipids, phospholipids, and glycogen; these constitute 85% of kidney cancers. Papillary renal carcinoma makes up approximately 10% of all kidney cancers, with the remainder being chromophobe, collecting duct, and miscellaneous histologic types. Papillary renal carcinoma has been divided into two morphologic subtypes, types 1 and 2. Collecting duct carcinoma is an unusual variant of renal cell carcinoma (RCC) that is characterized by a very aggressive clinical course. It is not uncommon for a patient with collecting duct carcinoma to present with locally or widespread advanced disease. Chromophobe carcinoma, described by Thoenes et al. in 1985, is characterized by large polygonal cells with pale reticular cytoplasm. Renal oncocytoma, which consists predominantly of eosinophilic cells in a characteristic nested or organoid pattern, is considered to be predominantly a benign lesion. Whether oncocyotma can occur in a malignant form or whether so-called malignant oncocyotma is actually a variant of chromophobe renal carcinoma is not completely understood.

The sarcomatoid variant, which can occur with any histologic subtype, is associated with a significantly poorer prognosis than are nonsarcomatous renal carcinomas. A median survival of only 6.6 months is reported for patients with sarcomatoid-type renal carcinoma, as compared to a 19.0-month median survival for patients with nonsarcomatous renal carcinoma. Although infrequently used in renal carcinoma, tumor grading may correlate with survival, particularly in patients with nonmetastatic cancer.

CLINICAL PRESENTATION

Renal carcinoma may remain clinically occult for most of its course. The classic presentation of pain, hematuria, and flank mass occurs in only 9% of patients and is often indicative of advanced disease. A tumor in the kidney can progress unnoticed to a large size in the retroperitoneum until a metastasis appears. Approximately 30% of patients with renal carcinoma present with metastatic disease, 25% with locally advanced renal carcinoma, and 45% with localized disease. Some 75% of patients with metastatic renal carcinoma have metastases to the lung, 20% to bone, 18% to liver, 8% to cutaneous sites, and 8% to the central nervous system. A considerable number of patients with renal carcinoma develop systemic symptoms of this disease (Table 34.2-3). Hypochromic anemia, due to either hematuria or hemolysis, has been observed in 29% to 88% of patients with renal carcinoma. Pyrexia is observed in 20% and cachexia, fatigue, and weight loss in 33%. Nonmetastatic hepatic dysfunction, initially described by Stauffer in 1961, is a reversible syndrome associated with renal carcinoma that tends to occur in association with fever, fatigue, and weight loss and resolves when the primary tumor is removed. Nonmetastatic hepatic dysfunction, which is usually associated with poor long-term prognosis, occurs in up to 7% of patients with renal carcinoma. Abnormal hepatic function is observed in up to 40%.

| Presenting Symptoms, Laboratory Abnormalities, or Abnormalities on Physical Examination and Their Relation to Survival Rate in 309 Consecutive Patients Undergoing Nephrectomy for Renal Carcinoma |
|---|---|---|
| Symptomatic of carcinoma | |  |
| Cancer, localized |  |  |
| Cancer, advanced |  |  |
| Nonmetastatic hepatic dysfunction |  |  |

TABLE 34.2-3. Presenting Symptoms, Laboratory Abnormalities, or Abnormalities on Physical Examination and Their Relation to Survival Rate in 309 Consecutive Patients Undergoing Nephrectomy for Renal Carcinoma
One to five percent of patients with kidney cancer have polycythemia. Renin levels often are elevated in patients with renal carcinoma but tend to return to normal after the kidney is removed. Whether the tumor itself produces renin or whether it induces renin production by compression of adjacent tissue is unclear. Immunocytochemical studies suggest that renal carcinoma may produce renin, which, however, may be biologically inactive. Plasma fibrinogen levels may be elevated in patients with renal carcinoma and may correlate with tumor stage, disease activity, and response to therapy. Acquired dysfibrinogenemia has also been reported in association with renal carcinoma and can be a sensitive plasma marker for the disease and for tumor progression.

SYSTEMICALLY ACTIVE TUMOR-PRODUCED FACTORS

In many patients with RCC, there is evidence of tumor-produced factors that have systemic effects. Pyrexia, cachexia, abnormal liver function, increased alkaline phosphatase levels, hypercalcermia, polycythemia, nephromyopathy, and amyloidosis have all been reported in association with RCC.

Humoral hypercalcermia of malignancy, frequently observed in patients with advanced RCC, is believed to be caused by a tumor-produced, systemically active bone-resorbing factor. A number of investigators have demonstrated that kidney cancer produces a factor with parathyroid hormone–like bioactivity. A parathyroid hormone–related protein that has been implicated in malignant hypercalcermia has been cloned from a human lung cancer cell line and is expressed in mammalian cells. Whether the parathyroid hormone–like factor induces paracrine or endocrine effects, such as bone resorption or hypercalcermia of malignancy, in patients with RCC is currently being studied.

<table>
<thead>
<tr>
<th>Type of Action</th>
<th>No. of Patients</th>
<th>% of Patients of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign tumors</td>
<td>58</td>
<td>58%</td>
</tr>
<tr>
<td>Metastatic renal cell carcinoma</td>
<td>7</td>
<td>7%</td>
</tr>
<tr>
<td>Cysts</td>
<td>17</td>
<td>17%</td>
</tr>
<tr>
<td>Adenomas</td>
<td>5</td>
<td>5%</td>
</tr>
<tr>
<td>Hemangiomas</td>
<td>3</td>
<td>3%</td>
</tr>
</tbody>
</table>

TABLE 34.2-4. Underlying Pathologic Conditions in 940 Asymptomatic Space-Occupying Lesions of the Kidney

RADIOGRAPHIC EVALUATION

Determining whether a space-occupying renal mass is benign or malignant can be difficult. A number of diagnostic modalities are used to evaluate and stage renal masses, including excretory urography, CT, arteriography, venography, ultrasonography, and magnetic resonance imaging (MRI). Excretory urography is infrequently used in the initial evaluation of renal masses but, because it is neither sensitive nor specific in RCC, a small to medium-sized tumor may be present when the excretory urogram appears normal. Excretory urography does provide important information about the location and function of the contralateral kidney and, while this is particularly useful when surgery is being considered, CT has replaced excretory urography in the evaluation of renal masses.

Ultrasound examination provides excellent staging and diagnostic information and can provide accurate anatomic detail of extrarenal extension of tumor, adrenal involvement, involvement of lymph nodes, and infiltration of adjacent viscera.

Renal arteriography is infrequently used in the evaluation of patients with a suspicious renal mass (Fig. 34.2-3). In a renal carcinoma, the arteriogram often will show neovascularity, arteriovenous fistulas, pooling of contrast medium, and accentuation of capular vessels. Epinephrine may be used as an aid in the diagnosis of an equivocal renal mass. When epinephrine is infused into a normal kidney during arteriography, the renal vessels constrict; in contrast, the vessels in a renal carcinoma do not constrict, owing to lack of musculature in the tumor vessels. A renal arteriogram may be useful in evaluating an indeterminate small renal mass and as an aid to the surgeon in defining the vasculature during the surgical removal of a large tumor. Although renal arteriography can be performed with minimal risk, false aneurysms, arterial emboli, hemorrhage, and decreased renal function secondary to contrast agent injection have been reported. Dual-phase three-dimensional magnetic resonance angiography can be a useful technique in depicting renal vessels before surgical therapy. This technique is very accurate for the detection of the renal arteries, renal vein involvement, and extension into the inferior vena cava.

FIGURE 34.2-3. Angiographic appearance of a renal carcinoma. A: Computed tomography demonstrates a right renal carcinoma (m) with a large contralateral adrenal metastasis (a). B: Early phase of the arteriogram demonstrates vascular changes indicative of a malignancy, with puddling and tortuosity (arrows). C: Late phase of the arteriogram demonstrates that the tumor (m) is relatively avascular despite its early appearance.

CT is a useful imaging technique for renal carcinoma (Fig. 34.2-4). CT and ultrasonography have become the main modalities used to characterize renal masses. Although arteriography and CT are equivalent in depicting renal vein involvement, CT is better for demonstrating local nodal involvement. The use of contrast agent enhancement has greatly increased the sensitivity of CT for abnormal renal masses. Contrast-enhanced CT allows the clinician to detect very small changes in the density of a renal lesion that might indicate the presence of an early neoplastic lesion. In a companion study, dynamic CT was superior to standard CT arteriography, ultrasonography, and radionuclide scanning. Dynamic CT correctly demonstrated tumor involvement of the kidney, involvement of the renal fascia, or extension into adjacent organs in all of the 22 patients studied (see Fig. 34.2-4).
FIGURE 34.2-4. Renal vein invasion by a renal carcinoma as shown by computed tomography (CT) and magnetic resonance imaging. **A:** Nonenhanced CT scan shows large left renal mass with calcification (m) invading the left renal vein (arrow). **B:** T1-weighted magnetic resonance image demonstrates tumor (m) and vascular invasion (arrow). Flowing blood (v) in the left renal vein is black on this scan.

Inferior venacavography may be performed when a large renal tumor is present or when there is uncertainty about tumor involvement of the vena cava. Ultrasoundography, CT, and MRI can provide information about tumor involvement of the vena cava (Fig. 34.2-5) but, however, the inferior venacavogram is the most reliable means of accurately determining the precise extent of vena caval involvement by tumor. This information is important to the surgeon in planning the vascular aspect of the operative procedure. MRI can produce a unique three-dimensional picture of the tumor, which, in the case of a large lesion, may be an invaluable aid to the surgeon in planning the operative approach. In patients with tumor involving the inferior vena cava, transesophageal echocardiography has been shown to be an accurate diagnostic technique for tumor imaging to document the extent of involvement of the vena cava (see Fig. 34.2-5).

FIGURE 34.2-5. Invasion of inferior vena cava (IVC) by renal carcinoma demonstrated by magnetic resonance imaging and venography. **A:** Axial T1-weighted image demonstrates a large left renal carcinoma with extension into the left renal vein (m) with protrusion into the IVC (v). **B:** Sagittal T1-weighted image shows the relation of the tumor thrombus (m) to the IVC (v) in the lateral projection. **C:** An anteroposterior image of the inferior cavogram demonstrates tumor (arrows) in the medial aspect of the inferior vena cava.

No single imaging technique is best for all patients with renal carcinoma. Depending on the size of the primary tumor and the extent of extrarenal disease, excretory urography, CT, ultrasonography, arteriography, venography, and MRI each can provide unique information in an individual case. Because CT, MRI, and ultrasonography are outpatient procedures and are less invasive than arteriography, arteriography now is infrequently used. Multiple imaging modalities often are combined to provide the most complete information, particularly when surgical removal of a large tumor is being considered.

STAGING AND PROGNOSIS

Robson Classification

The staging system used in the past by most physicians in the United States is the Robson modification of the system of Flocks and Kadesky (Table 34.2-5). In the Robson classification, stage I renal carcinoma is confined to the kidney. Stage II carcinoma extends through the renal capsule but is confined to Gerota's fascia, and stage III carcinoma involves the renal vein or inferior vena cava (IIIA) or the local hilar lymph nodes (IIIB). In stage IV renal carcinoma, the tumor has spread to local, adjacent organs (other than the adrenal gland) or to distant sites. The Robson staging system is uncomplicated and widely used. A disadvantage of this system is that it combines stages that may have significantly different survival prognoses. In this classification system, renal inferior vena caval involvement (IIIA) is staged the same as is local lymph node metastasis (IIIB). Although patients with stage IIIB renal carcinoma experience a greatly decreased survival, the prognosis for patients with stage IIIA renal carcinoma is not markedly different from that for patients with stage I or stage II renal carcinoma. Patients who have disease that involves the inferior vena cava often have either locally advanced or micrometastatic disease. However, patients who are found to have no evidence of metastatic disease and who undergo complete surgical excision can expect to have a reasonable chance for 5-year survival.

<table>
<thead>
<tr>
<th>Findings</th>
<th>TNM Classification</th>
<th>Robson Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small tumor, involving Gerota's fascia</td>
<td>T1</td>
<td>A (I)</td>
</tr>
<tr>
<td>Large tumor, noninvasive</td>
<td>T2</td>
<td>A (I)</td>
</tr>
<tr>
<td>Perinephric or hilar invasion</td>
<td>T3</td>
<td>B (II)</td>
</tr>
<tr>
<td>Renal vein involved</td>
<td>T3</td>
<td>C (III)</td>
</tr>
<tr>
<td>Vein(s) involved</td>
<td>T4</td>
<td>C (III)</td>
</tr>
<tr>
<td>Extension to neighboring organs</td>
<td>T4</td>
<td>D (IV)</td>
</tr>
<tr>
<td>Nodal involvement</td>
<td>No</td>
<td>C (III)</td>
</tr>
<tr>
<td>Omental metastasis</td>
<td>No</td>
<td>B</td>
</tr>
</tbody>
</table>

TABLE 34.2-5. Comparison of the Two Classification Systems for Staging of Renal Carcinoma

Tumor, Node, Metastasis Classification

The TNM (tumor, node, metastasis) classification proves a more accurate method for classifying the extent of tumor involvement. In the TNM classification, T1 denotes a tumor 7 cm or less confined to the kidney, T2 denotes a tumor more than 7 cm in greatest dimension but that is still confined to the kidney, T3 denotes tumor that extends into the major veins or invades the adrenal gland or perinephric tissues but not beyond Gerota's fascia, and T4 denotes tumor that has extended beyond Gerota's fascia (Table 34.2-6).
TABLE 34.2-6. TNM Classification of Kidney Cancer

N1 denotes metastasis in a single regional lymph node; N2 denotes metastasis in more than one regional lymph node. M1 indicates distant metastasis. The 1997 TNM classification of renal carcinoma appears to provide improved stratification according to survival and may have enhanced clinical utility as compared with previous classification systems.

SURVIVAL

The 5-year survival initially reported by Robson et al. in 1969 was 66% for stage I renal carcinoma, 64% for stage II, 42% for stage III, and only 11% for stage IV. Except for stage I carcinoma, these survival statistics remained essentially the same for a number of years (Table 34.2-7). However, it has since been noted that while renal vein involvement does not have a markedly negative effect on prognosis, the 5-year survival for patients with stage IIIB RCC is only 18%. Recent studies have reported better survival for patients with tumor confined to the kidney: approximately 95% 5- and 10-year disease-specific survival for T1 renal carcinoma and an 88% 5-year and an 81% 10-year disease-specific survival for stage T2 disease. Patients with T3 renal carcinoma had a 59% 5-year survival, and those with T4 disease, a 20% 5-year disease-specific survival.

TABLE 34.2-7. Summary of Published Survival Rates in Renal Carcinoma Demonstrating Improvement in Survival Over Time

In patients with N0M0 tumors, studies have detected no statistically significant difference in survival in relationship to the T stage of the disease. The 5-year survival for patients with metastatic renal carcinoma continues to be low, from 0% to 20%.

With the expanded use of CT scans and ultrasonography, the rate of incidentally found carcinomas of the kidney has increased. The prognosis for patients whose tumor was diagnosed incidentally is more favorable than that for patients who present with symptoms, as the former group consists of patients with smaller tumors that usually tend to be confined to the kidney. Patients with metastatic renal carcinoma who present with humoral hypercalcemia of malignancy have a poor prognosis. Fahn et al. reported the median survival of patients with stage IV kidney cancer to be fewer than 50 days. Most studies show increased survival in patients in whom metastatic disease has been diagnosed and in whom the following conditions obtain: (1) a long disease-free interval between initial nephrectomy and the appearance of metastases, (2) presence of only pulmonary metastases, (3) good performance status, and (4) removal of the primary tumor.

SURGICAL TREATMENT

Surgery is the only known effective therapy for localized renal carcinoma. The first nephrectomy was performed by Eratus B. Walcott in Milwaukee on June 4, 1861, on a 58-year-old man with a kidney tumor who died 15 days after surgery. Professor Gustave Simon, after completing a number of experimental nephrectomies on dogs, undertook the first deliberate, planned, and successful nephrectomy in Heidelberg on August 2, 1889, in a patient with a persistent ureteral fistula. The first successful nephrectomy in a patient with kidney cancer was performed in 1883 by Grawitz. The standard procedure today for treatment of localized renal carcinoma is radical nephrectomy (Fig. 34.2-6). Radical nephrectomy involves complete removal of Gerota's fascia and its contents, including the kidney and the adrenal gland, and provides a better surgical margin than simple removal of the kidney. Owing to the rarity of ipsilateral adrenal metastasis and the potential morbidity associated with adenectomy, many surgeons believe that a macroscopically normal ipsilateral adrenal gland should not be removed with the kidney (see Fig. 34.2-4).

A number of different surgical approaches have been described for removal of kidney cancer. Common approaches are the anterior transperitoneal approach, the flank approach, and the thoracoabdominal approach. The choice of surgical approach depends on the location and size of the tumor and the body habitus of the patient. The type of incision is chosen to ensure that the tumor may safely be removed. A flank incision, with or without removal of a portion of the tenth or eleventh rib, is often used for small tumors without venous involvement. A subcostal transabdominal incision may be used when a large tumor occupies the middle or lower
aspect of the kidney or when vascular involvement is anticipated and access to the major vessels is essential. A thoracoabdominal incision often is required when a large middle or upper pole tumor is present.

In a thoracoabdominal incision, a rib is removed, the thoracic cavity is opened, and the diaphragm is incised. The incision then is carried down transabdominally to allow maximal exposure of the upper abdominal region and the great vessels. In removal of a right-sided tumor, the hepatic flexure of the colon is mobilized toward the midline away from the kidney and duodenum. The duodenum is also dissected up anteriorly and medially to the great vessels, and the renal artery and vein are identified. The renal vessels are divided and ligated early in the surgical procedure to decrease the vascularity of the tumor so that it may be removed with a minimum of blood loss. Following ligation of the vessels, Gerota’s fascia is incised away from the posterior abdominal wall, diaphragm, and liver (pancreas and spleen on a left-sided tumor) (see Fig. 34.2-6). Once Gerota’s fascia and its contents have been dissected away from the surrounding structures and the vasculature has been ligated with nonabsorbable suture, the specimen can be lifted out of the retroperitoneum. When there is tumor in the renal vein, the renal vein can be ligated distal to the tumor thrombus. If there is tumor extension into the vena cava, the vena cava may need to be partially resected. If the tumor has grown into the sidewall of the vena cava or if the vena caval involvement is too extensive for a simple partial wall resection, a portion of the vena cava itself may be resected. When the tumor is in the right kidney, the adjacent vena cava can often be resected safely. If, however, the tumor in the left kidney and the adjacent vena cava are resected, vascular reconstruction of the right renal vein may be needed to establish adequate venous drainage. If the suprahepatic caval extension of a renal tumor thrombus extends up to the right atrium, cardiopulmonary bypass may be required for tumor removal (Fig. 34.2-7).

FIGURE 34.2-7. Surgical removal of a kidney tumor in which there is tumor extension through the renal vein into the inferior vena cava.

Laparoscopic nephrectomy has been evaluated as a less invasive procedure for the removal of kidneys with a small volume of RCC. Walther et al. have also evaluated the use of laparoscopic cryoablation nephrectomy in patients with advanced RCC as preparation for interleukin-2 (IL-2) treatment. Regional lymphadenectomy often is performed at the time of radical nephrectomy, although its role in prolonging survival has not been demonstrated. In a regional lymphadenectomy, ipsilateral nodal tissue from the diaphragm to the bifurcation of the aorta as well as nodal tissue in the interaortocaval region at the hilum of the kidney is removed. Proponents of regional lymphadenectomy point out that 5-year survival in patients with node-positive renal carcinoma is greatly decreased, and there is no known effective therapy for metastatic renal carcinoma. If local nodes were the first site of metastasis, resection of microscopic disease might be of benefit. Long-term survival in patients with node-positive disease who underwent lymphadenectomy has been reported. The ultimate role of regional lymphadenectomy remains to be determined in further randomized trials. In patients with locally advanced RCC (node-positive), no evidence to date supports the theory that, postsurgical treatment of patients with an agent such as IL-2 or interferon-a (IFN-a) increases survival. In patients in whom all visible disease has been resected surgically, most physicians recommend treatment when residual or recurrent disease becomes detectable.

Bilateral Renal Carcinoma or Tumors in Solitary Kidneys

The treatment of patients with either bilateral renal carcinoma or renal carcinoma in a solitary kidney is challenging. Patients with tumor in a solitary kidney may be treated by either partial nephrectomy or nephrectomy followed by dialysis or transplantation (or both). In selected patients, nephron-sparing surgery may be recommended for patients with sporadic renal cell cancer, particularly those with a small tumor (£4 cm) or a tumor in a solitary kidney. Extracorporeal partial nephrectomy plus autotransplantation is an infrequently used technique that allows the surgeon accurately to remove large tumors from the center of a solitary kidney. This ex vivo procedure entails radical excision of the kidney and division of the ureter. The kidney then is placed on a table and is intermittently perfused with a chilled solution to enhance viability. Under optical magnification, the tumor is carefully dissected from the surrounding renal parenchyma. Care is taken to preserve the vascularity of the normal kidney, which has been defined by preoperative arteriography. A small rim of normal tissue is removed along with the tumor to provide a tumor-free margin of resection. After the kidney has been surgically reconstructed, it is autotransplanted back into the iliac space. Vascular anastomosis of the renal artery and vein to the iliac vessels and ureteroureterostomy are performed.

Surgical Management of Patients with Hereditary Forms of Renal Carcinoma

Patients with hereditary forms of renal carcinoma are often challenging to manage. Individuals with VHL syndrome or HPRC can have widespread renal involvement. Surgical management in these patients involves careful parenchyma-sparing surgery, which is recommended when the renal tumors reach a certain size threshold, generally 3 cm. The use of parenchyma-sparing surgery in these patients is based on a strategy designed to maintain the patient’s renal function as long as possible while decreasing the risk for metastasis.

Radiotherapy as an Adjuvant to Nephrectomy

The value of adjuvant external-beam radiotherapy for patients with RCC remains unclear. Previous reports have demonstrated increased complication rates using conventional radiotherapeutic techniques. In addition, several randomized studies performed 20 to 30 years ago showed no apparent survival benefit with adjuvant therapy. These considerations led to an overall lack of enthusiasm for using radiotherapy in this disease. However, recent studies have suggested that the use of more sophisticated radiation techniques is less likely to result in treatment-related complications. In addition, previous trials testing preoperative or postoperative radiotherapy for this disease may not have been designed in an optimal fashion to evaluate its potential benefit fully for improving outcome in high-risk patients.

Though some retrospective reports have indicated an improvement in local tumor control or overall survival with the addition of postoperative radiotherapy, subsequent randomized prospective trials could not confirm any benefit. In one randomized study reported by Finney et al., the incidence of local recurrence was 7% in both the adjuvant radiotherapy and control arms. In addition, no survival advantage was detected in the radiotherapy arm. In fact, a trend for an inferior 5-year survival outcome was observed for the adjuvant radiotherapy group (36% as compared to 47% for patients with nephrectomy), owing to a higher complication rate observed in these patients. Ten years later, a second randomized prospective trial comparing nephrectomy and postoperative radiotherapy to nephrectomy alone demonstrated identical results. In that study, the incidence of local recurrence was reduced from 25% to 3% with adjuvant local radiotherapy. Further, the incidence of treatment-related morbidity in these two randomized trials was unacceptably high. Severe complications were experienced in 20% to 44% of treated patients, with an associated increased mortality rate due to radiation-related toxicities. The potential value of preoperative radiotherapy has also been tested in two randomized trials, neither of which could demonstrate any advantage for improved local control or survival with adjuvant radiotherapy.

However, it is difficult to draw any meaningful conclusions about the safety and value of adjuvant therapy for patients with RCC who are at increased risk for local recurrence. Previously published postoperative studies used relatively crude radiation techniques, and the radiation dose per fraction of 250 cGy to cumulative doses of 5000 to 5500 cGy used in some reports likely directly contributed to the high gastrointestinal and liver-related toxicities observed. In addition, a significant percentage of patients treated in these trials did not have prognostic features indicating a high risk for local recurrence for which adjuvant radiotherapy may have been potentially beneficial. Based on patterns-of-failure studies after nephrectomy alone, the overall local recurrence rate is low, and routine administration of adjuvant local therapy for all patients on the basis of advanced stage only would not be expected to improve outcome. However, on 172 patients treated with nephrectomy alone to identify patterns of failure and risk factors for local recurrence. In that report, the 7-year actuarial local failure rate was 5%.
However, among patients with positive surgical margins or positive lymph nodes, the incidence of local recurrence was 21%. Advanced T-stage disease in the absence of these prognostic features did not predict for local recurrence and thus is not necessarily an indication for local adjuvant therapy.

More recent reports have demonstrated that with the application of more sophisticated radiotherapeutic planning techniques, the incidence of treatment-related complications has been minimized. Using CT scanning, Kooby et al. at the University of Pennsylvania retrospectively reported the outcome of postoperative radiotherapy for selected patients with positive surgical margins or perinephric disease extension. Doses ranged from 4140 cGy to 6300 cGy using conventional fractionation. The overall local failure and survival rates were 100% and 75%, respectively, as compared to 30% and 62%, respectively, for similar patients at the University of Pennsylvania who underwent nephrectomy alone. Despite the higher radiation doses used, no late complications were observed.

An additional limitation of prior studies is the relatively low postoperative doses used secondary to concerns of late radiation sequelae. Several reports have suggested that higher doses may be necessary in this disease to overcome the relative radioresistance of the renal cell histology.\(^{105-108}\) With the introduction of three-dimensional conformal radiotherapy and intensity-modulated treatment delivery systems, it now is possible to deliver higher radiation doses in the adjuvant setting with improved target coverage and lower normal tissue complications. The use of postoperative radiation for high-risk patients may prove to be an effective approach for the delivery of high radiation doses, with the ability to easily shield the adjacent normal gastrointestinal structures. Eble et al.\(^{107}\) and Frydenberg\(^{106}\) reported the results of a phase I study in 11 patients with advanced-stage or locally recurrent RCC that incorporated intraoperative radiotherapy (15 to 20 Gy) in combination with fractionated external-beam radiotherapy. The 4-year survival outcome was 75%, and no local relapses or complications were noted. In a limited number of patients with recurrent RCC, other investigators have reported the feasibility of postoperative, hyperfractionated, high-dose-rate brachytherapy using iodine 192 as a means of effectively delivering a high radiation dose to the postoperative bed.\(^{110}\)

The aforementioned studies would suggest that adjuvant radiotherapy may be of benefit for selected patients with high-risk features predicting for local recurrence after nephrectomy. Using modern external-beam and brachytherapy techniques, higher radiation doses can now be delivered more safely and may further improve the efficacy of radiotherapy for selected patients. Nevertheless, randomized trials limited to high-risk patients will be required to assess fully the local control benefit of postoperative radiotherapy in this clinical setting.

Metastatic Renal Carcinoma

Nephrectomy and Resection of Metastases

Cytoebductive Nephrectomy. Adjuvant or palliative nephrectomy is not infrequently performed in patients with metastatic RCC particularly those with pain, hemorrhage, malaise, hypercalcemia, erythrocytosis, or hypertension. Removal of the primary tumor may alleviate some or all of these abnormalities.\(^{106}\) Although there are isolated reports of regression of metastatic renal carcinoma after removal of the primary tumor, only 4 (0.8%) of 474 patients in nine series who underwent nephrectomy have been described as having "regression" of metastatic foci.\(^{111}\) deKernion et al.\(^{112}\) reported results in 26 patients with metastatic renal carcinoma who underwent palliative or adjuvant nephrectomy and found no increase in survival, as compared with survival in the entire group of 79 patients with metastatic renal carcinoma. Adjuvant nephrectomy is not recommended for the purpose of inducing spontaneous regression; rather, it is performed to decrease symptoms or to decrease tumor burden in preparation for subsequent therapy in carefully controlled environments.\(^{113}\) The recent use of laparoscopic nephrectomy\(^{114}\) provides a potentially less invasive method for cytoreduction as preparation for administration of systemic therapies such as IL-2.

Resection of Metastases. Of the approximately 30% of patients with RCC who present with metastases, fewer than 4% have solitary metastases.\(^{115}\) Patients with a solitary metastasis synchronous with a primary lesion experience decreased survival when compared with patients who develop metastasis after the primary tumor is removed.\(^{115}\) Surgical resection is recommended in selected patients with metastatic renal carcinoma. In a study of 59 patients with renal carcinoma who underwent surgical resection for a solitary metastasis, 45% had a 3-year survival, and 34% survived 5 years.\(^{116}\) O'Dea et al.\(^{117}\) reported on patients who presented with primary tumor in place and a solitary metastasis. Of the patients who underwent nephrectomy and who later developed metastasis, 23% lived more than 5 years after removal of the metastatic lesions. Three of the 26 patients were alive 58, 94, and 245 months after resection of the metastatic lesions.\(^{118}\) Nephrectomy and resection of metastases will render few cures but frequently will produce some long-term survivors.

Role of Radiotherapy. Palliative radiotherapy for patients with symptomatic metastatic osseous lesions can be effective. Previous reports have noted response rates of 50% to 70% after local palliative radiotherapy for patients with metastatic RCC.\(^{119}\) In a randomized trial assessing various fractionation schemes for the palliation of symptomatic bone metastases, renal cell histology was found to respond less favorably to standard palliative radiation regimens as compared to metastatic breast and prostate cancers.\(^{117}\) In light of the relative radioresistance of this histology, higher radiation doses are critical to achieve adequate palliation. In general, doses of at least 50 Gy are required to achieve durable palliation. To deliver these higher doses safely, complex treatment planning often is necessary to minimize treatment-related toxicity. Investigators from the Jefferson College of Medicine have shown that higher radiation doses were associated with an improved palliative response.\(^{120}\) In a multivariate analysis, a higher baseline performance status and the use of higher radiation doses predicted for a greater likelihood for significant pain relief after radiotherapy for painful osseous lesions. Large-volume metastatic lesions such as those found within the renal bed require higher radiation doses to achieve palliation and, in general, this therapy is successful in fewer than 50% of treated patients.

Brain metastases from RCC are often hemoragic in nature, and the rapid initiation of palliative radiotherapy may be necessary to halt potential neurologic progression. Surgery should be considered for solitary lesions of the brain or spine, followed by postoperative radiotherapy. The results of routine administration of short-course whole brain radiotherapy using the conventional fractionation of 3000 cGy in ten fractions has been disappointing.\(^{121}\) Investigators from the Memorial Sloan-Kettering Cancer Center have reported that in the majority of treated patients with short-course whole brain radiotherapy, the cause of death was neurologic deterioration.\(^{122}\) For selected patients with good performance status or solitary lesions, radiosurgery alone or in combination with whole brain radiotherapy provides an opportunity to deliver higher doses and should be considered.\(^{123}\) Pomer et al.\(^{124}\) have shown that for patients with metastatic RCC, radiosurgery was more effective among those with a Karnofsky performance score in excess of 70 and among those with a greater than 1-year interval from diagnosis to manifestation of central nervous system metastases.

Osseous lesions in weight-bearing areas such as the femora should be considered for initial orthopedic stabilization, followed by postoperative radiotherapy. Treatment with radiotherapy alone should be exercised with some caution owing to the potential for posttreatment fracture.

Systemic Chemotherapy for Renal Cell Carcinoma

Limited options are available for the systemic therapy of RCC, and no hormonal or chemotherapeutic regimen is accepted as a standard of care. Reviews surveying phase II clinical trials for RCC have appeared at intervals (1967, 1973, 1983, 1995, and 2000).\(^{125-127}\) without a change in the final conclusion: No systemic chemotherapy or hormonal approach has provided a reasonable level of activity.

A comprehensive review by Yagoda et al.\(^{128}\) encompassed 4542 patients enrolled in 83 clinical trials published from 1983 through 1993. Among 4093 evaluable patients, a 6.0% response rate was recorded, with 53 complete responses (CRs; 1.3%) and 192 partial responses (PRs; 4.7%). Response rates in excess of 25% were noted in eleven trials; in each case another trial incorporating the same or a comparable treatment regimen reported lower or zero response rates.

Three agents warrant particular mention: floxuridine, 5-fluorouracil (5-FU), and vinblastine. One of the most intensively studied agents has been infusional floxuridine, which, studied in both standard and circadian schedules, appears to have a level of activity above the background. Fourteen trials yielded response rates ranging from 10% to 13%, with an overall average rate of 12%. Seven trials had response rates of less than 10%, and four had response rates exceeding 20%. For 5-FU, which has been primarily used in combination with immunotherapy, response rates were somewhat fewer, with an overall response rate of 10% for infusional 5-FU alone and 19% for 5-FU in combination with interferon. Similar results were reported for vinblastine, an agent initially thought to have activity in RCC. In the Yagoda series,\(^{128}\) seven trials incorporating infusional vinblastine yielded an overall response rate of 7%, whereas three trials reported no responses. Since 1993, further results with vinblastine have been equally discouraging. As the control arm for a multidrug resistance modulator trial, vinblastine produced one PR in 80 patients; as the control arm for an interferon trial, vinblastine produced one complete and one PR among 81 patients.\(^{129}\)

The 83 trials reported in the review by Yagoda\(^{128}\) included compounds from every class of anticancer agent: antimetotics (paclitaxel and docetaxel); vinca alkaloids (vinblastine, vincideine, and vinoreline); anthracodines (epirubicin, doxorubicin, and idarubicin); anthrancenediones (mitoxantron, bisantrene); alkylating agents (both nitrosoureas and sulfonylefuranes, as well as ifosfamide and melphalan); metals (carboplatinum and gallium nitrate); pyrimidines (fluoruridine, 5-FU, and gemcitabine);
and purines (6-thioguanine, fludarabine, and 2-deoxycoformycin). Yagoda et al. concluded that the responses may be mediated by an indirect effect on the immune system. Considering that the response rates in these trials are higher than the frequency of spontaneous remissions, and observing the occasional complete remission, one could speculate that the responses involve an effect triggered by the chemotherapy but mediated by the immune system. However, scientific evidence to support this thesis is lacking. Although the majority of patients experiencing a complete remission were noted in trials including cinetidine, vinblastine, 5-FU, and fluorouracil, the CR rate ranges between 2% and 4%, which is not very different from the 1.3% CR rate noted in the entire series. These considerations favor a conclusion that little, if any, cytotoxic activity has been exerted in renal cell cancer. It can be concluded that the best recommendation for patients with this disease, after immunotherapy, is participation in clinical trials studying new agents or new approaches.

**Hormonal Therapy in Renal Cell Cancer**

Hormonal agents have also been used in systemic therapy. This strategy had its origins in studies showing that progesterone could inhibit the development of estrogen-induced renal cell cancers in Syrian hamsters and in the observation that both estrogen and progesterone receptors could be found in a portion of human kidney cancers. Subsequently, medroxyprogesterone acetate (Megace) became conventional treatment for renal cell cancer. However, multiple studies have concluded that hormonal therapy is of no definite benefit. A series of studies collected from 1967 through 1976, using progestins or androgens included 644 patients. Response rates were highest (17%) in the earliest studies. With more stringent response criteria used in the studies conducted after 1971, an overall rate of 2% was observed. Except for its value in appetite stimulation, the use of Megace cannot be recommended in the treatment of renal cell cancer today.

Studies with antiestrogens in more recent years have yielded similar results. An overall response rate of 7% (three patients with CR) was identified in four studies treating 146 patients with high-dose tamoxifen (100 mg/m²/d or more). More recently, two CRs (3%) were reported in 63 patients receiving 40 mg of oral tamoxifen daily in the control arm of a randomized study. Similar activity was suggested also in a pilot study of high-dose toremifene (300 mg/d), a novel antiestrogen with activity in breast cancer. Thus, reported responses to treatment with hormonal therapy most likely mimic the same level of inactivity identified with most chemotherapeutic agents.

**Recent Chemotherapy Trials in Renal Cell Cancer**

More recently, an effort has been made to identify new treatment targets in cancer. A limited search for phase II single agents examined in renal cell cancer and reported since 1993 (and thus not included in earlier reviews) identified 23 published studies. These compounds, shown in Table 34.2-8, are from various pharmaceutical classes, including taxanes, camptothecins, anthracyclines, antifolateis, and alkylating agents. In recent abstracts from the American Society of Clinical Oncology, an additional nine new agents were tested. Once again, the refractory nature of renal cell cancer is observed. One new study—the combination of gemcitabine and 5-FU—warrants mention. In a study reported by Vogelzang at the University of Chicago, 7 PRs (17%) were observed among 39 patients receiving gemcitabine at 600 mg/m² on days 1, 8, and 15 and continuous-infusion 5-FU at 150 mg/m²/d for 21 days in 28-day cycles.

Table 34.2-8. Phase II Studies in Renal Cell Cancer: 1993–1999

To some extent, the refractory nature of renal cell cancer highlights a general problem with anticancer agents developed over the last three decades. A review of cytotoxic drugs introduced into clinical trial by the National Cancer Institute between 1970 and 1985 found that half of the 47 new agents adequately studied in phase II trials could be rated as having anticancer activity. Among these active compounds, 74% were active in lymphoma, 35% in leukemia, 22% in breast cancer, and 18% in ovarian cancer. Only one drug was active in colon cancer; no activity was reported with any of the 25 drugs properly tested in renal cell cancer. These data suggested that the prevailing screening strategies for anticancer agents were biased toward agents active in leukemia and lymphoma and were not likely to identify agents active in solid tumors. Thus, the drug screen was reorganized and a 60–cell line in vitro screen was established in 1990 with cell lines derived from solid tumors including RCC. It is hoped that this effort, along with compounds under development for defined intracellular and extracellular targets, will identify agents with activity in those tumors that are most difficult to treat. The antiangiogenesis agents currently being developed are examples of compounds with a novel approach to this difficult problem.

**Chemotherapy Combined with Interferon in Renal Cell Cancer**

Interferon, one of two immunotherapeutic agents widely used in the treatment of renal cell cancer (as discussed later, in Biologic Therapy), has a modest response rate and confers a survival advantage as a single agent. Numerous trials have been conducted combining interferon with cytotoxic chemotherapy in the hope that the immunologic benefit from interferon would improve the response to chemotherapy. With identified response rates ranging from 0% to 45% among 315 patients in 11 trials combining vinblastine with IFN-a, the response rates were highest in the oldest trials, where less stringent response criteria were used. Randomized studies have failed to provide any evidence for combining interferon with vinblastine (Table 34.2-9).

Table 34.2-9. Randomized Phase III Trials with Interferon and Chemotherapy

Interferon has also been combined with fluorouracil or 5-FU in multiple studies, with several reporting higher response rates than usually reported with either agent alone. However, more recent, nonrandomized, multinstitutional studies have been disappointing, suggesting little or no benefit from combining interferon with fluorouracil given over 14 days or with 5-FU.

A similar evolution occurred with the combination of interferon and cis-retinoic acid; Motzer et al. originally observed a 30% response rate for the combination.
Cell cancer is a major challenge for the new millennium. It is most likely that new agents directed against novel targets will be subject to the same mechanisms of tumor-based mechanisms, while resistance in even the tiniest pulmonary nodule suggests cellular mechanisms. A detailed understanding of drug resistance in renal cancer is a remarkable refractory solid tumor. More resistant than most other cancers, new phase II agents have failed time and again. The explanation for this drug resistance may lie within the tumor as an entity or within the individual cells. The broad spectrum of drugs to which RCCs are resistant suggests that resistance in kidney cancer. Factors that influence drug delivery include blood flow, permeability of tumor vasculature, and drug diffusion into the interstitium, which is affected both by properties of the drug and by interstitial pressure within the tumor. Thus, ample evidence for intracellular mechanisms of resistance exists in RCC. The challenge is to determine the importance of such mechanisms and to identify strategies for their circumvention.

Drug Resistance in Renal Cell Cancer

The ineffectiveness of chemotherapy can be ascribed to the primary, or intrinsic, resistance to chemotherapy, which, although poorly understood, is a hallmark of RCC. Overexpression of the 170-kD drug transporter P-glycoprotein (P-gp) and its encoding gene, MDR-1, has been most frequently cited as a mechanism of resistance. Expression of P-gp in RCC is related to its normal tissue expression in the cell of origin, the renal proximal tubule; and the level of expression correlates with differentiation. Fojo et al. reported high levels of expression of this transporter in kidney cancer and in vitro sensitization of kidney cancer cell lines to vinblastine with the antagonists verapamil and quindine. Chemosensitivity studies with fresh tumor specimens demonstrated high levels of resistance in 30 of 35 samples, and overexpression of P-gp in 70% of cases. Together, these findings suggest that P-gp expression could explain, at least in part, the notorious resistance of RCC.

However, efforts to modulate P-gp by treating patients with antagonists have met with disappointing results to date. Except for a single phase I study with doxorubicin, most of the trials have attempted modulation of vinblastine (Table 34.2-10). Though the studies, at face value, suggest no role for P-gp in RCC, it can be argued that this question is not fully resolved. Most of the reversal agents used in the trials were first-generation agents with low potency, selected because they were already in clinical use for other indications. Most of the trials incorporated vinblastine. Although vinblastine is a substrate for P-gp, renal cancers may have other mechanisms of resistance to vinblastine that were not addressed by these studies. P-gp may represent an avenue to increase intracellular concentrations of an agent, but that agent must have intrinsic activity for successful resistance reversal.

**Table 34.2-10. Trials Testing the Reversal of P-glycoprotein–Mediated Resistance**

**ABC TRANSPORTERS.** The broad nature of clinical resistance in renal cell cancer suggests that P-gp may be one of multiple resistance mechanisms. Recent studies have identified the existence of an increasing number of ATP-binding cassette (ABC) transporters, of which P-gp is the prototype. These include the family of multidrug resistance–associated proteins (MRP1 through MRP6), which have organic anion transport activity and a half-ABC transporter designated MDR/BCRP/ABCP1. These transporters may confer mitoxantrone and camptothecin resistance, bringing to three the number of transporter families expressed in renal cell cancer and potentially linked to drug resistance. If these transporters are confirmed as being active in renal cell cancer, their inhibition offers a future strategy for increasing drug accumulation in kidney cancer cells.

**INTRACELLULAR MECHANISMS.** While drug transporters would directly affect intracellular concentrations of drug, other mechanisms of drug resistance have been identified that confer resistance to the levels of cell survival pathways, drug metabolism, and the drug target. Many of these have been examined in renal cell cancer, but the findings are preliminary and must be validated. Cell survival in RCC may be linked to the frequently observed overexpression of the epidermal growth factor receptor and its homologue, ErbB2, or to overexpression of the antiapoptosis protein, Bcl-2. Alternatively, increased metabolism of anticancer agents may be promoted by higher levels of enzymes of the cytochrome P-450 family in concert with glutathione and glutathione transferases. Finally, decreased levels of topoisomerase II have been observed in RCC, which could confer resistance to agents that impair cell division through inhibition of topoisomerase II.

Thus, ample evidence for intracellular mechanisms of resistance exists in RCC. The challenge is to determine the importance of such mechanisms and to identify strategies for their circumvention.

**DRUG DELIVERY.** To some, the generalized resistance just described supports an argument that drug resistance in RCC is not based primarily on cellular mechanisms. Although investigators have worked principally in other model systems, studies evaluating tumor drug delivery may cast light on the problem of drug resistance in kidney cancer. Factors that influence drug delivery include blood flow, permeability of tumor vasculature, and drug diffusion into the interstitium, which is affected both by properties of the drug and by interstitial pressure within the tumor. Strategies aimed at identifying and reducing these physiologic barriers to drug delivery are under investigation and could have a particular relevance to the very large tumor masses seen in renal cell cancer.

**Prognostic Factors**

Clinical prognostic factors relating to survival after nephrectomy have been well defined. Molecular prognostic factors that may reflect chemosensitivity have been examined but, without reliable and effective therapy for RCC, their value cannot be determined. It could be predicted from experience in other cancers that correlation obtained in the good and poor prognosis would generally relate to the inherent biology of the tumor cell in the absence of effective therapy. Thus, markers of differentiation and indolent biology will confer a better prognosis at the present time because of the limitations of current therapy. A frequently identified poor prognostic factor is expression of PCNA (proliferating cell nuclear antigen) or MiB-1/Ki-67, antigens associated with cell proliferation. Disease-free and prolonged survival is more likely in tumors with a low proliferation index. Patients with diploid tumors are more likely to have longer disease-free intervals. Interestingly, response to interferon treatment is also more likely to occur in patients whose tumors manifest a more indolent biology. That finding is in contrast to laboratory observations with chemotherapy in which a slower growth rate is associated with increased drug resistance. When effective treatment for renal cell cancer is identified, tumor markers relevant to response to treatment can then be identified.

Although patients who have stage IV disease experience a reported median survival of 12 to 24 months, the range of survival times in this group of patients is very broad. A variety of studies have looked at the parameters that predict survival in patients with metastatic renal cancer, and performance status is the most commonly used marker. Other factors that have been identified in some studies as predictors of poorer survival of patients with stage IV disease are a short interval from initial diagnosis, multiple organ involvement, recent weight loss, previous chemotherapy, anemia, and an elevated serum lactate dehydrogenase level. Such factors should be considered in evaluating survival in nonrandomized studies.

**Summary**

In conclusion, RCC is a remarkably refractory solid cancer. More resistant than most other cancers, new phase II agents have failed time and again. The explanation for this drug resistance may lie within the tumor as an entity or within the individual cells. The broad spectrum of drugs to which RCCs are resistant suggests tumor-based mechanisms, while resistance in even the tiniest pulmonary nodule suggests cellular mechanisms. A detailed understanding of drug resistance in renal cell cancer is a major challenge for the new millennium. It is most likely that new agents directed against novel targets will be subject to the same mechanisms of...
resistance that have plagued treatment of this disease for decades.

**BIOLOGIC THERAPY**

The primary therapies for widespread metastatic RCC involve the use of biologic agents. IFN-α and IL-2 are the predominant agents used, yet several major questions remain about their application. The optimal dose and schedule have not been determined for either agent, the relative efficacy of combination therapy versus single-agent therapy is not known, and the factors that predict or produce dramatic, durable responses in a minority of patients have not been elucidated. There has even been debate as to whether these agents truly have benefit for patients with metastatic renal cell cancer or whether long-term survival results from chance or spontaneous tumor regression. The experience from two decades of biologic therapy for renal cancer has clarified this latter issue, made biologic agent administration safer, and defined the role of a number of cellular agents used in renal cancer therapy. The principle that immunotherapy can cause the complete and durable regression of large burdens of metastatic renal cancer and melanoma in some patients has been conclusively established. The most significant goal not yet accomplished is to increase significantly the percentage of patients who achieve these regressions. This objective will require improvements in our understanding of current agents as well as the development of new modalities that target different biologic mechanisms.

**Spontaneous Tumor Regression**

Although it does not represent a bona fide treatment modality, much has been made of the phenomenon of spontaneous tumor regression in patients with advanced renal cancer, and the mechanism is presumed to be immunologic. The practice of nephrectomy in patients with metastatic disease in the hope of inducing a spontaneous regression has been largely abandoned owing to the disappointingly low incidence of success of this method. In reviews of spontaneous tumor regression, another striking feature is that the majority of regressions are short-lived. In one randomized study of IFN-α in patients with RCC, the placebo control population demonstrated a surprisingly high response rate of 6%, but the duration of these regressions were 2 to 13 months with only one ongoing response of 9 months at the time of publication. Other larger reviews show that the true incidence of this phenomenon is probably less than 1% and that the vast majority of documented spontaneous regressions will relapse with progressive metastatic disease and require other therapy. In addition, the few well-documented cases of durable regressions often occurred in patients in whom life-threatening infectious or inflammatory events were possible instigators of their regression. These data indicate that spontaneous regression of RCC is often transient and is not a phenomenon that should be relied on as therapy. Furthermore, spontaneous regression clearly cannot account for the consistent fraction of patients who achieve complete and durable regressions with some immunotherapies.

**Interferons**

Early studies of leukocyte interferon in the treatment of cancer reported sporadic responses in patients with RCC. Subsequently, increased dosages and larger studies were possible using recombinant IFN-α, and this experience was repeated and confirmed. The response rates in the largest studies ranged from 0% to 29% (Table 34.2-11), with few CRs and few long-term survival data. In a review of the literature in 1989, Quesada reported an overall response rate of 16% for 654 patients. Factors that seemed to increase the likelihood of responding included good performance status, prior nephrectomy, and metastases confined to the lungs. Nevertheless, these factors could not be used to identify patients without a significant possibility of response, and so they should serve only as general guidelines.

Few data exist on the long-term results from interferon therapy but, from the very small number of completely responding patients, it is safe to conclude that interferon has no significant curative potential in RCC.

**TABLE 34.2-11. Treatment of Metastatic Renal Cell Cancer with Interferon**

Recently, randomized prospective studies have been performed to measure the benefit of IFN-α in patients with advanced renal cancer. A randomized comparison of IFN-α versus medroxyprogesterone acetate in 335 patients demonstrated a significant prolongation of median survival (6 months for medroxyprogesterone acetate and 8.5 months for IFN-α). This modest, albeit statistically significant, prolongation of survival was offset by greater symptoms and lesser quality of life in patients receiving IFN-α. In addition, responses did not appear durable, with estimated progression-free survival at 2 years of 5% or less for both groups.

Many different types and preparations of interferons have been used in clinical trials. Early trials with “natural” interferon produced from donor leukocytes and subsequent trials with different subtypes of recombinant IFN-α have not suggested a difference in efficacy among these preparations. Recent trials using IFN-b and IFN-g have indicated that these agents have either similar or less activity than IFN-α. A randomized comparison of IFN-α and placebo showed no difference in response rates or survival.

Interferon is one of the few biologic agents that has been tested in a randomized adjuvant study after nephrectomy. Two hundred and ninety-four patients with completely resected T3 or T4a or N1, N2, or N3 disease were randomized to observation or to 9 months of subcutaneous lymphoblastoid interferon. With a median follow-up of 4.4 years, patients receiving interferon had similar recurrence rates and significantly worse survival than patients randomized to observation only. In view of the limited response rate to biologic therapy and the absence of any indication that responses are related to lesser tumor burdens, there is currently no rationale for recommending adjuvant biotheraphy outside of a protocol setting.

One important consideration in evaluating interferon therapy is that the optimal dose, schedule and route of interferon administration is not yet known. Although refinement of schedules may have the potential of increasing response rates somewhat, in view of the small benefit demonstrated to this point, it is unlikely that randomized studies will ever be done to effectively optimize these parameters. In summary, disseminated renal cell cancer shows a small but consistent response rate to interferon (primarily IFN-α), but these benefits must be weighed against the toxicity of chronic therapy and the lack of documented long-term benefit.

**Interleukin-2**

After its discovery in 1976 and the demonstration of its activities as a T-cell growth factor and activator of T cells and natural killer cells, IL-2 was used in clinical trials against a variety of malignancies. From the first trials in 1984, renal cell cancer was identified as a tumor that could respond to IL-2 (Fig. 34.2-8, Fig. 34.2-9, and Fig. 34.2-10). These early trials rapidly escalated the dose of IL-2 to the maximum tolerated dose and then added lymphokine-activated killer (LAK) cells to the therapy, based on preclinical results. These trials initially reported response rates of 33% in RCC and, in a subsequent multicenter experience, the response rate was 16%. The remarkable feature of many of these responses is that they appear complete and durable. Median follow-up of greater than 10 years is available from those early studies, and a review of the follow-up data indicates that 7% to 8% of all patients (nearly half of all those responding) had a CR and the majority of those completely responding patients have never relapsed (see Fig. 34.2-8). This constitutes the most convincing evidence that IL-2 has clinical benefit in the treatment of metastatic renal cell cancer and led to the approval of IL-2 by the U.S. Food and Drug Administration as the only currently approved therapy for this disease in the United States. It should be emphasized that it is the curative potential of these responses and not their frequency that is of value (Fig. 34.2-11).
FIGURE 34.2-8. Radiographs of two patients with long-term complete regressions of pulmonary metastases from renal cancer in response to high-dose therapy with interleukin-2 alone. In most studies, patients with only pulmonary metastases appear to have a slightly higher probability of response.

FIGURE 34.2-9. Abdominal computed tomography scans of a patient with a durable, ongoing complete response to high-dose interleukin-2 therapy, which included the regression of extensive liver metastases.

FIGURE 34.2-10. Regression and recalcification of a large lytic metastasis of the lateral femoral condyle in a patient with widely metastatic renal cell cancer. This patient also had a durable complete response of all soft tissue metastases with interleukin-2–based immunotherapy.

FIGURE 34.2-11. Complete responses to high-dose interleukin-2 in patients with metastatic renal carcinoma are typically durable. An actuarial curve of response duration for patients with metastatic renal cell carcinoma responding to high-dose bolus interleukin-2 is shown. Among completely responding patients, 81% have not experienced relapse (median follow-up, 7 years), and no patients have experienced relapse beyond 3 years. Partial responses can be sustained for years but, in this study, all partially responding patients eventually experienced relapse. (Adapted from ref. 143.)

Since those early studies, several developments have occurred. The use of LAK cells with IL-2 has been critically examined in randomized studies, and many investigators have explored the use of lower-dose IL-2 regimens to avoid the toxicity of high-dose IL-2. Although murine models predicted that the addition of LAK cells to IL-2 would substantially increase therapeutic efficacy, this has not proved to be true in clinical studies. A randomized comparison of high-dose intravenous bolus IL-2 with and without LAK cells showed an insignificant difference in response rate (21% for IL-2 and 31% for IL-2 combined with LAK cells) with no difference in survival. Other studies have confirmed this and, currently, there is no evidence to support the use of LAK cells in patients with RCC.

The initial rapid escalation of IL-2 to its maximum tolerated dose identified as the maximum tolerated dose 600,000 to 720,000 IU/kg by intravenous bolus given every 8 hours. On that schedule, patients tolerated approximately seven to nine consecutive doses before treatment had to be stopped for vascular leak syndrome, hypotension, multiorgan dysfunction, and a variety of other toxicities. These effects rapidly reversed after therapy was stopped but, with hypotension requiring vasopressor support, pulmonary edema, and potential infectious complications, a 2% to 4% treatment-related mortality was initially encountered (see Fig. 34.2-10). Since then, increased experience with IL-2, prophylactic antibiotics (when indicated), and patient screening for occult coronary disease have dramatically decreased this mortality rate. A recent report cites 809 consecutive patients who received high-dose bolus IL-2 without a treatment-related mortality. A statistic unattainable with most multiagent chemotherapeutic regimens.

Nevertheless, the expense of intensive care unit care and the precipitous nature of toxicities on high-dose IL-2 led many investigators to try lower-dose regimens. In particular, daily subcutaneous self-administration was adopted as a convenient and inexpensive route. In a scenario that has been replayed many times during the development of IL-2, a multitude of small phase II studies were performed that reported short-term response rates similar to those seen with high-dose IL-2. An outpatient, daily, self-administered regimen using an initial week (Monday through Friday) of 18 million IU (fixed dose) followed by 5 weeks at half that dose was well tolerated and produced a response rate of 23% in 26 evaluable patients. Later, continued experience with a modification of this regimen showed a 20% overall response rate, with one ongoing CR in 47 patients; another group of investigators achieved an 18% response rate with a similar regimen. Others reported on the use of continuous-infusion IL-2, describing a similar response rate with less toxicity (and less overall IL-2 given over the same period). A review of the literature
(Table 34.2-12) shows response rates to IL-2 monotherapy or IL-2 and LAK cells, delivered on many different schedules and at different doses, ranging from 8% to 35%, and it is clear that smaller, nonrandomized studies cannot discern whether one schedule is more effective than another. Nevertheless, lower-dose schedules have been widely adopted before being critically evaluated. There is no question that patients with metastatic RCC can respond to these regimens and that patients with other significant medical conditions may not be able to tolerate high-dose IL-2. In these cases, lower-dose options represent a reasonable therapeutic choice. For those patients who are able to tolerate any of the published IL-2 regimens, it remains crucial to determine whether the added toxicity of high-dose IL-2 is associated with any improvement in clinical efficacy.

TABLE 34.2-12. Therapy with IL-2 Alone or with LAK Cells

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Response Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-2 alone</td>
<td>16.5</td>
</tr>
<tr>
<td>IL-2 and LAK cells</td>
<td>20</td>
</tr>
</tbody>
</table>

Such a study is under way, and an interim analysis is available. This study randomized patients to receive IL-2 at either 720,000 IU/kg or 72,000 IU/kg every 8 hours by intravenous bolus to maximum tolerance (up to 15 consecutive doses). The lower dose was selected as the maximum dose that still resulted in a well-tolerated regimen not requiring intensive care unit care and vasoppressor support. This two-arm comparison constitutes the most precise determination of whether the dose of IL-2 is important. Subsequently, a third arm was added to the trial to evaluate the widely used subcutaneous route of administration. This arm delivered 250,000 IU/kgiday for 5 days in the first week and then half that dose 5 days per week for the subsequent 5 weeks. Of course, only concurrently randomized patients are compared in this two-phase trial. With 228 randomized patients of a projected study population of 400, it is evident that the two lower-dose regimens are associated with lower toxicity, especially in the areas of hypotension requiring pressors (43% of courses of high-dose intravenous IL-2 vs. 4% of courses of low-dose intravenous IL-2 and 0% with subcutaneous IL-2), thrombocytopenia, pulmonary distress, and disorientation. It is important to note that there have been no deaths in any of the treatment arms. The interim response rates are shown in Table 34.2-13. In the two-arm comparison of high- and low-dose intravenous bolus IL-2, the respective response rates are 19% and 10% (P < .06). The durations of the responses bear watching, as seven of nine patients completely responding to high-dose IL-2 remain in CR beyond 2 years, whereas two of five patients completely responding to low-dose IL-2 maintained their response at 2 years. The three-arm comparison including subcutaneous IL-2 is still preliminary, with response rates of only 16%, 4%, and 11% for high-dose intravenous, low-dose intravenous, and subcutaneous IL-2 reported.

TABLE 34.2-13. A Randomized Study of High-Dose versus Low-Dose Interleukin-2 in Patients with Metastatic Renal Cell Cancer

Because the clinical benefit of IL-2 resides in the long-term CRs achieved, any interpretation of this study will require prolonged follow-up and survival analyses after full accrual. As a drug that conveys great benefit to a minority of patients (who happen to possess the unidentified tumor or immune system qualities that allow them to respond), IL-2 is unlikely to affect the median survival of patients in randomized studies, and study design must take this into account.

Other studies have addressed the issue of continuous-infusion IL-2 versus bolus IL-2. The initial nonrandomized studies using continuous-infusion IL-2 reported response rates similar to those for bolus IL-2 but with lesser toxicities. In a subsequent randomized study in which all patients received LAK cells, there was a randomization to receive either continuous-infusion IL-2 at 18 to 22.5 million IU/m²/day or 600,000 IU/kg/dose by bolus every 8 hours (the cumulative daily dose by bolus was more than three times the dose by continuous infusion). Both of these doses represented the respective maximally tolerated doses for these regimens, and the few significant differences in toxicities did not favor either regimen. In this study, patients receiving LAK cells and bolus IL-2 had a 20% major response rate, as compared to a 15% response rate for patients given LAK cells and continuous-infusion IL-2; the difference was not significant. Fortunately, it has been established that the CRs to high-dose continuous-infusion IL-2 can be of long duration. A single-institution study of 123 patients (some also receiving LAK cells) with follow-up of 1 to 109 months reported an overall response rate of 19%, with 7% CRs and 78% of those patients sustaining their CRs at 42 to more than 109 months.

A more complex issue is whether any combination of cytokine or chemotherapy added to IL-2 is superior to IL-2 alone. Here again, small, nonrandomized phase II studies have clouded this issue. Innumerable small studies have combined IL-2 with interferon and chemotherapy, and sometimes both agents, and reported improved short-term response rates with large, overlapping confidence intervals (see Table 34.2-9). The combination of IFN-α and IL-2 is especially appealing because both agents have independent activity against RCC, and preclinical animal models predict synergistic benefit from combining these agents. Early reports suggested that the response rate for patients with metastatic RCC might rise from 18% to 20% with high-dose IL-2 alone to as much as 31% with high-dose IL-2 plus interferon. However, further accrual and long-term follow-up of the patients in this study did not show sufficient improvement in either response rate or survival (when compared to historical controls from the same institution) to warrant the additional toxicity seen (see Fig. 34.2-11).

Other investigators have been using this combination of cytokines to reduce the dose of IL-2 needed for a response and, thus, to limit toxicity. Most have employed outpatient, subcutaneous schedules, as widely described by Atzpodien et al. The initial nonrandomized reports on this regimen emphasized lesser toxicities but similar response rates to high-dose IL-2 monotherapy. Yet when others have tried the same or similar regimens, their response rates as well as their toxicity profiles have not been as favorable. Without randomized studies, it is impossible to reconcile these disparate results.

Some experience in randomized evaluations of IL-2 and interferon is available. Negrier et al. randomized 425 patients to receive continuous-infusion, high-dose IL-2 alone, subcutaneous IFN-α three times weekly, or both agents simultaneously. There was a significantly higher response rate to the combination (18.6%) than to only IL-2 (6.5%) or interferon (7.5%), but this increased response rate did not translate into improved survival. This study demonstrated an unusually low response rate to IL-2 alone, and patients with tumor progression crossed over between therapy arms. Other small randomized studies of IL-2 and interferon have also failed to demonstrate an advantage to combination therapy, but these studies are largely underpowered.

In a further effort to enhance the efficacy of IL-2 by adding other agents, investigators have tried to exploit the reported synergy between 5-FU (which has a low single-agent response rate against RCC) and interferon by adding this agent to IL-2 and interferon. Again, early phase II studies reported major increases in response rates, but later studies did not always substantiate these findings. In fact, an attempt to reproduce the initial studies exactly with 5-FU, IFN, and IL-2 (which had a
phenazone, and caffeine. Between analgesic abuse and renal pelvic tumors, other reports have shown that a patient with a bladder tumor initially has a 2% to 3% chance of developing an upper tract tumor. If, however, the patient has both a renal pelvic tumor and a ureteral tumor simultaneously, there is a 75% chance that a bladder tumor will develop in this patient. Alternatively, a urinary tract carcinoma is a multifocal process; patients with cancer at one site in the upper urinary tract are at greater risk of developing tumors elsewhere. Carcinoma of the renal pelvis is a relatively rare tumor that accounts for 5% of all renal tumors. It occurs more frequently in men than in women (2:1 to 3:1). Upper tract urothelial tumors are highly vascularized and angiogenic. This angiogenic potential may contribute to the growth of these tumors. The field of angiogenesis and its role as a target for cancer therapy has burgeoned in the last decade. New inhibitors of angiogenesis such as endostatin and angiostatin have been discovered, and old compounds such as thalidomide have found new life as antiangiogenic agents. RCC presents an attractive target for antiangiogenic therapy. Although this is a field of intense activity and interest, it is not yet clear whether a single antiangiogenic agent will be sufficient to interrupt the vascular supply of a tumor. It may be that tumors use a variety of angiogenic pathways and that only with carefully combined multilagent therapy will clinically significant tumor arrest or regression be achieved.

ANTIANGIOGENIC AGENTS

The field of angiogenesis and its role as a target for cancer therapy has burgeoned in the last decade. New inhibitors of angiogenesis such as endostatin and angiostatin have been discovered, and old compounds such as thalidomide have found new life as antiangiogenic agents. RCC presents an attractive target for antiangiogenic therapy. Although this is a field of intense activity and interest, it is not yet clear whether a single antiangiogenic agent will be sufficient to interrupt the vascular supply of a tumor. It may be that tumors use a variety of angiogenic pathways and that only with carefully combined multilagent therapy will clinically significant tumor arrest or regression be achieved.

SUMMARY

In the last two decades, a burgeoning supply of new biologic agents has been made available in amounts sufficient for clinical trials by recombinant gene technology. Most of these new agents have met the unprecedented expectations generated by preclinical work and entrepreneurial publicity. In the face of these disappointments, several important principles were established in the treatment of renal cell carcinoma and melanoma that should not be overlooked. It has been established that purely immunologic therapy, which has no direct, intrinsic antitumor activity, was able to cause the regression of large, metastatic tumors by stimulating host immune cells. Even more crucial was the demonstration that some of these regressions were potentially curative, with a small but consistent fraction of patients maintaining their CRs to IL-2 beyond 10 years. These results argue effectively that predicted pitfalls to immunotherapy such as tumor heterogeneity and antigen loss, immunosuppression by the cancer-bearing state or tumor microenvironment, and a lack of tumor-specific antigens in human cancers are not insurmountable problems. To increase the frequency of successful immune attack on renal cell carcinoma, it will be important to understand the mechanisms and cellular elements that are responsible for these few dramatic responses. Both immune effector factors as well as tumor characteristics are likely to be involved in the successful interplay that occurs in responding patients. The treatment of patients with renal cell cancer is likely to contribute to our future understanding of these factors and to continue at the forefront of progress in biologic therapies for cancer.

CARCINOMA OF THE RENAL PELVIS AND URETER

CARCINOMA OF THE RENAL PELVIS

Carcinoma of the renal pelvis is a relatively rare tumor that accounts for 5% of all renal tumors. It occurs more frequently in men than in women (2:1 to 3:1). Upper urinary tract carcinoma is a multifocal process; patients with cancer at one site in the upper urinary tract are at greater risk of developing tumors elsewhere. The probability of multifocal occurrence is greater in patients with larger lesions and in those with carcinoma in situ. A patient with one upper tract urethral tumor has a 30% to 50% chance of developing a bladder tumor as well. Some 2% to 4% of patients with an upper tract urethral tumor develop bilateral renal pelvic tumors. If a patient has both a renal pelvic tumor and a ureteral tumor simultaneously, there is a 75% chance that a bladder tumor will develop in this patient. Alternatively, a patient with a bladder tumor initially has a 2% to 3% chance of developing an upper tract tumor.

ETIOLOGIC FEATURES AND GENETICS

Recent studies have demonstrated that the major cause of cancer of the renal pelvis is smoking and that cessation of smoking can eliminate a large number of these tumors. A significant increase in risk for upper genitourinary (GU) tract urothelial cancer is found in smokers, the risk being highest among the heaviest smokers. In 1965, Hultgren et al. first identified a connection between epithelial tumors of the renal pelvis and abuse of compound analgesics. Since then, a number of other reports have come from Sweden, Australia, the Netherlands, Denmark, Italy, Germany, and the United States. They have demonstrated an association between analgesic abuse and renal pelvic tumors. Most of the patients ingested a small amount (5 kg) of compound analgesic, usually containing phenacetin, phenazone, and caffeine. Typically, upper GU tract tumors occur in patients in whom prolonged and heavy analgesic ingestion is followed by renal papillary necrosis.

There is also an association between cancer of the renal pelvis and dentulous endemic familial nephropathy (Balkan nephropathy). Balkan nephropathy is a slowly
progressive inflammation of the interstitium of the kidney that ultimately results in renal failure. This disorder, which is prevalent in the Balkan countries (Yugoslavia, Romania, Bulgaria, and Greece), is associated with multifocal, slow-growing, superficial, low-grade tumors of the renal pelvis. The cause of Balkan nephropathy is unclear; however, a number of potential etiologic agents such as fungal toxins, viruses, silicates, and heavy metals have been studied.

An association has been observed between renal pelvic tumors and urban residence as well as occupation in the aniline dye, textile, plastics, and rubber industries. Chronic inflammation and irritation are associated with the development of renal pelvic tumors, particularly in patients who have upper urinary tract stones.

There are reports of kindreds exhibiting a hereditary pattern in the development of transitional cell carcinoma of the urinary tract. Of the affected family members, 22% had upper GU tract tumors, 59% had bladder cancer, and 18% had both upper and lower GU tract tumors. Upper GU tract urothelial tumors are found in patients with hereditary nonpolyposis colorectal cancer, which is associated with a germline abnormality in DNA mismatch repair genes. Studies of the molecular and cellular aspects of urothelial transformation should provide further insight into the etiology and mechanisms of progression and metastasis of this disease.

### Pathology

Transitional cell carcinoma accounts for 90% of the tumors of the renal pelvis and can be in situ, papillary, or planar (Table 34.2-14). Squamous cell carcinoma, which usually is associated with chronic inflammation or infection of the renal pelvis, accounts for 7% of renal pelvic tumors. Squamous cell cancer of the renal pelvis often is deeply invasive and is associated with a worse prognosis than is transitional cell carcinoma. Adenocarcinoma of the renal pelvis has been reported in few patients and occurs in association with inflammation, infection, or calculi.

### Diagnosis and Staging

Hematuria is the initial pelvic presenting symptom in the majority of patients with renal pelvic carcinoma. Gross hematuria is present in 62% to 75%, and microscopic hematuria is seen in 10%. The triad of flank mass, pain, and hematuria is encountered infrequently, in 20% or fewer cases, and is often associated with advanced disease. Excretory urography frequently is used in the initial evaluation of patients with renal pelvic tumors and will often reveal a filling defect in the collecting system. There may also be either a hydronephrotic or a nonfunctional kidney due to obstruction by a blood clot or mass. Retrograde pyelography (in which contrast medium is injected into the ureter through an endoscope) accurately delineates upper GU tract filling defects. If there is uncertainty about the nature of a renal pelvic lesion, CT performed before and after administration of intravenous contrast material will differentiate a tumor from another radiolucent mass such as a stone. Angiography is not used often in the diagnostic evaluation of a suspected renal pelvic tumor. However, a renal mass that lacks the characteristic neovascularity of a renal carcinoma may be the first indication of a renal pelvic tumor invading the renal parenchyma.

Urinary cytology is useful in evaluating a renal pelvis mass, and endoscopically obtained barbotage specimens allow an accurate diagnosis to be made in approximately 80% of cases. Tissue can also be obtained by introducing a biopsy brush into the ureter and removing a specimen for cytologic or histologic examination. Brush biopsy increases diagnostic accuracy to between 80% and 90%. Endoscopic ureteroscopy and percutaneous nephroscopy are techniques that have dramatically improved the diagnosis of upper tract tumors. Endoluminal sonographic evaluation may also be useful for diagnosis and staging. With currently available endoscopic instruments, the renal pelvis can be inspected visually in more than 90% of patients.

The most significant prognostic factors for survival of patients with renal pelvic carcinoma are stage and grade of tumor. Renal pelvic upper urinary tract cancer is divided into four stages by the TNM classification (Table 34.2-15). The primary tumor is classified as low-stage (Ta, limited to mucosa; T1, lamina propria invasion) and high-stage (T2, muscularis involvement; T3, tumor beyond the muscularis). Renal pelvic tumors are graded from 1 to 3. The median survival for patients with high-stage tumors is 14 to 16 months as compared with 67 months for patients with low-stage tumors. Median survival for patients with high-stage tumors is 13 months, whereas median survival for patients with low-stage tumors is 91 months. Invasion of the renal hilum occurs in 95% of patients who ultimately develop metastases.

### Surgical Treatment

Carcinoma of the renal pelvis may be treated with a radical nephrectomy that includes removal of Gerota's fascia and its contents, total removal of the ipsilateral ureter, and removal of a cuff of bladder. When transitional cell carcinoma of the renal pelvis invades the renal vein or vena cava, an extensive surgical procedure including thrombus extraction or partial vena cava resection may be required.

More conservative endourologic surgical excision is advocated by some who note that renal pelvic carcinoma can be bilateral and that survival of patients with low-stage, low-grade renal pelvic carcinoma treated with a conservative surgical procedure is approximately the same as in patients treated with more radical surgery. The incidence of low-stage, low-grade renal pelvic carcinoma is approximately 8%, and that of bilateral disease is 2%. Often there is also a long latent period prior to recurrence. Papillary, low-grade, low-stage tumors of the upper urinary tract often are considered amenable to endoscopic resection. However, most clinicians offer radical surgery to patients with high-stage endoscopically defined lesions. Currently, most clinicians consider that local, partial excision is potentially...
appropriate for patients with a solitary kidney, with bilateral renal pelvic carcinoma, or with renal insufficiency. Treatment strategies involving percutaneous or ureteroscopic resection of renal pelvic tumors followed by either laser irradiation or supplemental intracavitary therapy are currently being evaluated. 212,214 and 215

Follow-Up
Conscientious follow-up after surgery for renal pelvic carcinoma is essential. Urinalysis, urine cytology, and cystourethroscopy are performed every 3 months for 2 to 3 years and then less frequently. For patients who undergo a conservative upper tract procedure, periodic retrograde pyelography and ureteroscopy also are performed.216

URETERAL CARCINOMA
Ureteral carcinoma is an uncommon neoplasm that accounts for only 1% of all malignancies of the upper GU tract. Ureteral carcinoma was first described by the French pathologist Rayer in 1841; the first ureteral carcinoma to be removed by nephroureterectomy was reported by Vorphl in 1905. Ureteral carcinoma tends to occur in the older age groups, predominantly in the sixth, seventh, and eighth decades of life. The male-female ratio is 2:1. The most common site for the occurrence of a ureteral tumor is in the lower one-third of the ureter, with a lesser incidence higher up.

Histology and Etiology
Ninety percent of malignant tumors of the ureter are transitional cell carcinomas; 20% have squamous or glandular differentiation. Eight percent of the tumors are pure squamous cell carcinomas, and 1% are adenocarcinomas. Tumors of the ureter share embryologic, morphologic, and etiologic characteristics with renal pelvic tumors. As with renal pelvic tumors, there is an increased incidence of ureteral carcinoma associated with Balkan nephropathy, prolonged exposure to phenacetin, or prolonged exposure to environmental agents such as aniline dyes.218

Clinical Presentation: Grade and Stage
Hematuria is the most common presenting symptom and is present in 75% of patients with ureteral carcinoma. The hematuria is usually painless; however, colicky pain due to obstruction by clot or by tumor occurs in up to 35%. Urinary frequency or dysuria, present in only 10% of patients with renal pelvic carcinoma, occurs in up to 50% of patients with ureteral carcinoma.219

As in pelvic carcinoma, the primary ureteral carcinoma is classified as grades 1 through 3 and stage Ta (limited to the mucosa), T1 (lamina propria invasion), T2 (muscularis involvement), or T3 (invasion beyond the muscularis).220 Although up to 100% of grade 1 tumors and 85% of grade 2 tumors may be noninvasive, only 30% of grade 3 and 8% of grade 4 tumors are noninvasive.221,222

Diagnosis
Excretory urography is an initial part of the evaluation of a suspected ureteral mass lesion. On excretory urography, the upper tract above the tumor may be completely normal or there may be hydronephrosis or complete nonfunction. Retrograde pyelography may be performed to delineate accurately the precise location of the ureteral lesion. Urine is collected for cytologic examination, and brush biopsy may be performed to obtain tissue for histologic examination. Advances in ureteroscopic techniques have revolutionized the diagnosis and treatment of upper tract transitional carcinomas.223 The flexible endoscope has greatly improved the surgeon's ability to visualize and perform a biopsy of ureteral lesions, and its use is now part of the standard management of this disease.222,224 Abdominal CT also provides useful staging information, particularly with regard to extension of the tumor outside the ureter.

Treatment
Carcinoma of the ureter has historically been treated by either nephroureterectomy or partial ureterectomy. The advantage of a partial ureterectomy is that the more conservative procedure preserves the kidney. However, mapping studies of the urothelium have demonstrated that carcinoma of the upper urinary tract is a multifocal disease. Often atypia and carcinoma in situ are noted in multiple areas of the urothelium, particularly in high-grade, high-stage carcinomas. Small, solitary, low-grade tumors are most often treated by endoscopic resection, fulguration, or laser photocoagulation, which allows acceptable survival and renal preservation, particularly in patients with a solitary kidney, bilateral tumors, a poor operative risk, or impaired renal function.225,226 Nephroureterectomy is recommended for patients with high-grade or high-stage tumor and for those with disease at an unresectable location.

The surgical procedure of radical nephrectomy plus ureterectomy entails removal of the kidney and the entire contents of Gerota's fascia, the ureter, and a cuff of bladder including the ureteral orifice and intramural ureter (Fig. 34.2-12). Regional lymph nodes may be removed, particularly if there is indication that they are involved. This surgical procedure may be performed using one or two incisions, depending on the patient's body habitus and the surgeon's preference. When partial ureterectomy is performed, urinary tract continuity is reestablished with either ureteroureterostomy or ureteroneocystostomy.

FIGURE 34.2-12. The patient who will undergo a nephroureterectomy with lymph node dissection should be placed in a modified flank position and an incision made through either line a or line b. The area of dissection is as indicated in the middle panel, being divested from the superior mesenteric artery to the bifurcation. The ureter is removed by opening the bladder, circumscibing the orifice, and sharply dissecting the ureter from the surrounding detrusor muscle. The defect in the bladder then is closed appropriately. (From ref. 225, with permission.)

Results of Therapy
The 5-year survival of patients with ureteral carcinoma is determined primarily by the grade and stage of the disease. Thorough endoscopic follow-up is essential at regular intervals to rule out recurrences.227 Endourologic techniques combined with conservative treatment of ureteral transitional cell carcinoma can be effectively and safely used as first-line therapy for selected individuals.228 Patients with Ta or T1 ureteral carcinoma can experience a 90% to 100% 5-year survival rate; those with T2 disease, a 45% to 85% 5-year survival rate; and patients with T3 disease, a 25% to 30% 5-year survival rate. The 5-year survival for patients with metastatic disease is currently 0% to 5% (Table 34.2-16).
ADJUVANT RADIOTHERAPY FOR CARCINOMA OF THE RENAL PELVIS AND URETER

In the absence of randomized prospective data, there is no consensus regarding the need for adjuvant radiotherapy for patients with renal pelvis or ureteral cancers. Brookland and Richter\(^2\) reported on 23 patients with stage III to IV transitional cancers of the upper GU tract. Postoperative radiotherapy (45 to 50 Gy) was given to 11 patients. Among these 11, 5 patients (45%) developed a local recurrence, as compared to 1 of 9 patients (11%) treated with a nephroureterectomy alone (P = .23). Cozal et al.\(^3\) reported on 67 patients with stage I through IV upper tract transitional cell tumors. Though the authors demonstrated a reduction in the crude local relapse rate with the administration of 45 to 50 Gy of postoperative radiotherapy as compared to patients who did not receive adjuvant therapy (26% vs. 10%), these differences were not significant (P = .42). Other recent retrospective reports could not demonstrate a significant benefit for adjuvant therapy for advanced-stage disease.\(^2\) and \(^3\) These authors have highlighted the systemic nature of stage III and IV disease—namely, the high risk of distant metastases and the relative infrequent incidence of isolated local recurrences after initial local aggressive surgical therapy, which likely explain the lack of conclusive evidence that adjuvant radiotherapy is of any benefit. Nevertheless, as most patients in these reports were followed without the benefit of routine CT evaluations, the true incidence of a local failure for advanced-stage patients remains unclear. Until more effective systemic regimens are available for patients with locally advanced disease, distant metastasis appears to be the predominant mode of failure, and routine administration of adjuvant local radiotherapy is not recommended.

CHEMOTHERAPY FOR METASTATIC CARCINOMAS OF THE RENAL PELVIS AND URETER

Except for its role in the conservation and preservation of the bladder, considerations for systemic treatment of cancer of the ureter and renal pelvis are identical to those of bladder cancer. It is believed that the biology of transitional cell carcinomas of the renal pelvis, ureter, and bladder is the same, with comparable etiology, pathology, and pattern of spread. This paradigm is supported by the frequent occurrence of multifocal neoplastic sites in the transitional epithelium. Systemic chemotherapy for upper urinary tract cancers mirrors that for bladder cancer and has been administered in the metastatic, adjuvant, and neoadjuvant setting. Indeed, patients with carcinomas of the renal pelvis and ureter usually are included in clinical trials for bladder cancer, because the chemoresponsiveness of both upper and lower urothelial cancers is considered to be comparable. A retrospective review of 203 patients in five trials of methotrexate, vinblastine, doxorubicin (Adriamycin), and cisplatin (M-VAC) from the Memorial Sloan-Kettering Cancer Center could identify no difference in response or survival between patients with bladder and nonbladder primary sites (Table 34.2-17).\(^2\) Because the incidence of cancer of the upper urinary tract is a fraction of that of cancer of the bladder, chemotherapeutic trials do not address the upper urothelium separately. Hence, this section will briefly outline the issues relating to systemic treatment of upper urinary tract cancer, drawing from the bladder cancer literature. For a more extensive discussion, the reader is referred to Chapter 34.3.

<table>
<thead>
<tr>
<th>TABLE 34.2-16. Correlation of Survival Rate with Stage of Ureteral and Pelvic Tumors</th>
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<tbody>
<tr>
<td>Stage</td>
</tr>
<tr>
<td>I</td>
</tr>
<tr>
<td>II</td>
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<tr>
<td>III</td>
</tr>
<tr>
<td>IV</td>
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<p>| TABLE 34.2-17. Effect of Nonbladder Primary Site of Transitional Cell Carcinoma on Response to M-VAC |</p>
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<thead>
<tr>
<th>Primary Site</th>
<th>No. of Patients</th>
<th>Complete Remission</th>
<th>Partial Remission</th>
<th>No Response</th>
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<tbody>
<tr>
<td>Bladder</td>
<td>110</td>
<td>25 (22.7%)</td>
<td>65 (59.1%)</td>
<td>20 (18.2%)</td>
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<tr>
<td>Nonbladder</td>
<td>34</td>
<td>5 (14.7%)</td>
<td>18 (52.9%)</td>
<td>11 (32.4%)</td>
</tr>
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CHEMOTHERAPY FOR ADVANCED CANCER OF THE RENAL PELVIS AND URETER

Urothelial cancers are highly responsive to chemotherapy. After local recurrence or metastasis has developed, systemic chemotherapy is indicated. While combination chemotherapeutic regimens, including cisplatin, are most widely used, the single-agent activity for a variety of agents is sold. Response rates ranging from 25% to 35% have been reported for cisplatin, methotrexate, cyclophosphamide, and paclitaxel.\(^2\) Most recently, single-agent activity of 28% for gemcitabine has been reported.\(^3\) Table 34.2-18 includes results from both combined and single-agent chemotherapy trials.

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<thead>
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<th>TABLE 34.2-18. M-VAC and New Agents for Urothelial Cancer</th>
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<td>Agent</td>
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<td>Vinblastine</td>
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<td>Cyclophosphamide</td>
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As with other cancers that are responsive to chemotherapy, combination regimens elicit a higher response rate than do single-agent regimens. Although others have described, the most widely accepted regimen for bladder and other urothelial cancers has been M-VAC (methotrexate, 30 mg/m\(^2\) on days 1, 15, and 22; vinblastine, 3 mg/m\(^2\) on days 2, 15, and 22; Adriamycin, 30 mg/m\(^2\) on day 2; and cisplatin, 70 mg/m\(^2\) on day 2, in a 28-day cycle), originally described in 1985 with a 70% overall response rate.\(^4\) A single-institution randomized trial comparing M-VAC with cisplatin, cyclophosphamide, and Adriamycin (CISCA) confirmed a 65% response rate for M-VAC, including 35% of patients with a complete remission.\(^4\) Among 110 patients enrolled in the study, 81 had a primary bladder tumor, 14 had cancer of the renal pelvis, and 6 had cancer of the ureter. The site of origin of the tumor had no influence on response rate. A randomized intergroup study comparing
M-VAC with cisplatin monotherapy also demonstrated M-VAC to be significantly superior with regard to both response rate (39% vs. 12%) and survival (median 12.5 vs. 8.2 months). Long-term follow-up of this trial at 6 years confirmed the superiority of M-VAC over cisplatin alone. Escalation of methotrexate to 1000 mg/m² failed to improve response rate or median survival. M-VAC is associated with significant hematologic toxicity, and studies aimed at ameliorating the toxicity or supporting dose escalation with GM-CSF or granulocyte colony-stimulating factor have shown little benefit.

Patients experiencing a CR survive longer but, despite the regular occurrence of CRs, there is a high relapse rate. In the intergroup study, only 5 of 17 patients with CR remained disease-free from 8.5 to 39.5 months. Similarly, Igra et al. reported that among 51 patients who received M-VAC, 10 patients experienced CRs, but 8 relapsed, with a median duration of response of 11.9 months. These considerations have urged the pursuit of treatment that would provide more durable benefit with less toxicity.

For patients whose cancers progress after M-VAC, several newer agents have shown single-agent activity in urothelial cancer (see Table 34.2-18). Both paclitaxel and gemcitabine have response rates in the 20% to 30% range. Phase II combination studies of paclitaxel with carboplatin or gemcitabine with cisplatin have shown reproducible response rates, generally 50% to 60% in previously untreated (or adjuvant-only treated) patients. Although the response rates are lower than those seen in the original M-VAC trials, the results are comparable to the findings of the large intergroup trial of M-VAC, which demonstrated a 39% response rate and improved survival.

A recently reported phase I trial incorporated a sequential approach: doxorubicin plus gemcitabine for six 2-week cycles followed by ifosfamide, paclitaxel, and cisplatin in four 3-week cycles. A sequential approach such as this may allow the use of multiple known active agents without compromising doses, while minimizing toxicity.

Enrollment has been completed in a large randomized study comparing gemcitabine plus cisplatin with M-VAC in metastatic transitional cell carcinoma. A second randomized study conducted by the Eastern Cooperative Oncology Group is ongoing, comparing M-VAC with carboplatin and paclitaxel. Patients must be previously untreated and have advanced or metastatic urothelial cancer (from the renal pelvis, ureter, bladder, or urethra). This study should help to determine whether M-VAC can be challenged as front-line therapy in urothelial cancer.

PROGNOSTIC FACTORS IN UROTHELIAL CANCER

The randomized trial comparing M-VAC with cisplatin alone, encompassing 255 patients, was examined for prognostic factors. Factors that predicted a poor outcome included nontransitional cell histology, poor performance status, and liver or bone metastases. Overall, fewer than 4% of patients treated with M-VAC for advanced urothelial cancer were alive and disease-free at 6 years. Among 99 patients treated with M-VAC or CMV [cisplatin, methotrexate, and vinblastine], good performance status, low metallothionein expression, and high tumor grade were significant predictors of response to chemotherapy. Molecular factors important in tumor progression—p53, the retinoblastoma gene product (Rb), E-cadherin, and epidermal growth factor receptor—have also been identified in urothelial cancer. It is not known whether, beyond tumor progression, these factors may play a role in determining chemosensitivity.

ADJUVANT AND NEOADJUVANT CHEMOTHERAPY FOR CANCER OF THE RENAL PELVIS AND URETER

The responsiveness of urothelial cancer to chemotherapy offered the possibility that adjuvant or neoadjuvant chemotherapy could improve survival in patients undergoing curative resections. However, evidence for benefit of either strategy is limited, in part because of the large trial size that would be required to prove it. As in advanced disease, it is believed that upper urinary tract cancers have the same responsiveness to chemotherapy as do bladder cancers. A small adjuvant trial supporting this included 16 patients with bladder cancer and 10 patients with upper urinary tract cancer treated postoperatively with a combination of methotrexate, vincristine, cisplatin, cyclophosphamide, Adriamycin, and bleomycin. Disease-free survivals were comparable for both groups of patients.

Randomized adjuvant chemotherapy trials in bladder cancer have not provided clear support for the benefit of adjuvant treatment. Several factors can be cited for the failure of some trials to show benefit, including use of weaker chemotherapeutic regimens such as single-agent cisplatin. Treatment of node-negative populations, and small trial size. Neoadjuvant chemotherapy before cystectomy has also been studied in bladder cancer. A study from the M. D. Anderson Cancer Center compared neoadjuvant M-VAC (two cycles before cystectomy and three cycles afterward) with adjuvant M-VAC (five cycles after cystectomy). Randomizing 98 patients, no survival difference (60% vs. 63%) between the two strategies could be seen after the study was analyzed at 31.7 months. Neoadjuvant trials in bladder cancer, however, have also failed to provide conclusive evidence for the benefit of chemotherapy. Several studies, including a recently reported study from an international collaboration of trialists in which 976 patients were randomized between no chemotherapy and neoadjuvant chemotherapy consisting of three cycles of cisplatin, methotrexate, and vinblastine prior to curative local therapy. Median survival in the no-chemotherapy group was 37.5 months and, in the chemotherapy group, was 44 months. The absolute difference in 3-year survival was 5.5% (50% vs. 55.5%), an insufficient number to allow a broad recommendation for the inclusion of chemotherapy in the initial treatment of patients with urothelial cancer. One goal of neoadjuvant chemotherapy is the downstaging of tumor size, potentially allowing bladder preservation. In this regard, neoadjuvant chemotherapy is often used in patients with upper urinary tract cancer, as the only candidates for conservative surgery are patients with low-grade, superficial, noninvasive tumors in whom the prognosis is better (85% at 5 years) and the likelihood of benefit from chemotherapy is difficult to prove.

Most authors conclude that further randomized studies are required to prove a survival benefit for adjuvant or neoadjuvant chemotherapy in urothelial cancer. However, some clinicians administer adjuvant chemotherapy in the absence of convincing data because of the responsiveness to chemotherapy that has been observed in advanced disease and the incurability of recurrent or metastatic disease. Indeed, the current Eastern Cooperative Oncology Group Trial for adjuvant chemotherapy in urothelial cancer is not a randomized trial but rather an assignment to treatment with M-VAC or carboplatin and paclitaxel. In the absence of randomized data and specific data from upper urinary tract cancers, a decision in favor of adjuvant chemotherapy seems reasonable, particularly in patients in whom the risk of relapse is high, in whom tumors are invasive, nodal metastases are present, or the tumor grade suggests an aggressive biology.

SUMMARY

Cancer of the renal pelvis and ureter most frequently is a transitional cell carcinoma, as in carcinoma of the bladder. Because the biology of these urothelial cancers is considered to be identical, treatment recommendations have followed those for bladder cancer. At present, M-VAC is the mainstay of systemic chemotherapy for urothelial cancer; however, hematologic toxicity is significant and often results in reduced dosing. Thus, regimens with equal efficacy and less toxicity have been pursued, and several randomized trials are currently being evaluated. Insufficient data are available to define clearly subgroups of patients who will or will not benefit from adjuvant chemotherapy; many physicians opt for adjuvant treatment in the absence of randomized data because of the poor results that result from tumor recurrence.

CHAPTER REFERENCES

INTRODUCTION

Urinary bladder cancers represent a spectrum of neoplasms that can be grouped into three general categories: superficial, invasive, and metastatic. Each differs in clinical behavior, prognosis, and primary management. For treating superficial tumors, the aim is to prevent recurrences and progression to an incurable stage. For treating invasive disease, the issue becomes how to determine which tumors can be cured with single-modality therapies (e.g., surgery), which can be treated without surgical removal of the bladder, and which, by virtue of a high metastatic potential, require an integrated systemic approach to achieve cure. For treating metastatic disease, combination chemotherapy is the standard; yet, despite responses in more than 50% of cases, overall cure rates remain low. Recent progress with evolving chemotherapeutic regimens suggest that cure rates may improve in the future.

A unique aspect of bladder cancer treatment is that repeated surgical biopsy is an integral part of routine patient management, thus permitting molecular genetic studies of tumors from specific stages of the disease. The results of these studies suggest that bladder cancers develop and progress along at least two discrete pathways, which may account for differences in invasiveness and metastatic potential. It may also explain why some tumors recur on the surface, without invasion, while others metastasize with minimal infiltration below the epithelial layers. These considerations, along with identifying several chemotherapeutic agents active in patients who have progressed on cisplatin-based combinations, have led to clinical trials seeking to define new standards of care. It is hoped that incorporating molecular genetic factors into the currently used staging systems will change the paradigm of treatment so that the probability of cure is optimized and the quality of life maintained.

EPIEDEMOLOGY

Bladder cancer is the fourth most common cancer in men and the seventh most common in women. More than 54,000 cases (in 29,500 men and 14,900 women) were diagnosed in 1999, and 12,500 individuals (8400 male and 4100 female) succumbed. Bladder cancer, primarily a disease of men older than age 65, is rarely diagnosed before the age of 40. White men receive diagnoses twice as often as black men. Additionally, the diagnosis rate is higher in urban than in rural areas. Bladder cancer death rates declined substantially for both whites and blacks of both genders from 1973 to 1996, approximately 24% overall. This decrease is likely to be the result of more cases being diagnosed at a noninvasive stage and more effective therapies.

Cigarette smoking is the most important risk factor, although work in the dye, rubber, or leather industries is also strongly associated with bladder cancer. The latency period from initial exposure to the development of a urothelial tumor is a median of 18 years. Cigarette smoking is believed to contribute to upward of 50% of the cancers in men and 33% of the cancers in women. Overall, smokers have a two- to fourfold higher relative risk of bladder cancer than nonsmokers. Smoking contributes to the field change of the urothelium, because the urothelium from individuals who “never smoked” shows atypia in only 4% of cases versus up to 50% in “smokers.” Discontinuing smoking decreases risk, although a higher risk than nonsmokers remains for up to 10 years after smoking cessation. A high fluid intake is associated with a decreased incidence of bladder cancer in men, and lesser intake of daily fluids proportionally increases the risk of bladder cancer.

Dietary components consumed in high quantities, such as fried meats and fats, are associated with bladder cancer. Vitamin A supplements appear to be protective. Coffee consumption and artificial sweeteners confer little or no risk. Several drugs (e.g., phenacetin) are implicated in the development of urothelial tumors, and cyclophosphamide, used as an oncolytic or immunosuppressive agent, can increase risk ninefold.

Exposure to Schistosoma haematobium, a parasite found in many developing countries, is associated with an increased risk of both squamous and transitional cell carcinomas of the bladder. A link between a history of urinary tract infection and squamous cell carcinoma of the urinary bladder has been shown, particularly in paraplegics and those with bladder stones or indwelling Foley catheters. An association is not identified between infection and transitional cell tumors.

CLINICAL PRESENTATION AND DIAGNOSIS

The frequencies of a specific symptom at diagnosis parallel the occurrence of the three clinical subtypes. At presentation, 75% of tumors are superficial, 20% are invasive, and up to 5% have de novo metastases. Although hematuria is the presenting sign in 80% to 90% of cases, urinary frequency, the result of irritative symptoms or a reduction in overall bladder capacity, is common. Depending on a lesion’s location and depth of invasion, ureteral obstruction may develop, resulting in flank pain, discomfort, and overall reduced renal function. In rare cases, pain from a metastatic bone lesion or local progression of disease is the presenting sign.

Individuals older than 40 years of age who develop hematuria should have a urine specimen for cytology and undergo cystoscopy and imaging of the urinary tract with an intravenous pyelogram or computed tomographic (CT) scan. Screening of asymptomatic subjects for hematuria has not been shown to affect overall survival, although it does increase the probability of diagnosing the disease at an earlier stage. Prospective studies are ongoing to assess the role of screening in high-risk populations. Other urine assays have been used to diagnose disease and to follow up patients, including flow cytometry, blood group antigens (i.e., Lewis X), cyclokeratins, the bladder tumor–associated test, and tests for nuclear matrix protein, fibrin degradation product, and telomerase. None is sensitive or specific enough to replace cystoscopy and urine cytology.

CYSTOSCOPY

The cystoscopic examination forms the mainstay of diagnosis and staging. It begins with an examination under anesthesia to determine whether a palpable mass is present and, if present, whether it is movable. A cystoscope is then inserted into the bladder, and urine is obtained to determine the presence or absence of malignant
cells. The bladder is inspected visually, and a detailed notation of the size, number, location, and growth pattern (papillary or solid) of all lesions is recorded. The status of uninvolved mucosa is also noted. These data are recorded on a detailed bladder map for future reference (Fig. 34.3-1). Biopsy specimens are taken from visible tumors or resected in stages to determine the histologic subtype and depth of invasion into the submucosa and muscle layers of the bladder. In cases where there is suspected or minimal tumor invasion, a repeat biopsy is advised to ensure that all visible tumor is completely resected and to detect the presence of muscle invasion.  

The major difference is that the TNM system provides for the two patterns of growth and clinical behavior of superficial lesions and delineates more precisely the depth of invasion within the bladder wall. The presence or absence of distal metastases can be documented with physical examination, CT, a chest radiogram, and a radionuclide bone scan. Because bladder tumors occur in elderly individuals, a general medical evaluation is essential to document significant comorbid conditions.

PATHOLOGY AND NATURAL HISTORY

Transitional cell carcinomas (TCCs) constitute 90% to 95% of the urothelial tumors in the United States. They occur anywhere along the urinary tract from the renal pelvis to the ureter, bladder, and proximal two-thirds of the urethra, at which point a squamous epithelium predominates. More than 90% of tumors originate in the urinary bladder and 8% in the renal pelvis; primary tumors of the ureter and urethra constitute the remaining 2% of tumors in these locations. Pure squamous cell tumors, defined by the presence of keratinization in the pathologic specimen, comprise 3%, adenocarcinomas 2%, and small cell carcinoma fewer than 1% of tumors that develop in this region. Tumors of mixed histology, consisting of transitional cell and squamous or adenocarcinomatous elements, can also be identified. These are considered variants of the transitional cell lesion, and they do not portend a worse prognosis. Adenocarcinomas may occur in the embryonal remnant of the urachus on the bladder dome or in the perirectal tissues, or they may assume a signet cell histology. In rare cases, a lymphoma or melanoma develops in the bladder.

Approximately 70% of newly diagnosed cases have exophytic papillary tumors that are confined to the mucosa (stage Ta) or invade the submucosa (stage T1). They tend to be friable, with a high propensity to bleed. These tumors may recur at the same part or in other portions of the bladder and at the same or at a more advanced stage and grade. They are generally managed endoscopically by complete resection. An estimated 50% to 70% of patients with a tumor confined to the mucosa have a recurrence or a new occurrence of a TCC within 5 years, whereas 5% to 20% of superficial tumors progress to a more advanced stage. An important area of research is determining which tumors will recur, which will progress to a higher stage, and which will metastasize.

GRADING

Bladder tumors are classified as low-grade (G1) or high-grade (G2, G3). Grading is more important for noninvasive tumors because almost all invasive neoplasms (T1 or greater) are high-grade. The epithelium has a thickness of less than five to seven layers, normal polarity of nuclei, and no pleomorphism. Papillary carcinomas of low grade are considered to be relatively benign tumors that closely resemble the normal urothelium. They have more than seven layers of urothelium, normal nuclear polarity in more than 95% of the tumor, and no or only slight pleomorphism. More important, they rarely progress to a higher stage. High-grade papillary tumors show loss of polarization of the nuclei and moderate or prominent pleomorphism. Progression to higher-stage lesions is frequent. For invasive tumors, stage is the most important independent prognostic variable for progression and overall survival.

Primary CIS (Tis), without a concurrent exophytic tumor, constitutes 1% to 2% of newly detected cases of bladder cancer. CIS is found in more than one-half the bladders with multiple papillary tumors, either adjacent to or involving mucosal sites remote from papillary lesions. CIS is, by definition, high-grade and believed to be a predominant precursor of invasive tumors. Left untreated, CIS will develop invasive disease in 5 years in more than 50% of patients.

STAGING

The most commonly used staging systems are the Jewett-Strong-Marshall and TNM (tumor-node-metastasis) systems. They were developed from pathologic studies of cystectomy specimens in which the association between depth of invasion and clinical course was first identified. They are contrasted in Table 34.3-1 and Table 34.3-2. The major difference is that the TNM system provides for the two patterns of growth and clinical behavior of superficial lesions and delineates more clearly the extent of extravesical spread. Because of this, it is more widely used.
Ta lesions grow as exophytic lesions and tend to recur but generally do not invade. If a tumor invades the layer below the mucosa, the submucosa, or lamina propria, it is a T1 tumor. A breakpoint in both classifications is invasion into muscle, at which point surgical removal of the bladder is considered standard therapy (Table 34.3-3). Once invasion into the muscle layer is documented, the risk of nodal and subsequent distant metastases increases. The TNM system divides muscle-infiltrating (T2) disease into superficial (T2a) or deep (T2b) invasion but confined within the bladder. In clinical practice, the accuracy of determining the degree of muscle infiltration is modest, at best. Even in experienced hands, the correlation between depth of invasion, based on the cystoscopic evaluation, and the final bladder removed by cystectomy is only 70%. As treatment outcomes are further evaluated, it is becoming apparent that the most important determination is whether the tumor is organ-confined (T2 or less) or non–organ-confined (T3 or greater). The T3 category includes tumors that extend to the perivesical fat. In some cases, surgeons take specimens from deep in the bladder wall, rendering it possible for the pathologist to determine the boundary between muscle and perivesical fat. CT scans or magnetic resonance imaging may help to identify disease that has spread outside the bladder.

The TNM system differentiates tumors extending into adjacent organs from those extending into perivesical fat. A tumor that grows into the prostate, vagina, uterus, or bowel is classified as T4a, and a tumor fixed to the abdominal wall, pelvic wall, or other organs is a T4b lesion. Urothelial tumors may also grow into the prostate, along the prostatic ducts—noninvasive lesions with a good prognosis when resected—or directly invade the prostatic stroma, which harbors a worse prognosis. A similar bleak prognosis is also apparent for patients with metastases, whose median survival rates range from 6 to 9 months; few patients survive 5 years.

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PATHOGENESIS

The natural history of a urothelial tumor is recurrence. Recurrences may develop at any time, at the same or separate site of the urothelial tract, and at the same or a more advanced stage. This is termed polychronotopism and has led investigators to postulate that a field defect occurs in the urothelial tract, resulting in a genetically unstable urothelium that facilitates the continued development of new lesions. The observation of atypia in the urothelial lining of smokers is consistent with this view.

An area of controversy is whether tumors that occur in separate sites in the urothelial tract are derived from the same clone or are polyclonal in origin. Reports by Sidrinsky et al., demonstrating the clonality of multiple bladder tumors from different sites, and by Miyao et al., showing concordant genetic alterations in asynchronous tumors from individual patients, suggest that disparate urothelial tumors are derived from the same neoplastic clone.

Studies of different stages and grades of bladder cancer have shown a higher frequency of genetic abnormalities in advanced-stage lesions. The changes are classified as primary chromosomal aberrations if they are associated with the development of the disease or as secondary if they are associated with progression to a more advanced stage. These changes represent the activation of protooncogenes by point mutation, amplification, or translocation that results in a gain of function and the inactivation of tumor suppressor genes, primarily by allelic deletion and point mutation of the contralateral allele, which results in a "negative" event. In general, deletions of 17p (the TP53 locus) and the RB gene locus are seen in patients with invasive disease, whereas aberrations of 9q occur predominantly in superficial tumors.

Several studies report associations between specific pathologic and molecular markers and prognosis. More significantly, tumor markers are beginning to be incorporated into clinical practice. Caution is advised when interpreting the results of different studies because of the different sensitivities of the technique used, the specific stage of the tumor included, the number of patients, and the follow-up interval on which the conclusions are based. An example of the differences is provided by the reported results evaluating p53 alterations. These have variable been assessed by immunohistochemical staining, single-strand conformational polymorphism analysis, and direct sequencing of different gene exons. With a panel of antibodies that recognize the mutated p53 protein, nuclear overexpression correlated with grade, stage, vascular invasion, and the presence of nodal metastases. Multivariate analyses showed that p53 mutation is associated with a higher frequency of progression to a more advanced stage and a higher rate of death from bladder cancer.

The status of p53 is currently being used to stratify patients for risk of metastasis, probability of nonmetastasis, and response to specific chemotherapeutic regimens. Whether determinations of p53 can provide more information than staging and grade for the choice between different treatment modalities remains to be investigated in comparative trials.

TREATMENT

Treatment selection is based on the extent or stage of disease. For certain patients, one therapeutic modality is sufficient. For others, a combined-modality approach is required. For superficial tumors, cystoscopic resection with and without intravesical therapy is preferred. Once invasion into muscle is documented, the standard treatment involves removing the bladder (cystectomy), and disease in the bladder is considered incipient. Medical intervention may be advised. Developing standards of care beyond single-modality approaches has been hampered by inconclusive clinical trials. Demonstrating the superiority of one treatment approach over another requires large numbers of patients and long follow-up to be clinically meaningful. Furthermore, the higher the morbidity of the "new" approach, the greater the reluctance to offer it to patients.

SUPERFICIAL DISEASE

The standard initial treatment of superficial bladder tumors is a complete cystoscopic resection. The majority of patients develop new tumors over time, 30% of which progress to a higher stage. As a result, vigilant follow-up with cystoscopy, urine cytology, and repeat transurethral resections (TURs) as needed are performed every 3 to 6 months, at least for the first 5 years of follow-up. Depending on the number of lesions, the size, the depth of invasion, and the number of prior tumors in that individual, intravesical therapy may or may not be recommended. Intravesical treatment is rarely advised for the first Ta tumor that is low-grade, although it is recommended for high-grade Ta, Tis, and T1 lesions.

Intravesical therapies are used for two indications: therapeutic and adjuvant or prophylactic. The former refers to the clinical situation in which residual disease remains in the bladder despite an attempt at a complete endoscopic resection. This is relatively infrequent except in cases with CIS. Prophylactic or adjuvant therapy is applied when a patient has shown a repeated tendency to develop new lesions in the bladder. The recurrences may represent new papillary lesions, CIS, or a combination of both. Intravesical instillations have been performed with chemotherapeutic agents, such as thiotepa, doxorubicin (Adriamycin), and mitomycin C; immunologic agents, such as interferon- 

Intravesical instillations have been performed with chemotherapeutic agents, such as thiotepa, doxorubicin (Adriamycin), and mitomycin C; immunologic agents, such as interferon- (IFN-), and interferon- (IFN-). For all agents, the mechanism of action is debated. Although the rationale for instilling chemotherapeutic agents initially was a postulated direct toxic effect on the tumor cells, a nonspecific inflammatory reaction is also believed to be contributory. Side effects include the local toxicities based on the instillation itself and whether the drug is systemically absorbed. The latter depends partly on the size of the molecule, the pH at the time of instillation, and the timing of the instillation relative to the diagnostic and therapeutic cystoscopy. All intravesical treatments have common side effects in common, especially those related to bladder irritation, such as dysuria and frequency, but also other unique side effects specific to a particular drug, such as myelosuppression or contact dermatitis. BCG differs in one important aspect from the chemotherapeutic agents: A small proportion of patients develop a systemic "BCGnosis" requiring treatment with tuberculostatic agents and steroids. Deaths have been reported. Allowing 2 to 3 weeks for healing after the endoscopic resection has been performed and before chemotherapy or BCG is administered reduces the chance of severe local or systemic toxicities.

Indications for intravesical instillations vary. Generally, the indications for adjuvant therapy include two or more tumor recurrences in a given year, the presence of diffuse Tis or multiple papillary tumors, or the identification of T1 disease that carries a high risk of stage progression. The risk of tumor recurrence and progression is associated with tumor type (Ta, T1, or Tis), tumor grade (low vs. high), length of follow-up (5 or more years), and treatment (TUR alone or TUR plus chemotherapy or BCG). The majority of papillomas and TaG1 tumors recur within 5 years, but they rarely invade or cause a cancer death. Recurrent tumors are treated with TUR or fulguration (as outpatient procedures) and are a low biologic risk. On the other hand, almost all high-grade (G3) Ta tumors recur within 2 to 3 years, 20% progress in stage within 5 years, and 30% to 40% progress by 10 years. All adjuvant treatments using thiotepa, doxorubicin, mitomycin C, or BCG decrease the probability of tumor recurrences over TUR alone. BCG has been shown to delay tumor progression to a more advanced stage, to decrease the need for cystectomy, and to improve survival.

Tis is generally treated by a combination of endoscopic resection followed by the intravesical instillation of BCG. This recommendation is based on the results of large-scale randomized comparisons showing its proven superiority relative to doxorubicin and mitomycin C. In the past, thiotepa was the most widely used agent, but it is now used less frequently because of limited efficacy and high frequency of myelosuppression. BCG is typically instilled weekly for 6 weeks. BCG eradicates Tis for more than 1 year in 70% of cases and prevents subsequent disease for 5 years in 60% of cases and for up to 10 years in 40% of cases.

Tissue-predictive information is provided by follow-up evaluation after 3 and 6 months and whether the bladder has been rendered tumor free, both endoscopically and cytologically. If it is not, some urologists recommend a repeat course of treatment. The maintenance role of BCG treatments has been debated. Some feel that regular treatment beyond the initial 6-week course further delays tumor recurrence and progression. Others believe that continued BCG not only increases the frequency of complications but fails to reduce tumor progression. Patients who have recurrent or persistent tumors after one or two cycles of intravesical therapy are often considered for cystectomy.

TUR alone is generally sufficient for noninvasive papillary (Ta) tumors. In some patients, the disease does not recur and, if no disease is documented after several sequential 3-month evaluations, the follow-up can be restricted to a yearly examination. In other cases in which recurrences are documented, more frequent and longer follow-up is recommended. In these cases, intravesical therapy has shown both the probable efficacy and the number of tumors documented at a given recurrence. Because the probability of progression to a more advanced stage is low, however, no definitive benefit of delayed progression or improved survival has been shown. The decision to administer such therapy must be balanced by the adverse effects and potential benefit of therapy. Intravesical therapy is commonly recommended if the number of recurrent episodes during a 24-month period exceeds two and if a large part of the urinary bladder wall is covered with tumors. Repeat cystoscopic examinations are generally advised at 3- to 6-month intervals, depending on the number of tumor recurrences, for the first 5 years, and annually thereafter in the absence of tumor recurrence.

Were it possible to determine which tumors were destined to progress to an invasive stage, early cystectomy would be preferred. Currently, no single factor or combination of factors has been useful in guiding treatment selection for patients with superficial disease. Some surgeons suggest radical surgery in patients with...
multiple tumors and frequent recurrences, especially if such tumors recur despite BCG therapy. Other agents undergoing clinical trials for BCG-refractory bladder tumors include gemcitabine, taxanes, broperimine, and valrubicine (AD 32).

Recurrences after intravesical treatment can develop anywhere that transitional epithelium exists, including the renal pelvis, ureters, and urethra. In fact, one consequence of the "successful" treatment of tumors in the bladder is an increase in the frequency of extravesical recurrences. In patients with multifocal CIS, the risk of developing an upper tract tumor is 15% at 5 years, 25% at 10 years, and 33% with 15-year follow-up. Tumor involvement of the prostatic urethra and ducts may be detected in 10% to 15% of cases in 5 years and in 20% to 40% within 10 years. Patients with a positive cytology and no obvious tumor in the bladder need careful monitoring of the upper tracts. Tumors of the upper tracts are particularly difficult to manage, because contact between a topical therapeutic agent and the diseased urethra is limited. The development of tumors in extravesical sites is cited as evidence of the "field change" theory of carcinogenesis. Selected tumors in the ureter or renal pelvis may be managed by ureteroscopic resection or, in some cases, by instilling BCG through the renal pelvis. Tumors of the prostatic urethra are frequently managed by cysectomy, particularly if a complete resection cannot be accomplished.

The prevalence of panurothelial tumor diathesis suggests that chemoprevention strategies will be needed as an adjunct to active therapy directed against the primary bladder tumors. Broperimine, an interferon inducer, and fenretinide (4-HPR), a synthetic retinoid, are being investigated as oral chemoprevention agents, but neither appears to be effective (National Cancer Institute and Bladder Cancer Italian Trial Group [BLINST], unpublished data, 1999).

**T1 DISEASE**

The T1 tumor is an invasive (lamina propria) neoplasm. Virtually all are high-grade, and one-half the cases have associated Tis. Recurrence rates are 50% by 1 year, 80% by 3 years, and 90% within 5 years. Considering progression, 50% of T1G3 cases develop invasive disease within 5 years; this number rises to 80% if associated Tis is in the pathologic specimen. Because of the high risk of progression, T1 tumors are generally treated with intravesical therapy. BCG reduces tumor recurrence in 50% of patients and reduces the progression rate to 15% at 5 years and 50% at 10 years. These rates mean that 50% of patients with T1 tumors will develop a muscle-invasive cancer in 10 years, despite the best available conservative therapy. Each present and recurrent T1 tumor has a 5% to 10% probability of distant metastasis. The survival rate is 70% at 5 years with BCG therapy and resembles that achieved after immediate radical cysectomy. On the other hand, patients who relapse with recurrent T1 tumors within 6 months to 1 year after an adequate trial of TUR and BCG (one or two courses) are best treated currently with cysectomy.

**MUSCLE-INVADING TUMORS**

Therapies for muscle-infiltrating disease can be divided into bladder-sparing and non–bladder-sparing (see Table 34.3-3). The standard treatment is surgical removal of the entire organ by radical cysectomy. In appropriately selected cases, an aggressive TUR may be adequate, although this is controversial. In other cases, a resection is combined with radiation or chemotherapy. These combined-modality approaches are limited to selected cases. End points include time to recurrence, in either the primary or a distant site, disease-free status, and overall survival.

Radical cysectomy achieves the best local control of invasive bladder cancer. The exact indications vary between institutions. Most physicians recommend cysectomy for (1) muscle-invasive tumors unsuitable for segmental resection, (2) low-stage tumors unsuitable for conservative management (i.e., because of multicentric and frequent recurrences resistant to intravesical instillations), (3) high-grade tumors (T1G3) associated with Tis, or (4) bladder symptoms, such as frequency or hemorrhage, rendering the patient a "bladder cripple." Survival distributions are expected to vary for patients who undergo treatment for these indications.

**SURGICAL APPROACHES**

Radical cysectomy in men involves the en bloc removal of the bladder, prostate, seminal vesicles, and proximal urethra, with a wide margin of pelvic adipose tissue and peritoneum. Loss of sexual function is often a consequence of the operation. In women, the procedure involves an anterior exenteration to remove the bladder, urethra, uterus, fallopian tubes, ovaries, anterior vaginal wall, and surrounding fascia. Pelvic lymph nodes are also removed.

Urinary flow is directed through a conduit diversion or a continent reservoir, a bladder substitute. In the standard ileal conduit, urine drains directly from the ureters through a segment of ileum to the skin surface, where it is collected. No internal reservoir is created. A few patients with this form of diversion develop hypochloremic acidosis, hyperkalemia, hyponatremia, and uremia. Ureteral obstruction and urinary tract infection are also relatively common. Continent reservoirs are becoming increasingly popular and include external continent stomas, which the patient self-catheterizes at regular intervals, and internal, orthotopic neobladders that can be fashioned in both men and women. All involve the creation of a low-pressure reservoir from a detubularized segment of bowel that is then anastomosed to either abdominal wall (Indiana pouch) or the urethra (neobladder) (Fig. 34.3-2). When an anastomosis to the urethra is created, primarily in men without urethral disease, the patient can void in the natural position. Complication rates are acceptable and most patients achieve urinary continence. An indication for urethrectomy precludes the creation of a urethral anastomosis, such as documented CIS or exophytic tumor in the urethra but also tumors that involve the bladder neck, rendering the urethra likely. In addition, elderly or infirm patients or those with locally extensive tumors who are at high risk of local recurrence are better served with an ileal conduit. An ileal stoma has fewer complications than continent diversions and is less demanding on the patient for daily care.

![FIGURE 34.3-2. The ileoneobladder (A) and the Indiana reservoir (B).](image)

Medical clearance before cysectomy is essential and includes optimizing cardiac medication and nutritional status. Complications of the operation include those typical for major surgery and those specific to the cysectomy. Among the former are adverse reactions to the agents used during anesthesia, blood loss and complications secondary to blood transfusions, pulmonary depression, myocardial damage secondary to prolonged anesthesia time or blood loss, and wound infection. Complications specific to cysectomy include rectal perforation and pelvic abscesses. Early and late complications associated with the urinary diversion procedure include intestinal obstruction, acute pyelonephritis, ureteral obstruction, stomal stenosis, intestinal fistula, renal calculus, and ureteral outlet urinary leakage. Outcomes are usually reported on the basis of 5-year survival rates. As Table 34.3-4 and Table 34.3-5 show, survival rates vary inversely with depth of invasion and lymph node status. In most cases, patients succumb to distant disease, believed to be the result of the continued growth of micrometastases present at the time of surgery. Thus, in turn, has led to the integration of systemic chemotherapy to manage these tumors. Survival is also improved and complications are minimized in patients who undergo cysectomy by experienced surgeons in centers that treat a high volume of bladder cancer.

**RADIOThERAPY AS DEFINITIVE TREATMENT**

In some countries, external-beam radiotherapy is considered standard but not in the United States. It is also recommended for patients deemed unfit for cysectomy, based on either comorbid conditions or disease extent. In most series, despite negative selection, results are inferior to those observed with radical surgery. These
results are partially because of the difficulty of rendering the bladder tumor-free by external-beam radiation alone and the continued risk for developing new tumors in the retained bladder.

In most cases, treatments are delivered in five daily fractions a week, ranging from 2.0 to 2.5 Gy to a total treatment dosage of 55 to 65 Gy without interruptions. In designing the radiation fields to treat a patient with bladder cancer, the target is best defined by information from the planning cystogram, the CT scan, the cystoscopic and bimanual examinations, and having the bladder empty to assist setup reproducibility and adequate coverage of the tumor at each treatment. Even with these efforts, a prospective CT study from Manchester reported significant movement in the bladder target volume, with possible underdosing of the tumor in one-third of the evaluated patients. Thus, care must be taken to ensure that the target volume is well defined and adequate margins are included, especially posteriorly.

The initial complete response (CR) rate (T0), based on clinical restaging with a cystoscopy and biopsy after conventional radiation, is 40% to 52% (Table 34.3-6). For patients who do not respond completely or whose disease progresses locally without metastases and who are medically fit, a salvage cystectomy is performed. When radiation is used in patients with T2 to T4 disease, the probability of keeping the bladder free of disease at 5 years ranges from 35% to 45%, overall survival is from 23% to 46%. Toxicities are classified as acute or chronic, with radiation delivery to the rectum and bladder being dose-limiting, and include symptoms of an irritated bowel and bladder, inflammation of the skin, and fatigue. A persistent proctitis, with bleeding and secretion of mucus, is rare but does occur, and bowel obstruction may be severe enough to require a colostomy. A markedly reduced bladder capacity resulting from fibrosis may render a cystectomy or urinary diversion necessary. Sexual function can also be impaired. Occurrence of secondary tumors in the urinary bladder or the surrounding tissue is a potential late complication. Radiation techniques have evolved with surgical techniques, encouraging the therapeutic index to improve in both increased radiation dosage to tumor and decreased exposure of normal tissue with three-dimensional treatment planning.

TABLE 34.3-6. Local Control Based on Clinical Staging Radiotherapy Alone

<table>
<thead>
<tr>
<th>Local Control</th>
<th>Clinical Staging</th>
<th>Radiotherapy Alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR Rate (T0)</td>
<td>40% to 52%</td>
<td></td>
</tr>
<tr>
<td>Overall Survival</td>
<td>35% to 45%</td>
<td></td>
</tr>
<tr>
<td>Radiation Delivery</td>
<td>Rectum and Bladder</td>
<td>Dose-limiting</td>
</tr>
</tbody>
</table>

Evolving Standards of Care for Muscle-Invasive Disease: Combined-Modality Approaches

Developing treatment guidelines for tumors of a specific stage is easier than applying guidelines to an individual patient. For example, although the standard treatment of an invasive bladder tumor is radical cystectomy, numerous reports in the literature of selected series of patients treated by TUR alone, partial cystectomy, external-beam radiotherapy, chemotherapy, or combinations of these appear to have comparable survival rates. Given the choice, most patients prefer a bladder-sparing approach, yet cumulative results suggest that some of these alternatives produce inferior survival rates as compared to radical surgery if salvage cystectomy for local recurrence is not done promptly. Refining the choice of treatment to optimize quality of life without compromising cure is difficult, because preservation of a tumor-free bladder still has some risk of the subsequent development of a superficial or an invasive tumor. In the 1970s and 1980s, four randomized phase III trials compared preoperative irradiation and immediate cystectomy to external-beam radiotherapy with cystectomy deferred for recurrence. Three of the four trials (involving a total of 442 patients from the United Kingdom, Denmark, and the United States National Bladder Cancer Group) found no significant difference in survival. However, a trial of 67 patients from the M. D. Anderson Cancer Center (MDACC) is the only phase III study, to our knowledge, that shows a statistically significant survival advantage to immediate versus deferred cystectomy. Combined-modality treatment with bladder preservation as an alternative to cystectomy is still investigational, and we recommend that such therapy be administered by dedicated multimodality teams. This treatment may be considered a reasonable alternative, if careful cystoscopic surveillance is conducted, in patients who are deemed unfit for cystectomy and for those definitely seeking an alternative to radical cystectomy.

Strong inferential data also suggest improved outcomes for which randomized trials are not truly definitive. The role of postoperative or adjuvant chemotherapy is one such scenario. Difficulties are encountered in interpreting both negative and positive outcomes. In a negative-outcomes trial designed in 1980 with the best available therapy at the time, for example, only 19% of patients enrolled actually received full doses of the planned chemotherapy. Not administering treatment virtually guarantees failure. Instead of concentrating on correlation of bladder cancer patients as a whole, many trials enroll only highly selected patients. This situation is illustrated in a study in which only 17 of 41 randomly selected patients completed therapy in a specific treatment program; these patients were derived from 453 patients with invasive disease seen at the treating institution over the same interval. Extrapolating these results to all patients can be misleading. If a treatment is associated with significant morbidity or may increase mortality, the question becomes: What is the level of benefit a physician requires to adopt the approach as a standard? Considering the difficulties encountered in completing clinical trials in this disease, a more effective developmental strategy might be conducting trials in populations who have specific high-risk factors for developing metastatic disease and in whom treatment effects can be discerned rapidly.

Preoperative Radiotherapy

In the 1970s, moderate-dose preoperative radiation, with specific 20 Gy by accelerated fractionation or 40 to 50 Gy with conventional fractionation, was the standard. The results showed that radiotherapy alone could eradicate disease in the resected specimen and the regional lymph nodes in a small but definite proportion of patients. The technique was largely abandoned when no survival benefit was observed in randomized comparisons.

A recent trial at the MDACC identified a clinical subset for whom radiotherapy might be beneficial. The trial included 135 patients with clinical stage T3 tumors who were treated by either preoperative radiotherapy and cystectomy (92 patients) or cystectomy without irradiation (43 patients), using modern-day surgical techniques and adjunctive multiagent chemotherapy. Although no survival benefit was observed, the results showed a significant decrease in pelvic recurrence rates from 28% to 9% at 5 years for patients with T3 disease who received radiation. No difference was observed for patients with T2 disease. Because the true rate of pelvic recurrences after radical surgery is not known, as disease in most patients who experience relapse systemically is not restaged locally, the study raises the question whether preoperative cystectomy might be an option for patients who present with extravesical tumors. With drawbacks including the potential effect on the ability to create internal urinary reservoirs with irradiated bowel, the question requires prospective evaluation.

Postoperative Radiotherapy

When a positive surgical margin is documented after cystectomy, local recurrence rates are high with or without chemotherapy. However, no randomized trial has evaluated the use of postoperative radiation for patients with transitional cell tumors. A Radiation Therapy Oncology Group (RTOG) phase II trial of postoperative irradiation reported the incidence of small bowel obstruction or fistula in 30% of patients. Recently, investigators using multivariate analysis in a retrospective study of 92 patients from Milan reported that patients without evidence of nodal metastases receiving 50.4 Gy after radical cystectomy had significantly improved cancer-specific and disease-specific survival rates. With a median follow-up of 36 months, one of 32 irradiated patients has required reoperation for bowel toxicity. While encouraging, this result requires longer follow-up to be considered for further prospective evaluation. One randomized trial evaluating postoperative radiotherapy has been completed in Egypt for patients with squamous cell carcinomas. In this trial, the rate of pelvic recurrences was reduced from 50% to 10% in the irradiated patients. It must be noted that squamous cell tumors seen in the Middle East tend to recur locally and have a low metastatic rate as compared to the transitional cell tumors that occur in North America, which have a high metastatic rate.
Deferred Cystectomy: Treatment with External-Beam Radiation and Salvage Cystectomy

Four randomized trials have addressed the question of whether a regimen of preoperative radiation and immediate cystectomy compares with one of external-beam radiotherapy followed by a salvage cystectomy for radiation failures. A small trial with 67 patients showed a difference in survival at 5 years, and a second showed a lower frequency of pelvic recurrence but no survival difference with combined modality therapy. Based on the sample sizes, a 25% difference, either negative or positive, could not be excluded (Table 34.3-7; S. D. Cutler, personal communication, 1983). Nevertheless, the trials do suggest that deferring a cystectomy until local progression is documented does not appear to affect adversely the rate of metastases or to compromise overall survival.

TABLE 34.3-7. Randomized Trials of Irradiation Plus Cystectomy versus Radiation and Deferred (Salvage) Cystectomy

INTEGRATING SYSTEMIC CHEMOThERAPY

The major cause of death in patients with invasive bladder cancer is metastatic disease. In most cases, the course of tumor relapse supports the concept that micrometastases are present at the time of initial therapy. The primary role for chemotherapy in the perioperative setting is to increase survival. Additionally, a substantial number of studies address the use of chemotherapy alone and concurrent with radiotherapy to preserve the native bladder. Specific considerations in evaluating chemotherapy’s role in patients presenting with invasive disease include the activity of the various combinations of multiagent therapy—as judged by the proportion of patients with known metabolic diseases who achieve complete remissions and are ultimately cured—and the number of patients needed to prove the benefit of currently available therapies. Reviewing the activity of chemotherapy in metastatic disease provides insight into the studies exploring perioperative chemotherapy.

Chemotherapy

Urothelial cancer is a chemotherapy-sensitive neoplasm. A broad number of single agents with different mechanisms of action are effective (Table 34.3-8). Complete responses using older agents are rare; most produce partial responses, with response durations of approximately 3 to 4 months. Recently, several agents were identified as active in phase I and II studies, including docetaxel, paclitaxel, gemcitabine, piritrexim, and ifosfamide. Observations distinguishing these new, active agents from older drugs are moderate activity as both first- and second-line therapy; favorable toxicity profiles; drug metabolism independent of renal excretion; and CR in metastatic disease to a single agent.

TABLE 34.3-8. Cumulative Results with Single-Agent Chemotherapy Used in Metastatic or Unresectable Disease

Combination Chemotherapy: Randomized Trial Results

Clinical outcomes (i.e., response and survival) are better for multiagent therapy than those observed with single-agent treatment in advanced TCC. The regimens most extensively studied in the 1980s were cisplatin, cyclophosphamide, and Adriamycin (CISCA); cisplatin, methotrexate, and vinblastine (CMV); and methotrexate, vinblastine, Adriamycin, and cisplatin (M-VAC; Table 34.3-9). These regimens demonstrate strikingly similar CR and overall response proportions in 20% to 22% and 50% to 60% of patients, respectively. The comparable efficacy and toxicity of the various regimens were discerned by randomized trial results. The CMV combination was superior to methotrexate and vinblastine without cisplatin; CMV was associated with significantly longer progression-free survival (4.5 months vs. 2.5 months) and 1-year survival (28% vs. 16%). M-VAC was superior to single-agent cisplatin in both response and survival. In the only direct comparison of cisplatin-based combinations, M-VAC was superior to CISCA. Despite the popularity of the CMV regimen, median survival in one randomized trial was only 7 months; CMV has not been directly compared with M-VAC. It is concluded from these studies that cisplatin-based therapy should be the primary consideration for all patients requiring chemotherapy, and that M-VAC should be the regimen of choice.

TABLE 34.3-9. Cisplatin- and Carboplatin-Containing Regimens Used to Treat Urothelial Carcinoma
NEW CHEMOTHERAPEUTIC REGIMENS. Development of new agents and combining agents is necessary if improvement in long-term survival or reduction of chemotherapy-associated toxicity (or both) is to be achieved. In combination chemotherapy trials, several cytotoxic agents introduced in this decade are undergoing evaluation for treating urethral tumors. The most extensively studied agents are gemcitabine, a deoxycytidine analog with structural similarities to cytarabine, and the taxanes: paclitaxel and docetaxel.

Most combination regimens include a platinum analog, either cisplatin or carboplatin, in part because of the reported complementary or synergistic actions of these new agents with platinum analogs. The single-agent activity of carboplatin in urothelial cancer appears less than that observed with cisplatin (see Table 34.3-3). Controversy exists as to whether the efficacy of carboplatin combinations compares favorably with cisplatin combinations. A small, randomized phase II trial compared M-VAC with the carboplatin-based regimen of methotrexate, carboplatin, and vinblastine. Relative to M-VAC, the carboplatin-containing regimen produced a lower response proportion (52% vs. 39%) and shorter median survival (16 vs. 9 months). Criticism of the trial included the phase II nature of the study (i.e., a small number of patients) and the lack of doxorubicin in the carboplatin arm.

Cisplatin combinations are associated with greater renal, neurologic, and auditory toxicity; they are more difficult to administer to patients who have renal impairment or other medical comorbidities. In contrast, carboplatin is not only more feasible in the patient with impaired renal function or medical comorbidities, it is more easily administered in the outpatient setting. Although carboplatin has greater myelosuppression, this toxicity is easily managed by adjusting the dose according to the patient’s creatinine clearance to provide a predetermined area under the plasma concentration–time curve (AUC) of the drug. The controversy surrounding the efficacy of carboplatin–versus cisplatin-containing therapy in phase II trials is being addressed by ongoing and planned randomized phase III trials.

NEW TWO- AND THREE-DRUG COMBINATIONS AS FIRST-LINE THERAPY. The combinations of either paclitaxel (42% to 55% single-agent activity) or docetaxel (31% activity) with cisplatin (at 70 to 75 mg/m²/course) have been evaluated in four phase II trials. Three trials evaluating paclitaxel at 135 to 175 mg/m² over 3 hours in combination with cisplatin produced overall response rates ranging from 62% to 72% and CR rates ranging from 10% to 34%. These studies demonstrated that it is possible to increase drug delivery by as much as 60% over standard-dose M-VAC either by increasing the doses of the individual agents or decreasing the cycling intervals (or both). Toxicities seen with the dose-intense regimens range from side effects that resemble standard-dose M-VAC to substantially increased toxicity and an increased toxic death rate. Despite more intensive chemotherapy, the CR proportions for these studies still approximate 20%, suggesting no marked improvement in survival. A randomized phase III trial in the European Organization for Research and Treatment of Cancer (EORTC) is evaluating whether dose-intense M-VAC improves survival over standard-dose therapy.

The two-drug combination is active, generally well tolerated, and can be given in the outpatient setting. Docetaxel (75 mg/m²) and cisplatin had a major response in 60% of patients; 7 of 25 (28%) patients achieved CR, with a median survival rate of 13.6 months. The most predominant toxicity was granulocytopenia, but fluid retention, neuropathy, and mucositis were also observed. No plans exist to compare further the paclitaxel-cisplatin or the docetaxel-cisplatin doublet to standard therapy.

The paclitaxel-cisplatin doublet has been evaluated in numerous phase II trials. The initial phase I–phase II trial exploring paclitaxel doses of 150 to 225 mg/m² in a 3-hour infusion plus cisplatin at a AUC of 6 every 3 weeks reported an overall response rate of 51%. Trials 90 through 97 of more than 200 patients treated with paclitaxel (150 to 225 mg/m²) and carboplatin (AUC of 5 to 6) have provided several important observations. The regimen is well tolerated; myelosuppression is the most common toxicity, but granulocytopenic fever and cycling delays for hematologic toxicity are uncommon. Neurotoxicity is commonly observed but is not severe. Response rates vary, ranging from 14% to 65%, with CR rates ranging from 0% to 40%. Efficacy is highest among patients with lymph node metastases, but patients with lung and liver metastases also respond. No clear dose-response correlations exist for either paclitaxel or carboplatin. Mature results are not available for all studies, but the survival rate ranges from 8.5 to 9.5 months in the three trials reporting survival data. It is as yet unclear whether this doublet has survival inferior to the approximately 1-year survival seen with M-VAC or that the reported phase II results are affected by pretreatment prognostic factors, the small number of patients resulting in wide confidence intervals of efficacy parameters, or the inclusion of previously treated patients.

The three-drug combination of ifosfamide, paclitaxel (Taxol), and cisplatin (platinum) (ITP) recycled every 4 weeks was reported by MSKCC investigators to be effective and tolerable in previously untreated patients with advanced TCC. Thirty of 44 (68%) assessable patients (95% confidence interval, 52% to 81%) demonstrated a major response (10 complete [23%], 20 partial [45%]), with durations of response ranging from 4 to 36 months. At a median follow-up of 28 months, the median survival was 20 months. Eleven (25%) patients are disease-free. The median survival of 20 months in this trial is the best reported result for urethral tumors with metastatic TCC receiving chemotherapy and is greater than previously observed experiences with M-VAC (median survival, 12 to 13 months).
months). The possibility exists that adding ifosfamide to a cisplatin-based combination may enhance survival; alternatively, the improved survival may be a consequence of favorable pretreatment prognostic factors and aggressive postchemotherapy surgery.

The combinations of gemcitabine, paclitaxel, and either cisplatin or carboplatin have been reported in two separate trials. The cisplatin-containing triplet, reported for 29 assessable patients, demonstrated a 79% response proportion. Myelosuppression and asthenia were the predominant toxicities. Investigators at Wayne State University explored the paclitaxel-gemcitabine-cisplatin regimen, building on prior experience with the paclitaxel-cisplatin regimen. In 19 assessable patients, 11 (58%) had a major response.

Tu et al. evaluated paclitaxel, cisplatin, and methotrexate every 3 weeks in 25 previously treated patients. Partial responses lasting from 2 to more than 9 months were achieved in ten patients (40%), including three of seven patients with liver metastases. The primary toxicity was hematoLogic, with 8 of 25 patients experiencing severe neutropenia, resulting in six episodes of severe febrile requiring hospitalization. Severe thrombocytopenia, defined as grade 3 or greater, occurred in 8 of 25 patients. Meyers et al. evaluated the triplet of paclitaxel-cisplatin-methotrexate in 23 assessable patients. Adjunctive care included leucovorin and granulocyte colony-stimulating factor (G-CSF). Fourteen of 23 patients (61%) responded, including four complete responses, resulting in a median survival of 16 months. The principal toxicities were neutropenia and neurotoxicity. Leucovorin was subsequently eliminated from the regimen, and reduction of the carboplatin dose to AUC 5 allowed deletion of G-CSF.

Gallium nitrate as second-line therapy sponsored first-line combinations. The initial report of the three-drug regimen of vinblastine, ifosfamide, and gallium nitrate had a 67% major response rate. Activity was confirmed in the Eastern Cooperative Oncology Group (ECOG) trial, with 44% of patients responding. Toxicity was substantial; ocular blindness, arrhythmias, and myelosuppression were reported. A separate randomized phase II study examined the efficacy of gallium nitrate plus fluorouracil versus dose-intense M-VAC, finding only marginal activity for the gallium combination (12% major response proportion). The toxicity profile and the cost of administering gallium nitrate on a 5-day inpatient schedule limit further study. Seven of 14 (51%) patients obtained a major response to the combination of paclitaxel, vinblastine, and gallium. Calvo et al. evaluated the paclitaxel-cisplatin-methotrexate triplet in both chemotherapy-naive and previously treated patients. Among 12 patients, eight partial (67%) responses were observed, for an overall response rate of 75%. Grade 3 or 4 toxicity included neutropenia, thrombocytopenia, mucositis, diarrhoea and vomiting, and paralytic ileus.

SECOND LINE THERAPY AND FIRST-LINE REGIMENS WITHOUT PLATINUM ANALOGUES. Regimens devoid of a platinum analog have not been extensively studied. Sweeney et al. reported the combination of ifosfamide, 1000 mg/m² days 1 to 4, plus paclitaxel, 135 mg/m² by 24-hour infusion on day 4 of a 3-week cycle, using G-CSF support. Twenty-six patients were evaluable for response: Two of 13 patients (15%) treated in a second-line setting responded with CR, as did 4 (1 CR, 3 PR) of 13 patients (31%) previously treated with ifosfamide. Thus, the combination did not add to paclitaxel activity as first-line therapy and that paclitaxel did not increase the second-line activity of ifosfamide. The ECOG is currently exploring the combination of docetaxel and gemcitabine in chemotherapy-naive patients, and the Hoosier Oncology Group is evaluating the combination of paclitaxel and gemcitabine.

Limited experience exists for the paclitaxel-cisplatin combination in patients with primary therapy, or preexisting renal impairment. Otto et al. performed a phase II trial of this doublet in combination with an antimitotic agent (acelular pertussis vaccine) in 18 patients with cisplatin- and methotrexate-resistant metastatic cancer; 4 (22%) patients responded, including 2 CR (11%). It is implied from these studies that multiple-agent regimens offer no advantage over single-agent therapy in patients eligible for second-line therapy.

**Randomized Trials: Developing a New Standard of Chemotherapy for Advanced Disease**

**NEOADJUVANT AND ADJUVANT CHEMOTHERAPY ROLES IN MUSCLE-INVASIVE DISEASE.** Given the chemosensitivity of urothelial cancer, attempts to improve the survival of patients with muscle-invasive disease have focused on administering chemotherapy at the time of definitive treatment of the primary tumor, most often in the form of chemotherapy followed by surgery. However, the benefit observed by this approach is likely a consequence of favorable pretreatment prognostic factors and aggressive postchemotherapy surgery. Thus, the focus of these trials has been to determine whether the combination or combination regimens compared to either alternating chemotherapy regimens or combination chemotherapy in which maximal doses of each agent are limited by overlapping toxicity.

**GEMCITABINE-CISPLATIN DOUBLET.** The sequence of Adriamycin plus gemcitabine (AG) followed by the ITP combination is under evaluation for treating unresectable metastatic TCC. A randomized comparison of the 5-FU, interferon-a, and cisplatin combination and M-VAC regimens in chemotherapy-naive patients is ongoing at the MDACC. The second trial compared chemotherapy plus the paclitaxel-cisplatin doublet that has a favorable toxicity profile. The combination is easy to administer, has activity in phase II studies, and is frequently used in clinical practice. However, questions remain regarding the efficacy of this regimen in relation to M-VAC; this controversy is being addressed by comparing the paclitaxel-cisplatin regimen to standard M-VAC to determine whether this new doublet has similar efficacy with less toxicity. The phase II data for combination of gemcitabine, paclitaxel, and cisplatin have been encouraging.

A randomized international randomized trial has been proposed to compare this triplet to standard therapy.

**A Chemotherapy Hypothesis to urothelial cancer is being tested at MSKCC. The Norton-Simmon model, a mathematical prediction of chemotherapy sensitivity based on gompertzian growth rates displayed by malignant tumors, predicts that efficacy is increased with sequenced "dose-dense" therapy using either single agents or combination regimens compared to either alternating chemotherapy regimens or combination chemotherapy in which maximal doses of each agent are limited by overlapping toxicity.**

**Gemcitabine dose of 2000 mg/m² followed by ITP is associated with an encouraging CR proportion of more than 30%**. The survival distributions with early follow-up are encouraging, but long-term survival rates were not available. Drug tolerance and toxicity profiles favored the gemcitabine-cisplatin doublet.

**The two-drug combination was associated with delivery of a greater number of chemotherapy cycles, a smaller incidence of treatment-related death, and a lower incidence of infectious complications.** Based on the results of this randomized trial, gemcitabine and cisplatin should be considered a conventional chemotherapy standard for TCC.

**Two randomized trials are ongoing. 5-Fluorouracil (5-FU) combined with interferon-a alone and together with cisplatin has been reported to be active. A randomized comparison of the 5-FU, interferon-a, and cisplatin combination and M-VAC regimens in chemotherapy-naive patients is ongoing at the MDACC. The second trial compared chemotherapy plus the paclitaxel-cisplatin doublet that has a favorable toxicity profile. The combination is easy to administer, has activity in phase II studies, and is frequently used in clinical practice. However, questions remain regarding the efficacy of this regimen in relation to M-VAC; this controversy is being addressed by comparing the paclitaxel-cisplatin regimen to standard M-VAC to determine whether this new doublet has similar efficacy with less toxicity. The phase II data for combination of gemcitabine, paclitaxel, and cisplatin have been encouraging.**

**A national randomized international trial has been proposed to compare this triplet to standard therapy.**

A chemotherapy hypothesis novel to urothelial cancer is being tested at MSKCC. The Norton-Simmon model, a mathematical prediction of chemotherapy sensitivity based on gompertzian growth rates displayed by malignant tumors, predicts that efficacy is increased with sequenced "dose-dense" therapy using either single agents or combination regimens compared to either alternating chemotherapy regimens or combination chemotherapy in which maximal doses of each agent are limited by overlapping toxicity.

**The sequence of Adriamycin plus gemcitabine (AG) followed by the ITP combination is under evaluation for treating unresectable or metastatic TCC. A phase I study explored the feasibility of doxorubicin at 30 to 50 mg/m² plus gemcitabine at 1000 to 2000 mg/m² every 2 weeks for six treatment cycles with G-CSF in the AG/ITP sequence. Among the 14 patients assessable for response to the entire sequence, complete regression was observed in 3 (21%), and more than 50% regression occurred in 6 (43%), for an overall response rate of 64%. All six patients at the highest dose levels responded. The most common grade 3 and grade 4 toxicities were anaemia and neutropenia. A preliminary report of an MSKCC phase II trial of AG at a doxorubicin dose of 50 mg/m² and gemcitabine dose of 2000 mg/m² followed by ITP is associated with an encouraging CR proportion of more than 30%. An attempt to confirm the high CR proportion of this sequenced approach has been proposed in the cancer and leukemia group B.**

**NEOADJUVANT AND ADJUVANT CHEMOTHERAPY ROLES IN MUSCLE-INVASIVE DISEASE.** Given the chemosensitivity of urothelial cancer, attempts to improve the survival of patients with muscle-invasive disease have focused on administering chemotherapy at the time of definitive treatment of the primary tumor, most commonly in the perioperative setting. This approach attempts to enhance cure based on the putative advantages of greater efficacy in a smaller volume of disease and greater cure rate in patients whose disease is restricted to nodal sites rather than visceral sites.

Several considerations arise in analyzing the trial data. First, the odds of reducing mortality by perioperative chemotherapy are independent of the absolute odds of that event occurring in the absence of chemotherapy. For example, a group of pt4 or N+ patients (or both) would be expected to have an 80% death rate, and the hypothetical 20% chemotherapy benefit in mortality will reduce the actual mortality from 80% to 64% (i.e., survival improves from 20% to 36%). However, the same 20% chemotherapy benefit in mortality will reduce the actual mortality from 80% to 64% for patients with stage IV disease, provided the chemotherapy is administered in an adjuvant or neoadjuvant setting. Lessons learned in treating other malignancies show that if chemotherapy is effective, subsequent chemotherapy is conferred in either setting. However, such data do not extend to urothelial cancer, and advantages and disadvantages of such approach...

**DILEMMA: ADJUVANT OR NEOADJUVANT CHEMOTHERAPY.** If a survival benefit is conferred by perioperative chemotherapy, that benefit should be evident when the chemotherapy is administered in an adjuvant or neoadjuvant setting. Lessons learned in treating other malignancies show that if chemotherapy is effective, subsequent chemotherapy is conferred in either setting. However, such data do not extend to urothelial cancer, and advantages and disadvantages of such approach...
Adjuvant Chemotherapy. The major advantages for adjuvant chemotherapy are the following: (1) The risk of relapse is best predicted by pathologic stage, (2) the removal of the bladder eliminates the risk for new tumors, and (3) any potential risk of delay in surgery that may compromise cure is reduced. Radical cystectomy allows the treatment decision regarding chemotherapy to be based on the pathologic risk of recurrence, restricting chemotherapy to patient subsets most likely to benefit from chemotherapy, such as patients with pT3 to pT4 or positive lymph node (N+) disease. In addition to removing the bladder and reducing the risk of new tumor formation, repeated cystoscopy is not needed to evaluate for recurrent tumor.

The major disadvantages are that (1) drug delivery may be more difficult after surgery and (2) response to chemotherapy cannot be objectively measured. Clinical trials evaluating adjuvant chemotherapy do not have a surrogate end point for response; therefore, long patient follow-up is necessary to determine disease recurrence and survival. Historically, patients have had more difficulty in tolerating adjuvant chemotherapy after a radical cystectomy, so drug delivery, particularly cisplatin-based therapy, may be more difficult to give in the adjuvant setting.

Nonrandomized data suggest a survival benefit for adjuvant chemotherapy. In a study performed at MDACC, patients who did not receive adjuvant chemotherapy (not referred for chemotherapy, refused chemotherapy, or were considered medically unfit) were subdivided into a high-risk subgroup (defined as having resected nodal metastases, extravesical involvement of tumor, lymph-vascular permeation of the primary tumor, or pelvic visceral invasion) and a low-risk subgroup (having none of the above). These untreated patients were compared to those in a second high-risk group that received adjuvant chemotherapy with cisplatin, doxorubicin, and cyclophosphamide. The 5-year, disease-free survival for the treated high-risk group was twice that of the untreated high-risk group and equaled that observed for the low-risk group. These data imply that adjuvant chemotherapy is beneficial for high-risk treated patients, but the absence of randomization and patient selection may have biased the results.

Five randomized trials have examined adjuvant therapy in muscle-invasive disease (Table 34.3-10). Three trials have not shown benefit of single-agent cisplatin; the combination of cisplatin, vinblastine, and methotrexate; or a regimen of 5-FU and doxorubicin. Two trials suggest a benefit for chemotherapy over observation alone after cystectomy. In a University of Southern California (USC) trial, patients with pT3 or pT4 or node-positive disease were randomly assigned to either observation or four cycles of cyclophosphamide, doxorubicin, and cisplatin. A significant delay in time to progression was observed for patients who received chemotherapy (70% compared to 46% disease-free survival at 3 years; P < .001), and the improvement in survival (4.3 years vs. 2.4 years) was also statistically significant (P = .0062). Flaws in this trial include (1) low numbers of patients, (2) premature termination of the study, (3) the statistical methodology, and (4) the use of nonstandardized chemotherapy. Investigators in the Mainz trial studied 49 patients with pT2 to pT4 or node-positive TCC who were randomly chosen to receive M-VAC or CMV and either doxorubicin or epirubicin or to undergo observation. However, patients in the observation arm did not routinely receive chemotherapy at relapse. A significant reduction in the risk of tumor recurrence was observed in the adjuvant chemotherapy arm: 3 of 18 (17%) patients who received chemotherapy experienced relapse as compared to 18 of 23 (78%) untreated patients (P = .0007). A survival benefit was reported in a follow-up report with additional patients entered into the study.

Collectively, these trials fail to prove definitively that adjuvant chemotherapy provides a survival benefit in muscle-invasive TCC. The trials performed to date are substantially flawed. Problems encountered in the interpretation of results include (1) insufficient numbers of patients, raising the possibility of false interpretation, (2) inadequate chemotherapy, or (3) premature closure. Despite the reported activity of cisplatin-based chemotherapy in more advanced disease over the last 15 years, the hypothesis that multigent chemotherapy may be beneficial after cystectomy for muscle-invasive disease has not been adequately tested. Both nonrandomized and randomized data suggest that adjuvant chemotherapy delays tumor progression; however, a survival benefit has not been definitively proven. The MSKCC approach for nonprotocol patients with muscle-invasive disease is to consider four cycles of adjuvant M-VAC for patients with at least T3,N0 pathologic features, and any patients with node-positive disease provided that they can tolerate aggressive chemotherapy. If such patients cannot tolerate M-VAC therapy, chemotherapy is recommended. These treatment recommendations are based on the following data: (1) Cure can be achieved in patients with node-positive disease treated with chemotherapy followed by cystectomy; (2) M-VAC must be considered the most efficacious regimen based on randomized comparisons to single-agent cisplatin and to the combination of cisplatin, doxorubicin, and cyclophosphamide; and (3) independent prognostic factors for survival in the advanced disease setting are a good performance status (reflecting lower tumor burden) and disease restricted to lymph nodes; cure is greatest in patients with both features.

Neoadjuvant Chemotherapy. The major advantages of the neoadjuvant approach are the response of the primary lesion, which has prognostic importance, and the degree of response, which can be used to recommend further treatment. Response of a primary lesion to combination therapy is associated with improved long-term survival. In a report of 125 patients with multiple trials of cisplatin-based therapy followed by definitive surgery, 91% of the responders (2 of 21 at cystectomy) were disease-free, in contrast to only 37% of nonresponders (pT2 at cystectomy). A major response to neoadjuvant chemotherapy can also result in preservation of the bladder by repeated and aggressive transurethral resections or by a partial cystectomy. Patients whose disease is not responding appropriately can be referred for definitive cystectomy.

Major disadvantages of neoadjuvant chemotherapy include a marked discordance between the clinical and pathologic response to chemotherapy and persistent risk of new bladder tumor formation in the preserved bladder. Approximately 30% of bladder tumors staged as pT2 at cystectomy will recur after completing neoadjuvant chemotherapy will have persistent muscle-invasive disease if a cystectomy is performed. Second, even in the patient whose tumor is in complete pathologic response after chemotherapy, the bladder remains at risk for new muscle-invasive bladder tumors that may result in the need for cystectomy. Herr et al. reported a 56% incidence of new bladder tumors in patients 10 years after bladder preservation with neoadjuvant M-VAC and conservative surgery; 30% of the patients had invasive disease requiring a cystectomy.

Studies evaluating chemotherapy in the neoadjuvant setting include both phase III trials examining survival advantage and phase II studies examining response or potential bladder preservation (or both). The latter studies are not controlled for patient selection, cystoscopic resection, staging and restaging techniques, and chemotherapeutic regimens. Most randomized studies of neoadjuvant chemotherapy failed to show a survival benefit for chemotherapy (Table 34.3-11). Similar to the adjuvant trials, these studies suffer from suboptimal regimens of chemotherapy or small sample size. The only reported trial with enough power to detect a 10% difference in survival is the intergroup trial performed by the Medical Research Council and the EORTC evaluating CMF for three cycles followed by the participating institutions' recommended management of the primary lesion versus similar primary tumor management without neoadjuvant chemotherapy. Primary tumor management in this trial included cystectomy, radiotherapy, or both. With an accrual of 976 patients, a 5.5% advantage in 3-year survival for patients receiving neoadjuvant CMF was observed. The survival advantage was not statistically significant, because the trial was powered to detect a 10% survival advantage, the minimal benefit discerned by these collaborating investigators to substantiate the routine use of chemotherapy. Trial interpretation is difficult, as not all patients underwent similar treatment of the primary tumor: it is possible that benefit might be different in patients treated with cystectomy versus those treated with radiotherapy.

### Table 34.3-10. Randomized Trials of Adjuvant Chemotherapy versus Observation in Patients with Muscle-Invasive Urothelial Cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Patients</th>
<th>Treatment</th>
<th>Follow-up</th>
<th>Survival Advantage</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>218</td>
<td>M-VAC</td>
<td>3 years</td>
<td>50% vs. 33%</td>
<td>.0062</td>
</tr>
<tr>
<td>B</td>
<td>49</td>
<td>CMV</td>
<td>3 years</td>
<td>50% vs. 33%</td>
<td>.0062</td>
</tr>
<tr>
<td>C</td>
<td>125</td>
<td>Cisplatin</td>
<td>3 years</td>
<td>91% vs. 37%</td>
<td>.0001</td>
</tr>
</tbody>
</table>

**Adjuvant Chemotherapy: P = .001, and the improvement in survival (4.3 years vs. 2.4 years) was also statistically significant (P = .0062). Flaws in this trial include (1) low numbers of patients, (2) premature termination of the study, (3) the statistical methodology, and (4) the use of nonstandardized chemotherapy. Investigators in the Mainz trial studied 49 patients with pT2 to pT4 or node-positive TCC who were randomly chosen to receive M-VAC or CMV and either doxorubicin or epirubicin or to undergo observation. However, patients in the observation arm did not routinely receive chemotherapy at relapse. A significant reduction in the risk of tumor recurrence was observed in the adjuvant chemotherapy arm: 3 of 18 (17%) patients who received chemotherapy experienced relapse as compared to 18 of 23 (78%) untreated patients (P = .0007). A survival benefit was reported in a follow-up report with additional patients entered into the study.**

**Neoadjuvant Chemotherapy: The major advantages of the neoadjuvant approach are the response of the primary lesion, which has prognostic importance, and the degree of response, which can be used to recommend further treatment. Response of a primary lesion to combination therapy is associated with improved long-term survival. In a report of 125 patients with multiple trials of cisplatin-based therapy followed by definitive surgery, 91% of the responders (2 of 21 at cystectomy) were disease-free, in contrast to only 37% of nonresponders (pT2 at cystectomy). A major response to neoadjuvant chemotherapy can also result in preservation of the bladder by repeated and aggressive transurethral resections or by a partial cystectomy. Patients whose disease is not responding appropriately can be referred for definitive cystectomy.**

**Major disadvantages of neoadjuvant chemotherapy include a marked discordance between the clinical and pathologic response to chemotherapy and persistent risk of new bladder tumor formation in the preserved bladder. Approximately 30% of bladder tumors staged as T0 after completing neoadjuvant chemotherapy will have persistent muscle-invasive disease if a cystectomy is performed. Second, even in the patient whose tumor is in complete pathologic response after chemotherapy, the bladder remains at risk for new muscle-invasive bladder tumors that may result in the need for cystectomy. Herr et al. reported a 56% incidence of new bladder tumors in patients 10 years after bladder preservation with neoadjuvant M-VAC and conservative surgery; 30% of the patients had invasive disease requiring a cystectomy.**

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A Nordic Cooperative Bladder Cancer Study Group trial explored doxorubicin plus cisplatin, and the ongoing Southwest Oncology Group (SWOG) trial is evaluating neoadjuvant M-VAC. The Scandinavian trial explored doxorubicin and cisplatin prior to low-dose preoperative radiotherapy and cystectomy. This trial with 325 patients reported nonsignificant survival differences in patients treated with adjuvant chemotherapy (59% in the chemotherapy arm vs. 51% in the control arm (P = 1), with cancer-specific survival rates of 64% and 54%, respectively). The authors reported a 15% survival benefit in the subset of patients with T3 and T4 disease (P = .03) but no differences in patients with TI and T2 disease. A multivariate analysis revealed that chemotherapy and T stage were independent prognostic factors for survival and that the relative death risk for patients who received chemotherapy was 0.69 as compared to the control group. Results from the SWOG trial of neoadjuvant chemotherapy are awaited with great interest. This neoadjuvant trial evaluates the use of M-VAC chemotherapy, a regimen that many feel is the optimal conventional standard, for three cycles followed by cystectomy versus cystectomy alone. The accrual goal was reached in 1998, and results should be available in the year 2001.

Ongoing Clinical Trials Evaluating Adjuvant and Neoadjuvant Chemotherapy. The combination of paclitaxel and carboplatin is active in urothelial cancer and well tolerated when carboplatin is dosed to a predetermined AUC according to the patient's renal function. The activity and tolerance of this regimen are the basis of a randomized adjuvant trial designed by the ECOG. This proposed trial will randomly choose approximately 330 patients with either pT4NM0 or pT(any)N+M0 tumors after cystectomy and pelvic lymph node dissection to receive either four cycles of M-VAC or four cycles of paclitaxel plus carboplatin.

Current MSKCC trials are testing the hypothesis of maximizing individual drugs or combinations of agents devoid of overlapping toxicities according to the model originally proposed by Norton and Simon. After local control surgery, enrolled patients receive sequential, dose-intensive gemcitabine and doxorubicin, then either paclitaxel and cisplatin or paclitaxel and carboplatin, depending on renal function. The studies are designed to determine the feasibility, drug delivery, specific toxicity, and the noncomparative efficacy of a dose-intensive sequential chemotherapeutic regimen for high-risk resectable transitional cell urothelial cancer (extravesical, extraperitoneal, extrapelvic disease or positive regional lymph nodes).

**BLADDER PRESERVATION**

Evolving data show that the categorical recommendation of surgically removing the bladder in all cases with invasive disease is outdated. It is nevertheless important to stress that the primary goal of treatment is survival, and sparing the bladder is justified only when (1) it has a high likelihood of eradicating the tumor in the bladder, (2) the risk of recurrence is low, and (3) bladder function is not compromised. A patient who has had multiple recurrences before an invasive tumor developed may not be an appropriate candidate for such an approach because of the potential risk of future recurrences. Thus, for patients with invasive bladder cancer after multiple prior superficial tumors or for those with poor bladder capacity, surgical removal of the bladder and creation of an internal urinary reservoir, if possible, is preferable. Many groups have reported favorable cure rates with bladder-preserving methods in selected patients with tumors who meet certain criteria, with cystectomy reserved for those who do not meet the criteria. Because it is uncertain which factors predict a favorable outcome if the bladder is left in situ, any approach inevitably requires both physician judgment (selection) and some patient risk. With these caveats in mind, factors that have been associated with a favorable outcome include tumor size (≤4 cm), confined to the bladder (stage T2), and a CR to initial therapy as judged by a cystoscopy and biopsy performed after induction therapy. Selection by tumor response allows for prompt cystectomy. If the disease is persistent, and minimizes the risk of metastatic dissemination from failed initial local therapy. Importantly, any patient in whom the bladder is left in place must be monitored continually for recurrent disease in the bladder, because virtually all series show new tumors, both superficial and invasive, developing after successful bladder-sparing treatments.

**MONOTHERAPIES**

**Transurethral Resection Alone**

Three studies suggest that a maximal or aggressive TUR alone may control some muscle-invasive bladder tumors. One study evaluated 466 consecutively referred patients with muscle-invasive disease by a repeat TUR. Twenty-five percent (118 patients) were followed up conservatively after the second TUR failed to document residual muscle invasion. Of these 118 patients, 77 (65%) remained free of invasive tumor beyond 5 years with an intact bladder. The overall 5-year survival rate of these 77 patients was 83%. Tumors most amenable to TUR alone tended to be papillary, solitary, 2 cm or less in size, minimally invasive into muscle, and not associated with Tis, a palpable mass, or hydronephrosis. These are the same tumor characteristics that are most favorable for bladder preservation in general.

**Partial Cystectomy**

Approximately 5% to 10% of invasive tumors develop in a location where a curative resection by partial cystectomy is possible. This is most frequently accomplished when a lesion develops on the dome of the bladder, where a 2-cm margin of resection can be obtained, no association with CIS in other bladder sites exists, and bladder capacity is adequate once the tumors are removed. Tumors in the bladder neck and trigone are relative contraindications to the procedure. A wide segmental resection of the bladder's dome is the recommended surgical procedure for urachal carcinoma.

**Radiotherapy Alone**

Several series of patients treated with radiotherapy alone provide the benchmark against which new treatment approaches are judged. As noted, responses based on clinical grounds alone range from 40% to 52%, of which 30% to 40% are durable (see Table 34.3-6). The most consistently reported factors predictive for a successful outcome are clinical stage (T2), tumor size (<5 cm maximum diameter), and the absence of ureteral obstruction. A wide segmental resection of the bladder's dome is the recommended surgical procedure for urachal carcinoma. Most recent data suggest that the proportion of complete responses may be improved with accelerated fractionation schemes. In an older randomized trial with 168 patients unsuitable for cystectomy with T2 to T4 tumors, hyperfractionated (not accelerated) external-beam irradiation alone (i.e., 1.0 Gy three times daily to a total dose of 84 Gy) was shown to be superior to conventional treatment (e.g., 2.0 Gy daily to 64 Gy) with respect to survival at 5 years (27% vs. 18%) and CR rate (41% vs. 25%), without a significant increase in toxicities. In a series at the Royal Marsden Hospital, 86% (58 of 65) of patients were found to be tumor-free after a cystoscopic examination was performed 3 to 6 months after treatment of twice-daily fractions of 1.8 to 2.0 Gy, 5 days per week, to a dosage of 57.6 to 64 Gy. Prospective trials are ongoing, and the published results of a phase III trial from the United Kingdom are expected in 2000.

**Interstitial Brachytherapy**

Interstitial brachytherapy combined with external-beam irradiation and conservative surgery has been used successfully in some European centers in highly selected cases. The approach requires close cooperation between urologists and radiation oncologists. Candidates include patients with solitary, nonrecurrent, or clinical stage T2 and T3a tumors less than 5 cm in diameter, with adequate bladder capacity. Local control rates are 75% to 80%, with 5-year survival rates of 50% to...
The demonstration of CRs in advanced disease led to subsequent trials evaluating preoperative or neoadjuvant chemotherapy in patients with invasive disease in the 1980s. A prerequisite for safe bladder preservation is eradicating the tumor in the bladder. Published reports based on clinical (cytoscopic) staging showed CRs in up to 50% of cases; however, when the same reports are evaluated for the proportion of tumors free of disease at cystectomy, a more modest 20% to 30% rate based on pathologic grounds alone, pathologic complete response (PCR) is observed. Of equal concern is that the ability to predict which bladders clinically free of tumor by cystoscopic staging (T0) will actually be pathologically free of tumor at cystectomy (P0). Undertaging in up to 30% to 40% of cases has been observed in selected series. Thus, cumulative data show that chemotherapy alone is inadequate therapy to control the primary tumor for most patients. Analyses also show that the proportion of bladders rendered free of tumor varies inversely with T stage. PCR rates are less than 10% in patients with pT3 to pT4 disease or a palpable mass at presentation. Cumulatively, the data show that chemotherapy alone is inadequate as monotherapy if the primary goal is to preserve bladder function.

Bladder Sparing: Combined-Modality Approaches

The 20% to 40% success rates achieved with single-modality approaches are, when used nonselectively, inferior to contemporary cystectomy series in which local control rates for pelvic disease approach 90%. The evolution of combined-modality approaches aimed at bladder preservation began with reports suggesting that the combination of an aggressive TUR followed by radiation alone or in combination with multidrug systemic chemotherapy could increase the proportion of bladders that are rendered tumor-free. These strategies are based on the principle that final treatment of the bladder is determined by the response to initial therapy, whether unimodality or multimodality.

Table 34.3-12 shows results of combined-modality therapies for survival and survival with a bladder preserved. The ideal candidate for bladder preservation has clinical stage T2 primary tumor, no associated ureteral obstruction, visible complete TUR, and a documented CR after induction by chemotherapy or chemoradiation. Combined-modality treatment as an alternative to cystectomy is still investigational; it is recommended that such therapy be administered by dedicated multimodality teams.

Chemotherapy Followed by Partial Cystectomy

Only 5% to 10% of invasive tumors present in a location amenable to a curative resection by partial cystectomy at diagnosis. In appropriately selected cases, the approach has the advantage of surgically removing the diseased portion of the bladder, with definitive staging of the bladder and lymph nodes. After a response to chemotherapy, less extensive surgery may be necessary to achieve control. The proportion of tumors that could be removed by partial—as opposed to radical—cystectomy increased to 27% after M-VAC was used. Early results, confirmed by Sternberg et al., were excellent for this highly selected patient group. However, the long-term risk of recurrent disease is substantial. Herr et al. reported that salvage cystectomy was necessary in one-third of the patients, owing to new muscle-invasive neoplasms.

Chemotherapy Combined with Radiotherapy

The strategy of combining chemotherapy and radiotherapy evolved from clinical trials performed in the 1980s, which showed the importance of a complete endoscopic resection of the tumor within the bladder before radiation and, in a randomized comparison, a higher rate of local control in the bladder using concurrent cisplatin and radiotherapy versus radiotherapy alone. At the same time, laboratory studies demonstrated that several cytotoxic agents, particularly cisplatin and 5-FU, could sensitize tumor tissue to radiation and increase the killing of tumor cells in a synergistic fashion.

Chemotherapy has been combined with radiotherapy in concurrent, sequential, and alternating fashions. No optimal schedule has been defined. Nevertheless, several reports show that radiation adds to TUR and systemic chemotherapy to maintain the bladder free of tumor. These reports suggest a higher response rate after TUR and chemoradiation therapy (74%) than after TUR and chemotherapy (20% to 30%) as well as 5-year survival rates with the bladder (range, 36% to 44%), which are within the limits of comparing nonrandomized series. These survival rates appear to be superior to those reported with conservative surgery and chemotherapy alone (20% at 5 years and 33% at 30 months (median follow-up)). When the results are analyzed, the number of patients with tumor-free bladders must be considered in the context of the total number of patients entered into a study, as was done in the previously mentioned series (see Table 34.3-12). Considering the number of retained bladders relative to the number of patients who complete therapy artificially inflates the outcome. Finally, it must be remembered that the results of contemporary trials, though encouraging, do not exclude the possibility that a bladder-sparing approach may result in reduced survival compared to radical surgery.

The highly selective nature of patients treated with combined-modality approaches limits the comparison of survival distributions between these patients and those treated by more conventional means. These caveats notwithstanding, in contemporary combined-modality series, 5-year survival rates in the range of 45% to 52% have been reported. Three included radiation with a cisplatin-based regimen. Perhaps a reason why the survival rates with complete TUR of the bladder and chemoradiation are higher than those of other reported experiences is that patients who are at high risk for local failure are identified early and are referred for immediate cystectomy. At what point the patient is designated to have experienced failure of treatment and is referred for cystectomy is controversial. For example, in the Massachusetts General Hospital (MGH) series, patients first undergo an aggressive TUR followed by two cycles of CMV chemotherapy. A cystoscopy is performed 8 weeks from the initial TUR, and the response is assessed. All patients therefore undergo a cisplatin-based regimen. A third cystoscopy is performed and, if residual disease is documented, the patient is referred for cystectomy. In this series, 41% of the patients without a CR (T0) after TUR and chemoradiation at cystoscopy were rendered tumor-free by concurrent radiation of 40 Gy. The policy of referring nonresponding patients for surgery before definitive radiation doses has been effective and used successfully by other groups.

Evidence that the optimal dose and schedule of chemoradiation have not been developed is provided by a nevertheless encouraging report from Paris evaluating chemotherapy alone [20% at 5 years and 33% at 30 months (median follow-up)]. When the results are analyzed, the number of patients with tumor-free bladder is 76%, 173, 172 and 173. The approach has not been widely adopted in the United States because it is judged more invasive than transurethral surgery followed by chemotherapy and radiotherapy.
only 10% of these have developed new tumors within the preserved bladder. In the MGH, RTUG, and Erlangen studies, CR rates at cystectomy are 50% to 75% of patients may subsequently develop superficial tumors. These tumors are usually amenable to standard management with TUR and intravesical agents. Of 18 patients (24%) who developed muscle-invasive Ta or Gis among the 76 patients with initial bladder presentation at MGH, 14 have been maintained in remission for 4 to 10 years without evidence of tumor recurrence. A trial for TUR of the urinary bladder with malignant cells, followed by 15 to 20 years of follow-up development of their superficial tumor. Obviously, patients treated by multimodal therapy may experience a substantial benefit compared to those treated with standard therapy alone. CASE SELECTION Developing a coherent strategy for treating invasive bladder tumors will ultimately require designing and completing comparative trials. The Medical Research Council–EORTC international study, involving more than 1,000 patients, was a landmark trial in that it was the first study with a sufficient number of patients to detect a survival difference for chemotherapy. Similarly, the SWOG intergroup trial evaluating neoadjuvant chemotherapy is also important because it tests M-VAC, shown to be the most active chemotherapeutic regimen, with a sufficient number of patients to detect a survival difference. A novel approach in selecting patients for perioperative chemotherapy is incorporating prognostic markers of the primary tumor to allow for a more precise definition of metastatic risk. Clinical prognostic factors predicting adverse outcome include depth of invasion, presence of a palpable mass, and presence or absence of hydrenephrosis. Several molecular markers have also been investigated. Invasive bladder tumors that have a dysfunctional retinoblastoma (Rb) gene product or mutant p53, S and 11 implied by immunohistochemistry assays, are at increased risk of metastatic disease. These molecular markers must be validated in clinical trials of appropriate stage to determine their clinical utility. Two ongoing investigational trials explore the use of p53 mutations in urinary bladder tumors. Studies at USC determined that patients whose tumors had mutant p53 were more likely to have disease recurrence and death (P < 0.0001) than patients whose primary tumor had wild-type p53. At MSKCC, the p53 status of the tumors in patients treated with neoadjuvant chemotherapy was similar. Patients whose primary tumor had mutant p53 by immunohistochemistry, which implied mutant p53, were three times more likely to die from disease than were those whose tumors whose staining was consistent with wild-type p53. In the latter study, the use of both clinical stage and p53 status could predict patients with a favorable outcome. Patients with good prognostic features (i.e., wild-type p53 and low stage of disease (T2 tumors)) had a 77% survival at 5 years after neoadjuvant chemotherapy; bladder preservation and survival were more frequent in patients whose tumors had wild-type p53. A prospective trial comparing bladder preservation in patients with muscle-invasive bladder cancer and mutant p53 tumors, JRCG 8841, showed that testing a different hypothesis; preliminary retrospective data from their center suggest that adjuvant chemotherapy enhances survival in patients whose tumors have mutant p53. Based on these data, patients with mutant p53 tumors are randomly assigned to receive either adjuvant M-VAC chemotherapy or observation after cystectomy to assess a survival advantage associated with adjuvant chemotherapy. SUMMARY Urinary bladder cancer is a common disease, with increasing incidence but a decreasing mortality. Several carcinogens of the urothelium and risk groups have been identified, such as aromatic amines, combustible gases, a dietary component in meat or fat, the drug phenacemin, and tobacco smoking. An understanding of the pathogenesis of the disease is evolving, and at least two pathways lead to urinary bladder cancer. Mutations in p53, Rb, and as yet uncharacterized genes on chromosome 9 are common and probably important. Urinary bladder cancers typically present with macroscopic hematuria. The clinical course of the disease is strongly heterogeneous. Superficial TaG1 lesions almost never progress and can easily be handled with an endoscopic resection. Recurrent and high-grade superficial bladder tumors can be controlled in most cases with repeated TURs and intravesical BCIG, with cystectomy reserved for refractory tumors. Muscle-invasive disease may require both a locally aggressive therapy and systemic therapy of micrometastases for cure. Metastatic urinary bladder cancer is a fatal disease and often lethal, characterized by the presence of metastatic disease. In the last stage, only palliation is possible. Immunochemotherapy regimens may improve survival of patients with advanced disease. Current reagents in therapy include identifying subgroups of patients with superficial disease in whom the intensity of follow-up can be reduced or intravesical therapy is needed. For muscle-invasive disease, efforts are being made to identify patients for whom organ preservation is possible without compromising overall survival, as well as those with subclinical micrometastases for whom systemic therapy is needed for cure. Efforts continue to make chemotherapy better surgical techniques, combine three-dimensional treatment planning for more precise delivery of external-beam radiotherapy, and the incorporation of newly identified chemotherapeutic agents into combination regimens. For most patients, combination-modality approaches are essential to optimal management. It is likely that the improved overall survival observed during the last two decades will continue. With the increasing focus on preventive measures, such as the cessation of smoking and reducing exposure to known carcinogens, the incidence of the disease is likely to decrease, and the current trend of reduced bladder cancer mortality is likely to continue. CHAPTER REFERENCES 1. Cordon-Cardo C, Balbagni G, Sarkis AS, Reuter VE. Genetic alterations associated with bladder cancer. In: DeVita VT, Hellman S, Rosenberg SA, eds. Important advances in oncology. Philadelphia: JB Lippincott Co, 1994:71. 2. Landsd L, Murray T, Bolton S, Wingo PA. 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INTRODUCTION

Prostate cancer is a significant health care problem in the United States due to its high incidence and mortality, the costs associated with its detection and treatment, and the fact that no consensus exists on what constitutes the best form of treatment for any stage of this disease. Excluding superficial skin cancers, prostate cancer is the most common malignancy afflicting American men.

Since the advent in the late 1980s of prostate-specific antigen (PSA) level as an effective screening test, the medical community has witnessed a dramatic increase in the incidence of prostate cancer cases. Between 1985 and 1992, the age-adjusted incidence in the United States more than doubled, reaching a peak of more than 190 cases per 100,000 in 1992.1 Perhaps reflecting stage migration or more effective treatment for localized disease, 5-year cancer survival rates have increased from approximately 70% in the early 1980s to more than 90% a decade later.1 Since 1992, the incidence rate has steadily declined.

To date, no conclusive data confirm that screening reduces disease morbidity and mortality. Observations that support screening and early detection include the following: PSA screening improves detection of clinically important tumors without significantly increasing the detection of unimportant tumors; the disease is more burdensome at later stages; most PSA-detected tumors are curable using current techniques; and there is no cure for metastatic disease. However, until properly conducted trials of screening are completed, the benefits and risks of prostate cancer's early detection and the associated treatment methods should be discussed carefully with patients.

NORMAL PROSTATE ANATOMY AND HISTOLOGY

The prostate is an ovoid structure located between the urinary bladder superiorly and the pelvic floor inferiorly (Fig. 34.4-1). The urethra traverses this gland, entering its base below the bladder neck and exiting at the narrowed apex at the level of the urogenital diaphragm. The anterior surface of the prostate is attached to the pubis, and the posterior surface is flattened with a midline depression that lies against the rectal ampulla. The lateral and inferior surfaces of the gland are in contact with the levator ani muscles. The levator ani muscles have an almost vertical orientation, funneling inferiorly to surround the rectum and bracket the striated urethral sphincter and middle and apical portions of the prostate.2 The ejaculatory ducts enter the posterior surface laterally and pass obliquely toward the midline, where they end at the verumontanum on the posterior surface of the prostatic urethra. Because of the gland’s location deep within the pelvis behind the pubic bone, surgical as well as radiation-based approaches to expose and target the prostate and protect surrounding structures may be challenging.

FIGURE 34.4-1. Prostate and regional anatomy.
The prostate's anterior surface and the adjacent lateral pelvic floor are covered by the periprostatic fascia, which is formed by the prostatic and levator fasciae. Lateral to the base, this layer is called the endopelvic fascia, and it covers both the pelvic floor and important underlying neurovascular structures. The prostatic venous plexus (of Santorini), a rich network of tributary veins that serve as the primary venile drainage, is seen within this fascial covering. Erectile nerves to the corpora cavernosa travel out through the prostatic capsule in the lateral pelvic fascia between the prostate and the rectum (see Fig. 34.4-1). The cavernous nerves arise from the pelvic plexus, contain both sympathetic and parasympathetic fibers, and pass beneath the arcus pubis to supply the corpora cavernosa and the corpus spongiosum. These end in a network of nerve fibers around the cavernous vessels at the penile hilum. Appreciating these anatomic relationships intraoperatively is essential to avoid unnecessary injury and bleeding. The prostatic capsule, composed of condensed smooth muscle and connective tissue, blends with the prostatic stroma along the interlobular septa and Denovilliers' fascia. The posterior surface of the prostate is adjacent to the posterior rectal wall. The outer prostatic ligaments extend anterolaterally from the surface of the gland to fix the apex of the prostate to the pubis. At both the apex and base, no clear capsule separates the prostate from the striated urethral sphincter or bladder neck, respectively. Prostatic glands can be seen in the substance of the urethral sphincter, and smooth muscle fibers from the detrusor blend with the muscular coat of the prostate. Separating the prostate from the rectum is a layer of fascia, Denovilliers' fascia, derived from two layers of pelvic peritoneum in the retrovesical space.

While voluntary control of voiding begins with relaxation of the striated sphincter in the membranous urethra, smooth muscle components of the bladder neck and prostate contribute to continence in men. The prostatic sphincter is composed of muscle elements from the bladder. These muscles encircle the urethra and travel along and insert into the urethra more distally. The striated sphincter provides intrinsic resistance to urine leakage and newergrade seminal ejaculation. A passive prostatic sphincter is located distal to the verumontanum and is related closely to the striated muscle elements of the prostatomembranous sphincter.

The prostatic striated sphincter forms a thin muscle layer over the anterior surface of the gland. Distally, these fibers almost completely surround the gland, except for a posterior gap at the apex, and merge with muscles of the membranous urethral sphincter. Fibers of the membranous striated sphincter encircle the urethra, originating at the anterior decussation of the prostatic sphincter and inserting at the perineal body at the level of the perineal membrane. These sphincteric fibers insert broadly over the surface of the prostatic fascia near the apex and play an important role in regaining continence after radical prostatectomy. 

The primary arterial supply to the prostate comes from the prostatovesical artery that descends inferiorly along the bladder base. The origin of this artery is variable, but it usually comes from the anterior division of the internal iliac artery. The prostatic artery divides at the base of the prostate into the large posterolateral branch and anterior branch. The superolateral gland may receive arterial supply from the middle and superior rectal arteries. Urethral branches from the prostatic artery enter the capsule posterolaterally below the bladder neck to supply the transitional zone and periurethral glands. Capsular branches, traveling in the neurovascular bundle posterolaterally to the gland, enter the capsule more distally and laterally, to supply the central and peripheral zones. Prostate parenchymal veins, as well as veins draining all deep pelvic structures, intercommunicate with the prostatic venous plexus lying within the periprostatic fascia on the anterior surface of the gland. The deep dorsal vein of the penis emerges beneath the symphysis pubis between the puboprostatic ligaments to join this plexus. The majority of venous blood drains directly into the prostatic and inferior vesical veins to the internal iliac veins.

Semen emission is a neural process mediated within the prostate. With sexual activity, parasympathetic nerves stimulate the prostatic acini to produce secretions. Sympathetic nerve activity closes the preprostatic sphincter, preventing retrograde ejaculation, and increases smooth muscle tone in both the prostate parenchyma and capsule to deposit secretions in the urethra (emission). Ejaculation occurs with contraction of the striated bulbouspomouscle.

Preganglionic sympathetic nerves to the preprostatic sphincter and smooth musculature of the prostate gland originate at spinal level L2-3 and pass through the sympathetic chain ganglia to the superior hypogastric plexus. Here they synapse with postganglionic noradrenergic nerves, the cell bodies of which lie in the pelvic plexus lateral to the bladder and prostate. Parasympathetic innervation to the prostatic epithelium originates in the pelvic splanchnic nerves from spinal levels S2-4. These preganglionic nerves synapse in the prostatic plexus, located between the seminal vessels and the prostate, and send short postganglionic fibers into the prostate stroma. Somatic motor output from the pudendal nerve arises from S1-3 and innervates the pubococcygeus muscle of the external striated sphincter. Some contributing to ejaculatory function may also come from the sympathetic preganglionic nerve which includes sympathetic, parasympathetic, and somatic fibers. The parasympathetic nerve engulfs the neuromuscular junction of the prostate base. This nerve continues posteriorly along the prostatic base and divides into apical branches and a branch to the ejaculatory duct. The main branches pierce the prostatic capsule, then travel along the fibromuscular trabeculae of asacinar branches before reaching their terminals at muscular and glandular cells. Afferent nerves from the prostate travel through the pelvic plexus to reach sensory tracts in the cordal lymph.

Lymph capillaries emerge from the fibrous stroma and endoneurium to form a lobular network of channels. The major route of lymphatic drainage occurs along the prostatic artery to the obturator and internal iliac nodes. Secondary lymphatic drainage originates at the base of the prostate, where lymphatic trunks travel along the medial border of the seminal vesicles to drain into the external iliac nodes. Two more minor routes are along capsular lymphatics on the posterior surface of the gland to the sacral and internal iliac lymph nodes.

The internal structure of the prostate has been organized into lobes or zones. Early descriptions of five lobes were based on the embryologic concept of the prostate beginning as five groups of epithelial buds that branch off of the urogenital sinus between gestational weeks 11 and 16. By successively branching and rebranching, a complex system of ducts is formed circumferentially around the urethra, forming anterior, posterior, median, and two lateral lobes. However, the zonal description of prostate structure is more commonly used in clinical practice today. According to this scheme, prostate tissue consists of two primary areas: the peripheral zone and the transitional zone. The peripheral zone is composed of the more gland cells of the prostate than the transitional zone. About 5% of the prostate mass is made up of transitional zone. The transitional zone, an anterior fibromuscular segment, and a preprostatic sphincter zone. It is well recognized that prostate cancer occurs primarily in the peripheral zone, while the adenomatous growth of benign prostatic hyperplasty occurs primarily in the transitional zone.

The prostate parenchyma is composed primarily of glandular epithelium, yet 30% of its mass is composed of muscular elements. The secretory epithelium of the prostate is contained within tubuloalveolar glands with a simple branching architecture. These glands are lined with simple cuboidal or columnar epithelium under which lie flattened basal cells. Stromal smooth muscle and connective tissue surround most of the acini. Ducts draining each gland enter the urethra in several locations. Periurethral glands, not connected to the deep network of acini, drain into the urethra.

**PATHOLOGY AND PATTERNS OF PROGRESSION OF PROSTATE CANCER**

Approximately 75% of prostate cancers will arise in the peripheral zone of the gland. Another 15% may occur in the central zone, and 10% to 15% will be located in the transitional zone. Cancers arising within the transition zone are usually smaller and are discovered on digital rectal examination (DRE), as firm nodules or induration. However, it is not uncommon for cancers to be nonpalpable. Gross examination of cancerous tissue in prostatectomy specimens often reveals a similarly firm and gritty texture of the gland.

The prostate's anterior surface and the adjacent lateral pelvic floor are covered by the periprostatic fascia, which is formed by the prostatic and levator fasciae. Several grading systems have been proposed, of which the Gleason system is the most commonly used. This grading system recognizes the fact that prostate cancer is a multifocal disease with heterogeneous glandular patterns. Thus, two individual cancers, each grading 4+3, result in a Gleason score of 7. This score is then assigned to the patient to represent the most common grading in the primary tumor. The Gleason system is the most useful in assessing the prognosis of prostate cancer. The Gleason score is determined by the percentage of each Gleason pattern, with a score of 5 indicating a predominance of well-differentiated tumor (Gleason grade 1) and a score of 10 indicating a predominance of poorly differentiated tumor (Gleason grade 5).

To the pathologist, the Gleason score gives an indication of the aggressiveness of the tumor. A score of 1 to 3 indicates a well-differentiated tumor, whereas a score of 8 to 10 indicates a poorly differentiated tumor. The Gleason score is an important prognostic factor, as patients with higher Gleason scores are at greater risk for recurrence and progression of their disease. Treatment options, such as radical prostatectomy, radiation therapy, or hormone therapy, are often based on the Gleason score. Overall, the Gleason score is a critical factor in determining the prognosis and treatment approach for patients with prostate cancer.
Prostate cancer may spread locally or distantly. Cancers can invade the seminal vesicles and bladder base proximally and the urethra distally. Extension through the Denonvilliers' fascia. Lymphatic spread often occurs in a stepwise manner and follows the normal pattern of lymphatic drainage. The obturator nodes are the primary sites of lymphatic metastases, followed by the perivesical, hypogastric, iliac, presacral, and paraaortic nodes. Hematogenous metastases primarily affect the proximal femur, pelvis, thoracic spine, ribs, sternum, and skull. Bone metastases are typically osteoblastic (80%). Osteolytic (5%) and mixed osteoblastic-osteolytic bones and occur in up to 85% of patients who die of prostate cancer.

TABLE 34.4-1. Examples of Nonadenocarcinoma Prostate Cancer Cell Types

<table>
<thead>
<tr>
<th>Type</th>
<th>Characteristics</th>
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| Endometrioid carcinoma        | Prostatic urethra and periurethral prostatic ducts in the region of the verumontanum. Histologically, it resembles endometrial adenocarcinoma of the uterus with complex glands lined by stratified columnar epithelium. Clinically, this variant is more aggressive than simple adenocarcinoma and often is associated with metastases and a poorer prognosis. Another epithelial variant is mucinous adenocarcinoma. It is characterized by large accumulations of extracellular mucin and luminal distention. Overall prognosis is similar to that of adenocarcinoma. Signet-ring cell carcinoma is characterized by large cytoplasmic vacuoles that displace the nucleus and frequently is associated with poorly differentiated and aggressive adenocarcinoma. Associations with mucinous adenocarcinoma are not uncommon, and vacuoles may or may not be filled with mucin. The prognosis for patients with primary signet-ring cell carcinoma is poor, with a 3-year survival rate of 27%. Comedocarcinoma is characterized by nests of cells with central necrosis. Comedocarcinoma resembles poorly differentiated adenocarcinoma (Gleason grade 5) and usually carries a poor prognosis. A rare variant with a better prognosis is adenoid cystic carcinoma. Histologically, lesions resemble basal cell hyperplasia, and disease usually is organ-confined.

Squamous cell carcinoma of the prostate accounts for 0.5% to 1% of all prostate cancers and sometimes is difficult to differentiate from disease originating from the bladder and urethra. Such histologic features as keratinization and intercellular bridging are seen, as is the lack of glandular differentiation. Clinically, patients present in fashions similar to those with adenocarcinoma; however, serum tumor markers such as acid phosphatase and PSA will remain normal. This epithelial variant is more aggressive than adenocarcinoma, with an average survival after diagnosis of approximately 14 months. Primary transitional cell carcinoma (TCC) of the prostate has also been reported, although secondary spread from the bladder is much more common. Primary prostatic TCC does not respond to hormonal therapy but has been shown to respond to combination therapy. Prognosis is variable, and TCC is best treated with primary surgery or combinations of chemotherapy, radiation therapy, and surgery. Neuroendocrine tumors of the prostate are rare and can present with paraneoplastic syndromes. Most patients tend to present with advanced disease at the time of diagnosis.

Nonadenocarcinomas of the prostate are rare. Sarcomas represent fewer than 0.1% of prostate cancers and tend to occur in younger patients. The two most common types are rhabdomyosarcoma and leiomyosarcoma. The former is the most common prostatic tumor in the pediatric age group, whereas the latter tends to occur in adults. Both are extremely aggressive and tend to invade locally and hematogenously. Pathologically, rhabdomyosarcomas are solid neoplasms, with a histologic appearance that ranges from primitive mesenchyma to well-differentiated, myofiber-type cells. Leiomyosarcomas tend to be bulky, with diffuse infiltration into the peri-prostatic soft tissues. Histologically, lesions show interfacing spindle cells, eosinophilic cytoplasm, and nuclear atypia accompanied by necrosis and hemorrhage. A multidisciplinary approach to treatment, including surgery, chemotherapy, and radiation therapy, is usually recommended. A third nonepithelial cancer of the prostate is malignant lymphoma. It usually affects young men and frequently is associated with non-Hodgkin's and Hodgkin's lymphoma. On histologic examination, lesions resemble lymph nodes consisting of small-cleaved lymphocytic cells or large diffuse lymphomas. Prognosis is usually poor, and prostatesctomy may not prolong survival. Other metastases to the prostate include leukemia and local extension from rectal or bladder primary cancers. Metastases from other organs are rare.

Prostate cancer may spread locally or distantly. Cancers can invade the seminal vesicles and bladder base proximally and the urethra distally. Extension through the prostatic capsule and into the periprostatic tissues is not uncommon; however, rectal invasion posteriorly is rare, owing to separation of the two organs by Denonvilliers' fascia. Lymphatic spread most often occurs in a stepwise manner and follows the normal pattern of lymphatic drainage. The obturator nodes are the primary sites of lymphatic metastases, followed by the perivesical, hypogastric, iliac, presacral, and paraaortic nodes. Hematogenous metastases primarily affect the bones and occur in up to 85% of patients who die of prostate cancer. The axial skeleton is particularly vulnerable, as the preprostatic and periprostatic venous complex communicates with Batson's plexus of the presacral veins. Osseous sites of involvement, in decreasing order of frequency, include the lumbar spine, proximal femur, pelvis, thoracic spine, ribs, sternum, and skull. Bone metastases are typically osteoblastic (80%). Osteolytic (5%) and mixed osteoblastic-osteolytic (15%) lesions are less common. Hematogenous spread to viscera can occur, but widespread visceral dissemination is rare. Lung and liver metastases are seen in approximately 25% and 20% of patients, respectively, with end-stage prostate cancer. The current tumor, node, and metastasis (TNM) staging system for prostate cancer recognizes six T categories, six N categories, and three M categories.
cancer is presented in Table 34.4-2.

### TABLE 34.4-2. Prostate Cancer Staging

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
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<tr>
<td>A1</td>
<td>Disease is well differentiated and involves less than 5% of a pathologic specimen. Stage A2 involves more than 5% of a specimen or is moderate to poorly differentiated. Stage B (T2) cancers are clinically palpable but confined to the prostate. Stage B1 cancers are 1.5 cm in diameter or smaller and involve only one lobe of the prostate. Stage B2 involves either several nodules in both lobes or a lesion larger than 1.5 cm. Stage C (T3 and T4) tumors are non–organ-confined with invasion of soft tissue outside the prostate. Stage C1 tumors invade through the prostatic capsule but have a negative surgical margin. Margins are positive for stage C2 tumors, and C3 tumors invade the seminal vesicles. Stage D cancer is metastatic, with D1 referring to microscopic pelvic lymph node involvement and D2 to disease involving bones or distant organs (or both). Most clinicians use the TNM system.</td>
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The DNA content (ploidy) of cancerous lesions may correlate with patient outcomes. Patients with diploid cancers generally have better survival outcomes than do those with aneuploid cancers. In a study of nearly 900 patients with pathologically non–organ-confined disease (pT3), Hawkins et al. showed that DNA ploidy was a significant prognostic factor for both cancer-related death and biochemical failure–free survival. Others have reported that immunohistochemical staining for p27, a nuclear protein inhibitor of the cell cycle, may be of value. Decreased p27 expression is seen with more aggressive disease. Cheville et al. showed that patients with low p27 expression had higher-grade tumors, increased tumor aneuploidy, and higher incidences of seminal vesicle and nodal invasion than did men with normal p27 expression.

### STAGING

In addition to histologic examination, staging is also important in patient risk assessment and prognosis. The two most commonly used staging systems are the tumor, node, and metastasis (TNM) system and the Jewett staging system (see Table 34.4-2). In the Jewett staging system are four stages of prostate cancer. A to D, with subclassifications within each stage. Stage A disease is clinically nonpalpable disease found incidentally during surgery for benign prostatic hyperplasia (BPH). Stage A1 disease as well differentiated and involves less than 5% of a pathologic specimen. Stage A2 involves more than 5% of a specimen or is moderate to poorly differentiated. Stage B (T2) cancers are clinically palpable but confined to the prostate. Stage B1 cancers are 1.5 cm in diameter or smaller and involve only one lobe of the prostate. Stage B2 involves either several nodules in both lobes or a lesion larger than 1.5 cm. Stage C (T3 and T4) tumors are non–organ-confined with invasion of soft tissue outside the prostate. Stage C1 tumors invade through the prostatic capsule but have a negative surgical margin. Margins are positive for stage C2 tumors, and C3 tumors invade the seminal vesicles. Stage D cancer is metastatic, with D1 referring to microscopic pelvic lymph node involvement and D2 to disease involving bones or distant organs (or both). Most clinicians use the TNM system.

Given that autopsy studies show a high prevalence of histologic evidence of prostate cancer in men (>30%) who die of other diseases, there is some concern that many cancers currently detected may be "insignificant" or of such low biologic potential that treatment is not necessary and possibly harmful. Cancer grade, cancer stage, serum PSA level, and the age and health of the patient most often define the risk associated with a prostate cancer. Tumor volume also correlates with risk, although it cannot be determined in vivo with precise accuracy as yet. Generally, those cancers that exceed 0.5 mL are more likely to be associated with extraprostatic disease as compared to smaller cancers. Approximately 20% of autopsy or incidental cancers exceed this size. Similarly, higher-grade cancers (Gleason score 4 or 5) are also more likely to be associated with extracapsular disease and cancer progression as compared to lower-grade cancers. According to criteria of cancer size, grade, and stage, the vast majority of cancers currently identified by early detection efforts appear to be clinically significant. Indeed, at least one-third have adverse features, including extracapsular extension (ECE), seminal vesicle invasion, lymph node metastases, or very high-grade histology, all of which are associated with a significant risk of cancer progression, certainly without treatment and often with treatment.

### EPIDEMIOLOGY

Excluding superficial skin cancers, prostate cancer is the most common malignancy afflicting American men. In 1999, some 179,300 new cases were diagnosed, and an estimated 37,000 prostate cancer deaths occurred, making it the second most common cause of cancer death, after lung cancer, in American men.

Beginning in the late 1980s, PSA screening became a common practice, and the incidence of prostate cancer cases increased dramatically as a direct result. Between 1985 and 1992, the age-adjusted incidence in the United States more than doubled, reaching a peak of more than 190 cases per 100,000 in 1992. This increase was not unanticipated, as the introduction of any effective screening test should lead to detection of earlier-stage disease in more patients (i.e., stage migration). Stage migration has, in fact, occurred in the United States, and approximately three-fourths of prostate cancer cases diagnosed now are recognized while the disease is still clinically organ-confined, as compared to only one-fourth prior to the introduction of PSA screening. Perhaps reflecting patients' earlier disease stage at presentation and more effective treatment for localized disease, 5-year cancer survival rates have increased from approximately 70% in the early 1980s to more than 90% a decade later. Since 1992, the incidence rate has declined steadily as the pool of men with no previous diagnosis of lower-stage disease became slowly exhausted. Incidence rates today are approaching those before PSA screening.

Worldwide, prostate cancer ranks third in cancer incidence and sixth in cancer mortality among men. There is, however, a notable variability in incidence and mortality among world regions. The incidence per 100,000 is low in Japan and China at 8.51 and 1.08, respectively, and is intermediate in regions of Central America (24.77) and Western Africa (23.85). In North American countries, where PSA screening is widely adopted (e.g., in the United States), the incidence may be as high as 95.1 per 100,000.

Predominantly a disease of elderly men, the clinical diagnosis of prostate cancer is rare before age 40 but increases steadily thereafter. Autopsy studies worldwide have shown that histologic disease increases with age and that roughly three-fourths of men older than 80 years will have some evidence of latent disease. In parallel, more than 80% of clinically apparent disease occurs in men older than 65 years. In the United States, it is estimated that 1 in 55 men between the ages of 40 and 59 will develop clinically apparent disease. This incidence climbs almost exponentially to 1 in 7 for men between 60 and 79. This association is also reflected in mortality rates, as prostate cancer accounts for 10.8% of cancer-related deaths in men between 60 and 79 years of age and 24.6% in those older than 80. As the proportion of older men increases in our population, the impact of prostate cancer will continue to grow. In fact, the doubling of age-adjusted mortality rates in
Ethnic and racial differences are also seen in disease incidence and mortality. African Americans are in the highest-risk group, with an incidence of 224.3 cases per 100,000 for the period between 1990 and 1995. The incidence in white and Asian counterparts during that same period was considerably lower at 150.3 and 82.2 per 100,000, respectively. In addition, African Americans tend to present with more advanced disease and may have poorer overall prognosis than their white counterparts. It has been reported that African Americans are 1.3 to 1.8 times more likely to present with distant disease and, stage for stage, African Americans have lower survival rates. The underlying cause for this difference has been attributed to social, economic, educational, hereditary, and dietary differences. Migrant studies, particularly of Asian men, also suggest an environmental, social, or dietary etiology in prostate cancer. When migrants from a low-risk country such as Japan move to the United States, a high-risk nation, their prostate cancer incidence and mortality become several-fold higher than native Japanese counterparts. Investigators have found a positive correlation between the number of years since migration to the United States and cancer risk. Although diagnostic biases exist between countries, the upward shift in risk nevertheless seems real. This rise in clinically detectable disease may be related to differences in diet. In the prostate, high fat intake has been positively associated with increased risk in these studies and may, in part, explain the rising incidence of prostate cancer in Japan, as dietary habits become more Westernized.

Family history of prostate cancer also contributes to risk. It has been reported that men with prostate cancer are two to three times more likely than controls to have at least one first- or second-degree relative with prostate cancer. and Keetch et al. reported that a patient with prostate cancer is 3.1 and 4.3 times more likely than a control to have a history of prostate cancer in his father and brother, respectively. Together with the observation that clustering of prostate cancer cases exists in some high-risk families, a hereditary component clearly exists. However, the role of specific gene activity and molecular mechanisms of disease remains largely unsolved and continues to be an area of active research. A word of caution is warranted in interpreting family history studies, however, as they are subject to recall, self-selection, and socioeconomic biases.

The role of vasectomy and prostate cancer risk remains controversial. Retrospective and prospective cohort epidemiologic studies have demonstrated a relative risk of approximately 1.6 in men who underwent vasectomy. However, others could not confirm these findings and suggest that earlier studies were flawed by detection, control selection, and publication biases.

In summary, prostate cancer is a disease of older men worldwide. It is more common in Westernized countries, in those with a family history of the disease, and in African Americans. The cause is likely multifaceted, with genetic, dietary, and social modifiers. Further investigation is necessary to elucidate the role and significance of each factor in prostate cancer induction and progression.

CHEMOPREVENTION AND DIET

Chemoprevention is the administration of medicines or other agents to prevent, slow, or reverse cancer progression. The concept of primary chemoprevention for prostate cancer has gained much interest in the 1990s because of the disease's high prevalence, slowly progressive nature, and long latency period. The ideal therapeutic intervention would arrest disease progression during this latency period and decrease the incidence of clinical disease. The success of chemoprevention, however, depends on consideration of several important factors. First, because "healthy" men are treated, the therapeutic agent must offer low to no toxicity and side effects and must require a single dosing regimen. Second, epidemiologic and laboratory evidence should support the agent's efficacy. Finally, the ideal patient is one at high risk for developing clinical disease and motivated to adhere to chronic dosing of chemopreventive agents.

To date, several promising chemopreventive agents have been identified and are under laboratory and clinical investigation. Finasteride is among the agents now being tested in a large, phase III, randomized clinical trial, the Prostate Cancer Prevention Trial (PCPT). A joint effort of the Southwest Oncology Group (SWOG), the Eastern Cooperative Oncology Group (ECOG), and the Cancer and Leukemia Group B (CALGB), the PCPT is a 10-year study of 18,882 men, aged 55 or older, with normal DRE and a PSA level of less than 3.0 ng/mL, who have been randomized to either placebo or the 5a-reductase inhibitor finasteride (5 mg/d). Given prostate cancer's slowly progressive nature, the endpoint of prostate cancer mortality will not be pursued because of long study duration and large sample size requirements. Instead, the primary end point of prostate cancer period prevalence, as determined by sextant prostate biopsy, is used. The PCPT is designed to have greater than 90% power in detecting a 25% reduction in period prevalence of biopsy-proven disease when it reaches its end point in mid-2004.

The use of finasteride to prevent disease seems rational, given that prostate cancer is androgen-responsive. An inhibitor of 5a-reductase, finasteride blocks the conversion of testosterone to its active metabolite dihydrotestosterone (DHT) and lowers the prostatic androgen levels. Bologna et al. have shown that finasteride can attenuate in vitro prostate cancer cell growth in a dose-dependent manner, and others suggest that the lower incidence of prostate cancer among Japanese men as compared with their western counterparts may be associated with lower 5a-reductase activity. As shown, as a chemopreventive agent taken chronically, finasteride is well absorbed orally and does not appear to have any clinically relevant drug interactions or toxicity. The frequency of side effects is low and includes decreased libido, impotence, and decreased ejaculate volume.

Dietary manipulations have also gained much interest. Epidemiologic studies have shown that the incidence of clinically significant prostate cancer is much lower in parts of the world where people eat a predominantly low-fat, plant-based diet. In addition, migrant studies demonstrate that when men from a low-risk country move to the United States and begin eating a Westernized diet, their rates of prostate cancer increase severalfold and approach that of the host country.

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Dietary fat intake is positively associated with prostate cancer risk and may be a target for chemoprevention. In a case-control study from the Physicians' Health Study, those who had higher plasma a-linolenic acid levels (a fatty acid found in animal fat) had a two- to threefold increase in prostate cancer risk as compared to those with lower a-linolenic acid levels. Similarly, in a prospective cohort study of more than 47,000 men, Giovannucci et al. found that fat intake was directly correlated with risk of advanced disease and, specifically, animal fat, red meat, and a-linolenic acid were associated with the greatest risk [relative risk (RR) = 1.63, 2.64, and 3.43, respectively]. Others have studied saturated fat and reported an attributable risk of 13% for saturated fat intake in excess of 26 g/d as compared to diets with less than 13 g/d. This suggests that 13% of prostate cancer cases may be preventable by reducing saturated fat intake to less than 13 g/d.

In a recent meta-analysis, Keetch et al. found that fat intake inversely associated with saturated fat intake. As compared to men ingesting less than 10.8% of dietary calories from saturated fat, those ingesting more than 13.2% had three times the risk of dying from prostate cancer (RR = 3.13) and were more likely to develop bone metastasis (RR = 3.4) at a median follow-up of 5.2 years.

Evidence supporting a relationship between prostate cancer and dietary fat also comes from animal studies. Wang et al. injected prostate cancer cells (LNCaP) into mice and placed them on a "typical American" diet containing 40% fat. In 3 weeks, prostate tumor growth was noted. The researchers then divided the animals into five groups receiving diets containing approximately 40%, 30%, 20%, 10%, and 0% of calories as fat. Progression of prostate cancer ceased or was reversed in some animals placed on 10% to 20% fat diets. This was in contrast to continued tumor growth in groups ingesting higher amounts of fat. PSA levels were also lower in mice consuming 20% fat diets compared to those on the 40% fat diet.

On a molecular level, much remains unknown. Myers and Ghosh recently postulated that the risk seen with high fat intake may be linked to 5-lipoxygenase products of arachidonic acid (a ubiquitous fatty acid found in animal fat) and that inhibition of 5-lipoxygenase could lead to prostate cancer cell death and apoptosis. However, the significance of genetic polymorphisms for 5-lipoxygenase and the role of other fatty acid metabolic pathways in prostate cancer risk remain elusive.
of Korea, where prostate cancer incidence and mortality are just a fraction of that in North America, consumption of soy in the form of tofu, soy milk, temeph, and miso is noted to be up to 90-fold higher than soy consumption in the United States. In a cross-national study of more than 40 nations, Hebert et al. found soy, on a per-calorie basis, to be the most protective dietary factor. This protective role may be associated with soy's phytoestrogenic components genistein and daidzein. Genistein and daidzein are isoflavonoids with weak estrogenic effect that may have the ability to delay growth of precancerous prostate lesions and prostate tumors. Davis et al. showed that genistein inhibits prostate cell growth in culture and induces apoptosis through cell-cycle gene regulation in a dose-dependent manner. Others have demonstrated that genistein is an inhibitor of tyrosine kinase and suggest that genistein may act through inhibition of up-regulated tyrosine kinases in proliferative cancerous states. Although the association between soy and cancer risk seems convincing, a causal role remains obscure and awaits the rigor of prospective randomized studies. However, given that soy products are generally well tolerated and provide a cost-effective source of isoflavonoids, the scientific community's interest in soy as a chemopreventive agent will likely continue.

To explain the difference in cancer incidence and mortality between nations, researchers have also suggested a chemopreventive role for green tea, a beverage consumed in high quantities in Asia. In vitro studies by Yang et al. showed that polyphenol extracts from tea inhibited growth of cancerous cell lines and induced cellular apoptosis in a dose-dependent manner. Furthermore, in vivo studies by Mohan and Gupta et al. found that tea polyphenols inhibited ornithine decarboxylase, a testosterone-induced enzyme that is up-regulated in prostate cancer. Tea polyphenols' inhibition of ornithine decarboxylase in effect attenuates testosterone in the prostatic milieu and may be an important target for chemoprevention.

Tomatoes are rich sources of the carotenoid lycopene. With its potent antioxidant activity, lycopene may protect cellular components from reactive oxygen radical species and lower prostate cancer risk. Epidemiologic data show that lycopene consumption is associated with decreased risk as well as a possible reduction in prostate tumor growth. In a cohort study of approximately 14,000 Adventist men over a 6-year period, consumption of tomato products was associated with lower prostate cancer risk. This finding was substantiated in a prospective cohort study from the Health Professionals Study, where lycopene intake from tomato-based foods was found to be inversely associated with risk. The investigators reported that men ingesting two or more servings of tomato sauce per week had a 36% reduction in cancer risk as compared to counterparts who did not consume tomato sauce. Little is known, however, regarding lycopene's exact mechanism of action or the specific role of different isomers in prostate tissue metabolism.

The role of another antioxidant, vitamin E, as a chemopreventive remains controversial. Epidemiologic and in vivo data are often conflicting, despite promising in vitro studies. Part of the difficulty in elucidating vitamin E's effect in chemoprevention is that oral supplements frequently contain different forms of vitamin E than that found naturally in foods. Given the fact that vitamin E exists as potentially eight different compounds, and that isotomers such as γ-tocopherol have been shown to have greater inhibitory effects on prostate cancer cell growth than α-tocopherol, further evaluation of vitamin E is warranted.

Selenium has also been reported to lower prostate cancer risk. In a double-blinded clinical trial designed to determine whether selenium could lower skin cancer recurrences, Clark et al. found that men randomized to receiving selenium had a 63% reduction in prostate cancer incidence as compared to those randomized to receiving placebo. Similar findings were demonstrated in a nested case-control trial of the Health Professionals Follow-Up Study. The investigators found that higher selenium intake, as reflected in nail selenium levels, was significantly protective (odds ratio = 0.35 when comparing the highest and lowest quintile). In vivo studies in the human prostate cancer cell line have also shown that selenium inhibits cancer cell growth at physiologic doses and that its protective effect may be mediated through an androgen-sensitive gene that encodes for a selenium-binding protein.

Attention has also focused on vitamin D's antiproliferative and prodifferentiation effect on the prostate. Investigators have demonstrated that 1,25-dihydroxyvitamin D₃ [1,25(OH)₂D₃], the active metabolite of vitamin D, inhibits cellular proliferation in primary prostate cancer tissue cultures and in prostate cancer cell lines such as PC3, DU145, and LNCaP. Moreover, epidemiologic evidence shows an inverse relationship between prostate cancer risk and ultraviolet radiation, the primary source of endogenous vitamin D synthesis. This observation has led some to suggest that higher rates of prostate cancer in the elderly may be due in part to decreased sun exposure or a decline in the body's ability to synthesize 1,25(OH)₂D₃ with aging. Similarly, others have proposed that the higher risk in men of African descent may be related to higher skin melanin content, which would decrease endogenous vitamin D production. Taken together, vitamin D and its synthetic analogues may prove to be useful chemopreventive agents for prostate cancer.

Although a relationship between diet and prostate cancer is apparent, whether manipulating the diet will lead to changes in cancer risk is the subject of ongoing clinical trials. In considering the future development of rational chemoprevention trials and test compounds, one must appreciate the interdependence between the practical aspects of clinical trial design and the mechanisms in disease progression. A better understanding of the latter may lead to clinical trials that are less restrained by the need for large sample populations and prolonged follow-up. For example, it has been shown that urokinase-mediated cell surface proteolysis and angiogenesis in human prostate cancer cells are important in metastasis and that specific inhibition could decrease the metastatic potential of cancerous cells. From this work, one could postulate the design of a chemopreventive agent aimed at preventing metastasis in patients who present with localized disease. As compared to primary chemoprevention, this may be easier to implement clinically as patients are more likely to be motivated and compliant with chronic therapy. Thus, a multidisciplinary approach that reflects our understanding of prostate carcinogenesis and tumor invasion is critical to study design of future chemoprevention trials.

**PROSTATE CANCER EARLY DETECTION**

Prostate cancer screening or early detection has been accomplished using DRE, measurement of serum PSA (and its various forms), transrectal ultrasonography (TRUS), and combinations of these tests. Although DRE can detect prostate cancer, it detects fewer cancers than does PSA testing and, unfortunately, many cancers detected using DRE are either locally or regionally advanced. Although serum PSA is a better screening test than DRE, DRE should not be abandoned, as it may detect some cancers associated with a normal serum PSA level. Therefore, DRE should be combined with serum PSA testing. TRUS should not be used as a first-line screening study as it lacks high specificity, is relatively expensive, and adds little information to that already gained by the use of serum PSA testing and DRE. TRUS is used to guide prostate biopsy in those patients who have an elevated serum PSA level, an abnormal DRE, or both (Fig. 34.4.3).

**FIGURE 34.4.3.** Transrectal ultrasound image showing a characteristic hypoechoic abnormality (arrow) consistent with prostate cancer.

PSA is a serine protease produced by benign and malignant prostate tissues. Although it is produced in small amounts elsewhere, including breast tissue, endometrium, and in a few malignancies other than prostatic cancer, it should be considered to be organ-specific clinically. PSA circulates in the serum as uncomplexed (free or unbound) or complexed (bound) forms. Serum PSA is largely complexed by endogenous protease inhibitors, the most common being α-antichymotrypsin. Other proteins bind a smaller fraction.

Serum PSA may be elevated transiently in cases of prostatitis and after endoscopic urethral manipulation, prostatic biopsy and, to a more limited extent, ejaculation. Routine DRE actually has little effect on serum PSA, but most physicians defer PSA testing after such an examination. The half-life of serum PSA is 2.2 to 3.2 days. Therefore, one should wait approximately 4 to 8 weeks after significant prostate manipulation, such as that which occurs with prostatitis or prostate biopsy, before obtaining serum PSA. It should be emphasized that the most common cause for an elevated serum PSA level is BPH, the incidence of which...
increases with age, as does the incidence of prostate cancer.

Serum PSA concentrations can be decreased by treatment with agents that lower serum testosterone, such as luteinizing hormone–releasing hormone (LHRH) agonists and antagonists, antiandrogens such as flutamide, and the 5a-reductase inhibitor finasteride, which is used for the management of presumed BPH and male-pattern baldness. Finasteride also lowers PSA levels by an average of 50%. Therefore, one can correct for the effect of finasteride on PSA by doubling the PSA level. Use of α-adrenergic antagonists such as terazosin (also used to manage obstructive voiding symptoms) has no appreciable effect on serum PSA levels.

**USE OF TOTAL SERUM PROSTATE-SPECIFIC ANTIGEN LEVEL AND DIGITAL RECTAL EXAMINATION FOR PROSTATE CANCER EARLY DETECTION**

The risk of prostate cancer correlates with serum PSA concentrations and DRE findings. The positive predictive value of a serum PSA level between 4.0 ng/mL and 10 ng/mL is approximately 20% to 30%.

For levels in excess of 10 ng/mL, the positive predictive value increases to 42% to 71.4%. The use of DRE complements serum PSA testing (Table 34.4-3).

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**TABLE 34.4-3. Probability of Prostate Cancer Based on Serum Prostate-Specific Antigen and Digital Rectal Examination**

The majority of cancers (>80%) detected by serum PSA are clinically significant as defined by cancer grade and volume. In contrast to the use of DRE alone for early detection of prostate cancer, the majority of PSA-detected cancers are confined clinically. However, as many as 40% of cancers detected by the use of serum PSA and DRE may have evidence of ECE, usually centrally localized, if the prostate is removed surgically and examined pathologically.

The frequency of PSA testing remains a matter of some debate. In men with a normal DRE and a PSA level in excess of 2.5 ng/mL, PSA testing should be performed annually, as approximately 50% of these patients may convert to having a PSA level exceeding 4.0 ng/mL. The test can be performed biannually in those with a normal DRE and serum PSA level lower than 2.5 ng/mL, as the likelihood of ECE is much less likely.

The likelihood of curable prostate cancer, either organ-confined or with low-to-intermediate grade cancer, is similar in men who have prostate cancer associated with serum PSA levels lower than 4.0 ng/mL and in those with levels of 4.0 to 5.0 ng/mL. Therefore, cure is not likely to be compromised in those with very low serum PSA levels initially who experience a limited rise in the PSA level over time.

**Enhancing Prostate-Specific Antigen Test Performance**

A number of different strategies have been developed to enhance PSA test performance, by increasing sensitivity in certain populations or specificity in others. These strategies include use of age-specific reference ranges, PSA velocity, PSA density, and the molecular forms of PSA (free or complexed PSA).

PSA density is a measurement that attempts to correct for elevated PSA levels due to BPH. PSA density is defined as the total serum PSA level divided by the prostate gland volume (in milliliters) measured by TRUS.

As prostate gland volume increases with increasing amounts of BPH, PSA should rise as well. Prostate cancer releases more PSA into the serum than does BPH. The use of PSA density is limited by the need to perform TRUS, variations in the accuracy of TRUS to measure volume, and the fact that PSA levels due to BPH are a product of the ratio of both the stromal and epithelial components of BPH, which vary from patient to patient. Some have suggested that a PSA density cutoff of 0.15 may better discriminate between patients with elevated serum PSA levels due to BPH and those with elevated levels due to cancer. Catalona et al. showed that as many as 50% of prostate cancers may be missed if one uses this PSA density cutoff to determine the need for prostate biopsy. Still others have failed to show any utility for the use of PSA density in men with a normal DRE and PSA levels between 4.0 and 10.0 ng/mL. As BPH tends to occur in the transitional zone of the prostate and not in the central or peripheral zones, attempts to improve prostate cancer detection using transitional zone PSA density have been developed. However, like PSA density, these calculations are subject to error, require TRUS, and do not seem to be superior to the use of PSA testing alone in most patients. In addition, the failure to identify prostate cancer in those with larger prostate glands may simply be a product of biopsy sampling errors rather than true absence of the disease.

Age-specific PSA reference ranges are an attempt to compensate for the fact that the standard reference range of 0.0 to 4.0 ng/mL does not reflect age-related variations in the prostate due to BPH. A single cutoff may, therefore, be inappropriate for all ages. Many investigators have proposed age-related reference ranges to improve test sensitivity in younger men (who have less BPH and, therefore, would be expected to have lower levels of PSA) and to improve test specificity in older men (who are more likely to have BPH and higher PSA values that accompany it). Race may also have an impact on PSA levels, an issue that has been addressed by several authorities (Table 34.4-4). Using age-specific reference ranges, cancer detection rates will increase 8% to 18% in men younger than 60 years and will decrease 4% to 22% in older men. Use of age-specific reference ranges decreases the overall biopsy rate in men undergoing screening. The biopsy rate has been shown to decrease approximately 21% in older men undergoing screening if age-specific reference ranges are used. However, the overall cancer detection rate will also decrease, as fewer elderly men, the group most likely to have prostate cancer, will undergo prostate biopsy. In one series, the overall cancer detection rate fell from 5.7% using the standard PSA cutoff point of 4.0 ng/mL to 3.8% using age-specific reference ranges. Of the T1c or nonpalpable cancers missed in the older patient population, the vast majority have favorable pathologic features suggesting that they may be of low biologic potential in this age group and that failure to detect them may have little impact on patient mortality or morbidity.

**TABLE 34.4-4. Age-Adjusted Prostate-Specific Antigen Reference Ranges**

![Graph](image-url)
PSA velocity refers to the rate of changes in serum PSA over time. PSA velocity is calculated using the following equation: 1/2 (PSA2 – PSA1/time1) + (PSA3 – PSA2/time2), where PSA1 is the first, PSA2 the second, and PSA3 the third PSA measurement. Time represents the interval (in years) between PSA measurements. At least three PSA measurements obtained over 24 months or at least 12 to 18 months apart are required for maximal accuracy. In the initial study, significant differences in PSA velocity were noted in patients found to have cancer and BPH many years before cancer diagnosis. Carter et al. reported that a PSA velocity exceeding 0.75 ng/mL was highly predictive of prostate cancer using one assay (sensitivity 72% and specificity 95%). The use of PSA velocity is limited by the fact that multiple measurements using the same assay over a relatively long period are necessary for accuracy. In addition, there is substantial biologic and laboratory variability in serum PSA testing, and some suggest that only increases in serum PSA greater than 25% are likely to represent changes due to prostatic disease (BPH or cancer).

Perhaps the greatest enhancement of PSA testing has been based on the knowledge that PSA exists in the serum in both free (or unbound) and complexed forms (bound to serum proteins). Stenberg et al. made the observation that the free form of serum PSA exists in a higher fraction in men without prostate cancer than in those with the disease. Others observed that the specificity of PSA testing for the detection of prostate cancer could be enhanced by calculating the free-to-total PSA ratio as compared to using total PSA alone. Partin et al. conducted a multifstitutional trial evaluating the performance of both total and free-to-total PSA for the detection of prostate cancer in men with serum PSA levels between 4.0 and 10.0 ng/mL using the Hybritech assay (Hybritech, Inc., San Diego, CA). All men had a normal DRE and underwent systematic TRUS-guided prostate biopsy. Of 773 men, 379 (49%) were ultimately found to have prostate cancer. As expected, the total PSA was higher and free fraction was lower in those with prostate cancer as compared to those without the disease. Using a free PSA cutoff of 20% to provide 95% sensitivity, these researchers could achieve a specificity of 20%, eliminating 20% of unnecessary biopsies. For patients who had a normal DRE and total PSA concentration between 4.0 and 10.0 ng/mL, the probability of prostate cancer was 56%, 20%, and 8% for those with free PSA fractions of 0% to 10%, 15% to 20%, and more than 25%, respectively. Catalona et al. also demonstrated that the use of the percentage of free PSA in men with total serum PSA concentrations between 4.0 and 10 ng/mL could eliminate 29% of unnecessary biopsies, if a cutoff of 20% free PSA was used as an indicator for prostate biopsy. Others have performed similar studies using the same or different assays and patient populations (i.e., ranges of total PSA). These studies, the specificity and sensitivity for cancer detection varied from 71% to 100% and 24% to 95%, respectively, using cutoff points ranging from 14% to 28%.

As 13% to 20% of men with serum PSA concentrations between 2.6 and 4.0 ng/mL (upper limit of normal) will be found to have prostate cancer within 5 years, some have examined the usefulness of percentage of free PSA for the early detection of prostate cancer in these men. Catalona et al. used percentage of free PSA to screen 914 men aged 50 years or older who had normal DREs and total PSA concentrations between 2.6 and 4.0 ng/mL. Using a cutoff point of 27% free PSA, 90% of cancers were detected and 18% of unnecessary biopsies were eliminated. The positive predictive value of percentage of free PSA at this cutoff point was 24%, and 81% of 52 men who underwent radical prostatectomy were found to have organ-confined cancers. Of these cancers, 63% were considered to be clinically significant based on cancer volume, stage, and grade. Others have shown similar findings using a different PSA cutoff point. The percentage of free PSA may also be of value in predicting cancer aggressiveness. Carter et al. measured both total and percentage of free PSA serially in men from whom serum had been stored before the diagnosis of prostate cancer. Stored sera from men with aggressive cancers as defined by stage (T3, nodal or bone metastases), grade (³7), or positive margins at the time of radical prostatectomy were compared to sera from men with less aggressive cancers (none of the previously mentioned features). Although total PSA levels were not different between both groups measured serially before the diagnosis, a statistically significant difference between the two groups with respect to percentage of free PSA was noted. All eight patients with aggressive cancers from whom serum was available for testing 10 years before diagnosis had free PSA fractions of 14% or less.

Clinicians should be aware of several issues when determining whether to use percentage of free PSA and in interpreting results of the assay. Age, prostate volume, and method of serum storage before processing may influence PSA ratios. Samples should be processed within 3 hours or stored at ~70°C if processing is delayed; otherwise, the free PSA fraction may be degraded. Lower free PSA cutoff points may be possible in smaller gland volumes (i.e., =40 cm3) while still maintaining an acceptable detection sensitivity of 90%. Several analytical issues must be understood. Assays performed by different methods may yield different results. The percentage of free PSA cutoff point advised by manufacturers of these assays varies. Therefore, clinicians must be well acquainted with the methods used for free PSA testing before interpreting the results. Finally, it must be emphasized that use of percentage free PSA improves specificity of detection; some cancers will be missed. Both physicians and patients must be aware of this, as some will find any decrement in sensitivity unacceptable. Percentage of free PSA testing may be used best when determining the need for a second prostate biopsy in patients with a normal DRE, a total serum PSA between 4.0 and 10 ng/mL, and a previously negative biopsy.

**Future Refinements**

Similar to use of percentage of free PSA, several investigators have assessed the measurement of complexed PSA (PSA bound to a α-antichymotrypsin) for the detection of prostate cancer. Brewer et al. measured total, complexed, and free PSA in 75 men with prostate cancer and in 225 who had benign findings on prostate biopsy. At 95% sensitivity, the specificities of total, free, and complexed PSA were 21.8%, 15.4%, and 26.5%, respectively. Sokoll et al. reported similar findings and improved specificity for complexed PSA as compared to total PSA in men with total serum PSA concentrations between 4.0 and 10.0 ng/mL.

The ProstAsure Index (Horus Global HealthNet, Hilton Head Island, SC) examines the relationships between several variables, such as PSA, age, and prostatic acid phosphatase, using an artificial neural network to predict the risk of prostate cancer. Babaian et al. compared the ProstAsure Index with percentage of free PSA for prostate cancer detection in 54 men with prostate cancer, 77 with BPH, and 94 with no evidence of either. A comparison of the receiver operating characteristic curves for both tests demonstrated that the area under the curve for the ProstAsure Index was higher than that for percentage of free PSA (0.95 vs. 0.86, respectively), suggesting a small but significant advantage for the index. Other serum proteins have been identified that may, in the future, play a role in prostate cancer detection and evaluation. Prostate-specific membrane antigen (PSMA) is a 750–amino acid type 2 transmembrane glycoprotein distinct from PSA. Serum levels of PSMA are increased in patients with prostate cancer. Human kallikrein-2 is a 750–amino acid type 2 transmembrane glycoprotein distinct from PSA. Serum levels of PSMA are increased in patients with prostate cancer. Human kallikrein-2 is a serum protease that bears considerable homology to PSA. Neither PSMA nor human kallikrein-2 currently is being used routinely for prostate cancer early detection, but refinements in development of serum assays, as well as novel imaging and treatment techniques targeting these and yet-to-be discovered proteins, may have a significant impact on prostate cancer early detection, staging, and treatment.

**PROSTATE BIOPSY AND ITS IMPACT ON RISK ASSESSMENT**

Prostate biopsy is indicated in men with an elevated serum PSA level, an abnormal DRE, or a combination of the two. Prostate biopsy is best performed under TRUS guidance using a spring-loaded biopsy device coupled to the transrectal probe. Although prostate biopsy can be done using a transperineal approach, the transrectal approach facilitates more accurate needle placement and tissue sampling. Rather than just sampling an area abnormal on the basis of DRE or TRUS imaging, systematic biopsy strategies have been developed that improve cancer detection and risk assessment. DRE and TRUS each lack the sensitivity and specificity to guide performance of lesion-directed biopsy only. Traditionally, several sextant biopsy schemes have been used in most patients along a parasagittal line between the lateral edge and the midline of the prostate at the apex, midgland, and base bilaterally. Recently, several investigators have assessed the impact of increasing the number of biopsies as well as sampling specific portions or zones of the prostate. Investigators have shown that more laterally directed biopsies of the peripheral zone will increase detection rates by 14% to 20% over the more traditional sextant technique. Chang et al. analyzed a biopsy scheme that included an additional number of eight sites, including bilateral apex, midgland, parasagittal midgland, and lateral base. They found that the parasagittal biopsies at the base added very little unique information to this scheme.
As up to 30% of lesions may originate in the transitional zone, many investigators have examined the utility of specific transitional zone biopsies. Most have found that routine transitional zone biopsies add little unique information to that gained from routine peripheral zone biopsy schemes. Therefore, transitional zone biopsy should be considered in those with a high suspicion of prostate cancer based on serum PSA level and who have undergone previous peripheral zone biopsy without cancer detection. Patients should be advised that a negative prostate biopsy does not completely exclude cancer, as 13% to 31% of patients with an initially negative biopsy will be found to have cancer on subsequent biopsy.

Although the primary goal of prostate biopsy is cancer detection, the information gained from the results, if positive, can be of considerable value in initial risk assessment. The number of cores with cancer as well as the cancer grade determined by biopsy correlate with the risk of ECE and cancer progression. As biopsy samples only a portion of the prostate, accurate grading may be hampered by sampling errors. Grade as measured by biopsy will correlate exactly with that determined by analysis of the entire prostate after radical prostatectomy. Most often, needle biopsy underestimates cancer grade. Grading errors appear to be more limited with the use of contemporary biopsy schemes, which have increased (≥6) the number of cores taken. Prostate cancer volume correlates with both the risk of extracapsular disease and outcome after treatment. Although cancer volume currently is not well assessed by imaging, analysis of the number of biopsy cores involved with cancer as well as the extent of cancer within each core appears to be of value in this regard. Patients with multiple positive biopsies are at an increased risk of both ECE and recurrence after initial therapy. One series reported on 257 consecutive radical prostatectomy patients and demonstrated that the number of positive sextant biopsies and the Gleason score correlated with ECE (P ≤ .001 and P = .004, respectively) in a comparison of patients with and without ECE. With respect to serologic recurrence, patients with fewer than three positive biopsies and a Gleason score of less than 7 were at a low risk for recurrence irrespective of preoperative PSA levels (14% risk with a mean follow-up of 2 years). Other investigators have substantiated these findings, noting that patients in whom more than 50% of biopsy cores are involved with cancer are at an increased risk of both ECE and disease recurrence after radical prostatectomy. Knowledge of the number of cores involved may give important information not provided by analysis of the PSA level, Gleason grade, and local T stage alone. Although TRUS-guided prostate biopsy usually is very well tolerated by patients, approximately 24% of those undergoing the procedure will find it very painful. Hematopteremia and hematouria are common, occurring in approximately 40% to 50% of patients. High fever is rare, occurring in 2.9% to 4.2% of patients. Antibiotic prophylaxis is commonly given, although the necessity for it has been questioned by some. Recent use of aspirin or nonsteroidal antiinflammatory agents is not a contraindication for this procedure.

**TO SCREEN OR NOT TO SCREEN?**

The case for prostate cancer screening is supported by the following facts: The disease is burdensome; PSA testing improves detection of clinically important tumors without significantly increasing the detection of unimportant tumors; most PSA-detected tumors are curable using current techniques; and there is no cure for metastatic disease. In addition, several investigators have shown a reduction in cause-specific mortality with screening. In a community-based, prospective, randomized trial of men between the ages of 45 and 80 years, Labrie et al. showed that patients randomized to PSA screening had a cause-specific mortality equal to one-third that of unscreened men. However, this study must be interpreted with caution, as fewer than 20% of men in this study were randomized to screening. In an independent, population-based, case-control study that looked at screening with DRE, Jacobsen et al. showed an association between decreased mortality and screening. However, the causal relationship between screening and decreased mortality remains to be proven. In the Prostate, Lung, Colon, Ovarian Trial supported by the National Cancer Institute, men are randomized to screening (with DRE and PSA testing) and to no screening, with cancer-specific mortality as the end point. In this study, the number of cores involved with cancer was at an increased risk of both ECE and disease recurrence after radical prostatectomy. Knowledge of the number of cores involved may give important information not provided by analysis of the PSA level, Gleason grade, and local T stage alone. Although TRUS-guided prostate biopsy usually is very well tolerated by patients, approximately 24% of those undergoing the procedure will find it very painful. Hematopteremia and hematouria are common, occurring in approximately 40% to 50% of patients. High fever is rare, occurring in 2.9% to 4.2% of patients. Antibiotic prophylaxis is commonly given, although the necessity for it has been questioned by some. Recent use of aspirin or nonsteroidal antiinflammatory agents is not a contraindication for this procedure.

### TABLE 34.4-5. Average Life Expectancy and Life Expectancy Correlated with Patient's Perception of Health Status

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>Average Life Expectancy</th>
<th>Good Health</th>
<th>Fair/Poor</th>
</tr>
</thead>
<tbody>
<tr>
<td>65</td>
<td>15</td>
<td>15-28</td>
<td>4-8</td>
</tr>
<tr>
<td>70</td>
<td>12</td>
<td>15-28</td>
<td>4-8</td>
</tr>
<tr>
<td>75</td>
<td>19</td>
<td>15-28</td>
<td>4-8</td>
</tr>
<tr>
<td>80</td>
<td>7</td>
<td>8-11</td>
<td>3-4</td>
</tr>
</tbody>
</table>

(From ref. 75 with permission.)
FIGURE 34.4-5. Algorithm for the early detection of prostate cancer. *Whether one uses total prostate-specific antigen (PSA) or its variations (i.e., percentage free or age-referenced prostate-specific antigen testing) for the initial screening for the disease is a matter of debate (see text). DRE, digital rectal examination; PIN, prostatic intraepithelial neoplasia; TRUS, transrectal ultrasonography.

INITIAL CANCER STAGING AND RISK ASSESSMENT

Historically, initial risk assessment was based on clinical staging—that is, the assessment of anatomic extent of the disease on the basis of physical examination and imaging. Although clinical stage (TNM) correlates with outcome, in a large percentage of patients who are believed to have organ-confined disease, evidence of disease beyond the prostate is identified at the time of radical prostatectomy. Alternatively, some patients with high-risk pathologic features may not experience disease recurrence. Therefore, many clinicians have focused their efforts on better risk assessment schemes that predict the likelihood of disease recurrence if patients are treated and the likelihood of clinical progression if patients undergo initial surveillance. This more modern concept of risk assessment is a product of the knowledge that disease may be better characterized by analyzing many criteria (e.g., serum PSA level, Gleason grade, cancer volume) in combination with clinical stage, as compared to the use of staging alone.

An accurate assessment of risk before definitive treatment is attempted would allow for a more realistic assessment of the likelihood of cure with various treatment options and, therefore, better treatment selection. In addition, such assessment would allow for more accurate prediction of who may be candidates for neoadjuvant or adjuvant treatment or novel clinical trials owing to the presence of high-risk cancer features.

IMAGING

Imaging plays an important role in staging. Both cross-sectional imaging of the pelvis and imaging of the bones (with radionuclide bone scanning) often are performed. However, imaging can be costly, and patients at low risk of advanced disease can be spared the cost and morbidity of cross-sectional imaging and radionuclide bone scanning. With the advent of widespread screening for prostate cancer, considerable stage migration has occurred, and the incidence of metastatic and regionally advanced prostate cancer has decreased. Several investigators have proposed guidelines for prostate cancer imaging that limit costs without compromising significantly the accuracy of staging. However, a recent analysis of the use of cross-sectional imaging [computed tomography (CT) or magnetic resonance imaging (MRI)] and bone scanning in a large cohort of patients cared for by urologists suggests that bone scans, CT, and MRI are overused, certainly in low-risk patients (i.e., PSA <10 ng/mL, stage <T2c, grade <7). In this latter group, 66% of patients were undergoing bone scans, and 24% either CT or MRI.

Radionuclide bone scanning has replaced the use of plain films for the detection of prostate cancer metastases. Although sensitive, bone scans have a low specificity. False-positive scans can occur due to trauma, degenerative disease, or Paget's disease. Lee and Oesterling et al. have conducted investigations to assess the ability of serum PSA level to predict bone scan findings (Fig. 34.4-6). In a cancer population representative of newly diagnosed patients in the United States, serum PSA level was the best predictor of bone scan results. Of 652 patients with newly detected prostate cancer, 66% had a serum PSA concentration of less than 10 ng/mL. The likelihood of a positive bone scan due to metastases was 0.6% and 2.6% for those with serum PSA concentrations between 10.1 and 15 ng/mL and 15.1 and 20 ng/mL, respectively. Use of tumor grade, local tumor stage, or a combination of these variables did not enhance the predictive power of PSA testing. Many others have confirmed these results. On the basis of these results, one can omit the bone scan in patients with newly diagnosed, untreated prostate cancer who are asymptomatic and have serum PSA concentrations of less than 20 ng/mL and certainly in those with serum PSA concentrations of less than 15 ng/mL. Given that there is some risk of bone metastases in this population, it is reasonable to perform a bone scan in those patients with either very high-grade or very high-stage disease.

FIGURE 34.4-6. Radionuclide bone scan showing increased uptake consistent with prostate cancer metastases.

Cross-sectional imaging of the pelvis with CT or MRI in patients with prostate cancer generally is performed to exclude lymph node metastases in patients who are believed to be candidates for definitive local therapy (Fig. 34.4-7). However, the incidence of lymph node metastases is currently low (<5%), and imaging is costly and its sensitivity limited. One review of the literature encompassing 15 series and 1354 patients with an incidence of lymph node metastases of 22% revealed a sensitivity of CT and MRI of approximately 36% and a specificity of 97%. The authors of this review suggested that only those patients with a very high risk of lymph node metastases (i.e., 45%) would benefit from cross-sectional imaging. Such patients would include those with a normal bone scan, Gleason score greater than 7, a palpable abnormality on DRE (i.e., T2 to T4 disease), and a serum PSA level of greater than 25 ng/mL.

FIGURE 34.4-7. A computed tomography scan showing the presence of retroperitoneal adenopathy due to metastatic prostate cancer.

Radionucleolabeled monoclonal antibodies directed at PSA have been used to stage newly diagnosed patients and identify sites of cancer recurrence after definitive therapy. Prostascint (Cytogen Corporation, Princeton, NJ) uses a murine monoclonal antibody labeled with indium 111 for the detection of lymph node and other soft tissue metastases. Imaging is performed 72 to 120 hours after administration of the agent. The sensitivity, specificity, and positive predictive value of the test in one patient population with a 37% incidence of nodal metastases was 75%, 86%, and 79%, respectively. In a more recent study of 160 patients imaged before pelvic lymph node dissection, the sensitivity, specificity, and positive and negative predictive values for immunoscintigraphy were 62%, 72%, 62%, and 72%, respectively. The authors found the test, when considered in conjunction with certain combinations of PSA level and Gleason score, was effective in predicting the risk of lymph...
node metastases. The test has not gained wide popularity owing to difficulties with accurate interpretation, its cost, and the fact that similar information about risk may be gained by use of the serum PSA level, cancer grade, and cancer stage.

Whereas metastatic and regionally advanced disease are relatively uncommon at presentation, ECE and seminal vesicle invasion are not uncommon, occurring in approximately 20% to 40% and 8% of patients at presentation, respectively. Such patients are at an increased risk of recurrence with various forms of local therapy, and pretreatment knowledge of ECE would allow for more effective local therapy to be delivered (e.g., widespread surgical excision, wider field, higher dose or combination radiation therapy). Whereas CT is a less reliable and efficient test for assessment of ECE or seminal vesicle invasion, as compared to other imaging modalities, both MRI using an endorectal probe and TRUS are used commonly to assess the integrity of the prostatic capsule and seminal vesicles. The performance of CT, MRI (body coil alone and endorectal coil), and TRUS in this regard is reviewed in Table 34.4-6 and Table 34.4-7. Given the wide range of test performance noted, other parameters of risk such as cancer grade, serum PSA level, and the number of positive biopsy samples must be taken into account when interpreting the results of either endorectal MRI or TRUS. Whereas TRUS is performed at the time of biopsy, endorectal MRI is, for the most part, used for staging only after a diagnosis has been made. Endorectal MRI may be of some value in staging intermediate-risk patients but provide little additional information in both low- and high-risk patients.

**TABLE 34.4-6.** Accuracy of Imaging for the Detection of Extracapsular Extension

<table>
<thead>
<tr>
<th>Imaging Technique</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI</td>
<td>91%</td>
<td>92%</td>
</tr>
<tr>
<td>TRUS</td>
<td>89%</td>
<td>91%</td>
</tr>
</tbody>
</table>

The routine use of endorectal imaging is limited due to problems with interobserver variability and variable diagnostic accuracy. The development of endorectal surface coils has allowed the application of three-dimensional magnetic resonance spectroscopy (MRS) to the evaluation of prostate cancer. Significantly higher choline and lower citrate levels are observed in areas of prostate cancer as compared with either normal prostate tissue or BPH [Fig. 34.4-8]. Therefore, MRS may allow for estimation of prostate cancer volume and may improve sensitivity and specificity of cancer detection when combined with endorectal MRI. The addition of MRS to MRI recently was evaluated with respect to any improvements in cancer staging and localization. When more than 4.5 voxels per slice of prostate were involved with cancer, the risk of extracapsular invasion was 43%. If more than 6 voxels were involved, this risk rose to 75%. The impact of MRS on the accuracy of staging (detection of ECE) was most apparent when inexperienced readers were evaluating the images, suggesting that the use of such technology may be most helpful in improving the accuracy of radiologists with less experience in magnetic resonance interpretation. With regard to cancer localization in patients with biopsy-proven prostate cancer, MRS in conjunction with MRI allows for improved ability to localize cancer to a sextant. When either MRI or MRS was positive for cancer, a sensitivity of 91% was achieved. When both were positive at the same site, a specificity of 92% was achieved. Nonetheless, more experience with this technique is necessary before it can be used routinely to guide and deliver treatment.

**FIGURE 34.4-8.** A: Representative reception-profile corrected T2-weighted fast spin-echo axial image taken from a volume data set demonstrating a large tumor in the right midgland: low T2-weighted signal intensity (arrow). B: T2-weighted fast spin-echo axial image with overlying point resolved spectroscopy (PRESS) selected volume (bold white box) and phase-encoded grid (fine white line) taken from a three-dimensional array of spectra. C: Corresponding 0.24-mL proton spectra with the major prostate metabolites (choline-, creatine-, and citrate-labeled). Spectra in regions of cancer (left side of image) demonstrate elevated choline and reduced citrate relative to regions of healthy peripheral zone tissue. The prostate metabolite levels that are observed in different regions of zonal anatomy, benign prostatic hypertrophy, and cancer are described in detail in the text. D: Images can also be created from prostatic metabolite levels and overlaid on the corresponding anatomic images. The red area is where (choline + creatine) citrate ratios were greater than 3 standard deviations of healthy peripheral zone values.

**TABLE 34.4-7.** Accuracy of Imaging for the Detection of Seminal Vesicle Invasion

<table>
<thead>
<tr>
<th>Imaging Technique</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI</td>
<td>90%</td>
<td>91%</td>
</tr>
<tr>
<td>TRUS</td>
<td>89%</td>
<td>91%</td>
</tr>
</tbody>
</table>

**PRETREATMENT SERUM PROSTATE-SPECIFIC ANTIGEN LEVEL, TUMOR STAGE, CANCER GRADE, AND VOLUME**

Pretreatment serum PSA level is used extensively in both pretreatment risk stratification and in predicting the outcome after definitive local treatment. The serum concentration of PSA correlates well with cancer volume and stage. However, considerable overlap exists, making use of serum PSA alone inaccurate for clinical staging in most patients. Use of serum PSA level in conjunction with cancer grade and stage adds considerable sensitivity and specificity to the prediction of lymph node status as compared to the use of PSA level alone. Investigators have published nomograms and probability curves that aid in predicting pathologic cancer stage. Use of such nomograms allows a better assessment of preoperative risk and more appropriate selection of initial treatment. It is important to note, however, that these aids in predicting the pathologic extent of disease and not necessarily the cure rates with treatment. In addition, they do not take into account other cancer features that may be predictive. As mentioned earlier in Prostate Biopsy and Its Impact on Risk Assessment, the number of positive prostate biopsies correlates with risk: Those patients in whom more than 50% of biopsy specimens prove positive or in whom two to three of three biopsy specimens on one
side are positive are more likely to have ECE.

Table 34.4-9 is a summary of the findings from multiple analyses and can serve as a broad-based guide for pretreatment risk stratification. Future refinements in imaging and the use of molecular markers may further improve risk assessment. \textsuperscript{245,270} and \textsuperscript{271}

THE IMPACT OF RISK ASSESSMENT ON TREATMENT SELECTION

The information presented suggests that risk assessment is possible and that it provides both patients and clinicians with important information. Low-risk patients are very good candidates for definitive local therapy using standard techniques. On the basis of age, comorbidity, and the long natural history of this disease in some cases, certain patients may be candidates for surveillance alone. High-risk patients are unlikely to be cured with standard therapy and are ideal candidates for clinical trials. Combined-modality therapy may be especially important in this group of patients. \textsuperscript{257} Intermediate-risk patients are candidates for modifications of standard therapy, given a significant risk of recurrence and the emerging knowledge that wide surgical excision and adjuvant radiation therapy may be useful after radical prostatectomy and that dose escalation, improved targeting, and combined-modality radiation therapy may have value over standard radiation therapy techniques in this population. \textsuperscript{255,272,273} and \textsuperscript{277}

TREATMENT SELECTION FOR NONMETASTATIC (T1–T3N0M0) DISEASE

There is no consensus as to what constitutes the best form of treatment for any stage of prostate disease. Treatment is indicated in those who are symptomatic and those who are at high risk of dying of prostate cancer or developing symptoms of the disease. Given that most patients in whom the disease is currently being detected fall into either the low- or intermediate-risk groups, immediate and aggressive treatment may not be necessary in some patients. Such patients must be informed of the potential risks and benefits of all forms of treatment as well as surveillance, which is an option for some patients. Treatment decisions should be based on cancer stage and grade as well as patient age and health. Both patient and physician bias may play a strong role in treatment selection, inasmuch as precise guidelines for treatment are not available for the majority of patients. Given the protracted and, in some cases, indolent nature of the disease, disease progression may be avoided using a variety of treatment methods. Indeed, the morbidity of different treatment regimens may guide treatment selection in some patients.

Both patients and physicians must interpret the results (morbidity and cancer control rates) of various forms of treatment with caution. Often, the morbidity of treatment is reported using physicians’ estimates. However, physicians generally underestimate the impact of the disease in almost all health-related quality-of-life domains. \textsuperscript{274} Given the protracted nature of prostate cancer, only a limited number of patients may die of their disease. Therefore, outcome often is assessed using end points other than cause-specific survival, the most common being PSA levels. After radical prostatectomy, the PSA level should fall to undetectable, usually within 6 weeks of surgery. A persistently detectable PSA level predicts clinical recurrence, although disease may not return for many years and may not lead to death. \textsuperscript{275} After cryotherapy and radiation therapy, PSA continues to be produced in most patients. What constitutes an acceptable PSA level after either form of treatment is a matter of some debate. Whereas some argue that low (i.e., <0.5 ng/mL) nadir levels should be reached, the American Society for Therapeutic Radiology and Oncology (ASTRO) defines biochemical recurrence after radiation therapy as three consecutive rises in serum PSA level above nadir. \textsuperscript{276} Failure cannot occur until nadir is reached. This method of defining outcome is very sensitive to the length of follow-up and the frequency of PSA testing.

NATURAL HISTORY AND SURVEILLANCE ALONE

Certain prostate cancers may grow slowly. In addition, many patients with this disease are elderly and may have concomitant illnesses. Therefore, watchful waiting or surveillance alone may be an appropriate form of management for selected patients with prostate cancer. Contemporary series documenting the true natural history of untreated prostate cancer are limited. Many series are composed of only carefully selected patients, many of whom may have received some form of treatment, often androgen deprivation, during follow-up.

Several investigators have reported the likelihood of local and distant tumor progression in patients who were untreated or who were treated with noncurative intent (i.e., androgen deprivation) (Table 34.4-10). The risk of local progression in these series ranges from 8% to 84%, while the risk of progression to metastatic disease ranges from 8% to 74%. The results should be interpreted with caution, as most patients were older (i.e., >70 years old) and had low-grade or low-stage disease (or both). Furthermore, follow-up in these studies ranged from 4 to 14 years after diagnosis, and such differences likely account for the wide range of local and distant progression reported. Therefore, the results may underestimate the risk of disease progression in the general population of patients with prostate cancer, most notably in those who present at a younger age (i.e., <65 years). The definition of local progression in the majority of these series was based on changes in DRE, which is an imprecise measure. Two studies by Egawa et al.\textsuperscript{277} and Rana et al.\textsuperscript{278} have defined local progression by the development of bladder outlet obstructive symptoms necessitating surgical intervention. These were the only studies in which distant progression exceeded local progression. Finally, it must be emphasized that the use and timing of androgen deprivation therapy varied between studies. \textsuperscript{279} and \textsuperscript{280}
The risk of prostate cancer due to prostate cancer in these series varies. Prostate cancer caused or contributed to death in 34% to 62% of the patients who died. In a study of 514 prostate cancer patients, all of whom died between 1988 and 1991 and received immediate or deferred androgen deprivation therapy only, Aus et al. found that prostate cancer caused or contributed to death in 62% of the study population. When analyzing only those patients with clinically localized disease at diagnosis (M0), 93% still died as a result of prostate cancer. Gronberg et al. examined 6514 similar patients, in all of whom prostate cancer was diagnosed in Northern Sweden between 1971 and 1987. Follow-up in this series ranged from 7 to 23 years after initial diagnosis. Fifty-five percent of the patients who died during this time died as a result of prostate cancer. In a series of 451 prostate cancer patients from the Connecticut Tumor Registry, Albertsen et al. reported that prostate cancer was the underlying cause of death in 34% of those who died after a mean follow-up of 15.5 years.

Brasso et al. found that prostate cancer caused a significant excess mortality in untreated patients, with the number of actual deaths being approximately 1.6-fold greater than the expected number of deaths in the general population. Similarly, Rana et al. reported that actuarial survival was 17% less at 5 years and 15% less at 10 years after diagnosis for 199 prostate cancer patients who were managed conservatively, as compared to age-matched controls. Others have shown that patients with prostate cancer may lose a significant number of years of life expectancy. Of note, disease-specific survival at 10 years after diagnosis was 87% in 186 prostate cancer patients who were managed with delayed androgen deprivation after transurethral prostatectomy, as compared to a 10.2-year life expectancy for age-matched controls. Finally, several investigators have reported disease-specific survival for prostate cancer patients who were untreated or treated with noncurative intent. Disease-specific survival ranged from 60% to 98% at 5 years, 34% to 92% at 10 years, and 62% to 81% at 15 years after diagnosis (Table 34.4-11).

Patients with metastatic disease at the time of diagnosis fare significantly worse than do patients with clinically localized disease at presentation. Brasso et al. reported that the median survival was 3.7 years for patients with clinically localized prostate cancer, 1.8 years for patients with regionally advanced disease, and only 1.1 years for patients with metastatic disease at diagnosis. In the subset of patients surviving for at least 10 years after diagnosis, prostate cancer was the underlying cause of death in 61% of patients with clinically localized disease and in 76% of patients with advanced disease at diagnosis. Johansson et al. reported outcomes for 642 patients, most of whom were treated with immediate or delayed androgen deprivation. While the 15-year corrected survival was 81% for patients with clinically organ-confined disease (stage T0 to T2) and 57% for patients with clinical stage T3 or T4 disease at diagnosis, the 15-year corrected survival was only 6% for patients with metastases at diagnosis. In a study of 514 prostate cancer patients treated with immediate or delayed androgen deprivation, Aus et al. reported that the median survival of patients with localized disease at diagnosis was 82 months, as compared to only 26 months for patients with metastases at diagnosis. In those with clinically localized disease, T stage correlates with outcome. The risk of local and distant cancer progression and, ultimately, death rises with T stage. The risk of metastatic progression at 10 to 15 years after diagnosis is approximately 25% to 34% for those with T3 disease, whereas it is 13% to 20% for those with stage T1 and T2 disease. Similarly, 10- to 15-year overall and disease-specific survival is better for those with T1 and T2 disease (82% to 90%), as compared to that associated with T3 and T4 disease (57% to 70%). It should be noted that the risk of progression from stage T1 or T2 disease to T3 disease is approximately 70% at 10 years in those managed conservatively. Aus et al. found that 10% of patients with clinical stage T1a disease, 47% with clinical stage T1b disease, 52% with clinical stage T2a disease, 53% with clinical stage T2b to T3 disease, and 70% with clinical stage T4 disease ultimately died of prostate cancer.

Tumor grade may be the most important factor predicting disease progression and survival in prostate cancer patients managed conservatively. In a review of 828 prostate cancer patients obtained from six nonrandomized studies of men treated with observation and delayed androgen deprivation, Chodak et al. reported that poorly differentiated disease was the single most important predictor of disease-specific survival. The likelihood of remaining metastasis-free 10 years after diagnosis for patients with well-, moderately-, and poorly differentiated tumors was 81%, 58%, and 26%, respectively. Disease-specific survival 10 years after diagnosis was 87% for patients with well- or moderately differentiated disease and only 34% for patients with poorly differentiated disease. Similar results with respect to disease-specific survival and prostate cancer-related death have been reported in a number of other studies (Table 34.4-12). In these studies, the relative risk of prostate cancer–related death ranges from 2.6 to 3.6 for patients with moderately differentiated disease and from 6.1 to 12.9 for patients with poorly differentiated disease as compared to patients with well-differentiated prostate cancers.

### TABLE 34.4-10. Estimates of Local and Metastatic Tumor Progression in Prostate Cancer Patients Who Remain Untreated and in Those Who Are Treated with Noncurative Intent

<table>
<thead>
<tr>
<th>Disease</th>
<th>Untreated</th>
<th>Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local</td>
<td>10%</td>
<td>5%</td>
</tr>
<tr>
<td>Metastatic</td>
<td>25%</td>
<td>5%</td>
</tr>
</tbody>
</table>

### TABLE 34.4-11. Estimates of Disease-Specific Survival in Prostate Cancer Patients Who Remain Untreated and in Those Who Are Treated with Noncurative Intent

<table>
<thead>
<tr>
<th>Stage</th>
<th>Untreated</th>
<th>Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>81%</td>
<td>82%</td>
</tr>
<tr>
<td>T2</td>
<td>57%</td>
<td>53%</td>
</tr>
<tr>
<td>T3</td>
<td>13%</td>
<td>20%</td>
</tr>
<tr>
<td>T4</td>
<td>6%</td>
<td>0%</td>
</tr>
</tbody>
</table>
In one of the best-performed studies on prostate cancer natural history done to date, Albertsen et al. examined the impact of tumor grade on long-term survival among prostate cancer patients who were treated with either observation or immediate or delayed androgen deprivation. In their initial study, these authors determined that tumor grade correlated with death due to prostate cancer. Nine percent of patients with well-differentiated, 28% of patients with moderately differentiated, and 51% of patients with poorly differentiated disease died as a result of their prostate cancer within 15 years of diagnosis. These authors also compared the survival of prostate cancer patients treated conservatively with the expected survival of the general population. Age-adjusted survival for men with well-differentiated, Gleason score 2 to 4 tumors was not significantly different from that of the general population. In contrast, the maximum expected loss-of-life expectancy was 4 to 5 years for men with Gleason score 5 to 7 tumors and 6 to 8 years for men with Gleason score 8 to 10 tumors as compared to the general population. In a subsequent study, these authors developed a competing risk analysis to estimate the probability of dying from prostate cancer in 767 men, aged 55 to 74 years, all of whom remained untreated or received immediate or delayed androgen deprivation only. Tumor grade had the most important impact on the risk of prostate cancer–related death for these patients: 4% to 7% of men with Gleason score 2 to 4 disease, 6% to 11% of patients with Gleason score 5 disease, 18% to 30% of patients with Gleason score 6 disease, 42% to 70% of patients with Gleason score 7 disease, and 60% to 87% of patients with Gleason score 8 to 10 disease died of prostate cancer within 15 years of diagnosis. Others have reported similar findings (see Table 34.4-12).

Watchful waiting or surveillance alone for prostate cancer is an option for all patients with the disease. However, progression is likely in many, and the risk correlates with cancer stage and grade. Patients best suited for this approach may be those who are older and have low-grade or low-stage disease and in those with significant comorbidity. In such patients, the morbidity of treatment may outweigh the risks of significant disease progression. Patients being followed up with surveillance only need to be advised that end points for intervention for those on watchful waiting regimens have not been defined.

### RADICAL PROSTATECTOMY

Radical prostatectomy can be performed through a lower abdominal incision (radical retropubic prostatectomy) or through a perineal incision (radical perineal prostatectomy). With the former technique, lymphadenectomy can be performed simultaneously. With radical perineal prostatectomy, lymphadenectomy can be performed through a separate incision, laparoscopically, or deleted in those at very low risk of lymph node metastases. Recently, a laparoscopic approach to radical prostatectomy has been developed. Although early reports suggest that this technique is feasible and is associated with limited morbidity and acceptable positive margin and biochemical control rates, long-term follow-up in suitable patient populations is not yet available.

Contemporary series of patients with localized prostate cancers suggest that few patients harbor lymphatic disease (4% to 9%), and the risk of lymph node metastases can be quantitated as described previously in Imaging. Whereas high-risk patients benefit from lymphadenectomy, low-risk patients may forgo lymphadenectomy and be treated with definitive local therapy, whether irradiation or radical prostatectomy.

Lymphadenectomy should be considered if the Gleason score is 5 to 6 and the PSA level is at least 20 ng/mL or if the Gleason score is 7 or higher and the PSA level is at least 15 ng/mL. Patients with clinical stage C (T3) disease should also be considered as candidates for the procedure.

Radical retropubic prostatectomy is performed through a lower midline incision. The rectus abdominis muscles are separated in the midline, and the retropubic space is entered. A fixed retractor is placed. Lymphadenectomy may be performed selectively as described. Lymph node dissection has been modified over the last several years to include lymph node tissue in areas most likely to harbor disease. The limits of dissection, therefore, most often include the obturator nerve posteriorly, the common iliac artery superiorly, the circumflex iliac vein inferiorly, and the internal aspect of the external iliac vein laterally.

Exposure of the prostate when performing a radical retropubic prostatectomy is undertaken by first incising the endopelvic fascia from the area of the puboprostatic ligaments along the lateral edge of the prostate to its base (Fig. 34.4-9). Fibers of the levator ani are separated from the apex of the prostate. The fascia and overlying dorsal vein complex generally are gathered and suture-ligated to facilitate exposure and prevent bleeding from the complex once it is cut to allow access to the urethra (Fig. 34.4-10). The puboprostatic ligaments, which provide anterior support of the urethra, are left intact over the urethra, but any attachments to the prostate are incised. Preservation of the puboprostatic ligaments facilitates earlier and more complete return of urinary continence as compared to previous techniques, which incised these ligaments over the urethra. Care is taken during the apical dissection of the prostate simultaneously to preserve the urethra's distal continence mechanism and to excise all prostate tissue. The urethral incision should be carried posteriorly beyond the urethra to include Denovilliers' fascia, thereby ensuring complete cancer excision.

**TABLE 34.4-12. Outcome of Conservative Management of Prostate Cancer According to Histologic Tumor Grade**

<table>
<thead>
<tr>
<th>Tumor Grade</th>
<th>4% to 7%</th>
<th>6% to 11%</th>
<th>18% to 30%</th>
<th>42% to 70%</th>
<th>60% to 87%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gleason score 2 to 4</td>
<td>Death</td>
<td>Death</td>
<td>Death</td>
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<tr>
<td>Gleason score 5</td>
<td>Death</td>
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<tr>
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<td>Death</td>
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<tr>
<td>Gleason score 7</td>
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<tr>
<td>Gleason score 8 to 10</td>
<td>Death</td>
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</tr>
</tbody>
</table>

Penile erection is a neurovascular phenomenon, and the nerves and arterial blood supply (neurovascular bundles) crucial to potency run posterolaterally along either side of the prostate (Fig. 34.4-11). These bundles may be spared during surgery in an effort to preserve potency. However, ECE, when it does occur, may occur in the region of the neurovascular bundles. These bundles should be preserved cautiously in those at high risk of ECE. In addition, return of potency after a nerve-sparing
radical prostatectomy is not only a function of technique but also of patient age and preoperative function. Older patients and those with poor preoperative potency may not benefit from a nerve-sparing approach. The neurovascular bundles can be located using anatomic landmarks. During nerve-sparing radical prostatectomy, the lateral prostatic fascia is incised. The neurovascular bundles run deep to this fascia at approximately the 5- and 7-o'clock positions along the posterolateral surface of the prostate. Small vascular branches to the prostate may be taken using small clips or sutures. The neurovascular bundles are at the most risk for damage at the time of urethral dissection and transection, ligation of the lateral pedicles, and dissection of the seminal vesicles. However, a nerve stimulation device may facilitate identification and preservation. Electrical stimulation may result in smooth muscle relaxation of penile tissue and expansion of corporal sinusoids, resulting in increased penile blood flow, girth, and length. Either intracavernous pressure or penile circumference monitoring can note such changes. Early experience using a commercially available intraoperative, nerve-stimulating device and continuous monitoring of penile circumference during stimulation suggests that use of such a device may allow for better preservation of erectile function.

The lateral pedicles, branches of the prostatic and rectal arteries, are located alongside the prostate. Dissection proceeds superiorly, exposing the seminal vesicles and ampullae of the vas deferens. The ampullae are clipped or tied before being cut, and each seminal vesicle is excised in its entirety. The prostate then is separated from the bladder neck circumferentially. Once the prostate is removed, the bladder neck is closed to a smaller size, if necessary. The bladder neck is sutured to the urethral stump using interrupted suture material over a urethral catheter. Hospitalization is limited to 2 or 3 days in most situations. The urethral catheter is removed generally between 5 and 14 days after the procedure. Approximately one-half of patients will gain almost immediate urinary control. In the remaining patients, continence will return progressively within 3 to 6 months, rarely longer. Little additional urinary control occurs beyond 12 months. Erectile function in those who have undergone a nerve-sparing approach generally takes longer to return than does urinary continence. Patients may require use of sildenafil (Viagra), vacuum devices, or intracavernous injection therapy, at least initially.

Radical prostatectomy for patients with clinically localized disease is generally well tolerated, with excellent outcomes. In a series of more than 600 men treated with prostatectomy, Trapp et al. reported a 10-year crude survival rate of 96% and a cause-specific survival of 94%. In an independent analysis of 3170 men treated at a different institution, Zincke et al. reported similar 10-year crude and cause-specific survival rates of 75% and 90%, respectively. In addition, Zincke's group found that crude survival rates at 10 and 15 years after surgery were similar to those of age-matched men from the general population. This finding suggests that carefully selected patients with clinically localized prostate cancer that is treated with prostatectomy can expect to live as long as cohorts without prostate cancer in their community.

However, clinical disease staging is far from perfect, as up to 50% of patients believed to have organ-confined prostate cancer at the time of surgery are later found to have disease beyond the prostate. In addition, cancer recurrences are not uncommon in intermediate- to high-risk patients. The protracted nature of this disease and the fact that residual and recurrent disease may respond to salvage therapy such as radiation or hormonal ablation, postoperative follow-up with sensitive serum PSA assays has become increasingly important. Today, most clinical investigators report patient outcomes in terms of freedom from biochemical failure as well as clinical disease-free survival, in addition to crude and cause-specific survival. Biochemical failure is defined as either the persistence of a detectable PSA level postoperatively or the elevation of postoperative PSA to a detectable from a previously undetectable postoperative level. Total serum PSA has a half-life of 2 to 3 days, and its clearance follows first-order elimination kinetics; thus, the duration between surgery and PSA nadir generally takes several weeks and varies as a function of the patient's preoperative PSA level. Postoperative follow-up regimens reflect PSA elimination kinetics and usually consist of symptom assessment and measurement of serum PSA every 3 months for the first year, biannually for the second year, and third year, and annually thereafter. Clinical disease-free survival refers to freedom from detectable local or metastatic disease as assessed by the physician using physical examination, DRE, needle biopsy, radioisotope studies, and other traditional imaging modalities. Of note, studies from the early PSA era frequently used higher PSA cutoffs (e.g., 0.6 ng/mL). However, as the sensitivity of PSA assays improved over the last decade, most clinical investigators now use much lower cutoff points.

In the majority of cases, the first sign of disease recurrence or persistence is biochemical failure. In two contemporary prostatectomy series from the Cleveland Clinic and Johns Hopkins Hospital totaling more than 2000 patients, not one patient showed signs of clinical disease in the absence of PSA failure. Indeed, with the current patient follow-up regimen, nearly all recurrent clinical and metastatic disease is preceded by a rising PSA level, and only a few sporadic cases have been reported in the absence of detectable serum PSA. After biochemical (PSA) failure, up to 68% of men will progress to detectable clinical disease at a median follow-up of 19 months. With androgen deprivation therapy, the rate of progression to clinical disease is reportedly lower, at 21%. Metastatic disease after PSA failure occurs in 34% of patients without adjuvant or salvage therapy, and investigators have reported a median actuarial time to metastases of 8 years from the time of PSA failure. For those who develop metastatic disease, the median actuarial time to death was 5 years from the time of metastasis.

Several academic institutions have reported their experience in treating patients with clinically localized disease. The overall 5- and 10-year actuarial PSA progression-free rates range from 59% to 83% and 47% to 74%, respectively (Table 34.4-13). The variability in outcomes likely reflects differences in patient selection, surgical technique, and definition of biochemical failure, as those with higher preoperative serum PSA levels, Gleason scores, disease stage, and positive surgical margin status tend to fare worse than counterparts with lower values or negative margins. Reflecting the natural history of disease progression, clinical disease-free rates are higher, at 84% to 88% (5 years) and 72% to 78% (10 years).

TABLE 34.4-13. Comparison of Actuarial Survival Outcomes for Patients Treated with Radical Prostatectomy

The risk of disease progression and adverse outcomes varies directly with increasing pathologic disease stage, preoperative PSA level, and prostatectomy Gleason
scores.132,324,325,327,328,329 Whereas PSA relapse-free survival is approximately 80% to 84% for those with T2 disease, it falls to 57% to 67% for those with T3 disease. If one looks at all 7 stages, those patients with serum PSA levels of 10 ng/mL or less have PSA relapse-free survival rates of 80% to 95%, as compared to those with initial serum PSA levels of 10.1 to 20 ng/mL (48% to 75%) and those with levels in excess of 20 ng/mL (31% to 55%). Cancers with Gleason scores of 6 or less are associated with PSA relapse-free survival rates of 75% to 92%, as compared to PSA relapse-free survival rates of approximately 62% to 67% and 38% to 51% for Gleason scores of 8 and 9 to 10, respectively. PSA relapse-free survival correlates with the risk assessment scheme outlined in Table 34.4-5. At the University of California at San Francisco (UCSF), 92%, 75%, and 44% of low-, intermediate-, and high-risk patients, respectively, managed by radical prostatectomy were free of relapse at 5 years. DNA aneuploidy, seminal vesicle invasion, and positive surgical margin status have also been reported to influence survival outcomes negatively.132,324

Complications

With increasing experience, the morbidity and mortality associated with radical prostatectomy has declined dramatically. Perioperative mortality in academic centers is exceedingly rare, at approximately 0.2%.132,324,327,328,329,331 and 332 Across three institutions that included nearly 3000 patients, approximately 90% will be continent at 1 year, when continence is defined as no regular use of pads or no leakage with moderate exercise.132,325,327,328,330 In a multivariate analysis of risk factors for urinary incontinence, Eastham et al.132 reported that decreasing age, preservation of both neurovascular bundles, an absence of an anastomotic stricture, and use of a modified surgical technique about the striated urinary sphincter were independently associated with superior urinary outcomes. Continence appears to be equally well preserved with both the retropubic and perineal approaches.132,333 Severe and persistent incontinence, defined as leakage with normal activity or the need for three or more pads per day, occurs in 1% to 6% of patients, and the use of an artificial sphincter, collagen injection therapy, or surgical sling procedure should be considered in such patients.132,324,325,327,328,330 and 332

A rare complication of surgery is fecal incontinence. Defined as involuntary loss of liquid or solid stool, fecal incontinence may be caused by direct injury to the internal and external sphincters during perineal prostatectomy or by delayed retraction of these segments during the procedure leading to neurotrophic compromise. However, the exact mechanism of injury remains elusive. In a validated patient survey, Bishoff et al.132 initially evaluated 227 patients treated at two institutions and reported new-onset fecal incontinence rates of 5% and 18% for patients treated with the retropubic and perineal surgical approach, respectively. Although fecal incontinence was most often very transient, patients treated with perineal prostatectomy fared worse in terms of incontinence frequency and volume of leakage. Given the negative impact on patients’ quality of life and that patients with fecal incontinence may not report their problem to health care providers, physicians must take a proactive role in assessing this complication.

Maintenance of sexual function has been a major concern for patients and physicians alike. With the advent of the nerve-sparing approach to radical retropubic prostatectomy, more than two-thirds of preoperatively potent patients treated by an experienced surgical team can anticipate return of potency without sacrificing cancer control.132,325,326 Rates of potency recovery vary according to many factors, including neurovascular bundle preservation, reconstructive surgery, patient and surgeon experience. With current refinements in technique, significant urinary incontinence is rare, and preservation of potency is possible in selected patients. Patients most likely to benefit from this approach are those who have lost life expectancies and have either organ-confined disease or limited ECE, which can be excised completely.

Recurrence after Radical Prostatectomy and Role of Neoadjuvant and Adjuvant Therapy

Given the cancer recurrence and secondary treatment rates after radical prostatectomy, some investigators have tested the hypothesis that these rates could be reduced by neoadjuvant androgen deprivation.132 Such therapy could decrease the likelihood of positive surgical margins, leading to a decrease in local recurrence rates. Every randomized trial performed to date has shown that neoadjuvant androgen deprivation significantly decreases the rate of positive surgical margins.132,347 and 348 The rates of positive surgical margins were decreased by approximately 40% to 60% with neoadjuvant androgen deprivation. Unfortunately, this has not translated into any improvement in clinical or biochemical control rates. In a contemporary trial reported by Klotz and other members of the Canadian Urologic Oncology Group,132 213 patients with localized prostate cancer were randomized to radical prostatectomy alone (n = 101) or 12 weeks of cyproterone acetate followed by surgery (n = 112). The probability of biochemical progression at 36 months was similar for the groups treated by surgery alone or cyproterone acetate followed by surgery: 30.1% versus 40.2% (P = .3233), respectively. This and similar trials are ongoing. Failure to demonstrate a small, but significant, benefit to neoadjuvant therapy may be due to insufficient follow-up, short duration of androgen deprivation, insufficient power of some trials to demonstrate a benefit, or inclusion in the trials of low-risk patients. Some investigators have suggested that the patients most likely to benefit from neoadjuvant therapy are those who are young, potent, and sexually active and have focal disease. It also appears that return of spontaneous erections after nerve-sparing surgery may be improved with early use of either sildenafil or intracavernous injection therapy.132,349

In summary, radical prostatectomy is a safe operation for properly selected patients and offers excellent cancer control. Cause-specific survival at 10 years is greater than 90% for patients with organ-confined disease,132 and 330,333,334 such rates are constant, as a function of Gleason.132,331,332,333,334 Patients who undergo radical prostatectomy for locally advanced disease will exceed 4.0 cc in patients with pathologically capsule-confined prostate cancer will exceed 5.75 if (1) the cancer is confined to the surgical specimen, PSA level is at least 7.3, and Gleason score is 10; (2) there is ECE with positive margins or seminal vesicle invasion, PSA level is at least 5.4, and the Gleason score is 7; or (3) there is ECE with positive margins or seminal vesicle invasion and the Gleason score exceeds 8. A second model for patients with pathologically capsule-confined prostate cancer has been proposed by D'Amico et al.132 The model was defined as: V = cancer-specific PSA/PSA testa leak into serum per cubic centimeter of cancer. Variables were defined as follows: cancer-specific PSA = PSA (preoperative) – [0.2 + 0.3 × T2c cancer] × testa leak is a constant, as a function of Gleason.132,332,333,334 Patients who underwent radical prostatectomy for locally advanced disease will exceed 4.0 cc in patients with pathologically capsule-confined prostate cancer if (1) Gleason score is 6 and PSA level exceeds 18, (2) Gleason score is 7 and PSA level exceeds 14, or (3) Gleason score is 8, 9, or 10. Recently, Kattan et al.132 developed a preoperative nomogram for disease recurrence after radical prostatectomy. The nomogram is used by locating a patient's position on a number of
potential for local tumor cure. Indeed, a recent outcome assessment involving the use of postirradiation biopsies provided conclusive evidence for the effects of

and to calculate precisely the dose delivered at each point. It uses advanced imaging technology for tumor and normal organ segmentation, new algorithms for dose

Advances in computer technology have enabled the implementation of three-dimensional conformal radiation therapy (3D-CRT) as an approach to overcome some of

tumor underdosage have continued to contribute to a high frequency of local tumor failure.

required to eradicate the tumor.

indicated a need for higher doses to achieve maximal local tumor control,

radiographic images and frequently were inaccurate.

Failure of radiation therapy to control localized prostate cancer results most frequently from resistance of tumor clonogens to the dose levels used and from failure to
cover the entire target volume with the prescribed tumor dose. Before CT became available for treatment planning, tumor target volumes were assumed from planar

TABLE 34.4-14. Likelihood of Maintaining an Undetectable Serum Prostate-Specific Antigen in Patients with a Positive Surgical Margin

To date, no published studies have compared immediate versus delayed treatment in a prospective randomized fashion. Although the Southwest Oncology Group has

Radiation therapy was introduced as a curative modality for localized prostate cancer in the 1950s, largely due to the work of Malcolm Bagshaw 422,423 of Stanford

Radiation therapy may be given after surgery (adjuvant radiation), on the basis of adverse disease characteristics such as positive surgical margins, or after a
documented disease recurrence (therapeutic radiation), on the basis of either biopsy-proven recurrence or biochemical failure alone. Proponents of adjuvant radiation
argue that treatment is more effective when the local tumor burden is minimal and that series to date show that patients who undergo adjuvant radiation have been
shown to achieve and maintain an undetectable serum PSA level in 77% to 94% of such cases. 222,223,224 However, despite improved local tumor control, no

The impact of positive surgical margins on outcome is a matter of controversy. Despite careful case selection before radical prostatectomy, between 14% and 41% of

patients have tumor extending to the surgical margin on final pathologic analysis, with 33% to 62% of these patients failing radical prostatectomy based on the

presence of a detectable serum PSA level. 264,265,266,267

Radiation therapy may be given after surgery (adjuvant radiation), on the basis of adverse disease characteristics such as positive surgical margins, or after a
documented disease recurrence (therapeutic radiation), on the basis of either biopsy-proven recurrence or biochemical failure alone. Proponents of adjuvant radiation
argue that treatment is more effective when the local tumor burden is minimal and that series to date show that patients who undergo adjuvant radiation have been
shown to achieve and maintain an undetectable serum PSA level in 77% to 94% of such cases. 222,223,224 However, despite improved local tumor control, no

survival advantage has been demonstrated with adjuvant radiation. Studies have shown that between 42% and 70% of patients with positive surgical margins will

maintain undetectable serum PSA levels without adjuvant therapy (Table 34.4-14). 222,223,224,225 Pathologic factors such as the location, extent, and number of

positive margins may have an impact on the likelihood of disease recurrence in this setting. 226

RADIATION THERAPY

Curative Potential of Radiation Therapy

Radiation therapy was introduced as a curative modality for localized prostate cancer in the 1950s, largely due to the work of Malcolm Bagshaw 422,423 of Stanford

University. Using emerging techniques of megavoltage radiation therapy, it became possible to deliver tumoricidal dose levels to prostate tumors without excessive
damage to the skin and the normal tissues surrounding the prostate. 222,223 This approach continues to represent the basic tenet of curative radiation therapy in

prostate cancer, although systems of treatment planning and delivery have since advanced to improve precision and decrease toxicity. The ability of radiation to cure

localized prostate cancer has thus improved consistently over the past three decades. 424,425,426,427,428,429,430

Failure of radiation therapy to control localized prostate cancer results most frequently from resistance of tumor clonogens to the dose levels used and from failure to
cover the entire target volume with the prescribed tumor dose. Before CT became available for treatment planning, tumor target volumes were assumed from planar

radiographic images and frequently were inaccurate. 431 To compensate for target volume uncertainties, treatment volumes were classically increased to include a

wide safety margin, thus including substantial portions of bladder and rectum in the high-dose region. Because of the high sensitivity of pelvic organs to radiation, the

ability to deliver prostate doses exceeding 70 Gy with conventional megavoltage techniques was seriously compromised. 432,433 Whereas clinical data have

indicated a need for higher doses to achieve maximal local tumor control, 434 conventional radiation therapy techniques have, in many cases, fallen short of the levels

required to eradicate the tumor. 435 Further, while CT-assisted treatment planning has significantly improved the anatomic definitions of the tumor target, 436,437 wide

safety margins have remained a common practice to compensate for uncertainties in patient positioning and organ motion. Finally, because computers available for

treatment planning were, until recently, slow and limited in performance, calculations of dose distributions were restricted to a limited number of planes within the

target volume, and the dose to the rest of the tumor was assumed based on reasonable, albeit imprecise, projections. Hence, the problem of geographic misses and
tumor underdosage have continued to contribute to a high frequency of local tumor failure.

Advances in computer technology have enabled the implementation of three-dimensional conformal radiation therapy (3D-CRT) as an approach to overcome some of

these problems. 438,439 Three-dimensional treatment planning is based on the ability to define each pixel anatomically within the entire 3D space of irradiated tissues

and to calculate precisely the dose delivered at each point. It uses advanced imaging technology for tumor and normal organ segmentation, new algorithms for dose

calculations, and computer-aided optimization to generate treatment plans that conform the prescribed dose to the tumor while maximally excluding the adjacent

normal organs. The ability to exclude the normal tissues from the volume receiving high-dose irradiation has permitted significant increases in tumor dose without a

concomitant increase in normal tissue toxicity. 432 The improved precision also decreased the risks of anatomic tumor misses and underdosage, further improving the

potential for local tumor cure. Indeed, a recent outcome assessment involving the use of postirradiation biopsies provided conclusive evidence for the effects of

3D-CRT and dose escalation on the local cure of prostate cancer, thus defining new standards for curative radiation therapy in this disease. 440
Effect of Dose on Local Tumor Control

Several studies have addressed the relationship between radiation dose and local control in prostate cancer. 433,434,435,436,437,438,439,440 The biologic effects of radiation on tumor and normal tissues result in dose-response patterns that translate into sigmoid-shaped curves when plotted graphically. 434,435,436 Because human tumors consist of heterogeneous clonogen populations with regard to radiosensitivity, 436 it was suggested that tumor control curves would be relatively shallow, representing population averages for clones of different radiosensitivities. 433,434 The available clinical data mostly confirm this hypothesis, reporting tumor control curves with g50 values of approximately 2. 436,437,438,439,440,441 The validity of this model to prostate cancer was confirmed recently at the Memorial Sloan-Kettering Cancer Center (MSKCC) in a postirradiation biopsy study of 150 patients who did not receive neoadjuvant androgen deprivation therapy. 439,440 The diagnostic accuracy of posttreatment biopsies depends, among other factors, on the time interval from completion of treatment to biopsy. 432,433,434,435 For example, Scardino and Wheeler 434 reported that 32% of patients with a positive biopsy at 12 months after radiation therapy had a negative pathologic specimen at 24 months. As recommended by the ASTRO consensus statement, 432 biopsies were performed in the MSKCC study at 2.5 years or longer after 3D-CRT. The tumor dose was increased gradually in consecutive groups of patients, from 64.8 Gy to 81.0 Gy by increments of 5.4 Gy. Figure 34.4-12 shows that the rate of negative biopsies increased linearly from 48% in patients receiving 64.8 Gy to 94% after 81 Gy. The calculated g50 value for this set of data is 2.22. There was a concomitant increase in PSA relapse-free survival in patients receiving the high-dose range, providing further evidence for a significant effect of dose escalation on the cure of human prostate cancer.

Serum Prostate-Specific Antigen as a Surrogate for Defining Tumor Control after Radiation Therapy

After pelvic irradiation, serum PSA generally declines over 1 to 2 years, but usually it is not reduced to undetectable levels, as 70% of patients receiving radiation therapy for rectal or other nonprostatic tumors have PSA levels of less than 1.0 ng/mL for extended periods after irradiation. 441 On the basis of these data, it was suggested that cure of localized prostate cancer with radiation would be associated with maintained PSA profiles of less than 1.0 ng/mL. 441,442 It also was suggested that an increased serum PSA level from such postirradiation nadir values can serve as an indicator of disease relapse. Reviewing the emerging data in the field, the ASTRO consensus statement 441 has established a definition for PSA relapse as three consecutive rising PSA values from an established nadir value. The date of failure was defined as the midpoint between the last postiradiation nadir value and the first of the three consecutive increases. This guideline did not stipulate a specific nadir value that is associated with a complete response. However, multiple studies employing multivariate analyses have indicated that a PSA nadir of less than 1.0 ng/mL represents an independent variable in predicting long-term PSA relapse-free survival. 443,444,445 For example, Kavadi et al. 443 reported that the 5-year PSA relapse-free survival for patients who achieved nadir levels of less than 1.0 ng/mL was 17%, as compared to 70% for patients with posttreatment nadir levels exceeding 1.0 ng/mL. In this study, nadir levels of 90.5 ng/mL did not provide for improved prediction of outcome. The Eastern Virginia Medical School, 444 however, reported 5-year PSA relapse-free survival of 91% and 72% in patients with postiradiation nadir levels of less than 0.5 ng/mL and 0.5 to 1.0 ng/mL, respectively (P = .06).

Shipley et al. 445 defined the long-term pattern of PSA response in an outcome study of a multinstitutional pooled cohort of 1765 patients with T1 to T2 prostate cancer, treated with advanced external-beam techniques to doses ranging from 63 to 79 Gy (median dose, 69.4 Gy). Nadir posttreatment PSA values of £1.0 ng/mL were recorded in 80% of the patients, and only 12.8% had values in excess of 2.0 ng/mL. The overall 5-year PSA relapse-free survival was 65.8%, and of the 448 patients followed for more than 5 years, only 5% relapsed from the fifth to the eighth year. Though this study provided evidence that the majority of PSA relapses occur within the first 5 years after radiation therapy, it did not provide evidence that PSA relapse connotes anatomic relapse and that a nonrising profile correlates with lack of tumor relapse. The MSKCC posttherapy biopsy study 445,446 did, however, address this issue. Of patients undergoing biopsy at more than 2.5 years after treatment, 50 of 51 (98%) with a posttreatment PSA nadir of not more than 1.0 ng/mL and a nonrising PSA profile had negative biopsies, as compared with only 21 of 42 (50%) of those with a similar nadir but with a rising PSA profile (P = .001). Of patients with a PSA nadir of more than 1.0 ng/mL, 7 of 10 (70%) of those with a nonrising PSA profile and 21 of 47 (45%) with a rising PSA profile had negative biopsy specimens (P = .2). Taken together, these data strongly suggest that in early-stage patients in whom PSA levels of not more than 1.0 ng/mL are nadir, a maintained PSA relapse-free profile serves to indicate a 95% likelihood of permanent tumor control after radiation therapy.

Definition of Target Volume

Carcinoma of the prostate is frequently multifocal, involving more than one lobe of the gland. 445 Therefore, the clinical target volume (CTV) for irradiation consists of the total prostatic gland, including the seminal vesicles, as visualized on CT. Capsular involvement with or without periprostatic invasion has been demonstrated in 15% to 66% of radical prostatectomy specimens from patients with stage T1 or T2 disease. 446,447 For example, Schempp et al. 448 reported no significant differences in local control and survival (median follow-up of 12 years). The actuarial rates of local relapse at 12 years were 27% for prostate irradiation alone and 22% for prostate plus pelvic irradiation (P = .2), and the actuarial survival rates were 43% and 38%, respectively (P = .4). Based on these observations, it is generally accepted that elective pelvic irradiation is unlikely to affect the outcome of treatment, and pelvic lymph nodes generally are not included in the CTV for treatment planning.

Simulation and Treatment Planning

![Figure 34.4-12](https://example.com/figure34.4-12.png)

**Figure 34.4-12.** Tumor control curve, showing effect of radiation dose on the rate of negative prostate biopsies.
CONVENTIONAL (TWO-DIMENSIONAL) EXTERNAL-BEAM RADIATION THERAPY. Treatment is most frequently planned in the supine position at 100 cm source-axis distance, and immobilization devices are increasingly used to reduce patient motion during treatment. Localization skin marks are placed on the patient that correspond to a standardized treatment isocenter, a midline point near the center of the prostate located 1 cm inferior and 6 cm posterior to the upper border of the symphysis pubis. Simulation radiographs are obtained in the treatment position from the level of L5-S1 to 1.0 cm caudal to the ischial tuberosities. The target volume and the surrounding normal organs are drawn on orthogonal planar radiographs produced on conventional simulators or on digitally reconstructed radiographs generated from CT images obtained by CT simulators. To assist in defining the PTV, it is customary to use urinary bladder and rectal catheters and contrast media. A No. 16 Foley catheter is introduced into the bladder, and the balloon is inflated with 5 mL of 90% Hypaque solution. The balloon is pressed against the bladder trigone with light pressure, and the catheter is taped to the thigh. In addition, 30 mL of low-density Hypaque (30%) is introduced into the bladder. A second Foley catheter is placed in the rectum and the balloon is inflated with air and pressed against the internal sphincter of the rectum to indicate the location of the anus. Low-density Hypaque (30%) is also placed in the rectum to outline the rectal wall.

The superior border of the prostastic field usually is located approximately 2 cm above the Foley balloon and includes nearly 30% of the bladder detected by the contrast media (Fig. 34.4-13A and Fig. 34.4-13B). The inferior border is located short of the internal anal sphincter. The anterior margin is at the posterior cortex of the pubic bone, and the posterior border extends 6 to 10 mm posterior to the anterior rectal wall, sparing the posterior rectal wall. The right and left lateral margins are usually marked at 3.5 to 4.0 cm from the isocenter (see Fig. 34.4-13A and Fig. 34.4-13B). When there is an indication to treat the pelvic nodes, the inferior border usually is extended to the ischial tuberosities and the superior border to the top surface of L5 (see Fig. 34.4-13C and Fig. 34.4-13D). The lateral borders are placed approximately 1 cm lateral to the widest diameter of the pelvic inlet, but the superior and inferior corners are trimmed to protect as much bone marrow as possible. The anterior border of the lateral field extends to the posterior aspect of the pubic bones, as the anterior border of the lateral field extends to the posterior aspect of the pelvic bones, as the anterior border of the lateral field extends to the posterior aspect of the pelvic bones as the posterior border. The daily prostate dose is 1.8 to 2.0 Gy, delivered five times per week with all fields treated at each session, to a total dose of 65 to 70 Gy in 7 to 8 weeks. When the pelvic nodes are treated, radiation is planned first to the entire pelvic field to a dose of 45 to 50 Gy in 5 weeks. The prostate PTV then is boosted to a dose of 20 Gy, raising the dose to the primary prostastic tumor to a total of 65 to 70 Gy. To improve the tolerance of treatment, a “sandwich” technique has been proposed in which the dose to the large pelvic field is split and the small boost field is delivered in between. This technique permits a rest period and a partial recovery of the bowel and bladder from the toxic effects of the initial pelvic field irradiation.

THREE-DIMENSIONAL CONFORMAL RADIATION THERAPY. Although 3D treatment-planning systems vary in detail, all are based on common principles. The simulation consists of a combination of conventional and CT-assisted procedures. Conventional simulators can be used to determine the positioning of the patient, to define a provisional isocenter, and to produce reference localization skin marks. CT images are used to segment the prostate and normal organs and to generate high-resolution 3D reconstructions. The CT data are also used in calculations of dose distribution, as modern dose calculation formalisms are based on electron density ratios of the anatomic structures included in the treatment fields. Several algorithms are in use for 3D dose calculations, but the more advanced methods, such as the pencil-beam convolution algorithm with pixel-by-pixel inhomogeneity corrections, are required for maximal accuracy.

Treatment plans typically consist of an isocentric four-field box, designed to include the prostate, seminal vesicles, and periprostatic tissues. The cross sections of the beams may be shaped with Cerrobend blocks to protect, surrounding normal tissues in the simulation permits. The daily PTV dose is 1.8 to 2.0 Gy, delivered five times per week with all fields treated at each session, to a total dose of 65 to 70 Gy in 7 to 8 weeks. When the pelvic nodes are treated, radiation is planned first to the entire pelvic field to a dose of 45 to 50 Gy in 5 weeks. The prostate PTV then is boosted to a dose of 20 Gy, raising the dose to the primary prostastic tumor to a total of 65 to 70 Gy. To improve the tolerance of treatment, a “sandwich” technique has been proposed in which the delivery to the large pelvic field is split and the small boost field is delivered in between. This technique permits a rest period and a partial recovery of the bowel and bladder from the toxic effects of the initial pelvic field irradiation.

TREATMENT PLANNING. Although 3D treatment-planning systems vary in detail, all are based on common principles. The simulation consists of a combination of conventional and CT-assisted procedures. Conventional simulators can be used to determine the positioning of the patient, to define a provisional isocenter, and to produce reference localization skin marks. CT images are used to segment the prostate and normal organs and to generate high-resolution 3D reconstructions. The CT data are also used in calculations of dose distribution, as modern dose calculation formalisms are based on electron density ratios of the anatomic structures included in the treatment fields. Several algorithms are in use for 3D dose calculations, but the more advanced methods, such as the pencil-beam convolution algorithm with pixel-by-pixel inhomogeneity corrections, are required for maximal accuracy.

Treatment is planned in the supine or prone position. Within individually fabricated immobilization casts to ensure reproducible positioning during repeated treatment sessions. Because prostastic displacement during a course of radiation therapy was shown to be affected by a rectal and bladder volumes, some studies have recommended that the simulation and each treatment session be carried out with the patient’s bladder and rectum emptied, to reduce daily variations in prostate location and geometry. The tumor target and the critical normal structures are segmented on every CT slice where they appear. The PTV extends from 1.0 cm caudal to the external anal sphincter to the superior aspect of the pelvic inlet, and the PTV is positioned 2.0 cm inferior to the superior aspect of the pelvic inlet, but the superior and inferior corners are trimmed to protect as much bone marrow as possible. The anterior border of the lateral field extends to the posterior aspect of the pelvic bones, as the anterior border of the lateral field extends to the posterior aspect of the pelvic bones as the posterior border. The daily prostate dose is 1.8 to 2.0 Gy, delivered five times per week with all fields treated at each session, to a total dose of 65 to 70 Gy in 7 to 8 weeks. When the pelvic nodes are treated, radiation is planned first to the entire pelvic field to a dose of 45 to 50 Gy in 5 weeks. The prostate PTV then is boosted to a dose of 20 Gy, raising the dose to the primary prostastic tumor to a total of 65 to 70 Gy. To improve the tolerance of treatment, a “sandwich” technique has been proposed in which the delivery to the large pelvic field is split and the small boost field is delivered in between. This technique permits a rest period and a partial recovery of the bowel and bladder from the toxic effects of the initial pelvic field irradiation.

FIGURE 34.4-13. Simulation radiographs of a case planned for treatment with four-field conventional technique. A: Anteroposterior localization film of the prostate planning target volume (PTV) and the planned rectangular treatment field. Contrast material (Hypaque) has been placed in the urinary bladder and the rectum, and the balloons of the Foley catheters placed in the bladder and rectum. The setup point (SP) is marked on the patient’s skin. The center point for the treatment field is designated (R). B: Lateral localization of the prostastic PTV and the prostastic field (Q) and (B). Pelvic fields designed in this patient to treat the pelvic lymph nodes effectively. (From ref. 464, with permission.)

The planned treatment consists of one pair of lateral and two pairs of oblique fields. The dose distribution is shown on (A) axial, (B) sagittal, and (G) coronal.
compared tomography reconstructions of the prostate and surrounding normal tissue at the mid-plan of planning target volume (PTV). The boundaries of the PTV are shown in yellow dots. The red region represents the prescription isodose distribution, and the yellow region corresponds to approximately 70% to 80%, green to 45% to 70%, and blue to 45% or less of the prescription dose.

**INTENSITY-MODULATED RADIATION THERAPY.** For details of simulation and treatment planning using intensity-modulated radiation therapy (IMRT), see Chapter 29.4.

**Tolerance of Treatment and Late Complications**

Doses of 70 Gy or less, when delivered with conventional (two-dimensional) external-beam irradiation, are fairly well tolerated. However, grade 2 [RTOG/European Organization for Research and Treatment of Cancer (EORTC) scoring scheme; Table 34.4-15] or higher acute rectal morbidity or urinary symptoms requiring medication (or both) occur in approximately 60% of patients. Symptoms typically appear during the third week of treatment and resolve within days to weeks after its completion. Acute gastrointestinal symptoms, especially those associated with whole pelvis irradiation, are most commonly relieved with diet manipulations. Otherwise, medications such as diphenoxylate hydrochloride (Lomotil®) are appropriate to relieve symptoms. Internal and external hemorrhoids may become inflamed during a course of 3 weeks. These symptoms are best treated with sitz baths and corticosteroids. Acute urinary symptoms are treated with phenazopyridine hydrochloride (Pyridium), nonsteroidal antiinflammatory agents, or α-adrenergic blockers such as terazosin. Zielensky et al. recently reported that α-adrenergic blockers were significantly more effective than nonsteroidal antiinflammatory agents, resulting in significant resolution of urinary symptoms in 66% and moderate improvement in 22%; in only 12% was minimal relief to no improvement observed. In contrast, among patients treated with ibuprofen, only 16% experienced significant symptom relief, 26% exhibited moderate improvement, and 58% demonstrated minimal to no response.

Late complications develop within 3 to 6 months after completion of radiation therapy. Zielensky et al. reported that the median time to onset of grade 2 or worse late rectal toxicity was 12 months, with a range of 3 to 18 months. Similarly, Teshima et al. from the Fox Chase Cancer Center reported median times to occurrence of grade 2 and 3 rectal toxicities at 13 and 18 months, respectively. The incidence of late complications in patients receiving conventional radiation therapy doses of 70 Gy is low. An analysis of 1020 patients treated in two large RTOG trials demonstrated an incidence of chronic urinary sequelae (i.e., cystitis, hematuria, urethral stricture, or bladder contracture) requiring hospitalization in 7.3% of cases, but the incidence of urinary complications requiring major surgical interventions was only 0.5%. More than one-half of chronic urinary complications were urethral strictures, occurring mostly in patients who had undergone a previous transurethral radical prostatectomy. The incidence of chronic intestinal sequelae (chronic diarrhea, proctitis, rectal or anal stricture, rectal bleeding, or ulcer) requiring hospitalization for diagnosis and minor intervention was 3.3%, with only 0.6% of patients experiencing bowel obstruction or perforation. Fatal complications were extremely uncommon (0.2%).

The risk of late complications increases when radiation doses exceed 70 Gy. Leibel et al. reported 6.9% grade 3 to 4 complications in 174 prostate cancer patients treated with doses exceeding 70 Gy, as compared with 3.5% after treatment with less than 70 Gy. Sandler et al. reported that the actuarial incidence of grade 3 to 4 rectal toxicity for patients who received doses in excess of 68 Gy was 9% at 3 years, as compared to 2% for those who received lower doses. Schulteis et al. reported late toxicity in 712 patients treated with conventional or conformal radiation techniques. The risk of late toxicity strongly correlated with the central axis dose. The 5-year incidence of grade 2 or 3 late rectal toxicity was 27%, 35%, 43% for central axis doses of 71 to 74 Gy, 74 to 77 Gy, and 77 Gy or more, respectively, (P < .001).

Rectal complications have also been correlated with the volume of anterior rectal wall receiving a given dose (the so-called volume effect). Benk et al., from the Massachusetts General Hospital, reported dose-volume patterns and their relationship with rectal bleeding in patients treated with 50.4 Gy whole pelvis photon-beam radiation therapy followed by 25.2 cobalt-gray equivalents (CGE) delivered via a 160-MeV perineal proton beam boost. A logistic regression analysis revealed ten dose-volume combinations that were more likely associated with late rectal bleeding, ranging from 60 CGE delivered to 70% of the anterior rectal wall to 75 CGE involving 30% of the rectal wall. When portions of the anterior rectal wall were exposed to 75 CGE, the actuarial incidence of bleeding at 40 months was 61% when 40% or more of the wall received this dose, as compared with 19% when less than 40% of the wall was exposed (P = .0036). Lee et al. reported that among patients receiving PTV doses of less than 76 Gy, the use of a rectal block significantly reduced the incidence of grade 2 to 3 rectal toxicity, from 22% without a block to 7% with a block (P = .003). These data indicated the need to spare the rectal wall maximally when protocols of high-dose therapy are implemented, to improve the local outcome in prostate cancer.

**TABLE 34.4-15. Radiation Therapy Oncology Group–European Organization for Research and Treatment of Cancer Scoring Scheme for Acute and Late Rectal and Bladder Morbidity**

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3-D CRT has been developed, in part, to address this issue. The ability of the 3-D approach to reduce rectal and bladder toxicities has been demonstrated in several studies. The Fox Chase Cancer Center reported acute grade 2 gastrointestinal or genitourinary morbidity with 3-D CRT in 84 of 247 patients (34%), as compared with 93 of 162 patients (57%) treated with conventional radiation therapy techniques (P < .001). Dearnaley et al. randomized patients to receive a dose of 64 Gy with conformal or conventional techniques. The late grade 2 rectal toxicity was 5% for 3-D CRT patients, as compared with 15% for the conventional plan (P = .01). Leibel et al. have recently updated the MSKCC series of 1100 patients treated with 3-D CRT. In consecutive groups of patients, the tumor dose was gradually increased from 64.8 Gy to 86.4 Gy by increments of 5.4 Gy. The rate of grade 3 rectal bleeding requiring one or more transfusions or one or more laser coagulation procedures was 1%, and the rate of grade 3 urethral stricture was 1%. All strictures occurred in patients who previously underwent transurethral prostate resections. The 5-year actuarial risk of grade 2 rectal bleeding for patients receiving 64.8 to 70.2 Gy was 6%, as compared to 17% for those treated with 75.6 to 81 Gy (P < .001).

The rating of grade 2 rectal bleeding with increasing 3-D CRT dose indicated that dose escalation would require improved 3-D CRT techniques to decrease the volume of exposed rectal wall and decrease the risk of rectal toxicity. IMRT provides this option. A recent study from MSKCC compared 20 patients in whom concomitant 3-D CRT and IMRT were planned. Only 9% ± 3% of the rectal wall would have received 75 Gy with the IMRT plan, as compared with 14% ± 3% with a routine six-field 3-D CRT plan (P < .01). There was also a significant improvement of the percentage PTV receiving the prescription dose (81 Gy) with IMRT. These data indicated that IMRT significantly improves the conformity of the radiation treatment in prostate cancer. To validate the expected decrease in toxicity, the incidence of rectal bleeding was recorded in 61 patients treated to 81 Gy with routine six-field 3-D CRT and was compared with the rates in 171 patients treated to the same dose with IMRT. Figure 34.4-15 shows that the 2-year actuarial risk of grade 2 to 3 rectal bleeding was 2% for IMRT and 10% for conventional 3-D CRT (P < .001). Only one patient in each treatment group developed grade 3 rectal bleeding.
Sexual function is preserved in 73% to 82% within the first 12 to 15 months after irradiation, but erectile potency diminishes with advancing time, with only 30% to 61% of patients maintaining their potency at 5 years or longer after irradiation. The etiology of erectile dysfunction after radiation therapy appears to be related to vascular disruption caused by treatment as opposed to radiation damage to the nerve bundles. Doppler blood flow studies of the corporal vasculature in patients with erectile dysfunction after radiation therapy suggested that arteriogenic rather than cavernosal or neurogenic dysfunction underlie this toxicity. Patients who develop impotence after radiation therapy can be effectively treated with intracavernosal prostaglandin injection therapy. Preliminary observations with sildenafil in these patients demonstrated a 74% response rate. Improved responses to the medication were noted among patients with normal erectile function prior to radiation therapy, as compared to those with declining pretreatment function.

Results of Treatment

Before the PSA era, the outcome of radiation therapy was assessed by DRE, radiography, and isotope scans. Although outcome assessment by this method is somewhat imprecise, especially with regards to local control, it nonetheless appeared that the long-term results of radiation therapy in T1 and T2 disease were similar to those observed with radical prostatectomy. Using a hazard function over successive 5-year intervals, Coleman et al. reported that with the exception of very small tumors, there was a similar constant risk of relapse for surgery and radiation therapy throughout a follow-up period of 20 years. Stage for stage, the survival outcome was similar for the surgical and radiation series. Hanks et al. reported a 14% 10-year cause-specific mortality in 104 lymphadenectomy-staged patients with stages T1b to T2N0 disease treated in the RTOG trial 77-06. Eighty-seven percent of the patients were clinically free of local recurrences, 79% were free of distant metastases, and 67% were free of any failure. The survival rate was nearly identical to the expected survival in a life table for an age-matched control population throughout the 10 years of observation (63% observed vs. 59% expected at 10 years). It has been frequently stated that although the results of radiation and radical surgery are comparable up to 10 years, at longer follow-up periods there may be a selective, rapid decrement in survival and disease-free survival for irradiated patients. Table 34.4-16 summarizes published long-term results with conventional external-beam irradiation, indicating outcome data for irradiated patients at 15 years that are similar to published data for radical prostatectomy.

With the introduction of PSA level as a surrogate for defining tumor control after definitive therapy, it became evident that more failures can be documented after definitive therapy than had previously been appreciated. For example, Zietman et al. reported clinical relapse-free survival of 65% at 10 years in 504 T1 or T2 patients, as compared with freedom from PSA relapse in 40% of patients. Other studies have confirmed that PSA relapse precedes evidence of anatomic relapse, frequently by more than 2 years. The study by Zietman et al. also reported that of the 60% of patients who exhibited a PSA relapse, local progression by 10 years was found in only 13%. These data suggest that most of the rise in PSA level originates from distant metastases. However, Zagars et al. reported that in 80% of PSA relapsing patients, the rise in PSA was associated with a local failure only. The latter study also reported that the rate of PSA relapse in stage T1 or T2a patients was 26% at 5 years, suggesting that radiation therapy cure may occur substantially less frequently than had previously been assumed.

This issue was addressed further by Kupelian et al., who reviewed 298 stage T1 or T2 patients treated with radical prostatectomy and 253 treated with radiation therapy. The 5-year PSA relapse-free survival rates for radiation versus surgery were 43% and 57%, respectively. Multivariate analysis of time to failure showed that pretreatment PSA level and biopsy Gleason scores were independent predictors of PSA relapse. Based on these parameters, a low-risk (pretreatment PSA of 10.0 ng/mL and Gleason score 6) and high-risk (PSA >10.0 ng/mL or Gleason score 7) were defined. For low-risk patients, the 5-year PSA relapse-free survival rates for radiation versus surgery were 81% and 80%, while for the high-risk group the rates were 26% versus 37%, respectively. Zagars et al. reported 94% 6-year PSA relapse-free survival in T1 or T2 patients with a PSA level of 4 ng/mL or less and a Gleason score of 2 to 6, 70% for patients with a PSA level of 4 ng/mL or less and a Gleason score of 7 to 10, or a PSA level of 4 to 10 ng/mL and a Gleason score of 2 to 7, and 60% for patients with a PSA level exceeding 4 and a Gleason score of 8 or more.

Sexual function is preserved in 73% to 82% within the first 12 to 15 months after irradiation, but erectile potency diminishes with advancing time, with only 30% to 61% of patients maintaining their potency at 5 years or longer after irradiation. The etiology of erectile dysfunction after radiation therapy appears to be related to vascular disruption caused by treatment as opposed to radiation damage to the nerve bundles. Doppler blood flow studies of the corporal vasculature in patients with erectile dysfunction after radiation therapy suggested that arteriogenic rather than cavernosal or neurogenic dysfunction underlie this toxicity. Patients who develop impotence after radiation therapy can be effectively treated with intracavernosal prostaglandin injection therapy. Preliminary observations with sildenafil in these patients demonstrated a 74% response rate. Improved responses to the medication were noted among patients with normal erectile function prior to radiation therapy, as compared to those with declining pretreatment function.

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Combined with the results of posttreatment biopsies obtained in patients followed for 2.5 years (see Fig. 34.4-12), these data suggest that at least 81 Gy may be required for a maximal probability of cure. The data also demonstrate that a significant proportion of patients with unfavorable prognostic indicators may still have disease that is confined to the prostate and therefore is potentially curable with radiation alone.

**FIGURE 34.4-16.** Risk of treatment failure after three-dimensional conformal radiation therapy. (Data from refs. 415, 442.)

Investigators from the Fox Chase Cancer Center338 have reported a direct relationship between radiation dose and 5-year PSA relapse-free survival in patients treated to doses ranging from 66 to 79 Gy. The study matched by stage and grade 357 patients treated with at least 74 Gy 3D-CRT and 357 patients treated with less than 74 Gy with either conventional or conformal techniques. The 5-year PSA relapse-free survival rates were 71% and 56% for the high- and low-dose groups, respectively (P < .003). There was also a dose effect on 5-year freedom from distant metastases (97% vs. 88%; P = .0004), cause-specific survival (99% vs. 94%; P = .007), and overall survival (88% vs. 79%; P = .01). Roach et al.339 reported an advantage for using higher doses of 3D-CRT in patients with poorly differentiated histologies. Among 50 patients with pretreatment PSA levels of less than 20 ng/mL, the PSA relapse-free survival at 3 years was 83% for patients treated with more than 71 Gy and 5% for those treated to lower doses (P = .003).

Zagars et al.332 also observed a dose effect on the outcome in a retrospective analysis of 94 patients with localized prostate cancer treated with high-dose 3D-CRT (74 to 78 Gy) and 844 patients treated with conventional-dose irradiation (60 to 70 Gy). For analysis, patients were divided into three groups reflecting low (<67 Gy), intermediate (67 to 77 Gy), and high (>77 Gy) treatment dose. The 3-year PSA relapse-free survival rates were 61%, 74%, and 96%, for the low, intermediate, and high-dose groups, respectively (P < .01). When patients were stratified by the pretreatment PSA level, clinical stage (T1 or T2 vs. T3 or T4), or Gleason score (6 vs. 7 to 10), statistically improved PSA outcome was observed in all subgroups except for those with pretreatment PSA levels of less than 4.0 ng/mL. To further prove the impact of dose on the outcome, these investigators randomized 304 patients to receive either 70 Gy using a four-field conformal technique or the same treatment plus a six-field conformal boost to a total dose of 78 Gy.340 The overall 4-year PSA relapse-free survival was 72% for the 70-Gy patients and 77% for the 78-Gy patients (P = .21). A significant difference was nonetheless observed in patients with a pretreatment PSA level exceeding 10 ng/mL (47% for the 70-Gy and 68% for the 78-Gy patients; P < .01), with the most striking effect observed in T1 and T2 patients in this subgroup (85% for the 70-Gy and 93% for the 78-Gy patients; P < .003). The difference in the PSA outcome for patients with a pretreatment PSA level of less than 10 ng/mL was not significant. Further follow-up will be required to assess the impact of dose on the latter group of patients.

**ANDROGEN ABLATION PLUS RADIATION THERAPY**

The discovery that both normal and tumor prostate cells are sensitive to androgen ablation has led to its use as either neoadjuvant or adjuvant treatment in combination with radiation therapy. The rationale for this neoadjuvant approach is to debulk large prostate glands prior to irradiation and thus possibly to sensitize the tumor to the lethal effect of radiation, while the adjuvant approach is designed to reduce residual individual disease, remove and control locally or remotely uncontrolled disease, or both. Several groups have demonstrated the effectiveness of neoadjuvant androgen deprivation in decreasing the size of the prostate prior to radiation therapy, thus improving the ability to deliver maximal radiation doses without exceeding normal tissue tolerance.337,341-343 For example, Zelefsky et al.342 demonstrated that 3 months of leuprolide acetate and flutamide (Eulexin) reduced the prostate PTV by a mean of 25% (range, 3% to 52%). Further, two posttreatment biopsy series demonstrated improved local control when androgen ablation therapy was used, suggesting either an additive effect or a sensitizing effect induced by androgen deprivation. Zelefsky et al.338 reported a 10% incidence of positive biopsies (3 of 31) in patients pretreated for 3 months with androgen deprivation, as compared with 46% (48 of 105) in those patients who received radiation therapy alone (P < .001). The relative distribution of the prognostic risk groups and the prescribed dose did not differ significantly between the two groups. Laverdiere et al.344 reported preliminary results of a randomized trial of stage T2 and T3 prostate cancer patients who underwent biopsy at 24 months after radiation therapy. Patients treated for 3 months with neoadjuvant androgen deprivation followed by 64 Gy of radiation therapy had a 28% incidence of tumor-positive biopsy specimens, as compared to a 65% incidence in those patients receiving radiation alone. However, androgen deprivation given for 3 months before and 6 months after 64-Gy radiation therapy was associated with only a 5% rate of positive biopsy specimens, consistent with an additive rather than a radiation-sensitizing effect.

The clinical value of the neoadjuvant approach was tested in RTOG trial 86-10.345 Patients with large T2, T3, and T4 prostate tumors were randomized to either receive 2 months of leuprolide and Eulexin before and during radiation therapy or without androgen ablation. The cumulative incidence of local progression at 5 years was 46% for patients undergoing androgen ablation and 71% for patients receiving radiation alone (P < .001). Progression-free survival rates, including the ability to maintain normal PSA levels, were 36% and 15%, respectively (P < .001). There was, however, no difference in survival. The use of neoadjuvant androgen ablation in patients with locally confined disease (stage T1 to T2a) and a good prognosis is currently being tested by RTOG trial 94-08. Patients are stratified by risk of treatment failure after three-dimensional conformal radiation therapy. (Data from refs. 415, 442.)

Use of the androgen ablation approach has been tested in two prospectively randomized studies. RTOG trial 85-31 involved 977 T3 or T4 patients treated with whole pelvic irradiation to 45 Gy plus a prostate boost to 20 to 25 Gy. Patients were randomized to receive adjuvant goserelin initiated during the last week of radiation and continued indefinitely until relapse or initiated on evidence of postirradiation relapse. Actuarial local relapse-free survival at 5 years was 84% for the adjuvant arm and 71% for the radiation-alone arm (P < .001). The corresponding rates for freedom from distant metastases and disease-free survival were 83% versus 70% (P < .001) and 80% versus 44% (P < .001). The actuarial 5-year PSA relapse-free survival was 53% for the adjuvant group versus 20% for the radiation-alone group (P < .0001). There was, however, no difference in the overall 5-year survival (75% vs. 71%; P = .52). In contrast, EORTC trial 22983 did show a survival advantage for patients who received adjuvant androgen ablation.346 In this study, 415 patients with locally advanced prostate cancer were randomly assigned to receive radiotherapy alone (50 Gy to the pelvis plus a 20-Gy prostatic boost) or radiotherapy plus goserelin initiated after radiation therapy and continued after irradiation until relapse. The actuarial 5-year disease-free survival (clinical) was 85% in the combined-treatment group and 48% for the radiation therapy group (P < .001). The local recurrence-free survival was 97% versus 77% (P < .001), PSA relapse-free survival was 81% versus 43% (P < .001), and metastasis-free survival was 98% versus 56% (P < .001), respectively. The overall survival at 5 years was 79% for the adjuvant group versus 62% for the radiation alone group (P = .001). The validity of the latter observation has been questioned, because the survival level for the radiation-alone group (62%) appears significantly lower than published rates in similar patients.347 Hence, while addition of androgen ablation to definitive radiation therapy has been associated with a highly significant improvement in local control and freedom from disease progression, its impact on survival remains an open question.

**INTERSTITIAL THERAPY**

The basic paradigm of interstitial brachytherapy is based on the principle that deposition of radiation energy in tissues decreases exponentially as a square function of the distance from the radiation source. Thus, while tumor tissue infiltrated with radioactive sources would receive maximal doses of radiation, there will be a rapid falloff of the dose in surrounding normal tissues. Over the years, a range of isotopes (e.g., $^{125}$I, $^{103}$Pd, $^{131}$I, $^{109}$Rh, $^{125}$I) have been tested, and the techniques have evolved from free-hand implantation to ultrasonography- and CT-guided template systems.348-351 Retropubic implantation of the prostate with $^{125}$I sources was the technique of choice until a decade ago.348 Long-term follow-up, however, indicated that local failure was significantly increased within nearly all stages as compared with external-beam–treated patients.352-355 The causes for local failure in these patients are not fully known, but difficulties in achieving a
Patients who undergo cryosurgery alone rarely require hospitalization, and the procedure usually is performed on a “come and go” basis. A urethral catheter is left in
and cancer, allows for even distribution of the cryoprobes, eliminates steep temperature gradients between the probes, reduces bulky extracapsular disease, and may
may be placed in any area of gross ECE.
are performed, certainly in the area of cancer. In addition, if the ice ball does not adequately extend to the apex of the prostate, the cryoprobes are pulled backward
placement of five or more cryoprobes. Generally, two probes are placed anteromedially, two posterolaterally, and one posteriorly. Liquid nitrogen is circulated through
sloughing of tissue postoperatively. This device circulates heated water. An ultrasound transducer is inserted into the rectum, and volume measurements are made of
The ice balls generated by current methods are elliptic in shape, with the maximal radius at the tip. The radius is directly proportional to the rate of flow of liquid
–40°C may be necessary to ensure complete freezing of the intracellular compartment. This fact has important clinical implications to the urologist performing
cooling rate during freezing and the lowest temperature achieved.
Freezing of the prostate is carried out using a multiprobe cryosurgical device. Two parameters that correlate with the likelihood of cell destruction are the
cooling rate during freezing and the lowest temperature achieved. Damage may occur due to chemical injury or intracellular ice formation. Cellular destruction
occurs as a result of freezing of the extracellular compartment and withdrawal of water from the cells occurring at ~15°C, intracellular ice formation occurring at ~20°C
to ~25°C. Cell death results in ice formation within the cell and eventual cell death. The minimal temperature required to freeze tissue to ~0°C is ~30°C, and at ~40°C
may be necessary to ensure complete freezing of the intracellular compartment. This fact has important clinical implications to the urologist performing
cryosurgery, as the hyperechogenic edge of the ice ball visualized is 0° to ~2°C, and temperatures as low as ~20° to ~40°C are inside this edge. Therefore, one must
extend the ice ball well beyond the edge of the prostate to ensure adequate tissue ablation. Rapid freezing allows for minimal loss of intracellular water and, therefore,
the maximal chance of intracellular ice formation. Passive warming, which occurs slowly (over 15 to 20 minutes) after the cryoprobes are allowed to thaw, results in
formation of larger ice crystals, a process called recrystallization, and this process further destroys tissues. After one episode of freezing, the cells are very vulnerable
to additional cycles, and a second freezing cycle will allow for destruction of surviving cells. The protective process may be facilitated by thrombosis of small vessels
and the resulting tissue anoxia.
The ice balls generated by current methods are elliptic in shape, with the maximal radius at the tip. The radius is directly proportional to the rate of flow of liquid
nitrogen. At high flow rates, the gradient from the outer edge—which, as mentioned, is at 0°C—to the zone at 20°C is narrow, approximately 2 mm. At low flow rates,
this gradient is widened. The ice ball is approximately 4 cm long. Therefore, it is frequently necessary to pull the cryoprobes back toward the apex of the prostate
at the initial freezing to the base, to ensure complete destruction of the gland.

Patients, after induction of regional or general anesthesia, are placed in the lithotomy position. A urethral warning device is placed to preserve the urethra and avoid
shriveled toxic injury. The device circulates cooled and heated water. An ice ball larger than 5 cm is required to freeze the prostate. Cell death results in ice formation
between ~20° and ~25°C. However, temperatures are measured at least 6°C above the prostate or cancers. Using a needle guide, an 18-gauge, hollow-core needle is inserted into the prostate under TRUS guidance. Once in position, a 0.038 J-tipped guidewire is advanced through the needle to the proximal extent of the prostate capsule. Cannulas and dilators are passed over the wires to facilitate placement of the radioactive seeds. Generally, 150 seeds are inserted into the prostate. Liquid nitrogen is circulated through these needles, and the resulting freezing zones,
or ice balls, can be monitored by ultrasonography. The anterior probes are activated first and allowed to extend posteriorly and laterally. Once these have reached the desired position, thawing is begun, and the posterior probes are activated. Most often, two freeze-thaw cycles are performed, certainly in the area of cancer. In addition, if the ice ball does not adequately extend to the apex of the prostate, the cryoprobes are pulled backward

Androgen deprivation before cryosurgery should be considered in patients with large glands or extensive local disease, as such therapy serves to shrink the prostate
and cancer, allows for even distribution of the cryoprobes, eliminates steep temperature gradients between the probes, reduces bulky extracapsular disease, and may
allow for widening of the periprostatic space and better protection of surrounding structures.

Patients who undergo cryosurgery alone rarely require hospitalization, and the procedure usually is performed on a “come and go” basis. A urethral catheter is left in
place for 3 weeks, as such a period of urethral catherization appears to be associated with a lower likelihood of postoperative tissue sloughing and urinary retention
as compared to use of a suprapubic tube alone or shorter periods of urethral catherization. Patients are followed with serial PSA measurements and assessment of
symptom scores. TRUS-guided biopsies of the prostate should be considered in most patients at 6 to 12 months after the procedure, certainly in those who fail to reach PSA nadirs of less than 0.4 ng/mL or in those whose serum PSA falls to a low level initially but rises later.

The efficacy of various forms of treatment for prostate cancer can be assessed by analyzing several end points. Commonly, patients who have been treated with cryotherapy report prostate biopsies repeated prostate biopsies repeat prostate biopsies at 6 to 12 months after the procedure. The positive biopsy rate after cryoablation ranged between 7.7% and 25%. These results must be analyzed cautiously as not all patients underwent biopsy, some patients received neoadjuvant androgen deprivation (which could have affected biopsy data), and false-negative biopsy results are not uncommon, certainly in those with limited disease before treatment. Not surprisingly, there is a relationship between clinical stage and the likelihood of a positive posttreatment biopsy after cryotherapy. The likelihood of a positive biopsy is approximately 9% for those with clinical stage T1 or T2 disease and at least 21% for those with clinical stage T3 disease. Interestingly, benign epithelium, often very focal, has been seen in up to 71% of patients after cryotherapy. The significance of benign epithelium is unknown, and such findings may represent areas of the prostate not frozen to low temperatures, perhaps, in the area of the urethral warmer.

It must be recognized that certain areas of the prostate or seminal vesicles are likely to be sites of treatment failure. It appears that recurrence is more common in cancers located at the apex (9.5%) and seminal vesicles (43.8%), in contrast to those located in the midgland (4.1%) and base (0%). Similarly, Bahn et al. noted that the apex and, to some extent, the seminal vesicles were more likely to harbor residual disease as compared to the rest of the prostate.

Serum PSA levels after definitive treatment such as radical prostatectomy or radiation therapy have been shown to be an important determinant of eventual outcome. What constitutes an acceptable PSA level after cryotherapy has not been well evaluated. Radiation or cryotherapy does not result in complete destruction of all prostate tissue. Detectable levels of PSA may be due to either malignant or benign epithelial elements. Therefore, a low but stable PSA after cryotherapy may not be associated with disease progression. A similar situation has been noted for patients who undergo radiation therapy. This issue was addressed recently at UCSF by Shinohara et al., who correlated the rates of biochemical and biopsy failure with the PSA nadir after cryosurgical treatment of prostate cancer in 132 patients who underwent cryosurgical ablation procedures. Follow-up included PSA testing at 3, 6, and 12 months and every 6 months thereafter. Biopsies were performed at 6 months, and biochemical failure was defined as a PSA nadir of at least 0.5 ng/mL or subsequent PSA elevation of at least 0.2 ng/mL. Biochemical and biopsy failures were correlated with PSA nadir values after cryosurgery (<0.1 ng/mL, 0.1 to 0.4 ng/mL, 0.5 to 1.5 ng/mL, and >1.5 ng/mL). Biochemical failure (subsequent rise in PSA of 0.2 ng/mL or more) was lowest in those who achieved PSA nadirs of less than 0.1 ng/mL (21%) but was common in those with higher nadir values. Biopsy failure was lowest in those with nadirs of less than 0.1 ng/mL (1.5%) and in those with nadirs of not more than 0.4 ng/mL (10%). In contrast, 55% of the patients with nadir values of 0.5 ng/mL or more had biopsy failure. Both biochemical and biopsy failure tended to occur within the first 12 months after treatment (i.e., 96% and 88% of the biochemical and biopsy failures, respectively). Based on this single study, a PSA nadir of not more than 0.4 ng/mL should be achieved after cryotherapy. Higher values are associated with a significant risk of continued PSA elevation and a high likelihood of residual disease detected on prostatic biopsy.

Greene et al. similarly showed that a serum PSA level in excess of 0.5 ng/mL was highly predictive of biopsy and biochemical failure after cryoablation. Long recently analyzed a very well-characterized series of 145 patients. The crude rates of maintaining either a negative biopsy or a serum PSA level of less than 0.3 ng/mL at 6 and 24 months after the procedure were 87% and 73%, respectively. However, the overall actuarial rate at 42 months of maintaining a serum PSA level of less than 0.3 ng/mL was 59%.

Koppie et al. recently reported intermediate-term results of cryotherapy in 176 patients who underwent 207 cryosurgical procedures for clinically localized (stages T1 through T4) prostate cancer using a multiprobe cryosurgical device. The patient population was composed of men who generally had intermediate- or high-risk disease (T3 or T4 disease in 61%). Actuarial biochemical recurrence-free survival rates at 1 year and 3 years after treatment for those patients undergoing primary cryosurgery (excluding repeat procedures and patients who failed previous radiation or radical prostatectomy) were 62% and 49%, respectively. PSA nadir (P = .001) and pretreatment serum PSA level (P = .008) were significantly associated with outcome after cryosurgery. Outcome correlated with pretreatment risk status. Actuarial biochemical recurrence-free survival 1 year after cryosurgery was 82% and 69% for low-risk patients and 58% and 45% for intermediate- to high-risk patients, respectively (P = .048). Neoadjuvant androgen deprivation was not shown to improve outcome significantly after cryosurgery. Prostate biopsy was performed after 167 procedures and proved to be positive in 64 (38%) such cases.

Impotence is the most common complication of cryotherapy, occurring in more than 80% of the men who are potent before cryotherapy and who undergo complete (bilateral) treatment of the prostate. Impotence results from damage to the neurovascular bundles during the freezing process. Clearly, some patients who are impotent just after the procedure will regain erectile function with time. However, this number appears to be limited, and most men who become impotent after the procedure require long-term treatment for this condition.

Sloughing of tissue occurs in approximately 3% to 10% of patients. The likelihood of either urinary retention due to necrotic tissue obstruction or stricture formation is related to the type of urethral warmer used. Sloughing of urethral tissue, urinary retention, incontinence, and stricture disease are much less common in those patients treated with effective, commercially available urethral warming devices. In addition, leaving the urethral catheter in place for a prolonged period rather than relying on suprapubic urinary drainage will further decrease the likelihood of this complication. Sosa et al., in a multicenter review, reported the following incidence of early complications: urinary retention for longer than 6 months, 6.8%; pain, 9.4%; fistula formation, 1.4%. Complications are much more common in those who undergo cryoablation for management of local disease recurrence after radiation therapy. In this patient population, urinary incontinence is common, occurring in 42% of patients, and is usually moderate to severe in nature. Resolution of incontinence will occur in approximately one-half of these patients within 1 year of treatment. Therefore, early and aggressive treatment of incontinence should be delayed until it is ascertained that resolution will not occur. Options for treatment of incontinence, should it persist, are limited. Collagen injection should be delayed 12 to 15 months after the procedure to allow for healing. Although complete resolution of incontinence is unlikely, significant improvement may be noted in some patients after collagen injection. The use of an artificial sphincter is an option, but additional endoscopic procedures may be necessary, and revision is likely in some patients.

MANAGEMENT OF LOCAL FAILURE AFTER SURGERY, RADIATION THERAPY, AND CRYOTHERAPY

A significant number of men who undergo standard local treatment for prostate cancer will experience biochemical recurrence, which may herald the development of clinical recurrence in some. A recent analysis of patients enrolled in a disease registry of prostate cancer patients demonstrated that 22% of patients who received initial treatment with radical prostatectomy, radiation therapy, or cryotherapy required a second form of prostate cancer treatment within 3 years of initial therapy. Similar results have been reported by others.

Serial PSA measurements provide the most reliable method of detecting recurrence, as tumor progression rarely occurs in the absence of PSA elevation. Distinguishing between local recurrence and distant failure is crucial to subsequent treatment decisions. Physical examination of the prostate or surgical bed by DRE is neither sensitive nor specific for the detection of local recurrence after any form of local therapy. PSA kinetics, in conjunction with pretreatment pathologic stage and grade, appear to be the best means of identifying patients at risk of local recurrence. PSA values at the time of initial treatment are most at risk for local recurrence, whereas those with seminal vesicle invasion, high-grade cancers (Gleason score >7), positive lymph nodes, or initial serum PSA levels exceeding 20 ng/mL are more likely to experience failure distantly. A PSA velocity of less than 0.75 ng/mL/y is observed in 94% of patients with local recurrence after radical prostatectomy. Conversely, more than 50% of men with metastatic disease had a PSA velocity greater than 0.75 ng/mL/y.

Patients with detectable or increasing PSA levels after surgery or other forms of treatment for prostate cancer, respectively, may be candidates for local imaging complemented by TRUS-guided biopsy. After surgery, anastomotic biopsy may be positive for local recurrence in 40% to 50% of patients with detectable levels of PSA. However, a recent series of 70 patients undergoing surgery for locally advanced disease demonstrated that the necessity of all pretreatment biopsies for TRUS-guided biopsy after either radiation or other forms of focal therapy such as cryotherapy are not clear. Most would agree that such biopsies should be considered in those patients treated with radiation therapy or cryotherapy who show serial elevations in serum PSA level after reaching a PSA nadir. Nadir levels of PSA usually return to normal within 8 to 18 months after 21-Gy brachytherapy and within 3 months after cryotherapy. Both endorectal MRI complemented by spectroscopy and monoclonal antibody imaging may complement the use of PSA kinetics to define the site of recurrence after local therapy. However, CT, MRI, and bone scans rarely are required in the early evaluation of asymptomatic patients with biochemical failure after radical prostatectomy, radiation therapy, and cryoablation (Fig. 34.4-17). In the absence of symptoms, the probability of a positive bone scan due to metastatic disease is less than 5% until the serum PSA level is 5 ng/mL or greater. Radionuclide bone scans used in the past to stage PSA-positive patients as a means to guide treatment are no longer recommended. When scans are performed, they add little prognostic information other than gained by analysis of posttreatment PSA.
Treatment options after radical prostatectomy include surveillance alone, systemic therapy, or radiation to the prostatic bed. In general, 30% to 65% of men who undergo therapeutic, or salvage, radiation therapy after radical prostatectomy will develop and maintain undetectable PSA levels (Table 34.4-17). Schild et al. reported an overall 50% disease-free survival at 3 years; however, 76% of those patients with a pre–radiation therapy PSA level of less than 1.0 ng/mL were disease-free, whereas only 18% of men with a PSA level greater than 1.0 ng/mL remained disease-free. Others have reported similar findings, suggesting that therapeutic radiation after surgery should be applied early. Patients most likely to benefit from salvage radiation after prostatectomy include those with low- to moderate-grade tumors with an undetectable postoperative PSA that rises after more than 1 year. The exact timing of radiation therapy has yet to be determined, although a pre–radiation therapy PSA cutoff of 2.0 ng/mL currently appears reasonable. Such therapy is usually well tolerated, although transient changes in bowel and bladder function may occur. In a study of 294 men who underwent radiation therapy after surgery, no significant long-term impact of postoperative radiation was seen on either urinary continence or erectile dysfunction. Although both brachytherapy and cryotherapy have been used to manage local recurrences after radical prostatectomy, the experience with these modalities is very limited.

Androgen deprivation is the most common form of secondary treatment (88%) after radiation therapy. Such therapy generally is considered palliative rather than curative. Curative forms of secondary treatment should be considered in properly selected patients. Salvage radical prostatectomy is one option. Cause-specific survival after this procedure ranges from 70% to 90% and 30% to 50% at 8 to 10 years, respectively. In a series from Tefill et al., all patients with organ-confined disease were disease-free at 34 months. Amling et al. reported a 10-year disease-free survival of 43% in 108 patients, similar to the results from Rogers et al. and Moul et al. DNA ploidy, preoperative serum PSA level, and Gleason score were significant predictors of outcome postoperatively. Those patients most likely to benefit from salvage surgery include those with favorable disease characteristics before radiation therapy and those with PSA kinetics after radiation therapy consistent with local rather than distant recurrence. Complications of salvage prostatectomy are more common than after primary prostatectomy. Urinary incontinence is seen in 20% to 60% of patients, bladder neck contracture occurs in approximately 20%, and impotence is virtually universal. Rectal injury occurs in fewer than 10% of patients and rarely necessitates fecal diversion. Contemporary series report better outcomes due to improved patient selection, earlier identification of failure, and improved surgical technique.

The largest series of patients treated with cryoablation for local recurrence after primary radiation therapy was reported by Greene and Pisters et al. from the M. D. Anderson Cancer Center. Negative sextant biopsies were noted in 77% of patients 6 months after cryoablation. However, only 45 of 150 patients (30%) had a persistently undetectable PSA level with a mean follow-up of 13.5 months. Incontinence was common, and up to 50% of such patients may require transurethral resection for urinary retention and obstructive voiding symptoms. Impotence occurred in at least 80% of men. An effective urethra warming device was determined to be essential to minimize tissue sloughing. Complications such as urethrectal fistula, abscess formation, and urethral stricture were rare. Additional radiation is an option also.

Grado et al. followed 49 patients treated with brachytherapy after biopsy-proven primary radiation therapy failure. Actuarial biochemical-free survival was 34% at 5 years and was associated with a post-salvage PSA nadir of less than 0.5 ng/mL. Local disease control was 98%; only a single patient demonstrated local, clinical failure. These results are encouraging, especially given the treatment population. The median age was 73.3 years, and 71% had locally advanced disease at initial presentation. Ninety percent of the cancers were moderately to poorly differentiated on prebrachytherapy biopsies. Complications were similar to those seen in patients undergoing primary brachytherapy.

For those patients whose cancers recur after cryotherapy, the choice of secondary treatment is not well defined. Repeat freezing has been reported, as has salvage prostatectomy. In the subset of patients at UCSF who underwent multiple cryotherapy procedures, 87% had no cancer on subsequent biopsies but only 33% achieved long-term, favorable PSA values. Radical prostatectomy is an option, but morbidity may be significant. Radiation treatment can be used after cryoablation and, unlike cryotherapy after radiation, salvage radiation therapy after cryoablation appears to be associated with minimal morbidity.

New forms of salvage therapy are being developed and refined. Both high-intensity focused ultrasonography and radiofrequency interstitial ablation are being studied and appear to have promise in local control of prostate cancer. These methods induce coagulative necrosis of tissue. In preliminary studies, primary high-intensity focused ultrasonography achieved short-term, local control in 60% to 80% of patients. Radiofrequency ablation was able to produce predictable lesions in prostate prior to radical prostatectomy. The long-term efficacy and morbidity of these new forms of focal therapy require further study.

Finally, many patients in whom local therapy fails, as evidenced by rising PSA levels, may not develop clinical evidence of disease. Therefore, observation alone is an option in low-risk, asymptomatic patients in whom primary therapy fails. In such patients, the morbidity and cost of secondary therapy must be carefully considered and compared to the risk of clinical progression of disease.

### Table 34.4-17. Probability of an Undetectable Prostate-Specific Antigen Level after Therapeutic Radiation for a Detectable Prostate-Specific Antigen Level after Prostatectomy

| Radiation Therapy | No. of Patients | Follow-up | Follow-up No. 1
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>External Beam RT</td>
<td>108</td>
<td>10 years</td>
<td>43%</td>
</tr>
<tr>
<td>Brachytherapy</td>
<td>150</td>
<td>8 years</td>
<td>30%</td>
</tr>
<tr>
<td>Cryoablation</td>
<td>49</td>
<td>6 months</td>
<td>77%</td>
</tr>
</tbody>
</table>

### Algorithm for evaluation of those with biochemical failure after radical prostatectomy (RP), radiation therapy (RT), or cryotherapy for presumed localized prostate cancer. PSA, prostate-specific antigen.
TREATMENT SELECTION FOR ADVANCED DISEASE: METASTATIC AND LOCAL REGIONAL DISEASE

The spectrum of advanced prostate cancer has changed considerably over the last 10 years since the introduction and widespread use of PSA screening. Prostate cancer is diagnosed in fewer patients at a time when their disease is overtly metastatic. Most cancers are detected earlier, frequently at an asymptomatic stage. Nonetheless, a large number of patients still die of prostate cancer despite earlier detection, which reflects the existence of occult metastatic disease. A redefinition of advanced disease in the current era would seem appropriate, given these changes. Advanced disease might include patients who, at time of diagnosis, have poor-risk features but no overt metastases. One might include two other subsets of patients as having advanced disease: patients who demonstrate progression of prostate cancer (or prostate cancer therapy or androgen deprivation therapy) by a rise in the serum PSA level or by imaging evidence of bone metastases, the presence of appendicular bone disease in addition to axial bone disease, and higher serum alkaline phosphatase levels. Serum PSA levels are not consistently a predictor of response duration or survival. This apparent paradox may reflect the high variability in PSA production between tumors at the cellular level. In addition, the fact that less well differentiated tumors produce less PSA may muck a direct relationship. As a posttreatment dynamic factor, some studies indicate a large number of patients who have PSA levels at the time of diagnosis. Prostate cancer cell mass, presumably through induction of cell death pathways. It is likely that the remission sustained by the vast majority of patients reflects a composite of all of these phenomena, although conceivably one or another mechanism may dominate in any one individual.

The majority of circulating androgen is produced by the testicles in the form of testosterone, and the remainder is produced by the adrenal glands, which synthesize the so-called adrenal androgens. These adrenal androgens may contribute to 40% of the androgen detected within the prostate.

Androgen deprivation remains the mainstay of therapy for patients with advanced prostate cancer. Because androgen may play a role as both a survival factor and a growth factor for prostatic carcinoma cells, interference with the androgen-signaling pathway will generate clinically meaningful remissions in the majority of patients. These remissions are manifest by a reduction in symptoms related to disease, if they exist, and a reduction in the serum PSA level. A decline in serum PSA level reflects, in part, a decrease in the cellular production of PSA, as the PSA gene promoter is, in part, androgen-regulated. Thus, withdrawal of androgen will reduce the production of PSA. These factors should be considered in the context of management of patients with rising serum PSA levels after local therapy. It is likely that the remission sustained by the vast majority of patients reflects a composite of all of these phenomena, although conceivably one or another mechanism may dominate in any one individual.

Although these three studies suggest that early androgen deprivation therapy may confer a survival advantage over delayed therapy, these studies do not define the optimal timing of androgen deprivation therapy for patients in the modern era. Little justification can be made for withholding androgen deprivation therapy when radiographic evidence of metastatic disease is present. However, for patients earlier in their disease course (i.e., patients who have undergone definitive local therapy but who are at high risk of relapse or patients with rising serum PSA levels after local therapy), the appropriate timing of treatment remains to be defined. Given the heterogeneity in the biologic behavior of tumors in the patient population with rising serum PSA levels after local therapy, several factors should be considered during decision making regarding the treatment. These factors include those that predict the probability of androgen receptor expression, the presence of PSA lint, tumor grade, and the time since local therapy was implemented. In addition, patient factors that potentially affect quality of life should be taken into account. These include patient anxiety, on the one hand, and the short-term and long-term impact of androgen deprivation, on the other.

Timing of Androgen Deprivation Therapy

Although it is assumed that androgen deprivation therapy is life-prolonging, this has never been formally proven. Nonetheless, it is likely that androgen deprivation therapy delays the onset of radiographic progression or symptoms in an otherwise asymptomatic man, presumably by reducing the overall tumor cell mass. Whether the earlier initiation of androgen deprivation therapy increases survival duration has long been debated. In theory, it seems reasonable that the earlier the initiation of androgen deprivation therapy, the better the outcome. A decline in serum PSA level reflects, in part, a decrease in the cellular production of PSA, as the PSA gene promoter is, in part, androgen-regulated. Thus, withdrawal of androgen will reduce the production of PSA. These factors should be considered in the context of management of patients with rising serum PSA levels after local therapy. It is likely that the remission sustained by the vast majority of patients reflects a composite of all of these phenomena, although conceivably one or another mechanism may dominate in any one individual.

The third study that supports earlier intervention is a study by Messing et al., in which 98 men who had undergone a radical prostatectomy and were found to have histopathologically documented metastatic disease to lymph nodes were randomized to receive either early androgen deprivation therapy (LHRH analogue or orchectomy plus an antiandrogen) or deferred therapy. A dramatic and statistically significant difference in survival duration in favor of the early androgen deprivation therapy arm was found. After a median of 7.1 years, 7 of 47 men in the immediate therapy arm, as compared to 18 of 51 men in the delayed therapy arm, had died (P = .02). Three men died of prostate cancer in the immediate therapy arm, as compared to 16 men in the delayed therapy arm (P < .01). At the time of the last follow-up, 36 men in the immediate treatment arm versus 9 in the delayed treatment arm were alive without evidence of detectable serum PSA or clinical evidence of disease (P < .001).

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Prognostic Factors

Most of the studies that have analyzed predictive and prognostic factors of response and survival in patients undergoing androgen deprivation therapy have done so in patients with radiographic evidence of metastatic disease (M+). In such studies, factors that reflect more extensive disease are associated with a poorer prognosis. However, the absence of symptoms is a poor predictor of survival. Two such factors are presence or absence of symptoms. More quantitative parameters include the number of bone metastases, the presence of appendicular bone disease in addition to axial bone disease, and higher serum alkaline phosphatase levels. Serum PSA levels are not consistently a predictor of response duration or survival. This apparent paradox may reflect the high variability in PSA production between tumors at the cellular level. In addition, the fact that less well differentiated tumors produce less PSA may muck a direct relationship. As a posttreatment dynamic factor, some studies indicate a large number of patients who have PSA levels at the time of diagnosis. Prostate cancer cell mass, presumably through induction of cell death pathways. It is likely that the remission sustained by the vast majority of patients reflects a composite of all of these phenomena, although conceivably one or another mechanism may dominate in any one individual.
normalized (PSA <4) more frequently in men receiving the combination treatment, no difference in survival between the two arms was seen. Patients with visceral metastases and patients with lower serum testosterone levels prior to treatment appear to have a poorer outcome. To date, no molecular markers that predict response and response duration to androgen deprivation therapy have been identified.

**Monotherapy**

**ORCHIECTOMY.** Surgical castration (orchiectomy) remains the standard for patients who will require permanent androgen deprivation therapy. It has the advantages of convenience and cost (as compared to other modalities) and abrogates compliance issues. In addition, clinical response is rapid after the procedure is performed. In patients with symptomatic metastatic disease, significant improvement in symptoms can be achieved within 24 to 48 hours after orchiectomy. Many patients will choose alternative treatments because of the psychological impact of surgical castration or the desire to be treated with androgen deprivation in an intermittent fashion.

**LUTEINIZING HORMONE–RELEASING HORMONE ANALOGUES.** Peptide analogues of LHRH, which possess partial agonistic or antagonistic affects, have been used extensively in the treatment of prostate cancer. The commercially approved agents goserelin and leuprolide are partial agonists. These agents will initially cause a transient increase in luteinizing hormone (LH) and follicle-stimulating hormone production, followed by a decline. Consequently, serum testosterone levels decrease within weeks of initial administration. In patients with radiographic evidence of metastases, there is concern that this “flare” in serum LH and testosterone levels within the first few weeks of therapy is inappropriately high. These agents are generally used in combination with an antiandrogen such as flutamide, nilutamide, or bicalutamide, which blocks lipid binding to the androgen receptor. In one trial, flutamide was shown to abrogate the clinical effects of the serum LH and testosterone flare.

The LHRH analogues are as effective as other modalities in the treatment of patients with advanced prostate cancer. Randomized studies have demonstrated the equal efficacy of LHRH analogues to orchiectomy and to diethylstilbestrol (DES). Depot formulations have been developed that permit monthly or, alternatively, every-3- and -4-month administration. Depot formulations allowing yearly dosing will soon become available. Pure LHRH antagonists have been developed and are currently in clinical trials. Their niche may be in the treatment of patients with symptomatic metastatic disease who are initiating androgen ablative therapy. Because an LH flare should not occur with these agents, their use may obviate the need for concomitant use of an antiandrogen.

**ESTROGENS.** Estrogens such as DES inhibit LHRH production by the hypothalamus and LH production by the pituitary and, thus, reduce serum levels of testosterone. Whereas the role of estrogen in suppressing testosterone as a result of estrogen deprivation is well established, the role of estrogen in suppressing testosterone as a result of other independent mechanisms remains unknown. The presence of estrogen receptors in prostate epithelium suggests that there may be a direct effect. Estrogen therapy was the first exogenous therapy for prostate cancer. In the first Veterans Administration Cooperative Urological Research Group study (VACURG I), patients were randomized to one of four arms: DES, 5 mg alone; orchiectomy alone; DES, 5 mg plus orchietomy; or DES, 5 mg, plus placebo. Although the overall survival of patients randomized to DES was inferior to orchietomy randomized to a subsequent cancer control group, the cancer-specific mortality was lower in the DES-treated group. In this study, the possible therapeutic benefit of DES, 5 mg/d, was offset by an increase in cardiovascular mortality. In VACURG II, patients were randomized to different doses of DES (0.2 mg, 1 mg, and 5 mg) or placebo. The survival of men treated with 1 mg and 5 mg was equivalent, but there was greater toxicity with 5 mg. In another study, men were randomized to leuprolide, 1 mg/d, or to DES, 3 mg/d. Equal efficacy was seen, although the cardiovascular complication rate was higher with DES, 3 mg/d, as compared to leuprolide. Although DES, 1 mg/d, appears to be effective in patients with advanced disease, a significant proportion of men do not achieve castration levels of serum testosterone. In practice, estrogens are used infrequently because of their side effects and their lack of availability, although there is a resurgence of interest in agents that target the estrogen receptor.

**ANTIANDROGENS.** The antiandrogens are competitive inhibitors of testosterone at the androgen receptor. Two classes of antiandrogen are in clinical use, the first of which is the steroidal antiandrogens, which include cyproterone acetate (Androcur) and megestrol acetate (Megace). The second group is nonsteroidal antiandrogens, which include flutamide (Eulexin), bicalutamide (Casodex), and nilutamide (Anandron). The steroidal antiandrogens have broader activity than their nonsteroidal counterparts. In addition to their effect on the androgen receptor, they possess progestational and glucocorticoid activity. The steroidal antiandrogens suppress testosterone through their feedback effects at the pituitary and hypothalamus. As monotherapy, neither cyproterone acetate nor megestrol acetate is capable of suppressing serum androgen levels completely or indefinitely and, as a result, these agents rarely are used as monotherapy.

In contrast, nonsteroidal antiandrogens act principally through the androgen receptor. Through these agents’ stimulation of the hypothalamus, serum testosterone levels may increase or remain unchanged as compared to pretherapy levels. The nonsteroidal antiandrogens have been used in three clinical settings: first, as part of combined androgen blockade (in conjunction with surgical or chemical castration); second, as salvage monotherapy in patients who were previously treated with androgen deprivation therapy; and third, as initial therapy without surgical or chemical castration. When used in this last setting, they have the potential advantage of allowing potency to be maintained as serum levels of testosterone are maintained. Small clinical trials have been conducted that demonstrated both their efficacy (as determined by their ability to lower serum PSA levels) as sole agents and in combination with 5α-reductase inhibitors (which inhibit conversion of testosterone to the more potent form, DHT) and their ability to preserve potency in a proportion of men. However, in two randomized studies, nonsteroidal antiandrogens were found not to be as effective as castration. In one study of 92 patients with M+ prostate cancer, flutamide (250 mg i.d.) was compared to DES (1 mg i.d.). A significant difference in survival was observed in favor of DES. Median survival was 43.2 and 26.5 months, respectively (P = .04). In another study, orchietomy was compared to 50 mg/d of bicalutamide. In this study, survival duration was superior with orchietomy. It should be noted that, in retrospect, this dose of bicalutamide was suboptimal. Another study in which patients were randomized to goserelin plus fluoxymesterone or to bicalutamide, 150 mg/d, was conducted. Progression-free and overall survival were equivalent in both arms. In two other studies that were combined for publication, bicalutamide, 150 mg/d, was equivalent to orchietomy or goserelin for M0 patients but proved inferior for M+ patients. Antiestrogens should therefore not be used as monotherapy in patients with M+ disease. Their use as monotherapy in patients with earlier disease may be equivalent to castration; however, longer follow-up is needed.

**COMPARISON OF MONOTHERAPEUTIC AGENTS.** Numerous trials have compared the efficacy of the various monotherapy agents. The most comprehensive analysis of these studies was performed by the Technology Evaluation Center, an evidence-based practice center for the Agency of Health Care Policy and Research. The conclusions, based on a metaanalysis of ten trials that included 1908 patients, were that no difference in survival existed between patients treated with LHRH agonists or patients treated with orchietomy or DES and no difference in survival existed between patients treated with the different LHRH agonists.

**Combined Androgen Blockade**

The role of adrenal androgens in supporting prostate cancer cell growth is uncertain. The adrenal androgens are relatively weak as compared to testosterone. The adrenal androgens are capable of suppressing serum androgen levels completely or indefinitely and, as a result, these agents rarely are used as monotherapy. Their use as monotherapy or patients treated with orchiectomy or DES and no difference in survival existed between patients treated with the different LHRH agonists.

In the EORTC trial, 326 men were randomized to either goserelin or leuprolide, 1 mg/d SC, or to leuprolide plus flutamide, 250 mg PO i.d., or to leuprolide plus flutamide, 250 mg PO i.d. An improvement in median survival was again observed with CAB (34.4 months vs. 27.1 months, P = .02). In the other study, 457 men were randomized to orchietomy or to orchiectomy plus nilutamide. An improvement in survival was again observed (37.1 months vs. 29.8 months, P = .04) in favor of CAB.

Most randomized studies to date, however, have not shown an advantage of CAB, although some of these studies have been criticized for being too small, having inadequate follow-up, or for using steroidal antiandrogens. The largest study to date (INT-105) was a study of 1387 men with M+ prostate cancer in which orchietomy was compared to orchiectomy plus flutamide. Interestingly, although there was a difference in the frequency with which patients achieved a serum PSA level of less than 4.0 ng/mL (74% [95% CI, 69.4 to 78.2] vs. 61.5% [95% CI, 56.4 to 66.4]; P < .001), there was no difference in overall survival between the two groups.

A metaanalysis was performed by the Prostate Cancer Trialsists’ Collaborative Group, which sought to reconcile all the studies of CAB. Overall, no benefit was observed for CAB. Critics of this particular metaanalysis included the validity of combining studies in which steroidal and nonsteroidal antiandrogens were used and the inclusion of trials that used LHRH analogues but did not use short-term antiandrogen therapy to block the flare. In a second metaanalysis, which excluded studies published only as abstracts, those that did not present data on survival, and those that used short-term antiandrogens, a benefit was seen for CAB (RR 0.78;
In one caveat in drawing conclusions from these studies is that the majority of patients who were randomized were patients with M+ disease. Far fewer M0 patients were included. Thus, while it is reasonable to conclude that the benefits of CAB in patients with M+ prostate cancer is minimal, at best, for patients with earlier disease, it is less clear that CAB is not of any benefit for patients with M+ disease. In M+ patients, antiandrogens are of uncertain value when an orchietomy is performed. However, for patients with earlier forms of disease, given the paucity of relevant data, CAB is a reasonable option. Furthermore, it is important to note that the binding affinity of the currently used antiandrogens for the androgen receptor is relatively low. As more potent or specific antiandrogens are developed, these issues may need to be readdressed.

**PERIPHERAL ANDROGEN BLOCKADE.** The efficacy of antiandrogens as monotherapy may be less than that of chemical or surgical castration. Nonetheless, this therapy has the potential appeal of sparing sexual function and reducing other treatment-related side effects, including hot flashes. The strategy of combining an antiandrogen with a 5a-reductase inhibitor (which reduces the conversion of testosterone to DHT) has also been explored. In M+ patients, an antiandrogen (e.g., flutamide) added further antiandrogenic effect to that which already was achieved by an antiandrogen alone, as measured by a further reduction in serum PSA level after the achievement of a nadir with flutamide. Other studies have demonstrated PSA responses and the maintenance of potency in men treated with the combination. In one randomized phase II study, there was no difference in the percentage of decrease in serum PSA level when flutamide plus fluramide was compared with flutamide alone (although appealing, such studies should be regarded as experimental). Larger studies have not yet been completed, nor have phase III randomized studies yet been performed that compare this strategy to standard therapies, with survival as an end point.

**SECONDARY HORMONAL THERAPY.** The scientific basis for intermittent hormonal therapy is that hormonally dependent clones of prostate cancer cells may potentially prevent the growth of hormonally independent cells through the elaboration of growth inhibitory factors. Alternatively, the reintroduction of androgen after androgen withdrawal may result in the generation of differentiated tumor cells. It might be advantageous, therefore, to allow the reintroduction of androgen after androgen withdrawal to delay the emergence of an androgen-independent phenotype. This has been substantiated in some tumor models (Shionogi and LNCaP) but not others (Dunning). Practically speaking, this treatment involves continuing androgen ablation until adequate testosterone suppression is achieved and then maintaining suppression for some time. This is followed by the discontinuance of therapy and then readministration of therapy at an arbitrary point determined by serum PSA progression. A number of pilot studies testing the feasibility of this approach have been performed. In general, these studies have suggested that the quality of life of patients treated with this approach may be better and that patients can be maintained off of androgen deprivation therapy for significant periods. Although this wide appeal, it should be regarded as investigational. A large, randomized intergroup study is now under way comparing continuous hormonal therapy to intermittent hormonal therapy.

**SIDE EFFECTS OF THERAPY.** Although there is a growing appreciation of the breadth and significance of side effects of androgen ablation, comprehensive prospective studies are lacking and, therefore, the frequency of side effects is difficult to quantify. The most frequently described side effects of testosterone suppression are loss of libido, decreased sexual performance, and hot flashes. It appears that the majority of patients are so affected. More subtle, nonquantifiable effects include fatigue and mood changes. The fatigue that results is probably probabilistic. Decreases in serum testosterone level result in a reduction of muscle and red cell mass. In addition, psychological effects, which result in fatigue, may be operable. Other observable side effects are decreased body hair, peripheral edema, and gynecomastia. Peripherally edema appears to be more common with LHRH analogues, whereas gynecomastia is more frequent and more severely associated with estrogens, with antiandrogen monotherapy, or with combined antiandrogen and 5a-reductase inhibitor use. The observed incidence of cardiovascular events, including thromboembolic events, is relatively low with all agents and may be the anticipated rate in the generally elderly population having an underlying malignancy. The exception to this is estrogens, which reproducibly are associated with higher rates of thromboembolic and cardiovascular events. This effect may depend on dose and route of administration. Although the incidence of osteopenia and vitamin D deficiency in middle-aged and elderly men has been underappreciated, androgen ablatative therapy is likely associated with further bone loss, which may result in the greater potential for osteoporotic fractures. Whether bisphosphonates or other agents will prevent these side effects or whether selective androgen receptor modulators will decrease the degree of bone loss is under investigation.

**Recurrent Disease after Primary Androgen Ablative Therapy**

After androgen ablation, the serum PSA level almost always decreases and achieves a nadir value. This nadir is maintained for a variable period, reflecting (presumably) the inherent composition of the tumor with regard to sensitivity to androgen ablation and the growth kinetics of the remaining androgen-independent cell population. The earliest manifestation of relapse, in most circumstances, is a rise in serum PSA level. Although some patients will manifest a clinical relapse without a rise in their serum PSA level, this is unusual and may be more frequently associated with prostate cancers that exhibit neuroendocrine differentiation. It is important to note that although the serum PSA level in general correlates with tumor cell mass in all stages of disease, this relationship is altered after androgen deprivation therapy. Serum PSA levels generally are lower per tumor volume as compared to pretherapy levels. The velocity of serum PSA increase at the time of relapse after androgen therapy may or may not parallel the serum PSA velocity prior to androgen deprivation therapy, presumably reflecting the kinetics of the tumor in these two phases. In general, however, the prostate volume may increase before a clinical relapse. Two studies have compared the outcomes of patients in a retrospective fashion if primary androgen deprivation was maintained. In one study, discontinuation of androgen deprivation after failure was an independent predictor of survival, while it failed to be a factor in another study. It is current practice to maintain androgen deprivation (castrate levels of testosterone) even after primary androgen withdrawal stops working. Tumor progression after primary androgen ablation is poorly understood mechanistically and is largely based on clinical grounds. A small subset of patients who experience relapse actually have noncastrate levels of testosterone. Therefore, it is reasonable to check serum testosterone levels at this point and to recommend surgical castration if castrate levels have not been achieved. It had not been until the advent and use of PSA testing that there was some appreciation of the utility of secondary hormonal manipulations after primary androgen ablation therapy had failed. The implication of secondary therapy has not yet been studied in, general, for the sake of consistency, a 50% decline in serum PSA level in this setting has been considered a benchmark for response.

**Antiangiand Withdrawal Responses**

One of the most interesting observations made in the last decade was the recognition that the withdrawal of antiandrogen therapy (while maintaining testosterone suppression) may be associated with (PSA) and, in some cases, symptomatic and objective responses. Such responses were described initially in the context of withdrawal of flutamide and nilutamide. Withdrawal responses occur in approximately 25% of patients (range, 15% to 50%). The likelihood of response may correlate with the duration of exposure to the antiandrogen. Other factors such as the type of initial therapy used, whether the antiandrogen was used as part of CAB or was added at the time of disease progression, and other clinical variables have not proven to be predictive of an antiandrogen withdrawal response. Antiangiand responses generally are observed within a few weeks after withdrawal of the antiandrogen. Responses that occur after withdrawal of bicalutamide may occur later (i.e., up to 8 weeks), perhaps because of this agent's longer serum half-life. The typical duration of antiandrogen withdrawal response is 3 to 4 months, although withdrawal responses may last several years. The mechanism of antiandrogen withdrawal has not yet been defined; however, it is likely that at least one mechanism is the emergence of prostate cancer cells with mutated androgen receptors that respond to an antiandrogen as an agonist rather than an antagonist. In fact, when studies have been performed looking for mutated androgen receptors, they are almost exclusively detected in the context of treatment with CAB. Because of the potential benefit of discontinuance of the antiandrogen and the fact that this maneuver is nontoxic and usually is required for enrollment into most clinical trials, it is very reasonable to initiate antiandrogen withdrawal as the first
approach for patients whose disease is progressing while they are being treated with antiandrogen therapy. Whether subsequent reintroduction of the same antiandrogen is useful has not been studied.

As mentioned, secondary hormonal maneuvers will elicit responses in patients whose tumors are progressing while they are on primary androgen ablative therapy. The only proven treatment to improve survival and delay disease progression is hormone withdrawal. Further reduction in testosterone levels to castration levels results in a longer time to disease progression in those patients who have not achieved a complete reduction of testosterone, (2) blockade of the effect of residual serum androgens through binding of the antiandrogen receptor, (3) reduction in adrenal androgen production, and (4) binding of agents to other nuclear receptors, such as the estrogen receptor, in the prostate cancer cell.

**Antiandrogens**

Although the nonsteroidal antiandrogens bind the androgen receptor, it is interesting that non–cross-resistance exists between these agents. Scher et al. treated 51 patients who had tumor progression after primary androgen ablative therapy with bicalutamide (200 mg/d). Twelve (24%) patients responded. More frequent responses (in 10 of 26 patients, or 38%) were seen in patients previously treated with flutamide. In another study, Joyce et al. treated 31 patients with bicalutamide, 150 mg/d. Seven patients responded, six of whom had received prior flutamide. Interestingly, the two most impressive responses were those patients who had experienced a flutamide withdrawal response. Responses to nilutamide after flutamide have also been noted. However, no reports of flutamide activity after bicalutamide treatment have been published.

**Adrenal Androgen Inhibitors**

The rationale behind using adrenal androgen inhibitors is that approximately 5% to 10% of circulating androgen is derived from the adrenal gland and that a higher proportion of androgen within prostate cancer cells may be of adrenal origin. The two most commonly used agents in this setting are aminoglutethimide and ketoconazole, both of which have frequently been used in conjunction with corticosteroids. Therefore, it is difficult to ascertain the true activity of aminoglutethimide and ketoconazole as single agents, as corticosteroids have activity in this disease. Ketoconazole, which inhibits cytochrome P-450 and suppresses both testicular and adrenal androgen production, has significant activity. In one study of men treated with ketoconazole (1200 mg/d) plus hydrocortisone, 30 of 48 patients experienced a decline in serum PSA of greater than 50%. The median duration of response was 3.5 months. Ketoconazole is active at lower doses (i.e., 200 mg t.i.d.) and less toxic, though the comparative efficacy of lower versus higher doses has not been studied. The need to combine ketoconazole with a corticosteroid particularly at the lower dose is uncertain. Because ketoconazole requires an acidic stomach pH for optimal absorption, patients are instructed not to take antacids, 

**Glucocorticoids**

Glucocorticoids also have significant activity in prostate cancer. Kelly et al. treated 30 men with hormone-refractory prostate cancer with hydrocortisone, 40 mg/d, and observed a response rate of 20%. Tannock et al. compared prednisone, 10 mg/d, to prednisone plus mitoxantrone. Twenty-two percent of patients treated with glucocorticoids alone responded. This was also seen in a CALGB study comparing hydrocortisone, 40 mg/d, to hydrocortisone plus mitoxantrone. Twenty-two percent of patients responded (PSA decline) to hydrocortisone alone. In another study, 16% of 230 patients receiving hydrocortisone responded, as assessed by declines in serum PSA level.

Megestrol acetate has very modest activity in prostate cancer. Dawson et al. found that, in a randomized study of 160 mg versus 640 mg of megestrol acetate, 12% of patients responded (PSA decline). Because megestrol acetate, which is more commonly used to treat anorexia or hot flashes, may cause a clinical flare in disease, patients in whom this agent is used should be monitored closely.

**Estrogens**

DES has activity as secondary therapy in patients with hormone-refractory prostate cancer. In one study, 9 of 21 (43%) patients responded by PSA criteria. Interestingly, PC-SPES, a nutritional supplement consisting of eight different herbs, clearly has activity in prostate cancer. DiPaola et al. demonstrated that this concoction had estrogenic activity in vitro and serum PSA-lowering activity in men with prostate cancer. It was associated with estrogen-like side effects, including gynecomastia. Interestingly, however, Kameda et al. treated with PC-SPES 34 patients with androgen-independent prostate cancer; all patients had rising PSA levels. Eight of 24 patients achieved a decline in PSA after PC-SPES was introduced. In one study of men treated with ketoconazole plus hydrocortisone, patients who achieved a greater than 50% decline in PSA level survived longer than those who did not. A 75% decrease in PSA level was not associated with better survival than was a 50% decline. In this study, minor (<50%) declines in PSA level were not associated with altered survival.

These studies formed the foundation for the consensus report of the PSA working group in assessing clinical trials in hormone-refractory prostate cancer. The benchmark was set at a minimum 50% decline in PSA level. Although this is a useful benchmark, it is important to note that some potentially effective agents may not decrease PSA. It also is important to note that some agents have direct effects on PSA production such that it may be difficult to assess their activity through serum PSA changes alone.

**PROGNOSTIC FACTORS**

The main utility of prognostic factors in patients with advanced cancers is that they help to stratify patients into groups entering into clinical trials. In addition, use of prognostic factors may give some insight into predictive factors for response. Although many studies have addressed this issue, few have been useful. In a recent review, nine studies contained sufficient numbers of patients to perform multivariate analysis, 

**CHEMOTHERAPY**

The traditional view of cytotoxic chemotherapy for prostate cancer is that it had little or no impact on the natural history of the disease. In 1985, Eisenberger et al. reviewed 17 randomized clinical trials that involved 1484 patients. The complete and partial response rate in these trials was 4.5%. In a review of 26 chemotherapeutic trials performed between 1987 and 1991, the overall response rate was 8.7%. Over the last 5 to 10 years, however, increasing evidence of clinical efficacy of chemotherapy in prostate cancer has emerged. Nonetheless, no trial to date has demonstrated a survival benefit for patients treated with chemotherapy for prostate cancer. The perception of increased efficacy of chemotherapy is the result of several factors. Increased use of the serum PSA level in monitoring activity in clinical trials has suggested that some of the older drugs that previously were believed to be inactive are, in fact, active in this disease. Patients are being placed on clinical trials at an earlier stage because of the recognition that elevations in serum PSA level precede clinical relapse. Furthermore, newer drug combinations have been developed that have greater activity and, finally, better supportive measures, including antienemics and growth factor support, have allowed clinicians to treat a relatively elderly population in a safer fashion.

Two recently published phase III trials demonstrated the utility of mitoxantrone plus a corticosteroid in hormone-refractory prostate cancer. The first study compared...
prednisone (10 mg/d) and prednisone (10 mg/d) plus mitoxantrone (12 mg IV every 3 weeks). One hundred and sixty-one patients with hormone-refractory prostate cancer and pain requiring a nalgesics were entered into the trial. The primary end point in this trial was a significant impact on pain as measured by a drop of 2 points on a 6-point pain scale. Twenty-three (29%) of 80 patients who received mitoxantrone plus prednisone, as compared to 10 (12%) of 81 patients who received prednisone alone, achieved this palliative response (P = .01). In addition, the duration of the palliation was longer for those patients who received mitoxantrone plus prednisone (median duration: 12 weeks) than for those who received prednisone alone (median duration: 8 weeks; P = .001). In another study, hydrocortisone given as a split dose of 30 mg in the morning and 10 mg the evening was compared to hydrocortisone plus mitoxantrone, 14 mg/m² given every 3 weeks. Two hundred and forty-two patients with metastatic hormone-refractory prostate cancer were randomized in this trial. The primary end point for this study was an improvement in survival with mitoxantrone plus hydrocortisone as compared to hydrocortisone alone. No difference in survival was observed (12.6 months vs. 12.3 months). More patients responded (as measured by a greater than 50% decline in PSA level) with mitoxantrone plus hydrocortisone than with hydrocortisone alone (39% vs. 22%; P = .008). Pain responses were more frequent in the combination arm. These two studies led to U.S. Food and Drug Administration approval of mitoxantrone for the treatment of hormone-refractory prostate cancer.

**Estramustine-Based Chemotherapy**

Estramustine is a conjugate of estrogen mustard and estradiol. Originally synthesized to permit the selective delivery of an alkylating agent into an estrogen receptor–positive cancer cell, more recent studies have shown that estramustine possesses little alkylating activity and may work by inhibiting mitosis through binding microtubules in the nuclear matrix. Estramustine preferentially enters cells that possess the estramustine-binding protein, a protein in high concentration in prostatic epithelial cells. As a single agent, estramustine has modest activity. Its activity is related in part to its estrogenic properties but, in addition, perhaps to its microtubular inhibitory properties. Eighteen phase II trials involving 634 patients with hormone-refractory disease demonstrated an objective response rate to estramustine of 19%. When it was realized that estramustine had microtubular inhibitory properties, in vitro studies were performed that demonstrated synergy of this drug with other agents involved in microtubular assembly. Three trials were conducted involving estramustine and vinblastine. The doses chosen in these studies generally were estramustine, 10 mg/kg/d, along with weekly vinblastine, 4 mg/m². Of 92 patients entered into these three phase II studies, PSA responses were observed in 44 of 88 patients (50%), and objective responses were seen in 6 of 25 patients (24%) with measurable disease. The value of adding estramustine to vinblastine was questioned in a randomized study in which 201 patients with hormone-refractory prostate cancer were randomized to either vinblastine alone, 4 mg/m² wk, or vinblastine plus estramustine, 600 mg/m² qd. Although there was a difference in median survival between the two groups—11.9 months for the combination versus 9.2 months for vinblastine alone—this did not reach statistical significance (P = .08). Patients who were treated with the combination had a longer progression-free survival (3.7 months vs. 2.2 months, P = .001). PSA responses were more frequent in the combination arm (25.2% vs. 3.2%; P < .0001). Interestingly, more frequent gastrointestinal toxicity but less frequent granulocytopenia was seen in the estramustine arm. This study supported the concept that estramustine added activity to vinblastine.

Other estramustine combinations have been investigated. The combination of estramustine and etoposide also showed in vitro synergy. Four trials have been conducted with this combination, enrolling a total of 205 patients. PSA responses were seen in 106 of 190 patients (56%), and measurable responses were noted in 40 of 82 patients (49%). Estramustine was combined with vinorelbine in three trials. One of seven patients with measurable disease responded, and 21 of 47 patients (45%) had a PSA response. Another strategy has been to combine estramustine with the taxanes. Interestingly, one small study of 23 patients with hormone-refractory prostate cancer examined the activity of taxol given as a 24-hour constant infusion at a dose of 135 to 170 mg/m². In that study, one patient had a partial response, but no patient had a decline in serum PSA level of greater than 50%. In the one published study in which estramustine was combined with paclitaxel, 4 of 9 patients (44%) had a measurable response, and 17 of 32 (53%) had a PSA response. In a parallel strategy, docetaxel was combined with estramustine. Picos and Schultz demonstrated that docetaxel, when given alone, was active in prostate cancer. In this study, 16 of 35 patients (46%) responded to docetaxel (75 mg/m²) given every 3 weeks. Petylak et al. treated 34 patients with estramustine, 280 mg i.d., plus docetaxel, 40 to 80 mg/m² every 21 days. Twenty of 34 patients (59%) had more than a 50% decline in PSA level. Kreis et al. observed that 14 of 17 patients (82%) treated with estramustine, 14 mg/kg, and docetaxel, 40 to 80 mg/m², responded. The dose-limiting toxicity was grade IV leukopenia and grade III fatigue and diarrhea. CALGB completed a phase II study of estramustine and docetaxel in 40 patients with hormone-refractory prostate cancer. Eleven of nineteen men (58%) who were evaluable for response had a PSA response. Because of the significant activity seen with estramustine plus docetaxel, a comparative study is now under way comparing docetaxel plus estramustine to mitoxantrone plus prednisone. Three-drug regimens have emerged, including estramustine, etoposide, and paclitaxel. In a study of 40 patients, 10 of 22 patients (45%) with measurable disease responded, and 21 of 47 patients (45%) had a PSA response. Another strategy has been to combine estramustine with the taxanes. Interestingly, one small study of 23 patients with hormone-refractory prostate cancer examined the activity of taxol given as a 24-hour constant infusion at a dose of 135 to 170 mg/m². In that study, one patient had a partial response, but no patient had a decline in serum PSA level of greater than 50%. In the one published study in which estramustine was combined with paclitaxel, 4 of 9 patients (44%) had a measurable response, and 17 of 32 (53%) had a PSA response. In a parallel strategy, docetaxel was combined with estramustine. Picos and Schultz demonstrated that docetaxel, when given alone, was active in prostate cancer. In this study, 16 of 35 patients (46%) responded to docetaxel (75 mg/m²) given every 3 weeks. Petylak et al. treated 34 patients with estramustine, 280 mg i.d., plus docetaxel, 40 to 80 mg/m² every 21 days. Twenty of 34 patients (59%) had more than a 50% decline in PSA level. Kreis et al. observed that 14 of 17 patients (82%) treated with estramustine, 14 mg/kg, and docetaxel, 40 to 80 mg/m², responded. The dose-limiting toxicity was grade IV leukopenia and grade III fatigue and diarrhea. CALGB completed a phase II study of estramustine and docetaxel in 40 patients with hormone-refractory prostate cancer. Eleven of nineteen men (58%) who were evaluable for response had a PSA response. Because of the significant activity seen with estramustine plus docetaxel, a comparative study is now under way comparing docetaxel plus estramustine to mitoxantrone plus prednisone.

**Other Agents**

A number of other drugs are active in patients with hormone-refractory prostate cancer, including cyclophosphamide. Raghaven et al. treated 30 patients with hormone-refractory prostate cancer with oral cyclophosphamide at a dose 100 mg/m² for 14 days. Eighteen (60%) had significant improvement in symptoms, whereas 6 (20%) had objective responses. Doxorubicin has been used in the context of hormone-refractory prostate cancer as well. No study has looked at a single-agent doxorubicin regimen in the post-PSA era. However, this drug has been combined with other agents. A popular regimen was the combination of 5-fluorouracil, doxorubicin, and mitomycin C. In one trial, 48% of 62 patients (i.e., 30 patients) responded. However, in two larger, multicenter studies, response rates were much lower. Another combination that has been tried is doxorubicin and cyclophosphamide. In one study, 5 of 15 patients (33%) with measurable disease had a response, and 46% of patients enrolled had a greater than 50% decline in PSA levels.

A regimen popularized at the M. D. Anderson Cancer Center has been a combination of doxorubicin and ketorezoloz. In one study, 39 patients were treated with weekly doxorubicin (20 mg/m²) and daily ketorezoloz (1200 mg/id). A PSA decline of greater than 50% was seen in 21 of 38 patients (55%). Seven of twelve patients had objective responses. The regional has been used as an alternating regimen with estramustine and vinblastine. In one study at the M. D. Anderson Cancer Center, 46 patients with hormone-refractory prostate cancer, 31 patients (67%) had a greater than 50% decline in PSA level, and 12 of 16 patients (75%) had a measurable response.

**PALLIATION**

**Bisphosphonates**

Prostate cancer has a strong propensity to spread to bone. Osteoblastic metastases are seen most commonly, principally in the axial structures (pelvis, vertebral bodies) but also in the appendicular structures (long bones, ribs, etc.). This propensity has been a subject of research for many years. One explanation was that tumor cells gained access to vertebral and pelvic bones by retrograde flow through Batson's plexus of paravertebral veins. Other explanations include a similarity between the growth factor requirements that support prostate cancer cell growth and osteoblast growth. Some such factors include osteopontin, osteonectin, insulin-like growth factor (IGF), fibroblast growth factor, transforming growth factor-β, and endothelin-1 (ET-1). Although prostate cancer is primarily an osteoblastic disease, as evidenced by the predominance of sclerotic bone lesions, it is not uncommon to see mixed blastic and lytic disease. The extent of bone turnover of metastatic bone sites, as measured by a variety of parameters, is high. Bone resorption is mediated through various factors via osteoclastic activity. The value of bisphosphonates in reducing biochemical and clinical parameters of prostate cancer–mediated bone disease is uncertain. Several large, multinational, randomized trials have now been completed that should clarify these issues. Bisphosphonates have also been used in the context of preventing osteoporosis in patients undergoing androgen
Radiopharmaceuticals

Radiopharmaceuticals in use are of two general types. The first type are bone-seeking radioisotopes. Strontium 89 is the only approved agent of this type. In a randomized study, strontium 89 was shown to be superior to placebo with respect to bone pain palliation. Pain relief usually occurs within a few weeks after treatment, although 15% of patients will experience a flare in pain within the first 2 weeks. Strontium 89 requires redosing every 3 months. It is generally well tolerated, although progressive bone marrow suppression may occur with repeat dosing. The mechanism of its activity is uncertain, but it is rare to see pain relief coupled with a decline in serum PSA level.

Two trials have been completed that test the value of adding strontium 89 at the time of radiation therapy for symptomatic bone pain relief. In one study, 305 patients with symptomatic bone pain were randomized, after receiving radiation therapy, to receive strontium 89 or hemibody radiation. Twelve weeks after treatment, there was no difference in the degree of improvement in bone pain. However, fewer patients developed new painful areas when strontium 89 was used (47% vs. 65%, p<0.01). In another trial, patients who had undergone palliative radiation therapy to a bone lesion were randomized to either strontium 89 therapy or no further therapy. There was no difference in overall survival. However, analgesic consumption was reduced when strontium 89 was used. Fewer patients had new painful lesions, and the interval before additional radiation therapy was needed was longer for those receiving strontium 89.

The second general type of radiopharmaceutical in clinical use is a radioisotope coupled to a bisphosphonate. For these agents, homing to bone is based on the ability of bisphosphonate to adhere to the surface of bone. The currently approved agent in this class is samarium 153 ETDMP (ethylenediaminetetramethylene phosphonate) which, in addition to emitting short-range particles, is a g- particle emitter as well. Because of this, imaging is possible.

FUTURE THERAPIES: NOVEL TARGETS

GROWTH FACTOR AND GROWTH FACTOR RECEPTORS AS TARGETS

Some of the most promising targets for cancer therapy are growth factors and growth factor (tyrosine kinase) receptors. Some of the relevant pathways include such growth factors and receptors as epidermal growth factor (EGF), transforming growth factor-b, IGF-1 and IGF-2, and platelet-derived growth factor (PDGF). For several reasons, these growth factors and their receptors can be viewed as potential targets in prostate cancer. First, epidemiologic studies suggest that growth factor levels may be related to the development or progression of prostate cancer (e.g., IGF-1). Second, some of these growth factors or receptors are dysregulated in different stages of prostate cancer. Third, therapies such as small molecules and antibodies have been developed against these targets. Finally, there is evidence that targeting these pathways will be effective in cancer therapy. Specifically, an inhibitor of the Ab1 tyrosine kinase used for the treatment of chronic myelogenous leukemia has been shown to be effective. Furthermore, Herceptin, an antibody directed against Her-2/neu, is an effective therapeutic agent when coupled with chemotheraphy in the treatment of breast cancer.

A number of growth factors and receptors are potential targets in prostate cancer, as altered expression of growth factor or receptor can be demonstrated particularly in the context of hormone-refractory prostate cancer. Her-2/neu overexpression can be demonstrated in prostate cancers. Overexpression of Her-2/neu may be a mechanism of androgen-independent growth, perhaps through activation of the androgen receptor pathway. Clinical trials involving Herceptin alone and combined with chemotherapy have demonstrated a survival benefit. PTEN, a dual-specificity phosphatase, when activated by EGF or TGF-a, can stimulate prostate epithelial cell growth. Mechanistically, this may occur through activation of the androgen receptor pathway, suppression of p27, or activation of mitogen-activated protein (MAP) kinase. The EGF pathway is a potential target for prostate cancer. Antibodies directed against the receptor (C225), as well as small-molecule inhibitors, have been developed and are in clinical trials.

PDGF has been shown to regulate prostate epithelial stromal interactions in a paracrine fashion. The receptor may be overexpressed in metastatic, hormone-refractory disease. Small-molecule inhibitors have been developed, but clinical trials have not yet been reported.

Nerve growth factor (NGF) is highly concentrated in the prostate. NGF and a related family of peptides, the neurotrophins, influence proliferation, differentiation, and survival of epithelial cells through activation of trk receptors. Trk receptors are expressed in most malignant prostate epithelial tumors. Trk receptor antagonists have been developed and are in clinical trials.

IGF-1 levels may be related to prostate cancer development and progression. In vitro, IGF-1 is mitogenic to prostate cancer cell lines. Although the development of specific IGF-1 receptor inhibitors is in progress, none are in clinical testing. Somatostatin analogues have been used because of their ability to lower serum IGF-1 levels. Thus far, no activity has been noted.

ET-1, a potent vasconstrictor and mitogen for malignant epithelial cells, is overexpressed in the prostatic epithelium. Receptors for ET-1 are expressed in the stroma (ET-B) and epithelium (ET-A). ET-1 plasma levels are higher in patients with advanced disease as compared to those with localized disease or normal controls. An ET-A receptor antagonist, ABT-627, has recently undergone clinical testing and has shown promising results with respect to pain control and disease stabilization.

SIGNAL TRANSDUCTION PATHWAYS

The downstream target pathways of the cell surface growth factor receptors are the MAP kinase, phosphoinositide 3 (PI3) kinase, and phospholipase C pathways. For example, PDGF has been shown to regulate prostate epithelial-stromal interactions in a paracrine fashion. The receptor may be overexpressed in metastatic, hormone-refractory disease. Small-molecule inhibitors have been developed, but clinical trials have not yet been reported.

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DIFFERENTIATION THERAPY

Differentiation therapy refers to a form of treatment that causes cancer cells to differentiate into a less malignant phenotype or to undergo programmed cell death. This has been demonstrated to be an effective modality for the treatment of promyelocytic leukemia. Several agents are currently in clinical trials in prostate cancer, including phenylacetate and phenylbutyrate and several nuclear receptor agonists, including vitamin D analogues, retinoic acid analogues, and peroxisome proliferator-activated receptor gamma (PPARgamma) analogues.

Phenylacetate and phenylbutyrate cause growth arrest and differentiation of prostate cancer cells in culture. These agents have a range of effects including histone acetylation, inhibition of isoprenylation, glutamine depletion, alterations in lipid metabolism, and DNA methylation. Both agents have shown activity in early clinical trials in prostate cancer patients.

The retinoids are compounds that bind to two classes of nuclear receptors, the retinoic acid receptors and the retinoid X receptors. The retinoids cause differentiation of epithelial cells. In vitro, the activity of different retinoids is variable, ranging from growth inhibition to growth stimulation. Thus far, clinical trials with retinoids in prostate have been disappointing. The drug liarazole, which has a range of activities including inhibition of retinoid acid metabolism, has shown activity in prostate cancer. In one phase III study comparing liarazole to cyproterone acetate, 20% of patients with hormone-refractory prostate cancer responded to liarazole.

Interest in vitamin D and its analogues is based on epidemiologic data linking low levels of vitamin D and vitamin D receptor polymorphisms to prostate cancer.


Mazur P. Cryobiology: the freezing of biological systems. Semin Radiat Oncol 1998;8:5.


SECTION 34.5
Cancer of the Urethra and Penis

INTRODUCTION

Primary cancer of the urethra and penis is uncommon. The rarity of tumors involving the penis and urethra has contributed to the lack of a standardized approach in the management of patients with these neoplasms.

Squamous cell carcinoma is the most common cancer in the penis and urethra. The patterns of spread, treatment approaches, and prognosis are related to the extent of disease and the region of the urethra or penis involved by the tumor. When metastasis occurs, it follows a stepwise pattern; first, to the inguinal (groin) lymph nodes and, second, to the pelvic lymph nodes. Distant dissemination occurs later. A favorable natural history permits cure of most localized penile cancers and of many with inguinal metastases. Urethral carcinoma in both males and females tends to invade locally and metastasize to regional lymph nodes early in its evolution. Most of these tumors are far advanced locally when diagnosed. This feature accounts for the relative poor prognosis of urethral cancer despite aggressive management.

CARCINOMA OF THE MALE URETHRA

Carcinoma of the male urethra is extremely rare. Approximately 600 cases have been reported. Urethral carcinoma has been reported in boys as young as 13 years of age and in men in their 90s, although most patients are older than 50 years of age. Significant etiologic factors have not been identified, but chronic inflammation appears to play a role in the initiation of disease, because many patients have prior sexually transmitted disease, urethritis, or urethral stricture. The incidence of urethral stricture in men with carcinoma of the urethra ranges from 24% to 76%. The most frequent site of stricture and malignancy is the bulbomembranous urethra. No racial predisposition has been noted.

SYMPTOMS

The lesion is often insidious at onset with symptoms attributed to benign urethral disease with stricture rather than to malignancy. Men often present with a palpable urethral mass or obstructive symptoms. On occasion, pain associated with urethral fistula or periurethral abscess may herald the presence of a male urethral cancer. Urethral stricture or bleeding in a man without a history of trauma or venereal disease should suggest the possibility of urethral carcinoma. Because of the nonspecific nature of the symptoms, diagnosis is often delayed. The most common presenting symptoms are listed in Table 34.5-1. Most reflect local involvements by the lesion.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Number of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palpable urethral mass</td>
<td>30 (2)</td>
</tr>
<tr>
<td>Obstructive symptoms (both or without stricture)</td>
<td>30 (2)</td>
</tr>
<tr>
<td>Pain</td>
<td>10 (1)</td>
</tr>
<tr>
<td>Urethral fever or pain</td>
<td>10 (1)</td>
</tr>
<tr>
<td>Hematuria</td>
<td>10 (1)</td>
</tr>
<tr>
<td>Pyuria</td>
<td>9 (9)</td>
</tr>
</tbody>
</table>

TABLE 34.5.1. Cancer of the Urethra and Penis

PATHOLOGY

Tumors of the male urethra can be categorized according to histology of the cells lining the anatomic region of origin (Fig. 34.5-1). The epithelium of the prostatic urethra gives rise to transitional cell carcinoma that is histologically and clinically distinct from adenocarcinoma commonly associated with the prostatic glands, but that is identical to the bladder urothelium. Tumors originating in the area of the trigone or bladder neck with direct extension into the prostatic urethra may be mistakenly diagnosed as primary urethral carcinoma unless careful examination and biopsy excludes the vesical neck as the site of origin. Male urethral carcinoma occurs in the bulbomembranous urethra in 60%, penile urethra in 30%, and prostatic urethra in 10%. Histologically, 80% of male urethral cancers are squamous cell carcinoma, 15% are transitional cell carcinoma, and approximately 5% are adenocarcinoma and undifferentiated tumors.
Male urethral carcinoma spreads by direct extension to adjacent structures and usually involves the vascular spaces of the corpus spongiosum and the periurethral tissues. Carcinoma of the bulbomembranous urethra extends to the urogenital diaphragm, prostate, perineum, and scrotal skin. Hematogenous spread is uncommon except in advanced disease. Metastasis occurs by lymphatic embolization to regional lymph nodes. The lymphatics from the anterior urethra drain into the superficial and deep inguinal lymph nodes and occasionally to the external iliac lymph nodes. The lymphatics from the posterior urethra drain into the external iliac, obturator, and hypogastric nodes. Tumors of the anterior urethra usually metastasize to the inguinal nodes, and tumors of the posterior urethra most commonly spread to the pelvic nodes, although exceptions occur. Palpable inguinal lymph nodes occur in approximately 20% of cases and almost always represent metastatic disease.

**EVALUATION AND STAGING**

The diagnosis is made by transurethral biopsy. The extent of local involvement is determined by careful inspection and palpation of the external genitalia and perineum at the time of cystourethroscopy and by bimanual examination with the patient under anesthesia. Needle biopsy is occasionally helpful in determining local extent of neoplasm. Cytologic studies of voided urine may be helpful for diagnosing some patients. Computed tomography (CT) or magnetic resonance imaging (MRI) may help to evaluate the pelvic and paraaortic nodes. Local soft tissue and bone extension are best evaluated by an MRI scan.

The tumor, node, and metastasis (TNM) staging system is commonly used to assess carcinoma of the urethra (Table 34.5-2). The TNM staging classification is based on depth of invasion of the primary tumor, the presence or absence of regional lymph node involvement, and distant metastasis.

**TREATMENT**

Surgical excision is the primary therapy for carcinoma of the male urethra. The extent of surgery depends on the location and stage of the tumor. In general, anterior urethral carcinoma is more amenable to surgical control and has a better prognosis than posterior urethral carcinoma. Although some instances of tumor control by irradiation have been reported, in general, radiation has been reserved for patients with early-stage lesions of the anterior urethra who refuse surgery. Radiation therapy has the advantage of preserving the penis but may result in urethral stricture and chronic edema and does not prevent new tumor occurrences in the retained urethra. Combination chemotherapy has achieved encouraging results in patients with metastatic urothelial cancer and is now being integrated more frequently with irradiation and definitive surgery in patients with locally advanced urethral carcinomas.

**SURGERY**

Table 34.5-3 shows 5-year survival rates in cancer of the male urethra according to stage, site, and surgical treatment.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Site</th>
<th>Site</th>
<th>Percent</th>
<th>Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Sagittal</td>
<td>Reconstructed urethra</td>
<td>92</td>
<td>9 (6)</td>
</tr>
<tr>
<td>I</td>
<td>Iliac</td>
<td>Excision</td>
<td>72</td>
<td>1 (4)</td>
</tr>
<tr>
<td>II</td>
<td>Pubis</td>
<td>Excision</td>
<td>60</td>
<td>2 (1)</td>
</tr>
<tr>
<td>II</td>
<td>Suburethral</td>
<td>Excision</td>
<td>65</td>
<td>2 (1)</td>
</tr>
<tr>
<td>II</td>
<td>Perineum</td>
<td>Excision</td>
<td>70</td>
<td>2 (1)</td>
</tr>
</tbody>
</table>

**Carcinoma of the Distal Urethra**

Carcinoma of the penile urethra may be treated by transurethral resection (TUR), local excision, partial amputation, or radical amputation with or without emasculation. For a superficial papillary or an in situ tumor, TUR and fulguration is sufficient. For a tumor infiltrating the corpus and localized to the distal half of the penis, a partial amputation with a 2-cm margin proximal to the visible or palpable tumor is the accepted treatment. If the infiltrating tumor is located in the proximal penile urethra or involves the entire urethra, radical amputation is necessary. This procedure may involve emasculation if the scrotal skin or genitalia are involved. Iliinguinal groin node dissection is indicated only if the inguinal nodes are palpable. There is no evidence of benefit from prophylactic groin dissection. Carcinoma involving the distal or penile urethra generally enjoys a more favorable prognosis than cancers involving the entire or more proximal regions of the urethra.
Carcinoma of the Bulbomembranous Urethra

Transurethral or segmental resection may be adequate for treatment of early superficial tumors involving the bulbomembranous urethra, but such cases are rare. Most patients present with an infiltrating bulky tumor with invasion of surrounding structures. Approximately one-third of these patients are locally understaged and later prove to have pelvic or groin metastasis. The overall survival of patients in this group is poor despite a distinctly radical surgical approach, but radical excision offers the best opportunity for long-term disease control and the lowest incidence of local recurrence. Postoperative morbidity is high. Despite the dismal prognosis, experience suggests that when local control of the tumor can be achieved, overall long-term results are favorable. Such tumors tend to be locally extensive and are apt to recur locally with inadequate local treatment. Metastasis appears to be a late event, which has led to aggressive combined therapy approaches in patients with bulky posterior urethral carcinoma.

Treatment Results for Carcinoma of the Bulbomembranous and Anterior Urethra

Surgery alone gives suboptimal results in the management of male urethral carcinoma. In the Dinney et al. series, two of five patients with tumors of the anterior urethra and none of the four patients with tumors of the bulbomembranous urethra were alive after being treated by surgery alone. In the Dalbagni et al. series, 17 of 18 patients (94%) with tumors of the anterior urethra are disease-free, and 4 of 26 patients (15%) with tumors of the bulb urethra are disease-free.

Radiation therapy alone was ineffective, as summarized by Zeidman et al. Patients who receive radiation therapy followed by salvage surgery seem to fare worse than if surgery was performed in integrated fashion. A combination of preoperative irradiation (20 to 60 cGy) followed by surgical excision of the inferior pubic rami with partial symphysectomy, anterior perineum, urogenital diaphragm, and genitalia, en bloc with the pelvic organs and lymph nodes, may improve local control and survival. Results suggest that approximately one-third of patients undergoing such extended excision of locally advanced neoplasms can be salvaged.

The integration of chemotherapy used as systemic therapy, and radiosensitization followed by surgery, can be successful in both the bulbomembranous and prostatic urethra. Anecdotal reports document successful treatment using M-VAC (methotrexate, vinblastine, Adriamycin, doxorubicin, and cisplatin) for transitional cell tumors and 5-fluorouracil (FU) plus either mitomycin-C or cisplatin for squamous cell carcinoma. Three reports substantiate the use of mitomycin-C plus FU chemotherapy integrated with radiation therapy and surgery for squamous cell carcinoma. Baskin and Turzanski reported the first case of penile-preserving surgery for carcinoma of the male urethra with combined FU plus mitomycin-C and radiotherapy followed by distal urethrectomy. Licht et al. reported one complete response among two patients treated with similar chemotherapy and radiation for a squamous cell carcinoma of the urethra with lymph node metastasis. Oberfield reported good local preservation in two patients with an invasive urethra with this chemotherapy regimen plus radiation. In the series by Gheiler et al., four patients with high-stage tumors were treated with neoadjuvant chemotherapy and radiation before surgery, two of whom were rendered disease-free. Success using cisplatin and FU has been reported in both squamous cell carcinoma and adenocarcinoma.

Primary Carcinoma of the Prostatic Urethra

Primary carcinoma arising from the prostatic urethra is rare. Tumors may be transitional or adenocarcinoma, and the diagnosis is based on a solitary tumor in the prostatic urethra without associated coexisting or preexisting urothelial tumors within the bladder and the bladder neck. There are no characteristic symptoms of this lesion. Patients generally present with hemorrhia or obstructive urinary symptoms. Prostatic induration on rectal examination represents advanced disease. The serum prostate-specific antigen and acid phosphatase values are normal. Diagnosis depends on transurethral biopsy of the prostate.

Superficial lesions of the prostatic urethra are managed successfully by transurethral resection in the majority of patients. However, such tumors are uncommon. In most instances, the tumor involves the bulk of the prostate with variable extension to the bulbomembranous urethra or to the bladder neck and trigone. In this situation, cystoprostatectomy and urethrectomy is the treatment of choice. In limited experience, the overall 5-year survival rate of patients treated with radical surgery, with or without preoperative irradiation, is poor. Combined modality therapy offers a prospect for improved results. For example, a total of 11 patients with advanced tumors of the prostate, prostatic urethra, or bulbomembranous urethra received neoadjuvant chemotherapy (i.e., M-VAC). Of ten evaluable patients, four (40%) were downstaged to complete clinical remission, including three of five with transitional cell tumors of the prostate and prostatic urethra. In selected responding patients, conservative transurethral resection or prostatectomy rather than pelvic exenteration can be entertained. Most patients, however, are best treated with a combination of aggressive surgery, irradiation, and chemotherapy, although the optimal strategy using these modalities is not established.

RADIATION THERAPY

Radiation therapy alone and postoperative radiation are rarely implemented in the management of men with urethral carcinoma. The most common approach has been external-beam radiotherapy, using various techniques to deliver 50 to 60 cGy in 5 to 9 weeks. The long-term results of radiotherapy have been mixed, with the best results reported for patients with distal lesions, for whom the outcome is similar to that reported with surgery.

CARCINOMA OF THE FEMALE URETHRA

Carcinoma of the urethra is unusual among genitourinary tract neoplasms in that it occurs more often in women than in men. Tumors present most commonly in postmenopausal and older women, with 75% of patients older than 50 years of age. The disease is more prevalent among whites than other races.

ETIOLOGY

The cause of urethral carcinoma in women has not been established with certainty, although a causal relationship is reported with chronic irritation, urinary tract infection, and malignancy. Proliferative lesions, such as caruncles, papillomas, adenomas, and polyps, have been associated with subsequent malignancy. Leukoplakia of the urethra is considered a premalignant lesion and is treated with wide local excision.

SYMPTOMS

Most patients present with urinary frequency, hesitancy, obstruction, and a palpable urethral mass. Tumors may present as a papillary growth within the urethra and may later become a soft fungating mass that bleeds easily. Ulcerative lesions may produce a foul-smelling discharge. The lesion may be detected first as a submucosal mass in the anterior wall of the vagina. Spread from the primary lesion is by local extension and infiltration with subsequent involvement of the bladder neck, vagina, or vulva. It may be difficult on initial physical examination to differentiate malignant tumors of the urethra from those of the vulva or vagina.

Lymphatics of the anterior urethra and labia drain to the superficial and then deep inguinal nodes, whereas the posterior urethra drains to the external iliac, hypogastric, and obturator lymph nodes. These boundaries are not distinct, and anatomic crossovers are possible. Clinically palpable inguinal nodes are found in one-third of patients, but histologic confirmation of malignancy is made in more than 90% of this group. Pelvic node involvement occurs in 20%, and an additional 15% of patients develop metastatic nodal disease during follow-up. Metastasis outside the pelvis at the time of initial presentation is uncommon.

PATHOLOGY

Stratified squamous epithelium lines the distal two-thirds of the female urethra, and transitional epithelium lines the proximal one-third. The submucosa of the urethra contains numerous periurethral glands. Tumor histology is a reflection of the site, with squamous cell carcinoma being the predominant tumor type and usually presenting in the proximal two-thirds of the urethra. In general, carcinomas of the anterior urethra are low grade and less extensive. Carcinomas of the proximal or entire urethra are of higher grade and locally advanced. Squamous cell carcinoma accounts for approximately 60%, transitional cell carcinoma, 20%, adenocarcinoma, 10%; undifferentiated tumors and sarcomas, 5%, and melanoma, 2%. Histologic characteristics do not appear to significantly affect the prognosis, and different histologic types are often treated in a similar fashion.
EVALUATION AND STAGING

A pelvic examination under anesthesia combined with urethroscopy, cytoscopy, and biopsies is performed. Cytologic evaluation of the urine may be of value.

Radiographic evaluation consists of a chest x-ray and CT scan of the abdomen and pelvis. A barium enema and bone scan should be obtained in symptomatic patients.

There has been no universally accepted staging system for female urethral carcinoma. The TNM staging system has been adapted to female urethral cancer (see Table 34.5-2), but the practical fact is that staging, treatment, and prognosis are simplified by dividing tumors into anterior and low-stage versus posterior or entire urethra and advanced stage.

TREATMENT

The most significant prognostic factor for local control and survival is the anatomic location and extent of the tumor. Treatment is based primarily on the tumor stage at the time of presentation. Table 34.5-4 shows 5-year survival rates in female urethral cancer of both early and advanced stage after treatment.

![Figure 34.5-2. Anatomy and pathology of female urethral carcinoma.](image)

### TABLE 34.5-4. Five-Year Survival Rate in Female Urethral Cancer

<table>
<thead>
<tr>
<th>Stage</th>
<th>Rate</th>
<th>Painless</th>
<th>Painless</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early</td>
<td>64%</td>
<td>99%</td>
<td>99%</td>
</tr>
<tr>
<td>Radical</td>
<td>56%</td>
<td>86%</td>
<td>86%</td>
</tr>
<tr>
<td>Surgery</td>
<td>54%</td>
<td>88%</td>
<td>88%</td>
</tr>
<tr>
<td>Radical plus surgery</td>
<td>43%</td>
<td>74%</td>
<td>74%</td>
</tr>
<tr>
<td>Advanced</td>
<td>49%</td>
<td>80%</td>
<td>80%</td>
</tr>
<tr>
<td>Radical plus surgery</td>
<td>34%</td>
<td>69%</td>
<td>69%</td>
</tr>
</tbody>
</table>

Most urethral cancers in women are locally advanced when detected and involve the proximal one-third or entire urethra. Such lesions clearly do worse than localized, low-grade, anterior urethral lesions. Poor prognosis attributed to urethral cancers in women is because of the advanced stage (high tumor volume), adjacent organ involvement, inability to obtain a clear surgical margin (because of soft tissue infiltration), nodal disease, morbidity of extensive treatment, and inadequate systemic therapy for metastatic tumor. Single-modality therapy often fails for advanced cases and is successful only in selected cases.

SURGERY

Local excision is often sufficient in selected patients with carcinoma of the distal urethra. For example, meatal tumors, if diagnosed early, are associated with an excellent 5-year survival rate. Such tumors are superficial and well localized. The incidence of lymph node metastasis with distal urethral carcinoma is low. Local excision controls the primary tumor, and urinary continence is maintained.

For tumors involving the proximal urethra or extending beyond the urethra into the adjacent structures, more aggressive treatment is required. When surgery is considered, extensive resection is necessary, including total urethrectomy, cystectomy with pelvic lymph node dissection, and removal of most (if not all) of the vagina. Extended excision to include resection of adjacent pubic symphysis and urogenital diaphragm similar to that for proximal male urethral cancer has resulted in local control of a few cases of far advanced urethral carcinoma. Even extensive surgery, however, often fails because of soft tissue infiltration by the tumor beyond the confines of the bladder neck, urethra, and vagina. Local recurrence after surgery alone is common. Anterior exenteration alone led to 10% to 17% 5-year survival and a local recurrence rate of 67%. Garden et al. reported 41% and 31% 5- and 10-year actuarial survival rates, respectively, with a 5-year local control rate of 64% with radiation therapy. Dalbagni et al. reported an overall 5-year survival rate of 32%—that is, the rates were 78% for low-stage and 22% for high-stage tumors, 54% for tumors of the anterior urethra, and 25% and 18% for tumors of the posterior and whole urethra, respectively. No difference was found in survival between women treated with radiation or surgery.

In cases of palpable inguinal nodes, inguinal lymphadenectomy has been advocated. Inguinal lymph node dissection is usually not performed in the absence of palpable disease in the groin.

RADIATION THERAPY

Irradiation alone, as with surgical excision, may control small lesions in the distal urethra. Radiation of these small lesions can be accomplished with brachytherapy without additional external-beam irradiation. Interstitial or intracavitary irradiation delivering a 50 to 65 Gy tumor dose has been demonstrated to be sufficient to control small distal urethral lesions.

Tumors of the proximal urethra, bladder neck invasion, or involvement of the entire urethra require combined external irradiation and brachytherapy. External irradiation is delivered to the primary tumor site and regional lymph node. The groin should receive prophylactic irradiation to 50 Gy if there is no palpable adenopathy. In the presence of palpable inguinal lymph nodes, bolus is added to the groin and the total dose is increased from 60 to 65 Gy. The pelvis is treated to 50 Gy by the combined whole pelvis and split field technique. The pelvic side wall can be boosted to 60 Gy in the presence of lymphadenopathy as detected by CT scan. The primary tumor site is boosted with brachytherapy (one or two implants using iridium 192) to bring the total tumor dose from 70 to 80 Gy, depending on tumor size. Complications from irradiation include bowel obstruction, fistula formation, urethral stricture, and incontinence. Radiation therapy alone controls only approximately one-third of cases of advanced disease, and severe complications occur in 15% to 40% of patients.

COMBINED MODALITY THERAPY

Although the number of cases of advanced female urethral carcinoma is small, it is obvious that either extensive surgery alone or high-dose irradiation alone produces an unacceptably high morbidity rate and low tumor control rate. This fact has led to combined treatment strategies with chemotherapy, radiation therapy,
and surgery in women with advanced urethral cancer. M-VAC chemotherapy and irradiation followed by surgery have been used in patients with transitional cell carcinoma, and those with squamous cell carcinoma have received combined mitomycin-C and 5-fluorouracil and irradiation followed by surgery. Long-term results from combined modality therapy are unavailable.

**CANCER OF THE PENIS**

Carcinoma of the penis represents 2% of urogenital cancers. Although rare in North America, tumors of the penis account for 10% to 12% of all malignancies in males among populations in which circumcision is not a common practice.

Penile cancer is the most common genitourinary cancer in Paraguay, representing 45% to 76% of all genitourinary malignancies. In Uganda, where circumcision is usually not performed, penile cancer is the most commonly diagnosed cancer in males. Although malignant penile lesions have been found in young men, most patients are older than 50 years.

**ETIOLOGY**

Most penile cancers occur in uncircumcised men, suggesting an irritative effect of smegma combined with poor hygiene. Carcinoma is rare among men who were circumcised in the neonatal period, but circumcision performed at puberty or in adulthood does not have the same protective potential as circumcision at birth.

Although the annual age-adjusted incidence of carcinoma of the penis for males in the United States is only 1 per 100,000, the lifetime risk of penile cancer developing in uncircumcised males may be as high as 1 in 600. Smegma, the product of bacterial action on desquamated epithelial cells is carcinogenic in animal systems, although the specific component responsible for malignant degeneration in human males has not been identified.

Conflicting reports support and deny the association of penile cancer with cervical carcinoma in sexual partners or with herpetic infection. No compelling data support the assertion that penile cancer is a sexually transmitted disease. No persistent etiologic relation has been documented between carcinoma of the penis and the venereal diseases of syphilis, granuloma inguinale, or chancroid. Evidence that human papillomavirus (HPV) may be causative is scanty, although HPV transfection alters human epithelial cell differentiation in vitro and has not been ruled out as a potential cause of some cases of penile cancer.

**SYMPTOMS**

The most common presenting manifestation of penile cancer is a mass or persistent sore or ulcer of the glans, foreskin, or shaft of the penis. Most penile carcinomas are painless, and there may be significant ulceration and bleeding. Less commonly, the initial symptoms are related to inguinal lymphadenopathy.

It has been estimated that more than one-half of patients delay more than 1 year in seeking treatment after the appearance of the lesion, although such delays are uncommon in the United States. Any delay in the recognition, diagnosis, and therapy of penile carcinoma significantly worsens its prognosis.

**PATHOLOGY**

Penile carcinoma is most often squamous cell in origin, although malignant melanoma, basal cell carcinoma, Bowen's disease (carcinoma in situ), mesenchymal tumors (including Kaposi's sarcoma), metastatic lesions, and leukemic or lymphomatosis infiltrates may involve the penis. Several premalignant lesions have been identified.

**STAGING**

The initial diagnosis is made by incisional or excisional biopsy. Physical examination determines the extent of local invasion and the status of the inguinal lymph nodes that are essential to proper staging. A CT or MRI scan to evaluate the pelvic and abdominal lymph nodes may also be helpful. The TNM classification is used to determine the stage of the primary tumor and to quantify nodal metastasis. Nodal status is the most significant prognostic variable predicting survival. The incidence of groin metastasis (palpable or not) increases with T category of the primary lesion. Nodal disease occurs in 20% of T1 tumors and in 47% to 66% of T2–4 penile cancers.

**TREATMENT**

Treatment depends on the local extent of the primary neoplasm and the status of the regional lymph nodes. Wide excision or partial penectomy with or without inguinal lymph node dissection is the most commonly accepted treatment for small and well localized tumors. Radiotherapy may be effective for some patients with noninvasive small lesions and may avoid the functional sacrifice associated with penectomy. Radiation may be associated with necrosis or urethral stenosis, resulting in a nonfunctioning penis. Several investigations have demonstrated that local relapses after radiotherapy can be salvaged by a partial or total amputation of...
the penis without apparently affecting the prognosis, although this approach remains controversial.  

Paramount to treatment planning is a consideration of the lymphatic drainage of the penis (Fig. 34.5-3). The skin of the penis and the lymphatics of the prepucce drain primarily into the superficial inguinal nodes. Bilateral drainage occurs as a result of the freely anastomosing system and crossover at the base of the penis. The glans is drained by the superficial inguinal nodes, but along with those of the corpora, the lymphatics of the glans penis empty into the deep inguinal and iliac nodes. The superficial nodes are located in the deep portion of Camper's fascia above the deep fascia of the thigh, the fascia lata. The superficial lymphatics drain into the deep inguinal lymphatics surrounding the femoral vessels and then to the external iliac, common iliac, and paraaortic lymphatic channels. Tumor invasion of the corpora cavernosa or the posterior urethra may lead to deep pelvic lymphatic metastasis to internal iliac and obturator nodes.

![Figure 34.5-3: Lymphatic drainage of the penis.](image)

**FIGURE 34.5-3. Lymphatic drainage of the penis.**

**Surgery**

Surgery aims to control the primary neoplasm and is involved in the evaluation and therapy of nodal disease. Bilateral pelvic and inguinal node dissection is indicated, where possible, for any positive groin metastasis detected at the time of or within 6 months of treatment of the penile tumor. This is because lymphatic crossover at the base of the penis accounts for at least 60% contralateral groin metastasis, even in the face of unilateral palpable inguinal nodes. \[\text{Delayed (6 months or more)} \]

**Treatment of Primary Lesion**

Surgical therapy involves removal of the lesion with adequate margins to minimize the risk of local recurrence. Small tumors that are limited to the prepuce are treated by circumcision alone. Lesions that on physical examination involve only the skin may be treated by wide excisional biopsy. Local or total penectomy is indicated for lesions that because of their size, invasiveness, or location on the shaft are not amenable to more conservative treatment. Partial penectomy includes a 2-cm margin of normal shaft proximal to the primary tumor. For extensive lesions approaching the base of the penis, total penectomy is accomplished with excision of both corpora and creation of a perineal urethrostomy. Local recurrence after a properly planned and executed partial or total penectomy is rare.

**Management of Regional Lymph Nodes**

Several factors determine the role of regional lymphadenectomy in patients with penile cancer. First, 50% of patients with squamous cell penile cancer have palpable inguinal lymph nodes at diagnosis. In one-half of these cases, inguinal adenopathy represents benign inflammatory changes associated with ulcerated or infected penile lesions. Clinical assessment of the lymph nodes should be delayed until after a 4- to 6-week course of antibiotic therapy. Persistent adenopathy after 6 weeks warrants biopsy and therapy. Second, approximately 20% of patients with no palpable adenopathy have occult lymphatic metastases. Third, lymph node dissection can be curative for the majority of patients with isolated tumor-bearing inguinal nodes.

Overall, 50% of patients with positive inguinal lymph nodes can be rendered disease-free by surgical resection. \[\text{The volume of lymph node disease and its location appear to be important predictors of success. In one study of 119 patients, unilateral inguinal node involvement had a median 5-year survival rate of 56%, compared with 9% of patients with bilateral inguinal node metastases, extranodal spread, or pelvic node involvement.} \]

The primary controversy in the surgical management of penile cancer concerns the role of lymph node dissection if there is no clinically identifiable inguinal disease. The overall incidence of false-negative nodes in T1 and T2 disease is approximately 20%, but late nodal extension to the groin after adequate excision of the primary occurs in only 5% to 11% of patients. Routine lymph node dissection is therefore difficult to justify for low-stage primary disease. In patients with advanced (T3, T4) invasive primary tumors, the likelihood of nodal metastases increases, and in some series, two-thirds of patients with clinically negative nodes have histologically confirmed metastasis on lymph node dissection. The significant morbidity that may accompany groin dissection and the lack of controlled prospective studies to document the benefit of early "prophylactic" versus late "therapeutic" groin dissection has led many surgeons and centers to delay lymphadenectomy until clinical evidence of lymph node involvement exists.

Ekstrom and Edsmyr identified a 50% disease control rate among patients who had node dissection delayed until adenopathy was evident. Frew and colleagues could identify no cancer deaths among patients in whom lymph node excision was deferred until clinical node disease was found. Beggs and Spratt reported no significant adverse effect on survival in patients with delayed groin dissection. However, others have reported a significant decrease in 5-year survival rates in patients with therapeutic rather than prophylactic groin dissection and have suggested that delayed surgery is inappropriate. One study showed that 62% of patients survived 5 years if the lymph node dissection was done concomitantly with the primary therapy of the penile lesion, as opposed to an 8% survival rate among those who underwent lymphadenectomy when it became obvious that the nodes were pathologically involved. Most patients who benefited from groin dissection had locally advanced penile cancers. The current recommendation is that, among patients with low-stage (T1, T2) penile cancer and palpably negative groins, expectant management is reasonable in that delayed inguinal lymph node dissection for clinically positive nodes does not seem to compromise long-term survival when compared with patients who never develop inguinal lymphadenopathy. However, for locally advanced (T3, T4) tumors, a "prophylactic" bilateral lymph node dissection may result in improved survival among patients with clinically undetected inguinal metastasis.

Cabanas described a technique of "sentinel node" biopsy followed by formal node dissection if metastatic disease is found. In Cabanas' series, inguinal-femoral-iliac node involvement was not demonstrated without a positive sentinel node biopsy. However, Perinetti and colleagues have reported patients with negative sentinel node biopsies who later developed resectable bilateral groin disease. A modified or extended sentinel lymph node dissection node dissection has also been advocated to cure those patients with limited inguinal disease and to reduce the morbidity of a formal radical ilioinguinal lymphadenectomy. However, Pettaway reported that, among 14 patients who underwent a negative modified superficial inguinal dissection, 5 relapsed with incurable groin metastasis from 3 to 21 months later. Thus, radical ilioinguinal lymphadenectomy is the procedure of choice if groin dissection is indicated.

The operation is performed essentially as described by Whitmore and Vagiaiwa. Bilateral pelvic lymph node dissection is performed. The dissection limits are defined by the genitofemoral nerve laterally, the bladder medially, the bifurcation of the common iliac artery superiorly, and the fascia covering the obturator internus and levator ani muscles inferiorly. Cliveut's node is removed from the femoral canal.

The inguinal incision is planned to provide adequate margins surrounding lymph nodes containing obvious tumor and simultaneously to remove the area of skin at greatest risk of devitalization and necrosis. An elliptical incision is made over the inguinal ligament from the anterosuperior iliac spine to the pubic tubercle. The borders of the ellipse parallel the inguinal ligament and extend 4 to 6 cm in vertical diameter at the widest point. Because penile cancers appear to involve the inguinal lymph nodes by tumor embolization rather than through permeation of lymphatic channels, wide thin skin flaps and a thorough dissection, skeletonizing the femoral vessels as is required for malignant melanoma, are not required. The nodes in the superficial and deep inguinal areas are completely removed from the
chemotherapy for squamous cell carcinoma of other origins; they have not been pursued as yet in penile cancer. In summary, chemotherapy is sufficiently active in penile cancer. However, the analysis also showed that the overall sexual function was preserved or only slightly diminished in 10 of the 12 irradiated patients. Therefore, chemotherapy can only provide palliation for some patients.

Radiation Therapy

The main advantage for radiation therapy in penile tumors is that it provides an option of functional preservation of the penis. However, for radiation to represent an alternative to surgery, it must yield comparable local control rates with minimal toxic effects. Several series report initial rates of local control in 80% to 90% of patients treated with radiotherapy, but 10% to 20% eventually relapse and require surgical salvage. Furthermore, inadequate control of the primary tumor risks interval metastasis and a reduced cure rate.

Radiation techniques have included interstitial implantation of radium needles, radioisotopes, or external-beam radiotherapy. The use of brachytherapy has been limited to small tumors. Results from a series of 50 patients implanted with 125I seeds showed that the tumor was controlled in 95% of the patients with noninfiltrating tumors of 4 cm or less, with the penis conserved in 80% without major impairments of function. When external-beam radiotherapy is used, treatment is usually delivered with a custom-made plastic or wax mold to ensure a uniform dose distribution and to overcome the skin-sparing effects of supervoltage beams. Circumcision is usually recommended before radiotherapy to minimize radiation morbidity associated with cellulitis of the prepube and the adjacent structures. The whole shaft of the penis is treated to 40 Gy in 20 fractions in 4 weeks, and the primary lesion is boosted to a total dose of 60 Gy. Superficial small lesions can be treated with localized fields using superficial x-rays or electron beams carried to a similar dose.

External-beam radiotherapy of low-stage tumors usually produces 70% to 80% local success rates. Local failures appear in 20% of patients, but some can be salvaged with surgery. If prophylactic orchiectomy has been performed, external-beam radiotherapy to the inguinal and pelvic lymph nodes carried to 50 Gy may provide palliation for some patients.

The Royal Marsden Hospital has recently updated their experience with treating 101 patients with radiation for carcinoma of the penis. This group reported an 80% local recurrence rate in patients treated with at least 60 Gy of external-beam radiation therapy. However, local control was eventually achieved in 71 of 74 patients with stage I disease, which included retreatment with salvage surgery in 17 patients who had local recurrence following radiation. Unfortunately, very little quality of life information has been published following treatment of penile cancer. However, a recent study from the Norwegian Radium Hospital reports clear results of sexual performance using a formal prospective analysis. This study found that the overall sexual function was preserved or only slightly diminished in 10 of the 12 irradiated patients. However, the authors also showed that the overall sexual function was normal in only one of five men following wide local excision and in only two of nine men after partial penectomy.

Chemotherapy

Chemotherapy for urethral and penile carcinoma varies with the histology of the lesion. For patients with pure transitional tumors, cisplatin-combination regimens have shown efficacy. The results with chemotherapy for squamous cell tumors of the penis vary according to the extent of disease, with higher rates of response for locoregional (inguinal) than metastatic (pelvic and beyond) disease. Antitumor activity has been demonstrated with single-agent bleomycin, methotrexate, and cisplatin. Partial responses occur in up to one-third of patients, but complete remissions are rare. Large trials evaluating the role of multiagent chemotherapy in advanced carcinoma of the penis are uncommon. However, cisplatin-based regimens predominate the recent literature. Early trials evaluated the cisplatin/cyclophosphamide/bleomycin combination, with clinical responses seen in 4 of 13 patients; cisplatin was given by either the peripheral or the intraarterial route. The cisplatin/bleomycin/methotrexate regimen has been the most extensively studied. The M. D. Anderson Cancer Center experience was first reported by Dexeus and colleagues. Subsequently reported on 26 assessable patients with squamous cell carcinoma of the genitourinary tract, 20 of whom had penile cancer. The complete and partial response proportions were 15% and 50%, respectively; results were not characterized by the site of the primary tumor. Haas et al. reporting for the Southwest Oncology Group, evaluated this three-drug regimen in 40 patients with locally advanced or unresectable disease, none of whom had prior chemotherapy. Complete response was seen in 12.5% and a major response in 32.5% of patients. The median duration of response was 16 weeks, and the median survival was 28 weeks. Toxicity was substantial, including five treatment-related deaths. Other reports showed activity of cisplatin and 5-fluorouracil, a combination that has been extensively evaluated in head and neck tumors. Hussein and colleagues treated six men with recurrent or unresectable squamous cell carcinoma of the penis. Overall, one complete response and five partial responses were documented, including two patients with unresectable disease who were rendered disease-free by surgery. Fisher and coworkers treated five patients with biopsy-proven unresectable disease and reported major responses in four patients, including two men who were pathologically free of disease at surgery. Shammaas et al. treated eight patients, two of whom responded.

Most regimens studied in penile cancer use older agents. More recent studies have identified new, active agents in squamous cell carcinoma of the cervix and head and neck, including ifosfamide, paclitaxel, docetaxel, gemcitabine, and gemcitabine (Navelbine). Single and multiagent regimens that include these new drugs are now being used in other genitourinary cancers of other origins; they have not been used as yet in penile cancer. In summary, chemotherapy is sufficiently active in penile cancer to consider its inclusion in multimodality therapy for patients with bulky or fixed inguinal metastases.

CHAPTER REFERENCES

INTRODUCTION

Cancers of the testis make up a morphologically and clinically diverse group of neoplasms (Table 35-1). The overwhelming majority are primary in the testis, and most of these are germ cell tumors (GCTs). The management of each neoplasm is dependent on the histology and influenced by the anatomy of the testis and its lymphatic and vascular drainage. GCT is a highly curable disease requiring proper management at all stages.

TABLE 35-1. Histologic Classification of Testicular Neoplasms

BACKGROUND: INCIDENCE

GCTs are the most common solid tumor in men between the ages of 20 and 35 years. There are three modal peaks: infancy, ages 25 to 40, and approximately age 60. A solid testicular mass in a man aged 50 or greater is usually a lymphoma. The incidence of GCTs appears to be increasing. An estimated 7000 new cases (6900 testis) and 300 deaths caused by germ cell tumors of all primary sites will be reported in the United States in 2000. The incidence of testis cancer varies significantly according to geographic area. The reported incidence is highest in Scandinavia, Switzerland, Germany, and New Zealand; intermediate in the United States and Great Britain; and lowest in Africa and Asia. The rising risk of testicular GCT incidence is associated with a birth cohort effect in both the United States and Europe.
EPIDEMIOLOGY

GCTs are seen principally in young whites, and rarely in African Americans. The published ratio between white and African American patients is approximately 4:1 to 5:1, although it was closer to a 40:1 ratio in the U.S. military. In African Americans, GCT behaves similarly to that of the general population. Familial clustering has been observed, particularly among siblings.

The cause of GCT is unknown. Random genetic events occurring during the early stages of meiosis seem to be responsible for the malignant transformation of germ cells (see Biology, later in this chapter). A few congenital developmental defects predispose to the disease.

CRYPTORCHIDISM

The risk of GCT occurring in the cryptorchid testis is several times the risk in normally descended testes. Between 5% and 20% of patients with a history of cryptorchidism develop a tumor in the normally descended testis. An abdominal cryptorchid testis is more likely to develop GCT than an inguinal cryptorchid testis. The protective effect of orchiectomy is difficult to quantify, but most data suggest a reduced likelihood of GCT if orchiectomy is performed before puberty. If the testis is inguinal, hormonally functioning, and easily examined, surveillance is recommended. If the testis is not amenable to orchiectomy or cannot be adequately examined, orchiectomy is recommended.

DIETHYLSTILBESTROL

Exogenous administration of estrogens to pregnant mice causes testicular maldescent and dysgenesis in offspring. Cryptorchidism and dysgenesis have also been reported in the male children of women exposed to diethylstilbestrol or oral contraceptives. Despite anecdotes associating diethylstilbestrol exposure with the development of GCT, epidemiologic studies have failed to identify such an association.

KLINEFELTER’S SYNDROME

Klinefelter’s syndrome is characterized by testicular atrophy, absence of spermatogenesis, a eunuchoid habitus, and gynecomastia. It is diagnosed by a 47,XXY karyotype. Klinefelter’s syndrome patients have an increased incidence of mediastinal GCT.

OTHERS

A history of trauma is frequently noted by patients with testicular cancer; however, no evidence supports a direct causal relationship. Rather, the trauma usually prompts examination. Viral orchitis, usually secondary to mumps, may result in testicular atrophy. However, epidemiologic studies have failed to identify viral infection as a cause. More recently, testicular cancer has been reported in men infected with the human immunodeficiency virus. However, too few data support a higher incidence in individuals infected with human immunodeficiency virus, and the results of treatment are similar.

INITIAL PRESENTATION AND MANAGEMENT

SYMPTOMS AND SIGNS

The pathognomonic presentation of a primary testicular tumor is a painless testicular mass that may range in size from a few millimeters to several centimeters. However, the painless testicular mass occurs in only a minority of patients. The majority present with more diffuse testicular pain, swelling, hardness, or some combination of these findings. Since infectious epididymitis or orchitis, or a combination of the two, is more common, a trial of antibiotic therapy is often required in questionable cases. Acute testicular pain, simulating testicular torsion, occurs less frequently and may represent intratumoral hemorrhage. If the testicular discomfort does not abate or findings do not revert to normal within 2 to 4 weeks, a testicular ultrasound is indicated. On ultrasound, the typical testicular tumor is intratesticular and may produce one or more discrete hypoechoic masses. A pattern of multiple, diffuse calcifications in the testis has been associated with GCT.

DIAGNOSIS

A radical inguinal orchiectomy, using an inguinal incision with early high ligation of the spermatic cord at the deep inguinal ring, minimizes local tumor recurrence and aberrant lymphatic spread and is the only acceptable therapeutic and diagnostic procedure. The vasal and vascular components are doubly clamped and divided separately; their respective stumps are pushed into the retroperitoneal space to facilitate removal of the gonadal vessels at the time of retroperitoneal lymph node dissection (RPLND). The testicle and spermatic cord are removed en bloc, avoiding any spillage, and meticulous hemostasis is achieved. A transscrotal orchiectomy is contraindicated, because it permits the development of alternate lymphatic drainage pathways to the inguinal and pelvic lymph nodes and leaves intact the spermatic cord from the external to the internal ring. In the rare situation in which the diagnosis of a testicular tumor is in question, then an inguinal incision is required for an open biopsy. The tests can then be examined in situ in a sterile field and an appropriate biopsy taken with minimal risk of scrotal or inguinal contamination. Regardless of the preoperative diagnostic studies, all potential, primary testicular malignancies should be managed through an inguinal approach.

Extragonadal GCTs account for fewer than 10% of GCT. The mediastinum and retroperitoneum are the most common primary sites. Pineal tumors, occurring most frequently in children, are usually GCT. Because of their unique access to the meninges, the metastatic pattern of pineal GCT includes intradural sites along the neuraxis and is infrequently systemic. The management of extragonadal and testicular GCT is the same, and primary site is an independent factor in staging and risk classification.

HISTOLOGY

GCT is classified into two major subgroups: seminoma and nonsertoli. Three classifications are summarized in Table 35-2. The Mostofi adaptation of the Dixon/Moore classification was largely adopted by the World Health Organization and is the classification most commonly used in North America and Europe. The British Tumor Panel’s modification of the classification developed by Pugh is widely used in Great Britain and Australia.

TABLE 35-2. Comparison of Three Classifications of Germ Cell Tumors

<table>
<thead>
<tr>
<th>Classification</th>
<th>Mostofi (Bielack)</th>
<th>Pugh</th>
<th>Dixon/Moore</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seminoma</td>
<td>Seminoma</td>
<td>Seminoma</td>
<td>Seminoma</td>
</tr>
<tr>
<td>Embryonal sarcoma</td>
<td>Embryonal sarcoma</td>
<td>Embryonal</td>
<td>Embryonal sarcoma</td>
</tr>
<tr>
<td>Teratoma</td>
<td>Teratoma</td>
<td>Teratoma</td>
<td>Teratoma</td>
</tr>
<tr>
<td>Choriocarcinoma</td>
<td>Choriocarcinoma</td>
<td>Choriocarcinoma</td>
<td>Choriocarcinoma</td>
</tr>
<tr>
<td>All other tumors</td>
<td>All other tumors</td>
<td>All other tumors</td>
<td>All other tumors</td>
</tr>
</tbody>
</table>
CARCINOMA IN SITU

Carcinoma in situ (CIS) \(^{(C)}\) (intratubular germ cell neoplasia) precedes invasive testicular GCT in virtually all cases of typical and anaplastic seminoma and all nonseminomatous histologies in the adult. CIS is frequently present in retroperitoneal presentations and is rare, if ever, present in mediastinal presentations. It has not been described in spermatocytic seminoma and rarely in tumors arising in prepubertal patients. \(^{25}\) \(^{26}\) \(^{27}\) \(^{28}\) Cytologically, CIS preceding seminoma and nonseminoma is identical. The median time for progression of CIS to invasive disease is 5 years. \(^{29}\) \(^{30}\) In the general population, the incidence of CIS is low, \(^{31}\) whereas in men with impaired fertility, the incidence is approximately 0.5%. \(^{32}\) \(^{33}\) The incidence of CIS is 2% to 5% in both cryptorchid testes and the contralateral testes in patients with a documented prior testicular GCT. \(^{34}\) \(^{35}\) \(^{36}\)

SEMINOMA

Seminoma accounts for approximately 50% of all GCT and most frequently appears in the fourth decade of life. The typical or classic form consists of sheets of large cells with abundant cytoplasm and round, hyperchromatic nuclei with prominent nucleoli. A lymphocytic infiltrate, granulomatous reaction with giant cells, or both, are frequently present. Trophoblastic giant cells capable of producing human chorionic gonadotropin (HCG) are present in 15% to 20% of tumors. The presence of syncytiotrophoblastic giant cells in an otherwise pure seminoma does not influence prognosis or treatment. Anaplastic seminoma is an older term used when three or more mitotic figures are seen per high-power field, and it has no clinical or prognostic importance. Stage for stage, anaplastic seminoma is similar in response and prognosis to classical seminoma. \(^{37}\) \(^{38}\) \(^{39}\) \(^{40}\) \(^{41}\) \(^{42}\)

An anaplastic form of seminoma has been described with unusual immunohistochemical features. Although the cells cytologically resemble classical seminoma, lymphocytic infiltrate and granulomatous reaction are absent, necrosis is more common, and the nuclear to cytoplasmic ratio is higher. These tumors must be distinguished morphologically from solid variants of embryonal carcinoma and yolk sac tumor. Atypical seminoma frequently shows cytoplasmic expression of low-molecular-weight keratin or the type 1 precursor to the blood group antigens, whereas typical seminoma stains negative. \(^{43}\) \(^{44}\) Electron microscopic studies have shown that the individual tumor cells acquire cytoplasmic cytokeratin intermediate filaments, suggesting epithelial differentiation. There has been no specific association of atypical seminoma with an adverse prognosis, and its management is currently the same as any other seminoma.

Spermatocytic seminoma is a rare histologic variant seen almost exclusively in men above the age of 45. The relationship of spermatocytic seminoma to other GCTs is not clear, since it is not associated with CIS or bilaterality, does not express placental alkaline phosphatase (PLAP) (see Immunohistochemical Markers, later in this chapter), and has not been shown to have the same genetic abnormalities as other GCTs. Metastatic potential is minimal.

NONSEMINOMATOUS GERM CELL TUMORS

Nonseminomatous histology makes up approximately 50% of all GCTs and most frequently presents in the third decade of life. Most tumors are mixed, consisting of two or more cell types. Seminoma may be a component, but the definition of a pure seminoma excludes the presence of any nonseminomatous cell type. The presence of any nonseminomatous cell type (other than syncytiotrophoblasts) imparts the prognosis and management principles of a nonseminomatous tumor.

Embryonal Carcinoma

Embryonal carcinoma is the most undifferentiated somatic cell type. Individual cells are epithelioid in appearance and may be arranged in glandular or tubular nests and cords or as solid sheets of cells. Tumor necrosis and hemorrhage are frequently observed.

Choriocarcinoma

Choriocarcinoma, by definition, consists of both cytotrophoblasts and syncytiotrophoblasts. If cytotrophoblasts are not present, then the diagnosis of choriocarcinoma cannot be made. Pure choriocarcinoma is an extremely rare presentation usually associated with widespread hematogenous metastases and high levels of HCG. Hemorrhage into the primary tumor is frequent and is an occasional severe complication when it spontaneously occurs at a metastatic site. \(^{45}\) Elements of choriocarcinoma are frequently found in mixed tumors but appear to have no prognostic importance. \(^{46}\) Syncytiotrophoblastic giant cells can be seen as a component of any GCT (including pure seminoma). They impart no prognostic value by themselves.

Yolk Sac Tumor

Yolk sac tumor (endodermal sinus tumor) is often confused with a glandular form of embryonal carcinoma. This tumor mimics the yolk sac of the embryo and produces a-fetoprotein (AFP). The cells may have a papillary, glandular, microcystic, or solid appearance and may be associated with Schiller-Duval bodies, which are perivascular arrangements of epithelial cells with an intervening extracellular space. Rarely, embryoid bodies resembling the early embryo can be seen. Yolk sac histology is infrequently the only histologic subtype in adult GCT except in the mediastinum where pure yolk sac tumors account for a minority of primary tumors.

Teratoma

Teratoma is composed of somatic cell types from two or more germ layers (ectoderm, mesoderm, or endoderm) and is derived from a totipotential, malignant precursor cell (embryonal carcinoma or yolk sac tumor). Mature teratoma consists of adult-type differentiated elements such as cartilage, glandular epithelium, nerve tissue, or other differentiated cell types. Immature teratoma generally refers to a tumor with partial somatic differentiation, similar to that seen in a fetus. Both mature and immature teratomas are histologically benign. Teratoma with malignant transformation refers to a form of teratoma in which one of its components, either immature or mature, develops aggressive growth and histologically resembles another malignancy. These usually take the form of sarcomas (most frequently embryonal rhabdomyosarcoma), and, less frequently, carcinomas (e.g., enteric-type adenocarcinoma), neuroectodermal tumors, or combinations of these. \(^{47}\) Acute nonlymphocytic leukemias have arisen in the context of mediastinal nonseminomatous GCT, but not from other primary sites. \(^{48}\) In a review of 41 cases of pure mature or immature teratoma of the testis, 26 (63%) displayed retroperitoneal or systemic metastases, with or without increased levels of serum tumor markers. \(^{49}\) Therefore, a primary testicular tumor in a postpubertal boy or man that displays only histologically mature or immature teratoma must be considered to be a fully malignant GCT, and management should proceed as if malignant components are present.

BIOLGY

Adult human male GCTs make up a unique system for the study of the mechanism of transformation of a totipotential germ cell in lineage differentiation. The pluripotentiality of the tumor cells manifests as histologic differentiation into germ cell–like undifferentiated (seminoma), primitive yzygot (embryonal carcinoma), embryonal-like somatically differentiated (teratoma), and extraembryonically differentiated (choriocarcinoma and yolk sac tumor) phenotypes. Until fairly recently, the molecular mechanisms of germ cell transformation, GCT differentiation, or GCT chemotherapy sensitivity and resistance were poorly understood. More recent studies of GCTs have suggested that (1) overexpression of cyclin D2 is an early, possibly oncogenic, event in germ cell tumorigenesis; (2) differentiation in GCTs may be governed by several possibly interacting pathways such as loss of regulators of germ cell totipotentiality and of embryonic development, and genomic imprinting; and (3) chemotherapy sensitivity and resistance may be rooted in part in a p53-dependent apoptotic pathway.

Mechanism of Germ Cell Transformation

Genetic analysis of male GCTs has yielded important data relevant to the mechanism of germ cell transformation. \(^{50}\) Virtually 100% of tumors show increased copy number of 12p, as one or more copies of 12p2 as tandem duplications of 12p, in situ or transposed elsewhere in the genome \((\text{Fig. 36-1})\). \(^{51}\) This chromosomal marker has been observed as early as CIS, suggesting that it is among the earliest, if not the earliest, genetic change associated with the origin of these tumors. A candidate gene, CCND2, mapped to 12p13, has been identified as the possible driver gene on 12p whose deregulated expression may lead to GCT development. \(^{52}\) It is abundantly expressed in CIS as well as in many lineages of GCT. \(^{53}\) Cyclin D2 is one of the D-type cyclins that, along with the cyclin-dependent kinases cdk4, cdk6, or both, regulates the phosphorylation of pRB and controls the G1/S cell-cycle checkpoint. \(^{54}\) Disruption of this checkpoint through amplification or
achieved, as well as show how resistance may be circumvented in GCTs and other tumor types. The mechanisms whereby the unique apoptotic response to chemotherapeutic agents is achieved in GCTs will contribute to the understanding of how such a response is observed in somatically differentiated GCT cell lines, reflecting the relative resistance of teratoma elements of GCT specimens.

Overexpression of bcl-2 in a GCT cell line resulted in sensitization of the cell line to DNA damage-induced cell death. Associated with this sensitization was a decrease in endogenous expression of bcl-x. This decrease in bcl-x expression was observed in those cases where bcl-x overexpression was not associated with a decline in p53 levels, suggesting a potential role for bcl-x in the regulation of apoptosis in GCTs. However, the precise role of bcl-x in the regulation of apoptosis in GCTs remains to be elucidated.

Male GCTs offer a system in which the cellular factors portending exquisite sensitivity to chemotherapy can be studied. Some studies have suggested that the precursor of all GCTs is CIS; however, the stage of germ cell development at which transformation occurs is not known. Two models of origin of CIS cells have been proposed. One model proposed by Skakkebaek and colleagues suggested that gonocytes have been postulated to be susceptible to subsequent invasive growth through the mediation of postnatal and pubertal gonadotrophin stimulation. This hypothesis is based on a consideration of immunophenotypic markers expressed by gonocytes and CIS cells, types of abnormal germ cells seen in developmental disorders that predispose to GCTs, and epidemiology of GCT incidence. A second model proposed by Chaganti and colleagues takes into account four established genetic properties of GCTs, namely, increased 12p copy number, expression of cyclin D2 in CIS, consistent near triploid-tetraploid chromosome numbers, and abundant expression of wild-type p53. According to this model, aberrant chromatid exchange events during meiotic crossing over may lead to increased expression of D-type cyclins and overexpression of cyclin D2 in CIS. A possible mechanism by which embryonal and extraembryonal types of major differentiation paths are initiated in imprint-erased transformed germ cells may be differential oncogene activation.

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A great deal of effort has been directed toward understanding the mechanistic basis of decisions that determine the nature and regulation of proliferation and differentiation signals in the developing zygote. Among GCTs, seminoma can be viewed as transformed germ cells that have retained the inhibitory mechanism for zygotic-like differentiation, a feature of germ cells before fertilization. The in vivo expression patterns of kit receptor and stem cell factor in GCTs are consistent with such a view. Thus, the kit receptor, which normally is expressed by spermatogonia and primary spermatocytes, is expressed mainly by CIS and seminomas. On the other hand, nonseminoma appear to down-regulate kit and up-regulate stem cell factor, consistent with their loss of germ cell phenotype and acquisition of somatic fates. The key developmental difference between seminoma and nonseminoma appears to be the loss of ability to retain germ cell–like totipotentiality by the former.

The ability of GCTs to undergo an embryonal-like developmental program without the contribution of a maternal complement has obvious implications to genomic instability. A genetic abnormality often associated with tumor progression and resistance to therapy in human tumor development.

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Chemotherapy Resistance of Germ Cell Tumors

Molecular genetic studies of GCTs that are clinically resistant to cisplatin-based chemotherapy have identified a subset that harbors TP53 gene mutations. A molecular alteration not normally associated with GCTs. Evaluation of the cellular response to cisplatin in one GCT-derived cell line with a TP53 gene mutation indicated a relative resistance to cisplatin, in contrast to the extreme sensitivity of another GCT-derived cell line with wild-type TP53. Presumably, the cisplatin resistance of this subset of GCTs is rooted in their inability to mount an apoptotic response after drug exposure because of an inactivating TP53 gene mutation. On the whole, these tumors display higher than normal levels of TP53, in contrast to the lower levels observed in mature teratomas. Thus, somatic differentiation associated with a decline in p53 levels may make up a cellular setting for the operation of selective pressure for TP53 gene mutation.

A cohort of cisplatin-resistant GCTs has been analyzed for the presence of amplified DNA sequences, a genetic abnormality often associated with tumor progression and resistance to therapy. In this study, comparative genomic hybridization was performed on a panel of GCTs consisting of 17 resistant and 17 sensitive tumors. High-level amplification of eight chromosomal regions (other than 12p) was detected in five resistant tumors, but in none of the sensitive group. Evaluation of the cellular response to cisplatin in one GCT-derived cell line with a TP53 gene mutation indicated a relative resistance to cisplatin, in contrast to the extreme sensitivity of another GCT-derived cell line with wild-type TP53. Presumably, the cisplatin resistance of this subset of GCTs is rooted in their inability to mount an apoptotic response after drug exposure because of an inactivating TP53 gene mutation. On the whole, these tumors display higher than normal levels of TP53, in contrast to the lower levels observed in mature teratomas. Thus, somatic differentiation associated with a decline in p53 levels may make up a cellular setting for the operation of selective pressure for TP53 gene mutation.

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A role for cyclin D2 in the development of GCTs has also been suggested by Sicinski et al., through studies of mice homozygously inactivated (mutant) for the CCND2 gene, and expression of CCND2 mRNA in ovarian granulosa cells and testicular GCT cell lines. In germ cells that have re-entered cell cycle following cyclin D2 activation, downstream events such as loss of tumor suppressor genes (TSGs) brought about by genomic instability may lead to neoplastic progression. Extensive molecular genetic analysis has identified genomic, functional (expression), or both kinds of loss of several known TSGs such as RB1, DCC, and NME, and genomic loss at several previously recognized as well as novel chromosomal sites.

Embryonal-Like Differentiation in Germ Cell Tumors

Male GCTs display, albeit in a spatially and temporally abnormal manner, patterns of differentiation that mimic stages normally undergone by the developing zygote. Among GCTs, seminoma can be viewed as transformed germ cells that have retained the inhibitory mechanism for zygotic-like differentiation, a feature of germ cells before fertilization. The in vivo expression patterns of kit receptor and stem cell factor in GCTs are consistent with such a view. Thus, the kit receptor, which normally is expressed by spermatogonia and primary spermatocytes, is expressed mainly by CIS and seminomas. On the other hand, nonseminoma appear to down-regulate kit and up-regulate stem cell factor, consistent with their loss of germ cell phenotype and acquisition of somatic fates. The key developmental difference between seminoma and nonseminoma appears to be the loss of ability to retain germ cell–like totipotentiality by the former.

A great deal of effort has been directed toward understanding the mechanistic basis of decisions that determine the nature and regulation of proliferation and differentiation signals in the developing zygote. In this context, GCTs and derived embryonal carcinoma cell lines provide a unique opportunity to study embryonal versus extraembryonal pathways of differentiation, as well as development of somatic lineage. Analysis of genome-wide allelic loss in GCTs showed an overall higher loss in the highly differentiated teratomas compared with the less differentiated embryonal carcinomas. These studies identified chromosomal sites that may harbor effector genes such as transcription factors whose loss may prompt either induction of differentiation or lineage decision.

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IMMUNOHISTOCHEMICAL MARKERS

Seminoma do not display differentiation in vitro or in vivo and do not express markers of somatic differentiation such as low-molecular-weight keratins, vimentin, or blood group antigens. However, essentially all seminoma express PLAP and kit receptor CD117. Embryonal carcinoma and yolk sac tumor do display some somatic differentiation. Surface expression of low-molecular-weight keratins (e.g., AE-1, CAM 5.2) and the type 1 precursor substance of the blood group antigens is variable. Most embryonal carcinoma, but not seminoma, also express the CD30 antigen, originally described as a marker of Hodgkin's disease and anaplastic large cell lymphoma. Vimentin expression is limited to mesenchymal components of mature teratoma and interstitial and other support cells. In tumors of uncertain histogenesis, immunohistochemical studies that include PLAP, kit receptor, and low-molecular-weight keratins may be useful in establishing a diagnosis. It should be remembered that cytokeratins are expressed by all epithelial tumors, and PLAP immunoreactivity is present in a small subset of epithelial neoplasms, especially (but not limited to) those of Müllerian origin.

STAGING

A comprehensive evaluation is necessary to define the extent of disease and to determine the appropriate treatment, and should include pathologic examination of the primary tumor, physical examination, determination of serum concentrations of AFP and HCG, and radiographic studies.

Anatomic Considerations

The initial route of metastasis is lymphatic drainage to retroperitoneal lymph nodes (Fig. 35-2). From the testes, several lymphatic vessels emerge from the mediastinum testis and accompany the gonadal vessels in the spermatic cord. Where the spermatic vessels cross ventral to the ureter, some of these lymphatics diverge medially and drain into the retroperitoneal lymph node chain, whereas others follow the spermatic vessels to their origin. Lymph nodes located lateral or anterior to the inferior vena cava are called paracaval or precaval nodes, respectively. Interaoortocaval nodes are those nodes between the inferior vena cava and the aorta. Nodes anterior or lateral to the aorta are preaortic or paraaortic nodes, respectively. The primary landing zone for a right testicular tumor lies in the interaortocaval nodes immediately below the renal vessels, and the ipsilateral distribution includes the paracaval, preaortic, and right common iliac. The primary landing zone for a left testicular tumor lies in the true paraaortic nodes just below the left renal vessels, and the ipsilateral distribution for the left testis includes the paraaortic, preaortic, and left common iliac nodes. Metastatic nodal disease in more caudal areas such as the common iliac, external iliac, or inguinal lymph nodes is usually secondary to large volume of disease with retrograde spread. If the patient has undergone a heminephrectomy, vasectomy, or other transsurgical procedure unrelated to the tumor, additional attention should be paid to pelvic and inguinal lymph nodes.

Contralateral retroperitoneal metastasis is represented by involvement of nodes usually associated with a tumor from the opposite side. For example, paraaortic lymphadenopathy in the presence of a right-sided primary tumor is considered contralateral. Contralateral spread is more common with right-sided tumors, rare with left-sided primaries, and usually in the setting of large-volume disease.

Retroperitoneal lymphatics continue cephalad and empty into the cisterna chyle via the right and left lumbar trunks. Lymphatic involvement above the retroperitoneal nodes results in involvement of the retrocruclal nodes. Supradiaphragmatic spread occurs via the thoracic duct, leading to posterior mediastinal and left supraclavicular lymph node involvement. The anterior mediastinum is not part of this usual nodal hierarchy.

TUMOR IMAGING

Plain chest radiography and computed tomography (CT) are the most important radiologic investigations in determining extent of disease and treatment. The role of magnetic resonance imaging (MRI) is limited.

Computed Tomography

CT is the most effective radiographic technique for identifying metastatic involvement both above and below the diaphragm. Well-circumscribed pulmonary lesions less than 5 mm may be detected, and although these may represent metastases, many lesions in this size range represent benign processes, and their clinical importance depends on clinical stage. In seminoma, such lesions are usually benign.

CT scan of the abdomen is the best technique for identifying retroperitoneal lymphadenopathy and has replaced intravenous pyelography and lymphangiography. The abdominal CT scan is normal in 70% of newly diagnosed seminoma and at least one-third of newly diagnosed nonseminoma. Because GCTs may grow rapidly, treatment decisions should be made within 4 weeks of the last abdominal CT scan. Lymph nodes in the primary landing zones measuring 10 to 20 mm are involved by GCT approximately 70% of the time and those measuring 4 to 10 mm are involved 50% of the time. The duodenum and proximal jejunum must be adequately opacified by oral contrast. In evaluation of the postchemotherapy mass, the CT scan is unable to distinguish between residual malignant tumor, teratoma, and necrosis or fibrosis; a normal postchemotherapy CT scan does not preclude the presence of disease.

Magnetic Resonance Imaging

Like CT scanning, MRI can identify enlarged lymph nodes. Although MRI occasionally provides valuable preoperative information regarding vascular anatomy and the patency of the great vessels in patients with bulky retroperitoneal disease following chemotherapy, it adds little in the management of most patients with GCT. Both MRI and CT are equally unable to detect viable GCT after chemotherapy.

Lymphangiography

Historically, lymphangiography was used to determine the extent of retroperitoneal involvement in both seminoma and nonseminoma. In most patients, CT scanning has replaced it. The role of lymphangiography is limited to patients with stage I seminoma. In patients with seminoma, lymphangiography may reduce normal tissue irradiation by permitting more precise ports and identifying where a boost of radiation may be needed for abnormal nodes seen on lymphangiography but not evident on CT scan.

Positron Emission Tomography

Studies have compared positron emission tomography (PET) with CT for the evaluation of patients with newly diagnosed disease or residual disease after
chemotherapy. Although early studies suggest that PET may be more sensitive than CT, disease less than 0.5 cm was not detected. In patients with residual disease, PET has not been consistently able to identify residual viable malignant GCT and does not detect teratoma. Therefore, insufficient data exist to recommend PET as part of staging or in the evaluation of residual disease after chemotherapy.

### SERUM TUMOR MARKERS

#### a-Fetoprotein

AFP is a 70,000 molecular-weight glycoprotein produced in the liver, gastrointestinal tract, and fetal yolk sac, and its secretion in GCT is restricted to nonseminomatous histology, usually embryonal cell carcinoma or endodermal sinus tumor. AFP is detected by radioimmunoassay and reported in nanograms per milliliter. The normal adult concentration is usually less than 15 ng/mL. The serum half-life is 5 to 7 days. In patients with pure seminoma, elevated serum concentrations of AFP reflect an undetected nonseminomatous element. An increased serum AFP concentration is present in 10% to 20% of clinical stage I, 20% to 40% of low-volume clinical stage II, and 40% to 60% of high-volume disease. Because of stage migration, the frequency and degree of increased AFP concentrations in patients with advanced tumors has declined. Reproducible prognostic factors predicting retroperitoneal disease in seminoma have not been identified. A Princess Margaret Hospital study of seminoma patients treated with radiation therapy identified anaplastic histology, invasion of the tunica, and invasion of the epididymis as prognostic for relapse.

#### Human Chorionic Gonadotropin

HCG is a glycoprotein composed of two subunits and is produced by syncytiotrophoblasts. The a subunit is identical to that of luteinizing hormone, follicle-stimulating hormone, and thyroid-stimulating hormone. The b subunits of HCG, luteinizing hormone, follicle-stimulating hormone, and thyroid-stimulating hormone are homologous but have distinct amino acid sequences. Elevated serum concentrations can be found in patients with pure seminoma as well as those with nonseminomatous GCT. Most vendors have adopted the World Health Organization Third International Standard (code number 75/537) resulting in some uniformity in the radioimmunoassays to detect the HCG b subunit. The serum half-life is 18 to 36 hours.

Approximately 10% to 20% of patients have advanced pure seminoma have increased serum concentrations of HCG. False elevations of HCG secondary to either cross-reactivity of the antibody with luteinizing hormone, treatment-induced hypogonadism, or pituitary production of HCG have been reported.

#### Lactate Dehydrogenase

The serum level of lactate dehydrogenase (LDH) has independent prognostic significance in patients with advanced GCT and should be determined in all patients. Increases in the serum concentration are a reflection of tumor burden, growth rate, and cellular proliferation. LDH comprises multiple isoenzymes, but, in practice, the combined LDH value for all isoenzymes is used for clinical decision making. Comparison of one laboratory with another is possible by using ratios of the detected level to the upper limit of normal for the individual assay. Increased serum LDH concentrations are observed in approximately 60% of nonseminomatous GCT patients with advanced disease and in 80% of patients with advanced seminoma.

### STAGING CLASSIFICATIONS

Revised tumor, nodes, and metastases (TNM) and stage groupings of the American Joint Committee on Cancer and the Union Internationale Contre le Cancer were adopted in 1997 (Table 35-3A and Table 35-3B). For the first time, an S category for the serum concentrations of AFP, HCG, and LDH was incorporated because of its independent prognostic significance. Broadly, stage I disease is confined to the testis, stage II disease is restricted to the retroperitoneum, and stage III disease represents involvement of supradiaphragmatic or other nodal sites, or visceral disease. Levels of AFP, HCG, and LDH determine overall stage.

#### TABLE 35-3A. TNM Staging of Testis Tumors: American Joint Committee on Cancer

<table>
<thead>
<tr>
<th>T Stage</th>
<th>N Stage</th>
<th>M Stage</th>
<th>Stage</th>
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</thead>
<tbody>
<tr>
<td>T1</td>
<td>N0</td>
<td>M0</td>
<td>I</td>
</tr>
<tr>
<td>T2</td>
<td>N0</td>
<td>M0</td>
<td>II</td>
</tr>
<tr>
<td>T3</td>
<td>N0</td>
<td>M0</td>
<td>III</td>
</tr>
<tr>
<td>T4</td>
<td>N0</td>
<td>M0</td>
<td>IV</td>
</tr>
</tbody>
</table>

#### TABLE 35-3B. TNM Staging of Testis Tumors: American Joint Committee on Cancer

<table>
<thead>
<tr>
<th>T Stage</th>
<th>N Stage</th>
<th>M Stage</th>
<th>Stage</th>
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<tbody>
<tr>
<td>T1</td>
<td>N0</td>
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<td>I</td>
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<td>T2</td>
<td>N0</td>
<td>M0</td>
<td>II</td>
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<td>III</td>
</tr>
<tr>
<td>T4</td>
<td>N0</td>
<td>M0</td>
<td>IV</td>
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</tbody>
</table>

#### Factors Affecting Staging of the Primary Tumor (T Stage)

The T stage of the primary lesion (not size), histology, and serum tumor marker concentrations predict the likelihood of retroperitoneal disease. For nonseminomatous GCT, the presence of either lymphatic or vascular invasion or both has been associated with a higher likelihood of retroperitoneal metastases (approximately 50%) and is now included in the definition of T2. Invasion through the tunica albuginea into tunica vaginalis (also T2), spermatic cord (T3), or scrotum (T4) is an additional adverse feature.

Reproducible prognostic factors predicting retroperitoneal disease in seminoma have not been identified. A Princess Margaret Hospital study of seminoma patients treated with radiation therapy identified anaplastic histology, invasion of the tunica, and invasion of the epididymis as prognostic for relapse. However, other studies have failed to confirm these findings. Similarly, the presence of increased serum concentrations of HCG are not consistently associated with a poor prognosis.
Factors Affecting Staging of Regional (Retroperitoneal) Nodes (N Stage)

Metastatic disease to retroperitoneal lymph nodes is considered to be stage II disease. The classification of retroperitoneal lymph node involvement is based either on pathologic evaluation after RPLND or clinical evidence of retroperitoneal lymph node involvement (see Table 35-3A and Table 35-3B).

PATHOLOGIC STAGING. The number and size of retroperitoneal lymph nodes found at RPLND have prognostic importance. Most retrospective studies report a less than or equal to 35% incidence of recurrent disease when fewer than six nodes are involved with tumor, and the largest node is less than 2 cm, and no extranodal tumor extension is evident. More extensive tumor involvement is generally associated with a recurrence rate of greater than or equal to 50%. Once lymph node involvement is demonstrated, the histology of the primary tumor, and the presence or absence of vascular invasion in the primary tumor do not appear to add prognostic value.

CLINICAL STAGING. The transverse diameter of the largest lymph node has been used to subcategorize stage II disease (see Table 35-3A and Table 35-3B). For seminoma, the size of retroperitoneal adenopathy usually dictates the treatment modality. Relapse proportions after definitive radiation therapy for seminoma increase progressively from approximately 15% for nodes less than 5 cm to approximately 40% to 60% for nodes greater than 5 cm. In nonseminoma, treatment decisions are based on retroperitoneal lymph node size, location of the adenopathy, and the presence and degree of increase in serum tumor marker concentrations.

Prognostic Factors in Advanced Disease

Because 70% to 80% of patients with advanced GCT are cured with modern cisplatin-based chemotherapy, it has become necessary to stratify patients according to the likelihood of cure. Although survival is the best reflection of cure, complete response is often used as a surrogate for cure, since few patients relapse after being rendered free of disease. Histology, metastatic site, primary site, and serum tumor marker concentrations are independent prognostic variables and have been shown to predict the likelihood of cure. Patients who are more likely to be cured (good-risk or good-prognosis subgroup) constitute the majority of GCT patients with advanced disease and should be treated with regimens that have maximum efficacy with minimal toxicity. In contrast, patients who are unlikely to be cured (poor risk or poor prognosis) constitute the minority of patients. For them, more effective therapy is needed; toxicity is an important but secondary issue.

Between 1980 and 1997, several classification algorithms were used to assign good- and poor-risk status based on the extent of disease, specific sites of disease, pretreatment serum tumor marker concentrations, or all these factors. The Memorial Sloan-Kettering Cancer Center (MSKCC) and Indiana University allocation criteria were the most frequently used criteria in the United States and Medical Research Council and European Organization for the Research and Treatment of Cancer (EORTC) criteria in Europe (Table 35-4). A comparison of these four risk criteria in advanced nonseminomatous GCT demonstrated marked differences and revealed that the allocation to either good- or poor-risk categories was in agreement in only 56% of patients. Substantial numbers of patients assigned good-risk status by stringent criteria were classified as poor risk by those that were less stringent. The proportion cured in the poor-risk group increases with less stringent algorithms.

### TABLE 35-4. Comparison of Four Poor-Risk Classification Algorithms

The International Germ Cell Cancer Collaborative Group (IGCCCG), representing GCT clinical trialists from Europe, North America, and Australia, analyzed data from over 5000 patients treated with platinum-based chemotherapy in order to develop a common classification system. The IGCCCG found that the independent prognostic factors for progression-free survival for patients with nonseminomatous GCT included pretreatment levels of LDH, HCG, and AFP; site of the primary tumor (i.e., mediastinal vs. testis or retroperitoneal); and the presence of nonpulmonary visceral metastases (such as bone, brain, or liver metastases). Nonpulmonary visceral metastasis was the only significant prognostic factor in seminoma patients. Investigators agreed on three strata of good-, intermediate-, and poor-prognosis criteria in Europe (Table 35-4). A comparison of these four risk criteria in advanced nonseminomatous GCT demonstrated marked differences and revealed that the allocation to either good- or poor-risk categories was in agreement in only 56% of patients. Substantial numbers of patients assigned good-risk status by stringent criteria were classified as poor risk by those that were less stringent. The proportion cured in the poor-risk group increases with less stringent algorithms.

### MANAGEMENT OF CLINICAL STAGE I DISEASE

#### SEMINOMA

**Radiation Therapy**

Radiation therapy remains the treatment of choice for patients with clinical stage I seminoma. The ipsilateral hemiscrotum does not require therapy unless gross tumor spillage has taken place. A randomized trial shows that a simple paraaortic portal excluding the ipsilateral iliac and pelvic nodes is as effective as the dog-leg portal in overall survival. Although more pelvic relapses may be seen, the toxicity appears less (Fig. 35-3A). This more restricted portal may be considered a standard of care. Conventional fractionation for clinical stage I disease is 150 to 180 cGy/d for five sessions per week using high-energy linear accelerator beams to a total dose of 2500 to 3000 cGy. Elective, prophylactic radiation therapy to the mediastinum is contraindicated. The contralateral testes should be shielded during treatment. Proper shielding results in an exposure less than 1% of the total dose. For left-sided primary testicular tumors, the left renal hilum must be encompassed. Treatment of pelvic lymph nodes is sometimes required for T4 primary tumors or for scrotal violations with tumor spillage. An involved spermatic cord margin at the internal ring...
may also require field extension. The relapse rate within the irradiated portal after adequate radiation therapy is negligible. The systemic relapse rate, usually presenting as a supraclavicular mass, averages 4% to 5% (Table 35-6), and the death rate is under 2%. 95,109,110,111,112,113,114,115

FIGURE 35-3. A: Paraaortic portal for clinical stage I seminoma. B: Contoured anterior and posterior radiation treatment fields for men with clinical stage IIA or IIB left testicular cancer. The diagonally shaded area is an individually made, 8-cm-thick Cerrobend block.

TABLE 35-6. Treatment of Seminoma with Radiation Therapy: Outcome and Relapse Patterns

<table>
<thead>
<tr>
<th>Stage</th>
<th>Radiotherapy</th>
<th>Surgery</th>
<th>Other or Med. (0%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>18/24</td>
<td>21/26</td>
<td>15/20</td>
</tr>
<tr>
<td>IIA</td>
<td>14/21</td>
<td>17/25</td>
<td>13/19</td>
</tr>
<tr>
<td>IIB</td>
<td>17/24</td>
<td>21/25</td>
<td>10/17</td>
</tr>
<tr>
<td>III</td>
<td>20/26</td>
<td>23/26</td>
<td>16/22</td>
</tr>
</tbody>
</table>

As a consequence, surveillance has been studied as the only management after orchiectomy, to be followed by chemotherapy at relapse (Table 35-7). 93,117 The relapse rate is approximately 15%, but the median time to relapse is approximately 12 months, longer than that observed for nonseminomatous GCT. Moreover, relapses have occurred at intervals more than 5 years from diagnosis. 93 In addition, over 5 years of follow-up, surveillance is also approximately 30% less expensive. 118 Therefore, in the United States, observation for clinical stage I seminoma is not considered routine.

TABLE 35-7. Observation in the Management of Clinical Stage I Germ Cell Tumors

NONSEMINOMATOUS GERM CELL TUMORS

Nonseminomatous GCT is thought to be radioresistant, although one randomized trial reported no retroperitoneal relapse after radiation therapy. 119 However, radiation therapy plays no role in its initial management, since chemotherapy for subsequent relapse might be compromised and the systemic relapse rate is higher than for seminoma. 119 If a patient has clinical stage I disease at the conclusion of initial staging, the choice of management options depends on specific histologic features and the status of serum tumor marker concentrations.

Retroperitoneal Lymph Node Dissection

Because of predictable lymphatic metastatic spread, the conventional approach to patients with clinical stage I nonseminomatous GCT has been the modified, bilateral RPLND (Fig. 35-4A). Adequate exposure for RPLND can be achieved through either a thoracoabdominal or transabdominal approach. The standard bilateral infrarhilar RPLND template, which remains the standard against which therapeutic alternatives are judged, includes the precaval, paracaval, interaortocaval, paraaortic, paraaortic, and common iliac lymph nodes bilaterally.

Nerve-sparing RPLND may be of two types: nerve-dissecting or nerve-avoiding. Despite pathologic evidence of new disease, chemotherapy is often not limited to the retroperitoneum.

In the past, most patients undergoing bilateral RPLND experienced retrograde ejaculation and subsequent infertility. An improved understanding of the neuroanatomy of seminal emission and ejaculation, the pattern of retroperitoneal metastasis for right- and left-sided tumors, and surgical mapping studies led to modification of infraradical surgical boundaries and techniques.

NEUROANATOMY. Antegrade ejaculation requires coordination of three separate events: (1) closure of the bladder neck, (2) seminal emission, and (3) ejaculation. The sympathetic fibers that mediate seminal emission emanate primarily from the T-12 to L-3 thoracolumbar spinal cord. In the midretropitoneum, after leaving the sympathetic trunk, the fibers converge toward midline and form the hypogastric plexus near the aortic bifurcation. From the hypogastric plexus, sympathetic fibers travel via pelvic nerves to innervate the vas deferens, seminal vesicles, prostate, and bladder neck. Ejaculation is mediated by combined autonomic and somatic innervation originating at the sacral and lumbar spinal cord levels. Sym pathetic stimulation tightens the bladder neck, while pudendal somatic innervation from S-2 to S-4 causes relaxation of the external urethral sphincter and rhythmic contraction of bulbourethral and perineal muscles. Preservation of ejaculatory capacity requires preservation of paravascular sympathetic ganglia and their fibers, which converge at the superior hypogastric plexus around the aortic bifurcation. Sympathetic and parasympathetic sympathetic fibers can be prospectively identified, meticulously dissected, and preserved.

NERVE-SPARING RETROPERITONEAL LYMPH NODE DISSECTION. Nerve-sparing RPLND may be of two types: nerve-dissecting or nerve-avoiding. Despite pathologic stage II disease in patients selected for this procedure, recurrences in the retroperitoneum are rare. Modified, nerve-avoiding RPLND templates were designed to avoid the hypogastric plexus and contralateral sympathetic fibers responsible for ejaculation in clinical stage I or IIA disease. These templates do not attempt to identify specific nerve fibers. Rather, their design minimizes trauma to the hypogastric plexus by limiting the contralateral dissection to the level above the takeoff of inferior mesenteric artery. This method avoids transaction of the contralateral nerves and results in preservation of ejaculation rates in approximately 50% to 80% of patients. These rates are higher for a right-sided, nerve-avoiding template dissection compared with modified, left-sided dissection.

Preservation of ejaculation appears to be more successful when nerves are prospectively identified and spared, compared with modified template dissection, although duration of operation is usually longer for the former. With nerve dissection, approximately 95% of patients are left with normal ejaculatory status postoperatively.

For patients with clinical stage I disease experiencing a late relapse (greater than 2 years after initial treatment), the retroperitoneum was the most common site of recurrence. Furthermore, 11 of 12 patients with low-volume retroperitoneal disease and three with high-volume disease had received adjuvant cisplatin-based chemotherapy.

Several investigators have reported that laparoscopic retroperitoneal lymph node dissection (LRPLND) for clinical stage I nonseminomatous testicular cancer is technically feasible. After a lengthy learning curve, postoperative morbidity, operative blood loss and length of hospital stay may be significantly less compared with open surgery. However, several important points must be emphasized. First, surgical templates are limited to the ipsilateral side with omission of interaortocaval dissection for left-sided tumors. Second, therapeutic efficacy is difficult to assess, since all patients with retroperitoneal disease, regardless of tumor volume, were treated with postoperative chemotherapy, including two patients with microscopic metastases who received three cycles of cisplatin, etoposide, bleomycin (BEP). Finally, available follow-up is short. Late relapses are potentially catastrophic with inadequate control of the retroperitoneum. In patients with clinical stage I disease experiencing a late relapse, the retroperitoneum was the most common site of recurrence. Furthermore, 11 of 12 patients with low-volume retroperitoneal disease and three with high-volume disease had received adjuvant cisplatin-based chemotherapy.

Therefore, LRPLND is not routine and should only be considered by those who are experts.

Obsevation

The driving forces for observation studies in clinical stage I patients were the infertility resulting from RPLND (due to retrograde ejaculation), the frequent absence of therapeutic benefit (i.e., orchiectomy was a curative procedure or systemic disease occurred in the absence of retroperitoneal disease), and the ability of chemotherapy to cure systemic disease. Approximately 25% of patients with T1N0M0 disease and normal serum tumor markers relapse during observation (see Table 35-7). However, several important points must be emphasized. First, surgical templates are limited to the ipsilateral side with omission of interaortocaval dissection for left-sided tumors. Second, therapeutic efficacy is difficult to assess, since all patients with retroperitoneal disease, regardless of tumor volume, were treated with postoperative chemotherapy, including two patients with microscopic metastases who received three cycles of cisplatin, etoposide, bleomycin (BEP).

Finally, available follow-up is short. Late relapses are potentially catastrophic with inadequate control of the retroperitoneum. In patients with clinical stage I disease experiencing a late relapse (greater than 2 years after initial treatment), the retroperitoneum was the most common site of recurrence. Furthermore, 11 of 12 patients with low-volume retroperitoneal disease and three with high-volume disease had received adjuvant cisplatin-based chemotherapy. Therefore, LRPLND is not routine and should only be considered by those who are experts.

Chemotherapy

There are limited data regarding chemotherapy as initial treatment of clinical stage I disease when the risk of retroperitoneal disease is high. In three reports of patients receiving two cycles of cisplatin-based chemotherapy, fewer than 5% relapsed and approximately 1% died of GCT. Although this approach avoids RPLND and the duration of therapy is brief, these patients are exposed to the transient (e.g., myelosuppression), permanent (e.g., neuropathy), and delayed (e.g., Raynaud’s phenomenon, acute leukemia) toxicities of chemotherapy.

Rarely, patients with clinical stage I disease are found to have persistently elevated serum concentrations of AFP, HCG, or both after orchiectomy. If these markers increase or plateau at an elevated level after a period of observation, metastatic disease is present. This group of patients should receive initial systemic chemotherapy, since the disease is often not limited to the retroperitoneum. An RPLND should be done only if clinical studies at the conclusion of therapy demonstrate new disease.

MANAGEMENT OF CLINICAL STAGE II (Low Tumor Burden)

SEMINOMA

Low-tumor-burden stage II seminoma includes all patients with retroperitoneal metastases measuring less than 5 cm in maximum transverse diameter (clinical stages...
IIA and IIB; see Table 35-6). Radiation therapy is the treatment of choice for most patients with these stages of disease. A dog-leg radiation portal is used. Fractionation is the same as that of patients with clinical stage I disease, except that a boost of approximately 500 to 750 rads is administered to involved lymph nodes (see Fig. 35-1B). Relapses occur in from 5% to 15%, and death from seminoma is rare. Prophylactic mediastinal radiation therapy is not indicated, since relapses solely in the anterior or posterior mediastinum are infrequent (see Table 35-6). The combination of supradiaphragmatic and infradiaphragmatic radiation therapy results in chemotherapy intolerance, a high rate of treatment-related mortality due to chemotherapy, and a greater than expected death rate from disease due to the inability to administer adequate doses of chemotherapy.

There are exceptions to the need for radiation therapy for clinical stage I and nonbulky clinical stage II seminoma. (1) A horseshoe kidney is a contraindication to retroperitoneal radiation therapy due to the high likelihood of radiation-induced renal failure. Observation is preferred in clinical stage I, and primary chemotherapy is the treatment of choice for clinical stage II. (2) Patients who develop a second metachronous testicular GCT and who have undergone a prior RPLND or received radiation therapy should be observed frequently if clinical stage I disease is present and undergo primary chemotherapy in the unlikely event that the disease is confined to residual retroperitoneal lymph nodes. (3) Inflammatory bowel disease may also be a contraindication to radiation therapy. A discussion with an experienced radiation oncologist is indicated under such circumstances. If the decision is not to administer radiation therapy, then the management policies noted previously for patients with a horseshoe kidney should be followed.

**NONSEMINOMATOUS GERM CELL TUMORS**

Low-tumor-burden clinical stage II nonseminomatous GCT encompasses disease ipsilateral to the primary tumor, at or below the renal hilum, not associated with tumor-related back pain, and limited to the primary landing zone. The presence of suprahilar or retrocrural lymphadenopathy, bilateral retroperitoneal nodal masses, or contralateral back pain, or contralateral lymph nodes (even if the ipsilateral lymph nodes do not appear to be involved) generally implies unseetable disease (e.q., tumor-associated back pain) or a higher likelihood of metastatic disease (suprahilar and retrocrural adenopathy), and initial chemotherapy is preferred. Ipsilateral solitary lymph nodes less than 3 cm are best handled by RPLND. Lymph nodes between 3 to 5 cm, even if solitary, may be associated with more extensive disease than can be detected on abdominal CT scan.

**Retroperitoneal Lymph Node Dissection**

The standard approach to patients with clinical stage IIA and some IIB tumors has been RPLND. The priority is to perform a definitive therapeutic operation, following which there is a minimum likelihood of infiel recurrence. Margins of resection should not be compromised in an attempt to maintain eualutory function. Nerve-sparing dissection may be possible, depending on the location and volume of disease.

An important exception to this approach may be patients with clinical stage IIA or IIB and elevated serum tumor markers. Investigators at MSKCC reported that elevated serum tumor markers pre-RPLND were the most significant predictor for (1) relapse in patients with low-volume (pN1) retroperitoneal disease who did not receive adjuvant chemotherapy, and (2) for persistent nonseminomatous GCT (usually persistent marker elevation) despite complete resection of high-volume (pN2, pN3) retroperitoneal disease. Elevated serum tumor markers usually reflect systemic disease, and these patients should be considered for primary cisplatin-based chemotherapy. However, for patients with apparent low-volume disease and normal markers, RPLND is often therapeutic and cost effective.

**Adjuvant Chemotherapy**

Surveillance is a treatment choice for compliant patients with fewer than six involved nodes and none greater than 2 cm (Table 35-8). Surveillance requires close monitoring, and chemotherapy is reserved for patients who relapse. Patient compliance, psychological factors, age, or other issues may make adjuvant chemotherapy the preferred choice in rare patients. Three or four cycles of cisplatin-based therapy are required at relapse according to disease status at that time.

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**TABLE 35-8.** Pathologic Stage II Nonseminomatous Germ Cell Tumors: Surveillance for Minimal Nodal Involvement at Retroperitoneal Lymph Node Dissection

Adjuvant chemotherapy remains a strong consideration in patients when greater than or equal to six nodes are involved, any node is greater than 2 cm, or there is extranodal extension. In the late 1970s, treatment programs based on cisplatin, vinblastine, and bleomycin were given as adjuvant therapy following RPLND, and nearly 100% of patients survived relapse free. Considerable treatment-related morbidity was associated with these regimens, prompting efforts to reduce toxicity. Two cycles of cisplatin-based chemotherapy are nearly always effective in preventing relapse (Table 35-9). A randomized trial showed that observation with standard treatment at relapse and two cycles of adjuvant chemotherapy had equivalent survival. Etoposide has replaced vinblastine in adjuvant regimens. A more recent study showed that etoposide plus cisplatin alone is adequate, and that bleomycin is unnecessary as part of adjuvant therapy.

**TABLE 35-9.** Cisplatin -Containing Adjuvant Chemotherapy Trials

**IDENTIFICATION OF RELAPSE**

Careful periodic follow-up after locoregional therapy is required after radiation therapy for clinical stage I, IIA, and IIB seminoma during observation for clinical stage I nonseminomatous GCT, and after RPLND without adjuvant chemotherapy. After radiation therapy, a chest radiograph, determination of serum concentrations of AFP and HCG, and a physical examination should be performed every 6 weeks to 3 months in the first year, every 3 to 4 months in the second year, and less frequently thereafter. An abdominal CT scan should be done at the conclusion of radiation therapy. Following RPLND, a chest radiograph, determinations of serum concentrations of AFP and HCG, and a physical examination are required every 1 to 2 months in the first year, every 2 to 3 months in the second, and less frequently thereafter.
in the third year and beyond, with annual visits to detect late relapse and second primary tumors after the fifth year. Provided that follow-up has been adequate, virtually all of these patients relapse with low-volume disease and are cured with chemotherapy.

MANAGEMENT OF STAGE II AND STAGE III DISEASE (HIGH TUMOR BURDEN)

High-burden disease includes all patients with extensive or bulky retroperitoneal, supradiaphragmatic nodal or visceral metastases, including patients with stage IIC seminoma. This last group has a high relapse rate with radiation therapy alone (see Table 35-6).

Cisplatin-based chemotherapy cures 70% to 80% of those patients. Early clinical trials developed effective regimens such as cisplatin, vinblastine, and bleomycin, which eliminated maintenance therapy, and replaced vinblastine with etoposide. Adjunctive surgery was shown to be essential to achieving a disease-free state. Although the majority of patients was cured, significant adverse events were observed, including treatment mortality, myelosuppression, pulmonary fibrosis, Raynaud's phenomenon, coronary artery disease, nephrotoxicity, and intestinal ileus. Good- and poor-risk allocation algorithms were developed and clinical trials performed to address issues represented by different risks of treatment failure. The commonly used standard treatment regimens are summarized in Table 35-10.

Table 35-10. Commonly Used Chemotherapy Regimens for Metastatic Germ Cell Tumors

GOOD-PROGNOSIS GERM CELL TUMOR

Good-risk patients are those with a high likelihood of cure. All good-risk allocation criteria identify patients with a high probability of complete response. Response proportions range from 88% to 95% with favorable survival distributions. Since the advent of good-risk stratification, trials have focused on eliminating bleomycin from treatment regimens, reducing the number of cycles of therapy, and substituting carboplatin for cisplatin (Table 35-11).

Table 35-11. Randomized Trials in Good-Prognosis Germ Cell Tumors

A randomized trial performed by Indiana University examined the duration of therapy in 184 patients who received either four cycles of BEP administered over 12 weeks or three cycles administered over 9 weeks. Bleomycin was discontinued for any clinically evident pulmonary toxicity. A disease-free status was achieved by 98% of patients receiving three cycles, and 92% survived, compared with a 97% disease-free status and 92% survival among patients treated with four cycles.

Three randomized clinical trials have evaluated the elimination of bleomycin from regimens containing etoposide and cisplatin. Etoposide and cisplatin (EP) for four cycles was compared with a five-drug, bleomycin-containing regimen (cisplatin, vinblastine, bleomycin, dactinomycin, and cyclophosphamide) in 164 evaluable patients and was found to be therapeutically equivalent. A subsequent analysis evaluated late relapse in patients receiving EP, and none were observed with a median follow-up of 5 years. A randomized trial of cisplatin and etoposide (BEP) and without bleomycin (EP) was performed by the EORTC in 395 patients. The dose of etoposide in this study was 360 mg/m^2 per cycle, with the dose modifications for thrombocytopenia in contrast to 500 mg/m^2 per cycle without dose attenuations in American trials. The bleomycin arm was more toxic, including Raynaud's phenomenon in 8% of patients and two patients who died of pulmonary toxicity. Complete response was lower in EP patients (87% vs. 95%, P = .0075), but no differences were observed in relapses, time to progression, or survival with 7 years of follow-up. It can be concluded from this study that bleomycin cannot be deleted from good-risk therapy when European doses of etoposide are used.

A French trial directly compared three cycles of BEP to four cycles of EP in 250 patients. This trial used standard doses of bleomycin (30 U/week days 1, 8, and 15 of each cycle) and an etoposide dose of 100 mg/m^2 on days 1 through 5 (total 500 mg/m^2/cycle) in both arms of the trial. The criteria for good risk were those developed by the Institute Gustave Roussy: 97% of patients were good-risk by the IGCCCG criteria. With a median follow-up of 24 months, the survival was similar in both arms [97% for BEP (three cycles) vs. 96% for EP (four cycles)]. Finally, three cycles of BEP were compared with three cycles of EP in 166 patients. The number of patients with persistent or progressive carcinoma, relapse or viable cancer at postchemotherapy surgery was the end point. An interim analysis revealed an increased number of adverse events in the two-drug arm, resulting in early termination of the study.

Two randomized trials have evaluated the substitution of carboplatin for cisplatin in a multiminstitutional trial of 265 patients, four cycles of carboplatin plus etoposide were compared with four cycles of EP. Although the proportions of complete response did not differ significantly, patients receiving carboplatin plus etoposide had an inferior event-free (complete response or relapse) (P = .02) and relapse-free (P = .005) survival, and significantly worse myelosuppression requiring platelet transfusions and hospitalization for granulocytopenic fever. In subset analysis, carboplatin plus etoposide was inferior to EP in both seminoma and nonseminoma patients. The Medical Research Council and EORTC conducted a confirmatory, randomized trial comparing carboplatin, etoposide, and bleomycin with BEP in 598 patients. Bleomycin was administered at 30 U once every 3 weeks. Complete response was greater in patients allocated to BEP (94% vs. 87%, P = .009). Survival was inferior in carboplatin, etoposide, and bleomycin (P = .003), with BEP patients experiencing a 3-year survival of 97% compared with 90% for carboplatin, etoposide, and bleomycin. Conventional dose carboplatin therapy is inferior to cisplatin therapy in GCT patients.

Although good-risk studies differ in eligibility criteria, an efficacy threshold has been reached. Cisplatin-based therapy (greater than or equal to 100 mg/m^2/cycle) is required; there is no role for carboplatin-based therapy. Four cycles of EP and three cycles of BEP using a 500 mg/m^2 cumulative dose of etoposide per course are therapeutically equivalent in randomized comparison.
In the retroperitoneum, necrosis and fibrotic debris make up 45% to 50% of pathologic findings, teratoma another 35%, and viable GCT the remaining 15% to 20%.

**MANAGEMENT OF RESIDUAL DISEASE**

**High-Dose Therapy**

The success of high-dose, carboplatin-containing chemotherapy in the treatment of patients with refractory disease led to its incorporation into initial therapy. Stringent selection criteria for high-dose retroperitoneal resection are required to minimize treatment-related morbidity and mortality. Two pilot studies clarify high-dose therapy requirements in this setting. In these studies conducted at MSKCC, 58 poor-risk patients were first identified based on clinical presentation, and further selected to receive high-dose therapy based on the clearance of AFP, HCG, or both from serum during standard induction therapy. If the half-life was prolonged, treatment was changed to two-drug, high-dose therapy (etoposide and carboplatin). Hematopoietic reconstitution was rapid, only one treatment-related death was observed, and an improved survival trend was observed when this approach was compared with historic poor-risk experience with conventional dose, cisplatin-based combination therapy.

One randomized trial of dose-intensified therapy failed to show a therapeutic benefit. Greater treatment-related morbidity and mortality and lower survival were observed in the high-dose therapy arm. However, the trial was flawed because of a lower dose intensity of cisplatin and a lower total dose of cisplatin in the high-dose arm. Since cisplatin, 200 mg/m², is not superior to cisplatin 100 mg/m², the choice of cisplatin over carboplatin did not permit an adequate dose escalation to overcome resistance.

An ongoing national randomized trial is comparing four cycles of BEP to two cycles of BEP followed by two cycles of three-drug, high-dose therapy in poor- and intermediate-risk patients, and patients should participate if possible.

**Retropertioneum**

NONSEMINOMATOUS GERM CELL TUMORS. In the retropertioneum, necrosis and fibrotic debris make up 45% to 50% of pathologic findings, teratoma another 35%, and viable GCT the remaining 15% to 20%.

**TABLE 35-12. Results of Randomized Trials in Patients with Poor-Risk Germ Cell Tumors**

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**TABLE 35-13.** A bilateral RPLND is required, and retrograde ejaculation is the principal long-term consequence.
There is general agreement over the need to resect all sites of measurable residual disease. Since nearly 50% of resected residual retroperitoneal tumors have only necrosis and fibrosis, many studies have attempted to predict their presence. Among 80 patients with sequential CT scans before and after chemotherapy at Indiana University, necrotic viable GCT or teratoma was found among 15 patients if no teratoma was present in the primary tumor and the retroperitoneal tumor volume (not diameter) by CT scan had decreased by less than or equal to 90%. Conversely, teratoma in the primary tumor predicts the presence of teratoma or viable GCT in the postchemotherapy resection despite regardless in the original tumor mass. Other data suggest that RPLND may be needed regardless of the definition. A small percentage of patients requires operation at multiple sites, usually the retroperitoneum and lung and (less frequently) the neck.

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Lung and Mediastinal Resections

Lung and Mediastinal Resections

Careful observation is an alternative, but relapse with subsequent ifosfamide-based salvage chemotherapy has a low cure rate. Consequently, peroperative morbidity has been reported to be higher for seminoma than for nonseminomatous GCT. If viable carcinoma is present, it is partially drug-resistant and will progress. The cure rate of relapsed disease to ifosfamide-based therapy is approximately 25%. If viable disease is completely resected and two additional cycles of cisplatin-based therapy are administered, the cure rate is 50% to 70%. Teratoma may be found in metastatic sites despite its absence in the primary tumor. Toner et al. reported that among 75 patients without teratoma in the primary tumor who underwent resection of a residual mass, 25 (33%) had teratoma at a metastatic site. Mature teratoma may grow rapidly (growing teratoma syndrome), become unrespectable, or cause vascular or ureteral obstruction. Malignant transformation of teratoma (i.e., the development of non–germ cell malignant elements such as sarcoma or carcinoma) is present in a minority of resected retroperitoneal teratoma. These are clonal in origin with the original GCT and do not represent second primary cancers. Surgery is the only therapy (except for leukemia) for this subset of tumors that would otherwise recur and fail to respond to additional chemotherapy. Late local recurrence (defined as greater than 2 years after therapy) of both teratoma and viable GCT is more common when teratoma is present at a metastatic site. No postoperative deaths occurred. Conversely, among 74 tumors measuring less than 3 cm in diameter, no viable tumor was identified, and there were no in-hospital recurrences. The best oncologic approach in patients requiring postchemotherapy RPLND remains a bilateral dissection with a nerve-sparing approach limited to a minority of patients.

In summary, all residual retroperitoneal disease should be resected. The need for postchemotherapy RPLND is controversial when the postchemotherapy CT scan, usually of the retroperitoneum, is interpreted as normal. Multivariate analyses show that approximately 20% of patients predicted to have necrosis (fibrosis) have either teratoma or viable GCT. No single criterion or combination of criteria predict a negative pathology with sufficient accuracy to eliminate the risk of residual teratoma or viable GCT and obviate postchemotherapy RPLND. The risks of residual teratoma must be weighed against the growth and metastatic potential of viable GCT and the morbidity of the procedure.

SEMINOMA. The approach to the patient with pure seminoma and a postchemotherapy residual mass is controversial. Two important features distinguish seminoma from nonseminomatous tumors. First, teratoma in the residual mass is rare. Second, a complete RPLND following chemotherapy is often not technically feasible, secondary to the severe desmoplastic reaction and obliteration of tissue planes. Consequently, peroperative morbidity has been reported to be higher for seminoma than for nonseminomatous GCT.

A number of studies evaluated this issue in seminoma patients. Loehrer et al. reported that among 62 patients, 13 underwent attempted surgical excision of residual disease and three (23%) had residual malignancy. The size of residual mass was not considered predictive. Fossa et al. reported 39 patients, 15 of whom received prior radiation therapy. Twelve patients underwent exploration for residual disease; three (25%) had viable seminoma. One postoperative death due to pulmonary toxicity was observed. In a cohort of 45 patients, the size of residual mass was highly correlated with the site of the initial tumor but was not associated with the risk of recurrence. These data support the notion that the majority of patients with persistent radiographic abnormalities do not have residual malignant disease.

The experience at MSKCC differed. Bilateral RPLND was not usually possible or attempted; surgery was often limited to resection of the residual mass or multiple biopsies of the residual radiographic abnormality. In an initial cohort of 104 patients, 8 of 30 (27% of patients with a residual mass greater than 3 cm) relapsed or had residual seminoma. No postoperative deaths occurred. Conversely, among 74 tumors measuring less than 3 cm in diameter, no viable tumor was identified, and only two patients (3%) relapsed at the site of residual disease. Neither of these had undergone operation. Fewer tumors greater than 3 cm were present among patients treated after 1987 compared with those treated before 1987. Those investigators concluded that resection or biopsy of the residual masses greater than or equal to 3 cm was preferable to observation. If viable seminoma was documented, additional therapy was required.

In summary, residual masses less than 3 cm should be observed. Controversy exists regarding the minority of patients with a residual mass measuring greater than or equal to 3 cm. Radiation therapy to the area of residual disease is feasible, but approximately 75% of patients would receive it unnecessarily and it did not appear to reduce the likelihood of recurrence. Careful observation is an alternative, but relapse with subsequent ifosfamide-based salvage chemotherapy has a low cure rate. Size of the pretreatment and the postchemotherapy pulmonary nodule does not correlate with final histology. Different histologies may also be present in each lung. Therefore, residual intrathoracic disease should always be resected.

Lung and Mediastinal Resections

Resection of residual disease at sites other than the retroperitoneum is less controversial. There is a higher likelihood of teratoma, viable cancer at nonretropertoneal sites, or both, with the highest likelihood seen in the mediastinum, probably because residual disease in the mediastinum is usually associated with a mediastinal primary tumor. Size of the pretreatment and the postchemotherapy pulmonary nodule does not correlate with final histology. Different histologies may also be present in each lung. Therefore, residual intrathoracic disease should always be resected.

Other Procedures

A small percentage of patients requires operation at multiple sites, usually the retroperitoneum and lung and (less frequently) the neck. Histology at different sites is not predictable based on histology at one site. When the histologic specimen from the retroperitoneum is compared with that from a second site, the histologies are
dissimilar in approximately 35% of cases. 

When the lung and retroperitoneum are simultaneously involved, multiple, separate procedures may be required, but simultaneous bilateral thoracic and retroperitoneal resections are possible. If a primary testis tumor is present and an orchidectomy is not performed before chemotherapy, then it should be performed after chemotherapy, as that testis may harbor viable residual disease. Studies confirm that all sites of residual disease should generally be resected regardless of histologic findings at the initial procedure.

MANAGEMENT OF RELAPSE AFTER CHEMOTHERAPY

Twenty percent to 30% of patients with advanced GCT relapse or fail to achieve a complete response to conventional cisplatin-based chemotherapy. Effective (and curative) second- and third-line salvage offer further treatment options.

CONVENTIONAL DOSE SALVAGE THERAPY

After the single-agent activity of ifosfamide was identified, it was combined with cisplatin and etoposide or cisplatin and vinblastine in patients whose disease was resistant to two prior regimens (Table 35-14). In this heavily pretreated group, between 25% and 35% of patients achieved a complete response, and 15% to 27% remained in durable complete remission. Nephrotoxicity and severe neutropenia were extremely common. Results suggesting an improved complete response rate when paclitaxel is substituted for vinblastine await completion of ongoing phase II studies.

TABLE 35-14. Ifosfamide-Based Salvage Regimens for Relapsed and Refractory Germ Cell Tumors

HIGH-DOSE THERAPY

The chemosensitivity of GCT, the dose-response phenomena for individual drugs, the rare occurrence of bone marrow metastasis, and a young patient population permit consideration of high-dose therapy. More recent studies have included carboplatin and etoposide with or without an oxazaphosphorine (cyclophosphamide or ifosfamide) and show that a proportion of patients can be cured. In three relatively large series conducted in patients with refractory, progressive GCT, 15% to 21% of patients remained alive and disease-free with long-term follow-up. While these series demonstrate the curative potential of high-dose therapy, the majority of patients with cisplatin-refractory GCT die of disease, and new drugs and strategies are still needed. Studies incorporating paclitaxel are ongoing.

TABLE 35-15. High-Dose Carboplatin-Containing Chemotherapy in Patients with Refractory, Progressive Germ Cell Tumor

The major toxicities of dose-intensive therapy are hematologic and infectious, with most studies reporting a 10% to 12% treatment-related death rate. Hematopoietic growth factor support decreases the duration of neutropenia and hospitalization. Peripheral blood-derived stem cells have largely replaced the use of autologous bone marrow, and a randomized trial showed that peripheral blood-derived stem cells result not only in rapid neutrophil reconstitution but also faster platelet engraftment.

PROGNOSTIC FACTORS: SALVAGE CHEMOTHERAPY

Despite an occasional cure, the majority of patients receiving salvage chemotherapy fail to achieve a durable complete response and are subsequently considered for high-dose chemotherapy. Prognostic factors can be used to predict which patients are most likely to benefit from conventional dose salvage therapy. Patients with a testis primary site and a prior complete response have a better prognosis, and conventional dose cisplatin salvage therapy (vinblastine, ifosfamide, and cisplatin) is reasonable in these patients. Patients with an incomplete response to initial therapy or a relapsing extragonadal nonseminomatous GCT have a less than 10% 3-year survival response to conventional dose, cisplatin-containing salvage therapy. In these circumstances, a dose-intensive program, a novel treatment strategy, or a new agent should be considered. The contribution of serum tumor marker concentrations to prognosis in this group of patients has not been established.

Prognostic factors can also be used to identify patients most likely to benefit from salvage high-dose, stem cell–supported, carboplatin-containing chemotherapy. Patients with primary mediastinal GCT refractory to initial and salvage chemotherapy, patients with absolute refractory disease (rising markers or radiographic evidence of progressive disease within 4 weeks of cisplatin therapy), and patients with high HCG levels rarely achieve a complete response. These patients should be considered for phase II studies. All other patients are candidates for a high-dose approach.

NEW AGENTS

A number of single-agent trials have been conducted against refractory GCT. Because paclitaxel is synergistic with cisplatin and oxazaphosphorines in vitro, it is being studied in dose-intensive therapy with peripheral blood-derived, stem cell support, and in conventional dose therapy with ifosfamide plus cisplatin. Oral etoposide plays a palliative role in refractory GCT.

ROLE OF SURGERY

Histologic findings of resected masses following second-line or salvage chemotherapy differ from those observed following primary therapy. Viable tumor occurs in...
indicating that this group of midline tumors has a heterogeneous histogenesis. Therefore, genetic analysis using conventional and molecular techniques has both complete plus partial response proportion to cisplatin-based therapy and longer survival were associated with the presence of a GCT genetic marker. Extragonadal GCT was suggested despite the absence of increased serum concentration of AFP, HCG, or both in most cases. This phenomenon. Occurs in the absence of cisplatin (albeit less frequently). Vascular toxicity, most prominently as Raynaud's phenomenon, occurs in a minority (less than 10%) of patients receiving bleomycin administered by weekly bolus. It is greatest after 10 years. Pulmonary toxicity from bleomycin is rare but can be fatal. In one randomized trial, it resulted in approximately one-half of the treatment-induced deaths. In good-risk patients, a reduction in the number of bleomycin doses from 12 to 9 resulted in no bleomycin-related, treatment-related deaths. Pulmonary function tests (vital capacity and diffusion capacity of carbon monoxide) have been used to dictate changes in bleomycin administration. However, the diffusion capacity of carbon monoxide may not predict clinically significant bleomycin-induced lung damage. Vascular toxicity, most prominently as Raynaud's phenomenon, occurs in a minority (less than 10%) of patients receiving bleomycin administered by weekly bolus. It occurs in the absence of cisplatin (albeit less frequently). The substitution of etoposide for vinblastine did not reduce the incidence of Raynaud's phenomenon. Erectile dysfunction may be associated with Raynaud's phenomenon as a sign of microvascular angiopathy. Other vascular events include pulmonary embolism, angina and myocardial infarction. Coronary artery disease resulting from mediastinal radiation therapy is well recognized and emphasizes the need to avoid mediastinal radiation therapy in the management of patients with seminoma. Infertility is an important consideration. A minority of patients is infertile at diagnosis. Reduced spermatogenesis and higher follicle-stimulating hormone levels compared with healthy men are frequent in newly diagnosed patients. A similar impairment of testicular function occurs in men with CIS (intratubular germ cell neoplasia). However, paternity in patients on surveillance for clinical stage I disease did not seem to be reduced. A standard, modified bilateral RPLND causes retrograde ejaculation in nearly all patients. Nerve-dissecting and nerve-avoiding RPLND reduce, but do not eliminate, that risk. Chemotherapy may affect the germinal epithelium directly, and Leydig cell insufficiency is frequent. After chemotherapy, persistent oligospermia and abnormal forms and motility have been reported, but may occur despite oligospermia. Second malignancies are rare. Metachronous GCT appearing in the contralateral tests occurs in approximately 2% to 3% of all patients. After the second orchietomy, replacement testosterone is required to maintain normal serum testosterone levels, secondary sexual characteristics, and sexual function. Etoposide causes secondary leukemia characterized by translocations involving chromosome 11q in fewer than 0.5% of patients receiving a total dose less than 2000 mg/m². And as many as 6% of patients receiving total etoposide doses of greater than 3000 mg/m². However, reports showed acute leukemia in 0.8% to 1.3% of patients receiving median cumulative etoposide doses greater than 2400 mg/m². The latent period is short, averaging 2 to 4 years. The incidence of gastrointestinal malignancies increased after radiation therapy or radiation therapy plus chemotherapy. The relative risk increases with time and is greatest after 10 years. Stomach cancer is the most prevalent gastrointestinal tumor. An excess of soft tissue sarcoma has also been observed. The latent interval is long, and radiation therapy was implicated in the majority. These second malignancies do not outweigh the enormous benefits of treatment intervention. Along with the risk of recurrence, these second primary neoplasms emphasize the need for long-term follow-up of treated patients. Sarcoïdosis appears more frequently in GCT patients. Strictly speaking, it is not a sequel of therapy. It occurs both before and after GCT diagnosis. Paratracheal adenopathy or pulmonary nodules without retroperitoneal adenopathy or elevated serum tumor marker levels, particularly in patients with seminoma, suggest the possible presence of sarcoïdosis and should lead to biopsy.

MIDLINE TUMORS OF UNCERTAIN HISTOGENESIS

A subset of patients with poorly differentiated carcinoma of unknown histogenesis and uncertain primary site achieve complete response and long-term survival following treatment with cisplatin-combination therapy. In a series of 220 patients, 26% of patients achieved a complete response; the 10-year actuarial survival was 16%. Because of cisplatin sensitivity, predominant midline tumor distribution, and occurrence in relatively young patients, the presence of unrecognized extragonadal GCT was suggested despite the absence of increased serum concentration of AFP, HCG, or both in most cases. Since 12(p) is a specific chromosomal marker characterizing GCT, genetic analysis was undertaken. (12p) and chromosome 12 aneuploidy were identified by conventional or molecular cytogenetic analysis or Southern blot analysis for 12p copy number, permitting a diagnosis of GCT in approximately 30% of such tumors. A significantly greater complete plus partial response proportion to cisplatin combination and longer survival were associated with the presence of a GCT genetic marker. Genetic analyses also identified other tumors such as primitive neuroectodermal tumors, lymphoma, desmoplastic small cell tumor, melanoma, and clear cell sarcoma, indicating that this group of midline tumors has a heterogeneous histogenesis. Therefore, genetic analysis using conventional and molecular techniques has both
CHAPTER REFERENCES


OTHER TESTICULAR TUMORS

LEYDIG CELL TUMORS

Leydig cell (interstitial cell) tumors account for approximately 2% of testicular tumors. Approximately 75% appear in adults who present with a palpable mass or testicular swelling indistinguishable from GCT. A minority has gynecomastia or decreased libido. The remaining 25% of cases present in children, sometimes with signs of sexual pseudoprecocity such as pubic hair, voice change, or enlarged genitalia. A testicular mass associated with virilization in a prepubertal patient is a Leydig cell tumor until proven otherwise. There is no association between Leydig cell tumors and cryptorchidism. These tumors consist of tightly packed polygonal cells with eosinophilic granular cytoplasm and round nuclei with prominent nucleoli. Characteristic intracytoplasmic inclusion bodies (Rinke crystals) are seen in approximately 25% to 40% of cases. A radical inguinal orchietomy is required, and clinical staging includes a chest radiography, CT scan of the abdomen and pelvis, and studies for urine and serum steroids.

Most Leydig cell tumors are benign. Malignant potential is difficult to predict. Vascular invasion, cellular atypia, tumor necrosis, infiltrative margins, increased mitotic rate, tumor size less than 5 cm and older age at presentation have been reported to be predictive of malignant potential. Metastases are the only reliable criteria of malignancy. The most frequent sites of metastatic spread are the regional lymph nodes followed by lung, liver, and bone. RPLND is reasonable in selected cases with adverse features. Metastatic Leydig cell tumors are radiosensitive and chemoresistant. For metastatic disease, particularly that which secretes steroids, ortho-para-DDD, a potent inhibitor of steroidogenesis, has produced responses, but cure is not possible.

SERTOLI CELL TUMORS

Sertoli cell tumors (SCT) account for fewer than 1% of primary testicular neoplasms. They are subclassified into classic, large cell calcifying (LCCSCT), and sclerosing. SCT present as a painless, enlarging mass requiring a radical inguinal orchietomy. LCCSCT are noted for multifocality, familial tendency, and bilaterality. An association has been reported between LCCSCT, pituitary adenoma, adenocortical hyperplasia, cardiac myxoma, and pigmented skin and mucosal lesions. Precocious puberty is commonly noted in boys with LCCSCT, whereas feminization occurs in approximately 25% of classical SCT but is rare in LCCSCT. A testicular mass associated with feminization in a prepubertal patient is a classic SCT until proven otherwise.

Most SCT are benign and require RPLND only if accompanied by retroperitoneal adenopathy. Metastases are the only reliable indicator of malignancy, occurring in fewer than 10% of cases. The most common sites for metastatic spread are retroperitoneal lymph nodes, mediastinal nodes, lungs, liver, and bone. Sclerosing SCT and LCCSCT have minimal metastatic potential. Radiation therapy and chemotherapy are ineffective.

GRANULOSA CELL TUMORS

Granulosa cell tumors histologically resemble adult-type granulosa cell tumors of the ovary. Gynecomastia and increased estrogen secretion are common. These tumors are extremely rare; their metastatic potential appears limited. Radical orchietomy is required.

Juvenile granulosa cell tumors are the most common gonadal stromal neoplasms in early childhood, and the morphology may be confused with a yolk sac tumor. These patients usually present with maldescended testes, ambiguous genitalia, and an abnormal karyotype.

GONADOBLASTOMA

Gonadoblastoma are composed of sex cord elements admixed with germ cells. Often bilateral, they occur in men with chromosome abnormalities and those with dysgenetic gonads. Metastases from the GCT element may occur.

MESOTHELIOMA

Mesothelioma of the tunica vaginalis may invade the testis and frequently extend to the internal ring. Surgical intervention requires radical orchietomy and complete excision of the spermatic cord and hemiscrotum. Retroperitoneal or inguinal metastases may occur if the testis is invaded or if vascular invasion is present. Aggressive surgery is the only useful therapy.

SARCOMAS

ADENOCARCINOMA OF THE RETE TESTIS

This highly malignant neoplasm arises from the collecting system of the testis. Located posteriorly, it often invades adjacent structures such as the cord and epididymis. Over one-half of patients present with metastatic disease. Survival rates are poor, with 30% to 50% dying within 1 year. These tumors generally do not respond to either radiation therapy or chemotherapy. Following radical orchietomy, RPLND may be curative in some patients with minimal retroperitoneal involvement.

EPIDERMOID CYST

Epidermoid cysts of the testis usually present between the second and fourth decades. They are usually asymptomatic and discovered incidentally. These tumors are round, firm, and sharply demarcated on gross examination. Microscopically, the cyst is lined with stratified squamous epithelium. The adjacent testicular parenchyma is benign, and no CIS is present. The histogenesis of these tumors is uncertain. The clinical behavior of these tumors is uniformly benign; consequently, patients require no further therapy following resection. Testicular ultrasound may be diagnostic, in which case enucleation of the mass is sufficient treatment. Nevertheless, thorough histologic sampling must be performed to rule out a mature teratoma.

LYMPHOMA

Lymphoma is the most common secondary tumor of the testicle and the most frequent testicular neoplasm in men older than age 50. Approximately 40% of patients report systemic symptoms such as fatigue, weight loss, and fever. Painless testicular enlargement is common, whereas bilateral involvement occurs in approximately one-third of patients. Radical orchietomy establishes the diagnosis and cures a small subset of patients. However, most cases are associated with systemic disease. Central nervous system as well as bone marrow diseases are common. Survival is generally poor. Management of lymphoma is discussed in Chapter 45.

Metastatic Carcinoma

Metastatic carcinoma to the testicle is rare and usually associated with diffuse systemic disease. Bilateral involvement is noted in 15% of cases. The most common primary sites include prostate, lung, melanoma, and kidney. Treatment may include radical orchietomy with further therapy dictated by the primary tumor.

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Gene amplification did not underlie all cases of HER-2/Overexpression of HER-2/mutation-dependent and -independent inactivation of p53 is observed in the large majority of UPSC cases.

Asian women, as well as in colon cancers. Studies of endometrial cancers arising in women in the United States, however, show the prevalence of such mutations to

K-ras activating point mutations in codons 12 and 13 have been implicated in the development of atypical endometrial hyperplasias and endometrioid carcinomas in Asian women, as well as in colon cancers. Studies of endometrial cancers arising in women in the United States, however, show the prevalence of such mutations to be significantly lower. Notable was the almost complete absence of K-ras mutations in UPSC when compared to the usual endometrioid tumors. In contrast, mutation-dependent and -independent inactivation of p53 is observed in the large majority of UPSC cases.

Overexpression of HER-2/neu has been associated with advanced-stage, deep myometrial invasion, and poor survival in endometrial cancers in several studies. Gene amplification did not underlie all cases of HER-2/neu overexpression, although both gene amplification and overexpression were each associated with poor
outcome. When multivariate analysis was used to determine whether HER-2/neu was an independent prognostic factor in endometrial cancers when taking into account other molecular features such as DNA ploidy, epidermal growth factor receptor (EGFR), or p53 status, HER-2/neu did not achieve significance. Both c-myc gene amplification and c-ffs overexpression also have been associated with advanced-stage and high-grade endometrial cancers.

HORMONE-RELATED MOLECULAR ABNORMALITIES

Estrogen acts as a tumor promoter for the classic endometrioid cancers, with the well- and moderately differentiated tumors containing significant levels of estrogen or progesterone receptors or both. Aromatase cytochrome P-450 is part of the complex responsible for conversion of C19 steroids to estrogen; its increased expression in endometrial cancers but not in normal endometrium suggests a role in promotion of neoplastic proliferation. Two different functional isoforms of both the estrogen and progesterone receptors have been described that may account for some of the tissue-specific differences in the effects of hormones and their antagonists on the breast as compared with the endometrium.

Tamoxifen, an estrogen receptor antagonist/agonist, has been associated with an increased risk of development of endometrial cancers. Although studies using murine models have been generally reassuring in regards to the safety of the selective estrogen receptor modulator, raloxifene, on the endometrium, clinical studies to date have been plagued by short follow-up. The molecular mechanisms for the antiestrogenic actions of raloxifene relate to a specific molecular perturbation at aspartate 351 of the ligand-binding domain of the estrogen receptor, on its binding to raloxifene.

MOLECULES INVOLVED IN ADHESION AND INVASION

Integrin (cell adhesion molecules) expression inversely correlates with grade in endometrial cancers, with the loss of the b1, integrin associated with lymph node metastases. Variant forms of CD44 (a molecule important for cell adhesion and migration) are less frequently expressed in endometrial cancers than in normal endometrium, and its absence was significantly associated with an increased propensity for lymph-vascular space invasion. These data suggest that CD44 may play an important role in the function of the normal endometria, where it is strongly expressed near the basement membrane, and its loss may be related to invasion and metastasis.

OVARIAN CANCER

Most of the breakthroughs in understanding the molecular basis for ovarian cancer have been in the area of hereditary epithelial ovarian cancer syndromes, which affect 5% to 10% of ovarian cancer patients. Much work is still needed to understand the biology underlying sporadic ovarian cancers, which invariably present as advanced-stage disease and have a poor long-term outcome.

CLONALITY

In the search for the precursors of invasive epithelial ovarian cancer, molecular studies have been performed on normal ovaries; on benign, borderline, and invasive cancers; and on cancers with adjacent benign-appearing cysts. Such studies have been greatly aided by the ability to culture normal, immortalized, and transformed ovarian surface epithelial cells, as well as transformed cells originating from benign ovarian neoplasms. Evidence for a unifocal origin for these cancers appears to predominate, with bilateral ovarian cancers and metastases sharing common molecular features. Studies of microsatellite instability (which occurs in 17% of cases but apparently not related to family history) and studies of X chromosome inactivation support the clonal origin of these cancers. This is contrasted to the multifocal origin proposed for a proportion (25%) of the papillary serous carcinomas of the peritoneum; these tumors of multifocal origin are associated with germline BRCA1 (breast cancer gene) mutations. Interestingly, loss of heterozygosity studies, and K-ras and p53 mutation analyses, do not demonstrate shared findings between borderline or benign neoplasms and invasive cancers, suggesting that these entities are not the precursors of invasive epithelial ovarian cancers. For instance, frequent loss of heterozygosity of a portion of 9q on the inactive X chromosome was seen in borderline tumors, but not in low-grade invasive ovarian cancers. Notably, p53 mutations, which are absent in solitary borderline and benign neoplasms, are present along with allelic loss of chromosome 11p in benign-appearing cysts adjacent to the invasive cancers. Similarly, common genetic alterations (such as loss of heterozygosity involving the same allele) were observed in endometrioid and clear cell ovarian carcinomas and adjacent endometriosis.

BRCA1 AND BRCA2 GENES

Unlike most epithelia, division of normal ovarian surface epithelial cells gives rise to two daughter cells with equal growth potential. This provides a mechanism for the involvement of tumor suppressor genes in the development of ovarian cancer, in that repeated division of these cells can unmask such recessive mutations. In addition to being a tumor suppressor gene, BRCA1 may function as a transcription factor, as well as conferring protection against DNA damage. The latter mechanism also has been proposed as a function of BRCA2. Mutations of BRCA1 (unlike BRCA2) can account for the large majority of the familial cases of breast-ovarian cancer syndrome. Among breast-ovarian cancer families, there is significant evidence for heterogeneity of risk among BRCA1-mutation carriers. Assuming two BRCA1 alleles exist, one would confer a lifetime breast cancer risk of 62% and an ovarian cancer risk of 11%, whereas the other allele confers a 39% breast cancer risk and a 42% ovarian cancer risk by age 60 years, with the first allele representing 71% of the mutations. BRCA1 mutations specifically localized to the 5' region may increase the risk for ovarian cancer in these patients. BRCA2 mutations confer susceptibility to ovarian cancer with a significantly lower penetrance than for BRCA1. Compared to population-control cases, familial ovarian cancer in general, including disease associated with BRCA1 or BRCA2 mutations, are more frequently associated with advanced stage and, hence, a poorer clinical outcome. Stage for stage, however, BRCA1 mutations do not appear to result in a survival difference. Serous tumors appear to be a hallmark of BRCA1 mutation-associated ovarian cancers, and germline BRCA1 mutations have been reported to occur in papillary serous carcinomas of the peritoneum with a frequency comparable to that in epithelial ovarian cancers. However, no morphologic changes can differentiate normal ovaries removed prophylactically from carriers of a BRCA1 or BRCA2 mutation from ovaries removed from noncarriers; thus, identification of a premalignant lesion remains elusive.

In sporadic ovarian cancer, which represents 95% of ovarian cancer cases, few mutations of BRCA1 or BRCA2 were detected, whereas frequent allelic losses that included the BRCA1 region of chromosome 17q were demonstrated (see Table 36.1-1 for regions of chromosomal abnormalities commonly associated with ovarian cancer). These and other data suggest the involvement of additional tumor suppressor genes in the etiology of most of the sporadic ovarian cancers, including one or two that possibly are localized distal to the BRCA1 gene. An intriguing finding is the fact that, present in the germline of patients with sporadic ovarian cancer, is a Taq1 restriction fragment length polymorphism in an intron within the sequences encoding the hormone-binding domain of the progesterone receptor gene. This finding may be associated with coding region mutations of the gene and may contribute to tumorigenesis.

OTHER TUMOR SUPPRESSOR GENES

Functional wild-type p53 has been shown to be required for sensitivity to a variety of chemotherapeutic drugs and radiation, playing a crucial role in the execution of the common end pathway of apoptosis. p53 mutations of one allele predisposes the cell to the loss of wild-type p53 function, which has been shown in ovarian cancer cells to lead to the development of platinum resistance in vitro. In ovarian cancers, p53 mutations, which are seen in 50% of advanced cases, are associated with high grade and poor survival, but not with clinical chemoresistance. p53 mutations appear to arise before the onset of ovarian cancer metastasis, but are not present in the germline of patients with familial ovarian cancer phenotypes. p53 has been explored as a target for gene therapy in ovarian cancer by several groups. Similarly, other proapoptotic genes, such as the BAX gene, have been the focus of gene therapy efforts at ovarian selective tumor expression.

Other putative tumor suppressor genes in ovarian cancer include GPC3 (whose promoter is hypermethylated leading to gene silencing), Nox2 (ARH1, an imprinted tumor suppressor gene), OVCA1, and DOC-2, among others. The widespread loss of heterozygosity found in invasive ovarian cancers indicates that there may be several other tumor suppressor genes inactivated during tumorigenesis. The search for such genes (and likewise oncogenes) in ovarian cancer has been greatly facilitated by the advent of technologies such as complementary DNA microarray, comparative genomic hybridization, differential display, and serial analysis of gene expression.

ONCOGENES AND GROWTH FACTORS

Cytokines which may act via autocrine or paracrine routes on ovarian cancer cells include EGF, TGF-b, tumor necrosis factor, interleukin-6 (IL-6), lysophosphatidic acid (LPA), heregulin, vascular endothelial growth factor (VEGF), and the macrophage colony-stimulating factor (CSF-1). Ovarian cancer cells have been shown to
contain receptors for these cytokines and thus are capable of responding by phenotypic change, including growth stimulation or inhibition depending on the stimuli.

Coexpression of CSF-1 and the protooncogene c-fms (which encodes for the CSF-1 receptor) in ovarian cancer metastases portends a poor outcome.

Other oncogenes activated in ovarian cancer include K-ras (mutated in 40% of mucinous tumors), HER-2/neu (which does not appear to be related to poor prognosis in ovarian cancer, unlike breast cancer), c-myc, PKCα [the catalytic subunit of phosphatidylinositol 3-kinase (PI3-kinase)], and AKT-2 (which is activated by several mitogenic growth factors and serves as a downstream effector of PI3-kinase). Of interest, BRCA1- or BRCA2-related ovarian cancers do not appear to develop through mutations of K-ras or amplification of HER-2/neu, c-myc, or AKT-2. Both tyrosine kinase growth factor receptors and protein tyrosine phosphatases (PTP) may also play an important role: overexpression of PTP1B in ovarian cancer cells has been correlated with the expression of the tyrosine kinase receptors EGFR, HER-2/neu, and c-fms.

DRUG RESISTANCE

The phenomenon of platinum resistance remains the most germane for ovarian cancer patients, although with the inclusion of paclitaxel in first-line therapy, acquired classical multidrug resistance (mdr) is also a relevant mechanism. The first relationship between genomic aberrations in ovarian cancer (gains at specific loci on chromosomes 1q and 13q) and platinum resistance has been described.

Augmented DNA repair at several levels appears to contribute significantly to platinum resistance. In ovarian cancers, elevated levels of ERCC-1 and XPA, ranging from DNA repair genes, are found in clinically platinum-resistant tumors. However, overexpression of ERCC-1 in vitro leads to increased platinum sensitivity, the relative role of the different DNA repair genes in this process remains unclear. Elevated intracellular levels of glutathione, which lead to increased intracellular detoxification of platinum, generally correlate with intratumor platinum resistance and have been reported to confer poor survival. In platinum-resistant ovarian cancer cells, an elevated level of glutathione synthetase, an enzyme that contributes to biosynthesis of glutathione, is associated with increased drug resistance.

On the other hand, overexpression of BAX is associated with chemosensitivity to platinum and paclitaxel, as well as an improved disease-free survival rate in ovarian cancer. p53 mutations result in the loss of ability of p53 to transactivate BAX in platinum-resistant ovarian cancer cells. IL-1α, through inhibition of DNA repair, also sensitizes the activity of platinum in ovarian cancer cells and tumor necrosis factor, an apoptosis inducer, can ameliorate platinum resistance in ovarian cancer cells. Transfection of the cytokeratin 18 gene, which encodes an intermediate filament protein into platinum-resistant ovarian cancer cells, leads to a marked increase in platinum sensitivity.

The prevalence of MDR-1 overexpression in ovarian cancer appears to depend on the sensitivity of the methodology used. There is agreement, however, that mutated mdr is clinically relevant for these patients. Mutated p53 can contribute to classic mdr because it can transcriptionally activate the MDR-1 promoter, a phenomenon that is repressed by wild-type p53. Proteins associated with the mdr phenotype and expressed in MDR-1–negative cancers are MRPs (MDR-associated protein involved in glutathione conjugate transport) and LRPs (lung resistance protein). LRP appears to correlate with clinical chemoresistance (remarkably, both to agents associated with classic mdr, as well as to the class of platinum/alkylating agents) among ovarian cancer patients.

Aside from mdr, the other major mechanism of paclitaxel resistance involves stimulation of expression of the β-tubulin genes in the resistant ovarian cancers. Antisense down-regulation of β-tubulin sensitizes these cells to paclitaxel.

MOLECULES INVOLVED IN ADHESION, MOTILITY, INVASION, ANGIOGENESIS, AND METASTASIS

The cell adhesion molecules CD44 and E-cadherin both are expressed when ovarian cancer cells are attached to peritoneal mesothelium, but such expression is lost when the cells are found in ascites fluid. The β1 integrin is also found to be an important mediator of ovarian cancer cell adhesion to peritoneal cells.

Urokinase-type plasminogen activator is the primary plasminogen activator found in ovarian cancer tissues and, along with the matrix metalloproteinases (in particular, MMP-2 and -9), are important to the biology of invasion and metastasis of ovarian cancer. Inhibitors of urokinase have been shown to block invasive capacity of ovarian cancer cells, whereas a synthetic matrix metalloproteinase inhibitor decreases tumor burden (an effect that is even more pronounced in the presence of urokinase) in mice bearing human ovarian cancer xenografts. Urokinase has been shown to be inducible by CSF-1, a cytokine important to in vivo metastasis of ovarian cancer with CSF-1–induced invasion being mediated by urokinase activity. CSF-1–induced motility is being mediated by PAI-1 activity.

Urokinase-stimulated invasion is also induced by LPA, which also enhances drug resistance. VEGF, a critical mediator of tumor angiogenesis, is expressed in abundant amounts in ascites and in the malignant ovary. It is notable that molecules important to these related biologic phenotypes, such as E-cadherin and nm23 (associated with absence of lymph node metastasis), also may have putative tumor suppressor function, based on loss of heterozygosity studies or sequence analysis.

CERVICAL AND VULVAR CANCER

The study of the role of viruses in the carcinogenesis of lower genital tract malignancies (thought to be a field effect) has focused on cervical cancer, the third most common gynecologic cancer in the United States. Extension of those studies to vulvar cancer have led to support for two separate etiologies of vulvar cancer: one related to human papillomavirus (HPV), with epidemiologic risk factors similar to that for cervical cancer, and the other not appearing to be HPV-related.

HUMAN PAPILLOMAVIRUS

That HPV is a critical factor for cervical cancer and that the HPV E6 and E7 genes are oncogenic is clearly established. Infection of human keratinocytes by the oncogenic HPV subtypes leads to abnormalities in differentiation and growth; however, only after long-term culture of immortalized cells does an occasional clone become neoplastic in nude mice, suggesting that viral oncogenes are the principal genetic factor in cervical carcinogenesis. This theory is supported by data from transgenic mouse studies, in which E6/E7 genes can give rise to hyperplastic and neoplastic lesions of epithelial cell types after a latent period; however, epidermoid cervical cancers have not been noted. Cervical cancers of mesenchymal origin were noted to arise after a long latent period in some of the female progeny of transgenic mice into whom HPV-18 LCR/E6/E7 was introduced.

Both tyrosine kinase growth factor receptors and protein tyrosine phosphatases (PTP) may also play an important role: overexpression of PTP1B in ovarian cancer cells has been correlated with the expression of the tyrosine kinase receptors EGFR, HER-2/neu, and c-fms.

With the retinoblastoma (Rb) protein, E7, a potent viral oncoprotein that cooperates with activated ras in transforming assays, frees key cell-cycle proteins from Rb-imposed negative transcriptional regulation. Whereas for the high-risk HPV subtypes 16/18, E7/Rb binding is five- to tenfold more efficient than for HPV 6/11, mutations that affect E7 binding to Rb do not interfere with the capacity to confer immortalization. Similarly, mutations that interfere with E7's transforming properties do not appear to affect Rb binding; thus, the picture is complex.

Likewise, the mechanism for E6 promotion of oncogenesis is not clear. E6 promotes ubiquitin binding to p53, which tags such cells for degradation; thus, on DNA damage, the normal cellular response of induction of wild-type p53 is not seen in HPV-infected cells. Experimental evidence suggests that a p53 polymorphism with
arginine at codon 72 is more susceptible to E6-induced degradation in vivo than with proline at that site. However, the observation that individuals homozygous for the arginine-encoding allele are more susceptible to HPV-associated squamous cell cancers than heterozygotes has not been confirmed by larger studies. The suggestion has been made that, instead, this p53 polymorphism may predispose to the development of cervical adenocarcinomas in Asians. Although E6 binds to p53 protein in HPV 16/18 subtypes (not in HPV 6/11), no such correlation is seen in vivo between low p53 expression and E6 overexpression. Furthermore, there is evidence that endogenous p53 protein in HPV-infected cancer cells is competent to activate a downstream target gene, despite coexpression of the viral E6 protein.

The development of HPV vaccines has been an intense focus of investigation. Prophylactic HPV vaccine strategies have used nononcogenic, non–viral DNA-containing, antigenic papilloma virus–like particles. Development of therapeutic HPV vaccines has been somewhat more problematic in that sustained cellular immunity against oncogenic E6 or E7 protein has been difficult to achieve. New approaches include the use of autologous dendritic cells pulsed with HPV-specific tumor antigens, such as E7, to stimulate tumor-specific cytotoxic T lymphocytes (CTLs). Dendritic cells are thought to be effective stimulators not only to produce and maintain primary CTLs, but also to stimulate established CTL lines.

MOLECULAR COFACTORs IMPORTANT TO CERVICAL CARCINOGENESIS

Because HPV infection is not sufficient for cervical carcinogenesis, attention has focused on molecular cofactors important to this process, such as co-infection by herpes simplex virus 2, and the presence of activated Ha-ras; the latter results in rearrangements and amplifications of the HPV-16 sequence. Many positive and negative transactivation factors of E6/E7/TAT expression have been identified. The presence of the glucocorticoid receptor in HPV-positive cervical cells may underlie the clinical progression of HPV infection seen in pregnancy. Although retinoic acid represses HPV transcription in normal and malignant cells, its induction of retinoic acid receptor beta is restricted to normal cells. Both the retinoic acid receptor beta gene and a locus on chromosome 11q23 may have tumor-suppressive properties in squamous cell cancers. Loss of heterozygosity studies demonstrate allelic loss of many chromosomes, including 11q, but most frequently involving 3p, 6p, and 18q (see Table 36.1-1). The immune response is likely to be key in determining malignant transformation of HPV-infected cervical epithelium. The consequences of human immunodeficiency virus (HIV) infection include a dramatic increase in the risk for cervical dysplasia and invasive cancer, the degree of which correlates with the level of immunosuppression. Loss of expression of HLA class I alleles, along with interference with the transporter associated with antigen presentation in cervical cancers, is common; such changes may influence specific immunogenic presentation by tumors. In addition, the finding of certain HLA class II haplotypes in the cancer (when compared to cervical DNA from controls), which may influence the immune response to specific HPV-encoded epitopes, may contribute to the development of cervical neoplasia. The HLA-DQB1 locus shows evidence of allelic association with invasive cervical cancer in HPV-positive patients. This genotype thus appears to increase the risk for development of cervical cancers in these patients. Similar findings seen when HLA class II haplotypes in CIN were compared to controls; the HLA-DQB1 haplotype was significantly more highly associated with CIN.

In general, more than 90% of squamous cell cervical cancers contain HPV DNA, and only rarely are p53 mutations seen. Nuclear c-myc expression is correlated with the presence of HPV; c-myc can transactivate the HPV-16 promoter, as it can transactivate HIV-1 and c-myc. In most studies, HPV status was not a strong independent prognosticator of outcome in cervical cancer patients; however, there appears to be a trend for HPV-negative tumors to do worse. Among HPV-negative cancers, p53 mutations appear to be more common, although HPV-negative cancers that do not contain p53 mutations exist. The latter also do not contain MDM2 gene (capable of binding to p53) amplifications. Among HPV-negative tumors, c-myc overexpression has been associated with an increased risk of metastasis in early-stage disease.

MOLECULAR ABNORMALITIES IN CERVICAL ADENOCARCINOMAS

The presence of both HPV-16 and -18 has been demonstrated in cervical adenocarcinomas, with HPV-18 predominating in cervical adenocarcinoma cell lines. p53 mutations in this disease are associated with advanced-stage and high-grade cases, whereas those tumors containing HPV DNA tend to be of an early stage and low grade. Overexpression of HER-2/neu is seen in 25% of cervical adenocarcinomas, which is strongly associated with advanced stage. Reduced expression of nm23 and DAP kinase may be correlated with poor survival. Further, the loss of HLA-DQ B1 locus shows evidence of allelic association with invasive cervical cancers in HPV-positive patients. This genotype thus appears to increase the risk for development of cervical cancers in these patients. Similar findings seen when HLA class II haplotypes in CIN were compared to controls; the HLA-DQB1 haplotype was significantly more highly associated with CIN.

Expression of cell-cycle genes, such as bcl-1 and bcl-2, have been studied in cervical cancer. Bcl-1 (cyc1 D1) is capable of binding to the Rb protein and is overexpressed or amplified in the majority of cervical and vulvar cancer cell lines; its level of expression is elevated by activated c-fms. Overexpression of bcl-2, which protects against apoptosis and differentiation, was not found to relate to HPV status but was more likely to be seen in CIN 3 rather than low-grade dysplasias. Thus, its expression may be an early event important to malignant transformation. In vitro, increased bcl-2 expression is noted in cervical cancer cell lines which contain an inactive p53.In vivo, overexpression of bcl-2 is strongly correlated with radioreistance, and on multivariate analysis, poor outcome. Overexpression of EGFR also is found to be an independent predictor for poor prognosis in cervical cancer.

Proteins capable of degrading extracellular matrix may underlie the propensity of cervical cancer to invade adjacent tissues. Both the expression and activity of metalloproteinases have been described in cervical cancers, with more activity seen in this disease than in ovarian or endometrial cancers. Expression of MMP-2 is correlated with that of TIMP-2 in cervical cancer cells, and their coexpression is associated with advanced stage and poor survival. The opposite finding is seen for expression of TIMP-1 (the specific inhibitor of the matrix metalloproteinases). In fact, the ratio of specific metalloproteinases to TIMP-1 is increased in those cervical cancers and their surrounding stroma that have a poor prognosis. Furthermore, morphologic and immunohistochemical markers of angiogenesis correlate with poor outcome in cervical cancer. Many cervical cancers secrete significant levels of VEGF, the adenocarcinomas in particular.

MOLECULAR ABNORMALITIES IN VULVAR CANCERS

Molecular studies support two etiologies of vulvar cancer: (1) vulvar intraepithelial neoplasia grade 3 associated with basaloid and warzy carcinomas, the majority of which appear to be associated with the presence of HPV and epidemiologic risk factors similar to that seen for cervical cancer, such as smoking and herpes simplex virus 2 infection; and (2) keratinizing squamous cell carcinomas, which contain little HPV DNA. Thus, HPV is detected less often in vulvar cancers (approximately 10%). However, positive HPV-16 DNA testing has a high positive having a low false-positive rate. Similar to cervical cancers, there is higher prevalence of p53 mutations in HPV-negative vulvar cancers when compared to HPV-positive tumors, and p53 overexpression in vulvar cancers appears to relate to poor overall survival. Vulvar squamous cell carcinomas exhibit a broad range of allelic losses, irrespective of HPV status. Furthermore, the divergent patterns of loss of heterozygosity observed suggest that only some, but not most, genetic alterations in adjacent vulvar epithelium or vulvar intraepithelial neoplasia are related to the invasive cancers.

CHAPTER REFERENCES

CARCINOMA OF THE CERVIX

EPIDEMIOLOGY

The American Cancer Society estimated that 12,800 new cases of invasive cervical cancer would be diagnosed in the United States in 1999. During the same year, 4800 patients were expected to die of cervical cancer; this represents approximately 1.8% of all cancer deaths in women and 18% of deaths from gynecologic cancers. However, for women aged 20 to 39 years, cervical cancer remains the second leading cause of cancer deaths after breast cancer. In the United States, age-adjusted death rates from cervical cancer have declined steadily since statistics on the disease were first collected in the 1930s. Although this improvement is primarily because of the adoption of routine screening programs including pelvic examinations and cervical cytologic evaluation, the death rates from cervical cancer had begun to decrease before the implementation of Papanicolaou (Pap) screening, suggesting that other unknown factors may have played some role.

Squamous cell carcinoma of the cervix and its intraepithelial precursor follow a pattern typical of sexually transmitted disease. The risk of cervical cancer is increased in prostitutes and in women who have first coitus at a young age, have multiple sexual partners, have sexually transmitted diseases, or bear children at a young age. Promiscuous sexual behavior in male partners is also a risk factor. Other factors that may be associated with cervical cancer include cigarette smoking, immunodeficiency, vitamin A or C deficiency, and oral contraceptive use. In the United States, the incidence of cervical cancer is greatest in American Indian, African American, Vietnamese, and Hispanic women.

International incidences of cervical cancer tend to reflect differences in cultural attitudes toward sexual promiscuity and the penetration of mass screening programs. Some of the lowest incidences are in the United States, China, North Africa, and the Middle East, where estimated crude rates of cervical cancer are less than 10 per 100,000. However, cervical cancer continues to be the leading cause of cancer deaths for women in many developing countries. Incidences are particularly high in Latin America, Southern and Eastern Africa, India, and Polynesia. In the United States, Hispanic women have approximately twice the incidence and Vietnamese women approximately five times the incidence of white women. The incidence is also higher in African Americans than in whites, although this difference has been steadily decreasing, particularly for women less than 50 years old.

A number of studies suggest that the incidence of cervical adenocarcinoma has been increasing, particularly among women in their 20s and 30s. Several investigators have reported a correlation between cervical adenocarcinoma and prolonged oral contraceptive use. However, the likelihood of a causative relationship is less certain because of the many potential confounding risk factors.

Molecular and epidemiologic studies have demonstrated a strong relationship between human papillomavirus (HPV), cervical intraepithelial neoplasia (CIN), and invasive carcinomas of the cervix. HPV DNA has been identified in more than 95% of cervical carcinomas; HPV DNA transcripts and protein products have also been identified in invasive cervical carcinomas. In high-grade CIN and invasive carcinoma, papillomavirus DNA is typically integrated into the human genome rather than remaining in an intact viral capsid. It has been theorized that integration of HPV DNA in the human genome, possibly at the E2 site, causes persistent transcription of the E6 and E7 genes. Functional inactivation of p53 by E6 protein or of Rb by E7 protein disrupts normal cell-cycle control mechanisms. As the sensitivity and specificity of tests for HPV DNA have improved, it has become increasingly apparent that most of the covariables that have historically been associated with an increased risk of cervical cancer (e.g., age at first coitus, number of partners, socioeconomic status, and so forth) are surrogates for HPV infection. Investigators have suggested a number of cofactors that may contribute to disease progression. However, in more recent epidemiologic studies, cigarette smoking was the only consistent independent contributor to the risk of cervical cancer development after controlling for HPV infection. Taken together, the molecular and epidemiologic data provide compelling evidence that HPV infection plays a central causative role in the development of cervical neoplasia.
TABLE 36.2-1. Relationship between Human Papillomavirus Type and Cervical Pathology

In 1993 the Centers for Disease Control and Prevention added cervical cancer to the list of acquired immunodeficiency syndrome–defining neoplasms. Although several studies suggest that the incidence of CIN is higher in HIV-positive women than in the general population, overlap in risk factors for the two diseases may influence these results. Although Serraino et al. reported a possible increase in the risk of invasive cervical cancer in European HIV-positive women, several studies in Africa and a large epidemiologic study in the United States have failed to reveal any significant linkage. However, changes in cell-mediated immunity may play a role in the development of cervical cancer, and some investigators have suggested that cervical cancer is a more aggressive disease in immunosuppressed patients. For these reasons, regular surveillance with Pap smears, pelvic examination, and colposcopy (when indicated) should be part of the routine care of HIV-positive women.

NATURAL HISTORY AND PATTERN OF SPREAD

Most cervical carcinomas arise at the junction between the primarily columnar epithelium of the endocervix and the squamous epithelium of the ectocervix. This junction is a site of continuous metaplastic change; this change is most active in utero, at puberty, and during a first pregnancy and declines after menopause. The greatest risk of neoplastic transformation coincides with periods of greatest metaplastic activity. Virally induced atypical squamous metaplasia developing in this region can progress to higher grade squamous intraepithelial lesions.

The mean age of women with CIN is approximately 15 years younger than that of women with invasive cancer, suggesting a slow progression of CIN to invasive carcinoma. In a 13-year observational study of women with CIN 3, Miller found that disease progressed in only 14%, whereas it remained the same in 61% and disappeared in the remainder. Syrjanen et al. reported spontaneous regression in 38% of high-grade HPV-associated squamous intraepithelial lesions. However, in a large prospective study, Richart and Barron reported mean times to development of carcinoma in situ of 58, 36, and 12 months for patients with mild, moderate, or severe dysplasia, respectively, and predicted that 96% of all dysplasias would progress to carcinoma in situ within 10 years.

Once tumor has broken through the basement membrane, it may penetrate the cervical stroma directly or through vascular channels. Invasive tumors may develop as exophytic growths protruding from the cervix into the vagina or as endocervical lesions that can cause massive expansion of the cervix despite a relatively normal-appearing cervical portio. From the cervix, tumor may extend superiorly to the lower uterine segment, inferiorly to the vagina, or into the paracervical spaces by way of the broad or uterosacral ligaments. Tumor may become fixed to the pelvic wall by direct extension or by coalescence of central tumor with regional adenopathy. Tumor may also extend anteriorly to involve the bladder or posteriorly to the rectum, although rectal mucosal involvement is a rare finding at initial presentation.

The cervix has a rich supply of lymphatics organized in three anastomosing plexuses that drain the mucosal, muscularis, and serosal layers. The lymphatics of the cervix also anastomose extensively with those of the lower uterine segment, possibly explaining the high frequency of uterine extension from endocervical primary tumors. The most important lymphatic collecting trunks exit laterally from the uterine isthmus in three groups (Fig. 36.2-1). The upper branches, which originate in the anterior and lateral cervix, follow the uterine artery, are sometimes interrupted by a node as they cross the ureter, and terminate in the uppermost hypogastric nodes. The middle branches drain to deeper hypogastric (oburator) nodes. The lowest branches follow a posterior course to the inferior and superior gluteal, common iliac, presacral, and subaortic nodes. Additional posterior lymphatic channels arising from the posterior cervical wall may drain to superior rectal nodes or may continue upward in the retrorectal space to the subaortic nodes overlying the sacral promontory. Anterior collecting trunks pass between the cervix and bladder along the superior vesical artery and terminate in the internal iliac nodes.

**FIGURE 36.2-1.** The lymphatic system of the female genital organs. [Reprinted from ref. 481, with permission; adapted from Meigs JV (ed). *Surgical treatment of cancer of the cervix.* New York: Grune & Stratton, 1954:90.]

**Table** 36.2-2 summarizes the reported incidences of pelvic and paraaortic node involvement for patients who underwent lymphadenectomy as part of primary surgical treatment or before radiotherapy for cervical carcinomas. Many series excluded patients with extrapelvic disease. Variations in the completeness of lymphadenectomies and histologic processing may also lead to underestimates of the true incidence of regional spread from carcinomas of the cervix.
TABLE 36.2-2. Rates of Lymph Node Metastasis in Patients with Carcinoma of the Cervix

Cervical cancer usually follows a relatively orderly pattern of metastatic progression initially to primary echelon nodes in the pelvis, then to paraaortic nodes and distant sites. Even patients with locoregionally advanced disease rarely have detectable hematogenous metastases at initial diagnosis of their cervical cancer. The most frequent sites of distant recurrence are lung, extrapelvic nodes, liver, and bone. Although early studies suggested that the lumbar spine was a relatively frequent site of skeletal metastases, more recent studies using abdominal imaging demonstrate that most patients with isolated lumbar spine involvement actually have direct extension of disease from paraaortic nodes.

PATHOLOGY

Cervical Intraepithelial Neoplasia

Several systems have been developed for classifying cervical cytologic findings (Table 36.2-3). Although criteria for the diagnosis of CIN vary somewhat between pathologists, the important characteristics of this lesion are cellular immaturity, cellular disorganization, nuclear abnormalities, and increased mitotic activity. The degree of neoplasia is determined on the basis of the extent of the mitotic activity, immature cell proliferation, and nuclear atypia. If mitoses and immature cells are present only in the lower third of the epithelium, the lesion is usually designated CIN 1. Lesions involving the middle or upper third are diagnosed as CIN 2 or CIN 3, respectively.

TABLE 36.2-3. Comparison of Cytology Classification Systems

The term cervical intraepithelial neoplasia, as proposed by Richart, refers only to a lesion that may progress to invasive carcinoma. Although CIN 1 to 2 is sometimes referred to as mild to moderate dysplasia, CIN is now preferred over dysplasia. Because the word dysplasia means “abnormal maturation,” proliferating metaplasia without mitotic activity has sometimes been erroneously called dysplasia.

The Bethesda system of classification, designed to further standardize reporting of cervical cytologic findings, was developed after a National Cancer Institute consensus conference in 1988 and was refined in 1991. This system, which separates condylomata and CIN 1, classified as low-grade squamous intraepithelial lesions, from high-grade squamous intraepithelial lesions, is meant to replace the Papanicolaou system and is now widely used in the United States. The Bethesda system introduced the term atypical squamous cells of undetermined significance. This uncertain diagnosis is now the most common abnormal Pap test result. In United States laboratories, 1.6% to 9.0% of Pap smears are reported as having atypical squamous cells of undetermined significance. Although most reflect a benign process, approximately 5% to 10% are associated with underlying high-grade squamous intraepithelial lesions, and one-third or more of high-grade squamous intraepithelial lesions are heralded by a finding of atypical squamous cells of undetermined significance on a Pap smear.

Adenocarcinoma In Situ

The diagnosis of adenocarcinoma in situ (AIS) is made when normal endocervical gland cells are replaced by tall, irregular columnar cells with stratified, hyperchromatic nuclei and increased mitotic activity, but the normal branching pattern of the endocervical glands is maintained and there is no obvious stromal invasion. Approximately 20% to 50% of women with cervical AIS also have squamous CIN, and AIS is often an incidental finding in patients operated on for squamous carcinoma. Because AIS is frequently multifocal, cone biopsy margins are unreliable.

Microinvasive Carcinoma

Because the definition of microinvasive carcinoma is based on the maximum depth and linear extent of involvement, this diagnosis can only be made after examination of a specimen that includes the entire neoplastic lesion and cervical transformation zone. This requires a cervical cone biopsy.

The earliest invasion appears as a protrusion of cells from the stromoeplithelial junction; these cells are better differentiated than the adjacent noninvasive cells and have abundant pink-staining cytoplasm, hyperchromatic nuclei, and small- to medium-sized nucleoli. As the tumor progresses, invasion occurs at multiple sites, and its depth and linear extent become measurable. The depth of invasion should be measured with a micrometer from the base of the epithelium to the deepest point of invasion. Lesions that have invaded less than 3 mm (International Federation of Gynecology and Obstetrics (FIGO) stage IA1) rarely metastasize; 5% to 10% of tumors that invade 3 to 5 mm (FIGO stage IA2) have positive pelvic lymph nodes.

Although investigators occasionally label small adenocarcinomas as microinvasive, the term probably should not be used for these tumors. Because invasive adenocarcinomas may originate either from the mucosal surface or from the periphery of underlying glands, no reliable method has been found for measuring the depth of invasion of these tumors. For this reason adenocarcinomas are generally classified as either AIS or invasive carcinoma (FIGO stage IB).

Invasive Squamous Cell Carcinoma

Between 80% and 90% of cervical carcinomas are squamous. A number of systems have been used to grade and classify squamous carcinomas, but none have consistently been demonstrated to predict prognosis. One of the most commonly used systems categorizes squamous neoplasms as large cell keratinizing, large cell nonkeratinizing, or small cell carcinoma. Small cell squamous carcinomas have small- to medium-sized nuclei, open chromatin, small or large nucleoli, and abundant cytoplasm. Most authorities believe that patients with small cell squamous carcinoma have a poorer prognosis than those with large cell neoplasms with or without keratin. However, small cell squamous carcinoma should not be confused with anaplastic small cell carcinoma. The latter resembles oat cell carcinoma of the lung because it contains small tumor cells that have scanty cytoplasm, small round to oval nuclei, small or absent nucleoli, finely granular chromatin, and high mitotic activity. Approximately 30% to 50% of anaplastic small cell carcinomas display neuroendocrine features. Small cell anaplastic carcinomas behave more aggressively than poorly differentiated small cell squamous carcinomas; most investigators report survival rates of less than 50% even for patients with early stage I disease.

Adenocarcinoma

Invasive adenocarcinoma may be pure or mixed with squamous cell carcinoma (adenosquamous carcinoma). A wide variety of cell types, growth patterns, and degrees of differentiation have been observed. Approximately 80% of cervical adenocarcinomas are made up predominantly of cells whose differentiated features...
resemble endocervical glandular epithelium with intracytoplasmic mucus production. The remaining tumors are populated by endometrioid cells, clear cells, intestinal cells, or a mixture of more than one cell type. By histologic examination alone, some of these tumors are indistinguishable from those arising elsewhere in the endometrium or ovary.

Minimal-deviation adenocarcinoma (adenoma malignum) is a rare, extremely well differentiated adenocarcinoma that is sometimes associated with Peutz-Jeghers syndrome. Because the branching glandular pattern strongly resembles normal endocervical glands, minimal-deviation adenocarcinoma may not be recognized as malignant in small biopsy specimens. Earlier studies described a dismal outcome for women with this tumor, but more recently, patients have been reported to have a favorable prognosis if the disease is detected early.

Young and Scully described a villoglandular papillary subtype of adenocarcinoma that primarily affects young women, appears to metastasize infrequently, and has a favorable prognosis. Gluckmann and Cherry were the first to describe glassy cell carcinoma, a form of poorly differentiated adenocarcinoma with cells that have abundant eosinophilic, granular, ground-glass cytoplasm; large round to oval nuclei; and prominent nucleoli. Other rare variants of adenocarcinoma include adenoid basal carcinoma and adenoid cystic carcinoma. Adenoid basal carcinoma is a well-differentiated tumor that histologically resembles basal cell carcinoma of the skin and tends to have a favorable prognosis. Basal cell carcinoma consists of basaloid cells in a cribiform or cleft or cylinder shaped pattern and tend to have aggressive behavior with frequent metastases, although the natural history of these tumors may be long. Whether the prognoses of these rare subtypes are different from those of other adenocarcinomas of similar grade is uncertain.

A variety of neoplasms may infiltrate the cervix from adjacent sites presenting differential diagnostic problems. In particular, it may be difficult or impossible to determine the origin of adenocarcinomas involving the endocervix and uterine isthmus. Although endometrioid histology suggests endometrial origin and mucinous tumors in young patients are most often of endocervical origin, both histologic types can arise in either site. Metastatic tumors from the colon, breast, or other sites may involve the cervix secondarily. Malignant mixed Mullerian tumors, adenocarcinomas, and leiomyosarcomas arise occasionally in the cervix but more often involve it secondarily. Primary lymphomas and melanomas of the cervix are extremely rare.

**CLINICAL MANIFESTATIONS**

Preinvasive disease is usually detected during routine cervical cytologic screening. Early invasive disease may not be associated with any symptoms and is also detected during screening examinations. The earliest symptom of invasive cervical cancer is usually abnormal vaginal bleeding, often following coitus or vaginal douching. This may be associated with a clear or foul-smelling vaginal discharge. Pelvic pain may result from locoregionally invasive disease or from coexistent pelvic inflammatory disease. Pelvic pain may be a symptom of hypereosinophilia, often complicated by pyelonephritis. The triad of sciatic pain, leg edema, and hypereosinophilia is almost always associated with extensive pelvic wall involvement by tumor. Patients with advanced tumors may have hematuria or incontinence from a vesicovaginal fistula caused by direct extension of tumor to the bladder. External compression of the rectum by a massive primary tumor may cause constipation, but the rectal muca is rarely involved at initial diagnosis.

**DIAGNOSIS, CLINICAL EVALUATION, AND STAGING**

**Diagnosis**

The long preinvasive stage of cervical cancer, the relatively high prevalence of the disease in unscreened populations, and the sensitivity of cytologic screening make cervical carcinoma an ideal target for cancer screening. In the United States, screening with cervical cytologic examination and pelvic examination has led to more than a 70% decrease in the mortality from cervical cancer since 1940. Only nations with comprehensive screening programs have experienced substantial decreases in cervical cancer death rates during this period.

Authorities disagree about the optimal frequency of cervical cancer screening. In a 1988 consensus statement, the American Cancer Society and other medical groups recommended annual Pap smears beginning at age 18 years or with the onset of sexual activity and added that, after three or more consecutive normal annual examinations, the cytologic evaluation could be performed less frequently at the discretion of the physician. For patients who have had repeated negative test results, the marginal gain from screening more often than every 3 years decreases sharply. Although these groups have suggested tailoring the frequency of Pap smears to patient risk, practical definitions of low and high risk remain controversial. As a result, most clinicians continue to recommend that their patients be screened more frequently than recommended by the national guidelines. The rate of false-negative findings on the Pap test is approximately 10% to 15% in women with invasive cancer. The sensitivity of the test may be improved by ensuring adequate sampling of the squamocolumnar junction and the endocervical canal; smears without endocervical or metaplastic cells are inadequate and must be repeated. Because AIS originates near or above the transformation zone, it may be missed with conventional cervical smears. Detection of high endocervical lesions may be improved when specimens are obtained with a brush. Also, because hemorrhage, necrosis, and intense inflammation may obscure the results, the Pap smear is a poor way to diagnose gross lesions; these should always be biopsied.

Patients with abnormal findings on cytologic examination who do not have a gross cervical lesion must be evaluated by colposcopy and directed biopsies. Following application of a 3% acetic acid solution, the cervix is examined under 10- to 15-fold magnification with a bright, filtered light that enhances the acetowhitening and vascular patterns characteristic of dysplasia or carcinoma. The skilled colposcopist can accurately distinguish between low- and high-grade dysplasia, but microinvasive disease cannot consistently be distinguished from intraepithelial lesions on colposcopy.

If no abnormalities are found on colposcopic examination or if the entire squamocolumnar junction cannot be visualized in a patient with an atypical Pap smear result, endocervical curettage should be performed. Some authorities advocate the routine addition of endocervical curettage to colposcopic examination to minimize the risk of missing occult carcinoma within the endocervical canal. However, it is probably reasonable to omit this step in previously untreated women if the entire squamocolumnar junction is visible with a complete ring of unaltered columnar epithelium in the lower canal.

Cervical cone biopsy is used to diagnose occult endocervical lesions and is an essential step in the diagnosis and management of microinvasive carcinoma of the cervix. The geometry of the cone is individualized and tailored to the geometry of the cervix, the location of the squamocolumnar junction, and the site and size of the lesion. Cervical cone biopsy yields an accurate diagnosis and decreases the incidence of inappropriate therapy when (1) the squamocolumnar junction is poorly visualized on cervical smear and a high-grade lesion is suspected, (2) a high-grade lesion is detected by direct bimanual examination, and (3) a high-grade lesion is detected on directed biopsy. The endocervical curettage specimens show high-grade CIN, or (6) the cytologic findings are suspicious for AIS.

**Clinical Evaluation of Patients with Invasive Carcinoma**

All patients with invasive cervical cancer should be evaluated with a detailed history and physical examination, with particular attention paid to inspection and palpation of the pelvis with bimanual and rectovaginal examinations. Standard laboratory studies should include a complete blood cell count and renal function and liver function tests. All patients should have chest radiography to rule out lung metastases and an intravenous pyelogram (or computed tomography (CT)) to determine the kidney's location and to rule out ureteral obstruction by tumor. Cystoscopy and either a proctoscopy or a barium enema study should be done in patients with bulky tumors.

Many clinicians obtain CT or magnetic resonance imaging (MRI) scans to evaluate regional nodes, but the accuracy of these studies is compromised by their failure to determine the kidney's location and to rule out ureteral obstruction by tumor. Cystoscopy and either a proctoscopy or a barium enema study should be done in patients with bulky tumors. All patients with invasive cervical cancer should be evaluated with a detailed history and physical examination, with particular attention paid to inspection and palpation of the pelvis with bimanual and rectovaginal examinations. Standard laboratory studies should include a complete blood cell count and renal function and liver function tests. All patients should have chest radiography to rule out lung metastases and an intravenous pyelogram (or computed tomography (CT)) to determine the kidney's location and to rule out ureteral obstruction by tumor. Cystoscopy and either a proctoscopy or a barium enema study should be done in patients with bulky tumors. Many clinicians obtain CT or magnetic resonance imaging (MRI) scans to evaluate regional nodes, but the accuracy of these studies is compromised by their failure to determine the kidney's location and to rule out ureteral obstruction by tumor. Cystoscopy and either a proctoscopy or a barium enema study should be done in patients with bulky tumors.
Clinical Staging

FIGO has defined the most widely accepted staging system for carcinomas of the cervix. The latest (1994) update of this system is summarized in Table 36.2-4. Since the earliest versions of the cervical cancer staging system there have been numerous changes, particularly in the definition of stage I disease. Preinvasive disease was not placed in a separate category until 1965, and the stage IA category for "cases with early stromal invasion" was first described in 1962. Cases of early stromal invasion and occult invasion were redistributed between stages IA1, IA2, and IB until several times until 1985, when FIGO eliminated stage IB and provided the first specific definitions of microinvasive disease (stages IA1 and IA2). In 1994 these definitions were changed again, and, for the first time, stage IB tumors were subdivided according to tumor diameter (see Table 36.2-4). Although these changes have gradually improved the discriminatory value of the staging system, the most fluctuations in the definition of stage IA and IB have been associated with the outcomes of patients with tumors whose invasion of the pelvic wall was treated during different periods. In addition, many gynecologic oncologists in the United States use the Society of Gynecologic Oncologists' definition of a microinvasive carcinoma (i.e., tumor that "invades the stroma in one or more places to a depth of 3 mm or less below the base of the epithelium and in which lymphatic or vascular involvement is not demonstrated"), a definition that still differs from the current FIGO classification.

Table 36.2-4. International Federation of Gynecology and Obstetrics Staging of Carcinoma of the Cervix (1994)

FIGO stage is based on careful clinical examination and the results of specific radiologic studies and procedures. These should be performed and the stage should be assigned before any definitive therapy is administered. The clinical stage should never be changed on the basis of subsequent findings. When it is doubtful to which stage a particular case should be allotted, the case should be assigned to the earlier stage. According to FIGO, "a growth fixed to the pelvic wall by a short and indurated, but not nodular, parametrium should be allotted to stage IIIb. A case should be classified as stage III "only if the parametrium is nodular to the pelvic wall or if the growth itself extends to the pelvic wall." In its rules for clinical staging, FIGO states that palpation, inspection, colposcopy, endocervical curettage, hysteroscopy, cystoscopy, proctoscopy, intravenous urography, and radiographic examination of the lungs and skeleton may be used for clinical staging. Suspected bladder or rectal involvement should be confirmed by biopsy. Findings of biliary edema or malignant cells in cytologic washings from the urinary bladder are not sufficient to diagnose bladder involvement. FIGO specifically states that findings on examinations such as lymphangiography, laparoscopy, CT scan, and MRI are of value for planning therapy but, because these are not yet generally available and the interpretation of results is variable, should not be the basis for changing the clinical stage. Examination under anesthesia is desirable but not required. The rules and notes outlined in the FIGO staging system are integral parts of the clinical staging system and should be strictly observed to minimize inconsistencies in staging between institutions.

Although most clinicians use the FIGO classification system, a number of European groups use a staging system that divides stage IB tumors according to the extent of parametrial involvement and divides stage III tumors according to whether there is unilateral or bilateral pelvic wall fixation. Until the mid 1980s most reports from The University of Texas M. D. Anderson Cancer Center used a similar staging system that also categorized patients with bulky endocervical tumors in a special category. Although surgical staging for cervical cancer has been performed since the earliest versions of the cervical cancer staging system there have been numerous changes, particularly in the definition of stage I disease.

Surgical Evaluation of Regional Spread

In the 1970s, studies of diagnostic preradiation lymph node dissection used a transperitoneal approach that led to unacceptable morbidity and mortality from radiation-related bowel complications, particularly after treatment with high radiation doses and extended fields. More recently, extraperitoneal dissection, which induces fewer bowel adhesions, has been recommended. With this approach, postradiation bowel complications occur in fewer than 5% of patients. A number of groups are currently investigating the use of laparoscopic lymph node dissection to evaluate patients with cervical cancer. This approach reduces the length of postoperative hospitalization. However, the rate of late complications from radiotherapy following laparoscopic lymphadenectomy has not yet been determined.

Although the indications for surgical staging are controversial, advocates argue that the procedure identifies patients with microscopic paraaortic or common iliac node involvement who can benefit from extended-field irradiation. Some investigators have also suggested, on the basis of first principles and encouraging results with regard to control of pelvic disease, that debulking of large pelvic nodes before radiotherapy may improve outcome. Because patients with radiographically positive pelvic nodes are at greatest risk for occult metastasis to paraaortic nodes, these patients may have the greatest chance of benefiting from surgical staging.

Some authors have advocated pretreatment blind biopsy of the scalene node in patients with positive paraaortic nodes and in patients with a central recurrence who are being considered for pelvic exenteration. The reported incidence of supraclavicular metastasis varies widely (5% to 25% or more) for patients with positive paraaortic lymph nodes.

Prognostic Factors

Although rates of survival and control of pelvic disease in cervical cancer patients are correlated with FIGO stage, prognosis is also influenced by a number of tumor characteristics that are not included in the staging system. Clinical tumor diameter is strongly correlated with prognosis for patients treated with radiation. The predictive value of the staging system itself may, in part, reflect an association between the stage categories and the primary tumor volume. Operative findings often do not agree with clinical estimates of parametrial or pelvic wall involvement, and some authors have found that the predictive power of stage diminishes or is lost when comparisons are corrected for differences in clinical tumor diameter.

![Graph](image-url)
Lymph node metastasis is also an important predictor of prognosis. For patients treated with radical hysterectomy for stage IB disease, survival rates are usually reported as 85% to 95% for patients with negative nodes and 45% to 55% for those with lymph node metastases. **Inoue and Morita** reported that survival was correlated with the size of the largest node, and several authors have reported correlations between the number of involved pelvic lymph nodes and survival. **Survival rates for patients with positive paraaortic nodes treated with extended-field radiotherapy vary between 10% and 50% depending on the extent of pelvic disease and paraaortic lymph node involvement (Table 36.2-5).**

**TABLE 36.2-5. Results of Extended-Field Radiation Therapy to the Paraaortic Nodes for Biopsy-Proven Paraaortic Node Metastases from Carcinoma of the Cervix**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Number of Patients</th>
<th>Pelvic Lymph Nodes Involved</th>
<th>Paraaortic Node Metastases</th>
<th>5-Year Survival Rate</th>
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</thead>
<tbody>
<tr>
<td>Chuang et al. 1968</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td>91%</td>
</tr>
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<td>Eifel et al. 1973</td>
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<td>2</td>
<td>1</td>
<td>75%</td>
</tr>
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<td>Faid et al. 1973</td>
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<td>1</td>
<td>0</td>
<td>74%</td>
</tr>
<tr>
<td>Godin et al. 1973</td>
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<td>0</td>
<td>0</td>
<td>90%</td>
</tr>
<tr>
<td>Ghrayeb et al. 1974</td>
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<td>0</td>
<td>0</td>
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<tr>
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<td>82%</td>
</tr>
<tr>
<td>Teibert et al. 1975</td>
<td>14</td>
<td>0</td>
<td>0</td>
<td>80%</td>
</tr>
</tbody>
</table>

**FIGURE 36.2-2. Relationship between tumor diameter and the disease-specific survival rates of 1526 patients with stage IB squamous cell carcinomas of the cervix treated with radiotherapy at M. D. Anderson Cancer Center. Numbers in parentheses represent the number of patients at risk at 10 or 20 years. (Reprinted from ref. 148, with permission.)**

Several investigators have reported similar survival rates for patients with squamous carcinomas and those with adenocarcinomas. However, other investigators have drawn the opposite conclusion, noting unusually high pelvic relapse rates in patients treated surgically for adenocarcinomas and poorer survival rates among patients treated with surgery or irradiation for cervical adenocarcinomas. In a multivariate analysis of 1767 patients treated with radiotherapy for FIGO stage IB disease, Eifel and colleagues reported a highly significant independent correlation between histologic features and survival. Using Cox regression analysis, the relative risk of death from cancer for 106 patients with adenocarcinomas 4 cm or more in diameter was determined to be 1.9 times that for patients with squamous tumors (P < 0.01) (**Fig. 36.2-3**). Pelvic disease control rates were similar for patients with squamous carcinomas and those with adenocarcinomas, but there was a significantly higher incidence of distant metastases in patients with adenocarcinomas. Although the prognostic significance of histologic grade has been disputed for squamous carcinomas, there is a clear correlation between the degree of differentiation and the clinical behavior of adenocarcinomas. **The strongest evidence that anemia plays a causative role in pelvic recurrence comes from a small 1978 randomized study conducted at the Princess Margaret Hospital. All patients were maintained at a hemoglobin level of at least 10 g/dl, but those in the treatment arm were maintained, through the use of transfusions, at hemoglobin levels of at least 12.5 g/dl. The locoregional recurrence rate was significantly higher for the 25 anemic patients in the control arm than it was for the patients who received transfusions. Unfortunately, the results of this small study have never been confirmed, and subsequent studies aimed at overcoming the theoretical radiobiologic consequences of intratumoral hypoxia (hypoxic cell sensitizers, hyperbaric oxygen breathing, neutron therapy) have not been able to show a significant benefit.**
The serum concentration of squamous cell carcinoma antigen appears to correlate with the stage and size of squamous carcinomas and the presence of lymph node metastases. However, investigators disagree about the independent predictive value of this test. Other clinical and biologic features that have been investigated for their predictive power, with variable results, include patient age, peritoneal cytology, platelet count, tumor vascularity, DNA ploidy or S phase, and HPV subtype.

In two studies of patients with histologically negative lymph nodes, investigators have reported higher rates of disease recurrence when a polymerase chain reaction assay of the lymph nodes was strongly positive for HPV DNA.

TREATMENT

A number of factors may influence the choice of local treatment, including tumor size, stage, histologic features, evidence of lymph node involvement, risk factors for complications of surgery or radiation, and patient preference. However, as a rule, intraepithelial lesions are treated with superficial ablative techniques; microinvasive cancers invading less than 3 mm (stage IA1) are managed with conservative surgery (excisional conization or extrafascial hysterectomy); early invasive cancers (stages IA2 and IB1 and some small stage IIA tumors) are managed with radical surgery or radiotherapy; and locally advanced cancers (stages IB2 through IVA) are managed with radiotherapy. Selected patients with centrally recurrent disease after maximum radiotherapy may be treated with radical exenterative surgery; pelvic recurrence after hysterectomy is treated with irradiation. The results of randomized trials have led to the addition of concurrent cisplatin-containing chemotherapy to radiotherapy for patients whose cancers have a high risk of local-regional recurrence.

Preinvasive Disease (Stage 0)

Patients with noninvasive squamous lesions can be treated with superficial ablative therapy (cryosurgery or laser therapy) or with loop excision if (1) the entire transformation zone has been visualized colposcopically, (2) directed biopsies are consistent with Pap smear results, (3) endocervical curettage findings are negative, and (4) there is no suspicion of occult invasion on cytologic or colposcopic examination. If patients do not meet these criteria, a conization should be performed.

With cryotherapy, abnormal tissue is frozen with a supercooled metal probe until an ice ball forms that extends 5 mm beyond the lesion. Because cryonecrosis tends to be patchy and may be inadequate after a single freeze, the tissue should be frozen a second time after it has visibly thawed. Another common and equally effective technique ablates tissue with a carbon dioxide laser beam. After laser ablation there is less distortion and more rapid healing of the cervix, but the procedure requires more training and more expensive equipment than does cryosurgery.

Many practitioners now consider loop diathermy excision to be the preferred treatment for noninvasive squamous lesions. With this technique, a charged electrode is used to excise the entire transformation zone and distal canal. Although control rates are similar to those achieved with cryotherapy or laser ablation, loop diathermy is easily learned, is less expensive than laser excision, and preserves the excised lesion and transformation zone for histologic evaluation. However, some authorities think that low-grade lesions may be overtreated with this method. Because loop excision may inadequately treat disease within the cervical canal and complicate further treatment, this technique should not be considered an alternative to formal excisional conization when microinvasive or invasive cancer is suspected or for patients with AIS.

Cryotherapy, laser excision, and loop excision are all outpatient office procedures that preserve fertility. Although recurrence rates are low (10% to 15%) and progression to invasion rare (less than 2% in most series), life long surveillance of these patients must be maintained. The risk of recurrence may be somewhat increased in women with HPV type 16 or 18. Treatment with vaginal or type I abdominal hysterectomy currently is reserved for women who have other gynecologic conditions that justify the procedure; invasive cancer still must be excluded before surgery to rule out the need for a more extensive operative procedure.

Microinvasive Carcinoma (Stage IA)

The standard treatment for patients with stage IA1 disease is total (type I) or vaginal hysterectomy. Because the risk of pelvic lymph node metastases from these minimally invasive tumors is less than 1%, pelvic lymph node dissection is not usually recommended.

Selected patients with tumors that meet the Society of Gynecologic Oncologists' definition of microinvasion (FIGO stage IA1 disease without LVSI) and who wish to maintain fertility may be adequately treated with a therapeutic cervical conization if the margins of the cone are negative. In 1991, Burghardt et al. reported one recurrence (which was fatal) in 93 women followed for more than 5 years after therapeutic conization for minimal (less than 1 mm) microinvasion. Morris et al. reported no invasive recurrences in 14 patients followed for a mean of 26 months after conization for tumors invading 0.5 to 2.8 mm. However, patients who have this conservative treatment must be followed closely with periodic cytologic evaluation, colposcopy, and endocervical curetage.

Diagnostic or therapeutic conization for microinvasive disease is usually performed with a cold knife or carbon dioxide laser on a patient under general or spinal anesthesia. Because an accurate assessment of the maximum depth of invasion is critical, the entire specimen must be sectioned and carefully handled to maintain its original orientation for microscopic assessment. Complications occur in 2% to 12% of patients, are related to the depth of the cone, and include hemorrhage, sepsis, infertility, stenosis, and cervical incompetence. The width and depth of the cone should be tailored to produce the least amount of injury while providing clear surgical margins.

For patients whose tumors invade 3 to 5 mm into the stroma (FIGO stage IA2), the risk of nodal metastases is approximately 5%. Therefore, a bilateral pelvic lymphadenectomy should be performed in conjunction with a modified radical (type II) hysterectomy. Modified radical hysterectomy is a less extensive procedure than a classic radical hysterectomy. The cervix, upper vagina, and para-cervical tissues are removed after careful dissection of the ureters to the point of their entry to the bladder. The medial half of the cardinal ligaments and the uterosacral ligaments are also removed. With this treatment, significant urinary tract complications are rare and cure rates exceed 95%.

FIGURE 36.2-4. The pelvic ligaments and spaces. Dotted lines indicate the tissues removed with a type II or type III hysterectomy. (Reprinted from ref. 541, with permission.)

Although surgical treatment is standard for in situ and microinvasive cancer, patients with severe medical problems or other contraindications to surgical treatment can be successfully treated with radiotherapy. Grigsby and Perez reported a 10-year progression-free survival rate of 100% in 21 patients with carcinoma in situ and in 34 patients with microinvasive carcinoma treated with radiation alone. Hamberger et al. reported that all patients with stage IA disease and 95 (96%) of 93 patients with small stage IB disease (less than one cervical quadrant involved) were disease free 5 years after treatment with intracavitary irradiation alone.
Stages IB and IIA

Early stage IB cervical carcinomas can be treated effectively with combined external-beam irradiation and brachytherapy or with radical hysterectomy and bilateral pelvic lymphadenectomy. The goal of both treatments is to destroy malignant cells in the cervix, paracervical tissues, and regional lymph nodes. Studies indicate that selected subgroups of patients who require radiotherapy also benefit from concurrent chemotherapy.  \(^{254,255}\)

Overall survival rates for patients with stage IB cervical cancer treated with surgery or radiation usually range between 80% and 90%, suggesting that the two treatments are equally effective (Table 36.2-7).  \(^{257,260,261}\) In their study, patients with stage IB or IIA disease were randomly assigned to receive treatment with type III radical hysterectomy or a combination of external-beam and low dose-rate intracavitary radiotherapy. In the surgical arm, findings of parametrial involvement, positive margins, deep stromal invasion, or positive nodes led to the use of postoperative pelvic irradiation in 62 (54%) of 114 patients with tumors 4 cm or smaller in diameter and in 46 (84%) of 55 patients with tumors measuring less than 4 cm. Patients in the radiotherapy arm received a relatively low total dose of radiation to the cervix, with a median dose to point A of 76 Gy. With a median follow-up of 87 months, the 5-year actuarial disease-free survival rates for patients treated in the surgery and radiotherapy groups were 80% and 82%, respectively, for patients with tumors that were 4 cm or smaller and 63% and 57%, respectively, for patients with larger tumors. The authors reported a significantly higher rate of complications in the patients treated with initial surgery, and they attributed this finding to the frequent use of combined modality treatment in this group.

For patients with stage IBI squamous carcinomas, the choice of treatment is based primarily on patient preference, anesthetic and surgical risks, physician preference, and an understanding of the nature and incidence of complications with radiotherapy and hysterectomy (described in detail here). For patients with similar tumors, the overall rate of major complications is similar with surgery and radiotherapy, although urinary tract complications tend to be more frequent after surgical treatment, and gastrointestinal complications tend to be rarer. A significant trend toward better survival has been noted with women under 40 years of age who were treated with radiotherapy because it permits preservation of ovarian function and may cause less vaginal shortening. Radiotherapy is often selected for older, postmenopausal women to avoid the morbidity of a major surgical procedure.

Some surgeons have also advocated the use of radical hysterectomy as initial treatment for patients with stage IB2 tumors.  \(^{258,259}\) However, patients who have tumors measuring more than 4 cm in diameter usually have high risk for deep stromal invasion and are at high risk for lymph node involvement and parametrial extension. Because patients with these risk factors have an increased rate of pelvic disease recurrence, surgical treatment is usually followed by postoperative irradiation, which means that the patient is exposed to the risks of both treatments. Consequently, many gynecologic and radiation oncologists believe that patients with bulky (stage IB2) carcinomas are better treated with radical radiotherapy.

Two prospective randomized trials  \(^{262,263}\) indicate that patients who are treated with radiation for bulky central disease benefit from concurrent administration of cisplatin-containing chemotherapy. A third study suggests that patients who require postoperative radiation because of findings of lymph node metastasis or involved surgical margins also benefit from concurrent chemoradiation.  \(^{255}\) These studies are discussed in more detail in the following sections.

RADICAL HYSTERECTOMY. The standard surgical treatment for stage IB and stage IIA cervical carcinomas is radical (type III) hysterectomy and bilateral pelvic lymph node dissection. This procedure involves en bloc removal of the uterus, cervix, and paracervical, parametrial, and paravaginal tissues to the pelvic side walls bilaterally, with removal of as much of the uterosacral ligaments as possible (see Fig. 36.2-4). The uterine vessels are ligated at their origin, and the proximal third of the vagina and paracolpium are resected. For women younger than 40 to 45 years, the ovaries usually are not removed. If intraoperative findings suggest a need for postoperative pelvic irradiation, the ovaries may be transected out of the pelvis.

Intraoperative and immediate postoperative complications of radical hysterectomy include blood loss (average 0.8 L), ureterovaginal fistula (1% to 2%), vesicovaginal fistula (less than 1%), pulmonary embolism (1% to 2%), small bowel obstruction (1% to 2%), and postoperative fever secondary to deep vein thrombosis, pulmonary infection, pelvic cellulitis, urinary tract infection, or wound infection (25% to 50%). Subacute complications include lymphocyst formation and lower extremity edema, the risk of which is related to the extent of the node dissection. Lymphocysts may obstruct a ureter, but hydroureteronephrosis usually improves with drainage of the lymphocyst. The risk of complications may be increased in patients who receive preoperative or postoperative irradiation.

Although most patients have transient decreased bladder sensation after radical hysterectomy, with appropriate management severe long-term bladder complications are infrequent. However, chronic bladder hypotonia or atony occurs in approximately 3% to 5% of patients, despite careful postoperative bladder drainage.  \(^{265,266}\) Bladder atony probably results from damage to the bladder’s innervation and may be related to the extent of the parametral and paravaginal dissection.  \(^{267}\) Radical hysterectomy may be complicated by stress incontinence, but reported incidences vary widely and may be influenced by the addition of postoperative radiotherapy.  \(^{268,271}\) Patients may also experience constipation and, rarely, chronic obstruction after radical hysterectomy.

RADIOTHERAPY AFTER RADICAL HYSTERECTOMY. The role of postoperative irradiation in patients with cervical carcinoma is still being defined. Most investigators have reported that postoperative irradiation decreases the risk of pelvic recurrence in patients whose tumors have high-risk features (lymph node metastasis, deep stromal invasion, insecure operative margins, or parametrial involvement).  \(^{272-277,279,282}\) However, because the patients who received postoperative radiotherapy in these studies were selected for the high-risk features of their tumors, it is difficult to determine the impact of adjuvant irradiation on survival.

The GOG  \(^{282}\) reported results of a prospective trial testing the benefit of adjuvant pelvic irradiation in patients who have an intermediate risk of recurrence after radical hysterectomy for stage IB carcinoma. Patients were eligible if they had at least two of the following risk factors: greater than one-third stromal invasion, lymphatic space involvement, or clinical diameter of at least 4 cm. Patients with metastases to the pelvic lymph nodes were excluded. After radical hysterectomy, 277 patients were randomly assigned to receive 46.0 to 50.6 Gy of adjuvant radiotherapy to the pelvis or no further treatment. Overall, there was a 47% reduction in the risk of recurrence with adjuvant radiotherapy (P = .008). In this preliminary analysis, follow-up was too immature for a significance level to be assigned to the overall survival comparison, but there were 18 deaths (13%) in the radiotherapy arm versus 30 (21%) in the radical hysterectomy only arm (relative mortality, 0.64).  \(^{283}\)

Although pelvic irradiation also reduces the risk of recurrence for patients with pelvic lymph node metastases or parametrial involvement, the risk of pelvic and distant recurrence remains high for these women.  \(^{272,273}\) Some authors have hypothesized that the dose of radiation that can be given safely after surgery may be inadequate to control microscopic disease in a surgically disturbed, hypovascular site.  \(^{284}\) If this were true, it would be an argument for primary radiotherapeutic management of
tumors with known high-risk features. Preliminary results of a prospective study conducted by the Southwest Oncology Group suggest that administration of cisplatin-containing chemotherapy concurrent with adjuvant pelvic irradiation may improve the rate of control of pelvic disease and the rate of survival for patients with lymph node metastases, parametrial involvement, or involved surgical margins.\textsuperscript{251}

The overall risk of major complications (particularly small bowel obstruction) is probably increased in patients who receive postoperative pelvic irradiation, but inconsistencies in the methods of analysis and the relatively small number of patients in most series make studies of this subject difficult to interpret.\textsuperscript{252, 253, 254, 255, 256, 257} and 258 Bandy et al.\textsuperscript{259} reported that patients who were irradiated after hysterectomy had more long-term problems with bladder contraction and instability than those treated with surgery alone.

**RADICAL RADIOTHERAPY.** Radiotherapy also achieves excellent survival and pelvic disease control rates in patients with stage IB cervical cancers. Eifel et al.\textsuperscript{260} reported a 5-year disease-specific survival rate of 90% for 701 patients treated with radiation alone for stage IB squamous tumors less than 4 cm in diameter. The central and pelvic tumor control rates were 99% and 98%, respectively. Disease-specific survival rates were 86% and 67% for patients with tumors measuring 4.0 to 4.9 cm or 5 cm or more in diameter, respectively. Pelvic tumor control was achieved in 82% of patients with tumors of 5 cm or more in diameter. Perez et al.\textsuperscript{261} and Lowery et al.\textsuperscript{262} reported similar excellent disease control rates for patients with stage IB tumors treated with radiotherapy. Survival rates for patients with FIGO stage IIA disease treated with irradiation range between 70% and 85% and are also strongly correlated with tumor size.\textsuperscript{263, 264, 265} For patients with bulky tumors, studies suggest that results may be improved further with concurrent administration of chemotherapy.\textsuperscript{266, 267}

As with radical surgery, the goal of radiation treatment is to sterilize disease in the cervix, paracervical tissues, and regional lymph nodes in the pelvis. Patients are usually treated with a combination of external-beam irradiation to the pelvis and brachytherapy. Clinicians balance external and intracavitary treatment in different ways for these patients, weighting one or the other component more heavily. However, brachytherapy is a critical element in the curative radiation treatment of all carcinomas of the cervix. Even relatively small tumors that involve multiple quadrants of the cervix are usually treated with total doses of 80 to 85 Gy to point A. The dose may be reduced by 5% to 10% for small superficial tumors. Although patients with small tumors may be treated with somewhat smaller fields than patients with more advanced locoregional disease, care must still be taken to cover adequately the obturator, external iliac, common iliac, and presacral nodes. Radiation technique is discussed in more detail in the next section.

**IRRADIATION FOLLOWED BY HYSTERECTOMY.** In a 1969 report from M. D. Anderson Cancer Center, Durrance and colleagues\textsuperscript{268} reported a lower pelvic recurrence rate for patients with bulky endocervical tumors (greater than or equal to 6 cm) treated with external-beam and intracavitary irradiation followed by extrafascial hysterectomy than for those treated with radiation alone. Many groups subsequently adopted combined treatment as a standard approach to bulky stage IB or IIA disease. However, in a 1992 update of the M. D. Anderson experience, Thorns and colleagues\textsuperscript{269} suggested that the differences observed in earlier reports may have resulted from a tendency to select patients with massive tumors (greater than or equal to 8 cm) or clinically positive nodes for treatment with radiation alone. When these patients were excluded, pelvic disease control rates were similar with the two approaches.

In 1991, Mendenhall et al.\textsuperscript{270} reported no difference in pelvic disease control or survival rates for patients treated before or after the University of Florida adopted a policy (in mid-1970s) of using combined treatment for patients with bulky (greater than or equal to 6 cm) tumors. In a study of 1526 patients with stage IB squamous carcinomas, Eifel and colleagues\textsuperscript{15} reported central tumor recurrence rates of less than 10% for tumors as large as 7.0 to 7.9 cm treated with radiation alone, suggesting that the margin for possible improvement with adjuvant hysterectomy is small. Perez and Kao\textsuperscript{271} also found that central recurrences were rare if adequate doses of irradiation (greater than 80 Gy to point A) were delivered. Addition of concurrent chemotherapy should further reduce the margin for improvement with adjuvant hysterectomy.\textsuperscript{272}

There is, therefore, no clear evidence that adjuvant hysterectomy improves the outcome of patients with a bulky stage IB or IIA tumor, although many clinicians continue to recommend combined treatment.\textsuperscript{273} When combined treatment is planned, the dose of intracavitary irradiation is usually reduced by 15% to 25%. A type I, extrafascial hysterectomy is usually performed, in which the cervix, adjacent tissues, and a small cuff of the upper vagina in a plane outside the pubocervical fascia are removed. This procedure involves minimal disturbance of the bladder and ureters. Infracervical hysterectomy is not used for cervical cancer because it does not remove all cervical tissue.\textsuperscript{274} and radical hysterectomy is avoided after high-dose irradiation because of an increased risk of urinary tract complications.\textsuperscript{275}

In 1991, the GOG completed a prospective randomized trial of irradiation with or without extrafascial hysterectomy in patients with stage IB tumors of 4 cm or more in diameter. Preliminary analysis demonstrated no significant improvement in the survival rate of patients who had an adjuvant hysterectomy.\textsuperscript{276}

**CHEMOTHERAPY FOLLOWED BY RADICAL SURGERY.** During the 1990s, a number of investigators reported the results of treating patients with bulky stage IB or stage II cervical carcinomas with a combination of neoadjuvant chemotherapy followed by radical surgery.\textsuperscript{277, 278 and 279} Neoadjuvant chemotherapy has usually included cisplatin and bleomycin plus one or two other drugs (Table 36.2-8). The results of uncontrolled studies cannot be easily compared with the results with more traditional treatments because the series are small and often have short follow-up and the criteria for patient selection are not always clear. Some or all of the patients in each of these series received postoperative pelvic irradiation, but detailed descriptions of this additional treatment are not always given. Only one prospective randomized trial has compared radical hysterectomy followed by postoperative radiotherapy with chemotherapy followed by surgery and irradiation.\textsuperscript{280} In this study, Sardi et al. observed similar outcomes with the two treatments for patients who had tumors smaller than 60 cm\textsuperscript{2} (measured ultrasonographically), but they reported a significantly better projected 4-year disease-free survival with neoadjuvant chemotherapy for patients who had larger tumors. However, most patients had been followed for less than 3 years at the time of the report. Ultimately, the cost and morbidity of this triple-modality treatment may only be justified if it proves to be more effective than treatment with radiation or chemoradiation alone. However, studies comparing these approaches have not yet been reported.

**TABLE 36.2-8.** Response Rates to Neoadjuvant Chemotherapy in Patients with Previously Untreated Locally Advanced Cervical Cancer

<table>
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<th>Stages IB, II, and IVA</th>
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<td>Radiotherapy is the primary local treatment for most patients with locoregionally advanced cervical carcinoma. The success of treatment depends on a careful balance between external-beam radiotherapy and brachytherapy, optimizing the dose to tumor and normal tissues and the overall duration of treatment. Five-year survival rates of 65% to 75%, 35% to 50%, and 15% to 20% are reported for patients treated with radiation alone for stage IIB, III, and IV tumors, respectively.\textsuperscript{281, 282, 283, 284, 285, 286, 287, 288, 289} In a French Cooperative Group study of 1875 patients treated with radiotherapy according to Fletcher guidelines, Barillot et al.\textsuperscript{289} reported 5-year survival rates of 70%, 45%, and 10% for patients with stage IIB, IIIB, and IV A tumors, respectively (Table 36.2-8). With appropriate radiotherapy, even patients with massive locoregional disease have a significant chance for cure.</td>
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External-beam irradiation is used to deliver a homogeneous dose to the primary cervical tumor and to potential sites of regional spread. An initial course of external irradiation may also improve the efficacy of subsequent intracavitary treatment by shrinking bulky endocervical tumor (brining it within the range of the high-dose portion of the brachytherapy dose distribution) and by shrinking exophytic tumor that might prevent satisfactory placement of vaginal applicators. For this reason, patients with locally advanced disease usually begin with a course of external-beam treatment. Subsequent brachytherapy exploits the inverse square law to deliver a high dose to the cervix and para-cervical tissues while minimizing the dose to adjacent normal tissues.

Although many clinicians delay intracavitary treatment until pelvic irradiation has caused some initial tumor regression, breaks between external-beam and intracavitary therapy should be discouraged, and every effort should be made to complete the entire treatment in less than 7 to 8 weeks. The favorable results documented in reports from large single-institution studies have been based on policies that dictate relatively short overall treatment durations (less than 8 weeks), and several studies in patients with locally advanced cervical cancer have suggested that longer treatment courses are associated with decreased pelvic disease control and survival rates. 345, 346 Therefore, clinicians and patients should be encouraged to complete the treatment as soon as possible. 347

EXTERNAL-BEAM TECHNIQUE. High-energy photons (15 to 18 MV) are usually preferred for pelvic treatment because they spare superficial tissues that are unlikely to be involved with tumor. At these energies, the pelvis can be treated either with four fields (anterior, posterior, and lateral fields) or with anterior and posterior fields alone (Fig. 36.2-6). When high-energy beams are not available, four fields are usually used because less-penetrating 4- to 6-MV photons often deliver an unacceptably high dose to superficial tissues when only two fields are treated. However, lateral fields must be designed with great care because clinicians’ estimates of the location of potential sites of disease on a lateral radiographic view may be inaccurate. In particular, standard anterior and posterior borders that have been described in the past may shield regions at risk for microscopic regional disease in the presacral and external iliac nodes and in the presacral and cardinal ligaments; care must also be taken not to underestimate the posterior extent of central cervical disease in patients with bulky tumors. 348, 349, 350

The caudad extent of disease can be determined by placing radiopaque seeds in the cervix or at the lowest extent of vaginal disease. Information gained from radiologic studies can also improve estimates of disease extent. Lymphangiograms are helpful in tailoring blocks, particularly at the anterior border of lateral fields. MRI and CT scans can improve clinicians’ understanding of uterine position and thus help clinicians design anterior and posterior field borders. In fact, some investigators have argued that these studies should be obtained routinely for patients with bulky disease to avoid errors in lateral field design. However, when all these factors are considered, differences in the volume treated with a four-field or a high-energy two-field technique may be small. For this reason, some clinicians prefer to use the simpler technique for patients with bulky tumors.

Tumor response should be evaluated with periodic pelvic examinations to determine the best time to deliver brachytherapy. Some practitioners prefer to maximize the brachytherapy component of treatment and begin as soon as the tumor has responded enough to permit a good placement (with very bulky tumors this may still require greater than or equal to 40 Gy). Subsequent pelvic irradiation is delivered with a central block. A somewhat higher total paracentral dose can be delivered with this approach, but greater reliance is placed on the complex match between the brachytherapy dose distribution and the border of the central shield. This may result in overdoses to medial structures such as the ureters or underdosage of posterior uterosacral disease. For these reasons, other clinicians prefer to give an initial dose of 40 to 45 Gy to the whole pelvis, believing that the ability to deliver a homogeneous distribution to the entire region at risk for microscopic disease and the additional tumor shrinkage achieved before brachytherapy outweighs other considerations. However, external-beam doses of more than 40 to 50 Gy to the central pelvis tend to compromise the dose deliverable to paracentral tissues and increase the risk of late complications. 354

ROLE OF PARAORTIC IRRADIATION. The role of extended field irradiation in the treatment of cervix cancer is still being defined. Numerous small series of patients with documented paraaortic node involvement demonstrate that some enjoy long-term survival (see Table 36.2-5). 355, 356, 357, 358, 359, 360, 361, 362, 363, 364 Patients with microscopic involvement have a better survival than do those with gross lymphadenopathy, but even 10% to 15% of patients with gross lymphadenopathy appear to be curable with aggressive management. Survival is also strongly correlated with the bulk of central disease. A 1991 study by Cunningham et al. reported a 48% 5-year survival rate in patients who had paraaortic node involvement discovered at exploration for radical hysterectomy that was then aborted. This experience with patients who had small, radiographically primary disease demonstrates that patients with paraaortic node metastases can often be cured if their primary disease can be sterilized. This indicates that patients may have extensive regional spread without distant metastases and provides an argument for surgical staging in high-risk patients.

Two randomized prospective trials have addressed the role of prophylactic paraaortic irradiation in patients without known paraaortic node involvement. In a study conducted by the Radiation Therapy Oncology Group, 367 patients with primary stage IIB or stage IIB or IIA tumors more than 4 cm in diameter were randomly assigned to receive either standard pelvic radiotherapy or extended-field radiotherapy before brachytherapy. No consistent method was used to evaluate the paraaortic nodes. For the 337 evaluable patients, absolute survival was significantly better for those treated with extended fields than for those treated with standard pelvic radiotherapy (67% vs. 55% at 5 years; P = .02) (Fig. 36.2-7). There was no significant difference in disease-free survival (P = .56).

FIGURE 36.2-5. Relationship between International Federation of Gynecology and Obstetrics stage and the actuarial survival rates of 1383 patients with invasive carcinoma of the cervix treated with radiotherapy. (Reprinted from ref. 25, with permission.)

FIGURE 36.2-6. Typical fields used to treat the pelvis with a four-field technique. When lateral fields are used to treat cervical cancers, particular care must be taken to adequately encompass the primary tumor and potential sites of regional spread in the radiation fields.
A second trial, from the European Organization for Research and Treatment of Cancer, involved a similar randomization between pelvic irradiation and extended fields but had very different eligibility criteria. This study included patients with bulky stage IIB (involving distal vagina or lateral parametrium) and III disease and patients with stage I disease or less bulky stage IIB disease who had positive pelvic nodes on lymphangiography or at surgery. The 4-year disease-free survival rates for patients treated with pelvic or extended fields were not significantly different (49.6% and 53.3%, respectively). However, the rate of paraaortic node recurrence was significantly higher in the pelvic field group, and for patients in whom local control was achieved, the rate of distant metastases was 2.8 times greater if treatment was with pelvic irradiation only ($P < .01$).

Both studies revealed an increased rate of enteric complications in patients treated with extended fields. In the Radiation Therapy Oncology Group study, 112 most small bowel obstructions occurred in patients who had undergone pretreatment transperitoneal staging. The European Organization for Research and Treatment of Cancer 112 did not mention a relationship between surgical staging and enteric complications.

Taked together, these data clearly indicate that some paraaortic metastases are not detected by radiographic studies and that patients with occult disease can be cured if the paraaortic nodes are included in radiation fields. However, the addition of concurrent chemotherapy to the regimen of many patients with locally advanced disease increases the importance of careful selection of patients for large field irradiation because of the greater acute toxicity when chemotherapy is combined with extended-field radiotherapy. 114 124

**BRACHYTHERAPY TECHNIQUE.** Fletcher described three conditions that should be met for successful cervical brachytherapy: (1) the geometry of the radioactive sources must prevent undosed regions on and around the cervix, (2) an adequate dose must be delivered to the paracervical areas, and (3) mucosal tolerance must be respected. 125 Although some clinicians have proposed a number of variations on the low-rate intracavitary brachytherapy techniques practiced at M. D. Anderson, Fletcher’s conditions continue to dictate the character, intensity, and timing of brachytherapy for cervical cancer.

Brachytherapy is usually delivered using afterloading applicators that are placed in the uterine cavity and vagina. A number of different intracavitary systems have been used; in the United States, variations of the Fletcher-Suit-Delclos low dose-rate system are still used most commonly. 126 127 128 129 130 The intrauterine tandem and vaginal applicators are carefully positioned, usually with the patient under anesthesia, to provide an optimal relationship between the system and adjacent tumor and normal tissues. Vaginal packing is used to hold the tandem and colpostats in place and to maximize the distance between the sources and the bladder and rectum. Radiographs should be obtained at the time of insertion to verify accurate placement, and the system should be repositioned if positioning can be improved. Encapsulated radioactive sources are inserted in the applicators after the patient has returned to her hospital bed, reducing exposure to personnel during applicator placement. Remote afterloading devices that further reduce personnel exposure are often used in departments that treat many patients with gynecologic disease. Although $^{253}$Ra was used to treat most patients before the 1980s, it has gradually been replaced by $^{137}$Cs, which produces a similar dose distribution and avoids the radiation protection problems caused by the radon gas by-product of radium decay.

**Brachytherapy Dose** Ideal placement of the uterine tandem and vaginal ovoids produces a pear-shaped distribution, delivering a high dose to the cervix and paracervical tissues and a reduced dose to the rectum and bladder (Fig. 36.2-8).

Treatment dose has been specified in a number of ways, making it difficult to compare experiences. Paracentral doses are most frequently expressed at a single point, usually designated point A. This reference point has been calculated in a number of different ways, but it is usually placed 2 cm lateral and 2 cm superior to the external cervical os, in the central plane of the intracavitary system (see Fig. 36.2-8). Point A lies approximately at the crossing of the ureter and the uterine artery, but it bears no consistent relationship to the tumor or target volume. Point A was originally developed as part of the Manchester treatment system (a modification of the earlier Paris system). It was meant to be used in the context of a detailed set of rules governing the placement and loading of the intracavitary system. Today this context is often lost.

Other measures have been used to describe the intensity of intracavitary treatment. $\text{mg-hrs}$ or $\text{mgRaEq-hrs}$ are proportional to the dose of radiation at relatively distant points from the system and therefore give a sense of the dose to the whole pelvis. In 1985 the International Commission on Radiation Units and Measurements recommended use of total reference air Kerma, expressed in mGy at 1 m, as an alternative to mg-hrs that allows for the use of various radionuclides. 125 The International Commission on Radiation Units and Measurements also defined reference points for estimating the dose to the bladder and rectum. These points have both been widely, although not universally, accepted. Although normal tissue reference points provide useful information about the dose to a portion of normal tissue, several studies have demonstrated that they consistently underestimate the maximum dose to those tissues. 126 127 128 129 130

Whatever system of dose specification is used, emphasis should always be placed on optimizing the relationship between the intracavitary applicators and the cervical tumor and other pelvic tissues. Source strengths and positions should be carefully chosen to provide optimal tumor coverage without exceeding normal tissue tolerance. However, optimized source placement can rarely correct for a poorly positioned applicator.

A detailed description of the characteristics of an ideal intracavitary system and of the considerations that influence source strength and position are beyond the scope of this chapter but can be found elsewhere. 127 128 130 However, an effort should always be made to deliver at least 85 Gy (with low dose-rate brachytherapy) to point A for patients with bulky central disease. If the intracavitary placement has been optimized, this can usually be accomplished without exceeding a dose of 75 Gy.
to the bladder reference point or 70 Gy to the rectal reference point, doses that are usually associated with an acceptably low risk of major complications. The dose to the surface of the lateral wall of the apical vagina should not usually exceed 130 to 140 Gy. Suboptimal placements occasionally force compromises in the dose to tumor or normal tissues. To choose a treatment that optimizes the therapeutic ratio in these circumstances requires experience and a detailed understanding of factors that influence tumor control and normal tissue complications.

A total dose (external-beam and intracavitary) of 50 to 55 Gy appears to be sufficient to sterilize microscopic disease in the pelvic nodes in most patients. It is customary to boost the dose to a total of 60 to 65 Gy in lymph nodes known to contain gross disease and in heavily involved parametria.

Brachytherapy Dose Rate Traditionally, cervical brachytherapy has been performed with sources that yield a dose rate at point A of approximately 40 to 50 cGy/h. These low dose rates permit repair of sublethal cellular injury, preferentially spare normal tissues, and optimize the therapeutic ratio. In an effort to reduce the 3 to 4 days of hospitalization needed to deliver an appropriate dose of low dose-rate irradiation, some investigators have explored the use of intermediate dose-rate brachytherapy (80 to 100 cGy/h). However, in a randomized trial, Haire-Meder et al. reported a significant increase in complications when the dose rate was doubled from 40 to 80 cGy/h, indicating that the total dose must be reduced and the therapeutic ratio of treatment may be compromised with higher dose rates. On the basis of laboratory studies, Amdr and Bedford have suggested that differences in the magnitude of the dose-rate effect between tumor and normal tissues may in part reflect differences in the half-times for repair of sublethal radiation damage.

During the past two decades, computer technology has made it possible to deliver brachytherapy at very high dose rates (greater than 100 Gy/min) using a high-activity 192Ir source and remote afterloading. High dose-rate intracavity therapy is now being used for radical treatment of cervical cancer by a number of groups, including several in Japan, Canada, and Europe, and more recently by some groups in the United States. Many of the retrospective reviews provide incomplete descriptions of tumor and treatment details. Two purported randomized trials also have been criticized for methodologic flaws. The use of high dose-rate brachytherapy for cervical cancer continues to be a source of controversy.

INTERSTITIAL BRACHYTHERAPY. Several groups have advocated the use of interstitial brachytherapy to treat patients whose anatomy or tumor distribution make it difficult to obtain an ideal intracavitary placement. Interstitial implants are usually placed transperineally, guided by a Lucrea template that encourages parallel placement of hollow needles that penetrate the cervix and paracervical spaces; needles are usually loaded with 60Co or 192Ir. Advocates of the procedure describe the relatively homogeneous dose distribution achieved with this method, the ease of inserting implants in patients whose uteri are difficult to probe, and the ability to place sources directly into the parametrium. Early reports were enthusiastic, describing these theoretical advantages and high initial local control rates, but these early reports rarely included sufficient numbers of patients or had long enough follow-up to provide long-term survival rates.

In two of the larger early series, Syed and colleagues reported an encouraging projected 5-year survival rate of 53% for 26 patients with stage IIIB disease, and Martinez and colleagues reported an 83% local control rate in 37 patients with stage IIB and IIIB disease. However, survival results from two more recent reports have been disappointing. In a 1995 review of the combined experiences of Stanford and the Joint Center for Radiation Therapy, the 3-year disease-free survival rates for patients with stage IIB and IIIB disease were only 36% and 18%, respectively. Local control rates were 22% and 44%, respectively, and for patients with local control, the rate of complications requiring surgical intervention was high. A 1997 report of the Irvine experience also described disappointing survival rates of 21% and 29%, respectively, for stage IIB and IIIB, again with a high rate of major complications.

Several groups have been exploring the use of transrectal ultrasound, MRI, or laparoscopic guidance, interstitial hyperthermia, and high-dose-rate interstitial therapy to improve local control and complication rates. However, outside of an investigational setting, interstitial treatment of primary cervical cancers should probably be limited to patients who cannot accommodate intrauterine brachytherapy and patients with distal vaginal disease that requires a boost with interstitial brachytherapy.

COMPLICATIONS OF RADICAL RADIOTHERAPY. During radiotherapy of the pelvis, most patients have mild fatigue and mild to moderate diarrhea that usually is controllable with antiarrheal medications; some patients have mild bladder irritation. When extended fields are treated, patients may have nausea, gastric irritation, and mild depression of peripheral blood counts. Acute symptoms may be increased in patients receiving concurrent chemotherapy. Unless the ovaries have been transposed, all premenopausal patients who receive pelvic radiotherapy experience ovarian failure by the completion of treatment.

Perioperative complications of intracavitary therapy include uterine perforation, fever, and the usual risks of anesthesia. Thromboembolism is rare. In a review of 4043 patients who had 7662 intracavitary applications for cervical cancer, Jhingan and Elfet reported 11 patients (0.3%) with thromboembolism, four of which were fatal. All four fatal pulmonary embolism were in patients with advanced pelvic wall disease.

Estimates of the risk of late complications of radical radiotherapy vary according to the grading system, duration of follow-up, method of calculation, treatment method, and prevalence of risk factors in the study population. However, most reports quote an overall risk of major complications (requiring transfusion, hospitalization, or surgical intervention) of 5% to 15%. In a report from the Patterns of Care Study, Lanciano et al. reported an actuarial risk of 8% at 3 years. In a study of 1784 patients with stage IB disease, Elfet et al. reported an overall actuarial risk of major complications of 7.7% at 5 years. Although the actuarial risk was greatest during the first 3 years of follow-up, there was a continuing risk to surviving patients of approximately 0.3% per year, resulting in an overall actuarial risk of 14% at 20 years. In a 1997 review of 1458 patients treated with radiation alone, Perez et al. reported a crude incidence of severe complications (requiring surgical intervention or more than 4 weeks of hospitalization) of 5% for patients with stage IB cervical cancer and 9% to 10% for patients with more advanced disease. During the first 3 years after treatment, rectal complications are most common and include bleeding, stricture, ulceration, and fistula. In the study by Elfet and colleagues, the risk of major rectosigmoid complications was 2.3% at 5 years. Major gastrointestinal complications were rare 3 years or more after treatment, but a constant low risk of urinary tract complications persisted for many years. The actuarial risk of developing a fistula of any type was 1.7% at 5 years.

Small bowel obstruction is an infrequent complication of standard radiotherapy for patients without special risk factors. The risk is increased dramatically in patients who have undergone transperitoneal lymph node dissection. However, there appears to be little added risk if the operation is performed with a retroperitoneal approach. Other factors that can increase the risk of small bowel complications in patients treated for cervical cancer include pelvic inflammatory disease, thin body...
Most patients treated with radical radiotherapy have some agglutination and telangectasia of the apical vagina. More significant vaginal shortening can occur, particularly in elderly, postmenopausal women and those with extensive tumors treated with a high dose of irradiation. \[^{136,137}\] Vaginal function can be optimized with appropriate estrogen support and vaginal dilatation.

**CONCURRENT CHEMORADIATION.** Reports of five prospective randomized trials \[^{132,229,371,372,373}\] have provided compelling evidence that the addition of concurrent cisplatin-containing chemotherapy to standard radiotherapy improves the pelvic disease control and survival rates in selected patients with local, regionally advanced cervical cancer. Although these studies differed in their inclusion criteria, treatment specifics, and control treatments, each demonstrated reduction in the relative risk of recurrence of 30% to 50% with cisplatin-containing chemoradiation (Table 36.2-9).

Individual investigators and multinational groups have been exploring combinations of chemotherapy and radiation in patients with cervical cancer for more than 25 years. However, until relatively recently, studies had failed to demonstrate a clear benefit. An early GOG study compared radiation alone with radiation and concurrent hydroxyurea. \[^{375}\] This study appeared to show some benefit from the combination, but it was criticized because many patients were treated without brachytherapy or with very low doses of radiation and because 93 (49%) of the 190 patients randomized were excluded from the analysis as ineligible or un evaluable. Nevertheless, the GOG continued to include hydroxyurea in the control arm of subsequent studies. The first of these \[^{376}\] compared hydroxyurea (80 mg/kg given twice per week during external-beam irradiation) with mitomycin, a nitrosourea hypoxic cell sensitizer that has since been demonstrated to be of no benefit in several trials that compared mitomune with a placebo. \[^{377}\] Final analysis of this study \[^{378}\] showed a marginal advantage in progression-free survival \((P = .05)\) and survival \((P = .07)\) for patients treated with hydroxyurea.

Two subsequent GOG studies \[^{377,379}\] randomly assigned patients with stage IIB to IVA disease to receive either hydroxyurea or cisplatin-containing chemotherapy during external-beam irradiation. All three of the cisplatin-containing arms had local control and survival rates superior to those for the control (hydroxyurea and radiation) arms. In a third study, \[^{379}\] patients with stage IIB tumors measuring at least 4 cm in diameter were randomly assigned to receive radiation alone or radiation plus weekly cisplatin before extrafascial hysterectomy. Patients who received cisplatin were more likely to have a complete histologic response and were more likely to be disease free at the time of preliminary analysis. A fourth study, cosponsored by the Southwest Oncology Group and the GOG, \[^{379}\] included patients who were treated with radical hysterectomy and were found to have pelvic lymph node metastases, positive margins, or parametrial involvement. Patients were randomly assigned to receive postoperative pelvic irradiation alone or combined with cisplatin and 5-fluorouracil (5-FU). In a preliminary analysis, patients who received chemotherapy in this study also had a better disease-free survival rate.

During this time, the Radiation Therapy Oncology Group \[^{229}\] also conducted a trial in which radiotherapy alone (including prophylactic paraaortic irradiation) was compared with pelvic irradiation plus concurrent cisplatin and 5-FU. This is the only study in which chemotherapy was administered during both the brachytherapy and external-beam components of treatment. The results of this trial were released early when highly significant differences were detected in the rates of local control, distant metastasis, overall survival, and disease-free survival favoring the treatment arm that included chemotherapy. Although acute toxic effects of treatment were greater with chemotherapy, the dose and duration of radiation were similar in the two arms, and in an early analysis, there was no significant difference in the incidence of late treatment-related complications.

This work clearly demonstrates that the addition of concurrent cisplatin-containing chemotherapy benefited patients with locally advanced cervical cancer who were treated with radiation in these studies. However, all of the studies explicitly excluded patients with evidence of paraaortic lymph node metastases, poor performance status, or impaired renal function. In the future, clinicians will be challenged to determine how these favorable results can be generalized to patients with cervical cancer who may not have been included in the prospective trials because of severe medical or social problems and to the developing nations where invasive cervical cancer is epidemic.

These studies raise other interesting questions that will undoubtedly be the subjects of future studies. Of four different cisplatin-containing regimens, only two were compared directly. It is unclear from the results which regimen achieves the most favorable therapeutic ratio and whether the inclusion of 5-FU in several of the studies contributed importantly to the results. However, smaller studies have suggested that 5-FU is an effective radiation sensitization in cervical cancers. \[^{376,377}\] and the GOG is currently comparing radiation plus continuous-infusion 5-FU with radiation and cisplatin in patients with locally advanced disease. Other drugs that are being studied for their radiosensitizing effects in patients with advanced disease are paclitaxel, \[^{359}\] carboplatin, \[^{365}\] and mitomycin C. \[^{366}\] Extended-field irradiation (including the aortic nodes) has proven effective in the treatment of patients with known or suspected aortic node metastasis, \[^{367}\] but the role of extended-field irradiation needs to be clarified in the context of these new results. Combinations of extended-field irradiation and chemotherapy appear to be feasible, but the acute toxicity is considerable, and late toxicity may be greater with extended-field radiation alone. \[^{368}\]

**NEOADJUVANT CHEMOTHERAPY.** A number of investigators have explored the use of neoadjuvant chemotherapy for locally advanced cervical carcinoma, trying to exploit the encouraging response rates that have been reported for multiple-agent, cisplatin-containing regimens in previously untreated patients (see Table 36.2-6). \[^{368,369}\] To test this approach, a number of prospective randomized trials were conducted comparing radiation alone with neoadjuvant chemotherapy followed by radiation (Table 36.2-10). \[^{370,371,372,373,374,375,376,377}\] Unfortunately, of the seven trials that have been published, five \[^{373,375,376,377}\] demonstrated no benefit from neoadjuvant therapy and two \[^{372,376}\] demonstrated a significantly better survival rate with radiation alone. In one small trial from South America, \[^{377}\] patients treated with bleomycin, vincristine, methotrexate, and cisplatin followed by radiation had a significantly poorer survival rate than those treated with radiation alone. In addition, patients who failed to complete radiotherapy (and were excluded from the analysis) were more frequent in the neoadjuvant chemotherapy arm. Bleomycin toxicity (responsible for four of the deaths) contributed to the poor survival rate of patients treated with neoadjuvant chemotherapy in this study. Tattersall and colleagues \[^{378}\] compared neoadjuvant chemotherapy (cisplatin and epirubicin) followed by radiotherapy with radiotherapy alone. This study was discontinued when an interim analysis revealed a significantly poorer outcome for patients who received neoadjuvant chemotherapy \((P = .02)\).
In another interesting study, published by Chauvergne and colleagues, 32 patients who had a complete or partial response to chemotherapy followed by radiotherapy had a significantly better outcome than did those who had a poorer response to neoadjuvant chemotherapy. However, there were no significant differences in the overall response rates, disease-free survival rates, or median survival between patients treated with neoadjuvant chemotherapy and those treated with radiation alone.

In summary, despite the high rate of response of locally advanced cervical cancers to initial chemotherapy, none of the randomized studies reported to date has demonstrated an improvement in outcome when neoadjuvant chemotherapy was added to radical radiotherapy. In many ways this recapitulates the experience with treatment of locally advanced head and neck cancers, in which it has been hypothesized that the failure of neoadjuvant chemotherapy to influence outcome may reflect cross-resistance of tumor cells to drugs and radiation or accelerated repopulation of tumor clones induced by neoadjuvant chemotherapy. 332, 333 and 334

More recently, a number of investigators have begun to explore combinations of neoadjuvant chemotherapy with radical surgery in patients with bulky central disease. 335, 336, 337 and 338 Only one randomized trial addressing this approach has been published, 339 although a number of other studies have been completed or are in progress. In their study, Sardi and colleagues 340 randomly assigned 205 patients to receive radical hysterectomy with or without neoadjuvant chemotherapy. All patients received postoperative pelvic irradiation. The authors reported a higher rate of resectability (100% vs. 85%) and a better survival rate (81% vs. 66%) for patients treated with neoadjuvant chemotherapy. There have not yet been any comparisons between this approach and radiotherapy alone or combined with chemotherapy.

INTRAARTERIAL CHEMOTHERAPY. Intraarterial infusion of chemotherapeutic agents delivered in the neoadjuvant setting, concurrent with radiotherapy, or as salvage treatment for recurrent disease has generated interest for some years because of the distinct arterial supply to the central pelvis. 341, 342 and 343 A number of drugs have been used in small pilot studies, but 5-FU and cisplatin have been the most popular in this setting. Unfortunately, this technique is difficult and invasive, the toxicity reported in some series has been substantial, and the results have been variable in several small series of patients. However, occasional optimistic reports have maintained some interest in this approach, particularly for concurrent intraarterial chemotherapy and irradiation.

Stage IVB

Patients who present with disseminated disease almost always have incurable disease. The care of these patients must emphasize palliation of symptoms with appropriate pain medications and localized radiotherapy. Tumors may respond to chemotherapy, but responses are usually short.

SINGLE-AGENT CHEMOTHERAPY. Many drugs have been studied for their activity in patients with recurrent or metastatic carcinoma of the cervix. Approximately 20 have yielded response rates (partial and complete) of at least 15% and may be of therapeutic value (Table 36.2-13). 344

Several of the platinum compounds have been evaluated in greater detail. Cisplatin has been studied in a variety of doses and schedules. 345, 346 and 347 These studies have demonstrated activity of the drug at a dose of 50 mg/m² given intravenously at a rate of 1 mg/min every 3 weeks. Although there appears to be a small but statistically significant increase in the response rate with a doubling of the dose to 100 mg/m², this has not resulted in a detectable improvement in the rates of progression-free or overall survival. More prolonged infusion of the same dose over 24 hours yields a similar response rate with less nausea and vomiting, although the development of more effective antiemetic agents reduces the clinical importance of this observation. The response rates with other platinum compounds (i.e., carboplatin and iproplatin) are lower than those observed with cisplatin, which remains the platinum compound of choice for patients with cervical carcinomas.

Ifosfamide has been studied as a single agent in patients with recurrent cervical cancer in at least five phase II trials. 348, 349 and 350. Response rates ranged between 33% and 50% in three studies that were conducted in patients who had received no previous chemotherapy. 351, 352 and 353 However, the response rates were much lower in two phase II trials that included patients who had received prior systemic chemotherapy, with only three partial responses (8%) in 38 patients. 354, 355

COMBINATION CHEMOTHERAPY. Most reports of combination chemotherapy for carcinoma of the cervix have described small, uncontrolled phase II trials of drug combinations that have included at least some agents with known activity. Although response rates have varied widely, data from these phase II studies provide no firm evidence that any of the studied combinations are superior to single-agent therapy for patients with disseminated or recurrent cervical cancer. 332, 333 However, combinations based on ifosfamide and cisplatin and those based on 5-FU and cisplatin have attracted significant interest and deserve further discussion.

Several small phase II studies have evaluated treatment with combinations of ifosfamide and either cisplatin or carboplatin in patients who had not received prior radiotherapy. Response rates for these combinations ranged between 50% and 62% (Table 36.2-12). 356 and 357 A number of investigators have combined bleomycin with ifosfamide and a platinum compound. Three studies that included patients who had not had prior radiotherapy reported response rates of 65% to 0% and 72% (Table 36.2-13). 358 and 359 Reports of treatment with these drugs in previously irradiated patients have yielded mixed but generally lower response rates of between 13% and

| Table 36.2-10. Results of Prospective Randomized Trials That Compared Neoadjuvant Chemotherapy Followed by Radiation Therapy with Radiation Therapy Alone in Patients with Locally Advanced Cervical Cancer |
|---|---|---|---|---|---|---|---|
| **Drug** | **Response Rate (Partial and Complete)** | **N. of Patients** | **Study** | **Results** | **Comments** |
| Cisplatin | 50% | 50 | 1 | Increase in response rate with doubling of dose to 100 mg/m². |
| Carboplatin | 33% | 30 | 2 | Lower response rates compared to cisplatin. |

| Table 36.2-11. Cytotoxic Drugs Active Against Squamous Cell Carcinoma of the Cervix (Response Rate *15%) |
|---|---|---|---|---|---|---|---|
| **Drug** | **Response Rate (%)** | **N. of Patients** | **Study** | **Results** | **Comments** |
| Cisplatin | 50 | 50 | 1 | Increase in response rate with doubling of dose to 100 mg/m². |
| Carboplatin | 33 | 30 | 2 | Lower response rates compared to cisplatin. |

*15%: The response rate is 15% or higher.*
Combinations of cisplatin and continuous infusion 5-FU, cisplatin and paclitaxel, or cisplatin and vinorelbine also produce high response rates in previously untreated patients. Again, response rates decrease significantly if patients have had previous irradiation.

In 1996, the GOG reported results of a large prospective randomized trial comparing cisplatin alone with cisplatin plus ifosfamide and cisplatin plus mitomycin in patients with advanced or recurrent cervical cancers. The addition of ifosfamide to cisplatin improved the response rate (33% vs. 19%, P = .02) and progression-free survival rate (4.8 vs. 3.2 months, P < .05), but was associated with significantly greater toxicity (leukopenia, peripheral neuropathy, renal toxicity, and anemia) and did not significantly improve the overall median survival. The addition of mitomycin did not improve the response rate or survival duration. Other phase III randomized trials that are ongoing or have been completed recently will evaluate the benefit of adding bleomycin to cisplatin and ifosfamide and will test the addition of paclitaxel or topotecan to cisplatin.

FALLATIVE RADIOTHERAPY. Localized radiotherapy can provide effective pain relief for symptomatic metastases in bone, brain, lymph nodes, or other sites. A rapid course of pelvic radiotherapy can also provide excellent relief of pain and bleeding for patients who present with incurable disseminated disease.

Special Problems

TREATMENT OF LOCALLY RECURRENT CARCINOMA OF THE CERVIX.

After Radical Surgery. Patients should be evaluated for possible recurrent disease if a new mass develops; if, in irradiated patients, the cervix remains bulky or nodular or cervical cytologic findings are abnormal 3 months or more after irradiation; or if symptoms of leg edema, pain, or bleeding develop after initial treatment. The diagnosis must be confirmed with a tissue biopsy, and the extent of disease should be evaluated with appropriate radiographic studies, cystoscopy, proctoscopy, and serum chemistry studies before treatment is administered.

The treatment of choice for patients who have an isolated pelvic recurrence after initial treatment with radical hysterectomy alone is aggressive radiotherapy. Treatment for patients with an isolated central recurrence is similar to that for patients with a primary carcinoma of the vagina. Most patients are treated with external-beam radiotherapy with or without brachytherapy. Implants may need to be inserted under laparoscopic or laparotomy guidance. Pelvic wall recurrences are often treated with external-beam irradiation alone, although intraoperative therapy may contribute to local control in selected patients. Reported survival rates usually range between 20% and 40% for patients treated with radical radiotherapy. Patients with central recurrence usually have a better prognosis than those with pelvic wall recurrence. Ijaz and colleagues reported a survival rate of 69% 5 years after radical radiotherapy for 16 patients who had isolated vaginal recurrences that did not involve the pelvic wall. Only 18% of patients who had recurrences that were fixed to the pelvic wall or that involved pelvic lymph nodes survived 5 years. Several authors have reported significantly lower salvage rates for patients with locally recurrent adenocarcinoma. Thomas and colleagues reported encouraging results in a group of patients treated with radiation and concurrent chemotherapy, but further studies will be needed to determine whether this approach is superior to radiotherapy alone.

After Definitive Irradiation. In some cases, patients who have an isolated central recurrence after radiotherapy can be cured with surgical treatment. Because the extent of disease may be difficult to evaluate and the risk of serious urinary tract complications from pelvic surgery is high after high-dose radiotherapy, surgical salvage treatment usually requires a total pelvic exenteration. Less extensive operations, such as radical hysterectomy or anterior exenteration, are reserved for selected patients with small tumors confined to the cervix or lesions that do not encroach on the rectum, respectively.

Tumor involvement of the pelvic sidewall is a contraindication to exenteration but may be difficult to assess if there is extensive radiation fibrosis. The triad of unilateral leg edema, sciotic pain, and ureteral obstruction almost always indicates unsectable disease on the sidewall. Although advanced age is usually considered a contraindication to pelvic exenteration, Matthews and colleagues reported a 5-year survival rate of 46% and an operative mortality of 11% for selected patients who underwent exenteration at the age of 65 years or older compared with a 5-year survival rate of 45% and an operative mortality of 8.5% for younger patients. In all cases, preparation for total pelvic exenteration must involve careful counseling of the patient and family regarding the extent of surgery and postoperative expectations.

The operation begins with a thorough inspection of the abdomen for evidence of intraperitoneal spread or disease in the pelvic sidewall or paraaortic lymph nodes. Despite careful preoperative evaluation, approximately 30% of operations are aborted intraoperatively. Frozen section biopsies are done of suspicious areas. If the biopsy findings are negative, the surgeon proceeds to remove the bladder, rectum, vagina, uterus, ovaries, fallopian tubes, and all other supporting tissues in the true pelvis. A urinary conduit, a transverse or sigmoid colostomy, and a neovagina are created.

Postoperative recuperation may take as long as 3 months. The surgical mortality is less than 10%, with most postoperative complications and deaths related to sepsis, pulmonary thromboembolism, and intestinal complications such as small bowel obstruction and fistula formation. Gastrointestinal complications may be reduced by using unirradiated segments of bowel and by closing pelvic floor defects with omentum, rectosigmoid colon, or myocutaneous flaps. Advances in low colorectal anastomosis and techniques for creating continent urinary reservoirs have improved the quality of life for selected patients.

The 5-year survival rates for patients who undergo anterior or total pelvic exenteration are 33% to 60% and 20% to 46%, respectively. Several groups are exploring the role of intraoperative irradiation to treat patients with recurrent disease that involves the pelvic wall. However, patients with bulky central disease, positive lymph nodes, or 1 year or less between initial treatment and exenteration have a poor prognosis.

TREATMENT AFTER SIMPLE HYSTERECTOMY WITH UNSUSPECTED INVASIVE CANCER. Every patient who undergoes a planned hysterectomy should be carefully screened to rule out invasive cervical cancer before the procedure. However, whenever an unexpected diagnosis of invasive cancer is made in a hysterectomy specimen, the patient should be immediately referred for additional treatment because pelvic radiotherapy produces excellent pelvic disease control rates and survival rates for most patients in this setting.

Patients may be classified according to the extent of disease at the time of referral for posthysterectomy treatment into the following groups: (1) microinvasive cancer, (2) tumor confined to the cervix with negative surgical margins, (3) positive surgical margins but no gross residual tumor, (4) gross residual tumor by clinical examination documented by biopsy, and (5) patients referred for treatment more than 6 months after hysterectomy (usually for recurrent disease). In a report of the results of radiotherapy in 123 patients, Roman et al. reported survival rates of 79% and 59% for patients in groups 2 and 3, respectively. In contrast, the survival rate for 30 patients with gross disease (groups 4 and 5) was 4% (P = .0001).

Patients with less than 3 mm of invasion without lymph-vascular invasion usually require no treatment after simple hysterectomy. Patients with more extensive involvement who have negative margins require 45 to 50 Gy of pelvic radiotherapy to treat the pelvic nodes and paracolpal tissues. Most clinicians follow this with

**TABLE 36.2-12. Platinum-Containing Chemotherapy Combinations Used to Treat Cervical Carcinomas: Contrast between Results in Patients Treated before or after Pelvic Irradiation**

<table>
<thead>
<tr>
<th>Combination</th>
<th>Before Irradiation</th>
<th>After Irradiation</th>
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<tr>
<td>cisplatin</td>
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<tr>
<td>5-FU</td>
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<tr>
<td>paclitaxel</td>
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<tr>
<td>vinorelbine</td>
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</tbody>
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Note: Additional combinations and results are listed in the text.
vaginal intraocular therapy, delivering an additional vaginal surface dose of 30 to 50 Gy. Patients with positive margins may benefit from a somewhat higher dose of external-beam irradiation through reduced fields designed to include the region at highest risk (e.g., parametrium, posterior bladder wall). Patients in groups 3 and 4 reported in the series by Roman and colleagues were usually treated with 65 Gy of external-beam therapy with or without intracavitary therapy. The role of interstitial therapy in this setting is not well documented.

CARCINOMA OF THE CERVICAL STUMP

Although supracervical hysterectomy was once a popular treatment for benign uterine conditions, enthusiasm for the procedure has declined since the 1950s and it is rarely performed today. As a result, carcinomas of the cervical stump are less common than they once were and are usually seen in elderly women. Tumors are usually subclassified as coincidental tumors (diagnosed within 2 years of supracervical hysterectomy) or true cervical stump carcinomas (diagnosed less than 2 years after hysterectomy). Tumors classified as coincidental were probably present at the time of supracervical hysterectomy and are said to have a relatively poor prognosis, although the number of cases in most series is small.

The natural history, staging, and workup of cervical stump carcinomas are the same as for carcinomas of the intact uterus. If possible, the cervix should be probed at the beginning of treatment to determine the length of the uterine canal. MRI may be an important aid to treatment planning in these patients.

Patients with stage I A1 disease may be treated with simple tracheectomy, and selected stage I A2 or small stage IB tumors may be treated with radical tracheectomy and pelvic lymph node dissection. However, most patients are treated with irradiation alone using a combination of external-beam therapy and brachytherapy.

The altered geometry and short uterine length in these patients complicate treatment planning. However, in most cases the endocervical canal is 2 cm or longer and, after a course of external-beam irradiation, patients can be adequately treated with intracavitary therapy. The endocervical canal is usually loaded with 20 to 30 mgRaEq of cesium, depending on the length of the endocervical canal, and vaginal ovoids are loaded according to their diameter and position. Remote afterloading systems provide somewhat greater flexibility in source loading. If the endocervical canal cannot accommodate any sources, a boost dose may be delivered to the tumor with interstitial therapy, transvaginal irradiation, or reduced fields of external-beam irradiation. However, brachytherapy should be used whenever possible.

Barillot et al. reported a survival rate of 81.5% for patients treated with combined brachytherapy and external-beam irradiation versus 38.5% for those treated with external-beam irradiation alone. Several authors have advocated interstitial therapy, using techniques described for apical vaginal carcinomas, for patients with bulkier lesions. Vaginal ovoids alone rarely deliver an adequate dose to the cervix.

Most investigators have reported survival rates similar to those for patients with carcinomas of the intact cervix. In a series of 263 patients, Miller and colleagues reported survival rates of 91%, 77%, and 40% for patients with stage I, II, and III tumors, respectively. Similar survival rates have been reported in other large series. Miller and colleagues reported a somewhat higher complication rate for cervical stump carcinomas than for carcinomas of the intact cervix, but others have not observed this difference.

CARCINOMA OF THE CERVIX DURING PREGNANCY

Estimates of the incidence of invasive cervical cancer during pregnancy range from 0.02% to 0.9%. Hacker and colleagues estimated the incidence of pregnancy in patients with invasive cervical cancer usually range between 0.5% and 5.0%. Hacker and colleagues reported an incidence of cervical carcinoma in situ of 0.013% in pregnant women.

Diagnosis is often delayed because bleeding is erroneously attributed to pregnancy-related complications. All pregnant patients should have a careful pelvic examination and Pap smear at their first antenatal visit. Any suspicious lesion should be biopsied. If the Pap smear result is positive for malignant cells and the diagnosis of invasive cancer cannot be made with colposcopy and biopsy, a diagnostic conization may be necessary. Because conization subjects the mother and fetus to complications, it should be performed only in the second trimester and only in patients with inadequate colposcopy and strong cytologic evidence of invasive cancer. Conization in the first trimester of pregnancy is associated with an abortion rate of up to 33%. Conservative conization under colposcopic guidance may reduce the risk.

It appears to be safe to delay definitive treatment of patients with carcinoma in situ or stage I A disease until the fetus has matured. Patients with less than 3 mm of invasion and no LVSI may be followed to term and delivered vaginally. A vaginal hysterectomy may be performed 6 weeks after childbirth if further childbearing is not desired. Patients with 3 to 5 mm of invasion and those with LVSIs may also be followed to term. The infant may be delivered by a cesarean section, which is followed immediately by modified radical hysterectomy and pelvic lymph node dissection.

Patients with more than 5 mm of invasion should be treated as having frankly invasive carcinoma of the cervix. Treatment depends on the stage of gestation and the wishes of the patient. Modified radical cesarean section offers a 75% survival rate at 28 weeks gestational age for those delivered at 32 weeks. Fetal pulmonary maturity can be determined by amniocentesis, and prompt treatment can be initiated when pulmonary maturity is documented. It is probably wise to avoid delays in therapy of more than 4 weeks whenever possible although this guideline is controversial. For most women with stage IB1 tumors, the recommended treatment is classic cesarean section followed by radical hysterectomy with pelvic lymph node dissection. There should be a thorough discussion of the risks and options with both parents before any treatment is undertaken.

Patients with stage II to IV tumors and some patients with bulky stage IB cervical cancers should be treated with radiotherapy. If the fetus is viable, it is delivered by classic cesarean section and radiotherapy is begun postoperatively. If the pregnancy is in the first trimester, external-beam irradiation can be started with the expectation that spontaneous abortion will occur before the delivery of 40 Gy. In the second trimester, a delay of therapy may be entertained to improve the chances of fetal survival. If the patient wishes to delay therapy, it is important to ensure fetal pulmonary maturity before delivery is undertaken.

Compared with other cervical cancer patients, those with cervical cancer during pregnancy have slightly better overall survival because an increased proportion have stage I disease. The diagnosis of cancer in the postpartum period tends to be associated with a more advanced clinical stage and a corresponding decrease in survival. However, studies differ in their conclusions about whether pregnancy has an independent influence on the prognosis of patients with cervical cancer. For most women with stage IB1 tumors, the recommended treatment is classic cesarean section followed by radical hysterectomy with pelvic lymph node dissection. There should be a thorough discussion of the risks and options with both parents before any treatment is undertaken.

Patients who are diagnosed with invasive cervical cancer shortly after a vaginal delivery appear to be at risk for recurrence in the site of their episiotomy. At least 13 cases demonstrating this unusual pattern of failure have been reported.

CARCINOMA OF THE VAGINA

Carcinomas of the vagina are rare, accounting for only approximately 2% to 3% of gynecologic malignancies. According to FIGO, cases should be classified as vaginal carcinomas only when “the primary site of the growth is in the vagina.” A tumor that is limited to the urethra should be classified as a primary urethral cancer, and a tumor that has extended from the vulva to involve the vagina should be classified as a primary vulvar cancer. Also, according to FIGO, any tumor that has extended to the cervical port or has reached the area of the external os should be classified as a cervical carcinoma. For this reason, in patients with an intact uterus, it is probable that many tumors that originated in the apical vagina are actually classified as cervical cancers. This may explain why a large percentage (30% to 50%) of patients diagnosed with vaginal carcinoma have had a prior hysterectomy (preventing classification of their tumors as primary cervical cancers).

More commonly, the vagina is a site of metastasis or direct extension from tumors originating in other genital sites, such as the cervix or endometrium, or from extragenital sites, including the rectum and bladder.

EPIDEMIOLOGY

Vaginal intraepithelial neoplasia (VAIN) often accompanies CIN and is thought to have a similar etiology. VAIN lesions are more often seen in the upper third of the vagina and may be either extensions from adjacent areas of CIN or separate lesions. Kalogiorgi and associates found 41 cases of VAIN in 993 patients followed with cytologic examination and colposcopy after hysterectomy for CIN. Most VAIN lesions were in the upper vagina, particularly in the vault angles of the suture line.
Because the vagina does not have a transformation zone of immature epithelial cells susceptible to HPV infection. HPV-induced vaginal lesions are thought to arise in areas of squamous metaplasia that develop during healing of mucosal abrasions caused by coitus, tampon use, or other trauma. Invasive vaginal carcinoma has also been associated with chronic irritant vaginitis, particularly that caused by chronic use of a vaginal pessary. Schraub et al. reported that 80% of vaginal cancers arising in patients who used pessaries were in the posterior fornix or posterior wall of the vagina. Investigators have also reported an association between vaginal carcinoma and infection with HPV similar to that found for invasive cervical cancer. Ikenberg and colleagues found HPV DNA in 10 of 18 patients with invasive vaginal cancer. Pride and colleagues suggested that pelvic irradiation might be a predisposing factor in some cases. However, viral and other risk factors independent of the mode of treatment undoubtedly place some of these patients at risk for multiple primary tumors. In a review of 301 patients with vaginal cancer, Chyle and associates found that 56 had a prior history of carcinoma in situ of the cervix, 22 had a history of invasive cervical cancer, and two had prior in situ carcinomas of the vagina.

Primary invasive carcinoma of the vagina is predominantly a disease of elderly women, with 70% to 80% of cases presenting in women older than 60 years. However, FIGO data suggest that the age of peak incidence may have decreased since the early 1990s, when the highest incidence was among women in their 80s. Except for clear cell carcinomas, which are associated with maternal diethylstilbestrol (DES) exposure, invasive vaginal carcinomas are extremely rare in women younger than 40 years.

In 1971, Herbst and colleagues first reported a highly significant association between clear cell carcinomas of the vagina and maternal ingestion of DES during pregnancy. This led to the establishment of a registry to gather information about cases of clear cell carcinoma in the United States. The peak number of DES-associated cases occurred in 1975, when 33 were reported to the registry. The peak risk period for exposed women in the United States is between the ages of 15 and 22 years; the youngest patient reported was 7 years old. The oldest patient reported so far was 42 years old at diagnosis, but the risk to women older than 40 years is still unknown because women in the first exposed cohort are just reaching their fifth decade. Because only approximately 1 of every 1000 women exposed to DES in utero develops clear cell carcinoma, investigators have tried to define other risk factors for development of the disease. The risk of clear cell carcinoma has been associated with initiation of DES early during pregnancy, a maternal history of early miscarriage, and premature birth. Sharp and Cole found a correlation between adolescent obesity in exposed girls and the development of vaginal clear cell carcinoma. Infection with HPV may be a cofactor in some cases. Among 14 cases of clear cell carcinoma studies by Waggner and colleagues, three contained HPV 31 DNA; ten of the remaining HPV-negative tumors had p53 protein detected by immunohistochemistry, suggesting a mutation of p53.

Although the risk of clear cell carcinoma of the vagina is small in DES-exposed women, 45% of these patients have areas of vaginal adenosis, and 25% have histologically normal uteri, cervico-vaginal margin, or vagina. Unfortunately, awareness of the risks of in utero DES exposure has led to a dramatic reduction in the use of high doses of estrogen to prevent miscarriage, and the number of young women who need to be followed for this problem is declining. There is as yet no evidence that DES-exposed women are at risk for malignancies other than clear cell carcinoma.

NATURAL HISTORY AND PATTERN OF SPREAD

Approximately 50% of vaginal cancers arise in the upper third of the vagina. Although Plentl and Friedman reported that tumors arise more commonly on the posterior wall, more recent reviews have reported a more even distribution of lesions arising on the anterior, posterior, and lateral walls. Exhibits may tumor exhibit an exophytic or ulcerative, infiltrating pattern of growth. Tumors may invade directly to involve structures such as the urethra, bladder, and rectum. Despite the proximity of these structures, fewer than 10% of vaginal cancers are found to be stage IVA at presentation. However, extensive infiltration of the suburethra or rectovaginal septum is common and frequently influences treatment planning. Vaginal cancers may also spread laterally to the paravaginal space and pelvic wall. Although tumors arising in the vagina undoubtedly spread superiority to involve the cervix and uterus, this usually leads to their classification as cervical cancers, according to FIGO convention. Plentl and Friedman summarized their description of the lymphatic drainage of the vagina with the comment that, except for the lateral external iliac group, all lymph nodes of the pelvis may at one time or other serve as primary sites of regional drainage for vaginal lymph. Few data are available concerning the incidence of spread of vaginal cancer to the pelvic lymph nodes. In a review of early reports, Plentl and Friedman quoted an overall incidence of positive nodes of 21%. More recent studies suggest that the incidence of positive pelvic nodes in patients with stage II disease is at least 25% to 30%, emphasizing the importance of regional treatment for these patients. Inguinal node metastases generally occur only in patients whose tumors involve the lower third of the vagina.

The most frequent site of hematogenous metastasis is the lung. Less frequently, vaginal cancers may metastasize to liver, bone, or other sites.

PATHOLOGY

Eighty percent to 90% of primary vaginal malignancies are squamous cell carcinomas. Grossly, these tumors may be nodular, ulcerative, or exophytic plaques of any size. Histologically, they are similar to squamous tumors from other sites. Approximately one-third of these tumors are keratinizing, and more than one-half are nonkeratinizing, moderately differentiated lesions.

Verrucous carcinoma is a rare variant of squamous cell carcinoma that presents as a warty, fungating mass. Histologically, verrucous carcinoma is composed of large papillary fronds covered by dense keratin. Its deep margin creates a pushing border of well-oriented rete ridges. This tumor rarely metastasizes but can extensively infiltrate into surrounding tissues, including the rectum and cecum. Wide surgical excision is the treatment of choice in this situation.

Approximately 5% to 10% of primary vaginal neoplasms are adenocarcinomas; however, the absence of women in the population who were exposed to DES in utero. Clear cell carcinomas of the vagina are usually polypoid, and may have tubulocystic or solid patterns. Adenocarcinomas not associated with DES exposure occur primarily in postmenopausal women. The differential diagnosis of adenocarcinoma occurring in the vagina is often difficult, as it must be distinguished from metastatic tumors originating in other sites. Histologic patterns include clear cell, mucinous, adenosquamous, papillary, and undifferentiated. It has been hypothesized that these tumors may arise in foci of adenosis, from mesonephric rests, or from foci of endometriosis in the vagina.

Primary small cell carcinomas of the vagina are rare; fewer than 20 cases have been reported in the literature. They are histologically indistinguishable from neuroendocrine small cell carcinomas of the lung and cervix and like these tumors may coexist with squamous or adenocarcinoma elements.

Primary vaginal melanomas represent approximately 3% of primary vaginal cancers and fewer than 20% of genital melanomas. Primary vaginal melanomas are thought to arise from melanocytes in areas of melanosis or atypical melanocytic hyperplasia. They usually originate in the lower third of the vagina and occur at a mean age of 55 years, with an age range of 22 to 83 years. They tend to have a poorer prognosis than vulvar melanomas, with 5-year survival rates of 15% to 20% after treatment with surgery, radiation, or both.

Approximately 3% of vaginal cancers are sarcomas; approximately two-thirds of these are leiomyosarcomas, but endometrial stromal sarcomas, malignant mixed Müllerian tumors, and other types have been reported. Embryonal rhabdomyosarcoma (sarcoma botryoides) is a highly malignant sarcoma that occurs in children up to 6 years of age. This tumor usually forms soft nodules that fill and protrude from the vagina. The prognosis for children with this tumor has improved with the use
DIAGNOSIS, CLINICAL EVALUATION, AND STAGING

Most patients with VAIN and approximately 10% to 20% of patients with invasive disease are asymptomatic at presentation; in these cases carcinoma is usually diagnosed during investigation of an abnormal Pap smear result. Cytologic examination of the case of abnormal cytologic findings should always include a detailed examination of the entire vagina and cervix, even when there is an obvious cervical lesion, because patients can present with multiple areas of abnormality. Women who have persistent positive Pap smear results after treatment of CIN should be examined carefully for VAIN.

Approximately 50% to 60% of patients with invasive cancer present with abnormal vaginal bleeding, frequently after coitus or vaginal douching. Patients may also present with complaints of vaginal discharge, a palpable mass, dyspareunia, or pain in the perineum or pelvis.

According to FIGO, the rules for clinical staging of patients with carcinoma of the vagina are the same as those for clinical staging of patients with cervical cancer. FIGO has suggested a TNM staging system that classifies patients with unilateral inguinal metastases as N1 (stage III) and those with bilateral nodes as N2 (stage IVA), but this system is rarely used. Patients with inguinal metastases are sometimes cured with locoregional treatment; Kucera and Vavra report uncorrected 5-year survival rates of 29% for patients with clinically suspicious inguinal nodes and 44% for patients with clinically negative groins.

TABLE 36.2-13. International Federation of Gynecology and Obstetrics Clinical Staging of Carcinoma of the Vagina

FIGO does not specify how tumors should be classified when the inguinal nodes are clinically positive. The stage descriptions state that tumors that have spread beyond the true pelvis should be classified as stage IVB, but many clinicians ignore inguinal node status in assigning stage and thus generate confusion in the literature on this subject. The American Joint Committee on Cancer has suggested a TNM staging system that classifies patients with unilateral inguinal metastases as N1 (stage III) and those with bilateral nodes as N2 (stage IVA), but this system is rarely used. Patients with inguinal metastases are sometimes cured with locoregional treatment; Kucera and Vavra report uncorrected 5-year survival rates of 29% for patients with clinically suspicious inguinal nodes and 44% for patients with clinically negative groins.

PROGNOSTIC FACTORS

The rates of local control, distant metastasis, and survival in vaginal carcinoma are all correlated strongly with tumor stage (Table 36.2-14). Approximately 50% to 60% of patients with invasive cancer present with abnormal vaginal bleeding, frequently after coitus or vaginal douching. Patients may also present with complaints of vaginal discharge, a palpable mass, dyspareunia, or pain in the perineum or pelvis.

TABLE 36.2-14. Carcinoma of the Vagina: Survival Rates According to Clinical Stage

Most investigators have been unable to find a correlation between tumor site and outcome. However, Chyle and colleagues reported higher rates of local recurrence and overall relapse in patients with posterior wall lesions, and Kucera and Vavra reported a better survival rate for patients whose tumors involved the upper third of the vagina. Tumors that involve the entire vagina tend to have a poorer prognosis, probably reflecting the larger size of these lesions. Exophytic tumors may have a better prognosis than those with infiltrating or necrotic lesions. Investigators disagree about the influence of histologic grade and type on outcome. Several investigators have reported a correlation between increasing grade of squamous carcinomas and recurrence, whereas others have found no correlation. Chyle and coinvestigators reported significantly poorer survival and local control rates for patients with adenocarcinoma, but other investigators found no difference in outcome for patients with squamous carcinomas or adenocarcinomas.

TREATMENT

Stage 0

Patients with only HPV infection or VAIN 1 do not require treatment. These lesions often regress spontaneously, are frequently multifocal, and recur quickly after attempts at ablative therapy. VAIN 2 is usually treated by laser ablation. However, VAIN 3 is more likely to harbor an invasive lesion. Hoffman and colleagues reported finding occult invasion in upper vaginectomy specimens from 9 (28%) of 32 patients who had surgery for VAIN 3. It has been recommended that VAIN
lesions located in dimples of the vaginal cuff of older patients be locally excised before definitive treatment to rule out occult invasion. VAIN 3 lesions that have been adequately sampled to rule out invasion can be treated with laser ablation. Cryosurgery should not be used in the vagina because the depth of injury cannot be controlled and inadvertent injury to the bladder or rectum may occur. Superficial fulguration with electrosurgical ball cautery may be used under colposcopic control, with the epithelial tissue wiped away as it is ablated to allow observation of the depth of destruction. Local excision is an excellent method of treatment for small upper vaginal lesions. Rarely, total vaginectomy is required for extensive VAIN 3 lesions. The vagina should then be reconstructed with a split-thickness skin graft. However, this aggressive treatment should not be used for VAIN 2.

Although progression of stage 0 lesions to invasive disease is uncommon, the risk is sufficient to warrant close follow-up of patients treated for VAIN. In a review of 136 cases of carcinoma in situ of the vagina, Benedet and Saunders found only four cases (3%) that progressed to invasive cancer with up to 30 years of follow-up. Cheng and colleagues reported four cases of invasive cancer that developed in 35 patients who were followed after wide local excision for VAIN.

VAIN can also be treated effectively with intracavitary radiotherapy, but this treatment is usually reserved for patients with multifocal, multiply recurrent disease or high operative risk. Treatment is usually delivered using Cs loaded in a plastic vaginal cylinder 3 to 4 cm in diameter. Chyle et al. reported a 17% recurrence rate at 10 years in 37 patients treated with a vaginal surface dose of 70 to 80 Gy. Perez et al. reported only one recurrence (5%) in 20 patients treated with a vaginal surface dose of 60 to 70 Gy. The single vaginal recurrence was distal to the region treated with brachytherapy, and the authors emphasize the importance of treating the entire vagina to avoid marginal recurrences. More recently, some authors have reported results using fractionated high-dose-rate interstitial therapy to treat VAIN. MacCloud et al. reported control of VAIN 3 in 11 of 14 patients followed for 30 to 115 months after treatment; in these patients, the vaginal surface was treated with a total dose of 34 to 45 Gy in four to ten fractions. One patient had progression to invasive disease. The authors observed no severe complications with this treatment. However, Ogino and colleagues reported adverse vaginitis and rectal bleeding in two patients treated to the entire vagina with a less conservative fractionation schedule.

**Stage I**

Radiotherapy is often the treatment of choice for stage I disease because if surgery is used, total vaginectomy or even exenteration may be needed to obtain satisfactory resection margins. However, surgery has a definite role in selected cases. Early tumors that involve the upper posterior vagina can be removed with a vaginal hysterectomy and partial vaginectomy (if the uterus is in situ) or with a radical upper vaginectomy (if the peritoneum is intact) and bilateral pelvic lymphadenectomy. Some surgeons advocate broader indications for surgical treatment of stage I disease. Stock and associates reported a 5-year disease-free survival of over 80% for 15 patients treated with surgery alone (local excision, partial vaginectomy, or radical vaginectomy). One patient in whom disease recurred had successful salvage treatment with irradiation, and two patients who received postoperative irradiation were cured of their disease. Among six patients in the series of Stock et al. who were treated with definitive irradiation, the disease-free survival rate was 80%; one patient in whom disease recurred had successful salvage treatment with peptinectomy. For patients with a prior history of pelvic irradiation, radical surgery (usually pelvic exenteration) is indicated and is often curative.

Disease-specific survival rates for patients with stage I disease treated with definitive irradiation range from 75% to 95%. Selected patients with small, superficial tumors may be treated with brachytherapy alone. Perez et al. achieved pelvic tumor control in 22 (88%) of 25 selected patients with stage I disease treated with brachytherapy alone. They recommended a dose of 60 to 70 Gy calculated 5 mm beyond the plane of the implant or vaginal mucosa (vaginal surface dose of 80 to 120 Gy). Thicker stage I tumors should be treated with a combination of external-beam irradiation and brachytherapy with an aim to deliver 40 to 50 Gy to the pelvic nodes and 70 to 75 Gy to the tumor.

**Stage II**

Because investigators rarely define their criteria for distinguishing stage I from stage II disease or for selecting patients for various treatments, different institutional experiences cannot be easily compared. Reported disease-specific survival rates range from 50% to 80%. Data suggest that most patients with stage II disease recur after irradiation of the external-beam treatment field and pelvic tumor control. Perez and colleagues reported a 17% local recurrence rate at 10 years in 37 patients treated with brachytherapy alone, compared with 54 (67%) of 81 patients treated with a combination of external-beam irradiation and brachytherapy. Chyle et al. reported a local recurrence rate (in the vagina) of 11% in 18 patients treated with brachytherapy alone, but did not report the rate of pelvic wall relapse in this patient subset.

Brachytherapy should be tailored to the volume and distribution of the tumor and its response to external-beam irradiation. For tumors that flatten to less than 5 mm in thickness, the dose to the vagina may be boosted using intracavitary sources in a vaginal cylinder. Because the thickness of apical vaginal tumors may be difficult to assess in patients who have had a hysterectomy, an examination under anesthesia is often needed to determine whether intracavitary therapy will cover the tumor adequately. Transvaginal ultrasound or MRI may also be helpful in treatment planning. When the uterus is intact, tumors high in the posterior fornix can often be treated with a tandem and ovoids. Larger tumors usually require a boost with interstitial therapy or additional external-beam irradiation. Most authors emphasize the importance of brachytherapy in the treatment of vaginal cancer. However, brachytherapy must be designed to treat the entire vaginal tumor. Chyle and colleagues argue that tumors that cannot adequately be covered with brachytherapy may often be cured with external-beam irradiation alone using carefully designed shrinking fields. They reported three (11%) vaginal recurrences in 26 patients with stage II disease treated with external-beam irradiation alone, compared with 12 (21%) recurrences in 58 patients treated with combined external-beam irradiation and brachytherapy.

Selected patients with stage II disease may be cured with radical surgery. However, total radical vaginectomy or pelvic exenteration is often required to remove the tumor, and results with radical surgery do not appear better than those achieved with radiotherapy alone. Primary radical surgery is usually indicated for patients who have previously had pelvic radiotherapy.

**Stages III and IVA**

Most authors report disease-specific survival rates of between 30% and 50% for patients with stage III disease and between 15% and 30% for patients with stage IVA disease. Stage III and IVA tumors are usually bulky, highly infiltrative lesions involving most or all of the vagina as well as the pelvic wall, bladder, or rectum. The extent of these tumors and the proximity of critical normal tissue structures make their management a formidable technical challenge. Pelvic recurrence rates are high in most series; the risk of distant metastasis is also relatively high, although distant relapse is often accompanied by locoregional recurrence.

All patients require treatment with external-beam irradiation. Most authors advocate the use of brachytherapy whenever possible. However, Chyle and colleagues reported a 17% rate of freedom from relapse (47% at 10 years) in a series of patients with stage III disease in which the majority of patients (40 of 55) were treated with external-beam irradiation alone. Brachytherapy is undoubtedly an important part of disease management in some patients. However, in some cases interstitial therapy does not provide adequate coverage of tumors that are large and intimately associated with critical structures. In these cases, it may be appropriate to place greater emphasis on external-beam treatment.

For selected patients with stage IVA disease who are in otherwise good medical condition, a pelvic exenteration with vaginal reconstruction using a gracilis flap or rectus abdominis myocutaneous flap may be the treatment of choice, particularly if a rectovaginal or vesicovaginal fistula is present. Radiotherapy technique. External-beam fields must include the primary lesion and the regional lymph nodes. Fields should be individualized according to the primary site. Radiopaque markers placed at the distal edge of the tumor help to define the lower border, which often includes a portion of the introitus. Treating the patient in an open (frog-leg) position can often reduce the severity of vulvar cutaneous reactions.

When tumors involve the lower third of the vagina, pelvic fields should be enlarged to include at least the medial inguinal lymph nodes. When four fields are used to treat the pelvis, care must be taken to cover all the draining lymph nodes. Lateral fields should adequately cover posterior perirectal nodules, particularly when the primary lesion involves the posterior vaginal wall.

Intracavitary brachytherapy is of little value in the treatment of locally advanced vaginal cancers because the dose falls off rapidly from the surface of a vaginal cylinder. In general, the dose at a 5-mm depth is only 50% to 65% of the dose at the vaginal surface. Intermittent brachytherapy can provide better coverage of thick
Evidence that HPV may play a role in the pathogenesis of cervical cancer has led investigators to look for HPV infection in patients with vulvar neoplasms. Eighty or that effective treatment of VIN has prevented a significant increase in the incidence of invasive disease.

Neoplasia (VIN) tends to occur in younger women; the median age of women diagnosed with VIN is 45 to 50 years. Although investigators have not demonstrated an approximately 65 to 70 years; the incidence peaks in women older than 75 years at approximately 20 per 100,000.

Invasive vulvar carcinoma is a rare disease that accounts for approximately 4% of gynecologic cancers. Because primary vaginal carcinomas are rare, few reports have specifically addressed the role of chemotherapy in the treatment of this disease. Chemotherapeutic management is usually based on extrapolations from experience with the treatment of carcinomas of the cervix. For this reason, patients who have metastatic or recurrent vaginal carcinoma that is no longer amenable to locoregional treatment are sometimes treated with cisplatin-based chemotherapy even though the efficacy of this treatment is not well documented in the literature. Thigpen and colleagues reported one complete and no partial responses in 16 patients treated with etoposide for advanced vaginal cancers. Reports of the use of neoadjuvant chemotherapy or concurrent chemoradiation are anecdotal.

Vaginal Clear Cell Carcinoma

The treatment of vaginal clear cell carcinoma is similar to that of squamous cell carcinoma. However, most women with vaginal clear cell carcinoma are young, so an effort should be made to preserve vaginal and ovarian function whenever possible. Conventional treatments for stage I and II disease include radical hysterec- tomy, vaginectomy, and lymphadenectomy with formation of a neovagina using a split-thickness skin graft, and radical radiotherapy. Senekjian and colleagues reported on the use of local therapy alone in 43 patients with stage I disease who were reported to the Registry for Research on Hormonal Transplacental Carcinogenesis. Patients treated with local excision alone had a recurrence rate of more than 40% at 10 years. However, 17 patients who were treated with local irradiation (brachytherapy or transvaginal orthovoltage cone irradiation) or with or without local excision had a 10-year recurrence rate of less than 10%. Of 41 assessable patients treated with local therapy in Senekjian and colleagues report, eight had had 15 pregnancies and 12 live births. Retropertioneal lymphadenectomy may be indicated when local treatment is considered for stage I lesions, which are reported to have an overall rate of pelvic lymph node metastases of 17%. When larger or more advanced lesions are treated with whole pelvic irradiation, ovarian transposition should be considered before radiotherapy.

The overall actuarial 10-year survival rate for patients treated for vaginal clear cell carcinoma is 79%. The survival rates for patients with stage I and II tumors are 90% and 80%, respectively. Most recurrences occur within 3 years of initial therapy. However, recurrences have been reported to occur as many as 10 to 20 years after treatment. Approximately one-third of relapses are first detected at distant sites, most commonly the lungs or extrapleural lymph nodes.

ROLE OF CHEMOTHERAPY.

Because primary vaginal carcinomas are rare, few reports have specifically addressed the role of chemotherapy in the treatment of this disease. Chemotherapeutic management is usually based on extrapolations from experience with the treatment of carcinomas of the cervix. For this reason, patients who have metastatic or recurrent vaginal carcinoma that is no longer amenable to locoregional treatment are sometimes treated with cisplatin-based chemotherapy even though the efficacy of this treatment is not well documented in the literature. Thigpen and colleagues reported one complete and no partial responses in 16 patients treated with etoposide for advanced vaginal cancers. Reports of the use of neoadjuvant chemotherapy or concurrent chemoradiation are anecdotal. However, vaginal carcinoma resembles cervical carcinoma in its location, pattern of spread, histologic appearance, relationship to HPV infection, and response to radiotherapy. It may therefore be reasonable to extrapolate from randomized trials demonstrating a benefit from concurrent chemoradiation in patients with locally advanced cervical cancer to justify a similar approach in selected patients with high-risk invasive vaginal cancers.

CARCINOMA OF THE VULVA

EPIDEMIOLOGY

Invasive vulvar carcinoma is a rare disease that accounts for approximately 4% of gynecologic cancers. In the United States, invasive vulvar cancer occurs with an average annual age-adjusted incidence rate of 1.2 cases per 100,000 woman-years. The median age of patients diagnosed with invasive vulvar cancer is approximately 65 to 70 years; the incidence peaks in women older than 75 years at approximately 20 per 100,000.

In contrast, vulvar intraepithelial neoplasia (VIN) tends to occur in younger women: the median age of women diagnosed with VIN is 45 to 50 years. Although investigators have not demonstrated an overall increase in the incidence of invasive vulvar cancer, studies in the United States and Europe suggest that the incidence of VIN has more than doubled since the early 1970s.

This increase has been particularly marked in women younger than 55 years. The relatively stable incidence of invasive cancer despite a steady increase in patients diagnosed with VIN could suggest that the etiologic factors for the two conditions are different, that diagnostic procedures have improved, or that effective treatment of VIN has prevented a significant increase in the incidence of invasive disease.

Evidence that HPV may play a role in the pathogenesis of cervical cancer has led investigators to look for HPV infection in patients with vulvar neoplasms. Eighty percent to 90% of VIN lesions contain HPV 16 or other HPV types. However, although more than 90% of invasive cervical cancers are associated with HPV, only 30% to 50% of invasive vulvar carcinomas are associated with evidence of HPV infection.

Epidemiologic, histopathologic, and viral data suggest that patients with invasive squamous cell carcinomas of the vulva can be divided into at least two groups whose tumors may have different etiologies: one that is associated with HPV infection and one that is not.
(35 to 55 years), are often associated with VIN, are frequently multifocal, and tend to form less keratin than do HPV-negative tumors. Patients with HPV-positive tumors are also more likely to have CIN and to have the risk factors typically associated with cervical cancers (multiple sexual partners, early age at first intercourse, low socioeconomic status, and cigarette smoking). In contrast, HPV-negative tumors usually occur in older women (55 to 85 years), are often associated with vulvar inflammation or lichen sclerosis (but rarely with VIN), are generally unifocal, and are usually well differentiated with exuberant keratin formation. Although a number of investigators have reported this distinct grouping of patients with vulvar cancer, others have found greater overlap.

Several investigators have reported a high incidence of p53 mutations in HPV-negative tumors. Lee and colleagues found missense mutations of p53 in four (44%) of nine HPV-negative tumors but in only one (8%) of 12 HPV-positive tumors. They postulated that alteration in p53 activity, either through point mutations or through E6-mediated loss of p53 function in HPV-infected cells, could be important in the development of vulvar neoplasms.

**NATURAL HISTORY AND PATTERN OF SPREAD**

The female external genitalia include the mons pubis, labia majora, labia minora, clitoris, vestibular bulb, vestibular glands (including Bartholin’s glands), and vestibule of the vagina. Together, these structures form the vulva. The region between the posterior commissure of the labia and the anus is termed the perineum. Approximately 70% of vulvar squamous carcinomas involve the labia majora or minora, most frequently the labia majora. Approximately 15% to 20% involve the clitoris, and a similar proportion involve or arise in the perineum. In approximately 10% of cases, the lesion is too extensive to permit determination of the original site, and in approximately 5% of cases, the lesion is multifocal. Vulvar tumors may extend locally to invade adjacent structures, including the vagina, urethra, and anus; advanced vulvar tumors may invade adjacent pelvic bones.

A rich network of anastomosing lymphatics that frequently crosses the midline drains the vulva. Even minimally invasive vulvar tumors may spread to regional lymph nodes (Table 36.2-15). In most cases, initial regional metastasis is to the superficial inguinal lymph nodes that are located between Camper’s fascia and the fascia lata; tumors may then metastasize secondarily to the deep femoral lymph nodes located along the femoral vessels and then to the pelvic lymph nodes (Fig. 36.2-11). However, metastases have been reported to the deep femoral lymph nodes without involvement of the superficial inguinal lymph nodes, especially from carcinomas of the clitoris and Bartholin’s glands. Theoretically, tumors involving the clitoris can also spread directly to the obturator nodes through lymphatics that follow the dorsal vein of the clitoris, although evidence of this route is rarely seen in practice. Despite the extensive anastomosis of lymphatics in the region, metastasis of vulvar carcinoma to contralateral lymph nodes is uncommon in patients with well-lateralized T1 lesions.

**TABLE 36.2-15. Relationship between Depth of Stromal Invasion and Inguinal Lymph Node Metastases in Patients with Squamous Cell Carcinomas of the Vulva**

<table>
<thead>
<tr>
<th>Depth of Invasion</th>
<th>Metastases to Inguinal Lymph Nodes</th>
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<tbody>
<tr>
<td>T1</td>
<td>Approximately 10%</td>
</tr>
<tr>
<td>T2</td>
<td>More than 10%</td>
</tr>
</tbody>
</table>

The lungs are the most common sites of hematogenous metastasis.

**PATHOLOGY**

As classified by the International Society for the Study of Vulvar Disease, nonneoplastic epithelial disorders of the vulva (previously termed vulvar dystrophies) include lichen sclerosis, squamous hyperplasia, and other dermatoses. Approximately 10% of these lesions have cellular atypia and are termed VIN. Histologically, VIN is characterized by disruption of the normal epithelial architecture, varying degrees of cytoplasmic and nuclear maturation, and giant cells with abnormal nuclei. VIN lesions are assigned a grade from one to three according to their degree of maturation. Invasive cancers have been associated with two types of VIN. The most common VINs contain nuclear atypia throughout the epithelial layers and are frequently associated with HPV. These lesions are sometimes subdivided into warty and basaloïd types, which have greater and lesser degrees of differentiation, respectively.

In the second subset of VINs, atypia is largely confined to the basal layers of the epithelium. These lesions tend to occur in older women and are not usually associated with HPV but are commonly adjacent to areas of lichen sclerosis or hyperplasia. Buscema and Woodruff estimated that approximately 4% of patients treated for VIN develop a subsequent invasive cancer.

Paget’s disease of the vulva, a rare intraepithelial lesion located in the epidermis and skin adnexa, accounts for 1% to 5% of vulvar neoplasms. Histologically, vulvar Paget’s disease is characterized by large, pale, mucopolysaccharide-rich cells that are positive for periodic acid–Schiff. Electron microscopic studies have suggested that Paget’s cells derive from apocrine cells in the stratum germinativum of the epidermis. Paget’s disease usually occurs in postmenopausal women, who often present with symptoms of vulvar pruritus and discomfort. Grossly, Paget’s lesions appear eczematoid or, when extensive, may be raised and velvety with persistent weeping. Approximately 5% to 10% of newly diagnosed Paget’s lesions are associated with underlying adenocarcinoma arising locally in a vulvar vestibular gland or skin appendage or from a distant site such as the breast or rectum. It has been suggested that Paget’s disease with underlying adenocarcinoma represents a different process than other types of intraepithelial Paget’s disease because the other types rarely progress to invasive adenocarcinoma.

The term microinvasive carcinoma of the vulva should be used with caution. The methods and criteria used to define microinvasive carcinoma of the cervix cannot be applied to carcinoma of the vulva. Stromal invasion by vulvar carcinomas is not measured in a uniform manner, and strict criteria for the diagnosis of microinvasive vulvar cancer have not been defined. VIN is not routinely seen adjacent to invasive vulvar cancer, and the transition from normal tissue to invasive cancer can be abrupt. Elongatedrete pegs may extend 6 mm or more from the basement membrane and are sometimes misconstrued as invasive cancer. The International Society of Gynecologic Pathologists recommends that the depth of stromal invasion be measured vertically from the most superficial basement membrane to the deepest tumor. Tumor thickness is defined as the distance between the granular layer of epidermis and the deepest tumor. Lymph node metastases from tumors less than 1 mm in depth or thickness are extremely rare (see Table 36.2-15). For this reason, FIGO now includes a stage IA subcategory in its staging system for...
More than 90% of invasive vulvar cancers are squamous cell carcinomas. Atypical keratinization is the hallmark of invasive vulvar cancer. Most squamous carcinomas are well differentiated, but mitoses may be noted. Approximately 5% of vulvar cancers are anaplastic carcinomas that may consist of large immature cells, spindle sarcomatoid cells, or small cells. Vulvar carcinomas consisting of small cells may resemble small cell anaplastic carcinomas of the lung or Merkel’s cell tumors and have demonstrated an aggressive biologic behavior in the few reported cases. Verrucous carcinoma is a rare, very well-differentiated form of vulvar carcinoma that usually presents in the fifth or sixth decade of life as a large, locally invasive lesion. On microscopic examination, the tumor has a papillary, exophytic appearance; tumor cells retain a normal appearance of maturation and demonstrate minimal atypia. Even with extensive local invasion, lymph node metastasis from verrucous carcinoma is rare.

The diagnosis of Bartholin’s gland carcinoma is based on clinical findings of a tumor arising in the anatomic location of Bartholin’s glands and on the histologic appearance. Biopsy of a tumor arising from a Bartholin’s gland usually reveals adenocarcinoma, but squamous cell carcinomas, transitional cell carcinomas (arising from the duct and histologically indistinguishable from transitional cell carcinoma of the bladder), and adenoid cystic carcinomas have also been reported.

Rare cases of primary mammary adenocarcinoma of the vulva have been reported, presumably arising in aberrant mammary tissue occurring along the embryonic milk line. Other rare carcinomas that may occur in the vulva include basal cell carcinomas and sebaceous carcinomas.

Malignant melanomas of the vulvar account for approximately 2% to 4% of primary vulvar malignancies and 1% to 3% of melanomas arising in women. Vulvar melanoma occurs most frequently in women older than 60 years of age, but 10% to 20% of vulvar melanomas occur in women younger than 40 years. Approximately 50% of vulvar melanomas involve the labium majus, but tumors may also arise in the labium minus, clitoris, or perineum. In a large Swedish series, 57% of vulvar melanomas were of the mucosal lentiginous type, 22% were nodular, and 16% were superficial spreading or lentiginous. Most investigators have reported a correlation between depth of invasion or Breslow thickness and outcome. However, because the vulvar epithelium sometimes lacks a well-developed papillary dermis, which makes it difficult to assign Clark’s levels of invasion, Chung and colleagues proposed a modification of the Clark system that is often used to categorize patients with vulvar melanoma. Other factors that have been associated with a poorer prognosis are ulceration, clinical aneuploidy, and older age. Diagnosis is made by biopsy of any suspicious pigmented or nonpigmented lesion, particularly if it is nodular or indurated or has a perilesional halo.

Vulvar sarcomas constitute 1% to 2% of vulvar malignancies and include leiomyosarcomas, rhabdomyosarcomas, angiosarcomas, neurofibrosarcomas, and epithelioid sarcomas. The prognosis appears to depend on three main determinants: lesion size, tumor contour, and mitotic activity. Lesions greater than 5 cm in diameter with infiltrating margins, extensive necrosis, and more than five mitotic figures per ten high-power fields are the most likely to recur after surgical resection.

DIAGNOSIS, CLINICAL EVALUATION, AND STAGING

Patients with VIN may complain of vulvar pruritus, irritation, or a mass, but up to 50% of these patients are asymptomatic at the time of diagnosis. Patients with invasive vulvar cancer usually complain of a vulvar mass and chronic vulvar pruritus. Advanced lesions may bleed and be exquisitely tender.

Because VIN can have many manifestations, any new vulvar lesion should be biopsied. Once the diagnosis of VIN has been established, the entire vulva, cervix, and vagina should be carefully examined because patients often have multifocal or multicentric involvement. Colposcopic examination may help to define the extent of disease.

Diagnosis of invasive vulvar lesions requires a wedge biopsy of the lesion with surrounding skin and with underlying dermis and connective tissue so the pathologist can adequately evaluate the depth of stromal invasion. This procedure may be usually performed in the physician’s office under local anesthesia. Excisional biopsy is preferred for lesions smaller than 1 cm in diameter.

Patients with invasive disease require additional evaluation for regional and metastatic disease. All patients with invasive disease require a careful physical examination including a detailed pelvic examination, chest radiography, and biochemical profile. Cystoscopy and proctoscopy should be performed in patients with advanced lesions or with tumors that are near the urethra or anus, respectively. Patients who complain of bone pain or who have tumor fixed to pelvic bones should have appropriate skeletal radiography. CT or MRI scans can be obtained to evaluate deep inguinal and pelvic lymph nodes for possible regional metastasis.

In 1983, FIGO adopted a clinical TNM staging system for vulvar cancer. This system was based on clinical assessment of the primary tumor and regional lymph nodes. However, several studies have demonstrated poor correlation between clinical assessment of the inguinal lymph nodes and pathologic findings. In a study of 588 patients with tumors that invaded 5 mm or deeper, Homesley and colleagues reported that although 93% of patients with fixed or ulcerated nodes had metastatic tumor, 24% of those with clinically negative nodes had inguinal lymph node metastases and 24% of patients with suspicious but mobile nodes had negative findings at lymphadenectomy. In 1988 the FIGO staging system was modified to incorporate the more accurate information gained from surgical assessment of regional lymph nodes. The staging system was revised again in 1994 to create a separate stage IA for minimally invasive lesions (see Table 36.2-16). Studies of the relationship between tumor grade and outcome have drawn varying conclusions, possibly reflecting the inconsistent criteria used to grade vulvar tumors. Some investigators appear to have a poorer prognosis than diploid tumors, but ploidy tends to be correlated with other prognostic factors and may not be an independent predictor of outcome.

Other factors that tend to be associated with prognosis include the amount of keratin, the mitotic rate, and the tumor growth pattern. Anaploid tumors appear to have a poorer prognosis than diploid tumors, but ploidy tends to be correlated with other prognostic factors and may not be an independent predictor of outcome. Several authors have reported that tumors containing HPV DNA have a poorer prognosis than HPV-negative tumors.
Prognosis is strongly correlated with the presence and number of inguinal node metastases (see Table 36.2-17). In a study of 586 patients treated in two GOG trials, Homeley and colleagues \(^{328}\) reported 5-year survival rates of 91% for patients with negative inguinal lymph nodes and 75%, 36%, and 24%, respectively, for patients with one or two, three or four, or five or six positive nodes. None of the 16 patients with seven or more nodes involved with tumor survived. Patients with bilateral nodal involvement had a survival rate of 25%, compared with 71% for those with unilateral node involvement. The authors did not state whether patients with bilateral nodal disease had a poorer prognosis than did patients with a similar number of unilateral metastases. Homeley and colleagues \(^{329}\) reported that patients with pelvic node metastases had a particularly poor survival rate: Among patients treated with surgery alone, 3-year survival rates were 23% for patients with pelvic node metastases versus 73% for patients with only inguinal node involvement. For this reason, FIGO has categorized tumors that have spread to the pelvic nodes as stage IV.

However, it should be remembered that most of these series include patients who did not receive postoperative irradiation. It is not possible from available data to define the prognosis of patients who received multidisciplinary treatment for vulvar cancer metastatic to pelvic lymph nodes.

In 1995, van der Velden and colleagues \(^{330}\) published a detailed study of nodal prognostic factors in 71 patients with inguinal node metastases from vulvar carcinomas. Patients with extranodal spread or more than two positive nodes received adjuvant radiotherapy at an unspecified dose. The most powerful predictor of outcome in their study was extranodal tumor extension: 28 (63%) of 44 patients with extranodal tumor died of disease versus three (14%) of 22 without this finding. In Cox regression analysis, none of the other factors studied (tumor size, number of nodes, FIGO stage, nodal size, degree of nodal replacement, laterality) added to the predictive power of extranodal extension. Origoni and colleagues reported similar findings in a series of 53 patients with positive nodes. \(^ {331}\)

Studying the relationship between surgical margins and tumor recurrence, Heaps and colleagues \(^ {332}\) reported no local failures in 91 patients whose closest tumor margin (deep or at the skin surface) was 8 mm or more in the fixed specimen. Ten (43%) of 23 patients with margins of 4.8 mm or less experienced a local recurrence, as did 8(62%) of 13 patients with margins between 4.8 mm and 8.0 mm.

### TREATMENT

The traditional operative approach to invasive carcinoma of the vulva, radical en bloc resection of the vulva and inguino-femoral nodes, was developed at the beginning of the twentieth century, was popularized during subsequent decades, and remained the standard of care until the early 1980s. \(^ {333}\) Radiotherapy was thought to have little role in the treatment of vulvar cancer. Although this surgical approach achieved 5-year survival rates of 60% to 70%, the surgery caused significant physical and psychological complications, and patients with multiple positive nodes continued to have a poor prognosis. In 1981, Hacker and colleagues \(^ {334}\) demonstrated that a less morbid surgical approach, operating through separate vulvar and groin incisions, achieved cure rates similar to those achieved with the traditional radical vulvectomy. Since then, there has been a continuing trend toward less radical surgery for early-stage disease. In addition, prospective and retrospective studies have established the role of radiotherapy in the curative management of locoregionally advanced disease.

### Preinvasive Disease (Vulvar Intraepithelial Neoplasia)

After invasive carcinoma has been excluded by a sufficient number of excisional biopsies, the treatment of VIN should be as conservative as possible. Focal lesions can be simply excised. Multiple lesions can be excised separately or, if confluent, with a larger single excision. This approach is generally well tolerated and provides material for histologic assessment. When there is more extensive VIN, the lesions can be vaporized with a CO\(_2\) laser. This method may provide an alternative to more extensive operations but does not yield a specimen for histologic inspection.

Extensive, diffuse VIN may require a wider excision, even when the histopathologic analysis demonstrates that the initial lesions were completely resected. Presumably this phenomenon reflects the multifocal nature of the condition. \(^ {335}\) In fact, VIN can recur within the donor skin from split-thickness grafts. \(^ {336}\)

#### T1 and T2

Invasive vulvar tumors can usually be treated effectively without the complications of en bloc radical vulvectomy and inguinal node dissection. Today, most gynecologic oncologists advocate an individualized approach to early invasive vulvar carcinomas. \(^ {337}\) Overall 5-year disease-specific survival rates for stage I (T1N0M0) and stage II (T2N0M0) disease are approximately 98% and 85%, respectively. \(^ {338}\) Most T1 and selected T2 lesions can be controlled locally with a radical wide local excision. A wide and deep excision of the lesion is performed, with the incision extended down to the inferior fascia of the urogenital diaphragm. An effort should be made to remove the lesion with a 2-cm margin of normal tissue in all directions unless this would require sacrifice of the anus or urethra. The surgical defect is closed in two layers. Small T1 lesions that invade 1 mm or less can be managed with local resection alone because the risk of regional spread is small (see Table 36.2-15). Patients with more invasive tumors must also have surgical or radiation treatment of the inguinal nodes as discussed above.

Larger T2 tumors may require radical vulvectomy to obtain adequate tumor clearance with negative margins. En bloc resection of the vulva and inguinal nodes was once believed to be necessary to prevent recurrences in the soft tissue intervening between the vulva and regional nodes; however, most surgeons now perform the operation through separate vulvar and groin incisions. Although recurrences have been reported in this tissue bridge, these appear to be rare, and the risk of complications is significantly decreased when separate incisions are used. \(^ {339,340}\)

Wound seroma is the most common acute complication of radical vulvectomy and inguinal node dissection, occurring in approximately 15% of cases. \(^ {341}\) Other acute complications include urinary tract infection, wound cellulitis, temporary anterior thigh anesthesia from femoral nerve injury, thrombophlebitis, and, rarely, pulmonary embolus. \(^ {342,343}\) The most common chronic complication is leg edema, but this risk has decreased from approximately 30% to 15% with the use of separate groin incisions. \(^ {344}\) Other chronic complications including genital prolapse, urinary stress incontinence, temporary weakness of the quadriceps muscle, and introital stenosis. Rare late complications include pubic osteomyelitis, femoral hernia, and rectoperineal fistula. These risks are less when separate incisions are used and are further reduced when radical local excision of the primary lesion is done instead of radical vulvectomy. \(^ {345}\)

#### T3 and T4

Primary tumors that involve the anus, rectum, rectovaginal septum, or proximal urethra pose a difficult problem because adequate surgical clearance can be obtained only by combining a pelvic exenteration with radical vulvectomy and bilateral groin node dissection. Although some patients may be cured with this ultraradical surgery, the risks of acute and long-term complications of the procedure are substantial. \(^ {346,347}\) For this reason, a number of investigators have explored the use of less morbid surgical approaches that permit fixing all pelvic and perirectal structures to the obturator internus muscle. A variety of techniques have been described, including local excision, radical vulvectomy, and pelvic exenteration with or without pelvic node dissection.
of combined surgery and irradiation to spare critical structures in patients with locally advanced disease.

In some cases, patients with T3 tumors that minimally involve the external urethra or anus can undergo initial vulvectomy without sacrifice of major organ function if close margins are accepted near critical structures. Postoperative radiotherapy can then be delivered to prevent local recurrence. Although local recurrences are frequently successfully controlled with additional surgery, Faul and colleagues reported an overall 5-year survival rate of only 40% after the first local recurrence and emphasized the importance of achieving local control. These authors reported a significant reduction in the local failure rate (from 59% to 16%) when tumors that were within 8 mm of the operative margins were irradiated after surgery. In such cases, the vulva may be treated with opposed anterior and posterior photon fields (if the inguinal regions also require treatment) or with an appositional perineal electron beam. The vulva should receive a total dose of 50 to 65 Gy depending on the proximity of disease to the surgical margin.

In the early 1980s, several investigators reported results of preoperative radiotherapy in small series of patients with locally advanced disease. These reports indicated that modest doses of radiation (45 to 55 Gy) produced dramatic tumor responses in some patients with T3 and T4 disease, permitting organ-sparing surgery without sacrifice of tumor control. Hacker and colleagues reported that four of eight patients with T3 to T4 tumors treated preoperatively with 44 to 54 Gy had no residual tumor in the vulvectomy specimen and that seven of these eight had local control of their disease. More recently, investigators have emphasized the use of concurrent chemoradiation in this setting.

**Chemotherapy in Locoregionally Advanced Disease**

To reduce the need for morbid ultraradical surgery and to improve locoregional control rates, a number of investigators have explored combinations of chemotherapy with radiation and surgery in patients with locally advanced vulvar carcinoma. Most studies have used combinations of cisplatin, 5-FU, and mitomycin C, extrapolating from the high response rates observed with use of this treatment for locally advanced carcinomas of the cervix and head and neck and from studies that have demonstrated the efficacy of these drugs as radiosensitizers in the treatment of carcinomas of the anus. Treatment schedules usually include a 4- to 5-day infusion of 5-FU combined with one of the other two drugs, with this course repeated every 3 to 4 weeks. Studies have usually included small numbers of patients with advanced local or regional disease. However, most investigators have observed impressive responses that often appear to be better than would be expected with radiation alone. Randomized trials have not been done and may be difficult to perform because of the small number of patients with locally advanced vulvar cancer. However, trials that demonstrated improved local control and survival when concurrent cisplatin-containing chemotherapy was added to radiation treatment of cervical cancers and improved colostomy-free survival when mitomycin C and 5-FU were added to radiation treatment of anal cancer suggest that this approach may be also be useful treatment of women with vulvar cancer.

![Image](image-url)

**TABLE 36.2-18. Concurrent Chemoradiotherapy in the Management of Locally Advanced or Recurrent Carcinoma of the Vulva**

| Treatment of Regional Disease | Effective regional treatment is the single most important factor in the curative management of early vulvar cancer. Although patients with vulvar recurrences can often have their disease successfully controlled with additional local treatment, patients who suffer inguinal recurrences are rarely curable. All patients with primary tumors that invade more than 1 mm must have their inguinal nodes treated. Traditional management includes a bilateral radical inguinal lymph node dissection. Today, this is usually performed through separate groin incisions. An ellipse of skin is removed 1 cm below and parallel to the groin crease. The greater saphenous vein is ligated and divided. The skin incision is extended down to the fascia lata and 2 cm above the inguinal ligament to remove the inguinal nodes. The saphenous vein is tied off, the fascia lata is split, and the femoral nodes are dissected. A suction drain is placed, and the wound closed in two layers. At one time, pelvic node resection was also performed in all patients with invasive vulvar cancer. When subsequent studies demonstrated that pelvic node metastases were found only in patients with clinically suspicious or multiple positive inguinal nodes, use of the procedure was limited to patients determined intraoperatively to have positive inguinal nodes. Then, in 1986, Homesley and colleagues published results of a randomized, prospective study that compared pelvic node resection with inguinal and pelvic irradiation in patients with inguinal node metastases from carcinoma of the vulva. All patients were initially treated with radical vulvectomy and inguinal lymphadenectomy. Patient randomization was done prospectively after frozen section evaluation of the inguinal nodes. This trial was closed prematurely, after 114 eligible patients had been entered, when interim analysis revealed a survival advantage for the radiation treatment arm (P = .03). The difference was most marked for patients with clinically positive or multiple histologically positive groin nodes. For patients with two or more positive nodes, the 2-year survival rates were 63% and 37% for the radiotherapy and pelvic node resection groups, respectively. Analysis of failure patterns reveals that the largest difference between treatment groups was in the number of inguinal failures. With the publication of this study, most practitioners abandoned routine pelvic node dissection, and postoperative radiotherapy became standard for most patients with inguinal node metastases.
FIGURE 36.2-12. Survival rates of 114 patients with invasive squamous cell carcinoma of the vulva who were entered on a Gynecologic Oncology Group protocol in which patients with positive groin nodes after radical vulvectomy and bilateral inguinal lymphadenectomies were randomly assigned to receive pelvic lymph node dissection or postoperative irradiation to the pelvis and inguinal nodes (P = .004). (From ref. 627, with permission.)

FIGURE 36.2-13. Sites of recurrence in 114 patients with invasive squamous cell carcinoma of the vulva who were entered on a Gynecologic Oncology Group protocol in which patients with positive groin nodes after radical vulvectomy and bilateral inguinal lymphadenectomies were randomly assigned to receive pelvic lymph node dissection or postoperative irradiation to the pelvis and inguinal nodes. (From ref. 627, with permission.)

Most of the serious acute and subacute complications of radical vulvectomy are related to the lymph node dissection, although these risks have decreased somewhat with the use of separate groin incisions. 

Complications include wound disruption or infection in 50% to 75% of cases, chronic lymphedema in 20% to 50%, and a perioperative mortality of 2% to 5%. Patients who undergo vulvectomy without inguinal node dissection have significantly shorter hospital stays and fewer complications.

Although radical inguinal lymphadenectomy has historically been considered the treatment of choice for regional management of invasive vulvar carcinoma, several retrospective studies have suggested that regional radiotherapy may be an effective and less morbid way of preventing recurrence in patients with clinically negative groins. In a review of 91 patients who had elective treatment of the inguinal nodes for cancers with primary drainage to the inguinal nodes, Henderson and colleagues observed only two recurrences after treatment with 45 to 50 Gy over 5 weeks, and both of these occurred outside the treatment fields. In a retrospective review of 42 patients with invasive vulvar carcinomas, Petereit and colleagues found no difference in the groin recurrence rate for patients with clinically negative inguinal nodes treated with radical lymphadenectomy or radiotherapy, even though the irradiated patients in their series had more advanced primary tumors. The complications of treatment, including lymphedema, wound separation, and infection, and the length of hospitalization were greater for patients who had had lymphadenectomy. Leiserowitz and colleagues reported no groin recurrences in 23 patients with locally advanced, clinically NO vulvar cancers after prophylactic treatment of the groins with concurrent chemoradiation.

In 1992 the GOG reported the results of a trial that randomly assigned patients with clinically negative inguinal nodes to receive inguinal node irradiation or radical lymphadenectomy followed by inguinalpovic irradiation in patients with positive nodes) after resection of the primary tumor. The study was closed after entry of only 58 patients, when an interim analysis demonstrated a significantly higher rate of inguinal recurrence and death in the irradiated group. The authors concluded that lymphadenectomy was the superior treatment, although the morbidity rate of lymphadenectomy was greater than that of groin irradiation. However, the radiotherapy techniques used in this study have since been criticized. CT scans were not consistently obtained to verify the position and size of inguinal nodes. Patients were treated with superior appraisal fields, the dose was prescribed at a depth of 3 cm, and the use of electrons (usually 12 meV) was emphasized. This method of treatment can lead to significant underdosage of the inguino femoral nodes, which frequently extend to a depth of more than 5 to 6 cm.

Because of these criticisms, the study’s results and the role of irradiation in the primary management of clinically negative inguinal nodes remains controversial.

Some surgeons have tried to reduce surgical complications by reducing the extent of lymph node dissections. Burke and colleagues reported four (5%) groin recurrences in 74 patients with T1 to T2 tumors treated with wide local excision and superficial inguinal lymphadenectomy (unilateral or bilateral depending on the location of the tumor). In a prospective study of patients with favorable primary lesions (T1, less than or equal to 5 mm thick, no LVSI), the GOG reported nine (7%) inguinal recurrences in 121 patients who had negative findings on ipsilateral superficial inguinal lymphadenectomy. A number of investigators have explored the use of intraoperative lymphatic mapping to identify a sentinel node that would predict the presence or absence of regional metastases.

Preliminary studies suggest that a sentinel node can be identified in most patients. Further study will be needed to determine whether this procedure can be used to more accurately identify patients who can be successfully treated without the morbidity of radical regional treatment. Treatment of Metastatic Disease

A number of reports document the use of single-agent chemotherapy in patients with metastatic or recurrent squamous cell carcinomas of the vulva. Several anecdotal reports published in the 1970s suggest that bleomycin may be an active agent, but the response rate has not yet been documented in a prospective phase II trial, and the optimal dose and schedule have not been determined. Single-agent phase II studies of cisplatin, etoposide, mitoxantrone, and piperazinedione have failed to document any objective responses.

Data on the use of combination chemotherapy in this setting are anecdotal, and no series includes more than nine patients. In the absence of reliable data specific to carcinoma of the vulva, clinicians often use combinations that have had some activity in the treatment of cervical cancer. However, there are as yet few data to indicate that chemotherapy can provide effective palliation for patients with metastatic or recurrent vulvar carcinoma that is not amenable to locoregional treatments.

CHAPTER REFERENCES


55. Frisch MD, Berek JS. Minimal cervical cancer: definition and histology.


SECTION 36.3
Cancers of the Uterine Body

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PATRICIA J. EIFEL
FRANCO M. MUGGIA

Endometrial Carcinoma
Clinical Overview
Epidemiology
Natural History and Routes of Spread
Diagnosis and Pretherapy Evaluation
Risk Factors
Staging
Treatment of Primary Disease
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Outcome and Survival
Uterine Sarcomas
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Chapter References

ENDOMETRIAL CARCINOMA

CLINICAL OVERVIEW

Tumors of the uterine fundus comprise the most common group of gynecologic malignancies. Annual incidence figures for the United States have remained stable at approximately 36,000 cases during the 1990s. Deaths from disease occur in 6000 women per year. The large proportion of survivors with these cancers reflects a disease course characterized by early onset of symptoms and well-established diagnostic guidelines. Nevertheless, women with high-risk or advanced disease have a poor prognosis and account for the most uterine cancer deaths.

A general classification of uterine fundal cancers is provided in Table 36.3-1. Approximately 90% of tumors arise within the epithelium of the uterine lining and are categorized as endometrial carcinomas. Within this group, 90% of cancers are typical endometrial adenocarcinomas. The typical endometrial carcinomas are further subdivided into three architectural grades based on the percentage of solid tumor growth: Grade 1 cancers have identifiable endometrial glands and are well differentiated (Fig. 36.3-1), whereas grade 3 tumors demonstrate a solid growth pattern and are poorly differentiated. Rare cell types, including papillary serous carcinoma, clear cell carcinoma, and mucinous carcinoma, account for the remaining 10% of cases. Adenosquamous carcinomas are now classified as typical endometrial adenocarcinomas with squamous differentiation. In general, all of these uncommon cell types are associated with a later age of onset, greater risk for extraterine metastases, and poorer prognosis when compared with typical grade 1 adenocarcinomas.

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Approximate Freq. (%)</th>
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<tbody>
<tr>
<td>Typical endometrial adenocarcinoma</td>
<td>90</td>
</tr>
<tr>
<td>Papillary serous adenocarcinoma, high grade</td>
<td>5</td>
</tr>
<tr>
<td>Mucinous carcinomas, low grade</td>
<td>5</td>
</tr>
<tr>
<td>Clear cell carcinoma</td>
<td>5</td>
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</tbody>
</table>

TABLE 36.3-1. Classification of Uterine Fundal Cancer

FIGURE 36.3-1. Adenocarcinomas of the endometrium are graded on the basis of their architectural pattern. A complex, branching, glandular pattern without solid areas, as seen in this photomicrograph, is characteristic of grade 1 cancers.

EPIDEMIOLOGY

The normal endometrium is a hormonally responsive tissue. Estrogenic stimulation produces cellular growth and glandular proliferation, which is cyclically balanced by the maturational effects of progesterone. Abnormal proliferation and neoplastic transformation of the endometrium has been associated with chronic unopposed exposure to estrogenic stimulation. It is currently believed that estrogen-associated endometrial cancers progress through a premalignant stage described as atypical adenomatous hyperplasia. This phase is characterized by increases in gland number and complexity as well as cytologic atypia. Although serial observations of women with adenomatous hyperplasia are scarce, it is estimated that at least one-third of such cases progress to carcinoma.

The best-recognized risk factors for the development of endometrial carcinoma can be related to chronic estrogen exposure. These include oral intake of exogenous estrogen (without progestins), estrogen-secreting tumors, low parity, extended periods of anovulation, early menarche, and late menopause.
Pregnancy represents a 9-month period of relatively intense progesterone stimulation by the placenta. Consequently, women with multiple pregnancies have a lower risk of endometrial lesions on the basis of this protective hormonal effect. Both menarche and menopause are commonly associated with absent or irregular ovulation, so women who experience early onset or late cessation of ovarian function are more likely to have additional estrogenic exposure. Morbidly obese women also have a greater risk of endometrial cancer, presumably because their adipocytes are able to convert androstenedione of adrenal origin to estrone, a weak circulating estrogen.

Epidemiologic studies have consistently identified women with diabetes mellitus and hypertension as having an increased risk of endometrial carcinoma. This risk remains independent of other known factors in multivariate analyses. It has not been possible to connect these relatively common medical conditions to the “estrogenic hypothesis” of endometrial carcinogenesis. Epidemiologic risk factors for endometrial cancer are listed in Table 36.3-7.

<table>
<thead>
<tr>
<th>Table 36.3-7. Epidemiologic Risk Factors for Endometrial Carcinoma</th>
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<tr>
<td><strong>Factor</strong></td>
</tr>
<tr>
<td>Diabetes</td>
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<td>Hypertension</td>
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<td>Obesity</td>
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<tr>
<td>Advanced age</td>
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<tr>
<td>Nulliparity</td>
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<tr>
<td>History of breast cancer</td>
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<tr>
<td>History of endometrial surgery</td>
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</tbody>
</table>

There is extensive current interest in the potential connection between long-term tamoxifen use as adjuvant therapy for women with breast cancer and the development of endometrial cancers. Although primarily an estrogen antagonist, tamoxifen also has some agonist properties. The diagnosis of endometrial cancer among a few women taking tamoxifen on the National Surgical Adjuvant Breast and Bowel Project trial has raised concerns about the safety of such therapy. Some pathology reviews of tamoxifen-associated endometrial tumors have identified a preponderance of poor-prognosis tumors, whereas others have noted a majority of low-risk lesions. A confounding variable is the known increased risk of endometrial tumors in women with breast cancer. This issue is complex and evolving. On the basis of current information, it seems reasonable to conclude that (1) if an association between tamoxifen and endometrial carcinoma exists, the overall risk is small compared with the risk of recurrent breast cancer, and (2) women receiving long-term tamoxifen therapy should be monitored carefully for uterine abnormalities. Ultrasonic assessment of the contour and thickness of the endometrium is frequently used to monitor such patients, but its value is unproven. Certainly, any woman with abnormal vaginal bleeding should be evaluated promptly by biopsy. Exposure to adjuvant tamoxifen therapy should be limited to 5 years. The development of new selective estrogen receptor modulators that do not have stimulatory effects on the endometrium should eliminate all such risk for women who may benefit from antiestrogen therapy.

**NATURAL HISTORY AND ROUTES OF SPREAD**

Endometrial carcinoma is a disease of postmenopausal women. The average age at diagnosis is usually about 60 years. Women with high-risk tumors, such as grade 3 adenocarcinoma, papillary serous carcinoma, and clear cell carcinoma, tend to be slightly older. All endometrial lesions originate in the glandular component of the uterine lining. Their initial growth forms a polyoid mass within the uterine cavity. This tumor mass is friable and often contains areas of superficial necrosis. Consequently, postmenopausal bleeding is the hallmark symptom for more than 90% of patients. Because most women and their physicians recognize that this as an ominous finding, prompt diagnosis is common.

**FIGURE 36.3-2.** Endometrial cancers develop as polyloid lesions that gradually expand to fill the uterine cavity. This well-differentiated tumor involves both the anterior and posterior uterine walls throughout the entire fundus. Scattered areas of superficial necrosis give rise to the hallmark symptom of postmenopausal bleeding.

With further growth, the primary tumor may extend to involve a greater proportion of the endometrial surface and ultimately extend to the lower uterine segment and cervix. Invasion into the myometrium occurs simultaneously. The uterus has a rich and complex lymphatic network. Channels draining the superior portion of the fundus parallel the ovarian vessels and empty into the paraaortic lymph nodes in the upper abdomen. Lymphatics from the middle and lower portions of the uterus travel through the broad ligaments to the pelvic nodes. A few small lymphatic vessels course through the round ligaments to the superficial inguinal nodes. As a result of this extensive network, nodal metastases can occur at any level and in any combination.

Tumors that penetrate the uterine serosa may directly invade adjacent tissues, such as the bladder, colon, or adnexae, or they may exfoliate into the abdominal cavity to form implant metastases. Small tumor fragments may also gain access to the peritoneal cavity by traversing the fallopian tubes. However, the clinical importance of this potential mechanism of spread is uncertain. Hematogenous dissemination is observed but uncommon. Sites of distant spread include lung, liver, bone, and brain.

**DIAGNOSIS AND PRETHERAPY EVALUATION**

A diagnosis of endometrial carcinoma should be considered in postmenopausal women with any vaginal bleeding, perimenopausal women with heavy or prolonged bleeding, and premenopausal women with abnormal bleeding patterns who are obese or oligo-ovulatory. Although a formal dilatation and curettage has been the standard technique for diagnosis, outpatient endometrial biopsy has replaced it in most situations. A correctly performed endometrial biopsy includes an adequate amount of tissue obtained from multiple passes through the uterus, and it has a diagnostic accuracy equivalent to that of surgical curettage under anesthesia. Operative sampling may be necessary in unusual patients, such as those with cervical stenosis, inadequate outpatient biopsy, or inability to tolerate an outpatient examination and procedure. Asymptomatic women with endometrial cancer occasionally have abnormal glandular components detected by routine cervical cytology (Fig. 36.3-3). Because the Papanicolaou (Pap) smear is designed to sample the cervical epithelium, this method of diagnosis is uncommon. Fewer than 50% of women with known endometrial cancer have an abnormal Pap smear.
Endometrial carcinoma is a surgically treated and staged tumor. Consequently, the focus of the pretreatment evaluation is on the detection of unresectable disease and a determination of operative risk. For patients with disease that is clinically limited to the uterus by physical examination, a straightforward evaluation that includes laboratory studies, a chest radiograph, and an electrocardiogram is adequate. A serum CA-125 assay should be considered in women with high-risk histologic types because it may be predictive of occult extruterine disease and may be useful as a tumor marker. More sophisticated imaging studies such as ultrasound, computed tomography, intravenous pyelography, and magnetic resonance imaging rarely provide information that is not determined after surgical exploration. These studies should be reserved for patients with advanced disease or prohibitive surgical risks. Many women with endometrial cancer are elderly and have associated medical conditions, particularly obesity, diabetes, and hypertension. The pretreatment medical evaluation should be individualized based on findings obtained from the medical history and general physical examination.

RISK FACTORS

Histopathologic risk factors have been extensively evaluated since the late 1970s. For convenience, these can be grouped into uterine and extraterine categories. Major prognostic factors associated with the uterine component of the tumor are grade or cell type, depth of myometrial invasion, and tumor extension to the cervix. Less important are extent of uterine cavity involvement, lymph–vascular space invasion, and tumor vascularity. Obviously, women whose tumors have spread beyond the uterus have a poorer prognosis. The major extraterine risk factors are adnexal metastases, pelvic or paraaortic lymph node spread, positive peritoneal cytology, peritoneal implant metastases, and distant organ metastases.

A detailed analysis of nearly 1000 patients has been presented by the Gynecologic Oncology Group (GOG). The relative risks for the various histologic factors evaluated in that study are summarized in Table 36.3-5. The risk for developing recurrent disease was greatest in women whose tumors had metastasized to pelvic or paraaortic lymph nodes, demonstrated gross intraperitoneal spread, or contained unequivocal lymph–vascular space invasion. Not surprisingly, an exceptionally high incidence of recurrence was noted in cases with two or more risk factors. Based on the findings of this and other surgical staging trials, the International Federation of Gynecology and Obstetrics (FIGO) adopted a surgical staging system for uterine fundal cancers in 1988.

In addition to the more classic histologic risk factors, several studies have examined archival specimens to evaluate a number of potential molecular markers. Data suggesting a prognostic role for DNA ploidy, S-phase fraction, oncogenes, tumor suppressor genes, AgNOR, and nuclear morphometric features should be considered preliminary. Further prospective study in larger numbers of fresh tissue specimens may lead to a refinement of risk assessment. This would be particularly useful if it permitted the identification of the small percentage of otherwise low-risk patients who are destined to develop recurrent disease. Data reported by Lim and colleagues suggest that this approach is possible using ploidy and p53 overexpression as markers.

Some women have a genetic predisposition for endometrial cancer. Endometrial tumors are a component of some of the cancer family syndromes identified and evaluated by Lynch and colleagues. Within these unique families, the risk of developing endometrial cancer may approach 50%. However, cancer syndromes account for relatively few cases of endometrial carcinoma overall. Endometrial cancer is also more common in women with a previous cancer of the breast, colon, or ovary. Dual neoplasms may occur simultaneously or metachronously. The time interval between the diagnosis of the two neoplasms may be as long as 10 years.

STAGING

Before 1988, uterine fundal cancers were staged clinically. The clinical staging system stratified patients with early disease on the basis of a fractional biopsy specimen from both the endocervix and the endometrium as well as the depth of the uterine cavity and physical examination (Table 36.3-3). These techniques for assessment of disease volume and spread were found to be erroneous in as many as one-third of cases when compared with histopathologic findings at the time of laparotomy. In addition, women with small-volume disease in retroperitoneal nodes or the peritoneal cavity were rarely identified during clinical staging. The clinical system was abandoned because the accumulating data from surgical staging reports was more accurate and allowed stratification of similar risk groups for adjuvant and adjunctive therapy trials. Consequently, the surgical staging system approved at the 1988 FIGO meeting is currently used for most patients with uterine fundal cancers (Table 36.3-4). Risk factors incorporated into this system include depth of myometrial invasion, tumor extension to the cervix, tumor spread to adnexal organs, peritoneal cytology, retroperitoneal lymph node metastases, and spread to abdominal or distant sites. The clinical staging criteria have been retained for patients who do not undergo surgical exploration as a part of their initial treatment. Patients in this group are those with obviously advanced cancers who would not benefit from tumor resection by hysterectomy and those with medical conditions that preclude an operative procedure.
TABLE 36.3-3. Clinical Staging of Uterine Fundal Tumors

TABLE 36.3-4. Surgical Staging of Uterine Fundal Tumors

TREATMENT OF PRIMARY DISEASE

Surgical Resection and Operative Staging

Resection of the primary tumor by total abdominal hysterectomy and bilateral salpingo-oophorectomy is the mainstay of therapy for uterine cancers. Because endometrial cancer originates in the fundus, adequate surgical margins can usually be achieved by simple extravesicale hysterectomy. Salpingo-oophorectomy is recommended because the ovary is a relatively common site of occult metastasis and because most women are already postmenopausal and no longer have hormonal function from the organ. Removal of the uterus is curative treatment for most stage I cases. The more extensive radical hysterectomy has been recommended for selected patients with gross tumor involvement of the cervix. However, combined therapy, using both external-beam pelvic irradiation and extravesicale hysterectomy, is more frequently used in such cases. The increased expansion of endoscopic surgery has permitted its application in endometrial cancer. The staging portion of the operation is performed endoscopically followed by a transvaginal hysterectomy. Among surgical teams skilled in these techniques, the results appear to be equivalent to those obtained by open laparotomy. Some evidence also suggests that aggressive cytoreduction may improve survival in women with extrauterine disease.

The surgical staging system for uterine fundal tumors identifies certain histopathologic prognostic features for stage and substage assignment but does not define a specific surgical approach required to accomplish staging. The additional operative procedures associated with surgical staging produce a small, but definite, increase in operative risk. Most reported complications are related to organ injury during biopsy or hemorrhage from vascular injury during node sampling. Patients who have extensive intraperitoneal staging procedures also have a greater risk of bowel injury if they receive postoperative external irradiation.

Who should undergo surgical staging? Some advocate an extended staging procedure for all women with endometrial cancer. Our approach has been to limit surgical staging to patients at risk for occult disease spread. We routinely perform staging procedures in women with grade 2 or 3 adenocarcinomas and those with variant histologic tumor types. This group typically represents approximately one-third of cases. For patients with grade 1 adenocarcinoma, we estimate the depth of myometrial invasion intraoperatively by making a visual estimate and evaluating a frozen section. Extended staging procedures are only performed when significant myometrial invasion (more than 50%) is identified. Using this stratified approach to surgical staging minimizes surgical risk for patients with low-risk tumors while maximizing the chance for detecting occult extrauterine disease in those patients at risk.

FIGURE 36.3-4. The depth of myometrial invasion can be estimated by visually examining a cut section of the uterine wall taken at the level of the tumor. A clear line distinguishes polypoid tumor growth from myometrium in this surgical specimen. The accuracy of intraoperative visual estimates can be enhanced by using frozen section analysis in selected cases.

FIGURE 36.3-5. Schematic representation of a staging algorithm. Patients with grade 1 (G1) typical endometrial adenocarcinoma have an exploratory laparotomy with peritoneal cytology, total abdominal hysterectomy (TAH), and bilateral salpingo-oophorectomy (BSO). The depth of myometrial invasion and extension to the cervix
An equally important question is what procedures constitute an adequate staging effort. After the collection of cytopathology specimens and completion of the hysterectomy, the staging assessment is focused on two general areas—the peritoneal cavity and the retroperitoneal lymph nodes. Many gynecologic oncologists have adopted a staging approach similar to that used for women with epithelial ovarian carcinoma. Evaluation of the peritoneal cavity begins with a careful visual and palpatory inspection. Abnormal areas from peritoneal or serosal surfaces are biopsied. In the absence of obvious disease spread, random biopsies from multiple peritoneal sites are obtained. Cytopathology or histology samples, or both, are also taken from the diaphragm. A portion of the omentum is removed. When we examined our peritoneal staging procedures in a group of at-risk women, we found that occult peritoneal spread is relatively uncommon. 52 Although directed biopsy of palpably suspicious areas often detected metastatic disease, random biopsies were rarely positive. Peritoneal cytology and omental biopsy, coupled with directed biopsy from abnormal sites, provided accurate and reliable information regarding intra-peritoneal disease.

The primary goal of surgical staging is to provide an accurate assessment of disease spread at the time therapy is initiated. For patients with tumors confined to the uterus, those in the low-risk subgroup (grade 1 tumor with superficial myometrial invasion) are adequately treated by hysterectomy alone. Fortunately, such cases account for most women with endometrial carcinoma. Women with tumors demonstrating high-risk features have an incidence of recurrent disease of 25% to 40% and are excellent candidates for adjuvant therapy trials. Patients with more advanced disease warrant additional postoperative adjunct treatment.

Radiotherapy

HISTORICAL PERSPECTIVE. Within a few years of Marie Curie's discovery in 1895, radium was used to treat uterine cancers. Early reports of pathologic complete responses to radiation, encouraging survival rates with combined treatment, and the reduction of postoperative vaginal recurrences fueled enthusiasm for combined treatment. 55-56 By the 1950s, preoperative irradiation followed by hysterectomy had become standard treatment for early-stage endometrial cancer in the United States and other countries, although a few clinicians argued the advantages of selective postoperative irradiation. 57-58 The development of megavoltage radiotherapy in the 1950s reduced the risk of pelvic irradiation and increased the use of this modality to prevent pelvic recurrences. In more recent years, clinicians increasingly have come to appreciate the value of operative findings as a guide to the selection of adjuvant treatment. Because preoperative irradiation has never been proven to be more effective than tailored postoperative radiation therapy, its use has declined in favor of treatment with initial surgery. 59-60 Moreover, although radiation therapy has been clearly demonstrated to reduce the rate of pelvic disease recurrence after hysterectomy, the influence of adjuvant irradiation on the survival rate of patients with endometrial carcinoma has never been clearly determined. As a result, investigators continue to disagree about the role that adjuvant radiotherapy should play in the management of uterine carcinomas.

Several factors have made it difficult to study the value of adjuvant treatment. Because most newly diagnosed endometrial carcinomas are clinically confined to the uterus, with cure rates of 80% to 90% after treatment with hysterectomy alone, the margin for improvement is small. To detect any advantage from adjuvant treatment, studies must have many patients or must be confined to subgroups that are at high risk for recurrence. The influences of physicians' biases on the selection of patients for adjuvant treatment have limited the value of retrospective studies. Retrospective experiences are also difficult to compare because of changes that have been made in the classification systems for staging and grading neoplasms and the relatively recent recognition of special high-risk histologic subtypes. For these reasons, the selection of treatment is based primarily on clinicians' understandings of the risk factors for recurrence and the natural history of the disease, impressions gained from inconclusive studies, and physician or patient preference.

PREOPERATIVE IRRADIATION. The primary goal of preoperative intracavitary irradiation is to prevent vaginal recurrences. Bedwinek et al. 61 observed an inverse correlation between the dose of intracavitary treatment and the incidence of distant metastases in their patients, but other investigators have not confirmed this result. Intracavitary applicators are usually loaded with 35 to 40 mgRaEq of cesium and left in place for approximately 72 hours for a total exposure of 3500 to 4000 mgRaEq-hr. Vaginal applicators are loaded to deliver 60 to 70 Gy to the surface of the apical vagina over the same period. Inserting additional sources in the form of Heyman or Simon capsules may increase the dose to the fundus. After this dose of radiation, hysterectomy can be safely performed within 2 to 3 days. 62-64 Immediate hysterectomy is usually preferred because important prognostic information about the depth of tumor infiltration is retained. Although the popularity of preoperative irradiation has declined, some groups still support its use for patients with grade 2 or 3 tumors. Preoperative irradiation is not indicated for patients with grade 1 tumors that are clinically confined to the uterus, because low-grade carcinomas are usually superficial and have a very low risk of recurrence after treatment with hysterectomy alone.

The theoretical arguments for preoperative irradiation are strongest for patients with uterine cancers that grossly involve the cervix, because preoperative intracavitary techniques deliver a greater dose to the paracervical tissues than is possible with postoperative vaginal irradiation. Combined preoperative external-beam and intracavitary irradiation may be indicated for patients with nonserous tumors that extensively infiltrate the cervix. However, when external-beam irradiation is given preoperatively, hysterectomy should be delayed 4 to 6 weeks.

Because radiation therapy has been used to treat high-risk endometrial carcinoma for many years, few unselected series of patients treated with surgery alone have been reported. In early series, overall vaginal recurrence rates were as high as 15% to 25%. 2,6,10 However, changes in the staging of disease and methods of reporting results make it difficult to relate these results to current experience. A few authors have reported much lower vaginal recurrence rates after surgery alone and have suggested that the wide range of reported local recurrence rates may, in part, reflect variations in surgical technique that influence the risk of tumor cell implantation. 65

Most data suggest that irradiation reduces the incidence of vaginal recurrence from 10% to 15% to less than 5% for patients with high-risk disease. In a compilation of series published between 1967 and 1973, Jones 65 reported an overall incidence of vaginal recurrences of 4.6% in patients treated with preoperative radium compared with 10.6% in patients treated with surgery alone. Subsequent series reported vaginal relapse rates of 0% to 5% for patients with clinical stage I disease treated with preoperative intracavitary irradiation (Table 36.3-5). 66-68-75-77-80-81 However, these results cannot be compared with the recurrence rates of patients not treated with radiation because, in nearly all studies, patients who had a higher risk of recurrence were selected to receive combined treatment (Table 36.3-4).

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<th>Table 36.3-6. Rates of Vaginal Recurrence for Patients Treated with Hysterectomy for Endometrial Carcinoma</th>
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POSTOPERATIVE REGIONAL IRRADIATION. For many years, the only prospective randomized study that had evaluated the benefit of postoperative pelvic irradiation was one conducted at the Norwegian Radium Hospital and published in 1980. Patients with clinical stage I adenocarcinomas underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy. Those proven to have metastases at laparotomy were excluded from the study, but no consistent surgical evaluation was performed. The remaining 540 patients received 60 Gy with brachytherapy to the surface of the apical vagina and were then randomized either to receive 40 Gy of pelvic radiotherapy or no further treatment.

Although patients who received pelvic irradiation in this study had a lower rate of pelvic recurrences, there was no significant improvement in overall disease-specific survival. The data suggested that the survival rate of patients with deeply invasive grade 3 tumors may be improved with radiotherapy, but the number of patients in this subset was small, and the result was not statistically significant. The authors suggested that regional irradiation may have failed to improve the survival rate because patients whose pelvic disease was controlled recurred instead at distant sites. However, local control appeared to be most improved for patients with tumors that deeply invaded the myometrium, whereas the higher rate of distant metastases was seen primarily in irradiated patients with superficial or no muscle invasion. However, although the Norwegian study is one of the largest published series of patients with endometrial cancer, few patients with high-risk disease and relatively few disease-related deaths were reported. As a result, the study was unable to demonstrate or rule out moderate differences in survival rates between patient subgroups.

Several studies that document 80% to 90% survival rates for patients with high-risk disease treated with postoperative radiotherapy provide indirect evidence of the efficacy of regional irradiation. Carey and colleagues reported an 81% 5-year relapse-free survival rate for 157 patients with clinical stage I disease who were treated with postoperative pelvic radiotherapy alone. Kucera et al. reported a survival rate of 88% for 229 patients who had infiltration of the outer one-third of the myometrium or grade 2 or 3 tumors that involved the middle third of the myometrium. Schink et al. reported that tumors measuring less than 2 cm in diameter rarely involved pelvic nodes, whereas those involving the entire uterine cavity had a high risk of pelvic nodal involvement and disease recurrence even when the outer half of the myometrium was not invaded. Patients with intermediate-risk factors in the uterus who have had extensive nodal dissections without demonstration of nodal involvement are less likely to benefit from regional irradiation, particularly in view of the possible increased risk of late complications in patients who have had staging lymphadenectomies.

The GOG completed a randomized trial comparing surgery with surgery plus pelvic radiation therapy in 448 women with intermediate risk endometrial adenocarcinoma. The dose of pelvic radiation was 50.4 Gy, and brachytherapy was not used in either arm. All patients underwent complete surgical staging and only those with FIGO stage IB, IC, or occult stage II disease were eligible. With a median follow-up of 56 months, the estimated 2-year progression-free survival rate was 79% in the group of patients who received adjuvant radiation therapy versus 88% for those treated only with surgery (P = .004). Disease recurred in the pelvis in three patients treated with adjuvant radiation and in 17 patients treated with surgery alone. Overall survival rates for patients treated with or without adjuvant radiation were 96% and 89%, respectively, at 36 months; this difference was not statistically significant (P = .09). This study clearly confirms the ability of postoperative irradiation to reduce local recurrence, although some patients may have been achievable with brachytherapy alone. Opponents of adjuvant irradiation argue that survival was not improved by adjuvant treatment. However, follow-up of this study is still incomplete, and the inclusion of patients with very favorable (e.g., stage IB, grade 1) tumors may dilute a survival benefit to remaining patients (if it exists).

These studies suggest that pelvic radiotherapy is indicated for patients with endometrioid or mucinous tumors that are confined to the pelvis and have features that predict a high risk of recurrence in the pelvis. The potential benefit of treatment should be carefully balanced against the risk of complications, particularly for patients with a history of pelvic infection, multiple abdominal surgical procedures, or severe diabetes mellitus. Patients whose tumors invad the myometrium by more than 50%, involve peritoneal surface or local stroma, lymph–vascular spaces, or pelvic lymph nodes are at highest risk for pelvic recurrence and are usually treated with external-beam radiation to the true pelvis. Other risk factors may be used to select treatment for tumors with intermediate risk factors (e.g., grade 2 tumors invading to the middle third of the myometrium). Schink et al. reported that tumors measuring less than 2 cm in diameter rarely involved pelvic nodes, whereas those involving the entire uterine cavity had a high risk of pelvic nodal involvement and disease recurrence even when the outer half of the myometrium was not invaded. Patients with intermediate-risk factors in the uterus who have had extensive nodal dissections without demonstration of nodal involvement are less likely to benefit from regional irradiation, particularly in view of the possible increased risk of late complications in patients who have had staging lymphadenectomies.

Pelvic radiotherapy is usually delivered using a four-field technique or anteroposterior opposed fields with 15 to 20 MV photons to a total dose of 40 to 50 Gy. Serious complications are observed in 2% to 5% of patients who receive this treatment, but complications may be greater for patients who have had a staging lymphadenectomy. Corn and colleagues also reported a correlation between external-beam irradiation and the risk of complications. Some clinicians give additional intracavitary irradiation to the vaginal cuff after pelvic radiotherapy, although investigators disagree about the benefit of this treatment. Bliss and Cowie reported a lower vaginal recurrence rate (10% vs. 0%) in patients who had intracavitary irradiation added to external-beam irradiation, but gastrointestinal toxicity was also increased. In contrast, Randall et al. reported no difference in local control or complication rates when the vaginal cuff received an intracavitary radiation boost. Several authors have reported increased complication rates when an intracavitary boost was added to 45 to 50 Gy of external-beam radiotherapy to the pelvis; however, these groups tended to give relatively high doses (more than 50 Gy) or rapid dose rates (more than 70 cGy/hr) to the vaginal surface.

EXTENDED-FIELD IRRADIATION. Extended-field irradiation appears to be effective treatment for patients with nonserous endometrial cancer metastatic to paraaortic nodes. Between 30% and 50% of patients survive 5 years with this treatment (Table 36.3-7). Survival rates are not clearly different for patients with gross or microscopic nodal involvement. In their review of 50 patients, Corm et al. reported a lower rate of recurrence in paraaortic lymph nodes in patients who had a lymph node dissection in addition to extended-field irradiation. However, multivariate analysis suggested that the risk of recurrence was not significantly decreased by combined-field treatment. In another study, Onda and colleagues reported a 5-year survival rate of 75% for 20 patients treated with lymphadenectomy followed by cisplatin-containing chemotherapy and extended-field irradiation. Further study is needed to determine whether this excellent survival rate is reproducible.

TABLE 36.3-7. Survival Rate of Patients Treated with Extended-Field Irradiation for Endometrial Carcinoma Metastatic to Paraaortic Lymph Nodes

WHOLE ABDOMINAL IRRADIATION. The poor prognosis of uterine papillary serous carcinomas and their tendency to spread and recur intraabdominally have led radiation oncologists to explore the value of treatment with whole abdominal irradiation. The 68% abdominal recurrence rate reported by Greven et al. in patients with pathologic stage III papillary serous or clear cell carcinomas after treatment with pelvic or extended-field radiotherapy demonstrate why smaller radiation fields are usually inadequate for this disease. Although whole abdominal radiotherapy is accepted by many clinicians as a standard treatment for papillary serous carcinomas, it is rarely used because of the high risk of complications, particularly in patients with endometrioid or clear cell adenocarcinomas. Whole abdominal irradiation appears to be effective treatment for patients with nonserous endometrial cancer metastatic to paraaortic nodes. Between 30% and 50% of patients survive 5 years with this treatment (Table 36.3-7). Survival rates are not clearly different for patients with gross or microsco.
carcinoma, there are as yet only anecdotal reports supporting its efficacy. Potish et al. reported long-term survival in five (57%) of nine patients who had intraperitoneal spread from uterine papillary serous carcinoma at diagnosis, and Malpiedi et al. reported survival durations of 102 to 133 months in five of ten patients treated with whole abdominal irradiation. Three of the patients who survived more than 5 years had been diagnosed with pathologic stage IIa disease. Treatment techniques are similar to those used to treat patients with primary ovarian carcinomas.

Some authors have advocated the use of whole abdominal irradiation for patients with tumors of other histologic subtypes. The number of patients treated in these series is insufficient to determine whether the treatment is better than locoregional irradiation or even whether it is beneficial. Most studies suggest that intraabdominal dissemination is an uncommon pattern of spread in patients with nonserous histologic subtypes, even when malignant cells are seen in peritoneal washings taken at the time of hysterectomy. Although some have advocated whole abdominal irradiation to treat patients with positive peritoneal cytology, there is little evidence that this finding predicts a pattern of intraabdominal recurrence in patients with the more common endometrioid subtypes of endometrial carcinoma. Thus, treatment directed specifically at the positive cytology may not be warranted.

The GOG is comparing whole abdominal radiation therapy with chemotherapy (cisplatin and doxorubicin) for patients with FIGO (1988) stage III and IV disease (less than 2 cm residual). This study will be of particular interest for its comparison of the two treatments in patients with papillary serous tumors, although it will also include patients with nonserous stage III tumors for whom the risk of intraabdominal dissemination is probably small.

POSTOPERATIVE VAGINAL IRRADIATION. Some patients with minimally invasive grade 2 or noninvasive grade 3 tumors have a significant risk of vaginal recurrence despite a relatively low risk of pelvic node metastases. Implantation of tumor cells in the vaginal cuff incision may be an important mechanism of recurrence in these cases.

Postoperative intracavitary irradiation appears to be a very effective method of preventing vaginal cuff recurrences. Calais et al. reported no differences between the survival and vaginal recurrence rates of patients treated with preoperative or postoperative intracavitary irradiation. Reported rates for central recurrence range from 0% to 5% for patients treated with postoperative intracavitary irradiation alone, with the variation partly reflecting the different selection criteria used by various groups.

A variety of different types of intracavitary applicators have been used to treat the vaginal cuff. Radioactive sources are usually placed in vaginal oviducts or in a plastic dome-shaped vaginal cylinder. The arrangement of sources and shape of the cylinder are designed to deliver a homogeneous dose to the apical vaginal surface. Additional sources may be used to treat the mid-vagina if desired. Because the dose of radiation decreases rapidly to approximately 50% to 60% of the surface dose at a depth of 0.5 cm beneath the vaginal mucosa, the dose to adjacent normal tissues is substantially less than the vaginal surface dose.

In the past, radiation was usually administered at low dose rates. Typically, the apical one-third to one-half of the vaginal surface was treated to a total dose of 60 to 70 Gy (30 to 40 Gy at 0.5 cm depth) at a dose rate of 90 to 100 cGy/hr (60 to 60 cGy/hr at 0.5 cm depth). With this treatment, most investigators report a risk of major complications of approximately 1% to 2%. The complication rates tend to be higher with higher total doses and when more than one-half of the vaginal length is treated, although this has not been studied rigorously.

Today, fractionated high dose-rate intracavitary irradiation is increasingly being used as an alternative to low dose-rate irradiation to treat the vaginal cuff. This approach is more convenient for the patient and less costly than inpatient low dose-rate irradiation. The use of high dose-rate brachytherapy has been less controversial in this setting than in the treatment of primary cervical cancer because only a modest dose of radiation is needed to prevent tumor recurrence in the vagina and because placement of the vaginal cylinder requires little manipulation and no sedation.

There is no clear consensus about the ideal dose or fractionation schedule for high dose-rate vaginal brachytherapy. Sorbe and Smeds compared four fractionation schemes—4 × 9.0 Gy, 5 × 6.0 Gy, 6 × 5.0 Gy, and 6 × 4.5 Gy, prescribed at a tissue depth of 1.0 cm—in 404 patients who received intracavitary irradiation alone (without external-beam irradiation) after hysterectomy. The rates of acute and late complications were strongly correlated with fraction size. Eighty-eight percent of patients treated with 4 × 9.0 Gy had significant late rectal complications. Because the authors prescribed treatment at 1.0-cm depth, the total dose and dose per fraction at the mucosal surface were much higher than the specified dose.

Most authors have recommended more conservative fractionation schemes. Treatment is usually prescribed at the surface or 5 mm beneath the mucosa. When the dose is prescribed at 5 mm beneath the mucosa, it should be remembered that the rectal mucosa will receive a total dose (and dose per fraction) that is similar to the prescribed dose. In some reports, investigators have recommended a number of fractionation schemes including, for example, 6 × 6 Gy, 3 × 7 Gy, 4 × 8.5 Gy, and 2 × 16.2 Gy, with doses specified at the vaginal surface. All have reported vaginal recurrence rates of less than 1.5% for patients with relatively favorable tumors.

RADIOTHERAPY ALONE. Although hysterectomy is the primary treatment of most endometrial carcinomas, radiotherapy alone is also an effective treatment that is sometimes indicated for patients who are medically inoperable or who have unsectable disease. Most authors report disease-specific survival rates of 75% to 85% and local recurrence rates of 10% to 20% for patients with clinical stage 1 to II disease treated with radiation alone. Prognosis is usually correlated with clinical stage and histologic grade. Some authors have recommended a number of fractionation schemes including, for example, 6 × 6 Gy, 3 × 7 Gy, 4 × 8.5 Gy, and 2 × 16.2 Gy, with doses specified at the vaginal surface. All have reported vaginal recurrence rates of less than 1.5% for patients with relatively favorable tumors.

Brachytherapy must cover the uterine fundus adequately when treatment will not include a hysterectomy. A single uterine tandem with increased activity in the highest fractionation schemes includes, for example, 6 × 6 Gy, 3 × 7 Gy, 4 × 8.5 Gy, and 2 × 16.2 Gy, with doses specified at the vaginal surface. All have reported vaginal recurrence rates of less than 1.5% for patients with relatively favorable tumors.

Historical Background. The original observations by Kelley and Baker documenting the responsiveness of metastatic endometrial adenocarcinoma to progestogens encouraged the organization of the Endometrial Surgical Adjuvant Study Group in 1965, the forerunner of the GOG. This group's initial trial failed to demonstrate an effect of medroxyprogesterone acetate (MPA) on recurrences after surgical treatment of stage I endometrial cancer. Nevertheless, it stimulated the interest of gynecologic oncologists in collaborative clinical trials and led directly to a grant application in support of GOG activities that began in May 1971. More recent studies

### Systemic Adjuncts

**HORMONES.**

**Historical Background.** Justification for follow-up treatment has been based on studies that have suggested a relationship between the presence of a hormonally receptive tumor and a better prognosis after treatment. The most commonly used hormone regimen is tamoxifen, an estrogen antagonist. Tamoxifen is effective in postmenopausal women, but its use in premenopausal women is limited by significant side effects, including hot flashes and mastodynia. A variety of other hormonal agents have been studied as systemic adjunc-
Adjuvant Hormonal Studies. Progestogens have been widely used to treat metastatic endometrial carcinoma. Although no adjuvant effect of MPA was shown in the initial randomized study, optimistic results were obtained using adjunctive progestogens in women with stage I endometrial cancer compared retrospectively with patients treated only with local modalities. Subsequent randomized studies, however, again failed to demonstrate survival differences. Accordingly, some have argued for performing clinical trials on a better-selected population—for example, those with a greater chance of recurrence or with features that might render them more responsive to progestogens. However, such selection criteria produce the paradox that higher-risk tumors are less likely to be hormone responsive. Subset analyses have documented an unfavorable relative survival in “receptor-poor” versus “receptor-rich” stage I endometrial cancer treated with MPA. Studies have been initiated in Germany comparing higher doses of MPA (1000 mg orally daily) with tamoxifen and with observation in patients with stage I cancer and with nonrandomized use of MPA in women with stage II disease. However, because no fully published results from such newer adjuvant therapy trials have appeared, adjuvant hormonal therapy can only be recommended in the context of clinical trials. Similarly, nonrandomized experience with progestogens given as induction therapy before, or in lieu of, surgery in patients with preinvasive or minimally invasive disease, or in patients who are poor surgical risks, attests to their biologic activity but does not represent an established indication.

In addition to the use of adjuvant progestogens alone, a large Italian study of women with FIGO stage I cancers randomized patients with invasion beyond one-third of the myometrium to either external radiation or external irradiation plus MPA. No differences were seen among arms.

Cytotoxic Chemotherapy. Cytotoxic chemotherapy has been considered as an adjuvant treatment in certain circumstances when the risk of distant recurrence exceeds 20%. These circumstances include (1) any stage II tumor, (2) clear cell or papillary serous histology, (3) absence of hormone receptors, (4) preoperative finding of elevated CA-125, and (5) selected stage I disease with deep myometrial invasion. A study from the M. D. Anderson Cancer Center in patients with some of these adverse prognostic factors reported a favorable experience after adjuvant cisplatin, doxorubicin, and cyclophosphamide therapy. Confirmation from randomized studies is lacking, however.

Because the only randomized study of adjuvant chemotherapy yielded negative results (GOG 34, a study comparing adjuvant doxorubicin to no further therapy after surgery and radiation for stage I and occult stage II high-risk endometrial cancer), the GOG has subsequently launched studies to evaluate other adjuvant modalities. In July 1995, GOG 99, which randomized all cell types (except papillary serous and clear cell) of surgical stage I or occult stage II endometrial cancers to either no additional treatment or pelvic radiotherapy, was closed to accrual. In a simultaneous trial, GOG 94 treated all papillary serous and clear cell tumors, regardless of stage, with whole abdominal irradiation. Patients with other cell types and optimally debulked clinical stage III or IV were also eligible for this study.

New clinical trials have been proposed to compare combination chemotherapy (doxorubicin and cisplatin) and pelvic irradiation in stage I and II patients with advanced-stage disease. A resurgence of interest in consolidation therapy with simultaneous irradiation and chemotherapy is likely as paclitaxel and cisplatin are more tolerable in such situations than doxorubicin. In addition, drug combinations have been proposed before local irradiation in high-risk patients (those with papillary serous/clear cell histology, pathologic stage III and IVA disease, and earlier stages beyond IA if they have at least any two of the following unfavorable risk factors: grade 3 disease, more than one-third myometrial invasion, cervical stromal invasion, and vascular space involvement).

TREATMENT OF RECURRENT DISEASE

Treatment Failure

Treatment failure in low-risk patients is exceedingly rare. In our series investigating surveillance strategies, we had only one failure in this group. Tumor recurrence is most common in women with advanced-stage disease or those with high-risk features in their primary tumor. Late recurrence is uncommon, and virtually all failures are clinically evident within 3 years of original diagnosis.

One-half of patients whose tumors recur are symptomatic. A targeted examination and diagnostic evaluation should readily lead to the correct diagnosis. The remaining group with treatment failure have their recurrence detected during routine surveillance. Although the Pap smear and chest radiograph may detect an asymptomatic recurrence, this clinical scenario is rare. Most recurrences are detected by physical examination. Serum CA-125 levels may be useful in monitoring patients for the development of recurrent disease, especially those who have papillary serous carcinomas or intraperitoneal disease. Follow-up intervals of 6 to 12 months coupled with prompt evaluation of symptomatic patients seems to be an appropriate approach to surveillance. Routine use of diagnostic studies beyond cytology and the selective use of CA-125 is probably not cost effective.

The patterns of recurrence depend on initial disease distribution. Patients with advanced primary disease tend to have abdominal or systemic failure. Approximately one-third of recurrences seen in women whose primary tumors were confined to the uterus are limited to the pelvis; the remaining two-thirds have some component of distant failure. It is important to identify those cases with isolated pelvic recurrence because some can be salvaged by radiotherapy or ultrasonic therapy.

Systemic Agents

Hormone Therapy.

Overview of Clinical Studies. Progestogens have been used in the management of recurrent endometrial cancer after the original report by Kelly and Baker in 1961 used the parenterally administered hydroxyprogesterone caproate. Beneficial results from these trials were mostly confined to a subset of patients with well-differentiated tumor, metastases to the lung, and a long disease-free interval between diagnosis of the primary tumor and the development of metastases. Subsequent trials, using MPA or megestrol acetate, explored the use of high-dose progestogen therapy on better-selected patients through the study of hormone receptor content of tumors and limiting therapy to receptor-positive cases, paralleling breast cancer strategies. Overall, fewer than 30% of patients (even with the best selection) show objective responses, and the survival of patients with metastatic disease is disappointingly short, except for a rare, extremely hormone-responsive patient. Earlier series reporting very long median survival rates reflect carefully selected patients or loose criteria of response.

No dose-response effect for progestogens has been proven. Although some responders have very long survival rates, the median duration of response in most studies does not exceed 10 months. The results of treatment with tamoxifen are generally inferior to those obtained with progestogens.

Other hormonal manipulations are increasingly under study. These include not only combinations of tamoxifen and MPA, but also other selective estrogen receptor modulators such as raloxifene, luteinizing hormone–releasing hormone (LHRH) agonists and antagonists, aromatase inhibitors, and miscellaneous other drugs (Table). It is likely that the same subset of patients responds to these hormonally directed therapies, and no obvious advantage of one agent over another has emerged to date. Moreover, results from small studies may be discordant, reflecting the importance of patient selection in maximizing the probability of response.
Cancers, secondary cytoreduction after failure of primary therapy has no real role because of the lack of effective regional or systemic therapy. Two legitimate

Surgery plays a limited role in the management of recurrent endometrial cancer. Although cytoreduction is probably valuable for women with advanced primary cancers, secondary cytoreduction after failure of primary therapy has no real role because of the lack of effective regional or systemic therapy. Two legitimate

TABLE 36.3-9. Selected Series of Hormonally Based Therapy in Women with Advanced Endometrial Cancer

Biologic and Pharmacologic Considerations. The presence of estrogen and progesterone receptors in tumors has been shown to correlate with well-differentiated cancers and with response to progestogens. 182,183,191 and 192 Sequentially alternating tamoxifen and MPA or megestrol acetate regimens are based on the concept of up-regulation of progesterone receptors by the antiestrogen. 182 Other laboratory studies indicate the presence of specific binding sites for LHRR and for androgen receptors. 182 Supplementing clinical observations with molecular correlates of response may bring out some differences that are currently not apparent and also possibly lead to crossover hormonal therapies, a concept that has been useful in breast cancer treatment. The rational selection of specific hormonal manipulations from laboratory findings may become more feasible with the wider applicability of molecular immunohistochemical probes.

CYTOTOXIC CHEMOTHERAPY.

Overview of Clinical Trials. Most women with recurrent or stage IV endometrial cancers, except for those with well-differentiated and receptor-positive metastases, must be assessed for treatment with cytotoxic chemotherapy. Doxorubicin and its analogue epirubicin have shown reproducible antitumor activity in phase II and III trials 193,194 These phase III studies have indicated that the addition of cyclophosphamide to doxorubicin improves neither response nor survival rates and suggest that the incorporation of progestogens does not improve results 195,196 and 197 (Table 36.3-5). A number of other drugs studied by the GOG and others also have shown little efficacy but often have been used in combinations. On the other hand, cisplatin and carboplatin both show consistent antitumor activity, 197,198,199,200,201,202 and 203 and a phase III study combining cisplatin with doxorubicin showed superior progression-free survival over doxorubicin alone. 204 However, the overall median survival rate for patients receiving doxorubicin plus cisplatin was not improved. Other agents with single-agent activity include paclitaxel, 205,206 ifosfamide, 204 and oral etoposide. 207,208 Paclitaxel (250 mg/m²) given on a 24-hour infusion schedule and requiring cytokine support with filgrastim showed remarkable activity, 209 with four complete responses and six partial responses among 28 patients. A 24-hour infusion of 150 mg/m² 209 is being tested in phase III studies in combination with doxorubicin. Shorter infusions of paclitaxel have activity with less myelosuppression 209 and are often used in combination with carboplatin 210 or in three-drug combinations. 211 Regimens of platinum and taxanes also have activity against papillary serous cancers 212 and are, therefore, replacing doxorubicin-containing regimens in this condition. 213 On the other hand, the addition of intraperitoneal cisplatin to doxorubicin plus cyclophosphamide did not have an encouraging outcome. 214 In ongoing pilot studies with radiation, platinum and particularly cisplatin are favored. 214

TABLE 36.3-9. Cytotoxic Drug Trials Showing Activity in Women with Endometrial Carcinoma

Carboplatin is the preferred drug when added to paclitaxel because of its lower incidence of severe neurotoxicity relative to cisplatin.

Biologic and Pharmacologic Considerations. Laboratory and clinical studies should better define the role of systemic chemotherapy in relation to various known biologic factors in an analogous way to how pathologic features and hormone receptors have assisted in refining hormonal therapies. Endometrial cancers commonly express P-glycoprotein (Pgp). Studying the mechanisms of drug resistance mediated by multidrug resistance gene 1(MDR1)-mediated Pgp may assist in identifying doxorubicin- and paclitaxel-resistant tumors. 191 Moreover, mutations in p53 occur somewhat concordantly with the expression of Pgp and may help to define a more resistant subpopulation. A relationship between progestosterone and the expression of Pgp also has been postulated, 195 prior progestogen therapy might lead to changes in Pgp expression. The epidermal growth factor receptor and HER-2/neu are also likely to be important in determining chemosensitivity and outcome, as well as therapeutic targets. 196,197 Studies are beginning to focus on special subtypes, such as papillary serous and clear cell carcinomas, that not only have a propensity to metastasize early but may also have altered drug sensitivities. Several investigators have known that p53 mutations are more frequent in these cell types and are indicative of poor prognosis. Microsatellite instability, persistence of bcl-2, 219 and high proliferation indices may also be of prognostic significance.

Radiotherapy

Vaginal recurrences of endometrial carcinomas can often be successfully treated with radiation therapy if there is no evidence of extrapelvic disease. For patients whose initial treatment was hysterectomy alone, vaginal recurrence is usually treated with a combination of external-beam irradiation and intrauterine or interstitial brachytherapy, depending on the extent and distribution of disease. Technical considerations are similar to those for primary vaginal carcinoma.

With this treatment, reported 5-year survival rates for patients who have isolated recurrences in the vaginal apex are usually 40% to 60%. 213,214,215,216,217,218 Outcome is correlated with the recurrent tumor’s grade, size, and extent and the time to recurrence. 215,216,217,219,220,221 Sears et al. 219 reported 5-year survival rates of 74% and 30% for patients with tumors measuring 2 cm or less, or more than 2 cm, respectively, which suggests that early detection and treatment may be important. These authors also reported significantly better survival rates for patients who had a portion of their treatment given with brachytherapy. Distal vaginal recurrences are less common but may also be cured with irradiation if there is no other evidence of recurrent cancer. 213,214,215,216,217,218 If possible, the inguinal nodes should be treated when the distal vagina is involved.

The prognosis is much poorer for patients who have recurrent tumor on the pelvic wall. 213,214,215,216 However, there are anecdotal reports of prolonged disease-free survival after locoregional treatment. 213,214 Recurrence isolated to inguinal nodes should be treated aggressively because cures have been reported after treatment with irradiation. 216

Surgery

Surgery plays a limited role in the management of recurrent endometrial cancer. Although cytoreduction is probably valuable for women with advanced primary cancers, secondary cytoreduction after failure of primary therapy has no real role because of the lack of effective regional or systemic therapy. Two legitimate
indications for surgical management are attempted curative resection of central pelvic recurrence by exenteration and palliative treatment in selected clinical situations.

Historically, ultraradical resection of recurrent endometrial cancer has not been recommended because of the perception that systemic spread was too common. However, reviews that have examined carefully evaluated patients have identified a subset of women whose recurrence is limited to the pelvis. Cure rates of 40% to 50% have been obtained after resection by pelvic exenteration. These values are comparable to those reported for the treatment of central recurrence in patients with cervix cancer. Consequently, patients who have recurrent disease that is clinically limited to the central pelvis and have not been successful with radiotherapy should be considered candidates for curative resection. A diligent search for subclinical metastatic disease should be carried out before exploration and at the time of operation.

Palliative surgery is largely limited to patients with intraabdominal recurrences causing bowel obstruction or pain. Candidates for palliative operations must have realistic expectations as to the goals of surgery, and the planned procedure should have a reasonable chance of achieving the desired goal. The patient's life expectancy and clinical status should be adequate for the proposed procedure and the anticipated recovery. The operation performed should be the minimum procedure with the lowest risk capable of correcting the problem. Heroic operations attempted in patients with no chance for long-term survival are pointless.

**OUTCOME AND SURVIVAL**

Long-term survival of patients with endometrial cancer is clearly related to their surgical stage and substage. Representative 5-year survival rates by stage are 90% for stage I, 60% for stage II, 40% for stage III, and 5% for stage IV. Because the vast majority of patients have stage I disease and because there is a wide variation in survival based on risk profile within this stage, most research into postoperative adjuvant therapy is aimed at subsets of stage I patients. It is anticipated that the routine use of surgical staging will result in a more homogeneous subgrouping of similar risk patients and allow a more reliable prediction of survival potential. Selected patients with advanced disease that can be encompassed by surgical resection with or without adjunctive irradiation can be cured. However, few patients meet such criteria. Although patients with disseminated disease frequently respond to cytotoxic therapy, such responses tend to be short and provide a limited improvement in progression-free survival. As was suggested earlier, posttreatment surveillance for recurrence should be used to identify candidates for clinical trials of new agents or therapeutic approaches.

**UTERINE SARCOMAS**

**TUMOR TYPES**

Tumors with a malignant mesenchymal component account for approximately 10% of uterine fundal neoplasms. Pure uterine sarcomas of the homologous type arise from native elements, as is seen in endometrial stromal sarcoma, leiomyosarcoma, and sarcomas of nonspecific supporting tissues (fibrous tissue, vessels, lymphatics). Heterologous sarcomas may contain elements with nonnative differentiation, such as skeletal muscle, bone, and cartilage. The malignant mixed Müllerian tumor (MMT) is a mixture of carcinoma and sarcoma. Although any combination is possible, serous carcinoma admixed with endometrial stromal sarcoma is the most common histologic type. The adenosarcoma is a rare mixed tumor in which a benign epithelial component is mixed with a sarcomatous element.

**CLINICAL PRESENTATION**

Uterine sarcomas exhibit the typical gross features of similar tumors at other sites—firm, fleshy growth with areas of hemorrhage and necrosis. The initial growth phase of most sarcomas is within the fundal portion of the uterus. If the tumor involves the endometrial cavity, postmenopausal or abnormal vaginal bleeding is common. Tumors that have a polypoid growth configuration may prolapse through the cervix to present as an upper vaginal mass. This presentation is most often seen with MMTs.

Extensive local growth is another common clinical presentation. Once the tumor has penetrated the uterine serosa, it can rapidly attach to adjacent pelvic structures or loops of bowel positioned in the pelvis (Fig. 36.3-6). This locally advanced pelvic tumor presentation is typical of leiomyosarcoma. Patients with locally advanced cancers have symptoms related to an expanding pelvic mass (fullness, pressure, pain, urinary frequency) or to entrapment and destruction of adjacent organs (hematuria, tenesmus, rectal bleeding, bowel obstruction, fistula).

**FIGURE 36.3-6.** Uterine sarcomas tend to present as large, fleshy central pelvic tumors. This leiomyosarcoma has replaced most of the uterine fundus and penetrated the serosa to engulf the adnexa and directly contact intraperitoneal structures.

As is seen for epithelial tumors of the uterus, distant spread from uterine sarcomas may occur by a variety of mechanisms. Intraabdominal and retroperitoneal nodal metastases are frequently associated with the MMT. This is not as surprising because the epithelial component is usually papillary serous carcinoma and predominates within metastatic sites. Consequently, patients with advanced MMT follow a clinical pattern similar to that of women with epithelial ovarian cancer. All uterine sarcomas have a propensity for hematogenous dissemination. Pulmonary metastases are most frequently observed. Other sites include liver, bone, and brain. Women with distant spread at the time of diagnosis have symptoms and examination findings based on the location of their disease.

**EVALUATION**

Uterine sarcoma should be suspected in any postmenopausal women with an enlarging central pelvic mass. If the tumor projects into the uterine cavity or has partially prolapsed through the cervix, an endometrial or direct biopsy should provide a tissue diagnosis. Evaluation by an experienced pathologist is critical because uterine sarcomas are rare and the biopsy material is often fragmented or necrotic. Tumors originating within the uterine wall require exploratory laparotomy and hysterectomy to establish a diagnosis. Because primary therapy usually includes hysterectomy, the preoperative evaluation should focus on a search for disease at common metastatic sites and assessment of operative risk.

When the diagnosis of sarcoma is known or suspected, the pretreatment evaluation should include a careful history and physical examination, chest radiograph, and laboratory studies. The CA-125 level may be elevated in some cases, particularly in MMT tumors with peritoneal spread. Other markers have not been consistently useful. Computed tomography of the abdomen and pelvis may be helpful in identifying occult extraperitoneal disease. Cystoscopy, proctosigmoidoscopy, and barium enema should be performed in patients with advanced pelvic disease. Brain, bone, or liver imaging should be considered in patients with abnormal physical or laboratory findings.

**TREATMENT**

Surgery
Patients in whom the diagnosis of uterine sarcoma is not anticipated often undergo hysterectomy for a presumed diagnosis of uterine leiomyoma or “central” pelvic mass. Although most of these cases are not surgically staged, many are apparently stage I tumors. When the diagnosis of sarcoma is established and hysterectomy is technically feasible, surgical resection of the primary tumor should be attempted. Such surgery may be curative for tumors confined to the uterus. Because of the overall poor prognosis associated with uterine sarcomas, we proceed with extended surgical staging similar to that used for patients with endometrial adenocarcinoma when disease is clinically limited to the uterus. Although a survival benefit to surgical staging has not been demonstrated, knowledge of the true extent of disease is helpful in selecting therapy options.

In more extensive disease cases, resection or debulking of the central tumor can provide important palliation of bleeding and pain. Tumor reduction may enhance the ability of postoperative adjunctive therapy to extend survival, but this concept is not as well established as in epithelial ovarian tumors. The aggressiveness of the surgical approach must include a balance between the desire to remove as much tumor as possible and the risks of additional operative procedures. Patients with widespread or bulky unresectable disease should not be subjected to high-risk operations under the guise of cytoreduction.

Occasionally, surgical intervention is indicated in women with advanced or recurrent disease, but such situations are clinically uncommon. Some women have obtained long-term survival and apparent cure after resection of an isolated pulmonary metastasis. Exploration to palliate bowel obstruction or fistula is appropriate in selected refractory disease patients who have a good performance status and reasonable projected survival time. Potentially morbid palliative operations in women with terminal disease should be avoided whenever possible.

Radiotherapy

MIXED MÜLLERIAN TUMOR. The role of radiation therapy in the management of carcinosarcoma is controversial. Patients are frequently treated with postoperative pelvic radiotherapy, but irradiation has never been proven to influence survival. Retrospective comparisons of treatments are invariably biased by physicians’ tendencies to select treatment on the basis of known prognostic indicators. No randomized study has directly compared patients with similar prognostic features who were treated with or without radiotherapy.

Most retrospective reviews of patients with carcinosarcoma have demonstrated a lower rate of pelvic tumor recurrence in patients who received postoperative pelvic irradiation. In most cases, this has not resulted in a demonstrable improvement in the survival rate. However, few studies have evaluated risk factors that could have influenced treatment selection. Potential bias and the small number of patients in most studies have made it impossible to determine the efficacy of treatment.

The GOG retrospectively evaluated its experience in two studies. Hornback et al. reviewed the influence of pelvic radiotherapy in a study originally designed to evaluate the role of doxorubicin. In this study, radiotherapy was given at the discretion of the investigator. In 109 patients with stage I or II disease (95 of whom had carcinosarcoma), the pelvis was the first site of recurrence in 49 patients (10%) who had radiation therapy versus 14 of 60 patients (23%) treated with surgery alone. However, irradiated patients had a higher rate of distant metastasis, and no significant difference in the 2-year survival rate was reported. In a more recent review of another GOG study, the pelvis was reported to be the first site of recurrence in 17% and 24% of patients with carcinosarcoma treated with or without postoperative irradiation, respectively. The overall relapse rates were not significantly different. As with other reviews, because the tumor stage, grade, and depth of invasion and rates of lymph node involvement were not compared for patients receiving different treatments, the efficacy of radiotherapy cannot be determined from these studies.

LEIOMYOSARCOMA AND ENDOMETRIAL STROMAL SARCOMA. Few studies have separately reported control rates for patients treated with radiotherapy for leiomyosarcoma, and the numbers of patients are too small to evaluate efficacy. Patients with close surgical margins may benefit from postoperative irradiation. Because lymph node metastasis from leiomyosarcoma is uncommon, treatment of the operative bed (usually the lower pelvis) may be sufficient in most cases.

Several authors reporting small series of patients with endometrial stromal tumors have commented on the role of radiotherapy, either suggesting that it is effective or ineffective. Berchuck et al. reported dramatic responses in two of three patients who had measurable tumor. One patient remained free of disease for more than 10 years after treatment. However, reports of radiotherapy for these tumors are little more than anecdotal, and further study is needed to define the role of radiotherapy adequately.

Chemotherapy and Hormonal Therapy

Differences in the management of metastatic uterine leiomyosarcomas and MMMTs with respect to systemic chemotherapy have been established, and separate trials are conducted for these two entities (Table 36.3-10 and Table 36.3-11). Endometrial stromal sarcomas are less common and usually not included in clinical trials. Because antitumor activity of chemotherapy regimens has been documented in advanced stages, several trials are ongoing or planned in earlier stages of disease. Evidence to support the use of chemotherapy as an adjuvant to surgery is not yet forthcoming. One randomized study of the addition of doxorubicin after surgery in stage I and II uterine sarcomas yielded no advantage for the adjuvant chemotherapy group.

<table>
<thead>
<tr>
<th>TABLE 36.3-10. Selected Cytotoxic Drug Trials in Uterine Leiomyosarcomas</th>
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<td>TABLE 36.3-11. Selected Cytotoxic Drug Trials in Uterine Mixed Mesodermal Tumors</td>
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In mixed mesodermal tumors of stage I, II, and III, a GOG trial begun in 1983 is comparing whole abdominal radiation to chemotherapy with cisplatin and ifosfamide. These trials require several years to complete, a difficulty compounded by the evolving nature of the adjuvant treatments that are applied.

LEIOMYOSARCOMA. Doxorubicin was shown to be an effective drug against leiomyosarcomas arising in the uterus. Drug combinations were claimed to improve results, but both childhood and adult sarcomas of extraterine origin, but the addition of dacarbazine to doxorubicin did not improve the survival of patients with metastatic uterine sarcomas beyond that obtained with doxorubicin alone. Response rates were, however, significantly better in the doxorubicin plus dacarbazine arm. A subsequent randomized study also performed by the GOG failed to show that the addition of cyclophosphamide in modest doses was advantageous over doxorubicin by itself. The alkylating agent ifosfamide has modest activity, but does not add substantially to the therapeutic efficacy of doxorubicin. Other drugs, such as cisplatin, etoposide, and paclitaxel, have also been evaluated and have modest to minimal activity. A combination of ifosfamide, etoposide, and dacarbazine had antitumor activity without major toxicities.

MIXED MüLLERIAN TUMOR. Ifosfamide and cisplatin have greater antitumor activity against uterine MMT than does doxorubicin. Accordingly, the two drugs in combination have been explored in all stages and also compared with ifosfamide alone in advanced, persistent, or recurrent disease. The results indicate an improvement in survival in terms of progression-free survival, but nearly equivalent median survival at a cost of increasing toxicity. The combination is being administered to completely resected stage I and II MMTs of the uterus (GOG 117), but the assessment will require a comparison to historical controls. Taxanes, such as paclitaxel, have been evaluated, and this agent has already formed part of an active combination with the pegylated liposomal doxorubicin, Doxil. Experience with a number of other platinum-based combinations has been reported in very small series. These should be regarded as leads for future trials rather than a reliable indicator of activity.

ENDOMETRIAL STROMAL SARCOMA. The systemic treatment of endometrial stromal sarcoma is guided by reports from individual institutions (23,24,25,26) and case reports.27 The tumor’s relative rarity does not support the conduct of clinical trials. Because of the presence of hormonal receptors in low-grade (fewer than ten mitoses per high-power field) tumors, hormonal therapy has been advocated.28 However, high-grade tumors are treated with chemotherapy,29 investigation of biologic and pharmacologic issues may point for the hypothesis-driven drug trials.

BIOLoGIC AND PHARMACOloGIC CONSIDERATIONS. The growth of benign leiomyomas is under both estrogenic and progesterone control.30,31 Accordingly, the study of receptors and hormone-action inhibitors for antitumor activity may be relevant to the management of malignant smooth muscle tumors.32 Receptors and hormone action have also been studied in endometrial stromal sarcomas.33,34 and justify exploration of inhibition or depletion of hormonal mediators in the management of these tumors. Overexpression in MDR2 and p53 have been noted in some uterine sarcomas, but not in leiomyomas.35 For the development of cytotoxic therapy, the role of MDR1-mediated Pgp expression in determining resistance to doxorubicin has been investigated in a cell line from a leiomyosarcoma of the uterus and its doxorubicin-resistant derivative.36 Drugs that are substrates for Pgp may restore sensitivity to doxorubicin in this resistant variant. Trials of such resistance-reversing agents, including the cyclosporin analogue PSC-833, may lead to a reassessment of the potential for drugs such as doxorubicin, taxanes, and vinca alkaloids in the treatment of these traditionally refractory tumors.

OUTCOME AND SURVIVAL

Stage is the most significant predictor of outcome for women with uterine sarcoma. Patients whose tumors are confined to the uterus have a survival rate of 60% to 70% after surgical resection. Major sites of failure include the pelvis, upper abdomen, and lung. Few well-conducted prospective adjuvant therapy trials have been accomplished, so a precise role for either adjuvant irradiation or chemotherapy remains undefined. As has been noted for endometrial carcinoma, adjuvant pelvic irradiation may reduce the rate of pelvic failure without improving survival if more patients succumb to distant failure. Pelvic irradiation and local tumor control may be an important issue in tumors with extension to the cervix. However, so few patients are placed in this category that meaningful treatment data are not available.

Very few patients with tumor spread outside of the uterus can be curatively treated. Some women with small-volume regional disease have obtained long-term survival after external-beam irradiation. However, most patients with advanced or recurrent disease ultimately experience disease progression and die. These women are excellent candidates for new therapeutic trials.

REFERENCEs


Clinical Features and Staging

Choriocarcinoma

Finally, the ratio of serum to cerebrospinal fluid b-HCG has been used to identify brain metastases if such a ratio is less than 60:1.

Other tumor marker measurements may assist in the management of gestational trophoblastic disease: The placental-site trophoblastic tumor produces low levels of HCG in the presence of luteinizing hormone. Normally, HCG peaks at 10 to 12 weeks of gestation, and actual levels and serial changes in b-HCG are essential to

Persistence may...
Metastatic disease occurs in 4% of patients after local management of hydatidiform moles and very rarely after term pregnancies (1 in 40,000) or abortions. Rapid growth and a high propensity for hemorrhage make this tumor a medical emergency. Metastases are found in lung (80%), vagina (30%), pelvis (20%), brain (10%), and liver (10%). Other rare sites are the spleen, kidneys, and gastrointestinal tract. The lungs are often involved with multiple lesions, and at times this involvement is massive at presentation, leading to respiratory insufficiency. On the other hand, early detection in the asymptomatic state may take place through computed tomography in cases with persistent moles. The central nervous system is seldom involved in the absence of pulmonary metastases.

Anatomic staging of choriocarcinoma (I, confined to corpus; II, metastases to pelvis and vagina; III, pulmonary metastases with or without uterine, pelvic, or vaginal involvement; and IV, other metastases, such as brain, liver, kidneys, or gastrointestinal tract) is seldom used. Therapeutic planning relies on the scoring system based on prognostic factors that was developed at the Charing Cross Hospital by Bagshawe and later adopted by other groups, including the World Health Organization (Table 36.4-1). The importance of this scoring system lies in the identification of a high-risk choriocarcinoma that requires more intensive use of drug combinations to achieve cures and prevent emergence of resistance.

### Table 36.4-1: Prognostic Scoring System for Gestational Trophoblastic Disease

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The total score for a patient is obtained by adding the individual scores for each prognostic factor, with a score of 4 being considered low risk, a score of 5 to 7 as intermediate risk, and a score of greater than 7 as high risk.

### Treatment

Chemotherapy is highly effective for all forms of gestational trophoblastic disease. The curative effects of methotrexate in a disease that had previously resulted in the death of 60% of patients with disease confined to the uterus and 90% of patients with metastatic disease heralded the era of modern chemotherapy. The current challenges are to provide the proper follow-up after evacuation of hydatidiform moles, to balance drug administration with surgical interventions when more invasive trophoblastic disease is present, and finally to tailor the type of chemotherapy to the risk group of gestational trophoblastic disease that has been identified. The scoring system in Table 36.4-1 assists in reaching decisions, but the expertise of a multidisciplinary team cannot be overemphasized. In particular, hysterectomy and single-agent chemotherapy must be considered in stage I disease depending on the patient's desire for future fertility. In this circumstance, chemotherapy reduces dissemination during surgery and treats any occult metastases not previously detected.

The therapeutic regimens for low-risk disease based on the scoring that has been developed have sought to maximize efficacy while minimizing toxicity. As shown in Table 36.4-2, these regimens have consisted of methotrexate by itself or with leucovorin rescue or daunorubicin. Monitoring with b-HCG to document a prompt 1 log reduction in the titer in 18 days, along with continued monthly monitoring of negative values for 1 year, is standard practice. In small series, most patients failing to achieve a satisfactory response to methotrexate were adequately treated with daunorubicin or etoposide. Myeloid leukemia and secondary cancers are a concern with etoposide, which is not encouraging for its use in low-risk patients. Therefore, current Gynecologic Oncology Group studies for low-risk disease are comparing methotrexate with daunorubicin and also assessing daunorubicin in patients not responding to methotrexate.

### Table 36.4-2: Drug Regimens for Gestational Trophoblastic Disease

In intermediate- and high-risk patients, combination chemotherapy is the treatment of choice, and the serum EMA-CO (etoposide, daunorubicin, and folinic acid; vincristine and cyclophosphamide) combination (see Table 36.4-2) is most commonly used. This combination was introduced after recognition of the activity of etoposide, even after failure of other drug regimens, including those for low risk plus cyclophosphamide, vincristine, doxorubicin, hydroxyurea, and 5-fluorouracil. The Gynecologic Oncology Group has used a combination of methotrexate, daunorubicin, and chlorambucil (MAC) with excellent results in intermediate risk patients. Familiarity with one regimen ensures greater safety and proper application.

Results with EMA-CO are excellent in intermediate risk and most high-risk disease patients. However, approximately 20% of patients, predominantly high-risk or intermediate risk who are methotrexate resistant, do not show a complete response. Some of these patients may be salvaged, or could be treated when methotrexate resistance is identified, with regimens containing cisplatin. Deaths from choriocarcinoma usually result either from very late presentations leading to complications such as respiratory failure or central nervous system hemorrhage, or from the development of drug resistance if the tumor burden is excessive at the outset or if treatment has not been sufficiently aggressive. In any event, for germ cell tumors and other gynecologic cancer, resistance to cisplatin determines an unfavorable outcome. Experimental strategies to overcome such resistance include dose intensification, analog development, and use of new drugs such as taxanes and topoisomerase I inhibitors, although experience is limited. In addition, radiation and surgical resection of metastases may play a role. Specifically, radiation given concomitantly with chemotherapy has been advocated from the outset in patients who have brain metastases to decrease the risk of hemorrhage. A dose of 3000 cGy given over 10 fractions has been found satisfactory.

### Chapter References


OVARian CANcer

On the basis of distinct clinical and pathologic features, ovarian carcinomas can be separated into three major entities: epithelial carcinomas, germ cell tumors, and stromal carcinomas. The vast majority of ovarian carcinomas are epithelial in origin, accounting for more than 90% of the estimated 25,200 new cases of ovarian cancer diagnosed in 1999 in the United States.1 Fallopian tube carcinomas and extraovarian peritoneal carcinomas are much less common, but because of marked similarities to ovarian epithelial carcinomas in their biology and clinical presentation, these tumors also are considered in this chapter. Approximately 14,500 women died in the United States of ovarian cancer in 1999, making this tumor the leading cause of death from a gynecologic cancer.2 Overall, ovarian cancer accounts for 4% of all cancer diagnoses and 5% of all cancer deaths. The lifetime risk of further development of ovarian cancer is approximately 1.5%, and 1 woman in 100 will die of the disease.3

The vast majority of epithelial ovarian carcinomas are diagnosed in postmenopausal women, and the median age at diagnosis is 63 years. The age-specific incidence increases from 15 to 16 per 100,000 in the 40 to 44 age group to a peak rate of 57 per 100,000 in the 70 to 74 age group.4 Since the late 1970s, there has been little change in incidence or mortality rates.5 However, a statistically significant increase in 5-year survival rates has been seen—36% in 1970 versus 50% in 1994.6 This improvement in survival is likely the result of more effective platinum-based chemotherapy and improvements in surgery and supportive care. African American women in the United States have a lower incidence (10.3 per 100,000 women) compared with white women,7 and the stage-specific 5-year survival rates for white and African American women are similar: localized disease, 96% versus 91%; regional, 80% versus 78%; and advanced disease, 28% versus 24%, respectively.8

The biology and carcinogenesis of ovarian cancer is detailed elsewhere in this text (see Chapter 36.1). Hormonal, environmental, and genetic factors all have been identified as playing an important role in the development of ovarian cancer.

A family history is the single most important risk factor for the development of ovarian cancer. However, the vast majority of ovarian cancers are sporadic in nature. Fewer than 10% of cases can be defined as hereditary ovarian cancer (at least two first-degree relatives with ovarian cancer) in which predisposition for the disease follows a classic pattern of autosomal dominant transmission with a variable degree of penetrance. Two distinct clinical syndromes associated with hereditary ovarian cancer have been identified in which there is a germline inheritance of a mutant gene that is transmitted in an autosomal dominant manner and leads to increased susceptibility to ovarian cancer. The hereditary breast-ovarian cancer syndrome (HBOC) is the most common of these and accounts for 85% to 90% of all hereditary ovarian cancer cases currently identified.9 The majority of these tumors are associated with mutations of the BRCA1 locus, in which more than 100 mutations have been thus far identified. A second breast-ovarian cancer susceptibility gene, BRCA2, has been localized to chromosome 13q12.10 BRCA2 shares structural and functional similarities with BRCA1 and also appears to be involved in cell progression and cell differentiation.

Initial family pedigree studies revealed multiple cases of ovarian cancer without any increase in breast cancer, and this finding led to the possibility of a site-specific form of ovarian cancer.11 However, linkage studies have failed to identify additional loci other than BRCA1, which suggests site-specific manifestation is not a distinct hereditary syndrome but rather represents a variant of HBOC in which early-onset breast cancer is infrequent.12 It also has been demonstrated that hereditary ovarian cancer is a component of the hereditary nonpolyposis colorectal cancer syndrome (HNPPC).13 HNPPC is an autosomal dominant genetic syndrome that is also known as Lynch syndrome II.14

Ovarian cancer associated with germline mutations of BRCA1 appears to present with distinct clinical and pathologic features compared with sporadic ovarian cancer.15 The vast majority of BRCA1-associated cancers are serous adenocarcinomas, with an average age at diagnosis of 48 years. BRCA1-associated cancer may have a more favorable course than sporadic ovarian cancer. In a study by Rubin et al.,16 they reported a median survival of 77 months in 43 patients with advanced BRCA1-associated disease compared with 29 months for matched controls. These results have been confirmed in some, but not all, retrospective studies. A large prospective study is currently in progress by the Gynecologic Oncology Group (GOG) to compare the clinical course of sporadic ovarian cancer with that associated with BRCA1 and BRCA2 mutations.

Close surveillance and screening with transvaginal sonography is frequently used in women at high risk for hereditary ovarian cancer, although there is no evidence yet that such an approach decreases mortality.17 The National Institutes of Health Consensus Development Panel has recommended that prophylactic oophorectomy be strongly considered in women with hereditary ovarian cancer at age 35 years or after childbirth is completed. However, an increased risk remains for peritoneal carcinomatosis in women with hereditary ovarian cancer, which persists after prophylactic oophorectomy. Oral contraceptives, however, may reduce the risk of ovarian cancer in women with mutations in the BRCA1 or BRCA2 gene. Narod et al.18 demonstrated that use of oral contraceptives for 6 or more years is associated with a 60% reduction in risk in a study of 207 women with hereditary ovarian cancer with 161 of their sisters as controls. These data strongly suggest that oral contraceptive use should be considered in the prevention of cancer in women with BRCA1 or BRCA2 mutations. In addition, it is essential that patient education and counseling by trained geneticists be part of any risk-assessment program.

PATHOGENESIS

The common epithelial tumors account for 60% of all ovarian neoplasms and for 80% to 90% of ovarian malignancies. The remaining tumors arise from germ or stromal cells. The epithelial tumors arise from the surface epithelium, or serosa, of the ovary. During embryogenesis, the lining of the celomic cavity consists of mesothelial cells of mesodermal origin, and the gonadal ridge is covered by serosal epithelium. Müllerian ducts, which give rise to the fallopian tubes, uterus, and...
vagina, are the result of invagination of the mesothelial lining. When the epithelium becomes malignant, it can express a variety of Müllerian-type differentiations. Serous carcinomas can resemble the fallopian lumen, mucinous tumors the endocervix, endometrioid carcinomas the endometrium, and clear cell tumors can resemble endometrial glands occurring in pregnancy. It is thought that germ cell tumors originate in a primitive streak and can migrate to the gonads. The mesenchyma gives rise to the ovarian stroma, and stromal tumors arise from this cell type.

The most common form of dissemination of epithelial tumors throughout the peritoneal cavity is by exfoliation of malignant cells through the surface of the ovarian capsule. The circulation of the peritoneal fluid to the undersurface of the right hemidiaphragm facilitates the widespread dissemination of malignant tumor cells. All intraperitoneal surfaces are at risk. In addition, the omentum is a frequent site of tumor growth. Tumor spread also occurs via the lymphatics from the ovary. A primary source of drainage follows the ovarian blood supply in the infundibulopelvic ligament to lymph nodes around the aorta and vena cava to the level of the renal vessels. There is also lymphatic drainage through the broad ligament and parametrial channels; consequently, pelvic sidewall lymphatics, including the external iliac, obturator, and hyperaortic chains, are also frequent sites of lymphatic metastases from ovarian primary tumors. More rarely, spread may occur along the course of the round ligament, resulting in involvement of inguinal lymph nodes. Spread to lymph node is common, and approximately 10% of patients with ovarian cancer that appears to be localized to the ovaries have metastases to paraaortic lymph nodes. Retroperitoneal lymph node involvement is found in the majority of cases of advanced ovarian cancer when the disease has spread throughout the peritoneal cavity.

The dissemination of ovarian cancer can be clinically occult. As is described later in the section Staging, surgical staging requires meticulous histologic examination of visually normal tissues throughout the peritoneal cavity because microscopic disease frequently is detected in the undersurfaces of the diaphragm and other peritoneal sites. Hematogenous metastases to extraabdominal sites can occur but is uncommon. There can be direct extension of the tumor from the ovary to involve the peritoneal surfaces of the bladder, rectosigmoid, and pelvic peritoneum.

HISTOLOGIC CLASSIFICATION OF EPITHELIAL TUMORS

Table 36.5.1 details the classification of common epithelial tumors that has been developed by the World Health Organization and the International Federation of Gynecology and Obstetrics. The nomenclature for these tumors reflects the cell type, location of the tumor, and degree of malignancy, ranging from benign epithelial tumors to tumors of low malignant potential to invasive carcinomas. Tumors of low malignant potential (“borderline malignancy”) have an excellent prognosis compared with invasive carcinomas, and their clinical behavior and management is described later in the section Borderline Tumors. Tumors of low malignant potential are characterized by epithelial papillae with atypical cell clusters, cellular stratification, nuclear atypia, and increased mitotic activity. The differentiation between these tumors and carcinomas is primarily made on the architectural basis of invasion. Frankly malignant tumors are characterized by an infiltrative destructive growth pattern, with malignant cells growing in a disorganized pattern and dissection into stromal planes.

Table 36.5-1. World Health Organization Classification of Malignant Ovarian Tumors

The invasive epithelial carcinomas are characterized by histologic type and grade (the degree of cellular differentiation). The histologic type has limited prognostic significance independent of clinical stage. Histologic grade is an important independent prognostic factor in patients with early-stage epithelial tumors. Grading systems have been based on cytologic detail or a pattern grading classification based on the degree to which a tumor forms papillary structures or glands versus solid tumor. The relative prognostic value of histologic subtype and grade compared with other surgical and biologic factors is discussed in the section Prognostic Factors.

DIAGNOSIS AND SYMPTOMS

Epithelial cancers of the ovary have been described as a silent killer because the overwhelming majority of patients present with disease that has spread outside of the ovary and indeed outside of the pelvis at the time of initial presentation. Approximately 70% of patients with epithelial cancers of the ovary present with stage III or IV disease, whereas 70% of patients with germ cell ovarian malignancies present with stage I disease. Unlike epithelial cancers, ovarian germ cell malignancies tend to stretch and twist the infundibulopelvic ligament, causing severe pain while the disease is still confined to the ovary. Functioning ovarian tumors of the sex cord–stromal type may present with symptoms suggestive of excessive endogenous estrogen or androgen production. Granulosa cell tumors occurring in premenarchal women present with precocious puberty. Women in the reproductive years with granulosa cell tumors present with amenorrhea, and postmenopausal women may present with postmenopausal bleeding. Sertoli-Leydig cell tumors may present with symptoms of virilization.

Abdominal discomfort and bloating are the most common symptoms experienced by women with epithelial ovarian cancers, followed by vaginal bleeding, gastrointestinal symptoms, and urinary tract symptoms. Patients presenting with nonspecific lower abdominal discomfort and bloating require a prompt and careful pelvic examination. Not performing routine rectovaginal pelvic examinations may result in women with relatively early-stage ovarian cancer having a delay in diagnosis. Papanicolaou smear screening is inadequate for identifying ovarian cancer, although 1% to 2% of women seen at the Yale–New Haven Medical Center with ovarian cancer have an abnormality on their Papanicolaou smear suggesting the presence of an adenocarcinoma not of cervical origin.

Barber and Graber have recommended that a palpable ovary in a postmenopausal woman is an indication for surgery. This report in 1971 predated the modern era of ultrasonic technology. The identification of an adnexal mass on routine pelvic examination is now an indication for diagnostic ultrasonic evaluation. Advances in endovaginal ultrasound and color Doppler flow techniques have resulted in identifying characteristics of pelvic masses that either make them highly suggestive to be benign or highly suggestive for malignancy (Fig. 36.5-1). Morphology indices have been developed to indicate the likelihood of pelvic masses being malignant. Kurjak et al. have reported that particular color Doppler flow patterns and resistive indices are characteristic of malignant pelvic masses. Taylor and Schwartz have presented data suggesting that resistive indices and pulsatility indices are not always effective in distinguishing benign masses from pelvic masses. As a general rule, an adnexal mass suspicious for malignancy by ultrasound morphology criteria is probably the best technique available short of biopsying the mass to identify which masses are most likely malignant.

FIGURE 36.5-1. Endovaginal ultrasound with color Doppler flow studies demonstrating an epithelial ovarian cancer. (Courtesy of Dr. Kenneth J. W. Taylor.)
The most common complaints associated with ovarian malignancies in the pediatric population are pain, abdominal swelling, and pelvic mass. Ovarian masses in premenarchal women require prompt evaluation and an exploratory laparotomy, because functional cysts do not occur in this group. Most premenarchal women with adnexal masses have benign disease.

Small ovarian cysts are often identified with use of ultrasound examinations of postmenopausal ovaries. Approximately 8% to 9% of postmenopausal women who do not have clinically palpable ovaries are found by ultrasound examination to have ovarian cysts between 1.5 to 3.0 cm in size. These cysts do not need to be removed if they appear to be unilocular and are associated with a normal level of CA-125 and normal color Doppler flow studies. Postmenopausal women with complex pelvic masses, simple cysts in association with elevated serum CA-125 levels, or simple cysts in association with abnormal color Doppler flow studies should undergo prompt surgery.

Enlarged ovaries in reproductive-age women are relatively common and frequently are due to either functioning ovarian cysts, such as endometriomas and corpus luteum cysts, or to benign ovarian cysts. Women found to have such cysts are evaluated with serum CA-125 levels. CA-125 levels are often elevated in such patients and can be misleading if one uses the standard cutoff of 35 U/mL to distinguish benign cysts from malignancy in menstruating women. Studies suggest that a CA-125 cutoff from 65 to 200 U/mL is necessary to distinguish benign cysts from malignant cysts in premenopausal women.

Cysts that appear by ultrasound criteria to be functional in nature may be followed through several menstrual cycles. Often they disappear over this short observation interval. Functional cysts may also disappear when oral contraceptives are used. Neoplastic cysts do not disappear under the influence of oral contraceptives. Rising values of serial CA-125 assays obtained during the observation period are an indication that a malignancy may be present. In turn, CA-125 values that are stable or declining generally reflect the presence of a functional cyst. CA-125 assays should always be obtained when a woman is not actively menstruating, because menses have been associated with marked elevation of serum CA-125.

Computed tomographic (CT) scans are useful in preoperatively evaluating the extent of disease when a pelvic mass is present. CT scans are most useful when combined with oral and intravenous contrast. They allow assessment of retroperitoneal lymph nodes in the paraaortic area and the identification of intraperitoneal and mesenteric implants.

Diagnostic laparoscopy is now being used for evaluation of unexplained pelvic pain and small adnexal masses. The difficulty with the laparoscopic approach to the evaluation of pelvic masses is rupturing a malignant tumor. In general, if a stage IA ovarian tumor can be removed intact, there is little evidence that additional therapy has a major impact on survival. Survival in this situation is extremely good. However, once an ovarian malignancy has been ruptured, patients are treated with either radiation therapy or cytotoxic chemotherapy. Both treatment modalities carry with them physical as well as psychological trauma. Although there is no solid evidence that rupture of an early-stage ovarian malignancy decreases survival, avoidance of rupture of an ovarian neoplasm should be the routine method of approaching ovarian masses suspicious for malignancy.

Another technique for the diagnosis of ovarian cancer is peritoneal cytology. Aspiration of obvious ascites for cytologic assessment is routinely performed to identify malignant cells. If no ascites is present, saline may be instilled percutaneously or through the vaginal apex to flush the abdominal cavity and pelvis. The fluid is then withdrawn and sent for cytologic assessment. This diagnostic technique is quite uncomfortable for the patient and has been associated with poor patient acceptance and high false-positive results. Culdocentesis is not routinely used in the United States for the evaluation of a woman with possible ovarian cancer.

Serum CA-125 is the gold standard for tumor markers in the evaluation of pelvic masses, particularly epithelial ovarian cancers. Serum α-fetoprotein (AFP) and human chorionic gonadotropin (HCG) have been helpful in recognizing preoperatively the presence of an endodermal sinus tumor, embryonal carcinoma, choriocarcinoma, or mixed germ cell tumor. However, most young women with these diseases are not recognized preoperatively to have a malignancy. Levels of AFP and HCG are best applied in serially monitoring the effectiveness of therapy. Failure to identify preoperatively elevations of these markers does not preclude one from using them postoperatively in determining efficacy and duration of treatment for these diseases.

In summary, a woman suspected of having ovarian cancer requires a preoperative workup that should include a CT scan to evaluate the extent of disease in both the pelvis and the upper abdomen and to rule out occult alternative primary sites for the origin of the disease, such as the pancreas. A serum CA-125 measurement is useful because 80% of women with advanced ovarian cancer have elevations of CA-125. The marker may be used as a secondary support for ovarian cancer being present preoperatively, and it may be used postoperatively to confirm the effectiveness of therapy. Radiologic studies of the upper intestinal tract as well as the lower tract are not routinely recommended unless the patient is having symptoms related to the intestinal tract. A barium enema or Hypaque enema can be very helpful in determining whether there is compromise of the sigmoid colon lumen in women with obstructive symptoms.

Patients with a preoperative evaluation consistent with the diagnosis of ovarian cancer would do best if referred to a gynecologic oncologist. Survival data suggests that those patients operated on by gynecologic oncologists for early-stage and late-stage disease do better in terms of progression-free and overall survival, at least in part because of more aggressive cytoreductive surgery performed by gynecologic oncologists and more appropriate surgical staging of the patient before initiating treatment.

**STAGING**

Ovarian cancer is a surgically staged disease. Thus, it is important for physicians to be thoroughly familiar with the International Federation of Gynecologists and Obstetricians (FIGO) staging system for primary carcinomas of the ovary (Table 36.5-2). As described earlier in the section Pathogenesis, ovarian cancer spreads by direct extension to neighboring organs by exfoliating cells into the peritoneal cavity that can implant on pelvic and visceral peritoneum throughout the peritoneal cavity. It also disseminates by lymphatic spread, particularly to the pelvic sidewall lymph nodes (external iliac and obturator chains) and along the gonadal vessels to the upper common iliac and paraaortic lymph node chains (Fig. 36.5-2). Surgical staging procedures must evaluate sites to which ovarian cancer is likely to spread.

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Complete surgical staging is a necessity to properly evaluate the patient and to determine whether additional therapy should be recommended. Proper surgical staging requires that a vertical incision be made that extends from the pelvis into the upper abdomen. Subumbilical incisions do not allow the surgeon to perform complete surgical staging. On entering the peritoneal cavity, any fluid present should be aspirated and sent for cytologic studies. Peritoneal fluid, even if limited to the pelvis, is more likely to yield malignant cells than are cytologic washings. If no fluid is present, however, one should routinely irrigate the pelvis and paracolic spaces with normal saline. The fluid is then aspirated and sent to the cytology lab for evaluation. Careful inspection of the abdominal cavity should then be performed. Adhesions should be lysed to restore normal anatomy. Samples of the adhesions should be sent for microscopic evaluation.

If intraperitoneal carcinomatosis is not present, it is most appropriate to first resect the ovarian tumor and then to proceed with surgical staging. For women who are operated on for a tumor seemingly limited to one ovary, if preservation of fertility is an issue, the grossly normal opposite ovary should be biopsied or any implants on the ovarian surface should be excised. Preservation of fertility should be considered in any women of reproductive age with either a borderline malignant tumor of the ovary or an invasive epithelial cancer grossly confined to one ovary. A frozen section assessment of any abnormality involving the contralateral ovary helps guide the surgeon in determining whether to remove that ovary. Samples of pelvic peritoneum from the area of the ipsilateral infundibulopelvic and round ligaments, the cul-de-sac of Douglas, and urinary bladder are obtained. Pelvic retroperitoneal lymph nodes are removed in all patients with unilateral tumors. Patients in whom bilateral disease is suspected undergo bilateral pelvic lymph node sampling. Any enlarged pelvic retroperitoneal lymph nodes are removed, regardless of their locations. Lymphadenectomy is an important part of staging ovarian cancers, particularly when the disease is grossly limited to one ovary. In this situation, up to 20% of women have been found to have paraaortic lymph node metastases.

The vertical incision is then extended to assess disease in the upper abdomen. If gross disease is not present in the omentum, an intracolic omentectomy is sufficient for diagnostic purposes. When disease is present in the omentum, the omentum should be excised from the greater curvature of the stomach (Fig. 36.5-3). The upper abdominal evaluation continues with a careful inspection of the right hemidiaphragm, liver serosa, and parenchyma. If no disease is visually present, a 1 cm X 2 cm piece of peritoneum is excised off of the suprahepatic diaphragm, care being given to remove underlying musculature and create a pneumothorax. The spleen is then carefully inspected, as is the left diaphragm. The paracolic spaces are then evaluated, and large strips of peritoneum (3 cm X 5 cm) are removed from the left and right paracolic spaces if no obvious disease is present. The large bowel is then carefully inspected. The small intestine is evaluated, and any implants present on bowel or its mesentery are removed. The colon, either the ascending or the descending colon, is then mobilized to expose the paraaortic area. If the peritoneal cavity has been freed of bulky tumor such that the maximum residual tumor is less than 1 cm in stage III patients, retroperitoneal lymph nodes are removed by taking the fat pad from the upper half of the common iliac artery up to the level of the renal vessels. However, if bulky residual disease (greater than 1 cm) is left in the upper abdomen, there is no role for paraaortic lymphadenectomy. An international prospective randomized trial is now being conducted to determine the role of systematic pelvic and paraaortic lymphadenectomy for advanced ovarian cancer in women with 1 cm or smaller intraperitoneal residual tumor. In postmenopausal women or women in whom fertility is no longer desired, one should routinely perform a bilateral salpingo-oophorectomy and total abdominal hysterectomy. The hysterectomy is performed because the serosal surface of the uterus is a large peritoneal surface for implantation of malignant cells. In addition, field effects may be present whereby the epithelium of the fallopian tubes or uterus are involved with premalignant or malignant processes. The latter changes cannot be grossly recognized at the time of surgery.


POSTSURGICAL STAGING

Understaging occurs rather frequently at the time of the initial surgery for ovarian malignancies, especially when the preoperative diagnosis is that of a benign process. This leads to use of inappropriate incisions that does not allow complete surgical staging when the diagnosis of a malignancy is recognized intraoperatively. At other times, it is due to a lack of familiarity with commonly accepted surgical staging procedures.

The issue of the inadequately staged early-stage patient with ovarian cancer is a difficult one. The simplest solution for such patients is to subject them to a properly performed staging laparotomy performed by a gynecologic oncologist. However, if this is not possible or practical, an alternative is to obtain a CT scan and a CA-125. If the CT scan and CA-125 are normal and the tumor was one of low malignant potential, no further therapy is recommended at the Yale–New Haven Medical Center. If the tumor is an invasive epithelial malignancy, we would consider giving single-agent chemotherapy, such as carboplatin, to such a patient. However, no prospective randomized series of patients have been reported using this approach. If the CT scan is positive, a surgical procedure to remove gross disease should be performed.

Postoperative reevaluation by laparotomy or laparoscopy has been advocated by some authors. Earlier laparoscopic surgical staging papers revealed that as much as 30% to 40% of patients originally thought to have FIGO stage I or II disease actually had disease in the upper abdomen. Complications as a result of earlier laparoscopic procedures had been relatively limited and included pneumothorax, bleeding requiring transfusions, wound infections, and hypotension. More recently, more thorough laparoscopic techniques have been described that allow for paraaortic lymph node dissections and omentectomies. As the degree of the aggressiveness of laparoscopic surgical procedures advances, the complications become more significant.

SCREENING

Successful screening for ovarian cancer, by definition, would decrease mortality and morbidity from the disease. With currently available tests, routine screening for ovarian cancer cannot be recommended. Successful screening for any malignancy requires detection either at a time when the disease is in its early stages or in a precancerous stage without invasive features. Although the patterns of spread of ovarian cancer have been well defined, the precise natural history is poorly

TABLE 36.5-2. International Federation of Gynecologists and Obstetricians Stage Grouping for Primary Carcinoma of the Ovary (1998)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Tumor limited to the ovary or peritoneum</td>
</tr>
<tr>
<td>II</td>
<td>Tumor extends beyond the ovary to involve the pelvic peritoneum</td>
</tr>
<tr>
<td>III</td>
<td>Tumor extends beyond the pelvic peritoneum to involve the paraaortic lymph nodes</td>
</tr>
<tr>
<td>IV</td>
<td>Tumor extends beyond the paraaortic lymph nodes to involve distant sites</td>
</tr>
</tbody>
</table>

understood. It has not been established that untreated stage I routinely progresses to more advanced stages. Even if an orderly progression from stage I to stage IV takes place, the time frame for such a progression remains to be established. The entire peritoneum is at risk because peritoneal carcinomatosis may develop after an oophorectomy. Furthermore, the syndrome of extraperitoneal carcinomatosis is characterized by widespread intraperitoneal epithelial carcinoma in the presence of histologically normal ovaries. In addition, there is no direct evidence for a premalignant lesion in ovarian cancer. As noted, no experimental data suggest that an ovarian cyst can progress to a borderline tumor that can, in turn, lead to an invasive carcinoma.

The primary reason that screening is not recommended, however, is because the currently available screening techniques (ovarian palpation, transvaginal ultrasonography, and serum CA-125 determinations) are not sufficiently accurate for general screening. These tests have been limited by their sensitivity and specificity. Because a laparotomy is required to diagnose ovarian cancer, the positive predictive value (PPV) for screening is the primary consideration due to the cost, morbidity, and even mortality associated with unnecessary laparotomies for a false-positive screening test. 22 The PPV is defined as the ratio of a true-positive test (laparotomy) to true-positive plus false-positives. Most investigators think that the PPV of a laparotomy should be at least 10%. 22

Whereas pelvic examinations continue to be routinely recommended for women, ovarian palpation has not been established as a useful screening procedure. Most screening studies have used either serum tumor markers or ultrasonography or both. Although serum CA-125 levels correlate with progression or regression of established disease 23 and are also useful in the preoperative evaluation of a pelvic mass, the test does not have sufficient specificity to be used as a routine screen for ovarian cancer. 23 Besides ovarian cancer, many other conditions can be associated with an elevated CA-125 level, including cimtosir, peritonitis, pancreatitis, endometriosis, uterine leiomyoma, benign ovarian cysts, and pelvic inflammatory disease.

In a Swedish study, 24 CA-125 levels were measured annually in 550 women older than 40 years. In women with levels greater than 30 U/mL, sequential CA-125 levels were obtained every 3 months, along with pelvic examinations and transabdominal ultrasounds performed every 6 months. In this study, 175 women were found to have elevated CA-125 levels, and six ovarian cancers were detected.

Transvaginal ultrasonography is a more specific alternative to both transabdominal ultrasonography 25 and CA-125 screening. In studies from the University of Kentucky of more than 3000 asymptomatic postmenopausal women, the PPV was less than 10%. 25 In an effort to improve the unacceptable high rate of false-positive results with transvaginal ultrasonography, color Doppler imaging also has been studied in an effort to identify areas of vascularization that are associated with malignancy. 26 However, the addition of color Doppler imaging has not yet been established to improve the overall efficacy of ultrasonographic screening.

Several large screening trials have used a sequential combination of serum CA-125 and ultrasonography. In an English study, 22,000 volunteers without a family history of ovarian cancer underwent screening with serum CA-125 that was followed by abdominal ultrasonography for elevations of greater than 30 U/mL. 26 Women underwent a laparotomy for any detectable ovarian abnormality. In this study, 11 women had ovarian cancer, seven with stage III or IV disease. The PPV was less than 10% for early-stage disease. Table 36.5-3 summarizes the results of uncontrolled trials of ovarian cancer screening in more than 36,000 women. 27 A total of 41 cases of ovarian cancer were identified, but only 12 were in women with stage I disease. In the 29 women who were diagnosed with advanced-stage ovarian cancer, it is unlikely that survival would have been significantly improved by an earlier diagnosis because the disease had already spread throughout the peritoneal cavity. Screening may ultimately be more effective in women with a positive family history of ovarian cancer. 27 At this point, however, no evidence shows that even screening such a high-risk population has an impact on morbidity and mortality.

TABLE 36.5-3. Uncontrolled Trials of Ovarian Cancer Screening

<table>
<thead>
<tr>
<th>Country</th>
<th>Reference</th>
<th>Participants</th>
<th>Stage I</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nebraska</td>
<td>58</td>
<td>56</td>
<td>2</td>
<td>58</td>
</tr>
<tr>
<td>Utah</td>
<td>51</td>
<td>54</td>
<td>5</td>
<td>54</td>
</tr>
<tr>
<td>Utah</td>
<td>56</td>
<td>51</td>
<td>5</td>
<td>51</td>
</tr>
<tr>
<td>Utah</td>
<td>22</td>
<td>22</td>
<td>1</td>
<td>22</td>
</tr>
<tr>
<td>Total</td>
<td>124</td>
<td>124</td>
<td>12</td>
<td>136</td>
</tr>
</tbody>
</table>

(From: S. W. Lands, et al.)

Several large ovarian cancer screening trials are currently in progress. The National Cancer Institute's Prostate, Lung, Colon, Ovarian Cancer (PLCO) trial compares screening with an annual CA-125 measurement, transvaginal ultrasonography, and pelvic examination to usual medical care in 76,000 women aged 60 through 74. The participants in the study will be followed for 10 years. A European multicentric study headquartered at St. Bartholomew's Hospital in London will evaluate 120,000 postmenopausal women randomized to receive no screening or screening with transvaginal ultrasound followed by color flow Doppler examinations in women with abnormal transvaginal ultrasonograms. In additional, serial CA-125 levels will be used to determine which participants should go on to the next stage of screening. Studies are also in progress to identify more sensitive tumor markers. Macrophage colony-stimulating factor (M-CSF) has been detected in epithelial ovarian tumors and in 70% of the serum or ascites of patients with diagnosed carcinomas. 28 Serum M-CSF levels, together with CA-125 levels, may be more predictive than CA-125 levels alone. Similarly, OVX-1 is a newly developed antibody that may also complement CA-125. 29 The combination of these two antibodies has been more accurate in predicting the presence of residual disease at second-look surgical procedures. Furthermore, a panel of CA-125, M-CSF, and OVX-1 was shown to identify early-stage ovarian cancer with extremely high sensitivity and moderate specificity in preliminary studies. 29 The levels of these tumor markers and their rate of change over time are being prospectively analyzed to help identify an individual's risk of ovarian cancer. Lysophosphatidic acid, which had previously been shown to be elevated in malignant ascites, may also have utility as a predictive biomarker for ovarian cancer, because an elevated level was found in nine of ten patients with early-stage disease. Additional studies of sensitivity and specificity are in progress.

Inasmuch as screening has not been effective in diagnosing early-stage ovarian cancers, prophylactic oophorectomies have been advocated by some for women in high-risk groups. However, women still are at risk for peritoneal carcinomatosis even after normal ovaries have been removed. A multicenter prospective evaluation of the role of prophylactic oophorectomy in high-risk individuals is in progress. Preliminary results support a protective effect of an oophorectomy, although peritoneal carcinomatosis occurs at a higher rate in this group of women than in the general population. 30 Karlan et al. 31 have reported on the findings of peritoneal serous papillary carcinoma in women at high risk by family history for ovarian cancer. These investigators performed BRCA1 and BRCA2 gene mutation studies on four patients who developed serous carcinomas of the peritoneum and found that three of the four had BRCA1 mutations. None of the patients with peritoneal serous papillary carcinomas was recognized before intraabdominal carcinomatosis was evident. 31

PROGNOSTIC FACTORS

At the conclusion of a comprehensive laparotomy, the clinical findings and the histology are used to select postoperative therapy. In addition, new prognostic factors are being evaluated that may be used to identify groups of patients in whom more specific biologic treatments or more aggressive therapy is indicated.

Clinicopathologic findings determined to be clinically useful include the following:

- FIGO stage
- Histologic subtype
- Histologic grade
- Factors associated with tumor dissemination
- Malignant ascites
- Malignant peritoneal washings
- Tumor excrescences on ovarian surface
- Ruptured capsule
Management of Early-Stage Disease

The tumor stage remains the most important prognostic variable. Few trials provide an accurate assessment regarding the long-term survival of patients with early-stage ovarian cancer because earlier studies often included inadequately staged patients. Stage I patients with well- or moderately well–differentiated tumors have a greater than 90% 5-year survival rate. Patients with stage I disease with poor prognostic features are often included in treatment protocols for patients with stage II disease. This group of patients has been termed early-stage disease with unfavorable characteristics. However, limited information is available regarding the actual survival impact of some of the factors used to characterize patients as having an unfavorable prognosis. Rupture of the capsule increases the stage to IC. In a Swedish series, however, no adverse effect on survival could be established for early-stage patients in whom the capsule was ruptured during surgery. Furthermore, in contrast to the established adverse effect of malignant ascites, there is limited information regarding the prognostic significance of positive peritoneal cytology.

Recently, tumor adherence in the presence of dense adhesions has also been considered an adverse prognostic factor, and such patients should be considered as having stage II disease even in the absence of pathologic confirmation. Tumor size, bilaterality, and cytologically negative ascites have no prognostic significance. The most reliable long-term survival data on accurately staged early-stage ovarian cancer patients is derived from studies of the GOG. In these studies, unfavorable prognostic early-stage ovarian cancer patients have a 5-year survival rate of approximately 80%. Patients with stage III disease have a 5-year survival rate of approximately 15% to 20% that is dependent in large part on the volume of disease present in the upper abdomen. Patients with stage IV disease have less than a 5% 5-year survival.

Volume of residual disease after cytoreductive surgery for patients with advanced ovarian cancer has a significant impact on survival. After the administration of postoperative cisplatin-based combination chemotherapy, 5-year survival rates for patients with optimal stage III disease (defined as no residual nodule greater than 1 cm in diameter) is approximately 35%.

The true prognostic impact of histologic subtype and grade in patients with epithelial ovarian cancer remains to be determined. In patients with early-stage ovarian cancer, grade is an accepted determinant of risk and used to assign postoperative therapy as discussed earlier in the section Management of Early-Stage Disease. In advanced-stage patients, mucinous histology and clear cell histology also have been shown to have an adverse prognostic significance. In a GOG analysis, no negative second-look laparotomies in patients with mucinous or clear cell tumors were performed. Some studies have also demonstrated that histologic grade has an impact on survival in patients with advanced-stage disease.

Serum CA-125 levels frequently reflect the volume of disease and, as such, in multivariate analysis, preoperative levels have not exerted an independent prognostic effect on survival. However, postoperative CA-125 levels were shown to be an independent prognostic variable. Most studies also have demonstrated that serum CA-125 levels after three cycles of chemotherapy are accurate predictors for the probability of a patient achieving a complete remission. However, the CA-125 level after three cycles of chemotherapy cannot be used as a guide for treatment decisions because of the lack of predictive power.

The prognostic significance of age on survival of patients with ovarian cancer has been recognized. Median survival is at least 2 years longer in women younger than age 65 compared with those older than 65.

The prognostic significance of DNA ploidy and S-phase fraction have been examined in ovarian cancer. Investigators in Europe have now included aneuploidy in their selection of high-risk early-stage ovarian cancer patients for adjuvant therapy. Controversy remains, however, as to the nature of the relationship between histologic grade and degree of aneuploidy. In the GOG, aneuploidy has not been included as a criteria for risk in early-stage disease.

A series of new molecular factors have been proposed to have prognostic significance in ovarian cancer (Table 36.5-4). These factors include markers of proliferation, drug resistance, serum cytokine levels, growth factor receptors or signal transduction pathways, genes associated with metastases, and oncogene expression. Most of these factors have been identified in retrospective studies without multivariate analysis or confirmation in larger studies. These factors were developed from experimental studies in the biology of ovarian cancer (described in Chapter 36.1). Currently, none of these markers is routinely used to select therapy for patients with ovarian cancer.

### TABLE 36.5-4. Experimental Prognostic Factors in Ovarian Cancer

#### MANAGEMENT OF EARLY-STAGE DISEASE

A subset of patients with early-stage ovarian cancer definitely has been shown not to require any additional postoperative therapy after a comprehensive staging laparotomy. Patients with stage IA or IB disease with well- or moderately well–differentiated tumors have a 5-year survival rate of more than 90% without any adjuvant treatment. Patients with favorable prognosis early-stage ovarian cancer (stage IA and IB with grade 1 and 2 tumors) were randomized in an earlier GOG study to receive no treatment or oral intermittent melphalan (0.2 mg/kg daily for 5 days) with repeat cycles every 4 to 6 weeks for a total of 12 courses or 18 months of therapy. With a median follow-up of more than 6 years, only six deaths have been reported in 81 patients: four in the observation group and two in patients who received melphalan. Disease-free survival and overall survival is shown in Figure 36.5-4. Patients with favorable prognosis early-stage ovarian cancer can be spared the acute and chronic toxicities of chemotherapy, including myeloproiferative disorders such as leukemia.
The optimum treatment of early-stage ovarian cancer patients with unfavorable prognosis remains an area of controversy. Opinions differ as to not only what modality of treatment should be used (external-beam radiotherapy, intraperitoneal radioisotopes, or chemotherapy) but also with regard to the role of immediate therapy or to delay of treatment until disease progression. Furthermore, as noted, consensus has not been established as to the prognostic significance of some clinicopathologic features, such as positive peritoneal cytologies and a surgically ruptured capsule with contamination of the pelvis with cyst fluid. Clinicopathologic factors currently used by the GOG to define unfavorable prognosis early-stage disease include FIGO stage II and IC, clear cell histology, and grade 3 tumors.

External-Beam Radiotherapy

Although cisplatin- or paclitaxel-containing chemotherapy has become the standard initial treatment for patients with unfavorable prognosis early-stage ovarian cancer in all but a few centers, a number of studies have demonstrated that carefully applied whole abdominal radiotherapy is also a highly effective treatment for some patients.

Early nonrandomized studies suggested that pelvic disease control and survival were improved when patients with early-stage ovarian carcinoma were treated with postoperative pelvic radiation. In particular, patients with stage II disease had consistently better survival rates if the pelvis was treated (Table 36.5-5). However, these studies also demonstrated the importance of the coelomic pattern of metastatic spread, which limited the benefit of pelvic irradiation.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Surgery alone (%)</th>
<th>Surgery + Radiation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Koo and McKenney</td>
<td>0/12 (9)</td>
<td>14/10 (10)</td>
</tr>
<tr>
<td>Yeh and O'Reilly</td>
<td>2/2 (100)</td>
<td>2/2 (100)</td>
</tr>
<tr>
<td>Koo</td>
<td>0/11 (0)</td>
<td>5/10 (50)</td>
</tr>
<tr>
<td>MacLennan</td>
<td>0/5</td>
<td>5/10 (50)</td>
</tr>
<tr>
<td>Delius</td>
<td>0</td>
<td>7/10 (70)</td>
</tr>
<tr>
<td>Rees</td>
<td>0/2 (0)</td>
<td>4/4 (100)</td>
</tr>
<tr>
<td>Gatty</td>
<td>0/1 (0)</td>
<td>1/1 (100)</td>
</tr>
</tbody>
</table>

Table 36.5-5. Results of Early Series Comparing Postoperative Pelvic or Lower Abdominal Radiation versus Surgery Alone for Stage II Carcinoma of the Ovary

On the basis of these findings and encouraging responses of ovarian carcinoma to alkylating agents, investigators at the M. D. Anderson Cancer Center conducted a prospective trial that compared pelvic and whole abdominal irradiation with pelvic irradiation and single-agent chemotherapy (melphalan). Patients who had stage I to III ovarian carcinomas with less than 2 cm of residual disease after surgery were included. Abdominal treatment was delivered with cobalt (60Co) using the moving strip technique. Each strip was treated with 26 to 28 Gy in 8 to 12 fractions with partial shielding of the liver and kidneys. The authors reported that survival rates were similar for patients treated in the two arms, but the rate of serious bowel complications was higher for patients who received whole abdominal irradiation. It was concluded that chemotherapy was a superior treatment, and subsequent clinical trials at the M. D. Anderson Cancer Center and throughout the United States focused on the search for more effective chemotherapy.

Four years later, Dembo and associates published the results of a similar prospective randomized study conducted at the Princess Margaret Hospital in Toronto. Patients with stage IB or II ovarian cancer were randomized to one of three treatment arms: pelvic irradiation, pelvic plus whole abdominal irradiation, or pelvic irradiation plus single-agent chemotherapy. Patients with “asymptomatic” stage III disease were randomized only between the last two arms. Although the treatment arms were similar to those of the M. D. Anderson trial, the details of the treatments differed significantly from that study. Patients on the chemotherapy arm received chlorambucil, an alkylating agent that has since been demonstrated to yield poorer response rates than melphalan. The total dose of abdominal strip irradiation (22.5 Gy) and the daily fraction size (2.25 Gy) were less than those used in the M. D. Anderson trial, but the liver was not shielded and particular care was taken to include the domes of the diaphragm in the treatment fields.

Of 190 patients entered on the study, 132 had a hysterectomy and bilateral salpingo-oophorectomy performed at their initial laparotomy. Of these 132 (who were considered to have minimal residual disease), the 50 who received whole abdominal irradiation had significantly better rates of survival and abdominal disease control than did patients who received pelvic irradiation with chlorambucil (Table 36.5-6). Although the study has been criticized for using inconsistent surgical staging methods, it undoubtedly demonstrates the efficacy of abdominopelvic irradiation for at least some subsets of patients with minimal residual disease. Subsequent analysis of patients treated at Princess Margaret Hospital demonstrated that patients who had grade 1; stage I or II, grade 2; or stage I or II, grade 3 disease and no gross residual tumor after surgery were most likely to have a prolonged disease-free interval after abdominopelvic irradiation (Table 36.5-7).
Differences in the chemotherapy and radiotherapy techniques described above may explain the apparently contradictory results of the two trials. An imbalance in the proportion of stage I A patients may have favored the chemotherapy arm in the M. D. Anderson trial, but subset analysis by stage also failed to suggest an advantage with whole abdominal irradiation. The high total dose and fraction size per strip used at M. D. Anderson may explain the high rate of severe enteric complications compared with the 3% to 4% rate reported at Princess Margaret Hospital.

A number of other reports document that patients with postoperative residual disease have been cured with abdominopelvic irradiation alone; relapse-free survival rates of 40% to 60% at 10 to 15 years have been reported for patients with residual gross disease measuring less than 2 cm (Table 36.5-8). Collectively, these studies demonstrate the efficacy of abdominopelvic irradiation and its superiority over pelvic radiotherapy alone. They also indicate that irradiation alone is insufficient treatment for most patients with gross residual disease, particularly when the residuum is extrapelvic.

Randomized data comparing abdominopelvic irradiation with modern cisplatin- or paclitaxel-based chemotherapy have been difficult to obtain. Although retrospective studies do not demonstrate a clear advantage of one treatment over the other for patients with minimal residual disease, physician biases are strong and several multiinstitutional trials addressing this question have been closed prematurely because of inadequate patient accrual. In 1993, Redman and coworkers published the results of a randomized trial comparing abdominopelvic irradiation with single-agent cisplatin in 40 patients with microscopic residual disease, stages IC to III. The 5-year survival rates were 56% and 62% in the two arms, respectively, but the power of the study was weak because of the small number of patients. In 1994, Chiris and colleagues reported results of a second study comparing whole abdominal radiotherapy with cisplatin and cyclophosphamide in 70 patients with high-risk stage I or II disease. This study was compromised by poor accrual and protocol violations; 8 (24%) of the 34 patients assigned to receive radiotherapy were treated with chemotherapy. Projected 5-year survival rates for those treated with radiation (25 patients) or chemotherapy (44 patients) were 53% and 71%, respectively (P = .16).

However, these studies still leave us with an incomplete understanding of the role of radiotherapy in initial management of ovarian cancer. Although pelvic irradiation was routinely added to early treatments with single alkylating agents, it has generally been abandoned since platinum-containing regimens became standard. Early studies of pelvic radiotherapy alone and the success of whole abdominal irradiation in selected patients indicate that irradiation is still used by some practitioners for a selected group of patients with minimal disease. The isotope that is usually used is chromic phosphate (32P).

The characteristic transcolonic pattern of dissemination of ovarian cancer first led clinicians to treat patients with intraperitoneal isotopes in the 1950s, and this approach has never been abandoned. Some clinicians believe that this route of administration is superior to intraperitoneal injection because the excretion of 32P is more complete. However, isotopes that are given intraperitoneally decay rapidly in the peritoneal cavity. Those that are not absorbed by the large bowel should be excreted in the stools, but a delayed excretion is likely to occur in some patients. Chromic phosphate is still used by some practitioners for a selected group of patients with minimal disease. The isotope that is usually used is chromic phosphate (32P).

**TABLE 36.5-8. Evidence for Cure of Ovarian Cancer by Abdominopelvic Radiotherapy: Long-Term Outcome in Patients with Stage II and III Disease and Macroscopic Residuum**

<table>
<thead>
<tr>
<th>Study Center</th>
<th>No. of Patients</th>
<th>End Point</th>
<th>Overall Survival Rate (% at 5 Years)</th>
<th>Chemotherapy</th>
<th>Whole Abdominal Radiotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOG, 1990</td>
<td>141</td>
<td>25 patients</td>
<td>53 (29)</td>
<td>70</td>
<td>80</td>
</tr>
<tr>
<td>GOG, 1994</td>
<td>70</td>
<td>25 patients</td>
<td>56 (29)</td>
<td>66</td>
<td>63</td>
</tr>
<tr>
<td>M. D. Anderson, 1993</td>
<td>44</td>
<td>25 patients</td>
<td>71 (41)</td>
<td>53</td>
<td>71</td>
</tr>
</tbody>
</table>

Patients should always be simulated under fluoroscopy, and fields should provide a 1-cm margin on the maximum cephalad excursion of the diaphragmatic domes under quiet respiration. It is often necessary to flash the lateral abdominal wall to include the entire bony pelvis in whole abdominal fields to avoid excluding peritoneal surfaces. In obese patients with poor abdominal tone, the fields may need to extend laterally beyond the bony pelvis. This is particularly true when the patient is treated in the prone position. The thickness of the abdominal wall should be considered in choosing the energy of the radiation beam. When fields are designed using CT scans of the whole abdomen, coverage of peritoneal surfaces can be assured. The total dose of whole abdominal irradiation varies between 22 and 30 Gy depending on the fractionation scheme, use of concurrent chemotherapy, and patient tolerance. Posterior kidney blocks are placed to limit the renal dose to 15 to 18 Gy, and a portion of the liver may be shielded during part of the treatment, limiting the dose to 22 to 25 Gy. The true pelvis is usually treated to a higher dose of 45 to 50 Gy, either after whole abdominal irradiation or concurrently as a “field within a field” (not to exceed a total daily dose to the pelvis of 180 cGy). Martinez and coworkers have suggested boosting the dose to the paraaortic nodes and mediastinal nodes with a T-shaped field in selected patients. Chemotherapy that is given before or after irradiation can influence normal tissue tolerance and should be considered in estimations of organ tolerance.

**Intrapерitoneal Radioisotopes**

The characteristic transcolonic pattern of dissemination of ovarian cancer first led clinicians to treat patients with intraperitoneal isotopes in the 1950s, and this treatment is still used by some practitioners for a selected group of patients with minimal disease. The isotope that is usually used is chromic phosphate (32P). Chromic phosphate decays with a half-life of 14.3 days, emitting β-particles with a mean energy of 0.69 MeV. Because the average penetration of these particles in soft tissue is less than 1 mm, treatment with chromic phosphate is inappropriate for patients who have macroscopic residual disease. The isotope that is usually used is chromic phosphate (32P).

A GOG study, published in 1990, randomized 141 patients with poorly differentiated stage I A to B, stage IC, or completely resected stage II disease to receive either melphalan (0.2 mg/kg/d for 5 days, repeated every 4 to 6 weeks for 12 cycles) or intraperitoneal 32P (15 mCi at the time of surgery). The 5-year survival rates of 81% and 78% for patients treated with melphalan or 32P, respectively, were not significantly different. Toxic effects were acceptable for most patients with both therapies. However, four (6%) patients treated with 32P required an operation for small bowel obstruction, and two (3%) patients treated with melphalan developed leukemia. The authors concluded that intraperitoneal 32P was the preferred treatment for these patients because of its limited toxicity and no known risk for causing leukemia. Three randomized studies have compared 32P with cisplatin-containing chemotherapy; none demonstrated a significant difference in survival between the two treatments. Varghese and colleagues randomized 347 patients who had no gross residual disease after laparotomy to receive intraperitoneal 32P (7 to 10 mCi) or...
cisplatin (six courses of 50 mg/m² each). The estimated 5-year survival rates were 83% and 81%, respectively (P = .6). Although the dose of cisplatin was relatively low, 12 (9%) of 136 patients who had this treatment experienced small bowel obstructions compared with 2% of patients treated with cisplatin. For this reason, the authors recommended cisplatin as standard treatment.

In a GOG study, Young and colleagues compared intrabdominal cisplatin with combination chemotherapy (cisplatin and cyclophosphamide) for patients with high-risk early-stage disease. The 5-year survival rates were 76% and 84%, respectively (P = .08). One toxic death was reported in each treatment arm, but these authors also concluded that the greater risk of bowel complications with cisplatin outweighed the hematologic complications of chemotherapy; on this basis, the authors recommended chemotherapy as the preferred treatment.

The most common complication of cisplatin administration is transient abdominal pain in 15% to 20% of patients. Chemical or infectious peritonitis is a rare complication that occurs in 2% to 3% of patients. The most serious late complication of treatment is small bowel obstruction, which has been reported in 5% to 10% of patients treated with cisplatin alone. This risk increases to an unacceptable rate of 20% to 30% when intraperitoneal cisplatin is combined with external-beam radiotherapy, an approach that is no longer recommended.

These clinical trials, however, did not establish whether any form of adjuvant therapy was, in fact, superior to no immediate treatment for patients with early-stage ovarian cancer with unfavorable prognostic features. The Italian Inter-regional Cooperative Group of Gynecologic Oncology has conducted a randomized trial with a no-treatment arm in patients with stage I or IB, grade 2 or 3 tumors who are randomized to receive cisplatin (50 mg/m² for six cycles) or to observation. With a median observation time of 76 months, overall survival rates between the two treatment arms is similar (88% with cisplatin vs. 82% in the control group), although there is a marked improvement in disease-free survival for patients treated with cisplatin (83% vs. 65%). The absence of a larger difference in overall survival reflects the ability of cisplatin-based chemotherapy to salvage patients at the time of recurrence. Two additional trials, in which there is a no-treatment arm, are also in progress in Europe for early-stage ovarian cancer patients (Table 36.5-9). The Scandinavian randomized trial is similar in design to that of the Italian study. In an English trial, however, the randomization is between observation and treatment with single-agent carboplatin. Unlike the Scandinavian study, the English trial has no requirement for extensive surgical staging.

**TABLE 36.5-9. Clinical Trials in Early-Stage Ovarian Cancer**

<table>
<thead>
<tr>
<th>Study/Region</th>
<th>Study Period</th>
<th>Treatment Details</th>
<th>Stage IV Disease</th>
<th>Survival Rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Italian Inter-regional Cooperative Group of Gynecologic Oncology</td>
<td>5 years</td>
<td>Cisplatin (50 mg/m² for 6 cycles) or observation</td>
<td>58% ± 10</td>
<td>84% ± 10</td>
</tr>
<tr>
<td>Scandinavian</td>
<td></td>
<td>Cisplatin (6 courses of 50 mg/m² each) or observation</td>
<td>58% ± 10</td>
<td>84% ± 10</td>
</tr>
<tr>
<td>English trial</td>
<td>5 years</td>
<td>Cisplatin (6 courses of 50 mg/m² each) or observation</td>
<td>58% ± 10</td>
<td>84% ± 10</td>
</tr>
</tbody>
</table>

The current GOG trial for patients with early-stage ovarian cancer with unfavorable prognosis compares three cycles against six cycles of a treatment with paclitaxel and carboplatin (see Table 36.5-9). The details of this combination are discussed later in the section Paclitaxel Combination Therapy.

It is apparent that the optimum postoperative treatment for patients with early-stage ovarian cancer with unfavorable prognostic features remains to be established. Pending the results of the ongoing clinical trials, treatment options include chemotherapy with cisplatin or carboplatin, total abdominal and pelvic irradiation, and paclitaxel-based chemotherapy. In addition, a no-treatment option can be considered, although this choice has been shown to be associated with a decrease in disease-free survival. Second-look operations after completion of adjuvant therapy are not routinely recommended.

**TREATMENT OF ADVANCED-STAGE OVARIAN CANCER**

The generally accepted treatment for patients with either stage III or IV (advanced stage) ovarian cancer has been similar—cytoreductive surgery, when feasible, followed by chemotherapy.

**Cytoreduction**

Aggressive surgery to remove virtually all gross tumor (i.e., cytoreductive surgery or tumor debulking surgery) has become an integral part of initial surgery for management of ovarian cancer. The theoretic benefits of cytoreductive surgery are to remove large necrotic tumors with poor blood supplies and to remove large tumors that are in a slower growth phase, leaving behind tumors that are more sensitive to the effects of chemotherapy. Theoretically, all patients with stage III and IV disease are candidates for cytoreductive surgery. Stage IV patients, based on the presence of parenchymal liver disease, enlarged retroperitoneal lymph nodes, supraventricular lymph nodes, mediastinal metastases, and parenchymal lung metastases may not be candidates for optimal cytoreductive surgery. In addition, we have found that women who have disease on CT scan that involves the porta hepatitis or is associated with suprarenal lymphadenopathy or omental metastases that extend into the hilum of the spleen frequently have such advanced disease at the time of the cytoreductive surgery that the likelihood of optimal cytoreductive being accomplished is virtually nil. Women with stage IV disease only based on the presence of malignant pleural effusion have been able to undergo optimal cytoreductive surgery. Its impact on their survival has been questioned. Studies have suggested that an optimal surgical cytoreductive effort should be performed in women with stage IV disease, even when parenchymal liver disease is recognized preoperatively. If patients can be optimally cytoreduced to less than 1 to 2 cm maximum diameter of residual tumor, their median survival has varied from 25 to 40 months, whereas those women who were suboptimally cytoreduced had median survival rates of 10 to 18 months. Interestingly, the stage IV patients optimally cytoreduced in three of the four series had a superior survival to optimally cytoreduced patients with stage III ovarian cancer treated in prospective randomized trials by the GOG.

Successful surgical management of stage III or IV ovarian cancer requires meticulous attention to surgical techniques to avoid complications and a thorough knowledge of abdominal and pelvic anatomy to allow the successful accomplishment of cytoreductive surgery. In general, it is wisest to start with an incision in the lower abdomen to free the pelvis of cancer, then work up into the upper abdomen to attempt to clear it of cancer, then complete the procedure with paraaortic and pericaval retroperitoneal lymph node sampling or resection if optimal cytoreduction has been accomplished within the peritoneal cavity. The goal of optimal cytoreductive surgery is complete removal of all palpable or visible tumor. A minimal goal of cytoreductive surgery is to reduce the residual tumor to less than 1 cm and preferably less than 0.5 cm in maximum diameter.

On entering the abdominal cavity, normal anatomy is restored by lysing adhesions and freeing organs from adherent tumor. Frequently the pelvis is completely filled with tumor, and sometimes the entire peritoneal cavity is involved with metastatic disease. The peritoneum, along with the attached vessels down to the tumor mass, and dissection of the ovarian mass off of, or with, the underlying peritoneum to elevate the mass from the pelvic sidewall. By dividing the utero-ovarian ligaments and fallopian tubes, one can then remove the uterus and ovaries. It is necessary to take the uterus out en bloc with the ovarian tumor. Implants in the cul-de-sac may be resected using retroperitoneal dissection. Sigmoid colon implants usually involve epiploic appendices, which can be resected without performing a sigmoid colon resection. Retroperitoneal lymph nodes are routinely removed from the external iliac artery and vein, hypogastric arteries, and the obturator fossa. An appendectomy is routinely performed. An en bloc resection of peritoneum, along with the attached vessels down to the tumor mass; and dissection of the ovarian mass off of, or with, the underlying peritoneum to elevate the mass from the pelvic sidewall. By dividing the utero-ovarian ligaments and fallopian tubes, one can then remove the uterus and ovaries. It is necessary to take the uterus out en bloc with the ovarian tumor. Implants in the cul-de-sac may be resected using retroperitoneal dissection. Sigmoid colon implants usually involve epiploic appendices, which can be resected without performing a sigmoid colon resection. Retroperitoneal lymph nodes are routinely removed from the external iliac artery and vein, hypogastric arteries, and the obturator fossa. An appendectomy is routinely performed. Having resected the pelvic disease, a complete omentectomy is performed and large masses implanting on peritoneal surfaces, including the omentum, are removed. Once the abdomen has been cleared of disease, or the maximum residual disease is less than 1 cm, the fat pad overlying and surrounding the aorta and vena cava is removed, as are lymph nodes involved with metastatic disease in this area. In general, if large residual tumor volume is left within the peritoneal cavity,
there is not much benefit in resecting retroperitoneal disease. However, when intraperitoneal disease has been optimally cytoreduced to less than 1-cm maximal residual tumor volume, retroperitoneal lymphadenectomies are appropriate.

Impact of Primary Cytoreductive Surgery

The clinical rationale for cytoreductive surgery has been ascribed to Griffiths, who demonstrated in 1974 that survival was directly effected by the initial degree of cytoreductive surgery for women with advanced-stage ovarian cancer. In a retrospective review, patients with no residual disease had a mean survival of 39 months compared with 29 months for residual disease of less than 0.5 cm, 18 months for residual disease of 0.6 to 1.5 cm, and 11 months for those who were not cytoreduced below 1.5 cm. None of the latter patients survived beyond 26 months. Women who underwent optimal cytoreductive surgery had similar survival rates to women who had minimal-size abdominal metastases at the initial surgery. Subsequent to that report, numerous series have confirmed that aggressive cytoreductive surgery to 2 cm of residual tumor or less significantly enhances survival for patients. Most patients participated in trials in which multidrug chemotherapy was used, usually involving cisplatin-based chemotherapy. A review of nine reports, in which primary cytoreductive surgery resulted in disease of less than 2 cm or greater than 2 cm, demonstrated a mean survival in the optimally cytoreduced group of 29.4 months compared with 13.4 months in the group in whom cytoreductive surgery was suboptimal. 

Two metaanalyses gave conflicting views on the survival impact of cytoreductive surgery. Hunter et al. reviewed a total of 58 separate studies containing 6962 patients to determine whether maximum cytoreduction surgery benefits the survival of women with advanced ovarian cancer. These authors looked at the median survival times of groups of women with advanced ovarian cancer and used multiple linear regression techniques to analyze the effects on median survival. The variables studied were the proportion of each cohort undergoing maximum cytoreductive surgery, the use of cisplatin chemotherapy, the dose intensity of the chemotherapy, the proportion of each cohort with stage IV disease, and the year of publication of the study. The use of cisplatin chemotherapy resulted in an increased survival time of 33% (95% confidence intervals [CI], 35% to 73%). For each 0.2 unit increase in dose intensity, the increase in median survival time was 11.1% (95% CI, 6% to 17%, P = .001). Stage IV disease had a negative impact on survival. For each 10% increase in the number of stage IV patients in the study, a negative survival increase of 2.6% (95% CI, –0.1% to –5.4%) was found. For each 10% increase in the percentage of women who underwent maximum cytoreductive surgery, the increase in survival was only 4.1% (95% CI, –0.6% to 9.1%, P = .089) (Fig. 36.5-5). This study concluded that cytoreductive surgery has only a small effect on the survival of women with advanced ovarian cancer and that the type of treatment used (i.e., cisplatin) was far more important.

Allen et al. performed metaanalyses on 12 reports of women with stage III ovarian cancer in which they could determine that patients either had no residual disease, residual disease less than or equal to 2 cm, or residual disease greater than 2 cm, and on four reports of stage IV ovarian cancer for which similar analyses were possible. The results of these metaanalyses were consistent with survival benefits accruing to patients with no residual disease and residual disease less than or equal to 2 cm after surgery for stage III and IV disease when compared with patients with residual tumor masses greater than 2 cm. These authors, however, indicated that the survival benefit for women with small residual tumor probably reflects more the biology of the tumor and suggests that less-invasive tumors may be more chemotherapy-sensitive than those tumors in which optimum cytoreductive surgery was not possible. To date, no prospective randomized trials have been performed assessing the value of cytoreductive surgery in advanced ovarian cancer.

Three GOG studies give important insight into the impact of cytoreductive surgery in advanced ovarian cancer. The first demonstrated that removing all gross tumor defines true optimal cytoreductive surgery. Women treated with cisplatin-based chemotherapy who had no gross disease left had a progression-free interval of 42 months compared with 20 months for those with residual disease of less than 1 cm. The second study revealed that women who had 1 to 2 cm residual tumor had a significant survival improvement compared with those who had more than 2 cm of residual tumor. This third study refuted early data suggesting that women undergoing optimal cytoreductive surgery have similar survival as those patients initially found at surgery to have low-volume disease. The latter study reported on 348 women with 1 cm or less residual tumor, 200 of whom initially had abdominal disease of 1 cm or less. When implants were present on peritoneal or visceral peritoneum, even when optimally cytoreduced, survival rates significantly decreased. Indeed, the best survival for stage III patients observed were those whose initial macroscopic tumor was less than 1 cm in the omentum and associated with either no disease or microscopic disease in other abdominal sites (P = .0001). Those with the poorest survival had tumors initially greater than 1 cm involving omentum and had gross disease in other abdominal sites (Fig. 36.5-6). This study refutes early data suggesting that women undergoing optimal cytoreductive surgery have the same survival as those patients initially found at surgery to have low-volume disease. The study demonstrates that biologic factors responsible for bulk disease may be as important as technical ability to resect the disease.
Aggressive cytoreductive surgery incurs complications. Chen and Bochner\(^2\) reported on 60 patients who underwent optimal cytoreductive surgery. These patients had a 5% operative morbidity. Blythe and Wahl\(^2\) have looked at quality of life in optimal residual disease (less than 2 cm in diameter) and suboptimal residual disease (more than 2 cm in diameter) and found that 75% of the optimal group were judged to have good or good-to-fair quality of life, but only 18% of the suboptimal group achieved this quality of life. It has been argued that perhaps those women who are able to be optimally cytoreduced have biologically less virulent disease than those patients in whom optimal cytoreductive surgery cannot be achieved. This question has yet to be answered as there are no data from prospective randomized trials available.

CT scans have been used to identify the extent of ovarian cancer metastases and, in particular, to identify disease in the upper abdomen that may result in technical difficulties leading to significant residual tumor at the completion of attempted cytoreductive surgery. These sites include parenchymal liver disease, confluent sheets of tumor on the diaphragm and serosa of the liver, porta hepatitis infiltration, omental replacement with metastatic tumor that extends into the hilum of the spleen, and supramesocolic lymph node metastases. Although it is possible to resect some of these sites, CT scan findings in general reflect less than the actual findings at the time of surgery, but CT scan findings frequently reproduce and can be routinely induced by cytoreductive surgery. Therefore, CT scan findings alone should not be used in isolation to determine primary cytoreduction candidacy.

The development of carboplatin as a less toxic analogue led to several prospective randomized trials comparing single-agent carboplatin to cisplatin in previously untreated patients with advanced disease. The longest study currently has a minimum follow-up of 8 years, and no statistically significant differences in survival have been found—5-year survival rates of 15% and 19% for cisplatin and carboplatin, respectively. Similarly, an updated metaanalysis that included all clinical trials comparing single-agent carboplatin with single-agent cisplatin has also failed to detect any significant differences in progression-free survival or in overall survival for these drugs. In addition, combination chemotherapy regimens containing carboplatin have been compared with cisplatin-containing regimens. The GOG in North America, the Southwest Oncology Group, and the National Cancer Institute of Canada. No survival differences were reported in these trials. However, some investigators have suggested that in certain subsets of patients, the cisplatin treatment may be superior. A European trial compared CHAP-5 (cyclophosphamide, hexamethylmelamine, Adriamycin, and cisplatin) with CHAC, in which carboplatin replaced cisplatin. Complete remission rate for the cisplatin regimen was 32% compared with 27% for the CHAC combination. A trend toward improved survival was seen for patients with less than 1 cm of disease who were randomized to the cisplatin regimen. In patients with bulky disease, no survival differences were found.

In these studies, platinum-based regimens were routinely administered for six cycles. Prospective randomized trials have compared five cycles with ten cycles\(\text{11}\) or six with 12,\(\text{11}\) and no statistically significant differences have been reported in survival for patients treated with the greater number of cycles. However, numerous questions remain regarding the role of dose and dose intensity of these agents in the overall treatment of patients with ovarian cancer. Cisplatin dose intensity (expressed as mg/m\(^2\)/wk) was studied retrospectively in 33 published trials in ovarian cancer.\(\text{11}\) This retrospective analysis provided evidence for the importance of dose with regard to response and survival. Doses of cisplatin beyond 100 mg/m\(^2\)/cycle have been associated with unacceptable toxicity, primarily neurotoxicity. Several prospective clinical trials have compared differences in cisplatin dose intensity (\(\text{Table 36.5-1}\)). In the GOG trial, 485 patients with bulky stage III or IV disease were randomized to receive either eight cycles of cisplatin (50 mg/m\(^2\)/cycle) plus cyclophosphamide (500 mg/m\(^2\)/cycle) every 3 weeks, or four cycles of cisplatin (100 mg/m\(^2\)/cycle) plus cyclophosphamide (1000 mg/m\(^2\)/cycle) every 3 weeks.\(\text{11}\) This study demonstrated that a regimen could be administered at double the dose intensity of cisplatin with increased grade 3 and 4 myelotoxicity. However, no significant difference was noted in overall response rate or survival for patients who received the higher-dose regimen. Two similar studies from Italy also were not able to demonstrate any improvement for patients who received double-dose intensity of cisplatin.\(\text{11}\) In contrast, the study from the West Scotland's Clinical Trial Group compared two different cisplatin plus cyclophosphamide regimens and initially reported an improvement in survival for patients receiving the higher-dose intensity.\(\text{11}\) In this trial, patients with stage IC to IV disease were randomized to treatment with either 50 mg/m\(^2\) (low dose) or 100 mg/m\(^2\) (high dose) cisplatin, with all patients receiving 750 mg of cyclophosphamide. With the longer follow-up, the differences in survival appear to be decreasing.\(\text{11}\) There currently is no evidence that a dose of cisplatin greater than 75 mg/m\(^2\)/cycle should be routinely used in combination chemotherapy.
for patients with advanced ovarian cancer.

### Table 36.5-12

<table>
<thead>
<tr>
<th>Study</th>
<th>Comparator</th>
<th>Median Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOG 132</td>
<td>PAC</td>
<td>31.2 months</td>
</tr>
<tr>
<td>GOG 132</td>
<td>CP</td>
<td>38.9 months</td>
</tr>
</tbody>
</table>

In contrast to cisplatin, carboplatin is rapidly excreted in the kidney. The area under the concentration-time curve is dependent on glomerular filtration rate (GFR). Retrospective studies have identified a correlation between response and toxicity and area under the curve (AUC), with a plateau for response at an AUC of 6 to 7. Formulas have been developed to individualize dose based on AUC and patients' renal function. In Calvert's formula, the dose (mg) = AUC × [GFR + 25].

In these studies, GFR was estimated by $^{125}$I/EDTA clearance. Creatinine clearance, however, can be used to approximate GFR and can be measured or estimated with age and serum creatinine. Progressive randomized trials have been performed in which patients with advanced ovarian cancer have been randomized to different AUCs covering a twofold difference in dose intensity. In a study from the Danish Ovarian Cancer Study Group, there was no increased efficacy for patients randomized to receive an AUC of 4 versus 8. All patients in this trial also received cyclophosphamide. In the trial from the United Kingdom, patients received carboplatin dosed to an AUC of 6 or 12. Greater grade 4 toxicity in patients scheduled to receive an AUC of 12 subsequently was found, which led to substantial dose reduction.

Several randomized trials also have explored cisplatin plus cyclophosphamide versus doxorubicin-containing combinations. In the GOG trial, 349 patients with advanced disease were randomized to receive either cisplatin plus cyclophosphamide or a PAC combination (cisplatin, doxorubicin, and cyclophosphamide). No significant differences were reported with regard to complete remission rates (30% vs. 33%), progression-free interval (median, 22.7 months vs. 24.6 months), or overall survival rate (median, 31.2 vs. 38.9 months). In contrast, a large Italian trial has reported a significantly higher, surgically confirmed, complete remission rate (62% vs. 40%) and a 10-month increase in median survival for patients treated with PAC compared with cyclophosphamide and cisplatin (CP). Two separate metaanalyses pooling the data from these clinical trials has identified a survival benefit between 5% and 7% from years 2 to 6 for patients with the doxorubicin regimens. Direct comparison of these regimens, however, has been somewhat limited by differences in toxicity and dose intensity. Only the GOG study was performed with regimens that produced comparably hematologic toxicity. Although the metaanalysis suggested that the addition of doxorubicin slightly prolonged survival, a large prospective comparison [International Collaborative Ovarian Neoplasms (ICON) trial III] of single-agent carboplatin (AUC = 5) versus the PAC regimen did not demonstrate any differences in either progression-free survival or overall survival rates.

Before the demonstration of the role of paclitaxel in the initial chemotherapy of patients with advanced ovarian cancer, standard chemotherapy regimens in the United States consisted primarily of either cisplatin (75 mg/m$^2$) or carboplatin (dosed to an AUC of 6 to 7, or approximately 350 mg/m$^2$) together with cyclophosphamide (at a dose of 600 to 750 mg/m$^2$). In contrast, many clinicians in Europe continue to use the PAC regimen or single-agent carboplatin.

### Paclitaxel Combination Chemotherapy

Taxanes are a new class of cytotoxic agents with a unique mechanism of action. Paclitaxel and docetaxel both have been demonstrated to have activity in platinum-resistant patients. The taxanes exert their cytotoxicity primarily by their effect on microtubules. Taxanes bind to microtubules and shift their equilibrium toward microtubular assembly, leading to a cell-cycle arrest in G$_2$M. Premedication with steroids, cimetidine, and diphenhydramine has essentially eliminated the hypersensitivity reactions that limited early phase I trials. Of particular importance in the phase II trials, which demonstrate an overall response rate of 30% to 40%, was the observation that paclitaxel was active in patients who had disease progression while receiving cisplatin or had a duration of remission of less than 6 months. In the GOG trial of 43 patients, 27 were defined as platinum-resistant. The overall response rate in this subset of patients was 33%, compared with the overall response rate of 37%. Toxicities of paclitaxel include alopecia, myalgia, and myelosuppression (primarily neutropenia with little effect on platelets). The activity of paclitaxel was confirmed in other phase II trials.

Based on these results, a series of prospective randomized trials have compared platinum and paclitaxel versus regimens without paclitaxel (Table 36.5-12). The GOG study randomized almost 400 patients with suboptimal stage III and IV disease to paclitaxel plus cisplatin or to cyclophosphamide plus cisplatin. The paclitaxel regimen was superior with regard to response rate, complete remission, second-look rate, progression-free survival, and overall survival (Fig. 36.5-7). In this group of patients with poor prognosis and advanced disease, a 14-month improvement in median survival (24 months vs. 38 months) is seen in patients treated with the paclitaxel combination. The results of this study were confirmed by a European/Canadian trial that had a similar randomization. In this trial, however, paclitaxel was administered at 175 mg/m$^2$ in a 3-hour infusion instead of the 24-hour infusion used in the GOG trial. Furthermore, in the latter trial, in contrast to GOG 111, patients initially randomized to the nonpaclitaxel combination were frequently crossed over at the time of disease progression if they were initially randomized to cisplatin plus cyclophosphamide. Nevertheless, the results of this trial also showed a 10-month improvement in overall survival for patients treated initially with paclitaxel plus cisplatin. The subsequent trial by the GOG in the same group of patients was a three-arm study in which patients were randomized to receive single-agent cisplatin (100 mg/m$^2$), single-agent paclitaxel (200 mg/m$^2$), or the combination of cisplatin plus paclitaxel as described earlier in this section. In this protocol (GOG 132), most patients randomized to single-agent treatment actually received both drugs in sequence, as patients were routinely crossed to the other arm before clinical progression was noted through either persistent disease radiographically or findings of residual disease at second-look laparotomy. Although no difference was found in median survival between any treatment approach and GOG 132, six cycles of combination chemotherapy were judged to be the preferable regimen because of decreased toxicity.

### Figure 36.5-7

Disease-free (A) and overall (B) survival of patients with suboptimal stage III and IV ovarian cancer randomized to treatment with cisplatin plus cyclophosphamide (solid line) or cisplatin plus paclitaxel (dotted line). (From ref. 133, with permission.)
The preliminary results of the European trial (ICON III) comparing carboplatin plus paclitaxel versus cisplatin plus paclitaxel in advanced ovarian cancer were randomized in a two-by-two bifactor design to receive paclitaxel by 24- or 3-hour infusion and one of two different doses of paclitaxel (175 mg/m² or 135 mg/m²). A 3-hour infusion at 175 mg/m² was the preferred paclitaxel dose schedule for patients with ovarian cancer because of decreased neutropenia and a trend toward increased efficacy at the higher dose. The GOG pilot study demonstrated the safety and efficacy of paclitaxel (175 mg/m²) in a 3-hour infusion together with carboplatin (dosed to an AUC of 7.5). The overall response rate to this combination was 75%, with 67% of 24 patients with measurable disease achieving a clinical complete remission. The median dose of carboplatin was 470 mg/m² when using the Calvert formula to select an AUC of 7.5 (Fig. 36.5-8). This dose of carboplatin, even when combined with paclitaxel at 175 mg/m², was higher than that usually used in combinations when the drug is empirically dosed based on body surface area (300 to 350 mg/m²).

![Comparison of carboplatin dosage by area under the curve (AUC) and body surface in ovarian cancer patients receiving combination chemotherapy with paclitaxel and carboplatin. Most patients received an AUC of 7.5, which corresponds to a mean dose (based on body surface area) of 471 mg/m². (From ref. 140, with permission.)](image)

**TABLE 36.5-12.** Randomized Trials of Paclitaxel plus Platinum in Advanced Ovarian Cancer

The overall response rate to this combination was 75%, with 67% of 24 patients with measurable disease achieving a clinical complete remission. The median dose of carboplatin was 470 mg/m² when using the Calvert formula to select an AUC of 7.5 (Fig. 36.5-8). This dose of carboplatin, even when combined with paclitaxel at 175 mg/m², was higher than that usually used in combinations when the drug is empirically dosed based on body surface area (300 to 350 mg/m²).

![Comparison of carboplatin dosage by area under the curve (AUC) and body surface in ovarian cancer patients receiving combination chemotherapy with paclitaxel and carboplatin. Most patients received an AUC of 7.5, which corresponds to a mean dose (based on body surface area) of 471 mg/m². (From ref. 140, with permission.)](image)

**TABLE 36.5-13.** Randomized Trials of Carboplatin plus Paclitaxel versus Cisplatin plus Paclitaxel

All three randomized trials comparing cisplatin plus paclitaxel versus carboplatin plus paclitaxel have been presented in preliminary form and all have come to the same conclusion. GOG 158 was the largest of these trials and was different from the European studies in that only patients with optimal stage III disease were eligible. More than 800 patients were randomized to cisplatin (75 mg/m²) plus paclitaxel (135 mg/m² at 24-hour infusion) versus carboplatin (AUC = 7.5) plus paclitaxel (175 mg/m² in a 3-hour infusion). Patients were well balanced for prognostic factors. No difference was found in median times to progression between these two regimens, and the hazard ratio was 0.90 (95% CI, 0.76 to 1.11), which essentially excludes the possibility that carboplatin plus paclitaxel is inferior to cisplatin plus paclitaxel. In addition, increased metabolic and gastrointestinal toxicity was associated with the cisplatin regimen. Survival comparisons between the two treatment arms await further penetration of the data. The Arbeitsgemeinschaft Gynaekologische Onkologie trial 139 incorporated the quality-of-life instrument in its comparison of cisplatin plus paclitaxel versus carboplatin plus paclitaxel and demonstrated the superiority of the carboplatin combination. Based on these clinical trials, carboplatin plus paclitaxel is now generally accepted to be the preferred platinum regimen for treatment of patients with advanced ovarian cancer.

Numerous issues still remain regarding the optimal use of paclitaxel with carboplatin in patients with ovarian cancer. The importance of dose and schedule of paclitaxel has not been established. Phase II trials of high-dose paclitaxel (250 mg/m²) had reported a response rate of 48%, 141 which was higher than other phase II trials using lower doses. The GOG has completed a randomized trial of two different doses of paclitaxel. This trial showed that high-dose paclitaxel (250 mg/m²) had only a modest effect in patients with recurrent ovarian cancer. 142 The overall response rate was 36% versus 27.5% for a 175 mg/m² dose. Survival was similar—12.5 months versus 11.9 months. However, even with granulocyte colony-stimulating factor (G-CSF) support, substantially greater toxicity was seen with the higher dose schedule. Additional studies are currently in progress in Europe in previously untreated patients with advanced ovarian cancer who are randomized to receive two different doses of paclitaxel, with all patients receiving the same carboplatin dose. No survival data are yet available from these trials. The optimal number of cycles of paclitaxel plus carboplatin to be used as initial therapy for patients also remains to be determined. No evidence suggests that increasing the number of cycles of cisplatin plus cyclophosphamide improves outcome. Prospective randomized trials are, however, in progress in which patients who achieve a clinical complete remission with paclitaxel plus carboplatin are randomized to maintenance paclitaxel therapy for 3 to 12 months. Until the completion of these trials, standard chemotherapy for patients with advanced ovarian cancer consists of six cycles of paclitaxel (175 mg/m² in a 3-hour infusion) plus carboplatin dosed to an AUC of 5.0.
Management after Induction Chemotherapy

The majority of previously untreated patients achieve a clinical complete remission after induction chemotherapy. Clinical complete remission is defined as no evidence of disease on physical examination or by radiographic studies, together with a normal CA-125. However, between 50% and 75% of advanced-disease patients ultimately relapse from a clinical remission. Even patients who are surgically confirmed to be in a complete remission (negative second look) still remain at high risk with a relapse rate of 30% to 50% after platinum-based chemotherapy.

SECOND-LOOK SURGERY. Second-look surgery is a carefully planned systematic surgical approach to evaluating patients who have completed a program of chemotherapy and who, by clinical examination and by diagnostic imaging studies, are free of evidence of persistent cancer. The purpose of the second-look operation is to completely explore the abdominal cavity, sample any abnormalities found, and biopsy peritoneal surfaces where microscopic ovarian cancer is likely to be found. If disease is present, additional therapy should be routinely recommended.

Second-look operations were originally introduced by Wangenstein et al. for evaluating patients with colon cancer. It was then applied in a series of studies to ovarian cancer management. The surgery is performed through a vertical incision that allows access to the peritoneal cavity from the pelvis to the diaphragm. On exploring the abdominal cavity, washings of the paracolic and pelvic spaces are performed. Adhesions are lysed and sent for histologic assessment. Sampling then begins in the pelvis with removal of large strips of peritoneum (2 cm x 3 cm) from the pelvic side walls in the areas of the round ligaments and the infundibulopelvic ligaments, from the bladder flap peritoneum, and from the cul-de-sac peritoneum. Epiploic appendages of the sigmoid colon are removed. The retroperitoneal spaces are examined, and any residual lymph node or fatty tissues surrounding the external iliac artery, vein, or hypogastric artery are removed.

Remnants of omentum are then removed, as are large strips (3 cm x 5 cm) of peritoneum in the right and left pericolic spaces. The diaphragm is carefully inspected; any abnormalities are removed. If no abnormalities are present, a strip of peritoneum overlaying the inferior surface of the diaphragm also is removed. The bowel is carefully inspected. Any nodules on the bowel surfaces are removed. Any mesenteric implants are removed. The retroperitoneal space is then explored by mobilizing the bowel. The paraaortic and vena cava areas are explored, and nodularities and fat pads are removed. The anterior abdominal wall peritoneum is also sampled. At the completion of the procedure, somewhere between 20 and 40 biopsies of peritoneum and fat pads, including the retroperitoneal lymph node-bearing areas, should have been obtained. The thoroughness of the second-look operation is determined less by the number of samples obtained and more by the size of the sheets of peritoneum that are stripped off. The larger the volume of tissue available for the pathologist to inspect, the greater the chances are that occult disease will be identified.

The most important factors determining whether a second-look operation is negative are cancer stage at the initial operation and the volume of residual disease at that operation. Patients with stage I disease have a very high incidence of negative second-look operations, whereas those with advanced disease have a significantly lower incidence of negative second-look surgeries. Patients with no residual disease after primary cytoreductive surgery have a 77% incidence of negative second-look operations. Those with less than 2 cm of residual disease have an approximately 45% incidence of negative second-look surgeries, and those with more than 2 cm of residual disease have a 15% incidence. The timing of second-look surgery has changed over the years. With the introduction of cisplatin and doxorubicin chemotherapy in the 1970s, prolonged chemotherapy was no longer indicated. As noted, randomized clinical trials did not demonstrate any improvement after six cycles of platinum-based treatment. Second-look operations only are routinely recommended for women participating in clinical trials.

Second-look operations are not without complications. A report by Rubin and Lewis analyzing 682 second-look surgeries suggested that the overall rate of morbidity was approximately 19%. A typical problem associated with this operation is infections in the surgical incision, the urinary tract, and the lungs. Some reports also have indicated the presence of bleeding and the need for blood transfusions. Experience at the Yale–New Haven Medical Center would suggest that incidence of recurrent ovarian cancer after a negative second-look operation was in the 15% to 20% range; however, others have reported recurrence rates as high as 50% within 1 year.

The greatest value of second-look surgery is assessing patients on clinical protocols in which an answer to a question regarding therapeutic efficacy is being asked or for patients who are willing to go on to second-line therapy in a research format when the status of their cancer is important to answer clinical research questions.

Advances in laparoscopic surgery have led to recommendations for laparoscopy as an alternative to laparotomy. Laparoscopic surgery can be useful if the patient is found to have disseminated miliary-type cancer and can avoid a laparotomy. However, if the patient has focal disease, it may be missed at second-look laparoscopy because of technical reasons, or it may not be resectable through a laparoscope and a second-look laparotomy must be performed. Gynecologic oncologists skilled with advanced laparoscopic techniques are now providing data suggesting that, in their hands, laparoscopic second-look operations are comparable to laparatomies.

Patients at highest risk for recurrent disease after achieving a complete remission are those who had large-volume disease before initiation of chemotherapy and those with more poorly differentiated tumors. The overall survival rate for patients with recurrent ovarian cancer is poor, and it depends on a multiplicity of factors, the most important being the length of the initial disease-free interval. However, the vast majority of patients with recurrent ovarian cancer ultimately succumb to their disease. Consequently, numerous clinical strategies are being studied in an effort to prevent or delay recurrences in patients who achieve a clinical complete remission.

RADIOTHERAPY AFTER OR COMBINED WITH CHEMOTHERAPY. Numerous small phase I and II studies have used whole abdominal irradiation as salvage treatment for patients with minimal residual disease after chemotherapy. Some authors have reported 3-year progression-free survival rates as high as 25% to 35% and occasional 10- to 15-year disease-free survivors among patients treated with abdominal irradiation after an incomplete response to chemotherapy. However, others have reported high complication rates and have been discouraged by the short duration of most remissions, particularly for patients with high-grade disease or macroscopic residual tumor. Reported 5-year survival rates for patients treated with abdominal irradiation after a negative second-look laparotomy have been approximately 60% to 70%, but are not clearly different from reported survival rates with platinum-based chemotherapy alone.

Two randomized trials have compared whole abdominal irradiation with additional consolidative chemotherapy for patients with minimal disease after surgical cytoreduction and platinum-containing chemotherapy. Bruzzone and associates randomized patients who had minimal or no residual disease after chemotherapy [doxorubicin, cyclophosphamide (Cytotoxan), and cisplatin or carboplatin] to receive whole abdominal irradiation or three more cycles of chemotherapy. The study was closed after accruing only 41 patients because disease progression had been observed in 55% of patients treated with radiation versus 28% of those treated with additional chemotherapy (P = .08). The authors recommended treatment with chemotherapy, but the small number of patients and short median follow-up weaken the conclusions of their study. In a second study by Lambert and coworkers, 254 patients with stage IIIB or IV disease received five monthly courses of carboplatin and second-look laparotomy. The 117 patients who had residual disease of 2 cm or less after secondary cytoreduction were then randomized to receive either additional courses of carboplatin or whole abdominal irradiation (24 Gy in 5 weeks). The authors reported no statistical difference in survival or disease-free survival rates between the two treatment arms.

Although a small proportion of patients treated with whole abdominal irradiation for microscopic residual disease after chemotherapy enjoy long disease-free intervals, the control rates appear to be much poorer than those reported for patients treated with initial radiation for a similar volume of residual disease. A number of factors may contribute to these disappointing results. Patients who have not responded completely to chemotherapy may have disease that is inherently more aggressive than that of patients chosen for primary treatment with whole abdominal irradiation. Radiotherapy is often compromised because of poor hematologic tolerance after aggressive chemotherapy, which further decreases the probability of the tumor being sterilized. It also has been suggested that cytoknortropic treatments (surgery, irradiation, or chemotherapy) may stimulate the proliferation of clonogenic tumor cells. Consequently, to overcome rapid repopulation, higher doses of radiation may be required to sterilize tumor cells that remain after a course of chemotherapy.

Hoskins and colleagues have reported encouraging results for a regimen that integrated whole abdominal irradiation in the initial treatment of patients with minimal residual disease after cytoreduction. In their study, radiation was given after the first three of six cycles of cisplatin and cyclophosphamide. Comparison with the results of similar studies performed during a later time with six cycles of chemotherapy alone favored the alternating regimen, particularly for patients with stage I disease (P = .04).

Clinical trials of other modalities focused on preventing or delaying recurrence after initial chemotherapy are in progress: consolidation with high-dose chemotherapy,
whole abdominal irradiation, intraperitoneal 37P, intraperitoneal chemotherapy with cisplatin, intraperitoneal immunotherapy, and additional cycles of systemic chemotherapy and hormonal therapy with agents such as tamoxifen. Randomized trials addressing these modalities have been limited by slow accrual, and currently there is no evidence that consolidation treatment is able to improve survival after six cycles of initial treatment with paclitaxel plus a platinum compound.

TREATMENT OF RECURRENT OVARIAN CANCER

The selection of treatment modalities and drug regimens for patients with recurrent ovarian cancer is based on the initial chemotherapeutic regimen used and on the nature of the initial response to treatment. Patients with recurrent ovarian cancer can be broadly divided into two subsets with a markedly different prognosis. Patients whose disease recurs with a disease-free interval of less than 6 months have a worse prognosis that approaches that of patients who progress while receiving their initial chemotherapeutic regimen. In contrast, patients who have a disease-free interval of more than 6 months or 1 year have a markedly improved prognosis, primarily because of the increased efficacy of salvage chemotherapy. In patients with a long disease-free interval, secondary cytoreductive surgery can be considered in select subsets of patients.

Secondary Cytoreductive Surgery

Primary cytoreductive surgery has well-documented benefits in the management of women with advanced ovarian cancer. The possibility that secondary cytoreductive surgery (i.e., surgery performed to remove known persistent or recurrent disease after initiating chemotherapy) may be beneficial to patients has been suggested by numerous authors. Berek et al. reported that secondary cytoreductive surgery could be performed on 12 of 32 patients (38%), and their tumors were reduced to less than 1.5 cm of residual disease. The median survival for that group was 20 months, compared with 5 months for the 20 patients whose disease could not be optimally cytoreduced. The patients most likely to undergo optimal cytoreductive surgery were those who previously had optimal primary cytoreduction, less than 1000 mL of ascites, and a tumor size of less than 5 cm at the second operation. The interval from the primary to secondary surgery should be longer than 12 months. Factors that did not have an impact on secondary cytoreductive surgery included patient age, tumor grade, type of chemotherapy, and the presence or absence of bowel obstruction. Subsequently, Segna et al. reported their experience with secondary cytoreductive surgery. They too were able to show that if optimal secondary cytoreductive surgery could be performed, patients lived longer before succumbing to ovarian cancer. Factors that influenced successful efforts in cytoreductive surgery were a time interval of more than 1 year between the original operation and the secondary cytoreductive surgery and having optimal cytoreductive surgery performed at the initial operation. It is the current recommendation at the Yale–New Haven Medical Center that women who would be suitable for secondary cytoreductive surgery at the time of recurrence are those who have had more than a 1-year time interval between the initial operation and the diagnosis of recurrence. These women preferably had optimal cytoreductive surgery performed at the initial operation. However, if a review of the operative report suggests that an aggressive attempt at optimal cytoreductive surgery was not performed, this would make them suitable for secondary cytoreductive surgery.

Neijt et al. compared the survival of women who underwent optimal cytoreductive surgery with the survival of women who were unsuccessfully optimally cytoreduced but in whom, generally after three cycles of cisplatin-based chemotherapy, a secondary cytoreductive surgery was attempted. Those patients who underwent optimal secondary cytoreductive surgery had a statistically improved survival rate compared with those who were unable to undergo optimal secondary cytoreductive surgery. However, those patients who were optimally secondarily cytoreduced did not have a survival rate comparable to those patients who had optimal cytoreduction performed at the initial operation (Fig. 36.5-9).

van der Burg et al. reported on the European Organization for Research and Treatment of Cancers (EORTC) experience with debulking surgery after induction chemotherapy for advanced ovarian cancer. Three hundred nineteen of 425 patients with advanced epithelial ovarian cancer who had more than 1 cm in diameter of residual tumor after primary surgery received three cycles of cyclophosphamide and cisplatin and were randomized to undergo secondary cytoreductive surgery or no surgery. Both groups received additional chemotherapy. The progression-free and overall survival rates were both significantly longer in the group that underwent surgery (P = .01) (Fig. 36.5-10). The difference in survival was 6 months. At 2 years after initial diagnosis, 56% of the group that underwent surgery were alive, as opposed to 46% of the group that did not. In an update, the 5-year survival rate was 23% for the surgery group and 12% for the nonsurgery group. A multivariate analysis determined that debulking surgery was an independent prognostic factor (P = .012) for survival. After adjusting for all other prognostic factors, the risk of dying was reduced by 33% (95% CI, 10% to 50%; P = .008). This study statistically confirmed improved survival with optimal secondary cytoreductive surgery. However, secondary cytoreductive surgery does not make up for inadequate cytoreductive surgery performed at the initial operation.

Palliative surgery may be necessary in women with advanced ovarian cancer. This surgery may involve a colostomy for relief of a large bowel obstruction, lyses of adhesions, and surgical management of small bowel obstruction. Small bowel obstruction is a common complication as ovarian cancer advances and becomes refractory to chemotherapy. In considering surgery to relieve small bowel obstruction, the time from the original diagnosis and treatment of the ovarian cancer to the time of the obstruction is important, as is the adequacy of the initial cytoreductive surgery. Women who present as small bowel obstruction during the initial course of chemotherapy and who have not undergone optimal cytoreductive surgery generally have biologically aggressive tumors for which the role for surgery of the small bowel is minimal. A palliative gastrostomy tube may be most appropriate in this situation. In turn, women who have had prolonged periods during which they were free of disease, usually lasting more than 1 year from the original diagnosis, do benefit from small bowel surgery to relieve obstruction. However, a pseudo–small bowel obstruction pattern can be seen in women with advanced ovarian cancer with intraabdominal carcinomatosis, which occurs when ovarian cancer cells infiltrate the
myenteric plexus of the small bowel. Surgery generally plays no role in management of these patients. Medical treatment with metoclopramide, which stimulates motility of the upper gastrointestinal tract without stimulating gastric, biliary, or pancreatic secretions, may at times be helpful. Large bowel obstruction, particularly sigmoid colon obstruction, is relieved by performing colostomies and can allow the patient to have significant prolongation of life and improved quality of life if the disease is confined to the pelvis.

Chemotherapy for Recurrent Disease

Patients with ovarian cancer who had a response to chemotherapy and then relapsed after a disease-free interval of more than 6 months are considered drug sensitive. These patients are routinely retreated with single-agent carboplatin or paclitaxel. The likelihood of achieving a secondary response to either of these agents is based on the length of the disease-free interval. Single-agent carboplatin has a more favorable toxicity profile than cisplatin and remains the preferable platinum compound for treatment of recurrent disease. Some studies have suggested that the weekly administration of paclitaxel may be superior to the use of the traditional 3-week schedule in patients with recurrent ovarian cancer, although prospective randomized trials comparing these two different schedules are currently in progress. In addition to the “platinum-free” interval, the probability of response to second-line chemotherapy is related to additional clinical factors. Eisenhauer et al. identified three factors in a multivariate analysis of 704 patients who received prior treatment with platinum-based chemotherapy as independent predictors of response: serum histology, number of disease sites, and tumor size. Time from last treatment, when evaluated as a continuous variable, was not found to be an independent prognostic factor and was highly correlated with tumor size.

Retreatment with combination chemotherapy also has been used in patients with recurrent ovarian cancer. Rose et al. reported that second-line therapy with paclitaxel plus carboplatin produced a 70% complete clinical remission rate, with an additional 20% of patients achieving a partial response in patients who had previously demonstrated sensitivity to this combination when used as initial treatment. The majority of patients developed recurrence with a median interval of 9 months. Although the response rate with combination chemotherapy appears to be higher than reported for single agents, this study does not establish a clinical necessity for using combination chemotherapy in drug-sensitive ovarian cancer patients at the time of recurrence. It is possible that the same long-term survival rates could have been achieved by use of these drugs in sequence. For most patients, the appropriate choice of second-line treatment consists of single-agent chemotherapy with combinations reserved primarily for patients who have a prolonged disease-free interval.

For patients who did not respond to platinum- or paclitaxel-based retreatment or who developed resistance to these drugs when used as second-line agents, numerous other agents have been shown to have an active role. However, response rates are significantly lower in patients who have platinum- or paclitaxel-resistant cancers. Several agents, such as pegylated liposomal doxorubicin, gemcitabine, and vinorelbine, have been studied in patients with platinum- and paclitaxel-resistant ovarian cancer. Combined retreatment has been extensively evaluated in patients with recurrent ovarian cancer. In a phase III randomized comparison with paclitaxel, similar response rates were reported in patients who had received initial therapy with an alkylating agent and platinum.

Topotecan, a second-generation semisynthetic camptothecin analogue, has been extensively evaluated in patients with recurrent ovarian cancer. In a phase III randomized comparison with paclitaxel, similar response rates were reported in patients who had received initial therapy with a platinum-containing agent and paclitaxel. Bookman et al. reported on 139 patients with recurrent ovarian cancer in whom 81% had resistant disease. The overall response rate was 13.7%, with a 12.4% response rate in platinum-resistant patients. Median survival was 47 weeks. Grade 4 neutropenia was the primary toxicity that occurred in 82% of the patients. The GOG performed a phase II trial of oral etoposide in both platinum-sensitive and platinum-resistant patients. Among 41 platinum-resistant patients, a 27% response rate, including a 7% clinical complete response rate, was noted. Median survival time in the platinum-resistant patients was 10.8 months. Grade 3 or 4 hematologic toxicity was common. Gemcitabine, a novel cytidine analogue with activity against other solid tumors, including lung cancer and pancreatic cancer, was shown in phase II studies to have significant activity in patients resistant to platinum or to the combination of platinum and paclitaxel. Similarly, with liposomal doxorubicin, a response rate of 26% was observed in platinum-resistant patients with a median progression-free survival rate of 5.7 months. Grade 3 and 4 nonhematologic skin and mucosal toxicities were common.

In addition to these newer drugs, older agents, such as hexamethylmelamine and ifosfamide, also have activity in platinum-resistant patients, although it appears that in patients with resistance to both platinum and paclitaxel, the response rates are low (approximately 10%).

Hormonal therapy has long been used in the treatment of patients with refractory ovarian cancer. The overall response rate of progesterational agents and antiestrogens has been approximately 10% to 15%. A large GOG study, however, reported an 18% response rate for tamoxifen administered at a dose of 20 mg orally twice per day, including a 10% clinical complete remission rate. The majority of patients achieving a response in this study had elevated levels of estrogen receptor. Hormonal therapy continues to be a viable therapeutic option for patients who cannot tolerate or who have been unsuccessful with numerous cytotoxic regimens. Tamoxifen also has been recommended as the initial salvage therapy for patients who have a rising CA-125 level as the only manifestation of their disease. Although a rising CA-125 level in a patient in a clinical complete remission is highly predictive of a symptomatic recurrence (median time to physical or radiographic evidence of recurrent disease is 4 to 6 months), there is no evidence that immediate treatment with salvage chemotherapy is more effective than reserving such treatment for when other manifestations of recurrent disease appear. A trial is ongoing in the United Kingdom in which patients with elevated markers are randomized to immediate systemic therapy or to treatment at the time of symptomatic progression.

Palliative Radiotherapy

Radiotherapy can play an important role in palliation of patients with incurable ovarian cancer. Symptoms from a growing pelvic mass frequently dominate the final months of life for patients with terminal ovarian cancer, causing pain, bleeding, and rectal narrowing. Palliative pelvic radiotherapy can provide rapid relief and, in some cases, may prevent or delay the need for diverting colostomy. Palliative treatment courses are designed to be convenient and to achieve rapid symptom relief. At the M. D. Anderson Cancer Center, palliation of pelvic disease has been achieved using two single-fraction treatments of 10 Gy each to the true pelvis delivered 1 month apart. Treatment is delivered using 18 to 25 MeV photons. In a report of 42 patients who had advanced ovarian cancer and were treated with this approach, Adelson and coworkers reported that tumors in 19% of patients partially or completely responded to irradiation after one fraction and 75% responded after two fractions. Toxicity was minimal if treatment was limited to two fractions (20 Gy). However, they reported major hemorrhagic complications in four of eight patients who survived more than 6 months after three fractions. Spans and colleagues reported a high rate of gastrointestinal complications (49% in 1 year) in patients who were treated with three fractions of 10 Gy each and misonidazole for a variety of advanced pelvic malignancies. The Radiation Therapy Oncology Group investigated the efficacy of a multiple daily fraction split-course regimen (14.8 Gy delivered at 3.7 Gy per fraction in 2 days) in patients with advanced pelvic malignancies. Treatment was repeated every 2 to 4 weeks for a total dose of up to 44.4 Gy. A complete or partial tumor response was reported in 34% of patients (42% of those completing three courses), and toxic effects were acceptable. The interval between fractions had no significant influence on the response rate.

Other authors have reported relief of pelvic pain, bleeding, large bowel obstruction, pulmonary compromise, bone pain, and other symptoms of metastatic disease with radiotherapy using a variety of fractionation schemes. Patients with isolated cerebral metastases should be treated with combined surgical resection, postoperative whole brain irradiation, and chemotherapy, if possible. With this treatment, some patients survive for more than 3 years. Survival after treatment with radiation alone is usually less than 6 months.

Intrapерitoneal Chemotherapy

Clinical trials evaluating direct intraperitoneal installation of antineoplastic agents were based on the biology of ovarian cancer and on pharmacologic modeling studies. In studies that compared intraperitoneal chemotherapy with combinations reserved primarily for patients who have a prolonged disease-free interval.

Intraperitoneal Chemotherapy

Clinical trials evaluating direct intraperitoneal installation of antineoplastic agents were based on the biology of ovarian cancer and on pharmacologic modeling studies. In studies that compared intraperitoneal chemotherapy with combinations reserved primarily for patients who have a prolonged disease-free interval.
patients who had microscopic disease before intraperitoneal paclitaxel achieved a response to therapy.

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**TABLE 36.5-14. Pharmacokinetic Advantage Associated with Intraperitoneal Administration of Selected Cytotoxic Agents**

Phase II trials demonstrated that cisplatin had the highest activity when administered via the intraperitoneal route to patients with recurrent ovarian cancer. Intraperitoneal chemotherapy had no advantage in patients with bulky disease. However, in patients with small-volume residual ovarian cancer, responses were observed (40%) in those patients who had prior response to intravenous cisplatin. Because this is the same group of patients who also had the greatest benefit from retreatment with systemic cisplatin, the possibility remained that the primary benefit of intraperitoneal therapy in these trials was due to systemic absorption and delivery to the tumor via the microcirculation.

More recently, intraperitoneal chemotherapy has been compared with intravenous therapy in randomized trials. A large prospective randomized study of intraperitoneal cisplatin (100 mg/m²) combined with intravenous cyclophosphamide (600 mg/m²) compared with intravenous cisplatin (100 mg/m²) and intravenous cyclophosphamide in patients with optimal advanced ovarian cancer was initiated in the late 1980s (Table 36.5-15). Patients eligible for this intergroup study all had residual tumor masses of less than 2 cm at the completion of cytoreductive surgery. The intraperitoneal arm was considered to be superior based on pathologically confirmed complete remission (40% vs. 31%, \( P = .10 \)) and patient survival (median survival, 49 months vs. 41 months) and a decrease in the death-hazard ratio to 0.76 for the patients treated with intraperitoneal therapy. In addition, clinical hearing loss and neutropenia were more frequent and more severe in patients receiving intravenous cisplatin. During the long duration of this study, standard intravenous chemotherapy for ovarian cancer has changed from cisplatin plus cyclophosphamide to carboplatin plus paclitaxel. Consequently, it remains to be determined whether intraperitoneal cisplatin produces a similar advantage when combined with intravenous paclitaxel. A prospective randomized trial comparing intravenous cisplatin and paclitaxel to an experimental arm consisting of two cycles of carboplatin dosed to an AUC of 9 followed by six cycles of intraperitoneal cisplatin and intravenous paclitaxel has been completed. Recurrence-free survival was increased in the experimental arm by 5.1 months, although there is no statistically significant difference in overall survival. The experimental arm had significantly increased toxicity. Based on these results and the activity of intraperitoneal paclitaxel, the GOG is conducting another randomized trial in which patients with optimal stage III disease are comparing standard intravenous paclitaxel plus cisplatin to an experimental regimen of intravenous paclitaxel on day 1, intraperitoneal cisplatin on day 2, and intraperitoneal paclitaxel on day 8.

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**TABLE 36.5-15. Intraperitoneal Cisplatin in Previously Untreated Ovarian Cancer**

A separate phase III trial of intraperitoneal chemotherapy is in progress in Europe. Patients with a surgically confirmed complete remission to standard induction chemotherapy are randomized to receive six cycles of intraperitoneal cisplatin as a consolidation regimen compared with observation. No results are available from this trial.

**EXPERIMENTAL THERAPY**

**High-Dose Chemotherapy with Hematologic Support**

Standard-dose chemotherapy produces response rates in more than 70% of patients with advanced ovarian cancer. However, most patients develop disease recurrence, at which point salvage therapy has limited curative potential. Because of the high response rate to standard-dose chemotherapy and because of retrospective studies identifying a relationship between dose intensity and response, numerous clinical studies have evaluated high-dose chemotherapy with hematologic support. However, no established role has yet been determined for high-dose chemotherapy with hematologic support in the routine treatment of patients with advanced ovarian cancer.

The initial trials used autologous bone marrow rescue in heavily treated patients who were treated with single agents followed by transplantation. Subsequently, combinations of high-dose alkylating agents and platinum compounds were evaluated. Shpall et al. summarized the results of phase I and phase II trials in ovarian cancer patients. The overall response rate is approximately 70% to 80%; however, the median duration of response is less than 10 months.

More recently, Stiff et al. reported on the results with high-dose chemotherapy with hematologic support in 100 patients with recurrent or persistent ovarian cancer. They performed a univariate and multivariate analysis to identify factors associated with prolonged survival after high-dose chemotherapy. Cisplatin sensitivity and bulk of disease were identified as the best predictors for progression-free survival. Median progression-free and overall survival rates for 20 patients with platinum-sensitive disease with less than 1 cm of volume were 19 and 30 months, respectively. In the absence of a prospective randomized trial, there is no evidence that this approach produces superior results in patients with platinum-sensitive small-volume disease compared with what could be achieved with traditional second-line chemotherapy.

In this and other studies, it is apparent that the most favorable group of patients in whom additional trials with high-dose chemotherapy are indicated consists of patients who have both chemotherapy-sensitive tumors as well as a low tumor burden. Preclinical and clinical studies also suggest that multiple applications of high-dose chemotherapy may be superior to single courses. The combination of peripheral stem cell transplantsions with hematopoietic growth factors has permitted the evaluation of multiple courses of high-dose therapy in patients with ovarian cancer. Investigators at the Memorial Sloan-Kettering Cancer Center performed phase I and II studies of dose escalation of paclitaxel with high-dose cyclophosphamide and peripheral blood stem cell transplantsions in chemotherapy-naive patients with advanced ovarian cancer. Induction therapy consisted of two cycles of cyclophosphamide (3 g/m²) plus escalating doses of paclitaxel (from 150 to 350 mg/m²) followed by G-CSF and leukopheresis to harvest peripheral stem cells. Patients then received four courses of rapidly cycled carboplatin and cyclophosphamide (1500 mg/m² per course) with hematopoietic rescue. Multiple cycles of high-dose chemotherapy could be safely administered with hematopoietic support. The overall...
Antibody conjugates (either with antineoplastic drug, biologic toxin, or radioisotopes) also have been evaluated in early trials in ovarian cancer patients. On the basis of lymphokine activated killer cells, peritoneal toxicity was unacceptable. Single agent administered intraperitoneally or as part of adoptive immunotherapy together with lymphokine activated killer cells. In initial studies with IL-2 and therapies targeting antigens and surface receptors present on tumor cells. Interleukin-2 (IL-2) has been studied extensively in ovarian cancer patients, either as a single regimen or in combination with other drugs. These regimens have included (1) chemotherapy alone; (2) chemotherapy plus IL-2; and (3) IL-2 alone. The use of IL-2 as a single agent has been limited by late toxicity, particularly in patients with bulky disease. The preliminary results of in vitro studies have suggested that IL-2 may be effective in reversing drug resistance in ovarian cancer cells. In a pilot trial, IL-2 was administered while producing an 80% reduction in growth-stimulating hormone levels in circulating lymphocytes in the majority of drug-resistant patients. Furthermore, growth-stimulating hormone depletion in tumor cells was also documented in this study. In the phase II trial, drug-resistant patients are receiving the combination of buthionine sulfoximine plus melphalan.

Additional clinical trials aimed at reversing drug resistance to platinum compounds are focused on DNA repair pathways. In platinum-resistant tumors, increased expression of the von Hippel-Lindau tumor suppressor gene is seen, which leads to partial cross-resistance to be challenging to treat. Platinum resistance is multifactorial and includes alteration in molecular species and levels of tubulin, which may be more important than MDR. Clinical studies have identified the association of MRP expression and drug resistance. The frequency of MRP expression in ovarian cancer remains to be determined. One study suggests that an associated drug-resistant protein (LRp) may have prognostic significance in ovarian cancer.

**Immunotherapy and Gene Therapy in Ovarian Cancer**

Genetic alterations in oncogene and suppressor gene function and the immunobiology of ovarian cancer are reviewed elsewhere in this text. Abnormalities in suppressor gene function, particularly TP53, are common in ovarian cancer. Cisplatin sensitivity is associated with TP53 function, with loss of function usually resulting in resistance. Loss of TP53 function may inhibit the drug-induced pathways of apoptosis. In experimental models of gene therapy, sensitivity to cisplatin can be restored in resistant cell lines by reintroduction of p53 into tumor cells. An additional potential gene therapy in ovarian cancer relates to molecular chemotherapy in which a gene product can selectively sensitize tumor cells to an agent not ordinarily toxic. Adenoviral-mediated delivery of herpes simplex virus thymidine kinase has been shown to selectively sensitize human ovarian cancer cells to ganciclovir, and clinical evaluation is planned for this combination.

The immunotherapy of ovarian cancer has evolved from the administration of nonspecific immunostimulants, such as Corynebacterium parvum to more specific therapies targeting antigens and receptors on tumor cells. Interleukin-2 (IL-2) has been studied extensively in ovarian cancer patients, either as a single agent administered intraperitoneally or as part of adoptive immunotherapy with lymphokine activated killer cells. In initial studies with IL-2 and lymphokine activated killer cells, toxicity was unacceptable. Subsequent trials with lower doses of IL-2 produced acceptable toxicity, and the preliminary report described apparent durable responses in selected patients with recurrent ovarian cancer treated with intraperitoneal IL-2.

Antibody conjugates (either with antineoplastic drug, biologic toxin, or radioisotopes) also have been evaluated in early trials in ovarian cancer patients. On the basis of prolonged survival observed in a pilot study in patients with small-volume residual disease treated with iodine 131-labeled monoclonal antibody directed against an ovarian cancer phosphatase, a larger confirmatory trial of this conjugate is planned in Europe.
**BORDERLINE TUMORS**

Epithelial tumors of low malignant potential (borderline malignant potential tumors), are unusual in that they have the capacity to metastasize yet the required treatment seems to be limited to surgery for the overwhelming majority of patients. The different pathologic and biologic natures of these tumors were not recognized by FIGO until 1971 and the World Health Organization in 1973. Borderline malignant potential tumors are distinguished from benign mucinous and serous tumors by the presence of epithelial budding, multilayering of the epithelium, increased mitotic activity, and nuclear atypia. However, they are also associated with absence of stromal invasion. These tumors can be quite large in size, with the serous tumors having mean diameters varying between 7 and 12 cm and bivalutery ranging from 33% to 75%. Mucinous tumors of borderline malignant potential tend to be larger, with a mean diameter of 17 to 20 cm, and can be associated with pseudomyxoma peritonei. One must always be certain to rule out the possibility of a synchronous appendiceal primary tumor when dealing with the latter entity.

Borderline malignant potential tumors represent approximately 4% to 14% of all ovarian malignancies. The mean age of women developing tumors of low malignant potential is approximately 20 years younger than the mean age for women with epithelial cancers of the ovary. Ovarian tumors of low malignant potential have been associated with infertility and ovulation induction.

Ovarian tumors of low malignant potential are staged in the same manner as epithelial cancers (see Table 36.5-1). However, their survival rate, stage for stage, is far superior. Klemi and Trimble reported that the survival for 538 women with tumors of low malignant potential who had stage I disease was 99% with a mean follow-up of 7 years. The survival for 415 women with stage II and III disease was 92% with a mean follow-up of 7 years. The causes of death in this review were radiation-associated complications in three patients, chemotherapy-associated complications in nine, and bowel obstruction in eight. Eight women died from invasive carcinoma, and 18 died of disease without any additional information. Noteworthy was the fact that more patients died of treatment-related complications than died of bowel obstruction from progressive disease.

Management of patients with low malignant potential tumors of the ovary is similar to that of the surgical management of invasive cancer. However, preservation of fertility should be routinely performed in young women. Tazelaar et al. found no evidence of microscopic disease in grossly normal ovaries that were bivaluted in 61 patients with stage I low malignant potential tumors of the ovary. Women with advanced disease or who have completed childbearing should undergo total abdominal hysterectomy and bilateral salpingo-oophorectomy with complete cancer staging. If intraabdominal disease is present, aggressive cytoreductive surgery should be performed.

The evidence is scant to suggest that treatment beyond that of the initial surgery has any beneficial role. This is true for stage II and III disease as well as for stage I disease. Appropriate adjuvant therapy has yet to be identified in the management of women with tumors of low malignant potential. Trope et al. studied adjuvant therapy in 253 women with stage I and II ovarian tumors of low malignant potential in four randomized trials at the Norwegian Radium Hospital between 1970 and 1985. Patients were randomized to receive (1) cisplatin or carboplatin, (2) interventional radioactive gold or phosphorus followed by no further treatment or thiota; (3) thiota versus no further treatment; and (4) cisplatin versus intraperitoneal phosphorus. No differences in the two arms in any of the four randomized studies could be identified. It was recommended that adjuvant radiation and chemotherapy were not indicated in patients with stage I or II ovarian tumors of low malignant potential. A series of 94 patients reported by Chambers et al. from Yale–New Haven Medical Center did not reveal any significant advantage to adjuvant therapy. Barnhill et al. reported on 146 women with stage I ovarian tumors of low malignant potential. No adjuvant therapy was offered, and with a median follow-up of 42.4 months (range 1.6 to 108.0), no patient has developed a recurrence.

Attempts to identify women who might be at increased risk for recurrence based on flow cytometry studies have not demonstrated consistent results. Evidence has yet to be presented confirming that routinely treating patients whose tumors is aneuploid provides survival benefit. Surgery should be the main treatment approach for this disease. Chemotherapy should be reserved for progressive disease that does not respond to surgical management.

**SEX CORD–STROMAL TUMORS**

Ovarian sex cord–stromal tumors represent approximately 5% of all ovarian cancers. In general, they tend to present with stage I disease and frequently are associated with hormonal effects, such as precocious puberty, amenorrhea, postmenopausal bleeding, or virilizing symptoms. Granulosa cell tumors are the most common of the sex cord–stromal tumors and may be associated with endometrial hyperplasia and endometrial carcinoma. One cannot always tell the steroid production of the malignancies based on histologic appearance. For example, granulosa cell tumors have been reported to be associated with virilization. Sertoli–Leydig cell tumors have been associated with endometrial cancer. Pascale et al. have demonstrated that, in virilized women, the findings of increased serum testosterone with normal gonadotropin levels and gonadotropin-releasing hormone agonist suppression of gonadotropins leading to normalization of testosterone levels suggest that variable ovarian androgen-secreting tumors are not autonomous but apparently depend on gonadotropin stimulation.

Willemsen et al. reported on 12 patients who developed granulosa cell tumors. All patients in the series underwent ovarian hyperstimulation for the treatment of infertility. All patients received clomiphene citrate and gonadotropins or both. Willemsen et al. postulated that granulosa cell tumors may already be present in the ovaries and are simply exposed by a hormone trigger or that the increased follicle-stimulating-hormone concentrations used in ovulation induction are oncogenic to granulosa cells. However, it is also possible that the discovery of granulosa cells during ovarian stimulation is coincidental.

Surgical staging of sex cord–stromal tumors is the same as that for epithelial ovarian cancers (see Table 36.5-1). Surgical management of sex cord–stromal tumors is based on the stage of the tumor as well as the age of the patient. In general, premenarchal women or patients presenting in the reproductive years tend to have stage I disease in most series. A unilateral salpingo-oophorectomy is all that is routinely necessary for the management of this disease. The role for adjuvant therapy in younger women has not been demonstrated. However, in women who have completed childbearing, surgery should be more aggressive, including a bilateral salpingo-oophorectomy and total abdominal hysterectomy along with standard surgical staging. Women older than age 40 at diagnosis are more likely to have stage II disease. Appropriate adjuvant therapy has yet to be identified in the management of women with tumors of low malignant potential. Trope et al. reported that the survival for 538 women with tumors of low malignant potential who had stage I disease was 99% with a mean follow-up of 7 years. The survival for 415 women with stage II and III disease was 92% with a mean follow-up of 7 years. The causes of death in this review were radiation-associated complications in three patients, chemotherapy-associated complications in nine, and bowel obstruction in eight. Eight women died from invasive carcinoma, and 18 died of disease without any additional information. Noteworthy was the fact that more patients died of treatment-related complications than died of bowel obstruction from progressive disease.

Patients with advanced-stage disease (i.e., stage II to IV) may benefit from additional therapy. Cisplatin-based combination chemotherapy has been the most frequently used treatment. However, few series have been reported, and they involve small numbers of women with granulosa cell tumors. Colombo et al. demonstrated that primary treatment of six women with advanced granulosa cell tumor was effective using cisplatin, vinblastine, and bleomycin (the PVB regimen). However, their experience with the PVB regimen in five patients with recurrent disease was complicated by significant toxicity, leading to two deaths. Pascale et al. reported on 10 patients with advanced or recurrent granulosa cell tumor treated with cisplatin, Adriamycin, and cyclophosphamide (CAP). Five complete and one partial response was obtained. One of the pathologically complete respondents, however, relapsed 48 months after the onset of chemotherapy. Homesley et al. reported a collaborative group experience using bleomycin, etoposide, and cisplatin combination chemotherapy in the treatment of women with sex cord–stromal tumors. Forty-eight of the 57 tumors were granulosa cell tumors. For the series as a whole, 35 patients (61.4%) receiving this combination chemotherapy regimen had complete responses. Eighteen of the 35 underwent second-look surgery. Fourteen of the 18 patients had pathologically negative second-look results, four patients had a partial response, 14 patients had stable disease, and two patients had progression of disease among the 55 patients evaluable for response. Sixteen patients received the chemotherapy after primary surgery, nine of whom had received the chemotherapy because of positive peritoneal cytology and seven for the treatment of potential 40 years, approximately 20 years earlier than the mean age for women with epithelial cancers of the ovary. Ovarian tumors of low malignant potential have been associated with infertility and ovulation induction.

The overall survival in two large series of granulosa cell tumors was 85% and 90%, with one series reporting 100% survival for stage I disease and the other reporting 94% survival for stage I disease at 5 years. The current recommendations at Yale–New Haven Medical Center for women with early-stage granulosa cell tumors are surgery only for those younger than 40 and surgery followed by etoposide and carboplatin chemotherapy for women older than 40 who have stage I disease. For women older than 40 or for any woman with advanced-stage or recurrent disease, we recommend doxorubicin, cisplatin, and etoposide. Serum inhibin levels may be useful in monitoring for relapse. However, there is at least anecdotal experience that it may be elevated for unexplained reasons. Another tumor marker, Müllerian inhibiting substance (MIS), is usually undetectable in females before puberty. Gustafson et al. reported that elevated MIS levels dramatically declined in two girls with granulosa cell tumors after surgery. MIS may be an effective marker for granulosa cell tumors and Sertoli-Leydig cell tumors. Lane et al. have demonstrated preoperative elevations of MIS in six of eight subjects (75%) with juvenile granulosa cell tumors and seven of nine (78%) with adult granulosa cell tumors. None of 21 women with normal or
nonetheless, MIS levels developed recurrent granulosa cell tumors, but incompletely resected or recurrent disease was associated with elevated MIS levels in 6 of 15 patients. Roush et al performed flow cytometric DNA ploidy and S-phase fraction analysis on 18 women with granulosa cell tumors of the ovary. Eleven of the tumors were diploid and 7 were aneuploid. Only one of ten (10%) with euploid tumors died of disease, whereas four out of five (80%) with aneuploid tumors died of the disease. This observation did not reach statistical correlation. Perhaps in the future flow cytometric studies may be useful in identifying which group of patients might benefit from adjuvant therapy as opposed to observation.

Serott-LEYDIG cell tumors occur much less often than granulosa cell tumors yet are the second most common sex cord–stromal tumor. Their management is the same as that of granulosa cell tumors in terms of staging, surgical management, and adjuvant chemotherapy. Rare forms of sex cord–stromal tumors include sex cord tumors with annular tubules associated with the Peutz-Jeghers syndrome that are usually confined to the ovaries and can be treated with surgery alone. Thecomas rarely are malignant. Malignant thecomas would be treated in the same manner as granulosa cell tumors.

Recurrent sex cord–stromal tumors are treated with surgical resection followed by adjuvant therapy. If the recurrence is isolated and could be encompassed in a radiation field, older literature suggests that radiation therapy may be of value if the malignancy is a granulosa cell tumor. The natural history of granulosa cell tumors is to be slowly growing. Although late recurrences occur, it is difficult to know for certain whether it is the resection of the recurrent cancer or resorption followed by the radiation therapy that has had an impact on prolonging patient survival. Patients with extensive recurrences should be treated with cisplatin-based combination chemotherapy.

**EXTRAOVARIAN PERITONEAL CARCINOMA**

The diagnosis and management of women who present with intraperitoneal carcinomatosis can represent a diagnostic and therapeutic problem. In some patients, the primary site is unknown, and peritoneal carcinomatosis can present as part of the syndrome of adenocarcinomas of unknown primary site. Adenocarcinomas of unknown primary site who present with peritoneal carcinomatosis can respond to chemotherapy with platinum-based regimens. In a series of 18 women treated with a platinum-based regimen, median survival was 23 months, and five patients had complete remissions and long-term survival. The histologic classification and nomenclature of peritoneal carcinomatosis has been unclear and has included terms such as mesothelioma, peritoneal papillary serous carcinoma, extravascular serous carcinoma, and paraovarian cystadenocarcinoma. Although embryologically the germinial epithelium of the ovary and the mesothelium of the peritoneal cavity are derived from the same germ cell epithelium, a subset of peritoneal carcinomas may be morphologically identified that have a more favorable clinical behavior in response to therapy compared with peritoneal mesotheliomas. It has been proposed that the former disease process be termed peritoneal adenocarcinoma (serous) of Mullerian type. The serous type of peritoneal carcinomatosis is the most common. However, other histologic types of peritoneal carcinomatosis resulting from the common ancestry of ccelomic epithelium are possible, including mucinous, endometrioid, clear cell, and mixed peritoneal adenocarcinoma of Mullerian type. Using the proposed terminology, when an uncommon subtype other than serous is present, it can be encompassed in the description. Malignant mesotheliomas have a different histologic pattern and, in most cases, can be separated from the Mullerian-type peritoneal adenocarcinomas. Peritoneal mesotheliomas are more aggressive tumors, with a survival rate of usually less than 1 year. Furthermore, in women they are relatively less common than peritoneal adenocarcinomas of Mullerian type.

Most patients with extraperitoneal peritoneal carcinomatosis have signs and symptoms similar to those women who present with advanced-stage ovarian cancer. At surgery, these women frequently have ascites with diffuse peritoneal carcinomatosis. Attempts at cytoreductive surgery usually are made, although no evidence supports survival benefit in those women with peritoneal carcinomatosis who undergo optimum cytoreductive surgery. This may be due to the fact that although no tumor nodule larger than 1.5 cm is left behind, these women have innumerable such nodules throughout the peritoneal cavity and their actual tumor burden after cytoreductive surgery remains substantial. It appears that approximately 50% of patients with peritoneal carcinomatosis can be successfully surgically cytoreduced. Survival for patients with Mullerian peritoneal adenocarcinomas is similar to that reported for advanced ovarian cancer. In a large study from the University of California, Los Angeles, the median survival of patients who received chemotherapy after primary cytoreductive surgery was 28.4 months. Patients who received cisplatin-based chemotherapy had a substantially longer survival rate (57% living longer than 23 months) than patients who were not treated with cisplatin-based regimens. Based on the pattern of metastases and chemosensitivity to platinum-based chemotherapy, it seems prudent that current therapy for this group of patients should include cytoreductive surgery followed by chemotherapy with paclitaxel plus a platinum compound.

**GERM CELL TUMORS OF THE OVARY**

Germ cell tumors of the ovary are much less common than epithelial ovarian neoplasms. However, because they are highly curable and because they affect primarily young women of childbearing potential, appropriate management by specialists is exceedingly important. Germ cell tumors account for 2% to 3% of all ovarian cancers in Western countries. They almost always occur in younger women, and their peak incidence is in the early 20s. An increased incidence of germ cell tumors is found in Asian and black societies, and these tumors represent as many as 15% of all ovarian cancers in these populations.

**PATHOLOGY**

Table 36.5-1 provides the World Health Organization classification for germ cell tumors of the ovary. Serum tumor markers for HCG and AFP are useful in the diagnosis and management of these tumors. They are often divided clinically into dysgerminoma and nondysgerminoma germ cell tumors.

**DIAGNOSIS**

Abdominal pain, pelvic fullness, and urinary symptoms are common in patients with germ cell tumors of the ovary. In a minority of patients (approximately 10%), abdominal pain can be severe, usually the result of hemorrhage, rupture, or torsion of the tumor. Abdominal distention can also be a symptom and often is associated with ascites. Patients frequently have a palpable adnexal mass that should be ultrasonographically evaluated. Surgical exploration is usually required in masses of 8 cm or larger. Serum levels of HCG and AFP are useful in the diagnosis of some germ cell tumors.

**PATTERNS OF METASTASIS**

In contrast to epithelial tumors, approximately 60% to 70% of germ cell tumors are stage I at diagnosis. Stage II and IV are relatively uncommon, and stage III accounts for approximately 25% to 30% of tumors. Primary germ cell tumors can be very large and often are greater than 20 mL in size. With the notable exception of dysgerminoma, bilateral ovarian involvement is not common. Multiple peritoneal surfaces are often involved in addition to frequent lymph node involvement. These tumors also appear to have a greater tendency for hematogenous metastases compared with epithelial tumors, and liver and lung involvement can be observed. Ascites is infrequent (approximately 20% of cases).

**SURGICAL MANAGEMENT**

The importance of initial surgical approach for the treatment of germ cell tumors of the ovary cannot be overemphasized. Most patients can have fertility preserved, and the type of operative procedure is dictated by operative findings. In most cases, the contralateral ovary and the uterus can be preserved. Even in those situations of dysgerminoma in which the incidence of bilaterality is more common, bilateral oophorectomy is not routinely necessary because postoperative chemotherapy is curative and fertility can be preserved. In cases in which the contralateral ovary is grossly abnormal, oophorectomy or biopsy can be performed and bilateral salpingo-oophorectomy performed in the case of a dysgenetic gonad.

The principles with regard to surgical staging of germ cell tumors are similar to those described for epithelial tumors. After a large transverse incision, the entire peritoneal cavity should be carefully inspected. In the absence of ascites, peritoneal washings should be obtained and all fluids should be histologically examined. If disease is grossly confined to the pelvis, random biopsies should be performed analogous to surgical staging of early-stage epithelial ovarian carcinomas. Particular emphasis should be paid to paraaortic and pelvic lymph nodes because these are more commonly involved than in epithelial tumors. Although sampling of suspicious nodes is indicated for staging, no evidence suggests that lymphadenectomy is beneficial. Cytoreductive surgery is recommended as for epithelial tumors of the ovary. However, it must be emphasized that, even in the presence of widespread metastatic disease, because of the efficacy of chemotherapy, the contralateral ovary can be preserved.
There is no role for routine second-look operations in patients with a germ cell tumor who are clinically free of disease after chemotherapy. In particular, if the primary tumor was completely resected and did not contain teratoma, second-look procedures after chemotherapy are of no established benefit (Table 36.5-16). In some patients with a teratomatous tumor, however, a second-look procedure may be beneficial. Such patients may have residual mature teratoma; particularly if the initial resection was incomplete and postchemotherapy removal of benign teratomas is beneficial. Unresected teratomas in males with testicular cancer have been known to progress and lead to significant morbidity unless completely resected. Although experience with germ cell tumors of the ovary is not as extensive, the presumption remains that teratomas can lead to life-threatening complications and should be removed after initial chemotherapy.

MANAGEMENT OF DYSGERMINOMAS

Dyserminomas are the most common malignant germ cell tumors of the ovary and often have been considered the female equivalent of a seminoma. In contrast to nondysgerminomatous tumors, dysgerminomas are more frequently stage I, involve both ovaries, spread to retroperitoneal lymph nodes, and are markedly sensitive to radiotherapy. Because these tumors are also exquisitely sensitive to cisplatin-based chemotherapy, the role of curative radiation therapy has decreased. Furthermore, current chemotherapy usually does not result in ovarian ablation.

The vast majority of patients with dyserminoma are diagnosed with early-stage disease. Because preservation of fertility is an important issue for most of these women, all carefully staged patients with stage IA disease can be observed without compromising cure because only 15% to 25% of patients recur and they can be successfully salvaged. Until the demonstration that metastatic dyserminoma could be cured with cisplatin-based chemotherapy, most patients with stage I disease and all patients with higher stages were treated with radiotherapy. Virtually all early-stage patients were cured of their disease. Even in patients with stage III disease treated with radiation therapy, the 5-year survival rate was 80% to 90%, although recurrence-free survival was substantially lower.

The GOG evaluation of platinum-based chemotherapy in dysgerminomas has followed reports on the efficacy of different regimens in testicular cancer. In the early 1980s, ovarian germ cell tumors were treated with the PVB regimen. Subsequently, based on studies in testicular cancer that demonstrated increased efficacy and less toxicity for the bleomycin, etoposide, and cisplatin (BEP) regimen, this regimen has been used in patients with metastatic germ cell tumors, including dyserminoma (see Table 36.5-16). With a median follow-up of more than 2 years, 17 of 18 patients with advanced-stage dysgerminoma treated with one of these platinum-based regimens are disease free. Based on these results in advanced disease, the current approach within the GOG is to examine the role of carboplatin (400 mg/m²) and etoposide (120 mg/m² on days 1 to 3) in completely resected stage IB to III patients with dysgerminoma.

![TABLE 36.5-16. Second-Look Laparotomy in Germ Cell Tumors of the Ovary](image)

### Table 36.5-16. Second-Look Laparotomy in Germ Cell Tumors of the Ovary

<table>
<thead>
<tr>
<th>Initial Therapy</th>
<th>Second-Look Results</th>
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<tbody>
<tr>
<td>Chemotherapy</td>
<td>Laparotomy</td>
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<td></td>
<td>Findings</td>
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<td></td>
<td>Malignant Teratoma</td>
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<td>Benign Teratoma</td>
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<td></td>
<td>Normal Tissue</td>
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<tr>
<td>Complete excision of tumor at initial therapy</td>
<td>10</td>
</tr>
<tr>
<td>Incomplete excision of tumor at initial therapy</td>
<td>10</td>
</tr>
<tr>
<td>No resection to primary tumor (IB patients)</td>
<td>6</td>
</tr>
<tr>
<td>Tumor recurrence in primary tumor (II patients)</td>
<td>4</td>
</tr>
</tbody>
</table>

**NONDYSGERMINOMATOUS GERM CELL TUMORS**

The vast majority of nondysgerminomatous germ cell tumors of the ovary are treated with surgery followed by combination chemotherapy.

The immature teratomas are the second most common germ cell malignancy, accounting for 10% to 20% of all ovarian tumors seen in women younger than 20 years. The tumors rarely occur in postmenopausal women and most commonly occur between the ages of 10 and 20 years. These tumors contain elements resembling embryologically derived tissues and can occur in combination with other germ cell tumors (mixed germ cells). Occasionally, they are the source of excessive steroids, and patients can present with sexual pseudoprecocity. Tumor markers for AFP and HCG are negative unless a mixed germ cell tumor is present.

The most important prognostic feature, and that which is used to dictate therapy, is the grade of the lesion. In stage IA, grade 1 lesions, 5-year survival rates are greater than 90%, and no evidence suggests that chemotherapy improves outcome. However, this is the only subset of patients with immature teratomas in whom chemotherapy should not be used. Even patients with stage IA, grade 2 and 3 disease have such a high relapse rate that postoperative chemotherapy is indicated.

In patients whose tumors are confined to the ovary, unilateral oophorectomy or salpingo-oophorectomy should be performed. As noted, contralateral tumor involvement is rare in germ cell tumors other than dysgerminoma. The most frequent sites of dissemination are the peritoneum and retroperitoneal lymph nodes. Widespread dissemination to lungs, liver, or brain are uncommon. Before the development of effective chemotherapy, prognosis for patients with advanced-stage germ cell tumor was poor. The same combination that was found to be curative in disseminated testicular cancer quickly replaced nonplatinum regimens such as vincristine, daunorubicin, and cyclophosphamide. The PVB regimen produced a survival rate of 71% in a heterogeneous group of germ cell patients. The current chemotherapy regimen of choice for patients with nondysgerminomatous germ cell tumors is the BEP regimen (Table 36.5-17). In the GOG trial, 89 of 93 stage I, stage II, and stage III patients with completely resected tumor are disease free after three courses of this regimen.

### Table 36.5-17. Bleomycin, Etoposide, and Cisplatin Regimen in Germ Cell Tumors

<table>
<thead>
<tr>
<th>Cisplatin</th>
<th>Etoposide (NSG)</th>
<th>Bleomycin</th>
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<tbody>
<tr>
<td>20 mg/m² x 4 d</td>
<td>120 mg/m² x 4 d</td>
<td>25 units/ml</td>
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</table>

Although no prospective comparison has been performed between PVB and BEP in patients with advanced-stage germ cell tumor of the ovary, the latter regimen is preferred because of the results of the randomized trial in patients with advanced testicular cancer in which the superiority of BEP was established. In that trial, PVB produced a 70% 4-year survival rate in patients with metastatic, far-advanced testicular tumors, which was inferior to results obtained with BEP. Furthermore, the BEP regimen was less toxic than PVB because of elimination of vinblastine-related neuromuscular toxicities.
Endometrial sions (yolk sac) tumors are derived from the primitive yolk sac and are the third most frequent germ cell tumor of the ovary. These tumors secrete AFP, which can be used as a marker for response and recurrence. Similar to other germ cell tumors, a unilateral oophorectomy can be performed because the tumors are rare, if ever, bilateral. Most patients have early-stage disease, but all patients, regardless of stage and extent of initial surgery, are treated with platinum-based chemotherapy. No evidence supports a correlation between extent of initial surgery and survival. Before the development of effective chemotherapy, 2-year survival was only 20%. However, with platinum-based chemotherapy, the complete response rate is approximately 60%.

Embryonal carcinoma and nongestational chorionic choriocarcinoma of the ovary are both extremely rare. Embryonal carcinomas can secrete both AFP and HCG, whereas pure yolk sac tumors secrete only HCG. Both tumors are associated with chemotherapy resistance and have a poor prognosis. The recommended treatment approach consists of unilateral oophorectomy or salpingo-oophorectomy followed by combination chemotherapy with the BEP regimen. Similarly, mixed germ cell tumors of the ovary may consist of two or more elements and should also be treated with surgery followed by combination chemotherapy. Diagnosis in mixed germ cell tumors is related to the relative amount of the most aggressive component. The most frequent combination consists of elements of endodermal sinus tumor and dysgerminoma. Mixed germ cell tumors may secrete any combination of markers, depending on the histologic components of the tumor.

FALLOPIAN TUBE CANCER

Primary malignant neoplasms of the fallopian tube are exceedingly rare, and only a few hundred new cases are diagnosed annually in the United States, making it the least common site of origin for a malignant neoplasm of the female genital tract. Most fallopian tube carcinomas present as papillary serous adenocarcinomas. Intraperitoneal dissemination of fallopian tube carcinomas is similar to that observed with epithelial ovarian cancer. However, there appears to be a higher propensity to spread outside the pelvic cavity. Survival has been shown to be dependent on the depth of invasion of the tumor in the fallopian tube. For intermuscular lesions, 5-year survival is 91%, compared with 53% for tumors with mucosal wall invasion, and less than 25% in those situations in which the tumor has penetrated the tubal serosa. In addition to the depth of invasion, histologic differentiation and lymphatic capillary space involvement also have been shown to be of prognostic significance. In cases of metastatic disease, the distinction between metastatic ovarian carcinoma can be difficult. Criteria frequently used to confirm the diagnosis of a primary fallopian tube carcinoma include histologic pattern reproducing the epithelium of the mucosa with a papillary pattern, evidence for transition between benign and malignant tubal epithelium in the wall, and less tumor in the ovaries than in the tubes. In difficult cases, tumors are at times referred to as tubo-ovarian carcinomas. A minority of fallopian tube carcinomas are bilateral at the time of diagnosis. In contrast to patients with ovarian cancer, the majority of patients with tubal carcinoma are diagnosed with disease confined to the tubes and pelvic structures.

Patients with fallopian tube carcinomas appear to have a shorter history of symptoms compared with those with epithelial ovarian carcinomas. The most common symptom is postmenopausal vaginal bleeding. Abdominal pain and leukorrea are also common. Tubal distention produces more intense pain than is usually reported by patients with ovarian cancer, and these symptoms may present for the fact that more patients present with earlier stage carcinoma than patients with epithelial ovarian cancer. Currently, no data have been reported on the role of paclitaxel in this tumor. However, based on similar responses to cisplatin-based chemotherapy, it appears that the combination of paclitaxel plus a platinum compound should be considered the current chemotherapy regimen of choice for fallopian tube carcinoma.

The surgical management of patients with fallopian tube carcinoma is identical to that of epithelial ovarian cancer. Survival is improved in that group of patients in whom survival is similar to that of patients with early stage epithelial ovarian cancer. However, many patients present with later stage cancer, and these tumors may be symptomatic for the fact that more patients present with earlier stage carcinoma in whom the absence of specific symptoms may account for more disseminated disease.


Molecular Biology of Breast Cancer

FAMILIAL DISEASE

The purpose of this chapter is to provide an introduction to the cellular, genetic, biochemical, and molecular bases of breast cancer. Although the roles of steroid hormones have occupied breast cancer researchers since the 1950s, the roles of growth factors did not begin to emerge until the 1980s. The 1980s also saw the discovery of many of the oncogenes and suppressor genes driving progression of the disease and highlighted the connections to growth factor and steroid regulatory pathways. The 1990s witnessed the discovery of genes causing the familial forms of breast cancer. The final decade of the twentieth century also ushered in major advances in our understanding of the cell cycle, DNA repair, and cell death (apoptosis) and their regulation.

Much excitement has been generated over the successes in identifying the inherited defects in somatic genes responsible for hereditary and familial breast cancers (Table 37.1-1). Although hereditary breast cancers occurring in defined syndromes are characterized by a very high penetrance of multiple types of cancer, breast cancer families may also display a lower penetrance and not be so clearly associated with elevated risk for multiple other types of cancer. The incidence of the former category is estimated at 1% of breast cancer cases, whereas the latter make up approximately 5% to 10% of cases. Most researchers in the field of hereditary genetics of breast cancer have focused on genes that confer to the two-hit hypothesis, which states that a point mutation might be inherited in one allele of a candidate gene at a putative susceptibility locus and that loss of heterozygosity (LOH) or another genetic alteration might occur in the other allele of that locus later in life, leading to cancer.

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<th>TABLE 37.1-1. Major Genetic Defects in Breast Cancer</th>
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The first triumph in the identification of genes leading to the multicancer syndromes that include breast cancer was the demonstration that the TP53 gene (on chromosome 17p13) is responsible for the Li-Fraumeni syndrome of hereditary breast cancers, sarcomas, and other tumor types.\(^2\)\(^3\)\(^4\)\(^5\) As is discussed later in the section The Cell Cycle and Cell Death, mutations in this gene had been previously described in the context of progression of sporadic cancers of the breast and other organs. More recently, mutations in the PTEN (or MMAC1) gene (on chromosome 10q22-23) have been described in Cowden's syndrome of hereditary breast cancers and multicullaneous lesions.\(^6\) This gene also is discussed later in the context of growth factor signal transduction, but it may not be commonly mutated in sporadic breast cancers. Other studies have implicated mutations of the STK11/LKB1 gene (on chromosome 19) in the Peutz-Jeghers syndrome of hamartomatous polyps, breast cancers, gastrointestinal cancers, and reproductive cancers.\(^7\) and the MLH1 and MLH2 genes in the Muir-Torre syndrome of gastrointestinal and genitourinary tumors and breast cancer.\(^8\) Finally, although initially proposed to do so, mutations in the ataxia telangiectasia gene do not appear to contribute to the risk of developing breast cancer.\(^9\)

Two important genes that confer risk for the more pervasive, familial forms breast cancer have been identified. Carriers of these mutant genes may display a wide range of levels of increased risk of cancer, and the genes are quite prevalent in certain populations. King and coworkers first localized BRCA-1 (for breast cancer and ovarian cancer-1) to chromosome 17q21. The gene was subsequently cloned and found to be novel, containing an amino terminal, a zinc- and DNA-binding “ring finger” motif, a carboxy-terminal BRC (BRCA carboxy terminal) domain, and a nuclear localization sequence as recognizable motifs.\(^1\) Interestingly, mutations in this gene are particularly prevalent in breast cancer of Ashkenazi Jewish women; however, some of these women belong to families nearly devoid of multiple afflicted members.\(^1\) The detection of BRCA-1 mutations in women with no familial association of the disease also has been reported in other studies comparing different carrier populations, emphasizing the variable penetrance of inherited risk conferred by this gene. Mutations in the BRCA-1 gene have been verified in familial breast and ovarian cancer patients, but surprisingly, mutations have not been detected in sporadic breast cancers. Thus, BRCA-1 does not appear to be a classic tumor suppressor gene of relevance to both tumor onset and progression. However, studies have observed that the BRCA-1 protein may have an aberrant, cytoplasmic localization in breast cancer cells line from sporadic tumors, suggesting that a nonclassic mode of functional inactivation could be at work in this tumor type.\(^1\) Other studies have suggested that decreased expression of the BRCA-1 protein also occurs during the progression of sporadic breast cancers.\(^1\) Consistent with these findings are observations that antisense oligonucleotides directed against the BRCA-1 messenger RNA (mRNA) enhance the proliferation of breast tumor cells and mammary epithelial cells in culture in vivo. Correspondingly, other studies have demonstrated that retroviral transfer of the nonmutated BRCA-1 gene selectively inhibits growth of breast cancer cells in vitro and in vivo in nude mice.\(^1\)

A separate body of work has identified a separate locus, termed BRCA-2 (on chromosome 13q13), which is associated with familial cancers of the female and male breast and, to a lesser extent, of the ovaries. This gene also has been cloned; it shares homology with BRCA-1 and its encoded protein is now thought to function biochemically in a fashion very similar to BRCA-1. However, although BRCA-2 confers risk of female breast cancer, its effects on risk of ovarian cancer appear smaller than the risk conferred by BRCA-1. In addition, mutations of BRCA-2 confer risk of male breast cancer and (to a more limited extent) several other cancers, such as prostate cancer, pancreatic cancer, non-Hodgkin's lymphoma, basal cell carcinoma, bladder carcinoma, and fallopian tube tumors. Breast cancers of BRCA carriers are, overall, of similar prognostic significance when matched for other characteristics to the sporadic cases of breast cancer in noncarriers, although they also...
PR-positive epithelial cell populations are distinct from the majority of proliferative cells in the normal gland, in cancer these cells grow rapidly. It is of interest that in precisely the same subpopulation of ductal and lobular luminal cells, although this supposition is considered to be likely. It is of interest that the ER and PR appear PR expression also has been shown to be positively regulated by estrogen.

Estrogen-regulated PR protein is now routinely performed. In many breast tumor cell lines and in normal ER-containing tissues, such as the endometrium and brain, it has been repeatedly noted that these assays do not provide perfect prognostic tools for the disease. Although more than 60% of human breast cancers are designed as radioligand techniques, they are more commonly performed today using radioimmunoassay and immunohistochemical technologies. Although extremely responsive genes.

The steroids are also well known for their ability to modulate directly the expression of cell-cycle regulatory genes known as protooncogenes, regulator cyclin D1 (product of the CCND1 gene) also interacts with the ER to promote its transcriptional activity. Superimposed on this complexity, each estrogen receptor is able to adopt multiple conformations, depending on the characteristics of interaction of the steroid (or nonsteroid ligand) with the receptor binding pocket. For example, estrogen receptor α interacts with the nuclear transcription factor NF-κB, the major transcription factor of MYC, and the pre-S/p53 kinase regulator CCND1. A significant role of estrogen receptors is to modulate multiple aspects of mammalian gene expression.

The estrogen and progestrone receptors are dimeric, gene-regulatory proteins. Estrogen and progesterone are well-established endocrine steroid regulators that modulate multiple aspects of mammalian gene expression. These two hormones work together to drive mammalian epithelial growth, differentiation, and survival. Although both steroids are commonly thought to be of primary importance for tumors arising in the reproductive years, in addition to the TP53 gene (also known as p53), the two BRCA-1 and the two BRCA-2, are known to have specific regulatory functions. LOH, genetic regions identified as frequently rearranged, amplified, deleted, or otherwise altered have been commonly detected on chromosomes 1, 3, 6, 7, 8, 9, 11, 13, 15, 16, 17, 18, and 20. More recently, the powerful techniques of comparative genomic hybridization and chromosome painting followed by spectral karyotyping have allowed implication of additional chromosome regions, including areas of 10, 12, and 22. Although they have only begun to be used in this type of study, the techniques of comparative genomic hybridization and chromosome painting followed by spectral karyotyping can be applied to all human tumors, and have been used to identify other potentially important oncogenes in breast cancer. For example, DNA gains are common on 6q, 8p, 9q, 11q, 17q, and 20q. In each of these cases, however, the specific genes involved in driving the chromosome amplification process are still under active investigation.

The most common genetic abnormalities in the progression both of sporadic and familial breast cancers (as in many other types of solid tumors) appear to be losses of heterozygosity at multiple loci (see Table 37.1). As noted earlier, an LOH event uncovers the functional consequences of a mutation in an allele of a tumor suppressor gene. In the context of the dominant-negative model of breast cancer progression, at the TP53 gene has been identified, and the two BRCA-1 and the two BRCA-2, are known to have specific regulative functions.

Cytogenetic studies, except for those of malignancy, are thought to be governed by a series of genetic and resultant phenotypic changes in the pathways regulating cellular proliferation, differentiation, death (apoptosis or necrosis), DNA repair, tissue compartmentalization, and responses to therapy. Although several selective genetic alterations (discussed later in Oncogenes and Suppressor Genes of Breast Cancer Progression) have been identified with high frequency and proven relevance, the identity of the susceptibility DNA damage.

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Oncogenes and Suppressor Genes of Breast Cancer Progression

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It is not clear what relationship exists between ER-positive and ER-negative forms of the disease. Several ER-negative breast cancer cell lines do not transcribe the expression of TGF-α, and the expression of angiogenesis-related growth factors in these cell lines. It has been observed that circulating mouse salivary gland–derived EGF may potentiate spontaneous mammary tumor formation in the mouse model.

Increased expression and altered isozyme patterns of the family of cellular enzymes termed protein kinase C (PKC) also have been implicated during malignant progression and may play a role in development of resistance. This enzyme family can act to down-modulate ER mRNA, to activate ER function, to independently induce some estrogen-responsive genes with AP-1 sites in their promoters, and to allow expression of more invasive cellular characteristics. The PKC family contains at least nine cytoplasmic-nuclear enzymes, each of which possesses serine-threonine specificity for phosphate in addition to other cellular proteins. Different isotypes serve different cellular functions. The activity of PKC is known to be regulated by hormones and growth factors during normal lactational differentiation and to contribute to the regulation of casein expression. PKC activity has been suggested to be elevated in ER-negative and drug-resistant breast cancer relative to ER-positive breast cancer.

Treatment of ER-positive breast cancer with an activator of PKC, such as the phorbol ester 12-O-tetradecanoylphorbol-13-acetate, leads to rapid down-regulation of ER, destabilization of its mRNA, and phosphorylation of the ER protein, coincident with modulation of its function. Phosphorylation of ER and PR (induced by estrogen itself) by growth factor pathways (such as IGF-1), heregulin, cAMP, dopamine agonists, and other hormones may also constitutively activate the steroid receptors. Other current studies have suggested that receptors for other steroids (potential cancer prevention agents, retinoids, vitamin D) may modulate ER/PR function by modulating their chromatic interactions.

**GROWTH FACTOR PATHWAYS IN THE NORMAL AND MALIGNANT GLAND**

The natural secretory products of the mammary epithelial cell, colostrum and milk, are abundant sources of growth factors. Growth factors in the normal gland probably serve multiple purposes in the development of the newborn, in mammary growth, and in mammary carcinogenesis. A large body of literature has shown that estrogen, antiestrogens, progestins, and antigestins strongly regulate certain growth factors and receptors of the EGF and transforming growth factor-β (TGF-β) families, as well as growth factors, receptors, and secreted binding proteins of the EGF family of proteins (Table 37.1.4–2). EGF, apparently the most abundant milk-derived growth factor, is an important regulator both of the proliferation and the differentiation of the mouse mammary gland in vivo and of mouse mammary explants in vitro. It also has been observed that circulating mouse salivary gland–derived EGF may potentiate spontaneous mammary tumour formation in the mouse model and promote the growth of the tumors once they are formed. EGF, or other members of this growth factor family, are also required supplements for the clonal anchorage-dependent growth, in vitro, of normal human mammary epithelial cells. In contrast, human breast cancer cells in culture are largely independent of this exogenous requirement. However, most breast cancer cell lines retain EGFRs and appear to be stimulated in their growth by their own autocrine or paracrine production of this family of factors.

**TABLE 37.1.2. Sex Hormone Regulation of Growth Factor Systems in Breast Cancer**

Direct modulation of signal transduction pathways of EGF and its family members, as well as their indirect regulation by other unrelated growth factors are proving to be critical during mammary development. The EGF family consists of, at present, four receptors and more than six growth factors in mammals, and an additional half dozen growth factors encoded only by certain mammalian viruses. TGF-α and amphiregulin, close structural and functional homologs of EGF, can produce qualitatively the same proliferative effects as EGF in mouse mammary explants and in cultured human and mouse mammary epithelial cell lines. Each of these factors is also produced in proliferative, early ductal development, amphiregulin is also produced in the lobuloalveolar development of pregnancy. However, the detailed localization patterns and functions of each family member differ. For example, an immunohistochemical study in the mouse gland has revealed that expression of TGF-α is highest in the basal epithelial, proliferative end-bud cap cells, whereas expression of EGF is in scattered ductal luminal secretory cells. Hepatocyte growth factor, a non-EGF family factor, also appears to be involved in ductal morphogenesis. The EGF-related neuregulin subfamily of isoforms (including heregulin) is expressed primarily in the mammary stroma and appears to modulate the lobuloalveolar development of pregnancy. TGF-α, a heparin-binding family member termed amphiregulin, and their common receptor, the EGFR, are all detected in vitro in proliferating human mammary epithelial cells in culture. TGF-α mRNA levels are relatively low in explanted, primary cultures of resting epithelial organoids; the entire system appears tightly coupled to proliferation in the normal gland. TGF-α and amphiregulin are known to act as autocrine autostimulatory growth factors in normal and immortalized human mammary epithelial cells in mass culture, an anti-EGF antibody or heparin, respectively, reversibly inhibited proliferation. Although the majority of work on the biology
The development of transgenic technology has allowed additional correlation of expression of TGF-a, amphiregulin, and cripto-1 (another EGF family member, but with an unrelated receptor type) with mammary tumors induced by a wide range of oncogenes. This technology also has allowed study of the effect of overexpression of TGF-a under the control of mammary-specific mouse mammary tumor virus (MMTV) or metallathionine promoters in the mammary glands of mice. The multiple conclusions of these studies implicate TGF-a–induced proliferation, TGF-a–blocked differentiation, and TGF-a–suppressed, postlactational glandular regression in mammary hyperplasia and tumorigenesis. More recently, transgenic expression of the EGF subfamily known as neuregulins also has been shown to lead to mammary tumorigenesis.

Although observations of overexpression of EGF family growth factors have led to significant biologic insights into breast cancer, the greatest clinical impact has come from the study of the transforming growth factor (TGF)-a receptor. Gene expression of TGF-a receptor (TGF-aR) is downregulated in a direct correlation among TGF-a production, expression of the c-erbB oncogene, and malignant transformation was demonstrated in vitro. In vivo, subsequent work in breast cancer and in benign proliferative breast disease has also established that TGF-a overexpression is very common.

The role of TGF-a in breast cancer has been reviewed.\(^\text{14a}\) TGF-a is a cytokine secreted by many cell types in the breast, including epithelial cells and fibroblasts, and modulates cellular behavior, including cell adhesion, spreading, growth, and migration. TGF-a is one of many cytokines that modulate mammary gland function. Activation of TGF-a is controlled by its extracellular matrix (ECM) interactions and ECM mediators. The TGF-a signaling cascade comprises multiple receptors and signaling pathways. TGF-a signaling is regulated by multiple factors, including proteases, protease inhibitors, and ECM interactions. In mammalian cells, TGF-a signaling is mediated by two types of receptors: TGF-aR1 and TGF-aR2.

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It should be noted that, at present, several dozen other growth factors have been identified in breast cancer, but their consideration is beyond the scope of this chapter; this information is reviewed elsewhere. To summarize some of these data, prolactin and mammary-derived growth factor-1 might be autocrine positive factors in breast cancer, and mammary-derived growth inhibitor and mammastatin may serve negative growth functions. In addition, hepatocyte growth factor has been shown to synergize with estradiol-derived paracrine factors in the stimulator of epithelial growth and of tumor angiogenesis. Finally, vascular endothelial growth factor, pleiotropin, and platelet-derived growth factor may serve as angiogenic, vascularization-inducing factors in breast cancer. Other growth factors under hormonal regulation in breast cancer probably remain undiscovered; future investigations should evaluate this possibility. Many studies have also established that steroid regulation of growth factors is important in the uterus and, possibly, the prostate gland, as well as in the breast.

SIGNAL TRANSDUCTION AND NUCLEAR ONCOGENES

Unifying, mechanistic links between the proliferative actions of growth- and survival-modulatory steroids, growth factors, and intergins in diverse tissues are represented by the multiple classes of nuclear protooncogenes and other transcription factors (see Table 37.1-1). These transcription-regulating proteins mediate convergent pathways of regulatory stimuli directly through steroidal action, through growth factor–induced-mitogen-activated protein (MAP) kinases, through other tyrosine kinase pathways (C–PKC), through cyclic-AMP–induced JAK-STAT pathways, through TGF-b–induced SMAD molecules, and through estrogen–induced Fak/ Src pathways. The MAP kinase pathways are central pathways for the proliferative and survival stimuli exerted through the EGFR, the erbB, the ER, and these pathways through autophosphorylation and downstream binding to src homology 2 (SH2/SH3) or phosphorytrosine-binding (PTB) domains of signal transduction adaptor proteins. After mitogenic growth factor treatment of many types of cells, including normal and malignant epithelial cells, and a cascade of protein phosphorylations, c-Myc, AP-1–acting (c-fos, c-Jun, and Jun B), c-Myb, and Ets protooncogenes and ATF, EIK, SRF, and NFkB transcription factors are commonly observed to be induced. The protein products of at least three nuclear protooncogenes, c-MYC, c-FOS, and c-JUN, are also induced by both estrogen and progesterone in breast cancer. Progesterone additionally induced c-ERB2. Not surprisingly, tamoxifen down-modulates c-MYC expression during treatment-induced regression of patient tumors. c-MYC, c-FOS, and c-JUN induction also have been observed to occur in human mammary epithelial cells in vitro and in the rat uterus in response to estrogen treatment. In vivo, c-MYC, c-FOS, and c-JUN, are also induced by both estrogen and progesterone in breast cancer. Progesterone additionally induces c-ERB2. Several other c-Myc–interactive proteins exist in addition to the TATA binding protein and Max; they include TRRAP, BIN1, DAM, p107, YY1, MIZ1, and TFII-1. Thus, the c-Myc protein in breast cancer may function in breast cancer to allow growth factors or hormones to act to drive aberrant, transformed growth.

The c-Myc protein and, therefore, act in multiple systems to regulate gene expression, promote cell proliferation, inhibit differentiation, modulate cell adhesion, and effect immune recognition. Central to these effects is its role to specifically regulate initiation of DNA replication. Overall, gene regulatory functions of the protein also encompass both activation and suppression of gene expression; modulation of the cell cycle; activation of apoptosis, and chromosomal stability, depending on the cellular context and degree of expression. Myc-Max interaction with the TATA binding protein represents one transcriptional mechnism to stimulate basal transcription. A second specific transcriptional mechnism involves E-box promoter genes such as those encoding the CAD (carboxamyl phosphate synthetase–aspartate transcarbamoylase–dihydroorotate), DHFR (dihydrofolate reductase), and ODC (ornithine decarboxylase) enzymes. However, multiple c-Myc–regulated genes do not appear to possess E-boxes, and E-box–interactive sequences do not appear to be required for c-Myc effects on proliferation and apoptosis.

Several other c-Myc–interactive proteins exist in addition to the TATA binding protein and Max; they include TRRAP, BIN1, DAM, p107, YY1, MIZ1, and TFII-1. Thus, multiple other potential mechanisms may exist for transcriptional and transcriptional suppressive effects of c-Myc. Estron and progesterone induce c-Myc; the latter appears to stimulate the mammary epithelial cell cycle both by inducing the synthesis of cyclin E and the CDK2-p3a phosphatase and by triggering the degradation of p27 (kip1), resulting in an active CDK2. Activation of CDK2 results in inhibitory phosphorylation of Rb and promotes cell-cycle progression through G1/S. Additional primary effects of breast cancer appear to be induction of cyclin A to activate CDK2 and induction of the E_F, transcription factor to promote cell-cycle progression through S.

Although much is known about the cellular and molecular biology of c-Myc, it is clearly an understudied oncogene in breast cancer. It appears to be central to the disease in two respects. First, antiestrogen oligonucleotide directed against the c-Myc mRNA have been used to block estrogen-induced proliferation in breast cancer cells. Second, amplification of the c-Myc gene is now known to be one of the most common genetic alterations in breast cancer; approximately one-fifth of breast cancers contain this genetic change. A putative (but currently unidentified) suppressor gene on chromosome 1p32-pter is proposed to control amplification of other genes, (e.g., cyclin E, c-Myc, or the simian virus 40T nuclear oncoproteins (but not v-Ras), alter cellular resistance to in vitro -platinum and other DNA strand scission–inducing drugs, and is associated with poor prognosis, high S phase, and postmenopausal disease. Although the latter has not been confirmed.

Based on several investigations in various epithelial malignancies, including those of the ovary and liver, c-Myc activity is thought to cooperate with TGF-a and EGRF overexpression and with downstream signaling pathways. Thus, dual stimulation of the EGRF pathway and c-Myc may serve a general cooperative function in epithelial transformation.

The c-Myc protein may, therefore, act in multiple systems to regulate gene expression, promote cell proliferation, inhibit differentiation, modulate cell adhesion, and effect immune recognition. Central to these effects is its role to specifically regulate initiation of DNA replication. Overall, gene regulatory functions of the protein also encompass both activation and suppression of gene expression; modulation of the cell cycle; activation of apoptosis, and chromosomal stability, depending on the cellular context and degree of expression. Myc-Max interaction with the TATA binding protein represents one transcriptional mechanism to stimulate basal transcription. A second specific transcriptional mechanism involves E-box promoter genes such as those encoding the CAD (carboxamyl phosphate synthetase–aspartate transcarbamoylase–dihydroorotate), DHFR (dihydrofolate reductase), and ODC (ornithine decarboxylase) enzymes. However, multiple c-Myc–regulated genes do not appear to possess E-boxes, and E-box–interactive sequences do not appear to be required for c-Myc effects on proliferation and apoptosis.

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certain chromosomes could suppress malignancy in vitro in cell hybrid studies.\(^1\) This concept has led to the discovery of several tumor suppressor genes in breast cancer, some regulating the cell cycle and cell death, and others regulating different aspects of the progression of the disease.

The first tumor suppressor gene shown to confer risk of an inherited breast cancer syndrome was termed TP53, and more recently, the PTEN gene was implicated in this respect. Also, the two BRCA genes (see Table 37.1-1) are responsible for a larger group of patients with an inherited pattern of breast cancer (BRCA-2) and breast plus ovarian cancers (BRCA-1). It is now widely accepted that BRCA-1, BRCA-2, and PTEN all function as tumor suppressor genes. However, in contrast to TP53, their mutations are uncommon in sporadic breast cancers. Conversely, three other well-established tumor suppressor genes, CDKN2 (p16), RB-1, and CDH1 (E-cadherin), are commonly altered (mutation, methylation, LOH, and deletion) in sporadic breast cancer but do not appear to be involved in conferring familial risk of the disease (see Table 37.1.1).

During the malignant progression of breast cancer to its fully metastatic state, mutation, inactivation, loss, or down-regulated expression of tumor suppressing genes commonly occurs. Estimated incidences of these processes for the relevant, known suppressor genes are as follows: TP53, 30% to 40%; RB-1, 15% to 20%; CDKN2, 20% to 30%; and CDH1, 20% to 30%.\(^1\) Tumor suppressor genes appear to function in four major ways: as antiproliferative or antisurvival factors, as DNA-repair inducers, and as differentiation-promoting agents. BRCA-1 and BRCA-2 serve roles to directly repair damaged DNA. The ATM protein (described earlier as a suspected tumor suppressor) detects the damage and transmits the signal to the BRCA proteins, while multiple other proteins, such as Rad51 and p53, serve roles downstream of the BRCAes.\(^1\) E-cadherin, a suppressor that works through an unrelated pathway, serves to strengthen homotypic interactions of mammary epithelial cells and maintain their differentiated status; in addition, it promotes sequestration of β-catenin (a proliferation-promoting protein that regulates the T-cell factor (TCF) class of transcription factors).\(^1\) p53, by inducing the p21 protein (Waf-1/CIP-1), also inhibits proliferation, whereas the p16 protein also serves to inhibit the cell cycle; both p53 and p16 suppressor proteins ultimately promote phosphorylation and inactivation of Rb to block G₁ and G₂/S transit of the cell cycle.\(^1\)\(^2\) Although Rb is thought to be a central tumor suppressor protein in breast cancer, it appears to be understudied at present, particularly with respect to its mutation status. PTEN serves to suppress cell survival and proliferation by dephosphorylating phosphoinositides to prevent their activation of the three AKT signal transduction kinases.\(^1\)\(^2\)\(^3\)\(^4\) Beyond the scope of this chapter is the consideration of literally dozens of additional candidate tumor suppressor genes that also function on these cellular pathways (see also the section Process of Malignant Progression)\(^1\)\(^3\).

Study of the TP53 gene has provided remarkable insights into multiple aspects of cancer biology. TP53 is a tumor suppressor gene, but when mutated in one of several sensitive regions, its conformation changes, its stability increases, and its regulatory properties are radically altered. Mutation can confer a loss of tumor suppressor activity and gain of tumor promotion function.\(^1\)\(^2\) The nonmutated p53 gene product is an oligomeric DNA binding protein that functions to trigger cellular responses to DNA damage; it has been termed the "guardian of the genome."\(^1\)\(^2\)\(^3\)\(^4\)\(^5\)\(^6\) p53 functions both by protein-protein interactions and by regulation of transcription. The p53 protein appears to function in the context of DNA damage as a G₁/S and G₂/M checkpoint controller to slow cell growth and induce DNA repair; cell death is triggered in a process termed apoptosis if damage is too severe for repair. It is of particular importance for the progression of many cancers, including breast cancer, that mutation of p53 is associated with enhanced genetic instability.\(^1\) Certain viral proteins, although they are probably not relevant to breast cancer, are known to inactivate p53 as a critical event in viral carcinogenesis.\(^1\)

It is not yet fully clear what molecular events induce (through protein stabilization) the p53 protein. However, it is well known that UV irradiation and double-strand DNA breaks are strong inducers of p53 stabilization through the DNA-dependent protein kinase and the ATM gene product. ATM is a signal transduction protein with high homology to phosphatidylinositol-3-kinase.\(^1\)\(^2\)\(^3\)\(^4\) Of uncertain masses of basic objects are observations that inhibitors of PKC inhibitors, serine-threonine phosphatases, and cAMP can prevent undiminished response. On a molecular level, p53 induces growth arrest in multiple processes of the cell cycle through induction of p21, a multipotent inhibitor of cyclin-dependent kinases (CDKs), which blocks cell-cycle progression (discussed later in Cyclins, Cyclin-Dependent Kinases, and Inhibitors);\(^1\) p21 also blocks a catalytic inhibitor of a DNA replication termed proliferating cell nuclear antigen (PCNA). A very important, specific consequence of p21 induction is the inhibition of cyclin E–CDK2-catalyzed phosphorylation of the Rb protein. Hyperphosphorylation of Rb allows its function as an additional cell-cycle inhibitor.\(^1\) p53 is also thought to directly modulate translation of the Rb and to directly bind a partner of Rb (termed p70) at the protein level.\(^1\) Additionally, p53 induces transcription of genes encoding cyclin G, ERCC (excision repair cross-complementing), and Gadd 45 (growth arrest DNA damage), all proteins thought to be involved in DNA repair. A third general process triggered by p53 is apoptotic death. This process is quite distinct from necrotic death in that it requires ATP, the cell condenses the DNA breaks are strong inducers of p53 stabilization through the DNA-dependent protein kinase and the ATM gene product. ATM is a signal transduction protein with high homology to phosphatidylinositol-3-kinase.\(^1\)\(^2\)\(^3\)\(^4\) Of uncertain masses of basic objects are observations that inhibitors of PKC inhibitors, serine-threonine phosphatases, and cAMP can prevent undiminished response. On a molecular level, p53 induces growth arrest in multiple processes of the cell cycle through induction of p21, a multipotent inhibitor of cyclin-dependent kinases (CDKs), which blocks cell-cycle progression (discussed later in Cyclins, Cyclin-Dependent Kinases, and Inhibitors);\(^1\) p21 also blocks a catalytic inhibitor of a DNA replication termed proliferating cell nuclear antigen (PCNA). A very important, specific consequence of p21 induction is the inhibition of cyclin E–CDK2-catalyzed phosphorylation of the Rb protein. Hyperphosphorylation of Rb allows its function as an additional cell-cycle inhibitor.\(^1\) p53 is also thought to directly modulate translation of the Rb and to directly bind a partner of Rb (termed p70) at the protein level.\(^1\) Additionally, p53 induces transcription of genes encoding cyclin G, ERCC (excision repair cross-complementing), and Gadd 45 (growth arrest DNA damage), all proteins thought to be involved in DNA repair. A third general process triggered by p53 is apoptotic death. This process is quite distinct from necrotic death in that it requires ATP, the cell condenses the

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Although quite complex, the balance of life/ apoptosis is critically regulated in cancer progression and response to therapy (see Table 37.1-3). Estrogen, progesterone, TGF-α, EGF, and insulin all appear to suppress apoptosis and promote survival of breast cancer model systems. Antiestrogens, antiangiogenesis, TGF-b, and the overexpressed c-Myc oncoprotein can induce apoptosis without countered with a survival-promoting, environmental influence. Current research is focused on how these factors regulate the apoptotic pathways.\(^1\)\(^2\) The system has clear implications for response of breast cancer to radiation, anthracyclines and biologic therapies, chemotherapy, and even gene therapy. For example, it has been suggested that estrogen promotes chemotherapeutic resistance of induction of p53 mutation results in resistance to chemotherapy;\(^1\)\(^2\)\(^3\)\(^4\) and that experimental gene therapy with bclx can differentially kill tumor cells and sensitize them to chemotherapy but spare bone marrow cells.\(^1\)\(^2\)\(^3\)\(^4\)\(^5\)\(^6\) Gene therapy addressing the p53 gene directly has also been proposed.\(^7\)

The RB-1 gene product also has tumor suppressor functions and is a nuclear protein. When mutated in one of several critical regions, the function of the gene product is inactivated. The RB protein is also functionally inactivated by phosphorylation; this phosphorylation is catalyzed by one or more cyclin-dependent protein kinases. It is of interest that a large number of cellular growth regulatory proteins, such as members of the c-Myc, CDK, and E₂/F-1 families, bind the RB protein or its family members. RB appears to function to restrict cellular entry into the S phase of the cell cycle (Table 37.1-4).\(^7\)\(^8\) Hypophosphorylated Rb binds E₂/F-1 and DF-1 family members to restrict access of these transcription factors to the chromatin. This is a blockade of transcription from genes involved in G₁/S progression and S phase in the cell cycle.\(^9\)\(^10\)
Almost certainly, the most important consequences of these molecular changes initially relate to limited effectiveness of antihormonal therapy, chemotherapy, and predominate in early breast cancer, potentially causing the chromosomal type of instability. Defects appear to be associated primarily with later stages of progression and metastasis of breast cancer. In contrast to colon cancer, centrosomal defects appear to mechanisms for genetic instability and accumulation of further mutations in other cancers, such as colon cancer, have been proposed to initially depend on genetic changes occurs, resulting from overall genomic and chromosomal instability. Familial disease may bypass one or more steps in this cascade. The next steps in tumorigenesis almost entirely involve spontaneous gene amplification, LOH, and mutations, which arise because of overactive cell cycles or tumorigenic progression—replicative immortality.

As important regulators of the epithelial cell cycle in breast cancer, tyrosine kinase receptor-acting growth factors and sex steroids induce both c-Myc and cyclin D1. c-Myc itself appears to suppress D1 in cycling cells, induce cyclin E (and possibly CDC25A), and trigger the proteosome-mediated destruction of the CDK1 p27 (kip1) and activation of CDK2. Cyclin D1–CDK4 is inhibited by the CDK inhibitor p15 (INK4), by the tumor suppressive CDK1 p16 (MTS1 or INK4b), and by p18 and p19, more recently defined CDKIs of the same family. Cyclin D–CDK4 and cyclin E–CDK2 are also each inhibited by the CDK1 termed p27 (Waf1/CIP-1), which is induced by p53; by p27 (kip1); and by p27 (kip2), which may be involved in cellular senescence. It has been shown that synthesis of CDK4 is inhibited by TGF-b; overexpression of CDK4 leads to TGF-b resistance. p27 is also of note because it is induced by growth-inhibitory TGF-b. Rb is phosphorylated and inactivated both by the cyclin D–CDK4 and by the cyclin E–CDK2 kinases. Many effects of multiple regulators of G_s and G_2/S are thus integrated by their collective effects on phosphorylation of Rb. c-Myc also degrades S phase by inducing cyclin (to activate CDK1) and E_sF-1. P53 also functions later in the cycle; its mutation not only abrogates the G_1/S checkpoint, but also a post-M spindle assembly checkpoint. Evidence is rapidly accumulating that the development of cancer is a process that not only involves disregulation of proliferative factors and activation of oncogenes but also disregulation of inhibitoty factors and loss of suppressor gene function (Fig. 37.1-1). Studies in breast cancer have served to underscore the role of germline deletion or mutation of suppressor genes in the familial forms of the disease, and somatic gene amplifications, mutations, deletions, and rearrangements during malignant progression of the disease. Malignant progression of breast cancer involves a progressive deterioration of the normal mechanisms of cell-cycle progression. DNA repair, apoptotic controls, and tissue compartmentalization break down (through angiogenesis and tumor invasion) until the highly abnormal state of metastatic disease is reached. Early aberrations in proliferation probably only slightly perturb the pathways activated by systemic hormones (estrogen and progesterone) and local growth factors (such as TGF-b). The actual mechanisms for these early hyperactive proliferative controls to induce benign breast disease or premalignant atypical ductal or lobular carcinoma are not at all clear at the present time. Some studies have shown that genetic damage is minimal in these early lesions, although this area of study is only in its earliest stages.

**CYCLINS, CYCLIN-DEPENDENT KINASES, AND INHIBITORS**

Growth factors and inhibitors, as well as oncogenes and tumor suppressors, function to a large extent in the G_s phase of the cell cycle. The cell cycle (see Table 37.1-4) is directly controlled by an ordered series of CDKs, their positive regulatory subunits (cyclins), and their inhibitors. Early G_s is driven by the three cyclin D family members bound to CDK4 and CDK6. In the next portion of the cycle, the G_2/M transition is driven by cyclin E–CDK2. The S phase is driven by cyclin A–CDK2, and then the G_1/M transition is directed by cyclin B/A–CDK2 (CDK1).

**TABLE 37.1-4. The Cell Cycle**

**Fig. 37.1-1.** Summary of the genetic and phenotypic alteration of mammary epithelial cells associated with the onset and progression of breast cancer.

An interesting, current area of research into mechanisms of onset of breast cancer involves the DNA replication–associated enzyme telomerase. High levels of expression of this enzyme have been shown to lead to cell immortalization, a widely hypothesized early step in human tumorigenesis. One study has implicated the catalytic subunit of this enzyme (hTERT) plus two oncogenes—simian virus 40T (a viral oncogene that inactivates both p53 and Rb) and the mutant form of the signal transduction protein c-RasH—in converting human embryonic kidney cells to cancer. Telomerase overexpression has been detected in the earliest stages of breast cancer; it is known to be induced both by estrogen and by c-Myc. Thus, telomerase dismutation may serve a subtle, early function in breast tumorigenesis—replicative immortality.

The next steps in tumorigenesis almost entirely involve spontaneous gene amplification, LOH, and mutations, which arise because of overactive cell cycles or defective cell death that are largely due to abnormal cell-cycle checkpoint controls. Once these types of genetic alterations begin to occur, a cascade of further genetic changes occurs, resulting from overall genomic and chromosomal instability. Familial disease may bypass one or more steps in this cascade. The mechanisms for genetic instability and accumulation of further mutations in other cancers, such as colon cancer, have been proposed to initially depend on overexpression of a mutator gene termed MSH2. To date, however, these mechanisms have not been fully evaluated for breast cancer, and mismatch repair defects appear to be associated primarily with later stages of progression and metastasis of breast cancer. In contrast to colon cancer, centrosomal defects appear to predominate in early breast cancer, potentially causing the chromosomal type of instability.
radiation therapy. The mechanisms of failure of adjuvant therapy in hormone receptor–positive disease may potentially relate to sensitization of the tumor to very low levels of sex hormones and to the extrap Computer-aided 3D models have been shown to indicate good prognosis for an erbB 1 receptor 155,156. However, the ultimate event that leads to mortality from breast cancer is metastasis. Two separate but apparently interactive cellular processes seem to occur to allow metastasis of the disease: tumor angiogenesis and loss of proper tissue compartmentalization (invasion). It is not yet fully established whether genetic or phenotypic changes underlie these alterations. However, several molecular determinants have been proposed to relate to each process. Loss of cell-cell attachment, altered cell substrate attachment, and altered cytoskeletal organization play a role in regulating cellular invasion. In addition, cell locomotion, proteolysis, and the ability to survive and proliferate at distant sites also contribute. 152,154,155 Although acquisition of this group of characteristics is responsible for a cancer to locally invade host tissue, the ability of a tumor to distribute itself to distant sites also requires the development of a tumor vasculature—the complex process of angiogenesis. 152,157 Some studies have shown that metastatic alterations may have at least some genetic basis 158 and that distant metastases are more likely to exhibit dominance of a malignant clone than primary tumors. 159 Because of space limitations, we cannot discuss the processes of angiogenesis and metastasis further here; the reader is directed to the more general chapter covering some of these processes earlier in this volume (Chapter 9).

**IMPLICATIONS OF MOLECULAR BIOLOGY FOR TUMOR PREVENTION, EARLY DETECTION, PROGNOSIS, AND RESPONSE TO THERAPY.**

A major hope in the study of genetic changes in breast cancer is that they lead to development of new prevention and early detection strategies, therapies, and prognostic tools. In the area of prevention, there is much current work to establish more rapid, accurate, and cost-effective assays of BRCA-1 and BRCA-2 mutations to better identify women with a familial propensity for breast cancer. In addition, the gene(s) responsible for a significant number of breast cancer families remain to be identified, and the genotype (and therefore environmental) for the variable penetrance of the BRCA genes remains to be determined. Women at high risk will undoubtedly be the population of emphasis for future prevention trials. Although the benefits of prophylactic mastectomy and oophorectomy are now established, tamoxifen is also known to be an effective prevention strategy. A major, current trial is comparing tamoxifen to raloxifene (an antiestrogen thought to produce fewer endometrial cancers and to provide other benefits). However, new pharmacologic or dietary strategies are needed, particularly to prevent ER-negative breast cancer. 160,161,162

In the area of early detection, we now know that overproduction of growth factors such as TGF-a and hepatocyte growth factor are very common, but they have not yet been shown to distinguish benign proliferative disease from malignant disease. 163,164,165,166 However, exciting results have been reported in the area of chromosomal instability. It is possible that detection of telomerase expression or the ability to detect subtle genetic alterations will provide useful new approaches for marking the onset of cancer. Development of new nipple aspirate methodologies and blood and urinary assays for growth factors, growth factor receptors, autoantibodies to oncoproteins, and tumor DNA are also currently under way. 167,168,169,170

In the area of prognosis and response to therapy, much hope has been vested in development of more accurate and rapid methods for immunohistochemical and fluorescence in situ methodologies for characterization of oncoproteins, suppressor genes, and related proteins. 171,172 Serum and plasma assays for growth factors are also of interest, in addition to more classical tumor markers of CA15.3 and CEA (carcinoembryonic antigen) for the variable penetrance of the BRCA genes remain to be determined. Women at high risk will undoubtedly be the population of emphasis for future prevention trials. Although the benefits of prophylactic mastectomy and oophorectomy are now established, tamoxifen is also known to be an effective prevention strategy. A major, current trial is comparing tamoxifen to raloxifene (an antiestrogen thought to produce fewer endometrial cancers and to provide other benefits). However, new pharmacologic or dietary strategies are needed, particularly to prevent ER-negative breast cancer. 160,161,162

A large group of studies have confirmed that 20% to 30% of breast tumors contain an amplification of the c-ERBB2 gene and overexpress the encoded receptor protein. c-ERBB2 is also overexpressed in a very high portion of ductal carcinoma in situ. 173,174 Expression of the c-erbB protein is associated with an elevated mitotic rate; it correlates with poor clinical response to certain chemotherapeutic and antiherm drug (5-fluorouracil, methotrexate, Cytoxan, and tamoxifen-containing regimens) and insensitivity to tamoxifen in vitro. 175,176 c-erbB expression is also associated with poor prognosis in patients who do not receive treatment with chemotherapy or antiherm drugs. 177,178,179,180,181 Although one might postulate that c-ERBB2 gene amplification directly modulates metastatic capacity based on data with tissue models, its association with poor prognosis would appear to relate to other features of tumor biology still to be fully elucidated.

The c-erbB2 protein also holds significant interest for breast tumor immunology. Certain antibodies to the extracellular domain of the c-erbB2 protein seem to sensitize cells to killing by cisplatinum, carboplatinum, and doxorubicin in vivo. It is thought that the mechanism of this effect is interference with DNA repair mechanisms. 182,183 The extracellular domain of c-erbB2 protein may represent a useful, antitumor, blood-borne marker of breast cancer burden. 184,185 and the c-erbB2 protein itself may be a new target of immunotherapy of cancer. 186,187 as with EGFR. 188 Specifically, a humanized, anti-c-erbB antibody termed herceptin is showing promise in clinical trials. 189 More recent results also suggest the possibility of active immunotherapy targeting the c-erbB protein; a lymphoplasmaclastotic infiltrate in breast cancer was shown to indicate good prognosis for an erbB-2–positive subset of patients. This study noted production of growth-inhibitory antibodies by peripheral lymphocytes from these patients. 190

Although many studies have demonstrated the prognostic significance of c-erbB expression for lymph node–positive patients, the role of the oncoprotein in the malignant process is not clear. For example, many established human breast cancer cell lines overexpressing c-erbB are frequently of poor tumorigenicity in the nude mouse. This fact could theoretically be due to a lack of coexpression of a heterodimeric receptor partner or a ligand, or to coinduction of a suppressive phosphatase. 191 Overexpression of c-erbB in immortalized breast epithelial and breast cancer cell lines has suggested that it is only weakly transforming in vitro, and...
It has not significantly induced or enhanced a tumorigenic phenotype in vivo in several studies.\[23\] However, in the transgenic mouse, c-erbB-2 expression results in long-latency, metastatic breast tumors.\[24\] Association of the c-erbB-2 protein with, and activation of, the c-Src oncogene in this model are thought to be critical in the tumorigenic pathway. Because the c-erbB-2 protein can heterodimerize with other receptor family members, co-overexpression of all family members and cross-dimerization must eventually be taken into account in prognostic and therapeutic studies. Of interest in this respect are studies identifying a constitutively active, variant form of EGRF in human cancers.\[25\]

As we have emphasized, nuclear protooncogenes are common mechanistic links between the actions of growth-promoting steroids and growth factors in diverse tissues. Although amplification of the c-MYC nucleic protooncogene is one of the most common genetic alterations in breast cancer (approximately 20% of breast cancers contain this amplification), it must be the target of much future investigation because of its central role in a diversity of cellular processes.\[19\] \[20\] \[21\] \[22\] \[23\] Study of c-MYC gene expression in breast cancer has been hampered by immunologic and statistical difficulties in measuring the protein in tumor biopsies, but new fluorescence in situ hybridization techniques and polymerase chain reaction methodologies are likely to improve c-MYC studies in human breast cancers.\[22\] \[23\] c-MYC amplification occurs with c-ERBB2 amplification in primary breast cancers,\[24\] but much additional study still needs to apply high-throughput mutation analysis to routine assay. TP53 also is widely observed as a potential gene for genetic therapy trials of cancer. Three regulators downstream of c-MYC are also of interest. \[25\] \[26\] \[27\] \[28\] More studies must be carried out on RB-1 mutation analyses and detection of other Bcl family members. Finally, a new area of study is the identification of genes responsible for resistance-to-therapy by use of high throughput complementary DNA chip assay analyses. Such studies have the potential to improve breast diagnosis and prognosis.\[29\] \[30\]

Another major effort in better understanding breast tumor progression and response to therapy surrounds the genes involved in controlling cell death and DNA repair. Specifically, the TP53 gene, whose protein product has the potential to mediate apoptotic death induced by virtually all forms of adjuvant therapy, is easily measured by immunohistochemical methodology. A major caveat is that pathologists cannot be certain that the amplification of p53 protein they measure is due to mutation rather than to induction from a proapoptotic stimulus. Much effort will go into improvements in p53 methodology. Data, so far, clearly indicate that TP53 overexpression and genetic alteration are common in breast cancer and chemotherapy resistant tumors. Although proper interpretation of these results remains poor, additional studies must be carried out to apply high-throughput mutation analysis to routine assay. TP53 also is widely observed as a potential gene for genetic therapy trials of cancer. Three regulators downstream of c-MYC are also of interest. \[25\] \[26\] \[27\] \[28\] More studies must be carried out on RB-1 mutation analyses and detection of other Bcl family members. Finally, a new area of study is the identification of genes responsible for resistance-to-therapy by use of high throughput complementary DNA chip assay analyses. Such studies have the potential to improve breast diagnosis and prognosis.\[29\] \[30\]

Studies of metastasis have suggested that quantification of tumor angiogenesis and deposition of the extracellular matrix protein (termed tenascin) may be of value in evaluating the likelihood of metastasis. Angiography, biopsy measurements that may be useful in clinical trial for blockade of angiogenesis.\[31\] Metastasis itself seems to depend on the elaboration of proteases (such as urokinase/plasminogen activator and matrix metalloproteases), the most promising of which for prognostic significance is the cognate inhibitor urokinase PAI-1 (plasminogen activator inhibitor-1). New drugs, such as marimastat, are currently in clinical trials studying blockade of proteolytic activity. This will be a very active area of future drug development.\[32\] \[33\] \[34\] Finally, the adhesive changes that metastatic cells undergo are of major interest. Loss of expression of E-cadherin (and acquisition of a mesenchymal phenotype marked by the intermediate filament vimentin), loss of α, integrin, overexpression of a 67-kD laminin binding protein, and overexpression of a variant form of the hyaluronic acid receptor (CD44) are all more promising. \[35\] \[36\] \[37\] \[38\] More studies must be carried out on RB-1 mutation analyses and detection of other Bcl family members. Finally, a new area of study is the identification of genes responsible for resistance-to-therapy by use of high throughput complementary DNA chip assay analyses. Such studies have the potential to improve breast diagnosis and prognosis.\[29\] \[30\]

In summary, although a very large number of genetic and phenotypic alterations have been suggested in breast cancer, only a handful have been fully identified and brought to clinical study. It is quite encouraging that study of each of these genes and phenotypic changes has provided its own unique perspective to the biology of the disease. The challenge for the future, however, is to take advantage of this knowledge to improve detection of familial risk; develop prevention strategies; improve early detection, clinical diagnosis, and premenopausal detection; and rapidly apply novel biologic therapeutics.\[39\] \[40\] \[41\] \[42\] \[43\] \[44\] \[45\] \[46\] It is our prediction that future discovery in breast cancer will focus on the molecular processes of processes involved in treatment failure—invagination, angiogenesis, metastasis, and resistance to therapy. Central to these hopes are the development of new technologies for high throughput analyses of pathologic material (such as laser capture microdissection techniques, fluorescence in situ hybridization, and other molecular cytogenetic methods), complementary DNA chip array assay methods, SAGE (serial analysis of gene expression), and other cutting-edge RNA and protein analysis techniques. It is essential that new technologies be brought to improve tumor microdissection techniques, fluorescence in situ hybridization, and other molecular cytogenetic methods.}

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Jaffe E. Factors 1.9.5.


INTRODUCTION

Breast cancer has a major impact on the health of women. Approximately 183,000 women are diagnosed with invasive breast cancer each year and nearly 41,000 women die of the disease. In American women, breast cancer is the most frequently diagnosed cancer and the second leading cause of cancer death in women aged 40 to 55. Breast cancer is the leading cause of all mortality. There has been a slight decline in breast cancer mortality overall, which can be attributed both to the success of early detection programs and to advances in treatment, particularly developments in systemic therapy. Data from the Surveillance, Epidemiology, and End Results (SEER) program indicate that white women in the United States have a 13.1% lifetime risk of developing breast cancer, whereas African American women have a 9.6% lifetime risk. It is estimated that in situ carcinoma was diagnosed in almost 40,000 women in the United States.

For several decades there had been a dramatic increase in the incidence of invasive breast cancer. While the incidence of invasive breast cancer has leveled off, the number of in situ cancers, particularly ductal carcinoma in situ (DCIS), has been on the rise. SEER data indicate that there was a 130% increase in in situ cancers in whites and a 190% increase in African Americans from 1983 to 1996. It is estimated that in situ carcinoma was diagnosed in almost 40,000 women in the United States.
States in 1999. The increase in in situ cancers, particularly DCIS, is largely a result of the increasing use of screening mammography.

In this chapter, we describe the salient features of breast cancer, stressing practical information of importance to clinicians and findings that are new since the last edition of this text. The increasing incidence of in situ cancer and the more complex management issues surrounding DCIS are reflected in an expanded section dealing with these issues. For more details about breast cancer, the interested reader is referred to a related textbook in this series devoted exclusively to diseases of the breast.

RISK FACTORS FOR BREAST CANCER

Multiple factors are associated with an increased risk of developing breast cancer, including increasing age, family history, exposure to female reproductive hormones (both endogenous and exogenous), dietary factors, benign breast disease, and environmental factors. The majority of these factors convey a small to moderate increase in risk for any individual woman. It has been estimated that approximately 50% of women who develop breast cancer have no identifiable risk factor beyond increasing age and female gender. Since breast cancer is such an overwhelmingly female disease, gender is often not even considered among the risk factors. The importance of age is sometimes overlooked as well. Many women, particularly young women, overestimate their chances of developing breast cancer. As can be seen in Table 37.2-1, age plays a major role in breast cancer risk.

In women under 30, breast cancer is extremely uncommon. From 1992 to 1996, the incidence of breast cancer in women aged 35 to 39 was 59 per 100,000; however, in women 55 to 59, the incidence was 296 per 100,000. The annual incidence continues to rise, albeit more gradually, as a woman enters her 60s and 70s.

FAMILIAL FACTORS

A family history of breast cancer has long been recognized as a risk factor for the disease. The majority of women diagnosed with breast cancer do not have a family member with the disease, and only 5% to 10% have a true hereditary predisposition to breast cancer. Many women with a positive family history overestimate their risk of developing breast cancer, and women considering genetic testing have been shown to overestimate their chance of having a mutation. Overall, the risk of developing breast cancer is increased 1.5- to 3.0-fold if a woman has a mother or sister with breast cancer. Family history, however, is a heterogeneous risk factor with different implications depending on the number of relatives with breast cancer, the exact relationship, the age at diagnosis, and the number of unaffected relatives. For example, there may be minimal elevation in breast cancer risk for a woman whose mother was diagnosed with breast cancer at an advanced age and who has no other family history of the disease. In contrast, a woman who has multiple family members diagnosed with early-onset breast cancer is at a much higher risk of developing the disease. Even in the absence of a known inherited predisposition, women with a family history of breast cancer face some level of increased risk, likely from some combination of shared environmental exposures, unexplained genetic factors, or both. For women with a limited family history, assessment tools such as the Gail model may be helpful in providing a quantitative estimate of breast cancer risk. Of note, the Gail model was used in the National Surgical Adjuvant Breast Project (NSABP) breast cancer prevention study with tamoxifen.

INHERITED PREDISPOSITION TO BREAST CANCER

The identification of the two tumor suppressor genes BRCA1 and BRCA2 has provided new insights into the understanding of breast cancer genetics. When a woman has a mutation in either of these genes, she faces a markedly increased lifetime risk of developing breast cancer. The possibility of a mutation in either BRCA1 or BRCA2 should be considered when breast cancer is diagnosed at a young age (i.e., less than 45 to 55), when multiple relatives are affected, when there is a history of other cancers in the family (particularly ovarian cancer), or any combination of these factors. Although an increased risk of ovarian cancer is seen in families with both BRCA1 and BRCA2 mutations, the presence of ovarian cancer in a family member of a woman with breast cancer is more consistent with a mutation in BRCA1. Both BRCA1 and BRCA2 are inherited in an autosomal dominant manner and can be passed to offspring through either paternal or maternal lineage. A number of models have been developed to help clinicians estimate the chance of identifying a gene mutation.

In 1990, chromosome 17q21 was identified as the likely location for a breast cancer susceptibility gene. The BRCA1 gene was ultimately cloned in 1994. Mutations in BRCA1 are associated with a 50% to 85% risk of developing breast cancer during a woman's lifetime, with a particularly striking predisposition to early-onset breast cancer. The risk of ovarian cancer is elevated, though not to the same extent as breast cancer. Nevertheless, the presence of both early-onset breast cancer and ovarian cancer in either a single individual or within a family is highly suggestive of a BRCA1 mutation. Men with BRCA1 mutations do not appear to be at increased risk of breast cancer, but are probably at increased risk of prostate cancer and possibly of colon cancer. The BRCA1 gene is large, with 24 coding regions and 1833 amino acids; hundreds of mutations have been described throughout the gene. As a result, screening for a mutation in BRCA1 is costly and time consuming. Polymorphisms in the gene are not uncommon and probably do not convey an elevated cancer risk.

BRCA2 is located on chromosome 13 and is an even larger gene than BRCA1. Women with BRCA2 mutations are thought to be at a similar risk of developing breast cancer as those with BRCA1 mutations. There is an increased risk of ovarian cancer in women with BRCA2 mutations, although to a lesser degree than with BRCA1. Men with BRCA2 mutations develop breast cancer with a lifetime incidence that is estimated to be 6%. In addition, there are a variety of other cancers that appear to be associated with BRCA2; however, studies to date remain limited.

In the general population, it is estimated that between 1 in 500 and 1 in 800 individuals carry a BRCA1 mutation. BRCA2 mutations are even less common. In contrast, mutations in either BRCA1 or BRCA2 occur in approximately 1 in 40 individuals of Ashkenazi Jewish background. Within this population, three founder mutations (185delAG and 5382insC in BRCA1 and 6174delT in BRCA2) appear to have been passed on for generations. Because of the high frequency of the founder mutations in this group of individuals, genetic testing can begin with an assessment for the presence of the three mutations. In Ashkenazi Jewish women diagnosed with breast cancer at age 40 or earlier, it has been estimated that 20% or more have a mutation.

Genetic testing should be preceded by a careful evaluation of an individual's personal cancer history and family history. The implications of genetic testing for both the individual and the extended family are considerable, and these issues should be addressed in genetic counseling session(s) before any testing. A more extensive discussion of this issue is found elsewhere in this text.

There are many unanswered questions about both BRCA1 and BRCA2. Since the genes are large and mutations can be highly variable in location, an important issue is whether all mutations convey the same level of risk. It is unknown to what extent breast cancer risk is modified by other genes, hormonal factors, or environmental exposures. For example, preliminary reports have suggested that early pregnancy is not protective, although oophorectomy appears to lower breast cancer risk. For women with mutations who have not developed breast cancer, a variety of strategies have been considered to lower risk and are described later in Breast Cancer.
Women with BRCA1-associated breast cancers are thought to have a high proportion of breast-high grade, hormone receptor–negative cancers, although it is not clear that their overall outcome is different from that of women with sporadic breast cancer. The tumors in women with BRCA2 mutations do not appear to have distinctive features and bear a closer resemblance to sporadic breast cancer. At this time, it is not known whether a woman’s genetic status should influence management decisions when breast cancer is diagnosed. Women with mutations have a higher risk of developing contralateral cancers, but their clinical course otherwise has not been shown to be different from other women with breast cancer. For this reason, there are insufficient data to indicate that either local or systemic management of the patient with a mutation should differ from what is the standard of care based on stage, tumor grade, receptor status, and general health status.

Breast cancer is also observed as part of other familial syndromes, including Li-Fraumeni syndrome, Cowden syndrome, Muir syndrome, and ataxia-telangiectasia.

HORMONAL FACTORS

The development of breast cancer in many women appears to be related to female reproductive hormones. Epidemiologic studies have consistently identified a number of breast cancer risk factors, each of which is associated with increased exposure to endogenous estrogens. Early age at menarche, nulliparity or late age at first full-term pregnancy, and late age at menopause increase the risk of developing breast cancer. In postmenopausal women, obesity and postmenopausal hormone therapy, both of which are positively correlated with plasma estrogen levels and plasma estradiol levels, are associated with increased breast cancer risk. Furthermore, in utero exposure to high concentrations of estrogen may also increase breast cancer risk.

The age-specific incidence of breast cancer increases steeply with age until menopause. After menopause, although the incidence continues to increase, the rate of increase decreases to approximately one-sixth of that seen in the premenopausal period. This dramatic slowing of the rate of increase in the age-specific incidence curve suggests that ovarian activity plays a major role in the etiology of breast cancer. The relative risk of developing breast cancer for a woman with natural menopause before age 45 is one-half of that woman whose menopause occurs after age 55. There is substantial evidence that estrogen deprivation via iatrogenic premature menopause can reduce breast cancer risk. Epidemiologic studies have shown that premenopausal women who undergo oophorectomy without hormone replacement have a markedly reduced risk of breast cancer later in life. Oophorectomy before age 50 decreases breast cancer risk, with an increasing magnitude of risk reduction as the age at oophorectomy decreases. In a small study of women undergoing ovarian ablation as part of adjuvant breast cancer treatment, contralateral breast cancer rates were reduced compared with women not undergoing ovarian ablation. Recent data from women with BRCA1 mutations suggest that early oophorectomy has a substantial protective effect on breast cancer risk in this population as well.

Age at menarche and the establishment of regular ovulatory cycles are strongly linked to breast cancer risk. Earlier age at menarche is associated with an increased risk of breast cancer; there appears to be a 20% decrease in breast cancer risk for each year that menarche is delayed. Of note, hormone levels through the reproductive years in women who experience early menarche may be higher than in women who undergo a later menarche. Additionally, late onset of menarche results in a delay in the establishment of regular ovulatory cycles, although there is some controversy over whether this delay confers any additional protective effect. From these data regarding menarche and menopause, it seems likely that the total duration of exposure to endogenous estrogen is an important factor in breast cancer risk.

The relationship between pregnancy and breast cancer risk appears more complicated. Age at first full-term pregnancy clearly influences breast cancer risk. Based on epidemiologic studies, women whose first full-term pregnancy occurs after age 30 have a two- to five-fold increase in breast cancer risk in comparison with women who have a first full-term pregnancy before approximately age 18. Nulliparous women are at greater risk for the development of breast cancer than parous women, with a relative risk of about 1.4. During pregnancy, mammary cells differentiate into mature breast cells prepared for lactation. After this differentiation, these cells have a longer cell cycle, allowing more time for DNA repair in G1. Breast cancer risk increases transiently after a pregnancy. The increased risk, which lasts approximately 10 years, is then associated with a more durable protective effect. The reason for the increased risk has been hypothesized to be the increase in proliferation, growth, and survival of breast cells preparing for lactation, leading to the development of mutations. Alternatively, risk may increase secondary to the effect of high levels of hormones on subclinical cancers.

Studies of lactation on breast cancer risk have had inconsistent results. Studies have suggested that a long duration of lactation reduces breast cancer risk in premenopausal women. The effect of abortion, whether spontaneous or induced, on breast cancer risk is less clear. Several studies have found that termination of a pregnancy not only negates any protective effect, but, in fact, increases breast cancer risk. More recent studies, including a large population-based cohort comprised of 1.5 million Danish women, show no increase in long-term risk after early termination of a pregnancy. These apparently contradictory effects of pregnancy on risk have been explained in a variety of ways. As breast tissue undergoes differentiation as a result of hormonal changes of a full-term pregnancy, these fully differentiated cells may be less likely to undergo malignant transformation. In incomplete pregnancy, the breast is exposed only to the high estrogen levels of early pregnancy. These unopposed high levels theoretically could be responsible for an increased risk in women who do not carry the pregnancy to term and thus do not experience the full mammary differentiation in preparation for lactation. Despite these theoretical arguments, at this time there is no conclusive evidence that early termination of a pregnancy has any effect on breast cancer risk.

The effects of exogenous hormones, in the form of hormone replacement therapy and oral contraceptives, on breast cancer risk have been studied extensively. Metaanalyses of the effect of hormone replacement therapy demonstrate small, but statistically significant, increases in risk (relative risks, 1.02 to 1.35) for users. Risk appears to increase with current use and duration of use. This finding is consistent with studies demonstrating that postmenopausal women with higher concentrations of endogenous estrogen levels have a greater risk of developing breast cancer than women with lower estrogen levels.

More recent studies have found statistically significant increases in risk in women taking both estrogen and progestin compared with those taking estrogen alone for hormone replacement. It is of interest that several more recent studies suggest that breast cancer arising in women on hormone replacement therapy may be histologically more favorable. Furthermore, the increased risk of breast cancer appears to be reduced after cessation of hormone replacement therapy and may actually disappear after approximately 5 years.

Overall, there is no convincing evidence of a significantly increased risk of breast cancer in women who have used oral contraceptives. Some studies suggest that a slightly increased risk of breast cancer is seen in women who are younger than 35 and who use oral contraceptives, possibly related to duration and/or recency of use.

Studies of subsets of patients, including those with a family history of breast cancer or a history of benign breast disease, have not produced consistent findings.

LIFESTYLE AND DIETARY FACTORS

A possible relationship between breast cancer and diet has been suggested by the large international variation in breast cancer incidence rates. Studies of immigrant Japanese women immigrating to the United States and first-generation American-born Japanese women were found to have an incidence of breast cancer almost equal to that of whites in the same area and considerably higher than that of women in Japan. Because national per capita fat consumption correlates with incidence and mortality from breast cancer, many investigators have sought to determine the relationship between fat intake and breast cancer risk. Kinlen compared breast cancer rates of nuns who ate no or very little meat with single British women who ate regular diets and observed no differences. Breast cancer mortality among Seventh Day Adventists, a group that adheres to a diet low in animal fats, is not significantly lower than expected when compared with the general population. A pooled analysis of seven prospective cohort studies involving 337,819 women demonstrated no difference in breast cancer risk between women in the highest and lowest quintile of fat intake. Furthermore, this study and other more recent studies have also been unable to detect any relation between risk of breast cancer and consumption of specific types of fats. Thus, over the range of fat intake seen in western societies, there is no apparent association between breast cancer risk and fat intake in adults. Any effect of fat intake during childhood or adolescence, however, cannot be ruled out based on available data.

Examination of the relationship between energy balance and breast cancer has been more revealing. Data have been consistent for a positive association between...
birth weight and breast cancer. Most case-control and cohort studies of attained height, a variable highly correlated with age at menarche, and risk of breast cancer suggest a positive relationship. Although being overweight during early adult life has been associated with a lower incidence of premenopausal breast cancer, weight gain after age 18 is associated with a significantly increased risk in postmenopausal breast cancer. The protection conferred by increased weight early in life is thought to be secondary to increased irregularity of menstrual cycles in these women, suggesting their exposure to endogenous estrogens is decreased. The increased risk with weight gain in later adult life has been explained by increased estrogen levels in these women secondary to increased production in adipose tissue. These findings are also consistent with the possible influence of physical activity on breast cancer risk. A premenopausal woman's level of physical activity, even if moderate, can have an effect on the likelihood of ovulatory cycles and, for this reason, may alter breast cancer risk. Furthermore, physical activity influences body fat stores, the principal source of estrogen in postmenopausal women.

Multiple studies suggest a positive association between alcohol intake and breast cancer risk. A large metaanalysis demonstrated a relative risk of 1.1 for one drink per day, 1.2 for two drinks per day, and 1.4 for three drinks per day. Additional data from prospective studies confirm this increase in risk. The effect of alcohol intake, which is associated with increased estrogen levels, appears to be mitigated by high folate acid intake.

Many investigators have examined the effects of specific dietary components on breast cancer risk. Despite the lack of evidence that fiber or individual vitamins and minerals confer any significant protective effect, it appears that a diet high in fruits and vegetables may decrease breast cancer risk.

**BENIGN BREAST DISEASE**

Benign breast lesions are classified as proliferative or nonproliferative. Nonproliferative disease is not associated with an increased risk of breast cancer, whereas proliferative disease without atypia results in a small increase in risk (relative risk, 1.5 to 2.0). Atypical hyperplasia is associated with a greater risk of cancer development (relative risk, 4.0 to 5.0).

Dupont and Page found a marked interaction between atopia and a family history of a first-degree relative with breast cancer. This subgroup of patients had a risk 11-fold that of women with nonproliferative breast disease. The absolute risk of breast cancer development in women with a positive family history and atypical hyperplasia was 20% at 15 years, compared with 8% in women with atypical hyperplasia and a negative family history of breast carcinoma. Proliferative breast disease appears to be more common in women with a significant family history of breast cancer than in controls, further supporting its significance as a risk factor.

Of note, however, the majority of breast biopsies done for clinical indications demonstrate nonproliferative disease. In Dupont and Page's study of 10,000 breast biopsies, 69% had nonproliferative changes and only 3.6% demonstrated atypical hyperplasia. No increased risk of breast cancer development has been observed in women with a diagnosis of proliferative disease who have used estrogens after breast biopsies.

**ENVIRONMENTAL FACTORS**

Exposure to ionizing radiation, either secondary to nuclear explosion or medical diagnostic and therapeutic procedures, increases breast cancer risk. Because of the long latency period for radiation-induced breast cancers, in addition to the increased sensitivity to mutagenic damage in a developing breast, radiation exposure after age 40 produces a minimal increase in risk, while exposure early in life carries the greatest risk. A markedly increased risk of breast cancer development has been reported in women who received mantle irradiation for the treatment of Hodgkin's disease before age 15. Other environmental factors, including exposure to electromagnetic fields and organochlorine pesticides, have been suggested to increase breast cancer risk, but further data are needed before drawing firm conclusions.

**MANAGEMENT OF THE HIGH-RISK PATIENT**

A woman's risk of developing breast cancer is influenced by a range of factors. There is no formal definition of what constitutes high risk. Without question, women who carry mutations in either BRCA1 or 2 or who have a family history consistent with genetically transmitted breast cancer are considered to be at higher risk than those in the general population. A second and much less common group of high-risk women consists of those individuals who have received mantle irradiation, usually for treatment of Hodgkin's disease. Women with lobular carcinoma in situ (LCIS) or atypical hyperplasia on breast biopsy are also considered high risk. Although a variety of hormonal factors (e.g., early menarche, late age at first full-term pregnancy) affect breast cancer risk on a population basis, these conditions have a relatively small effect on risk for any individual woman.

In approaching women concerned about breast cancer risk, it is important to recognize that many women overestimate their risk of developing breast cancer. In one study, respondents overestimated their probability of dying from breast cancer within 10 years by more than 20-fold. A number of studies have demonstrated that overestimation of risk is associated with psychological morbidity and, in some cases, avoidance of proven screening measures. Providing women with an accurate assessment of breast cancer risk may have a number of benefits, including allaying anxiety and facilitating treatment decisions.

**TABLE 37.2-2. Potential Benefits of Breast Cancer Risk Assessment**

The first step in determining a woman's risk of developing breast cancer is to take a thorough history, evaluating for the presence of known risk factors. Of these, family history, age, and the presence of a premalignant lesion on previous breast biopsy are probably the most significant. Because of the substantially higher risk of identifying a BRCA1 or BRCA2 mutation in women of Ashkenazi Jewish descent, ethnic background should also be established. It can be helpful to provide women who are concerned about their breast cancer risk with a numeric risk estimate. A number of models for risk assessment are available, of which the Gail model and a model developed by Claus and colleagues from the Cancer and Steroid Hormone Study are the most frequently used. The Gail model, which calculates a woman's risk of developing breast cancer based on age at menarche, age at first live birth, number of previous breast biopsies, the presence or absence of atypical hyperplasia, and the number of first-degree female relatives with breast cancer, has been used in the NSABP breast cancer prevention trials. Efforts to validate the Gail model in different settings have produced variable results. In the Nurses' Health Study cohort, the Gail model was found to overestimate breast cancer risk, although, in other settings, it has proven to be more accurate. In the NSABP prevention trial, the Gail model performed extremely well, with a ratio of observed to expected cancers in study participants of 1.03 (95% confidence interval, 0.88 to 1.22). In general, the Gail model is thought to underestimate risk in women with strong family histories, at least in part because it only incorporates a family history in first-degree relatives. The Claus model, on the other hand, takes into account both first- and second-degree relatives, although it does not include other risk factors. Not surprisingly, the numeric assessments produced by different models may produce discordant estimates. The widespread use of the Gail model as part of the NSABP prevention trials has led to its general acceptance in clinical practice. In communicating model-based estimates to high-risk women, the limitations of these models should be emphasized. Clinicians should also be aware that women who are anxious about their breast cancer risk may continue to overestimate their risk of developing the disease even after receiving individualized counseling.
Although there is extensive literature on breast cancer screening in the general population, there are few data available on which to base screening recommendations in women with inherited susceptibility genes or other factors that markedly increase breast cancer risk. For high-risk women over the age of 40, annual mammography is recommended. The area of greatest controversy is in screening women under the age of 40. An expert panel has recommended that women with an inherited susceptibility gene should perform monthly breast self-examinations, undergo a clinical breast examination once or twice a year, and have annual mammograms beginning between the ages of 25 and 35. The role of more frequent mammograms (i.e., twice annually), digital mammography, or magnetic resonance imaging (MRI) is uncertain. Ongoing studies are addressing these issues.

**BREAST CANCER PREVENTION**

The identification of risk factors associated with the development of breast cancer has led to an effort to prevent breast cancer in women at increased risk. Numerous strategies have been considered, including risk factor modification, lifestyle alteration, drug therapy, and prophylactic surgery. Only preliminary evidence suggests that behavioral approaches can be used to alter breast cancer risk, and, unfortunately, most of the known risk factors for breast cancer are not easily modifiable. Few women would be willing to modify the age at which they have a first pregnancy in an effort to lower breast cancer risk. While early menopause may be associated with lower breast cancer risk, there are adverse psychological and physical consequences of premature menopause. Some investigators have attempted to alter a woman's natural hormonal milieu to lower breast cancer risk, and it is possible that such approaches might have future promise. To date, however, most efforts to lower a woman's risk of developing breast cancer have focused on pharmacologic interventions.

**SELECTIVE ESTROGEN RECEPTOR MODULATORS**

Adjuvant trials of tamoxifen have demonstrated clear reductions in the development of contralateral breast cancers in women treated with tamoxifen. These data, as well as preclinical evidence supporting a role for tamoxifen in breast cancer prevention, led to the development of the NSABP's Breast Cancer Prevention Trial and to various studies in Europe.

The NSABP trial, known as P-1, randomized over 13,000 patients to either tamoxifen for 5 years or to a placebo. To be eligible, women 35 years of age or older had to have at least a 1.66% chance of developing breast cancer over the ensuing 5 years based on the Gail model. Because of the elevated risk associated with age, any woman over the age of 60 was eligible for the trial. Overall, women randomized to 5 years of tamoxifen experienced a 49% decrease in invasive breast cancer, with similar risk reduction seen in women both younger than 50 and older than 50. The benefits of tamoxifen were seen across all patient subgroups (Table 37.2-3) and were highly statistically significant. Despite the high level of statistical significance, the absolute benefit from tamoxifen is of relatively small magnitude, even if one also considers the cases of DCIS prevented by tamoxifen (69 cases in the placebo arm and 35 in women on tamoxifen). To date, the benefit seen with tamoxifen only applies to the prevention of estrogen receptor (ER)–positive cancers; in P-1, there was no reduction in the risk of ER-negative cancers. While there is reason to believe that the beneficial effects of tamoxifen may extend beyond 5 years, it is unknown to what degree a 5-year course of tamoxifen affects a woman's lifetime risk of developing breast cancer.

<table>
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<tr>
<th>Table 37.2-3. Incidence of Invasive Breast Cancer in Women Participating in P-1</th>
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<td>The benefits associated with tamoxifen must also be balanced against the potential risks, in terms of both serious toxicities and adverse consequences with respect to quality of life. Increases in both endometrial cancer and thromboembolic events were seen in women on tamoxifen, although more commonly in older women (50 and older) than their younger counterparts. Based on these findings, it is thought that tamoxifen may be most beneficial in younger women with an elevated risk of developing breast cancer.</td>
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The findings from NSABP P-1 must also be considered in light of two European studies evaluating tamoxifen. Both the Royal Marsden Hospital chemoprevention trial and the Italian prevention trial failed to demonstrate a protective effect of tamoxifen. The studies were considerably smaller than P-1 (2494 in the Royal Marsden trial and a total of 5408 in the Italian), and a number of explanations have been offered to explain the negative results. The Royal Marsden trial, for example, may have included a substantial number of women from families with BRCA1 and BRCA2 mutations, and the Italian study results could have been compromised by poor compliance with the study medication. Nevertheless, the European findings provide a sobering counterpoint to the P-1 study. These results, as well as recognition of the limitations of what has been learned from P-1, underscore the need for further research in this area. At present, the need to individualize decision making about tamoxifen in the prevention setting cannot be overemphasized.

Raloxifene, another selective ER modulator, has also been shown to lower the risk of developing invasive breast cancer. In a randomized trial in postmenopausal women with osteoporosis, two doses of raloxifene (60 or 120 mg) were compared with placebo. Treatment with raloxifene not only led to an improvement in bone density and fracture risk, but also appeared to prevent breast cancer. Among 5129 women randomized to raloxifene, there were a total of 13 cases of breast cancer, compared with 27 cases among 2576 women assigned to placebo (relative risk, 0.24; 95% confidence interval, 0.13 to 0.44). Like tamoxifen, raloxifene increased the risk of thromboembolic disease (relative risk, 3.1; 95% confidence interval, 1.5 to 6.2) but did not appear to increase the risk of endometrial cancer. The follow-up of patients on the trial was relatively short (median, 40 months), and women participating in the trial were generally not at increased risk of developing breast cancer (apart from the increased risk associated with increasing age). The NSABP is now conducting a second-generation prevention trial (P-2) in which tamoxifen and raloxifene are being compared directly in postmenopausal women who are at increased risk of developing breast cancer. Until the results of that trial or additional data are available, the routine use of raloxifene to lower a woman's risk of developing breast cancer cannot be recommended.

**OTHER PHARMACOLOGIC AGENTS TO LOWER BREAST CANCER RISK**

Ongoing trials are evaluating a wide range of other agents to lower a woman's risk of developing breast cancer. A randomized Italian study indicated that fenretinide, a differentiating agent in the retinoid family, lowers the risk of contralateral cancers. Unfortunately, symptomatic nyctalopia is a problem for approximately 10% of patients taking this agent. A U.S. Intergroup trial comparing tamoxifen plus placebo versus tamoxifen plus N-(4-hydroxyphenyl) Retinamide was stopped prematurely, making it unlikely that there will be a definitive answer as to whether N-(4-hydroxyphenyl) Retinamide plays a role in a woman's risk of developing breast cancer. Trials involving other differentiating agents, aromatase inhibitors, and vaccines are ongoing, but it is unlikely that there will be any commercially available agent to lower breast cancer risk in the near next several years.

**PROPHYLACTIC MASTECTOMY**

For years it has been assumed that prophylactic mastectomy would lower a woman's risk of developing breast cancer. Since a small amount of breast tissue remains following mastectomy, the level of protection was debated. In a retrospective but rigorously conducted analysis at the Mayo Clinic, Hartmann et al. have demonstrated a 90% reduction in breast cancer risk as a result of prophylactic mastectomy. Most women and their physicians consider prophylactic mastectomy to be an extreme procedure; however, for certain high-risk women, such as those with an inherited genetic predisposition, it is currently an option. Modeling studies have
demonstrated that prophylactic mastectomy in women with BRCA1 mutations may result in a modest improvement in survival. The decision to proceed with prophylactic surgery should be considered carefully. Unlike many other choices that high-risk women may face, this is one that is irreversible and should not be made without carefully considering all the available options. Women who are considering prophylactic mastectomy with reconstruction should also recognize the potential short- and long-term complications associated with breast reconstruction (see Breast Reconstruction, later in this chapter).

### BIOPSY TECHNIQUES FOR SUSPICIOUS BREAST LESIONS

In this section, the various techniques employed to biopsy suspicious palpable and mammographic breast lesions are described. The major techniques used to diagnose palpable breast masses are fine-needle aspiration (FNA), core-cutting needle biopsy, and excisional biopsy. (Incisional biopsy is occasionally used to diagnose large breast masses, but this technique has largely been replaced by the less invasive aspiration or core biopsy.) The advantages and disadvantages of the three techniques are listed in Table 37.2.4. Both FNA and core biopsy are office procedures. Excisional biopsy, with rare exceptions, is an outpatient procedure that can be done using local anesthesia.

#### TABLE 37.2.4. Biopsy Techniques for Palpable Masses

The main issue surrounding the use of FNA is the risk of false-negative results. Large series of FNA have demonstrated a sensitivity of 87%, an incidence of insufficient specimens ranging from 4% to 13%, and a false-negative rate of 4.0% to 9.6%. Fibrotic tumors, infiltrating lobular, tubular, and cribriform histologies, and physician inexperience have all been found to be sources of false-negative aspirate results. False-positive aspirates are extremely uncommon and are reported in fewer than 1% of cases in most large series. FNA does not, however, reliably distinguish invasive cancer from DCIS, potentially leading to the overtreatment of gross DCIS.

Core-cutting needle biopsy has many of the advantages of FNA, in addition to which it provides histologic details of the lesion. The accuracy of core biopsy is similar to that reported for FNA, with sensitivities of 79% to 94%. Shabot et al. prospectively compared the diagnostic accuracy of FNA and core-cutting needle biopsy in 81 women. The accuracy of FNA was 96%, compared with 79% for the core-cutting needle technique. No false-positive results were observed in any of these reports.

Excisional biopsy has been the standard technique used in diagnosing breast masses. This method affords the physician complete evaluation of tumor size and histologic characteristics before selecting definitive local therapy. When an excisional biopsy is performed, an attempt should be made to remove a small margin of grossly normal tissue around the tumor. Kearney and Morrow used such an approach in 239 patients with cancer and obtained negative margins in 95% of cases, thus obviating the need for a reexcision as part of definitive breast-conserving therapy. Proper specimen handling with inking of the margins facilitates this approach. There is no evidence that a one-step procedure (i.e., biopsy under general anesthesia followed by definitive surgery if positive) is associated with any survival benefit compared with biopsy followed by definitive surgery at a later time.

Until relatively recently, nonpalpable, mammographically detected lesions have been routinely approached by needle-localized excisional biopsy. The most important factor in the success of this approach is how close the localizing needle is placed to the mammographic abnormality. Gallagher et al. reported wire placement to within 2 mm of the target in 96% of cases, allowing excision with a median specimen volume of 6.0 cm, and 96% of the lesions were removed with a single specimen. Specimen radiography is an essential part of the biopsy procedure done for microcalcifications in order to confirm that the calcifications are present in the biopsy specimen. Although nonpalpable masses can frequently be identified grossly at the time of biopsy, specimen radiography is also useful to ensure that the gross lesion corresponds to the mammographic abnormality. Failure to excise the mammographic lesion is reported in fewer than 5% of cases in most modern series. When this occurs, persistence of the lesion on mammogram should be confirmed and repeat biopsy undertaken.

Frozen section is generally reliable in the diagnosis of palpable breast masses, but indications for its use in the evaluation of nonpalpable breast lesions are limited. The abnormalities being sought by needle-localization biopsy are usually small and are often histologically borderline and difficult to diagnose on frozen section. Sacchini et al. noted a discordance rate of 12% between the frozen-section diagnosis and the final histologic diagnosis in a study of 403 nonpalpable lesions. Errors in distinguishing atypical hyperplasia from DCIS accounted for most of the discrepancies. Tinnemans et al. had two false-positive results in a series of 297 nonpalpable lesions diagnosed by frozen section, as well as a 3% incidence of false-negative results. Because needle-localization biopsy is rarely undertaken with a plan to proceed to definitive therapy at the same operation, a careful examination of the entire lesion with paraffin sections is generally the more prudent course.

An alternative approach to the diagnosis of nonpalpable abnormalities is the image-guided breast biopsy, using either stereotactic mammography or ultrasound to guide needle placement. The choice of technique is dependent on the visibility of the lesion. In general, ultrasound guidance is more rapid and does not require breast compression, making it better tolerated. Stereotactic guidance is reserved for lesions not visualized on ultrasound.

A review of seven series comparing stereotactic core biopsies with surgical excision demonstrates sensitivities ranging from 71% to 100% for the core-biopsy technique in a selected group of patients. In a series in which core biopsy was performed using automated 14-gauge biopsy devices, sensitivities of 92% to 100% were reported, and insufficient specimens were rare. Extensive experience has been gained with these techniques, and a number of indications for surgical biopsy after core biopsy have been identified. These include lack of concordance between the radiographic finding and the histologic diagnosis, a diagnosis of radial scar, or atypical hyperplasia on a core biopsy is associated with DCIS in 30% to 50% of cases. While radial scar may be difficult to distinguish from a well-differentiated carcinoma that has elicited a fibrous reaction.

For mammographic abnormalities that are benign, core biopsy is clearly less traumatic and more cost effective than needle localization and excision. For highly suspicious abnormalities (BI-RADS 5), the benefits are less clear. Two studies have demonstrated that, for experienced surgeons, the likelihood of obtaining negative margins with a single operative procedure for excision of nonpalpable abnormalities is the same whether or not a core-biopsy diagnosis of carcinoma is obtained before surgery. However, Morrow et al. prospectively evaluated the number of operations needed to complete local therapy in 409 patients with nonpalpable cancer approached initially with core biopsy or needle localization and excision. Core biopsy reduced the number of operations for all types of lesions except when patients were treated by lumpectomy alone. This suggests that for small calcified lesions with a high likelihood of being pure DCIS, surgical excision may remain the diagnostic procedure of choice.

### DUCTAL CARCINOMA IN SITU

DCIS, also known as *intraductal carcinoma*, is an entity distinct in both its clinical presentation and its biologic potential from LCIS, the other lesion classified as noninvasive carcinoma. The widespread use of screening mammography has resulted in a significant increase in the detection rate of DCIS, and the acceptance of breast-conserving therapy for the treatment of invasive carcinoma has led to changes in the management of women with DCIS. Uncertainty exists as to the proportion of women with mammographically detected DCIS who will develop invasive carcinoma during their lifetimes. This has led to a debate regarding whether all DCIS
An abnormally mammographic report of clustered microcalcifications is currently the most common presentation of DCIS. DCIS can also present as a mass or pathologic nipple discharge, or can be identified as an incidental finding in a breast biopsy. In many reports of mammographically directed biopsies, DCIS accounts for one-half or more of the malignancies identified.

The widespread use of screening mammography has resulted in a remarkable increase in the incidence (or detection rate) of DCIS. This increase in the incidence of DCIS has been observed in women both younger than and older than 50 years of age, and in both white and African American women. This dramatic increase in the incidence of DCIS has led some authors to suggest that screening results in the detection of biologically indolent DCIS that is unlikely to become clinically significant during a woman's lifetime. The findings that patients with lesions detected by screening have a higher frequency of grade 3 lesions than patients with lesions not detected by screening and that the risk factors for DCIS and invasive carcinoma are similar argue against this point.

DCIS is characterized pathologically by a proliferation of presumably malignant epithelial cells within the mammary ductal-lobular system, without light microscopic evidence of invasion into the surrounding stroma. However, DCIS encompasses a heterogeneous group of pathologic lesions that differ in their growth pattern and cytopathic features. At present, there is no universal agreement as to how best to subclassify these lesions. Proposed classification schemes for DCIS have variously emphasized (1) architectural features or growth pattern of the neoplastic cells within the ductal-lobular system, (2) cytoplastic features of the neoplastic cells, and (3) clinical factors, such as patient age and in combinations. The traditional system for classifying DCIS was based primarily on architectural pattern and recognized five major subtypes: comedo, cribriform, micropapillary, papillary, and solid. DCIS is commonly subdivided into the comedo type and the noncomedo type (which encompasses the other variants). This is based on the observation that the comedo type usually appears more malignant cytopathologically and is more often associated with invasion; the other DCIS types. Classification systems based primarily on architecture have a number of limitations: (1) many DCIS display a mixture of patterns, (2) the correlation between architecture and nuclear grade is not very high, and (3) interobserver reproducibility in the categorization of DCIS lesions by architectural pattern is poor. Several newer systems classify DCIS lesions primarily on the basis of nuclear grade, necrosis, or both, with architectural pattern given secondary or no consideration. In 1997, a consensus conference was convened in an attempt to reach agreement on the classification of DCIS. While the panel did not endorse any one system of classification, there was agreement that certain features be routinely documented in pathology reports of DCIS lesions. These include nuclear grade (low, intermediate, or high grade), the presence of necrosis (comedo or punctate), cell polarization, and architectural pattern(s).

A number of biologic markers in DCIS lesions have been evaluated. These studies have generally shown that comedo or high-grade lesions more frequently than noncomedo or low-grade lesions lack estrogen and PR, overexpress the HER-2/neu (c-erbB-2) oncogene, and show mutations of the p53 tumor suppressor gene with accumulation of its protein product. and demonstrate angiogenesis in the surrounding stroma.

Auxiliary lymph node involvement in patients with mammographically detected DCIS is a rare event. In one series of 189 patients with DCIS, most of whose tumors were detected by mammography alone, none showed metastases on axillary dissection. A National Cancer Data Base review of 10,946 patients with DCIS who had an axillary dissection by 1985 and 1991 demonstrated that only 406 (3.6%) of this group had axillary metastases.

A frequently encountered issue related to DCIS is the identification of small foci of invasive carcinoma, so-called microinvasion. Unfortunately, this term has not been applied in a consistent, standardized manner, and the histologic diagnosis of microinvasion is not straightforward. In the 1997 edition of the AJCC Staging Manual, microinvasion is defined for the first time as "the extension of cancer cells beyond the basement membrane into the adjacent tissues with no focus more than 0.1 cm in greatest dimension" and are staged as T1mic, a subset of T1 breast cancer. The staging manual further states that "when there are multiple foci of microinvasion, the size of only the largest focus is used to classify the micro-invasion" and that the size of the individual foci should not be added together. Given the problems with both the definition and pathologic diagnosis of microinvasion, the clinical significance of this lesion is controversial. The reported incidence of axillary lymph node involvement in patients given the diagnosis of microinvasion ranges from 0% to 20%. and The management of this condition is discussed in the next section, Treatment Options.

TREATMENT OPTIONS

A variety of local treatments, ranging from excision alone to mastectomy, have been proposed for DCIS. Making comparisons among retrospective reports is difficult because of differences in patient populations, lack of standardization of surgical and radiotherapeutic techniques, and changes in treatment practice over time.

Mastectomy is a curative treatment for approximately 98% to 99% of patients with DCIS, whether gross or mammographic. and If note, patients with initial biopsies that showed DCIS but who later had invasive carcinoma identified in the mastectomy specimens were excluded from these reports. Recurrences after mastectomy are almost all invasive carcinomas and may present as a chest wall or axillary recurrance or as distant metastases without evidence of local recurrence. Mastectomy is a highly effective treatment for DCIS, but it is a relatively radical approach to a lesion that may not progress to invasive carcinoma during the patient's lifetime. It also seems somewhat paradoxical that a woman with an invasive carcinoma should be able to preserve her breast, whereas the reward for screening and early detection is a mastectomy. The acceptence of breast-conserving therapy for the treatment of invasive carcinoma has led to its use also as a treatment for DCIS.

Treatment of DCIS by mastectomy has not been directly compared with treatment by excision and irradiation, and it is unlikely that such a trial will ever be done. In many cases, the assumption has been made that since these two treatments result in equivalent survival for patients with invasive carcinoma, the same will be true for patients with DCIS. This assumption is flawed because it implies that the disease between patients with invasive carcinoma and between those with DCIS is different. In patients with invasive carcinoma, the risk of metastatic disease is largely present at diagnosis and is not greatly altered by local recurrence in the breast. In patients with DCIS, on the other hand, the risk of metastases at diagnosis is negligible, and an invasive local recurrence carries with it the potential risk of breast cancer metastases. The staging manual further states that "when there are multiple foci of microinvasion, the size of only the largest focus is used to classify the micro-invasion" and that the size of the individual foci should not be added together. Given the problems with both the definition and pathologic diagnosis of microinvasion, the clinical significance of this lesion is controversial. The reported incidence of axillary lymph node involvement in patients given the diagnosis of microinvasion ranges from 0% to 20%.

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Because one-half of the local failures seen after breast-conserving therapy for intraductal carcinoma are invasive carcinoma, the outcome of salvage treatment of these recurrences is important. In a separate report, Solin and coworkers described 42 cases of local failure in 274 cases of DCIS treated with excision plus irradiation. The follow-up rate was 3.7 years. Nineteen of the recurrences (45%) were DCIS, and 14 of these were detected by mammography alone. All of the women with DCIS recurrences remain free of disease after mastectomy, with a median follow-up of 4.7 years. Five patients with invasive recurrence had developed distinct metastases, either simultaneously with the recurrence (one patient) or subsequently (four patients). Chest wall recurrences were noted in three of these cases, and all had involved lymph nodes at the time of recurrence. Of the entire group of 42 women with recurrence, 36 patients (86%) were alive and free of disease, 4 patients (10%) died of disease, 1 patient is alive with disease, and 1 patient died of other causes. Similarly high rates of salvage have been reported in other studies; however, the ultimate breast cancer mortality resulting from breast-conserving therapy cannot yet be assessed given the available follow-up in these studies.

Because breast-conserving therapy of patients with mammographically detected lesions from this series (n = 110) did not reveal a significantly lower rate of local failure than that seen in the group as a whole, a finding also reported by Hiramatsu et al.

A number of investigators have also examined the use of excision alone as a treatment. and patients treated with this approach are highly selected, usually on the basis of low histologic grade, small lesion size, or both. The percentage of patients with DCIS in the study population meeting these selection criteria is not usually stated, making it unclear how many women with DCIS are candidates for this type of treatment. In general, the results show rates of local recurrence less than that seen with excision combined with irradiation. In a 1999 publication by Solin and associates, it was suggested that the rate of local recurrence would be low if there are an adequate margin of resection (defined as greater than 10 mm). There are, however, several limitations of the study that are worth noting.

First, the group of 93 treated patients by wide excision alone who had margins greater than 10 mm is highly selected. The median size of the lesion was only 9 mm, and only 23% showed comedo necrosis. The patients were cared for by a dedicated team of surgeons, radiologists, and pathologists, and the specimens were routinely handled by total sequential embedding, an ideal technique for assessing margins, but unlikely used because of its expense. In addition, since these patients were seen more recently in the series compared with the irradiated patients, their follow-up time is shorter, estimated to be approximately 5 years as a median, with many less than 3 years. Therefore, this data set does not allow the conclusion that the full range of DCIS lesions can be managed by wide excision.
To date, there have been two clinical trials with published results in women with DCIS randomized to excision alone or excision plus radiation therapy (RT) (Table 37.2-6). Both trials involved patients with DCIS treated with an excision yielding histologically negative surgical margins defined as tumor-filled ducts not touching an inked surface. The NSABP has reported the 8-year results of trial B-17. In this study, 818 women were randomized to excision alone or excision plus 5000 cGy of irradiation to the breast. Eighty percent of the women in the study had tumors detected by mammographic screening. At 90 months of follow-up, a persistent reduction was seen with RT. The 8-year incidence of invasive recurrence was significantly reduced from 13.4% to 3.9% by irradiation, and the incidence of recurrent DCIS was also significantly reduced from 13.4% to 8.2%. The European Organization for Research and Treatment of Cancer has reported the 4-year results of trial 10853. In this study, 1010 women were randomized to excision alone or excision plus 5000 cGy of irradiation to the breast. Seventy-one percent of the women in the study had tumors detected by mammographic screening. With a median follow-up of 51 months, a 38% reduction in the annual incidence of ipsilateral breast recurrence was observed in the irradiation group. The 4-year incidence of invasive recurrence was significantly reduced from 8% to 4% by irradiation and the incidence of recurrent DCIS was also reduced from 8% to 5%. The overall survival is the same for the two groups, as is the incidence of distant metastases. Of note, the baseline recurrence rate with excision alone was similar in the two trials, but the reduction with RT was somewhat greater in the NSABP trial (59% reduction) compared with the European Organization for Research and Treatment of Cancer trial (38% reduction). In addition, the local benefit of RT for both DCIS trials is lower than that seen for trials of RT for invasive cancers treated by excision.

The identification of women at high risk of developing invasive carcinoma after breast-conserving therapy for apparently localized DCIS would be extremely helpful. The NSABP has reported the results of two analyses of the pathologic features of 623 of the 824 patients enrolled in protocol B-17. In the initial report, moderate or marked comedo necrosis and uncertain or involved margins were associated with an increased risk of local failure. While radiation reduced the risk of failure in all subgroups, the absolute benefit was greatest in those patients at highest risk for recurrence. After 8 years, an analysis of nine histologic features, including margins, histologic type, nuclear grade, tumor size, and comedo necrosis, demonstrated that only comedo necrosis significantly predicted for an increased risk of ipsilateral breast recurrence in multivariate analyses. Breast recurrence was much greater in unirradiated patients with moderate or marked comedo necrosis compared with patients with absent or slight comedo necrosis. The addition of RT eliminated most of the risk associated with this factor, with 13% of those with absent or slight comedo necrosis and 14% with moderate or marked comedo necrosis recurring after RT at 8 years. Margin involvement was of borderline significance, but only a minority of patients had involved margins.

Several studies have suggested that age may influence the risk of local recurrence after breast-conserving therapy. Solin et al. noted a 25% incidence of local failure in patients aged 50 or younger treated with excision and irradiation compared with 2% in patients older than 50, in spite of the fact that nuclear grade, tumor size, and margin status did not differ between groups. The median time to local failure was also shorter in the younger patients (4.9 vs. 8.7 years). Similar findings using a cutoff of 40 years was noted by Van Zee et al. and Fourquet et al. Other studies have suggested that a family history of breast cancer may affect the risk of local failure after excision and irradiation. Attempts have been made to incorporate the size of the lesion, its histologic features, and the extent of the surgical excision into a prognostic index that would direct treatment selection. One such index is the Van Nuys Prognostic Index, which assigns equally weighted scores of 1, 2, or 3 for histologic type, width of the surgical margin, and size of the lesion. Lesions with low Van Nuys Prognostic Index scores are said to be suitable for excision alone; those with intermediate scores (5 to 7) require the addition of irradiation; and those with high scores require mastectomy. While such a simplification of the decision-making process is attractive, there are a number of limitations to this index. As noted previously, the latest information from this group now suggests that margin width is the key prognostic factor, with lesion size and histologic type much less important. Until the Van Nuys Prognostic Index is validated, it should not substitute for an individualized assessment of the risks and benefits of the available treatment options for DCIS.

Tamoxifen has been shown to reduce the risk of both invasive and intraductal carcinoma in women at increased risk for breast cancer development and to reduce contralateral breast cancer incidence when used as an adjuvant treatment in women with breast cancer. The initial results of NSABP protocol B-24, in which 1804 patients with DCIS treated by lumpectomy and RT were randomized to tamoxifen (20 mg daily) or placebo for 5 years, have been reported with a mean follow-up of 62 months. Overall, the risk of ipsilateral recurrence of any type (invasive or noninvasive) or of new contralateral breast cancers was reduced from 13.0% to 8.8% at 5 years, a highly significant reduction. These benefits need to be weighed against the potential risks of treatment, which are lowest in patients aged less than 50 and those who have had a prior hysterectomy.

### TABLE 37.2-6. Results of Randomized Clinical Trials Testing the Value of Radiation Therapy after Excision

<table>
<thead>
<tr>
<th>Trial</th>
<th>Population</th>
<th>Results</th>
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<tbody>
<tr>
<td>NSABP B-17</td>
<td>818 women</td>
<td>8-year incidence of invasive recurrence reduced from 13.4% to 3.9% by irradiation, incidence of recurrent DCIS reduced from 13.4% to 8.2%</td>
</tr>
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</tr>
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Table 37.2-6. Results of Randomized Clinical Trials Testing the Value of Radiation Therapy after Excision
In contrast with DCIS, which is heterogeneous in its histologic appearance, the histologic features of LCIS show little variation and are usually easily recognized. LCIS is also an uncommon finding in autopsy studies. LCIS is also a poorly defined pathologic entity. Similar to DCIS, it is being diagnosed more frequently because of the increased use of screening mammography. As previously discussed, microinvasive carcinoma has been a poorly defined pathologic entity. Similar to DCIS, it is being diagnosed more frequently because of the increased use of screening mammography. The limited available data on patients with microinvasive carcinoma suggest that axillary lymph node metastases are infrequent and the prognosis after surgical treatment is excellent. Clinical trials currently in design or open for accrual in the United States include (1) a randomization following excision to clear margins of 3 mm and tamoxifen to RT or no RT (Radiation Therapy Oncology Group, Intergroup) and (2) trials of wide excision alone (Harvard, Eastern Cooperative Oncology Group).

**MICROINVASIVE CARCINOMA**

The available information on DCIS suggests that, although all patients can be treated with mastectomy, many are candidates for treatment with excision and irradiation, and a smaller group may be appropriately treated with excision alone. When thinking about treatment selection, it is useful to consider (1) the risk for breast cancer recurrence, (2) the risk for an invasive breast cancer, and (3) the risk for dying of breast cancer as well as the patient’s perception of the risks and benefits of the treatment options. The available data on breast-conserving treatment (BCT) with irradiation generally show recurrence rates of 10% to 15% at 10 years. Approximately one-half of these recurrences are invasive carcinoma, for a 10-year risk of 5% to 7%. Assuming that the risk of dying of breast cancer is one-third or less the risk of developing an invasive cancer, the risk of breast cancer death with BCT is approximately 2% at 10 years. If the risk of local recurrence is 5% to 10%, then the breast cancer mortality risk is reduced proportionally. The risk for death 10 years after a mastectomy for DCIS is 1% to 2%, with nearly all breast cancer mortality seen by that time. In contrast, given the long-term risk of a breast cancer recurrence after BCT, comparisons of breast cancer mortality 30 years after treatment could show greater differences in survival between women having mastectomy and those treated with excision and RT. However, the use of tamoxifen will significantly reduce the risk of invasive recurrence. Whether RT is necessary for all patients with DCIS treated with a breast-sparing approach remains uncertain. Retrospective data indicate that highly selected patients, usually those with small, low-grade (none or slight comedo necrosis) DCIS with widely negative margins, have a low local recurrence rate after excision alone. The effect of tamoxifen on recurrence when RT is not given is uncertain, since this approach has not been directly studied in clinical trials.

While developments in molecular biology may one day allow us to predict more precisely which lesions progress to invasive carcinoma, efforts must now be directed toward minimizing local recurrence in women treated with a breast-conserving approach. The initial step in the evaluation of patients with DCIS is determination of the extent of the lesion. Because most patients with DCIS have nonpalpable mammographic lesions, careful mammographic evaluation before treatment selection is critical. The routine use of magnification views as part of the mammographic evaluation allows the detection of additional calcifications that reduce the discrepancy between the pathologic and the mammographic extent, particularly for well-differentiated DCIS. The goals of surgery are to remove all suspicious microcalcifications and to achieve negative margins of resection. Needle localization should be used to guide the biopsy, and, if the calcifications are extensive, bracketing wires are useful to aid in complete excision. Specimen mammography is essential to confirm the excision of calcifications. In cases in which calcifications are extensive or adjacent benign breast tissue, postexcision mammography is useful to confirm the removal of all suspicious calcifications. It is important to recognize that, although DCIS lesions are not clinically detectable, they may be quite large. Morrow et al. found that concomitantly microinvasive carcinoma was present in 33% of patients with DCIS compared with only 10% of patients with stage I invasive carcinoma. Extensive disease, which could not be encompassed with a cosmetic resection, was the major contraindication to BCT in patients with DCIS.

A detailed pathologic evaluation is also needed and should include orientation and inking of the specimen before sectioning as well as measurement of both specimen and, if present, tumor size. Because accurate measurement of microscopic DCIS is often difficult, reporting the number of blocks in which DCIS is present and the biopsy level at which DCIS is found is helpful. If DCIS is present on only one side, then it is useful to note its size. The correlation of microcalcifications with DCIS (i.e., calcifications noted in DCIS, calcifications in adjacent benign breast tissue, or both) and the margin status should be noted. If margins are involved, the extent of involvement should be stated, and when negative, the proximity of the lesion to the margin should be noted. Clinical trials currently in design or open for accrual in the United States include (1) a randomization following excision to clear margins of 3 mm and tamoxifen to RT or no RT (Radiation Therapy Oncology Group, Intergroup) and (2) trials of wide excision alone (Harvard, Eastern Cooperative Oncology Group).

**SUMMARY**

DCIS represents a heterogeneous group of lesions of varying malignant potential. Total (simple) mastectomy is associated with a cure rate of 98% to 99% for all types of DCIS. Patients with localized DCIS are candidates for breast-sparing surgery and irradiation. Detailed mammography and careful pathologic evaluation are essential to confirm the localized nature of the lesion and judge the adequacy of resection. The goals of surgery are to remove all suspicious microcalcifications and to achieve negative margins of resection. Excision alone may be an appropriate treatment for selected women with small (less than 1 to 2 cm) low-grade DCIS lesions with clearly negative margins. Axillary dissection is not indicated in DCIS. In women with large high-grade lesions undergoing mastectomy, a low axillary sampling obviates the need for reoperation if invasion is identified. The use of tamoxifen should be considered to reduce the risk of ipsilateral breast tumor recurrence after breast-conserving surgery and to reduce the risk of contralateral breast cancer. A detailed discussion of the risks and benefits of the various options must be undertaken to allow each woman with DCIS to make an informed treatment choice.

**LOBULAR CARCINOMA IN SITU**

LCIS is not detectable on macroscopic examination and is always an incidental microscopic finding in breast tissue removed for another reason. Given this, the incidence of LCIS in the general population is unknown. Reviews of large series of benign breast biopsies done for clinical abnormalities have found that only 0.5% to 3.6% are LCIS. LCIS is also an uncommon finding in autopsy studies. In all reports, LCIS is noted to be more common in younger women, with the mean age at diagnosis usually reported to be between 44 and 46 years, with 80% to 90% of cases of LCIS occurring in premenopausal women. LCIS is reported to occur approximately ten times more often in white women than in African American women in the United States. The frequency with which LCIS is diagnosed is increasing, with one series reporting a 15% increase in the number of cases seen from 1973 to 1988. Although some of this increase is due to greater recognition of LCIS as a pathologic entity, the major factor responsible appears to be the increased number of breast biopsies that are performed as a result of screening mammography. A review of 826 mammographically generated biopsies showed that LCIS was present in 2.3% of total cases, accounting for 9.8% of mammographically detected lesions classified as malignancies. No specific mammographic findings are associated with LCIS. Several studies have examined the distribution of LCIS in an involved breast and the contralateral breast. Multicentric LCIS is identified in 60% to 80% of mastectomy specimens. In addition, LCIS is frequently noted to be bilateral. In contrast with DCIS, which is heterogeneous in its histologic appearance, the histologic features of LCIS show little variation and are usually easily recognized. LCIS is most often characterized by a solid proliferation of small cells, with small, uniform, round-to-oval nuclei, and variably distinct cell borders. Some cases of LCIS are,
The observations that most women with LCIS do not develop breast cancer, that the risk for breast cancer is bilateral, and that most tumors are infiltrating ductal carcinomas give credence to the hypothesis that LCIS is a risk factor for cancer development. One management option for the woman with LCIS is careful observation, as would be done for any woman known to be at increased risk for breast cancer development due to a positive family history or prior personal history of breast cancer. The use of tamoxifen in women electing observation only is worthy of consideration. An alternative for women unwilling to accept the risk for breast cancer development (approximately 1% per year) associated with a policy of careful observation is bilateral simple mastectomy, usually with immediate reconstruction. Treatment strategies addressing one breast, such as unilateral simple mastectomy with contralateral biopsy, would seem illogical because the risk of LCIS is bilateral regardless of the findings of the contralateral biopsy. The effectiveness of a program of careful follow-up in detecting potentially curable carcinoma in a population of high-risk women is uncertain. A metaanalysis of 389 reported cases of LCIS followed for a mean of 10.9 years reported a breast cancer mortality of 2.8%, although 16.4% of the group developed carcinoma. In contrast, of 391 women treated initially with mastectomy, breast cancer mortality was 0.9%. However, many of these series antedate the use of modern mammography, and uniform clinical follow-up was not used.

Wide surgical excision and histologically negative margins are not needed when careful follow-up is chosen given that LCIS is known to be a multifocal lesion. Similarly, RT has no role in the management of LCIS. When observation is elected, it is recommended that women with LCIS be examined at 4- to 6-month intervals and obtain annual mammograms. Because the increased risk of breast cancer persists indefinitely, observation must last for the patient's lifetime. The choice between careful observation with or without tamoxifen and bilateral prophylactic mastectomy can only be made by the patient who thoroughly understands the risk she assumes. Surgical treatment of LCIS is not an emergency, and detailed discussions of treatment options are important for patients to overcome the confusion often associated with this diagnosis.

STAGING OF BREAST CANCER

Staging refers to the grouping of patients according to the extent of their disease. It is useful in (1) determining the choice of treatment for individual patients, (2) estimating their prognosis, and (3) comparing the results of different treatment programs. Staging can be based on either clinical or pathologic findings. Currently, staging of cancer is determined by the American Joint Committee on Cancer (AJCC), which is jointly sponsored by the American Cancer Society and the American College of Surgeons. The AJCC system is a clinical and pathologic staging system and is based on the TNM system, in which T refers to tumor, N to nodes, and M to metastasis. The current edition, the fifth, published in 1997, is given verbatim below. It provides rules for classification, definition of the anatomy, and stage groupings. Of particular note in the 1997 classification are the new changes: (1) the designation of T1mic for invasive cancers with microinvasion measuring 0.1 cm or less in greatest dimension, and (2) the designation of pN1a for nodal micrometastasis (none larger than 0.2 cm).

The many changes in the AJCC system over time and its complexity have limited its use and usefulness. In addition, the current system does not address present-day issues, such as a patient's suitability for BCT or the risk of distant relapse with and without systemic therapy. In practice, most clinicians simply use the tumor size and the histologic findings of axillary dissection, often grouped for convenience into negative, one to three positive nodes, four to nine positive nodes, and ten or more positive nodes.

AMERICAN JOINT COMMITTEE ON CANCER RULES FOR CLASSIFICATION

Clinical Staging

Clinical staging includes physical examination, with careful inspection and palpation of the skin, mammary gland, and lymph nodes (axillary, supravacular, and cervical), imaging, and pathologic examination of the breast or other tissues to establish the diagnosis of breast carcinoma. The extent of tissue examined pathologically for clinical staging is less than that required for pathologic staging (see next section, Pathologic Staging). Appropriate operative findings are elements of clinical staging, including the size of the primary tumor and chest wall invasion, and the presence or absence of regional or distant metastasis.

Pathologic Staging

Pathologic staging includes all data used for clinical staging, surgical exploration, and resection as well as pathologic examination of the primary carcinoma, including not less than excision of the primary carcinoma with no macroscopic tumor in any margin of resection by pathologic examination. A case can be classified pT for pathologic stage grouping if there is only microscopic, but not macroscopic, involvement at the margin. If there is tumor in the margin of resection by macroscopic examination, it is coded TX because the extent of the primary tumor cannot be assessed. If there is no clinical evidence of axillary metastasis, resection of at least the low axillary lymph nodes (level 1; i.e., those lymph nodes located lateral to the lateral border of the pectoralis minor muscle) should be performed for pathologic (pN) classification. A case of complete axillary dissection ordinarily includes six or more lymph nodes. Metastatic nodules in the fat adjacent to the mammary carcinoma within the breast, without evidence of residual lymph node metastases are classified as regional lymph node metastases (N). Pathologic stage grouping includes any of the following combinations: pT pN pM, or pT pN cM, or cT cN pM.

ANATOMY
Primary Site

The mammary gland, situated on the anterior chest wall, is composed of glandular tissue within a dense fibroareolar stroma. The glandular tissue consists of approximately 20 lobes, each of which terminates in a separate excretory duct in the nipple.

Regional Lymph Nodes

The breast lymphatics drain by way of three major routes: axillary, transpectoral, and internal mammary. Intramammary lymph nodes are considered with, and coded as, axillary lymph nodes for staging purposes; metastasis to any other lymph node is considered distant (M1), including supraclavicular, cervical, or contralateral internal mammary. The regional lymph nodes are presented here:

1. Axillary (ipsilateral): interpectoral (Rotter's) nodes and lymph nodes along the axillary vein and its tributaries that may be (but are not required to be) divided into the following levels:
   a. Level I (low axilla): lymph nodes lateral to the lateral border of pectoralis minor muscle
   b. Level II (midaxilla): lymph nodes between the medial and lateral borders of the pectoralis minor muscle and the interpectoral (Rotter's) lymph nodes
   c. Level III (apical axilla): lymph nodes medial to the medial margin of the pectoralis minor muscle including those designated as subclavicular, infraclavicular, or apical

   Note: Intramammary lymph nodes are coded as axillary lymph nodes.

2. Internal mammary (ipsilateral): lymph nodes in the intercostal spaces along the edge of the sternum in the endothoracic fascia

Any other lymph node metastasis is coded as a distant metastasis (M1), including supraclavicular, cervical, or contralateral internal mammary lymph nodes.

Metastatic Sites

All distant visceral sites are potential sites of metastasis. The four major sites of involvement are bone, lung, brain, and liver, but this widely metastasizing disease has been found in many other sites.

TUMOR, NODE, METASTASIS CLASSIFICATION

Primary Tumor

The clinical measurement used for classifying the primary tumor (T) is the one judged to be most accurate for that particular case (e.g., physical examination or imaging such as a mammogram). The pathologic tumor size for classification (T) is a measurement of only the invasive component. For example, if there is a 4.0-cm intraductal component and a 0.3-cm invasive component, the tumor is classified T1a. The size of the primary tumor is measured for T classification before any tissue is removed for special studies, such as for ERs.

Microinvasion of Breast Carcinoma

Microinvasion is the extension of cancer cells beyond the basement membrane into the adjacent tissues with no focus more than 0.1 cm in greatest dimension. When there are multiple foci of microinvasion, the size of only the largest focus is used to classify the microinvasion. (Do not use the sum of all the individual foci.) The presence of multiple foci of microinvasion should be noted, as it is with multiple larger invasive carcinomas.

Multiple Simultaneous Ipsilateral Primary Carcinomas

The following guidelines are used when classifying multiple simultaneous ipsilateral primary (infiltrating, macroscopically measurable) carcinomas. These criteria do not apply to one macroscopic carcinoma associated with multiple separate microscopic foci: (1) Use the largest primary carcinoma to classify T. (2) Enter into the record that this is a case of multiple simultaneous ipsilateral primary carcinomas. Such cases should be analyzed separately.

Simultaneous Bilateral Breast Carcinomas

Each carcinoma is staged as a separate primary carcinoma in a separate organ.

Inflammatory Carcinoma

Inflammatory carcinoma is a clinicopathologic entity characterized by diffuse brawny induration of the skin of the breast with an erysipeloid edge, usually without an underlying palpable mass. Radiologically there may be a detectable mass and characteristic thickening of the skin over the breast. This clinical presentation is due to tumor embolization of dermal lymphatics. The tumor of inflammatory carcinoma is classified T4d.

Paget's Disease of the Nipple

Paget's disease of the nipple without an associated tumor mass (clinical) or invasive carcinoma (pathologic) is classified Tis. Paget's disease with a demonstrable mass (clinical) or an invasive component (pathologic) is classified according to the size of the tumor mass or invasive component.

Skin of Breast

Dimpling of the skin, nipple retraction, or any other skin change except those described under T4b and T4d may occur in T1, T2, or T3 without changing the classification.

Chest Wall

Chest wall includes ribs, intercostal muscles, and serratus anterior muscle, but not pectoral muscle.

DEFINITION OF TUMOR, NODE, METASTASIS CLASSIFICATION

Definitions for classifying the primary tumor (T) are the same for clinical and for pathologic classification (Table 37.2-9). The telescoping method of classification can be applied. If the measurement is made by physical examination, the examiner will use the major headings (T1, T2, or T3). If other measurements, such as mammographic or pathologic, are used, the telescoped subsets of T1 can be used.
The published results of modern, prospective randomized clinical trials comparing CS and RT and mastectomy have all shown equivalent survival between the two approaches, as well as by considering the integration of local and systemic treatment.

This section describes the multidisciplinary approach to the local management of breast cancer by addressing the use of mastectomy, conservative surgery (CS), and RT in a coordinated fashion, as well as by considering the integration of local and systemic treatment.

Modified radical mastectomy is still the most common surgical treatment for patients with invasive breast cancer in the United States. The term modified radical mastectomy is used to describe a variety of surgical procedures, but all involve complete removal of the breast, the underlying pectoral fascia, and some of the axillary nodes. Whereas the modified radical mastectomy may not seem to differ significantly from the radical mastectomy, it represents a major departure from Halstedian principles of en bloc cancer surgery. The switch to modified radical mastectomy occurred when it became recognized that treatment failure after breast cancer surgery usually is caused by the systemic dissemination of cancer cells before surgery, rather than an inadequate operative procedure. In addition, by the 1970s, fewer patients with large tumors with fixation to the pectoral muscle were being seen, making modified radical mastectomy feasible for most women. Two prospective randomized trials demonstrated no difference in survival between patients treated with modified radical and radical mastectomy. These findings were confirmed in two prospective randomized trials. Perhaps the most influential of the studies refuting the Halstedian concept was the NSABP B-04 trial. In this trial, clinically node-negative patients were randomized to radical mastectomy, simple mastectomy and nodal irradiation, or simple mastectomy with axillary observation and delayed dissection if positive nodes developed. The failure of this trial to demonstrate a difference in survival between groups was the final proof that the Halstedian concept of breast cancer did not apply to the majority of patients and was a landmark in our understanding of the local therapy of breast cancer. Today, there are few, if any, indications for radical mastectomy.

The strategy behind BCT is to remove the bulk of the tumor surgically and to use moderate doses of radiation to eradicate any residual cancer. The application of this strategy requires an understanding of the extent and distribution of cancer in a breast with an apparently localized tumor. This issue has been clarified as a result of the work of Holland and coauthors. In their initial study, mastectomy specimens with unicentric tumors 4 cm or less in size were evaluated using 5-mm sections, radiography of these thin slices, and an average of 20 blocks per specimen for histologic evaluation. Only 39% of specimens showed no evidence of cancer beyond the reference tumor. In 20%, there was additional cancer, but this was confined to within 2 cm of the reference tumor. Forty-one percent of cases had residual cancer more than 2 cm from the reference tumor; of these, two-thirds had pure intraductal carcinoma and one-third had mixed intraductal and invasive carcinoma. Local recurrence in the breast occurs at or near the site of the primary tumor in most cases, emphasizing that this multifocal involvement is biologically important. In a subsequent study, the amount of residual intraductal carcinoma was evaluated. Approximately 10% of patients had prominent intraductal carcinoma (defined as a total of six or more low-power fields of intraductal carcinoma) extending more than 2 cm from the reference tumor. These studies indicate that the extent and amount of microscopic cancer in the vicinity of a primary tumor, known as multifocality, is variable. These results imply that the extent of surgical resection required in BCT varies from patient to patient.

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These data demonstrate that survival for most breast cancer patients is not dependent on choice of local therapy. In addition to the results of these trials, numerous reports from centers in Europe and North America on the use of CS and RT have demonstrated high rates of local tumor control with satisfactory cosmetic results. Studies indicate that fewer than 50% of women with stage I and II breast carcinoma are treated with BCT. The available data indicate that a minority of patients have contraindications to BCT, and that these are readily identified with standard clinical tools, such as physical examination and mammography including magnification views. National studies indicate that physicians continue to use inappropriate selection criteria for BCT.

The rates of recurrence in the breast at 7 to 18 years ranged from 7% to 19% in the randomized studies using widely varying surgical and RT techniques. In the corresponding patients treated with mastectomy, 4% to 14% of patients developed local recurrence, emphasizing that mastectomy does not guarantee freedom from local recurrence, even in women with clinical stage I and II breast carcinoma. The nonrandomized studies with the longest follow-up describe a persistent risk of recurrence in the breast through 20 years of follow-up. These results have been contrasted to those seen after mastectomy, in which most local failures occur in the first 3 years following surgery. The annual incidence rate for a recurrence at or near the primary site is constant for years 2 through 7 after treatment, and then decreases to a low level by 10 years after treatment. In contrast, the annual incidence rate for recurrence elsewhere in the breast increases slowly to a rate of approximately 0.7% per year at 8 years and remains stable. Recurrences in the skin of the treated breast are a rare event associated with a poor prognosis. Whole breast irradiation is effective at eradicating multicentric breast carcinoma, but it does not prevent the subsequent development of new cancers.

A number of factors have been identified that influence the risk for local recurrence after BCT. Young age has consistently been observed to be associated with an increased risk of local recurrence after breast-conserving surgery and RT. In young women with a family history suggestive of an inherited breast cancer susceptibility, BCT is associated with a higher rate of opposite breast cancer compared with young women without such a family history. This is consistent with the findings of an increased risk of opposite breast cancer in young patients with mutations undergoing mastectomy. The rate of local recurrence in young patients with a positive family history is, if anything, lower than in patients with a negative family history. This might be explained by the findings linking BRCA1 and 2 with radiation repair genes, or by a greater likelihood of localized (extensive intraductal component–negative) cancers in patients with mutations compared with patients without mutations. However, patients with mutations appear to be at risk for late new primaries in the treated breast. Of note, patients with a mutation do not appear to be at an increased risk for adverse effects from RT. Thus, BCT appears to be an acceptable option for patients with a suspected or known mutation, although these patients need to be apprised of the increased risk of a second breast cancer, either in the opposite or, over time, in the treated breast. Many of these patients, particularly those with favorable presentations, elect bilateral mastectomy. A modeling study suggests that bilateral mastectomy may be associated with a modest gain in survival.

An extensive intraductal component has been shown to be an important risk factor for local recurrence when margins of resection are not evaluated. An extensive intraductal component has been found to be a marker for a large residual tumor burden in the involved quadrant of the breast such that moderate-dose RT is not able to eradicate it. In such patients, a larger breast resection is commonly required to ensure adequate removal. Results have shown that the microscopic margins of resection are the major selection factor for BCT (Tables 37.2-11 and 37.2-12). Patients with negative margins of excision (typically defined as the absence of either invasive or ductal in situ disease directly at an inked surface) have generally been observed to have low rates of local recurrence following treatment with CS and RT. In particular, patients with an extensive intraductal component, but with negative inked margins of excision, are not at an increased risk of local recurrence. The outcome of patients with close margins of excision has been less clear. In part, this reflects variability in the definition of close margins and, perhaps, the effect of institutional policies calling for escalated radiation doses based on the proximity of cancer cells to the margin of resection. In the Joint Center for Radiation Therapy (JCRT) experience shown in Table 37.2-12, there was no significant difference in recurrence rates between patients with close margins (less than or equal to 1 mm) compared with patients with margins greater than 1 mm using similar doses. Some studies have suggested a high rate of local recurrence at 10 years in patients with close margins; however, the number of patients in these series and the actual follow-up time is limited.

**TABLE 37.2-11.** Recurrence Rates (%) following Conservative Surgery and Radiation Therapy by Margin Status

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**FIGURE 37.2-2.** Overview analysis of trials of conservative surgery and radiotherapy versus mastectomy. The squares represent the odds ratio of the annual death rate in the radiotherapy group compared with the control group. The vertical line is an odds ratio of 1, and the 99% confidence interval (CI) is shown by the horizontal line. Squares to the right of the vertical indicate a survival benefit for mastectomy. BCG, Breast Cancer Group; BCT, breast-conserving treatment; BMFT, Bundesministerium für Forschung und Technologie; CRC, Cancer Research Campaign; EORTC, European Organization for Research and Treatment of Cancer; INT, Instituto Nazionale per lo studio e Cura dei Tumori; IT, Instituto Tumori; NCI, National Cancer Institute; NSABP, National Surgical Adjuvant Breast Project; SE, standard error. (Reprinted from Anonymous. Effects of radiotherapy and surgery in early breast cancer. An overview of the randomized trials. Early Breast Cancer Trialists Collaborative Group. N Engl J Med 1995;333(22):1444, with permission.)
Long-term data on the use of BCT in patients with positive margins are more limited. In most analyses, positive margins have been associated with a high risk of breast cancer recurrence. 275-277,278,279 and 280,281,282,283 At the JCRT, patients with positive margins had a considerably higher risk of breast cancer recurrence than patients with negative margins. 282 The 8-year crude rate of breast recurrence was 18% for patients with positive margins. However, patients with focally positive margins (any invasive or in situ ductal carcinoma at the margin in three or fewer low-power microscopic fields) had a 14% rate of recurrence compared with a 27% rate in patients with greater than focally positive margins. These data suggest that patients with focally positive margins can be considered for BCT. As discussed in this section, the use of adjuvant systemic therapy results in a large reduction in local recurrence in patients treated with CS and RT. In the JCRT series, among the 45 patients with focally positive margins who received adjuvant systemic therapy, the 8-year local recurrence rate was 8% (95% confidence interval, 1% to 18%). 281 Additional experience is needed to confirm this finding. Patients with more than focally positive margins require more surgery given the significantly higher rate of breast cancer recurrence. 

The use of adjuvant systemic therapy is an important factor associated with recurrence in the breast when used in conjunction with CS and RT. This is most clearly demonstrated in three randomized clinical trials. In the NSABP B-13 trial, node-negative, ER-negative patients were randomized to chemotherapy or to a no-treatment control group. Among the 235 patients treated with CS and RT, the 8-year rate of recurrence in the ipsilateral breast was 13.4% without chemotherapy and only 2.6% with chemotherapy. 282 Similar results are seen with adjuvant tamoxifen. In NSABP trial B-14, node-negative, ER-positive patients were randomized to tamoxifen or to a placebo. Among the 1062 patients treated with CS and RT, the 10-year rate of recurrence in the ipsilateral breast was 14.7% without tamoxifen and only 4.3% with tamoxifen. 283 A similar result was seen in the Stockholm Breast Cancer Study Group among node-negative patients randomized to tamoxifen or to a placebo. 284 Among the 432 patients treated with CS and RT, the 10-year rate of recurrence in the ipsilateral breast was 12% without tamoxifen and only 3% with tamoxifen.

GUIDELINES FOR PATIENT SELECTION

Based on the extensive information available from prospective and retrospective studies, there is a general consensus on the criteria for patient selection for the use of BCT. It is now established that, in most cases, BCT results in a cosmetically satisfactory breast and that it provides survival rates equivalent to those seen after mastectomy. The American College of Surgeons, the American College of Radiology, the College of American Pathologists, and the Society of Surgical Oncology have jointly provided standards of care for BCT and most recently published their report in 1998. 285 Key portions of this report are summarized here and additional comments are provided in parentheses.

CONTRAINDICATIONS FOR BREAST-CONSERVATION TREATMENT WITH RADIATION THERAPY

Absolute Contraindications

- Women with two or more primary tumors in separate quadrants of the breast or with diffuse malignant-appearing microcalcifications are not considered candidates for breast-conservation treatment.
- A history of previous therapeutic irradiation to the breast region that, combined with the proposed treatment, would result in an excessively high total radiation dose to a significant volume is another absolute contraindication.
- Pregnancy is an absolute contraindication to the use of breast irradiation. However, in many cases, it may be possible to perform breast-conserving surgery in the third trimester and to treat the patient with irradiation after delivery.
- Finally, persistent positive margins after reasonable surgical attempts absolutely contraindicate BCT with radiation. The importance of a single focally positive microscopic margin needs further study and may not be an absolute contraindication (see updated results from the JCRT in Local Management of Invasive Breast Cancer, earlier in this chapter).

Relative Contraindications

- A history of collagen vascular disease is a relative contraindication to BCT because published reports indicate that such patients tolerate irradiation poorly. 286 Most radiation oncologists will not treat patients with scleroderma or active lupus erythematosus, considering either an absolute contraindication. In contrast, rheumatoid arthritis is not a contraindication. 287
- Patients with multiple gross tumors in the same quadrant and indeterminate calcifications must be carefully assessed for suitability because studies in this area are not definitive.
- Tumor size is not an absolute contraindication to BCT, although few reports have been published about treating patients with tumors larger than 4 to 5 cm. However, a relative contraindication is the presence of a large tumor in a small breast in which an adequate resection would result in significant cosmetic deformity.
- Breast size can be a relative contraindication. Women with large or pendulous breasts can be treated by irradiation if reproducibility of patient setup can be ensured and it is technically possible to obtain adequate dose homogeneity.

NONMITIGATING FACTORS

- The presence of clinical or pathologic involvement in axillary nodes should not prevent the treatment.
- Completion of the surgical procedure being able to detect a recurrence is not a contraindication. The changes associated with recurrence can usually be detected at an early stage by physical examination and mammography.
- The delivery of irradiation to the breast does not result in a meaningful risk of second tumors in the treated area or in the untreated area.
- Tumor location is not a factor in the choice of treatment. Tumors in a superficial subareolar location occasionally may require the resection of the nipple-areolar complex so that negative margins can be achieved, but this does not affect outcome. The patient and her physician need to assess whether such a resection is preferable to mastectomy.
- A family history of breast cancer is not a contraindication to breast conservation. Little is known about the risk of breast recurrence in patients with hereditary breast cancer, but currently this is not a contraindication to BCT. (However, such patients should be apprised of their increased risk of a second breast cancer.)
- A high risk of systemic relapse is not a contraindication for breast conservation, but is a determinant of the need for adjuvant therapy.

CONSERVATIVE SURGERY WITHOUT RADIATION THERAPY

An unresolved question is whether RT is necessary in all patients with invasive breast cancer after CS. Six randomized clinical trials with published results have compared CS alone with CS and RT in patients with early-stage breast cancer. 281,282,283,284 and 285,286 These trials vary with regard to patient selection, the details of the surgery and RT, the use of adjuvant systemic therapy, and the length of follow-up. The results of these various trials are shown in Table 37.2-13. These trials all show a large reduction in the rate of local recurrence after RT, with an average crude rate of reduction of about one third (range, 63% to 89%). None of the six trials shows a significant survival benefit for RT; however, in the trials with published data, the survival rate is slightly better for irradiated patients than for nonirradiated patients. A large trial (or perhaps a metaanalysis of multiple smaller trials) is necessary to detect a small, but clinically significant difference in survival, if it in fact
Attempts have been made to identify a subgroup of patients (based on various clinical and histologic features) that has a low risk of local recurrence after CS alone. It was not possible to identify such a subgroup within the Ontario and NSABP randomized trials. Local recurrence rates are generally lower in trials using more extensive surgery than in those using lumpectomy and in older patients than in younger patients. The JCRT attempted to identify such a subgroup in a prospective single-arm trial in which patients with favorable disease were offered the option of CS alone. The criteria for entry onto this protocol were tumor size of 2 cm or less, histologically negative axillary nodes, absence of both lymphatic vessel invasion and an extensive intraductal component in the cancer, and no cancer cells visualized within 1 cm of inked margins. All but one patient had a negative reexcision. This trial was stopped shortly before reaching its accrual goal of 90 patients because of stopping rules ensuring against an excessively high local recurrence rate. The latest analysis includes the results in 81 patients. The median age of patients in this trial was 66 years, and median pathologic size of the cancers was 9 mm. With a median follow-up of 92 months, 19 of the patients have developed a recurrence in the ipsilateral breast, for a crude local recurrence rate of 23%. Based on the results of this prospective study, it was concluded that, even in a highly selected group of breast cancer patients, there is a substantial risk of early local recurrence after treatment with wide excision alone.

The use of adjuvant systemic therapy substantially reduces the rate of local recurrence in patients treated with CS and RT, but does not seem to reduce greatly the rate of local recurrence after CS alone. There are no published trials directly comparing CS with and without either chemotherapy or tamoxifen. Information on this is available from indirect comparisons within randomized clinical trials for both adjuvant chemotherapy and tamoxifen. In the NSABP trial B-06, an indirect comparison of the effect of adjuvant chemotherapy can be made. Node-positive patients treated with lumpectomy and adjuvant chemotherapy but without RT had a 13% rate of local recurrence in the breast of 41% compared with only 5% for node-positive patients treated with 6% of 336 patients, RT, and chemotherapy (P < .001). In comparison, node-negative patients treated with lumpectomy without RT had a 12-year rate of recurrence in the breast of 32% compared with 12% for node-negative patients treated with lumpectomy with RT. A similar observation, suggesting that systemic therapy further decreases the rate of local recurrence when combined with RT, but not in its absence, is also seen in indirect comparisons within the Milan trials. In the Scottish trial, patients with ER-negative cancers were treated with adjuvant cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) chemotherapy. With a median follow-up of approximately 5.7 years, the crude rate of local regional recurrence was 44% among patients treated with CS, but without RT, compared with only 14% among patients treated with RT.

There is particular interest in avoiding RT in older patients. It is often less convenient for such patients to receive RT, and their local recurrence rate appears lower after CS alone compared with younger patients. The results of retrospective studies of CS alone with or without adjuvant tamoxifen have shown variable results. The Cancer and Leukemia Group B (CALGB) and other groups in North America have completed a prospective randomized clinical trial testing the value of RT in older breast cancer patients treated by CS and tamoxifen; at this time there are no results from the trial. In NSABP B-21, women with tumors smaller than 1 cm with negative axillary lymph nodes were randomized to tamoxifen alone, breast irradiation alone, or breast irradiation plus tamoxifen. With an average follow-up of 73 months, 24.4% of women in the tamoxifen-only arm had an ipsilateral recurrence, compared to 11.7% of women who received breast irradiation plus tamoxifen. The difference was highly statistically significant. Based on these results, the investigators thought it unlikely that tamoxifen could be substituted for radiation in this patient population.

In conclusion, the use of breast irradiation after CS is associated with a large reduction in the rate of local recurrence. The available data from the randomized trials do not show a survival benefit; however, none of the available trials has the statistical power to eliminate a small survival difference. A subset at low risk of local recurrence following CS has not been clearly identified, and RT is currently considered standard. The addition of adjuvant systemic therapy to CS alone has not been demonstrated to decrease local recurrence. In elderly patients, particularly those with significant comorbidity, RT is commonly omitted because of the practical difficulties of delivering such therapy in this group of patients.

PREOPERATIVE CHEMOTHERAPY

The successful application of preoperative chemotherapy in locally advanced breast cancer has led to a number of studies in patients with stage I and II breast carcinoma to determine if the use of preoperative chemotherapy would allow breast conservation in patients who would otherwise be treated with mastectomy. Early studies demonstrated a high response rate to preoperative chemotherapy in a number of patients initially thought to be unsuitable for BCT to be considered reasonable candidates for breast conservation. In addition to increasing the number of patients who can undergo BCT, a second goal of preoperative therapy is to improve survival. The available randomized trials suggest that the use of preoperative chemotherapy does reduce the use of mastectomy, but does not improve survival. Of note, however, in the NSABP trial B-18, an analysis of breast recurrence rates among patients initially eligible for lumpectomy and those who were eligible only after down-staging by chemotherapy demonstrated a local failure rate of 6.9% in those thought to be candidates for lumpectomy before chemotherapy compared with 14.5% in those who required down-staging (P = .04). Similar findings were noted in a trial from France. Further experience is therefore needed to identify down-staged patients who can be effectively managed by BCT. A major practical problem with the use of preoperative chemotherapy to increase rates of BCT is the determination of the extent of residual viable tumor that must be resected. The clinical assessment of response is relatively inaccurate using clinical examination and mammography. Given this, we approach these patients by initially resecting any clinically or mammographically abnormal tissue. If viable tumor is present throughout the specimen, a reexcision is carried out even if the initial margins are negative. If further viable tumor is present in the reexcised specimen, a reevaluation of the patient’s suitability for BCT is undertaken. Marking the extent of the tumor before chemotherapy with stereotactically placed clips or skin tattoos is useful for determining the tumor location in patients who have a complete clinical response and may aid in assessing the need for resection of residual abnormalities in patients with a partial response.

The definitive role of neoadjuvant therapy in operable breast cancer remains undefined. There appears to be no rationale, outside of a clinical trial, for its routine use in patients who are suitable candidates for BCT. Initial chemotherapy is appropriate when a large tumor in a small breast would necessitate mastectomy and the patient desires BCT. However, in the study of Morrow et al., this contraindication to BCT was present in only 6% of 336 patients with stage I and II carcinoma. The potential for a higher risk of breast recurrence should be discussed with the patient, and the pathology carefully reviewed before deciding that the patient is a suitable candidate for BCT.

TECHNIQUE AND COMPLICATIONS OF BREAST-CONSERVING SURGERY

The goal of breast-conserving surgery is to minimize the risk of local recurrence while leaving the patient with a cosmetically acceptable breast. The most common form of breast-conserving surgery used in the United States is referred to as lumpectomy. The surgical technique of lumpectomy differs from that used for mastectomy in that lumpectomy is not an en bloc cancer operation. Quadrantectomy is another type of breast-conserving surgery that is designed to remove an anatomic segment of breast tissue and frequently includes removal of the overlying skin and underlying pectoral fascia. Because excision of a large amount of breast tissue is the major factor responsible for a poor cosmetic outcome after BCT, lumpectomy is considered the appropriate initial surgical approach in the United States. Other surgical factors that influence the cosmetic outcome are the size and placement of the incision, the management of the lumpectomy cavity, and the extent of axillary dissection.
A number of technical aspects of lumpectomy are worth emphasizing. In general, the incision should be placed directly over the area of the tumor. This is true even when a biopsy is performed for a mammographically detected lesion. In the upper part of the breast, incisions should be curvilinear or transverse and follow the natural skin creases (Langer's lines) of the breast. In the lower part of the breast, the choice of a curvilinear or radial incision depends on the contour of the patient's breast, the distance from the skin to the tumor, and the amount of breast tissue to be resected. It is not necessary to remove skin (except for superficial tumors) or to remove needle tracks from core-needle biopsies or FNAs. Preservation of the subcutaneous fat and the avoidance of thin skin flaps is also important in maintaining normal breast contour. Raising flaps is necessary only to allow access to the tumor. Meticulous hemostasis is important because a large hematoma distorts the appearance of the breast and makes reexcision and follow-up evaluation more difficult. The presence of a postbiopsy hematoma, however, is not a contraindication to BCT, but it may result in distortion of the breast contour, which may not be apparent with the patient supine on the operating table. The best cosmetic results usually are obtained by allowing the lumpectomy cavity to fill in with serum and fibrin. Drainage of the lumpectomy cavity should be avoided. Finally, the incision should be closed with a subcuticular suture to avoid cross-hatching of the skin.

A critical step in lumpectomy is the evaluation of the completeness of excision of the tumor. To allow adequate histologic evaluation, the specimen should be removed as a single piece of tissue and should not be transected unless the pathologist is present. The use of marking sutures to orient the specimen for the pathologist allows reporting of the status of individual margins. Gross inspection of the specimen in the operating room allows identification of positive or close margins, facilitating immediate reexcision. Recognition of suspicious margins at the time of the first operation allows a more limited dissection and the possibility of a delayed second-look operation. Close communication between surgeon and pathologist is essential. The status of the first margin should be used to determine the patient's suitability for BCT.

When axillary dissection is performed as part of breast-conserving surgery, a separate incision should be used, except in patients with tumors high in the tail of the breast. A curvilinear incision at the edge of the hair-bearing axillary skin provides the best cosmetic result. The incision should not extend anterior to the fold of the pectoralis major or posterior to the latissimus dorsi.

The primary indications for a reexcision are positive or unknown histologic margins of resection on the initial excision. Several studies have demonstrated residual carcinoma in approximately one half of cases when reexcision is performed for positive or unknown margins.107,108 No consensus exists on the best technique for reexcision. When reexcision is done within 1 to 2 weeks of the biopsy, it is not usually possible to reexcise an entire biopsy cavity as a single specimen without sacrificing large amounts of breast tissue. Modified radical mastectomy is performed through an elliptical transverse incision, which encompasses the nipple-areola complex and the biopsy scar if an open biopsy has been performed. The nipple-areola complex and the biopsy incision must be removed, but the remainder of the skin of the breast can be preserved in early-stage breast cancer if needed for breast reconstruction. With a skin-sparing procedure, additional exposure to allow complete excision of the breast tissue is achieved by reexcision rather than excision of the skin. Skin flaps are created in the plane between the subcutaneous fat and the underlying breast tissue. Because of the variability in the amount of subcutaneous fat, no single thickness is appropriate for all skin flaps. To encompass all breast tissue, the dissection should extend superiorly to the inferior border of the clavicle, medially to the lateral border of the sternum, inferiorly to the superior extent of the rectus sheath, and laterally to the latissimus dorsi muscle. The fascia of the pectoralis major muscle can be safely preserved when needed for breast reconstruction. In general, however, excision posterior to the fascia provides a convenient plane for ensuring removal of most of the breast tissue. When the breast tissue is resected inferiorly and laterally, axillary dissection is carried out. Closed suction drains are then placed in the apex of the axilla and beneath the inferior skin flap. Skin closure is accomplished with a subcuticular suture. Pressure dressings are not needed with suction drains and may compromise blood supply.
Indications for Postoperative Radiation Therapy

Postoperative RT refers to the use of irradiation to the chest wall and draining lymph node regions as an adjuvant treatment after mastectomy. Postoperative RT has been clearly shown to reduce the rate of local regional tumor recurrence (i.e., recurrence on the chest wall or in the axillary, internal mammary, or supraclavicular lymph nodes) by treating residual microscopic disease that has spread beyond the margin of surgical resection. In the absence of postoperative RT, there is a substantial risk of local recurrence after modified radical (or even radical) mastectomy, principally related to the presence and extent of axillary nodal involvement. If axillary nodes are involved, local recurrence is seen in 10% to 30% of patients, whereas if axillary nodes are uninvolved, local recurrence is seen in only approximately 5% of patients. Once a local recurrence is clinically manifest, it can be effectively controlled in only approximately one-half of patients. Therefore, postoperative RT can benefit high-risk patients simply by preventing local recurrence.

Despite the clear-cut improvement in local control with adjuvant RT, its effect on survival remains controversial. Assessing the survival value of postoperative RT requires evaluation within large, prospective randomized clinical trials. There are six published trials in which patients were randomized after radical, modified radical, or total mastectomy to postoperative RT or no further treatment in the absence of systemic therapy. Some of these are among the earliest clinical trials performed in medicine. In many of these trials, RT was given using orthovoltage equipment and in most trials techniques were used that delivered considerable doses to the heart and are now considered outmoded. Despite this, the use of postoperative RT clearly reduced the incidence of local recurrence, but none of these trials demonstrated a clear-cut improvement in the survival rate. In addition, some of these trials showed a late increase in cardiac mortality in patients treated with RT compared with unirradiated patients. The most modern of these trials was conducted at the Radiumhemmet in Stockholm between 1971 and 1976. In this trial, 644 patients with operable breast cancer were treated with modified radical mastectomy and randomized to postoperative RT or no further treatment. With a median follow-up time of 16 years, negative-patient survivors had a decreased rate of local recurrence with postoperative RT, but there was no effect on distant metastases or survival. For node-positive patients, the use of postoperative RT was associated with not only a decrease in local recurrence, but also a decrease in distant metastases. An overview of randomized trials of postoperative RT after mastectomy with or without axillary dissection showed no difference in survival when patients treated with RT were compared with those treated without RT over the first 10 years after surgery. After 10 years, however, there was a lower rate of survival associated with the use of RT, but this was not statistically significant. When cause-specific mortality data were examined, there was an excess of cardiac deaths among patients treated with RT, but this was offset by a reduced number of deaths from breast cancer, especially in the more recent trials. An overview reanalysis published in 2000 showed similar results. These studies suggest that if increased cardiovascular mortality associated with adjuvant irradiation can be avoided by the use of appropriate techniques, a benefit in survival will be seen.

There are a number of studies that have examined the rate of local recurrence in patients treated with mastectomy and adjuvant chemotherapy, but without RT. In the largest of these, the rate of local recurrence in 2016 node-positive patients entered into Eastern Cooperative Oncology Group adjuvant systemic therapy trials was examined. The 10-year rate of local regional recurrence (with or without simultaneous distant failure) was 12.9% for patients with one to three positive nodes and 28.7% with greater than or equal to four positive nodes. Similar results are observed in the other studies. These studies, as well as the trials described here, demonstrate a moderate risk of local regional recurrence in node-positive patients treated with mastectomy and adjuvant systemic therapy, particularly when four or more nodes are involved.

A number of studies have examined the issue of adding postoperative RT to adjuvant chemotherapy (Table 37.2-14). In DBCG trial 82b, 1708 premenopausal patients who had undergone mastectomy for pathologic stage II or III breast cancer were randomly assigned to eight cycles of CMF plus local regional RT or to nine cycles of CMF alone. With a median follow-up of 114 months, the 10-year rate of local regional recurrence was reduced from 32% to 9% with RT, and overall survival was improved from 45% to 54% with RT (both P values <0.01) (Fig. 37.2-3). In DBCG trial 82c, 1375 postmenopausal patients who had undergone mastectomy for pathologic stage II or III breast cancer were randomly assigned to tamoxifen or to tamoxifen alone. With a median follow-up time of 123 months, the 10-year rate of local regional recurrence was reduced from 35% to 8% with RT, and overall survival was improved from 36% to 45% with RT (both P values <0.05) (Fig. 37.2-4). In a smaller trial from British Columbia, 319 node-positive premenopausal patients treated with modified radical mastectomy were similarly randomized to adjuvant CMF chemotherapy and postoperative RT or to chemotherapy alone. The results of the British Columbia trial were similar to those of the DBCG trial 82b. Of note, the magnitude of the improvement seen in these trials is similar to that seen with adjuvant systemic therapy (chemotherapy, hormonal therapy, or both) and suggests that all node-positive patients should receive postmastectomy RT. A metaanalysis published in 2000 showed a survival benefit for local regional RT in node-positive women treated with modified radical mastectomy and adjuvant systemic therapy. For a number of reasons, however, these trials have not resulted in the universal use of postoperative RT in node-positive patients, particularly those with one to three positive nodes. One reason is that the worldwide overview of all trials of postoperative RT only shows a small, but not statistically significant survival benefit. A more substantial reason relates to the issue of generalizing from these results due to differing surgical and systemic treatments. The extent of axillary surgery performed in these trials was less than that performed in the United States, and the rates of local regional recurrence, especially axillary recurrences, observed in the Danish trials were greater than observed in U.S. series. In particular, as noted previously, series of patients with one to three positive nodes treated by modified radical mastectomy and adjuvant chemotherapy from the United States show rates of local regional recurrence in the range of 10%, compared with approximately 30% in the two Danish trials. Also, systemic therapy in the Danish trials may have been suboptimal by current standards. What seems clear is that these trials address an important principle about the value of establishing local regional control in the presence of systemic therapy. Without detracting from the importance or validity of the principle, it is legitimate to question the clinical implications of these results for practice in the United States. The final reason for the failure of these trials to translate directly into clinical practice is the concern about long-term complications of postoperative RT, especially late cardiac mortality. This is especially relevant in patients receiving chemotherapy with potential cardiac toxins such as doxorubicin (Adriamycin). To address the issues raised by the available data on postoperative RT, the American Society of Therapeutic Radiology and Oncology sponsored a symposium on postoperative RT and invited a panel to hear the latest information on this topic and to develop a Consensus Summary Statement. The panel was composed of three radiation oncologists, a medical oncologist, a surgical oncologist, and a consumer activist.

### Table 37.2-14. Randomized Trials Testing the Value of Postoperative Radiation Therapy Used in Conjunction with Adjuvant Systemic Therapy

<table>
<thead>
<tr>
<th>Trial</th>
<th>Country</th>
<th>Patients</th>
<th>Treatment</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>DBCG 82b</td>
<td>Denmark</td>
<td>1708</td>
<td>CMF + RT vs. CMF alone</td>
<td>10-year LRR: 32% vs. 9%, OS: 45% vs. 54%</td>
</tr>
<tr>
<td>DBCG 82c</td>
<td>Denmark</td>
<td>1375</td>
<td>Tamoxifen + RT vs. Tamoxifen alone</td>
<td>10-year LR: 35% vs. 8%, OS: 36% vs. 45%</td>
</tr>
</tbody>
</table>

Fig. 37.2-4

With a median follow-up time of 123 months, the 10-year rate of local regional recurrence was reduced from 35% to 8% with RT, and overall survival was improved from 36% to 45% with RT (both P values <0.05) (Fig. 37.2-4). In a smaller trial from British Columbia, 319 node-positive premenopausal patients treated with modified radical mastectomy were similarly randomized to adjuvant CMF chemotherapy and postoperative RT or to chemotherapy alone. The results of the British Columbia trial were similar to those of the DBCG trial 82b. Of note, the magnitude of the improvement seen in these trials is similar to that seen with adjuvant systemic therapy (chemotherapy, hormonal therapy, or both) and suggests that all node-positive patients should receive postmastectomy RT. A metaanalysis published in 2000 showed a survival benefit for local regional RT in node-positive women treated with modified radical mastectomy and adjuvant systemic therapy. For a number of reasons, however, these trials have not resulted in the universal use of postoperative RT in node-positive patients, particularly those with one to three positive nodes. One reason is that the worldwide overview of all trials of postoperative RT only shows a small, but not statistically significant survival benefit. A more substantial reason relates to the issue of generalizing from these results due to differing surgical and systemic treatments. The extent of axillary surgery performed in these trials was less than that performed in the United States, and the rates of local regional recurrence, especially axillary recurrences, observed in the Danish trials were greater than observed in U.S. series. In particular, as noted previously, series of patients with one to three positive nodes treated by modified radical mastectomy and adjuvant chemotherapy from the United States show rates of local regional recurrence in the range of 10%, compared with approximately 30% in the two Danish trials. Also, systemic therapy in the Danish trials may have been suboptimal by current standards. What seems clear is that these trials address an important principle about the value of establishing local regional control in the presence of systemic therapy. Without detracting from the importance or validity of the principle, it is legitimate to question the clinical implications of these results for practice in the United States. The final reason for the failure of these trials to translate directly into clinical practice is the concern about long-term complications of postoperative RT, especially late cardiac mortality. This is especially relevant in patients receiving chemotherapy with potential cardiac toxins such as doxorubicin (Adriamycin). To address the issues raised by the available data on postoperative RT, the American Society of Therapeutic Radiology and Oncology sponsored a symposium on postoperative RT and invited a panel to hear the latest information on this topic and to develop a Consensus Summary Statement. The panel was composed of three radiation oncologists, a medical oncologist, a surgical oncologist, and a consumer activist.
The risk of contralateral breast cancer within 30 years is approximately 22% without RT and increases to approximately 25% to 26% with RT. Thus, the risk of younger, the risk of contralateral breast cancer within 15 years is approximately 11% without RT and increased to approximately 12% to 13% with the addition of RT. One possible complication of RT for breast cancer is the induction of another breast cancer. Breast tissue is known to be sensitive to radiation carcinogenesis. The latency period between exposure and the detection of induced cancers is at least 5 years, and this risk persists for many decades. The risk of carcinogenesis increases with doses up to 10 Gy, then seems to level off and decline so that for doses in the therapeutic range (greater than 45 Gy), the risk seems to be small. Because the dose to the opposite breast from a course of RT is in the range of 1 to 3 Gy, tumor induction in the contralateral breast is of greater potential concern than in the ipsilateral breast. Age at exposure to radiation is the other important risk factor for carcinogenesis in human breast tissue. Among women who survived for at least 10 years, RT was associated with a small, but marginally significant, elevation in the risk of a contralateral breast cancer (relative risk, 1.33). The increased risk associated with RT was evident among women who were younger than 45 years of age when they were treated (relative risk, 1.59), but not among older women (relative risk, 1.01). In another case-control study from Denmark, the incidence of a second primary breast cancer in the contralateral breast was examined among 56,540 women with a first primary breast cancer diagnosed between 1945 and 1978. In that study, RT was not associated with an increased risk of contralateral breast cancer (relative risk, 1.04). It is possible to estimate the increased absolute risk of contralateral breast cancer given the elevated relative risk for patients aged 45 or younger seen in the study by Boice et al. The risk may actually be lower, as is suggested by the Danish study. For patients aged 45 years or younger, the risk of contralateral breast cancer within 15 years is approximately 11% without RT and increased to approximately 12% to 13% with the addition of RT. The risk of contralateral breast cancer within 30 years is approximately 22% without RT and increases to approximately 25% to 26% with RT. Thus, the risk of contralateral breast cancer in young patients, which is already higher than that for older patients, is likely to be further increased to a small extent by the use of RT.
radiation-induced sarcoma is shorter than for others irradiaed for breast cancer, with some occurring before 5 years.

Lung cancer also appears to be increased in patients irradiated for breast cancer. The latency period from RT to diagnosis is approximately 10 years. In a case-referent study reported by Inskip and others, using the Connecticut Tumor Registry, there was a small increased risk of lung cancer among 10-year survivors of breast cancer associated with the use of postoperative RT (relative risk, 1.8; 95% confidence interval, 0 to 3.8). The relative risk for the period 15 years or more after RT was 2.8 (95% confidence interval, 1.0 to 8.2); however, it can be difficult to distinguish a late metastasis of breast cancer to lung from a new primary lung cancer even with a tissue specimen. This increased relative risk suggests that there would be approximately nine cases of RT-induced lung cancer per year among 10,000 breast cancer patients who survived at least 10 years. Similar findings were noted in a study using the SEER database. Another study from this same group suggested that the beneficial effects of smoking and RT are multiplicative, although this relationship has not been established with certainty. These studies all examined the risk of lung cancer after local regional irradiation and the risk may be less after more localized breast irradiation.

Sequencing of Systemic Therapy and Radiation Therapy

Clinicians are now commonly faced with the necessity of combining systemic therapy and RT in patients after surgery and mastectomy. Given (1) the variable agents, duration, and intensity of CT regimens, (2) variations in RT and surgical techniques, and, (3) the limited data from randomized clinical trials addressing this question, the optimal sequencing approach is unresolved. The major goal in sequencing is to obtain the highest rate of survival; however, additional important goals are the control of local recurrence and the rate of complications. The options for combining RT and CT are (1) CT first followed by RT; (2) RT first followed by CT; (3) RT and CT simultaneously; or (4) some number of cycles of CT, then RT, and then more CT (commonly referred to as sandwich therapy). In considering this issue, it would be useful to know whether a delay in either CT or RT decreases its effect, what the complication rate is for each sequence option, and whether the delay affects the ability to give maximal doses of CT. It seems plausible that delays in the initiation of CT will decrease its effectiveness; however, firm data demonstrating this are not available. As previously described, the use of preoperative CT has not clearly improved survival compared with conventionally timed adjuvant chemotherapy. Retrospective reviews of patients treated either with mastectomy or BCT examining the influence of the delay of CT on outcome have demonstrated conflicting results. The information available on whether a delay in the initiation of RT to give CT first leads to a increased local recurrence rate is also conflicting. RT preceded by CT followed by RT and, with a mean delay of 58 months, the 5-year crude incidence of first sites of recurrence suggested that local recurrence was greater with delayed RT and distant recurrence was greater with delayed CT. The overall actuarial rate of distant failure was higher in the RT-first arm (37% vs. 23% for the CT-first arm). The question of sequencing of systemic agents and negative patients is still not resolved. When sequencing occurs in patients with negative axillary nodes or when there are 12 weeks of chemotherapy. One can hypothesize that the effect of delay in the initiation of RT is related to the extent of the breast surgery and the final margin status, namely, a delay of 12 to 16 weeks is important only for patients with limited breast surgery and close or positive margins. This hypothesis is suggested by a subset analysis of the JCRT trial; however, this trial was not large enough to allow for such analysis. At this writing, there are no ongoing unpublished trials in France. In the Aroscin trial, approximately 700 patients treated with breast-conserving surgery will be randomized either to (1) mitoxantrone, cyclophosphamide, and fluorouracil given every 3 weeks for 6 cycles followed by RT, or (2) concurrent CT and RT using the same drugs. In the other trial, patients are randomized either to (1) epirubicin, cyclophosphamide, and fluorouracil followed by RT, or (2) concurrent mitoxantrone, cyclophosphamide, and fluorouracil and RT.

Another important question regarding sequencing is whether RT and CT can be given simultaneously without an increase in complications or a decrease in the cosmetic outcome. The use of simultaneous RT and CT has the advantage of eliminating the necessity for delaying one of the modalities and perhaps providing an additive or synergetic interaction between the RT and CT. It has been reported, however, that the concurrent use of CMF chemotherapy and full-dose RT can result in greater side effects compared with patients treated with sequential treatment; however, this was a decrease in the long-term cosmetic result. It may be possible to combine CMF and RT in other, more tolerable ways. At the University of Pennsylvania, 210 patients were treated with concurrent CF and RT, followed by six cycles of CMF, with excellent results. This trial has been questioned as a result of the addition of RT. The JCRT has conducted a prospective pilot study of a modified concurrent CMF and RT regimen using reduced doses of RT designed to lessen treatment side effects by anticipating the known interaction of CMF and RT. One hundred twelve patients with zero to three positive lymph nodes were entered into this prospective study. Patients received six cycles of CMF given every 28 days. On day 14 of cycle 1, patients started tangential field radiation, consisting of 47.5% had excellent, 43% had good, and 10% had fair cosmetic scores. Seventy-nine percent of patients (89 of 112) were evaluable for CMF dosages delivered; however, longer term data are required to substantiate this.

Doxorubicin and cyclophosphamide (AC) given every 3 weeks for 4 cycles are currently used more widely than CMF, given its shorter course and at least equivalent outcome. With the substantial interaction between doxorubicin and RT, it does not seem feasible to combine these modalities concurrently even with reduced doses of RT. When AC is used, the results of the JCRT Upfront-Outback trial provide strong support for the use of AC × 4 followed by RT in all moderate- to high-risk patients. Preliminary results suggest that AC × 4 may further improve outcomes compared with AC × 4 alone. The optimal sequencing of RT in this setting is uncertain. Given that the positive results in this trial were obtained using RT after completion of Taxol, it generally seems best to use this approach. Studies are under way testing the feasibility of AC × 4 followed by concurrent Taxol and RT; however, there is a report of early-onset pneumonitis using this approach and another report showing none.

Axillary Treatment

Axillary treatment in the form of a complete dissection was, for many years, standard management in patients with invasive breast cancer. As dictated by the Halscheidt concept of breast cancer spread, axillary dissection was considered a critical component of the surgical cure of the disease. The axillary nodes were considered the filter before spread of cancer cells to distant sites. Axillary dissection is also known to be useful in assessing prognosis and ensuring local tumor control in the axilla. By the 1970s, there was increasing evidence that axillary dissection had a limited effect on survival. This was most convincingly demonstrated in the NSABP trial B-04. In this trial, patients with clinically negative axillary nodes were randomized to randomized to radical mastectomy, total mastectomy with observation of the axillary nodes and a delayed dissection if positive nodes appeared, or total mastectomy with RT to the regional lymphatics. No statistically significant difference in the 10-year survival rate was found among the groups, despite the fact that approximately 40% of the patients undergoing axillary dissection had positive nodes and a similar percentage were presumed to have positive nodes in the observation-only arm. While this study emphasizes that axillary dissection is not of survival benefit for the majority of breast cancer patients with positive nodes, it can be difficult to distinguish a late metastasis of breast cancer to lung from a new primary lung cancer even with a tissue specimen. This increased relative risk suggests that there would be approximately nine cases of RT-induced lung cancer per year among 10,000 breast cancer patients who survived at least 10 years. Similar findings were noted in a study using the SEER database. Another study from this same group suggested that the beneficial effects of smoking and RT are multiplicative, although this relationship has not been established with certainty. These studies all examined the risk of lung cancer after local regional irradiation and the risk may be less after more localized breast irradiation.

With the general recognition that axillary dissection was principally a prognostic, rather than therapeutic, procedure, a number of studies were undertaken to determine the extent of axillary surgery needed to determine whether nodes were positive or negative. Many of these studies examined the likelihood of skip metastases (i.e., involvement of nodes in the upper axilla; level III) in the absence of involvement in the lower (level I or II) nodes. Involvement of level III is clearly rare. More recent retrospective analyses of large databases of patients treated with a level I and II dissection as part of BCT, axillary recurrence rates of less than 3% have been reported. When patients undergo more routine axillary sampling procedures, the likelihood of skip recurrence is related to the number of lymph nodes removed. The 5-year probability of an axillary recurrence is approximately 20% in patients with no lymph nodes examined and approximately 10% only when one to two negative nodes are removed. At least six to ten nodes need to be removed to avoid misclassification and to optimize local control in the axilla. While a level I and II dissection is generally well tolerated, there are occasionally complications. Major complications, including injury or thrombosis of the axillary vein and injury to the motor nerves of the axilla, are infrequent. Minor complications are more common and include seroma formation.
A number of developments have led to a reexamination of the need for axillary dissection in all patients. Under discussion is the routine use of adjuvant systemic therapy in many patients with node-negative breast cancer, the increasing use of BCT, and the increasing number of patients with small, mammographically detected cancers with a low risk of axillary metastases. One approach to avoiding axillary dissection is to identify cancers with a low risk of nodal metastases. The incidence of axillary nodal involvement is known to be related principally to tumor size. However, axillary node metastases are still seen in 12% to 37% of cancers measuring 1 cm or less.\textsuperscript{429,430,431,432,433,434} In a number of studies, the incidence of metastases does not decrease appreciably even with cancers 0.5 cm or smaller.\textsuperscript{429,432,434} The only groups of patients with invasive carcinoma regularly identified as having nodal metastases in fewer than 5% of cases are those with microinvasive tumors, those with grade 1 tumors less than 5 mm,\textsuperscript{432} and those with pure tubular carcinomas less than 1 cm.\textsuperscript{429,432,433,434} However, most patients continue to undergo axillary dissection, even in these favorable groups. Patterns of Care study examining axillary surgery in 17,151 patients with stage I and II carcinoma undergoing BCT in 1994 found that overall, 93% had an axillary dissection. Even in patients with grade 1 tumors, favorable histologic subtypes, or tumors less than 5 cm, 88% or more underwent axillary dissection.

The technique of lymphatic mapping and sentinel node biopsy offers the possibility of reliably identifying patients with axillary node involvement with a low-morbidity operation, allowing axillary dissection to be limited to patients with nodal metastases who can benefit from the procedure. The sentinel node is defined as the first node receiving lymphatic drainage from a tumor, and the absence of metastases in the sentinel node reliably predicts the absence of metastases in the remaining axillary nodes.\textsuperscript{435} This concept was popularized by Giuliano et al. in malignant melanoma and later adapted to breast cancer.\textsuperscript{435} Multiple studies have now confirmed that a sentinel node can be identified in more than 90% of cases, with experience, and predicts the status of the remaining nodes with 90% to 95% accuracy.\textsuperscript{436,437,438,439,440,441} (Table 37.2-15).

### TABLE 37.2-15. Studies of Lymphatic Mapping and Sentinel Node Biopsy

The sentinel node can be identified using isosulfan blue dye, radiolabeled colloids, or a combination of the two agents. Similar success rates are reported for the techniques, and a randomized trial demonstrated no difference in the rate of sentinel node identification, predictive value of the sentinel node, or learning curve for isosulfan blue dye alone compared with the blue dye plus technetium sulfur colloid.\textsuperscript{442} Approximately 20 to 30 cases appear to be necessary to master the sentinel biopsy technique, with individual learning curves varying widely.\textsuperscript{443,444,445,446}

A number of contraindications to sentinel node biopsy have been identified, including the presence of suspicious axillary adenopathy, evidence of locally advanced breast cancer, use of preoperative chemotherapy, receipt of local or regional therapy, prior axillary surgery, and a pregnant or lactating patient. In addition, virtually no information on accuracy of the procedure for tumors larger than 5 cm is available. Lymphatic mapping and sentinel node biopsy have prompted renewed interest in the role of the internal mammary nodes in breast cancer. A small number of internal mammary node metastases have been reported in patients whose lymphoscintigraphy results have failed to demonstrate axillary drainage, but the need for internal mammary node biopsy remains to be defined.

Sentinel node biopsy offers the pathologist the opportunity to perform a much more detailed examination of one or two nodes than is possible when evaluating an entire axillary specimen. It has been known for more than 30 years that approximately 20% of lymph nodes in which no tumor is seen after routine processing and light microscopy contain tumor cells that can be identified by serial sectioning or immunohistochemistry.\textsuperscript{447,448,449,450} Early studies did not find these micrometastases to be prognostically significant, and these techniques were not practical for use on an entire axillary specimen. With the ability to examine only one or two sentinel nodes, there is renewed interest in the possibility of using immunohistochemistry for ultra staging. However, prospective confirmation of the significance of tumor cells detected by immunohistochemistry is lacking. The retrospective studies that indicate prognostic significance show a wide variation in the magnitude of this effect,\textsuperscript{451,452} which may be due to differences in patient selection, making patient counseling difficult. The results of two prospective clinical trials being carried out by the American College of Surgeons Clinical Oncology Group and the NSABP to address these issues will provide important information regarding the clinical significance of micrometastases.

An additional important unresolved issue is the need for completion axillary dissection when a positive sentinel node is identified. The initial sentinel node studies demonstrated that the sentinel node is the only tumor-containing node in 40% to 60% of cases, and fewer than 20% of patients have more than three involved nodes.\textsuperscript{453,454,455,456} A positive sentinel node establishes the need for systemic therapy, and, in patients undergoing breast-conserving surgery, radiation of the breast includes a significant portion of the low axilla, helping to maintain local control. However, the possibility that axillary dissection has some therapeutic benefit for patients with involved nodes cannot be excluded, making abandonment of completion axillary dissection unwise. The need for axillary dissection in sentinel node–positive patients is being addressed in a prospective randomized trial by the American College of Surgeons Clinical Oncology Group and the NSABP to address these issues will provide important information regarding the clinical significance of micrometastases.

The initial results of lymphatic mapping and sentinel node biopsy are extremely promising. However, data on the long-term outcome of sentinel node biopsy alone in unselected populations and information on the ability of surgeons outside of centers of expertise doing a low volume of breast surgery are needed before it can be determined if sentinel node biopsy will replace axillary dissection as the standard of care for the node-negative or node-positive breast cancer.

### LOCAL RECURRENCE

#### LOCAL RECURRENCE AFTER MASTECTOMY

Local recurrence following mastectomy usually presents as one or more asymptomatic nodules in or under the skin of the chest wall, typically located in or near the scar of the mastectomy.\textsuperscript{457} A few patients present with diffuse chest wall involvement, more commonly seen in patients with locally advanced tumors originally. Carcinoma en cuirasse is a distinct form of diffuse infiltration of the skin or subcutaneous tissues of the chest wall with woody induration and spread of tumor well beyond the limits of standard surgical or RT boundaries. Approximately 80% of local recurrences appear by 5 years after mastectomy and nearly all occur by 10 years.\textsuperscript{458,459} However, local recurrences occurring 15 to 50 years after initial surgery have been reported. It is possible that some of these late recurrences may represent new secondary cancer arising in residual breast tissue.\textsuperscript{460}

It is unclear how often chest wall recurrences progress to be symptomatic. In some series, only 25% to 30% of patients develop significant morbidity.\textsuperscript{461,462} However, in one series of 100 patients with local regional recurrence, 62 had one or more significant symptoms before death.\textsuperscript{463} Despite aggressive local treatment, most patients with an isolated local recurrence following mastectomy eventually manifest distant metastases. In a series of patients with local, regional, or both local and regional recurrence treated at the JCRT, the 5- and 10-year actuarial rates of freedom from distant metastases were 30% and 7%, respectively.\textsuperscript{464} The corresponding rates of overall survival were 50% and 26%. However, patients surviving without death 15 or more years after treatment with mastectomy are more likely to have a recurrence that can be managed without further treatment. Recent series appear to include patients with more favorable disease and suggest that favorable subsets of patients with local recurrence can be identified based on factors discussed here.\textsuperscript{465,466,467,468}

A number of prognostic factors for survival following local recurrence have been identified.\textsuperscript{469,470,471,472} The interval between mastectomy and local recurrence (called the disease-free interval) is the most reliable indicator of the time to subsequent distant failure and overall survival. This likely reflects the intrinsic
growth rate of the tumor. For example, at the JCRT, the relapse-free survival at 3 years was 20% for patients treated with aggressive RT who had isolated local recurrences less than 24 months after initial surgery, compared with 36% in patients who had isolated local recurrences at 24 months or longer after surgery. The respective 10-year survival rates were 7% versus 36%, with similar results found in nearly all RT series. Lymph node status at the time of mastectomy and the number of sites and the size of recurrence also appear to influence prognosis. In patients with a long disease-free interval, limited disease capable of being resected, limited axillary involvement, or both limited disease and involvement, the prognosis may be favorable. 

Patients undergoing skin-sparing mastectomy do not appear to be at a greater risk of local recurrence than patients undergoing more conventional mastectomy, but further experience is needed to confirm this.

Patients with local recurrence after mastectomy should have a complete restaging to rule out distant metastases. In particular, a CT scan of the chest and abdomen and a bone scan is recommended since many patients have additional sites of involvement only discovered in this manner. MRI or positron emission tomography scans may provide additional information. Limited local excision has been used in some patients, with further local failure occurring in over one-half of patients so treated. For highly selected patients, local control rates in excess of 75% have been reported with wide local excision of skin and subcutaneous tissue or partial or full-thickness chest wall resection, with some patients surviving 5 years or more. RT has been the standard form of local treatment for patients with local recurrence after mastectomy. The volume of disease remaining at the time of RT is a critical determinant of the likelihood of achieving long-term local control, and gross excision is recommended if feasible. In patients with initially unresectable disease, the use of initial systemic therapy should be strongly considered. Patients with a recurrence in one portion of the chest wall or draining lymph node areas should receive RT to the entire chest wall. Patients with chest wall recurrence may subsequently have recurrences in the supracavicular region (where the axillary region if not previously dissected) if only the chest wall is irradiated. In general, the higher the dose of RT delivered, the less likely an in-field failure, and doses in the range of 60 Gy to the site of recurrence are recommended, even following gross excision. However, even with technically optimal RT, further local recurrence is seen in a significant minority of patients. Attempts to improve this have included the addition of hyperthermia; however, this treatment is still limited by technical limitations, complications, and insufficient support for its use in randomized trials.

Photodynamic therapy has shown some utility in previously treated patients, but its role in the primary treatment of local recurrence has not been established.

It is not clear whether using adjuvant systemic therapy in conjunction with local treatment can prolong disease-free or overall survival time. While a number of retrospective studies have suggested a benefit to adjuvant systemic therapy, the only randomized trial addressing this issue is from Switzerland and has only a limited number of patients (n = 167). Entry in this trial was restricted to patients with a positive or undetermined ER assay, disease-free interval greater than 1 year, and three or fewer nodules, each 3 cm or smaller in diameter, without fixation. Randomized patients underwent complete gross tumor resection and RT and were randomly allocated to receive either tamoxifen until relapse or to observation. With a median follow-up of 6.3 years, the 5-year relapse-free survival rates were 39% and 36% in the tamoxifen and observation arms, respectively (P = NS). However, this difference had nearly disappeared by 8 to 9 years, and the overall survival rates were the same in both groups. This trial was not large enough to suggest a clinically important advantage for adjuvant systemic therapy.

As previously noted, the large majority of recurrences in the treated breast following CS and RT are at or near the site of the primary tumor. The risk of this type of recurrence is substantially greater from years 1 to 5 than in the first 5 years. The prime treatment for such recurrences is wide local excision with or without adjuvant systemic therapy. The findings on physical examination associated with a recurrence may be subtle, especially when the primary tumor was of infiltrating lobular histology. Changes in the physical examination that occur more than 2 years following the completion of RT should be viewed as suspicious. Recurrence in the nipple areola, presenting as Paget's disease, can also occur. There can be substantial overlap in the radiologic appearance between benign and malignant lesions following treatment. Ultrasound is sometimes helpful in distinguishing benign and malignant masses. MRI scans may also be useful, but this is not yet established. In patients with suspicious findings, prompt biopsy is recommended. Mammographic or ultrason-directed core-needle biopsy is an increasingly used approach to confirm the diagnosis.

The large majority of breast recurrences are operable, and the majority of patients are alive 5 years after recurrence. The results appear to be better than for patients with local recurrence after mastectomy, except possibly for patients with early recurrence for whom prognosis is equal or poor after mastectomy and local recurrence. Limited local excision has been used in patients with operable disease are not well established. The most important prognostic factor in patients undergoing mastectomy in the JCRT experience was the histology of the recurrence. There was no further evidence of disease among the 24 patients with only noninvasive cancer or predominantly noninvasive disease with only focal areas of invasion. In contrast, 38% of patients (38 of 99) with predominantly infiltrating tumors developed a further recurrence, usually distant. A small minority of patients present with skin involvement following BCT, and these patients have a poor prognosis.

In patients with a breast recurrence, appropriate staging for distant metastases should be performed before definitive therapy. The standard treatment for an isolated breast recurrence is mastectomy. Subsequent chest wall recurrences occur in fewer than 10% of patients treated with mastectomy. Postoperative complications following mastectomy are rare. Wide local excision alone is associated with a substantial risk of further breast failure and uncontrolled local disease. There is limited experience with reirradiation for patients with a breast recurrence. Many patients treated with mastectomy for local recurrence desire breast reconstruction. Immediate reconstruction with a myocutaneous flap is psychologically advantageous and also promotes tissue healing. The risk of complications following reconstruction is slightly greater than in patients who have not had prior RT, and the overall cosmetic results may not be quite as favorable. Previously irradiated patients have tolerated submuscularly placed tissue expanders poorly.

The role of adjuvant systemic therapy following breast recurrence has not been established. In patients with an invasive recurrence, the risk of distant recurrence is substantial, and the use and concerns of adjuvant systemic therapy are similar to those described previously (see Local Recurrence after Mastectomy, earlier in this chapter).

BREAST RECONSTRUCTION

As discussed, breast reconstruction is an important option for a breast cancer patient undergoing mastectomy to consider and should routinely be discussed with the patient before definitive surgery. The only contraindications to breast reconstruction are the presence of significant comorbid conditions that would interfere with the patient's ability to tolerate a longer operative procedure in the case of immediate reconstruction or additional procedures in the case of delayed reconstruction. In patients who may require postoperative chest wall irradiation, implant reconstruction should be avoided since the risk of implant loss is high after RT. However, TRAM flap reconstructions appear to tolerate postoperative RT well. Patient age, need for adjuvant chemotherapy, or poor long-term prognosis are not contraindications to reconstruction.

The simplest technique for breast reconstruction involves the use of available tissue and placement of an implant. This approach is best for women with small or moderate-sized breasts with minimal piastra and requires adequate skin to cover an implant of a size similar to the contralateral breast. The use of limited skin excision, with operative exposure gained by incision, usually leaves enough skin to cover an implant. Oncologic surgeons generally agree that the only skin that it is necessary to excise for reasons of cancer control is the nipple-areola complex and the biopsy scar. If insufficient skin is available to achieve symmetry with the contralateral breast or for larger or plictic breasts, a tissue expander may be employed. This technique involves placement of a prosthesis that is only partially inflated beneath the pectoral muscle. Using a subcutaneous injection port, the prosthesis is gradually filled with saline over a period of weeks to months until the desired volume is achieved.
Silicone breast implants have been available for over 30 years. In January 1992, the U.S. Food and Drug Administration (FDA) declared that silicone gel-filled implants could not be used until more information was available about their long-term safety. This moratorium, however, did not apply to saline-filled implants, and the FDA later recommended that gel-filled implants be allowed in breast cancer patients pending the results of further study. The major recognized complication of implants is the development of capsular contracture, an excessive scar formation around the implant that may lead to deformity and pain of the breast. Other complications of implants include rupture of the implant and leakage of silicone through the intact implant capsule. The incidence of these complications is uncertain. A major concern regarding the use of silicone implants arose after uncontrolled reports suggested an increased incidence of connective tissue disease in women with implants.\(^{246,247}\) However, in 1995 the American Society of Rheumatologists concluded that scientific evidence does not support an association between implants and connective tissue disease. A metaanalysis of 13 epidemiologic studies and other publications on this topic identified a relative risk of 0.76 for any connective tissue disease and 0.98 for scleroderma in patients with breast implants.\(^{497,512}\) Similar risks were reported by Silverman et al.\(^{512}\) after a metaanalysis of 4000 cases.

Another technique of reconstruction is the use of myocutaneous flaps to transfer skin, fat, and muscle from distant parts of the body. The most commonly used flaps are the latissimus dorsi and TRAM flaps. The use of a flap for reconstruction requires a more lengthy and involved operative procedure than the implant method, and postoperative recovery is somewhat longer because there are two separate incision sites. The latissimus flap is often used in conjunction with a prosthesis because, in most cases, the flap alone provides insufficient bulk to achieve symmetry. With the latissimus flap, there is only a 1% incidence of complete flap loss. The TRAM flap, though, allows an adequate breast mound to be fashioned without the use of a prosthesis, but its blood supply is more tenuous than that of the latissimus flap, with major necrosis reported in 5% of patients and partial necrosis in as many as 31% of patients.\(^{248,249}\) For some patients, the removal of extra tissue from the lower abdomen is an advantage to this procedure. Abdominal wall herniation is seen in 2% to 5% of patients following this procedure, but this percent is dependent on the skill and experience of the operator. Long-term cigarette smoking (more than 20 pack-years) has an acute and chronic effect on microcirculation and, in many centers, is a contraindication to the procedure. If these myocutaneous flaps are not available or suitable for use, it is possible to transfer composite tissues from distant sites and to perform a microvascular anastomosis to nearby vessels.\(^{520}\) This technique, known as a free flap, requires a skilled microsurgeon and prolonged operating time and is only occasionally chosen for primary reconstruction. The potential benefits and complications of the various reconstructive procedures are listed in Table 37.2-16.

### Table 37.2-16. Types of Reconstruction after Mastectomy

Regardless of the technique of reconstruction chosen, the creation of a breast mound is the chief goal in breast reconstruction. Surgery on the contralateral breast, such as reduction or mastectomy, may be required to achieve symmetry. Reconstruction of a nipple-areola complex is another secondary procedure that some patients elect to undergo in order to improve cosmetic appearance. The patient's own nipple should not be used for this purpose because recurrent carcinoma due to persistence of breast tissue on the nipple has been reported. Microscopic involvement of the nipple is seen in 30% of mastectomy specimens, but is frequently not apparent at the time of gross pathologic examination. The nipple can be reconstructed using a variety of local flap techniques or by the use of full-thickness skin grafts. Tattooing of the grafts produces a color match to the patient's own areola and allows any site to be used as the donor.\(^{370}\) Tissue from the contralateral nipple should not be used for nipple reconstruction because of the concern of transferring breast tissue to the reconstruction site.

### SPECIAL THERAPEUTIC PROBLEMS

#### PAGET'S DISEASE OF THE NIPPLE

Paget's disease of the nipple is a rare form of breast cancer that is characterized clinically by eczematoid changes of the nipple. Associated symptoms include itching, erythema, and nipple discharge.\(^{242,243}\) Paget's disease is diagnosed histologically by the presence of large cells, with pale cytoplasm and prominent nucleoli (known as Paget's cells) involving the epidermis of the nipple. In approximately 45% of women with Paget's disease, a breast mass is detected at presentation, and in most of the remainder, infiltrating or intraductal carcinoma is identified in the mastectomy specimen.\(^{243,244}\) The average age of women with Paget's disease does not differ from that of women with other forms of breast cancer, but symptoms are frequently present for 6 months or more before diagnosis.\(^{243,245}\) The relation between the changes observed in the nipple and the underlying breast cancer remains a matter of controversy. One theory suggests that the nipple involvement represents the migration of malignant cells from the underlying breast tumor. The alternate hypothesis suggests that Paget's cells are a separate disease process originating in epidermis.

Paget's disease has traditionally been treated with mastectomy. The rationales for this approach are the need to sacrifice the nipple-areola complex, the fact that the subareolar ducts may be diffusely involved with tumor, and the observation that carcinoma may be found at a considerable distance from the nipple.\(^{252,253,254}\) A limited experience with breast-conserving procedures in the management of Paget's disease has been described. Paone and Baker reported five patients who underwent excision of the nipple with a wedge resection of underlying breast tissue, who remained free of disease at 10-year follow-up.\(^{255}\) Lagios and coworkers reported five patients with no palpable breast mass and negative mammogram results treated by excision of the nipple-areola complex, who remained free of parenchymal recurrence at a mean follow-up of 50 months.\(^{256}\) One patient, treated with only partial nipple excision, developed recurrent Paget's disease at 12 months, which was resected. In contrast, four of ten patients treated by Dixon et al. with excision alone had local recurrences after a median follow-up of 40 months.\(^{252}\) Twenty-seven patients with Paget's disease without clinical or radiologic evidence of parenchymal breast cancer were treated with RT alone or excision plus RT at the Institut Curie from 1960 to 1984.\(^{523}\) At a median follow-up of 7.5 years, three patients had recurrent disease in the nipple-areola region and were treated with mastectomy. The 7-year actuarial probability of survival with the breast preserved was 81%. Bulens et al., using similar selection criteria, reported no local or distant failures in a group of 13 patients treated with breast irradiation alone.\(^{523}\) Osteen collected a total of 79 patients treated by local excision with or without RT, with nine local recurrences.\(^{523}\)

When considering therapeutic options in Paget's disease, it is helpful to think of the condition as DCIS involving the nipple. Usually associated with additional intraductal or invasive carcinoma in the underlying breast parenchyma. The extent of the underlying involvement determines the patient's suitability for BCT. Detailed mammographic evaluation (including magnification views of the subareolar region) and histologic evaluation with margin assessment are essential components of this evaluation. For patients with evidence of diffuse involvement or disease at a distance from the nipple, mastectomy remains the standard therapy. In patients with disease localized to the subareolar area or the nipple-areola complex, BCT can be considered. This treatment requires removal of the entire nipple-areola complex and some of the underlying ducal region. In carefully selected patients, local failure rates with this approach appear to be similar to those reported for other breast carcinomas. The prognosis in Paget's disease is related to the stage of the disease and appears to be similar to that of women with other types of breast carcinoma. If invasive breast cancer is found, adjuvant systemic treatment should follow the same guidelines used for other patients with invasive cancer.

### MALE BREAST CANCER

Cancer of the male breast is an uncommon disease, accounting for less than 1% of all cases of breast carcinoma.\(^{512,513}\) According to SEER data, approximately 1600 cases of male breast cancer and 400 deaths were expected to occur in 1999.\(^{2}\) In one study, a family history of female breast or ovarian cancer was reported in 30% of men with breast cancer.\(^{327}\) As described previously (see Inherited Predisposition to Breast Cancer, earlier in this chapter), studies have demonstrated that germline...
mutations of BRCA2 are associated with an increased risk of male breast cancer, as well as early-onset breast cancer in women. In the absence of a family history, however, a BRCA2 mutation is unlikely to be found in a man with breast cancer. An initial report suggested that BRCA2 might account for approximately 15% of male breast cancer; however, a high percentage of patients in this study had a family history of female breast cancer. \[53\] The only population-based study using male patients from a cancer registry found a much lower (4%) incidence of BRCA2 mutations. \[51\] Other factors that increase the risk of male breast cancer include Klinefelter's syndrome, hepatic schistosomiasis, and radiation exposure. \[52\] \[53\] \[54\] Except for men with Klinefelter's syndrome, the presence of gynecomastia does not seem to be associated with an increased risk of breast carcinoma; however, microscopic changes of gynecomastia are commonly seen histologically in male breast cancer. \[55\] \[56\]

Male breast cancer typically presents as a mass beneath the nipple-areola complex. Ulceration of the nipple is a frequent sign, although isolated nipple discharge is uncommon. The mean age of men with breast carcinoma is between 60 and 70, slightly higher than that of women with the disease. Infiltrating ductal carcinoma is the most common tumor type, but Paget's disease of the nipple and inflammatory carcinoma have been reported in men. LCIS is not seen in the male breast, and infiltrating lobular carcinoma is rare. As many as 80% of male breast carcinomas are hormone-receptor positive, and an inverse correlation exists between receptor positivity and age, similar to that seen in women. \[57\] \[58\]

The standard local treatment for male breast carcinoma is mastectomy. If the tumor is not fixed to the pectoral muscle, a modified radical mastectomy can be performed. If muscle involvement is limited, a portion of this structure can be removed. For patients with extensive involvement of the pectoral muscle, a radical mastectomy may be required. \[59\] BCT for male breast carcinoma is rarely feasible given the small size of the breast and the subareolar location of the cancer in most men. Patients may, however, occasionally express an interest in this approach to therapy. \[60\]

The survival rate of men with breast cancer is similar to that of women after controlling for differences in stage. \[63\] As in women, axillary nodal status is the major predictor of outcome. In a report of 335 cases of male breast cancer, 84% of node-negative patients survived 10 years, compared with 44% of those with one to three positive nodes and 14% with four or more positive nodes, not dissimilar to that seen with female patients. \[64\] Age at diagnosis and tumor size were also significant in a multivariate analysis of prognostic factors in the study of Huhtinen et al. \[65\] Borgen and coauthors found that only duration of symptoms and axillary nodal status were significant predictors of outcome. \[66\] \[67\]

The benefit of adjuvant systemic therapy in male breast cancer has not been evaluated in randomized clinical trials, although men with metastatic breast cancer are thought to have a similar course and response to treatment as women with the disease. By extrapolation, this experience has guided the approach to adjuvant therapy in men with early-stage disease. The administration of adjuvant tamoxifen to men with stage II and III disease resulted in a 55% 5-year survival, compared with 28% in historic controls receiving no systemic treatment. Two small retrospective studies suggest that survival is improved by adjuvant systemic chemotherapy. In the absence of definitive data, guidelines for the use of adjuvant therapy in men should be the same as those employed in women and guided by age, stage, and hormone receptor status. Similarly, decisions about the use of radiation should parallel the treatment of female breast cancer. For those men who choose to have CS, radiation is mandatory. Postmastectomy radiation appears to decrease local regional recurrence, but does not have a substantial effect on survival. Two trials that report an overall survival for women undergoing postmastectomy radiation suggest that radiation should be considered following mastectomy in men with nodal involvement. \[68\] \[69\]

The use of systemic therapy in male patients with metastatic breast cancer should also follow the guidelines set for female patients. Tamoxifen, megestrol acetate (Megace), aromatase inhibitors, and surgical castration are the principal treatments, although antiangiogenes and lateleuízing hormone-releasing hormone agonists have been reported to be effective. \[70\] \[71\] \[72\] Response rates of 50% to 80% to hormonal therapy are reported, and responses to second-line therapy are commonly seen. \[73\] \[74\] The traditional method of hormonal manipulation has been orchectomy. A literature review found a 67% response rate to this treatment, which increased to 80% when only receptor-positive cancers were considered. Tamoxifen has a similar response rate and has become increasingly popular as a first-line hormonal manipulation, but tamoxifen may not be as well tolerated in men as in women. \[75\] \[76\] \[77\] Orchietomy is now often reserved for patients who have failed multiple other therapies. \[78\] \[79\] Chemotherapy is useful as palliative treatment. In general, the spectrum of activity with chemotherapeutic agents is similar to what has been seen in women with breast cancer, although much of the information is anecdotal. \[80\] \[81\]

**BREAST CANCER DURING PREGNANCY**

Breast cancer during pregnancy has been thought to be a particularly virulent disease, but much of the poor prognosis may be due to advanced disease at the time of diagnosis. After correction for tumor stage and age, most studies indicate that survival in women treated during pregnancy is similar to that seen in nonpregnant women. \[82\] \[83\] \[84\] A review of 416,441 pregnancies found an incidence of 2.2 breast cancers per 10,000 pregnancies. \[85\] The demographic changes that have led to delays in childbearing have increased the proportion of breast cancer cases that are now associated with pregnancy. It has been suggested that breast cancer may complicate 1 in 1000 pregnancies. \[86\]

The clinical presentation of breast cancer during pregnancy is typically a palpable mass. The mass or thickening may initially be attributed to the breast changes seen in women with breast cancer, although much of the information is anecdotal. \[87\] \[88\] \[89\] \[90\] \[91\] \[92\] \[93\]

Mammography is not as useful in pregnant patients as in those who are not pregnant because of the increased density in breast parenchyma associated with pregnancy. Moreover, the increase in breast size during pregnancy also may make detection more difficult. As is the case with nonpregnant patients, an unrewarding mammogram should not lead to a decision to forego biopsy in a patient with a palpable mass. Delays in diagnosis are not uncommon in pregnant women, most likely due to the difficulty of examining the breast of a pregnant woman and the reluctance of many physicians to suspect breast cancer in a relatively young, gravid patient. \[94\] \[95\]

Breast cancer during pregnancy has been thought to be a particularly virulent disease, but much of the poor prognosis may be due to advanced disease at the time of diagnosis. Petrek et al. compared 56 pregnant breast cancer patients treated at Memorial Hospital from 1960 to 1980 with 166 nonpregnant women of the same age treated in the same period. Sixty-one percent of the pregnant women and 38% of the nonpregnant women had positive lymph nodes; 31% of the pregnant women had T1 tumors compared with 50% of their counterparts. After correction for tumor stage and age, most studies indicate that survival in women treated during pregnancy is similar to that seen in nonpregnant women. \[96\] \[97\] \[98\] and \[99\] In the series by Petrek et al., no-dead pregnant patients had a 77% 10-year survival compared with 75% for nonpregnant patients. The corresponding 10-year survival figures for node-positive patients were 25% and 41%, respectively, and were not statistically different. In contrast, a multinstitutional study of 407 patients aged 20 to 29 at the time of cancer diagnosis found a relative risk of cancer death of 2.83 (95% confidence interval, 1.24 to 6.45) for the 26 patients whose children were diagnosed during pregnancy compared with those who had never been pregnant. \[100\]

After a diagnosis is made, the pregnant patient with breast cancer should meet with a multidisciplinary team, including a medical, surgical, and radiation oncologist, as well as an obstetrician. In addition, psychosocial support for the patient and her family is critical. An initial evaluation should include an assessment of the extent of the disease and a thorough physical examination. Evaluation should be performed safely throughout the course of pregnancy. Diagnostic studies, such as bone scans and CT scans, should be avoided early in the pregnancy, particularly during the period of organogenesis. These studies are not essential in the initial evaluation of most women with localized breast cancer. For women in the first or second trimester, the question of pregnancy termination is inevitably raised. While some treatment approaches are feasible during pregnancy, others are contraindicated. Depending on the patient's specific situation, continuing the pregnancy may or may not compromise the usual breast cancer treatment. Even when deviations from the usual treatment are required, it is unclear to what extent such changes or delays affect a woman's odds of remaining free from recurrent breast cancer. The concerns about compromising care must be balanced, by the woman, her family, and her physicians, with the desire to continue the pregnancy. The woman facing these issues must also consider the possibility that if she receives chemotherapy, her ability to conceive another child could be compromised. There is no clear evidence that pregnancy termination changes overall survival, but the limitations of all studies that have examined this issue should be recognized. In general, clinicians and patients must understand that the disease outcomes for pregnant women with breast cancer are less well understood than for the general population of women with breast cancer.
In the setting of a pregnancy, options for local therapy need to be considered carefully. Radiation to the breast is contraindicated at all times during pregnancy because of the inability to shield the developing fetus from scatter. If a woman is in her third trimester, the use of CS is reasonable as radiation can be administered after the delivery with only a minimal delay in treatment. For women who are in their first or second trimesters, delaying radiation for 3 to 8 months is of far greater concern as it may increase the risk of local recurrence. However, if a woman is going to receive a course of adjuvant chemotherapy during pregnancy, radiation may not be planned for several months. If the inability to administer radiation during pregnancy leads to a substantially longer time to the initiation of radiation than would usually be the case, careful consideration should be given to proceeding directly to mastectomy. Reconstruction with a TRAM flap is contraindicated because of the effect on the abdominal wall. Other forms of reconstruction are not generally recommended because of the additional anesthesia time required by reconstruction and the difficulty achieving symmetry in a pregnant woman.

The vast majority of young women with breast cancer receive some type of adjuvant systemic therapy as part of their treatment. Such treatment decisions are particularly complex in the pregnant patient. The potential benefits of treatments for the mother must be considered within the context of risks to the fetus. In general, all chemotherapy agents should be avoided during the first trimester because of the risk to the fetus. When chemotherapy is administered during the first trimester, there is an increased risk of spontaneous abortion, compromised fetal viability, and major organ malformations. Certain agents, such as methotrexate and 5-fluorouracil, appear to be particularly problematic in terms of fetal malformation. Cyclophosphamide and other alkylating agents have also been associated with fetal malformation in the first trimester. Exposure of the fetus to chemotherapy after the first trimester does not appear to increase the risk of major fetal malformation. However, there are reports of low birth weight, growth retardation, and fetal demise when exposure occurs after the first trimester. Chemotherapy does cross the placenta, so there is the potential for fetal bone marrow suppression and other organ toxicity. Fetal myocardial necrosis has been reported with the third-trimester administration of an anthracycline, but other fetal abnormalities have not been reported with this regimen. Many clinicians believe that the potential late cardiac effects of in utero anthracycline exposure to the fetus. There are no data concerning the safety of in utero taxane exposure.

When adjuvant chemotherapy is administered during pregnancy, many clinicians opt for an anthracycline-based regimen, such as four cycles of doxorubicin and cyclophosphamide. Chemotherapy should not be administered until the second trimester, and even then many physicians try to delay chemotherapy for as many weeks as possible to allow for further fetal development. Adjuvant chemotherapy for women in their third trimesters is often delayed until after delivery, often with the plan of delivering the baby several weeks early.

A regimen of fluorouracil, Adriamycin, and cyclophosphamide chemotherapy has been used by investigators at M. D. Anderson Cancer Center in a total of 24 pregnant women during their second and third trimesters. Birth weights, Apgar scores, and general health of the newborns were reported to be normal. In France, generally favorable short-term outcomes (median follow-up, 12-24 months) have been reported for children exposed to a range of chemotherapy regimens during the second and third trimesters. Adjuvant tamoxifen has not been shown to be safe in women during pregnancy.

In the rare situation that a gravida patient has metastatic disease, treatment decisions are even more difficult and must be tailored to the individual situation. For women with rapidly progressive disease, there may be few options apart from proceeding with systemic therapy, regardless of gestational age.

**OCCULT PRIMARY WITH AXILLARY METASTASES**

It is relatively uncommon for breast cancer to present as an axillary nodal metastasis without a palpable lesion in the breast. In a study of over 10,000 patients treated for primary breast cancer at Memorial Sloan-Kettering Cancer Center between 1975 and 1988, occult primaries with axillary metastases accounted for 0.35% of the cancers. Similarly, 0.5% of 12,000 breast cancers treated at the National Cancer Institute in Milan were found to be occult primaries with axillary metastases.

Although malignant axillary adenopathy may be secondary to a variety of primary solid tumors, as well as lymphoma, breast cancer is by far the most common diagnosis in a woman presenting with isolated axillary adenopathy. Before undergoing biopsy, a woman should have a complete physical examination and bilateral mammography. Chest radiography should be obtained, particularly in those with a smoking history. Once a diagnosis is established, additional radiologic studies looking for another primary tumor are rarely helpful in the absence of specific symptoms. The presence of positive hormone receptors further suggests a diagnosis of breast cancer, although other primary tumors (i.e., lung carcinoma) can also be positive for ER.

Several series suggest that MRI may be able to detect otherwise occult cancers in the breast and may be helpful in planning local therapy. In one small series, MRI identified the primary cancer in 9 of 12 patients presenting with axillary disease. In another series from the University of Pennsylvania, MRI of the breast detected occult cancers in 19 of 22 women with a mean size of 17 mm. These findings have important implications for BCT in these women, although it is likely that the use of MRI to detect occult cancers would decrease the proportion of women identified with unsuspected tumors at the time of mastectomy.

**TABLE 37.2.17. Results of Mastectomy in 228 Women with Axillary Disease in the Setting of an Occult Primary Tumor**

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Patients</th>
<th>Occult/Nonoccult</th>
<th>3-yr Survival Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ginzburg et al.</td>
<td>55</td>
<td>6/49 (12%)</td>
<td>78</td>
</tr>
<tr>
<td>Beck et al.</td>
<td>50</td>
<td>19/31 (61%)</td>
<td>75</td>
</tr>
<tr>
<td>Fink et al.</td>
<td>15</td>
<td>12/15 (80%)</td>
<td>75</td>
</tr>
<tr>
<td>Fitt et al.</td>
<td>21</td>
<td>9/17 (53%)</td>
<td>71</td>
</tr>
<tr>
<td>Ungar et al.</td>
<td>26</td>
<td>9/12 (75%)</td>
<td>66</td>
</tr>
<tr>
<td>Kevany et al.</td>
<td>26</td>
<td>9/17 (53%)</td>
<td>65</td>
</tr>
<tr>
<td>Tridon et al.</td>
<td>29</td>
<td>19/20 (95%)</td>
<td>64</td>
</tr>
<tr>
<td>Vannier et al.</td>
<td>20</td>
<td>19/20 (95%)</td>
<td>65</td>
</tr>
<tr>
<td>Drucker et al.</td>
<td>15</td>
<td>13/20 (65%)</td>
<td>64</td>
</tr>
<tr>
<td>Macmillan et al.</td>
<td>18</td>
<td>9/17 (53%)</td>
<td>61</td>
</tr>
<tr>
<td>Total</td>
<td>228</td>
<td>92/136 (67%)</td>
<td>64</td>
</tr>
</tbody>
</table>

There are a number of reports of using BCT in patients with occult primaries. The obvious objection to this approach is that there may be a relatively large tumor, multifocal disease, or both in the breast that might not be well controlled with radiation. Results with this approach have been mixed. A series of 44 patients treated at the Institut Curie with relatively high-dose whole breast irradiation (median dose, 60 Gy) reported a 5% risk of ipsilateral breast recurrence at 8 years. Elderbrook et al. reported a 17.5% 5-year actuarial rate of ipsilateral breast recurrence in a group of 16 women treated with breast conservation. There has been no apparent survival difference associated with breast conservation in comparison with mastectomy, but randomized trials in women with occult primaries have not been performed. Furthermore, the series are sufficiently small that it would be misleading to draw anything but the most tentative conclusions regarding the survival equivalence of this approach. Whether or not a mastectomy is performed, some form of axillary surgery should be performed in women presenting with palpable axillary disease because of the limited ability of radiation to control gross axillary disease.

Overall survival for women with occult primary tumors is similar to the survival of patients with comparable axillary involvement in the setting of known primary tumors. Some investigators have suggested that survival may even be slightly better for those with occult primary tumors (often with minimal disease in the breast) could have a slightly better prognosis than the general population of node-positive patients. Systemic treatment for patients with occult primary tumors and axillary involvement
Phyllodes Tumor

The term phyllodes tumor includes a complete group of malignant potential ranging from completely benign tumors to fully malignant sarcomas. Clinically, phyllodes tumors are smooth, rounded, multinodular lesions that may be indistinguishable from fibroadenomas. Skin ulceration is seen with large tumors, but this is usually due to pressure necrosis rather than invasion of the skin by malignant cells. Histologically, phyllodes tumor, like fibroadenoma, is composed of epithelial elements and a connective tissue stroma.

Phyllodes tumors are classified as benign, borderline, or malignant based on the nature of the tumor margins (pushing or infiltrative) and presence of cellular atypia, mitotic activity, and overgrowth in the stroma. There is disagreement about which of these criteria is most important, although most experts favor stromal overgrowth. The percentage of phyllodes tumors classified as malignant ranges from 22% to 50%. Axillary metastases are reported in less than 5% of cases, but are a poor prognostic sign when present. Metastases commonly follow the pattern seen with melanomas, with the lung as the most common site and histologically resemble sarcomas. They occur in 6% to 22% of cases and are considerably more common in the malignant subtype. Approximately 20% of phyllodes tumors recur locally if excised with no margin or a margin of a few millimeters of normal breast tissue, regardless of whether they are benign or malignant. A wide excision with a 2-cm margin of normal breast tissue is appropriate therapy for benign and borderline phyllodes tumors unless they are so large that this is not cosmetically feasible. In the past, many authors have advocated mastectomy for the management of malignant phyllodes tumors. Since phyllodes tumors are not multicentric, there is no clear-cut biologic rationale for mastectomy, and series have reported the successful treatment of malignant phyllodes tumors with wide excision.

The use of systemic therapy for malignant phyllodes tumors is guided by the primary treatment of treating sarcomas.

PROGNOSTIC AND PREDICTIVE FACTORS

Some of the key decisions in the current management of primary breast cancer involve the need for prognostication and the optimal selection of therapy. A prognostic factor is defined as a biologic or clinical measurement that is associated with disease-free or overall survival in the absence of adjuvant systemic therapy. A predictive factor is any measurement associated with response or lack of response to a particular therapy. Estrogen receptor status has been clearly shown to be a predictive factor for hormonal therapy, in both the adjuvant and metastatic disease settings. Prognostication is especially important in identifying patients whose prognoses are so favorable that adjuvant systemic therapy is unnecessary. Prognostic factors can also be useful in identifying patients whose prognoses with conventional treatment are so poor as to warrant consideration of more aggressive investigational therapies.

It should be stressed that evaluating potential prognostic and predictive factors requires caution. Individual studies often evaluate many factors and report only the statistically significant ones. To be useful, potential factors require validation in a separate large data set in which multivariate analysis allows for the assessment of the potential factor when adjusted for other known factors.

The most established prognostic factor is the number of positive axillary lymph nodes based on at least a level I or II axillary dissection and a detailed histologic evaluation. An adequate axillary dissection usually contains at least ten lymph nodes. As the number of involved lymph nodes increases, relapse rates increase, and survival rates decrease. Patients are often grouped as having negative nodes, one to three positive nodes, four to nine positive nodes, or ten or more positive nodes. Given the morbidity of axillary dissection and controversies about its therapeutic value, many patients are now undergoing sentinel node biopsy or no axillary surgery (see Axillary Treatment, earlier in this chapter).

Tumor size, one of the first prognostic variables accurately quantified, is also a valuable prognostic factor. Tumor size refers to the maximal size of the invasive component measured on microscopic sections. Tumor size correlates with the number of histologically involved nodes, but has independent prognostic significance. Tumor size is particularly useful in patients with pathologically negative nodes. Patients with negative nodes and tumor size less than 1 cm have a favorable prognosis.

Tumor grade is commonly provided on pathology reports, and several investigators have demonstrated that it is an important prognostic factor in individual series. The use of tumor grade, however, has been limited by poor reproducibility.

Among clinical factors, young patient age should be recognized to be an adverse prognostic factor by some, but not all, investigators. In two large series, breast cancer patients younger than 35 years of age had a worse prognosis than older patients. In both studies, young patients were more likely than older patients to have adverse prognostic factors, but young age remained a significant prognostic factor in multivariate analysis. At the 1996 St Gallen International Conference on Adjuvant Therapy of Breast Cancer, young patient age was first recognized as an adverse prognostic factor.

Of the biochemical measurements, the most important is the presence or absence of ER and PR in the tumor. In the past, the receptor status was determined by a dextran-coated charcoal biochemical assay. More recently, nearly all laboratories are using an immunohistochemistry assay (estrogen and progesterone receptor immunohistochemical assay, ERICA and PRICA). ERICA is preferable in that it does not require fresh tissue, allows correlation with histology, and can be performed even on very small lesions. Although hormone receptor status correlates with prognosis, it does so only weakly. Furthermore, several studies have reported that ER is a prognostic factor for 5-year disease-free survival, although the curves tend to merge with longer follow-up. This suggests that ER status is a measure of proliferation, rather than metastatic potential. Despite this, hormone receptor determination is of critical importance as a predictive factor for hormonal therapy. In addition, the 1998 Overview on the use of adjuvant chemotherapy (see Adjuvant Drug (Systemic) Therapy, later in this chapter) showed that its effectiveness was somewhat greater in ER-poor cancers than in ER-positive cancers, thus establishing ER as a weak predictive factor for adjuvant chemotherapy.

The identification of micrometastases in bone marrow using antibodies to various epithelial antigens has also been evaluated for its prognostic significance. A meta-analysis of 20 published studies reported in 1998, including 2494 patients using a variety of techniques, concluded that the presence of micrometastases did not contribute independent prognostic information. More recently, a group using a monoclonal antibody to bind an antigen on cytoeratins not present on bone marrow cells identified a strong correlation between the presence of cytokeratin-positive cells in the bone marrow and 4-year survival. This study raised the possibility that standardized procedures for (1) the preparation of bone marrow specimens, (2) the use of antibodies and staining technique, and (3) the criteria for defining positively stained cells may allow for the routine use of this procedure. Additional follow-up and future studies are needed to establish this before its use in routine clinical practice.

Measures of proliferation have been another area for the evaluation of prognostic factors. This includes mitotic index, thymidine labeling index, flow cytometry, and several antibodies to cell-cycle-associated antigens. One of the concerns in the use of these various measures of proliferation is ensuring standardization. The most thoroughly evaluated of these in the United States has been DNA flow cytometry. Flow cytometry can be performed on fresh tissue specimens, frozen biopsy samples, needle aspirates taken directly from the tumor, or paraffin-embedded tissues. The technique produces a measure of DNA content (DNA ploidy) and the distribution of cells in the cell cycle. Of particular interest has been the percent of cells in the S phase. In 1997, a review of the experience with S-phase fraction determined by flow cytometry concluded that standardization and quality control must be improved before it can be routinely used.

Studies are also under way to determine whether S-phase fraction is a predictive factor for the use of chemotherapy. Studies using antibodies to Ki-67 and proliferating cell nuclear antigen have shown encouraging early results but are not established. To date, there have been relatively few studies that have directly compared different measures of proliferation.

There has also been interest in the prognostic value of growth factors and their receptors. Of these growth factors, the greatest interest has been in HER-2/neu. The gene is located on chromosome 17q21 and is transcribed into a 4.5-kb mRNA, which is translated into a 185-kD glycoprotein. While multiple studies have demonstrated the negative impact of HER-2/neu overexpression on the progress of node-positive patients, the role of HER-2/neu in node-negative patients is less clear. There is evidence, however, that HER-2/neu may be a useful predictive factor. Several retrospective studies suggest that only patients whose tumors have little or no detectable levels of HER-2/neu derive considerable benefit from cyclophosphamide (Cytoxan), methotrexate, and 5-fluouracil regimens, and, in a study...
from CALGB, that patients whose tumors have high levels of HER-2/neu derive greater benefit from dose-intensive Cytoxan, Adriamycin, and 5-fluouracil regimens. A study from the NSABP that compared adjuvant treatment with and without Adriamycin demonstrated that patients with HER-2/neu-negative tumors had the same outcome with or without Adriamycin, whereas patients with HER-2/neu-positive tumors who did not receive Adriamycin had significantly worse prognoses. Similar results were also seen in a trial from the Southwest Oncology Group study. With the growing use of HER-2/neu testing, the most reliable method to determine HER-2/neu status must be established.

It has also been suggested that HER-2/neu status may predict response to endocrine therapy. Among patients treated with adjuvant tamoxifen, those with HER-2/neu-positive tumors tend to have shorter disease-free and overall survival times compared with patients with low HER-2/neu levels. However, the data supporting an interaction between HER-2/neu expression and adjuvant tamoxifen therapy is not conclusive, and patients with ER-positive and HER-2/neu-positive cancers should still receive adjuvant hormonal therapy. Ongoing trials are testing the combined use of tamoxifen and trastuzumab (Herceptin) in these patients.

There are a large number of investigations of other potential prognostic and predictive factors; however, it is beyond the scope of this chapter to review each of them. None has been established for routine use in clinical care, including nm23, p53, cathepsin D, and other measures of tumor invasiveness, measures of angiogenesis, and evolving microarray technology.

**ADJUVANT DRUG (SYSTEMIC) THERAPY**

It is thought that occult metastases (or micrometastases) are commonly present when patients first present with operable breast cancer. This view is based on the fact that, even following effective local treatment, many patients develop metastatic involvement over time and improvements in local control have been shown to provide, at best, only a small decrease in distant metastases. Given this, improving the long-term outlook for newly diagnosed breast cancer patients with early-stage disease can only be accomplished with improvements in systemic therapy.

Beginning more than three decades ago, many clinical trials were organized to test the value of various drugs as an adjunct or adjuvant to local treatment. These trials, described in detail here, have demonstrated significant improvements in survival for treated patients compared with controls. Adjuvant chemotherapy, hormonal therapy, or both are now in widespread use around the world. Since its introduction, there has been a decrease in the death rate from breast cancer, suggesting a beneficial effect on public health. In many populations, it has been difficult to distinguish the life-saving effects of screening mammography from those of adjuvant systemic therapy since these two interventions were introduced at approximately the same time. In one large population-based study from British Columbia in which this issue was studied, the use of adjuvant systemic therapy by itself had a direct beneficial effect on the death rate from breast cancer.

Over 100 prospective randomized clinical trials of adjuvant therapy have been conducted. More than 15 years ago, the Early Breast Cancer Trialists’ Collaborative Group was formed to organize this vast body of information. This group has provided a composite analysis of all randomized trials of the treatment of primary breast cancer performed worldwide. The major portion of this activity has focused on adjuvant drug therapy; the results of the 1995 Overview are summarized in Table 37.2-18. The 1995 Overview (published in 1998) provided important new insights related to the value of tamoxifen in premenopausal women and the utility of chemotherapy in postmenopausal women.

In the Overview, the number of events (either relapse or death) in the treatment and control arms of individual trials are scored to determine an expected-minus-observed value and an odds ratio indicative of the value of the treatment. When a treatment is beneficial in a given trial, the expected-minus-observed value is negative, and the odds ratio is less than 1.0. Similar studies are grouped together, and a combined expected-minus-observed value and overall odds ratio can then be calculated. In combining the results of similar studies, each expected-minus-observed value and odds ratio are weighted by the relative size of each experiment so that a large study with more events counts more. This statistical method provides an estimate of the effectiveness of a certain therapy based on the entirety of all available data from randomized trials (see Table 37.2-18).

In examining the results of the Overview, it is important to distinguish those results that are generated from a direct comparison of randomized arms and those results that are indirect comparisons of treatment results across different studies. For example, an indirect comparison would use data from trials comparing chemotherapy versus no treatment with trials comparing ovarian ablation versus no treatment to compare the relative benefits of chemotherapy versus ovarian ablation. The results of direct comparisons provides solid information for use in making treatment decisions, whereas the results of indirect comparisons should be used in generating hypotheses to be tested in additional studies.

The results of the breast cancer metaanalysis suggest an important principle; namely, that the proportional reduction in the risk of relapse as a result of a treatment is generally constant regardless of the patient's absolute risk of relapse (Table 37.2-19). To illustrate this, assume that a therapy reduces the annual odds of relapse by one-third. If we treat patients who are expected to have recurrences at a rate of 15% per year, we would lower the recurrence rate to 10% per year with therapy. In turn, the percentage of patients who develop recurrence would decline from 14% to 10% at 10 years. In this situation, the absolute improvement is only 4%. In some situations, such as a woman with a tumor that is less than 1 cm with negative nodes, the absolute benefits might be even smaller.

### TABLE 37.2-18. Adjuvant Drug Therapy: Percentage Reduction in the Annual Odds ofEither Recurrence or Death (from Any Cause)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Reduction in Annual Odds of Either Recurrence or Death (from Any Cause)</th>
<th>Reduction in Annual Odds of Either Recurrence or Death (from Any Cause)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10%</td>
<td>10%</td>
<td>10%</td>
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<td>15%</td>
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<tr>
<td>95%</td>
<td>95%</td>
<td>95%</td>
</tr>
</tbody>
</table>

### TABLE 37.2-19. Absolute Reduction in Mortality at 10 Years per 100 Patients Treated
Clinicians should consider the effect of an adjuvant therapy in terms of both disease-free and overall survival. Ultimately, the goal of adjuvant treatment is to prolong survival. Some clinicians would argue that an improvement in disease-free survival, in and of itself, justifies the use of adjuvant treatment since recurrence is often associated with substantial morbidity. Any improvement in disease-free survival must be considered in the context of the short- and long-term toxicity of adjuvant treatment. In general, improvement in disease-free survival usually translates into survival benefits as well. For this reason, it is reasonable to consider disease-free survival in making treatment decisions, particularly if the studies in question have a sufficiently short follow-up such that an overall survival advantage would not yet emerge.

**ADJUVANT TAMOXIFEN**

Tamoxifen was initially considered a promising candidate for adjuvant treatment because of its efficacy against advanced disease and relative lack of toxicity. In the Overview analysis, over 37,000 patients were randomized in 55 trials examining the effect of adjuvant tamoxifen at a dose of 20 to 40 mg/d for at least 1 year. The trial has yielded no clear evidence that 40 mg is superior to 20 mg, in addition to which, the higher dose is more expensive and possibly more toxic. As a result, the standard dose of tamoxifen is 20 mg/d.

As shown in Table 37.2-18, the benefits of tamoxifen are substantial and are seen in both premenopausal and postmenopausal women. Tamoxifen, taken for approximately 5 years, reduces the annual odds of disease recurrence by 47% and the annual odds of death by 26%. The degree of benefit is similar in younger and older women. The benefits of tamoxifen administered for 5 years were similar despite the presence or absence of chemotherapy. This finding represented a change from the previous Overview, at least for premenopausal women. Importantly, the benefits seen with tamoxifen were only seen in women with ER-positive tumors. There appeared to be no benefit from adjuvant tamoxifen in ER-poor patients in terms of either recurrence or death (Table 37.2-20).

<table>
<thead>
<tr>
<th>Hormone-Related Level</th>
<th>Reduction in Annual Odds of Recurrence (%)</th>
<th>Reduction in Annual Odds of Death (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor (0/10 fmol)</td>
<td>-3.5</td>
<td>-1.7</td>
</tr>
<tr>
<td>Moderate (11-99 fmol)</td>
<td>-6.9</td>
<td>-3.1</td>
</tr>
<tr>
<td>Positive (&gt;100 fmol)</td>
<td>-9.3</td>
<td>-5.1</td>
</tr>
<tr>
<td>HER-2/neu overexpression</td>
<td>-16.0</td>
<td>-9.3</td>
</tr>
</tbody>
</table>

**TABLE 37.2-20. Effects of Tamoxifen for 5 Years According to Estrogen-Receptor Level**

In terms of duration of tamoxifen therapy, 5 years of treatment is the standard of care (Table 37.2-21). Once women with ER-poor tumors were excluded from the analysis, indirect comparisons indicated that 5 years were superior to 2 years or less. This finding is supported by the results of two individual studies comparing 2 years versus 5 years of tamoxifen. It remains uncertain whether more than 5 years of tamoxifen could be superior to 5 years. In both the NSABP B-14 trial and a trial from Scotland, patients randomized to more than 5 years of therapy appeared to have a greater risk of recurrence. An Eastern Cooperative Oncology Group trial suggested that the continuation of tamoxifen beyond 5 years may delay relapse in ER-positive patients; however, there was no difference in survival in this study. At present, the available data would support stopping tamoxifen at 5 years. Of note, there are both preclinical and clinical data (withdrawal responses in the metastatic setting) to suggest that tamoxifen may act as a growth agonist after variable periods of exposure. If this is the case, it is not difficult to imagine that the withdrawal of tamoxifen could, in and of itself, be of benefit. Tamoxifen lowers the risk of disease recurrence even after it has been discontinued. Women randomized to 5 years of tamoxifen had a 33% annual reduction in recurrence after 5 years (when they were no longer taking tamoxifen) compared with women who never took tamoxifen. For mortality, the proportional reduction after 5 years was similar to the proportional reduction seen during the first 5 years.

**TABLE 37.2-21. Duration of Tamoxifen**

In general, tamoxifen appears to have greater benefit in women with strongly positive ERs. In the trials evaluating 5 years of tamoxifen, the proportional reduction in annual recurrence was 43% for patients who had moderately ER-positive tumors (less than 100 fmol) and 60% for women with strongly ER-positive tumors (greater than 100 fmol). Similar trends were seen for mortality. Despite the predictive value of progesterone receptors (PR) in patients with advanced disease, PR status did not appear to affect the benefits of tamoxifen in patients with ER-positive tumors. There were insufficient numbers of patients with ER-negative, PR-positive tumors in the Overview to draw any definite conclusions about the benefits of tamoxifen in this subgroup. In clinical practice, such patients are usually considered to have hormonally responsive disease, and similar recommendations for adjuvant tamoxifen therapy should be made for ER-negative, PR-positive patients as for those with ER-positive tumors. As noted previously, the substantial benefits of adjuvant tamoxifen appear to be confined to patients with positive hormone receptor results. This finding represents a change from previous publications of the Overview. A total of 8000 women with ER-poor tumors were randomized to tamoxifen or no tamoxifen. Although the 10% reduction in the annual odds of recurrence is statistically significant, the absolute benefit is of small magnitude. The proportional reduction in terms of mortality is even smaller, and there is no trend for improved outcome with longer duration of treatment. Given these results, women who are shown to have negative hormone receptor status should not be treated with tamoxifen to prevent a systemic recurrence.

With growing interest in the measurement of HER-2/neu or c-erbB-2, there has been concern raised about the role of tamoxifen in women with both positive hormone receptors and HER-2/neu overexpression. In the metastatic setting, trials have suggested relative resistance to hormonal therapy in patients with HER-2/neu overexpression. In the adjuvant setting, a retrospective analysis of the Italian GUN-1 trial suggested that patients with ER-positive, HER-2/neu overexpressing tumors had a worse outcome with tamoxifen than those who received no hormonal intervention. A retrospective analysis of a large CALGB trial failed to detect a negative interaction between tamoxifen and HER-2/neu. At this time, HER-2/neu overexpression does not preclude the use of adjuvant tamoxifen in a patient who is otherwise an appropriate candidate.

In addition to its effect on recurrence and mortality in trials of 5 years of therapy, tamoxifen has also been shown to reduce the incidence of contralateral tumors. There was a 47% reduction in the annual odds of developing a contralateral cancer. The reduction in contralateral tumors was independent of the hormone receptor status of the primary tumor. These findings are consistent with the results of individual trials in the NSABP tamoxifen prevention trial, and the results seen with the
use of tamoxifen in women with DCIS.\textsuperscript{204}

The serious toxicities of tamoxifen and the common side effects are listed in Table 37.2-22. In individual trials, the Overview, and the tamoxifen prevention trial, there has been an unequivocal increase in the incidence of endometrial cancer in women taking tamoxifen. The excess risk over 10 years is estimated to be four cases of endometrial cancer per 1000 women. In NSABP B-14, there was a 0.16% annual risk of developing endometrial cancer on tamoxifen.\textsuperscript{205} The breast cancer prevention trial has strongly suggested that endometrial cancer is primarily a problem for women over 50.\textsuperscript{206} Thromboembolic complications were also seen more frequently in older women.

<table>
<thead>
<tr>
<th>Serious, Any Event</th>
<th>Not Preme, Not Premenopause</th>
<th>Event Type</th>
<th>Any Common</th>
<th>Any Event, Premenopause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaginal Bleeding</td>
<td>Depressive</td>
<td>Endometrial cancer</td>
<td>Vaginal Discharge</td>
<td>Vaginal Discharge</td>
</tr>
<tr>
<td>Breathing Difficulty</td>
<td>Social Disturbance</td>
<td>Genital Abnormality</td>
<td>Normal</td>
<td>Social Disturbance</td>
</tr>
</tbody>
</table>

**TABLE 37.2-22.** Adverse Effects of Tamoxifen

Tamoxifen has been reported to have positive effects on bone density in postmenopausal women.\textsuperscript{207} In the NSABP prevention study, there was a reduction in osteoporotic fractures with tamoxifen that almost reached statistical significance.\textsuperscript{208} The clinical significance of this finding is uncertain, and the effects of tamoxifen on bone have not been compared with the bone effects of agents approved to prevent or treat osteoporosis. In premenopausal women, there has been concern raised about accelerated bone loss.\textsuperscript{209} Although tamoxifen does lower cholesterol levels,\textsuperscript{210} there was no improvement in cardiac or vascular events with tamoxifen in the Overview.\textsuperscript{211} In the NSABP prevention study, there was no difference in the frequency of fatal myocardial infarction, nonfatal myocardial infarction, or angina requiring surgical intervention.\textsuperscript{212}

In patients who are receiving chemotherapy, tamoxifen can be administered either following the completion of treatment or concurrently with chemotherapy. While there have been theoretical concerns raised about tamoxifen reducing tumor growth rates and interfering with the effects of chemotherapy,\textsuperscript{213} this has not been observed clinically. Clinical studies indicate that thromboembolic complications are increased when the two treatments are administered concurrently.\textsuperscript{214} Outside of a clinical trial, either approach is reasonable. A similar concern has been raised about a potential negative interaction of tamoxifen and radiation, but this has not been supported by clinical data. Tamoxifen, which was administered concurrently with radiation, lowered the rate of ipsilateral breast recurrences by 61% in NSABP B-14.\textsuperscript{215}

Which patients with invasive breast cancer should receive tamoxifen? It is possible to answer this question with less equivocation than in the past. All women who have positive lymph nodes or tumors greater than 1 cm in the setting of positive hormone receptors should receive adjuvant tamoxifen for a period of 5 years. For women with small tumors (T1a or T1b) and negative lymph nodes, the risk of a systemic recurrence is relatively low, and decisions about tamoxifen need to be considered carefully. For the majority of such women, the benefits of tamoxifen probably outweigh the risks. This is particularly the case for a woman who has undergone CS plus radiation and in whom tamoxifen will not only decrease the risk of a systemic recurrence but will also lower the chance of an ipsilateral recurrence or a new contralateral primary. Since the life-threatening toxicities of tamoxifen (endometrial cancer and thromboembolic disease) are more common in women over 50, these toxicities should be considered when making decisions about tamoxifen in this older group of women who are at low risk of recurrence. The decision to continue tamoxifen needs to be reevaluated in women who experience unpleasant side effects. While tamoxifen is usually well tolerated, some patients have a more difficult time with side effects than others. In summary, it is reasonable to consider the use of tamoxifen and to discuss the pros and cons of treatment in any woman diagnosed with a hormone receptor–positive or unknown breast cancer. Tamoxifen should not be administered to women with negative hormone receptor status unless the main goal of treatment is to prevent a second primary tumor. It should be recognized, however, that for the majority of women with invasive breast cancer, the risk of a systemic recurrence is far higher than the risk of developing a second primary tumor.

**HORMONAL INTERVENTIONS OTHER THAN TAMOXIFEN**

Although tamoxifen is the mainstay of adjuvant hormonal therapy for patients with breast cancer, questions still remain about the role of ovarian ablation in the management of women with stage I or II disease. If anything, this area has become even more complex in recent years as a result of new findings from clinical trials.

Twelve randomized trials using either surgical or radiation ablation were judged to be of adequate quality to be included in the Overview.\textsuperscript{216} Of these studies that included 3456 women, seven evaluated ovarian ablation as the sole adjuvant treatment and five looked at ovarian ablation in combination with chemotherapy. Many of the trials were underpowered; some included both premenopausal and postmenopausal women, and only the trials that included chemotherapy had information on ER assays. Despite the fact that most of the individual trials had failed to detect a difference in overall survival, the combined analysis of the 12 studies indicated a highly significant improvement in both recurrence rates and survival for ovarian ablation (Table 37.2-23).\textsuperscript{217} Not surprisingly, this benefit was confined to women who were under 50 at the time of randomization. There was no significant benefit seen with ovarian ablation in the 1354 women who were over 50, most of whom would have already experienced menopause. The absolute improvement in survival at 15 years associated with ovarian ablation in the older subgroup was 2.5%, a difference that was not statistically significant. Of interest, the benefits of ovarian ablation appeared to be far less dramatic in women who also received chemotherapy. The explanation for this finding may lie in the fact that at least some of the benefit associated with chemotherapy may be due to treatment-induced menopause that occurs in a substantial proportion of premenopausal women.

**TABLE 37.2-23.** Metaanalysis of the Effects of Ovarian Ablation

A U.S. Intergroup Trial prospectively studied the value of adding a luteinizing hormone–releasing hormone agonist to a course of adjuvant cyclophosphamide, Adriamycin, and 5-fluorouracil in premenopausal, receptor-positive, node-positive patients.\textsuperscript{218} Women were randomized to chemotherapy alone, chemotherapy plus 5 years of goserelin, or chemotherapy plus 5 years of goserelin and 5 years of tamoxifen. The addition of goserelin alone resulted in much smaller improvement in relapse-free survival that was not statistically significant. In a subset analysis, there was the suggestion of greater benefit with goserelin in women...
under the age of 40, who would be less likely to experience chemotherapy-induced menopause. The European studies have also addressed the role of ovarian ablation in women with early-stage breast cancer. Investigators in Sweden randomized 732 premenopausal women with positive hormone receptors to nine cycles of intravenous CMF every 3 weeks or ovarian ablation. After a median follow-up of 86 months, there was no difference in either disease-free or overall survival. In another trial, the combination of tamoxifen for 3 years and tamoxifen for 5 years was compared with six cycles of intravenous CMF (day 1, 8 every 28 days) in 1045 premenopausal women with hormone receptor-positive breast cancer. There was no difference in survival between the two arms, although patients on the hormonal therapy had a statistically significant improvement in relapse-free survival after a median follow-up of 42 months. Finally, in a smaller but more mature trial, there was no difference seen between intravenous CMF (every 3 weeks for six to eight cycles) and ovarian ablation in approximately 300 premenopausal women. In women with higher levels of ER expression, there was the suggestion of a better outcome with ovarian ablation; conversely, women with low ER expression appeared to have a better outcome with chemotherapy.

The results of these studies are of great interest, and indirect comparisons in the Overview suggest that ovarian ablation and chemotherapy are similar in the magnitude of their effects. It remains unclear where ovarian ablation fits into the treatment paradigm for women with early-stage breast cancer. Any conclusions must be tempered by the recognition that the database on ovarian ablation is far less extensive than on either chemotherapy or tamoxifen. While ovarian ablation may be comparable with chemotherapy in selected premenopausal patients, there are insufficient data to suggest that ovarian ablation should be substituted for chemotherapy as a routine practice. The potential negative consequences of ovarian ablation in women with breast cancer have not been fully investigated and could be even greater in some women than a course of chemotherapy. It also remains unclear to what extent ovarian ablation adds to benefits seen with tamoxifen in premenopausal women. For many clinicians, the pressing clinical question is whether ovarian ablation is of additional benefit in the premenopausal woman who has received chemotherapy, is taking tamoxifen, and continues to have menstrual cycles. In the absence of additional data, there are insufficient data to recommend such a treatment approach at this time.

Far more limited data are available about other adjuvant hormonal therapies. While toremifene has been shown to be equivalent to tamoxifen in the metastatic setting, its activity in the adjuvant setting has not been established. There are insufficient data to support the use of any other antiestrogens as adjuvant treatment for early-stage breast cancer, including raloxifene.

In premenopausal women, ongoing studies are evaluating aromatase inhibitors in place of tamoxifen, in conjunction with tamoxifen, and following 2 to 5 years of tamoxifen. Given the activity of aromatase inhibitors in the metastatic setting, these agents may ultimately play a role in the adjuvant therapy of premenopausal women.

**ADJUVANT CHEMOTHERAPY**

The first trials of adjuvant chemotherapy were launched in the 1950s, but it was not until the late 1960s that the first modern trials of combination chemotherapy were initiated. Since the 1970s, randomized trials have addressed many fundamental questions related to adjuvant chemotherapy. Adjuvant chemotherapy initially was administered to women with positive nodes; a series of trials published in the late 1980s extended the use of adjuvant chemotherapy to node-negative women as well.

Two early trials had a major effect on the care of women with breast cancer and the design of future studies. The NSABP compared the use of melphalan for 2 years versus no adjuvant therapy in 349 women with node-positive disease. At the same time, Bonadonna and colleagues in Milan evaluated 12 months of CMF versus no adjuvant treatment in 386 women. Both studies showed a statistically significant improvement in disease-free survival, with subset analyses strongly suggesting most of the benefit was in women under the age of 50. The studies demonstrated a trend toward improved survival with chemotherapy, although the survival comparisons did not reach statistical significance. CMF quickly became the standard care for node-positive patients, particularly those who were premenopausal at the time of diagnosis. Twenty-year follow-up of the Milan trial has demonstrated a persistent advantage for the premenopausal women who received CMF, with a difference in survival of 47% versus 22%.

Additional randomized trials have been completed since 1980. Many of these trials have been substantially larger than the early studies, thereby increasing the power of the trials to detect small but clinically meaningful differences. These trials have contributed to our understanding of the optimal duration of therapy, the role of anthracyclines, and the benefits of treatment in both node-negative and postmenopausal patients.

There are many unanswered questions about the optimal use of adjuvant chemotherapy in women with operable breast cancer, however, one can argue that more is known about adjuvant chemotherapy for women with breast cancer than almost any other topic in clinical oncology. At the present time, there is no woman with invasive breast cancer for whom we can say there is no benefit associated with adjuvant chemotherapy, but for many women the absolute benefit is exceedingly small. In such settings, the potential benefits of treatment need to be carefully balanced against the side effects and potential risks of treatment. Breast cancer is a heterogeneous malignancy with a highly variable natural history. While the extent of disease (or stage of disease) partially reflects the underlying biology of the cancer, a more comprehensive understanding of the molecular biology and genetics of breast cancer is needed. Ultimately, this understanding will allow us to tailor therapies for specific patient subgroups and to target therapies to different tissue types. Until we gain a better understanding of subgroup differences, we are forced to consider the risks and benefits of treatments across broad populations, as best exemplified by the Overview analysis.

It is difficult to overestimate the importance of the Oxford Overview analysis in furthering our understanding of the role that adjuvant chemotherapy plays in women with breast cancer. The results of 69 randomized trials involving approximately 30,000 women were included in the third and most recent analysis and publication of the Overview. Although any metaanalysis has limitations, the large number of women included in the analysis allows for comparisons that cannot be made in individual trials.

Table 37.2-24 outlines the benefits of polychemotherapy (combination chemotherapy) in comparison with no chemotherapy in a total of 47 trials involving 17,000 women. Although some of these trials, women received additional treatment (i.e., tamoxifen) as well, but all study participants were randomized to receive multiple courses of combination chemotherapy or no chemotherapy. As can be seen, there is a highly significant benefit for combination chemotherapy compared with no chemotherapy. For the population as a whole, polychemotherapy reduced the annual odds of recurrence by approximately 25% and the annual odds of death by approximately 15%. The reduction in recurrence as a result of chemotherapy was greatest during the first 5 years following diagnosis, although there was still a significant, although smaller, proportional reduction in recurrence as a result of chemotherapy even after 5 years. The effect of chemotherapy on survival was seen during the first 5 years and persisted to an equal or greater extent during the next 5 years. The fact that the survival curves continued to separate after 5 years is not surprising; recurrences of breast cancer during the first 5 years after a diagnosis may lead to death from breast cancer during the subsequent 5-year period. This finding underscores the importance of following women with early-stage breast cancer for an extended period of time to obtain a full picture of the effect of a therapy on long-term survival. The effect of adjuvant chemotherapy on women under age 50 is illustrated in Figure 37.2-5.

| Table 37.2-24: Effects of Combination Chemotherapy across Entire Patient Population in Overview Analysis |
In the Overview analysis, the proportional reductions in recurrence and mortality are similar in node-negative and node-positive patients. Given the better prognosis of node-negative patients, especially those node-negative patients with small tumors (i.e., less than 1 cm), the absolute benefit of therapy in women with negative lymph nodes is much smaller than in those who have positive nodes. It is estimated from the Overview data that an average node-negative patient under age 50 would have an absolute improvement in survival at 10 years of 7% (an improvement from 71% to 78%). In contrast, the absolute improvement for a node-positive patient under age 50 is estimated to be 11% (an improvement from 42% to 53%). Given the mix of trials included in the Overview, the actual benefits of chemotherapy may be somewhat greater in a compliant patient population without significant comorbidity in whom full doses are delivered.

There is a strong relationship in the Overview between age and the magnitude of benefit seen with chemotherapy, with younger women having a proportionally greater reduction in both recurrence and mortality than women aged 50 to 69. The Overview includes data on only approximately 600 women aged 70 or older, thus limiting any conclusions that can be drawn regarding this subgroup. Since over one-third of all women diagnosed with breast cancer in the United States are over the age of 70, it is unfortunate that additional data are not available. The reductions in recurrence and mortality by age are detailed in Table 37.2-25. Although the benefit of chemotherapy is less in older women, the Overview shows a statistically significant advantage for chemotherapy across all age groups (up to age 69).

TABLE 37.2-25. Effect of Age on Outcome with Adjuvant Chemotherapy

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Reduction % in Annual Recurrence</th>
<th>Reduction % in Annual Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>40-49</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>50-59</td>
<td>5%</td>
<td>2%</td>
</tr>
<tr>
<td>60-69</td>
<td>7%</td>
<td>3%</td>
</tr>
<tr>
<td>&gt;70</td>
<td>10%</td>
<td>4%</td>
</tr>
</tbody>
</table>

The age-related findings in the Overview are consistent with observations made in the earlier trials, suggesting that the benefit of chemotherapy is greater in younger women than in an older patient population. The more substantial benefit of chemotherapy in younger patients, as well as the established benefits of ovarian ablation in premenopausal women, suggests that adjuvant chemotherapy may be working both through a direct cytotoxic effect on the tumor and an endocrine effect by way of the induction of menopause (which occurs in a substantial number of premenopausal women receiving chemotherapy). It should be noted, however, that not all studies show a consistent relationship between the induction of menopause secondary to chemotherapy and disease outcome. It has been difficult to separate the effects of age and menopausal status because of their high degree of correlation. It is of interest, however, that in the Overview, postmenopausal women under the age of 50 appeared to derive a similar benefit from chemotherapy as did premenopausal women under 50. This finding would suggest that chemotherapy-induced ovarian ablation is not the primary factor leading to improvement in disease-free survival and overall survival with chemotherapy. If chemotherapy is less effective in older women, there are multiple possible explanations for this phenomenon apart from the ovarian ablation hypothesis. Women over the age of 50 may have a different biologic mix of tumors; the fact that there are age-related differences in tumor biology is suggested by the differences in hormone receptor status across age. Older women may also tend to receive lower doses of therapy and are more subject to competing causes of mortality. Finally, it should be noted that several studies have suggested that the age-related differences in outcome with adjuvant chemotherapy may be less significant than was previously thought.

Other subjects addressed in the 1998 Overview include the influence of hormone receptor status on decisions regarding therapy and the utility of tamoxifen in conjunction with adjuvant chemotherapy. While chemotherapy was beneficial to a highly significant degree in patients with both ER-negative and ER-positive tumors, there was a trend for greater benefit in women with ER-negative tumors. This finding was seen particularly in women aged 50 to 69 in whom the proportional reduction in recurrence was almost twice as great (30% ± 5 vs. 18% ± 4) in patients with ER-negative tumor compared with those who had ER-positive tumors. The administration of tamoxifen in addition to chemotherapy did not appear to have a substantial effect on the benefits of chemotherapy. In other words, the proportional risk reductions from chemotherapy were similar whether or not a woman received tamoxifen; however, the number of younger women receiving chemoendocrine therapy in the Overview was small.

The Overview has provided additional findings of clinical significance. Among these findings, shorter duration therapy (3 to 6 months) appears to be as effective as longer therapy. In addition, anthracycline-containing regimens appear to be superior to non-anthracycline-containing regimens. A total of 11 randomized trials involving 5942 patients compared CMF with an anthracycline-containing regimen. Overall, anthracycline-containing therapy resulted in a proportional recurrence reduction of 12% and a proportional mortality reduction of 11%. The mortality reduction, which resulted in an absolute improvement in survival at 5 years of 2.7%, was of borderline statistical significance. Finally, the Overview did not demonstrate a preponderance of deaths from other causes as a result of chemotherapy, including deaths from other neoplasms and deaths from vascular events.

USE OF ANTHRACYCLINES IN THE ADJUVANT SETTING

The use of anthracycline-based therapy merits further comment. The finding from the Overview, suggesting a small incremental benefit with anthracyclines, has been seen in some individual trials as well. A U.S. Intergroup trial involving almost 2700 patients compared six cycles of CMF with six cycles of cyclophosphamide, doxorubicin, and fluorouracil (CAF) in high-risk, node-negative patients. The trial demonstrated a 2% improvement (one-sided P = .03) in survival for the Adriamycin-containing arm in both premenopausal and postmenopausal women. A Canadian trial comparing CMF and CEF (cyclophosphamide, epirubicin, fluorouracil) demonstrated an improvement in both disease-free and overall survival for the epirubicin-containing arm. This trial led to the Food and Drug Administration’s approval of epirubicin as adjuvant chemotherapy in the United States. To date, epirubicin-containing adjuvant regimens have been much more popular in Europe than in the United States.

NSABP B-15 randomized node-positive patients to CMF or four cycles of AC administered every 3 weeks. Although there was no difference in disease-free survival or overall survival between the two arms, the AC arm has been widely adopted as a standard of care. The shorter duration of the treatment of the regimen and the relative ease of administration has led to the regimen’s popularity. Whether or not four cycles of AC (lasting approximately 3 months) is equivalent to one of the longer anthracycline-containing regimens (which have often included fluorouracil) remains uncertain. Of interest, using a nonanthracycline regimen, the International Breast...
Retrospective analyses from a number of studies suggest that the HER-2/neu status of the tumor may influence the relative benefit of anthracycline-containing regimens. Studies have suggested that either more intensive anthracycline-containing regimens or the mere addition of an anthracycline to a non-anthracycline-containing regimen may be particularly beneficial in patients whose tumors overexpress HER-2/neu. Patients who were HER-2/neu-negative in these studies appeared to derive far less benefit from the addition or intensification of an anthracycline. Small retrospective studies have also suggested relative resistance of HER-2-positive disease to CMF-type regimens. Given the retrospective nature of all of the analyses described previously, it remains uncertain to what extent the benefit of anthracyclines reported in individual trials and in the Overview is a function of HER-2/neu status. The use of an anthracycline-containing regimen has become the standard of care in patients with HER-2/neu overexpression (who are receiving chemotherapy) and in most patients with multiple positive lymph nodes. Although four cycles of AC followed by four cycles of paclitaxel have become a widely accepted standard program for node-positive breast cancer, there are many questions remaining about this regimen. First, is the improvement in women who received paclitaxel entirely due to paclitaxel itself or is it related to the longer regimen? This question is particularly relevant in the woman with positive receptors who has a small tumor, generally favorable prognostic factors, and a small number of positive lymph nodes. Finally, how will the use of other paclitaxel schedules (i.e., weekly treatment) and the use of docetaxel compare with the benefit seen in the study described previously? Ongoing trials are addressing these issues.

DOSE INTENSITY AND DOSE DENSITY IN ADJUVANT TREATMENT

Dose intensity in adjuvant therapy has been of major interest since 1980. A retrospective review of the initial Milan CMF study suggested that patients who received a greater proportion of the intended chemotherapy had a superior outcome to those who had more extensive dose reductions. This study, as well as trials in the metastatic setting and preclinical models, led to the development of a series of prospective randomized trials that tested the hypothesis that more dose-intensive treatment would improve clinical outcome for patients with node-positive breast cancer.

The Cancer and Leukemia Group B compared three doses and schedules of CAF chemotherapy. Approximately 1550 patients were randomized to either (1) four cycles of low-dose CAF; (2) six cycles of moderate-dose CAF; or (3) four cycles of high-dose CAF. The total doses in the moderate- and high-dose arms were identical, and the low-dose arm received one-half of the total dose of either of the other groups. The high-dose arm used doses of cyclophosphamide and Adriamycin (600 mg/m² and 60 mg/m², respectively) that are now considered the standard of care. A statistically significant improvement in disease-free survival and overall survival at a median follow-up of 9 years in favor of the moderate- or high-dose arms in comparison with the low-dose arm (P < .0001 and P < .004 for the two comparisons) was seen. The absolute improvement in 5-year survival between the high- and low-dose arms was 7% (79% vs. 72%). These results are consistent with either a dose-response relationship (progressive improvement in outcome with dose escalation) or a threshold effect.

Three additional trials have evaluated dose escalations with either cyclophosphamide, doxorubicin, or both. In an Intergroup trial, four cycles of AC chemotherapy were administered to over 3100 women with node-positive breast cancer. The dose of cyclophosphamide was fixed at 600 mg/m², but women were randomized to Adriamycin doses of 60 mg/m², 75 mg/m², and 90 mg/m². Despite increased acute toxicity with higher doses of doxorubicin, there was no evidence of an improvement in either disease-free survival or overall survival. Although the median follow-up from the trial is relatively brief, the results do not support the use of more than 60 mg/m² per cycle of Adriamycin. In two NSABP trials (B-22 and B-25), the dose of Adriamycin was kept constant at 60 mg/m², and women were randomized to receive 600 or 1200 mg/m² of cyclophosphamide. Despite the increased dose, there was no improvement in disease-free survival or overall survival. In B-25, the cyclophosphamide dose was escalated from 1200 to as high as 2400 mg/m² for four cycles. Toxicity on the higher dose arms appeared to be greater, including an increased number of cases of acute leukemia and myelodysplasia. Although a subset analysis of women with four to nine nodes suggested a slight improvement for the high-dose arm in terms of disease-free survival and overall survival, this was not seen in other nodal subgroups. Dose escalation of cyclophosphamide beyond 600 mg/m² (as part of combination adjuvant therapy is unlikely to be of substantial benefit and does not appear to be worth the added toxicity). While other studies have used higher than standard doses of cyclophosphamide, at present there is no established role for escalating doses above the 600 mg/m² cycle range in clinical practice.

The ultimate test of dose intensity has been the use of very high doses of chemotherapy, usually alkylating agents, in combination with autologous bone marrow or peripheral stem cell support. An initial report from Peters et al. suggested that this approach, when used in women with ten or more positive nodes, improved disease-free survival in comparison with historical controls. A series of randomized trials have been conducted over the past decade comparing high-dose chemotherapy with less intensive treatment programs. Many of these trials have been reported, while others are still accruing or maturing.

To date, there is little evidence that the use of high-dose chemotherapy with autologous bone marrow or peripheral stem cell support improves disease outcomes in the adjuvant setting. In the largest of the adjuvant trials, Peters et al. randomized over 800 women with ten or more positive lymph nodes to four cycles of CAF chemotherapy followed by an intermediate-dose consolidation versus the same induction therapy followed by high-dose cisplatin, carbustine, and cyclophosphamide with stem cell support. Although the median follow-up of 37 months, there was no significant difference in either event-free or overall survival (<0.0001 and P < .004 for the two comparisons). Of note, the overall survival in the intermediate-dose group was 70%, far higher than many would have anticipated from the historic controls. While there were fewer relapses in the high-dose arm, this difference was offset by an increase in the number of toxic deaths on the high-dose arm. Additional follow-up is still needed, but other randomized trials have failed to demonstrate a significant benefit for treatment with high-dose chemotherapy administered with bone marrow or stem cell support. It is premature to draw definite conclusions, but at this time, high-dose chemotherapy with peripheral stem cell support cannot be recommended as adjuvant therapy outside of controlled clinical trials.

### Table 37.2-26

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Low-dose CAF</th>
<th>Moderate-dose CAF</th>
<th>High-dose CAF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>6%</td>
<td>6%</td>
<td>7%</td>
</tr>
<tr>
<td>Overall survival</td>
<td>95%</td>
<td>93%</td>
<td>91%</td>
</tr>
<tr>
<td>Relapse</td>
<td>31%</td>
<td>19%</td>
<td>26%</td>
</tr>
<tr>
<td>Toxic deaths</td>
<td>6%</td>
<td>5%</td>
<td>9%</td>
</tr>
</tbody>
</table>

**TABLE 37.2-26. Results of Adjuvant Trial Comparing High-Dose Chemotherapy with Bone Marrow Support versus Intermediate-Dose Chemotherapy**

INCORPORATION OF THE TAXANES INTO ADJUVANT TREATMENT

Because of the demonstrated activity of the taxanes in the treatment of metastatic breast cancer, both paclitaxel and docetaxel have been incorporated into adjuvant chemotherapy trials. While the results of trials with docetaxel are not yet available, four cycles of paclitaxel have been shown to improve disease-free and overall survival in node-positive patients. Henderson et al. randomized women to AC × 4 followed by paclitaxel (175 mg/m² every 3 weeks × 4) or no additional treatment. The addition of paclitaxel resulted in a 22% proportional reduction in the risk of recurrence and a 26% proportion reduction in mortality. These data were recently updated at an FDA hearing; at 36 months of follow-up, 73% of patients randomized to AC were alive and disease-free compared with 69% in the group who received paclitaxel. The absolute improvement in survival was 3% (84% vs. 87%). The benefit of paclitaxel was similar in premenopausal and postmenopausal women, and women were randomized to receive 600 or 1200 mg/m² of cyclophosphamide and 75 mg/m² of docetaxel. Although the median follow-up from the trial is relatively brief, the results do not support the use of more than 60 mg/m² per cycle of Adriamycin. In two NSABP trials (B-22 and B-25), the dose of Adriamycin was kept constant at 60 mg/m², and women were randomized to receive 600 or 1200 mg/m² of cyclophosphamide. Despite the increased dose, there was no improvement in disease-free survival or overall survival. In B-25, the cyclophosphamide dose was escalated from 1200 to as high as 2400 mg/m² for four cycles. Toxicity on the higher dose arms appeared to be greater, including an increased number of cases of acute leukemia and myelodysplasia. Although a subset analysis of women with four to nine nodes suggested a slight improvement for the high-dose arm in terms of disease-free survival and overall survival, this was not seen in other nodal subgroups. Dose escalation of cyclophosphamide beyond 600 mg/m² (as part of combination adjuvant therapy is unlikely to be of substantial benefit and does not appear to be worth the added toxicity). While other studies have used higher than standard doses of cyclophosphamide, at present there is no established role for escalating doses above the 600 mg/m² cycle range in clinical practice.

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SELECTION OF ADJUVANT REGIMEN AND DECISION MAKING ABOUT ADJUVANT TREATMENT

There is no single adjuvant regimen that has emerged as the treatment of choice for all women with breast cancer. Although anthracycline-containing regimens have gained tremendous popularity in clinical practice and are, in some cases, superior to CMF, there remains a role for CMF-type regimens in many women with breast cancer. Table 37.2-27 lists the adjuvant regimens that are acceptable in a nonprotocol setting.

TABLE 37.2-27. Acceptable Adjuvant Regimens Outside of a Clinical Trial

It is impossible to identify a group of women with invasive breast cancer in which there is absolutely no benefit to be gained from adjuvant chemotherapy. In some patient subgroups, the benefits are of extremely small magnitude and should be carefully considered in light of the risks associated with treatment. Women with tumors less than or equal to 0.5 cm (T1a) with negative lymph nodes should not be treated with chemotherapy because of their favorable natural history. Because of the limited toxicities associated with tamoxifen, the reduction in recurrence risk as a result of tamoxifen treatment, and the possibility that chemotherapy may be somewhat less effective in patients with ER-positive tumors, the decision to add chemotherapy to tamoxifen in a woman who is at relatively low risk of recurrence can be particularly difficult. The acute side effects of chemotherapy (e.g., myelosuppression, emesis, mucositis, infection, fatigue) can have a substantial effect on short-term quality of life. In addition, the persistent or late effects of treatment, such as premature menopause, weight gain, and a slightly increased risk of leukemia, must also be considered.

Patient preferences play an important role in decision making about adjuvant therapy. Surveys have demonstrated that some women are willing to accept the side effects of chemotherapy for small improvements in their risk of recurrence or death from breast cancer. In one survey, the median acceptable life extension in exchange for a course of chemo-therapy was 3 to 6 months, and over one-half of those surveyed indicated that they would take chemotherapy for a survival benefit of 1% or less. It is unclear to what extent such surveys are representative of the general population, but there are clearly many women who accept the short-term toxicity and inconvenience of chemotherapy in exchange for a small improvement in outcome. In most preference studies, there is considerable variability across patients. Ultimately, it is hoped that adjuvant therapy will be better tailored to the tumor, so that women do not need to consider such tradeoffs (i.e., a toxic treatment for a small benefit). Until we succeed in this endeavor, it is incumbent on oncologists to describe the potential advantages and disadvantages of adjuvant treatment to their patients.

PREOPERATIVE CHEMOTHERAPY

For the past two decades, preoperative chemotherapy has been administered to patients with locally advanced breast cancer. More recently, a number of randomized trials have been performed in which preoperative therapy has been administered to women with operable disease. In general, preoperative therapy has been successful in downstaging tumors, both decreasing the size of the tumor and decreasing the number of axillary lymph nodes involved with tumor. It is extremely rare for tumors to progress during preoperative therapy, and the proportion of women who can undergo CS following preoperative treatment is increased. The response to preoperative therapy is a predictor of disease-free and overall survival. Ongoing studies may be helpful in determining whether the response to preoperative therapy can be used to individualize postsurgical treatment. Until additional data are available, the primary advantage of preoperative therapy is to increase the chance of breast-conserving CS in women who are otherwise borderline candidates for this procedure.

THERAPY OF LOCALLY ADVANCED AND INFLAMMATORY BREAST CANCER

The term locally advanced breast cancer encompasses a heterogeneous group of patients including those with neglected, slow-growing tumors as well as those with biologically aggressive disease. Locally advanced breast cancer is a relatively uncommon presentation in the economically developed world, accounting for only 5% of cases in major centers, and no more than 20% in other locations. In most other parts of the world, however, locally advanced breast cancer is more common, accounting for at least one-half of all cases. This difference is thought to be due to variations in public awareness and attitudes, as well as the availability of medical resources, including screening mammography. Biologic differences between populations may also play a role (as discussed later, in Inflammatory Breast Cancer). The relative infrequency of locally advanced breast cancer has limited the speed of clinical progress in this area.

The definition of locally advanced breast cancer is variable. All investigators include patients with inoperable stage III, stage IV by virtue of positive supraclavicular lymph nodes, or both. Management recommendations and prognosis might vary according to which of these definitions is used. For example, it might not be necessary to recommend preoperative chemotherapy for a patient with IIIA breast cancer that could be removed surgically. A reader of this literature needs to be certain which of the various definitions is used.

ROLE OF SYSTEMIC THERAPY

Historically, the results in treating patients with locally inoperable breast cancer using surgery and RT were uniformly poor. More aggressive local treatment did little to improve survival rates, but did result in increased complications. The results, however, improved greatly with the development of effective chemotherapy. This is related in part to the ability of chemotherapy to convert most cases of inoperable primary breast cancer to operable disease. In addition, these patients likely experience the same benefit in decreasing rates of recurrence and death as do patients with stage I and II disease treated with postoperative chemotherapy. Since systemic therapy results in a proportional reduction in the risk of systemic recurrence, the absolute benefit in patients with locally advanced disease may be considerable. In the Overview analysis, the benefit of systemic therapy was equally apparent in adjuvant trials that included stage III patients.

The response rates to preoperative chemotherapy are high, possibly related to the presence of an intact blood supply. The use of preoperative treatment allows (1) the opportunity to observe directly the response to treatment (an in vivo chemosensitivity assay), (2) to determine the optimal duration and sequencing of therapy for a small benefit). Until we succeed in this endeavor, it is incumbent on oncologists to describe the potential advantages and disadvantages of adjuvant treatment to their patients.

A wide variety of chemotherapy regimens have been used as preoperative treatment, with most incorporating doxorubicin. These regimens generally produce response rates in at least two-thirds of patients with a complete pathologic remission rate of approximately 10% to 20%. There is no evidence that one doxorubicin-containing regimen is better than another; neoadjuvant treatment is generally given to maximal response. The optimal duration and sequencing of
Contrary to what many patients expect,
more intensive screening (e.g., mammogram) or intervention (e.g., breast biopsy).

The high response rates seen with induction chemotherapy have stimulated interest in the use of BCT for selected patients with locally advanced breast cancer. Good results have been reported in some series, but the experience using this approach is still limited, and data from randomized, prospective trials are not available. Preoperative conservation is considered, and all of the usual considerations apply, including a mammographic evaluation that does not demonstrate diffuse disease. The conservative resection should obtain clear margins with an acceptable cosmetic result. Criteria for determining the extent of surgery in a conservative resection following induction chemotherapy have not been established, and the long-term local control rates remain uncertain.

In general, prognostic factors predictive of good outcome in patients with locally advanced breast cancer are the same as in lower stages of primary breast cancer: namely, smaller tumor size, slower growth rate, better differentiation, and fewer involved axillary lymph nodes. In addition to these classical factors, the response of locally advanced cancers to preoperative chemotherapy is an additional important prognostic factor. As noted, evidence from many series indicates that patients with rapid responding cancers and those who achieve a complete remission have a better outcome than patients who do not have a good response to chemotherapy.

Patients with inflammatory breast cancer appear to have a different clinical course than other patients with locally advanced cancer. An important distinction should be drawn between locally advanced disease by virtue of rapid growth and those that are locally advanced by virtue of neglect of a slowly growing cancer. Patients with these neglected cancers have a more indolent course than similarly staged patients with rapidly growing cancer. This distinction is better discerned by a careful history than by any laboratory study including flow cytometry.

INFLAMMATORY BREAST CANCER

Although frequently grouped with other locally advanced cases, inflammatory breast cancer is a distinct clinical and pathologic entity. It is defined by the presence of diffuse breast edema or ecchymosis, usually without an underlying palpable mass. The clinical presentation is due to tumor embolization of dermal lymphatics. While dermal lymphatic invasion is required for the diagnosis as specified by the current AJCC staging system, patients with the clinical presentation, but without evidence of dermal lymphatic invasion, also have a poor prognosis with local treatment only. It is common for patients with inflammatory breast cancer to give a history of breast cancer before their inflammatory breast onset. Inflammatory breast cancer is uncommon in the United States and in most of Europe, but it is more frequently in North Africa. European women living in Morocco have presented with this particularly virulent form of primary breast cancer, suggesting the existence of a specific etiologic agent. The identity of such a putative agent remains elusive. Inflammatory breast cancer becomes more common in the United States. Data from SEER show that between 1975 and 1977 and 1990 and 1992, the incidence doubled, increasing among whites from 0.3 to 0.7 cases per 100,000 person-years and among African Americans from 0.6 to 1.1 cases.

Nearly all patients with inflammatory breast cancer are dead within 5 years of the absence of systemic therapy. In addition, the historic results of surgical treatment are available. Surgery is often in obtaining clear margins and a high local recurrence rate. Preoperative chemotherapy in patients with inflammatory breast cancer produces a response rate in the vicinity of 80%, and most patients can go on to surgical resection with clear margins. As in other patients with locally advanced breast cancer, the most typical approach is to use an anthracycline-containing chemotherapy as induction, followed by surgery, then additional chemotherapy, and then consolidation RT. With the combined modality approach, over 70% of patients achieve local tumor control. This is particularly true in patients whose tumors respond well to initial chemotherapy. In patients with inflammatory breast cancer who successfully complete a combined modality treatment, prognosis is dramatically improved when compared with the prechemotherapy era. Currently, approximately one-half of patients treated with combined modality treatment survive for 5 years and approximately 35% of the patients have been reported to be disease free at 10 years. This improvement may reflect the biology of rapidly growing disease and its preferential effect of chemotherapy.

Improving the results in locally advanced breast cancer can be achieved by a number of means. It may be possible to decrease the incidence of locally advanced breast cancer by diminishing any socioeconomic factors that impede early diagnosis. Further improvements in the results of treating patients with locally advanced breast cancer require even better systemic therapy. In this regard, there is great interest in including patients with locally advanced disease in clinical trials of novel systemic therapies. Locally advanced disease affords a special research opportunity (i.e., the ability to obtain primary tumor tissue before and after chemotherapy to correlate with response and other clinical parameters).

FOLLOW-UP AFTER PRIMARY TREATMENT

There are over 2 million breast cancer survivors in the United States. As screening programs identify more patients with earlier stage disease, and as the number of women diagnosed with DCIS continues to rise, there will be even more women living with a personal history of breast cancer. Women with a history of invasive breast cancer are at risk of developing metastatic disease. Most recurrences are detected within 5 to 10 years after diagnosis, but later recurrences can occur. Women with both invasive and in situ breast cancer face a 0.5% to 1.0% annual risk of developing a contralateral cancer, and this risk is even higher in women with a first breast cancer at a younger age and those with an inherited predisposition. In addition, women who have been treated for breast cancer are at risk for complications related to their treatment and face a variety of health-related decisions (e.g., pregnancy, hormone replacement therapy, prevention of osteoporosis) that may need to be carefully considered in light of their breast cancer history.

Although extensive testing to identify early presentations of metastatic disease is probably not warranted, there is a strong rationale for having a physician knowledgeable about breast cancer care follow the patient after completion of treatment. While many follow-up visits after breast cancer treatment may seem routine to the physician, the visit provides both the clinician and the patient with the opportunity to address a wide range of issues. Table 37.2 outlines the specific goals of follow-up care.

TABLE 37.2-28. Goals of Follow-Up Care after Treatment for Early-Stage Breast Cancer

Contrary to what many patients expect, early diagnosis of metastatic disease by performing frequent, extensive, or both kinds of testing has not been shown to
improve survival. Two randomized trials have compared simple follow-up regimens consisting of periodic physical examination and routine mammography with more intensive evaluation including radiographic studies (chest radiography, bone scan, liver ultrasound) and laboratory studies (complete blood counts and liver function tests) in women after treatment of early-stage breast cancer. More intensive follow-up resulted in a slightly earlier time at which systemic recurrences were detected; however, there was no difference in overall survival. Some physicians have argued that more intensive follow-up schedules might improve quality of life by providing patients with added reassurance, allowing treatment of metastatic disease before a patient develops symptoms, or both. These arguments are not supported by quality-of-life assessments performed as part of one of the large randomized follow-up studies. With the development of ever more accurate methods of detecting low-volume metastatic disease (i.e., spiral CT or positron emission tomographic scanning), there is the potential to detect metastatic disease even earlier than in the randomized trials discussed previously. The routine monitoring of tumor markers may also allow for the detection of metastatic disease at an earlier point in a patient's clinical course. There is little reason to believe that early detection of metastatic disease as a result of monitoring tumor markers would result in an improvement in either survival or quality of life; the routine use of tumor markers in patients who have completed breast cancer therapy is generally not recommended and can be particularly problematic. An elevated marker may be the first sign of an impending recurrence, but a thorough search for metastatic disease may be negative even in the presence of an elevated marker. There is no treatment that has proven to be of benefit to patients with elevated tumor markers who have no evidence of disease, and such situations are almost always anxiety provoking for patients. Early intervention in asymptomatic patients with metastatic breast cancer has not been demonstrated to improve clinical outcome. For this reason, the identification of metastatic disease in an asymptomatic patient could theoretically lead to the initiation of toxic therapy that could have a negative effect on a patient's quality of life and, at the same time, not improve her overall survival.

The American Society of Clinical Oncology has published evidence-based recommendations for follow-up care after a diagnosis of breast cancer. A physical examination and history (emphasizing symptoms that could be due to metastatic disease) are recommended every 3 to 6 months for the first 3 years after diagnosis and every 6 to 12 months for the subsequent 2 years. Even for patients who are 5 or more years postdiagnosis, annual follow-up is recommended. Women should be advised to do breast self-examinations on a monthly basis and to have annual mammography and gynecologic examinations. Routine laboratory testing (including tumor markers) and radiologic studies are not recommended. Patients with signs or symptoms of recurrent disease should be rigorously evaluated. These recommendations have been issued in the context of the presently available therapies for patients with recurrent breast cancer. If treatments become available in the years ahead that can prolong the lives of women diagnosed with asymptomatic, low-volume, metastatic disease, recommendations for follow-up care will need to be altered.

MANAGEMENT OF PATIENTS WITH METASTATIC BREAST CANCER

The management of patients with metastatic breast cancer is a topic familiar to most medical oncologists. Although the majority of women diagnosed with breast cancer today will never experience a systemic recurrence, approximately 41,000 women in the United States will die of metastatic breast cancer in 2000. The median survival for women with metastatic breast cancer is in the range of 2 to 3 years, but there is great variability. Indeed, there are even a small number of patients with metastatic disease who will receive a course of chemotherapy and remain relapse-free for a decade or longer (Fig. 37.2-6). Factors that affect the prognosis of patients with metastatic breast cancer are (1) the patient's physical status, (2) the number and rate of organ system involvement, (3) the presence of marked laboratory abnormalities, (4) the type and extent of initial systemic therapy, (5) the presence of local disease, and (6) the presence of symptoms attributable to the disease. The two primary goals in the treatment of patients with metastatic breast cancer are (1) improvement or maintenance of quality of life and (2) prolongation of survival. The measurement of response rates in either clinical trials or clinical practice is useful only to the extent that response is a surrogate for survival, quality of life, or both. Maintenance of quality of life is achieved by controlling disease-related symptoms, minimizing toxicity from treatment, and limiting the intrusion of the patient's disease and treatment on her life. Historically, it has been difficult to demonstrate that treatment prolongs survival, but there has been an assumption on the part of many medical oncologists that treatment of metastatic breast cancer extends survival. More recently, several trials have demonstrated that more effective therapy has been able to prolong survival in women with metastatic breast cancer. These trials have included studies of hormonal agents, chemotherapeutic agents, and combinations of chemotherapy and Herceptin. While the median prolongation in survival has been a matter of months, these trials have demonstrated an important principle (i.e., more effective treatment of metastatic breast cancer can extend the lives of our patients). In selecting a treatment program, close attention must be paid to the patient's symptoms, the pace of her disease, and her preferences and ability to tolerate the therapy.
EVALUATION OF PATIENTS WITH SUSPECTED METASTATIC BREAST CANCER

All patients who are thought to have metastatic breast cancer should undergo a careful physical examination and a thorough history. Historically, it was considered mandatory to biopsy a first site of metastatic disease to confirm the diagnosis. In the case of patients with chest wall or lymph node involvement, pleural effusions, or other easily assessable disease, obtaining biopsy or cytologic proof of metastatic disease can be accomplished with minimal difficulty. If a more complicated procedure is needed, which could place the patient at greater discomfort or risk, physician judgment must be exercised. In the patient with a history of breast cancer who has unequivocal radiologic evidence of advanced breast cancer, a biopsy can often be deferred. If there is any question as to whether the patient has cancer or any suspicion that the patient may have a second primary (i.e., widespread pure lytic bone lesions and anemia suggestive of multiple myeloma) that would require alternative treatment, a biopsy is essential. In the case of a woman with a history of breast cancer who presents with a solitary pulmonary nodule, a resection of the lesion is usually required since a high percentage of these lesions may be primary lung cancers. A biopsy to establish metastatic disease provides an opportunity to reassess the hormone receptor status of the tumor. While few tumors evolve from ER negative to ER positive, more frequently there can be loss of hormone receptors over time. With the availability of Herceptin, the result of a HER-2/neu assay is often important in making treatment decisions, although this can often be assessed from specimens of the primary tumor.

Recommendations for the laboratory and radiographic evaluation of patients with newly diagnosed metastatic breast cancer have been established by the National Cancer Center Network. Routine blood work consisting of complete blood count and liver function tests are recommended. In addition, chest radiographs and bone scans are recommended. The decision to proceed with other radiographic studies can be based on symptoms, although many physicians obtain a baseline assessment of liver involvement with a CT scan or MRI, particularly if the presence of liver metastases would change treatment. Since intracranial involvement is extremely rare in newly diagnosed patients in the absence of CNS symptoms, a CT or MRI of the brain is not usually recommended for a woman with a new diagnosis in the absence of symptoms. The use of tumor markers in the management of patients with breast cancer remains controversial.

In certain situations, patients treated with local therapy for an isolated recurrence may also be considered for adjuvant systemic therapy. A phase II trial of fluorouracil, Adriamycin, and cyclophosphamide chemotherapy for patients with stage IV but no evidence of disease suggested an improvement in relapse-free survival in comparison with historic controls. It should be noted, however, that the majority of these patients had not received prior adjuvant chemotherapy. A retrospective review of 96 patients with isolated chest wall recurrence demonstrated an improvement in disease-free survival and overall survival for those patients who received some form of systemic therapy although the majority received hormonal therapy as opposed to chemotherapy. Other investigators have reported less promising results with the use of chemotherapy in this setting. In such situations, the toxicity of a course of chemotherapy must be balanced against the largely theoretical benefits. The use of chemotherapy in the patient with stage IV but no evidence of disease has its greatest appeal in the patient with a hormone receptor–negative tumor who has never received cytotoxic chemotherapy, but the benefits in this setting remain uncertain. In contrast, it is reasonable to have a lower threshold to prescribe a hormonal therapy in the patient with positive hormone receptors, with the hope that treatment will delay the time to progression. A randomized trial in 167 ER-positive patients with locoregional recurrence demonstrated an improvement in median disease-free survival (26 vs. 82 months) with the addition of tamoxifen to locoregional therapy in the patient with positive hormone receptors, with the hope that treatment will delay the time to progression. A randomized trial in 167 ER-positive patients with locoregional recurrence demonstrated an improvement in median disease-free survival (26 vs. 82 months) with the addition of tamoxifen to locoregional therapy.

LOCAL VERSUS SYSTEMIC THERAPY

Patients with a chest wall recurrence, a single site of bone involvement, pleural disease, or other localized sites can often be managed with local therapy alone. In such situations, systemic therapy may be delayed until there is evidence of disease progression. There is a small group of patients with isolated metastatic disease who remain disease-free for an extended period of time after local therapy to the involved site. This situation is best exemplified by the patient who presents with an isolated chest wall recurrence. Although patients with isolated chest wall recurrence should receive definitive local treatment, local therapy is not mandatory in minimally symptomatic patients who present with isolated sites of distant disease (i.e., a single bone lesion). As previously mentioned, isolated pulmonary nodules generally should be resected because these often represent a second primary. There are reports of resection of hepatic metastases, but this approach cannot be recommended as standard practice.

In patients with widespread disease, local therapy is often used to provide palliation for specific symptoms. Radiation to bone lesions, CNS disease, or, less commonly, soft tissue disease, can be effective in controlling disease. At times, local therapy is administered in conjunction with systemic therapy, although one must be careful about the potential increase in toxicity that may be seen with the concurrent administration of chemotherapy and radiation. Decisions about the use of local therapy in the patient with advanced disease can be complex. Such decisions should be guided by the patient’s symptoms or impending symptoms, the extent to which those symptoms can be relieved by supportive care, and the chance that a change in systemic therapy will provide effective palliation for the local disease.

Administration and Choice of Systemic Therapy

The vast majority of patients with metastatic breast cancer receive some form of systemic therapy. The initial question is whether to consider hormonal therapy or chemotherapy. Because of the limited toxicity with most hormonal therapies, patients who have hormone receptor–positive tumors and a limited to moderate disease burden should generally receive hormone therapy. Patients with both estrogen and progesterone receptor positivity are more likely to respond to hormonal therapy than those with ER-positive/PR-negative or ER-negative/PR-positive tumors. A trial of hormonal therapy may be justified even in the presence of negative hormone receptors since a small number of patients with ER-negative/PR-negative tumors respond to a hormonal intervention. The key issues that the clinician must consider in proceeding with initial hormonal therapy are whether or not the patient is likely to respond to the treatment and whether the patient would be adversely affected if she did not respond to treatment and was started on chemotherapy 2 to 3 months later. Visceral disease, particularly low-volume and asymptomatic disease, is not a contraindication to the use of hormonal therapy; however, the patient with extensive visceral disease is probably better served by chemotherapy. If a patient with a hormone receptor–positive tumor is initially treated with chemotherapy, the clinician should consider returning to hormonal therapy at some point in the future.

Table 37.2-30 lists the commercially available hormonal therapies for premenopausal and postmenopausal women. In general, there is little evidence that one hormonal therapy is substantially more effective than another. As a result, the ease of administration and tolerability usually dictates the choice of treatment.

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<tr>
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<td>Tamoxifen</td>
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TABLE 37.2-30. Hormonal Therapy for Women with Metastatic Breast Cancer

In premenopausal women who have never received hormonal therapy, tamoxifen is generally the treatment of choice. A small randomized trial has suggested that tamoxifen and ovarian ablation are equivalent in efficacy. In patients who respond to tamoxifen, the duration of response is often in excess of a year and may
extend for several years in a minority of patients. Medical or surgical ovarian ablation is usually the second-line hormonal therapy of choice in women who are premenopausal, particularly those who have responded to tamoxifen. European trials have evaluated the use of a combination of ovarian ablation and tamoxifen in patients with metastatic breast cancer. In some studies, there has been a suggestion of an improved overall response rate, but it remains unclear if this approach is superior to sequential therapy. Aromatase inhibitors are not active in premenopausal women because of the high levels of circulating estrogen from the ovaries. Aromatase inhibitors can be used in conjunction with ovarian ablation, although there is little published information about this combination. Megestrol acetate remains the usual third-line hormonal therapy. The subgroup of premenopausal women with hormone receptor–positive tumors can, at times, have an extended survival in the metastatic setting. Faulkson et al. have reported a median survival of approximately 5 years in a group of hormone receptor–positive, premenopausal women who were initially treated with chemotherapy plus oophorectomy. If anything, many clinicians may tend to undervalue the benefits of hormonal therapy in premenopausal women with positive hormone receptor status.

In postmenopausal women, tamoxifen remains the usual first-line therapy. In the metastatic setting, toremifene is an acceptable alternative based on the equivalence demonstrated between the two agents in randomized trials. Since many women with metastatic breast cancer have either developed disease progression on tamoxifen or have had a recent course of adjuvant tamoxifen, there are fewer and fewer patients receiving antiestrogens when they present with metastatic disease. The aromatase inhibitors (i.e., anastrozole, letrozole, and exemestane) have all been demonstrated in randomized clinical trials to be equivalent or superior to megestrol acetate. Exemestane, a steroidal aromatase inhibitor that irreversibly inhibits aromatase activity, has been shown to have a survival advantage in comparison with Megace. All three agents are generally well tolerated and are not associated with the bothersome weight gain that is seen with Megace. It is unknown, at this time, if one aromatase inhibitor is superior to another. A randomized trial demonstrated the equivalence of anastrozole (Arimidex) and tamoxifen in patients who had no prior hormonal therapy, making it reasonable to consider these agents as first-line therapy even in patients who have never received tamoxifen. Objective response rates to the aromatase inhibitors have been in the 10% to 20% range, but a substantial number of patients in these trials have had disease stabilization for 6 months or longer. Megestrol acetate remains a third-line therapy, and patients rarely are treated with either androgens or high-dose estrogen as fourth- and fifth-line therapy.

In both premenopausal and postmenopausal women, occasional responses can be seen with withdrawal of either high-dose estrogen (now rarely used), tamoxifen, or progestins. Withdrawal responses are relatively rare and are more commonly seen when a patient has had a prior response to the hormonal manipulation. The possibility of withdrawing tamoxifen (without additional therapy) can be considered in the patient with low-volume, indolent, ER-positive disease who has either been on adjuvant tamoxifen for several years or has had a documented response in the metastatic setting.

Assessing the response of patients to hormonal therapy can be complex. Many patients treated with hormonal therapy have bone-only disease, making response assessment complex. In addition, it can take up to several months to see a response in some patients, whereas others have more rapid disease regressions. A flare phenomenon with worsening bone pain, increasing soft tissue lesions, hypercalcemia, or all three is seen in a small percentage of patients who are started on hormonal therapy. Flares have been seen with high-dose estrogen, tamoxifen, progestins, and androgens and occur within the first days to weeks of treatment. A portion of patients who have a flare go on to respond to endocrine therapy. With either hormonal therapy or chemotherapy, there can be a rise in tumor marker levels, alkaline phosphatase, or both early in the course of therapy, with a subsequent decline. Clinicians should not continue hormonal therapy in patients with rapid or unequivocal evidence of disease progression. In the minimally symptomatic patient, it is often prudent to continue therapy for several months if there is an uncertainty concerning the response to treatment. In these situations, it is important to explain to patients that a change in therapy in the near future may be necessary, but that there is little to be lost by continuing the hormonal approach with close monitoring of disease status.

A question that often arises is how many hormonal regimens to administer before moving on to chemotherapy. In a patient who has had a prior response to (or extended disease stabilization with) hormonal therapy, there is a reasonable chance of observing a response with another hormonal approach. There are patients who respond to a second hormonal therapy, even if their disease progressed through a first agent. In making a clinical decision as to whether to consider a second third, or even fourth hormonal approach, the clinician needs to weigh the therapeutic index of another hormonal agent versus that of chemotherapy. The chance of observing a response with each successive hormonal regimen decreases. However, if the patient continues to have relatively indolent disease and will not be harmed by delaying therapy that may have a higher chance of producing an objective response (i.e., chemotherapy), it is reasonable to try another hormonal therapy, even if the likelihood of obtaining a response is small. For that matter, it is important to reconsider the potential advantages of another trial of hormonal therapy, even in a patient who has received intervening chemotherapy.

Resistance to hormonal therapies ultimately develops in virtually all patients with advanced disease. The mechanisms responsible for resistance to hormonal therapy are not fully understood, and are currently being investigated. Identifying new hormonal agents, such as pure antiestrogens, new selective ER modulators, and antiprogestins, is a priority. Ongoing studies are also addressing the potential of using hormonal therapies with other agents, such as differentiating compounds, to enhance disease control.

**CYTOTOXIC CHEMOTHERAPY FOR METASTATIC BREAST CANCER**

Although hormonal therapy is usually the treatment of choice for patients with hormone receptor–positive cancer, almost all patients eventually develop hormone-refractory disease, and many patients with metastatic breast cancer have negative hormone and receptor status. For these patients, chemotherapy is the treatment of choice, with the goal of ongoing symptom control and modest prolongation of survival. The use of chemotherapy for metastatic breast cancer has evolved since 1990. Multiple new agents are now available, many of which have a favorable toxicity profile. Clinical trials have addressed a variety of fundamental issues related to the administration of chemotherapy to patients with metastatic breast cancer, such as the value of single agents versus combination therapy and the appropriate duration of therapy.

**Table 37.2-31** lists the agents commercially available for patients with advanced breast cancer. While some of these have official Food and Drug Administration approval for the treatment of breast cancer, others have simply become part of the standard armamentarium as a result of general clinical acceptance. There is no rigid order in which agents or regimens should be administered. CMF and CAF were long considered the standard of care for initial chemotherapy treatment of advanced disease, but the development of the taxanes and a variety of other agents has given physicians and patients far greater flexibility in making treatment decisions. The taxanes and doxorubicin are usually considered the most active agents for the treatment of advanced disease, but the activity of any agent is most dependent on the characteristics of the patient population, particularly the extent of prior therapy. There are few compelling data that one regimen is markedly superior to another or promotes improved long-term survival. The precise order in which treatments are administered is unlikely to affect overall survival. The CALGB has demonstrated that initial treatment with an investigational agent (in patients who did not have visceral crisis) does not compromise either overall survival or response to a subsequent doxorubicin-based regimen. The availability of new agents, such as the taxanes, has improved overall survival, but the order in which treatments are delivered (i.e., taxane as first-line vs. second-line therapy) is unlikely to have a major effect on long-term outcome.

In patients who have received no prior chemotherapy in the metastatic setting, objective response rates of 25% to 55% have been seen in multicenter randomized trials. Higher response rates are seen in single-institution, phase II trials. It is likely that the percentage of patients who derive some palliative
benefit from chemotherapy is higher than the reported response rates in multicenter trials. The median duration of response with most first-line chemotherapy regimens is in the range of 6 to 12 months, with a shorter duration of response seen in patients who are treated in the second- and third-line setting.

**COMBINATION VERSUS SINGLE-AGENT CHEMOTHERAPY**

For several decades, the use of combination chemotherapy was considered the standard of care. More recently, several trials have compared combination therapy with the use of single agents in the treatment of advanced breast cancer. In a large Eastern Cooperative Oncology Group trial, Sledge and colleagues randomized patients to one of three arms: single-agent Adriamycin, single-agent paclitaxel, or a combination of the two. Patients initially randomized to the single-agent arms were crossed over to the alternate agent at the time of progression. Although there was a statistically significant improvement in response rate and time to progression on the combination arm, there was no difference in either survival or quality of life. If one considers the secondary responses with the crossover therapy, there is even less reason to view combination therapy as a superior approach. A Finnish trial that randomized patients to combination or single-agent therapy in both the first- and second-line setting also failed to show any appreciable difference in disease outcomes. A major advantage of single-agent therapy is the ability whether of a given agent is of benefit to the patient. When a patient responds to combination therapy, it is never clear whether she is benefiting from a single drug in the regimen or from all of the agents. While the administration of combination therapy remains a common practice, it is most appropriate in highly symptomatic patients in whom the higher response rate seen with combination chemotherapy may be worth the added toxicity. Numerous trials have also compared the use of chemotherapy alone versus the combination of chemotherapy and hormonal agents. In general, these trials have demonstrated either higher response rates, longer time to progression, or both with the combination treatment, as well as a benefit in terms of survival.

**DURATION OF CHEMOTHERAPY**

Several trials have examined how long chemotherapy should be continued in patients with stable or responding disease. Muns and colleagues treated 250 patients with initialCAF chemotherapy and randomized almost 150 women with stable or responsive disease to maintenance chemotherapy or observation. Although there was a 6-month prolongation in time to disease progression for women on maintenance therapy, there was no difference in overall survival. Findings from other investigators have been quite similar. Of note, a very brief course of treatment may not only shorten time to progression, but it may also compromise quality of life. Coates and colleagues randomized Australian patients to continuous chemotherapy versus intermittent therapy (three cycles only) with reinitiation of treatment at the time of disease progression. The two groups had an equivalent overall survival, but the intermittent group had a lower response rate, shorter time to progression, and inferior quality of life. Since the maximal response to chemotherapy occurs after approximately 4 to 6 months of treatment, one interpretation of this trial is that the failure to treat patients until they achieved a maximal response to therapy perhaps compromised quality of life.

The question of how long to continue chemotherapy is frequently raised in discussions with patients. Assuming a patient has had to 6 months of chemotherapy and has stable or responsive disease, there is no evidence that continuing treatment will have an effect on her overall survival. When a patient experiences progression of disease, treatment (at times with the same regimen) can always be resumed. In the patient who was initially symptomatic, has had excellent palliation of her symptoms, and has minimal toxicity with treatment, chemotherapy can be continued with the goal of delaying disease progression.

**DOSE AND SCHEDULE OF CHEMOTHERAPY**

A large number of trials have addressed questions that relate to either the dose or schedule of chemotherapy. In general, higher response rates have been seen with regimens that are in the standard-dose range than those in which the doses are reduced substantially. Low-dose CMF has been found to be inferior to standard-dose therapy (600 mg/m²; 40 mg/m²; 600 mg/m²). Lower responses rates or more rapid disease progression have been demonstrated with other agents when doses have been reduced below the usually accepted range. The clinician must balance the potential benefits and toxicities of different dose levels. To date, there is little convincing evidence to show that escalating doses of chemotherapy to levels that require growth factor support has a substantial effect on disease outcome. In addition, some of these regimens result in a marked increase in toxicity.

Questions exist about the optimal schedule for many cytotoxic agents. By changing the schedule of many agents, there is the suggestion that both efficacy and toxicity can be altered. The NSABP compared 3-hour versus 24-hour paclitaxel administration in patients with locally advanced or metastatic disease. Although a significantly higher response rate was observed with the longer infusion (54% vs. 44%), there was no difference in survival, and the longer infusion was much more inconvenient. Initial reports of weekly taxanes have been encouraging, and these dose-dense schedules are being compared with the standard every 3 week regimens in randomized trials of interest. A European trial compared classical CMF (day 1 and 8 with oral cyclophosphamide) with an every 3 week regimen. The classical regimen, which is more dose dense, resulted in a higher response rate and an improvement in overall survival. With the availability of oral fluorouracil agents and liposomally encapsulated agents, such as doxorubicin (Doxil), it is possible to increase the duration of exposure to cytotoxic agents without committing patients to ambulatory infusion pumps or frequent clinic visits.

**HIGH-DOSE CHEMOTHERAPY WITH HEMATOPOIETIC SUPPORT**

Beginning in the mid-1980s, trials were initiated evaluating the role of high-dose chemotherapy with autologous bone marrow support. These studies were based on preclinical models and the hope that dose escalation would result in prolongation of survival. Multiple phase I and II trials in women with metastatic breast cancer suggested that high-dose chemotherapy resulted in high response rates, generally in excess of 70%. In addition, a small proportion of patients (approximately 10% to 15%) remained free of disease progression for several years following therapy. In general, patients with a low disease burden, long disease-free interval, and absence of visceral involvement appeared to have the most favorable outcome after high-dose therapy. Based on preliminary trials, thousands of women in the United States underwent treatment with high-dose chemotherapy throughout the late 1980s and 1990s.

More recently, the nature of responses to a randomized trial comparing high-dose chemotherapy with prolonged conventional chemotherapy have been published. Stadtmueller and colleagues enrolled 553 women with metastatic breast cancer onto a trial designed to determine if high-dose chemotherapy would improve disease outcomes. Of the original cohort, 310 women had a response to initial chemotherapy, and 199 of these women were ultimately randomized to receive either high-dose chemotherapy with stem cell support versus prolonged treatment with CMF. With a median follow-up of 37 months, there was no evidence that high-dose therapy improved either time to progression or overall survival. Subgroup analyses looking at demographic variables, response (complete vs. partial response) to induction treatment, and disease characteristics failed to identify a population of patients that had a better outcome with high-dose therapy than with CMF. In another study, Berry et al. retrospectively compared the outcomes of 560 women registered with the Autologous Bone Marrow Transplant Registry with 657 patients who participated in a series of CALGB trials using conventional dose chemotherapy. All patients included in the analysis were 60 years of age or younger and had chemotherapy-sensitive disease. In a multivariate model, there was no difference in survival between the two groups of patients. The investigators could not identify any patient subgroup who had a better outcome with high-dose therapy. Thus, despite the initial enthusiasm for high-dose chemotherapy for metastatic breast cancer, this approach appears unlikely to have a substantial effect on the natural history of the disease.

**TRASTUZUMAB (HERCEPTIN)**

The development of Herceptin has been a major advance in the treatment of HER-2/neu–positive metastatic breast cancer. As previously noted, approximately 25% to 30% of all breast cancers overexpress HER-2/neu, a 185-kD transmembrane glycoprotein receptor. These tumors have a more aggressive natural history, a higher risk of recurrence, a higher frequency of visceral disease at first recurrence, and a lower likelihood of ER positivity. Herceptin, a humanized recombinant anti–HER-2/neu antibody, has been evaluated in a series of clinical trials as both a single agent and in combination with chemotherapy.

In a multinational trial, women with HER-2/neu–overexpressing metastatic breast cancer were randomized to receive chemotherapy alone or chemotherapy plus Herceptin. Patients who had not received an anthracycline in the adjuvant setting were randomized to AC with or without Herceptin. Those patients who had received an adjuvant anthracycline-containing regimen received paclitaxel with or without Herceptin. Chemotherapy was continued in stable or responding patients for a minimum of six cycles. In the absence of disease progression, Herceptin was administered weekly at a dose of 2 mg/kg for 1 year or longer. Table summarizes the results of the trial.
The benefit of Herceptin was seen both in patients who received AC and in those who received paclitaxel. In addition, the survival benefit was noted despite the fact that approximately two-thirds of the women randomized to chemotherapy alone ultimately received Herceptin on an open-label extension protocol at the time of disease progression. While Herceptin was generally well tolerated, there was a 19% incidence of grade III or IV cardiac dysfunction on the AC plus Herceptin arm; with the combination of Herceptin and paclitaxel, the frequency of serious cardiac toxicity was only 4%. In a large single-agent trial, Cobleigh and colleagues treated 222 women with refractory metastatic breast cancer (one or two prior chemotherapy regimens). As a single agent, Herceptin was well tolerated. Five percent of the study population developed cardiac dysfunction; however, all these patients had either received prior anthracyclines or had preexisting cardiac disease. The overall response rate in this group of pretreated patients was 15%, with a median duration of response of 9.1 months. In another single-agent trial, Vogel et al. reported a response rate of 25% in 112 women with HER-2/neu-overexpressing metastatic breast cancer. Although none of these patients had received chemotherapy in the metastatic setting, over one-half had received prior doxorubicin in the adjuvant setting. Taken together, these two trials clearly demonstrate the activity of Herceptin administered as a single agent.

There is compelling evidence to consider the use of Herceptin in the initial management of women with HER-2/neu-positive, hormone-refractory metastatic breast cancer; however, there are a multitude of unanswered questions about the use of Herceptin in clinical practice. It is unknown how long Herceptin should be administered, whether it should be continued with second-line chemotherapy after disease progression, or if single-agent therapy (followed by chemotherapy) is better or worse than combination treatment. Many of these questions will be answered through future clinical trials; others will depend on gaining a fuller understanding of the complex mechanism of action of Herceptin and its probable role in sensitizing breast cancer to the effects of chemotherapy. It is unlikely that there is any role for Herceptin in patients whose tumors do not overexpress HER-2/neu. Discussions continue regarding the optimal methods to assess HER-2/neu overexpression. Additional trials are needed to test combinations of Herceptin with other cytotoxic agents. Promising preliminary reports have appeared using combinations of Herceptin plus vinorelbine, Herceptin plus docetaxel, and Herceptin plus weekly paclitaxel. Finally, the role of Herceptin in both the neoadjuvant and adjuvant setting will be the focus of a number of clinical trials in the years ahead.

QUALITY OF LIFE AND SUPPORTIVE CARE ISSUES

A growing emphasis has been placed on quality-of-life issues in women with metastatic breast cancer. This interest has been reflected by an increasing effort to measure quality of life in clinical trials. Although only a small number of randomized trials in women with metastatic breast cancer have demonstrated differences in quality of life, this research has likely led to a greater awareness of quality-of-life issues in clinical practice.

Many of the newer chemotherapy and hormonal agents have fewer side effects, or at least a more manageable side-effect profile than agents that were available a decade ago. In many ways, the emphasis on single-agent therapy can be viewed as a step forward from a quality-of-life standpoint. There is also an ongoing effort to make breast chemotherapy more convenient for patients. Virtually all therapy is administered in the outpatient setting, and there is a growing interest in the development of oral chemotherapeutic agents. Patient surveys have documented a strong preference for oral treatment, but only if the oral therapy can be administered without compromising efficacy.

With the heightened interest in quality-of-life issues, there has also been a greater emphasis on supportive care measures. The use of bisphosphonates in women with lytic bone lesions has become a standard of practice. Treatment with bisphosphonates does not improve survival, but does have an important effect on the frequency of bone-related complications such as pain, the need for palliative radiation, and hypercalcemia. There is a growing awareness of fatigue, its relationship with anemia, and the potential benefits of treatment with erythropoietin. Nausea and vomiting, while still a problem with many chemotherapy regimens, are far better controlled with the judicious use of some of the newer antiemetic agents. While the availability of these newer supportive care measures represents a major advance in the care of women with breast cancer, the clinician needs to weigh carefully the advantages and disadvantages of each of these supportive care interventions.

NEW TREATMENT APPROACHES

It is difficult to know which of the therapies currently in development will have a future role in the treatment of women with breast cancer. There is renewed interest in immune-based treatments, including vaccines, monoclonal antibodies, and approaches using dendritic cells. Ongoing trials are evaluating a range of novel therapeutic strategies, including interacting agents and angiogenesis inhibitors. As our basic understanding of breast cancer grows, it is likely that there will be a whole new generation of targeted molecular therapies, allowing clinicians to increase the quality of care and decrease the toxicity of treatment for women with breast cancer.

CHAPTER REFERENCES

TABLE 37.2-32. Benefit of Herceptin When Added to Chemotherapy

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INTRODUCTION

Breast reconstruction after mastectomy has grown in popularity since the 1970s. The era of diagnosis with less extensive cancers has ushered in less extensive total mastectomies, including "skin sparing" with an incision only around the areola. Presently, the typical patient has many choices, not only regarding the cancer management but also regarding multiple surgical options after mastectomy.

The first consideration after mastectomy is whether to reconstruct the breast. Not performing breast reconstruction is the simplest approach. The patient then faces postmastectomy appearance and the need, in most women, for an external prosthesis to restore appearance and weight balance. Mastectomy forms first began as individually made cotton fluff-filled forms. Then foam rubber forms were manufactured with holes in the back for metal weights to add stability and gravity. Now almost all weighted breast prostheses are made of solid silicone materials. The variably shaped breast forms are also available in several skin colors. It is very rare, but possible, to require custom manufacturing of the form for the irregular mastectomy defects.

The external prosthesis is completely concealed in a bra with an adjustable built-in pocket specially constructed to accommodate it. Wearing the weighted prosthesis should help the body maintain its posture and balance and may prevent back and neck strain. With the concern that the prosthesis could become dislodged, even with such a specially fitted bra or swimsuit, adherent forms have now become popular. Using a variety of surgical adhesives, the form adheres to the chest wall or to a backing on the skin of the chest wall, so that the form can be removed every night while the backing can remain for a week or more. In retrospective studies, the differences among those opting for breast reconstruction, those wearing external prostheses, and those doing neither were explored.

The American Cancer Society sponsors the program Reach to Recovery (1-800-ACS-2345), which began in 1952, a time in which all volunteers had undergone mastectomy. Today, the survivor-to-patient outreach and support include volunteers who have had breast conservation and postmastectomy reconstruction. At the physician's request, trained volunteers meet with the patient to discuss several aspects of recovery, including physiologic, psychological, and cosmetic rehabilitation. Resources for the patient include breast prostheses information with knowledge of local resources, clothing suggestions, and even an exercise booklet and aids.

DELAYED VERSUS IMMEDIATE RECONSTRUCTION

If breast reconstruction is elected, the next decision is timing, immediate (at the time of the mastectomy) or delayed. The traditional concept of performing the mastectomy, proceeding with adjuvant therapy, and delaying reconstruction until the completion of adjuvant therapy is being supplanted by the increasing use of immediate reconstruction. In a mastectomy without immediate reconstruction, it is difficult to "save" any extra native breast skin because, with the volume of the breast missing, there is excess skin folding and wrinkling. The first large report of immediate reconstruction was in 1982 by Georgiade et al. In their series of 62 patients, the authors concluded that immediate breast reconstruction in selected patients offered the advantages of improved aesthetic results, decreased cost, less morbidity, and no adverse effect on cancer management.

Because the mastectomy and reconstruction are performed under a single anesthetic, the total hospital costs and convalescent time are reduced when compared to mastectomy and delayed reconstruction. Immediate reconstruction reduces physical morbidity by limiting the total number of anesthetics and reducing the need for a sympathectomy, a procedure on the opposite breast. Critical landmarks for optimizing breast form and symmetry are the inframammary fold, which is preserved, and the breast skin envelope, which can be preserved and maintained in its native state with immediate reconstruction.

Current methods of reconstruction can be broadly classified into autologous tissue or prosthetic material. Autologous tissue reconstruction uses the patient's own tissue (skin, subcutaneous tissue, and muscle) from another site to reconstruct the missing breast. Prosthetic reconstruction uses a process known as tissue expansion to create a "pocket" for the ultimate placement of a breast implant. There are occasional indications for a combination of both autologous tissue and an implant. The selection of the reconstructive technique is based on anatomic patient factors, including the laxity and thickness of the remaining chest wall skin, the condition of the chest wall musculature, the size of the opposite breast, and the availability of suitable autologous tissue donor sites. To identify the appropriate method of reconstruction, the anatomic factors are considered with cancer treatment goals and the patient's expectations, as well as, most important, clinical factors (diabetes, obesity, other chronic illnesses) because operative complexity and postoperative recovery varies.

PROSTHETIC RECONSTRUCTION

Breast reconstruction using prosthetic materials involves the use of tissue expanders and permanent breast implants. Initially, implants were placed directly under the skin in the mastectomy space, but the results were limited by the available skin envelope and capsular contracture. The development of tissue expanders allowed for greater control over the size of the skin envelope, thus resulting in the ability to use larger prostheses for symmetry. Current techniques use a complete submuscular placement of the tissue expander, with coverage by pectoralis major, serratus anterior, and occasionally the anterior rectus sheath.

A biodimensional textured surface tissue expander is placed either at the time of mastectomy, which increases the operative time of less than 1 hour, or in a delayed fashion, during a separate later operation. The area is allowed to heal for approximately 10 to 14 days, at which time fluid expansion is commenced. Using an integrated valve within the expander, saline is injected into the expander percutaneously until the appropriate size is reached. Adjuvant chemotherapy can be commenced during the expansion process. The exchange to a permanent breast implant takes place after the chemotherapy course. Using a two-stage method of implant reconstruction allows for maximum control of the implant pocket and optimal symmetry with the contralateral breast. When indicated, contralateral symmetry procedures such as augmentation mammoplasty, reduction mammoplasty, or mastopexy (breast lift), are accomplished when the tissue expander is exchanged to a permanent implant.
The author (J. J. D.) reported results with 770 consecutive patients undergoing tissue expansion over a 10-year period. In this series, premature removal of the tissue expander secondary to wound-related complications or persistent disease was necessary in only 1.8% of the patients. The advantages of tissue expander implant reconstruction are the simplicity, reliability, and avoidance of donor site morbidity. The disadvantages of this technique relate to the use of prosthetic material and include infection, leakage of the implant, capsular contracture, and differences in texture and symmetry when compared to the contralateral breast, which can lead to multiple surgical procedures on the opposite breast.

Breast implants available for reconstruction vary in size, shape, surface texturing, and fill material. In general, implants are either round or anatomic in shape, with a smooth or textured surface, and saline or silicone gel-filled. Currently, saline-filled breast implants are available, and use of silicone gel implants requires enrollment in a silicone adjunct study sponsored by the implant manufacturers, U.S. Food and Drug Administration, and the Institution Review Board where the procedure is being performed. Despite the moratorium placed on the general use of silicone gel implants, to date there is no convincing cause and effect between “human adjuvant disease” and the use of silicone gel implants.

AUTLOGOUS TISSUE RECONSTRUCTION

The most predictable results in breast reconstruction involve the use of autologous tissue. In general, use of the patient's own tissue results in a reconstruction that can closely match the opposite breast in size, shape, and texture. Depending on the volume of the tissue transferred and the volume of the contralateral breast, autologous tissue breast reconstruction sometimes also requires an implant.

Methods of autologous tissue breast reconstruction include local flaps and distant flaps. Local flaps, including the latissimus dorsi myocutaneous flap and the pedicled transverse rectus abdominus myocutaneous (TRAM) flap, rely on transposition of muscle, subcutaneous tissue, and skin into the mastectomy defect based on the attached native blood supply of the muscle. Distant flap breast reconstruction mandates the use of microvascular free tissue transfer. The most common distant tissue donor site is the free TRAM flap. Other donor sites include the inferior gluteal flap, the superior gluteal flap, the deep inferior epigastric artery perforator flap, and the Rubens flap. Reconstruction using these tissues relies on harvesting the flap with its discreet vascular pedicle. The vascular pedicle is then anastomosed using microsurgical technique to appropriate recipient vessels in the mastectomy site, usually the thoracodorsal and internal mammary vessels.

The latissimus dorsi myocutaneous flap with an overlying skin island can be transposed from the back into the mastectomy defect. The advantages of the latissimus flap are in its ease of harvest and minimal donor site morbidity, compared to other sites. The chief disadvantage of the latissimus flap is that concomitant use of a breast implant is often necessary due to the limited volume of tissue provided. Without a simultaneous implant placement, the latissimus dorsi flap is reserved for small breasts.
The most common method of autologous tissue breast reconstruction is with the TRAM flap because of the texture and the large volume, both of which match the other breast (Fig. 37.3-5). The blood supply to the skin island and lower abdominal fat is derived from perforating vessels through the underlying rectus abdominus muscle. Depending on the increasing volume necessary to match the other breast, the TRAM flap can be transferred on a single pedicle (usually the contralateral superior epigastric), double pedicle (using both rectus muscles and their associated superior epigastric vessels), or as a free flap (based on the deep inferior epigastric vessels) (Fig. 37.3-6).

The TRAM flap allows the reconstructive surgeon the most versatility and design. Thus, the flap can be sculpted to closely match the contralateral breast in unilateral reconstruction, or itself in bilateral reconstruction (Fig. 37.3-7). The use of a breast implant is rarely indicated with a TRAM flap, because an ample amount of tissue exists in properly selected patients. The lower abdominal donor site scar is easily hidden with conventional clothing. Despite the obvious advantages of the TRAM flap, not everyone is a candidate. Thin patients may not have an adequate amount of tissue at the donor site, whereas obese patients have a much higher risk for local and systemic complications. Total flap loss with the free TRAM flap can occur, but the risk is generally accepted to be less than 2%. Use of the rectus abdominus muscle results in 10% loss in abdominal wall strength in unilateral reconstruction and 40% loss when both muscles are harvested. Lower abdominal bulging and hernia formation occurs in fewer than 10% of patients and can be minimized by surgical techniques that maximize preservation of the rectus muscles.

Other methods of autologous tissue reconstruction include the gluteus free flap based on the superior or inferior gluteal vessels, and the Rubens flap based on the deep circumflex iliac artery. These techniques are technically demanding and do not offer the same high-quality tissue available with a TRAM flap. Therefore, their use is reserved for patients desiring breast reconstruction that are not candidates for more conventional methods.
Breast reconstruction after local failure in the irradiated breast presents a unique challenge for both the oncologic and reconstructive surgeon. The late effects of radiation are characterized clinically by a loss of skin elasticity, fibrosis, and decreased blood supply. The postradiation fibrosis severely limits the ability of the tissue expander to create a satisfactory pocket for the permanent implant. There is an increased incidence of infection, skin necrosis, and expander extrusion when attempting to expand the irradiated skin and muscle chest wall, as well as a high rate of capsular contracture in the final result. The lack of projection of the permanent implant and capsular contracture detracts from the final aesthetic result.

Increasing the success of breast reconstruction after prior irradiation involves the use of autologous tissue. Depending on the method, this procedure can be performed with or without a breast implant. The transfer of the ipsilateral latissimus dorsi muscle with a cutaneous skin island into the mastectomy defect delivers a large volume of healthy nonirradiated tissue into the defect. In conjunction with a tissue expander, the flap can be expanded without difficulty, and ultimately a permanent implant can be placed with improved aesthetics and a decreased incidence of complications.

In a series of 680 consecutive patients who underwent TRAM flap breast reconstruction, 108 patients had had previous irradiation, and no difference was found in flap survival in the two groups. There was, however, increased incidence of infection and fat necrosis in the radiated group, which detracts from the final aesthetic result. The effects of irradiation on the mastectomy flaps predisposes to ischemia and may increase scar formation.

SKIN-SPARING MASTECTOMY WITH IMMEDIATE RECONSTRUCTION

Although autologous tissue breast reconstruction can create a breast mound that resembles the breast in shape and consistency, one drawback is the color difference between the native breast skin and the flap skin (from the distant site), which conveys a “patch-like” appearance. The technique of skin-sparing mastectomy is accomplished through one incision around the areola with preservation of the entire breast skin envelope. When necessary, a counterincision in the axilla is used to expose blood vessels, to remove lymph nodes, or for microsurgical flap transfer. The skin island from the flap is confined to the zone of the nipple-areola complex. Subsequent nipple reconstruction covers the skin island completely, thereby virtually eliminating all visible scars, and the reconstructed breast is almost indistinguishable from the other. Importantly, long-term follow-up of selected patients has not shown a difference in local recurrence rates after skin-sparing mastectomy versus traditional mastectomy. Technical advances using complete skin-sparing techniques have resulted in reconstructed breasts that are virtually indistinguishable from the native breast in terms of color, texture, and appearance.

Aside from recurrence, lymphedema is the most dreaded sequela of breast cancer treatment. Approximately 15% to 20% of breast cancer patients have developed
lymphedema after breast cancer treatment. Therefore, of perhaps 2 million current breast cancer survivors after axillary dissection, approximately 400,000 cope daily with the disfigurement, discomfort, and disability of arm and hand swelling.

Lymphedema is the result of a functional overload of the lymphatic system in which lymph volume exceeds transport capabilities. The functioning lymph system removes large molecules that reach the interstitial space by filtration, cellular metabolism, or secretion. The buildup of interstitial macromolecules leads to an increase in oncotic pressure in the tissues, producing more edema, and the blocked lymphatic vessels raise hydrostatic pressure proximally in the system. Persistent swelling and stagnant protein eventually lead to fibrosis and provide an excellent culture medium for repeated bouts of cellulitis and lymphangitis. With dilation of the lymphatics, the internal valves become incompetent, causing further stasis.

The reported incidence of lymphedema has varied greatly and depends in part on the extent of axillary treatment, the interval between axillary treatment and measurement, methods used to define lymphedema, and the completeness of the patient population follow-up.

All reports on the incidence of lymphedema, including the seven selected ones from a review, are retrospective, and in each of these reports, the denominator (i.e., the number of patients at risk for developing lymphedema in a particular population) is imprecise or unknown. The incidence varied from 6% to 30%, with the lowest incidence of lymphedema having the shortest follow-up.  

**ETIOLOGIC FACTORS**

Almost all previous studies find that the incidence and degree of lymphedema is correlated to the extent of surgical dissection as more nodes are excised. However, two large studies could not demonstrate this relationship, perhaps because rather small differences in extent of axillary dissection were assessed. Regardless of the number of lymph nodes excised, surgeons should attempt to carefully preserve the fatty axillary tissue containing the invisible lymphatic trunks around the vein and to dissect the tissue only inferior to the axillary vein.

In every study that has evaluated this issue, the addition of radiation therapy directed to the dissected axilla was a strong predictor of lymphedema. Of particular importance is that even when the intent is to radiate the breast only (such as after lumpectomy), some radiation dosage may reach the axilla depending on radiotherapy technique and patient anatomy. Specific breast radiotherapy techniques with the goal to avoid the dissected axilla and the pathophysiology of radiation-related lymphedema have been reviewed. For precise radiation technique, it may be helpful for the surgeon to mark axillary dissection by radiopaque clips, and the area can then be seen on the simulation films.

It is biologically intuitive that sentinel lymph node biopsy of one or few nodes should decrease the risk of lymphedema. However, the sentinel node operation is not always so limited, and it is theoretically possible that indeed the sentinel node may be at the level of the axillary vein (and the lymph trunks), thereby theoretically predisposing the patient to lymphedema. The risk of lymphedema has not yet been assessed in the follow-up of patients treated with sentinel lymph node technology. Furthermore, if axillary radiotherapy is added after sentinel node biopsy, there is the risk of lymphedema. In series reporting axillary radiotherapy but no axillary surgery at all, lymphedema incidence ranged from 2% to 5%.

Beyond these two definite factors—extent of surgical dissection and radiation to the axilla—a wide range of possible etiologic factors has not been evaluated systematically. Older age at diagnosis was reported to be a significant factor in one study, but was unrelated to lymphedema incidence in another, and curiously was not noted in others. Similar disagreement holds for dominant hand on the operated side, obesity, surgical technique, and postoperative course.

**PREVENTION OF LYMPHEDEMA AFTER AXILLARY TREATMENT**

Because controlling lymphedema requires daily attention, and because “curing” lymphedema has not been accomplished, emphasis must be placed on prevention. Nevertheless, without evidence-based knowledge of etiologic factors, the list of posttreatment arm precautions is based on intuitive reasoning. As a background, it is important to remember that each woman has a congenitally different anatomy, which also is probably uniquely prone to degenerative conditions, similar to the remainder of the vascular system. This has been studied thus far in a limited fashion with lymphoscintigraphy. The individual patient factors, combined with surgical and radiation treatment factors, must be the main determinants, notwithstanding the fact that lymphedema may occur several years after treatment. Events or activities, such as exercise, in the subsequent years and decades have not been studied to state which are causative factors and to what degree.

Arm and hand precautions are loosely based on two overarching principles: (1) Do not increase lymph production, which is directly proportional to blood flow, and (2) do not increase blockage to lymph transport. Heat (such as that in a sauna), significant infections, and vigorous arm exercise increase blood flow in the arm and thereby increase lymph production. Obstruction of lymph flow may result from tight arm garments or from infections with ensuing fibrosis and stenosis of lymphatic vessels.

The patient is instructed as follows:

1. Avoid puncturing or injuring the skin in any way. Use meticulous skin and nail/cuticle care. Pay immediate attention and use standard first aid care.
2. Avoid vaccinations, injections, blood pressure monitoring, blood drawing, and intravenous administration in that arm.
3. Avoid constricting sleeves or jewelry and wear a padded bra strap (to avoid supraclavicular area compression).
4. Avoid heat, such as with sunburns or tanning, baths, and saunas.
5. Avoid violent exercises and strenuous exertion. Consider vigorous aerobic arm exercise only when compression garments support the arm.

No data govern any of these recommendations. In the only studies that reported on bilateral axillary dissections, there was no higher risk of lymphedema in those women over those who had unilateral axillary dissection. This calls into question whether blood drawing, intravenous administration, blood pressure monitoring, and injections are proven to hasten the development of lymphedema. On the other hand, breaking the skin barrier, even during medical procedures, could theoretically predispose to infection, and blood pressure monitoring could cause soft tissue trauma. Data for any of the other arm and hand precautions are also intuitive and not evidence-based.

All patients after axillary dissection are instructed in the arm and hand care precautions, which may, however, be too severe for those at low risk and yet not aggressive enough for those at highest risk. Because lymphedema development may occur even several decades after the axillary treatment, patients are admonished to follow these demanding precautions for the remainder of their lives.

**LYMPHEDEMA TREATMENTS**

Therapeutic nihilism (i.e., no treatment at all) is deplorable, although common. The fact that the average clinician is ill-prepared to recognize early signs of lymphedema must be remedied because the sooner the treatment is started, the less treatment is required to prevent further progression.

In the past, the treatment of established lymphedema has varied from none at all to a host of aggressive surgical procedures. Between the extremes are various combined conservative treatments, the most important of which are elevation, compression garments, centripetal massage and exercises, pneumatic compression devices, and the complete (or complex) decongestive physiotherapy (CDP) program.

**Complete Decongestive Physiotherapy**

CDP has been widely available in Europe for many years. The program was founded on the fact that lymphedema exists in an entire body quadrant, although it is most distressing in the arm or hand. The program includes skin care, gentle specific massage known as manual lymph drainage (MLD), low stretch multilayer compression bandaging (followed by a fitted compression garment when edema is reduced), and therapeutic exercises with the garment or bandages in place.

The modification and features of the various CDP programs by Vodder, Leduc, Foldi, and Casley-Smith have been reviewed in the 1998 American Cancer Society Workshop on Breast Cancer Treatment–Related Lymphedema. Although the principles followed are the same for each school, the massage techniques vary somewhat in the degree of pressure, motion, and timing of strokes. Additionally, the Leduc technique uses low intermittent pneumatic pressure (<40 mm Hg) pumps,
and the Casley-Smith group uses benzopyrone medication.

A typical program is given below. CDF must be performed by skilled, specially trained therapists. During the treatment phase, the patient is given one or two daily 75 to 90 minute treatments over 1 to 4 weeks. In the maintenance phase, which is continued indefinitely, the patient maintains and optimizes the results by applying some of the techniques learned in the treatment phase, such as wearing an elastic sleeve during the day, bandaging (as described below) the affected limb overnight, and exercising for 15 minutes a day while wearing the bandages.

MLD, or manual lymph therapy, is a delicate massage technique that stimulates lymph vessels to contract more frequently and that directs and channels fluid toward adjacent, functioning lymph basins. MLD begins with stimulation of the lymph vessels and nodes in unaffected and opposite basins (neck, contralateral axilla, ipsilateral groin). Edema fluid and obstructed lymphatics are made to drain toward functioning lymph basins across the midline of the body, down toward the groin, over the top of the shoulder, around the back, and so forth. Finally, in segmented order, massage of the involved trunk, then shoulder, upper arm, forearm, wrist, and hand is performed. Multilayer low-stretch bandaging is done immediately after MLD. Bandages are wrapped from the fingertips to the axilla with maximal pressure distally and decreasing pressure proximally. This is done by using many layers of manually elastic cotton bandages, beneath which layers of foam rubber padding are inserted to ensure uniform pressure distribution or to increase pressure in areas that are particularly fibrotic. The bandaged patient is next guided through exercises involving active range of motion with the muscles and joints functioning within the closed space of the bandaging. Isometric exercise is generally avoided.

After volume reduction has been accomplished, well-fitted custom-made compressive garments (see next section) continue ongoing control of edema. The patient should be re-measured and the garment replaced every 3 months. The prescribed exercises continue in the low-stretch multilayer bandages, which are also worn overnight. The patient and family is trained to continue the maintenance program at home. Follow-up visits to the center usually take place at least at 6-month intervals.

Although this increasingly popular technique appears more successful in reversing lymphedema than other modalities, the availability of patient services and treatment centers that can practice CDF are limited. The patient availability 12 and the professional education for physical therapists 12 has been reviewed. The theory and clinical application of the four schools of manual lymphatic technique are reviewed in the American Cancer Society monograph by their representative faculty. 45,46 and 47

### Elevation and Elastic Garments

Although elevation is helpful in reducing swelling through use of gravity, it is impractical. A patient with lymphedema should be fitted with an elastic sleeve from wrist to axilla, if the edema is mild, or after swelling reduction, if the edema is moderate. A separate gauntlet or handpiece allows the patient to wash her hands without removing the sleeve.

The compression classes are as follows:

- I. 20 to 30 mm Hg
- II. 30 to 40 mm Hg
- III. 40 to 50 mm Hg
- IV. 50 to 60 mm Hg

For upper extremity lymphedema, a class II or III support is generally required. The person measuring the lymphedematous arm and hand should be specifically trained in fitting such garments and in instructing the patient in proper application. A statistically significant reduction in edema has been reported in women who wore garments for 6 consecutive hours per day.12 Using these garments during exercise, physical activity, and air travel is recommended.

### Pneumatic Pumps

The standard sequential system is a multichamber pump that delivers the compression at the same pressure in each garment section from distal to proximal tissues. The gradient sequential system delivers pressures that differ by approximately 10 mm Hg between each chamber, with the higher pressures delivered to the distal chambers. Each pump session with the arm lifted is elevated, and lower pressures for longer periods are more effective than higher pressures for a shorter time. Individualized and tailored pumping programs should be prescribed by a physical therapist, based on measurable efficacy and tolerability, as known by the serial assessment before the patient is placed on a home program.

The various devices have been reported in several controlled studies 48,49 and 50 to reduce lymphedema. Although theoretically attractive to use machinery for the pumping action on the arm lymphatics, pumping has not been as clinically effective as would be hoped. It has been hoped that pneumatic compression devices or “pumps” could duplicate the beneficial effects of massage. However, the pumps force protein-rich edema fluid toward the shoulder but not through the axillary blockage. Rationale and controversies about pumps have been reviewed. 49,50

### MEDICATIONS

Diuretics are not effective in high-protein edemas such as lymphedema. Although the diuretics can temporarily mobilize water, the osmotic pressure from the increased protein in the interstitial space causes rapid re-accumulation of edema.

Benzopyrones belong to a group of drugs that include the bioflavonoids and the coumarins. The former occurs widely in nature, especially in fruits and vegetables. Benzopyrones may improve chronic lymphedema by stimulating macrophage activity for increased proteolysis and thereby removal of stagnant, excess protein in the tissue spaces, which results in less oncotic pressure and edema fluid. In 1993, a randomized, double-blind, placebo-controlled, crossover trial of 5,8-benzo-a-pyrene demonstrated its efficacy in an Australian study. 37 Although the effect was mild, it was statistically significant. However, in a similar study design, a larger number of breast cancer patients in an American multicenter study led by the Mayo Clinic were reported. No value was found among these study subjects beyond liver function tests.

### CHAPTER REFERENCES

In 1988, the specific genotype-phenotype correlations have been established to date. There are separate families. Approximately two-thirds of the reported mutations in the pancreas, thyroid, the gonads, and other tissues. Similar to the protein products of most previously described tumor suppressor genes, evidence has been provided that menin is a nuclear protein.

The diverse array of reported mutations includes missense, nonsense, frameshift, and mRNA splicing defects that are distributed throughout the nine coding exons as well as the intervening intronic sequences. The MEN1 gene mutations in a series of 25 separate kindreds with MEN 1 are depicted graphically in Figure 38.1-1. To date, more than 100 germline MEN1 mutations have been reported in the literature, and there are almost as many distinct mutations as there are separate families. Approximately two-thirds of the reported mutations in the MEN1 gene result in truncation of the C-terminal portion of the menin protein. No specific genotype-phenotype correlations have been established to date.

**INTRODUCTION**

The transformation of a cell from the normal to the malignant phenotype is a result of a stepwise accumulation of genetic defects that render the cell unresponsive to or independent of normal cellular growth signals. Defects in a variety of oncogenes and tumor suppressor genes have been described in endocrine neoplasms.

Characterization of these specific molecular defects has yielded insight into the mechanisms of tumorigenesis in these tissues and, in some cases, provided clinically applicable diagnostic or prognostic information. Identification of the germline mutations associated with the multiple endocrine neoplasia types 1 and 2 (MEN 1, MEN 2) syndromes has led to the advent of direct DNA testing for individuals at risk. In patients with a hereditary form of medullary thyroid carcinoma (MTC), early thyroidectomy may be performed on the basis of DNA mutational analysis at a time when the MTC is occult and likely curable. Finally, the molecular defects that occur in tumors arising in the familial endocrine neoplasia syndromes have been found to play an important role in tumorigenesis of sporadic neoplasms arising in the same endocrine tissues.

**MULTIPLE ENDOCRINE NEOPLASIA SYNDROMES**

**MULTIPLE ENDOCRINE NEOPLASIA TYPE 1**

**Clinical Features**

MEN 1 is characterized by the development of parathyroid hyperplasia, neuroendocrine tumors of the pancreas and duodenum, and adenomas of the anterior pituitary gland. In affected patients develop bronchial and thymic carcinoids, benign thyroid and adrenocortical tumors, subcutaneous lipomas, cutaneous angiofibromas, and spinal ependymomas with increased frequency. More than 90% of patients inheriting a MEN1 gene mutation develop hyperparathyroidism (HPT) by the second or third decade of life. Depending on the method of study, 35% to 75% of mutation carriers develop neuroendocrine tumors of the pancreas and duodenum that are frequently malignant. The neuroendocrine tumors in patients with MEN 1 result in symptoms due to either excess secretion of a specific hormone product or the effects of the tumoral process itself. The malignant duodenopancreatic tumors and intrathoracic tumors account for the majority of the disease-related morbidity and mortality in MEN1 gene mutation carriers.

**Genetics**

**MEN1 TUMOR SUPPRESSOR GENE.** In 1988, the MEN1 predisposition gene was mapped to chromosome 11q13 by a combination of studies of the loss of chromosomal sequences in tumor DNA and genetic linkage analysis using markers from chromosome 11. The frequent occurrence of chromosome deletions encompassing the 11q13 interval in tumor DNA supports the hypothesis that the MEN1 gene is a classic tumor suppressor gene. The normal protein encoded by a tumor suppressor gene is presumed to function as a negative control or "brake" on unregulated cellular growth and proliferation, such that complete elimination of its function by mutation or deletion of both homologous copies would be expected to result in unregulated cell growth. The multifocal involvement characteristically observed in affected endocrine tissues presumably reflects the chance occurrence of multiple "second hits." The MEN1 tumor suppressor gene encodes a predicted 610–amino acid protein product termed menin. The structure of the MEN1 gene consists of ten exons, with the first exon being untranslated. The 2.8-kilobase menin messenger RNA (mRNA) transcript is ubiquitously expressed and may be detected in lymphocytes, thymus, pancreas, thyroid, the gonads, and other tissues. Similar to the protein products of most previously described tumor suppressor genes, evidence has been provided that menin is a nuclear protein.

The diverse array of reported MEN1 mutations includes missense, nonsense, frameshift, and mRNA splicing defects that are distributed throughout the nine coding exons as well as the intervening intronic sequences. The MEN1 gene mutations in a series of 25 separate kindreds with MEN1 are depicted graphically in Figure 38.1-1. To date, more than 100 germline MEN1 mutations have been reported in the literature, and there are almost as many distinct mutations as there are separate families. Approximately two-thirds of the reported mutations in the MEN1 gene result in truncation of the C-terminal portion of the menin protein. No specific genotype-phenotype correlations have been established to date.
FIGURE 38.1-1. Germline mutations in the MEN1 gene in a set of 25 independent kindreds. The mutations are distributed throughout the nine coding exons of the gene. Five splicing defects and two missense mutations are depicted above the MEN1 gene, and seven nonsense and six frameshift mutations are depicted below the MEN1 gene. The position of the mutation is reported as the codon in which it occurs relative to the open reading frame. The position of the splicing defects are reported as the number of bases 3’ or 5’ to the nearest exon [(+) indicates 3’ direction and (–) indicates 5’ direction relative to the exon]. For the deletions, insertions, and splicing defects, uppercase letters refer to exon nucleotides and lowercase letters refer to intron nucleotides. *Previously reported mutations; †mutations that occur in more than one family. (Reprinted from ref. 16, with permission.)

CELLULAR BIOLOGY OF MENIN PROTEIN PRODUCT. The precise role of menin in the regulation of cell growth has yet to be elucidated. Menin binds to the JunD transcriptional regulation factor and may function to inhibit JunD-activated transcription. The nucleotide sequence of menin is highly conserved, with an overall homology of 97% between the human and murine genes. In the mouse embryo, MEN1 expression appears as early as gestational day 7 and ultimately is detectable at high levels in diverse tissue, including testis and the central nervous system. These findings support a broad role for the menin protein product in regulating cell growth that is not limited to the tissues affected in MEN 1. Lymphocytes from patients with a heterozygous germline mutation in the MEN1 gene have been shown to exhibit increased premature centromere division in cell culture when exposed to an alkylating agent. The finding of increased chromosomal instability suggests that the MEN1 gene product may normally function in part to maintain the integrity of DNA.

MULTIPLE ENDOCRINE NEOPLASIA TYPE 2 SYNDROMES

Clinical Features

The MEN 2 syndromes include MEN 2A, MEN 2B, and familial, non-MEN medullary thyroid carcinoma (FMTC). These syndromes are inherited in an autosomal dominant fashion and are caused by germline mutations in the RET protooncogene. The most consistent feature of MEN 2 syndromes is MTC, which is multifocal, bilateral, and usually occurs at a young age (Fig. 38.1-2). There is almost complete penetrance of MTC in these syndromes; almost all persons who inherit the disease allele develop MTC. Other features of the syndromes are variably expressed, with incomplete penetrance. These features are summarized in Table 38.1-1.


TABLE 38.1-1. Clinical Features of Sporadic MTC, MEN 2A, MEN 2B, and FMTC

MTCs are derived from the thyroid C cells, also called parafollicular cells, which migrate from the neural crest. C cells comprise 1% of the total thyroid mass and are dispersed throughout the gland, with the highest concentration in the upper poles (Fig. 38.1-3). The C cells are so named because of their unique ability to secrete the hormone calcitonin. Calcitonin is a specific tumor marker for MTC. It is extremely useful in the screening of individuals predisposed to the hereditary forms of the disease and in the follow-up of patients who have been treated. C cells also are capable of secreting other hormones, including carcinoembryonic antigen.
In 1987, the gene for MEN 2A was localized to the pericentromeric region of chromosome 10 (10q11.2) by linkage analysis. The RET protooncogene was first discovered based on its ability to transform mouse NIH 3T3 fibroblasts in culture. The transforming RET sequences first identified represented a rearrangement of RET that occurred in vitro during the transfection assay. Sequence analysis of the RET protooncogene showed that it is a member of the receptor tyrosine kinase gene family. 

**Figure 38.1-3.** Diagram of the RET gene product delineating locations of germline mutations found in multiple endocrine neoplasia type 2A and familial, non-MEN medullary thyroid carcinoma (ovals), germline mutations in multiple endocrine neoplasia type 2B (diamond), and mutations in hereditary Hirschsprung’s disease. (Reprinted from Moley JF, Lairmore TC, Phay JE. Hereditary endocrinopathies. Curr Prob Surg 1999;36:653, with permission.)

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**Table 38.1-2.** RET Mutations in Hereditary Medullary Thyroid Carcinoma

More than 30 missense mutations have been described in MEN 2A and FMTC kindreds (Table 38.1-2). Most of these mutations result in nonconservative changes in cysteine residues, although changes in Glu, Val, Met, Leu, and Tyr have also been described. Several of these mutations have been shown to result in “gain-of-function” in the RET protein product, with increased intrinsic tyrosine kinase activity or alterations of substrate recognition (or both) and transforming capability. The RET protooncogene encodes a protein with three domains: a cysteine-rich extracellular receptor domain, a hydrophobic transmembrane domain, and an intracellular tyrosine kinase catalytic domain (Fig. 38.1-4). The RET gene consists of at least 20 exons and is expressed as five major mRNA species. The RET gene product is expressed in a limited number of cell types in the normal individual, including the thyroid C cells, the adrenal medulla, and parts of the brain. The gene is important in the embryonic development of the enteric nervous system and the kidneys.

**Figure 38.1-4.** Photomicrograph of medullary thyroid carcinoma showing nests and sheets of small, uniform cells with scant to moderate amounts of amphophilic cytoplasm infiltrating around normal thyroid follicles. (Reprinted from Moley JF, Lairmore TC, Phay JE. Hereditary endocrinopathies. Curr Prob Surg 1999;36:653, with permission.)
(triangles). As mentioned in the text, the RET gene product is thought to create a dimer that forms a complex with glial-derived neurotrophic factor receptor-α or neurulin. The RET gene product is divided into the intracellular, transmembrane, and extracellular domains. ATP, adenosine triphosphate. (Adapted from Moley JF, Kim S, Molecular genetics in surgical oncology. Austin: RG Landes, 1994, with permission.)

Gial-derived neurotrophic factor (GDNF) and neurulin are ligands to the receptor domain of the RET gene product. 12,13,14 GDNF is a 32-kD protein dimer that was first purified from glial cell lines and is a potent neurotrophic survival factor for motor neurons. A glycosphosphatidylinositol-linked protein called GDNF receptor-α (GDNFR-α) is a cofactor in the signaling heterodimeric complex with RET. Current evidence suggests that GDNF binds directly to GDNFR-α and indirectly with RET. When triggered by ligand, wild-type RET dimerizes with another RET molecule, and this dimerization is responsible for phosphorylation and activation of the tyrosine kinase domain, with subsequent downstream signal transduction events. RET molecules that contain MEN 2A-type mutations are constitutively dimerized and therefore activated. In contrast, the mutation responsible for MEN 2B does not result in constitutive dimerization but changes the substrate specificity of the tyrosine kinase domain, which results in transformation.

OTHER RET GENOTYPE-PHENOTYPIC CORRELATIONS.

Cutaneous Lichen Amyloidosis. Interscapular lesions of cutaneous lichen amyloidosis (CLA) have been described in several families with MEN 2A. The total number of patients described with this entity is fewer than 100. In a 634Tyr mutation was reported in one family with MEN 2A and CLA, and in two other families, a 634Arg mutation was described that segregated with both MEN2A and CLA.

Hyperparathyroidism. HPT in MEN 2A is caused by parathyroid hyperplasia; the hypercalcemia is mild and often asymptomatic. HPT clusters in some families with MEN 2A. Whether specific MEN2A mutations are associated with a higher incidence of HPT remains controversial. Mulligan et al. previously described a strong correlation between C63AR mutation and HPT in families with MEN 2A, but other studies have been unable to confirm this relationship definitively.

Hirschsprung's Disease. Hirschsprung's disease is characterized by absence of autonomic ganglion cells within the distal colonic parasympathetic plexus, resulting in obstruction and proximal megacolon. Approximately 80% of Hirschsprung's disease cases are sporadic, and the remainder are familial. A subset of familial Hirschsprung's cases have been found to be associated with germline mutations of RET. 22,23 Most of these are inactivating and loss-of-function (frameshift and nonsense) mutations and are not associated with the MEN 2A phenotype. Several families, however, have been described in which Hirschsprung's disease cosegregates with either MEN2A or MTC (missense codon 618 or 620 mutations).

Additionally, a few Hirschsprung's disease patients have been described with missense mutations in codon 609 or 620 who have no evidence of MEN 2A or MTC. 22,23 It is interesting to note that the Hirschsprung's disease phenotype can be associated with either loss-of-function or gain-of-function mutations of RET. All patients with MEN 2B (missense codon 918 mutation) have megacolon and chronic colonic motility disturbances, though they usually do not require surgery for this (see 24).

RET Mutations in Sporadic Tumors. Mutations in the RET protooncogene have also been found in sporadic MTCs. 25-27 The most frequent mutation in sporadic MTCs is the M918T mutation found in MEN 2B. Mutations have been found in other regions of the extracellular and intracellular domains. Missense, deletions, and insertion mutations have been described. 24 Somatic RET mutations in sporadic pheochromocytomas are unusual but have also been described.

Other Dominant Oncogenes in Medulillary Thyroid Carcinomas and Pheochromocytomas. Absence of amplification of N-MYC, C-MYC, and ERBB2 has been reported in MTCs and pheochromocytomas. Roncalli et al. 28 reported that N-myc expression in more than 10% of tumor cells, as detected by immunohistochemistry, was associated with poorer survival, sporadic disease, and male gender. These investigators found no evidence of gene amplification and did not determine the basis for the overexpression.

Our group reported absence of mutation of the H-RAS, N-RAS, and K-RAS genes in a series of pheochromocytomas and MTCs analyzed by direct sequencing. 24 Likewise, examination of nerve growth factor and nerve growth factor receptor (p75) showed no abnormality at the DNA or RNA levels.

Other Tumor Suppressor Genes in Medulillary Thyroid Carcinoma and Pheochromocytoma. Several studies have evaluated loss of heterozygosity (LOH) at tumor suppressor loci in pheochromocytomas and MTCs; these are summarized in Table 38.1-3. The cumulative data indicate a higher-than-background incidence of LOH in pheochromocytomas on chromosome arms 1p, 3p, 17p, and 22q. 29,30 In MTCs, the report by Mulligan et al. 24 suggests a significant incidence of 1p LOH; however, evaluation of other chromosomal arms yielded no consistent findings. Lack of significant LOH on 1q, at the RET locus, supports the hypothesis that the RET protooncogene acts as a dominant oncogene as opposed to a tumor suppressor gene. 24 Chromosome 1 is the largest chromosome, and LOH analysis on 1p in pheochromocytomas suggests a very large region of deletion. Our studies have indicated that the entire short arm of 1p is lost in pheochromocytomas from patients with MEN 2A and MEN 2B. 24 Fine mapping of the region of deletion suggests a possible common breakpoint in the centromeric region defined by the markers D1S514 and D1S442.

Table 38.1-3. Loss of Heterozygosity in Pheochromocytomas and Medulillary Thyroid Carcinomas

The high rate of LOH on 3p in pheochromocytomas suggests an as-yet undefined tumor suppressor locus. 24,25 LOH on 17p suggests possible involvement of the TP53 gene. 24,25 Existing reports on TP53 mutations in pheochromocytomas are conflicting. Two Japanese groups reported no evidence of TP53 mutations in pheochromocytomas. 29,30 In contrast, a Chinese group reported TP53 mutations in five of six tumors tested. 24 Four of these mutations were in exon 4. Our group reported a series of 22 pheochromocytomas and 29 MTCs that were screened with four different markers for LOH on 17p. 24 S SCCV analysis of exons 4 through 9 of the TP53 gene was performed in 20 of the pheochromocytomas and in 22 of the MTCs. The expression of p53 was determined by immunohistochemistry in 19 pheochromocytomas and in 17 MTCs, using two different antibodies (D01 and D07) on both frozen and paraffin-embedded tissues. LOH was demonstrated on 17p in 4 of the 22 pheochromocytomas and in none of the MTCs. No mutations were detected in any of the tumors screened by SCCV analysis. Immunohistochemical staining of frozen and paraffin-embedded tumor sections did not show p53 overexpression in any of the tumors examined. These findings indicate that mutations in the TP53 gene are an uncommon event in the tumorigenesis of hereditary and sporadic pheochromocytomas and MTCs.

Pheochromocytomas also occur in neurofibromatosis type 1 (NF1) and von Hippel-Lindau (VHL) disease, both of which are caused by mutations in tumor suppressor genes. NF1 gene expression was decreased or absent in 7 of 20 pheochromocytomas from patients with MEN 2 and sporadic disease. 24 Because NF1 is ubiquitously expressed, its lack of expression indicates that NF1 may play a role in the development or progression of pheochromocytomas from patients who do not have NF1. Because of the extremely large size of the NF1 gene, mutational analysis has not yet been performed. Mutational analysis of the VHL gene in non-VHL pheochromocytomas has not been reported.

There have been no reports of the involvement of DNA repair genes (MLH1, MSH2) in development or progression of pheochromocytomas or MTCs, and replication error or repeats have not been a consistent finding in these tumors (J. F. Moley, unpublished data).
Preventive Surgery for MEN 2A Gene Carriers

Individuals with MEN 2A and FMTC are virtually certain to develop MTC at some point in their lives (usually before age 30 years). Therefore, at-risk family members who are found to have inherited a RET gene mutation are candidates for thyroideectomy, regardless of their stimulated plasma calcitonin levels. In a series from Washington University in St. Louis, Wells et al. reported the performance of preventive surgery in 13 asymptomatic RET mutation carriers. One hundred thirty-two individuals from seven different kindreds affected by MEN 2A were screened. Of the 132 individuals, 48 had an established diagnosis of MEN 2A, and 58 were at 50% risk for inheriting the disease but had no clinical evidence of endocrine neoplasia. Twenty-six unaffected spouses of MEN 2A kindred members served as controls. All individuals were evaluated for the presence of RET gene mutations. PCR- and sequence-based direct mutation analysis of genomic DNA from the 58 individuals at 50% risk for MEN 2A identified 21 individuals who had inherited a RET mutation associated with disease. The other thirty-seven family members had two normal RET alleles. All 26 unaffected control individuals had normal RET alleles. After meeting with genetic counselors, who informed them of the pattern of disease inheritance and the basis for the genetic tests, total thyroideectomy was offered to all 21 individuals who were found to have inherited a RET mutation. The patients ranged in age from 8 to 21 years (mean, 13.2 years). In 12 of the 21 patients (mean age, 12 years; range, 6–21 years), the stimulated plasma calcitonin levels were within normal limits. In the remaining nine patients (mean age, 15.1 years, range, 8–20 years), the stimulated plasma calcitonin levels were elevated.

Of the 12 genetically positive individuals with normal stimulated plasma calcitonin levels, 6 patients (or, in the case of minors, their parents) decided against having an immediate thyroideectomy, for reasons of convenience of timing or because they preferred to wait until calcitonin levels were elevated. Of the nine family members with elevated stimulated plasma calcitonin levels, two wished to delay thyroideectomy for several months for personal reasons. In the remaining 13 individuals (six with normal plasma calcitonin levels and seven with elevated levels), total thyroideectomy, lymph node dissection, and parathyroid autotransplantation were performed. After thyroideectomy and parathyroid autotransplantation, patients were placed on thyroid hormone, calcium, and vitamin D supplementation. Approximately 8 weeks after the operation, the oral calcium and vitamin D were stopped. Two weeks after the oral calcium and vitamin D replacement were stopped, the serum calcium concentration was within the normal range in each patient. Of the seven patients whose preoperative plasma calcitonin levels were elevated, each had microscopic evidence of MTC on histologic examination. Two of the seven had macroscopic disease. Of the six patients with normal preoperative plasma calcitonin levels, macroscopic MTC (n = 1), microscopic MTC (n = 2), or C-cell hyperplasia only (n = 3) was evident. A total of 212 lymph nodes were resected from the central zone of the neck (14.5% per patient), none of which was found, on histologic examination, to contain metastases. In each of the 13 patients, the stimulated plasma calcitonin levels were normal after total thyroideectomy.

Lips et al. in a series from the Netherlands, identified 14 young members of families affected by MEN 2A who had normal calcitonin testing but who were found to be MEN2A gene carriers by DNA testing. Thyroideectomy was performed on 8 of these 14, and foci of MTC were identified in all 8.

In a later report of preventive thyroideectomies in RET mutation carriers, Wells et al. reported on a series of 49 children with MEN 2A and MEN 2B. In this series, 14 children had a prophylactic thyroideectomy based on genetic testing. The average age of the children at the time of surgery was 10.5 years. Postoperative calcitonin levels were all undetectable, and no evidence of recurrent MTC was found during a mean follow-up of 1.3 years. In an interim report of 3-year follow-up of the earliest group of 18 patients, no recurrence of disease was noted.

The finding of carcinoma in the thyroid glands of many of these young patients with normal stimulated calcitonin testing indicates that the operation was therapeutic, not prophylactic. There is some urgency, therefore, to applying this genetic test to other at-risk individuals and performing thyroideectomy on those who test positive genetically. The ideal age for performance of thyroideectomy in those patients found to be genetically positive has not been determined unequivocally. It is reasonable to perform surgery in 6-year-old patients with MEN 2A and FMTC. Patients with MEN 2B should undergo thyroideectomy during infancy, because of the aggressiveness and earlier age of onset of MTC in these patients. Patient follow-up over the next decades will determine whether there is a significant rate of recurrence after preventive thyroideectomy. At present, it is advisable to follow up these patients with stimulated plasma calcitonin levels every 1 to 2 years. These patients must also continue to be followed for the development of pheochromocytomas and HPT.

MOLECULAR PATHOGENESIS OF SPORADIC THYROID NEOPLASMS

The thyroid follicular cell is highly differentiated, with the ability to concentrate iodide and synthesize thyroglobulin. Thyroid-stimulating hormone (TSH) is the major regulator of differentiated function of follicular cells and also functions as a growth factor for follicular cells via a cyclic adenosine monophosphate–mediated signal transduction pathway. In addition, thyroid cell growth and proliferation are influenced by a variety of growth factors and cytokines, as well as by the amount of iodine in the diet. Presumably, a host of genetic and environmental factors may result in unregulated growth or loss of differentiated function and confer a proliferative advantage to certain follicular cells, resulting in nodule formation.

Progression of benign adenomatous nodules to differentiated carcinoma is speculative at present, but good evidence exists for the development of anaplastic carcinomas from well-differentiated tumors. A schematic model of the proposed events in thyroid follicular cell tumorigenesis is shown in Figure 38.1-5.

FIGURE 38.1-5. Flow diagram of proven and postulated events in thyroid follicular cell tumorigenesis. Mutations in the RAS oncogene are believed to be early events in the genesis of follicular neoplasms. Activation of the RET and TRK receptor tyrosine kinases is specific to papillary thyroid carcinomas. The association of mutations in the TP53 tumor suppressor gene with undifferentiated thyroid tumors suggests that mutations in TP53 are a critical event in the progression of follicular carcinoma to anaplastic carcinoma.

EPIDEMIOLOGIC AND GENETIC FACTORS ASSOCIATED WITH THYROID NEOPLASIA

Papillary thyroid carcinoma accounts for 85% of differentiated thyroid carcinomas in iodine-sufficient countries. In areas of iodine deficiency or endemic goiter, an overall increased incidence of thyroid cancer is noted, attributable to a higher proportion of follicular carcinomas and anaplastic thyroid carcinomas (which often arise from preexisting follicular carcinomas). The incidence of thyroid neoplasia is also increased in certain hereditary syndromes, including familial adenomatous polyposis coli, Cowden's disease, and MEN 1. Exposure to external radiation in childhood is a strong risk factor for the subsequent development of benign and malignant thyroid nodules. Point mutations of K-RAS have been detected in 60% of radiation-related thyroid tumors.

FOLLICULAR ADENOMAS

A local proliferative advantage may be provided to a thyroid follicular cell by genetic mutational events, environmental factors, or the local influence of cytokines or growth factors. Clonal expansion of cells with a growth advantage leads to nodule formation.

Mutations in all three members of the RAS oncogene family (K-RAS, N-RAS, and H-RAS) have been detected in thyroid neoplasms. RAS mutations are detected with equal frequency in benign and malignant thyroid neoplasms and are believed to represent an early event in follicular cell tumorigenesis. RAS mutations occur predominantly in follicular thyroid carcinomas, with most of the mutations occurring at codon 61 of H-RAS and N-RAS. By contrast, RAS mutations are a rare event in papillary thyroid carcinomas. It appears that RAS mutations are not sufficient for transformation of the thyroid cell; additional genetic events are required. In
cooperation with other oncogenes. Transformation of thyroid cells in vitro with mutant RAS is associated with loss of differentiation, including decreased iodide uptake and expression of thyroid peroxidase.

Mutational events affecting receptors or intermediates along the adenylate cyclase–cyclic adenosine monophosphate signal transduction pathway may contribute to the formation of hyperfunctioning adenomas. A subset of hyperfunctioning adenomas has been shown to harbor somatic mutations in the TSH receptor (TSHR) that result in constitutive activation of downstream events. Mutations in the G protein intracellular mediator of adenylate cyclase (Gβγ) have been detected in 25% of hyperfunctioning thyroid nodules. Therefore, a unifying molecular theme in the pathogenesis of hyperfunctioning nodules is inappropriate activation of the TSH signal transduction pathway, which is a result of specific gene mutations altering a key mediator of an otherwise well-balanced cascade.

Finally, deletion of chromosomal sequences from the 11q13 region has been demonstrated in 14% of follicular adenomas, suggesting that inactivation of a tumor suppressor gene in this region may play a role in follicular-cell tumorigenesis in a subset of tumors.

**PAPILLARY THYROID CARCINOMA**

Activation of receptor tyrosine kinases (RET/PTC, NTRK1, MET), whether by chromosomal rearrangement or gene amplification, is associated with the transformation of follicular cells to papillary thyroid carcinoma. The RET protooncogene was first discovered based on its ability to transform mouse NIH 3T3 fibroblasts in culture. The transforming RET sequences first identified represented a rearrangement of RET that occurred in vitro during the transfection assay. Fusco et al. subsequently demonstrated that DNAs from 25% of papillary carcinomas or their lymph node metastases also were positive in transfection assays. The transforming sequences in papillary carcinomas, originally believed to be a unique oncogene termed PTC (for papillary thyroid carcinoma), were shown to represent in vivo chromosomal rearrangements that resulted in the juxtaposition of sequences encoding the intracellular tyrosine kinase domain of RET with 5′ sequences from one of three unrelated genes. The most frequent form of activated RET/PTC results from a paracentric inversion of chromosome 10q, which in turn incites the gene fusion of D10S170 (H4) sequences with the catalytic domain of RET (Fig. 38.1–4). The frequency of RET rearrangements in papillary carcinomas may be as high as 33%, but a lower frequency has been found in other studies, perhaps reflecting either racial or environmental factors influencing thyroid tumorigenesis in different geographic regions.

**FIGURE 38.1-6.** Chromosome 10q inversion in papillary thyroid carcinoma. A: Two representative chromosome 10 homologues from tumor cells of patients 1 and 2 showing inv(10)(q11.2q21) (arrow). B: Schematic view of the paracentric inversion of chromosome 10q generating the transforming sequence RET/PTC. (From ref. 116, with permission.)

Activation of NTRK1 (tropomyosin receptor kinase), which encodes a cell surface receptor for nerve growth factor, has also been detected in some papillary carcinomas. The NTRK1 oncogene is generated by a chromosomal rearrangement that juxtaposes the tyrosine kinase domain of NTRK1 and the 5′ region of the TPR gene, both mapping to chromosome 1q23-24. Finally, the MET oncogene, which also encodes a receptor tyrosine kinase, is amplified and overexpressed in 70% of papillary and poorly differentiated carcinomas but in only 25% of follicular carcinomas. Activation of MET by amplification and the presence of a rearranged, activated form of RET/PTC have been suggested as predictors of aggressive biologic behavior and poor prognosis in papillary carcinomas. However, because of the generally excellent prognosis of these tumors, larger studies will be required to confirm these observations.

Activation of receptor tyrosine kinases by the common mechanism of gene rearrangement that brings the tyrosine kinase domain under the control of inappropriate upstream regulators derived from any of several “activating genes” appears to be specific for the transformation of follicular cells into papillary thyroid carcinoma.

**FOLLICULAR THYROID CARCINOMA**

Numerous chromosomal deletions have been detected in thyroid neoplasms, suggesting a role for multiple tumor suppressor genes in the initiation or progression of these tumors. Although sporadic follicular thyroid tumors exhibit allelic chromosomal loss of chromosome 11q13 sequences with increased frequency, one study failed to find accompanying mutations in the MEN1 gene in the remaining normal allele, suggesting that a tumor suppressor gene other than MEN1 might be involved in tumorigenesis of these neoplasms. In addition to the 11q13 deletions described in follicular adenomas, Hermann et al. have presented evidence for chromosome 3p deletions specific to follicular carcinomas and proposed that inactivation of a tumor suppressor gene on chromosome 3p is important in the progression from follicular adenoma to carcinoma.

**ANAPLASTIC THYROID CARCINOMA**

Point mutations in the TP53 tumor suppressor gene are frequent in anaplastic thyroid carcinomas but not in differentiated thyroid tumors. This suggests that the TP53 mutation is a critical event in the progression of follicular carcinoma to anaplastic carcinoma. Wild-type TP53 encodes a nuclear phosphoprotein that functions as a transcriptional regulator believed to influence cell-cycle arrest or programmed cell death in response to genetic damage. Disruption of this protective function appears to be relevant to the progression of thyroid neoplasms to an aggressive, undifferentiated phenotype. Codons 273, 282, 248, and 277 are hot spots for TP53 mutation in anaplastic thyroid carcinoma.

**MEDULLARY THYROID CARCINOMA**

The molecular genetic alterations associated with sporadic medullary carcinoma of the thyroid were discussed earlier in other RET Genotype-Phenotype Correlations.

**GENETIC ABNORMALITIES IN PARATHYROID NEOPLASMS**

**BENIGN PARATHYROID NEOPLASMS**

Neoplasms of the parathyroid glands are almost always benign and occur with increased frequency in postmenopausal women, after neck irradiation, or as a component of several distinct familial syndromes. Benign parathyroid adenomas in patients with primary HPT have a proliferative defect (increase in cellular mass) as well as a defect in regulating parathyroid hormone (PTH) release in response to the extracellular calcium concentration (set-point abnormality). In different parathyroid tumors, at least three specific genetic defects have been uncovered, including activation of an oncogene, inactivation of the MEN1 tumor suppressor gene, and mutations in the cell surface calcium-sensing receptor.

**MUTATIONS IN THE MEN1 GENE AND ROLE OF OTHER TUMOR SUPPRESSOR GENES**
Patients with MEN 1 inherit one mutated copy of the MEN1 gene in the germline and therefore require only one chance additional somatic event (deletion, point mutation) to result in the loss of the remaining functional copy of the gene within an individual parathyroid cell. Presumably, the relatively likely combined occurrence of these genetic events leads to the asynchronous development of multiglandular parathyroid neoplasms (parathyroid hyperplasia) in affected individuals. LOH for markers within the MEN1 gene region has been demonstrated not only in MEN 1–related parathyroid tumors but also in approximately 30% of sporadic parathyroid adenomas. As previously suspected from studies of chromosome 11q13 LOH in DNA from sporadic parathyroid adenomas, loss of MEN1 gene function now is known to be responsible for a subset of the parathyroid adenomas in patients with sporadic primary HPT. In this subset, the occurrence of a sporadic parathyroid adenoma presumably requires the chance occurrence of two somatic inactivating events (one involving each homologous copy of the MEN1 gene).

A study by Heppner et al. identified somatic mutations in one allele of the MEN1 gene in tumor DNA from 7 of 33 parathyroid adenomas. In each of these tumors, a chromosome deletion was detected that eliminated the remaining wild-type copy of the MEN1 gene in tumor DNA. Farberno et al. screened 45 sporadic adenomas from 40 patients with nonfamilial HPT by LOH and SSCP analysis. LOH for chromosome 11q13 was present in 13 (29%) of the tumors and, in six of these cases, somatic mutation was detected in the remaining copy of the MEN1 gene. These findings suggest that a subset of sporadic parathyroid adenomas is caused by a combination of somatic genetic events within a parathyroid cell that inactivate both copies of the MEN1 tumor suppressor gene.

ACTIVATION OF THE PRAD1 PROTOONCOGENE BY CHROMOSOMAL GENE REARRANGEMENT

In a small subset of parathyroid adenomas (approximately 5%), a pericentromeric inversion of chromosome 11 has been detected that results in a gene rearrangement involving the PTH gene on 11p15 and the parathyroid adenoma 1 (PRAD1) oncogene or cyclin D1 on 11q13. As a consequence of the breakpoint and rejoicing in 11q13, the PTH transcriptional regulatory sequences and its noncoding exon 1 are placed immediately upstream of the PRAD1 protooncogene intact promoter and its five exons (Fig. 38.1-7). This rearrangement results in inappropriate or unregulated expression of PRAD1 in response to the parathyroid tissue–specific transcriptional regulatory elements of the PTH gene. It has been suggested that the subset of patients with the PRAD1 chromosomal rearrangement tend to have larger tumors and are more often symptomatic than are other patients with this disease.

OTHER GENETIC LOCI IMPLICATED IN FAMILIAL HYPERCALCEMIC SYNDROMES

FAMILIAL BENIGN HYPERCALCEMIA

Familial benign hypercalcemia (hypocalciuric hypercalcemia) is a dominantly inherited condition characterized by mild hypercalcemia, low urinary calcium excretion, and the absence of symptoms or the complications of hypercalcemia. The features of familial benign hypercalcemia are important to recognize and distinguish from other hypercalcemic disorders, because surgery fails to result in correction of the calcium level.

Pollak et al. demonstrated that mutations in the human calcium-sensing receptor gene are associated with familial benign hypocalcaemia as well as neonatal severe HPT (NSHPT). Parathyroid cells from patients with familial benign hypercalcemia are characterized by an abnormally increased set point for extracellular calcium.

The germline mutations that are associated with familial benign hypercalcemia are heterozygous, inactivating mutations in the calcium-sensing receptor gene. The reported mutations include point mutations, nonsense mutations, or insertions that are postulated to result in varying degrees of loss of the receptor's calcium-sensing function.

NEONATAL SEVERE HYPERPARATHYROIDISM

NSHPT is characterized by severe hypercalcemia, failure to thrive, dehydration, pathologic fractures and rib cage deformities, respiratory distress, and hypotonia in the newborn. The disorder usually requires urgent total parathyroidectomy in the first few weeks of life, although some have achieved a favorable outcome with intensive medical management.

In some cases, NSHPT results from homozygous mutations (mutations on both homologous alleles) that cause loss of function of the calcium-sensing receptor gene.

HEREDITARY HYPERPARATHYROIDISM–JAW TUMOR SYNDROME

The autosomal dominant inheritance of HPT without any associated features and without any apparent association to the MEN syndromes has been described in several families. HPT–jaw tumor syndrome (HPT-JT) is recognized as a distinct syndrome characterized by the autosomal dominant inheritance of recurrent parathyroid adenomas, fibrousosseus jaw tumors, Wilms' tumor, and parathyroid carcinoma. The onset of hypercalcemia typically occurs in childhood or the second decade of life. The association may not be recognized in many cases because the jaw lesions occur asynchronously in relation to the parathyroid tumors and may occur in some patients without HPT. The parathyroid tumors may be single or multiple but have a tendency toward recurrence after subtotal parathyroidectomy. The parathyroid adenomas in the familial HPT-JT syndrome often are cystic, a finding that occasionally is noted in primary sporadic HPT. The specific gene responsible for the HPT-JT syndrome remains to be identified.

PARATHYROID CARCINOMA

Molecular defects with a possible role in progression to the malignant phenotype have also been sought in tumor DNA from parathyroid carcinomas. Although one study failed to detect evidence of mutations in exons 5, 7, and 8 of the TP53 gene in parathyroid carcinomas, another study reported allelic loss of TP53 in two of six informative parathyroid carcinomas. None of 20 informative parathyroid adenomas exhibited deletions of TP53. Most recently, the retinoblastoma tumor suppressor gene has been shown to be inactivated in most parathyroid carcinomas but not in adenomas.

GENETIC ABNORMALITIES IN ADRENAL NEOPLASMS
SPORADIC PHEOCHROMOCYTOMAS

The molecular genetic alterations associated with sporadic pheochromocytomas were discussed earlier in this chapter.

FAMILIAL PHEOCHROMOCYTOMAS ARISING IN PATIENTS WITH VON HIPPEL-LINDAU SYNDROME AND NEUROFIBROMATOSIS TYPE 1

Pheochromocytomas occur in association with the VHL and NF1 syndromes. VHL syndrome is characterized by the development of retinal, cerebellar, and spinal hemangioblastomas, pheochromocytomas, renal cysts, renal carcinomas, pheochromocytomas, neuroendocrine tumors of the pancreas, epididymal cysts, and endolymphatic sac tumors. The original mapping of the VHL gene by positional cloning to chromosome 3p was reported in 1993. The VHL tumor suppressor gene encodes a protein that regulates the transcription of DNA to mRNA by RNA polymerase II. Clinical heterogeneity exists in patients with the VHL syndrome. In type 1, pheochromocytomas do not occur. Pheochromocytomas are associated with type 2a, but renal cell carcinoma do not form. In type 2b, both pheochromocytomas and renal cell carcinomas develop. The preceding classification has been related also to apparent genotype-phenotype correlations associated with mutations in the VHL gene.

Mutations in the tumor suppressor gene for NF1 on chromosome 17q were identified in 1990. Pheochromocytomas occur in approximately 1% to 2% of patients with NF1. Bilateral tumors occur with increased frequency compared with sporadic cases of pheochromocytomas.

ADRENOCORTICAL ADENOMAS AND CARCINOMAS

Several lines of evidence suggest a role for mutation or loss of the TP53 tumor suppressor gene in adrenal cortical cancers. First, LOH for markers from 17p has been consistently demonstrated in adrenal cortical cancers but not in benign adenocortical adenomas or hyperplasia. Frequent LOH has also been detected for markers on chromosome 11p and 13q. It is of interest to note that adrenocortical carcinomas occur with increased frequency in patients with the Li-Fraumeni syndrome, who have been shown to harbor germline mutations in TP53, and in patients with the Beckwith-Wiedemann syndrome, which is associated with a defect on chromosome 11p15. Sequence analysis has also demonstrated point mutations in the TP53 gene in adrenal carcinomas, but not in adrenal adenomas.

In one study of 35 adrenocortical lesions (six hyperplasias, 19 adenomas, ten adenocortical carcinomas), LOH at 11q13 was detected in 31% of the tumors analyzed. The frequency of LOH for this region was significantly greater in adrenocortical carcinomas (60%) than in benign lesions (11%). However, inactivating mutations of the MEN1 gene were demonstrated in almost none of the tumors with LOH at 11q13. The authors concluded that the MEN1 gene appears not to play a significant role in the development of benign or malignant adrenocortical neoplasms.

SUMMARY

A variety of genetic abnormalities in both oncogenes and tumor suppressor genes have been identified in endocrine tumors. The study of tumors developing in the inherited endocrine cancer syndromes has provided valuable insight into genetic events that likely play a role in the genesis of sporadic tumors developing in the same endocrine tissues. The advent of direct DNA testing for germline mutations in the RET proto-oncogene that are responsible for the MEN 2 syndromes has made possible early thyroidec- tomy at a time when hereditary MTC is likely occult and curable. The identification of germline mutations in the MEN1 gene will allow direct genetic testing and an enhanced understanding of the mechanisms of tumorigenesis of related endocrine tumors.

CHAPTER REFERENCES

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Introduction

Cancers of the endocrine glands or organs are rare, as they will account for only 1.5% of the estimated 1.22 million new cases of non–skin cancer and 0.21% of the estimated 563,100 cancer deaths in the United States in 1999. Thyroid cancer is overwhelmingly the most common type of endocrine malignancy, accounting for the majority of the deaths due to endocrine cancers. It was estimated that in 1999 there would be 18,100 new cases of thyroid cancer (more than 90% of the total new endocrine cancers) and 1400 deaths due to thyroid cancer, which is 60% of the total deaths due to endocrine malignancies (Table 38.2-1). Compared to the number of thyroid cancers, there are approximately 800 cases of endocrine pancreas tumors (not all malignant), 550 adrenal cancers, 130 pituitary gland cancers, and 65 parathyroid gland cancers. The discrepancy between the total number of cases of all endocrine cancers arising in the thyroid (91%) and the total proportion of endocrine cancer deaths (60%) reflects the relatively indolent nature and long-term survival associated with thyroid malignancies.

TABLE 38.2-1. Incidence and Proportion of All Endocrine Cancers and Relative Proportions of Different Primary Thyroid Cancer Subtypes

With the broad category of thyroid cancers, there are many types, each with a distinctive epidemiology, natural history, treatment, and prognosis. The general categories of thyroid cancer are well-differentiated malignancies, anaplastic cancer, medullary thyroid cancer (MTC), and other unusual cancers, such as lymphoma, sarcoma, and other rare malignancies. The normal thyroid is composed histologically of two main parenchymal cell types. Follicular cells line the colloid follicles, concentrate iodine, and are involved in the production of thyroid hormone. These cells give rise to well-differentiated cancers and, almost certainly, anaplastic thyroid cancer (ATC). The second cell type is the parafollicular or C cell, which produces calcitonin and is the cell of origin for MTC. Stromal and immune cells of the thyroid are responsible for sarcoma and lymphoma, respectively. Of the 18,100 new cases of thyroid cancer each year, approximately 90% of malignant thyroid nodules are well-differentiated cancers, 5% to 9% are MTC, 1% to 2% are anaplastic cancers, 1% to 3% are lymphoma, and fewer than 1% are sarcoma and other rare tumors.

Within the category of well-differentiated thyroid cancers, there are various histologic subtypes. These descriptive subgroupings have evolved since the 1980s with an improved understanding of the biology of these different types. Initial categories included papillary, follicular, and mixed tumor with variable areas of both papillary and follicular histology. Several studies have documented that these mixed tumors with any area of papillary features have the same natural history and prognosis as papillary thyroid cancer without follicular features. This category of mixed papillary and follicular carcinoma should be grouped with papillary carcinoma; even those that are composed entirely of follicles should be included (diagnosed as the follicular variant of papillary carcinoma). The major cytologic feature shared by all members of this group, regardless of the histologic pattern, is the characteristic nucleus. A third category of lesions grouped with differentiated thyroid carcinoma is the Hurthle cell or oncocytic carcinoma. Although there are controversies about whether Hurthle cell neoplasms can behave in a benign fashion, most authors now accept the concept of benign and malignant lesions with this cytoLOGY. The clinical behavior of these lesions is somewhat more aggressive than usual follicular carcinomas, and some authors prefer to include these lesions in the intermediate malignancy group. The distribution of well-differentiated thyroid cancer subgroups in some reports shows that 80% to 85% are papillary, with 10% to 15% of cases being follicular and 3% to 5% Hurthle cell carcinomas. These published figures may not reflect adequate pathologic recognition of the follicular variant of papillary carcinoma, and true follicular carcinoma may represent 5% or fewer of well-differentiated thyroid cancers in countries with iodine-sufficient diets. Therefore, as 90% of all thyroid cancers are well-differentiated and 85% to 90% of all well-differentiated tumors are papillary tumors, papillary thyroid cancer accounts for 75% to 80% of all thyroid cancers.

This chapter is organized to present the key clinical aspects of well-differentiated thyroid cancers, anaplastic cancers, MTCs, thyroid lymphoma, and secondary thyroid malignancies. As the vast majority of thyroid cancers present as thyroid nodules, yet only a minority of all thyroid nodules are malignant, a general discussion of the incidence, evaluation, and management of thyroid nodules precedes discussion of specific clinical conditions.

Thyroid Nodules

The prevalence of thyroid nodules depends on the population under study; gender, age, and history of exposure to ionizing radiation strongly influence the results of various large studies, as does the method by which the nodules are being detected (physical examination, ultrasonography, or pathology). There is clearly an age-dependent increase in thyroid nodules; in one pathologic study, up to 90% of women older than 70 years and 60% of men older than 80 years had nodular goiter. All studies show that women develop nodules more frequently than men, although reports of the female to male ratio vary from 1.2:1 to 4.3:1. An increased tendency to develop thyroid nodules is demonstrated in groups exposed to ionizing radiation, especially during childhood. In a study at the Michael Reese Hospital, 38.4% of patients who received radiation before age 16 years developed palpable thyroid nodules. In patients with Hodgkin’s disease treated with mantle radiation, 3% developed thyroid nodules....

Most thyroid nodules are found in asymptomatic patients either during routine physical examination of the neck or because the patient notices a mass in the neck. By...
obtaining information from the history and physical examination, one assesses the risk of malignancy in that individual. In general, there is a 5% to 10% chance of malignancy in all thyroid nodules for the total population; however, men and patients at the extremes of age are at higher risk for malignancy. Nodules found in a patient with a history of childhood neck irradiation carry a 33% to 37% chance of malignancy. The presence of a solitary nodule is of greater concern than a thyroid with multiple nodules; however, a dominante nodule or a nodule that changes size in the setting of a multinodular goiter should be investigated to exclude carcinoma. Patients with Graves' disease who develop a nodule may have a higher risk of cancer. Whether the co-occurrence of Graves' disease affects the aggressiveness of the thyroid carcinoma is a topic of controversy. However, the occurrence of carcinoma in autonomously functioning nodules is extremely rare.

Although not specific for malignancy, a history of rapid increase in size, dyspnea, dysphagia, hoarseness, and the development of a Horner's syndrome are worrisome symptoms. Tender nodules are more often associated with thyroiditis and are likely to be benign. A family history of thyroid cancer or pheochromocytoma should suggest MTC in the setting of multiple endocrine neoplasia type 2a (MEN 2A) or MEN 2B. Other inherited disorders to be aware of are Gardner's syndrome and Cowden's disease, both of which are associated with benign and malignant thyroid neoplasms. On examination of the neck, attention to the firmness, mobility, and size of the nodules, their adherence to surrounding structures, and the presence of adenopathy are important clues to the presence of carcinoma. However, these features, with the exception of cervical lymphadenopathy, lack specificity for malignancy.

Thyroid function testing should be performed to identify underlying thyroid pathology and not to differentiate benign from malignant nodules. Subclinical hyperthyroidism, sometimes seen only as a suppressed thyroid-stimulating hormone (TSH), may be secondary to an autonomously functioning nodule. In this case, one determines whether the nodule is functional with a radionuclide scan by iodine uptake. Tests of serum thyroglobulin (Tg) levels are not helpful in distinguishing benign from malignant thyroid nodules. Routine measurement of serum calcitonin may be useful to identify patients with sporadic medullary carcinoma of the thyroid preoperatively; however, the cost-effectiveness of this practice requires further evaluation. The majority of both benign and malignant thyroid nodules are hypofunctional when compared to normally functioning thyroid tissue; thus, the finding of a "cold nodule" on ¹²³I or ⁹⁹Tc scanning is nonspecific. Radionuclide scans are also helpful in determining the functional status of nodules in patients with multinodular thyroid disease to focus a biopsy on cold nodules. A hyperfunctioning or hot nodule is rarely malignant in an adult.

High-resolution ultrasonography is a useful adjunct to the clinical examination for size assessment of nodules, for the detection of multiple nodules not discerned by palpation, and for assisting in fine-needle aspiration biopsy (FNAB) of nodules. Despite advances in technology allowing more sensitive detection of blood flow in thyroid pathology, differences in echogenicity or vascularity cannot distinguish benign from malignant lesions. Ultrasonography identifies whether a lesion is cystic or solid, and the vast majority of cystic lesions are benign. A more cost-effective method to identify a cyst is fine-needle aspiration (FNA) with return of fluid and disappearance of the nodule after aspiration. Cysts larger than 4 cm in size and having a partially solid component and those that recur after three aspirations may warrant biopsy, as these conditions are more likely to be associated with malignancy.

The single most important study in the evaluation of thyroid nodules is the FNAB. The impact this procedure has had on clinical practice is reflected by a reduction of the total number of thyroid surgeries performed, a greater proportion of malignancies removed at surgery, and an overall reduction in the cost of managing patients with nodules. The accuracy of cytologic diagnosis from fine-needle biopsy ranges from 70% to 97% and is highly dependent on the skill of the person performing the biopsy and that of the cytopathologist interpreting it. The results of FNAB are most commonly divided into the following categories: benign or negative (colloid nodule or hyperplastic nodule), indeterminate (all follicular neoplasms, including those with Hurthle cell changes), suspicious or malignant (papillary, anaplastic, medullary, and lymphoma), and insufficient sample. Reviews of this technique provide insight into the results typically obtained at the time of fine-needle biopsy of the nodules: 70% are classified as benign (range, 53% to 90%), 4.0% as malignant (range, 1% to 10%), 10% as suspicious or indeterminate (range, 5% to 23%), and 17% as insufficient sample (range, 15% to 20%).

The malignant potential of follicular neoplasms cannot be determined by cytologic evaluation; thus, the biopsies from all such lesions are generally classified as suspicious or indeterminate, and most come to surgical resection. The cells from follicular adenomas and follicular carcinomas appear identical; only by identifying capsular or vascular invasion can cancer be diagnosed. Specimens with predominantly Hurthle cells must be treated in the same fashion; however, extensive Hurthle cell changes can be seen in Hashimoto's thyroiditis. Malignancy is found in 10% to 20% of follicular nodules that are classified as indeterminate biopsy.

Attempts to develop more discriminating cytologic subclassifications to improve the yield of malignancy found at surgery have not proven highly successful, nor are they easily adopted at other institutions. A new technique to improve the sensitivity of FNA in this situation has been to perform polymerase chain reaction analysis for Thyroglobulin. However, the occurrence of carcinoma in autonomously functioning nodules is extremely rare. False-positive results for malignancy occur in 3% to 6% of all biopsies. Thyroglobulin levels are not helpful in distinguishing benign from malignant lesions. The cytologic features of Hashimoto's thyroiditis frequently lead to these false-positive interpretations. With experienced cytopathologists, this false-positive rate should decrease to less than 1%.

Benign thyroid nodules can be followed up carefully by routine physical examination or, more precisely, by ultrasonography and do not generally require repeat biopsy. Thyroxine suppression therapy is widely used; however, the cost-effectiveness of this practice requires further evaluation. Specifically, median age at diagnosis in white women is between 40 and 41 years, whereas for white men, it is 44 to 45 years for papillary carcinoma. For follicular thyroid carcinoma, the median age at diagnosis is 48 for white women as compared to 53 for white men. Well-differentiated thyroid cancer has a greater incidence in whites than in blacks of both genders. The relative proportion of age-adjusted incidence rates is slightly more than twofold higher for whites. One significant difference in the incidence in terms of race is that the proportion of well-differentiated thyroid carcinomas that are follicular is increased greatly in blacks as compared to whites. It is reported that follicular carcinoma accounts for 15% of all well-differentiated tumors in whites as compared to 34% in blacks.

WELL-DIFFERENTIATED THYROID CARCINOMA

DEMOGRAPHICS AND EPIDEMIOLOGY

The incidence of both papillary and follicular thyroid carcinomas in terms of gender distribution is similar, with approximately a 2.5-fold excess in favor of female individuals as compared to male individuals (Table 38.2-2). The median age at diagnosis is earlier in women than in men for both papillary and follicular subtypes and tends to be earlier for papillary cancer as compared to follicular cancer in either gender (see Table 38.2-2). Specifically, median age at diagnosis in white women is between 40 and 41 years, whereas for white men, it is 44 to 45 years for papillary carcinoma. For follicular thyroid carcinoma, the median age at diagnosis is 48 for white women as compared to 53 for white men. Well-differentiated thyroid cancer has a greater incidence in whites than in blacks of both genders. The relative proportion of age-adjusted incidence rates is slightly more than twofold higher for whites. One significant difference in the incidence of both papillary and follicular thyroid carcinomas is that follicular is increased greatly in blacks as compared to whites. It is reported that follicular carcinoma accounts for 15% of all well-differentiated tumors in whites as compared to 34% in blacks.
ETIOLOGY

Radiation exposure to the thyroid gland is the only risk factor known definitively to increase the incidence of well-differentiated thyroid cancer. Thyroid exposure to radiation can occur in two ways: from external sources or from ingestion of radioactive material. Data regarding external exposure to the thyroid comes primarily from two sources. One is medically administered external-beam irradiation, and the second is environmental exposure, previously related to nuclear weapons attacks or weapons testing and, more recently, from nuclear power plant accidents. Internal exposure occurs by ingestion of radioisotopes of iodine that concentrate in the thyroid gland from either medical treatment with radioactive iodine or by ingestion of these radioisotopes from the fallout from nuclear weapons explosions or power plant accidents. The relative risks of radiation exposure from these different sources has been well studied, and variables, such as age at exposure, radiation dose, and latent period to developing cancers, have been defined. However, radiation accounts for only a small portion of the total annual cases of well-differentiated thyroid cancer. Other potential factors that may predispose to thyroid neoplasms include diet (particularly content of iodine), effects of steroid hormones, and other occupational exposures.

Case-control studies, as well as detailed institutional reviews of large populations of patients undergoing childhood irradiation, show that there is an inverse relationship between increased risk of thyroid cancer and age of exposure to radiation. Relative risk is also linearly related to exposure dose, at least up to 2000 rads. The latent period after exposure is at least 3 to 5 years, and there is no apparent drop-off in the increased risk even after 40 years after the radiation exposure. One of the best analyzed databases regarding childhood radiation for medical purposes comes from Schneider et al. at the University of Chicago. They have intensively analyzed more than 3000 patients who were irradiated between 1939 and 1962. More than one-third of these patients developed thyroid nodules, and 318 patients were documented to have thyroid cancer. The large populations studied by Schneider et al. showed that increased relative risk of thyroid carcinoma was low and thyroid cancers were rare between 5 and 10 years after radiation exposure. The majority of cases occurred between 20 and 40 years after exposure. However, even after 40 years, the relative risk compared to a nonirradiated population was still increased. For these reasons, the large cohort of patients who underwent childhood irradiation for benign medical conditions between 1920 and 1960 are now between the ages of 40 and 80, and this population still has an increased risk of developing thyroid carcinoma as compared to nonirradiated patients.

Although the use of radiation for benign conditions has not been practiced since the 1960s, there is increased use of radiation treatments for neoplastic conditions, including infants, children, and young adults. The majority of this patient population is made up of patients with either Hodkgin's or non-Hodkgin's lymphoma but also includes long-term survivors of Wilms' tumor of the kidneys or neuroblastoma in which there is some scatter to the thyroid gland. The young age at treatment for neuroblastoma and Wilms' tumor (mean age, 2 and 3 years, respectively) and the relatively high-dose of thyroid exposure (660 rads and 310 rads, respectively) has led to increased relative risk of 350 for neuroblastoma patients and 132 for survivors in relative risks for the development of thyroid cancer. Relative risks between 16 and 80 have been reported in this patient population of adolescents and young adults treated for lymphoma. In the adult patient population treated with therapeutic radiation for malignancies, there is a drop-off in risk reflecting the importance of age at exposure. A large study of more than 150,000 women treated with radiation for cervical cancer had an estimated thyroid exposure of 11 rads, with a relative risk of 2.35, compared to nonirradiated age-matched controls.

A second type of radiation exposure to the thyroid gland is via ingestion of radioisotopes that concentrate in the thyroid. These isotopes come from two sources: medical administration either for diagnostic or therapeutic purposes using radioactive iodine, and environmental exposure to fallout from nuclear weapons or nuclear accidents. The most common exposure is due to 131I administered for diagnostic thyroid scans. A typical nuclear medicine study exposes the thyroid to the equivalent of approximately 50 rads of external-beam radiation exposure. A large study of more than 35,000 diagnostic scans between 1951 and 1969 showed a very minimal increase in the number of thyroid cancers, with 50 actual cases versus 39.4 cases predicted. A second, more significant medical exposure is therapeutic 131I administered for ablation of thyroid tissue, with the equivalent of 6000 to 10,000 mL to treat Graves' disease. Despite this high radiation dose, there is a standardized increased incidence ratio of only 1.32 for thyroid cancer, as the high-dose 131I most likely destroys the thyroid parenchyma.

A more dangerous type of ingestion of radioisotopes of iodine comes from exposure to nuclear fallout. Data from fallout exposure comes from nuclear weapon–testing sites at the Marshall Islands and Nevada in the 1950s as well as the 1986 nuclear power plant explosion at Chernobyl. The positive results in these studies compared to the lack of risk of the medical use of 131I is most likely due to other high-energy short-lived isotopes, such as 132I and 133I to 131I present in fallout that are more damaging but are not present in radiisotope drugs. An early study completed 4.5 years after the event at Chernobyl suggested no increased risk of thyroid nodules. More recent studies show a steady sequential increase in the diagnosis of pediatric thyroid cancer as early as 3 years and increasing from 5 to now 10 years since the incident. This data reflect the importance of age at exposure, as this increased incidence occurs primarily in children.

The natural history and pathology of radiation-associated thyroid cancer has been well documented in the aforementioned epidemiologic studies. The vast majority of cases have a papillary histology, and these behave in the same way as nonradiation-associated papillary cancers.

Although the data relating radiation exposure of the thyroid gland and subsequent development of carcinoma are definitive, the majority of patients who developed well-differentiated thyroid carcinoma have absolutely no history of radiation exposure. A study from the Connecticut Tumor Registry shows that 9% of thyroid cancer could be related to radiation exposure, meaning 91% of cases have no identifiable risk factor. Other factors, including dietary influences, sex hormones, environmental exposures, or increased genetic susceptibility, have been studied, with very mixed results and no clear associations. Dietary influences have primarily focused on the level of iodine in the diet. Iodine-deficient diets or diets that include a large intake of vegetables from the crucifer family (which block iodine uptake) may lead to increased TSH levels and are considered goitrogenic, with a modest increase in follicular cancers. Increased iodine intake due to shellfish occurs in the geographic areas with the highest incidence of predominantly papillary thyroid cancer, such as Iceland, Norway, and Hawaii.

There is no clear familial syndrome or genetic disease associated with the development of well-differentiated thyroid cancer, although one study has suggested a propensity to multifocal well-differentiated thyroid cancer in a small number of families. However, none of the described oncogenes for well-differentiated thyroid cancer (RET, MNG-1, TCO) were found to be involved in evaluation of 56 kindreds. This contrasts with MTC, in which a variety of genetic syndromes now are being defined at the molecular level (see later in Treatment of Familial Medullary Thyroid Cancer and Table 38.2-10).

PATHOLOGY

Thyroid malignancies are derived from either follicular cells (papillary, follicular, Hürthle cell, and anaplastic carcinomas) or C cells (medullary carcinoma, described later in Medullary Thyroid Cancer). The degree of clinical malignancy varies greatly among the types of carcinoma: It is convenient to consider these tumors as falling into three categories with increasing clinical aggressiveness: well-differentiated (papillary carcinoma, follicular carcinoma), intermediate differentiation (Hürthle cell carcinoma, some variants of papillary carcinoma, insular carcinoma), and undifferentiated (anaplastic carcinoma).

Papillary carcinoma constitutes approximately 80% to 85% of malignant epithelial thyroid tumors in developed countries where sufficient iodine is present in the

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**TABLE 38.2-2. Age, Gender Distribution. Proportion of Papillary or Follicular and Extent of Disease at Presentation for Several Institutional Series of Well-Differentiated Thyroid Cancer**
Carcinoma is relatively increased, the majority (65%) still do not have malignant lesions. Well-Differentiated Thyroid Cancer: Surgery malignant lesions detected by FNA should undergo surgical resection. The extent of this resection is controversial and is discussed in detail later in against the goal of avoiding unnecessary surgical procedures for benign pathology. management options include careful observation typically combined with thyroid suppression, alternative or repeat diagnostic studies, or surgical excision. The goal of thyroid. For parathyroid disease or undergoing neck magnetic resonance imaging studies for cervical spine disease may have unappreciated nodular disease within the whom the nodule is not palpable but is diagnosed by imaging studies obtained for other clinical indications. Certain aspects of the clinical history are relevant to the differential diagnosis, including a prior history of radiation exposure (increased mass in the thyroid. Because most patients with well-differentiated thyroid cancer are euthyroid, complaints related to thyroid dysfunction are rare, and thyroid function laryngeal nerve, the trachea, and the esophagus, respectively. Certain variants of papillary carcinoma have been shown to be more aggressive clinically, but these make up a minority of all papillary carcinomas. The more aggressive variants include the so-called tall cell variant, in which the cells are at least twice as long as they are wide the columnar variant, which shows a curious clear cytoplasm; and the diffuse sclerosis variant, which is found more commonly in young individuals and adolescents. This sclerosis variant permeates the thyroid lymphatics and has a 100% incidence of regional lymph node metastases at the time of diagnosis. All these high-risk variants are associated with significant mortality at 5 years, ranging between 25% and 90%.

Well-differentiated thyroid carcinoma is a rare tumor comprising approximately 5% to 10% of thyroid malignancies in nonendemic goiter areas of the world. Before iodine prophylaxis via iodinated salt, follicular carcinoma was much more frequently diagnosed. In addition, the pathologic dictum—that any tumor with a pattern that is 50% or more characteristic of follicular carcinoma should be diagnostically placed in a follicular carcinoma category—has been shown to be incorrect. Indeed, most of the follicular pattern thyroid malignancies represent the follicular variant of papillary carcinoma and share its biological features, natural history, and prognosis. Follicular thyroid carcinoma is unifocal and thickly encapsulated and shows invasion of the capsule or the vessels. Because of the diagnostic confusion, it is difficult to collect statistics about the survival rate or the metastatic potential of true follicular carcinoma. Most studies show that if capsular invasion but not vascular invasion is present, the prognosis is excellent, with 85% to 100% of patients surviving at least 10 years of follow-up.

A variant of follicular neoplasms is the Hurthle cell neoplasm. In 1894, Hurthle described a thyroid cell that was later shown to be the parafollicular C cell. For this reason, the designation of cells and their tumors as Hurthle cells is historically incorrect as these lesions are actually derived from thyroid follicular cells. The preferred pathologic term is oncocytic. However, because a large body of literature exists on the subject of Hurthle cells and Hurthle cell neoplasms, this nomenclature will be used. The Hurthle cell tumor of the thyroid is one of the most controversial lesions in this organ. Initially, all such lesions, despite the histologic features, were considered to be malignant; hence, it was recommended that they all be treated aggressively. However, many studies have evaluated the clinical pathologic features of Hurthle cell tumors and have shown that, on average, only 33% show histologic evidence of malignancy or invasive growth and may metastasize. Hurthle cell tumors that do not demonstrate invasion microscopically behave as adenomas and may be treated conservatively.

Clinical Findings in Well-Differentiated Thyroid Cancer

The typical clinical presentation for a patient with well-differentiated thyroid cancer is development of an asymptomatic thyroid nodule. Other symptoms may infrequently precede or occur simultaneously with development of a nodule, including hoarseness, dyspnea, and dysphagia, reflecting local invasion of the recurrent laryngeal nerve, the trachea, and the esophagus, respectively. A small subset of patients present with palpable cervical lymphadenopathy without an identifiable mass in the thyroid. Because most patients with well-differentiated thyroid cancer are euthyroid, complaints related to thyroid dysfunction are rare, and thyroid function test results tend to be normal. Certain aspects of the clinical history are relevant to the differential diagnosis, including a prior history of radiation exposure (increased risk of papillary cancer), family history (increased risk of familial MTC), and rapid rate of growth of the thyroid nodule (increased likelihood of ATC or thyroid lymphoma), but may also represent a spontaneous hemorrhage into a benign cyst. A second category of patients diagnosed with thyroid nodules consists of those in whom the nodule is not palpable but is diagnosed by imaging studies obtained for other clinical indications. For example, patients undergoing ultrasonography for parathyroid disease or undergoing neck magnetic resonance imaging studies for cervical spine disease may have unappreciated nodular disease within the thyroid.

Any new palpable thyroid nodule or any lesion larger than 1.0 cm identified by neck imaging should be initially assessed by FNAB (described previously in Thyroid Nodules). Nodules smaller than 1.0 cm may be followed intermittently (6 to 12 months) with ultrasonography and should be subjected to biopsy only when the nodule becomes larger than 1.0 cm. Management decisions in these patients are based on the FNA results modified by certain factors of the clinical history. Potential management options include careful observation typically combined with thyroid suppression, alternative or repeat diagnostic studies, or surgical excision. The goal of management of these patients is to avoid missing an enlarging carcinoma that could be morbid to the patients if the disease is not recognized and treated balanced against the goal of avoiding unnecessary surgical procedures for benign pathology. An algorithm of management based on FNA as the initial procedure is shown in Figure 38.2-2. Decisions regarding patient management in four of the five categories of possible results from the FNA are relatively straightforward. Patients with malignant lesions detected by FNA should undergo surgical resection. The extent of this resection is controversial and is discussed in detail later in Treatment of Well-Differentiated Thyroid Cancer, Surgery. Patients with a benign FNA result should be followed up intermittently, and nodules that enlarge should be resubmitted to biopsy. Although common clinical practice is to suppress patients who have benign nodules by FNA using thyroid hormone, objective data that this practice alters the clinical course are lacking. Some investigators argue that patients with a prior history of radiation should have all thyroid lesions surgically resected once they are noted without a biopsy. Although the proportion of these patients with carcinoma is relatively increased, the majority (65%) still do not have malignant lesions.
Patients with an inadequate biopsy should submit to a repeat biopsy, as one-half of the time this provides definitive results. Often, patients with small lesions that are not discrete and are difficult to palpate as well as patients with large lesions with areas of necrosis or hemorrhage have inadequate sampling results. Repeat FNA with ultrasonographic guidance to ensure that the aspiration specimen is taken from a solid component of the lesion may be helpful. Nodules in patients in whom a diagnosis cannot be obtained by repeat FNA even with ultrasonographic assistance should be studied with nuclear medicine scans to determine the functional status of the nodule. Functional nodules have a small chance of being malignant, whereas hyperfunctioning nodules in adults are unlikely to harbor malignant lesions and require no further study other than close follow-up.

Cystic lesions should be aspirated until all the fluid is removed. After the cyst fluid aspiration, the area is studied with ultrasonography, and any residual solid component is sent for biopsy by FNA using ultrasound guidance. Cysts that have a complex cyst and solid component, are recurrent after three separate aspirations, and are larger than 4 cm may warrant open biopsy, as these conditions are more likely to be associated with malignancies. Patients who have a cyst resolve and then recur should undergo repeat cyst aspiration, with biopsy reserved for patients with recurrent lesions despite three prior successful aspirations.

Most investigators recommend surgical resection of lesions classified as indeterminate or suspicious by FNA to establish definitive diagnosis. Analysis of subgroups in this category show the majority of aspirates "suggestive of a follicular neoplasm" and, to a lesser extent, "suspicous for papillary" or "Hurthle cell features." In a large series from the M. D. Anderson Cancer Center, 22% of patients with suspicious FNA eventually were shown to have cancer; of these patients, virtually all biopsies suggested papillary cancer on the initial cytology report, and the majority with follicular or Hurthle features and who were older were the patients who proved to have malignant lesions. Analyses such as these may establish criteria for selective surgical management of patients with suspicious nodules on FNA. Any patients with an indeterminate or suspicious FNA with other risk factors, such as prior radiation exposure or local symptoms, should have nodules surgically resected. For patients with no risk factors and stable nodules, some investigators have advocated using nuclear medicine thyroid scans to determine patient management.

A cold mass clearly has a higher risk for being a carcinoma as compared to a warm or hot mass by this nuclear medicine scan, and patients with functional or hyperfunctioning nodules may be followed up clinically.

NATURAL HISTORY AND PROGNOSIS

The natural history and prognosis of well-differentiated thyroid cancer has been intensively studied since the 1980s. Clear definition of risk factors associated with poor outcome have allowed more selective and less morbid treatment recommendations. In general, well-differentiated thyroid cancer is one of the most indolent solid neoplasms, with favorable long-term survival. However, a small proportion of patients with papillary cancer and a slightly larger proportion of patients with follicular thyroid cancer do die from disease-related causes. As opposed to other solid neoplasms, one major difference is that regional lymph node metastases appear to have no strong correlation with overall survival in most, but not all, series but do consistently correlate with local recurrence.

At presentation, approximately two-thirds of patients have disease that is localized to the thyroid. The median size of tumors is between 2.0 and 2.5 cm in most large series. Patients with papillary carcinomas smaller than 1.0 cm are considered to have minimal or occult papillary thyroid cancer (papillary microcarcinoma). In North American studies, the incidence of occult papillary tumors ranges between 0.5% and 1.4%, with a greater proportional incidence in older age groups. Studies from Scandinavia report up to one-third of patients with minimal papillary thyroid cancers. There is clearly a large discrepancy between this incidence of one-fourth to one-third of patients having occult papillary thyroid cancer and the incidence of 40 per 1 million patient population of clinically significant disease. This discrepancy would argue strongly that these minimal lesions have a different biology than the clinically apparent thyroid cancers. For this reason, standard practice is not to investigate or submit to biopsy nodules that are smaller than 1.0 cm, except in the setting of familial FTC. However, a proportion of patients who present with metastases to cervical lymph nodes may have a clinically occult lesion.

Approximately 33% to 61% of patients with papillary thyroid cancer will have involvement of clinically apparent cervical lymph nodes at the time of diagnosis (see Table 38.2-2). The reported incidence of positive cervical lymph node metastases in follicular thyroid cancers is much lower, ranging between 5% and 20%, with a median of approximately 10%. However, this is probably an overestimate, as many series of follicular thyroid carcinomas include follicular variants of papillary carcinomas that have the natural history of papillary thyroid cancer and metastasize to lymph nodes with a high incidence. Some argue that the frequency of true lymphatic metastases from follicular thyroid carcinoma to regional lymph nodes may be extremely unusual, being less than 1%. Although one report from Memorial Sloan-Kettering Cancer Center (MSKCC) reported a 31% incidence of lymph node metastases in follicular carcinoma. If patients with papillary cancer have lymph nodes studied in detail, the incidence of micrometastases in lymph nodes increases to 80%. The clinical significance of these micrometastases in some ways parallels the significance of the microscopic foci of intrathyroidal disease, as it is very common but does not progress and change clinical outcome.

Hurthle cell neoplasms generally have the same natural history and survival as follicular tumors; however, the incidence of nodal metastases is greater than that of follicular carcinomas but not as high as papillary cancers. Another difference that may have an impact on outcome is that these lesions do not tend to take up radioactive iodine with the efficiency of papillary tumors.

Only a small minority of patients have metastatic hematogenous disease at the time of diagnosis. In a large series from Mazzaferrri and Jhiang, 1% to 2% of papillary thyroid cancer patients and 2% to 5% of follicular thyroid cancer patients had distant metastases outside the neck or mediastinum at the time of diagnosis. One series of 1038 patients from the MSKCC reported 44 patients (47%) presenting with metastases at diagnosis, including 2.3% of patients with papillary cancer and 11% with follicular cancer. Having distant metastases at the time of presentation is a strong predictor of very poor outcome. Between 50% and 90% of these patients die secondary to their thyroid malignancy. In the 44 patients in this category in the MSKCC series, there was a 43% long-term survival.

FIGURE 38.2-2. A flow diagram for management of thyroid nodules based on fine-needle aspiration as the initial procedure.

FIGURE 38.2-3. A flow diagram for well-differentiated thyroid cancer showing the extent of disease at the time of diagnosis, the natural history, and the
In the overall population with papillary thyroid cancer, there is a 90% to 95% long-term disease-free survival and a 70% to 80% long-term disease-free survival for patients with follicular cancers. The 20% of patients in this group who develop recurrent disease includes a majority with local cervical recurrences either in lymph nodes or the thyroid bed and a minority of patients with distant metastases to the lung, bone, and liver. \( ^{12} \) Once again, patients who do develop distant metastases have a poorer outcome, with 50% to 90% disease-specific deaths, whereas patients with locally recurrent disease in the neck have long-term survival between 70% and 90% even in the presence of persistent cervical disease. \( ^{12} \)

Overall survival in well-differentiated thyroid carcinoma from various institutional series shows a better 10-year survival for papillary cancer, ranging between 74% and 93% as compared to follicular cancer, with 10-year survival of 43% to 94%. \( ^{12} \) Although many institutions have reported their data based on these histologic subcategories, a more meaningful system is to categorize patients according to defined risk factors more pertinent to generating prognostic information. Groups at both the Lahey Clinic \( ^{41} \), \( ^{42} \) and the Mayo Clinic \( ^{44} \), \( ^{45} \) have considerable databases that define prognostic risk factors for well-differentiated thyroid cancer. The two dominant factors in both series are the age at diagnosis and the presence of distant metastases. \( ^{42} \) All systems also include some measurement of the size of the lesion and other factors, such as local invasion or grade of the tumor, which have impact on outcome. In general, younger patients do well with well-differentiated thyroid cancer. Cady and Rossi \( ^{42} \) defined low-risk age categories as men younger than 40 and women younger than 50 years. The Mayo Clinic takes age into account using a numerical factor in a formula calculating a prognostic score (PS) that does not discriminate according to gender. Although historical data report follicular cancer as having worse outcome than papillary thyroid cancer, Donohue et al. \( ^{12} \) showed that if one corrects for age and other prognostic variables, the outcome is similar within these two pathologic subcategories.

As stated, patients who have distant metastatic disease either at presentation or with recurrence do much worse. \( ^{12} \) Similarly, patients with local invasion or high-grade lesions have a worse prognosis. The risk categorization schema developed by the Lahey Clinic group incorporating these components carries the acronym AMES (age, metastasis, extrathyroidal extension, size) \( ^{12} \). Using this system, low-risk patients can be identified who have a long-term overall survival of 98% and overall disease-free survival of 95% as compared to 54% and 45%, respectively, for high-risk patients \( ^{12} \). A group from Canada added an assessment of DNA content by flow cytometry to the AMES categorization and showed that high-risk patients with aneuploid tumors have essentially zero long-term survival in a small number of patients. \( ^{12} \) The initial system developed by the Mayo Clinic group \( ^{12} \) carried the acronym AGES (age, tumor grade, tumor extent, tumor size; see \( \text{Table 38.2-3} \)). A mathematical formula to develop a PS with different weights on these factors was developed. The scoring system showed that patients with a PS of less than 4 had a 99% 20-year survival, whereas patients with a PS greater than 6 had a 13% 20-year survival, with graded categories in between \( ^{12} \) (see \( \text{Table 38.2-4} \)). A more recent modification of this system is seen in MACIS (metastasis, age at diagnosis, tumor extent subdivided into completeness of resection and invasion, and tumor size). \( ^{12} \) Using this system, the score of less than 6 yields a 20-year survival of 99%, and a score of more than 8 results in a 20-year survival of only 24%. On the basis of these scoring systems that have been verified by other institutions, the aggressiveness of treatment can be balanced against the possible treatment risks and costs. Clearly, if subgroups of patients with 99% 20-year survivals can be prospectively identified, aggressive therapy with potential life-long complications cannot be justified in this subpopulation. Sanders and Cady \( ^{12} \) reexamined the AMES criteria for a group of thyroid cancer patients treated between 1980 and 1990. Survival rate for the low-risk groups was 96% and for the high-risk group was 47%, consistent with data collected over the previous four decades. As has been published by this group before, there was no significant improvement in survival with total thyroidectomy or radioactive iodine therapy (discussed later in \( \text{Radioiodine Therapy} \)). \( ^{12} \)

### TABLE 38.2-3. Schema for Categorizing Patients with Well-Differentiated Thyroid Cancer by Prognostic Risk Categories

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Low Risk (%)</th>
<th>Intermediate Risk (%)</th>
<th>High Risk (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival</td>
<td>98</td>
<td>93</td>
<td>54</td>
</tr>
<tr>
<td>Local invasion</td>
<td>98</td>
<td>93</td>
<td>95</td>
</tr>
<tr>
<td>Distant metastases</td>
<td>98</td>
<td>93</td>
<td>95</td>
</tr>
<tr>
<td>DNA analysis</td>
<td>98</td>
<td>93</td>
<td>95</td>
</tr>
<tr>
<td>Risk score</td>
<td>1-3</td>
<td>4-6</td>
<td>7-9</td>
</tr>
</tbody>
</table>

### TABLE 38.2-4. Survival or Disease-Free Survival in Patients with Well-Differentiated Thyroid Cancer Based on Various Prognostic Classification Schemes

The Mayo Clinic group applied the AMES criteria to its long-term database, evaluating 1685 patients treated between 1940 and 1991 in the low-risk category with papillary thyroid cancer. \( ^{12} \) The 30-year rate for disease-specific mortality was 2%; for distant metastases, it was 3% in this patient population. With 20-year follow-up, there was a 4% rate of local recurrence and an 8% rate of nodal recurrence. These two reports verify the criteria established much earlier for prediction of outcome in well-differentiated thyroid cancer. \( ^{12} \) The importance of age, extrathyroidal extension, and distant metastases play an important role in the American Joint Committee on Cancer staging of thyroid cancer \( ^{12} \). \( ^{12} \)
There is no large database that has verified this adaptation of the AMES and MACIS staging system into the TNM (tumor-node-metastasis) classification used by the American Joint Committee on Cancer. However, a very similar staging system was developed by the National Thyroid Cancer Treatment Cooperative Study registry, which initiated collection of data in 1987. A report of more than 1500 patients analyzed by this staging system showed that 5-year disease-specific survival rates for papillary thyroid cancer in stage I and II were 100%, 93.8% for stage III, and 78.5% for stage IV (<0.0001). The disease-free survival similarly showed a high correlation with stages I through IV papillary carcinoma, having survivals of 94.4%, 92.5%, 82.7%, and 30%, respectively (P<.0001). A comparison of the ability of this prospective registry to predict for patients being disease-free over long-term follow-up produced slightly higher correlation values than the AMES classification but slightly lower than the MACIS and TNM classifications.

TREATMENT OF WELL-DIFFERENTIATED THYROID CANCER

Surgery

The real increased risk of performing a total thyroidectomy versus a lesser resection may be in the long-term incidence of hypocalcemia (Table 38.2-7). Acceptable surgical procedures to remove a thyroid neoplasm include a lobectomy, a subtotal thyroidectomy, a near-total thyroidectomy, and a total thyroidectomy. A near-total thyroidectomy usually depends on the particular anatomy of the thyroid in any given patient. There may be a small ledge of thyroid tissue, called the ligament of Berry, that every effort is made to excise all thyroid tissue, leaving no gross or macroscopic residual thyroid in either lobe. The difference between a total thyroidectomy and a near-total thyroidectomy is approximately 1 g in normal tissue that is left close to the ligament of Berry. This maneuver may offer some protection to the recurrent laryngeal nerve, but it offers minimal benefit in terms of preserving the blood supply of the upper parathyroid. A total thyroidectomy implies removal of the entire thyroid. In cases suspicious for a follicular variant of papillary carcinoma, the presence of specific nuclear features that define papillary thyroid cancer may be identifiable on frozen-section analysis. For this reason, patients with FNA results that are read as follicular neoplasm with some features of papillary nuclei should undergo lobectomy and intraoperative assessment (frozen section, touch preparation) to attempt identification of a follicular variant of papillary thyroid cancer.

A long-standing controversy among endocrine surgeons has existed regarding the extent of surgical resection for well-differentiated thyroid cancer. This question may never be answered definitively by a clinical trial, as the expense and number of patients needed for trials of this indolent low-risk disease are overwhelming. Acceptable surgical procedures to remove a thyroid neoplasm include a lobectomy, a subtotal thyroidectomy, a near-total thyroidectomy, and a total thyroidectomy.

The entire thyroid lobe on the side of the primary cancer is taken out as completely as possible for any of these procedures. The difference comes in the management of the contralateral lobe and how this choice relates to outcome as well as operative morbidity. Arguments typically put forth for either more conservative therapy or more aggressive surgery are listed in Table 38.2-6. In a thyroid lobectomy, the contralateral lobe is not dissected but is simply examined visually and by palpation for abnormalities. A subtotal thyroidectomy leaves a rim of 2 to 4 g of tissue in the upper lateral portion of the contralateral thyroid lobe. By leaving thyroid in this location, two things are accomplished. First, the recurrent laryngeal nerve as it enters the larynx at the ligament of Berry is not dissected and consequently does not present a risk for injury. Second, the blood supply to the superior parathyroid gland on that side is less likely to be disrupted by leaving a rim of tissue in this location. A near-total thyroidectomy leaves a much smaller amount of normal tissue (<1 g) immediately adjacent to the ligament of Berry. This maneuver may offer some protection to the recurrent laryngeal nerve, but it offers minimal benefit in terms of preserving the blood supply of the upper parathyroid. A total thyroidectomy implies that every effort is made to excise all thyroid tissue, leaving no gross or macroscopic residual thyroid in either lobe. The difference between a total thyroidectomy and a near-total thyroidectomy usually depends on the particular anatomy of the thyroid in any given patient. There may be a small ledge of thyroid tissue, called the superior or inferior parathyroid gland, that the surgeon has to work around to avoid injury.

Preoperative FNA and the Frozen-Section Test

Before the development and widespread use of preoperative FNA of thyroid nodules, surgeons frequently relied on frozen-section test results obtained during the procedure to guide them. The utility of frozen-section diagnosis for thyroid nodules is controversial. The situations in which the frozen section may be useful is for patients who have suspicious FNA results. Specifically, patients with suspicious cytology (e.g., follicular neoplasm or possible follicular variant of papillary carcinoma) or patients with a nondiagnostic FNA on repeated biopsies underwent surgical resection with an unknown diagnosis of malignancy. Most of the lesions in the inadmissible FNA category are follicular neoplasms, the majority of which are benign. As previously described in the section Pathology, capsular and vascular invasion define malignancy, and the ability to render an accurate interpretation on frozen-section analysis is very limited. A large series from Chen et al. at Johns Hopkins University examined this patient population. They reported that 87% of frozen sections rendered no useful information, whereas 5% gave inaccurate results. Their conclusions were that obtaining frozen sections did more harm than good in addition to the expense incurred. A similar series from Bonner et al. also reported that frozen-section interpretation of lesions diagnosed as follicular or Hurthle cell neoplasms on FNA is fraught with error. The recommended approach in this group of patients is to perform excision of the thyroid lobe harboring the nodule and to wait for the definitive pathologic report. If the lesion turns out to be a follicular carcinoma with characteristics that place a patient at high risk, such as significant capsular invasion or angioinvasion, a completion total or near total thyroidectomy is performed during a second operation to remove the contralateral thyroid lobe. In cases suspicious for a follicular variant of papillary carcinoma, the presence of specific nuclear features that define papillary thyroid cancer may be identifiable on frozen-section analysis. For this reason, patients with FNA results that are read as follicular neoplasm with some features of papillary nuclei should undergo lobectomy and intraoperative assessment (frozen section, touch preparation) to attempt identification of a follicular variant of papillary thyroid cancer.

The algorithm outlined in Figure 38.2-2 is a guide for deciding which patients should undergo surgical resection based on an initial assessment by FNA.

TABLE 38.2-6. Arguments for and against Conservative or More Radical Surgery for Well-Differentiated Thyroid Cancer

The real increased risk of performing a total thyroidectomy versus a lesser resection may be in the long-term incidence of hypocalcemia (Table 38.2-7). A study from the Mayo Clinic spanning the years between 1946 and 1970 reported a 32% incidence of permanent hypocalcemia after total thyroidectomy versus only a 0.3% incidence after a subtotal procedure. More recent series report much less permanent morbidity and show variable results comparing the patients undergoing subtotal with those undergoing total thyroidectomy. Virtually all experienced surgeons should be able to perform total thyroidectomies with less than 1% recurrent nerve injuries, with the long-term risk of hypoparathyroidism of 2% to 9%.
A very large review from the Mayo Clinic of 1685 patients with papillary thyroid cancer treated between 1940 and 1991 has been reported with a long-term follow-up. 131 Based on surgeons’ preference, 1468 patients underwent a near-total or total thyroidectomy (87%), while 195 patients (12%) had a unilateral resection. With a 20-year follow-up, the incidence of local recurrence with unilateral resection was 14% and, for bilateral resection, it was 2%. 126 Similarly, the incidence of recurrent cervical lymph node metastases after unilateral resection was 19% as compared to 6% after bilateral resection (P=0.0001). Despite this very clear difference in recurrence rates, there was no translation of benefit in terms of disease-specific survival or distant metastases. The overall mortality at 30 years for patients with either unilateral or bilateral resection and regional recurrence was 2%. These results further confirm the excellent predictive outcome of the AMES low-risk criteria with long-term follow-up. 115 The authors concluded that although no survival benefit is gained from bilateral thyroid resection, the significant improvement in local recurrence with a minimal operative morbidity in the hands of experienced surgeons would lead to recommendation of near-total or total thyroidectomy for even this low-risk category of patients. Some investigators have noted a positive correlation with lymph node metastases and outcome with cancer, 5 had positive lymph nodes (42%: 3 level VI, 2 level IV) for metastases and, in 2 patients, the sentinel node was the only node positive for cancer. Seventeen patients had thyroid mapping, with successful removal of sentinel lymph nodes in 15 (88%) and 2 failures due to retrosternal lymph nodes. Of 12 patients for whom a sentinel lymph node biopsy with frozen-section pathologic evaluation. If positive for metastatic cancer, these lymph node areas should be completely dissected.

TABLE 38.2-7. Long-Term Complications of Total versus Subtotal Thyroidectomy

The most compelling argument for performing a unilateral lobectomy or a subtotal thyroidectomy are the data that come from the definition of prognostic factors for this disease. These rating scales identified by the acronyms AMES or AGES have been used to evaluate thousands of patients (see later in Natural History and Prognosis). 107,126,127 A low-risk patient defined by the AMES criteria has a 20-year survival of 99% with a 20-year disease-free survival of more than 95%. 126 If prognostic factors can accurately diagnose patients with such excellent outcome, the added benefit of a total thyroidectomy as well as postoperative iodine therapy may not be worth the potential morbidity for the patient. However, careful medical surveillance for cancer in the contralateral lobe as well as recurrence must be maintained. Furthermore, in situations in which a small thyroid remnant is left, the true morbidity of treating this patient with ablative doses of 131I (if indicated) is relatively minimal. 125 In fact, it is typical for patients with a surgical report of a “total thyroidectomy” that there is residual thyroid tissue within the bed of the thyroid identified on the postresection diagnostic scan, as actually a near-total thyroidectomy was performed. This small thyroid remnant is then ablated with postoperative 131I treatments. Radioiodine ablation of an intact lobe of the thyroid lobectomy is associated with considerably more symptoms. 127

A different strategy was used by a group from Germany: For well-differentiated cancer, a modified radical neck dissection was performed routinely only for T4 lesions. 131 For other-stage primary tumors, if there were only positive cervical lymph nodes was a modified radical neck dissection performed at the time of initial surgery. 131 The main reason was that, because of regular follow-up of these patients with papillary thyroid cancer, the incidence of regional recurrence for T2 lesions was 45% in those without initial neck dissection versus 3% for those with an initial neck dissection; 77% of patients for T3 lesions without initial neck dissection had local recurrence as compared to 36% with initial dissection, and patients with T4 tumors had a 75% recurrence rate without initial neck dissection versus 35% with an initial neck dissection (P<0.0001). 131 It is not clear from this study with limited follow-up whether an increased regional recurrence risk for all patients with positive central neck lymph nodes at the time of initial therapy. Radioiodine Therapy

The postoperative treatment of patients with well-differentiated thyroid cancer, particularly relating to radioiodine therapy, is controversial. The lack of well-designed, randomized controlled studies and the low probability that any large multicenter treatment studies will ever come to fruition force the clinician to rely on retrospective studies and surveys of practice habits. 131,132 All patients who have undergone a total or near-total thyroidectomy for a follicular carcinoma or a papillary carcinoma larger than between 1.0 and 1.5 cm should be considered candidates for radioiodine ablation. 131 Ablation of residual normal thyroid is important after what is thought to be complete resection of the primary tumor to aid in the detection of metastatic disease and to destroy residual microscopic cancer. Normal thyroid tissue takes up 131I more avidly than does cancer and thus prevents visualization of the true extent of disease. Furthermore, 131I ablation removes the contribution of normal thyroid tissue serum Tg, an important tumor marker in the follow-up of postoperative patients. 131,142 Most important, many studies have documented that 131I ablation decreases cancer death, 131,135 tumor recurrence, 131 and development of distant metastases. 131,144 Despite such data for large patient populations, Cady and Rossi 131 and Sanders and Cady 131 observed that an enhanced survival has not been documented with the use of radioiodine ablation in the Lahey Clinic series, particularly in “low-risk” patients defined by AMES criteria.

The dose of 131I for ablation is not standardized. Some recommend low-dose ablation with less than 30 mCi given on an outpatient basis. This approach should be reserved for low-risk young patients who may benefit from an overall lower radiation exposure and who accept the fact that several low radioiodine doses may be necessary because of a tumor recurrence. Several studies demonstrating prognostic diagnostic preparation with sufficiently elevated TSH and adherence to a low-iodine diet describe rate of success of ablative ablation using less than 30 mCi ranging from 27% to 33%. 145,147 Higher ablative doses ranging from 100 to 150 mCi should be used for older, high-risk patients, particularly those known to have an incomplete resection of the primary tumor, an invasive primary tumor, or metastases. Beaenwaltes et al. 131 demonstrated that 87% of their patients were ablated with an initial dose of 100 to less than 200 mCi. No significant differences were noted when doses from 100 to 200 mCi or more were used, leading to a recommendation of an optimal ablative dose of...
The available recombinant human TSH has led to a large study that reported comparing diagnostic whole body iodine scans after standard thyroxine withdrawal compared to scans obtained with recombinant human thyroid-stimulating hormone (rhTSH). In 127 patients with a diagnosis of well-differentiated thyroid cancer in this study, rhTSH, 0.9 mg, was injected once daily intramuscularly for 2 days. The day after the final injection, patients received between 3 and 5 mCi of $^{131}$I and were scanned 48 hours later. At 4 weeks later, patients underwent standard thyroxine withdrawal with an endogenous TSH level at least as high as 25 U/mL. The results of several parameters of this study are shown in Table 38.2-8. There were 65 patients who had concordant negative scan results (51% of the patient population). The time to thyroxine withdrawal was significant ($P<.001$) and dysphoric mood states ($P=.03$) but not when radioiodine therapy was included in the analysis ($P=.048$). The degree of thyroid suppression in these cases is dictated by balance of the risk of recurrent thyroid cancer and the overall medical condition of patients, particularly their cardiovascular status.

The success of radioiodine therapy is dependent on residual thyroid tissue concentrating iodine avidly under the stimulation of rhTSH. Although it is clear that higher scanning doses improve visualization of thyroid remnants and metastases, even conventional scanning doses of 4 to 5 mCi of $^{131}$I were found to diminish therapeutic radioiodine uptake. Park et al. have suggested that diagnostic scanning with rhTSH may prevent the stunning effect. One strategy is to use a 5-mCi $^{131}$I diagnostic dose followed by a whole body scan at 48 hours, with treatment following in most cases. At 24 hours, the whole body scan may be obtained after 5 to 7 days to determine the extent of disease. Follow-up diagnostic scanning should be performed at 6- to 12-month intervals, and treatment should continue until there is no further uptake, the serum Tg is in the “athyreotic” range, or complications of $^{131}$I therapy arise.

Medical management of malignant lesions includes thyroxine therapy to suppress TSH, which is invariable in preventing tumor recurrences. The degree to which one suppresses TSH is a point of debate. It is advisable to keep the TSH at or below the normal range (range, 0.5 to 5 µU/mL) in patients who are thought to be without evidence of disease and to maintain a lower TSH (0.1 µU/mL) in patients with residual neck disease, metastases, or recurrent disease. A large review by the Cancer Treatment Cooperative Registry of 693 patients reported for all papillary thyroid patients that TSH levels did not predict disease progression. In high-risk papillary thyroid cancer, a TSH level of less than 0.1 µU/mL was included in the analysis ($P<.001$). The degree of thyroid suppression in these cases is dictated by balance of the risk of recurrent thyroid cancer and the overall medical condition of patients, particularly their cardiovascular status.

Thyroglobulin MEASUREMENTS. Tg, an important tumor marker in the follow-up of thyroid cancer patients, is the protein that provides a matrix for thyroid hormone synthesis within thyroid follicles and is critical in the storability of thyroid hormone within the thyroid gland. After successful thyroid ablation and ablation of residual normal or cancerous thyroid tissue by radioiodine, the Tg will be in the athyreotic range. Levels above the athyreotic range are indicative of persistent, functioning residual thyroid tissue or carcinoma. If there is no detectable serum Tg after suppressive thyroxine therapy, it is a true indicator of persistent or recurrent thyroid carcinoma. However, thyroxine may suppress Tg in patients with metastatic disease; therefore, the test is more sensitive in the setting of thyroid hormone suppressive therapy withdrawal and frank hypothyroidism documented by an elevated TSH. At the time of thyroid hormone withdrawal for both initial postoperative scans and for subsequent follow-up scans, Tg is measured in conjunction with the diagnostic whole body scan and may be more sensitive than the scan in detecting cancer, as demonstrated by several investigators. Pineda et al. treated 17 patients with 150 to 300 mCi $^{131}$I who had negative diagnostic whole body scan results but serum Tg measurements above 8 ng/mL (range, 8 to 480 ng/mL) detected at the time of hypothyroïdism. Posttherapy scan results were positive in the thyroid bed or at sites of distant metastases in 16 of 17 patients. After repeated therapeutic doses given under similar conditions, 8 of 13 patients had a positive scan result after a second therapeutic dose, and five of five were positive after a third treatment. Lowering of Tg was demonstrated as was a decrease in uptake demonstrated on subsequent posttherapy scans. Since this initial report, there has been a great deal of debate regarding the optimal management of patients who are whole body iodine scan–negative but Tg-positive. This debate has included discussions of the false-negative rate of Tg, and alternative imaging studies, including positron emission tomography (PET) scans as well as sestamibi, technetium-sestamibi scans, and thallium 201 scans. Without question, there are patients who have negative whole body iodine scan results but have definite recurrent and metastatic well-differentiated thyroid cancer. PET scans have been reported to have sensitivities of identifying the occult disease in 82% and 71% in this patient population. In the series of patients studied at MSKCC, the PET scan result changed clinical management in 19 of 37 patients. PET scans also had high negative predictive value of 92%; in patients with a low Tg value, PET scans had a negative predictive value of 93%. A study from the University of Southern California reported that 100% of patients imaged by PET with elevated or rising Tg had evidence of disease, although only 17 of these 24 patients had this recurrence confirmed (biopsy or alternative imaging studies). Alternative imaging methods, including sestamibi scans as well as $^{123}$I Tl scans, could detect thyroid cancer metastases even in patients with false-negative normal Tg level results.

The relatively routine use of radioiodine ablation in this patient population who are Tg-positive and whole body scan–negative has been debated in the literature. Most experts agree that a selective approach incorporating prognostic features of the primary tumor (age of patient, extrathyroidal extension) should come into play regarding management of these patients. It should also be understood that a variety of patients with autoantibodies to Tg may have spurious results that are most commonly false-negative results but also have the potential for false-positive test results. The controversy in this area speaks to the need for a randomized trial that may answer these questions. The North American Thyroid Registry of radiodine treatment in this patient population. An even more elegant approach is for all patients with metastatic disease treated with repeated therapeutic doses of $^{131}$I that will deliver no more than 200 cGy to the blood, with no more than 120 mCi retained at 48 hours or 80 mCi in the presence of pulmonary metastases. This decreases the risk of bone marrow damage and radiation fibrosis in patients with metastatic lung disease. The methods used to perform dosimetry are generally modifications of the protocol developed by Benua and Leeper and others. One recommended approach is for all patients with metastatic disease treated with repeated therapeutic doses of $^{131}$I to undergo dosimetric quantification of the highest, safe dose, using a ceiling of 300 mCi. Other investigators recommend a standard fixed dose that may vary according to the site of uptake. For example, a dose of 150 mCi is given for residual or recurrent thyroid bed carcinomas with or without metastases, up to 200 mCi for bone metastases, and a reduced dose of 75 mCi for diffuse pulmonary metastases to prevent radiation pneumonitis and fibrosis.

Lymph node metastases were found in up to 42% of patients at time of initial therapy in one large study by Mazzaferri and Jhiang. Radioiodine is indicated in these patients to decrease recurrences that may have an impact on long-term survival. Pulmonary metastases are frequently detected exclusively on radioiodine scanning. Solumbarger reported an increase in this observation, noting the rate of negative chest radiograph results in patients with metastatic disease to have increased from 13% to 43%. Earlier detection of pulmonary metastases before development of gross chest film abnormalities is thought to be due to the use of Tg screening and the enhanced sensitivity of $^{131}$I scanning. This same group reported on 23 patients who had diffuse pulmonary metastases seen only on radioiodine scanning, of which almost 90% had no further uptake and a decrease in the serum Tg after $^{131}$I therapy. Bone metastases may require several modalities for adequate therapy. Surgery may be needed for orthopedic stabilization or palliation of pain. External radiation may be used in combination with radioactive iodine in difficult cases.

Ablation of residual thyroid is typically performed at approximately 6 weeks after near-total or total thyroidectomy. Most, but not all, centers perform a diagnostic scan followed by ablative $^{131}$I therapy. To optimize uptake by both residual thyroid and thyroid cancer, patients are rendered hypothyroid with a goal of increasing TSH. To accomplish this, thyroid replacement after thyroidectomy is thyrotoxic, as it has a much shorter half-life than thyroxine, and it is discontinued 2 weeks before treatment. In response to this hypothyroid state, thyroid hormone suppression therapy should achieve levels of greater than 25 to 30 µU/mL to obtain optimal uptake of radioiodine. A low-iodine diet is instituted 1 to 2 weeks before scanning to enhance the uptake and retention of radioiodine.
The most common side effects from radioiodine therapy include sialadenitis, nausea, and temporary bone marrow suppression. Amifostine, (Ethyol) which has been used as a radioprotector of head and neck cancer, significantly reduced sialadenitis from radiation treatment for thyroid cancer. Testicular function and spermatogenesis are transiently impaired but appear to recover with time. In a study comparing fertility rates, birth rates, and prematurity between women treated with and those not treated, there were no significant differences. One noted that three of six patients who became pregnant within the first year after radioactive treatment had children with significant congenital anomalies.

There is a dose-dependent relationship between therapy and the development of leukemia. The incidence increases when the total cumulative dose is greater than 800 mCi and can be avoided by treating at widely spaced intervals (6 to 12 months) with activity between 100 and 200 mCi. A higher incidence of bladder carcinoma has been seen in patients who have received high cumulative doses of radioiodine. Urine dilution by adequate hydration and frequent voiding can reduce the radiation exposure to the bladder wall.

Chemotherapy and Radiation Therapy

The most effective nonsurgical treatment for well-differentiated thyroid cancer is, without question, ablation with radioiodine. Other conventional modes of neoplastic treatment—chemotherapy, and external-beam radiation therapy—demonstrate much poorer results and, consequently, are much less studied. The best single chemotherapeutic agent for this tumor is doxorubicin (Adriamycin) with partial response rates of 30% and up to 45% in some series. Combination therapy with Adriamycin and cisplatin has produced disappointing results that were no better than single-agent trials, and the toxicity was worse.

For surgically unresectable local disease that has not responded to radioiodine, the best treatment may be a combination of hyperfractionated radiation treatments plus Adriamycin. Response rates of more than 80% have been reported using this regimen, although even in this situation, complete responses are rare and limited in duration. Adjuvant radiation therapy for grossly resected well-differentiated thyroid cancer has not generally been thought to be beneficial until one recent retrospective study. This study by Farahhati et al. analyzed patients with T4 primary lesions (evidence of extrathyroidal extension) who underwent radiation (n = 99) compared to those who did not (n = 70). Patients received a uniform treatment course of total thyroidectomy with initial ablative radioactive iodine, with or without 5000 to 6000 rads of external-beam radiation therapy to the neck and mediastinum, followed by a second ablative dose of radioactive iodine. The group that had radiation treatments had recurrent disease in 4% of cases (3 of 75 patients), while the group who did not receive radiation had recurrences in 26% (13 of 50 patients; P = 0.001). This benefit for radiation extended only to the subgroup of patients with lymph node–positive disease. In patients with papillary thyroid cancer who were lymph node–negative, there were 1 of 47 patients (2%) with recurrence with radiation therapy and 2 of 21 patients (9.5%) without radiation therapy had recurrences, which was not statistically significant (P = 0.27). In patients with T4 lesions and positive lymph nodes who received radiation, there were 2 recurrences in 28 (7.1%) and there were 13 recurrences in 29 patients without radiation therapy (44.8%; P = 0.002). These results would suggest that patients with T4 papillary thyroid cancer, particularly with positive lymph nodes, should undergo external-beam radiation therapy to the neck. This patient population should be studied in a prospective manner to determine the benefit of that additional therapy. This retrospective review showed not only an improvement in local recurrence but an improvement in distant metastases in this subgroup.

ANAPLASTIC THYROID CANCER

ATC is one of the most aggressive and difficult human malignancies to treat and is one of the most lethal. As opposed to the excellent long-term survival for well-differentiated thyroid carcinoma, ATC in most series has a median survival of 4 to 5 months from the time of diagnosis, with rare long-term survivors. The proportional incidence of ATC compared to the total number of thyroid carcinomas is variable but appears to be declining over time. Historically, ATC was said to constitute 5% to 15% of all thyroid carcinomas in the United States and between 10% to 50% in European series. Current epidemiologic studies indicate that this lethal form of thyroid cancer has decreased to between 1% and 3% of the total number of cases. Institutional reviews over a distinct period support the apparent recent decrease in the incidence of ATC. One of the largest single-institution series, from the Mayo Clinic, spans the years 1946 to 1971. During that time, 1161 patients with thyroid cancer had their primary treatment at Mayo Clinic, including 82 cases of ATC or 7.1% of the total. Later single-institution series from Loyola (1966 to 1989) and Roswell Park (1968 to 1992) reported respective incidences of 5% and 2.7%. The decrease over time may be partially related to iodine prophylaxis and an overall decrease in endemic iodine-deficient goiter in North America. Patients with ATC differ epidemiologically from patients with well-differentiated thyroid neoplasms, with a median age two to three decades older and with a more equal gender distribution (Table 38.2-8). Median age at diagnosis ranges between 63 and 74 years. In most series, including the largest one from the Mayo Clinic with 82 patients, there are equal number of male and female patients, but some series show a predilection for women near the ratio that is commonly reported for well-differentiated thyroid cancer.

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**TABLE 38.2-8. Comparison of Whole Body Iodine Scans and Scans Obtained after Injection of Recombinant Human Thyroid-Stimulating Hormone**

**TABLE 38.2-9. Clinical Series of Anaplastic Thyroid Carcinomas with Demographic Data, Total Percentage of Thyroid Cancer, and Survival**
ATC is commonly related to a prior or a concurrent diagnosis of well-differentiated thyroid cancer or benign nodular thyroid disease. This association of ATC with prior or concurrent well-differentiated thyroid carcinoma suggests two features of the biology of this tumor. First, ATC may arise via the dedifferentiation of prior well-differentiated thyroid cancer, and the aggressive growth pattern of this anaplastic tumor may replace all previous evidence of well-differentiated tumor. Also, the close association between ATC and well-differentiated thyroid cancer suggests that the risk factors are similar.

The natural history, clinical presentation, and outcome of ATC reflect the biology of this tumor as an undifferentiated, rapidly growing neoplasm with invasive characteristics. The patients uniformly present with a palpable mass that is reported to be increasing in size during the period of observation. The median tumor size in patients with ATC from Roswell Park Cancer Institute was 8 to 9 cm, with a range of 3 to 20 cm as compared to the usual size of 2 to 3 cm for well-differentiated thyroid cancer. Invasion to the trachea, larynx, or recurrent laryngeal nerve leads to hoarseness at diagnosis and, in a subset of these patients, an invasion to the esophagus may cause dysphagia.

The majority of patients with ATC die from aggressive local regional disease, primarily with upper airway respiratory failure. At the time of diagnosis, 25% to 50% of patients may have synchronous pulmonary metastases. However, it is usually the local growth causing obliteration of the airway that causes the patient’s demise. For this reason, aggressive local therapy is indicated in all patients who can tolerate it and in whom it is technically possible. As opposed to well-differentiated thyroid cancer, ATC plays no role in the treatment of recurrent or metastatic disease for this tumor. Therefore, total or near-total thyroidectomy is not as important in ATC, except as needed to obtain local control.

Survival after the diagnosis of ATC is very poor. With the median survival in most series being less than 5 months from the time of diagnosis, this is one of the most rapidly lethal tumors known in clinical oncology. The majority of patients die due to local recurrence, although distant metastases occur primarily in lung, bone, and liver. External radiation has been used with limited success to treat locally recurrent ATC. One study from London reported 10 of 17 patients with an objective response to accelerated radiation (three complete responses and seven partial responses) but toxicity to the esophagus was considerable. In the mid-1980s, Kim and Leeper reported improved responses with a combination of radiation therapy and relatively low-dose Adriamycin as an apparent synergistic agent, achieving responses in 84% of 19 patients, although still having a median survival of only 12 months. Adriamycin is the single most effective chemotherapeutic for ATC, and it has been shown that Adriamycin plus platinum is more effective than Adriamycin alone. A review from the National Cancer Database reports a 10-year survival of 14% for ATC. Early diagnosis with aggressive surgical supplementation with anterior-beam radiation therapy and Adriamycin-based chemotherapy is the most appropriate treatment for patients with anaplastic thyroid carcinoma.

MEDULLARY THYROID CANCER

MTC was recognized in the 1950s by Hazard et al. as a distinct clinicopathologic entity. Since this description, sequential pathologic, biochemical, and molecular genetic studies have progressed to render this one of the best characterized solid malignancies of the thyroid. In 1959, Hazard described MTC as a solid thyroid neoplasm with no follicular histology but with a high degree of lymph node metastases that accounted for 3.5% of thyroid cancers in a review at the Cleveland Clinic. Over the next 10 years, investigators identified and described the parafollicular C cell that produces calcitonin, which lowers serum calcium. In 1966 and 1967, Williams suggested that MTC arose from this C-cell population. This hypothesis was confirmed by a number of investigators who documented elevated serum calcitonin from patients with MTC. During the decade of the 1970s, Wells et al. extended the measurement of calcitonin by defining a provocative test that rendered this hormonal tumor marker one of the most sensitive and specific in all of oncology. Understanding of the familial associations of MTC with corollary genetic studies reported in the 1980s and early 1990s has defined molecular changes that are important for inherited MTC and may have implications for sporadic MTC as well.

MTC constitutes as few as 3% or as many as 12% of most institutional series of detectible thyroid cancers. As opposed to well-differentiated thyroid cancer, MTC is not associated with radiation exposure, but it does occur in distinct familial syndromes. Sporadic or nonfamilial MTC accounts for 60% to 70% of cases, with three distinct familial syndromes accounting for the remainder. MTC is the most prominent clinical diagnosis in MEN 2a and MEN 2B (Table 38.2-10). In 1986, familial MTC with none of the associated features of MEN 2a or MEN 2B was described. Appreciation of this syndrome has shifted the percentage of incidence of sporadic MTC as a function of the total number of cases of MTC from 60% to 65% and even lower in some series. In addition to the presence or absence of other associated endocrine abnormalities, each of these familial forms of MTC has a unique natural history and prognosis. Furthermore, studies have identified specific genetic changes associated with each type (see Table 38.2-10).

Table 38.2-10. Characteristics of Sporadic and Various Familial Forms of Medullary Thyroid Cancer

Parafollicular, or C cells, arise embryologically from the neural crest and have characteristics shared with other cells with a similar origin. The C cells are located primarily in the upper and middle thirds of the thyroid lobes, with a particular concentration posteriorly. This feature is important to surgical therapy, as this is the location in which the recurrent laryngeal nerve passes under the ligament of Berry and enters the larynx. Therefore, complete thyroid resection is necessary for this condition, because MTC typically arises in this upper region of the thyroid gland where the C cells are concentrated. Grossly, MTC may be circumscribed or infiltrative and is usually yellow. Histologically, this tumor can be described as having a wide variety of patterns, including glandular, solid, spindle-cell, oncocytic, clear cell, papillary pattern, small cell, and giant cell. The nuclei of MTC resemble those of neuroendocrine tumors in other areas of the body. They are usually round and have a stippled “pepper-and-salt” chromatin. Pathologic features associated with a poor prognosis include presence of necrosis (P<.001), squamous pattern (P=.002), presence of oxyphil cells in the tumor and absence of cells with intermediate cytoplasm (P=.02), and less than 50% calcitonin immunoreactivity (P=.04).

CLINICAL PRESENTATION AND DIAGNOSIS

The clinical symptoms at the time of presentation vary, dependent on the situation for each patient. Patients with familial MTC who are identified by screening with stimulating tests or with molecular analysis are universally identified before any macroscopic mass or lesion. Sporadic patients typically present with an asymptomatic mass in the thyroid. Patients with bulky disease with extremely high levels of calcitonin may have severe secretory diarrhea as a principal symptom.

Before the definition of the molecular change for familial MTC, basal and stimulated serum calcitonin levels were used to screen patients. Sequential calcitonin testing is still important as a tumor marker for following up patients with MTC.

Various nuclear medicine imaging studies have been evaluated in patients with MTC to identify gross and occult metastases. MTC does not concentrate iodine, so thyroid scans are of no utility. Similarly, thallium as well as technetium scans have been used with minimal benefit in this disease. Metaiodobenzylguanidine scans have been useful in pheochromocytoma and neuroblastoma and have been studied for MTC but do not identify a large proportion of the lesions.
TREATMENT

General Approaches

Chemotherapy and external-beam radiation therapy are ineffective against MTC, rendering surgical resection the only definitive therapy.\(^{203}\) For patients with sporic MTC who are not identified by biochemical or genetic screening, the appropriate operation in most cases is total thyroidectomy with central node dissection. Total thyroidectomy is indicated in this sporadic setting because a small proportion of lesions may be bilateral and because it may not be clear at the time of operation whether a patient has an index case of familial disease. Because all familial syndromes have a high propensity for bilateral tumors, total thyroidectomy is indicated except possibly for patients having nonfamilial syndromes and small lesions (<1.0 cm).\(^{191}\) However, one report of 80 patients with sporadic MTC smaller than 1 cm showed that 11% had clinically involved lymph nodes, 31% had pathologically involved lymph nodes, and 5% had distant metastases.\(^{205}\) Combined with this thyroid resection, a central lymph node dissection is performed, removing lymphoid tissue from the level of the hyoid bone to the carotid sheath medially and laterally to the jugular vein. Lymph nodes lateral to the jugular vein are sampled and, if there is any evidence of metastatic spread in this area, a formal modified radical neck dissection is performed.\(^{191}\)

The incidence of positive lymph nodes correlates with the size of the primary lesion at the time of diagnosis. It has been reported that for lesions smaller than 1 cm, there can still be an 11% incidence of positive nodal disease, whereas in patients with tumors larger than 2 cm, 60% will have positive cervical lymph nodes.\(^{203}\) Combining all cases of MTC, between 15% and 75% have spread to the lymph nodes at the time of diagnosis.\(^{191}\) For this reason, Duh et al.\(^{206}\) advocated a formal modified radical neck dissection for any lesion larger than 2 cm on the side in which it is located, with a central node dissection on the contralateral side.

The incidence of distant metastases at the time of diagnosis varies according to the clinical setting. Twelve percent of patients with sporadic MTC have distant metastases, whereas 20% of those with MEN 2B have metastatic spread but only 3.3% of patients with MEN 2a.\(^{191}\) Patients with familial non-MEN MTC also have a favorable clinical condition similar to MEN 2a, with 2% of patients presenting with distant metastases.\(^{191}\) Moley et al.\(^{207}\) have instituted staging laparoscopy to identify liver metastases in patients undergoing thyroid resection and lymph node dissection. For MTC, liver metastases are often the site of metastatic disease and are often radioiodine occult.\(^{207}\) By performing laparoscopy, the incidence of biochemical cure has increased because patients with unexcised liver disease are eliminated from the therapy pool.

The outcome of treatment of patients with sporadic MTC has improved. An early review published in 1970 reported 5- and 10-year survival rates of 48% and 12%, respectively.\(^{208}\) More recent studies show a 5-year survival of between 80% and 90% and 10-year survival between 70% and 80% for combined series of familial and sporadic MTC.\(^{209,210}\) The series from the National Cancer Database confirms this improved survival, with a 75% 10-year survival for MTC.\(^{191}\) It is interesting to note that the natural history and prognosis for the various subtypes of MTC correlate with described genetic changes. The two groups with the worst outcome (sporadic and MEN 2B) have similar genetic changes in the RET oncogene, as do the two types with favorable outcome (familial non-MEN and MEN 2B).\(^{209}\)

One controversial area in the surgical management of patients with MTC is the proper approach to patients who have persistently elevated basal or stimulated calcitonin after resection of all gross disease.\(^{211,212,213,214,215}\) In many of these cases, imaging studies with conventional techniques of ultrasonography, computed tomography, or magnetic resonance imaging, plus newer techniques of somatostatin receptor scintigraphy,\(^{216}\) demonstrate no areas of disease. One strategy to identify the region from which elevated calcitonin is coming is to perform selected venous sampling with systemic pentagastrin or calcium stimulation.\(^{217}\) The key clinical question is: In these patients, who have occult MTC with no radiographic or clinical evidence by which to localise residual tumor but with persistently abnormal calcitonin levels, is the natural history altered by aggressive attempts to excise the occult disease surgically? Excision attempts generally do not produce normalization of calcitonin levels. The best results come from Tisell, who performs meticulous 12-hour neck dissections, often removing 40 to 60 additional cervical lymph nodes per operation.\(^{218}\) In a series of 11 patients, Tisell et al.\(^{218}\) had normalized calcitonin levels, with another four that had dramatic improvement in their calcitonin levels. However, even these improvements in the calcitonin levels do not necessarily translate into improved survival. Thirty-one patients were identified, all of whom had gross disease resected at initial operation at the Mayo Clinic but who had documented elevated postoperative calcitonin.\(^{219}\) With a median follow-up of almost 12 years, only 11 patients developed clinically or radiographically apparent recurrent disease, and these 11 patients were reoperated at that time. None of these patients normalized their calcitonin levels after reoperation. Importantly, it is the overall 5- and 10-year survival rates in this population were 90% and 86%, respectively, with only two patients dying specifically from MTC. Both patients had sporadic MTC with very aggressive invasive primary lesions and died of distant metastases 2 to 2.5 years after diagnosis. Even though there is no alternative therapy to surgical resection for MTC, the data regarding the prognosis of occult MTC plus the lack of success even with very extensive reoperations to normalize calcitonin would argue that the best course of action in this patient population is close follow-up and operation only when clinically apparent disease is present.

For patients with metastatic MTC, surgical resection may still offer the best chance of survival as well as long-term palliation. In 16 patients with metastatic MTC at Johns Hopkins, 21 palliative reoperations were performed. These procedures included neck reoperations in 11 cases but also removal of mediastinal masses and liver metastases as well as other miscellaneous lesions. All patients had clear relief of their index symptoms, typically diarrhea and fatigue, and had a median survival rate of 8.2 years.\(^{191}\)

The results of MTC treatment with external-beam radiation therapy,\(^{221}\) or chemotherapeutics are disappointing.\(^{218,219}\) Radiation administered at a dose of more than 5000 rads to a large Y-shaped anterior field without laryngeal shielding necessary to treat these patients causes significant local toxicity. Dysphagia as well as dyspnea can be severe in certain individuals. Furthermore, treatment with this radiation dose has not definitively been shown to decrease local recurrences. One large study from France of 59 patients reported local recurrences within the radiation field in 30% of patients.\(^{220}\) Chemotherapeutics used in treatment of MTC include Adriamycin, streptozocin, and 5-fluorouracil.\(^{221}\) Single-agent response rates are poor, with aggressive Adriamycin regimens producing 20% to 30% objective responses. A study of combination chemotherapy showed that a regimen of 5-fluorouracil, streptozocin, and dacarbazine produces objective responses in only 15%.\(^{218}\) The poor outcome of treatment of metastatic disease validates the treatment recommendation to diagnose patients with MTC early and treat with initial aggressive surgery.

Due to failure of chemotherapy and radiation therapy to offer significant benefit for patients with MTC, innovative therapeutic strategies for MTC have been developed, such as the use of gene therapy. This technique primarily uses adenovirus to transduce either interleukin-2 or suicide gene, such as herpes simplex virus thymidine kinase.\(^{221}\) Other more directed gene therapies would rely on the expression of calcitonin only from MTC and have use of selective promotor in front of a suicide gene or other targeted transgene.

Treatment of Familial Medullary Thyroid Cancer

An increasing number of patients are identified in one of the three familial settings of MTC that are diagnosed using biochemical or genetic screening.\(^{222}\) Routine use of provocative biochemical testing to diagnose MTC led to a significant decrease in the age of diagnosis, a significant decrease in the incidence of lymph node metastases, and a significant increase in the number of patients cured biochemically at these earlier operations.\(^{223}\) This strategy has been extended to an earlier stage with the description of the mutations in the RET oncogene present in the MEN 2a.\(^{224}\) At Washington University, Wells et al.\(^{225}\) use a molecular screening technique to identify patients who are carriers of the MTC2a mutation as infants or young children. Before any abnormality in basal or stimulated calcitonin, these patients undergo a total thyroidectomy, a total parathyroidectomy, and a parathyroid autograft. Pathologic evaluation on these children's thyroid identifies either C-cell hyperplasia or microscopic or macroscopic MTC. In the initial trial, no patients treated with this strategy had evidence of lymph node metastases, and this surgical strategy should be curative.

The genetic test for the mutations in the RET protooncogene have become commercially available, and many individuals are reporting series based on early operation for patients identified by RET mutation. A review has noted that in a total of 209 patients treated in this manner, 3.4% had normal thyroid glands with no evidence of C-cell hyperplasia or MTC.\(^{226}\) It was also noted that in these patients undergoing prophylactic operations, there was an 8.6% incidence of lymph node metastases. Based on these results, it is thought that a prophylactic central neck dissection should be performed at the time of this prophylactic thyroidectomy, based

Studies have used radiolabeled anti-carcinoembryonic antigen antibody or anticalcitonin antibody but with limited success. Several studies have used somatostatin receptor scintigraphy in the setting of MTC.\(^{227,228}\) Like other amine precursor uptake and decarboxylation (APUD) cells, C cells may express a high level of somatostatin receptors, and pharmacologic developments of radiolabeled agents, based on analogs that bind to somatostatin receptor, have been studied for use in treating MTC. In general, the results are better than any other nuclear medicine agent; however, occult lesions smaller than 1 cm as well as liver lesions still are missed with this technique.
on genetic basis. Because this oncogene was one of the first to be identified that led to a therapeutic approach, there has been appropriate attention paid to the understanding and more sophisticated diagnostic tools, such as immunohistochemistry, these patients are being correctly categorized as having thyroid lymphoma.

For the more clinically relevant situation in which the thyroid metastasis is detected premortem, the most common primary site is renal cell carcinoma, accounting for 23% of all cases combined from the literature. The next most common sites are breast (16%, 15%), melanoma (5%), and colon and larynx (4.5% each). Occasionally, the thyroid metastasis may be the initial presentation of an occult primary from a gastrointestinal source or renal primary. Because FNA biopsy is the diagnostic tool used to evaluate thyroid nodules as the initial step, an awareness of the potential of the secondary metastases is important for interpretation of these biopsy results.

Depending on the clinical situation, some of these patients may need thyroidectomy for palliation of local symptoms. Thyroid metastases may grow at a rapid rate and can range between 2% and 26% in autopsy series, probably depending on the thoroughness of the examination by the pathologists. From these biopsy series, the most prominent malignancies metastatic to the thyroid are breast and lung, each accounting for 25% of the total. Metastasis, renal cell carcinoma, and gastrointestinal tract malignancies each account for approximately 10% of these secondary metastases from autopsy studies. A variety of other miscellaneous diagnoses account for the remainder.

SECONDARY THYROID MALIGNANCY

Involvement of the thyroid gland by malignant metastases from other sites is rare, accounting for fewer than 1% of malignant thyroid malignancies in most clinical series involving surgical resection or FNA biopsies. On the other hand, the incidence of thyroid metastases identified on autopsy series is greater and can range between 2% and 26% in autopsy series, probably depending on the thoroughness of the examination by the pathologists. From these biopsy series, the most prominent malignancies metastatic to the thyroid are breast and lung, each accounting for 25% of the total. Metastasis, renal cell carcinoma, and gastrointestinal tract malignancies each account for approximately 10% of these secondary metastases from autopsy studies. A variety of other miscellaneous diagnoses account for the remainder.

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Depending on the clinical situation, some of these patients may need thyroidectomy for palliation of local symptoms. Thyroid metastases may grow at a rapid rate and can cause airway obstruction. In one large institutional series from Toronto, 8 of 11 patients derived benefit from a thyroidectomy after premortem diagnosis of secondary metastases.

CHAPTER REFERENCES


INTRODUCTION

Parathyroid neoplasia is a common endocrine problem, whereas parathyroid carcinoma is exceptionally rare. Parathyroid carcinomas, as opposed to other endocrine tumors that become less hormonally active when malignant, are hyperfunctional and characterized by severe elevations of serum calcium with associated renal and bone symptoms. The clinical course is variable, but typically follows a pattern of local recurrence in the neck with late distant metastases to lung, bone, and liver.

The initial report of a parathyroid carcinoma was made by de Quervain in 1909. He described a patient with a large locally invasive neck mass that was parathyroid on histologic evaluation. The tumor was definitely malignant as the patient developed lung metastases after removal of the neck mass, but no signs or symptoms of hypercalcemia were described. The initial description of severe hypercalcemia associated with parathyroid cancer was made three decades later by Armstrong. The rarity of parathyroid carcinoma limits reports to primarily small institutional series with occasional reviews of all experience reported in the medical literature. Even institutions such as the Massachusetts General Hospital or the Mayo Clinic with extensive clinical interest in this disease have only one to two dozen cases in clinical reviews spanning four to five decades. A detailed review by Obara and Fujimoto identified 270 cases of parathyroid carcinoma in the English literature between 1933 and 1991. An article from the National Cancer Database in the United States identified 286 cases of parathyroid cancer reported between 1985 and 1995. This single report more than doubles the number of cases in the literature for this rare disease. The epidemiology, pathology, clinical course, treatment, and prognosis of this rare malignancy is described in relation to the much more common diagnoses of parathyroid adenoma and hyperplasia.

PRIMARY HYPERPARATHYROIDISM

The vast majority of parathyroid cancers are functional with excess production of parathyroid hormone (PTH) which results in the clinical syndrome of primary hyperparathyroidism (HPT). The pathology of HPT can be grouped into three general categories: a single parathyroid adenoma (83% to 85% of cases), multiglandular hyperplasia (15%), and parathyroid cancer (0.5% to 3.0%). The proportion of HPT patients who truly have parathyroid cancer is likely to be well under the 2% of cases more recently quoted. The epidemiologic and pathologic characteristics of these three general categories of HPT are shown in Table 38.3-1.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenoma</td>
<td>83% to 85%</td>
</tr>
<tr>
<td>Hyperplasia</td>
<td>15%</td>
</tr>
<tr>
<td>Carcinoma</td>
<td>0.5% to 3.0%</td>
</tr>
</tbody>
</table>

TABLE 38.3-1. Comparison of the Various Causes of Primary Hyperparathyroidism

PATHOLOGY

Schantz and Castleman defined the pathologic criteria used to distinguish parathyroid carcinoma from benign parathyroid adenoma in a classic article in 1973. Thick fibrous bands, pleomorphic cells in a trabecular pattern, and a high incidence of mitotic figures are the chief distinguishing features (Fig. 38.3-1). Invasion of the glandular capsule and vascular invasion are also found with parathyroid carcinoma. However, as with other endocrine neoplasms, the diagnosis of parathyroid carcinoma strictly is difficult on histologic evaluation using the criteria outlined previously. There is a spectrum of these changes present in benign adenomas, atypical adenomas, and true carcinomas. Even histologic evidence of capsular or vascular invasion is not pathognomonic for parathyroid cancer as spontaneous hemorrhage in large benign parathyroid adenomas may result in a similar histologic appearance.

FIGURE 38.3-1. Pathologic characteristics that are used to define a lesion as a parathyroid carcinoma are shown in these two panels. A: A low-power view demonstrates dense fibrous bands with the cells arranged in a trabecular pattern (arrowheads) and evidence of capsular invasion (arrows). B: A high-power view documents a high number of mitotic figures (arrows) in one single field of view.
clinical presentation is discussed in greater detail here, but parathyroid carcinoma tends to have a higher serum calcium level, more marked symptoms of HPT, and larger lesions that may be palpable in the neck. The operating surgeon finds a large lesion that is more firm than typical adenomas. The color of parathyroid carcinoma is frequently gray-brown versus the red-brown of benign lesions, reflecting the increased fibrous stroma within these tumors. Most important, parathyroid carcinoma may locally invade into adjacent structures such as the ipsilateral thyroid gland or overlying strap muscles of the neck. This gross pathologic feature is infrequently seen with benign lesions. 16,17,18

In the past decade, several groups have used flow cytometry to analyze DNA content in parathyroid carcinomas compared with adenomas. In three series, a consistent proportion between 31% and 56% of parathyroid carcinomas were documented to be aneuploid. 13,14,15 The DNA content of parathyroid adenomas is not as consistent, with one group reporting no aneuploidy in 32 patients 16 and other groups reporting proportions in the range of one-third aneuploid similar to parathyroid carcinoma. A second piece of information that these studies report is that aneuploidy is a prognostic indicator for parathyroid carcinoma. August reported that four out of five patients with aneuploid parathyroid carcinoma died of disease with the fifth alive with extensive recurrence, while four of four patients with diploid parathyroid carcinoma were cured with no evidence of recurrence after parathyroid surgery. 13

EPIDEMIOLOGY

The incidence of parathyroid cancer is most commonly reported in the context of primary HPT. Most endocrine surgeons report 0.5% to 4.0% of all HPT as being parathyroid carcinoma (Table 38.3-2). Because the estimate of the annual incidence of primary HPT is reported to be 1 per 2000, 1 then if 1% of HPT is parathyroid carcinoma, the incidence of this malignancy would be approximately 0.5 per 100,000 persons. This incidence is clearly an overestimation as it would place the annual number of parathyroid cancers in the United States more than 1000 new cases, which greatly exceeds the actual number. Several tertiary institutions have reported their total experience with parathyroid carcinoma over several decades in the setting of more than 1000 cases of primary HPT. The Mayo Clinic, 1 the Cleveland Clinic, 2,3 and the University of Michigan 2,4 reported an overall proportion of parathyroid cancer in HPT of 0.6%, 0.47%, and 0.37% (see Table 38.3-2). However, even these numbers may be overestimates as these tertiary institutions are more likely to be referred these patients with this rare diagnosis. A review from a tertiary referral center in Padua, Italy, reported 5.2% of all patients operated on for HPT between 1980 and 1996 were parathyroid cancers. 2 This unusually high proportion does not appear to be an overestimation due to inaccurate pathology as 13 of 16 had metastases and two had multiple local recurrences. Thompson at the University of Michigan reported an incidence of two parathyroid carcinomas in 1450 initial parathyroid operations for HPT over the past two decades at the University of Michigan for 0.1% of HPT. 4 There is no American Joint Committee on Cancer Staging system for parathyroid cancer. The National Cancer Database reported 286 cases of parathyroid cancer in a 10-year period. This group believed that it captured 60% to 80% of all cancers in the United States during that time interval. If that estimate is correct, then there are only 36 to 48 cases of parathyroid cancer annually in the United States. With an incidence of 0.015 per 100,000 population, parathyroid cancer is one of the most rare of all human cancers. Because of this low incidence, there is no American Joint Committee on Cancer Staging system for parathyroid cancer. 2

### TABLE 38.3-2. Demographics, Proportion of Primary Hyperparathyroidism That Is Parathyroid Cancer, Tumor Size, and Calcium Levels in More Recent Institutional Series of Parathyroid Cancer

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Parathyroid Cancer</th>
<th>Nonparathyroid Cancer</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender distribution</td>
<td>Male (51%)</td>
<td>Female (49%)</td>
<td></td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td>45-51 years (55%)</td>
<td>19-81 years (66%)</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td>Caucasian (75%)</td>
<td>African American (25%)</td>
<td></td>
</tr>
<tr>
<td>Incidence</td>
<td>0.15 per 100,000</td>
<td>0.15 per 100,000</td>
<td></td>
</tr>
<tr>
<td>Difference in serum calcium level</td>
<td>15-16 mg/dL</td>
<td>11-12 mg/dL</td>
<td></td>
</tr>
</tbody>
</table>

The gender distribution is equal or has a slight female preponderance in most series and differs from benign parathyroid adenomas, which have a higher female predominance. 1-3 (see Table 38.3-2). The age at diagnosis can vary between 19 and 81 and the median age in most series is between 45 and 51 years. The large National Cancer Database series had essentially an equivalent gender distribution (51% male and 49% female subjects) and a mean and median age of 54.5 and 55.1 years, respectively. 5 The National Cancer Database had the largest proportion (76.2%) of non-Hispanic whites, 7.3% black, 7.3% Hispanic, and 4.2% others. 5 There are no documented etiologic causes for this malignancy, although there is a familial association in a few series. Parathyroid cancer has been reported and documented in members of multiple endocrine neoplasia 1 kindreds. 6 In this autosomal dominant disease, the predominant endocrine abnormality is multiglandular benign hyperplasia of the parathyroids. Familial non–multiple endocrine neoplasia 1 associated parathyroid cancer has been reported in siblings 27 and in one report, several relatives across two generations had parathyroid carcinoma. 5 This study also reported other relatives with primary HPT who had atypical adenomas, implying a connection between this benign pathologic entity and true parathyroid carcinoma. External radiation exposure has been correlated with parathyroid neoplasms, but virtually all reports describe an association between radiation and the more common parathyroid adenoma, although there are isolated case reports of patients with parathyroid carcinoma who had a history of radiation treatments in the distant past. 28 Patients with renal failure typically experience HPT with nonclonal hyperplasia of all parathyroid glands, but 13 cases of parathyroid cancer have been reported in the literature in this clinical setting. 28

**CLINICAL PRESENTATION**

Because virtually all parathyroid carcinomas are functional, meaning they produce high and unregulated levels of PTH, the signs and symptoms of this disease relate primarily to the consequences of this hormone excess. Specifically, various manifestations of renal disease associated with hypercalcemia and hypercalciuria such as renal stones, renal colic, nephrocalcinosis, renal insufficiency, or all of these manifestations occur in up to 90% of cases. 2,7,9 (Table 38.3-3). Also, the prevalence of bone disease related to calcium absorption with osteoporosis and bone pain is much greater in parathyroid carcinoma than in patients with parathyroid adenoma, 2,7,9 with up to 70% of patients manifesting the symptoms. In nonmalignant parathyroid disease, it is unusual to have both renal and bone symptomatology documented at the time of diagnosis. 29 However, these symptoms are present simultaneously in up to 50% of patients with parathyroid carcinoma (see Table 38.3-3). These amplified symptoms reflect the increased magnitude of the biochemical disturbances seen with parathyroid carcinoma. The level of total serum calcium is significantly elevated in virtually all series of parathyroid carcinoma, with the mean values between 15 and 16 mg/dL compared with 11 to 12 mg/dL seen with
parathyroid adenomas. Similarly, the PTH level in parathyroid carcinoma is consistently higher than for benign parathyroid disease, with more than 70% of patients having a greater than fivefold increase over the upper limits of normal for PTH. Because of the high degree of hypercalcemia, it is unusual for patients to be asymptomatic at presentation with parathyroid carcinoma compared with patients with benign causes of HPT who are asymptomatic in more than 50% of cases in some series. Up to 14% of patients with parathyroid carcinoma may present with hypercalcemic crisis manifested by a depressed level of consciousness, dehydration, and extreme hypercalcemia. The size of the typical parathyroid carcinoma is much larger than benign lesions. The median maximal diameter in most series is between 2 and 3.5 cm, compared with approximately 1.5 cm for benign adenomas. This large mass translates into a significant number of patients who present with a palpable neck mass ranging between 22% and 50% of cases. Again, it is extremely unusual for patients with benign lesions to have palpable abnormalities in the neck, and this is a clinical sign that strongly suggests parathyroid carcinoma. In 10% of cases, patients with parathyroid carcinoma present with symptoms of hoarseness caused by compression or invasion of recurrent laryngeal nerve and vocal cord paresis.

### NATURAL HISTORY

The best information regarding the natural history of parathyroid carcinoma comes from a detailed review of 163 cases reported between 1981 and 1989 (summarized in Table 38.3-4). At initial presentation, few patients with parathyroid carcinoma have metastases either to regional lymph nodes (less than 5%) or distant sites (less than 2%). In the National Cancer Database series of 266 patients, only 16 (6.1%) had lymph node metastases noted at the time of initial surgery. This report did not comment on the incidence of distant metastases and has a relatively short follow-up interval. A higher proportion of parathyroid carcinomas are locally invasive into the thyroid gland, overlying strap muscles, recurrent laryngeal nerve, trachea, or esophagus. Some patients are not identified preoperatively or intraoperatively as having parathyroid carcinoma and undergo parathyroid procedures as if to treat parathyroid adenoma. Only after review of the pathologist identifying this resection, or when these patients have either local recurrences or metastases is a correct diagnosis of parathyroid carcinoma made. The incidence of not recognizing parathyroid carcinomas at initial operation ranges between 11% from the Lahey Clinic series (one in nine), to 36% in the M. D. Anderson series (5 of 14), up to 86% in the Cleveland Clinic series (six of seven).

After surgical treatment, 40% to 60% of patients have recurrent disease at some point typically in the range of 2 to 5 years after the initial resection. Since parathyroid carcinomas are functional, serial measurements of calcium or PTH serve as ideal tumor markers for this malignancy. In patients followed closely, hypercalcemia precedes physical evidence of recurrent disease in most cases. The most common location of recurrence is regionally either in the tissues of the neck or in cervical lymph nodes, accounting for two-thirds of the recurrent cases. Often the local recurrences in the neck are difficult to identify as they may be small, multifocal, and involve the scar from the previous procedure. Use of ultrasound, sestamibi-thallium scanning, and more recently positron emission tomographic scanning may aid in this difficult diagnosis. Distant metastases occur in 25% of patients, primarily in the lungs but also in the bone and liver (see Table 38.3-4). More recently published series have reported a higher incidence of recurrence than prior studies. In nine patients from Brazil with parathyroid cancer with long-term follow-up, five had local or nodal neck recurrence (55%), three had lung metastases (33%), and one had bone metastasis (11%). In a study of 16 patients from Italy, 13 had distant metastases (nine lung alone, four lung plus bone) and 2 others had local neck recurrences. The reasons for this high incidence of recurrence between 94% and 100% may be due to more accurate pathologic diagnosis excluding patients with atypical adenomas.

Patients who experience parathyroid carcinoma typically die of metabolic consequences and not directly from malignant growth. For this reason, surgical treatment to debunk parathyroid carcinoma, if possible, is indicated as medical management of the hypercalcemia of parathyroid carcinoma is difficult (see Treatment, later in this chapter). The median survival after recurrent parathyroid cancer ranges between 3 and 5 years, with isolated case reports of patients surviving several decades with intermittent surgical debunking.

### DIFFERENTIAL DIAGNOSIS

Other non-HPT causes of hypercalcemia can be ruled out primarily by the biochemical studies of serum PTH simultaneous with total and ionized serum calcium. Secondary HPT in the setting of renal failure is clinically obvious by the concomitant renal disease. There are isolated reports of development of parathyroid carcinoma in this clinical setting as well, however. Once the diagnosis of primary HPT is established, the histopathologic diagnosis of parathyroid carcinoma may be difficult as discussed previously. Supporting evidence of malignancy comes from markedly elevated calcium levels (greater than 14.0 mg/dL) and larger gland sizes (greater than 3.0 cm). In most reported institutional series, it is likely that parathyroid carcinoma is overdiagnosed. In one such study, a careful review of the pathology in the context of the clinical course identified more than one-half of the patients with previously diagnosed parathyroid carcinomas as more appropriately considered as benign or atypical adenomas. This difficulty in correctly identifying parathyroid carcinoma is also reflected by the wide variation in clinical outcome between different series. Some series report long-term disease-free survival rates greater than 75%. One explanation for series in which outcomes are much better than the norm is that they include in their analysis patients with atypical parathyroid adenomas that were not truly malignant. Other investigators take an opposite approach and include only cases in their institutional reviews that recur locally or manifest distant metastases. This approach may underestimate the true incidence of cases of parathyroid carcinoma because there is a subgroup with this disease that may be cured with an aggressive initial resection.

Local recurrence of parathyroid neoplasms after initial resection does not necessarily establish the diagnosis of parathyroid carcinoma. Two patterns of benign lesions that recur locally have been described. First, patients with a single parathyroid adenoma may have partial or incomplete resection of a gland such that there is an isolated regrowth after the initial procedure in the exact position where the first abnormal gland was removed. The recurrent gland grows in an area of fibrosis and scar, and may give the gross appearance of an invasive carcinoma, but detailed pathologic analysis of the initial or recurrent specimen shows no evidence of carcinoma in terms of mitotic figures, cellular appearance, or fibrous bands. A second category of nonmalignant recurrent disease is a condition called parathyroblastoma. Parathyroblastoma is a diffuse seeding of the cervical tissue with parathyroid cells that implant and grow. This occurs when lesions that are being excised have the capsule ruptured and are spilled or when lesions are partially removed with a raw surface of the adenoma exposed to the field of dissection. This condition is much more difficult to treat than isolated local recurrence and is tantamount to a nonmetastasizing locally recurrent carcinoma, and this condition has been described with lesions that have absolutely no pathologic or clinical manifestations of parathyroid carcinoma.

### TREATMENT

The only effective treatment of parathyroid carcinoma is surgical resection. The most important component to achieve a favorable outcome is recognition by the operating surgeon that a lesion is likely to be a parathyroid cancer, which allows performance of the appropriate en bloc resection of the tumor with all potential areas of invasion at the initial operation. Patients with extremely high serum calcium levels (greater than 13.5 mg/dL) should lead the physician to suspect parathyroid cancer preoperatively. Other clinical features that suggest parathyroid cancer are a palpable mass and hoarseness. Intraoperatively, if a large lesion is identified, particularly if it is firm or scirrhous, then the operating surgeon should assume the lesion is parathyroid cancer and do an en bloc resection. The practice of minimizing invasive parathyroidectomy, which is appropriate in the vast majority of patients with HPT, should be altered in these clinical situations. Parathyroid cancer typically invades the ipsilateral thyroid lobe, and resection of the tumor with one or both thyroid lobes is frequently required to perform an adequate operation. In most series, long-term results in terms of local recurrence are significantly improved when an en bloc excision including thyroid is done as opposed to cases in which

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### REFERENCES

[1] Lahey Clinic series (one in nine). [2] M. D. Anderson series (5 of 14). [3] Cleveland Clinic series (six of seven). [4] Secondary HPT in the setting of renal failure is clinically obvious by the concomitant renal disease. There are isolated reports of development of parathyroid carcinoma in this clinical setting as well, however. Once the diagnosis of primary HPT is established, the histopathologic diagnosis of parathyroid carcinoma may be difficult as discussed previously. Supporting evidence of malignancy comes from markedly elevated calcium levels (greater than 14.0 mg/dL) and larger gland sizes (greater than 3.0 cm). In most reported institutional series, it is likely that parathyroid carcinoma is overdiagnosed. In one such study, a careful review of the pathology in the context of the clinical course identified more than one-half of the patients with previously diagnosed parathyroid carcinomas as more appropriately considered as benign or atypical adenomas. This difficulty in correctly identifying parathyroid carcinoma is also reflected by the wide variation in clinical outcome between different series. Some series report long-term disease-free survival rates greater than 75%. One explanation for series in which outcomes are much better than the norm is that they include in their analysis patients with atypical parathyroid adenomas that were not truly malignant. Other investigators take an opposite approach and include only cases in their institutional reviews that recur locally or manifest distant metastases. This approach may underestimate the true incidence of cases of parathyroid carcinoma because there is a subgroup with this disease that may be cured with an aggressive initial resection.

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only the parathyroid cancer is removed. The recognition and diagnosis of parathyroid cancer preoperatively correlates strongly with a favorable outcome. In a small series of seven patients from the Cleveland Clinic, six had parathyroid carcinomas that were not appreciated until after the procedure. All of these patients had recurrences, whereas the one case that was known to be a parathyroid cancer preoperatively underwent an en bloc resection with long-term disease-free survival. The recurrent laryngeal nerve may be intimately involved or invaded by the parathyroid cancer. In these situations, patients frequently have preoperative hoarseness due to the tumor invasion of the nerve. Because the nerve is at risk for loss of function due to the malignant process itself, it is appropriate to resect the recurrent laryngeal nerve if necessary to perform an en bloc excision during the initial procedure for parathyroid cancer. The increased potential for long-term local control achieved by this approach outweighs the complication of postoperative vocal cord paralysis, which can be improved with techniques such as Teflon injection into the paralyzed cord. Assessment of cervical lymph nodes, particularly level 6 paratracheal nodes and levels 3 and 4 internal jugular nodes, should be performed with node dissection only for enlarged or firm lesions.

For most cases of recurrent parathyroid carcinoma confined to the neck, the most appropriate treatment is aggressive resection. However, as opposed to the initial procedure in which the success rate is up to 40% to 60%, it is unusual to obtain long-term cures in patients who have to undergo resection. In a large series from the Mayo Clinic, no patients who underwent resection were cured. However, there are selective patients described in the literature who have disease-free intervals greater than 10 years after two or three local resections in the neck. The benefit of sacrificing the recurrent laryngeal nerve is greatly decreased in patients undergoing resection for recurrent parathyroid cancer as most recurrences are multifocal. If a recurrent nodule involves the recurrent laryngeal nerve, there are most likely other areas of parathyroid cancer that are adherent to the trachea, esophagus, and great vessels of the neck. Since it is impossible to remove all of these vital structures, one is unlikely to obtain a cure by taking the nerve. However, in certain circumstances in which there is an isolated local recurrence that is involving the nerve, it again should be sacrificed with an en bloc resection as those patients’ conditions, in rare instances, may be salvaged by an aggressive surgical procedure (see Fig. 38.3-2).

Nonsurgical forms of therapy for parathyroid carcinoma have generally poor results such that surgical treatment of distant metastases is appropriate in certain situations. Pulmonary metastases as well as bone metastases should be resected, if possible, primarily to debulk tumor to decrease the magnitude of the hypercalcemia. However, occasionally long-term salvage is achieved in this group of patients with aggressive surgical treatment.

Radiation therapy, in general, does not result in meaningful antitumor responses. Isolated case reports of long-term control exist, and radiation therapy should be used in patients with unresectable recurrent cervical disease. Various chemotherapeutic agents alone or in combination have been used for treatment of parathyroid carcinoma with limited success. Dacarbazine alone or in combination with 5-Fluorouracil and cyclophosphamide have been reported to result in objective responses, including one complete response in a patient with pulmonary metastases. Other combination therapies have resulted in rare responses. Part of the problem with the medical treatment of parathyroid carcinoma is that the rarity of this disease does not allow systematic evaluation of various combination therapies.

The second aspect of medical management for metastatic parathyroid carcinoma relates to the treatment of the hypercalcemia. Acute therapy of patients with hypercalcemic crises or high serum calcium levels is similar to that used for other causes of symptomatic hypercalcemia. Volume loading with loop diuretics causing a forced diuresis is the initial therapy. For patients with parathyroid carcinoma, the ultimate management of the hypercalcemia is directed at the tumor to decrease the level of PTH, if possible, by surgical treatment. In situations in which surgical resections are no longer possible, the treatment of hypercalcemia is difficult, and this metabolic abnormality is the primary cause of death for the majority of these patients. The most effective agents in this setting are the bisphosphonates that inhibit osteoclast bone resorption. Two agents available in the United States are etidronate and pamidronate. Other agents used in other settings of hypercalcemia such as plicamycin (formerly mithramycin) and calcitonin have limited benefit. Gallium nitrate has also been used as an inhibitor of bone reabsorption, but is limited by nephrotoxicity. All agents used to date in the setting of high tumor burden from parathyroid carcinoma have a limitation that the patients become refractory after initial treatment. Newer generations of more potent bisphosphonates may hold some promise for symptomatic management of this group of patients.

OUTCOME

The ability to achieve long-term survival in patients with parathyroid carcinoma ranges between 18% and 78% in various series. The 5- and 10-year overall survival rates for patients with resected parathyroid carcinoma are shown in Table 38.3-5. A summary of 251 patients analyzed shows a 5-year survival of 57% and a 10-year survival of 39%. The National Cancer Database reported a 5-year survival at 55.5% and a 10-year survival of 49.1% in 286 patients treated. These two large series accounted for the majority of cases of parathyroid cancer in the literature and provides an accurate assessment of outcome. The majority of patients who have recurrences after initial surgery ultimately succumb to this disease because there is a much lower rate of salvage after second or third procedures. For patients with local recurrences or distant metastases, only between 0% and 15% have long-term cures after secondary resections as there is no meaningful nonsurgical therapy.

TABLE 38.3-5. Five- and 10-Year Survival after Surgical Excision of Parathyroid Cancer

CHAPTER REFERENCES

Adrenal Tumors

PATHOLOGY OF THE ADRENAL CORTEX

HYPERPLASIA

The term hyperplasia is defined as an increased number of cells. It is a pathologic change associated with increased function or compensatory change. When a pituitary adrenocorticotropic hormone (ACTH)-secreting tumor produces hypercortisolism (Cushing's disease), the most common form of endogenous hypercortisolism, the adrenal gland is approximately twice normal size. The weight of each hyperplastic adrenal is between 6 and 12 g (normal adrenal weights between 3 and 6 g). Microscopically there is a widened inner zone of the compact zona reticularis and a sharply demarcated outer zone of clear cells. Adrenal glands in ectopic ACTH syndrome are larger in size, weighing between 12 and 30 g. Macronodular adrenal hyperplasia (3-cm adrenocortical nodules weighing between 30 and 100 g) usually is a secondary response of the adrenal to ACTH, but may occur with primary adrenal pathology. Primary pigmented micronodular adrenal hyperplasia (1- to 5-mm nodules with pigmented appearance and normal glandular weight) is more likely to be autonomous and to occur in children and can occur in a familial pattern.

ADRENAL CORTICAL ADENOMA

Adrenal adenoma is a benign neoplasm of adrenal cortical cells that may possess functional autonomy. In general, an adenoma does not exceed 5 cm in diameter nor 100 g in weight. Some cellular pleomorphism and tumor necrosis may be present, but is rare. It is not possible to describe the exact functional type of neoplasm based solely on histology, although there are consistent differences. Adenomas produce syndromes of hypercortisolism and hyperaldosteronism and seldom produce adrenogenital syndromes. Tumors larger than 6 cm that produce adrenogenital syndromes are usually carcinoma. Pleomorphism, tumor necrosis, and mitotic activity are more common in malignant tumors. The prognosis of adrenal cortical adenoma producing Cushing's syndrome is excellent, and surgical resection invariably produces cure. The prognosis of adrenal cortical adenomas producing hyperaldosteronism may not be as favorable. Resection is followed by a favorable response in blood pressure and serum level of potassium; however, 30% of patients develop recurrent hypertension. Adenomas that produce the adrenogenital syndrome have the least favorable outcome, because many of these tumors are really carcinomas.

ADRENAL CORTICAL CARCINOMA

Adrenal cortical carcinoma is a malignant neoplasm of adrenal cortical cells demonstrating partial or complete histologic and functional differentiation. Adrenal cortical carcinomas are rare and compose between 0.05% and 0.20% of all cancers. This incidence translates to a rate of only 2 per million in the world population. Women develop functional adrenal cortical carcinomas more commonly than men. However, men develop nonfunctioning malignant adrenal tumors more often than women. There is a bimodal occurrence by age, with a peak incidence less than 5 years and a second peak in the fourth and fifth decade. Adrenal cortical carcinoma has been described as part of a complex hereditary syndrome, including sarcoma, breast, and lung cancer. Studies suggest that loss of heterozygosity on the short arm of chromosome 11 (11p) may be important in the pathogenesis of adrenocortical cancer. Germ line P53 mutations do not appear to be involved. In a study from a region in Brazil with a tenfold higher incidence of adrenocortical cancer, eight of nine tumors had an increase in genetic material in the chromosomal region 9q34, suggesting that these changes may also be important. In addition, deficiency of 21-hydroxylase (P-450c21), an essential enzyme for zona glomerulosa and fasciculata function, has also been implicated. Prevalence of heterozygous germine mutations in the P-450c21 gene has been noted to be increased in patients with adrenocortical tumors. The myriad of genetic changes seen in different studies of these tumors may explain the association of adrenocortical cancer with complex hereditary syndromes.

Adrenal cortical carcinomas are greater than 6 cm in size and weigh between 100 and 5000 g. Areas of necrosis and hemorrhage are common. Invasion and metastases also occur. Microscopically, the appearance is variable. Cells with big nuclei, hyperchromatism, and enlarged nucleoli are all consistent with malignancy. Nuclear pleomorphism is more common in tumors larger than 500 g. Vascular invasion and many mitoses are diagnostic of malignancy. Broad desmoplastic bands are associated with metastatic potential of tumors. The diagnosis of malignancy in cortical tumors that weigh between 50 and 100 g is less certain. Furthermore, the distinction between adrenal and renal carcinoma may also be difficult. Immunostaining for vimentin, epithelial membrane antigen, cytokeratin, and blood group antigens may be used to distinguish the two diagnoses. Adrenal tumors stain positive for vimentin, whereas renal carcinoma is negative for vimentin but positive for the others. Although the difference in natural history between benign and malignant adrenal cortical neoplasms is clear, it is not always possible to histologically separate one from the other. The only reliable, single criterion is the presence of nodal or distant metastases. The data used to differentiate benign from malignant adrenocortical neoplasms include whether and what type of hormone is produced, amount of tumor necrosis, fibrosis, inhibin, 21-hydroxylase deficiency, vascular invasion, micoses, and tumor weight (Table 38.4-1). The detection of mitotic activity and venous invasion suggest a malignant tumor. Aneuploidy is also associated with cancer. Quantitative nuclear analysis demonstrates that nuclei from adrenal cancers are larger than adenomas, and DNA density is diploid in adenomas and aneuploid in carcinomas. A final criterion is based on the observation that cells from carcinomas produce abnormal amounts of androgens and 11-deoxysteroids. However, this is merely suggestive of malignancy, because only 10% of malignant tumors produce masculinization whereas the rest secrete cortisol, aldosterone, or nothing (see Table 38.4-1).
Urinary excretion of unmetabolized ("free") cortisol is directly proportional to the amount of free cortisol in the plasma. As the normal single-dose dexamethasone test and urinary free cortisol (less than 100 µg/d in most laboratories) virtually exclude the diagnosis of hypercortisolism. Cushing's syndrome whose levels suppress). This test may also have false-positives (3%), including depression, alcoholism, stress, and primary cortisol resistance. A hypercortisolism do not suppress and have cortisol levels greater than 5 µg/dL. The major disadvantage of this test is a 3% incidence of false-negatives (patients with endogenous hypercortisolism are not excluded). The most common cause of hypercortisolism is idiopathic administration of steroids to treat other diseases. The most common cause of endogenous hypercortisolism is a pituitary tumor that makes ACTH, or Cushing's disease. Hypercortisolism is not usually associated with multiple endocrine neoplasia type 1 (MEN 1), although it can be present in this familial syndrome. It has been reported to be present in 5% of patients with sporadic Zollinger-Ellison syndrome (ZES) and 19% of patients with ZES and MEN 1.

Progressive weight gain is the most universal symptom of patients with hypercortisolism. Obesity is usually truncal, and patients have thin extremities due to muscle wasting. Increased fat in the dorsal neck region combined with kyphosis secondary to osteoporosis gives the appearance of a "buffalo hump." Serial photographs show a rounding of the face. Increased blood pressure is mild and caused by excess mineralocorticoid secretion. Striae are reliable clinical signs of Cushing's syndrome. Hirsumism consists of excessive fine hair on face, upper back, and arms. Virilization, including clitoromegaly, deep voice, and balding, suggest adrenocortical carcinoma. Glucose intolerance with hyperglycemia is common, and patients may present with diabetes mellitus. Weakness secondary to muscle atrophy is a common complaint and is especially common in ectopic ACTH syndrome with hypokalemia. Menstrual irregularity or amenorrhea is common in women, whereas men with Cushing's syndrome have loss of libido or impotency. In children, the most common presenting sign is obesity and an arrest of normal growth with short stature. Dilatation of blood vessels and thinning of the subcutaneous tissue gives the face a ruddy appearance. Mental changes vary from mild depression to severe psychosis and appear to correlate directly with serum levels of cortisol and ACTH. Hypokalemia worsens the weakness associated with Cushing's syndrome and suggests the diagnosis of adrenocortical carcinoma or ectopic ACTH syndrome. Immunosuppression results in unusual infections, including cryptococcosis, aspergillosis, nocardiosis, Pneumocystis carinii, and necrotizing fasciitis. The early diagnosis of Cushing's syndrome depends primarily on a knowledge of the many different signs and symptoms of the disorder and a high clinical index of suspicion.

Workup and Diagnosis

The initial step in the workup of a patient with presumptive hypercortisolism is to establish biochemically whether hypercortisolism is, in fact, present. The second step is to determine whether the hypercortisolism is "pituitary dependent" or "pituitary independent," and the final step is to determine the exact etiology (see Fig. 38.4-1). Current laboratory testing allows the correct diagnosis in nearly every case. ESTABLISHING HYPERCORTISOLISM. Urinary excretion of unmetabolized ("free") cortisol is directly proportional to the amount of free cortisol in the plasma. As the cortisol-binding globulin becomes saturated (plasma cortisol levels of 20 µg/dL), small increases in cortisol secretion produce exponential increases in urinary free cortisol. This amplification effect makes 24-hour urinary free cortisol the single best measurement to discriminate normal from hypercortisolemic states. The overnight single-dose dexamethasone test (see Fig. 38.4-1) works because of lack of normal feedback (Fig. 38.4-2) that occurs in all forms of hypercortisolism. Normal subjects given 1 mg of dexamethasone orally at 11:00 p.m. have plasma cortisol levels of less than 5 µg/dL at 8:00 a.m. the next day. Patients with endogenous hypercortisolism do not suppress and have cortisol levels greater than 5 µg/dL. The major disadvantage of this test is a 3% incidence of false-negatives (patients with Cushing's syndrome whose levels suppress). This test may also have false-positives (3%), including depression, alcoholism, stress, and primary cortisol resistance. A normal single-dose dexamethasone test and urinary free cortisol (less than 100 µg/d in most laboratories) virtually exclude the diagnosis of hypercortisolism.
ETIOLOGY OF HYPERCORTISOLISM. Patients with pituitary tumor (Cushing's disease) respond to 1 µg/kg corticotropin-releasing hormone (CRH) by increasing plasma cortisol levels, whereas patients with depression or other stress diseases have a blunted ACTH response to CRH (see Fig. 38.4-1 and Fig. 38.4-2). The CRH test also distinguishes pituitary tumor from ectopic secretation of ACTH. Twenty-nine of 33 patients with Cushing's disease had increased plasma ACTH and cortisol levels after a CRH test, whereas none of 8 with ectopic ACTH responded. Patients with Cushing's syndrome have abnormalities in the diurnal rhythm of plasma levels of cortisol and ACTH. Serial samples over days are necessary because patients with Cushing's disease can have episodic secretion of cortisol. Nevertheless, a low midnight cortisol level (less than 2 µg/dL) excludes the diagnosis of endogenous hypercortisolism. Determination of plasma ACTH levels may also be helpful. Patients with primary adrenal tumors or hyperplasia have undetectable or low plasma ACTH levels, those with pituitary-dependent hypercortisolism have intermediate levels, and those with ectopic ACTH-producing tumors have very high levels; approximately 60% of these patients have ACTH levels greater than 300 pg/mL. Radioimmunoassays for ACTH in plasma have been difficult to perform reliably and interpret because of platelet-associated proteases that degrade ACTH. Secretion of ACTH must be collected using recommended procedures, including prechilled tubes on ice. Urinary 17-ketosteroids can help differentiate the differential diagnosis of hypercortisolism. Low levels (less than 10 mg/d) suggest an adrenal adenoma, and very high levels (more than 60 mg/d) occur more commonly in patients with adrenal cancer and ectopic ACTH. Hypokalemia is seen in most patients with ectopic ACTH (16 of 16 in one series) and in only 10% of patients with Cushing's disease.

The standard dexamethasone suppression test is the most useful test in establishing the cause of hypercortisolism (see Fig. 38.4-1 and Fig. 38.4-2). The expected results are that urinary free cortisol levels will be markedly suppressed when normal subjects receive a low dose (2 mg) of dexamethasone, but levels do not suppress in patients with Cushing's syndrome. High-dose dexamethasone (8 mg/d) suppresses urinary levels of free cortisol to less than 50% of baseline levels in patients with pituitary-dependent hypercortisolism (Cushing's disease), but it does not suppress levels in patients with primary adrenal causes of hypercortisolism or ectopic ACTH syndrome. This single test makes the diagnosis of Cushing's syndrome and determines the cause of hypercortisolism with an accuracy rate of approximately 95%.

The metyrapone test, which is a stimulation test in patients with pituitary Cushing's disease, can be complementary to the dexamethasone suppression test, and combining both tests results in greater accuracy than with either test alone.

RADIOLOGIC EVALUATION OF HYPERCORTISOLISM. Computed tomography (CT) scans of the sella detect a tumor in only 0% to 15% of patients with pituitary-dependent Cushing's disease. Adrenal CT can detect microadenomas in 23% to 60%. Most ACTH-secreting tumors are microadenomas (less than 5 mm). Pituitary magnetic resonance imaging (MRI) studies, even with gadolinium, have similar resolution. In patients with pituitary-dependent hypercortisolism, CT and MR may be normal, but bilateral petrosal sinus sampling for ACTH concentrations detects the side with a tumor in most cases. Data indicate that this is the single best method to differentiate a pituitary from an ectopic ACTH-producing tumor. The study requires bilobar sampling of the inferior petrosal sinus and peripheral veins for plasma ACTH levels before and after CRH. A petrosal sinus to peripheral plasma ACTH level of greater than 3 after CRH administration correctly identifies patients with Cushing's disease (sensitivity, 100%) with few false-positive results (specificity, 100%). Furthermore, petrosal sinus sampling provides correct localization of the ACTH-producing microadenoma in most patients. It is the study of choice both to diagnose and localize pituitary tumors in patients with Cushing's disease.

Adrenal CT can detect normal adrenal glands in most patients. CT can reliably distinguish cortical hyperplasia from tumor. CT has great sensitivity (more than 95%); however, it lacks specificity. In a patient with Cushing's syndrome, early detection of an adrenal neoplasm by CT simplifies the workup. CT can be used to image the primary tumor plus local and distant metastases in patients with cancer. In these cases, the primary tumor is usually greater than 6 cm. Approximately 15% of patients with Cushing's syndrome have a primary adenoma as the source of the hypercortisolism. Unilateral adrenal tumors require the detection of a normal adrenal gland on the contralateral side. Adrenal hyperplasia may also be detected if both glands appear enlarged. MRI may be able to add specificity to the sensitivity of CT. MRI may be able to distinguish adrenal adenoma from carcinoma and pheochromocytoma by the appearance on the T2-weighted image. Adenomas appear darker than the liver on the T2 MRI. Carcinomas, whether primary adrenocortical or metastatic, appear as bright as or slightly brighter than the liver on T2 image. Pheochromocytomas appear much brighter (three times) than the liver on T2 MRI.

Radioisotope imaging of adrenals using labeled iodocholesterol, such as 131I-6-b-kodimethylnorcholesterol, can be used to distinguish adrenoma from hyperplasia. It can help differentiate a benign cortical neoplasm (adenoma), which usually takes up iodocholesterol (images), from a malignant cortical neoplasm (carcinoma), which usually does not. This is not absolute, however, because adrenal cortical carcinomas may take up iodocholesterol and be "hot" on scan. Iodocholesterol scan can be helpful in micronodular hyperplasia in which bilateral uptake confirms the diagnosis. It can image ectopic rests of adrenal tissue. The disadvantages of radiodiodocholesterol scans are exposure to radiation, limited isotope availability, and poor imaging of malignant adrenal neoplasms.

INTERPRETATION OF WORKUP FOR CUSHING'S SYNDROME. Once the biochemical tests confirm endogenous hypercortisolism, the remainder of the workup can pinpoint its cause. If it is caused by an adrenal cortical neoplasm, the workup will produce the following results: (1) imaging of the tumor on CT and MRI, (2) low plasma ACTH levels with elevated serum cortisol levels, and (3) no suppression of urinary free cortisol level with high-dose dexamethasone. If criterion number 1 is absent but numbers 2 and 3 are present, primary cortical adenoma or carcinoma should be ruled out by iodocholesterol scan (see Fig. 38.4-1). If criteria numbers 1 and 3 are present but ACTH levels are consistently elevated, urine catecholamines, vanillylmandelic acid (VMA), and metanephrines should be measured because the patient may have an ACTH-producing pheochromocytoma.

In ectopic ACTH syndrome, one finds (1) enlargement of both adrenals on CT, (2) elevated plasma ACTH levels, (3) no suppression with high-dose dexamethasone, and (4) no evidence of pituitary ACTH secretion on petrosal sinus sampling. Bronchial carcinoid tumors are the most common site of ectopic ACTH secretion and are potentially curable. Lobectomy is required, because a significant proportion has nodal metastases. Some bronchial ACTH-producing carcinoid tumors may suppress with dexamethasone, but the false suppression of ectopic ACTH-producing tumors is rare. Malignant tumors, such as Ewing's sarcoma, have been rarely determined to secrete a CRH-like factor that causes Cushing's syndrome. Studies from the Netherlands suggest that Octreoscan (somatostatin receptor scintigraphy) may be useful to image the source of ectopic ACTH. It correctly identifies 80% of ACTH-secreting carcinoid tumors (either bronchial or thymic carcinoids).

In Cushing's disease (pituitary adenoma), one expects to find (1) bilateral hyperplasia of the adrenal glands, (2) normal or mildly elevated plasma ACTH levels, (3) no suppression with low-dose dexamethasone and suppression with high-dose dexamethasone, and (4) localization with petrosal sinus sampling. Occasionally (less than 5% of instances) results may be confused with ectopic ACTH syndrome. This is not common, however, and most studies show that petrosal sinus sampling eliminates the ambiguity.

CONN'S SYNDROME (PRIMARY ALDOSTERONISM)

Signs, Symptoms, and Diagnosis

Aldosterone overproduction with elevated plasma levels is the cause of hyperaldosteronism in patients with primary aldosteronism, or Conn's syndrome. The most common cause of primary aldosteronism is an aldosterone-producing adenoma; next is idiopathic hyperplasia and last is carcinoma. Secondary aldosteronism, which occurs with renal artery stenosis, cirrhosis, and conditions of decreased kidney perfusion, is diagnosed by an increase in plasma renin activity.

Hypertension, hypokalemia, hyperaldosteronism, and decreased plasma renin levels are essential for the diagnosis of primary aldosteronism. Primary hyperaldosteronism is also associated with weakness, muscle cramps, polyuria, and polydipsia. These clinical signs are due to hypokalemia. Hypertension is usually not severe and is mostly diastolic (diastolic pressure more than 90 mm Hg).

The serum potassium level is usually less than 3.5 mEq/L. Another possible diagnosis is essential hypertension treated with diuretics, although patients with that diagnosis seldom have potassium levels less than 3.5 mEq/L. All diuretics and antihypertensive medications should be stopped and 24-hour urinary potassium excretion measured. In most patients with primary aldosteronism, 24-hour urinary excretion of potassium is greater than 30 mEq. Patients with primary hyperaldosteronism have elevated plasma levels of aldosterone and low levels of renin activity. Measurement of messenger RNA (mRNA) in the kidney and adrenal
gland of patients with aldosteronoma also has demonstrated decreased levels of renin mRNA. The plasma aldosterone-renin ratio is usually greater than 30. Final evidence for the diagnosis of primary hyperaldosteronism relies on the inability to lower plasma aldosterone levels and raise plasma renin activity after captopril. The patient takes 25 mg of captopril orally in the morning. Two hours later, plasma levels of aldosterone and renin activity are measured. In normal subjects and patients with essential hypertension, captopril decreases plasma aldosterone levels and increases plasma renin activity. In patients with primary aldosteronism, plasma levels of aldosterone and renin activity do not change. A post-captopril plasma aldosterone level greater than 15 ng/dL and an aldosterone-renin ratio greater than 50 are diagnostic of primary aldosteronism (Table 38.4-2).

### Table 38.4-2. Diagnosis of Primary Aldosteronism

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenal venous sampling</td>
<td>96%</td>
<td>100%</td>
</tr>
<tr>
<td>CT</td>
<td>75% to 90%</td>
<td></td>
</tr>
<tr>
<td>Iodocholesterol scans</td>
<td>88%</td>
<td></td>
</tr>
</tbody>
</table>

### Adenoma versus Hyperplasia

Once the diagnosis of primary aldosteronism is established, the next important consideration is the etiology—whether the patient has idiopathic adrenal hyperplasia (IAH) or a tumor that produces aldosterone (Table 38.4-3). The exact cause is critical because drug treatment is indicated for IAH, and surgery is indicated for a neoplasm. Measurement of plasma aldosterone concentrations with respect to postural changes is a relatively quick biochemical test to differentiate between the two. A decrease or no change in the serum level of aldosterone measured at 8:00 a.m. and noon in the upright position after overnight recumbence is consistent with an adenoma. The accuracy of this test is between 75% and 100%.

### Table 38.4-3. Etiology of Primary Aldosteronism: Idiopathic Adrenal Hyperplasia (IAH) versus Neoplasm

CT can image approximately 75% to 90% of aldosteronomas. CT may miss small tumors. The contralateral adrenal cortex in a patient with an aldosteronoma appears thin on CT. Iodocholesterol scans with 131I-labeled norcholesterol can image 88% of aldosteronomas. The advantage of these nuclear studies over CT is the provision of functional information about the neoplasm. In patients with IAH, the scan shows symmetrical uptake in both adrenal glands; and in patients with adrenal carcinoma causing hyperaldosteronism, the study may show no uptake by the tumor, whereas in adenomas tumor uptake is usually evident.

The single study of choice to determine if hyperaldosteronism is caused by a tumor or hyperplasia is sampling of the adrenal veins for aldosterone. The procedure is performed by simultaneous selective catheterization of both adrenal veins and a peripheral vein. Serum levels of aldosterone and cortisol are measured at each site before and after ACTH. Aldosteronomas make aldosterone in response to ACTH. A unilateral elevation of aldosterone level or of the aldosterone-renin ratio indicates the presence of an aldosterone-secreting adenoma. Bilateral levels of aldosterone that are similar and greater than peripheral levels are consistent with IAH. Adrenal venous sampling for aldosterone (96%) is more sensitive than CT (75%) and adrenal venography (78%) in prospective comparisons. If CT is nondiagnostic, venous sampling is the study of choice to distinguish a tumor from hyperplasia.

### Treatment

The management of primary aldosteronism depends on the diagnosis. Idiopathic adrenal hyperplasia is best managed medically with spironolactone or amiloride in conjunction with other antihypertensive drugs. Another drug with potential for managing the hypokalemia and hypertension associated with primary aldosteronism (both IAH and adenoma) is the calcium channel blocker nifedipine. Because aldosteronomas are usually small benign adenomas, it is now preferable to use a laparoscopic approach for unilateral adrenalectomy in patients with aldosteronoma. The laparoscopic approach is associated with less pain and morbidity.

Results for resection of an aldosteronoma have not been entirely satisfactory. A high percentage of patients initially become normotensive and normokalemic postoperatively (approximately 95% dependent on accurate diagnosis). However, 20% to 30% of patients develop recurrent hypertension within 2 to 3 years. This has caused some physicians to advise against surgery and recommend long-term medical management. This therapy has been demonstrated to effectively control blood pressure and serum level of potassium in patients with aldosteronoma for periods of up to 5 years. Aldosterone-producing adrenocortical carcinomas are rare (2% of all carcinomas). Treatment is similar to other patients with adrenal carcinoma and is discussed later (see the section Treatment of Adrenal Cortical Neoplasms).

### INCIDENTAL ADRENAL MASS

High-resolution CT scans have resulted in a new diagnostic problem: an incidental adrenal mass detected by CT. Unexpected adrenal masses are seen in 0.6% of abdominal CT scans. The majority of these are benign adrenal cortical adenomas, which occur in 9% of autopsies. However, one report indicates that an asymptomatic 3-cm adrenal mass that was followed subsequently was found to be metastatic adrenocortical carcinoma. Of 311 incidentally discovered adrenal tumors, adrenocortical carcinoma was diagnosed in 21 cases (7%).

The suggested evaluation of an incidental adrenal mass (incidentaloma) is given in Figure 38.4-3. Two questions arise. Is the tumor functional? Is it cancer?
The first step in evaluation of an incidentally discovered adrenal mass is a careful history and physical examination, including blood pressure. The clinician should examine for evidence of weight change, weakness or hypokalemia. Cushing's syndrome, hypertension, virilization, feminization, change in menstruation, and evidence of occult malignancy (stool guaiac, pap smear, anemia). Laboratory evaluation should consist of a 24-hour urine collection for free cortisol, VMA, metanephrines, and catecholamines. Twenty-four-hour urinary levels of free cortisol are indicated to rule out Cushing's syndrome. Patients with incidentalomas and no stigmata of Cushing's syndrome have been identified who have occult hypercortisolism. These individuals are fairly uncommon but can be identified by measuring a 24-hour urine sample for free cortisol or a low-dose dexamethasone suppression test. If urinary levels of catecholamines or catecholamine metabolites are elevated, the diagnosis is pheochromocytoma (see the section regarding management in Pheochromocytoma, later). In addition, the serum potassium concentration is used to exclude an aldosteronoma. Plasma levels of aldosterone and renin activity should be measured in any patient with hypertension and hypokalemia. Hormonal screening for an excess of androgens or estrogens is limited to patients with clinical signs suggestive of these disorders.

The size of an adrenal mass on CT is an important determinant of a potentially malignant tumor. Adrenal cortical carcinomas are generally greater than 6 cm in diameter, and benign lesions are less than 6 cm. Nevertheless, a smaller lesion should not be totally ignored. Early diagnosis may lead to discovery of a small adrenal cortical carcinoma, which may lead to better prognosis and survival. Patients with primary adrenal cancers less than 5 cm in size have a better prognosis than those with larger tumors. Most recently, because of decreased morbidity with laparoscopic excision, some have advocated surgery for incidentalomas of 4 cm in size, especially in younger patients. CT can accurately image normal glands, hyperplastic adrenal glands, and neoplasms, but it can only distinguish benign from malignant neoplasms by criteria such as size, direct invasion, or distant metastases.

Fine-needle aspiration for cytology of an adrenal mass has limited ability to differentiate benign from malignant primary adrenal lesions. Fine-needle aspiration may be catastrophic in a patient with an unsuspected pheochromocytoma, so urinary catecholamines are indicated to exclude a pheochromocytoma before needle biopsy. In patients with suspected metastatic disease to the adrenal or lymphoma, needle aspiration may be helpful. In patients with known primary cancers, fine-needle aspiration can reliably diagnose adrenal metastasis. Because it cannot distinguish between benign and malignant primary adrenal tumors, fine-needle aspiration cytology is not routinely recommended.

The suggested approach to an asymptomatic adrenal mass is outlined in Figure 38.4-3. Biochemical assessment should be performed to exclude hormonal function of the tumor. The size of the tumor is assessed. Size greater than 4 cm is an indication for surgical resection, especially in a younger patient. The incidence of cancer in solid adrenal masses equal to or greater than 6 cm is estimated to be between 35% and 98%. Laparoscopic excision of smaller tumors is recommended because of less pain and morbidity.

Laparoscopic excision of large adrenal tumors (greater than 6 cm) is not recommended because a high proportion of these tumors are malignant. However, some suggest that size is not a contraindication to the laparoscopic approach. We prefer the open anterior approach to malignant adrenal tumors because of fewer long-term wound complications and higher likelihood of complete tumor excision. If the tumor is hormonally functional, adrenalectomy is indicated and is usually performed laparoscopically. If the patient has a history of cancer, fine-needle aspiration can be considered to exclude adrenal metastases. If the mass is smaller than 4 cm and nonfunctional, a repeat follow-up CT examination in 3 to 6 months is indicated to again determine size. If size increases, surgical excision is necessary. If there is no change at 6 months, it is most likely an adenoma, and subsequent CT scans are unnecessary. It is hoped that the evaluation provides early surgical intervention for functional or malignant adrenal masses and exclusion of nonfunctional benign adrenal adenomas.

SEX HORMONE EXCESS

Adrenocortical carcinoma may present with excessive sex hormone secretion. Virilization or feminization may be combined with hypercortisolism, or the tumor may produce only estrogen or testosterone. In children, the clinical signs of increased androgen production include increased growth, premature development of pubic and facial hair, acne, genital enlargement, increased muscle mass, and deep voice. In women, the clinical signs of excess androgen production include hirsutism, acne, amenorrhea, infertility, increased muscle mass, deep voice, and temporal balding. In children, the clinical signs of increased estrogen production include gynecomastia in boys and precocious breast enlargement and vaginal bleeding in girls. In adult men, hyperestrogenism presents with gynecomastia, decreased sexual drive, impotence, and infertility. In adult women, hyperestrogenism presents primarily with irregular menses in premenopausal women and dysfunctional uterine bleeding or vaginal bleeding in postmenopausal women. The workup requires 24-hour urinary 17-ketosteroids, 17-hydroxysteroids, urinary free cortisol and, depending on virilization or feminization, serum determination of testosterone or estrogen.

Virilization secondary to an adrenal neoplasm may accompany Cushing's syndrome, and if it does occur, it usually indicates adrenal cortical carcinoma. Virilization in the absence of Cushing's syndrome may also occur due to adrenal cortical adenoma or carcinoma. Of course, there are many other disorders that cause virilization in women and children; however, in working up a patient with virilization, an imaging study of both adrenals, either CT or MRI, is indicated to rule out an adrenal neoplasm.

TREATMENT OF ADRENAL CORTICAL NEOPLASMS

ADRENAL CORTICAL ADENOMA

The definitive treatment of benign adrenal adenoma is surgical resection of the adrenal gland with the adenoma. Laparoscopic adrenalectomy is rapidly becoming the procedure of choice to remove benign adrenal tumors. It is clearly indicated for smaller tumors (less than 6 cm) because it is associated with less pain and shorter convalescence. In patients who are undergoing resection of an adrenal tumor that causes Cushing's syndrome, steroid replacement during and after surgery is necessary. Glucocorticoid replacement is not required. Postoperative glucocorticoid replacement is indicated until complete recovery of the hypothalamic-pituitary-adrenal axis (see Fig. 38.4-2). Glucocorticoid replacement may be necessary for as long as 2 years. Surgical resection of an adenoma is curative. Larger lesions weighing between 50 and 100 g that appear benign histologically (no mitoses and no vascular invasion) need careful long-term follow-up to exclude carcinoma.

ADRENAL CORTICAL CARCINOMA

The mainstay of treatment of adrenal cortical carcinoma is complete resection of all gross tumor. If the carcinoma is intimately associated with the kidney, liver, or diaphragm on the right or pancreas on the left, it may be necessary to remove part or all of the contiguous structures at the time of definitive surgery. It is important to consider that the best time for curative resection is the initial time. The surgeon needs adequate imaging of the extent of disease, which can be achieved by CT, MRI, or both. CT or MRI should include the chest to rule out metastatic disease above the diaphragm. If the right adrenal is involved and the inferior vena cava is compressed, either an inferior vena cava contrast study or caval ultrasound is useful to assess tumor extension into the cava. If resection of one kidney is indicated, either an intrarenal approach or an intravenous contrast CT is necessary to be certain the contralateral kidney is functioning. A complete bowel preparation is used in case the tumor invades the bowel. Even though patients with hypercortisolism have impaired healing, adrenal tumor resection can be performed with acceptable morbidity and an operative mortality of 3%.

Adrenal cortical carcinoma can occur in adults and children. It occurs in children younger than 6 years, with a higher incidence in girls than boys. The median age in
children with adrenal cancer is 4 years. Virilization is the most common presenting feature (93%). Some children may also present with precocious puberty or Cushings syndrome. Some children with adrenal cancer can be cured by complete surgical resection. Approximately 65% of children with adrenocortical cancer can be cured by complete surgical resection of tumor. In a multivariate analysis of predictors of outcome, only primary tumor size greater than 200 cm independently identified a poor-prognosis group of children who may require more aggressive adjuvant therapy after surgery. One study of children with adrenocortical cancer demonstrated that virilization was the most common presenting symptom, followed by Cushings syndrome. The overall 5-year survival rate was 49%, and when all tumor was removed, it was 70%.

The second peak age of occurrence of adrenal cancer is between 40 and 50 years, and approximately 70% of these patients present with hormonal syndromes. The surgical staging of adrenal carcinoma is as follows:

I. Tumor less than 5 cm without local invasion, nodal, or distant metastases
II. Local invasion or positive lymph nodes
III. Tumor with local invasion or positive lymph nodes
IV. Tumor with local invasion and positive lymph nodes or distant metastases (Table 38.4-4)

Most patients (70%) present with stage III or IV disease. Some recommend adjuvant mitotane therapy after surgical resection to improve survival. Doses between 1.5 and 2.0 g/day are well tolerated and may prolong survival. However, others do not recommend mitotane therapy because it has not been proven to prolong survival. In an analysis of 105 adult patients with adrenal cancer, only 80 were able to undergo surgery for possible cure, and the median disease-free interval postoperatively was 12 months. The overall 5-year survival rate was 22%. In most series, the 5-year survival rate is between 20% and 35%. In a series from Italy, the 5-year survival rate after surgical resection in 129 cases was 35%. In another series from Goteborg, Sweden, complete surgical resection was routinely combined with 1 year of mitotane therapy. Sixteen patients were treated, and the 5-year survival rate was 58% based on the Kaplan-Meier method. Age over 40 years and the presence of metastases at the time of diagnosis correlated with a poor prognosis. If complete resection of tumor cannot be achieved, tumor debulking should be attempted to decrease the amount of corticosteroid-secreting tissue and to minimize complications due to tumor mass. Patients who undergo definitive resection surgery should undergo monitoring of steroid hormone levels postoperatively. Accurate measurement of urinary levels requires switching the glucocorticoid replacement therapy from hydrocortisone to dexamethasone. CT and MRI are also used to detect local recurrences and pulmonary metastases. If a recurrence is detected, it can be removed surgically. Prolonged remissions have been reported after resection of hepatic, pulmonary, and cerebral metastases from adrenal cortical carcinoma. Patients with recurrent adrenal cortical carcinoma who can be surgically resected have improved survival over those who cannot. In 52 cases of recurrent disease, the 5-year survival rate of reoperated cases was 50% versus 8% for nonoperated cases. When complete resection of tumor metastasis is not possible, near total resection may still be helpful in some hormonally productive, slow growing adrenal cortical cancers. Palliation of bony metastases may be achieved by radiation therapy. Abdominal radiation therapy may be useful in 65% of patients with local recurrences not amenable to resection, and the treatment has even relieved bowel obstruction. However, it does not appear to improve the duration of survival.

CHEMOTHERAPY

Once the patient has recurrent or metastatic adrenal cortical carcinoma, chemotherapy with o,p-DDD (mitotane) usually is started. Therapy is initiated at a dose of 2 to 6 g daily in two or three divided doses and increased until adverse reactions occur. Adverse reactions include gastrointestinal toxicity (anorexia, nausea, vomiting, and diarrhea), neurotoxicity (depression, dizziness, tremors, headache, confusion, and weakness), and skin rash. Seventy-nine percent of treated patients developed gastrointestinal toxicity, 50% developed neurotoxicity, and 15% developed a skin rash. Mitotane is associated with prolongation of the bleeding time and abnormal platelet aggregation. A decrease in urinary 17-hydroxysteroids and 17-ketosteroids occurs in 67% of patients treated due to a direct effect on steroid metabolism, and a partial response occurs in approximately 35% of patients treated with mitotane. It is important to measure blood levels of o,p-DDD and achieve levels of at least 14 µg/mL. In one study, patients who had blood levels of less than 10 µg/mL had no demonstrable therapeutic effects, whereas seven of eight patients who had levels greater than 14 µg/mL had objective responses and subsequently lived significantly longer. Unfortunately, the difference between efficacy and toxicity is small, and levels greater than 20 µg/mL are associated with symptoms of neurotoxicity.

Tumor responses usually occur in the first 6 weeks after the initiation of mitotane treatment. Although most patients who demonstrate an objective response to o,p-DDD subsequently relapse, there have been a few long-term survivors with metastatic adrenocortical carcinoma treated with mitotane. Mitotane may be an unpleasant drug, and when clinical toxicity is present, the dose must be adjusted to minimize side effects. Because patients with adrenocortical carcinoma are rare, there have been no controlled studies to establish that mitotane can significantly alter the natural course of adrenocortical carcinoma. Some suggest that adjuvant o,p-DDD improves survival after initial surgery for adrenocortical carcinoma, although most experts do not recommend it as an adjuvant drug after total resection of primary adrenocortical carcinoma. In a report of 59 patients with adrenal cancer who received mitotane therapy at a dose between 7 and 10 g/day, 37 patients were evaluable for tumor response. Of the 37 patients, only 8 (22%) had a documented partial response. Mitotane has been reported to have a 20% response rate. Most experts do not recommend mitotane for the management of patients with adrenocortical cancer. However, others argue that the dose of drug is critical and that the dose of mitotane must be pushed to toxicity to see reasonable response rates. When one achieves a measurable serum mitotane level greater than 14 µg/mL, mitotane appears to have a more favorable impact on survival. Lower serum levels have no impact at all. At best, the response rate with mitotane alone is 60%, and few complete responses have been reported. Mitotane has clear benefit to help control hypercortisolism. In one retrospective review, two inoperable patients were treated preoperatively with mitotane and streptozotocin, and each had a 50% reduction in primary tumor size. One patient also had complete regression of pulmonary metastases. Tumor was resected in both patients, and both were treated with more chemotherapy postoperatively. Both patients have remained completely free of disease for 5 and 9 years postoperatively. Chemotherapy has been combined with mitotane treatment. Eighteen patients with advanced adrenal cortical carcinoma were treated with etoposide (VP16), 100 mg/m²/day, and cisplatin, 100 mg/m², every 4 weeks plus mitotane. A complete response was seen in three cases and a partial response in three cases, for an overall response rate of 33%. Because of the in vitro finding that mitotane is able to reverse multidrug resistance, it has also combined with etoposide, doxorubicin, and cisplatin in a (n = 38) Italian multicenter trial of patients with advanced metastatic adrenal cortical carcinoma. A complete response was achieved in two patients and partial responses in 13, for an overall response rate of 54%. Patients treated with mitotane plus chemotherapy have prolonged survival over patients treated with chemotherapy alone.

Chemotherapy regimens besides o,p-DDD have been ineffective against adrenal cortical carcinoma. Partial responses have been reported with regimens based on doxorubicin and alkylating agents. Promising regimens include cisplatin and etoposide. In three studies including these drugs in patients with metastatic adrenal cortical carcinoma who failed mitotane, there were seven responses in eight patients, including one complete response, although the complete responder had a
duration of only 1 year. Another active regimen includes 5-fluorouracil, doxorubicin, and cisplatin, which has produced 3 responders in 13 patients treated. One patient had a complete response that lasted for 42 months. Patients who have not responded to mitotane have been effectively treated with a combination of cisplatin and etoposide. Suramin is known to inhibit the binding of growth factors, including epidermal growth factor, platelet-derived growth factor, and transforming growth factor-β, to tumor receptors and may reduce tumor growth by antagonizing these factors. It has been used as a phase 1 agent in 21 patients with metastatic adrenal cortical cancer who have failed other therapy, and 3 partial responses (14%) were seen with no complete responses. Suramin has toxicity related to blood coagulation, and some patients have had thrombotic events and hemorrhage (C. A. Stein, R. LaRocca, C. E. Myers, personal communication, 1991). In a study of nine patients with metastatic adren al cortical carcinoma treated with suramin, cumulative doses between 8 and 30 g were administered over 1 to 15 months. One-third had a partial response, and the remainder had progression or stabilization. Toxicity included polyneuropathy, coagulopathy, and thrombocytopenia. Suramin has had limited efficacy and serious toxicity. Suramin does not appear to be an effective agent in adrenal cancer.

In vitro studies in a soft agar system suggest that the new midazole tetraazoline compound 8-carbamoyl-3-methylimidazo(5,1-d)-1,2,3,5-tetrazin-4(3H)-1 (benzimidazole) is very active against adrenal cortical carcinoma. Paclitaxel also has been shown to be effective against the adrenocortical carcinoma cell line, human NCI-H295, in in vitro studies. Taxol also has been effective in in vitro studies against a steroid-secreting malignant adrenal cortical carcinoma cell line. Gossypol has been shown in experimental studies of adrenal cancer to inhibit tumor growth and prolong survival of mice. However, in phase 1 human studies with metastatic adrenal cancer, it had a partial response rate of 20%. One 5-year-old child with metastatic adrenal cancer had a near complete response to oncovin, cisplatin, epipodophyllotoxin, and cytoxan. Steroid hormone receptors have been detected in vitro in adrenal cortical carcinomas, indicating dependence on progesterone and glucocorticoid. However, in vivo studies of therapy related to manipulation of receptors have not been done. The available chemotherapeutic agents and results are summarized in Table 38.4-5. Mitotane is a first-line chemotherapy drug, and combination regimens including cisplatin and other drugs are the preferred second-line choices. Adrenal cortical carcinoma is rare and malignant. Most patients present with stage III and IV tumors (see Table 38.4-4). Metastatic sites of adrenal cancer are lymph nodes (68%), lung (71%), liver (42%), and bone (26%). Surgical cure may only be feasible in stage I or stage II tumors (tumors confined to the adrenal gland).

**TABLE 38.4-5. Chemotherapy Agents Used to Treat Adrenocortical Carcinoma**

In patients with invasion of contiguous structures at presentation, median survival is 2.3 years. Patients who present with stage I disease have a 50% 5-year survival rate compared with patients who present with either stage II or III disease, who have a 10% 5-year survival rate. In patients with tumors confined to the adrenal gland, the mean duration of survival is 5 years. For all patients, the 5-year survival rate is between 10% and 35%, indicating that most patients present with locally advanced or distant disease. Most clinicians still recommend aggressive surgical resection of locally recurrent or metastatic cancer in these patients, but one study demonstrates that, even with this aggressive intervention, the 5-year survival rate is only approximately 10% to 20%. These data indicate the poor prognosis of all patients with adrenal cortical carcinoma and support the use of adjuvant systemic chemotherapy or radiotherapy for resectable lesions (stages I to III). Based on the current evidence, however, adjuvant chemotherapy or radiation therapy is not recommended because effective regimens have not yet been documented. Future challenges for better treatment of adrenal cortical carcinoma include earlier diagnosis and better adjuvants than o,p-DDD. Earlier diagnosis can be facilitated by an index of suspicion of hormonal excess during history and physical examinations. Changes in body appearance and menstrual history are important clues to earlier diagnosis. The use of MRI to differentiate benign from malignant incidentalomas of the adrenal may help clinicians find early resectable adrenal cortical cancers. Drugs such as cisplatin and etoposide or mitotane combined with chemotherapy may be useful in the management of these difficult patients.

**ECTOPIC ADRENOCORTICOTROPIC HORMONE SYNDROME**

The first report of a patient who exhibited features of Cushings's syndrome had an oat cell carcinoma of the bronchus secreting a peptide now called corticotropin, or ACTH. Similar patients who had adrenal hyperplasia without pituitary tumors were reported over the next 30 years, but it was Christy and Liddle who established the presence of ACTH-like material in tumors other than pituitary tumors, in the blood, and in subnormal quantities in the pituitary itself. The name ectopic ACTH syndrome was introduced in 1962. The diagnosis of ectopic ACTH syndrome is based on the metabolic evidence of the patient who presents with hypercortisolism. An early clue to the diagnosis is the presence of Cushings's syndrome and severe hypokalemia (potassium level under 3.3 mEq/L). The diagnosis is based primarily on high plasma ACTH and cortisol levels, which do not change with high-dose dexamethasone or administration of CRH, and results of petrolatum sinus sampling that demonstrate low levels of ACTH draining the pituitary gland that do not change with CRH. Once the diagnosis is established, the primary therapeutic goal is to find and eradicate the neoplasm that is secreting ACTH. When this is accomplished by surgery, chemotherapy, or radiotherapy, long-term cures can be achieved. The main clinical problems have been finding the source of ectopic ACTH in some patients and treating the aggressive underlying tumor in others. The causative tumors, in approximate order of frequency, are as follows:

1. Oat cell or small cell lung cancer
2. Carcinoid tumor of the bronchus
3. Epithelial carcinoma of the thymus or thymic carcinoids
4. Pancreatic islet cell tumor
5. Medullary carcinoma of the thyroid gland
6. Pheochromocytoma
7. Gut carcinoids
8. Ovarian adenoscarcinoma
9. Pancreatic cystadenoma
10. Adrenocarcinoma of unknown site

Other than small cell carcinoma of the lung, the most common cause of ectopic ACTH syndrome is either bronchial or thymic carcinoid tumors. The recommended radiographic procedures to localize ACTH-producing tumors include chest and abdominal CT, chest and abdominal MRI, urinary catecholamines to screen for pheochromocytoma, plasma levels of calcitomin to rule out medullary thyroid carcinoma, and inferior petrosal sinus sampling with CRH in patients in whom the differential diagnosis of Cushings's disease (pituitary) is unclear. Any suspicious finding in the chest or abdomen can be unequivocally confirmed by fine-needle aspiration and radioummunoassay for ACTH in the aspirate.

The goal of therapy for patients with ectopic ACTH production is to find and treat (usually resect, unless it is oat cell carcinoma) the neoplasm that is the source of ACTH. Cancer resection is indicated for patients with bronchial carcinoid tumors (lobectomy with lymph nodes) because 50% will have positive lymph node
metastases. Despite this clear malignant potential, approximately 75% of patients are cured by surgical resection. The proper therapy for ACTH-producing neoplasms depends on the diagnosis (exact tumor that produces ACTH) and extent of disease.

Any of these tumors may be malignant and may metastasize. Therefore, in some patients with ectopic ACTH production, the primary disease cannot be eradicated and therapy must be directed toward correcting the life-threatening metabolic and hormonal abnormalities. Hypokalemia and excess mineralocorticoid activity may be managed with potassium supplementation and spironolactone. Hypercortisolism may be managed with metyrapone, aminoglutethimide, or mitotane. Bilateral adrenalectomy is recommended for patients who have ectopic ACTH secondary to tumors that cannot be localized despite diligent radiographic efforts and for patients who have stable, but unresectable, metastatic disease whose hypercortisolism cannot be managed medically.

### PHEOCHROMOCYTOMA

Pheochromocytomas are rare tumors that rise from chromaffin cells in the adrenal medulla and elsewhere. Pheochromocytomas secrete catecholamines and cause intermittent, episodic, or sustained hypertension. Pheochromocytomas can present with either lactic acidosis or unexplained fever. In autopsy series, only 0.005% to 0.1% of patients have unsuspected pheochromocytomas. When urinary catecholamines are measured in hypertensive patients, pheochromocytoma is present in only 0.1% of patients. Although these tumors are rare, it is important to diagnose and localize pheochromocytomas. Sustained hypertension caused by a pheochromocytoma is curable with tumor resection. Sudden death is associated with pheochromocytoma. Pheochromocytomas may be malignant. Earlier diagnosis and therapy may lessen the probability of death from malignancy and improve the prognosis. Incidence of malignancy in pheochromocytomas is as low as 5% and as high as 46% in different series. Extraadrenal tumors may be more commonly cancerous. Pheochromocytomas may be associated with endocrine and nonendocrine inherited disorders. Bilateral adrenal medullary pheochromocytomas are components of MEN 2a and MEN 2B. Some recommend unilateral adrenalectomy in some MEN 2a patients as long as careful follow-up of the contralateral adrenal gland with urinary catecholamines is maintained. Familial pheochromocytoma also has been described. Affected individuals have bilateral adrenal pheochromocytomas and no other manifestation of MEN syndromes. In other families, extraadrenal pheochromocytomas have been reported, sometimes in the same location (bladder, etc.) in affected individuals. Pheochromocytomas occur in approximately 25% of patients with von Hippel-Lindau (VHL) disease and in fewer than 1% of patients with neurofibromatosis and von Recklinghausen's disease.

Pheochromocytomas produce catecholamines, which result in clinical symptoms of anxiety attacks, episodic hypertension, or sustained hypertension. Severe, symptomatic paroxysmal hypertension with symptoms that are not related to stress or emotional distress are the most common presenting complaint of patients with pheochromocytoma. However, pheochromocytomas may also produce other hormones, including ACTH; therefore, patients may have concomitant Cushings's syndrome. Pheochromocytomas may produce many other peptide hormones, including somatostatin, calcitonin, oxytocin, and vasopressin.

### ONCOGENE

Pheochromocytomas originate from the neural crest and may develop by arrest at various points during normal differentiation. The ras oncogene does not appear to be involved in the tumor process of pheochromocytoma, because one study failed to detect any abnormality of ras gene sequence in ten pheochromocytomas. Loss of heterozygosity at specific loci may help localize tumor suppressor genes involved in the formation of various familial and sporadic pheochromocytomas. Of 41 tumors tested, significant allelic losses were found on chromosome 1p (42%), 3p (16%), 17p (24%), and 22q (31%). Furthermore, there appeared to be a correlation between loss of heterozygosity on chromosome 1p with urinary excretion of metanephrine and loss of heterozygosity on chromosomes 1p, 3p, and 17p with tumor volume. Because pheochromocytomas are part of the VHL syndrome, investigators have studies the role of the tumor suppressor gene CUL2, whose product interacts with the VHL tumor suppressor in the pathophysiology of sporadic pheochromocytomas. It does not appear to have a significant effect, because only 1 of 26 tumors had a mutation.

### PATHOLOGY

Pheochromocytomas arise from chromaffin cells. Chromaffin cells are widespread and associated with sympathetic ganglia during fetal life. After birth, most chromaffin cells degenerate, and the majority remain in the adrenal medulla. This may explain why approximately 90% of pheochromocytomas are in the adrenal medulla. Extraadrenal pheochromocytomas may arise anywhere, including the carotid body, intracardiac, along the aorta (both thoracic and abdominal), and within the urinary bladder. The most common extraadrenal location is the organ of Zuckerkandl, which is near the origin of the inferior mesenteric artery to the left of the aortic bifurcation. Extraadrenal pheochromocytomas may more often be malignant. Bilateral adrenal pheochromocytomas occur in familial syndromes, including MEN 2a and MEN 2B.

Data from series of patients with sporadic pheochromocytomas indicate that the right adrenal gland more commonly harbors a tumor than the left gland. Pheochromocytomas resected from hypertensive patients usually measure between 3 and 5 cm in diameter and weigh approximately 100 g. These tumors appear tan to gray in color and have a soft smooth consistency. Larger tumors may be cystic or have necrotic areas and often have calcification. Macroscopically, pheochromocytomas resemble the cell of origin. Tumors are usually arranged in cords or alveolar patterns. Tumors may be composed of cords of cells lining vascular structures that have an angiomatosus appearance. Tumors are generally clearly separated from the adrenal cortex by a thin band of fibrous tissue. Extension of the pheochromocytoma into the cortex or vascular invasion may occur in benign neoplasms.

The pathologic distinction between benign and malignant pheochromocytomas is not clear, and pathologists have relied on the reported benign natural history of most pheochromocytomas. However, some reports indicate that more pheochromocytomas than expected are malignant. In one large series, the tumor recurrence rate was 10%, and most recurrences occurred within 5 years. In another series, the recurrence rate was 23%, and in another it was 46%. Certainly these results partly reflect the referral pattern of tertiary institutions, but they may also reflect a true higher malignancy rate than originally suggested. Malignant tumors tend to be larger and weigh more, although this is not an absolute criterion. Staining for the nuclear proliferation marker MIB-1 is positive in 50% of malignant pheochromocytomas and negative in benign tumors. It is preliminary data, but it may be a useful marker for malignancy. The only absolute criterion for malignancy is the presence of secondary tumors in sites where chromaffin cells are not usually present and visceral metastases. Benign pheochromocytomas may demonstrate marked nuclear pleomorphism, whereas paradoxically, malignant ones demonstrate less. Malignant pheochromocytomas usually have many more mitoses than benign tumors, but capsular and vascular invasion occurs with equal frequency in both. Nuclear DNA ploidy may be a predictive indicator of malignant potential. Flow cytometry has been used to define a subgroup of patients with pheochromocytoma who have malignant tumor. Tumors whose DNA ploidy demonstrated secondary tumors in sites where chromaffin cells are not usually present and visceral metastases. Benign pheochromocytomas may demonstrate high significance of a malignant course than most tumors, which were normally diploid. It has been observed that neuroepitope Y gene expression by tumors may be used to distinguish benign from malignant pheochromocytomas. Neuropeptide Y mRNA was expressed in 9 of 9 benign tumors and only 4 of 11 malignant tumors, suggesting that expression of this gene is seen more often in benign pheochromocytomas.

Others have attempted to differentiate patients with benign and malignant pheochromocytomas by serum levels of neuron-specific enolase and neuropeptide Y, but observed differences were not significant. Finally, studies indicate that size of tumor (weight) correlated best with malignant potential, as did amount of necrosis (see Table 38.4-6).

<table>
<thead>
<tr>
<th>Pathologic Parameter</th>
<th>Benign</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitoses</td>
<td></td>
<td></td>
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<tr>
<td>Necrosis</td>
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<tr>
<td>Mitochondria</td>
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<tr>
<td>Vascular invasion</td>
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<tr>
<td>Capsular invasion</td>
<td></td>
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<tr>
<td>Necrosis</td>
<td></td>
<td></td>
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<tr>
<td>Tumor size</td>
<td></td>
<td></td>
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<tr>
<td>Histological features</td>
<td></td>
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<tr>
<td>Neuropeptide Y mRNA</td>
<td></td>
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<tr>
<td>Nuclear DNA ploidy</td>
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<tr>
<td>Neuroepitope Y gene</td>
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<tr>
<td>Neuron-specific enolase</td>
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<td>Neuropeptide Y mRNA</td>
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### DIFFERENTIATION OF BENIGN VERSUS MALIGNANT PHEOCHROMOCYTOMAS

<table>
<thead>
<tr>
<th>Differentiation</th>
<th>Benign</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuroepitope Y</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Neuropeptide Y</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Neuron-specific enolase</td>
<td>Low</td>
<td>High</td>
</tr>
</tbody>
</table>

TABLE 38.4-6. Differentiation of Benign versus Malignant Pheochromocytomas
Patients with pheochromocytomas can present with a range of symptoms, from mild labile hypertension to sudden death secondary to a hypertensive crisis, myocardial infarction, or cerebral vascular accident. The classic patient describes “spells” of paroxysmal headaches, pallor, palpitations, hypertension, and diaphoresis. In 50% of patients, the hypertension is intermittent, whereas in the others it is sustained. In 90% of children with pheochromocytomas, the hypertension is sustained. Patients may have signs of chronic hypovolemia, such as orthostatic hypotension or lactic acidosis secondary to excess a-catecholaminergic stimulation and vasoconstriction. Most patients have mild weight loss, but obesity does not rule out pheochromocytoma. Diabetes mellitus may be induced.

The diagnosis of pheochromocytoma is based on measuring catecholamines and metabolites in the urine (Fig. 38.4-4). If a pheochromocytoma is suspected clinically or a patient has a history of familial pheochromocytoma, MEN 2a, or MEN 2B, the best study is a 24-hour urine test for catecholamines, metanephrine, and VMA. In a report describing the testing of 64 patients, 30 of whom had pheochromocytomas, 24-hour urine collections for VMA, dopamine, epinephrine, and norepinephrine were analyzed. The 24-hour urinary levels of VMA and norepinephrine had the greatest sensitivity (97%), whereas the levels of VMA had the best specificity (91%). Another study also reports that urinary measurement of catecholamine, VMA, and metanephrine levels were the most sensitive screening test. Methods are now available to measure plasma catecholamines using a radioenzymatic assay. This can provide a more direct measurement of catecholamine excess, but there have been conflicting reports comparing the value of urinary or plasma catecholamines in the diagnosis of pheochromocytoma. As the plasma studies become more reliable, they may be a more sensitive and specific method than the urinary assay. However, it depends on the laboratory and the method, because studies still report that urinary measurements are more sensitive than plasma.

A-Methyltyrosine is a competitive inhibitor of tyrosine hydroxylase, the rate-limiting step in catecholamine biosynthesis. Treatment with a-methyltyrosine (metyrosine) is generally not used before anesthesia and surgery. The clonidine suppression test has become the test of choice to determine whether a patient with borderline urinary or plasma catecholamine level has a pheochromocytoma. It is the study of choice to diagnose pheochromocytomas in patients with plasma catecholamine concentrations between 500 and 2000 pg/mL. In normal subjects and patients with idiopathic hypertension, clonidine suppresses plasma levels of epinephrine and norepinephrine. In patients with pheochromocytoma, clonidine does not suppress levels. Only two incorrect diagnoses have been reported using the clonidine suppression test: one false-positive and one false-negative. An overnight method of this test has also been reported based on the measurement of urinary levels of norepinephrine and epinephrine.

CT and MRI are the two radiologic (nonnuclear medicine) procedures of choice to localize pheochromocytomas (see Fig. 38.4-4). Both are noninvasive and sensitive, being able to detect tumors approximately 1 cm in diameter. MRI may be more specific because of the increased signal intensity on the T2-weighted image. CT has some advantages over MRI. CT scanners currently have greater resolution and greater availability. In a Mayo Clinic study of 52 patients with pheochromocytoma, CT detected 51 of 52 tumors, including 9 of 10 bilateral tumors. In another study, unenhanced high-resolution CT detected pheochromocytomas in six of the six patients who had tumors found at surgery, including two extradural retroperitoneal tumors. MRI also has remarkable resolution. In seven patients with pheochromocytomas demonstrated on CT, MRI imaged all primary lesions as well as metastases to the chest, retroperitoneum, and liver. Because it has no radiation exposure, it can be used to image a pheochromocytoma during pregnancy. In one analysis, CT imaged 16 of 19 pheochromocytomas (84%), whereas MRI imaged 12 of 15 (75%) for comparable sensitivity. In addition, MRI successfully imaged an intrapericardial pheochromocytoma and distinguished it from the cardiac chambers and surrounding great vessels, which could not be determined by CT.

Another important technique for the localization of pheochromocytomas is nuclear scanning after the administration of labeled metaiodobenzylguanidine (MIBG) (see Fig. 38.4-4). The compound is similar to norepinephrine and is taken up and concentrated in adrenergic tissue. I-MIBG has been studied in 400 patients to localize suspected pheochromocytomas. The sensitivity of MIBG scanning was 78% in sporadic pheochromocytoma, 91% in malignant pheochromocytoma, and 94% in familial pheochromocytoma. The overall sensitivity was 87%. The specificity was nearly 100% in all categories and overall. I-MIBG at another institution demonstrated a sensitivity of 77% and a specificity of 96%, and two other institutions had similar findings. More recent data confirm previous studies and demonstrate that labeled MIBG is a useful diagnostic and imaging study for the detection and localization of pheochromocytoma. In three studies from three different institutions, it had a sensitivity of 86% and correctly diagnosed and imaged tumor in 71 of 83 patients. It appears that MIBG scanning is safe, noninvasive, and efficacious for the localization of pheochromocytomas, including those that arise in nonadrenal sites, and malignant disease. Metastatic bone involvement by pheochromocytoma can be imaged by I-MIBG, but standard bone scintigraphy may be more sensitive. In summary, MIBG scanning images catecholamine-producing tumors with a high specificity and sensitivity. Whereas CT and MRI reflect changes in morphology, scintigraphic imaging relies on tissue function. False-positive results with MIBG scintigraphy are rare (but tumors such as medullary thyroid carcinoma and neuroblastoma can image), which accounts for the high specificity (98% to 100%) of the study. False-negative results can occur and have an incidence of approximately 13% to 20%, which lowers sensitivity. It appears that these false-negatives may be more common with multiple tumors and metastatic disease in the same patient.

**FIGURE 38.4-4.** Flow diagram for diagnosis, localization, preoperative preparation, treatment, and follow-up of a patient with a pheochromocytoma. CT, computed tomography; MIBG, metaiodobenzylguanidine; MRI, magnetic resonance imaging; VMA, vanillylmandelic acid.

**CLINICAL MANIFESTATIONS AND DIAGNOSIS**

**Preoperative Preparation**

Once the diagnosis is established and the tumor localized, preoperative preparation includes a-adrenergic blockade. Patients are started on phenoxybenzamine, 10 mg orally two or three times daily (see Fig. 38.4-4). If tachycardia develops (heart rate more than 100 beats/min), a-adrenergic blocking agents (propranolol) are added before surgery. Propranolol should never be started before a blockade because unopposed vasoconstriction may worsen hypertension. Phenoxybenzamine increases the total blood and plasma volume in patients with pheochromocytoma. In addition, lactic acidosis may be present in patients with pheochromocytoma related to the effect of catecholamines on peripheral circulation. The measurement and correction of arterial blood pH should be performed in all patients before the induction of anesthesia and surgery.

a-Methyltyrosine is a competitive inhibitor of tyrosine hydroxylase, the rate-limiting step in catecholamine biosynthesis. Treatment with a-methyltyrosine (metyrosine) reduces catecholamine production by 50% to 80% in patients with pheochromocytoma. The usual dose is 250 mg four times daily, which may be increased to a maximum of 3 to 4 g/day. It has been used preoperatively to prepare some patients with pheochromocytoma and unusual cardiac complications for surgery, and it may be used to treat hypertensive crisis in patients with pheochromocytoma. Studies suggest that it is most effective when combined with phenoxybenzamine. Others have successfully used the calcium-antagonist nifedipine with phenoxybenzamine or nicardipine alone (60 to 120 mg every 24 hours) to control labile hypertensive episodes in patients with pheochromocytoma. Either of these newer drug strategies appear to work as well as or better than the more traditional strategy of phenoxybenzamine.
Intraoperative Management

If the patient is elderly or has had cardiac complications, he or she should be transferred to the intensive care unit the day before surgery and a Swan-Ganz catheter should be inserted. This allows correction of hemodynamic imbalances and optimization of cardiac performance. The morning of operation, an arterial catheter and peripheral intravenous catheters should be inserted. Arterial blood gas should be measured to rule out acidosis. During surgery, especially during manipulation of the tumor, marked increases in blood pressure may occur; hypertensive episodes should be controlled with either a-adrenergic blocking agents like regitine or agents that directly relax arterial and venous smooth muscle like sodium nitroprusside. Nitroprusside is the preferred drug because of its rapid onset and short duration. It is administered through a pump, and the blood pressure is continuously titrated to acceptable levels. The use of preoperative preparation with oral a-adrenergic blocking agents and intraoperative adjustment and regulation of blood pressure with nitroprusside has greatly facilitated the surgical resection of pheochromocytoma and has reduced operative morbidity and mortality.

The operation is performed using a transabdominal incision, either a bilateral subcostal or a long midline incision. Preoperative localization studies, such as CT, MRI, and 131I-MIBG, guide the exploration, but the entire abdomen should be carefully visualized and palpated. Others argue that localization procedures are so sensitive and specific that more direct approaches may be preferred. Small intraadrenal pheochromocytomas have been removed using laparoscopic techniques. Laparoscopic procedures appear to decrease pain and shorten the time to recovery. Most pheochromocytomas are well localized. However, in instances of malignant pheochromocytomas in pheochromocytomas, in extrarenal pheochromocytomas, in pheochromocytomas, in extrarenal pheochromocytomas, and in pheochromocytomas, some tumors may be missed. Extrarenal pheochromocytomas may be difficult to find. The most common locations of intraadrenal extraadrenal pheochromocytoma are in the hilar region of the kidneys and in the chromaffin tissue along the aorta from the celiac axis to the aortic bifurcation. The organ of Zuckerkandl at the aortic bifurcation is the most common extraadrenal location. Patients who have had described adrenals, metastatic tumors, and all surgical procedures are performed to complete exploration of the entire abdominal cavity. The “rule of ten” may be of value in the management of pheochromocytomas: Ten percent are malignant, 10% are extraadrenal, and 10% are bilateral. In patients with MEN 2, some suggest that nearly 100% either have or will develop bilateral benign adenyal medullary pheochromocytomas, whereas others suggest that the incidence of bilaterality, although high, may be significantly less than 70%.

MALIGNANT PHEOCHROMOCYTOMAS

Malignant pheochromocytomas are thought not to occur in MEN syndromes and to be present in approximately 10% of patients with pheochromocytomas. Two reports indicate that substantially more than 10% of sporadic pheochromocytomas may be malignant. In one study, 25 of 89 (36%) patients had malignant pheochromocytomas diagnosed by recurrent or metastatic disease; in another study using the same criteria, 81 of 176 (46%) patients with pheochromocytomas had malignant disease. In the later study, original histologic review by blinded pathologists did not discriminate malignant versus benign neoplasms with accuracy.

Pathologic analysis was not helpful in predicting which tumors were malignant. Patients who developed metastases did not develop them until 0.2 to 28.7 years after their initial surgery. Incidence of detection for the first 9 years was 5% per year. Males were more likely to develop metastatic pheochromocytoma. Imaging with 131I-MIBG was usually able to detect recurrent or metastatic pheochromocytoma. Some recommend yearly 131I-MIBG scans to detect recurrent disease in all patients after resection of pheochromocytoma. New studies indicate that octreotide scintigraphy may also be useful to image malignant metastatic pheochromocytoma. The tumor is imaged by somatostatin receptor scintigraphy, octreotide therapy may have potent antitumor effects. Others recommend lifelong follow-up with measurement of blood pressure and urinary levels of catecholamines. The detection of recurrent or metastatic pheochromocytoma should be based on the same methods as detection of primary or initial pheochromocytoma. These methods include urinary and serum catecholamine measurement, the chromaffin suppression test, CT scanning, MRI, and 131I-MIBG scanning. Careful follow-up requires some, but not necessarily all, of these studies on a yearly basis (see Fig. 38.4-4). It appears that with careful follow-up the incidence of malignant pheochromocytoma may be greater than 10% and may approach 30% to 50%.

The basic principles in the treatment of malignant pheochromocytoma have been to surgically resect recurrences or metastases whenever possible and to treat hypersensitive symptoms by catecholamine blockade. Even in pediatric patients, surgical resection of metastatic and recurrent pheochromocytomas has been shown to prolong survival. Painful bony metastases, which may be diagnosed by either 131I-MIBG scans or standard bone scans, respond well to radiotherapy. Soft tissue metastases generally respond well to radiation, but radiotherapy to areas of the bone may not be able to be administered. Localized or solitary soft tissue masses, even when metastatic to the liver or lung, may be successfully resected surgically. Standard chemotherapy regimens including doxorubicin plus streptozotocin and carmustine plus doxorubicin have not had much efficacy in the treatment of malignant pheochromocytomas.

Survival data of patients with malignant pheochromocytoma are difficult to obtain because of the rarity and indolence of the tumor. In a large series from the Mayo clinic, the 5-year survival rate was 36%. Others report a 5-year survival rate of 60% in 15 patients with malignant pheochromocytoma. In this study, patients were treated primarily by aggressive surgery and medical blood pressure control. In a final series, patients who succumbed from malignant pheochromocytoma did so within 3 years of the appearance of metastases.

The early success with streptozotocin in the treatment of neuroendocrine tumors of the gastrointestinal tract suggested that it might also be useful in the treatment of malignant pheochromocytomas. Streptozotocin has had mixed responses in patients with malignant pheochromocytoma. Initial work with streptozotocin was disappointing and suggested no role for it in the treatment of malignant pheochromocytoma. However, Feldman treated one patient with a good response and suggested a schedule might be useful. A study that provided additional support for this approach noted that the patient maintained an 85% reduction in urinary homovanillic acid levels and a 73% reduction in urinary VMA levels with normal renal function despite 66 g of streptozotocin. Other groups have tried this regimen and noted no response and deterioration of renal function. It may be that some patients with malignant pheochromocytoma respond to streptozotocin chemotherapy, but many do not, and it does not appear to play a major role in the treatment of patients with these rare tumors.

Because of the high sensitivity (85%) and specificity (100%) of 131I-MIBG to image pheochromocytomas, its use in higher doses to treat recurrent or metastatic pheochromocytomas has been implemented. Current imaging modalities of pheochromocytoma permit relatively accurate dosimetry to the tumor on the basis of the diagnostic dose of 131I-MIBG administered. If uptake by primary or metastases is high, it is possible to deliver very high radiation doses by increasing the administered activity. Specific activity of 131I-MIBG of 200 mcI in 5 mg has now been achieved. With the remarkable ability of MIBG to image tumors, one would expect its ability to treat metastatic or recurrent tumors to be equally effective; however, the results have not been very dramatic. Treatment response in patients with pheochromocytomas can be measured by catecholamine secretion and standard tumor size measurements. Blood pressure control of a few patients with malignant pheochromocytomas has been facilitated by 131I-MIBG therapy. One trial reports the use of 131I-MIBG therapy in 15 patients with malignant pheochromocytomas. Patients were treated with 131I-MIBG (specific activity 740 MBq/mg) every 3 months. The typical patients received three doses. The absorbed cumulative tumor dose was 12 to 155 Gy. A beneficial response to treatment was observed in nine patients (60%), four never responded, and others had a slight response. No complete responses were observed. Five patients had measurable partial responses to treatment, and seven had clear hormonal responses. Toxicity included pancytopenia in one patient that resolved after discontinuation of therapy. In another study of 12 patients treated with 131I-MIBG, 5 (42%) reduced catecholamine levels and 2 decreased tumor size (17%). Vetter and colleagues reported two patients with malignant pheochromocytomas treated with 131I-MIBG who had minor reduction in tumor size but no change in catecholamine secretion. There were no reported complete responses until more recently. Targeted radiotherapy with 131I-MIBG is effective in 58% of malignant pheochromocytomas. One report documented a 4-year biochemical and imagede complete response with 131I-MIBG treatment in one patient. Another report documents significant partial responses in three patients treated with 131I-MIBG.

Neuroblastomas are aggressive tumors of neural crest origin that occur in children and have no association with hypertension. All patients with neuroblastoma have high plasma levels of dopamine. Patients with benign pheochromocytomas have elevated plasma levels of norepinephrine or epinephrine, and none have elevated plasma levels of dopamine. A unique feature in patients with neuroblastoma is the similarity between malignant pheochromocytoma and neuroblastoma is further supported by the astonishing responsiveness of malignant pheochromocytoma to therapy that is effective in treating neuroblastoma. Combination of cyclophosphamide, vincristine, and dacarbazine has an 80% response rate for metastatic neuroblastoma. And has been used in patients with metastatic pheochromocytoma. The chemotherapy regimen consists of cyclophosphamide, 750 mg/m² intravenously, on day 1, vincristine, 1.4 mg/m² intravenously, on day 1, and dacarbazine, 600 mg/m² intravenously 14 days, on days 1 and 2, repeated every 21 days. Doses of cyclophosphamide and dacarbazine have been increased or decreased on the basis of neurotoxicity. This regimen has now been reported in 14 patients with metastatic pheochromocytoma. The ability to respond to the chemotherapy regimen correlated with plasma norepinephrine level before therapy. One patient had a catecholamine response (both biochemical and imagede) that lasted for 5 months. One other patient also had a biochemical complete response, and a total of eight (57%) patients had clear decreases in 24-hour levels of urinary catecholamines. Seven patients (50%) also had at least a 50% decrease in the measurable size of tumor. Biochemical response (urinary catecholamines) correlate well with response evaluated in imaging studies. The median duration of response was greater than
Patients with malignant pheochromocytomas have been treated with both chemotherapy and radioactive MiBb in a study protocol. Six patients with metastatic pheochromocytoma were treated with three doses of 131I-Mibb followed by a year of chemotherapy with CVD given in 21-day cycles. Three patients had significant partial responses to 131I-Mibb, and two patients had further partial responses to chemotherapy. The combination therapy produced additive antimutant effects. Two additional patients with metastatic pheochromocytoma also had partial CVD responses with partial volume response. Table 38.4-7 lists possible treatment regimens for metastatic pheochromocytoma.


**SECTION 38.5**

*Pancreatic Endocrine Tumors*

H. RICHARD ALEXANDER

ROBERT T. JENSEN

**Introduction**

Pancreatic endocrine (or neuroendocrine) tumors (PETs) are uncommon neoplasms that share a number of features. Histologically, they are classified as apudomas and share cytochemical features with melanoma, pheochromocytoma, carcinoid tumors, and medullary thyroid carcinoma. All amine precursor uptake and decarboxylation (APUD) neoplasms have the capacity to synthesize and secrete polypeptide products that have specific endocrine hormone activity. Except for insulinoma, each is malignant in most (more than 60%), if not all, cases (Table 38.5-1). Each type is a vascular tumor sharing with the other types a similar radiographic appearance and metastatic patterns of spread (primarily to regional lymph nodes and liver).

**INTRODUCTION**

PETs are considered functional if they are associated with a clinical syndrome due to ectopic hormone release or nonfunctional if not associated with clinical symptoms. In the latter category are pancreatic polypeptide (PP) tumors (PPomas), as the hormone causes no specific symptoms. In addition, some PETs are associated with no known hormone elevation and histologically are indistinguishable from functional tumors.

In general, PETs are uncommon. Functional PETs are reported to have a prevalence of 10 per million population. The prevalence in unselected autopsy studies is 0.5% to 1.5%, with fewer than 1 of 1000 being functional. The incidence of clinically significant PETs is 3.6 to 4 per million population per year; nonfunctional PETs or PPomas are reported to account for 15% to 30% of all PETs. Gastrinomas or PPomas are the most common malignant PETs, whereas insulinoma is the most common benign PET. Gastrinomas usually are clinically recognized because of the Zollinger-Ellison syndrome (ZES) and have been studied extensively.

This chapter presents information in a format that reflects the many similarities of PETs, though detailed discussions of each tumor type are provided for those tumors associated with unique issues.

**PATHOGENESIS, PATHOLOGIC FEATURES, AND TUMOR BIOLOGY**

**GENERALLY MALIGNANT NEOPLASMS**

In 1955, Zollinger and Ellison described two patients with severe peptic ulcer disease treatable only by total gastrectomy because of extreme hypersecretion of gastric acid associated with a non-beta islet cell tumor of the pancreas. Analysis of tumor extracts via enzymatic degradation and amino acid analysis demonstrated that the gastrin-secreting tumour was identical to human antral gastrin. Hence, these tumors are called gastrinomas. Studies estimate that the ZES occurs in one-half to three patients per million population per year and varies from half as common to 1.2 times as common as insulinomas.

Almost all the early clinical manifestations are due to gastric acid hypersecretion secondary to hypergastrinemia. Effective control of the gastric hypersecretion either medically or surgically abolishes all clinical manifestations such as peptic ulcer disease or diarrhea. Along with basal gastric acid hypersecretion, hypergastrinemia causes trophic changes in the gastric mucosa, with the result that patients with ZES have increased numbers of parietal cells and an increased maximum acid secretory capacity. Many patients with ZES have diarrhea and, in some patients, it is the sole presenting manifestation. The diarrhea is a result of acid hypersecretion causing direct injury to the small intestinal mucosa, inactivation of pancreatic lipase, and precipitation of bile acids. ZES patients with diarrhea become asymptomatic when the gastric acid hypersecretion is controlled, even though the hypergastrinemia remains unchanged.

Gastrin in both normal subjects and patients with ZES has been found in a number of different molecular sizes. In gastrinoma, gastrin 17 (G) is the major gastrin component, composing 74% to 80% of the total immunoreactivity, with "big gastrin" or gastrin 34 (G), making up most of the remainder. In contrast, in sera from normal subjects and patients without gastrinoma, G contributes more than 60% of the total gastrin immunoreactivity. In addition to G and G, smaller and larger forms of gastrin have been described in sera and gastrinomas from patients with ZES. Also, a large-molecular-weight progastrin has been described in plasma...
and tumors of patients with gastrinomas. High amounts of progastrin have been found in patients with gastrinoma metastatic to liver. The relative amount of G₁₇₇, the amount of NH₄-terminal fragments, and the ratio of the amount of G₁₇₇ carboxy-terminal immunoreactivity to the amount of G₁₇₇ carboxy-terminal immunoreactivity have been shown to be predictive of the extent of the gastrinoma by some investigators but not others.

In recent studies, the proportion of gastrinomas found at surgery in the duodenum and in lymph nodes near the pancreatic head has increased to greater than 50%, such that 85% to 90% of all gastrinomas found at surgery occur in the pancreatic head and duodenal area (Table 38.5-2). Gastrinomas have also been reported to occur occasionally in other sites such as the liver, stomach, jejunum, mesentery, common bile duct, heart, and spleen (Fig. 38.5-1). In women, ovarian gastrinomas can occur and are functionally indistinguishable from other gastrinomas.

### Table 38.5-2. Sites of Apparent Primary Gastrinoma

<table>
<thead>
<tr>
<th>Site</th>
<th>Frequency (%)</th>
</tr>
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<tbody>
<tr>
<td>Duodenum</td>
<td>65-80</td>
</tr>
<tr>
<td>Nephrectomy</td>
<td>15-18</td>
</tr>
<tr>
<td>Liver</td>
<td>15-20</td>
</tr>
<tr>
<td>Common bile duct</td>
<td>15-20</td>
</tr>
<tr>
<td>Jejunum</td>
<td>15-20</td>
</tr>
<tr>
<td>Stomach</td>
<td>15-20</td>
</tr>
<tr>
<td>Mesentery</td>
<td>15-20</td>
</tr>
<tr>
<td>Pancreas</td>
<td>15-20</td>
</tr>
<tr>
<td>Spleen</td>
<td>15-20</td>
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</table>

![Image](image_url)

**FIGURE 38.5-1.** Patient with a primary gastrinoma of the common bile duct, illustrating several important features of the disease. Computed tomography scan after selective angiography (A) shows a 1.5-cm enhancing nodule (arrow) at neck of gallbladder just above the head of the pancreas, which is also seen on somatostatin receptor scintigraphy (B). C: At surgical exploration, a discrete mass is seen within the wall of the common bile duct (arrow shows primary tumor; 1, gallbladder; 2, cystic duct; 3, common bile duct). The primary tumor after resection (D) was a primary intracholedochal gastrinoma (E), and the adjacent lumen of the bile duct (L) is lined by normal epithelium. The tumor showed typical aggregation of neuroendocrine cells and dense vasculature characteristic of neuroendocrine tumors (F). Immunoperoxidase stained positive for chromogranin, synaptophysin, and gastrin. (From ref. 28.)

At present, the cell of origin of gastrinomas and other PETs remains obscure. Recent studies have provided evidence that duodenal gastrinoma, which usually contains many well-differentiated gastrin-containing (G) cells (in contrast to pancreatic gastrinoma), originates from gastrin cells in the duodenal crypts and Brunner's glands. Because pancreatic gastrinomas are pleomorphic with heterogeneous cell types, it has been proposed that they originate from a multipotential, endocrine-programmed stem cell that undergoes somewhat inappropriate and incomplete differentiation toward the G cell. As G cells are not normally present in the adult pancreas, pancreatic gastrinomas are generally considered ectopic, whereas gastrinomas in areas that normally contain G cells (duodenum, stomach, jejunum) are considered entopic.

In early studies in which patients presented late in the course of their disease, gastrinomas were found at surgery in most patients with ZES (81% to 94%). In subsequent studies of patients undergoing potentially curative surgery, no gastrinomas were found in as many as 50% of patients. Recent studies have shown that almost all the missed gastrinomas were in the duodenum. Now that exploration of the duodenum is being performed routinely, gastrinomas are found in more than 90% of patients.

In early studies, 60% to more than 90% of patients with ZES had a malignant gastrinoma, whereas in recent studies only one-half of patients have a malignant gastrinoma at the time of diagnosis. Metastases usually are to peripancreatic lymph nodes and to the liver. Some metastases have been reported in approximately 30% of patients with metastatic gastrinoma in the liver. The diagnosis of malignancy is complicated by the fact that no histologic criteria predict malignancy, which can be established only by the presence of metastases. Even metastatic disease can be difficult to establish, because a number of cases of extrapancreatic gastrinoma localized in lymph nodes have been described with no evidence of primary tumor. Some of these cases have apparently been cured by excision of lymph nodes, which suggests that the gastrinoma was not metastatic but rather originated in the lymph node.

Numerous studies have attempted to identify predictors of malignancy in gastrinomas as well as other PETs. Clinically, tumor size has been shown to be an important predictor of liver metastases but not lymph node metastases. Liver metastases occurred in 4% of gastrinomas less than 1 cm in diameter, in 28% of tumors measuring 1.1 to 2.9 cm, and in 61% of tumors larger than 3 cm. In several prospective studies, duodenal gastrinomas have been found to be malignant with metastatic spread in 48% to 75% of cases. In one large study involving 90 patients with ZES with pancreatic or duodenal gastrinomas, an equal percentage had lymph node metastases (48% and 47%, respectively), showing that, as regards lymph node metastases, the malignant potential of ectopic and entopic gastrinomas does not differ. However, in this same study, 5% of patients with duodenal gastrinomas had liver metastases, which was significantly less than the 52% incidence in patients with pancreatic gastrinomas. Because most duodenal gastrinomas are small (80% <1 cm) and most pancreatic gastrinomas are large (70% ≥ 3 cm), it remains unclear whether tumor size and location are independent predictors.

Recent studies have attempted to use assessments of nuclear DNA to differentiate benign from malignant gastrinomas and other PETs. DNA ploidy analysis in some studies did not predict prognosis. However, in a study of 59 patients with gastrinomas, 54% were diploid, 15% near-diploid, 0% pure tetraploid, and 25% nontetraploid aneuploid, while another 5% exhibited multiple stem line aneuploidy. All patients with multiple stem line aneuploidy had widespread metastases, and the results of the DNA analysis correlated with disease extent. Silver staining of nuclear organizer regions, expression of the proliferating nuclear antigen, and expression of the cell cycle–associated antigen Ki-67, have all been reported to be potentially useful in differentiating benign from malignant PETs. Chromosomal abnormalities have recently been reported in PETs of five of nine patients, but such alterations were not associated with more aggressive tumor behavior. The protooncogene HER-2/neu recently was reported to be overexpressed in gastrinomas from 11 patients, with no mutations in the ras gene and a mutation in the p53 gene in only 1 of 11 patients. No correlation with malignancy and HER-2/neu was found, but a previous study by the same investigators on carcinoid tumors of the gastrointestinal tract found a trend toward increased HER-2/neu copy number and aggressiveness. Similarly, no abnormal expression of p53 protein was found in PETs in another study.

One study showed allelic loss on chromosome 11q13 in gastric carcinoids from patients with multiple endocrine neoplasia type 1 (MEN 1) and ZES, suggesting that the pathogenesis of these tumors is similar to that of the pancreatic and parathyroid tumors that develop in MEN 1 patients. Using positional cloning, the gene for...
MEN 1 has been located on chromosome 11q13, and approximately 30% of gastrinomas occurring in the sporadic setting have mutations in the gene.

Approximately 20% of patients with ZES have a familial form and demonstrate evidence of MEN 1 (Wermer's syndrome). MEN 1 is an autosomal dominant trait characterized by hyperplasia or tumors of multiple endocrine organs, hyperparathyroidism being the most common abnormality. Islet cell tumors of the pancreas are the second most common abnormality, occurring in 82% of MEN 1 patients, with 57% having ZES and 25% insulinomas. Pituitary and adrenal adenomas are less common. Patients with MEN 1 with ZES differ from sporadic cases in that they frequently present at a younger age; their tumors are almost always multiple and frequently small and, in some studies, patients with MEN 1 have an increased survival rate as compared with sporadic cases.

Immunocytochemical studies of tumors from patients with ZES have demonstrated gastrin in 90% to 100% in some studies and in 56% to 78% in others. This difference may be due to differences in tissue fixation or type of gastrin antibody used or to a low content of gastrin in small tumors. Recent studies have demonstrated that more than 50% of tumors also demonstrated other peptides, including PP in 17% to 50%, insulin in 20% to 33%, glucagon in 0% to 33%, somatostatin in 0% to 33%, and adrenocorticotropic hormone-like immunoreactivity in 0% to 30%. In one report that reviewed seven different immunocytochemical studies involving tumors from 75 patients with ZES, gastrin was found in 80%, insulin in 30%, human PP (HPP) in 35%, glucagon in 29%, and somatostatin in 21%. Therefore, it has become increasingly difficult, if not impossible, to determine which of the hormones found in a tumor by immunocytochemical study, as well as occasional ZES patients with a concomitant insulinoma or glucagonoma, no patient had increased amounts of these peptides in plasma in the aforementioned prospective study of 45 patients. The presence or absence of abnormal plasma levels of a particular peptide or the extent of elevation did not correlate with location of tumor, extent of tumor, or the presence or absence of a particular symptom. Adrenocorticotropic hormone (ACTH) production in PETs, particularly in ZES patients, is associated with a very aggressive tumor phenotype.

Elevated concentrations of human chorionic gonadotropin (HCG) subunits (a or b chains) in sera or in the tumor by immunocytochemistry occur in some patients with gastrinoma and may be predictive of malignancy. In a study of 30 patients with ZES, 57% of patients with malignant and 45% with benign disease had elevated concentrations of a-HCG in plasma. Seven patients had elevated levels of b-HCG in plasma, with four having malignant disease. This study demonstrates that elevated plasma concentrations of a- or b-HCG are not useful in predicting malignancy.

Chromogranin A is a 48-kD protein that is co-stored and co-released with peptide hormones from gastrointestinal tract endocrine cells and tumors and is not present in nonendocrine cells. Immunocytochemically, chromogranin A has shown its presence in gastrinomas, carcinoids, atrial G cells, and fundic enterochromaffin-like (ECL) cells of the stomach. Elevated levels in the plasma are reported to be one of the best markers for PETs, although chromogranin levels also are elevated in carcinoid and other neuroendocrine tumors. In a recent study of 72 patients with ZES or carcinoid tumors, 99% had elevated plasma chromogranin A levels, 88% chromogranin B levels, and 6% chromogranin C levels. In another study, plasma chromogranin A levels were measured in 112 patients with ZES, and the value correlated significantly with fasting serum gastrin (FSG) levels. However, there was no correlation between the plasma level of chromogranin A and the amount of tumor, presence or absence of metastatic disease, or presence or absence of MEN 1.

Histologic studies have demonstrated the general similarity of PETs and carcinoid tumors. Different histologic classifications have been proposed based on vascular patterns, including a glandular pattern, solid nests of cells (solid pattern), a trabecular or ribbon-like structure (gyriform pattern), and unclassified pattern. Similar patterns of neuroendocrine tumor from different organs, and the type of histologic pattern does not correlate with the type of hormone produced, clinical symptoms, or malignancy. Ultrastructural classifications have all been proposed on the basis of the type of granules seen, but this also does not correlate with malignancy or clinical features.

**GENERALLY BENIGN NEOPLASMS: INSULINOMA**

Insulinomas were first recognized by Whipple, who described 30 patients with hypoglycemia and pancreatic adenomas. Whipple's triad consists of the characteristic symptoms of hypoglycemia associated with blood glucose levels of less than 50 mg/dL and immediate relief after ingestion of glucose and have, for many years, remained the major criteria for the diagnosis of insulinoma. Insulinomas usually occur in patients between the ages of 20 and 75 years. The average age at presentation is between 44 and 46 years, and there is a preponderance of women in most series (60%).

Insulinomas are the opposite of gastrinomas, in that whereas 60% to 90% of gastrinomas are malignant, only 5% to 11% of insulinomas are malignant. Most insulinomas are found to be solitary benign pancreatic nodules, often encapsulated, with only 2% to 10% of patients having multiple tumors. In a patient with multiple insulinomas, MEN 1 should be suspected. Insulinomas are uniformly distributed throughout the entire pancreas and are usually less than 1.5 cm in maximum diameter.

**CLINICAL PRESENTATION AND DIAGNOSIS**

Resection is the only curative modality for patients with PETs, and the success of operation is contingent on establishing the correct diagnosis, determining whether a patient may belong to a MEN kindred, performing appropriate radiographic imaging studies to assess the location of the primary tumor and the extent of regional or metastatic spread, and ensuring adequate medical management of the functional sequelae of excess hormone production preoperatively.

**GASTRINOMA**

Gastrinomas are slightly more common in men (60%) than in women (40%). The mean age at diagnosis is 45 to 50 years, and approximately 20% of patients have MEN 1. The most common presentation in patients with ZES is abdominal pain in 26% to 58%, which usually cannot be differentiated from pain caused by other common gastrointestinal disorders. However, in some studies, a significant proportion of individuals (14% to 25%) have no peptic ulcer or abdominal pain at the time of diagnosis. Diarrhea is the initial symptom in 37% to 73% of patients and, in 15% to 18%, it is the only symptom. In one study involving 122 patients with ZES, esophageal symptoms, endoscopic abnormalities, or both were present in 61% of patients. In early studies, up to 93% of patients had a peptic ulcer and, in 36%, the ulcers were multiple or in unusual locations. Although the decreased severity of peptic ulcer disease at diagnosis suggests that in patients with ZES diagnoses are being made earlier, in almost all series a delay of 3 to 6 years still exists between the onset of symptoms and diagnosis. Intestinal perforation, especially of the jejunum, is a presenting event in up to 7% of patients with ZES. The diagnosis should be suspected on the basis of the clinical presentation and established in all patients by demonstrating elevated basal gastric acid secretion (basal acid output [BAO]) and fasting hypergastrinemia. Between 38% and 60% of patients have a solitary peptic ulcer, and 14% to 25% have no peptic ulcer. ZES should be suspected in the clinical setting of peptic ulcer with diarrhea, familial peptic ulcer, or ulcer in unusual locations, and recurrent or resistant peptic ulcer. ZES should be particularly suspected in patients with peptic ulcers that persist or recur despite treatment for Helicobacter pylori infection or with H2-receptor antagonists, in patients with severe esophagitis, and in patients with duodenal ulcers without H pylori infection. H pylori infection is present in 90% to 98% of patients with idiopathic duodenal ulcer disease, and 90% heal with H pylori eradication; in ZES, fewer than 50% of patients have H pylori infection. In all patients who have peptic ulcer disease severe enough to require gastric surgery, at least one preoperative FSG level should be obtained.

To make the diagnosis of ZES, it is necessary to demonstrate an FSG elevated above 200 pg/mL and an elevated BAO. The FSG concentration usually is obtained first, and only rarely do normal values occur in patients with ZES. Although nearly 32% of patients with ZES have an FSG of at least 1000 pg/mL, in the...
remaining two-thirds of the FSG is elevated but not to the level of 100 pg/mL. Two general types of disorders other than ZES are also known to cause elevation in FSG: those associated with gastric acid hypersecretion and those associated with hypochlorhydria or achlorhydria, including chronic gastritis, gastric cancer, and pernicious anemia and in postvagotomy patients. One of the most common causes of FSG elevation is drug-induced hypergastrinemia due to inhibition of acid secretion with H(2)-ATPase inhibitors (omeprazole, lansoprazole). Similarly, H pylori infection can, on occasion, cause elevations of FSG in the range seen in ZES. No absolute level of elevation in FSG distinguishes patients with disorders of acid hypersecretion versus hypochlorhydria; they can be distinguished only by direct assessment of acid output. If facilities are not available to measure the BAO, then a simple determination of the pH of the gastric contents (while the patient is not taking antacid medication) should be performed. A pH of 2.5 or higher virtually excludes the diagnosis of ZES.

The most commonly used secretory criteria for diagnosing ZES are a BAO of at least 15 mEq/h in patients who have not undergone previous acid-reducing operations and at least 5 mEq/h in patients who have had previous acid-reducing operations. The mean BAO in various series ranged from 34 to 53 mEq/h for patients with a history of previous acid-reducing surgery. A BAO of at least 15 mEq/h will include up to 99% of patients with ZES and exclude 90% of patients with routine duodenal ulcers. In patients who have undergone previous acid-reducing surgery, the mean BAO exceeds 5 mEq/h in most studies but, in 6% to 45% of ZES patients, is less than 5 mEq/h. Patients with ZES also have an elevated maximum acid output (MAO) and an elevated BAO/MAO ratio that often exceeds 0.6. However, diagnostic criteria based on the MAO or BAO/MAO ratio offer no advantage over an elevated BAO alone.

If a patient has an FSG of at least 1000 pg/mL and a gastric pH of less than 2.5, then the diagnosis of ZES generally is established. The only other disorder that can mimic ZES in this capacity is retained gastric antrum syndrome, an uncommon condition that occurs in patients who have undergone a Billroth II gastroenterostomy with a portion of antrum left attached to the excluded proximal duodenal stump. This diagnosis can be excluded in patients after gastric surgery by the secretin stimulation test and by gastric 99mTc pertechnetate scanning. In patients with only moderately elevated FSG levels and a gastric pH of less than 2.5, ZES must be differentiated from retained gastric antrum syndrome, H pylori infection, chronic gastric outlet obstruction, antral G-cell hyperplasia, massive small bowel resection and, rarely, chronic renal failure. These conditions are best distinguished from ZES by the use of various gastrin-provocative tests, including the secretin test, calcium infusion test, and meal test. The sensitivity of the secretin stimulation test is superior to the calcium and meal-provocative tests and is the one most commonly used. Gastrin levels after secretin increased by 110 pg/mL in 93%, by more than 200 pg/mL in 87%, and by more than 50% in 85% of patients with ZES. Because of its ease, lack of side effects, high sensitivity, and very low occurrence of false-positive outcomes, the secretin test is the diagnostic provocative test of choice; a rise in gastrin of 200 ng/mL is diagnostic. The calcium infusion test should be reserved for the rare patient in whom ZES is strongly suspected but the secretin test is negative.

Antral G-cell hyperplasia is reported to mimic ZES clinically, with elevated FSG and BAO. This syndrome frequently occurs in patients after vagotomy, is due to increased numbers of antral G cells, is curable by antrectomy, may be associated with H pylori infections, and is differentiated from ZES by a negative secretin test and an exaggerated (at least 100% increase) postmeal serum gastrin level. Antral G-cell hyperfunction is similar to antral G-cell hyperplasia except that there are normal numbers of G cells and the syndrome is frequently familial, with autosomal dominant inheritance, and is associated with hyperpepsinogenemia I. This syndrome was reported to be distinguishable from ZES by its association with a negative secretin test and an exaggerated increase in postprandial serum gastrin. In patients with ZES, only 30% had a greater than 100% increase and 10% had a greater than 150% increase in the postprandial serum gastrin level. Therefore, the meal test actually is frequently positive in patients with ZES and does not reliably differentiate ZES from antral syndromes.

Chronic gastric outlet obstruction can be difficult to distinguish from ZES because the obstruction can be caused by ZES or it can mimic ZES and be secondary to other causes of duodenal obstruction. ZES can be differentiated from the other causes of obstruction by a secretin test and prolonged gastric suction. Massive small bowel resection can cause a transient elevation of BAO and can be distinguished from ZES by history and the secretin test. Chronic renal failure and H pylori infections can cause hypergastrinemia, which is usually associated with acid hyposecretion, although occasionally it may be associated with acid hypersecretion and can be differentiated from ZES by the secretin test.

**INSULINOMA**

The clinical symptoms of insulinoma are due to hypoglycemia in almost all instances. Most symptoms are neuroglycopenic in nature and include visual disturbances (59%), confusion (51%), altered consciousness (38%), and weakness (32%). Seizures occur but are uncommon (23%). Symptoms also can occur due to excess catecholamine release (adrenergic symptoms), such as sweating (43%) and tremulousness (23%). In one study, 49% of patients had both neuroglycopenic and adrenergic symptoms, 38% had neuroglycopenic symptoms only, and 12% had adrenergic symptoms only. Symptoms are characteristically associated with fasting, a delayed meal, or exercise.

The diagnosis of insulinoma can be established only by documenting symptomatic hypoglycemia with inappropriately elevated serum insulin levels during a monitored fast (Table 38.5.3). Hypoglycemia usually is defined as a blood glucose level of less than 70 mg/dL in the fasting state. In healthy individuals, the blood glucose value usually does not decrease to less than 70 mg/dL after an overnight fast. In more than 97% of individuals, a supervised fast of 48 hours or less will be sufficient to diagnose insulinoma by the development of clinical symptoms and a plasma glucose level of less than 50 mg/dL. In addition, patients with the diagnosis will usually have serum insulin levels greater than 5 μU/mL, and 97% will have levels greater than 10 μU/mL. An insulin-glucose ratio greater than 0.3 is typical. In some normal obese subjects, because of hyperinsulinemia due to insulin resistance, the fasting plasma insulin-glucose ratio may be elevated and may mimic the pattern in insulinoma. In these patients, the fasting glucose is normal and, with prolonged fasting, the blood glucose level does not decrease to less than 55 mg/dL.

**NONFUNCTIONING PANCREATIC ENDOCRINE TUMORS**

Nonfunctioning PETs and PPomas present in the fourth and fifth decade of life. PPomas release the hormone pancreatic polypeptide, which has no known functional sequelae. Originally it was thought that nonfunctioning PETs did not release any hormone products, but these lesions have since been shown to secrete chromogranins, α-HCG or β-HCG subunits, or other peptides that do not cause symptoms. Increasingly, what in the past were believed to be nonfunctioning PETs

| Table 38.5-3. Common Diagnostic Criteria for Insulinoma |
|------------------|------------------|------------------|------------------|------------------|
| **Criteria**     | **Insulinoma**   | **Non-insulinoma** |
| Symptomatic hypoglycemia | Yes             | No               |
| Fasting glucose < 55 mg/dL | Yes             | No               |
| Serum insulin > 10 μU/mL | Yes             | No               |
| Insulin-glucose ratio > 0.3 | Yes             | No               |

A number of other conditions can cause fasting hypoglycemia with increased plasma insulin levels, including causes of organic hyperinsulinism due to pancreatic islet cell disease aside from insulinoma, factitious use of excessive insulin or hypoglycemia agents, or autoantibodies against the insulin receptor.

To differentiate insulinoma from these other conditions, additional tests are useful, including plasma determination of proinsulin, C-peptide level, antibodies to insulin, and plasma sulfonpyrazone levels. Because endogenous insulin is synthesized as a precursor, proinsulin, quantification of the higher-molecular-weight component, called the proinsulin-like component, is useful. In patients with surreptitious use of insulin or oral hypoglycemia agents, the proinsulin level is either normal or decreased.

The measurement of C peptide has proven useful in differentiating organic hypersecretion of insulin from patients surreptitiously using insulin because commercial insulin preparations contain no C peptide. In insulinoma, the characteristic finding is either an elevated or normal plasma C-peptide concentration, whereas in patients surreptitiously using insulin, the plasma insulin level is high and the C-peptide level low.
now are appreciated to have elevated plasma PP levels. In one study, one-half to three-fourths of PETs not associated with any clinical syndrome and classified as nonfunctioning were found to be PPomas. Elevated plasma PP is specific for endocrine pancreatic tumors; of 53 patients with adenocarcinoma of the pancreas, none had elevated plasma PP levels. Currently, no data are available to suggest that nonfunctioning PETs without elevated PP and PPomas differ in biologic behavior or presentation. Immunohistochemically nonfunctioning PETs and PPomas can stain positively for numerous other gastrointestinal peptides. In one series of 30 nonfunctioning tumors, 50% displayed insulin-like immunoreactivity, 30% glucagon, 43% PP, and 13% somatostatin, and only 13% stained for no peptide. With these tumors, symptoms arise largely from mechanical or mass effects of the neoplasm, and therefore the tumors are diagnosed late, when they are quite large and locally invasive.

They are usually solitary tumors except in patients with MEN 1, in whom multiple adenomas are seen. The tumors are distributed throughout the pancreas at a pancreatic head-body-tail ratio of 7:1:1.5. The malignancy rate varies from 64% to 92%.

Chromogranin A and B levels are elevated in almost all patients with nonfunctioning PETs. Elevated plasma levels of PP do not establish the diagnosis of a PPoma even when a pancreatic mass is present. Plasma PP levels are reported to be elevated in 22% to 71% of patients with functional PETs in various studies, as well as in nonfunctioning carcinoid tumors. Furthermore, elevated plasma levels of PP can occur in other situations such as old age; after bowel resection; with alcohol abuse; during certain infections; in chronic noninfectious inflammatory disorders, acute diarrhea, chronic renal failure, diabetes, chronic relapsing pancreatitis, and hypoglycemia; or after eating.

To increase the specificity of an elevated plasma level for a PPoma, an atropine suppression test may be used. In one study of 48 patients with elevated plasma PP levels, atropine (1 mg intramuscularly) did not suppress PP levels in any of the 18 patients with PETs but did suppress the level by 50% in all patients without tumors.

Patients present with abdominal pain in 36% and jaundice in 28% of cases; in 16% of patients, the tumors are found incidentally at surgery and, in the remaining patients, a variety of symptoms due to the tumor mass are present. The average delay from onset of symptoms until diagnosis varied from 5 months to 2 to 7 years.

### OTHER RARE PANCREATIC ENDOCRINE TUMORS

The VIPoma syndrome, also commonly called the Verner-Morrison syndrome, was first described by Verner and Morrison in 1958. Because of the resemblance of the diarrheal fluid to that seen in patients with cholesterola, the terms pancreatic cholesterola and endocrine cholesterola and the abbreviation WDHA3 (watery diarrhea, hypokalemia, and achlorhydria) have also been used for this condition. The tumors occur in a bimodal distribution. The mean age for adults at diagnosis is 50 years, with a range of 32 to 81 years. There is a female predominance. In children, the mean age at diagnosis is 2 to 4 years, with a range of 20 months to 9 years.

In adults, more than 80% of VIPomas are located in the pancreas, with rare cases caused by intestinal carcinoids or pheochromocytomas that produce vasoactive intestinal peptide (VIP). VIPomas are usually large solitary tumors. In one series, only 2% of tumors were multiple, with 50% to 75% reported to be in the pancreatic tail. One-to-two-thirds of patients with VIPomas have metastases at the time of diagnosis or surgery. Characteristically in children younger than 10 years, and rarely in adults (5% of cases), VIPoma syndrome is due to a ganglieneuroma or ganglieneuroblastoma. These extrapancreatic tumors are less often malignant (10%) than are pancreatic VIPomas.

Using immunocytochemical studies, 34% to 38% of VIPomas also stain for HPP, 19% for glucagon, 10% for somatostatin, 5% for insulin, and 0% for gastrin. VIPomas also elaborate the peptide histidine methionine (PHM-27), a 27–amino acid peptide that shares with VIP a common precursor peptide, pre-pro-VIP/PHM-27. The presence of immunoreactive VIP is strongly suggestive for VIPoma, as this peptide rarely is found in other pancreatic endocrine tumors (10 of 104 pancreatic endocrine tumors in one study).

Plasma levels of VIP are consistently elevated in patients with the VIPoma syndrome and appear to be responsible for the functional syndrome (Table 38.5-4).

A continuous infusion of VIP for 10 hours in normal human subjects to achieve plasma levels similar to those seen in patients with the VIPoma syndrome produced watery diarrhea in 6 to 7 hours. The principal features of VIPoma syndrome are the presence of severe secretory diarrhea associated with hypokalemia and dehydration. The diarrhea is copious, all patients with VIPoma producing >3 L/d. The diarrhea volume of less than 700 mL has been proposed to rule out the diagnosis of VIPoma. Cramping pain or colic is reported in 35% to 63% of patients. Gross steatorrhea usually is not present; in one study, none of 52 patients with VIPomas had 24-hour fecal fat greater than 15 g/d and, in another study, 84% of the patients did not have steatorrhea. Weight loss is almost universally present. Erythematous flushing of the head or trunk area is characteristic and reported in 23% of patients. The clinical laboratory studies invariably demonstrate hypokalemia (63% to 100%) and, to a lesser degree, hypercalcemia (41%), hypochlorhydria (70%), and mild hyperglycemia (18%). Hypokalemia is often severe, potassium levels being less than 2.5 mEq/L at some time in 93% of patients.

<table>
<thead>
<tr>
<th>VIPoma Syndrome</th>
<th>Other Causes</th>
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<td>Hypokalemia</td>
<td>Hypercalcemia</td>
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<tr>
<td>Weight loss</td>
<td>Hypochlorhydria</td>
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<tr>
<td>Erythematous flushing</td>
<td>Mild hyperglycemia</td>
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The diagnosis of VIPoma requires the documentation of an elevated plasma concentration of VIP and the presence of a large volume of secretory diarrhea. A large number of possible causes for the diarrhea can be excluded by fasting the patient because, in patients with VIPomas, the diarrhea persists during fasting. The diarrheal fluid should be characteristic of a secretory diarrhea, with rare cases caused by intestinal carcinoids or pheochromocytomas that produce vasoactive intestinal peptide (VIP). VIPomas are usually large solitary tumors. In one series, only 2% of tumors were multiple, with 50% to 75% reported to be in the pancreatic tail. One-to-two-thirds of patients with VIPomas have metastases at the time of diagnosis or surgery. Characteristically in children younger than 10 years, and rarely in adults (5% of cases), VIPoma syndrome is due to a ganglieneuroma or ganglieneuroblastoma. These extrapancreatic tumors are less often malignant (10%) than are pancreatic VIPomas.

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glucagonomas are within the pancreas; however, a glucagonoma associated with the typical clinical syndrome was found in the proximal duodenum. 117

Glucagonomas usually occur as a single tumor, although in 10% of patients in one series, multiple tumors or diffuse involvement by a single mass was found. 117

Glucagonomas usually occur in middle to late age, with only 16% of cases occurring in individuals younger than 40 years and most occurring at 50 to 70 years of age. 117 125 129 The typical dermatitis occurs in 64% to 90% of patients, diabetes mellitus or glucose intolerance in 83% to 90%, weight loss in 56% to 90%, diarrhea in 14% to 15%, abdominal pain in 12%, and thrombocytopenic purpura with venous thrombosis in 24% and with pulmonary emboli in 11%; occasionally, psychiatric disturbances also are seen (see Table 38.5-4). 117,118 and 119 Laboratory abnormalities include anemia in 44% to 85% of patients, hypoaminoacidemia in 26% to 100%, hypocholesterolemia in 80%, and renal glycosuria. 119

The pathophysiology of the glucagonoma syndrome is related to the known actions of glucagon. Glucagon stimulates glycogenolysis, gluconeogenesis, ketogenesis, lipolysis, and insulin secretion, as well as affecting gastrointestinal tract secretion, inhibiting pancreatic and gastric secretion, inhibiting intestinal motility, and increasing heart rate and contractility. Hyperglycemia in glucagonoma results from the increased hepatic glycogenolysis and gluconeogenesis. Weight loss has been attributed to the known catabolic effects of glucagon. 117 It has not been clearly established that the skin rash is due to the hyperglucagonemia per se, because in normal patients given large doses of glucagon over extended periods of time, the skin rash did not develop. 112 Possibly, the glucagon-induced hypoaminoacidemia that develops in 80% to 90% of patients may be involved, because correction of the hypoaminoacidemia has been shown to correct the dermatitis without changing plasma glucagon concentrations in some patients. 118,120 The similarity of the lesions to those seen in patients with zinc deficiencies has resulted in trials of zinc therapy in some patients, with observed benefit; however, plasma zinc levels are normal in most cases.

Glucagon is one of the most frequently recognized peptides in immunocytochemical studies of PETs, though in many cases it is not associated with any syndrome. In one series of 1366 autopsy cases, a frequency of 0.8% adenomas was reported, and all contained glucagon-producing cells. 59,60 The morphology of most glucagon-producing tumors demonstrates no general features that distinguish them from other PETs. 102 107 117

The presence of cutaneous lesions often precedes the diagnosis of the syndrome for long periods, with a mean of 6 to 8 years and a maximum of 18 years. Typically, the rash starts as an erythematous patch, usually at periocular or intriginous areas such as the groin, buttocks, thighs, or perineum, and then spreads laterally. The lesions later become raised, with superficial, central blistering. The top of the bullae frequently detach or rupture, leaving eroded areas that crust. The lesions tend to heal in the center, while the edges continue to spread with a crusting well-defined edge. Healing is associated with the development of hyperpigmentation. This entire sequence characteristically takes 1 to 2 weeks, so that while some new lesions are developing, others are healing; therefore, a mixed pattern of erythema, bullous formation with epidermal separation, crustation, and hyperpigmentation together with normal skin can occur. The histopathology can be as varied as the clinical presentation. 117,118 Glossitis or angular stomatitis is reported to occur in 34% to 68% of patients.

Once the diagnosis is suspected, it can be confirmed by establishing the presence of a marked elevation in plasma glucagon concentration. In most laboratories, the upper limit of normal for fasting glucagon concentration is 150 to 200 pg/mL. In one large review of glucagonomas, only two patients had a plasma glucagon level of 200 to 500 pg/mL, four patients had a level between 500 and 1000 pg/mL, and 52 patients had a level in excess of 1000 pg/mL. 126 These results are in agreement with another study; 127 in which the mean plasma glucagon concentration in 73 cases of glucagonoma was 2110 ± 334 pg/mL, with a range of 550 to 6600 pg/mL and no result of less than 200 pg/mL. Hyperglucagonemia (generally <500 pg/mL) is reported to occur in chronic renal insufficiency, diabetic ketoacidosis, prolonged starvation, acute pancreatitis, acromegaly, hypercortisolism, septicemia, severe burns, severe stress (trauma, exercise), familial hyperglucagonemia, and hepatic insufficiency. 117,118

Somatostatinomas release somatostatin, a hormone that inhibits numerous endocrine and exocrine functions. Release of almost all gastrointestinal tract hormones, including insulin, glucagon, gastrin, secretin, cholecystokinin, and motilin, is inhibited by somatostatin. In addition to the inhibition of endocrine secretions, somatostatin has direct effects on a number of target organs, including inhibition of gastric acid secretion, increased intestinal motility, and reduced intestinal absorption of fat. In 1977, the first two cases of somatostatinoma were described by Gandia et al. 112 and Larsson et al. 117 Somatostatinomas are the least common PET, fewer than 50 cases having been described. 122 Patients characteristically have diabetes mellitus, gallbladder disease, diabetes, weight loss, steatorrhea, and hypochloremia (see Table 38.5-4). 129,130 132

Somatostatinomas occur in the pancreas in 56% to 75% of cases, and the remainder occur in the upper small intestine. 129 The tumors have a predilection for the pancreatic head and occur there two to three times as often as in the body or tail. 129 In 90% of patients, the tumors are solitary 129 and range from 1.5 to 10.0 cm in diameter. Tumors demonstrate evidence of metastatic spread at diagnosis or operation in 70% to 92% of patients. 129 Metastases usually occur in the liver (75% of patients with metastases) but also in the regional lymph nodes (31%) and, less frequently, in bone. 129

Electron-microscopic studies show that the secretory granules are typical of those in D cells in 89% of the tumors examined. 129 Immunochemical analysis shows somatostatin-like immunoreactive material in tumors that, in addition, contained insulin (33%), calcitonin (27%), and gastrin (13%).

The mean age of patients is affected with somatostatinomas is 50 years. 129,130 A female preponderance (73%) is seen for all PETomas. Acromegalic features are indistinguishable from those of patients with acromegaly. 129 The known actions of GRF as a stimulant of growth hormone release account for the clinical presentation with acromegaly.

Hypochlohydria occurred in 83% to 100% of patients with pancreatic tumors and in 0% to 100% in other pathological studies, 129 130 131 although very few of these patients had acromegaly. The known actions of GRF as a stimulant of gastric hormone release account for the clinical presentation with acromegaly. 129,130,131

Patients are between 15 and 63 years old, the average age being 38. 129 129a 129b Patients with intestinal GRFomas tend to be younger, with two of three patients in one study being younger than 20 years. 129 A female preponderance (73%) is seen for all GRFomas. Acromegalic features are indistinguishable from those of patients with chronic renal insufficiency, diabetic ketoacidosis, and acute pancreatitis. 130 130a 130b The diagnosis should be suspected in any patient with acromegaly who does not have a pituitary adenoma imaged by magnetic resonance modalities or with an abdominal mass 129 and is confirmed by measuring plasma GRF levels.

**IMAGING AND LOCALIZATION OF PANCREATIC ENDOCRINE TUMORS**

Relatively precise localization of the gastrinoma has become an increasingly important factor in evaluating patients with ZES. 119 With the increased ability to control gastric acid hypersecretion with antisecretory drugs, emergency total gastrectomy rarely is necessary now, allowing the clinician time to determine the location and extent of the gastrinoma. The ability for long-term control of gastric acid hypersecretion has made tumor growth and possible metastatic spread an increasingly important determinant of long-term survival. 102,112,125 Preoperative imaging studies can identify patients with metastatic disease to the liver or other sites so that unnecessary surgery can be prevented. Gastrinomas frequently are multiple and extrapancreatic, and accurate imaging assists in determining the nature of the operative procedure. Imaging studies identify resectable metastatic disease to the liver in up to 15% of patients. 122 For insulinoma, the extent of preoperative imaging studies is often limited by the location of the tumor. 102
necessary to ensure an operative cure has not been clearly defined. It is generally agreed that some preoperative localization is essential, primarily because insulinomas are frequently small (<2 cm in diameter) and, to a lesser extent, because metastatic spread should be identified to prevent unnecessary surgery. However, the question of the extent of localization studies that should be performed in occult insulinomas has not yet been resolved.

A number of different techniques, including abdominal ultrasonography, computed tomography (CT) scanning, magnetic resonance imaging (MRI), selective abdominal angiography, selective venous sampling for gastrin from portal venous tributaries (PVS), intraarterial secretin with hepatic venous gastrin sampling (IAS), somatostatin receptor scintigraphy (SRS), endoscopic ultrasonography (EUS) preoperatively, intraoperative ultrasonography (IOUS), and intraoperative endoscopy (IOE) with transillumination of the duodenum at surgery have all been reported as helpful in localizing gastrinomas.

Ultrasonography has a low sensitivity for localizing both primary and metastatic tumors, but, in a prospective study, it was recommended that this imaging modality continue to be used because it has high specificity, is noninvasive and, on occasion, localizes gastrinomas not found by other modalities. The CT scan detects nearly 50% of all primary and metastatic liver disease; however, its ability to detect primary tumors has been shown to be directly related to tumor size, detecting 0% of tumors less than 1 cm in diameter, 30% of those between 1 and 3 cm, and 95% of tumors more than 3 cm in diameter. Frequently, small primary tumors, which are being increasingly found in the duodenum (<1 cm), are missed by CT. Furthermore, CT scan is less sensitive for detecting extrahepatic, extrapancreatic gastrinomas than pancreatic gastrinomas. In a large, prospective study, selective angiography was found to detect 68% of primary tumors and 86% of hepatic metastases. The ability to detect tumors was location-dependent: Of gastrinomas in the pancreatic head, 90% were found, as were 80% in the body, 45% in the tail, and 34% in the duodenum; 50% of extrapancreatic, extrahepatic, and extraduodenal tumors also were found. In a comparative study, angiography detected 20% more hepatic metastases than did CT scanning (68%), and the combination detected 96% of all liver metastases.

Improvements in the sensitivity of MRI have increased its usefulness in localizing gastrinomas and other PETs. A prospective study from the years 1986 to 1987 reported that MRI was less sensitive than either CT scanning or angiography, but a recent study using current, improved MRI technology was more sensitive than either angiography or CT scanning for metastatic disease. However, MRI remains less sensitive than angiography for primary tumor. For insulinomas, ultrasonography localizes 33%, MRI 46%, CT scanning 35%, dynamic CT scanning 66%, selective arteriography 63%, and all imaging studies combined 80%.

Pancreatic endocrine tumors frequently have a high density of somatostatin receptors, and scanning after injection of the radiolabeled long-acting somatostatin analog octreotide localizes pancreatic endocrine tumors. This technique is one of the most sensitive methods for localizing primary gastrinomas. This study included 100 patients with ZES. PVS correctly localized the tumor in 75% and 88% of cases, respectively. In another study of 35 patients with insulinoma in whom radiologic studies were obtained over SRS or current MRI techniques is unproven. Recently, EUS was reported to have a high sensitivity, localizing 80% of insulinomas, even though 15% of tumors less than 1 cm in diameter, 30% of those between 1 and 3 cm, and 95% of tumors more than 3 cm in diameter. Frequently, small primary tumors, which are being increasingly found in the duodenum (<1 cm), are missed by CT.

**FIGURE 38.5-2.** Example of somatostatin receptor scintigraphy sensitivity in detecting gastrinoma. A patient with biochemically confirmed Zollinger-Ellison syndrome underwent initial imaging studies. The magnetic resonance image (MRI) and computed tomography (CT) scan did not show any lesion. However, somatostatin receptor scintigraphy (SRS) showed a positive signal in the right upper quadrant, which was confirmed to be a 1.4-cm gastrinoma resected from the anterior lateral wall of the second part of the duodenum at surgical exploration. (From ref. 39.)

EUS is being used increasingly to localize PETs. It is reported to localize 75% of primary gastrinomas and to be particularly useful for intrapancreatic tumors. Whether EUS can image small duodenal gastrinomas is unclear. However, EUS is an invasive procedure, and the additional information obtained over SRS or current MRI techniques is unproven. Recently, EUS was reported to have a high sensitivity, localizing 80% of insulinomas, even though 15% of tumors less than 1 cm in diameter, 30% of those between 1 and 3 cm, and 95% of tumors more than 3 cm in diameter. Most gastrinomas (91%) demonstrate a paradoxical release of gastrin with intravenous injection of secretin. This characteristic has been used to localize gastrinomas selectively by injecting secretin intraarterially into various abdominal arteries and collecting venous samples from the hepatic veins for assays of gastrin. Injection into the arterial supply of the tumor area causes a marked increase in gastrin. In a recent comparative study, IAS was found to localize the gastrinoma as frequently as the much more technically difficult PVS.

PVS for insulin can accurately localize an insulinoma to the exact region of the pancreas (head, body, tail) in nearly all patients. PVS, which requires considerable expertise and is highly invasive, is now being replaced by the intraarterial injection of calcium (IAC) during angiography, with hepatic venous insulin sampling. A recent preoperative study reported that 80% of insulinomas could be localized using this method. In two studies, composed of 12 and 23 patients with insulinoma, PVS and IAC correctly localized the tumor in 75% and 88% of cases, respectively. In another study of 35 patients with insulinoma in whom radiologic studies imaged the tumors in 46%, PVS localized the tumor in 100%. PVS localizes tumors to only a general area of the pancreas, and the insulinoma may be so small that it cannot be localized by palpation at surgery within this area. However, IOUS has been increasingly reported to be useful in localizing insulinomas at the time of surgery. In one study of 12 patients with negative imaging studies in whom 75% had a PVS gradient localizing the insulinoma to the appropriate pancreatic area, at surgery insulinomas could be localized by palpation in only 41%. IOUS identified insulinomas in five additional patients and was the single best modality in locating the insulinoma at surgery.

The use of IOUS in a recent prospective study was demonstrated to change operative management in 10% of all ZES cases, either by localizing additional gastrinomas or by determining that a gastrinoma was malignant. IOUS localized 22 of 23 pancreatic gastrinomas found at surgery but only 7 of 12 extrapancreatic gastrinomas. All five of the gastrinomas were missed in the duodenum.

Even though gastrinomas frequently occur in the duodenum (see Table 38.5-2), they are rarely seen by routine upper gastrointestinal endoscopy because they are...
small and submucosal. IOE of the duodenum at surgery has been attempted and found useful in localizing small gastrinomas not found by other modalities. In a recent prospective study, 12 duodenal gastrinomas were found at surgery in 10 patients. IOE detected 10 of the 12 (83% sensitivity), which was significantly greater than either standard preoperative imaging, which detected 3 (25% sensitivity) or IOUS and palpation, which detected 5 (42% sensitivity). IOE with transillumination detects 20% more duodenal tumors than does palpation, and duodenectomy detects an additional 15%. Endoscopic transillumination also is often helpful in establishing the placement of the duodenotomy incision.

TREATMENT OF RESECTABLE DISEASE

GASTRINOMA

In ZES patients, gastric acid hypersecretion must be controlled because most patients will not be cured after surgical exploration. If acid hypersecretion is controlled, patients have an excellent quality of life; however, long-term prognosis is being increasingly determined by the malignant nature of the gastrinoma. As many as 90% of gastrinomas may be malignant; therefore, it is important to consider surgical therapy directed at the primary and metastatic disease, if feasible (Fig. 38.5-3).

![Flow diagram showing a proposed workup for patients with newly diagnosed sporadic Zollinger-Ellison syndrome (ZES).](image)

**Management of Gastric Acid Hypersecretion**

Years ago, patients with ZES required total gastrectomy to control gastric acid hypersecretion. Before effective medical management, the operation was commonly done as an emergency procedure and carried a mortality rate of 15%. Operative results were unsatisfactory for patients who had less than a total gastrectomy, with most patients developing recurrent ulcer disease, often with lethal complications, within days of surgery. With the development of increasingly effective medical therapy, the mortality for patients with ZES undergoing total gastrectomy has decreased. Though an early study claimed that total gastrectomy could lead to regression of the gastrinoma in some patients, subsequent studies have failed to substantiate this claim. There is no evidence that either medical therapy of gastric hypersecretion or total gastrectomy affects the growth rate of the gastrinoma.

Numerous studies have demonstrated that gastric acid hypersecretion can now be controlled medically over the long term in every patient who will reliably take oral medication—the H\(^+\)-ATPase inhibitor omeprazole or lansoprazole. The availability of these agents and their long duration of action have greatly simplified management because they can be taken once or twice per day. Therefore, most authorities recommend that total gastrectomy be reserved for patients who are unreliable, do not have access to routine medical follow-up, or cannot or will not take oral medication. In all other patients, medical therapy is the treatment of choice. Although partial cell vagotomy in patients with ZES in whom no tumor was found at surgery decreased the BAO by 66%, most patients still needed some antisecretory drug. At present, routine performance of parietal cell vagotomy is not recommended.

In patients with ZES and the MEN 1 syndrome, medical control of gastric hypersecretion can be greatly facilitated by correction of the hyperparathyroidism that is almost invariably present by the time ZES develops. Correction of hyperparathyroidism may reduce the FSG concentration, increase the responsiveness to a given dose of antisecretory medication, or decrease the BAO. Therefore, in patients with ZES and MEN 1 with hyperparathyroidism, parathyroidectomy should be performed before any contemplated surgical procedure to control acid hypersecretion.

The results of medical treatment of gastric acid hypersecretion have been reviewed extensively. H\(_2\) receptor antagonists (cimetidine, ranitidine, famotidine) alone or in combination with anticholinergic agents (propantheline, isopropamide) and, more recently, the substituted benzimidazole (omeprazole), which functions as an H\(^+\)-ATPase inhibitor, have been used successfully in the long-term treatment of gastric hypersecretion in ZES. The number of patients in whom medical therapy fails varies greatly in different series. For cimetidine, the reported failure rate varies from 0% to 65%. For ranitidine from 0% to 40%, and for omeprazole and lansoprazole from 0% to 7.5%. The failure rate for famotidine has been reported as 0% in several series. In general, studies have shown that relief of symptoms does not adequately reflect the effectiveness of antisecretory therapy. Most studies have demonstrated that in order to assess the adequacy of antisecretory therapy, gastric acid secretion must be measured while the patient is taking medication.

The amount of antisecretory medication varies widely from patient to patient; thus, the optimal dose of medication must be determined for each patient initially and must periodically be reevaluated. Recent studies have shown that if enough antisecretory drug is used to decrease gastric acid output to less than 10 mEq/h for the hour prior to the next dose of medications in patients with no history of gastric surgery and to less than 5 mEq/h in patients with a history of acid-reducing procedures or severe esophageal disease, peptic ulcers will heal and complications of peptic ulcer disease will be prevented.

In general, studies have shown that relief of symptoms does not adequately reflect the effectiveness of antisecretory therapy. Most studies have demonstrated that in order to assess the adequacy of antisecretory therapy, gastric acid secretion must be measured while the patient is taking medication.

The long-term use of omeprazole has caused concern about toxicity, because female rats given long-term omeprazole (or other potent inhibitors of gastric acid secretion) develop proliferation of gastric ECL cells and, in some cases, carcinoid tumors of the stomach. Results from a number of studies have led most investigators to conclude that the ECL hyperplasia and gastric carcinoid tumor formation in these animal models were most likely secondary to drug-induced achlorhydria and the resultant hypergastrinemia and not secondary directly to a toxic action of the antisecretory drug. Hyperplasia of gastric endocrine cells occurs in patients with ZES. Quantitative studies indicate that gastric ECL cells are increased approximately twofold, independent of administration of antisecretory agents. In studies in which omeprazole treatment was prolonged for up to 4 years, there was no statistical increase in gastric ECL cells owing to use of this drug. In 15 of the 16 patients reported with gastric carcinoids and ZES in whom the presence or absence of MEN 1 could be determined, 14 had MEN 1. These data suggest that the presence of MEN 1 may be an important predisposing factor to the development of gastric carcinoids in patients with ZES. In patients with ZES without MEN 1, 0.6% had gastric carcinoid tumors in one study and, in another study, 0% had gastric carcinoid tumors. In contrast, in patients with MEN 1, 13% in a U.S. study and 30% in a French study had gastric carcinoids. These data demonstrate further the importance of the presence of MEN 1 in...
determining the development of gastric carcinoids.

Most patients with ZES require H₂ antagonists every 4 to 8 hours to inhibit gastric secretion adequately, whereas omeprazole or lansoprazole has a very long duration of action (>48 hours), allowing most patients to require omeprazole only once or twice daily. The usual starting dose for omeprazole is 60 mg/d, although a proportion of patients are better controlled with a twice-daily dose. Patients with ZES with complicated disease (previous gastric surgery, moderate to severe esophageal disease, or MEN 1), usually require a higher dose and are best treated by starting with 40 mg twice daily. Recent studies show that in patients with uncomplicated ZES, the dose of omeprazole or lansoprazole can be reduced over time in more than 85% of patients. It is recommended, though, that because of these drugs' acid lability, patients not be started on these low doses until they are proven safe and effective.

For patients presenting with a complication who cannot take oral antisecretory medication and for patients undergoing surgery, it is important that acid secretion be adequately controlled parenterally. Studies have shown that continuous infusions of cimetidine (median dose, 3 mg/kg/h) or ranitidine (median dose, 1 mg/kg/h) or bolus doses of omeprazole (injectable, 60 mg every 12 hours; not yet available in the United States) are all effective. A recent, new parental proton pump inhibitor, pantoprazole, has been shown to produce a dose-dependent decrease in acid output in volunteers stimulated with pentagastrin. These drugs should be continued until oral antisecretory agents can be restarted.

SURGERY TO CURE GASTRINOMA

In a number of studies, the 5-year survival rate for all patients with ZES was 62% to 87%, and the 10-year survival was 47% to 77%. A recent comprehensive report from the National Institutes of Health cited long-term outcome in 151 consecutive ZES patients who underwent operation with curative intent. And in patients with gastrinoma, 34% were biochemically and radiographically free of disease at 10 years, as compared to no patients with MEN 1 and ZES. The overall 10-year survival was 94% (Fig. 38.5-4). In another study from the same institution, a multivariate analysis of factors associated with long-term (>5-year) cure was performed. Age, gender, duration of symptoms or disease, and severity of disease (as reflected by the level of BAO, FSG, or secretin stimulation test) did not predict outcome. Only a diagnosis of MEN 1 was inversely correlated with cure. In addition, the status of preoperative imaging studies (either positive or negative), tumor size, and number of tumors resected did not correlate with cure. However, a normal postoperative FSG and secretin stimulation test did independently and significantly predict cure.

Though the growth of gastrinoma is generally slow, in long-term studies of patients originally treated by total gastrectomy, 57% of deaths were due to tumor progression. Therefore, with the ability to control gastric acid hypersecretion, the malignant potential of the tumor is an increasingly important determinant of long-term prognosis. The extent of the tumor and whether MEN 1 is present or absent have been reported to determine survival rates. In patients with no tumor found at laparotomy or in whom tumor is completely resected, 5- and 10-year survival rates are 90% to 100%, respectively. Patients with liver metastases had a 5-year survival rate of 95%, and 10-year survival rates were 90%. In contrast, patients with liver metastases had a 5-year survival rate of only 53% and a 10-year survival of 30% (Fig. 38.5-5). In most studies in patients without liver metastases, a difference in survival is noted between patients whose tumors were resected completely and those in whom tumors were resected and recurred or in whom tumors were incompletely resected. There was, however, no difference in survival rate between patients with complete resection and those with no tumor found at surgery. In two studies, patients with MEN 1 are reported to have a better 5- and 10-year survival rate than patients without MEN 1. Whereas in other studies, the difference was not significant. One study demonstrated a significant difference in the percentage of patients with ZES with MEN 1 (6%) who presented with liver metastases, as compared with non–MEN 1 patients (22%, P = .03), with no difference in survival rate for the patients without liver metastases between MEN 1 and non–MEN 1 patients. The presence of concurrent Cushing's syndrome may also be associated with a poor prognosis.

A recent study has addressed the question of whether surgical resection of the tumor alters its natural history. In this study, only 3% of patients with ZES undergoing tumor resection developed liver metastases during follow-up, whereas significantly more patients treated medically developed liver metastases (28%, P < .003). Two deaths occurred owing to metastatic disease in the nonoperated group, as compared with no disease-specific deaths in the surgical group (P = .085). Although this was not a randomized study, the two groups did not differ in clinical or laboratory characteristics or time of follow-up (15.4 ± 1.5 years).
In most recent series, the improvement in outcome after surgical exploration and resection with curative intent is due to a number of factors. First, because gastric acid hypersecretion can be managed in all patients with antisecretory agents, surgical exploration can be done electively and safely. Second, patients can be effectively screened to eliminate occult metastatic unresectable disease, thereby improving patient selection for potentially curative surgery. Furthermore, the knowledge that small duodenal primary tumors are more frequent than previously was appreciated has resulted in increased detection and resection of these lesions than in earlier studies. In a 10-year prospective analysis of surgical outcome in patients with ZES, the overall percentage of patients free of disease at 5 years was 30%, consistent with the updated outcome from the same institution. In addition, ectopic gastrinoma can occur in a variety of other locations, including small bowel mesentry, common bile duct, and ovary.

At laparotomy, the entire pancreas as well as the duodenum should be dissected and exposed. Duodenum in the anterior wall of the second part of the duodenum also should be performed. In 42 patients, palpation alone identified 65% of duodenal gastrinomas, endoscopic transillumination an additional 20% of tumors, and duodenotomy an additional 15% of tumors not localized by any other modality. For duodenal tumors, 71% are in the first part of the duodenum, 21% in the second part, and 8% in the third part. Using this approach to carefully evaluate the duodenum, gastrinomas have been found in all patients undergoing operation, 71% of such lesions being duodenal. At laparotomy, if a gastrinoma is found as a solitary lesion in the liver, it should be removed, provided the resection can be performed safely. If gastrinoma is found in the pancreatic head, it should be enucleated. If extensive gastrinoma not amenable to eradication is found in the pancreatic head, performing a pancreatectoduodenectomy (Whipple's operation) for potential cure is controversial. A Whipple procedure cured 11 of 12 patients with tumors localized by imaging studies and PVS to the periampullary head area. However, no studies have demonstrated an increased survival rate overall in patients with ZES after pancreatectoduodenectomy. Because of the possible morbidity and mortality associated with this operation and the excellent long-term prognosis of these patients, it has not yet been established whether the adverse consequences of a pancreaticoduodenectomy might outweigh the adverse consequences of unresected occult gastrinoma. If no gastrinoma is found at surgery, as occurs in 7% to 30% of cases overall, a blind distal pancreatectomy should not be performed, because 65% to 90% of gastrinomas are now found in the pancreatic head or duodenum and because such an approach has not improved cure rates.

At surgery, the use ofIOUS is recommended to localize additional lesions, to confirm the significance of a palpated mass, and to establish the relationship between the tumor and the pancreatic duct. For either pancreatic or duodenal primary tumors, any abnormal or suspicious lymph nodes in that area should be excised. In some patients undergoing exploration, disease may be limited to one or more lymph nodes. Despite the inability to identify a primary site of disease in the duodenum or pancreas, long-term biochemical cures can be achieved. In one study of 13 patients who had disease limited to resected lymph nodes, 43% remained biochemically cured with a median follow-up of 5.3 years.

At present, the role of surgery in the treatment of patients with ZES and MEN 1 is unclear. A recent study reported that in eight patients (six surgical cases and two autopsy reports) with ZES and MEN 1, gastrinomas were found in the duodenum in all. In all six patients whose tumors were surgically resected, the gastrin values were normal postoperatively, and this study raised the possibility that these patients could be cured. However, a number of limitations exist for this study, for example, cure cannot be established without a secretin provocative test, which was not reported in this study. A recent prospective study involving ten consecutive patients with ZES and MEN 1 demonstrated that no patients could be cured by simple tumor enucleation after duodenotomy. Cure was not possible short of pancreatectoduodenectomy, because 30% of patients had more than 20 duodenal tumors and 86% of patients had positive lymph nodes. This study also demonstrated that 20% of patients with MEN 1 and ZES had pancreatic gastrinomas. Another recent study reported three patients with MEN 1 and ZES who were cured by a Whipple procedure. In 77 patients with MEN 1 and ZES, the only independent factor associated with the development of liver metastases was a pancreatic primary tumor measuring greater than 3 cm. Operation with curative intent in 118 patients did not influence survival. Currently, because of the excellent prognosis of these patients, the ability to control acid secretion medically, the presence of other pancreatic tumors, and the morbidity of this procedure, it is not routinely recommended. Our recommendation is to operate on patients with MEN 1 and ZES when a tumor of at least 2.5 cm is seen on imaging studies. This policy is based on the recent observation that metastases to the liver correlated with tumor size. If the tumor is in the pancreatic head, it is enucleated if possible, and, if in the pancreatic tail, it is resected and a duodenal exploration is performed. Because most patients with sporadic ZES undergoing operation and resection will have persistent or recurrent disease, the role of reoperation in these patients warrants consideration. In a series of 17 patients who had previously undergone an operation with curative intent, reoperations were performed on the basis of biochemically documented recurrent disease and one or more positive imaging studies. In those undergoing reoperation, it was possible to identify and resect disease in 17 of 18 cases, with biochemical cures in all, although median follow-up was short (34 months). Of note, the site of recurrent disease identified at reoperation was related to the initial operative findings. For example, in those in whom lymph node disease was resected initially, most patients had lesions identified in the duodenum at reoperation. In contrast, in those who had a primary duodenal or pancreatic lesion initially resected, recurrence was commonly identified in regional lymph nodes. Because of the increased potential risk of complications associated with reoperation in this setting, reoperation should be considered carefully.

**INSULINOMA**

**Medical Therapy for Hypoglycemia of Insulinoma**

The simplest form of nonsurgical treatment for insulinoma is dietary management. Many insulinoma patients begin ingesting frequent small meals to alleviate symptoms prior to seeking medical evaluation, and a significant percentage report weight gain in the year prior to diagnosis. Slowly absorbed oral nutrients such as cornstarch, bread, potatoes, and rice are recommended. A number of drugs have been reported to control the hyperinsulinemia, with octreotide and diazoxide being the most effective. Diazoxide, a benzothiazide analog, directly inhibits insulin release from β cells through stimulation of ATP-sensitive receptors and also has an extrapancreatic hyperglycemic effect, possibly by inhibiting cyclic adenosine monophosphate phosphodiesterase, which enhances glycogenolysis. The major side effects of diazoxide are sodium retention, gastrointestinal symptoms such as nausea and, occasionally, hirsutism. Edema can result from the sodium retention, and the addition of a diuretic such as triamterene, a benzothiazide derivative, can correct the edema as well as augment the hyperglycemic effect. Diazoxide should be initiated, with 150 to 200 mg given in two to three divided doses per day, and, if not effective, increased to a maximum of 600 to 800 mg/d. The calcium channel inhibitor verapamil has been used, either alone or in combination with other drugs, to help control hypoglycemia in a small number of patients, as has propranolol.
Phenyltoin (Dilantin) inhibits the release of insulin from β cells and has been used successfully to treat a small number of patients with refractory hypoglycemia.\textsuperscript{20} Maintenance doses of 300 to 600 mg/d are used, but it is reported that in only one-third or fewer patients is the hyperglycemic effect of phenyltoin of any clinical significance.\textsuperscript{20} Glucocorticoids (prednisone, 1 mg/kg) and glucagon, either alone or with diazoxide, have also been used in a few patients.\textsuperscript{21}

Octreotide controls symptoms and hypoglycemia in 40% to 60% of patients.\textsuperscript{22,23,24,25} This drug is generally well tolerated and usually is initiated at doses of 50 µg subcutaneously two or three times daily, which can be increased to 1500 µg/d.\textsuperscript{25} The main side effects are gastrointestinal, such as bloating and abdominal cramping, and include long-term side effects such as malabsorption and cholelithiasis.\textsuperscript{11,12} Besides improving symptoms, octreotide decreases plasma insulin levels in 65% of patients.\textsuperscript{26} However, most patients were treated for less than 1 week preoperatively, so the long-term efficacy is not known in a significant number of patients. Octreotide also decreases plasma glucagon levels and growth hormone secretion; hence, it may worsen the hypoglycemia in some patients.\textsuperscript{22}

Surgical Therapy

All insulinomas without evidence of metastases should be surgically removed, regardless of the severity of symptoms. Of all insulinomas, 80% to 90% are benign isolated lesions that are cured by complete surgical removal.\textsuperscript{27,28} The extent of preoperative imaging necessary for successful outcome of resection of presumed benign solitary pancreatic insulinoma is controversial.\textsuperscript{28,29} Because insulinomas are exclusively located within the pancreatic parenchyma, thorough exploration and intraoperative evaluation with inspection, palpation, and IOUS can result in successful resection in the vast majority of patients undergoing operation. IOUS has been advocated as an important adjunct in operation for insulinoma, not only in identifying lesions at the time of surgery but also in enucleating the lesion by identifying the relationship between the tumor in the pancreatic parenchyma and the adjacent pancreatic duct. This is particularly important in the case of lesions located in the head of the pancreas, where a resection other than enucleation would require pancreaticoduodenectomy. Selective arterial stimulation of the splanchic vessels supplying the pancreas using the secretagogue calcium can produce a subsequent rise in insulin levels obtained from catheters positioned at the orifice of the hepatic veins.\textsuperscript{30} The sensitivity of this test is almost 90% and allows one to direct attention to a particular region of the pancreas at the time of operation. Blind distal pancreatectomy has been used in the past in an attempt to cure insulinoma in patients in whom no lesion could be identified, based on the appreciation that insulinomas can be distributed anywhere in the pancreatic parenchyma and resection of a large portion of normal pancreatic tissue should therefore have a reasonable cure rate for occult disease. However, given the current status of available localization studies, this practice should be largely unnecessary. With careful inspection and the use of IOUS, the number of people with occult lesions that cannot be identified at the time of operation should be fewer than 5%.\textsuperscript{31,32} In this setting, our recommendation would be to proceed with distal pancreatectomy only in the face of a position insulin step-up in the hepatic veins after selective intraarterial stimulation with calcium demonstrates a bona fide step-up in the splenic artery as compared to the gastroduodenal or hepatic arteries.

The liver must always be explored for evidence of metastatic disease, and the entire abdomen must be explored to rule out rare extrapancreatic tumors that primarily secrete insulinoma-related growth factors (IGFs). IGF-secreting tumors that cause hypoglycemia usually are of mesodermal origin and have considerable tumor bulk by the time hypoglycemia symptoms occur.\textsuperscript{11} The entire pancreas must be explored for other tumors, since multicentral tumors occur in up to 10% of all cases.\textsuperscript{33,34} Isolated lesions of the tail may be enucleated or removed en bloc by distal pancreatectomy. Body and head lesions require enucleation with careful dissection to avoid damage to the main pancreatic duct and its attendant morbidity. Even in cases of documented metastatic disease, refractory debilitating symptoms may be an indication for debulking the pancreatic lesions, as metastases are not always secretory. Removal of peripancreatic lymph nodes may be curative for malignant insulinoma if no liver metastases are present.\textsuperscript{35,36}

The documentation of metastatic disease, either at the time of surgery or by imaging studies, is the only accurate means of diagnosing malignant insulinoma. Unlike all other PETs, malignant insulinomas are uncommon, occurring in only 5% to 11% of all cases of insulinoma. Malignant primary insulinomas usually are not occult and have a mean size of 6 cm, which is more than three times as large as benign insulinomas.\textsuperscript{36,37,38} The median disease-free survival after curative resection of malignant insulinomas was 5 years in one series.\textsuperscript{39} The recurrence rate was 63%, the median interval to recurrence was 2.6 years, and the median survival with recurrent tumor was 19 months. Palliative re-resection was associated with a median survival of 4 years, whereas median survival after biopsy was only 11 months.\textsuperscript{39} Surgical resection of primary and metastatic insulinomas is desirable when possible.\textsuperscript{39} Malignant insulinomas, like other PETs, may respond to chemotherapy and treatment with octreotide.\textsuperscript{40,41} The use of these agents for all malignant PETs is described later in Treatment of Metastatic Disease.

OTHER PANCREATIC ENDOCRINE TUMORS

The remainder of the PETs are relatively infrequent and include VIP-producing tumors (VIPomas), glucagonomas, ACTHomas, somatostatinomas, and GRF pancreatic tumors (GRFomas). Each of these PETs is usually malignant.

The treatment is surgical, if possible, even in the more than 60% of cases in which metastases are present at the time of diagnosis \cite{38, 57, 58}. Of 25 cases of nonfunctional PETs in one series, a Whipple procedure was performed in 20% of patients, partial or total pancreatectomy in 25%, and tumor excision in 10%.\textsuperscript{42} The survival rates were 60% at 3 years and 44% at 5 years in this series.\textsuperscript{42} The cure rate of these tumors at present is low because of their late recognition.

**FIGURE 38.5-7.** Flow diagram illustrating the general approach and management strategy for patients with pancreatic endocrine tumors (PET). Once the diagnosis has been established, initial staging studies are performed to determine the absence or presence of metastatic disease. A variety of palliative options are available to control the functional sequelae of hormone excess for increasing tumor burden. For those patients who have isolated liver metastases, resection should be performed when possible. Other regional therapies that may cause durable palliation of symptoms or disease control in the liver should be attempted. For those patients who have local regional disease, resection should be considered. MRI, magnetic resonance imaging.

The first treatment objective in patients with VIPomas, even before considering the diagnosis, is the replenishment of fluid and electrolyte losses to correct the profound hypokalemia, dehydration, and acidosis that usually are present. The patients may require 5 L/d or more of fluid and more than 350 mEq/d of potassium.\textsuperscript{43} In the past, numerous drugs have been reported to control, to varying degrees, the diarrheal output in small numbers of VIPoma patients; among these agents are prednisone (60 to 100 mg/d), clonidine, indomethacin, phenothiazines, lithium carbonate, propranolol, metoclopramide, loperamide, lidamidine, angiotensin II, and norepinephrine.\textsuperscript{11,31,44}

Octreotide, a long-acting somatostatin analog, can control the diarrhea in both the short and long term in 87% of patients with VIPoma, and it is now the agent of choice.\textsuperscript{45,46,47} In recent reviews of treatment of 20 and 25 patients with VIPomas with octreotide, the drug completely abolished diarrhea in 10% of patients in the first study and in 65% in the other and improved the diarrhea in 90% in the first study and in 95% in the other.\textsuperscript{48,49} In some patients, responses have been reported to octreotide, or a patient may respond initially to a low dose (50 to 100 µg three times daily) but subsequently may require a larger dose to control the diarrhea and may even become refractory to doses up to 1200 µg/d.\textsuperscript{49} In nonresponsive patients or in patients whose symptoms recur, the administration of glucocorticoids concomitantly with octreotide has proven effective in a small number of cases.\textsuperscript{50} With octreotide treatment, plasma VIP concentrations decreased in 80% to 88% of
patients. 

After imaging studies have been conducted to localize the primary VIPoma and determine the extent of the tumor, surgical excision for cure should be considered in all patients without metastatic disease. In one series, surgical resection of a pancreatic VIPoma relieved all symptoms in 17 patients (33%), and 30% were cured in another series. 

Surgical removal with complete control of all symptoms was possible in 78% of all patients with VIP-producing ganglioneuroblastomas. 

For patients with glucagonomas, medical therapy with octreotide improves dermatitis in 54% to 90% of patients, with complete disappearance of this symptom in up to 30%. 

In one study, diarrhea improved in four of six patients and resolved in two of six patients. Diabetes mellitus was not improved with octreotide treatment. 

The diabetes mellitus was severe enough to require oral hypoglycemia agents in 42% of patients and insulin in 27%. Plasma glucagon levels decreased in 80% to 90% of patients but only decreased to the normal range in 10% to 20% of patients on octreotide treatment. 

In 50% to 80% of patients, metastases are already present at the time of diagnosis. 

Surgical resection has been successful in a number of patients with resectable disease, but the exact percentage of cases that can be cured is not known. In one large review involving 92 cases of glucagonoma, only 16 of the malignant cases were treated by surgical resection alone. Seven cases exhibited normal plasma glucagon levels after resection and, in the five cases that had no evidence of metastatic spread, plasma glucagon levels postoperatively were normal in two. Even if a patient eventually develops a recurrence, an extended disease-free interval may be attained that is beneficial. 

A number of studies have reported a benefit to patients even if surgical debulking only can be accomplished. 

In patients with widely metastatic disease in whom surgical debulking is not possible, various chemotherapeutic agents are used and are discussed later in Treatment of Metastatic Disease. 

Most somatostatinomas are found at the time of laparotomy for cholecystectomy or during gastrointestinal imaging studies for various nonspecific complaints such as abdominal pain or diarrhea. 

The symptoms produced by somatostatinomas are less pronounced and less specific than those seen with other PETs and probably do not reach a detectable level until patients develop high somatostatin blood levels late in the course of the disease. Though the plasma levels of somatostatin usually are elevated in pancreatic somatostatinomas, in duodenal or small-intestinal tumors these levels may fail to be conclusive. 

Duodenal somatostatinomas are increasingly associated with von Recklinghausen's disease. In a recent review, 27 duodenal somatostatinomas with or without von Recklinghausen's disease were compared with pancreatic somatostatinomas without von Recklinghausen's disease. The cases of somatostatinomas with von Recklinghausen's disease were similar to the sporadic duodenal cases in that they rarely were associated with the somatostatinoma syndrome, additional hormone production was infrequent, and they were less frequently malignant (30% vs. 71%). 

The number of patients undergoing successful complete resection ranges from 60% to 80%. 

In one series, 65% of patients were reported to have undergone successful resection, but the percentage actually cured was not stated. 

In a number of patients, a combination of surgical resection and cytotoxic therapy was used. 

Of the 60% of the patients were alive 6 months to 5 years after diagnosis. Because of the malignant nature of these tumors, if imaging studies demonstrate a possible resectable tumor, results suggest that patients with somatostatinomas will benefit from surgical resection. 

In patients without metastatic disease, surgical resection of a GRFoma should be carried out. Surgical resection results in resolution of the GRFoma syndrome, but the long-term cure rate is unknown. Before surgery and in those patients with nonresectable lesions, various agents may reduce plasma growth hormone (GH) and GH-related symptoms. 

Somatostatin analogs have been used in patients with classic acromegaly, 

rarely is it possible to normalize plasma growth hormone levels in patients with GRFomas. 

Octreotide is now the agent of choice. 

In all cases thus far described, octreotide significantly suppressed or normalized growth hormone and IGF-1 levels and, in some cases, was associated with pituitary shrinkage. 

In 75% of cases, octreotide decreased plasma GH levels by more than 50%. 

In a few studies in patients with PETs secreting the peptide neurotensin, a neurotensinoma syndrome has been proposed. 

Clinical features of patients with possible neurotensinomas include hypokalemia, weight loss, diabetes mellitus, cyanosis, hypotension, and flushing in a patient with a PET. 

In a review of six cases, one-half of the patients were cured by resection of the pancreatic endocrine tumor, and the remaining one-half improved with chemotherapy. 

Elevated plasma neurotensin levels have been measured in patients with VIPomas, and their symptoms did not differ from those with normal levels; a similar result was found in patients with gastrinomas. 

Patients with PETs and Cushing's syndrome (ACTHoma) have been reported. 

In recent studies, 4% to 16% of Cushing's syndrome cases attributable to an ectopic ACTH syndrome originated from a pancreatic tumor. Cushing's syndrome is reported in 19% of patients with the ZES syndrome and MEN 1. In these patients, the disease was of pituitary origin and was mild. Cushing's syndrome also occurs in sporadic cases of ZES and, in one prospective study, it was found in 5% of all cases. 

In these patients, the Cushing's syndrome was severe due to the ectopic ACTH production and occurred with metastatic pancreatic endocrine tumors, which responded poorly to chemotherapy; hence, the disease was associated with a poor prognosis. 

The occurrence of Cushing's syndrome as the only manifestation of a PET occurs in 37% to 60% of cases and may precede any other hormonal syndrome. 

Hypercalcemia resulting from a PET secreting a parathyroid hormone–related protein or to an unknown hypercalcemia substance that mimics the action of parathyroid hormone and causes hyperparathyroidism has been reported. 

Clinical features of patients with parathyroid hormone–related protein-producing tumors include hypokalemia, weight loss, diabetes mellitus, cyanosis, hypotension, and flushing in a patient with a PET. 

The tumor is generally large and metastatic to the liver by the time of diagnosis, although in one recent case, radical resection of a pancreatic tail tumor with subsequent treatment with chemotherapy resulted in a total remission for 5 years. 

TREATMENT OF METASTATIC DISEASE 

The treatment of all metastatic PETs is considered as a unit because, in most respects, cytotoxic protocols and surgical approaches are the same. The long-term natural history of most functional PETs (malignant insulinomas, VIPomas, glucagonomas, GRFomas, somatostatinomas) is not known because, until recently, effective treatment for the functional syndrome did not exist and therefore patients often died of complications of the hormonal excess rather than from the tumor. 

In a study including 212 patients with ZES who had well-controlled gastric acid hypersecretion, 31% had died at a mean follow-up of almost 14 years. 

One-half of these deaths were due to tumor progression, particularly in bone and liver, and to ectopic ACTH production. In a recent large study involving 185 patients with ZES, in whom no patient died from acid-related problems, the 10-year survival rate was not significantly different among patients in whom no tumor was found (only 8%), patients in whom tumor was completely resected, and patients in whom tumor was resected without biochemical cure (84%, 96%, and 93%, respectively). 

However, in patients with unresectable disease, the 10-year survival rate was only 30%. This study demonstrates that the development of metastatic liver disease is the primary determinant of survival. 

Currently, no data are available to suggest that survival for patients with other PETs will differ from that for patients with ZES and, in fact, limited data from PPomas, of which most were metastatic, reported mean survival of 4.3 years and a 5-year survival rate of 44%, which is similar to patients with metastatic gastrinomas. Most authorities would agree that treatment directed to metastatic unresectable liver disease is indicated. However, at present, there is no agreement about when therapy should be started or the efficacy of various therapeutic options, because of the small numbers of patients treated with various protocols. Chemotherapy either alone or combined with cytoreductive surgery, hepatic arterial embolization alone or with chemotherapy, hormonal therapy with the long-acting somatostatin analog octreotide, interferon, or hepatic transplantation have all been reported to be useful in small numbers of cases. 

CHEMOTHERAPY 

Almost all studies that include significant numbers of patients and investigate the effects of chemotherapeutic agents on PETs include all types of PETs, often combined with carcinoids. Whether these results can be extrapolated to each histologic type is unclear at present. Three studies have demonstrated no difference in response rates of various PETs to streptozocin (STZ) and/or chemotherapy. 

However, only small numbers of patients with different type of PETs were included. Other studies have shown that vinblastine is a single-agent chemotherapeutic agent with dacarbazine (DTIC) or STZ, suggesting that differences may exist. 

Finally, other studies suggest that functioning tumors respond better than nonfunctioning tumors to vinblastine (BL) and, among functioning tumors, insulin and VIP-secreting PETs may be more sensitive to STZ-based therapies. 

Except for STZ or chlorozotocin, a single-agent chemotherapy with other various other agents (doxorubicin, etoposide, carboplatin, DTIC, and tuberculostatin) has had limited efficacy (Table 38.5-5). STZ, a glycosaminoglycan nitrosourea compound originally derived from a Streptomyces species, has been in clinical
use since 1967.\textsuperscript{25} In preclinical studies, it was found to have cytotoxic effects on pancreatic islet cells\textsuperscript{26} and has generally been used, usually in combination with other agents, for the treatment of metastatic PETs.\textsuperscript{27,28,29,30,31,32,33,34,35,36,37,38,39,40} The current first-line regimen is the combination of STZ and doxorubicin.\textsuperscript{20} This recommendation is based on a prospective study that demonstrated that STZ and doxorubicin were superior to STZ and 5-fluorouracil (5-FU) or chlorozotocin alone (response rates of 69%, 45%, and 30%, respectively).\textsuperscript{23} Median durations of response were 18 months for the doxorubicin combination, 14 months for the 5-FU combination, and 17 months for the chlorozotocin group. Survival for patients treated with the doxorubicin combination was significantly longer. In a previous prospective study, STZ alone in 42 patients produced a response rate of 36%, with 12% showing a complete response, whereas STZ plus 5-FU had demonstrated a response rate of 63%, with 33% of patients having a complete response.\textsuperscript{24}

These results suggest that the effect of interferon-a on PETs is similar to that of octreotide in that it has minimal tumoricidal activity, with PETs rarely regressing with interferon-a treatment either alone or in combination with other agents.\textsuperscript{20} Of 57 patients with PETs, 47% had a biochemical response and 12% experienced complete remissions, and no statistical difference in survival in responders versus nonresponders.\textsuperscript{28} In another study of a similar group of 22 patients, only 5% of patients demonstrated an objective decrease in tumor size.\textsuperscript{30} Therefore, the precise role and efficacy of chemotherapy in patients with metastatic gastrinoma has not been established.

Also, when chemotherapy should be initiated in a given patient with metastatic disease has not been clearly determined.\textsuperscript{23} Recently, it has become apparent that the time course of tumor progression in patients with metastatic untreated gastrinoma is highly variable.\textsuperscript{36} Of 19 patients evaluated, 26% showed no tumor growth over a mean follow-up of 29 months, 32% had marginal progression (<50% increase in tumor volume), and 42% had rapid growth in less than 1 year. Some patients have been followed up for 20 years with stable metastatic disease,\textsuperscript{37} although most die within 5 years, with the mean survival being 3 to 5 years.\textsuperscript{38,39} Of the two research groups with considerable experience with metastatic gastrinoma, one group proposed that patients be treated with chemotherapy when they become symptomatic.\textsuperscript{34} However, if gastric acid hypersecretion is controlled adequately, symptoms due to the tumor arise only very late in the course of the disease. Another group proposed that, after the initial evaluation, patients be reassessed in 3 to 6 months and those patients with evidence of increasing size of hepatic metastases be treated with chemotherapy.\textsuperscript{40} No studies have recommended chemotherapy for patients with metastases only to regional lymph nodes.

STZ causes nausea and vomiting in almost all patients, dose-related susceptibility (including proteinuria) in 20% to 70%, decrease in creatinine clearance in 20% to 70%, abnormalities in hepatic function in 29%, and leukopenia and thrombocytopenia in 6% to 9%.\textsuperscript{24,25,41} In one study, nine patients suffered from chronic renal failure, and seven required dialysis; thus, use of STZ must be carefully monitored.\textsuperscript{23} The nausea and vomiting can now be controlled in almost all patients using 5-HT3 antagonists such as ondansetron, so that the renal dysfunction is the major dose-limiting toxic effect. Chlorozotocin is structurally closely related to STZ,\textsuperscript{26,27} but it causes less nausea and vomiting than does STZ. Patient response to chlorozotocin alone\textsuperscript{25,26,28} or in combination with 5-FU\textsuperscript{25} is, in general, similar to that to STZ (see Table 38.5-5).

Etoposide, dacarbazine, and cisplatin alone have been used in a few cases but are generally not effective.\textsuperscript{20} The combination of etoposide and cisplatin was evaluated in 14 patients with metastatic PETs, and the results were compared with those in metastatic carcinoid tumors (13 patients) or anaplastic neuroendocrine tumors (18 patients: 6 pancreas; 8 stomach or intestine; 1 lung; 3 unknown).\textsuperscript{42} This study was performed because recent work has demonstrated that these two agents are effective in small cell lung cancer, which has neuroendocrine features histologically similar to those seen in PETs. Sixty-seven percent of the anaplastic neuroendocrine tumors, 14% of the PETs, and 0% of the metastatic carcinoid tumors demonstrated partial to complete regression.\textsuperscript{42}

Other etoposide combinations including doxorubicin, cisplatin, and 5-FU have been tried in a small number of patients with limited success (i.e., response rate of 20%).\textsuperscript{25} Glucagonomas are reported to respond frequently to dacarbazine.\textsuperscript{43} The current first-line regimen is the combination of STZ and doxorubicin (18 patients: 6 pancreas; 8 stomach or intestine; 1 lung; 3 unknown).\textsuperscript{44} In two previous studies, the response rate between patients with or without previous chemotherapy.\textsuperscript{20} Furthermore, interferon-a may stabilize the disease in a significant percentage of patients and possibly extend survival, although with PETs this has not yet been proven. Interferon-a has been used with 5-FU,\textsuperscript{24} octreotide,\textsuperscript{34} and 5-FU plus STZ,\textsuperscript{25} though in such small numbers of patients that clear assessment of any advantages of these combinations is not possible.

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<th>Table 38.5-5</th>
<th>Drug Therapy for Pancreatic Endocrine Tumors and Gastrinomas</th>
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<td>STZ combined with 5-FU or 5-FU plus doxorubicin causes an objective response in up to 80% of patients with metastatic gastrinoma. For all PETs, the combination of STZ plus 5-FU gave a response rate of 63%, which was significantly better than the 40% response rate with STZ alone.\textsuperscript{20} However, in a prospective study of ten patients with progressive metastatic gastrinoma to the liver, chemotherapy with STZ, 5-FU, and doxorubicin resulted in only a 40% objective response rate, no complete remissions, and no statistical difference in survival in responders versus nonresponders.\textsuperscript{28} In another study of a similar group of 22 patients, only 5% of patients demonstrated an objective decrease in tumor size.\textsuperscript{30} Therefore, the precise role and efficacy of chemotherapy in patients with metastatic gastrinoma has not been established.</td>
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<td>Interferon-a has been reported to be effective at controlling symptoms in patients with PETs.\textsuperscript{25} In a review of numerous series involving 322 patients with various neuroendocrine tumors, 43% of the patients showed a biochemical response (&gt;50% decrease in hormone levels) and 12% showed a decrease in tumor size with interferon-a treatment either alone or in combination with other agents.\textsuperscript{51} Of 57 patients with PETs, 47% had a biochemical response and 12% experienced decreased tumor size. The mean duration of the response was 20 months (range, 2 to 96 months). Disease stabilization was seen in 25%. There was no difference in the response rate between patients with or without previous chemotherapy.\textsuperscript{27}</td>
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In another study of 11 patients with metastatic gastrinoma to the liver that was increasing in size, interferon-a (5 million U/d) failed to decrease tumor size in any patients but slowed tumor growth in 3 patients.\textsuperscript{20} These results suggest that the effect of interferon-a on PETs is similar to that of octreotide in that it has minimal tumoricidal activity, with PETs rarely regressing with treatment. However, interferon-a may stabilize the disease in a significant percentage of patients and possibly extend survival, although with PETs this has not yet been proven. Interferon-a has been used with 5-FU,\textsuperscript{24} octreotide,\textsuperscript{34} and 5-FU plus STZ,\textsuperscript{25} though in such small numbers of patients that clear assessment of any advantages of these combinations is not possible.

Hepatic Artery Embolization
Hepatic artery embolization with or without postembolization chemotherapy has been used successfully in small numbers of patients with metastatic PETs to the liver. 110,27-29,31-33 Side effects include abdominal pain, nausea, vomiting, and fever usually lasting 3 to 10 days, with severe complications (including hepatic failure, infection, acute renal failure, and death) occurring in 10% to 15%. 122,129 Until recently, it was often difficult to establish the true extent of the metastatic disease and, therefore, to decide which patients might be most helped by this procedure. With the availability of SRS, it should be possible to accomplish this in most cases. In a patient with a symptomatic PET and diffusely metastatic disease to the liver but minimal or no bone metastases, in whom hormone symptoms cannot be controlled by octreotide, chemotherapy, or other medical treatment, hepatic artery embolization should be considered.

SURGICAL TREATMENT

Systemic removal of all resectable tumour has been recommended in general for PETs. 292,293,294,295 and, if possible, for VIPomas, glucagonomas, GRFomas, and somatostatinomas. 292 The data of Zollinger et al. 292 suggest that removal of all resectable tumour, termed debulking or cyrodebulking surgery, prolongs life expectation of patients who have had no more than 50% of their tumour resected for up to 8 years. It is important to differentiate between the possible benefit of such surgery in patients with gastrinomas or nonfunctional tumours and the potential benefit in patients with functional PETs for whom poor medical therapy for the hormonal excess state might ensue. In the former group, the procedure must extend life or relieve tumour symptoms to be worthwhile, whereas in the latter group, improved ability to control the hormonal excess state in situations without effective medical therapy may be a major benefit.

A number of studies have provided data dealing with this approach. 292,293,294,295 One study involved 17 patients with potentially resectable metastatic PETs, 292 and the second evaluated 74 patients with metastatic neuroendocrine tumours (50 carcinoid, 23 islet cell, and 1 atypical tumour). 295 In the first study, in 80% of cases, the tumour was completely excised at surgery, and the survival rate was 79% at 5 years, with a mean follow-up of 3 years. 292 In this study, patients with extensive metastatic disease were more likely to die of their disease than patients with limited disease (P = 0.02). In the second study, 36 hepatic lobectomies or extended hepatectomies and 38 nonanatomic liver resections were performed. Perioperative mortality was 2.7%, morbidity 24%, and 4-year survival 73%, 80% of patients experienced symptomatic improvement postoperatively. 295 Norton et al. 295 reported the successful resection of all tumour in one study in 5 of 20 patients with ZES with extensive disease, 2 of whom have maintained normal gastrin levels postoperatively. A series of 38 patients with PETs confined to liver who underwent resection was compared to 23 patients with comparable tumour burden but technically unresectable disease. 122 Survival was significantly longer in those who underwent resection, although other factors may also have influenced outcome. The conclusion of each of these studies was that resection of metastatic disease to liver should be considered in selected patients with neuroendocrine tumours. 292-294,295 It is important to remember that this may be possible in only a proportion (90%) in another study of all patients with metastatic PETs in the liver. Furthermore, at present, whether such an approach actually increases survival is not clear (see Fig. 38.5-3, Fig. 38.5-7). This approach may be required in patients with symptomatic tumours in whom octreotide or the use of chemotherapy alone is not reducing plasma hormone levels sufficiently, so that symptoms remain poorly controlled.

LIVER TRANSPLANTATION

Liver transplantation has been attempted in small numbers of patients with metastatic PETs. 296,297,298,299 Each of the reported series involves small numbers of patients. All these studies recommend that liver transplantation be considered in selected cases, especially patients without extrahepatic disease. In the largest series of 19 patients, active liver transplantation for neuroendocrine tumours, 15 were for carcinoid and 16 were for PETs. 296 Survival rates were significantly higher for the carcinoid patients (68% alive 5 years) than for the PET patients (8% alive 5 years). It appears from these studies that liver transplantation is uncommon, with recurrence to liver being most common. Whether liver transplantation is more effective in PET cases than in other metastatic tumours and whether it appreciably prolongs survival remains underdetermined.

CHAPTER REFERENCES


Carcinoid Tumors and the Carcinoid Syndrome

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PATHOLOGY AND TUMOR HISTOLOGY

Neuroendocrine tumors (NETs) are derived from the diffuse neuroendocrine system, which is made up of peptide- and amine-producing cells with different hormonal profiles depending on their site of origin. Carcinoids are classified as NETs and share cytochemical features with melanomas, pheochromocytomas, medullary carcinoma of the thyroid, and pancreatic endocrine tumors (PETs). Carcinoids are composed of monotonous sheets of small round cells with uniform nuclei and cytoplasm. Mitotic figures are rare. Oberndorfer introduced the term carcinoid in 1907 to describe tumors that behaved more indolently than adenocarcinomas. Pathologists cannot differentiate benign from malignant carcinoids based on histology, nor histologically can they differentiate PETs from carcinoids. Malignancy can only be determined if invasion or distant metastases are found. Ultrastructurally, carcinoids possess electron-dense neurosecretory granules, and they contain small clear vesicles that correspond to the synaptic vesicles of neurons. Carcinoids synthesize bioactive amines and peptides, including serotonin, dopamine, somatostatin, gastrin, pancreatic polypeptide, calcitonin, substance P, other various tachykinins (e.g., neuropeptide K), growth hormone–releasing hormone, bombesin, and various growth factors such as transforming growth factor-b (TGF-b), platelet-derived growth factor, and basic fibroblast growth factor.

Most carcinoids are tentatively identified on routine histology. However, these tumors are characterized by their histologic staining patterns due to their shared secreted products and certain cytoplasmic proteins. Characteristically, carcinoids either take up and reduce silver (argentaffin reaction) or take it up but do not reduce it (argyrophilic). The chromogranins (A, B, C) are acidic polypeptides that are the major component of the secretory granules of many neuroendocrine cells. Generally, chromogranin A immunoreactivity is more specific than the argentaffin reaction because the latter also identifies other intracellular proteins such as melanin. NSE, the gamma-gamma dimer of the glycolytic enzyme enolase, occurs in the cytoplasm of most neuroendocrine cells and is positive in most carcinoids as well as other APUD (amine precursor uptake and decarboxylation) tumors. The advantage of NSE as a marker is that its reactivity is unrelated to secretory granule content. However, NSE can be occasionally misleading because some tumors not considered neuroendocrine, such as fibroadenomas of breast carcinoma and certain lymphomas, may contain a considerable amount of NSE activity. Synaptophysin is a calcium-binding vesicle membrane glycoprotein that is expressed independently of other neuroendocrine proteins.

In addition to the general histologic NET markers, specific markers for carcinoids may identify the tumor as a carcinoid. Serotonin can be identified by various methods, including the use of the argentaffin reaction of Masson or using antibodies to serotonin. In general, the argentaffin reaction of Masson is usually positive, and the serotonin antibody localization is frequently weak or negative in midgut carcinoids, whereas in foregut and hindgut carcinoids, serotonin immunoreactivity is detected more often than the argentaffin reaction.

Williams and Sanders proposed classifying carcinoids according to their site of origin because carcinoids with similar sites of origin frequently share functional manifestations, histochemistry, and secretory products. Foregut carcinoids generally have a low serotonin [5-hydroxytryptamine (5-HT)] content, are argentaffin-negative but argyrophilic, occasionally secrete 5-hydroxytryptophan (5-HTP) or ACTH, can be associated with an atypical carcinoid syndrome, are often multihormonal, and may metastasize to bone. Although many foregut carcinoids synthesize peptides, clinical syndromes are rarely produced and elevated plasma hormone levels are generally not detected. Midgut carcinoids are argaffin-positive, have a high serotonin content, have smaller numbers of endocrine cells than foregut tumors, most frequently cause the classic carcinoid syndrome when they metastasize, release serotonin and tachykinins (substance P, neuropeptide K, substance K), rarely secrete 5-HTP or ACTH, and uncommonly metastasize to bone. Hindgut carcinoid tumors are argentaffin-negative, often argyrophilic, rarely contain serotonin, rarely cause carcinoid syndrome, contain numerous gastrointestinal (GI) hormones, rarely secrete 5-HTP or ACTH, and may metastasize to bone.

TABLE 38.6-1. Classification of Carcinoid Tumors

Carcinoids within the same site of origin, such as lung, thymus, and pancreas, can differ significantly in characteristics and behavior. Therefore, it has been proposed that the term carcinoid be replaced by the designation neuroendocrine tumor, and a new classification system has been drawn up. In this proposed classification, tumors are divided according to tissue of origin and subdivided by growth behavior. It is proposed that this new classification system better reflects the biology of...
Carcinoids can be ubiquitous, but most take origin in four sites: bronchus, appendix, rectum, and jejunum. In the past, carcinoids were most frequently reported in the appendix (approximately 40%); however, more recently the bronchus and lung are the most common site (32%) (Table 38.6-2). The distribution reported from analyses of two large National Cancer Institute databases from 1950 to 1971 and from 1973 to 1991 are contrasted in Table 38.6-2. A number of trends are apparent from comparison of the data from these two periods. The percentages of gastric carcinoids almost doubled, whereas the percentage of appendicular carcinoids decreased more than fourfold from 38% to 7.6%. Small intestinal carcinoids remained a large group comprising approximately 20% of all carcinoids. Overall, GI carcinoids remain the most frequent, comprising 74% of all carcinoids in the 1973 to 1991 Surveillance, Epidemiology, and End Results (SEER) data, with the respiratory tract being a distant second with 25%.

The clinical presentation of carcinoids far underestimates their occurrence, because many are asymptomatic. This fact is demonstrated by SEER data, which report an annual incidence rate of 2.8 per million population for small intestinal carcinoids, whereas in an autopsy study at the Mayo Clinic, 6500 cases per million were reported. In another study, the annual incidence of malignant carcinoids at autopsy was 21 per million population per year, whereas in a Swedish study calculated on autopsy and surgical results, the incidence was 84 cases per million population. The distribution of carcinoid tumors found in various surgical or clinical series differs markedly from that found at autopsy. As many as 76% of all carcinoids are found in the jejunum at autopsy, whereas they make up approximately one-fourth of cases in clinical and surgical series.

Approximately 1 in every 200 to 300 appendectomies result in discovery of a carcinoid. Most occur in the tip of the appendix. The majority (i.e., 90%) are less than 1 cm in diameter and are without metastases. In the SEER data of 1570 appendiceal carcinoids, 62% were localized, 27% had regional lesions, and 8% had distant metastatic disease. Approximately 50% of the carcinoids between 1 and 2 cm in size metastasize to lymph nodes.

Small intestinal carcinoids may be present in 70% to 87% of autopsies in patients with a history of peptic ulcer disease. In an analysis of 12 series, 47% (range, 0% to 100%) were associated with metastases, whereas 35% to 70% were associated with metastases in the National Cancer Institute studies (6%) (type II), which is almost always as part of multiple endocrine neoplasia type 1 (MEN 1).

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Carcinoids can be classified on their histologic growth patterns as insular, trabecular, glandular, undifferentiated, or mixed. The mitig carcinoids frequently possess the most typical morphology, with insular-like formation of regular tumor cells surrounded by fibroelastic stroma. Most foregut carcinoids show a more mixed growth pattern, with a solid, ribbon-like, trabecular, or acinar pattern. Hindgut carcinoids are frequently solid or trabecular. It has been demonstrated that the histologic types have prognostic significance. In one classification of decreasing order of median survival time in years, the growth pattern ranked as follows: mixed insulin plus glucagon (4.4 years), insulin (2.9 years), trabecular (2.5 years), mixed insulin plus trabecular (2.3 years), glucagon (0.9 years), and undifferentiated (0.5 years). In other studies, carcinoids are divided histologically into typical (well-differentiated neuroendocrine tumors) and atypical (nuclear atypia, necrosis, increased mitotic activity), and categorization has been shown to have prognostic significance.
MOLECULAR PATHOGENESIS

Little is known about the induction of malignant growth or the factors promoting the growth of carcinoids. For some gastric carcinoids, studies show that gastrin is an important growth factor. An increased occurrence of gastric carcinoids occurs in disease states (pernicious anemia, atrophic gastritis, Zollinger-Ellison syndrome) that result in hypergastrinemia. The hyperplastic effect of hypergastrinemia is restricted to gastric ECL cells. It has been proposed that, with prolonged hypergastrinemia, ECL hyperplasia (simple, linear, micronodular, adenomatoid), dysplasia, and carcinoid formation are increased. In pernicious anemia and atrophic gastritis, up to 4% to 11% of patients develop gastric carcinoids. Patients with Zollinger-Ellison syndrome also develop gastric carcinoids, although they are much more frequent in the subgroup with MEN 1. In patients with Zollinger-Ellison syndrome with MEN 1 with gastric carcinoids, allelic loss occurs at the MEN 1 locus on chromosome 11q13, and thus fundic gastric carcinoids are now included in the spectrum of MEN 1 tumors. Studies suggest that other important growth factors in some carcinoid tumors are TGF-α and TGF-β, insulin-like growth factor-1 (IGF-1), trefoil peptides (TFP1, TFP2, TFF3), platelet-derived growth factor, vascular endothelial growth factor, acidic and basic fibroblast growth factor, and epidermal growth factor.

Limited studies have been performed on carcinoids examining the possible role of mutations of protooncogenes and alterations of tumor-suppressor genes in their pathogenesis. Mutations in common oncogenes, such as K-ras, are uncommon in GI carcinoids. Overamplification of HER2/NEU, c-myc, and c-jun have been described in some cell lines derived from GI endocrine tumors and some carcinoids. In bronchial carcinoids, a high expression of c-fos, c-jun, and c-met occurs early, and a high expression of c-myc and L-myc occurs late. Alterations in the common tumor suppressor gene p53 are also uncommon in carcinoids, as are alterations in the retinoblastoma gene in typical carcinoids, although they may occur in atypical carcinoids. MEN 1 has been shown to be due to defects in a 10-exon gene on chromosome 11q13 that encodes for a 610-amino acid nuclear protein, MENIN. Loss of heterozygosity at this locus has been reported in 26% to 78% of carcinoids, and mutations in the MENIN gene were reported to be 18% in one study. Microsatellite instability is rare in carcinoids, however, by comparative genomic hybridization, both frequent gains (of chromosome 5, 14, 17q, 7) and losses (especially of chromosome 9p) are reported.

CLINICAL FEATURES

GENERAL CHARACTERISTICS

The age of onset ranges from 10 to 93 years, with a mean onset of 36 years of age for tumors of the cervix, 63 years for tumors of the small intestine and respiratory tract, and 68 years for tumors of the rectum.

CARCINOID TUMORS WITHOUT SYSTEMIC FEATURES

The presentation of carcinoids that do not cause carcinoid syndrome is diverse and related to the site of origin of the tumor as well as the malignant spread of the tumor. In the appendix (see Table 38.6-3), carcinoids are usually found incidentally during surgery for suspected appendicitis. Small intestinal carcinoids in the jejunum are the most common location for carcinoids of clinical significance. Most small intestinal carcinoids found in autopsy studies do not cause symptoms, but these tumors can cause fibrosis of the mesenteric, which results in kinking of the bowel, intestinal obstruction, and gut infarction or intussusception. The most common presenting symptoms due to the small intestinal carcinoids per se are periodic abdominal pain (51%), intestinal obstruction with ileus and invagination (3%), abdominal tumor (17%), or GI bleeding (11%). Because of the vagueness of the symptoms, the diagnosis is frequently delayed, with a median time of onset from symptoms to diagnosis of approximately 2 years and a range up to 20 years. Duodenal and gastric carcinoids are usually found incidentally during endoscopy. Rectal carcinoids are frequently found incidentally during endoscopy but can be symptomatic. The most common symptoms include melena and bleeding (39%), constipation (17%), and diarrhea (12%). Bronchial carcinoids are frequently discovered on chest radiograph. In one large series, 31% of patients were asymptomatic, and the carcinoid was incidentally discovered. The most common symptoms are pneumonia, hemoptysis, and cough. Thyroid carcinoids present as anterior mediastinal masses, usually on chest radiograph. Ovarian and testicular carcinoids may present as masses detected by physical examination or ultrasound. Most carcinoids present as an isolated disease, but associations exist between foregut carcinoids and MEN 1, gastric carcinoids and diseases causing hypergastrinemia, ampullary somatostatin-rich carcinoids and von Recklinghausen's disease, an intestinal carcinoid with myotonic dystrophy, a gastric carcinoid in a patient with primary biliary cirrhosis, and duodenal carcinoid tumors causing Zollinger-Ellison syndrome. Metastatic carcinoids in the liver, presenting as hepatomegaly, may be the initial presentation in a patient who is fully active and productive with minimal symptoms and normal or near-normal liver function tests.

CARCINOID TUMORS WITH SYSTEMIC FEATURES

The most common systemic syndrome caused by carcinoids is the malignant carcinoid syndrome. As already mentioned, carcinoids may contain and secrete a number of biologically active substances. Immunochemical and radioimmunoassay studies show that carcinoids can contain ACTH, gastrin, somatostatin, insulin, motilin, growth hormone, gastrin-releasing peptide, serotonin, calcitonin, neurotensin, melanocyte-stimulating hormone–b, tachykinins (substance P, substance K, acidic and basic fibroblast growth factor, and epidermal growth factor. Even though these GI peptides were present in the serum, it is not apparent that any of these peptides contributed to any clinical symptoms. Immunocytochemical and radioimmunoassay studies show that carcinoids can contain ACTH, gastrin, somatostatin, insulin, motilin, growth hormone, gastrin-releasing peptide, serotonin, calcitonin, neurotensin, melanocyte-stimulating hormone–b, tachykinins (substance P, substance K, acidic and basic fibroblast growth factor, and epidermal growth factor. Even though these GI peptides were present in the serum, it is not apparent that any of these peptides contributed to any clinical symptoms. Immunocytochemical and radioimmunoassay studies show that carcinoids can contain ACTH, gastrin, somatostatin, insulin, motilin, growth hormone, gastrin-releasing peptide, serotonin, calcitonin, neurotensin, melanocyte-stimulating hormone–b, tachykinins (substance P, substance K, acidic and basic fibroblast growth factor, and epidermal growth factor. Even though these GI peptides were present in the serum, it is not apparent that any of these peptides contributed to any clinical symptoms.

Forogut carcinoids are more likely to produce various GI peptides than midgut carcinoids. Ectopic ACTH production with Cushings syndrome is increasingly seen with foregut carcinoids, and in some studies, these tumors were the most common cause of the ectopic ACTH syndrome, accounting for 64% of all patients. Acromegaly due to release of growth hormone–releasing factors can occur with a number of carcinoids. The somatostatinoma syndrome due to somatostatin release can occur with duodenal carcinoids.

CARCINOID SYNDROME

CLINICAL FEATURES

Flushing attacks occur in 23% to 65% of carcinoid syndrome patients initially and in 63% to 78% at some time during the disease course. The typical flush is the sudden appearance of a deep red erythema of the upper part of the body, primarily the face and neck. Flushes are often associated with an unpleasant feeling of warmth, occasionally with lacerimation, itching, palpitations, facial or conjunctival edema, and diarrhea. Flushes may be spontaneous or precipitated by stress, alcohol, certain foods, such as cheese; exercise; or pharmacologically by injections of agents such as catecholamines, calcium, or pentagastrin. Flashes may be brief, lasting 2 to 5 minutes, especially initial, or may be prolonged for hours, especially later in the course. They are usually seen with carcinoids of midgut origin but can also occur in some patients with foregut tumors. With bronchial carcinoids, the flushes can be frequently prolonged, lasting for hours to days, reddish in color, associated with salivation, lacerimation, diaphoresis, facial swelling, palpitations, diffuse burning of the forehead, diarrhea, and hypotension. The flushing with bronchial carcinoids has a greater tendency to cause diffuse body involvement, and after repeated flushing of this type, patients may develop a constant red or cyanotic coloration. The flush associated with gastric carcinoids is also reddish in color but patchy in distribution over the neck and face. It is frequently provoked by food intake or pentagastrin, with erythema associated with blotches and wheals with central clearing, frequently occurring around the root of the neck and on the arms, and the lesions are frequently associated with pruritus.
Diarhoea is commonly present in 32% to 73% of patients initially and in 67% to 84% at some time during the disease course (see Table 38.6-3). Diarhoea usually occurs with flushing (85% of cases), but it may occur alone (15% of cases). The diarhoea is described as watery and, less commonly, as frothy or the pale bulky stool of steatorrhoea, with the stool number ranging from 2 to 30 per day, and 60% of patients have output of less than 1 L/d. Steatorrhoea is present in 67% and in 46% is more than 15 g/d. Abdominal pain may be present with the diarhoea or independently, and the frequency varies from 10% to 34% (see Table 38.6-3).

Cardiac manifestations occur in 11% to 66% of patients (see Table 38.6-3). The cardiac disease is due to fibrosis involving the endocardium, primarily of the right side of the heart, although left side lesions can also occur. The fibrous deposits are diffuse and are found most commonly on the ventricular aspect of the tricuspid valve and the associated chordae and less commonly on the pulmonary valve cusps. These fibrous deposits tend to cause constriction of both the tricuspid and pulmonic valves. At the pulmonic valve, stenosis is usually predominant, whereas at the tricuspid valve, the constriction results in the valve being fixed open, and tricuspid regurgitation is usually predominant. In two series, 80% of the patients with cardiac lesions had evidence of heart failure. Lesions on the left side occur in 30% of autopsy cases, are less extensive, and most frequently occur on the mitral valve.

Other clinical manifestations of carcinoid syndrome are wheezing or asthma-like symptoms in 8% to 25% of patients and pellagra-like skin lesions with hyperkeratosis and pigmentation in 2% to 5% of cases (see Table 38.6-3). Arthralgias, changes in mental state or confusion, and ophthalmic changes during flushing leading to vessel occlusion. A variety of noncardiac problems secondary to increased fibrous tissue have been reported, including retroperitoneal fibrosis leading to ureteral obstruction, or Peyronie’s disease of the penis; intraabdominal fibrosis; and occlusion of mesenteric arteries or veins. Sexual dysfunction is a common complaint of men with carcinoid syndrome. This may relate to the vascular effect of serotonin on pelvic blood vessels.

**PATHOBIOLOGY**

Carcinoid syndrome developed in 8% of 8876 patients with carcinoids, with an incidence of 1.7% to 18.4% in six different series. Carcinoid syndrome occurs only when sufficient concentrations of the hormonal products released by the tumor reach the systemic circulation. Its occurrence and severity are directly related to tumor size in an area that drains into the systemic circulation. In 91% of cases, this only occurs after distant metastases (especially to the liver) develop. Rarely, however, primary GI tumors with nodal metastases with extensive invasion retroperitoneally or drainage into the ovarian veins; pancreatic carcinoids with retroperitoneal lymph nodes; or carcinoids such as those in the lung or ovary, with direct access to the systemic circulation can produce the carcinoid syndrome without hepatic metastases. Rarely, medullary thyroid carcinoma, a duodenal adenoma, or small cell lung cancer also have been reported to cause carcinoid syndrome. Adenocarcinomas of the stomach do not have the same propensity to metastasize and to produce the carcinoid syndrome (see Table 38.6-2). Because midgut tumors are the most common and frequently metastasize, midgut tumors account for 60% to 87% of the carcinoid syndrome, foregut tumors for 2% to 33%, hindgut for 1% to 8%, and an unknown primary location for 2% to 15% (see Table 38.6-3).

Symptoms of carcinoid syndrome were originally attributed to secretion of 5-HT (serotonin) by the tumor. In one study of 380 patients with carcinoid tumors, 56% had evidence of serotonin overproduction; 18% of 500 patients in a second study and 88% of 103 patients with carcinoid tumors in a third study had elevated urinary 5-hydroxyindoleacetic acid (5-HIAA), the major metabolite of serotonin. When 44 consecutive cases were studied before any resection, 84% of the patients had serotonin overproduction. In various studies, 12% to 26% of patients with evidence of serotonin overproduction did not have symptoms of carcinoid syndrome. In one study of 44 consecutive patients with carcinoids, platelet and urinary serotonin, 5-HIAA, and seven catecholamine metabolites were measured. Platelet serotonin was elevated in 96%, 43%, and 0% of patients with midgut, foregut, and hindgut carcinoids, respectively. Urinary dopamine and catecholamine metabolites were elevated in 38% and 33% of midgut, 20% and 20% of foregut, and 7% and 14% of hindgut carcinoids, respectively. In a large review of 748 cases of carcinoid syndrome, 82% had increased serotonin activity.

**FIGURE 38.6-1.** Synthesis, secretion, and metabolism of serotonin [5-hydroxytryptamine (5-HT)] and 5-hydroxytryptophan in patients with typical and atypical carcinoid syndrome. (1) Tryptophan hydroxylase. (2) Aromatic 1-amino acid decarboxylase (dopa decarboxylase). (3) Monoamine oxidase. (4) Aldehyde dehydrogenase. Arrows indicate the sites of action of therapeutic agents used in the treatment of carcinoid syndrome. Somatostatin analogues include octreotide and lanreotide. Serotonin receptor subtype 3 antagonists (5-HT3) include ondansetron, tropisetron, and alosetron.

Patients may develop either a typical or atypical type of carcinoid syndrome (see Fig. 38.6-1). In patients with the typical carcinoid syndrome, the conversion of tryptophan to 5-HTP is the rate-limiting step. Once formed, the 5-HTP is rapidly converted to 5-HT in the tumor by dopa decarboxylase, either stored in the neurosecretory tumor granules or released into vascular compartments, and most is taken up and stored in the granules of platelets. A small amount remains in the plasma. The majority in the circulation is converted by monamine oxidase and aldehyde dehydrogenase to 5-HIAA, which appears in large amounts in the urine. Characteristically, patients with carcinoid syndrome have expansion of the serotonin pool size, increase in blood and platelet concentrations of serotonin, and elevations of 5-HIAA in the urine. This is the typical pattern in argentaffin- and argyrophil-positive tumors such as midgut carcinoids, which characteristically secrete large amounts of serotonin and which make up to 60% to 87% of all cases of carcinoid syndrome (see Table 38.6-3). Some carcinoids cause an atypical carcinoid syndrome and are thought to be deficient in the enzyme dopa decarboxylase; thus, they cannot convert 5-HTP to 5-HT (serotonin), and 5-HTP is secreted into the bloodstream (see Fig. 38.6-1). Plasma serotonin levels are normal in these patients, but urinary levels are usually elevated because some of the 5-HTP is decarboxylated in the kidney and excreted as 5-HIAA. Patients with this type of carcinoid tumor may have a marked increase in urinary 5-HT and 5-HTP levels but normal or only slightly elevated 5-HIAA levels. Foregut carcinoids are more likely to excrete high levels of 5-HT and 5-HTP in the urine and give the atypical carcinoid syndrome.
The exact cause of flushing in carcinoid syndrome remains unclear. 5-62 5-64 Flushing is not thought to be due to serotonin overproduction, because serotonin antagonists generally have no effect on the flushing. 5-66 A number of studies, including a randomised controlled trial, have suggested that the use of prophylactic antihistamines may be effective in reducing the frequency and severity of flushing. 5-68 One study 5-68 demonstrated that all patients with idiopathic flushing had elevated plasma serotonin levels; however, in a small subset of patients, flushing was not associated with elevated plasma serotonin levels. 5-69 5-51 Studies demonstrate that the pathogenesis of flushing in carcinoid syndrome is multifactorial, involving a combination of serotonin, histamine, and other vasoactive peptides. 5-70 Flushing is not thought to be due to an increase in circulating histamine, because histamine antagonists generally have no effect on the flushing. 5-72

Bronchial carcinoids are usually detected by chest radiography, CT or, occasionally, by bronchoscopy. The location of the primary tumor as well as tumor extent. 5-73 The presence of liver metastases and other distant metastases should be assessed. 5-74 Studies have shown that the presence of liver metastases is associated with a poorer prognosis. 5-75 The presence of liver metastases may also be associated with an increased risk of metastases to the lung, bone, or brain. 5-76

LOCALIZATION

A number of techniques, including GI endoscopy, barium radiographs, chest radiographs, imaging studies [ultrasound, computed tomographic (CT) scan, magnetic resonance imaging, angiography], endoscopic ultrasound, selective venous sampling for various hormones, positron emission tomography scanning, and various forms of radionuclide scanning [radiolabeled somatostatin receptor scintigraphy (SRS), iodinated metaiodobenzylguanidine (MIBG)], have all been used to determine the location of the primary tumor as well as tumor extent. 5-77 5-83

Bronchial carcinoids are usually detected by chest radiography, CT or, occasionally, by bronchoscopy. They appear frequently (37%) as opacities with sharp or indistinct margins. 5-84 They are slow growing and often induce airway compression with resultant atelectasis. Enlarged hilar lymph nodes and metastases are
Carcinoids possess high-affinity receptors for somatostatin in 88% to 100% of cases. The somatostatin receptors are present in both the primary tumor and metastases. Five subtypes (numbered sst1 to sst5) of somatostatin receptors have been described. Octreotide binds with high affinity to sst2 and with a lower affinity to sst1 and sst5 and has a very low affinity for sst3. Studies show almost all carcinoids (90% to 100%) possess sst1, 50% to 60% sst5, 10% to 100% sst2, 70% to 100% sst3, and 20% to 100% sst4. [111In-DTPA-DPhe] octreotide has been approved for localizing carcinoids using radionuclide scanning. SRS images tumor in 73% to 89% of patients with carcinoids. In one comparative study of 40 patients, SRS localized tumors in 78% and CT in 82%. SRS detected primary tumors in two patients missed on CT, and in 16% of cases it detected lesions not previously seen. Numerous other studies have demonstrated that SRS has greater sensitivity for localizing carcinoids, especially the extent of metastatic spread, than conventional imaging studies (Figure 38.6-2). More recent studies demonstrate that it has a higher specificity than bone scanning and equal or greater sensitivity. General, SRS has excellent specificity, but it is important to remember that high densities of somatostatin receptors exist on a number of other normal and abnormal cells that can lead to increased uptake and a false-positive response. These include granulomas (e.g., sarcoid, tuberculosis), activated lymphocytes (wound infections, lymphomas), thyroid diseases (goiter, thyroiditis), PEts, and other endocrine tumors. In one study, 12% of SRS localizations were false-positives; however, by considering the clinical context the number of false-positives was reduced to less than 4%. Because of its sensitivity and ability to image all body areas, SRS should be the initial imaging procedure to localize and establish the extent of carcinoids.

Bone metastases are increasingly being recognized in patients with metastatic carcinoid and other PEts. In one study of 30 patients with carcinoid tumors, bone metastases were found in four (13%) using SRS and bone scanning. In general, technetium 99m bone scanning and SRS have been found to be more sensitive than conventional radiographs for detecting bone metastases.

Positron emission tomography scanning with 5-hydroxtryptophan (11C-labeled 5-HTP) has been compared with CT in 16 patients with carcinoids. Positron emission tomography was more sensitive in ten of the patients than CT and was equally sensitive to CT in the others. During treatment, a close correlation (r = 0.91) was found between changes in the positron emission tomography scan transport rate constant and changes in urinary 5-HIAA, suggesting that positron emission tomography scanning may be useful for monitoring the results of therapy.

PROGNOSIS

Clinically, carcinoid syndrome is generally a manifestation of advanced disease. Two in every three patients with carcinoid syndrome have physical signs of cancer, such as an abdominal mass or hepatomegaly. A clear positive correlation exists between tumor mass and urinary 5-HIAA levels therefore, the laboratory test measuring 5-HIAA levels is a good marker for extent of disease.

Carcinoids from different locations not only differ in the percentage that are malignant and the percentage that develop carcinoid syndrome (see Table 38.6-2), but also in their aggressiveness. The percentage of carcinoids in different locations having localized disease, regional metastases, or distant metastases varies widely. The highest percentage of nonlocalized disease is with pancreatic (91%), colonic (77%), and small intestinal carcinoids (75%), whereas the highest percentage with localized disease is the larynx (100%), followed by the ovary, appendix, and rectum (62% to 95%). Overall metastases are present at the time of diagnosis in 45% of patients in the SEER group data. In one study, no difference was found in the overall 5-year survival rate of patients with foregut (60%) or midgut carcinoids (63%) (Figure 38.6-3).
Survival rates for different carcinoids depend on both the site and the extent of tumor.\(^\text{31,141}\) (Table 38.6-4, and Table 38.6-5; see Fig. 38.6-3C). For all 8305 patients in the SEER data\(^1\) with local disease only, the 5-year survival rate was 80%, varying from 0% for liver and 65% for small intestine and ileum to 94% for appendix. In patients with regional involvement, the 5-year survival rate was 51% overall, varying from 0% for the pancreas and gallbladder to 85% for the appendix. For patients with distant metastases, the overall 5-year survival rate was 22%, varying from 0% for the liver to 36% for the small intestine. In different studies for the common carcinoids, the 5-year survival rate was the highest for carcinoids of the appendix (86% to 100%), followed by lung (77% to 87%), rectum (62% to 72%),\(^1\) small intestine (42% to 73%),\(^1\) colon and stomach (42% to 75%).\(^1\)

### Table 38.6-4. Five-Year Survival Rates of Carcinoid Tumors by Site and Stage

<table>
<thead>
<tr>
<th>Site</th>
<th>5-Year Survival Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreas</td>
<td>57</td>
</tr>
<tr>
<td>Gallbladder</td>
<td>67</td>
</tr>
<tr>
<td>Liver</td>
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<td>37</td>
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<td>Large Intestine</td>
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<tr>
<td>Stomach</td>
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</tr>
<tr>
<td>Rectum</td>
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</tr>
<tr>
<td>Appendix</td>
<td>62</td>
</tr>
<tr>
<td>Stomach</td>
<td>65</td>
</tr>
<tr>
<td>Other</td>
<td>51</td>
</tr>
</tbody>
</table>

### Table 38.6-5. Prognostic Factors in Carcinoid Tumors

One of the main determinants of survival is the presence of liver metastases (see Table 38.6-4 and Fig. 38.6-5). In a multivariate analysis of 188 cases of patients with carcinoids,\(^2\) the one factor independently predictive of death was the presence of metastases. Additional prognostic factors are summarized in Table 38.6-5. The extent of hepatic metastases is also an important prognostic factor (see Fig. 38.6-3B). In one study,\(^1\) the survival rate was similar in patients with limited hepatic metastases (fewer than five) or no metastases, and it was significantly greater (\(P < 0.001\)) than for patients with extensive metastases. Female gender is associated with a better prognosis,\(^1,2\) as is younger age.\(^1,2,142,144\) The level of tissue invasion is an important predictor of the probability of developing liver metastases.\(^1\) The likelihood of finding regional invasion, metastatic disease, and decreasing survival rates is directly proportional to the size of the primary tumor.\(^1\) With carcinoids of less than 1 cm in diameter, fewer than 15% to 30% in the small bowel have metastatic disease; in the rectum, fewer than 0% to 20%; and in the appendix, fewer than 0% to 2%.\(^1,3,13,39\) In contrast, for those tumors more than 2 cm in diameter, 33% to 95% in the small bowel have metastases; in the rectum, more than 70% have metastatic disease; and in the appendix, 33% have metastatic disease.\(^1,2\)

The histologic features as well as the stage of the carcinoid have been shown to correlate with disease-specific survival and the risk of metastases (see Table 38.6-5 and Fig. 38.6-3C). In one study,\(^1\) for patients with bowel tumors invading only the submucosa (T1), the 5-year survival rate was 100%; with tumors invading the muscularis propria (T2), it was 81%; with tumors invading to the subserosa (T3), it was 70%; and with tumors involving the visceral peritoneum or directly invading other structures (T4), it was 52%. These results are consistent with numerous studies that have demonstrated that, for carcinoids, the probability of developing liver metastases is closely related to the level of tissue invasion.\(^1\) With bronchial carcinoids,\(^1\) the most important variables affecting prognosis are increasing age, tumor diameter larger than 3 cm, T stage, N stage, lymph node involvement, and number of lymph nodes involved. For all pulmonary NETs, which include typical and atypical carcinoids, and for large cell and small cell neuroendocrine carcinomas,\(^2\) the histologic features, number of mitoses, degree of necrosis, vascular invasion, and extent of nuclear pleomorphism all had a significant effect on survival.\(^2\) Histologic features such as necrosis, increased mitotic count, nuclear pleomorphism, vascular or lymphatic invasion, and undifferentiated growth pattern are used to classify carcinoids histologically as typical or atypical.\(^2\) and this variable can have a marked effect on survival (see Fig. 38.6-3C and Table 38.6-5). Measures of proliferation, such as Ki-67 activity or proliferative cell nuclear antigen expression, correlate with tumor aggressiveness or survival in some studies,\(^1,145,146\) but not in others.\(^1\) Flow cytometry has been used to attempt to define the malignant potential for both GI and bronchial carcinoids.\(^1,140,153,152,153,154,142,150\) In two studies\(^1,155\) of GI carcinoids, the presence of metastases or decreased survival correlated with the presence of aneuploidy,\(^1\) whereas in other studies,\(^1\) no correlation was found. In bronchial carcinoids, aneuploidy was reported to occur in 50% to 79%;\(^1\) and in some studies,\(^2,4,147,148,155\) but not others,\(^1\) the flow cytometric result was predictive of the presence of metastases or decreased survival. In one study,\(^1\) aneuploidy was seen significantly more frequently in atypical (74% of cases) than in typical (18%) bronchial carcinoids.

In various studies in the before-octreotide era,\(^1\) the median survival of patients with carcinoid syndrome from the time of onset of symptoms varied from 3.5 to 8.5 years, and the presence of carcinoid syndrome was associated with decreased survival. The mean survival after recognition of abnormal excretion of 5-HIAA was 23 months,\(^2\) and the 5-year survival rates after onset of symptoms in two studies were 30% and 67%.\(^2\) In a number of studies,\(^3,23\) the level of 5-HIAA excretion has been correlated with survival (see Table 38.6-5). In one study, patients excreting 10 to 49 mg/dL had a median survival of 29 months; those with 50 to 149 mg/dL had a survival rate of 24 months, and those with more than 150 mg/dL had a mean survival rate of 13 months.\(^2\) Octreotide treatment has been proposed to extend survival. Studies show the level of plasma chromogranin A elevation is predictive of survival,\(^1\) as is the plasma level of the tachykinin neuropeptide K,\(^1\) and in one study,\(^1\) patients with a plasma chromogranin A level of less than 5000 \(\mu\)g/L had significantly (\(P < 0.001\)) longer survival than those with higher values (56 months vs. 33 months, respectively). A number of studies\(^1\) have provided evidence that patients with carcinoids are at increased risk of developing a synchronous adenocarcinoma (7% to 10%), with the most common site being the large intestine. The development of a second malignancy is associated with a worse prognosis.\(^1\)

The most immediate life-threatening complication of carcinoid syndrome, the carcinoid crisis, is observed more frequently in patients who have intense symptoms from foregut carcinoids or who have greatly elevated urinary 5-HIAA levels (more than 200 mg per 24 hours).\(^2\) The carcinoid crisis may occur spontaneously, or it may be associated with stress, anesthesia, chemotherapy, or even biopsy of hepatic metastases.\(^1,13,18,25,26,32,34\) Patients usually develop flushing, diarrhea, and abdominal pain. Mentation is altered, ranging from light-headedness to coma. Cardiac abnormalities also occur, including tachycardia, hypertension, or profound hypotension.\(^1\) The carcinoid crisis may be successfully treated, but in some patients it may also be a terminal event.\(^1\) In one study,\(^1\) of 21 patients with abdominal carcinoids, of whom 80% had an elevated urinary 5-HIAA level, 80% had evidence of cardiovascular instability during surgery, primarily hypotension. In five cases pretreated with octreotide, the changes in blood pressure were lessened and responded easily to additional octreotide.\(^1\) Other investigators also have described the value of octreotide in the treatment and prevention of carcinoid crises.\(^1,13,15,16,44,155,156\)
TREATMENT

Many patients with hepatic metastases from carcinoid tumors remain active and well except for occasional episodes of flushing or diarrhea. Treatment of these patients includes avoiding stress and conditions or substances that precipitate flushing, and dietary supplementation with nicotinamide (Fig. 38.6-4). Heart failure may require diuretics; whereas may require oral bronchodilators such as salbutamol, a bronchodilator that interacts with b-adrenergic receptors and does not induce flushing, or aminophylline; and mild diarrhea may respond to antidiarrheal agents such as loperamide or diphenoxylate. If patients still have carcinoid syndrome symptoms, serotonin receptor antagonists or somatostatin analogues are the drugs of choice, although a number of other drugs also have been shown to be effective in small numbers of patients.172 (see Fig. 38.6-1, and Fig. 38.6-4).

These various agents act in a variety of ways, including by inhibiting the synthesis of serotonin (parachlorophenylalanine, a-methyldopa), by functioning as serotonin receptor antagonists and blocking the action of 5-HT on target tissues, or by inhibiting the release of various vasoactive substances (octreotide, interferon-a) (see Fig. 38.6-1 and Fig. 38.6-4). Parachlorophenylalanine, which blocks the hydroxylase enzyme that converts tryptophan to 5-HTP, relieves diarrhea and improves flushing in some patients and reduces urinary 5-HIAA.164 However, its side effects include hypereosinophilia, urticaria 5-HT and psychiatric disturbances, making it intolerable for long-term clinical use.127 a-Methyldopa blocks the conversion of 5-HTP to serotonin; however, its effect is partial. It occasionally relieves flushing, which may be secondary to inhibiting catecholamine-stimulated release of vasoactive substances, and has little effect on GI symptoms.24 Phenoxycarbimazole, an a-adrenergic antagonist, as well as phenoxyzines, possibly acting as a-adrenergic receptor antagonists, may block flushing provoked by alcohol or other agents, although patients frequently become refractory.194 Fourteen subclasses of serotonin (5-HT) receptors have been described.109 The 5-HT 4, and 5-HT 1 receptor antagonists methysergide,180 cyproheptadine,180 and ketanserin frequently decrease the GI symptoms but usually do not decrease the flushing. In one study, cyproheptadine sodium at a dose of 3 to 8 mg three times per day reduced diarrhea in 50% of patients, with minimal, if any, effect on flushing or excretion of 5-HIAA. Cyproheptadine also is reported to have antitumor activity.31 The use of methysergide is limited because it can cause or enhance retroperitoneal fibrosis. In various studies,162,174,175 ketanserin diminished frequency and severity of flushing in 6% to 100% and diarrhea in 30% to 100% of patients. 5-HT 2 receptor antagonists (ondansetron, tropisetron, alosetron) usually control diarrhea and nausea and, occasionally, flushing.55 A combination of histamine H1- and H2-receptor antagonists are effective in carcinoid syndrome that is caused by gastric carcinoids.24 Prednisone in doses of 20 mg/d gives occasional relief in some cases with severe flushing; however, it is ineffective in controlling the GI symptoms. Tamoxifen was reported to cause systemic improvement in two patients with carcinoid syndrome, however, in a study involving 16 patients with malignant carcinoid, no improvement or sustained reduction in 5-HIAA occurred with tamoxifen administration.153

Native somatostatin reduces symptoms in patients with carcinoid syndrome.175 However, its use is limited by its short half-life (2.5 to 3.0 minutes). With the availability of synthetic, long-acting somatostatin analogues, octreotide (half-life, 90 minutes),29 and lanreotide, treatment can be given subcutaneously every 6 to 12 hours.127 These drugs are now the drugs of choice to control the symptoms of patients with carcinoid syndrome.135 Somatostatin analogues are effective at relieving symptoms and decreasing hormone levels when self-administered every 6 to 12 hours subcutaneously in patients with carcinoid syndrome.172,175,176,177,178,179,180,181,182,183,184,185,186,187,188,189,190,191,192 These somatostatin analogues are effective at both treating these as well as preventing their possible development during known precipitating events, such as surgery, anesthesia, chemotherapy, or stress.180,185 It has been recommended27 that patients with carcinoids scheduled for surgery should be given 150 to 250 µg of octreotide subcutaneously every 6 to 8 hours beginning 24 to 48 hours before anesthesia. In patients receiving chemotherapy, 250 to 300 µg subcutaneously 1 to 2 hours before chemotherapy is recommended.25

Sustained-release preparations of somatostatin have been developed that facilitate treatment. These include monthly octreotide-LAR (long-acting release) or biweekly lanreotide-SR (sustained release) formulations.24,181,182,189 With octreotide-LAR (30 mg/month) a plasma level of 1 ng/mL or more is maintained for 25 days, whereas this requires three to six injections per day of the non-sustained-release form.128 Similar to the nondepot forms, the sustained-release preparations are highly effective at controlling symptoms of carcinoid syndrome.135,181 and 182

Short-term side effects of somatostatin analogues have been minimal, occurring in 40% to 50% of patients.24,135,136,137 Pain at the injection site and effects related to the GI tract (discomfort in 59% and nausea/diarrhea in 15%) are most common. Most are short-lived and therapy is not interrupted.23 Important long-term side effects include gallstone formation, steatorrhea, and deterioration in glucose tolerance.5,135,136,137 In various studies,135 the incidence of gallstones in patients treated long term with octreotide has varied from 5% to 80%, and in a review123 of 13 studies involving 2134 carcinoid patients, 29% developed gallstones.123 In a study29 of 45 patients with metastatic carcinoid or PETs treated long term with octreotide, the overall incidence of gallstones, biliary sludge, or both was 52%, with 7% having symptomatic disease requiring surgical treatment.

Interferon-a is effective in carcinoid syndrome, either alone 202 or combined with hepatic artery embolization.203 In more than 300 patients with carcinoids and carcinoid syndrome treated with interferon,212 the overall biochemical response rate was 42%. In 111 patients213 from one center given interferon-a (1.5 to 7.0 µL three to seven times per week), 42% had a biochemical response (a more than 50% decrease in tumor marker) with a median duration of 32 months. In 70% of patients, an improvement in flushing or diarrhea was seen. In another study,211 high doses of interferon-a were used (24 µM/µL); 39% of patients had a decrease in 5-HIAA secretion, flushing improved in 65%, and diarrhea improved in 33%. However, these responses were transient, lasting a median of only 7 weeks. Interferon-a has been combined with hepatic embolization212 in seven patients and compared with interferon given alone in 12 patients (5 µL/d) for the treatment of carcinoid syndrome. Evaluation after 1 year of treatment showed that, with interferon alone, 50% of patients had decreased urinary levels of 5-HIAA, and when combined with embolization, 71% of patients had a decrease. With interferon alone, 211 58% had decreased flushing and 67% had decreased diarrhea, whereas with the addition of embolization, 86% had decreased flushing and 43% had decreased diarrhea.

Patients with carcinoid syndrome who have no response to octreotide or interferon-a alone have been treated with a combination of both agents.184,214 In one study202

FIGURE 38.6-4. Algorithm for the treatment of malignant carcinoid tumors. Somatostatin analogues refer to the use of octreotide, lanreotide, or their long-acting depot formulations (long-acting-release octreotide or sustained-release lanreotide). 5-HT 3 hydroxytryptamine subtype 3.
involving 24 patients, all demonstrating increased urinary 5-HIAA levels and 19 having classic carcinoid syndrome, complete biochemical remission occurred in 18% and partial biochemical remission occurred in 59%. For a patient with severe carcinoid syndrome not responsive to other measures, hepatic artery embolization or ligation either alone or combined with interferon or chemotherapy may be effective. In two studies involving 32 patients with metastatic liver disease with carcinoid syndrome, embolization or ligation resulted in at least a 50% decrease in urinary 5-HIAA levels in 63% of patients. In two studies involving 42 patients who had disappearance of symptoms immediately after placebo treatment, at 1 year posttreatment 90% were free of symptoms. Chemoembolization, which is embolization with Gelfoam and simultaneous chemotherapy (doxorubicin, mitomycin C, cisplatin, 5-fluorouracil) or interferon, was reported to result in symptomatic improvement in a significant number of patients with carcinoid syndrome. In one large study involving 42 patients with carcinoid tumors, 83% had a decrease in 5-HIAA with chemoembolization followed by treatment with doxorubicin plus dacarbazine ([dimethyltriazeno]imidazole carboxamide; DTIC) and streptozocin plus 5-fluorouracil, and the mean decrease was 87%. Among patients responding, 98% had improvement in IMA levels and 83% had improvement in diarrhea. In another study involving 15 patients and 89% who had unsuccessfully treated with chemotherapy and somatostatin analogue, hepatic artery chemoembolization with 5-fluorouracil, Adriamycin, cisplatin, and mitomycin C controlled diarrhea in 75%, flushing in 58%, and pain in 75%. Hepatic artery occlusion or embolization can have significant side effects, with nausea, vomiting, liver pain, and fever. Major complications occurred in 12% to 17% of patients, including hepatoportal syndrome, sepsis, gallbladder perforation or necrosis, upper GI bleeding, and abscess formation. In two studies involving 75 patients with advanced abdominal carcinoids, all of whom underwent exploratory laparotomy [33% had debulking procedures (excluding liver)], demonstrated a significantly longer survival in those patients who underwent debulking mesenteric metastases and removal of compromised intestinal segments, even in the presence of liver metastases. In one study involving 138 patients, all of whom underwent full-scale cancer operation should be done. In the case of carcinoids of the appendix 2 cm or larger, a right hemicolecction is the operation of choice. In a tumor larger than 2 cm in the rectum or a small tumor with invasion through the musculairia propria, an abdominoperineal resection or a low anterior resection is necessary when anastomosis is recommended by some but not by others. In two studies involving 231 patients with rectal carcinoids larger than 2 cm, all patients died from or developed metastatic disease to the liver despite abdominoappendeal or low anterior resection, and the authors concluded that radical surgery is inappropriate if anorectal carcinoids can be removed by local excision. In the case of a small intestinal carcinoid 2 cm or more, a wide resection is recommended with en bloc resection of the adjacent lymph node-bearing mesentry. For carcinoids of the appendix 1 to 2 cm in size, simple appendectomy is recommended by some whereas others favor more aggressive surgery, such as partial cecectomy or formal right hemicolecction for those lesions located at the base of the appendix to ensure clear margins. In patients with invasion of the mesoappendiceal or vascular invasion. For carcinoids of the rectum 1 to 2 cm in size, it is estimated that 11% to 47% have metastases, and thus it is recommended by some that these tumors be locally excised with a wide, local, full-thickness excision and that those tumors found to invade the musculairia propria undergo abdominoappendeal or low anterior resection. In another study, however, 47% of these patients had metastases and 50% without metastatic disease developed metastases on follow-up, leading the authors to conclude that extensive surgical resection is not routinely warranted in these patients. With gastric carcinoids, treatment is generally stratified by whether hypergastrinemia is present (type I or II) or not (type III). In type I or II gastric carcinoids, if the tumor is larger than 2 cm or if there is local invasion, some recommend total gastrectomy whereas others recommend it be removed surgically with resection, with antrectomy performed for type I (pernicious anemia) lesions. For type I or II lesions of 1 to 2 cm, no general agreement has been reached on treatment; some recommend that these lesions should be treated surgically, whereas others recommend endoscopic treatment. In type III gastric carcinoids not associated with hypergastrinemia, which tend to be larger and more aggressive, if they are larger than 2 cm, excision and regional lymph node clearance is recommended. For type I or II lesions of 1 cm or less, no general agreement has been reached on treatment; some recommend that these lesions should be treated surgically, whereas others recommend endoscopic treatment. The approach of isolated hepatic metastases may also be beneficial or curative in select patients. In one study involving 22% of patients had unibolar disease and could have all tumor resected, whereas in other studies, fewer than 10% of patients were surgical candidates because of more disseminated disease. In the 20% with all metastatic disease resected, 5-HIAA levels were normal and 10-year survival was 100%. The role of cytoreductive or debulking surgery is complex in which the tumor cannot be removed is unclear. No prospective randomized trials have addressed this question. A number of retrospective analyses suggest that such an approach should be considered in selected cases. A number of studies involving 231 patients recommend debulking mesenteric metastases and removal of compromised intestinal segments, even in the presence of liver metastases. In one study involving 38 patients with midgut carcinoids of whom 51 patients were subjected to surgery with the principal aim of removing the primary tumor and debulking mesenteric metastases, the authors concluded that this surgery provided considerable symptomatic relief. A similar study involving 75 patients with advanced abdominal carcinoids, all of whom underwent laparotomy or formal right hemicolecction for those lesions located at the base of the appendix to ensure clear margins. In patients with invasion of the mesoappendiceal or vascular invasion. In patients with type I or II gastric carcinoids, if the tumor is larger than 2 cm or if there is local invasion, some recommend total gastrectomy whereas others recommend it be removed surgically with resection, with antrectomy performed for type I (pernicious anemia) lesions. For type I or II lesions of 1 cm or less, no general agreement has been reached on treatment; some recommend that these lesions should be treated surgically, whereas others recommend endoscopic treatment. In type III gastric carcinoids not associated with hypergastrinemia, which tend to be larger and more aggressive, if they are larger than 2 cm, excision and regional lymph node clearance is recommended. For type I or II lesions of 1 cm or less, no general agreement has been reached on treatment; some recommend that these lesions should be treated surgically, whereas others recommend endoscopic treatment. Because MIBG is frequently taken up by carcinoids and concentrated, the possibility of using radiolabeled MIBG therapeutically has been evaluated in a small number of patients. Iodine 125 MIBG or iodine 131 MIBG has been reported to decrease 5-HIAA urine concentrations and control symptomatic metastases in a small number of cases.
CHEMOTHERAPY

No general agreement has been reached about when, or even if, chemotherapy should be started in patients with malignant carcinoids. One group with considerable experience suggests that only patients with significant symptoms or disability from malignant disease or syndromes who have a poor prognosis should undergo chemotherapy. Chemotherapy for metastatic carcinoids has, in general, been disappointing (Table 38.6-4). Single-agent therapy with doxorubicin, streptozocin, 5-fluorouracil, DTIC, actinomycin D, cisplatin, alkylating agents, etoposide, streptozocin, and carboplatin has provided low tumor response rates of 0% to 10%. In general, the duration of responses is short, usually less than 1 year. Combination chemotherapy for metastatic carcinoid has not been shown to have any clear advantage compared with single-agent chemotherapy. Two-dose combinations have been used of streptozocin and 5-fluorouracil, streptozocin and cyclophosphamide, streptozocin and doxorubicin, etoposide and cisplatin, DTIC and 5-fluorouracil, and lomustine and 5-fluorouracil with low response rates of 0% to 40% and no apparent significant improvement over the use of single agents alone. Three-drug combinations with 5-fluorouracil, doxorubicin, and cisplatin, DTIC, 5-fluorouracil, and epirubicin, and streptozocin, cyclophosphamide, and 5-fluorouracil also gave low response rates of 10% to 31% and showed no additional therapeutic advantage over a single agent. Remissions were short-lived, with an average duration of 4 to 7 months. It can be concluded that no combination therapy has clearly had a beneficial effect in the treatment of malignant carcinoids. Given the inherent nature of the tumor, poor efficacy, and undisputed toxicity of chemotherapy and the availability of excellent symptomatic therapy (octreotide and interferon), chemotherapy usually is reserved for advanced tumors with evidence of progression late in the course of disease. Selective hepatic artery infusion of 5-fluorouracil had a similar response rate as that reported for systemic 5-fluorouracil.

**TABLE 38.6-6. Antitumor Drug Therapy of Carcinoids**

**BIOThERAPy**

Analogs such as octreotide or lanreotide, in addition to controlling symptoms and reducing secretion of 5-HIAA or various peptides, also have been assessed for their antitumor effects (176-180,182-184,202-206,217-219) (see Table 38.6-6). In general, these analogs have a poor tumoricidal effect, decreasing tumor size in only 0% to 17% of patients. However, both somatostatin analogues (lanreotide, octreotide) have a tumoristic effect, stabilizing the growth of metastatic disease and, in some studies, prolonging survival. The mean survival in the 68 patients treated with octreotide in the Mayo Clinic studies was 3 years, which was significantly longer than the 9 to 12 months in the 92 patients treated with chemotherapy in the Eastern Cooperative Oncology Group studies. Similarly, in a phase II study examining the effect of octreotide, 150 to 250 mg three times per day, on survival and tumor growth in 20 patients with metastatic carcinoids, 50% of patients had a CT-documented stabilization of metastatic disease that was maintained a minimum of 2 months (median, 5 months). The median survival was not reached at 20 months. Similar results were reported in prospective studies with octreotide or lanreotide in Germany, in Sweden, and in two studies in Italy, in which 45%, 70%, 80%, and 100% of the patients did not demonstrate tumor progression, respectively. No prospective study has proven that this tumor stabilization results in increased survival.

Studies (217-220,222,224,225) show that human leukocyte interferon or interferon-a causes a decrease in tumor size in a small number (0% to 20%) of patients with metastatic tumors (see Table 38.6-6). However, similar to octreotide, interferon appears to have a tumoristic effect, stopping further tumor growth and stabilizing the extent of metastatic disease, which may lead to prolonged survival. In a large prospective study of interferon-a in 111 patients with metastatic disease, 16 patients (14%) demonstrated a greater than 50% reduction in tumor size, whereas 66% demonstrated a stabilization of disease and 19% progressed. In this study, the survival of patients treated with interferon-a was evaluated compared with the survival of those treated with streptozocin and 5-fluorouracil. Interferon treatment (3 million to 9 million units three times per week) was associated with tolerable but significant side effects, including flu-like symptoms in 89%, fatigue in 70%, weight loss in 57%, reduction of blood counts in 31% (anemia in 31%, leucopenia in 3%, thrombocytopenia in 14%), increased serum levels of triglycerides in 32%, and increased liver enzymes in 31%. Clinical thyroid disease developed in 76% of patients with thyroid antibodies. In 12 patients, it was found that the induction of the enzyme 2′,5′-oligoadenylate synthetase with interferon treatment correlated with the development of a clinical response; however, it is unknown if this response is predictive of changes in tumor size with interferon treatment. The optimal dose for long-term treatment seems to be 5 to 10 μIU three to five times per week; subsequently, however, it is important to titrate the dose individually for each patient. It is recommended that the leukocyte count be used as an indication of the antiproliferative effect of interferon-a, with the goal of reducing the leukocytes to less than 3 × 10^9 per liter.

Because of their separate tumoristic effects and ability to control symptoms, the combination of octreotide and interferon-a were assessed in small numbers of patients with malignant carcinoid syndrome, either alone or in combination with other agents (see Table 38.6-6). With octreotide and interferon-a, interferon-a alone, or interferon-a plus 5-fluorouracil, interferon-a and doxorubicin, and streptozocin and doxorubicin and interferon-a, only low rates (0% to 10%) of decrease in tumor size occurred, which was similar to interferon-a alone. Although some of these combinations, such as octreotide and interferon-a, were more effective than either agent alone at controlling symptoms of the carcinoid syndrome or decreasing 5-HIAA excretion, no clearly increased tumoricidal effect was apparent. In one study involving 21 patients with metastatic NETs (including nine with carcinoids who were unresponsive to monotherapy with octreotide, an interferon-a plus octreotide combination caused inhibition of tumor growth in 67%. In one patient (6%), a decrease in tumor was noted, whereas in the other 61%, the response was a stabilization of tumor size without further growth over a median period of 12 months (range, 3 to 52 months).

Studies demonstrate that somatostatin analogues (lanreotide, octreotide), but not interferon, can induce apoptosis in carcinoid. In contrast, treatment with interferon-a caused an increased expression of bcl-2 in the carcinoids, whereas treatment with somatostatin analogues did not. It was proposed that this induced bcl-2 expression may contribute to keeping the malignant carcinoid cells at G0 phase; or as chemoembolization combined with chemotherapy with DTIC, cisplatin, doxorubicin, streptozocin, and 5-fluorouracil; or four-drug combinations of streptozocin, doxorubicin, cyclophosphamide, and 5-fluorouracil, or lomustine and 5-fluorouracil with low response rates of 0% to 40% and no apparent significant improvement over the use of single agents alone. Three-drug combinations with 5-fluorouracil, doxorubicin, and cisplatin, DTIC, 5-fluorouracil, and epirubicin, and streptozocin, cyclophosphamide, and 5-fluorouracil also gave low response rates of 10% to 31% and showed no additional therapeutic advantage over a single agent. Remissions were short-lived, with an average duration of 4 to 7 months. It can be concluded that no combination therapy has clearly had a beneficial effect in the treatment of malignant carcinoids. Given the inherent nature of the tumor, poor efficacy, and undisputed toxicity of chemotherapy and the availability of excellent symptomatic therapy (octreotide and interferon), chemotherapy usually is reserved for advanced tumors with evidence of progression late in the course of disease. Selective hepatic artery infusion of 5-fluorouracil had a similar response rate as that reported for systemic 5-fluorouracil.

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EMBOLIZATION AND CHEMOEMBOLIZATION

Surgical hepatic artery ligation or embolization via interventional radiology has been reported to reduce hepatic tumor bulk alone (207,208,210,212-215). Combined with interferon-a, or as chemotherapeutic combination with chemotherapy with DTIC, cisplatin, doxorubicin, 5-fluorouracil, or streptozocin, combined with interferon-a (207,208,210,212-215,224,225) (see Table 38.6-6). In one study of 29 patients with metastatic carcinoids, 38% had a decrease in tumor size after embolization; 38% had a greater than 50% decrease in hormone levels and 52% had either. Overall growth stabilization was achieved in 38% for a median duration of 7 months. In two other studies involving 31 patients, 19 patients had temporary liver dearterialization and 12 were treated with chemoembolization. After temporary liver dearterialization, 41% had a decrease in metastatic hepatic tumor size, whereas with embolization, 50% showed a decrease, and in almost all cases the reduction was present for more than 12 months. Hepatic artery occlusion with chemotherapy or chemoembolization may be more effective than embolization or hepatic artery occlusion alone (216). In one large study, the percentage of patients who had tumor regression after hepatic artery ligation alone was similar to that for patients receiving chemoembolization (treatment with DTIC and doxorubicin alternating with streptozocin and 5-fluorouracil) (67% vs. 69%, respectively) (see Table 38.6-6). However, the duration of the response was decreased (4 months vs. 18 months for the combination).
In nine recent studies involving chemoembolization (embolization combined with doxorubicin in ethiodized oil with or without fluorouracil, DTIC, doxorubicin, cisplatin, mitomycin C, or streptozocin), a decrease in tumor size was seen in 33% to 100% of the patients (see Table 38.6-6). The average decrease in size in one study was 84%. In one study, 47% of patients survived 2 years (median survival, 17 months), and in another study the median survival time was 15 months. Interferon has been compared with and without hepatic artery embolization in 42 patients with metastatic carcinoid tumors. Seventeen patients were randomized to interferon and the remaining 25 patients received only interferon. At 1 year, 82% with embolization had stable disease or decrease in metastases, whereas 64% of those treated with interferon had stable disease. Also at 1 year, all patients responding to interferon and those with stable disease were randomized to no interferone or continued interferone (3 n 3 doses per week). One year later, all patients receiving interferon had stable disease as compared with only 40% of those taking no interferon. Survival was significantly longer in patients remaining on interferon. Embolization combined with interferon caused a significantly higher rate of tumor shrinkage than embolization alone in this study but did not prolong survival.

**LIVER TRANSPLANTATION**

In contrast to other metastatic tumors to the liver in which liver transplantation has generally given poor results and has been largely abandoned, interest in liver transplantation is increasing for patients with metastatic carcinoids and PETS, [58, 59, 60, 61, 62, 63] In a review of 103 patients with malignant NETs who underwent liver transplantation (43 carcinoids, 48 PETS), the 2-year and 5-year survival rates were 60% and 47%, respectively. However, recurrence-free survival was less than 24%.[64] Univariate analysis defined favorable prognostic factors as age younger than 50 years, primary tumor in liver or bowel, and pretransplantation somatostatin therapy. Multivariate analysis identified the following factors: for patients with carcinoids, age begins to affect outcome combined with upper abdominal exenteration or Wilbrand's resection (P < 0.1). It was concluded that liver transplantation may be justified, particularly in young patients with only hepatic disease.

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SECTION 38.7
Multiple Endocrine Neoplasias

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INTRODUCTION
The multiple endocrine neoplasia (MEN) syndromes are a group of syndromes characterized by tumors of endocrine organs (Table 38.7-1). MEN 1 affects the parathyroid glands, endocrine pancreas, and pituitary gland, among other organs, whereas MEN 2 affects the thyroid gland, parathyroid glands, and adrenal glands. A great deal has been learned over the last 10 years about the genetics and genotype-phenotype relationships characteristic of these syndromes. Syndromes that were earlier thought to be completely separate [MEN 2B and familial medullary thyroid cancer, (FMTC)] are now known to be closely related to MEN 2A.

TABLE 38.7-1. Multiple Endocrine Neoplasia Syndromes and Familial Medullary Thyroid Cancer

MULTIPLE ENDOCRINE NEOPLASIA TYPE 1
Werner first described the familial occurrence of tumors involving the pituitary gland, parathyroid glands, and pancreatic islets. The syndrome was initially called Werner's syndrome, subsequently called multiple endocrine adenomatosis type 1, and now MEN 1. It is now clear that the parathyroid disease is always hyperplasia and that the endocrine parathyroid tumors may be malignant.

MEN 1 is inherited as an autosomal dominant trait. Chromosomal linkage studies localized the genetic defect to the long arm of chromosome 11 (11q13 locus). The gene has subsequently been identified and codes a protein called menin. This follows the two-hit theory of neoplasia of Knudson in which an inherited mutation in one chromosome is unmasked by a somatic deletion or mutation in the other normal chromosome, thereby removing the suppressor effect of the normal gene. These results are in contrast to patients without MEN 1 who develop pancreatic endocrine tumors, in whom the pancreatic neoplasms develop homozygous inactivation of the MEN 1 gene in 27% to 39% of cases.

Studies concerning the etiology of primary hyperparathyroidism in patients with MEN 1 suggest that there is a circulating factor in the plasma that stimulates bovine parathyroid cells to proliferate. Subsequently, analysis of plasma mitogenic activity in MEN 1 patients demonstrated that basic fibroblast growth factor or a closely related factor was present, and circulating antibodies to it have been identified. However, other studies have demonstrated that there is a monoclonal abnormality in the hyperplastic parathyroid glands of patients with MEN 1, suggesting that the hyperplastic process in these glands may not be totally dependent on a circulating factor but rather through inactivation of the MEN 1 gene in a precursor cell.

CLINICAL PRESENTATION
The peak incidence of symptoms in women with MEN 1 is during the third decade of life, whereas the peak incidence in men is during the fourth decade. In individuals from kindreds, its presence can usually be detected with screening by the age of 18. More than one-half of patients with MEN 1 have adenomas of more than one organ, and approximately 20% have three affected endocrine glands. The frequency of glandular involvement, in descending order, is parathyroid, pancreas, pituitary, adrenal cortex, and thyroid. Both the adrenal cortex and the thyroid typically have benign, nonfunctioning adenomas. Other clinically important tumors these patients develop include gastric carcinoids, bronchial carcinoids (primarily women), and carcinoid tumors of the thymus (primarily men). The frequency of clinical signs and symptoms, in descending order, is hypercalcemia, nephrolithiasis, peptic ulcer disease, hypoglycemia, headache, visual field loss, hypopiattism, acromegaly, galactorrhea-amenorrhea, and rarely Cushing's syndrome. Patients with MEN 1 have a decreased life expectancy, with a 50% probability of death by age 50. One-half of the deaths are due to a malignant tumor process or a sequel of the disease.

PARATHYROID GLAND INVOLVEMENT
Primary hyperparathyroidism is the most common abnormality in patients with MEN 1, occurring in 88% to 97% of affected patients. The diagnosis is dependent on the detection of elevated serum levels of calcium and parathyroid hormone. Primary hyperparathyroidism is usually the initially recognized clinical manifestation of patients with MEN 1, although in prospectively screened patients, other manifestations may be biochemically detected earlier. Occasional patients have clinical manifestations of Zollinger-Ellison syndrome (ZES) before primary hyperparathyroidism. Further, pituitary adenomas or hyperinsulinism may be identified before hypercalcemia. The pathology associated with primary hyperparathyroidism is always hyperplasia or multiple gland disease, although some glands may appear grossly normal. Basic fibroblast growth factor has been expressed in the hyperplastic parathyroid glands of patients with MEN 1. The surgical management requires removal of three and a half or four parathyroid glands to control the hypercalcemia. If four glands are removed, immediate autograft of some of the parathyroid tissue into the musculature of the nondominant forearm is recommended. The results of surgery have not been ideal. The incidence of
recurring or persistent hyperparathyroidism is 16% to 54%, and the incidence of hypoparathyroidism is between 10% and 25%. Primary hyperparathyroidism has been shown to adversely affect the medical management of the gastric acid hypersecretion in MEN 1 patients with ZES. Many clinicians recommend initial parathyroid surgery to control hypercalcemia because it facilitates the management of the gastric acid hypersecretion.

**PANCREATIC ENDOCRINE TUMORS**

Malignant pancreatic endocrine tumors are the most common MEN 1-related cause of death in MEN 1 kindreds (Table 38.7-2). Pathologic examination of the duodenum and pancreas in patients with MEN 1 demonstrates multiple neuroendocrine tumors. Tumors producing pancreatic peptide are the most common pancreatic endocrine tumor in MEN 1 patients, occurring in 80% to 100%.

These tumors cause symptoms only due to the tumor mass itself and thus often present when tumor growth is advanced. Many patients develop functional pancreatic endocrine tumors, sometimes coincident with pancreatic peptide-producing tumors, of whom most have gastrinoma, approximately 20% insulinoma, 3% glucagonoma, and 1% vasoactive intestinal peptide (VIPoma) (see Table 38.7-1).

![Somatostatin receptor scintigraphy](image)

**TABLE 38.7-2.** Multiple Endocrine Neoplasia Type 1–Related Causes of Death in the Washington University Series

<table>
<thead>
<tr>
<th>Cause</th>
<th>No. of Patients</th>
<th>Malignant Whipple’s disease: 12</th>
<th>User disease: 6</th>
<th>VIPoma: 5</th>
<th>Glucagonoma: 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year of death</td>
<td>1970–1982</td>
<td>18</td>
<td>6</td>
<td>5</td>
<td>3</td>
</tr>
</tbody>
</table>

A number of studies have suggested that most gastrinomas in patients with ZES and MEN 1 are in the duodenum and not in the pancreas. The ideal treatment of the ZES is surgical excision of the gastrinoma; however, in patients with MEN 1, excision of gastrinoma rarely results in normal serum gastrin levels. Because of the low probability of cure and the suggestion that the gastrinoma is less malignant in MEN 1, some have recommended that patients with MEN 1 do not undergo surgical excision. However, familial gastrinoma may still have a malignant course. Others recommend surgery if a localized gastrinoma is identified by a gastrin gradient or if the serum gastrin level is elevated.

Somatostatin receptor scintigraphy can be used to rule out distant metastases and to evaluate for other primary sites (Fig. 38.7-1). At present, the best approach is still unclear.

**FIGURE 38.7-1.** Somatostatin receptor scintigraphy can be helpful to identify sites of distant metastases or otherwise undetected second primary tumors in the lungs or mediastinum. In this patient with a malignant nonfunctional neuroendocrine tumor in the body of the pancreas (black arrow), the scintigram revealed a solitary metastasis in the left lateral segment of the liver (white arrow) that was not demonstrated on computed tomographic scan or magnetic resonance imaging.

To date, no studies have demonstrated that surgical resection of gastrinomas in MEN 1 is beneficial. One study suggests that surgical resection of primary gastrinomas in patients with and without MEN 1 decreases the probability of the development of liver metastases, which is the most important negative predictor of survival. Further, when followed for long periods of time, patients with gastrinoma and MEN 1 develop liver metastases at a rate similar to patients with sporadic disease. Therefore, we currently recommend that all patients with ZES and MEN 1 have extensive localization studies including somatostatin receptor scintigraphy. Only patients with unequivocally positive imaging studies and no metastases should undergo surgical exploration with intraoperative ultrasound. Tumors larger than 1 cm identified in the pancreatic head are enucleated, the duodenum is carefully explored by duodenotomy, and solitary or multiple tumors identified are resected; large tumors in the pancreatic body or tail are removed by distal pancreatectomy and splenectomy. Some studies suggest that nearly 50% of large tumors treated in this manner may have lymph node metastases. Other studies have shown that the primary tumor size is not necessarily correlated with the presence of lymph node metastases in particular. Resection of liver metastases from patients with MEN 1 may also be beneficial. Using this approach, cure of ZES is unusual, resection should reduce the risk of subsequent metastatic disease.

MEN 1 is present in 20% of all patients with ZES and 4% of patients with insulinoma. The exact percentage of patients with VIPoma, glucagonoma, or somatostatinoma with MEN 1 is not known, but is estimated to be low (less than 5%). The surgical management of insulinoma and VIPoma in MEN 1 patients has had more frequent biochemical cures than resection for gastrinoma. Medical management of the watery diarrhea in VIPoma is effective using either short-acting or depot somatostatin analogues. Hypoglycemia management in insulinoma is not reliable. Diazaize and octreotide are available and may be useful for short-term treatment. In patients with MEN 1, insulinoma and VIPoma are frequently solitary large lesions. Resection may result in cure.

**PITUITARY TUMORS**

Pituitary tumors occur in 54% to 80% of patients with MEN 1. Symptoms may be due to local encroachment including headache and visual field defects. In a review of series, the most common tumor was a prolactinoma (41% to 76%), followed by growth hormone–secreting tumor, nonfunctioning tumor, and rarely adrenocorticotropic hormone– or thyrotropic-stimulating hormone–secreting tumors. Men with prolactinoma may be unable to achieve a penile erection, whereas women may have galactorrhea. Growth hormone–secreting tumors (25%) result in acromegaly. In one study 20% of patients with MEN 1 and gastrinoma had Cushing's syndrome. In all cases in this series, the Cushing’s syndrome was of pituitary origin and was mild. Cushing's syndrome may also result from release of adrenocorticotropic hormone–like material from a pancreatic islet cell tumor or a foregut carcinoid tumor (ectopic adrenocorticotropic hormone). Prolactinomas are generally treated by dopamine receptor agonists ( bromocriptine, pergolide, cabergoline). Transphenoidal pituitary surgery may be indicated to control any detectable pituitary mass lesion in patients with MEN 1. Incompletely resected patients may also be treated with bromocriptine.

**ADRENAL AND THYROID TUMORS AND LIPOMAS**
Adrenal abnormalities may occur in 27% to 36% of patients with MEN 1.\cite{28,29} The most common abnormality is a benign, nonfunctional adrenal adenoma, although adrenal cortical carcinomas and hyperplasia may also occur.\cite{28,29} Adrenal cortical hyperfunction may rarely be found secondary to an adrenal tumor. Adrenal cortical neoplasms are usually nonfunctional in patients with MEN 1. Thyroid adenomas also occur in approximately 5% to 30% of patients with MEN 1 and have little clinical significance.\cite{28,29} Lipomas are seen with greater frequency in patients with MEN 1, as are cutaneous angiolipomas and collagenomas.\cite{28,29}

CARCINOID TUMORS

Gastric carcinoid tumors develop in 7% to 30% of patients with MEN 1 with ZES.\cite{28,29} They arise from gastric enterochromaffin-like cells and thus are also called ECLomas. Approximately 18% have metastases, they are usually multiple, and they generally pursue an indolent course.

Thymic carcinoids occur in 0% to 8% of patients with MEN 1, are almost exclusively in men, are usually asymptomatic, and are not associated with Cushings' or carcinoid syndrome.\cite{28,29} They pursue an aggressive course with distant metastases and are an increasing cause of death in older men with MEN 1.

Bronchial carcinoid tumors occur in 0% to 8% of patients with MEN 1. Eighty percent are in women and 74% are benign; however, they are an occasional cause of death.\cite{28,29}

FAMILIAL MEDULLARY THYROID CARCINOMA AND MULTIPLE ENDOCRINE NEOPLASIA TYPES 2A AND 2B

HISTORY AND PATHOLOGY

In 1959, Hazard and coworkers\cite{30} first described medullary thyroid carcinoma (MTC) and its striking histologic characteristics of cellular argentaffin staining and amyloid production. MTC is associated with three distinct familial syndromes: MEN 2A, MEN 2B, and familial non-MEN MTC, a disease characterized by hereditary MTC without associated endocrinopathies (see Table 38.7-1).\cite{30}

In 1961, Sipple reported the unusually high incidence of bilateral pheochromocytomas in patients with thyroid malignancy.\cite{30} These patients were later found to have MTC, and the familial disease was inherited as a mendelian autosomal dominant trait with high gene penetrance.\cite{30,31} Subsequently, primary hyperparathyroidism was also noted to be part of this syndrome.\cite{30} In 1968, this syndrome of medullary carcinoma of the thyroid gland, pheochromocytomas, and hyperparathyroidism was termed MEN 2; now it is called MEN 2A. In 1966 Williams and Pollock called attention to the finding that some patients had multiple mucosal neuromas, with or without marfanoid habitus, puffy lips, prominent jaw, pes cavus, and medullated corneal nerves with MTC and pheochromocytomas.\cite{30} For this group of patients the terms MEN 2B and MEN 3 were subsequently suggested.\cite{30} Patients with MEN 2B do not have parathyroid disease. The gene defect in patients with MEN 2A, MEN 2B, and familial MTC is a germline mutation in the RET protooncogene.\cite{30,31}

MTC is a malignant neuroendocrine tumor of the parafollicular thyroid cells or the calcitonin-secreting cells (C cells). Histologically, the MTC in patients with familial MTC, MEN 2A, and MEN 2B appears identical to the MTC occurring sporadically. However, in the familial form of MTC there is bilateral, multifocal involvement, and the cancer usually occupies a position in the superior lateral part of the thyroid lobe at the junction of the upper and middle third. In the sporadic setting, the MTC is usually unilateral. MTC is most malignant in MEN 2B, malignant in MEN 2A, and least virulent in MEN 2A.\cite{30,31} MTC accounts for 5% to 12% of all thyroid cancers, and only 10% of all MTC is familial.\cite{30} In MEN 2A, approximately 42% to 60% of patients develop pheochromocytoma.\cite{30,31}

The pheochromocytomas in patients with MEN 2A or MEN 2B usually present in the second or third decade of life and are often bilateral.\cite{30,31} The size of the tumor or tumors in patients with MEN 2A is usually less than 2 to 3 cm, while it is usually larger in patients with MEN 2B. Even in MEN 2A patients with apparent unilateral pheochromocytomas, the contralateral adrenal gland almost always demonstrates medullary hyperplasia on pathologic analysis.\cite{30,31} Patients with medullary hyperplasia rarely have symptoms of pheochromocytoma.\cite{30,31} I-metaiodobenzyl guanidine scans in patients with MEN 2A may be useful to predict the presence of a clinically significant pheochromocytoma and can be obtained preoperatively. Pheochromocytomas in patients with MEN 2A or MEN 2B are seldom malignant and are usually within the adrenal gland. Histologically, these tumors are indistinguishable from those occurring sporadically in a nonfamilial setting.

The parathyroid lesions in MEN 2A consist of generalized hyperplasia and should be managed like the parathyroid disease in MEN 1.\cite{30,31} Approximately 35% of patients with MEN 2A develop primary hyperparathyroidism.\cite{30,31} The primary hyperparathyroidism in MEN 2A is usually less clinically significant and causes fewer symptoms than the primary hyperparathyroidism in MEN 1.\cite{30,31}

CLINICAL PRESENTATION

Any of the neoplasms that make up the syndromes of MEN 2A or MEN 2B may be the presenting problem; however, MTC is a hallmark feature that occurs in nearly 100% of affected individuals. Of 164 patients with MEN 2A, each had MTC, 35 (21%) had pheochromocytomas, and 28 (17%) had primary hyperparathyroidism.\cite{30,31} In another study of patients with MEN 2A, each had MTC, 40% had pheochromocytomas, and 60% had parathyroid hyperplasia.\cite{30,31} In patients with MEN 2B, all have MTC and approximately 60% develop pheochromocytoma.\cite{30,31}

In patients with MEN 2B the MTC presents at an early age and appears more aggressive, since few patients live beyond 30 years of age.\cite{30,31} In some kindreds, the MTC in MEN 2B may be less malignant and individuals may live longer.\cite{30,31} The characteristic appearance of MEN 2B patients is often the first sign of disease (see Fig. 38.7-1) and may suggest the diagnosis before other clinical abnormalities. However, with investigation by measuring calcitonin, the MTC is always present at the time of clinical recognition (see Table 38.7-1).\cite{30,31}

Patients may initially seek medical advice because of episodic spells with headache, dizziness, or symptoms of irritability and nervousness. It is unusual for patients with MEN 2A to present with symptoms related to parathyroid disease.\cite{30,31}

PREOPERATIVE EVALUATION AND SCREENING

When a suspicion of FMT, MEN 2A, or MEN 2B exists, precise diagnosis depends on detection of missense mutations in the RET protooncogene in peripheral leukocytes. Several studies in individuals from families with MEN 2A have been able to predict the presence of MEN 2A by detection of missense mutations in RET.\cite{32,33,34,35} Screening of new patients or family members for mutations in RET involves polymerase chain reaction amplification and DNA sequence analysis for detection of known point mutations in exons 10 and 11 (codons 609, 611, 618, 620, and 634) for MEN 2A and FMT and exon 16 (codon 918) for MEN 2B. If a RET mutation is detected, each individual (100%) develops MTC. Further, if a RET mutation is absent, the individual does not need any additional testing. Virtually all patients with MEN 2B have either elevated basal or stimulated plasma levels of calcitonin (CT). Patients who present with clinically apparent disease usually have basal plasma CT levels exceeding 1 ng/mL.\cite{30,31} Generally, there is a direct correlation between the tumor mass of MTC and plasma calcitonin levels.\cite{30,31}

Minimal plasma elevations of plasma CT are indicative of MTC in patients who have no other clinical evidence of the neoplasm.\cite{30,31} Some patients with normal basal plasma CT levels have an increase to abnormal levels following calcium infusion (15 mg/kg over 4 hours) or by pentagastrin injection (0.5-mg/kg bolus). Short bolus calcium injection (2 mg of calcium gluconate per kilogram over 1 minute) also provokes elevated plasma CT levels in MEN 2B patients. The peak plasma CT levels in patients with MTC are highest with the combination test of calcium and pentagastatin injection.\cite{30,31}

The presence of inherited MTC can be currently diagnosed in individuals from kindreds before detectable elevations in plasma calcitonin levels. Surgery performed based solely on detection of RET mutations always demonstrates MTC or C-cell hyperplasia.\cite{30,31} It is necessary in patients with MEN 2A or MEN 2B to exclude a pheochromocytoma before undertaking surgery for MTC. Pheochromocytomas can be excluded by measuring normal urinary levels of epinephrine, norepinephrine, vanillylmandelic acid, and metanephrines. If an elevated level is detected, pheochromocytoma localization studies should be done. Abdominal computed tomography and magnetic resonance imaging are frequently helpful in localizing the pheochromocytoma, but additional more sensitive studies may be needed.\cite{30,31} Metanephrines are concentrated into pheochromocytoma cells and provides a means to functionally localize these tumors using scintigraphy.\cite{30,31}
Surgical management of familial MTC is total thyroidectomy with a central lymph node dissection. It is essential that a total thyroidectomy be performed, because the MTC is always bilateral.

Postoperative Follow-up

In patients with MEN 2A and MEN 2B, MTC is the disease that is most frequently lethal. The MTC in patients with MEN 2B seems to be more virulent than in patients with MEN 2A (see Table 38.7.1), although a group of children with MTC in the setting of MEN 2B have been reported, some of whom appear to be cured of MTC. Survival of patients with MEN 2A is dependent on the extent of MTC at initial surgical resection. Data suggest that the survival rate of patients with MTC in the presence of MEN 2A is excellent.

With the widespread availability of reliable radioimmunoassays for CT, an individual patient can be easily followed postoperatively. Detection of an elevated basal plasma CT level or the finding of an abnormal response to calcium and pentagastrin indicates recurrent or persistent disease. In patients with metastatic MTC, it is unclear whether radical thyroidectomy with or without 131I thyroid suppression, and radiation therapy have been helpful. MTC is relatively insensitive to chemotherapy. Because of the indolent nature of the tumor, most have chosen not to aggressively treat metastatic disease.

The 10-year survival of MTC is approximately 80% to 90%. Aggressive surgical resection has been used to locally control recurrent MTC, and one-third of individuals can be rendered biochemically disease free. However, it must be remembered that in patients with MEN 2A, the MTC may be well tolerated. The average life expectancy of patients with MEN 2A and MEN 2B is over 50 years. The current best therapy for familial MTC is early diagnosis and complete resection of intrathyroidal disease at initial surgery. Ablation of extrathyroidal disease when detected as persistent or recurrent elevations of plasma CT levels following total thyroidectomy requires the development of effective systemic adjuvant treatment.

CHAPTER REFERENCES

INCIDENCE

In the United States the incidence of soft tissue sarcoma is approximately 7800 new cases per year. A little more than 50% of these new patients go on to die of the disease. The relatively small number of cases seen and the great diversity in histopathologic presentation, anatomic site, and biologic behavior have made a comprehensive understanding of these disease entities extremely difficult. They are, however, ideal prototypes to demonstrate the important role of multidisciplinary management. It is clear that soft tissue sarcoma, diagnosed at an early stage, is eminently curable. When diagnosed at the time of extensive local or metastatic disease, soft tissue sarcoma is rarely curable.

Analysis of population based data from Connecticut suggests an increase in incidence in both men and women, greater for women.

ETIOLOGY AND GENETICS

Most soft tissue sarcomas have no clearly defined etiology, although multiple associated or predisposing factors have been identified (Table 39.1-1). Data suggest that genetic mutations in pluripotent mesenchymal stem cells give rise to malignant clones that differentiate along pathways that resemble normal histogenesis. Alterations in the RB-1 and p53 genes are detected in a substantial proportion of sarcomas. The importance of these cell regulatory genes in the pathogenesis of sarcoma is highlighted by the high incidence of germline mutations in patients with hereditary retinoblastoma, and by identification of germline mutations in p53 in the...
Li-Fraumeni syndrome. A genetic predisposition to soft tissue sarcoma has also been associated with neurofibromatosis, and familial adenomatous polyposis.

Table 39.1-2

### Radiation-associated soft tissue sarcoma

TABLE 39.1-1. Genetic Predisposition to Soft Tissue Sarcoma

The most common tumors in patients with neurofibromatosis are in the central nervous system. In a 42-year follow-up study, 47% of all malignancies were nervous system tumors. This review confirms the high incidence of malignant tumors in patients with neurofibromatosis: approximately 46% of all patients with this disease develop either a tumor or a benign central nervous system tumor. This prevalence is slightly higher in those with a family history of neurofibromatosis than in those with sporadic cases, but is common in both. Relatives of such patients, whether with a family history or not, are also at risk of developing malignant tumors. The development of phaeochromocytoma also is a complication of neurofibromatosis. Approximately 5% of patients with neurofibromatosis develop malignant peripheral nerve sheath tumors (MPNSTs).

Genetic predisposition to malignancy is well established in the form of an autosomal dominant gene in 8% to 9% of children with soft tissue sarcomas. Survivors of retinoblastoma with the associated RB gene abnormality often develop tumors later in life with a high incidence of sarcomas; the best documented is osteosarcoma. A follow-up study of members of Li-Fraumeni families with childhood rhabdomyosarcoma found additional cancers including carcinoma of the breast, soft tissue sarcomas, lung cancer, skin cancer, leukemia, pancreatic cancer, and brain tumors.

It is important to emphasize that in patients who have retinoblastoma, the increased risk of a second primary is enhanced by radiotherapy, which is dose dependent. Familial adenomatous polyposis, a subset of which is Gardner's syndrome, is commonly associated with the development of intra-abdominal desmoids. These tumors behave as low-grade fibrosarcomas, although constant debate exists as to the histopathologic classification and distinction between the desmoid tumor and aggressive fibromatosis (see below, in Pathologic Classification). However, their natural history of slow growth with accompanying invasion of contiguous structures increases the risk of subsequent mortality when managed inappropriately.

The development of soft tissue and bone sarcoma as a result of exposure to radiation has been known since 1922. Although uncommon, these sarcomas usually have a poor prognosis. In a review of 160 patients, the antecedent diseases for which the radiation was given were predominantly breast and cervical cancer and lymmphofibromatosis (Fig. 39.1-1). External radiation therapy was given to 99% of the patients, 14% of whom received additional treatment with temporary or permanent radioisotope implantation. One patient inadvertently ingested radium. The subsequent tumor that developed was most commonly an osteogenic sarcoma, followed by soft tissue tumors, particularly malignant fibrous histiocytoma (MFH) and angiosarcoma or lymphangiosarcoma (see also, in Pathologic Classification). No significant difference in survival was found between patients with bone tumors and those with soft tissue sarcomas. Survival was not affected by site, latency period, and the amount of radiation received initially, nor were there any differences for patients receiving chemotherapy for their sarcomas. The three factors in the Cox multivariate analysis that had a significant unfavorable association were presentation with metastatic disease (P = .017), incomplete or no operative resection (P = .004), and tumor size of at least 5 cm (P = .007). Tumor grade was not significant in any analyses, but only 6% of the patients had low-grade tumors.

Given the increased use of radiation therapy as a primary treatment modality for breast cancer, concern has been expressed that an increased incidence of sarcoma might be expected. In one study, all 122,991 women with breast cancer in Sweden from 1958 to 1992 were followed, and 116 soft tissue sarcomas were found. There were 40 angiosarcomas and 76 other sarcomas. As expected, angiosarcoma correlated with lymphedema [relative risk = 9.5 (3.2 to 28.0)] but not radiation therapy. For other sarcomas, there was a dose-response relationship with exposure to radiation therapy.

Lymphedema has long been established as a factor in the development of lymphangiosarcoma. The most well-recognized association is with the postmastectomy, postirradiated lymphedematous arm, described by Stewart and Treves. This is not a radiation-induced sarcoma because the lymphangiosarcoma develops in sites both inside and outside of the irradiated field, in the edematous extremity. Similar advanced sarcomas have been seen following filarial infection and chronic lymphedema. Lymphangiosarcoma can arise in filarial lymphedema and remain localized for relatively long periods of time.

The issue of trauma as a possible predisposing factor is more controversial. Often a minor episode of injury is the factor that draws attention to the presence of a mass, implying a causative association that is not real. Abdominal desmoid tumors commonly follow parturition. However, they can occur in the extremity and may be associated with antecedent vigorous physical activity. They may be multifocal.

Chemical agents have been implicated in the etiology of soft tissue sarcoma. Through the years there have been conflicting reports about the relationship between occupational exposures to phenoxyacetic acids found in some herbicides and chlorophenols (found in some wood preservatives) and soft tissue sarcomas, particularly malignant fibrous histiocytoma (MFH) and angiosarcoma or lymphangiosarcoma (see also, in Pathologic Classification). However, their natural history of slow growth with accompanying invasion of contiguous structures increases the risk of subsequent mortality when managed inappropriately.

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Chemical agents have been implicated in the etiology of soft tissue sarcoma. Through the years there have been conflicting reports about the relationship between occupational exposures to phenoxyacetic acids found in some herbicides and chlorophenols (found in some wood preservatives) (Table 39.1-2). Other authors have pointed to the inherent problems in occupational epidemiology in relationship to the source material for soft tissue sarcoma, among them, (1) possible recall bias in self-reported exposure data; (2) soft tissue sarcomas not consistently classified in the International Classification of Diseases, which is organ based; (3) variation in the operational definition of soft tissue sarcomas; and (4) because of their rarity, difficulty recruiting sufficient patients for a case-control study, and cohorts would have to be extremely large to identify an increase in risk. Nevertheless, some studies have suggested a link between phenoxy herbicide exposure in forestry workers, farmers, and railroad workers and subsequent development of sarcoma, whereas other studies from the United States, New Zealand,
and Finland have not confirmed this relationship.  

TABLE 39.1-2. Case-Control Studies of Relationship between Exposure to Phenoxy Herbicides and Incidence of Soft Tissue Sarcoma  

Interestingly, it has been suggested that such exposure may be tissue type specific (i.e., MFH and leiomyosarcoma having a herbicide association, but none being found for liposarcoma).

An increased incidence of soft tissue sarcomas was seen in a cohort of 1520 industrial workers exposed for more than 1 year to 2,3,7,8-tetrachlorodibenzo-p-dioxin, but other studies did not substantiate these findings.  

The issue of dioxin as a risk factor remains controversial. A population-based case-control study assessed the risk of soft tissue sarcomas in Vietnam veterans, including those potentially exposed to Agent Orange, which contains dioxin, and found no increased risk among any subset of veterans compared with control groups. Another study found no increased risk for Vietnam veterans compared with men who had never been in Vietnam. The risk for subgroups of veterans who were more likely to be exposed to Agent Orange, compared with their unexposed counterparts in Vietnam, was not statistically significant. Several chemical carcinogens have an established role in the development of hepatic angiosarcomas: thorotrast, vinyl chloride, and arsenic (including Fowler’s 1% arsenic solution.) A review of pesticides and cancer has again linked the phenoxy herbicides to soft tissue sarcoma and lymphoma, but again questions the causal relationship of these agents.

Chemotherapy for pediatric malignancies has been associated with the subsequent development of osteogenic sarcomas; a relationship with the development of soft tissue sarcomas has not been demonstrated.

CYTOGENETIC ABNORMALITIES

It is important to emphasize that extensive cytogenetic abnormalities occur in soft tissue sarcoma (Table 39.1-3). These are usually associated with high-grade tumors, but are not consistent between tumors. For example, an analysis of 36 tumors, pleomorphic soft tissue sarcomas were examined. Multiple complex karyotypes were identified and at least 24 recurrent abnormalities (defined by their presence in at least five cases) were detected. However, none of the selected rearrangements was specific for any one of a particular subgroup. It seems unlikely at the present time, therefore, that cytogenetic analysis can help differentiate the pleomorphic sarcomas. Conversely, specific changes have been identified in selected sarcomas. The best examples are the classical translocation in Ewing’s sarcoma (primitive neuroectodermal tumor), t(11;22)(q24;q11.2-12), and the translocation seen in synovial sarcoma t(X;18)(p11.2;q11.2). In these situations, these genetic abnormalities can be used as a diagnostic tool.

TABLE 39.1-3. Chromosomal Changes in Soft Tissue Sarcoma  

Multiple other studies of genetic abnormalities have been published. Abnormalities of INK4A (coding for p16 and p19ARF on 9p21) and INK4B have been correlated with poor survival. These chromosomal alterations occur in 15% of patients with high-grade sarcomas. In myxoid liposarcoma, the presence of the TLS-CHOP fusion protein has now been firmly established and is considered a definitive diagnostic tool for these tumors.

DISTRIBUTION

Soft tissue sarcomas can occur in any site throughout the body. Almost 50% of all soft tissue sarcomas appear in the extremities, with two-thirds of extremity lesions occurring in the lower limb, and 30% intraabdominally divided equally between visceral and retroperitoneal lesions.
PATHOLOGIC CLASSIFICATION

Soft tissue tumors generally are categorized according to the normal tissues they mimic. Many soft tissue neoplasms have been described, reflecting the diversity of soft tissue types. Although most soft tissues arise from embryonic mesoderm, tumors of the peripheral nervous system (ectoderm), and some tumors of uncertain histogenesis are included as soft tissue neoplasms.

TABLE 39.1-4. Histologic Classification of Soft Tissue Sarcoma

Soft tissue tumors may be benign or malignant, and a variety of borderline lesions are also recognized. The ratio of benign to malignant tumors is certainly more than 100:1. The soft tissue sarcomas are the malignant tumors that arise in soft tissues. The precise pathogenesis of the vast majority of the sarcomas is uncertain. Unlike carcinomas, sarcomas do not demonstrate in situ changes, nor does it appear that sarcomas originate from benign soft tissue tumors. An exception would appear to be the development of MPNST in patients with neurofibromatosis.

Although each of the sarcomas has distinguishing histologic characteristics, the different types of sarcoma have many common clinical and pathologic features. Sarcomas are characterized by local invasiveness. The pattern of metastasis of most sarcomas is hematogenous. Lymph node metastases are uncommon, with the exception of selected cell types usually associated with childhood sarcoma (Table 39.1-5). Grossly, most sarcomas are similar, with a pale tan flesh appearance (although liposarcomas may be soft and yellow). The clinical behavior of most types of sarcoma also is similar, determined more by anatomic location, grade, and size, than by specific histologic pattern.

TABLE 39.1-5. Soft Tissue Sarcomas: Histologic Type and Lymph Node Metastasis

GRADING OF SARCOMA

After establishing the diagnosis of sarcoma, the most critical piece of information the pathologist can provide to the clinician is histologic grade. The pathologic features that define grade include cellularity, differentiation, pleomorphism, necrosis, and number of mitoses. Unfortunately, the criteria for grading are neither specific nor standardized. Furthermore, several grading scales are used: a four-grade system (Broders), a three-grade system (low, intermediate, high) as recognized by the American Joint Commission on Cancer (AJCC), and a binary system (high vs. low) as used at Memorial Hospital. Even when there is agreement about the number of grades to be used, expert pathologists disagree about specific criteria for defining grade.

The possible clinical implications are obvious. In adjuvant chemotherapy trials high grade was defined differently at different centers, making comparison of results between trials, and combining results of multiple trials, extremely hazardous. For example, tumors of 240 patients who participated in the Scandinavian Sarcoma Group adjuvant trial for high-grade extremity sarcoma were reviewed by a panel of reference pathologists. A four-grade system was used in this trial; only patients with grade III or IV sarcomas were eligible. On review, 5% of the patients were considered ineligible because their tumors actually were low grade. Furthermore, although it did not influence eligibility, there was considerable discordance between the original pathologists and the reference pathologists with regard to whether a lesion was grade III or IV. Although the adjuvant regimen did not affect survival (see below), in adjuvant chemotherapy, a difference in survival was noted between patients with tumors of these two grades as assigned by the reference pathologists.

Many pathologists consider mitotic activity and degree of necrosis to be the most important pathologic features. To define a practical grading system, the European Organization for Research on the Treatment of Cancer (EORTC) studied the histologic features of tumors from 282 patients who participated in their adjuvant chemotherapy trial, and correlated the pathologic findings with outcome. In multivariate analysis, only mitotic count (less than 3, 3 to 20, and greater than 20 mitoses per 10 consecutive high power fields), the presence or absence of necrosis, and tumor size predicted survival.

Mutation of p53, nuclear overexpression of p53, and a high Ki-67 proliferation index are associated with high grade and poor survival. As yet, however, these biologic markers have not been shown to be independent indicators of prognosis and cannot be used to grade sarcomas.

Several tumors that are considered sarcomas have no recognizable normal tissue counterpart (e.g., alveolar soft part tumor, Ewing’s sarcoma, epithelioid sarcoma). These tumors often have unique clinical features and usually are not graded. However, note that Ewing sarcomas are considered high-grade, undifferentiated sarcomas.

DIFFERENTIAL DIAGNOSIS

In addition to sarcoma, the differential diagnosis of a soft tissue mass includes a variety of benign lesions, as well as primary or metastatic carcinoma, melanoma, and lymphoma. Accurate diagnosis requires an adequate and representative biopsy of the tumor, and the tissue must be well fixed and well stained. Antibodies for immunohistochemical staining are available commercially, and this technique is readily applicable to paraffin-embedded tissues. The most useful immunohistochemical markers are the intermediate filaments (e.g., vimentin, keratin, desmin, leukocyte common antigen, S-100). In addition, the pathologist should be prepared to process tissue from selected cases for electron microscopy, cytogenetic studies, or molecular analysis. This implies that certain diagnoses are considered by the clinician, that the diagnostic biopsy is obtained appropriately, and that the clinician and pathologist communicate before the biopsy is performed to...
ensure that the necessary steps are taken in handling the tissue.

Cyto genetic analyses reveal clonal chromosome alterations in the majority of sarcomas. Consistent chromosomal abnormalities have been identified in several soft tissue tumors, but cyogenetic analysis is labor intensive and requires short-term culture of the sarcoma cells. Fusion genes resulting from chromosomal rearrangements may be detected by reverse transcriptase polymerase chain reaction. This technique has been quite effective in diagnosing and distinguishing among the small cell sarcomas. Table 39.1-3 describes some of the genetic changes identified in soft tissue sarcoma. Fluorescent in situ hybridization using probes to locate specific chromosomal abnormalities may become clinically useful, but is unavailable for routine diagnostic use at this time. Supernumerary ring chromosomes, seen in mesenchymal neoplasms of low or borderline malignancy, such as dermatofibrosarcoma protuberans, may be identified with this technique.

As might be expected from a group of rare, diverse, but related tumors, there may be considerable disagreement among pathologists regarding the specific histologic diagnosis in individual cases. When pathologic material from 424 patients who entered into Eastern Cooperative Oncology Group (ECOG) sarcoma trials was reviewed by a panel of expert pathologists, 10% of cases were rejected as not being sarcoma, and for 14% of the remaining cases there was disagreement with respect to the histologic subtype. Similarly, in the Southeastern Cancer Group experience with 216 patients, 6% were determined not to have sarcoma, and in 27% the type of sarcoma was deemed incorrect by the reviewers. In the Scandinavian Sarcoma Group experience, the specific histologic diagnosis was disputed in 20%.

Overall, the three most common histopathologic subtypes are MFH, liposarcoma, and leiomyosarcoma. Some types of sarcoma occur with greater frequency in certain age groups or in specific locations, forming clinicopathologic syndromes that permit standardized treatment strategies. The distribution of common histologic types among different age groups is demonstrated in Figure 39.1-3. The most common extremity sarcomas are liposarcoma, MFH, tendosynovial sarcoma, and fibrosarcoma, although a variety of other histologic types are seen. Most retroperitoneal sarcomas are liposarcomas or leiomyosarcomas. The distribution of histologic type by site is shown in Figure 39.1-4.

![Figure 39.1-3. Age distribution of common histologic types of soft tissue sarcomas.](image)

![Figure 39.1-4. Predominant histology by site of soft tissue sarcomas in 3968 patients aged 16 or older admitted to Memorial Sloan-Kettering Cancer Center between July 1982 and July 1999. MFH, malignant fibrous histiocytoma; MPNT, malignant peripheral nerve tumor.](image)

The most frequently encountered chest wall sarcomas are desmoids, liposarcomas, and myogenic sarcomas. Virtually all gastrointestinal sarcomas were previously classified as leiomyosarcomas or leiomyoblastomas. It is now recognized that many gastrointestinal sarcomas do not express markers of myogenic differentiation and are better classified as gastrointestinal stromal tumors, or, if they exhibit neural differentiation, gastrointestinal autonomic nerve tumors (GANT). The pattern of recurrence is intraabdominal, including liver metastasis.

Overall, leiomyosarcoma is the most common type of genitourinary sarcoma in the adult and arises in the bladder, kidney, or prostate, usually in older individuals. Rhabdomyosarcoma arising in paratesticular tissues is a disease of young men. Three major types of uterine sarcoma are recognized: (1) leiomyosarcomas, tumors of the myometrium; (2) mesodermal mixed tumors (malignant mixed Müllerian tumors), composed of elements of carcinoma and sarcoma; and (3) endometrial stromal sarcoma, the least common, which arises from endometrial stroma and usually has an aggressive behavior.

Approximately 10% to 15% of all sarcomas occur in children. The majority of pediatric patients have small cell sarcomas, including embryonal rhabdomyosarcoma and the Ewing's sarcoma and primitive neuroectodermal tumor spectrum (see Chapter 44.2).

**CLINICOPATHOLOGIC FEATURES OF SPECIFIC TYPES OF BENIGN AND MALIGNANT SOFT TISSUE TUMORS**

**TUMORS OF FIBROUS ORIGIN**

There are a variety of benign tumors and tumor-like lesions of fibrous tissue that must be distinguished from true fibrosarcoma. These lesions may also be confused with reactive or reparative processes. A variety of names have been used to designate identical or overlapping entities. In addition, there are a variety of fibrous proliferations of infancy and childhood that resemble lesions in the adult, but are associated with a better prognosis. Features of lesions that may be mistaken for sarcoma are summarized in the following sections.

**Nodular Fasciitis**

Nodular fasciitis, also called pseudosarcomatous fasciitis, is a benign lesion usually seen in adults aged 20 to 40, although it has been reported in both older and younger patients. The typical lesion grows rapidly over several weeks reaching a size of 1 to 2 cm. Growth is usually self-limited, and lesions rarely are larger than 5 cm. Tenderness or soreness is a common complaint. The upper extremity is the most common site, especially the volar aspect of the forearm. Nodular fasciitis generally arises in the subcutaneous fascia or the superficial portions of the deep fascia. Histologically, the lesions are nodular, nonencapsulated masses, consisting of plump, immature fibroblasts arranged in short, irregular bundles or fascicles. Because of their cellularity, rapid growth, and high mitotic activity these lesions may be mistaken for fibrosarcoma. Recurrence is uncommon after simple excision.
Fibroma
Fibroma is a general term that has been applied to a group of defined benign lesions that arise in the skin or soft tissues. Most are effectively treated by simple excision. Fibroma of tendon sheath is a slowly growing dense fibrous nodule that is attached to the tendon sheath, found most frequently in the hands or feet. Recurrence may occur after local excision.

Elastofibroma
Elastofibroma is a rare, slow-growing benign tumor that characteristically arises between the lower portion of the scapula and the chest wall of older individuals. These lesions, which typically occur in workers who have done repetitive manual tasks for years, are thought to be reactive. Elastofibromas grow as ill-defined masses, often measuring 5 to 10 cm in diameter. They may occur bilaterally and rarely have a familial association. Histologically, these lesions consist of swollen eosinophilic collagen and elastic fibers, and stain intensely for elastin. Complete excision is curative.

Superficial Fibromatoses
Superficial fibromatoses arise from the fascia or aponeurosis and generally are small and slow growing. Palmar fibromatosis is associated with flexion contractures (Dupuytren's contracture), and is by far the most common form, affecting as many as one in five persons aged 65 and older. This condition is more common in men than in women and tends to be familial. Although benign, these lesions have a tendency to recur after simple excision. Plantar fibromatosis (Ledderhose's disease) tends to occur in a somewhat younger age group, but may occur with greater frequency in patients with palmar fibromatosis. Penile fibromatosis (Peyronie's disease), with its peculiar pattern of growth, is much less common. The fibrous mass in Peyronie's disease primarily involves fascial structures, the corpus cavernosum, and rarely, the corpus spongiosum. Peyronie's disease is more common in men with palmar and plantar fibromatosis than in the general population.

Desmoid Tumor
The desmoid was originally described as a tumor of the abdominal wall in women who had recently been pregnant, but these rare, slow-growing fibrous tumors may arise at any site in the body. The desmoids have been classified by location as abdominal, extraabdominal, intraabdominal, and mesenteric. As is the case for other sarcomas, site affects management, but it is unclear whether the distinction by site is biologically significant. The term aggressive fibromatoses, often applied to these lesions, especially when they occur in the retropertitoneum, belies their potential for invasion and progressive growth. Although desmoids do not metastasize, for clinical management these tumors are best considered low-grade fibrosarcomas. Retroperitoneal desmoids, along with fibromas, osteomas, and epidermoid cysts, are among the extracutaneous manifestations in patients with familial adenomatous polyposis coli that characterize Gardner's syndrome. Multifocal desmoids of the extremities have been recognized, usually in young women. In a clinicopathologic study based on Finnish hospital records, the incidence of desmoid was estimated at 2 to 4 cases per 100,000. Of the 89 cases, 49% involved the abdomen. Only one patient had Gardner's syndrome, although familial bone abnormalities were noted in some patients. Four populations were defined: juvenile (age 4.5 ± 3.5 years), fertility (27.2 ± 4.4 years), middle age (43.9 ± 6.9 years), and old (69.1 ± 4.4 years). The juvenile desmoid was primarily an extrabdominal tumor of girls, whereas abdominal wall tumors of women were dominant in the fertile age group. Among middle-aged patients, abdominal wall tumors predominated, but the proportion of men and women was equal. In the oldest age group, both abdominal and extraabdominal tumors occurred without a gender difference. These investigators reported that the growth rate in premenopausal women was statistically greater than the rate of growth observed in male patients.

Among 131 patients with desmoid tumors treated at Memorial Hospital, of whom 39% presented with recurrent disease, the female to male ratio was 1:6. Approximately one-half of these tumors arose in the extremity. 15% were retroperitoneal, 12% arose in the abdominal wall, and 10% were chest wall tumors. Four patients had Gardner's syndrome. In univariate analysis, local failure was more common among patients aged 18 to 30 years, those with marginal or inadequate excision, those who presented with recurrent disease, and those who did not receive radiation for gross residual disease. In multivariate analysis, only presentation with recurrent disease and inadequate margins of resection were independent prognostic features. Gender had no influence on recurrence. The probability of local failure following excision was estimated at 37%. Eleven deaths were attributable to recurrent disease, including one patient who developed pulmonary metastases; none of the 11 patients had an extremity primary. Management of patients with desmoid tumors is discussed later in this chapter in the section Desmoids (Aggressive Fibromatoses).

Fibrosarcoma
Fibrosarcoma may occur in patients of any age, but most commonly are seen persons aged 30 to 55 years. These tumors have no characteristic clinical findings. Pathologically, they consist of elongated fibroblast-like cells arranged in a uniform, vesiculated growth pattern. Intersection or interlacing of the fascicles often yields a herringbone pattern on light microscopy. Well-differentiated fibrosarcomas are rich in mature collagen.

FIBROHISTIOCYTIC TUMORS
These tumors, originally thought to arise from histiocytes that had fibroblastic potential, almost certainly are fibroblastic in origin. Thus, the term fibrohistiocytic is merely descriptive of their appearance.

Fibrous Histiocytoma
These benign tumors usually present as solitary, slowly growing nodules, although up to one-third are multiple. Histologically, they consist of fibroblastic and histiocytic cells often arranged in a cartwheel or storiform pattern. When such lesions occur in the skin, they are often called dermatofibromas or sclerosing hemangiomas. Superficially located lesions usually are cured by simple excision. Deeper lesions should be resected with a wider margin of normal tissue to prevent local recurrence.

Xanthoma
Xanthoma refers to a collection of lipid-laden histiocytes and is seen in diseases associated with hyperlipidemia. These lesions generally occur in cutaneous or subcutaneous locations, but may involve deep soft tissues. Presumably, xanthomas are reactive lesions.

Dermatofibrosarcoma Protuberans
Dermatofibrosarcoma protuberans is probably best considered a low-grade sarcoma. This lesion may occur anywhere in the body, but more than 40% occur on the trunk, 20% in the head and neck, and 40% on the extremities. This lesion typically presents in early or midadult life, beginning as a nodular cutaneous mass. The pattern of growth is usually slow and persistent, and as the lesion enlarges over many years, it becomes protuberant. Large lesions often are associated with satellite nodules. Dermatofibrosarcoma protuberans is histologically similar to benign fibrous histiocytoma, but grows in a more infiltrative pattern, spreading along connective tissue septa in deep areas. The central portion of the tumor consists of a uniform population of plump fibroblasts arranged in a distinct ordered pattern. Unlike fibrous histiocytoma, dermatofibrosarcoma protuberans stains positive for CD34, suggesting a neural origin. More than 75% of these tumors have a ring chromosome, probably of chromosome 17 origin, superimposed on a normal karyotype (see Table 39.1-3). Up to 50% recur after simple excision. Occasionally, areas of increased pleomorphism and mitotic activity occur, especially in recurrent lesions. Metastases occur rarely to lung or to lymph nodes. Because of their locally aggressive nature, these lesions may ultimately lead to amputation or even death because of extensive invasion. A variant with melanin pigmentation (Bednar's tumor) also is recognized.

Malignant Fibrous Histiocytoma
The term MFH was first introduced in 1963 to describe a group of malignant soft tissue tumors with a fibrohistiocytic appearance. Since then, this entity has become the most commonly diagnosed extremity sarcoma. A number of subtypes have been described, including myxoid, giant cell, inflammatory, angiomatoid, and pleomorphic types. With advances in pathological techniques, it has been claimed that a specific line of differentiation can be identified in the overwhelming majority of patients with pleomorphic MFH. Nonetheless, this designation has been useful clinically.

MFH characteristically is a tumor of later adult life with a peak incidence in the seventh decade, although it may occur in younger adults. MFH usually presents as a painless mass; the most common site is the lower extremity, followed by the upper extremity and the retroperitoneum. Nonetheless, this designation has been useful clinically.

**TUMORS OF ADIPOSE TISSUE**

**Lipomas**

Lipomas are the most common of all benign neoplasms and may arise in any location where fat is normally present. Lipomas may be deep seated in the mediastinum or retroperitoneum where they may attain massive size. Multiple lipomas are occasionally seen in a familial pattern. Lipomatosis is a term applied to a poorly circumscribed overgrowth of mature adipose tissue that grows in an infiltrating pattern.

Well-differentiated lipomas are composed of fat cells, but are demarcated from surrounding fat by a thin fibrous capsule. These tumors usually are found within subcutaneous fat, but may occur anywhere in the body. In spindle cell lipoma, mature fat is replaced by collagen-forming spindle cells; this lesion typically arises in the posterior neck and shoulder in men between the ages of 45 and 65. Pleomorphic lipoma is a closely related lesion. Local excision of lipoma and these variants is generally curative. The term atypical lipoma is used by some to describe these benign lesions; others use atypical lipoma to describe a well-differentiated liposarcoma that arises in a subcutaneous or intramuscular location.

Angiopomas present as subcutaneous nodules, usually in young adults. The most common site is the upper extremity. Angiopomas rarely reach more than 2 cm, but they often are painful, especially during their initial growth period. Microscopically, these tumors consist of adipocytes with interspersed vascular structures. Myxoid and fibrolastic angiopomas are recognized.

**Angiomyolipoma**

The term angiomyolipoma is used for a nonmetastasizing renal tumor that is composed of fat, smooth muscle, and blood vessels. Angiomyolipoma is more common in women than in men and is seen in association with tuberous sclerosis. Although angiomyolipoma is usually well demarcated from normal kidney, it may extend into the surrounding retroperitoneum. Angiomyolipomas may be solitary or multicentric and may produce abdominal pain or hematuria. Wide excision is curative. Angiomyolipomas of the liver have also been described.

**Hibernoma**

Hibernoma is a rare, slowly growing benign neoplasm that resembles the glandular, brown fat that is found in hibernating animals. The literature consists primarily of case reports, and in most of these the tumor arises within the thorax. Lesions of the trunk, retroperitoneum, or extremities also are reported. Excision is generally curative.

**Lipoblastoma and Lipoblastomatosis**

Lipoblastoma and lipoblastomatosis are peculiar variants of lipoma that occur almost exclusively in infancy and early childhood. They differ from lipoma by their cellular immaturity and their close resemblance to the myxoid form of liposarcoma.

**Liposarcoma**

Liposarcoma is primarily a tumor of adults with a peak incidence between age 50 and 65. Next to MFH, it is the most commonly diagnosed soft tissue sarcoma in adults. Liposarcoma may occur anywhere in the body, although the most common sites are the thigh and the retroperitoneum. As with other adult sarcomas, there are no characteristic clinical findings. Several types of liposarcoma are recognized and have different clinical outcomes. Well-differentiated liposarcoma is a nonmetastasizing lesion. It is often difficult to distinguish well-differentiated liposarcoma from atypical lipoma, and the distinction may be irrelevant to the clinician. Sclerosing liposarcoma, also a low-grade lesion, typically occurs in the retroperitoneum.

Myxoid liposarcoma accounts for 40% to 50% of all liposarcomas. The tumor consists of proliferating lipoblasts within a delicate capillary network and has a myxoid matrix. The amount and distribution of the mucoid material may vary widely. Although previously considered a low-grade lesion, it is now clear that a myxoid matrix can be seen in many high-grade liposarcomas. As with other sarcomas, pathologic nomenclature can vary widely between pathologists. Myxoid liposarcoma typically has a t(12;16)(q13-p11) translocation. Round cell (or lipoblastic) liposarcoma is characterized by excessive proliferation of small rounded cells. Round cell liposarcoma has the same translocation seen in myxoid liposarcoma, suggesting that these liposarcomas are variants of the same pathogenetic process. Fibrolastic liposarcoma is composed of slender, fibrolast-like cells, and, like round cell liposarcoma, is of higher grade than myxoid liposarcoma. Pleomorphic liposarcoma, as the name implies, is a highly malignant lesion. Mitotic activity is high, and hemorrhage or necrosis is common.

It is not unusual for large liposarcomas to consist of multiple nodules, some of which contain only low-grade elements and others containing intermediate- or high-grade elements. The term dedifferentiated liposarcoma has been used to refer to lesions that appear to begin as low-grade lesions, but progress to higher grade tumors and show evidence of nonlipogenic differentiation. This lesion is seen most frequently in the retroperitoneum.

**TUMORS OF SMOOTH MUSCLE**

**Leiomyoma**

Benign smooth muscle tumors are quite common in the uterus and in the gastrointestinal tract. Rare cutaneous leiomyomas arise from the piolecract muscles of the skin. Some occur on a familial basis. These lesions are often multiple and may be quite painful. Typically, these cutaneous leiomyomas develop in adolescence or early adult life as small discreet papules that eventually form nodules. The extensor surfaces of the extremities are most often affected, and the nodules may follow a dermatomal distribution. Although these tumors are histologically benign, recurrences after surgical incision are seen frequently, and often the lesions are so numerous that surgical excision is not possible. Leiomyoma may also occur deep within the extremities, abdominal cavity, or retroperitoneum.

Angiomyoma is a solitary form of leiomyoma. This lesion tends to occur on the extremity in people between the fourth and sixth decades of life. Women are more commonly afflicted than men.

Intravenous leiomyomatosis is a rare condition in which nodules of benign smooth muscle tissue grow within the veins of the myometrium and may extend into the uterine and hypogastrial veins. Typically, these tumors are histologically benign, recurrences after surgical incision are seen frequently, and often the lesions are so numerous that surgical excision is not possible. Leiomyoma may also occur deep within the extremities, abdominal cavity, or retroperitoneum.

**Leiomyosarcoma**

Leiomyosarcoma may arise in any location, but more than half are located in retroperitoneal or intraabdominal sites. These masses often reach quite large proportions, but present insidiously with nonspecific symptoms. In addition, most visceral sarcomas are leiomyosarcomas. Cutaneous leiomyosarcomas usually appear as small solitary extremity nodules. Deep extremity leiomyosarcoma most frequently arises in the thigh and may arise in association with medium or large veins. Although rare, leiomyosarcoma may arise in large vascular structures and present with symptoms of obstruction to the normal flow of blood. The most common arterial site is the pulmonary artery; patients present with symptoms of decreased pulmonary outflow. Leiomyosarcoma of the inferior vena cava, which may present with the
Budd-Chiari syndrome, is also described.

The typical cell of the leiomyosarcoma is elongated and has an abundant cytoplasm. Multinucleated giant cells are common. Epithelioid changes, in which the cells become rounded, with concomitant clear cell changes in the neoplasm, may occur in otherwise typical leiomyosarcomas. When the tumor is predominantly or exclusively epithelioid, the term leiomyoblastoma has been used. The term leiomyoblastoma, however, fails to convey any information with regard to clinical behavior.

Localisation of muscle antigens by means of immunohistochemistry proves the diagnosis of leiomyosarcoma. Desmin and smooth muscle actin are the most common immunohistochemical stains. Grading of leiomyosarcoma, however, can be quite difficult, although mitotic activity appears to be the best indicator of prognosis.

TUMORS OF SKELETAL MUSCLE

Benign tumors of striated muscle are rare. Several types of rhabdomyosarcoma are recognized. Embryonal rhabdomyosarcoma is a small cell tumor that usually arises in the orbit or genitourinary tract in children. The botryoid type of embryonal rhabdomyosarcoma, which frequently originates in mucosa-lined vesicular organs such as the vagina and the urinary bladder, generally grows as a polypoid tumor. These tumors may disseminate widely, but are responsive to chemotherapy and radiation. Embryonal rhabdomyosarcomas occasionally arise in adults. Although regression of tumor in response to pediatric chemotherapy regimens usually occurs, age is an important prognostic factor for survival, with worse outcomes in older patients. Extremity rhabdomyosarcoma in adolescents and young adults often has an alveolar histology. Alveolar rhabdomyosarcoma is composed of ill-defined aggregates of poorly differentiated round or oval cells that frequently show central loss of cellular cohesion and formation of irregular alveolar spaces. These tumors appear to have a worse prognosis than embryonal rhabdomyosarcoma in younger children, but not in adults. A specific translocation, t(2;13)(q37;q14) involving the PAX3 gene on chromosome 2 and the FKHR gene on chromosome 13, is seen in the majority of alveolar rhabdomyosarcomas. In other patients, the translocated chromosome 2 locus is different. Many pediatric studies include all types of rhabdomyosarcoma seen in the pediatric population.

In adults, pleomorphic rhabdomyosarcoma is the most common form of rhabdomyosarcoma. This high-grade lesion is not clinically distinguishable from other high-grade adult sarcomas.

VASCULAR TUMORS

Hemangioma

Hemangiomas are among the most common soft tissue tumors. Most hemangiomas are present at birth and regress spontaneously. Rapid growth with impingement on vital structures may occur, however, and treatment with intralesional injection of interferon has been life-saving. Pulmonary hemangiomas have been observed in rare adults, and diffuse microvascular proliferation in the lung, has been treated effectively with systemic interferon. cavernous hemangioma refers to a benign lesion consisting of large dilated blood vessels with a flattened endothelium.

Lymphangiomyomatosis

Pulmonary lymphangiomyomatosis is a disease of women of childbearing age. Patients present with cough, hemoptysis, and dyspnea. Grossly, the lungs demonstrate multiple small cystic lesions. On microscopic examination, there is proliferation of normal smooth muscle around the airways and the blood and lymphatic vessels. Tamoxifen does not appear to be useful, but responses to postgestational agents have been seen.

Epithelioid Hemangioendothelioma

As its name implies, epithelioid hemangioendothelioma is a vascular tumor that has an epithelial appearance. It has several forms. These lesions may appear as a solitary, slightly painful mass in either superficial or deep soft tissue. Metastases to lung, regional lymph nodes, liver, and bone are reported. Another pattern is that of a diffuse bronchoalveolar infiltrate or multiple small pulmonary nodules. This entity has also been called BIVAT (intravascular, bronchial, and alveolar tumor of the lung). Patients may present with cough and hemoptysis. Epithelioid hemangioendothelioma can also arise in the liver, often presenting as an incidental finding, or as part of a workup for mild elevation of liver enzymes or vague abdominal pain. Multiple liver nodules are the rule. Although these lesions can metastasize, they usually run an indolent course. Liver transplantation has been performed, even in patients with metastatic disease.

Kaposi's Sarcoma

Classic Kaposi's sarcoma is an unusual vascular sarcoma that occurs in the skin of the lower extremities of elderly men of Mediterranean or Jewish extraction. The disease is usually indolent, although it can spread to the lungs and the gastrointestinal tract. Cutaneous lesions can be palliated with radiation therapy when necessary. Another form of Kaposi's sarcoma occurs in Bantu men in Africa; it may also occur in African children in whom it runs a more aggressive course. Kaposi's sarcoma has arisen in renal allograft recipients who are receiving immunosuppressant therapy. Epidemic Kaposi's sarcoma is a complication of human immunodeficiency virus infection (see Chapter 59.1).

Angiosarcoma

Angiosarcomas may arise in either blood or lymphatic vessels. Cutaneous lymphangiosarcoma may develop in chronically lymphedematous extremities. The classic presentation is the Stewart-Treves syndrome, lymphangiosarcoma in the chronically lymphedematous arms of women who have been treated for breast cancer with radical mastectomy, and, often, axillary irradiation. Hemangiosarcomas are usually located in the skin or superficial soft tissue. Multicentric angiosarcomas occur on the scalp and face of elderly men, where unrelenting progression can cause severe ulceration and infection. Angiosarcoma of the breast is usually an aggressive lesion that recurs locally and may metastasize, primarily to lung; histologic grade has been of prognostic value. Angiosarcomas are known to occur in sites of prior irradiation without chronic lymphedema, in particular the pelvis of women who have received radiation therapy for gynecologic cancers. Soft tissue angiosarcoma, often with epithelial features, may arise on the extremities or within the abdomen.

PERIVASCULAR TUMORS

Glomus Tumor

Glomus tumors mimic the modified smooth muscle cells of the glomus body, a special form of arteriovenous anastomosis that is located in the skin and participates in thermal regulation. The glomus tumor generally presents as small, blue-red nodules in subcutaneous tissue or in the subungual region of the finger. These tumors are often associated with paroxysmal pain irradiating away from the tumor. Complete excision is the proper management.

Hemangiopericytoma

The cells of these tumors resemble pericytes, cells that normally are arranged along capillaries and venules. These rare tumors usually arise in adults, although an infantile hemangiopericytoma is recognized. The adult form is most common in the lower extremity, but also occurs in the pelvis or retroperitoneum or other sites. The tumors tend to be well circumscribed and consist of tightly packed cells around thin-walled vascular channels of varying calibers. The cells of hemangiopericytoma stain immunohistochemically with factor XIIa and HLA-DR antigen, but not with factor VIII-related antigen. Many hemangiopericytomas have an indolent behavior, although some behave like other high-grade sarcomas.

TUMORS OF SYNOVIAL TISSUE

Nodular Tenosynovitis

A variety of benign tumors and tumor-like lesions arise from the synovium. Nodular tenosynovitis (tenosynovial giant cell tumor) is a giant cell tumor that may occur at any age but is most commonly seen between the ages of 30 to 50. These tumors are somewhat more common in women. They occur with greatest frequency in the...
hand, but are also seen in the ankles and knees, among other sites. These slow-growing tumors grow as circumscribed lobulated masses and are usually diagnosed when they are less than 5 cm in diameter. Because of their location, excision is often done with close margins and local recurrence is seen in 10% to 20% of patients. A diffuse form occurs in and around joints, most commonly around the knee or ankle. In contrast to most giant cell tumors, this neoplasm grows in expansive sheets without a mature capsule. Malignant giant cell tumors of the tendon sheath are also recognized.

Synovial Sarcoma

Synovial sarcoma usually occurs in young adults. The most common site is around the knee. As opposed to most other soft tissue sarcomas, these lesions occasionally are painful. This tumor is composed of two morphologically distinct types of cells that form a characteristic biphasic pattern. The biphasic synovial sarcoma includes epithelial cells with a surrounding spindle or fibrous component. Calcification, with or without ossification, is seen in up to 30% of tumors. The spindle cells stain positive for keratin and epithelial membrane antigen. Vimentin is demonstrable in spindle cells but absent in epithelial cells. S-100 may be positive as well. Monophasic synovial sarcoma of both fibrous and epithelial types are recognized, although monophasic epithelial synovial sarcoma is extremely rare. Synovial sarcomas contain a characteristic chromosomal translocation, t(X;18)(p11.2;q11.2); a hybrid transcript has been identified.

TUMORS OF THE PERIPHERAL NERVES

Neurofibroma

Solitary neurofibromas are small, slow-growing cutaneous or subcutaneous nodules that usually arise during the third decade of life. By definition, these lesions are not associated with neurofibromatosis. Neurofibromatosis type 1 (NF1, peripheral neurofibromatosis, von Recklinghausen's disease) is one of the most common genetic disorders, affecting approximately 1 in 3000 live births. An autosomal dominant mutation at the 17q11.2 locus has been identified. The clinical features of NF1 include café au lait spots, Lisch nodules (pigmented hamartomas) of the iris, and neurofibromas of several types. Cutaneous neurofibromas, soft, fleshy growths, arise in the skin in all patients with NF1. These lesions may range in size from a few millimeters to 50 to 60 cm. Although some patients have only a few such lesions, others may have hundreds. Subcutaneous neurofibromas are firm and nodular and may be painful. Plexiform neurofibromas are large lesions that affect large segments of a nerve, thickening and distorting the nerve into a tortuous mass. They may cause severe dysesthetic pain.

Benign Schwannoma

Also called neurilemoma, this benign lesion occurs most commonly in people aged 20 to 50 years. Common sites include the head and neck and the flexor surfaces of the extremities. It grows slowly and is usually smaller than 5 cm when the diagnosis is made. This encapsulated nerve sheath tumor is distinguished from neurofibroma in that schwannoma consists of two components: a highly ordered cellular region (Antoni A area), and a loose, myxoid component (Antoni B area).

Cellular Schwannoma

This tumor is more cellular than classical schwannoma. It usually presents in patients during the seventh decade of life as a painless paravertebral mass. Complete excision is curative in most patients.

Granular Cell Tumor

The granular cell tumor (also called granular cell myoblastoma) is a rare tumor that probably is of neural origin. This tumor usually presents in adults as a small, poorly circumscribed subcutaneous nodule, although there are patients who have multiple lesions. This entity has a distinct histologic appearance and stains positive for S-100. Granular cell tumors usually run a benign course, but metastases have been reported.

Malignant Peripheral Nerve Sheath Tumors

MPNSTs have also been called malignant schwannoma, neurofibrosarcoma, or neurogenic sarcoma. The majority of MPNSTs are high grade and characteristically stain for the S-100 protein. The lower extremity and the retroperitoneum are the most common sites, but MPNSTs may arise anywhere in the body. These tumors originate from the nerve sheath, rather than from the nerve itself. Although higher estimates appear in the literature, approximately 5% of patients with NF1 develop MPNSTs.

Malignant peripheral nerve sheath tumors tend to have a similar outcome to other poor prognosis peripheral sarcomas. MPNSTs tend to present with a greater preponderance of large size and high grade than other soft tissue sarcomas, hence their reputation for aggressivity. The Triton tumor is a malignant peripheral nerve tumor with rhabdomyosarcomatous elements.

Because of evolving concepts and nomenclature, the literature is confusing with regard to MPNST and primitive neuroectodermal tumor. The latter, a small cell tumor of children and young adults, is a variant of Ewing's sarcoma.

Gastrointestinal Autonomic Nerve Tumor

GANT, also called plexosarcoma, presumably arises from the enteric plexus of the gastrointestinal tract. Clinically and microscopically, GANT resembles gastrointestinal leiomyosarcoma, but immunostaining is negative for markers of myogenic differentiation. Neurofilaments are seen by electron microscopy. GANT is usually considered a subset of gastrointestinal stromal tumors (GISTs) and characteristically demonstrates expression of the oncogene c-kit (CD117).

EXTRASKELETAL CARTILAGINOUS AND OSSEOUS TUMORS

Myositis Ossificans

This benign lesion is a self-limiting process that usually is associated with trauma. Despite its name, myositis ossificans is not necessarily confined to the muscle nor is inflammation a prominent feature. The condition usually presents in athletic young adults as a tender, soft tissue mass. Over a period of weeks, the mass usually becomes firm or rock hard. Radiographs show calcification several weeks after the lesion appears. Histologically, the mass consists of fibroblastic tissue, often with prominent mitotic activity. Nonetheless, this process is benign and may be managed conservatively. Obviously, it is important to distinguish between myositis ossificans and sarcoma, especially extraskeletal osteosarcoma.

Extraskelatal Chondrosarcoma

Myxoid chondrosarcoma (also called chordoid sarcoma) occurs most commonly in patients over the age of 35. More than two-thirds occur in the extremity. This tumor usually grows slowly, but late recurrence and metastasis is common. A nonrandom reciprocal translocation has been shown in these tumors.

Extraskeletal Osteosarcoma

Extraskeletal osteosarcomas are rare, high-grade sarcomas defined by their production of malignant osteoid and bone. By definition, they are not attached to the skeleton. Unlike typical osteosarcoma of bone, these tumors rarely occur in patients under the age of 20, and most patients are over 50 years of age. These high-grade tumors present like other soft tissue sarcomas. Most arise in the extremities, although osteosarcoma of other sites, including breast, retroperitoneum, urinary bladder, or other visceral organs have been reported. They are considered heterogeneously in the histologic appearance. Spindle cell varieties may resemble MFH, MPNST, or fibrosarcoma, whereas others have a more epithelioid appearance. Giant cells are a common feature. Some lesions that may contain bone or cartilage are hard to distinguish from MFH, but bone in MFH is well differentiated. Nonetheless, extraskeletal osteosarcoma resembles MFH in terms of
age, sites of distribution, and clinical behavior.

TUMORS OF UNCERTAIN HISTOGENESIS

Myxoma

Intramuscular myxoma is a rare tumor that occurs in adults, usually in the large muscles of the extremities. Myxomas consist of abundant mucoid material but few cells. Although these lesions often measure 5 to 10 cm, their clinical behavior is generally benign. Multiple intramuscular myxomas occur in association with fibrous dysplasia.

Aggressive angiomyxoma is a tumor that usually occurs in women, although male patients have been reported. The lesion generally presents as a mass in the perineal or pelvic area. Local recurrence can result in considerable morbidity given the location of these tumors, but distant metastases do not occur.

Mesenchymoma

Malignant mesenchymoma is defined as a malignant tumor showing at least two types of malignant mesenchymal differentiation in addition to a poorly differentiated fibrosarcomatous element. These rare tumors are generally thought to behave clinically in accordance with the predominant component, although one report suggests that their behavior is not as aggressive as might be expected.

Alveolar Soft Part Tumor

This rare tumor occurs most frequently in patients between 15 and 35 years of age. Women outnumber men, especially in patients less than 20 years of age. Prognosis is better in those patients who present at a younger age. These tumors often present in the lower extremities as slow-growing painless masses. Grossly, alveolar soft part tumors are poorly circumscribed. They typically grow in an organoid or nest-like arrangement. The alveolar spaces actually are necrotic areas. Considerable controversy regarding histogenesis persists. Neural derivation has been suggested, but other data suggest a myogenic origin. Lung, brain, and bone are the most common sites of metastasis. Although this tumor tends to grow slowly, the ultimate prognosis is quite poor. Patients may remain asymptomatic over years, however, even with metastatic disease.

Epithelioid Sarcoma

Epithelioid sarcoma is another tumor of adolescents and young adults. This tumor usually presents as a small, firm nodule in the subcutaneous tissue of the distal extremities. Multiple recurrences, which grow along tendons and fascial planes, are a characteristic feature. Unlike most other sarcomas, lymph node metastases are common, and the tumor may appear in the extremity in transit to the regional nodes. Lung is the most common site of distant metastasis.

Clear Cell Sarcoma (Malignant Melanoma of Soft Parts)

This tumor, also called clear cell sarcoma of tendons and aponeuroses, presents as a soft tissue mass. Because of the presence of intracellular melanin and the tendency for regional nodal metastasis, it has been suggested that this entity is better considered a melanoma than a soft tissue sarcoma. Despite these clinical features, clear cell sarcoma has a distinct chromosomal translocation, t(12;22)(q13;q13). Size is the most important prognostic factor. Treatment of the primary is similar to that of other sarcomas. There are few reported responses to chemotherapy.

Desmoplastic Small Cell Tumor

This newly appreciated entity is a tumor of adolescents and young adults. It usually presents in the abdomen, often with diffuse peritoneal implants. Because of its multifocal nature, complete resection is usually impossible. Chemotherapy regimens used in the treatment of Ewing's sarcoma have induced responses in patients with this disease, but are rarely curative. A specific translocation between chromosomes 11 and 22 that is different from the translocation of Ewing's sarcoma has been identified.

Follicular Dendritic Cell Sarcoma

This unusual lesion is thought to arise from lymphatic tissue and commonly occur in the neck, but has been described in other sites.

CLINICAL PRESENTATION

The presence of soft tissue sarcoma almost invariably is suggested by the development of a mass. This mass is usually large, often painless, and may be associated by the patient with an episode of injury. The majority present at a size greater than 5 cm. The size distribution for 3541 cases admitted to Memorial Sloan-Kettering Cancer Center (MSKCC) is illustrated in Figure 39.1-5. The focus of the clinical evaluation is to determine the likelihood of a benign or malignant soft tissue tumor, the involvement of muscular or neurovascular structures, and the ease with which biopsy or subsequent excision can be obtained. Size becomes an important feature (see Prognostic Factors for Outcome, later in this chapter) and definitive diagnosis is dependent on biopsy and histologic confirmation.

![Figure 39.1-5](image)

**FIGURE 39.1-5.** Distribution by size of soft tissue sarcomas in 3541 patients aged 16 years or older admitted to Memorial Sloan-Kettering Cancer Center between July 1982 and July 1999.

DIFFERENTIAL DIAGNOSIS

The major concern, when confronted with a soft tissue mass, is whether or not the lesion is benign or malignant. In most patients with small lesions, or even on occasion large lesions, the differentiation is from the most common soft tissue tumor, lipoma. This may be simple but becomes more difficult as the more aggressive and underappreciated inherently benign lesions are considered. Particularly difficult is myositis ossificans. The patient often has an antecedent history of trauma, and often presents with a large, firm to hard lesion that, on plain film, may have a telltale sign of intrinsic calcification. This does not preclude a malignant lesion. Tru-Cut (Travenol Laboratories, Deerfield, IL) needle biopsy or open biopsy is often accompanied by aggressive hemorrhage, suggesting a vascular neoplasm. In most cases, diagnosis can be made fairly accurately by either plain film (Fig. 39.1-6) or magnetic resonance imaging (MRI) (Fig. 39.1-7). Certainly, the diagnosis should be suspected when there is a significant history of trauma, the lesion is particularly hard, and there is inherent calcification.
Other difficult lesions are the angiomyolipoma and the rare angiomyxoma (Fig. 39.1-8A and Fig. 39.1-8B), which can also be vascular lesions, and the atypical schwannoma, which can be quite large and often is invasive (Fig. 39.1-9). They can often be quite destructive, causing ureteric obstruction and bone invasion. The management is as difficult as for any sarcoma. Conversely, unless absolutely imperative, multiple radical operations in inherently indolent lesions should be avoided.

FIGURE 39.1-8. Other similarly difficult lesions are angiomyxoma, here seen growing as a mass in the perineum (A) and pelvis (B) in a young woman.

FIGURE 39.1-9. Atypical schwannoma can be quite large and often invasive, as shown here in a man with a 20-year history of having undergone multiple resections for large invasive lesions.

**IMAGING STUDIES**

Imaging studies for soft tissue sarcoma vary, depending to some extent on the site. They involve evaluation both of the primary lesion and the potential site of metastasis. Evaluation of the primary lesion in the extremity, and head and neck, predominantly is either by computed tomography (CT) scan, or magnetic resonance imaging (MRI), which provides some increased definition. In the hands of a knowledgeable radiologist, MRI can provide information over and above that provided by CT. Nevertheless, a Radiology Diagnostic Oncology Group study comparing these modalities has shown no benefit of MRI over CT. What is clear in this era of cost containment is that multiple modalities, all focusing on the same entity, are not required.

An important issue for the primary clinician is identification of the relationship of the sarcoma to neurovascular structures. Angiography is rarely of value. For the primary intraabdominal lesion we prefer CT scan (Fig. 39.1-10), which can identify both primary and potential metastasis, although in lesions known to involve the intestinal tract, MRI may add information.
**Computed tomography of a massive intraabdominal liposarcoma.**

**Positron Emission Tomographic Scan**

While positron emission tomographic (PET) scan has been used as an investigational agent for several years, it has yet to gain universal acceptance. It does appear in some studies that grade can be distinguished by this modality. At present, it would appear that the role of PET is primarily in the identification of unsuspected sites of metastasis in patients with recurrent high-grade tumors.

**SITES OF METASTATIC DISEASE**

As important as imaging studies of the primary lesion is evaluation of possible sites of metastasis. This knowledge is essential. An analysis of patients at MSKCC reveals the common sites of metastasis that can guide investigation (Fig. 39.1-11). Metastatic disease from soft tissue sarcoma is also site-specific. For patients with extremity lesions, most metastases (70%) go primarily to the lung. For patients with retroperitoneal or visceral lesions, a much more common site for metastases would be the liver parenchyma, with lung only a secondary site. Nevertheless, no site is immune from soft tissue sarcoma metastasis, and other unique patterns can be identified (e.g., the unusual presentation of intraabdominal metastasis following an extremity liposarcoma).

**BIOPSY**

The primary thrust of biopsy is to obtain adequate tissue for definitive histopathologic confirmation, to evaluate grade, and to identify prognostic factors that would alter the approach to definitive treatment. In the main, for lesions that are less than 5 cm, particularly those that are superficial, excisional biopsy is the preferred approach.

**VALUE OF TRU-CUT BIOPSY**

Several studies have examined this issue, and a summary of the accuracy of Tru-Cut, incisional and frozen section biopsies is included in Table 39.1-6. In the main, the important issue is the adequacy of the sample. Sufficient viable tissue is required that is both representative of the lesion and available for all histopathologic evaluation, immunohistochemistry, and where necessary, electron microscopy. As molecular markers become a factor in prognosis, meticulous attention to the adequacy of biopsy, tissue preservation, and evaluation is paramount. Histopathologic interpretation varies from center to center and may be a major variable in decision making. As with other relatively rare lesions, it is essential that review of the histopathology be made by an experienced group. In a paper from a major center, members of the Musculoskeletal Tumor Society were surveyed and the diagnostic accuracy of biopsies and the consequences of errors made in diagnosis were tabulated. More recent studies, however, show improved diagnostic accuracy and confluence of opinion at least for malignancy and grade.

**TABLE 39.1-6. Accuracy of Tru-Cut Biopsy**

<table>
<thead>
<tr>
<th>Tru-Cut</th>
<th>Percutaneous</th>
<th>Frozen Section</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>60</td>
<td>43</td>
</tr>
<tr>
<td>Accuracy (%)</td>
<td>93</td>
<td>100</td>
</tr>
<tr>
<td>Gastrointestinal (GI)</td>
<td>95</td>
<td>100</td>
</tr>
<tr>
<td>Cervical (C)</td>
<td>69</td>
<td>69</td>
</tr>
<tr>
<td>Gynecologic (G)</td>
<td>86</td>
<td>86</td>
</tr>
</tbody>
</table>

**FINE NEEDLE ASPIRATION CYTOLOGY**

Fine needle aspiration cytology (FNA) has been examined by a number of authors, but is usually confined to the confirmation of recurrence, rather than for the primary diagnosis. In the hands of some, however, it has been a consistent tool. Kindblom performed a study of 18 soft tissue tumors, 5 bone tumors, and 3
metastatic carcinomas thought to be primary soft tissue tumors to examine the relative advantages of a technique using both light and electron microscopy rather than conventional light microscopic aspiration cytology. In their hands FNA was a valuable adjunct used in this manner, but is rarely employed in most centers, other than to identify expected recurrent lesions.

Some authors have argued that biopsy itself is not justified if FNA is available. Rydholm has suggested that no open biopsy is ever really indicated, the argument against its use suggesting the possibility of risking local tumor spread. The author is concerned that antecedent open biopsy increases both the magnitude of the subsequent operation and the need for adjuvant radiation therapy. The author argues that without biopsy, radiation therapy is not needed in the majority of cases and limits the need for more extensive resections. Using FNA, the surgeon proceeds directly to open operation. The author points out, however, that this requires referral before antecedent biopsy, a relatively uncontrollable event in the United States. In addition, other authors suggest that this results in ten patients with benign lesions referred for every sarcoma patient, certainly an untenable situation under the present system.

In addition, this approach presupposes that all that is required is a malignant sarcoma diagnosis and the type or grade of sarcoma does not determine therapy. At MSKCC for extremity lesions we use brachytherapy (BRT) for high-grade lesions and external-beam radiation therapy for low-grade lesions, particularly of large size, that would preclude such an approach. The authors themselves conclude the difficulty if patients should be candidates for pretreatment neoadjuvant therapy to improve survival. However, they argue that immunohistochemistry, electron microscopy, DNA cytology, and chromosomal analysis, all of which can be performed on FNA, ensure the appropriateness of this approach. We still favor adequate tissue from Tru-Cut, excisional, or incisional biopsy to begin such a procedure.

FROZEN SECTION

In some institutions, frozen section is relied on as the diagnostic tool of choice. For many institutions, however, this is unavailable. Our results for frozen section are described in Table 39.1-6. For diagnosis of malignancy, frozen section is accurate but for histopathologic subtypes and grade it is inferior to permanent sections of either Tru-Cut or incisional biopsy.

STAGING

There have been significant changes in the staging of soft tissue sarcoma. The original 1992 staging system was based on a review published in 1977. That staging system has since been considerably modified. The major difference was the inclusion in the original staging system of a subcategory grade [i.e., patients with small (less than 5 cm) lesions that were high grade, were considered as stage IIIA]. Several reviews, however, have suggested that such lesions (small, high grade) have a much more favorable prognosis than outlined in the original 1977 proposal. Reports from two separate institutions suggest that survival of these patients is certainly better than 80% and in many patients, 90%. Consequently, size, which had been historically considered a subcategory of grade, was redefined. Clearly, however, size is a continuous variable and the decision to divide tumors into less than 5 cm or greater than 5 cm is clearly arbitrary. An analysis of greater than 1000 patients with localized extremity sarcoma seen at MSKCC between 1982 and 1997 has been published. The new staging system, however, now includes both size and depth. Our analysis of the present modified 1997 staging system makes it more clear that stages IB (low-grade, large superficial tumors) are uncommon as are stage IIC (high-grade, large, superficial tumors). They are in such a minority that the ability to use them meaningfully in a staging system must be questioned. In addition, this would suggest that depth, although significant in multiple, overall analyses, is of less value when incorporated with other prognostic factors such as size. In addition, it is clear that size itself is a continuous variable as mentioned previously, and for the high-risk tumors (i.e., the large, less than 5-cm, deep tumors), they can be meaningfully divided into tumors of greater than 5 cm or greater than 10 cm. Using this approach then, distant metastasis-free survival can be quite clearly distinguished into four discriminating groups (Table 39.1-7).

![Table 39.1-7. Primary Extremity Soft Tissue Sarcoma: Distant Metastases by Stage, Memorial Sloan-Kettering Cancer Center, July 1, 1982 through December 31, 1997 (n = 1059)](image)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Grade</th>
<th>Tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>G2+</td>
<td>T1A-B or SA</td>
</tr>
<tr>
<td>II</td>
<td>G2</td>
<td>T2B</td>
</tr>
<tr>
<td>III</td>
<td>G3</td>
<td>T3-A or SB</td>
</tr>
<tr>
<td>IV</td>
<td>G2</td>
<td>T4B</td>
</tr>
<tr>
<td>V</td>
<td>G3</td>
<td>T4C</td>
</tr>
</tbody>
</table>

![Table 39.1-8A. Newer Approaches to Staging System of Soft Tissue Sarcoma: Stage Groupings](image)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Patient Survival</th>
<th>Disease-Free Survival</th>
<th>Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>76.6%</td>
<td>77.8%</td>
<td>86.7%</td>
</tr>
<tr>
<td>II</td>
<td>59.1%</td>
<td>56.2%</td>
<td>66.2%</td>
</tr>
<tr>
<td>III</td>
<td>28.6%</td>
<td>25.6%</td>
<td>31.0%</td>
</tr>
</tbody>
</table>

![Table 39.1-8B. Local Recurrence, Disease-Free Survival and Overall Survival in Patients with Modified Staging](image)
Stage IV disease from lymph node metastasis, which as previously alluded to, is rare in the majority of adult soft tissue sarcomas, is equivalent to any other metastasis. For example, if one takes patients with lymph node metastasis only or lymph nodes plus other metastasis and contrasts those to other systemic metastasis, then the disease-specific survival is essentially the same (Fig. 39.1-13). Finally, it is important to emphasize that prognostic factors can vary with time. For early recurrence, it would appear that grade is predominant, whereas for late recurrence, size assumes a progressively more important role. 54,185

Whether or not age should be a determinant in a staging system is as yet unclear. Certainly, when age is examined as an outcome for overall survival, the older patient has a shorter survival than the younger patient. This has usually been arbitrarily divided into less than 50 or greater than 50 years, with a patient over 50 having a worse prognosis. Conversely, a distinction into three groups can show some separation, which we thought were, in the main, disease-dependent rather than age-dependent (Fig. 39.1-14). It certainly seems clear that patients under the age of 16 (i.e., the pediatric age group) have a far different prognosis and a far different response to treatment with sarcoma than do the adults, and this should not be included in the current adults’ staging system. An analysis of the most common histopathologic type in children, rhabdomyosarcoma, suggested that the soft tissue sarcomas in children behave in a somewhat different manner than those in adults. It does appear that the early stage of disease and the late stage of disease are similar in both children and adults, but the intermediate stage lesions have a better prognosis in children, which does not appear solely due to their ability to tolerate extent of treatment. Site is also a clear determinant of outcome. Patients with retroperitoneal and visceral sarcomas certainly do worse than patients with extremity lesions (Fig. 39.1-15).

<table>
<thead>
<tr>
<th>Study</th>
<th>Log Rank Test</th>
<th>Wilcoxon Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local recurrence</td>
<td>P = .5</td>
<td>P = .5</td>
</tr>
<tr>
<td>Disease-free survival</td>
<td>P = .001</td>
<td>P = .001</td>
</tr>
<tr>
<td>Overall survival</td>
<td>P = .001</td>
<td>P = .001</td>
</tr>
</tbody>
</table>

TABLE 39.1-8C. Statistical Test on Three Stages

FIGURE 39.1-12. Distant metastasis-free survival for patients with primary extremity soft tissue sarcoma (n = 1059 patients admitted to Memorial Sloan-Kettering Cancer Center between July 1982 and January 1998) by stages, incorporating 1A/1B/2A versus 2B/2C versus 3A versus 3B. Significance describes the overall difference between the curves. (From ref. 183, with permission.)

FIGURE 39.1-13. Disease-specific survival for patients with soft tissue sarcoma with metastases (n = 711 patients admitted to Memorial Sloan-Kettering Cancer Center between July 1982 and July 1997); lymph node metastases alone versus lymph node metastases with other metastases versus all other metastases. (From ref. 183, with permission.)

FIGURE 39.1-14. Overall survival for extremity soft tissue sarcoma by age group in 1813 patients aged 16 years or older admitted to Memorial Sloan-Kettering Cancer Center between July 1982 and July 1999 (P < .001). Significance describes the overall difference between the curves.
Disease-specific survival by site of soft tissue sarcoma in 3968 patients aged 16 years or older admitted to Memorial Sloan-Kettering Cancer Center between July 1982 and July 1999 ($P < .001$). Patients with retroperitoneal or visceral sarcomas did worse than patients with extremity lesions. Significance describes the overall difference between the curves.

Conversely, there are factors that affect our ability to treat specific sites such as difficulty of radical resections for head and neck tumors and the limitations of radiation therapy in intraabdominal sites.

It does appear that site is a significant factor in survival. However, it is difficult to separate site from adequacy of treatment. It is clear that patients with retroperitoneal sarcoma can and do die of local recurrence, an uncommon event in extremity lesions. The intraabdominal visceral leiomyosarcomas still maintain a high metastatic rate as the primary cause of death.

Bone invasion by soft tissue sarcoma with neurovascular invasion has historically been considered a bad prognostic feature. However, as bone invasion is relatively uncommon in soft tissue sarcoma, it has not been uniformly included in any staging system, but should certainly be considered as a poor prognostic factor.

As of the present time, the innumerable molecular markers that have been included and defined for soft tissue sarcoma, some with prognostic implications, have not been included in staging systems, but one that we would expect to become an increasingly important variable.

MANAGEMENT OF EXTREMITY AND SUPERFICIAL TRUNCAL SOFT TISSUE SARCOMA

Surgical Treatment

A suggested algorithm is shown in Figure 39.1-16. Where appropriate, alternative approaches are discussed in the text (e.g., for patients with lesions less than 5 cm and positive microscopic margins not able to be resected without major morbidity, radiation therapy can be selectively used). The mainstay of treatment for all soft tissue sarcomas of the extremity and trunk is surgical excision. The issues of debate concern how extensive that surgical excision should be and whether it should be preceded or followed by adjuvant therapy.

Wide en bloc resection is used most often. Historical attempts to resect all muscle bundles from origin to exertion have now been supplanted by an encompassing resection, aiming to obtain 2 cm of all uninvolved tissue in all directions. This is often unrealistic, however, because the limiting factor is usually neurovascular juxtaposition or, occasionally, bony juxtaposition. Because most soft tissue sarcomas tend not to invade bone directly, only rarely does bone need to be resected. Soft tissue sarcomas only uncommonly involve the skin, so major skin resection should be limited. In situations of primary or recurrent tumors where skin is involved, or the tumor is so extensive that skin is involved, then consideration of free flap or rotational flap closure becomes important, particularly in those patients who are candidates for subsequent adjuvant radiation therapy.

EXTENT OF SURGICAL RESECTION

The most extensive resection is clearly amputation. This should be only rarely indicated in soft tissue sarcoma at the present time because limb-sparing operations are possible in at least 95% of patients. Experience over the last 25 years at MSKCC indicates that the 50% amputation rate in the late 1960s is now less than 5% (Fig. 39.1-17). Amputation should be reserved, in the main, for tumors not able to be resected by any other means, without evidence of metastatic disease and the propensity for good long-term functional rehabilitation. Often these are patients with large, low-grade tumors with considerable cosmetic and functional deformity, who can be rendered free of symptoms by a major amputation.

Limb-sparing surgery (LSS) versus amputation for all patients, primary and recurrent. Trends in management over time based on the experience at Memorial Sloan-Kettering Cancer Center from 1968 to 1998.
Major amputation has been contrasted to limb-sparing surgery combined with adjuvant radiation. Local recurrence can occur after the limb-sparing operation, and follow-up data on this study confirm that this is almost invariably salvaged, but there is no effect on long-term survival. The issue of amputation versus limb-sparing surgery for extremity lesions has been addressed by a prospective randomized trial at the National Cancer Institute (NCI). In patients entered into this trial, follow-up is now available for more than 10 years. Although local recurrence is greater in those undergoing limb-sparing operation plus irradiation compared with amputation (Fig. 39.1-18), survival overall is not different (Fig. 39.1-19).

![FIGURE 39.1-18. Soft tissue sarcoma, local recurrence according to treatment. Limb-sparing surgery (LSS) plus irradiation (RT) compared with amputation (AMP) at the National Cancer Institute. (Courtesy of J. C. Yang and S. A. Rosenberg.)](image1)

![FIGURE 39.1-19. Soft tissue sarcoma, disease-free survival according to treatment. Limb-sparing surgery (LSS) plus irradiation (RT) compared with amputation (AMP) at the National Cancer Institute. (Courtesy of J. C. Yang and S. A. Rosenberg.)](image2)

**SIZE**

Because size is a prognostic factor for outcome both in terms of local recurrence and subsequent metastatic disease, the approach to these lesions can be varied. In patients with small approach to these lesions can be varied. In patients with small lesions less than 5 cm, complete surgical excision is usually sufficient, adjuvant therapy being reserved for only those with recurrent lesions. Given the high risk of recurrence and of systemic disease for lesions larger than 10 cm that are high grade, these patients are candidates for investigational approaches, especially neoadjuvant chemotherapy (see below, in Adjuvant Chemotherapy). All patients with lesions larger than 5 cm should be considered for adjuvant radiation therapy as a proven method of limiting local recurrence.

**RADIATION THERAPY**

Before discussing the role of radiation therapy in the management of soft tissue sarcoma, it is important to differentiate between radiosensitivity and radioresponsiveness. Radioresponsiveness refers to the inherent response of cancer cells to radiation, and radioresponsiveness refers to how quickly a tumor regresses after radiation. These two parameters do not always correlate.

Unfortunately, the slow rate of regression of soft tissue sarcomas even after high doses of radiation, an example of poorly radioresponsive tumors, is often mistaken for radioresistance. This in turn has lead to an extensive debate about the effectiveness of radiation therapy in soft tissue sarcomas. This debate was not settled until the recent past, even though the use of x-rays for the treatment of sarcoma was first proposed in 1902. The fact that soft tissue sarcomas are radiosensitive tumors has not only been proven clinically, but it has also been shown in radiobiologic experiments. Radiation sensitivity of cell lines derived from sarcomas, measured in vitro, is not less than that of epithelial cancer cell lines.

The discussion in this section is focused primarily on the role of radiation in the management of soft tissue sarcoma of the extremity and superficial trunk. The role of radiation in other sites is discussed separately in other sections of this chapter. Radiation therapy is mainly used as an adjuvant treatment to surgery in the form of BRT or external-beam radiation and rarely used alone for patients with unresectable disease.

**ADJUVANT RADIATION**

The effectiveness of adjuvant radiation has been clearly shown not only through retrospective data but also through three prospective randomized trials that have compared surgery alone with surgery and radiation. Therefore, the question that we should be asking is not whether radiation is useful, but rather which form of radiation is the most effective in terms of tumor control and function preservation.

**POSTOPERATIVE EXTERNAL-BEAM RADIOTHERAPY**

The use of postoperative external-beam radiotherapy in soft tissue sarcoma of the extremities has served as an early model for function preserving approach in oncology.

Historically, amputation was considered the standard surgical treatment for soft tissue sarcoma of the extremity, but data that evaluated more conservative surgery followed by postoperative external-beam radiotherapy emerged as a reasonable alternative. These encouraging results lead the NCI to perform a randomized prospective trial that compared amputation with wide local excision and postoperative radiation in patients with high-grade soft tissue sarcoma of the extremity. Twenty-seven patients were randomized to conservative surgery and radiotherapy, and 16 received amputation (2:1 randomization). There were four local recurrences in the limb-sparing group and none in the amputation group (P = .06). However, there were no differences in disease-free survival rates (71% and 78% at 5 years; P = .75) or overall survival rates (83% and 88% at 5 years; P = .99) between the limb-sparing group and the amputation treatment groups. In a subsequent trial, investigators at the NCI wanted to determine if adjuvant radiation was needed after wide local excision. Ninety-one patients with high-grade lesions were randomized; 47 to receive radiotherapy and 44 to not receive radiotherapy. With a median follow-up of 9.6 years, a highly significant decrease (P = .0028) in the probability of local recurrence was seen with radiation, but no difference in overall survival was shown. Of 55 patients with low-grade lesions (24 randomized to resection alone and 26 to resection and postoperative radiotherapy), there was also lower probability of local recurrences (P = .016) in patients receiving radiotherapy, again, without a difference in overall survival.

The importance of technical aspects of postoperative radiation in soft tissue sarcoma of the extremity has been clearly emphasized in the literature. The volume at risk...
has generally varied from including the whole compartment from origin to insertion, to giving a generous margin around the tumor bed, scar, and drainage sites. However, whether such generous margins are always needed has been challenged. In particular, the results of adjuvant BRT suggest that radiation treatment directed to the tumor bed plus a 2-cm margin might be adequate. In addition, some retrospective data showed no added benefit in terms of local control between field margins of 5.0 to 9.9 cm versus margins of greater than 10 cm or inclusion of the entire compartment. During the design of the radiation field and irrespective of length of field, it is important to spare as much circumference of the limb as possible in order to avoid chronic edema. The use of all preoperative images and CT-based treatment planning to ensure adequate coverage of the target volume with sparing of surrounding normal structures is important.

The optimal dose of radiation in the postoperative setting is also undergoing some debate. The traditional dose of postoperative external-beam radiotherapy is usually 60 to 66 Gy. A dose less than 63 Gy has been advocated by some authors, but this remains controversial.

In summary, the effect of postoperative external-beam radiation on local control for soft tissue sarcoma of the extremity, whether it is high or low grade, has been shown in two prospective randomized trials. Most authors recommend that the tumor bed, including scar and drainage site plus at least 5 to 7 cm margins be included in the initial field of treatment. Then, one or two further reductions in the treatment volume should be done to allow maximum sparing of normal tissues. The total dose is usually 60 to 70 Gy depending on tumor grade, size, margin status, and location.

ADJUVANT BRACHYTHERAPY

Although most of the initial experience with adjuvant radiation has revolved around external-beam radiation, BRT is becoming an attractive alternative. With BRT, patients usually leave the hospital having completed all their treatment in approximately 2 weeks compared with a 6- to 7-week course of external-beam radiation. The evaluation of the tumor bed at the time of the operation by both the surgeon and the radiation oncologist can far exceed any imaging modality in its accuracy, and the rapid dose fall off with BRT spares more normal tissue than external radiation. In addition, Janian et al. reported savings of $1000 per patient treated with BRT as compared with external irradiation.

The initial experience with adjuvant BRT at MSKCC was reported by Hilaris et al. in 1982 and based on these encouraging results a prospective randomized trial was initiated at that time. The aim of this trial was to determine whether adjuvant BRT was needed after complete gross resection. One hundred sixty-four patients were enrolled in that trial; 78 patients were randomized to adjuvant BRT and 86 patients to no further therapy. With a median follow-up time of 76 months, the 5-year actuarial local control rates were 82% and 69% in the BRT and no BRT groups (P = .04), respectively (Fig. 39.1-20). This improvement in local control, however, was limited to patients with high-grade histology. For this group, local control for the BRT arm was 89% versus 66% for surgery alone (P = .0025). There was no improvement in local control for patients with low-grade tumors. The 5-year freedom from distant recurrence rates were 83% and 76% in the BRT and no BRT groups (P = .6), respectively. Analysis by histologic grade did not demonstrate an effect of BRT on the development of distant metastasis or survival.

Even though adjuvant BRT did not show an improvement in local control in patients with low-grade tumors, the local recurrence rates were 22% (no BRT) and 27% (BRT), indicating the need for adjuvant external irradiation in those patients.

FIGURE 39.1-20. Results of a prospective randomized trial at Memorial Sloan-Kettering Cancer Center of adjuvant brachytherapy (BRT) in patients undergoing limb-sparing surgery (n = 3968 patients admitted to Memorial Sloan-Kettering Cancer Center between July 1962 and July 1992, follow-up to July 1999; P = .4). Patients who received adjuvant BRT had a statistically significant improvement in local control. (Updated from ref. 192, with permission.)

Other institutions have also reported encouraging results in their experience with BRT in soft tissue sarcoma. In most of those cases, BRT was used as a boost in combination with external-beam irradiation, but whether this combination is needed in all patients is unclear. Alekhteyar et al. reported on 105 patients with primary or locally recurrent high-grade soft tissue sarcomas who were treated with wide local excision and BRT (87 patients) or BRT and external-beam irradiation (18 patients). With a median follow-up of 25 months, there was no statistically significant difference in the 2-year actuarial local control rates between the two groups; 86% in the BRT group compared with 90% in BRT plus external-beam irradiation group (P = .32). At MSKCC, external-beam irradiation is added to BRT only when the geometry of the implant is suboptimal or there is a positive surgical margin.

One of the most attractive aspects of BRT is the ability to deliver further radiation in previously irradiated patients who may otherwise need amputation in order to obtain good local control. Nori et al. and Pearlstone et al. reported a local control rate of 82.5% (33 of 40) and 65% (17 of 26), respectively, when using conservative surgery and reirradiation with BRT. Catton et al., on the other hand, reported a local control of only 36% (4 of 11) for patients treated with conservative surgery and no further irradiation.

The technical aspects of BRT are different from external-beam radiotherapy. At the time of the operation, the radiation oncologist and the surgeon jointly evaluate the tumor bed, and the radiation target area is determined by adding 2 cm margin longitudinally and 1.0 to 1.5 cm circumferentially. The radiation oncologist then implants this target area with an array of afterloading catheters, placed percutaneously and spaced 1 cm apart. The loading of the catheters takes place no sooner than the fifth postoperative day to allow enough time for wound healing. Unlike with postoperative irradiation, no attempts are usually made to treat large margins or to include the scar and the drainage site. In patients treated with BRT alone, the dose is usually 45 Gy given over 4 to 6 days, and when given as boost the dose is usually 15 to 20 Gy plus 45 to 50 Gy with external-beam irradiation. The most common isotope used is the low-dose-rate iridium 192; however, high activity iodine 125 is occasionally used in young patients or to protect the gonads. More recently, high-dose-rate iridium 192 has been advocated by some authors to take advantage of its radiation safety aspects as well as its dose-optimization capabilities. Further follow-up, however, is still needed to determine its long-term morbidity and overall...
Of the three types of adjuvant radiation, preoperative external-beam irradiation is the only modality that has not been tested against surgery in a randomized trial. There is, however, a great deal of interest and enthusiasm for this approach. Some of the potential advantages of preoperative external-beam radiation therapy include decreased intraoperative seeding of tumor cells, a smaller radiation target volume compared with postoperative irradiation, and tumor shrinkage that might facilitate later surgery. Sutliff et al. evaluated the relationship between tumor size and the sequencing of radiation and showed that preoperative radiation was superior to postoperative radiation in terms of local control for patients with tumors greater than 15 cm. Other investigators have shown no difference in overall survival. Pollack et al. from the M. D. Anderson Cancer Center compared the sequencing effect, not only according to size, but also according to presentation. For patients who presented to their institution with gross disease, the 10-year local control rate was 88% for preoperative radiation compared with 67% with postoperative radiation (P = .01). In contrast, for those presenting after an excision elsewhere, the 10-year local control was better with postoperative radiation (88% versus 73%, P = .07). It is important to note, however, that on multivariate analysis for predictors of local control for the entire population, the type of radiation was not a determinant of local control. It is evident from this discussion that there are no conclusive data on which adjuvant radiation produces the best results in terms of local control; indeed the results are similar. Therefore, the only way to adequately answer this question would be through a randomized prospective trial. Such a trial was just concluded at the Princess Margaret Hospital in Toronto, Canada, where patients with extremity soft tissue sarcoma were randomized to preoperative versus postoperative radiation. With 1.9 years median follow-up, six cases manifested local relapse and metastatic outcome and survival were similar. Outcome analysis must await longer follow-up.

The technical aspects of preoperative radiation for the large part are similar to postoperative irradiation. The typical margin around the target volume is 5 to 7 cm in the longitudinal axis and 1.5 to 2.0 cm circumferentially. The definition of the target volume is different in the preoperative setting since it only includes the gross tumor volume identified on imaging, preferably MRI. This volume usually receives 50 Gy in 5.0 to 5.5 weeks. Surgery is usually performed 2.5 weeks later. Most institutions that use the preoperative approach do not add a boost except in patients with positives margins, where an additional 15 Gy is given.

**SPECIAL CONSIDERATIONS**

**POSITIVE MARGINS OF RESECTION**

Positive microscopic margin was found to be an independent adverse prognostic factor for local relapse in 1041 patients with localized soft tissue sarcoma of the extremity (P = .0001). Although adjuvant radiation has been shown to improve local control in soft tissue sarcoma of the extremity, its effect on patients with positive microscopic margin has not been clearly defined. Data from the Princess Margaret Hospital and Massachusetts General Hospital on patients treated with adjuvant radiation have shown a 10% to 16% increase in the 5-year local recurrence rates in patients with positive margins compared with those with negative margins despite the use of adjuvant irradiation. In our trial of adjuvant BRT a total of 29 patients with positive margins were randomized: 15 to the BRT arm and 14 to the no BRT arm. Five local failures were noted in each group (P = .98). These findings then beg the following questions, when compared with surgery alone; does adjuvant irradiation improve local control in patients with positive margins of resection? Aklektayar et al. evaluated 110 patients with primary high-grade soft tissue sarcoma of the extremity who were treated at MSKCC with surgery alone (19 patients) or with surgery and radiation (91 patients). The 5-year actuarial local control for the whole group was 71%. In the group that received adjuvant radiation the 5-year local control rate was 75% compared with 56% in those treated with surgery alone (P = .01). Adjuvant radiation also retained its significance as an independent prognostic factor for local control when multivariate analysis was performed (P = .01). Whether any radiation modality is better than another in those patients is debatable possibly due to the paucity of data. Aklektayar et al. demonstrated a trend toward improvement in local control if BRT was supplemented with external-beam radiotherapy in patients with positive margins (90% vs. 59%, P = .08). However, others showed no difference in local control between external-beam irradiation and BRT boost.

**SMALL SOFT TISSUE SARCOMAS**

Despite the fact that two randomized trials that compared surgery alone with adjuvant radiation have shown an improvement in local control in all patients, there is still considerable debate in the literature on whether all patients need adjuvant irradiation. Two large-scale studies that have looked at prognostic factors in soft tissue sarcomas of the extremity have failed to show a correlation between local control and tumor size in multivariate analysis. However, in the Geer study, the effect of adjuvant radiation was only analyzed in the subset of patients with negative margins. In fact, patients with positive margins in that study had a 5-year local control rate of only 56% versus 88% in those with negative margins (P = .01). Similar finding were reported by Fleming et al. from the M. D. Anderson Cancer Center. It is also our policy to treat patients with positive margins of resection at the time of preoperative radiation. If the tumors were less than or equal to 5 cm, the other factor that should be considered is whether the patient has had a prior unplanned excision. Naria et al. found a significantly higher rate of local recurrence in patients who were treated after unplanned excision on the outside compared with patients who receive their treatment at their institution (22% vs. 7%, P = .03). It is important to remember that the previously mentioned scenario is common in the community settings when small soft tissue lesions are excised under the presumption that they are benign. Therefore, its is our policy to attempt a reexcision if at all feasible, otherwise patients are strongly considered for postoperative irradiation.

**SOFT TISSUE SARCOMAS OF THE HANDS AND FEET**

Soft tissue sarcomas of the distal extremity deserve special consideration since they pose a formidable challenge to the treating oncologist. For a start, a true wide local excision is the exception rather than the rule in these sites due to the lack of muscular bulk and the proximity to neurovascular structures and bone. In addition, the overall prognosis has been shown to be inferior to other sites in the extremity. Brien et al. showed that even in patients with hand tumors that are less than or equal to 5 cm, the survival rate was significantly lower than other extremity sites (P = .0008). In the past, the use of adjuvant irradiation was fraught with debate about the functional outcome in regions that have traditionally been considered poorly tolerant of radiation. However, more recently data to the contrary have been demonstrated. Talbert et al. treated 78 patients with nonmetastatic soft tissue sarcoma of the distal extremity with conservative surgery and radiation therapy. The 10-year local control rate was 74% and the salvage rate was 85% in patients who failed locally using this approach. The rate of amputation from complications was 8%. Bray et al. also reported on 25 patients with soft tissue sarcoma of the hand and forearm. Twenty received adjuvant radiation and with a mean follow-up of 37 months, the local control rate was 88%. In addition, 88% of those who survived and did not require amputation were able to return to occupational and activities of daily living with minimal or no functional limitation. Therefore, conservative surgery and adjuvant radiation should be considered as an acceptable treatment modality for distal soft tissue sarcomas. Special attention, however, needs to be paid to radiation treatment technique in order to minimize complications and preserve function.

**DEFINITIVE RADIATION**

Surgery remains the main treatment for patients with sarcomas of the extremity, and every effort should be made to attempt resection. However, in some patients with unresectable disease definitive radiation could be considered due to medical reasons or to achieve some palliation. Since sarcoma may be radioresistant in terms of cell killing but not radioresponsive in terms of shrinkage of the mass, this can be perplexing, as such masses could give the false impression that little has been accomplished. Whereas in reality the mass is mainly made up of sterilized tumor cells and debris. Tepper and Sult reported on 51 patients treated with definitive photon beam irradiation to a total dose of 64 to 66 Gy. The 5-year local control and survival rate were 33% and 25%, respectively. Local control was better for tumors less than 5 cm (87.5%) than in tumors 5 to 10 cm (53%) or greater than 10 cm (30%). Slater et al. showed similar findings in 57 patients treated with definitive photon irradiation to 44 to 88 Gy. The 5-year local control was 28%.

More recently, hyperfractionated photon radiation was combined with intravenous iododeoxyuridine as a radiosensitizer. Goffman et al. reported on 36 patients
treated in this fashion, and with a median follow-up of 4 years the local control rate was 60%. 

Other investigators have looked at using neutron radiotherapy either alone or in combination with photon beam radiation. Schwarz et al. reviewed the European experience with such an approach and reported a local control rate of 50%, but the rate of severe complications ranged from 6.8% when neutron therapy was used as a boost to 50% when used alone.

**ADJUVANT CHEMOTHERAPY**

Surgery remains the mainstay of therapy for soft tissue sarcoma in the control of local disease. As discussed previously, radiation therapy also plays a role in the local control of soft tissue sarcomas. Nonetheless, as many as one-half of all patients with adequate local control of disease develop distant metastasis, usually to the lungs (extremity sarcomas) or liver (abdominal primary). As has been demonstrated in other cancers such as breast and colorectal cancer and osteosarcoma, it was hoped that adjuvant chemotherapy would help decrease the frequency of distant metastases, thus increasing overall survival. At least 15 studies of adjuvant therapy for soft tissue sarcoma have been performed. Since anthracyclines are the most active agents in sarcoma therapy in the metastatic setting, they have been used in nearly all of the adjuvant trials, alone or in combination. Most of these studies are small, and therefore lack the statistical power to detect small changes in overall survival. Accordingly, metaanalyses have been performed on the randomized trials for adjuvant chemotherapy in soft tissue sarcoma. In the following section the data from the individual studies and metaanalyses are examined (Table 39.1-9). Single-agent chemotherapy trials are considered first, followed by studies with combination chemotherapy.

### Table 39.1-9. Adjuvant Studies in Soft Tissue Sarcoma

**RANDOMIZED ADJUVANT STUDIES OF DOXORUBICIN ALONE**

One of the earliest studies to accrue patients in a randomized trial of adjuvant chemotherapy was performed by the Gynecologic Oncology Group for patients with uterine sarcomas. Two hundred twenty-five patients with stage I or II uterine sarcomas of any histopathologic subtype were treated surgically for local control. Radiation was added at the discretion of the physician for local control, then patients were randomized to doxorubicin, 60 mg/m² every 3 weeks for eight cycles, or to observation alone. Of 156 evaluable patients, disease-free survival was not different between the two groups, nor was there a statistically significant difference in overall survival (73.7 months in the treated arm versus 55.0 months in the control arm). The addition of radiation therapy did not affect survival, although there was a lower rate of vaginal relapse in the group treated with radiation.

Between 1978 and 1982, the Dana-Farber Cancer Institute, Brigham and Women's Hospital, and Massachusetts General Hospital enrolled AJCC stage IIB to IVA patients in a study in which local therapy consisted of radical surgery, or wide en bloc excision followed by radiation. Forty-two patients were randomized to receive five doses of doxorubicin, 90 mg/m², every 3 weeks, versus observation. The timing of chemotherapy varied between Dana-Farber Cancer Institute/Brigham and Women's Hospital and Massachusetts General Hospital, with former patients receiving both radiation and chemotherapy postoperatively, and the latter patients receiving radiation and two of the five cycles of chemotherapy before surgery. There was no significant difference in local control, relapse-free survival, or overall survival in this study, although there was a trend (not statistically significant) toward better overall survival of patients with extremity sarcomas who received chemotherapy compared with the patients who did not receive chemotherapy.

Similarly, the ECOG enrolled 47 AJCC stage IIB to IVA patients in a study in which local therapy consisted of radical surgery or wide en bloc excision followed by radiation. Patients with local recurrence were permitted on the study as well. Thereafter, patients received doxorubicin, 70 mg/m² every 3 weeks for seven cycles. Thirty-two were eligible for analysis. There was no difference in local control, relapse-free survival, or overall survival in the treatment and control arms.

The Intergroup Sarcoma Study Group also examined AJCC stage IIB to IVA patients treated with surgery for local control. Seventy-eight eligible patients were randomized to observation or to doxorubicin at 35 mg/m² given as daily bolus doses on two consecutive days. Six cycles of doxorubicin were given at 3-week intervals in the chemotherapy arm. There was no significant difference in local recurrence, disease-free survival, or overall survival in the chemotherapy arm compared with the control arm. A trend was noted toward improved disease-free survival for extremity lesions that was of borderline statistical significance (P = .06). However, pooling the data from the Boston, ECOG, and Intergroup studies demonstrated no survival benefit for adjuvant doxorubicin.

The Scandinavian Sarcoma Group performed the largest study of doxorubicin as an adjuvant to local therapy for soft tissue sarcomas. Two hundred forty patients were treated with surgery with the option of adjuvant radiation for local control. Patients were then randomized to receive either doxorubicin, 60 mg/m², every 4 weeks for nine cycles, or no chemotherapy. Chemotherapy was started within 6 weeks of surgery when radiation was not used for local control, or within 10 weeks when radiation was used. One hundred eighty-one patients were evaluable; at a median follow-up of 40 months, there was no difference in local control, disease-free survival, or overall survival for the evaluable patients. Survival data was also assessed for the entire 240 patient cohort; again, there was no difference in disease-free survival or overall survival.

The Istituto Ortopedico Rizzoli examined a heterogeneous group of 77 patients with high-grade extremity sarcomas. As has been demonstrated in other cancers such as breast and colorectal cancer and osteosarcoma, it was hoped that adjuvant chemotherapy would help decrease the frequency of distant metastases, thus increasing overall survival. At least 15 studies of adjuvant therapy for soft tissue sarcoma have been performed. Since anthracyclines are the most active agents in sarcoma therapy in the metastatic setting, they have been used in nearly all of the adjuvant trials, alone or in combination. Most of these studies are small, and therefore lack the statistical power to detect small changes in overall survival. Accordingly, metaanalyses have been performed on the randomized trials for adjuvant chemotherapy in soft tissue sarcoma. In the following section the data from the individual studies and metaanalyses are examined (Table 39.1-9). Single-agent chemotherapy trials are considered first, followed by studies with combination chemotherapy.

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RANDOMIZED ADJUVANT STUDIES OF COMBINATION CHEMOTHERAPY

In 1983 the NCI published the first in a series of publications on adjuvant chemotherapy for soft tissue sarcoma of different anatomic sites. A pilot study examined 26 patients with extremity sarcoma grades II and III, treated for local control with amputation or limb-sparing surgery with radiation. These patients were treated postoperatively with escalating doses of cyclophosphamide (500 to 1000 mg/m²) and doxorubicin (50 to 70 mg/m²) every 28 days, with a maximum cumulative dose of 550 mg/m² of doxorubicin. This combination was followed by six cycles of intermediate dose methotrexate (50 to 250 mg/kg with dose escalation). Patients were randomized to receive chemotherapy with or without C. parvum adjuvant immunotherapy, and were compared with historic controls. There was no effect of the immunologic adjuvant, but the overall survival at 5 years was 73%, better than the 45% seen in the historic controls.

These initial data led to examination of adjuvant chemotherapy alone in a second cohort of patients with extremity sarcomas. Sixty-five patients underwent similar local control as described previously, then were randomized to observation or to the same cyclophosphamide, doxorubicin, and methotrexate regimen of the pilot study. Initial data indicated that disease-free survival and overall survival were improved in the chemotherapy arm. With longer follow-up (median, 7.1 years), 5-year disease-free survival was still improved (75% vs. 54% in the control arm), but the difference in overall survival (83% vs. 60% in the control arm) was not statistically significant. Local control was improved in the chemotherapy arm. In long-term follow-up there has been non–tumor-related mortality; there continues to be no survival advantage in either treatment arm (J. Yang, S. Rosenberg, unpublished results).

Fourteen of the 101 patients treated with the NCI regimen developed clinical congestive heart failure. Other patients had radioveno-occlusive performed confirming a subclinical decrease in cardiac ejection fraction at rest or with exercise. In all, there was an overall event rate of 46% clinical or subclinical cardiomyopathy in the 75 evaluated patients. The high rate of cardiomyopathy led to a third trial examining the same cyclophosphamide, doxorubicin, and methotrexate combination versus a regimen without methotrexate and a doxorubicin ceiling cumulative dose of 350 mg/m². No difference in 5-year overall survival was observed (69% for low dose, 75% for high dose), nor was there a difference in 5-year disease-free survival. There was no clinical congestive heart failure documented in the low-dose arm, and the decrease in cardiac ejection fraction by nuclear medicine study was less pronounced than with the high-dose arm.

The NCI has also examined adjuvant chemotherapy for other sites in two other trials, using the same cyclophosphamide, doxorubicin, and methotrexate combination regimen. In one study, some of the 37 patients with retroperitoneal sarcoma (15 of whom were prospectively randomized) were given adjuvant chemotherapy. Patients given chemotherapy had a trend to poorer overall survival compared with the control group (P = .06). Analysis of this study is difficult because of the small number of patients and lack of prospective randomization for all patients. A separate NCI study using the same chemotherapy regimen examined 31 patients with soft tissue sarcoma of the head and neck, breast, and trunk. All patients had resection and postoperative radiation, then were randomized to receive chemotherapy or no further therapy. Six patients received C. parvum adjuvant immunotherapy. A trend toward improved disease-free survival was seen in the chemotherapy patients, but there was no statistically significant difference in overall survival.

The M. D. Anderson Cancer Center started one of the earliest adjuvant trials for soft tissue sarcoma. Because of their high local relapse rate, patients with head and neck or abdominal sarcomas all received surgery, radiation, and chemotherapy in this study. Forty-three eligible patients with trunk and extremity sarcomas were treated with local therapy (surgery and radiation) with or without chemotherapy. The chemotherapy regimen consisted of vincristine, oral cyclophosphamide, and doxorubicin every 4 weeks. After seven cycles of doxorubicin-based therapy, actinomycin D was substituted for doxorubicin in a maintenance phase to complete 2 years of chemotherapy. The initial results demonstrated poorer disease-free survival in the chemotherapy arm (76% vs. 83% for the control arm, P value not significant) and double the rate of metastasis in the chemotherapy arm (but P > .3), and the study was stopped. However, the original study stratified patients by histology, not by tumor grade. In a reanalysis of this data of the patients with truncal or extremity sarcomas, disease-free survival was improved in the chemotherapy arm (55% vs. 35% at 10 years, P = .05), although there was no difference in overall survival in the two groups.

Another early study of combination chemotherapy was reported by the Mayo Clinic. Sixty-one patients with sarcomas of the trunk or extremities were treated with surgery alone for local control, then randomized to no further therapy or to chemotherapy. The chemotherapy regimen alternated between cycles of vincristine, actinomycin D, and cyclophosphamide and cycles of vincristine, doxorubicin, and dacarbazine, given at 6-week intervals for eight courses. Thirteen patients (randomly selected from either arm) were given bacille Calmette-Guérin methanol extraction residue adjuvant nonspecific immunotherapy, but this was discontinued owing to ulceration at the injection site. There was no benefit in overall survival in the chemotherapy arm, and there was a high local recurrence rate, likely due to the omission of radiation in the local control phase of therapy. The chemotherapy regimen used in this study had low dose intensity by today’s standards.

The largest single study of adjuvant chemotherapy in soft tissue sarcoma was performed by the EORTC. Four hundred sixty-eight patients (excluding only very low grade sarcomas) were treated with surgery for their primary sarcoma, and with adjuvant radiation used for margins less than 1 cm. Patients were randomized to receive or not receive combination chemotherapy with cyclophosphamide, vincristine, doxorubicin, and dacarbazine (CyVADIC, Table 39.1-10), given every 28 days for eight cycles. Disease-free survival and local control were both better in the chemotherapy arm, but overall survival was not significantly different between the two arms. Improvement in local recurrence rates was limited to patients with head, neck, and trunk sarcomas and was not observed for patients with extremity sarcomas. Some criticism has been raised as to the long accrual time of the study (11 years), inability of nearly half of patients to complete all eight cycles of chemotherapy, and the relatively large number of patients ineligible for analysis, which most commonly was due to inappropriate radiation therapy.

Initial data indicated that disease-free survival and overall survival were improved in the chemotherapy arm. With longer follow-up, this difference in disease-free survival remained (P = .002). In a reanalysis of the data from the EORTC study, patients were treated with chemotherapy sooner after surgery, and on 21-day cycles, as opposed to 28-day cycles in the EORTC study, that patients were treated with local therapy with surgery and radiation, 59 eligible patients with AJCC stage III to IVA tumors were randomized to receive no chemotherapy or CyVADIC chemotherapy, in doses similar to the EORTC study. In comparison with the EORTC trial, patients were treated with chemotherapy sooner after surgery, and on 21-day cycles, as opposed to 28-day cycles in the EORTC study. More patients with extremity sarcomas were in the chemotherapy group, and the histology of the treated groups was different (e.g., more MFH and no undifferentiated sarcoma in the chemotherapy arm). In contrast to the EORTC trial, local control, distant metastases-free survival (P = .003), and overall survival (P = .002) were better in the chemotherapy arm than the control arm. However, in comparison with the EORTC study, the chemotherapy arm fared better (5-year survival 85% vs. 68% for the EORTC study), and the control group performed more poorly (5-year survival under 37%, compared with 63% in the EORTC trial).

TABLE 39.1-10. Combination Chemotherapy for Sarcoma: A Comparison of Formulations

A smaller study from the Fondation Bergonié also examined the CyVADIC regimen as adjuvant therapy. Following local therapy with surgery and radiation, 59 eligible patients with AJCC stage III to IVA tumors were randomized to receive no chemistry or CyVADIC chemotherapy, in doses similar to the EORTC study. In comparison with the EORTC trial, patients were treated with chemotherapy sooner after surgery, and on 21-day cycles, as opposed to 28-day cycles in the EORTC study. More patients with extremity sarcomas were in the chemotherapy group, and the histology of the treated groups was different (e.g., more MFH and no undifferentiated sarcoma in the chemotherapy arm). In contrast to the EORTC trial, local control, distant metastases-free survival (P = .003), and overall survival (P = .002) were better in the chemotherapy arm than the control arm. However, in comparison with the EORTC study, the chemotherapy arm fared better (5-year survival 85% vs. 68% for the EORTC study), and the control group performed more poorly (5-year survival under 37%, compared with 63% in the EORTC trial).

The Italian Sarcoma Study Group reported in abstract form the only trial to date to examine an anthracycline plus ifosfamide as adjuvant therapy for extremity sarcoma. After surgery with or without local radiation, 104 patients were randomized to receive no chemotherapy or to receive ifosfamide (1.8 g/m² on 5 consecutive days) with epirubicin (60 mg/m² on 2 consecutive days), with filgrastim support. Interim analysis in 1996 led to early conclusion of the trial. At a median follow-up of 36 months, disease-free survival in the chemotherapy arm was 72% compared with 55% for the control arm (P = .002). This investigation is promising for its use of the two most active agents against sarcoma in an appropriate cohort of patients. Review of the final data will be necessary to assess patient selection and follow-up before conclusions can be drawn concerning this data.

CONCLUSIONS FROM INDIVIDUAL ADJUVANT CHEMOTHERAPY STUDIES
Clearly, the small size of these trials makes interpretation on an individual basis difficult, since such studies have no statistical power to detect small (e.g., 10% to 20%) changes in overall survival. In many of the studies, a significant proportion of patients was ineligible for analysis, raising the question of selection bias. A second example of selection bias arises from the fact that patients who are enrolled on clinical trials are healthier overall than nonrandomized patients, and survive longer, as demonstrated in the Mayo study. Historic controls are inadequate for comparison as there continue to be advances in diagnosis, specific therapy, and supportive care that could affect outcome.

Beyond general problems with randomized studies, staging and dose intensity also affect our ability to draw conclusions about individual studies. A number of patients with high-grade sarcomas or small tumors are included in the trials described previously. Patients with high-grade sarcomas do well as long as the primary disease is small (less than 5 cm). The improved overall survival with smaller high-grade tumors has been incorporated into the most recent staging system for sarcoma. Future studies must focus on patients with large tumors at high risk of relapse. Furthermore, dose intensity of doxorubicin is low to moderate in many studies of adjuvant chemotherapy to date, and largely do not have growth factors such as fstatism available. It is reasonably clear that doxorubicin and ifosfamide show dose-dependent responses, and with better supportive care more intensive therapy may lead to improved survival. It is hoped that the first studies evaluating the use of adjuvant chemotherapy using an anthracycline combined with ifosfamide with growth factors will go further direction to future studies in the adjuvant therapy of sarcomas.

METAANALYSES OF RANDOMIZED TRIALS OF ADJUVANT CHEMOTHERAPY FOR SARCOMA

Given the lack of statistical power of the existing randomized trials, it was hoped that combining the data from individual studies of adjuvant chemotherapy for sarcoma would reveal improvement in overall survival that could not be detected in smaller studies. For example, to detect a 10% difference between control group and treatment group with a power of 0.90 would require approximately 1000 patients to be enrolled in a randomized study.

Antman and colleagues pooled the data from three randomized studies (ECOG, Dana-Farber Cancer Institute/Massachusetts General Hospital, and the Intergroup studies). The 168 eligible patients examined in this study made up a smaller group than the EORTC adjuvant trial, but were followed for up to 11 years in some cases. Patients with extremely lesions fared better than those with other sites of disease (P = .02), but there was no difference in overall survival in those receiving chemotherapy versus control patients.

Zalupski et al. examined overall and disease-free survival in patients with extremity sarcoma obtained from ten of the adjuvant studies mentioned previously. Data was stratified for the text and combined data included disease-free survival (71% to 81%, P = .0005) and 15% improvement in disease-free survival (53% vs. 68%, P = .0001). Criticism of this metaanalysis includes the fact that potentially inappropriate patients were included (e.g., the Rizzoli and UCLA studies who received preoperative chemotherapy). In addition, some of the data were relatively immature as well, such as the EORTC and Bergonie studies.

Tierney and colleagues assessed 15 published studies 2 years later and converted the survival data into the odds of recurrence based on the latest available publication from each trial. Standardization was performed to account for different lengths of follow-up. In all, 1546 patients were included in the study, which showed improved survival at 2 years and at 5 years in the 13 and 11 studies eligible for analysis at each time point, respectively. In contrast to the previous metaanalysis from Zalupski et al., the Rizzoli data were included in this study, but not the data from UCLA.

The most rigorous metaanalysis was published in 1997. In this study, 23 potential studies were considered, and 14 ultimately included: only 31 potential patients were omitted due to unavailability of data, giving a cohort of 1658 patients to examine. Aprcausal had to be complete by the end of 1992, which excluded one trial. Histology for each patient was recorded, but pathology review was not centralized. Median follow-up was 9.4 years. Analyses were stratified by trial, and hazard ratios were calculated for each trial and combined, allowing for an assessment of the risk of death or recurrence in comparison with control patients. Disease-free survival at 10 years was found to be improved from 45% to 55% and was statistically significant (P = .001). Local disease-free survival at 10 years also favored the chemotherapy group (from 75% to 85%, P = .0005). However, the most significant improvement was seen at 10 years (60% vs. 75%, P = .12). The largest difference in overall survival was found in subgroup analysis of the 866 patients with extremity sarcomas, in which absolute overall survival was shown to increase 7% in the group receiving chemotherapy (P = .029).

CONCLUSIONS: ADJUVANT CHEMOTHERAPY FOR SOFT TISSUE SARCOMAS

The data from the metaanalyses described previously must be examined with caution. Although the most recent metaanalysis is a useful tool, it still combines studies with different designs, diverse criteria for enrollment, variations in pathologic assessment such as grading, different chemotherapeutic regimens, and different end points. In particular, only one-fourth of the specimens from the 1997 metaanalysis underwent review of tumor grade; approximately 60% were reviewed for histologic subtype. Of 15 published adjuvant studies, only two, the Rizzoli and Bergonie studies, show improved overall survival in the chemotherapy arm. Only one small study included in the 1997 metaanalysis used ifosfamide, another active agent in sarcoma.

If there is a benefit for the adjuvant use of chemotherapy, it appears modest, based on the previously mentioned data. Given no statistically significant benefit in a population of patients typically healthier than patients not enrolled on protocols, the data do not support the routine use of adjuvant chemotherapy for soft tissue sarcoma outside of the setting of a clinical trial. However, moderate to large extremity lesions represent one situation in which adjuvant chemotherapy may be considered in the adjuvant arm of randomized clinical trials. The subset analysis of the 1997 metaanalysis indicates this is one situation in which adjuvant chemotherapy can be considered. However, subset analyses are used to generate hypotheses and do not necessarily give definitive results. Publication of the more recent Italian study of epirubicin and ifosfamide as adjuvant therapy for extremity sarcomas may clarify this situation further. With clear definition of a population at high risk for metastatic disease, identification of relatively sensitive histologic subtypes of sarcoma, and use of combinations of active agents, it is hoped that future studies will delineate which clinical situations merit use of adjuvant chemotherapy.

PREOPERATIVE CHEMOTHERAPY

Preoperative chemotherapy has been successful in the management of predominantly pediatric sarcomas such as Ewing's sarcoma and osteosarcoma. With this success, the concept was extended to use in adult soft tissue sarcomas. Preoperative neoadjuvant chemotherapy can make subsequent surgery easier and potentially treat micrometastatic disease earlier before acquisition of resistance. Treating with chemotherapy before surgery also leaves primary vascular intact for drug delivery. In addition, preoperative chemotherapy can guide postoperative treatment based on pathologic review of the tissue after chemotherapy. In experimental models, preoperative chemotherapy eliminates a postoperative surge in growth of metastases noted after resection of primary tumors. There is relatively little evidence concerning the use of neoadjuvant chemotherapy in the treatment of soft tissue sarcomas. Rouesse et al. retrospectively examined a group of 34 patients with locally advanced sarcomas for whom only amputation or mutilating surgery was feasible. However, subset analyses are noted in over one-third of patients; not surprisingly, those patients who had a complete response by any means had a better overall survival than those who did not respond completely. Local recurrence was common in the responding group, as well.

A retrospective trial of 46 patients from M. D. Anderson Cancer Center examined preoperative chemotherapy using cyclophosphamide, doxorubicin, and dacarbazine. Sixty percent of patients demonstrated complete, partial, or minor responses to chemotherapy and had better rates of survival than the patients who did not have an objective clinical response to chemotherapy.

A prospective trial was performed at MSKCC in which 29 patients with large, high-grade, primary or recurrent metastases were given two cycles of combination chemotherapy before definitive therapy with surgery and radiation. Clinical and radiologic studies were performed before chemotherapy, and the specimen was assessed for response after surgical resection. Only 1 of 29 patients demonstrated a clinical partial response, although liquefaction, cystic necrosis, and hemorrhage into the tumor were noted regularly in the resected specimen, with three tumors showing greater than 90% necrosis. Most patients did not elect to receive postoperative chemotherapy after surgery, and survival results from this study did not differ significantly from studies of adjuvant doxorubicin or of no chemotherapy.

Assessing the response to preoperative chemotherapy in primary soft tissue sarcomas is difficult. Some softening or liquefaction can be noted clinically without significant change in tumor size, but in the trial from MSKCC neither CT nor MRI provided information that predicted long-term outcome. It appears that there are
significantly fewer cases of complete response compared with preoperative adjuvant chemotherapy for sarcoma of bone (osteosarcoma or Ewing’s sarcoma), and it is difficult to objectively evaluate responses grossly or microscopically after chemotherapy. Other imaging modalities may demonstrate changes consistent with chemotherapy effect (MRI spectroscopy, PET, gallium scan, thallium scan), but these modalities remain investigational.

In sum, preoperative chemotherapy is given to some patients with potentially sensitive sarcoma subtypes such as synovial sarcoma or other high-grade lesions. It is clear from the present AJCC staging system that larger, deep, high-grade lesions have a high risk of metastasis. Thus, it is conceivable that local control could improve with adjuvant chemotherapy, without significantly changing overall survival. Nonetheless, preoperative chemotherapy may be considered during an attempt to maintain function of an extremity, with the possibility that more aggressive surgery could be performed later if needed. Selected patients have had responses that allow for a more conservative resection, avoid an amputation, or both.

INTRAARTERIAL CHEMOTHERAPY

There have been many studies examining the role of intraarterial chemotherapy, with doxorubicin, cisplatinum, or both; in some situations other drugs have been used as well. This infusional approach is to be differentiated from local limb perfusion, discussed later in this section. Hyperthermia and Limb Perfusion. Intraarterial chemotherapy has the potential benefit of providing higher doses of chemotherapy to the limb in a first-pass effect. However, pharmacokinetic data have not shown an advantage over intravenous chemotherapy.

Intraarterial chemotherapy has been used in conjunction with radiation as well. Mention has already been made of the UCLA adjuvant study in which patients received 3 days of intraarterial doxorubicin before administration of 35 Gy of external-beam radiation over 10 days, or 17.5 Gy administered over 5 days. Patients were then randomized to receive postoperative doxorubicin intravenously or no further chemotherapy. No difference in survival or local control was noted in this study. Therefore, a randomized trial by the same group examined preoperative intravenous intraarterial chemotherapy before radiation (28 Gy given over 8 days) followed by wide excision. There was no difference in local recurrence or survival between the 45 patients receiving intraarterial doxorubicin and the 54 patients receiving intravenous doxorubicin.

A number of studies have examined intraarterial chemotherapy before radiation and surgery. Doxorubicin alone, or in combination with other drugs such as cisplatin, single agent intraarterial cisplatin, or intraarterial doxorubicin in combination with intravenous doxorubicin or other agents. Doxorubicin with simultaneous radiation has also been examined. In these studies, some patients have been able to avoid amputation. Infusional chemotherapy has its attendant complications as well, including arterial thromboembolism, infection, gangrene, and problems with wound healing, itself requiring amputation. Pathologic fractures have been reported in patients receiving chemotherapy and relatively large doses of radiation. One study reported ten major complications in 13 patients treated intraarterial chemotherapy with simultaneous radiation, emphasizing the investigational nature of this approach. Although there are situations in which such therapy should be considered, intraarterial chemotherapy at present has a limited role in the treatment of extremity sarcomas.

HYPERTHERMIA AND LIMB PERFUSION

In contrast to systemic intraarterial chemotherapy infusion, perfusion of limbs requires isolation of the arterial and venous system of the limb by means of a tourniquet and obtaining access to arteries and veins supplying the limb. The arterial and venous supply of the limb is connected to an extracorporeal circulation system to isolate the limb from the rest of the body. Recirculation of the blood from the limb is performed by a heart-lung machine to oxygenate the blood. Care is taken after isolation of the limb to ensure no leakage of the circuit into the systemic circulation; technetium-labeled albumin is injected into the circuit and a probe is used over the heart to ensure isolation of the bypass circuit. Since mild hyperthermia may make chemotherapy more effective in some clinical settings (as mentioned in this section), the blood of the circuit is often warmed to 39° to 40°C.

A number of chemotherapeutic agents have been used for limb perfusion, such as melphalan, nitrogen mustard, actinomycin D, and doxorubicin. The most effective agents to date have been melphalan when given with tumor necrosis factor (TNF). The greatest experience with this technique comes from Eggermont et al. Two hundred forty-six patients with primary or recurrent sarcomas that would otherwise require amputation or marked loss of function were treated with one and occasionally two isolated limb perfusion sessions. After isolation of the extremity, melphalan (10 to 13 mg/L limb volume) was perfused into the limb with a dose of TNF an hour after starting the procedure. Melphalan was administered for 4 hours under mild hyperthermic conditions. In early studies interferon-a was included in the regimen, but was later dropped, as it did not appear to improve results over melphalan and TNF alone. Both components of the regimen appeared important; the omission of TNF led to a decrease in tissue dose of melphalan, probably from its effects on the tumor vasculature. Surgery to remove residual tumor was performed 2 to 4 months after limb perfusion. With a median follow-up of 3 years, 71% of patients had successful limb salvage.

It is difficult to compare this approach with standard chemotherapy, given the heterogeneity of patients between the two types of studies. In aggregate, the response rate does appear higher in the perfusion studies than in the infusion studies. However, isolated limb perfusion requires substantial expertise and specialized dedicated equipment. Complications of this technique include shock (from systemic leak of TNF); infection; chronic damage to skin, muscles, and nerve; persistent edema; and arterial or venous thrombosis. Experience has led to a decrease in the incidence and severity of complications. Isolated limb perfusion does appear to hold promise for at least a subset of patients who would otherwise require amputation for local control and has been approved for such patients in Europe. Studies are underway to examine the utility of regional limb infusion, which would not require bypass machines, as a simplified means of treating otherwise unresectable extremity sarcomas.

Hyperthermia has been used in other ways to enhance the effects of chemotherapy in patients with locally advanced disease. Whole body hyperthermia using extracorporeal heating of blood has been combined with ifosfamide and carboplatin intravenous chemotherapy, and responses have been seen in patients with otherwise refractory small cell sarcomas. Regional hyperthermia provided through an external magnetic field (phased array) has been examined in combination with ifosfamide and etoposide. Similarly, hyperthermia achieved with an external electromagnetic field has been combined with ifosfamide, etoposide, and doxorubicin. In both studies, partial and complete responses in patients with locally advanced sarcoma have been observed. The hyperthermia used in these protocols is more aggressive than that used with limb perfusion; higher temperatures have led to a higher rate of local complications. Isolated limb perfusion has not been compared directly with simultaneous hyperthermia and chemotherapy. In sum, isolated limb perfusion and hyperthermia-enhanced chemotherapy represent novel ways of attempting to preserve function of limbs in what otherwise would be situations in which amputation would be necessary. In the United States, such procedures remain investigational at present.

SPECIAL FEATURES OF THE MANAGEMENT OF SARCOMAS OF NONEXTREMITY SITES

MANAGEMENT OF VISCERAL/RETROPERITONEAL SARCOMA

Clinical Presentation

Most patients present with an asymptomatic abdominal mass (Fig. 39.1-22). On occasion pain is present and, less commonly, gastrointestinal bleeding, incomplete obstruction, or neurologic symptoms relating to retroperitoneal invasion or pressure on neurovascular structures are present. Weight loss is uncommon and incidental diagnosis is often the norm. In one report, neurologic symptoms related primarily to an expanding retroperitoneal mass were identified in 27% of patients.

Fig. 39.1-22
On physical examination, a large abdominal mass is often present. Important issues of differential diagnosis, particularly in the young, are the presence of a germ cell tumor or a primary retroperitoneal tumor arising from the adrenal. Most of such lesions, however, are tumors of mesenchymal origin, either benign or malignant.

### USE OF IMAGING STUDIES

In the main, CT remains the primary modality for evaluation of retroperitoneal and visceral sarcomas. Because the most likely site of visceral metastasis is the liver, a CT scan of the abdomen and pelvis usually encompasses description not only of the primary lesion, but also of the most likely source of metastasis. For retroperitoneal lesions, the incidence of metastatic disease to the liver is possible but still low.

Of the histopathologic types, leiomyosarcoma and liposarcoma predominate (see **Fig. 39.1-4**), whereas other types seen in the extremity, such as MFH, are very uncommon. Most retroperitoneal tumors are high-grade lesions because of the predominance of leiomyosarcoma in the visceral lesions. The retroperitoneal liposarcoma is often predominantly low grade and overall the more common tumor. Nevertheless, with increasing frequency we note the mixed cellularity and grade of some retroperitoneal sarcomas.

Primary surgical resection is the dominant therapeutic modality. Preoperative bowel preparation is important, not because of tumor invasion, but often because of the frequent difficulty of resection without en bloc resection of the retroperitoneum, evaluation of renal function, particularly the establishment of contralateral adequate renal function, is important, to allow nephrectomy where appropriate.

Although resection of adjacent organs is common, proof that a more extensive resection of adjacent organs has an effect on long-term survival seems limited. It is clear that complete surgical resection is the primary factor in outcome (**Fig. 39.1-23**). Once complete resection is accounted for, the predominant factor in outcome is the grade of the lesion.
of neuropathy than the experience of the NCI, and this dose of external-beam irradiation should result in lower risk of radiation enteritis. Alekliar et al. reported on 32 patients treated with such an approach. 274 With a median follow-up of 33 months, the 5-year actuarial local control and overall survival rates were 62% and 45%, receptively. The rate of peripheral neuropathy was 6% and the rate of gastrointestinal toxicity was 19%.

MANAGEMENT OF HEAD AND NECK SARCOMA

Soft tissue sarcomas of the head and neck in adults are rare. They represent approximately 1% of all head and neck malignancies and 10% of all soft tissue sarcomas. Most of these tumors present as a painless subcutaneous or submucosal mass. Any histologic type of soft tissue sarcoma could originate in the head and neck area, but there is preponderance of angiosarcoma in this site. Multimodality approach is the cornerstone for most soft tissue sarcomas of the head and neck. Surgery is the main treatment for these tumors, and every attempt should be made to obtain at least gross total resection, otherwise the results are usually poor. However, unlike extremity sarcomas, head and neck sarcomas are not amenable to wide local excision with generous margin of normal tissue due to anatomic constraints. Therefore, the use of adjuvant radiation is more liberal in this site because local recurrence could be the cause of death in a substantial proportion of patients.

Eeles et al. reported on 103 patients with soft tissue sarcoma of the head and neck area treated by surgery with or without radiation. The 5-year survival rate was 50% and the local control rate was 47%. The only independent prognostic factor for survival was surgery other than biopsy ($P = .003$). For local control the combined use of surgery and radiation as opposed to single modality was also an independent prognostic factor ($P = .002$). In addition, local tumor was the cause of death in 63% of cases. 275 Willers et al. reported on 46 patients with soft tissue sarcoma excluding angiosarcoma who were treated by radiation with or without surgery. The 5-year survival and local control rates were 74% and 69%, respectively. On multivariate analysis survival correlated with low grade, recurrent presentation, and lack of direct extension ($P = .001, .01, .03$, respectively). For local control the only independent prognostic factor was the T stage ($F = .55$). There was also a 15-fold increased risk of dying for patients whose tumor had recurred locoregionally, compared with controlled sarcomas ($P = .004$). 276

Le et al. reported on 65 patients treated by surgery with or without radiation and found the 5-year survival and local control rates to be 56% and 66%, respectively. On multivariate analysis the independent predictors of improved survival were age less than 55 ($P = .009$), low grade ($P = .0002$), extent of resection ($P = .008$), and negative margin ($P = .0009$). For local control smaller tumor size ($P = .004$) and grade 1 to 2 ($P = .01$) were independent predictors. 277

Angiosarcoma of the head and neck deserve special consideration due to their poor prognosis compared with other sarcomas in that region. 278,279 Some of the difficulties in managing this disease have to do with its notorious propensity to infiltrate throughout the dermis beyond what is clinically apparent, making wide local excision with negative margins difficult to achieve. In addition, they display a higher incidence of regional lymph node metastasis than other sarcomas with a reported rate of 10% to 15%. 278

Morrison et al. reported on 14 patients with angiosarcoma of the head and neck treated by radiation with or without surgery. The 5-year overall and distant metastasis-free survival rates were 29% and 37%, respectively. The 5-year above clavicle local control rates were 24% for definitive radiation compared with 40% with adjuvant radiation ($P = .03$). 279 Similar findings were reported by Willers et al. on 11 patients with 5-year overall, distant metastasis-free, and local recurrence-free survival rates of 31%, 42%, and 24%, respectively. 277

MANAGEMENT OF BREAST SARCOMA

Primary soft tissue sarcomas of the breast are rare, representing approximately 1% of all breast malignancies. They usually present as a painless mass with no distinctive findings on mammography. The main treatment is surgery and the extent of resection is debatable, but most authors believe that wide excision with generous negative margin is adequate. 280 North et al. reported on 25 patients treated by surgery with or without radiation. The 5-year overall survival rate was 61%, which did not vary significantly between those treated with wide excision compared with those who underwent mastectomy ($P = .9$). Five patients received adjuvant radiation and none of them developed local recurrence. 281

Gutman et al. showed similar findings in 60 cases of breast sarcoma treated by surgery with or without radiation. 282 Johnstone et al. reported on 10 patients treated with mastectomy and adjuvant radiation. The 5-year survival rate was 66% with no local or regional failures. 283

SERIOUS COMPLICATIONS OF PRIMARY TREATMENT

WOUND COMPLICATIONS

It is well established that radiation and chemotherapy inhibit wound healing. Early studies defined the effects of doxorubicin and x-ray treatment on wound healing in animal models. 284 The authors demonstrated that the timing and the combination of multiple antineoplastic agents were critical to inhibiting wound healing. They suggested that radiation or antineoplastic drugs delivered more than 7 days on either side of the wound were accompanied by minimal inhibition of wound healing. Conversely, the application of radiation or chemotherapy just before, or in close juxtaposition to, the time of wounding, resulted in significant impairment of wound healing. With a median follow-up of 33 months, the 5-year actuarial local control and overall survival rates were 62% and 45%, respectively. 274

More recently, wound complications (wound infection or the need for further operative intervention) were analyzed in the randomized BRT trial at MSKCC. 285 The overall rate was 24% in the BRT arm compared with 14% in the control arm ($P = .13$). However, the rate of reoperation was higher in the BRT group, 10% versus 0% ($P = .006$). The other covariable that contributed to wound reoperation was the width of the excised skin. If the width was greater than 4 cm the rate was 10%, but if the width was less than or equal to 4 cm the rate was 1% ($P = .02$). These types of complications are not unique to BRT but have been shown with external-beam irradiation as well. 286,287,288 In a randomized trial from Princess Margaret Hospital comparing preoperative and postoperative irradiation, wound complication was a primary end point of study. Wound complications were defined as secondary wound surgery, hospital admission for wound care, and deep packing or prolonged dressings within 120 days following tumor resection. The investigators found that preoperative radiation had a significantly higher rate of wound complications (35% vs. 17%; $P = .01$). 289

In situations in which wound complications may be anticipated because of the magnitude of the wound, extent of the resection, prior radiation, and so forth, serious consideration should be given to bringing fresh vascularized tissue in the form of either transpositional or free grafts into the area to cover the defect before the placement or delivery of radiation therapy. With this approach, postoperative morbidity can be markedly diminished.

OTHER COMPLICATIONS

The effect of adjuvant radiation and chemotherapy on the development of bony fracture has been reported in the literature but the data are scant. Stinson et al. reported on 145 patients with soft tissue sarcoma who underwent limb-sparing surgery and postoperative radiation with or without chemotherapy and found a 6% fracture rate. 290 For patients treated with adjuvant BRT in the MSKCC randomized trial, the rate of fracture was 4% compared with 0% in the control arm. This difference, however, was not statistically significant ($P = .2$). 274 Grant et al. reported a 7.8% rate of pathologic fracture in patients treated with preoperative radiation. 269

Lin et al. evaluated 205 patients with soft tissue sarcoma of the thigh to determine the contributing factors to pathologic fracture of the femur in patients treated with adjuvant radiation. The 5-year actuarial risk was 8.5%, which on univariate analysis correlated with periosteal stripping ($P = .0001$), location in the anterior compartment ($P = .008$), female sex ($P = .01$), the use of chemotherapy ($P = .02$), age greater than or equal to 50 ($P = .03$), and the use of external-beam radiation instead of BRT ($P = .04$). On multivariate analysis only periosteal stripping retained significance ($P = .01$). 274

Le et al. reported a 7.6% rate of pathologic fracture in patients treated with preoperative irradiation. 275 The other covariable that contributed to pathologic fracture was positive resection margin ($P = .02$). There was a 17% rate of at least one complication ($P = .006$). The other covariables that contributed to wound reoperation were the width of the excised skin ($P = .01$), and the use of chemotherapy ($P = .01$). Yet another factor that contributed to fracture was the width of the excised skin ($P = .01$). The authors emphasized the importance of the agents used and the timing of delivery.

In our studies of adjuvant BRT and WRT complications, we also demonstrated that when particular attention is paid to the timing of delivery of radiation via afterloading catheters to beyond the fifth postoperative day, the major wound complication rate approaches that with surgery alone. 274,285

With a median follow-up of 33 months, the 5-year actuarial local control and overall survival rates were 62% and 45%, receptively. The rate of peripheral neuropathy was 6% and the rate of gastrointestinal toxicity was 19%.
The other type of complication encountered with adjuvant radiation is peripheral nerve damage. In the control arm of the MSKCC randomized trial the rate was 7% compared with 9% in the BRT arm \( (P = .8) \). LePechoux et al. reported a rate of 1.6% of peripheral nerve damage in 62 patients treated with postoperative radiation. Brant et al. reported a 3.4% rate for patients treated with preoperative radiation.

**PROGNOSTIC FACTORS FOR OUTCOME**

As more sophisticated approaches to the analysis of outcome become more widely employed, it becomes clear that the variables being investigated provide different information. Prognostic factors for local recurrence, metastasis, disease-specific survival, and overall survival may all be fine gradations of differing factors, all of which provide considerably different information.

An analysis of long-term follow-up for over 1000 patients with localized soft tissue sarcoma of the extremity has been provided from our group. From prospective data collected from 1041 patients over the age of 16, we have determined the clinical pathologic factors that influence local recurrence, distant recurrence, and disease-specific and overall survival. The 5-year survival rate was 76%, with a median follow-up of 4 years. Factors that increased the risk of local recurrence were age greater than 50 years, recurrent disease at the time of presentation, positive histologic primary margins, histologic subtypes of fibrosarcoma (including desmoid), and malignant peripheral nerve tumors (Table 39.1-11).

### TABLE 39.1-11. Relative Risk Influence on Recurrence of Localized Extremity Soft Tissue Sarcoma *

<table>
<thead>
<tr>
<th>Factor</th>
<th>Relative Risk Influence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.1 (1.05 - 1.15)</td>
</tr>
<tr>
<td>Recurrence-positive patients</td>
<td>1.7 (1.1 - 2.6)</td>
</tr>
<tr>
<td>Malignant peripheral nerve damage</td>
<td>1.5 (1.0 - 2.4)</td>
</tr>
<tr>
<td>Sarcoma (all grades)</td>
<td>1.7 (1.0 - 2.9)</td>
</tr>
<tr>
<td>High-grade sarcoma</td>
<td>1.4 (1.0 - 1.9)</td>
</tr>
<tr>
<td>Leiomyosarcoma</td>
<td>1.4 (1.0 - 1.9)</td>
</tr>
</tbody>
</table>

Factors that increased distant recurrence rates were tumor size greater than 5 cm, high histologic grade, deep location, recurrent disease at the time of presentation, and histologic subtype leiomyosarcoma. Histology of liposarcoma was favorable for decreased distant recurrence rate when compared with other histologies.

For disease-specific mortality, large tumor size, high histologic grade, deep location, recurrent disease at presentation, positive histologic margins at the time of resection of the primary, lower extremity site, and the histologic types of leiomyosarcoma and malignant peripheral nerve tumor were all factors.

Postmetastasis survival for most patients is independent of factors involved in the primary presentation, although large tumor size has been associated. The determination of recurrence rates and survival rates can depend on which factor is examined. For example, high-grade lesions have a much greater cumulative hazard rate of developing a distant metastasis in the first 30 months. Low-grade lesions, however, have a continued slow but inexorable progression to a continuing long-term rate of metastasis. This raises the interesting biologic question of whether lack of recognition of the metastatic potential of low-grade sarcomas is caused by inherent sampling error in low-grade lesions, where small foci of potentially metastatic cells are not appreciated. Alternatively, all soft tissue sarcomas may be inherently imbued with metastatic potential. One thing is clear: 5-year survival does not guarantee cure. An analysis of patients who were disease-free 5 years after the diagnosis and treatment of extremity lesions showed 9% would go on to have a further recurrence in the next 5 years (Fig. 39.1-24).

**QUALITY OF LIFE AND FUNCTIONAL OUTCOME**

Quality of life assessment has gained so much importance in recent years that many randomized trials in the field of oncology are evaluating that issue either as the primary end point or secondary to outcome. This issue is obviously of great significance in patients with soft tissue sarcoma of the extremity who are being treated with conservative surgery and adjuvant therapy in order to preserve function and potentially improve the overall quality of life.

However, in order to determine the effect of adjuvant therapy it is important to look at other potential contributing factors as well. One such factor is the extent of surgical resection. Sugarbaker et al. found no evidence of improved quality of life in patients treated with conservative surgery and adjuvant radiation compared with amputation, but more recently Davis et al. showed a significantly higher levels of handicap in amputated patients compared with those treated with conservative surgery. In patients treated with conservative surgery, the effect of the extent of surgery on functional outcome is not clearly defined. Robinson et al. reported on 54 patients who were disease-free 2 or more years after limb-conserving treatment for soft tissue sarcoma of the leg or pelvic girdle. The extent of surgery was not an independent prognostic factor for limb function, although univariate analysis suggested an association with range of movement \( (P < .025) \). On the other hand, Bell et al. showed that neural sacrifice performed at the time of wide local excision was associated with poorer outcome on univariate \( (P = .002) \) and multivariate analysis \( (P = .019) \). Conventional chemotherapy has not been shown to affect the functional outcome of patients with extremity sarcomas.

The effect of adjuvant radiation and some of its parameters on functional outcome have been studied more extensively. Yang et al. reported that adjuvant postoperative external-beam radiation compared with surgery alone resulted in significantly worse limb strength and edema and range of motion, but these deficits were often transient and had few measurable effects on activities of daily life or global quality of life. Schapuk et al. reported on a group of patients who underwent rigorous psychofunctional testing and were part of the BRT randomized trial at MSKCC. There were no significant differences in the functional outcome between the BRT group and the no BRT group. The psychofunctional scores, however, revealed a higher level of anxiety, depression, and appreciation of illness in patients who received adjuvant BRT. Karasek et al. evaluated 41 patients who were treated with surgery and radiation and showed that 83% of them had good or excellent functional outcome. But there was a correlation between volume irradiated to greater than or equal to 55 Gy and poorer functional score, strength, fibrosis, and skin changes. Robinson et al. also found that doses in excess of 60 Gy resulted in increased fibrosis and a worse functional outcome.
TREATMENT OF LOCAL RECURRENT

The treatment of locally recurrent soft tissue sarcoma in almost any site that is amenable to low morbidity surgical resection is reresection. Local recurrence, however, remains a significant factor in long-term morbidity and mortality. In cases in which surgical resection can be achieved, then adjuvant radiation therapy should be considered in the vast majority of patients with recurrent disease. In patients undergoing systemic recurrence, again surgical resection should be considered.

Analyses of patients undergoing local resection of intraabdominal lesions have been extensively reviewed. It is clear that when complete gross resection can be achieved, operation for local recurrence should be attempted along with investigational approaches such as IORT (see Technical Issues, earlier in this chapter). Intrapерitoneal chemotherapy following debulking of peritoneal metastases has been advocated, but remains an investigational approach.

MANAGEMENT OF ADVANCED DISEASE

Control of the primary site can be achieved in the vast majority of patients with soft tissue sarcoma, but ultimately close to one-half of patients succumb to metastatic or locally advanced disease. Unfortunately, the most active chemotherapeutic options are of limited value and are associated with serious and potentially life-threatening toxicity. Median survival from the time metastases are recognized is 8 to 12 months, although 20% to 25% of patients with metastatic sarcoma are alive 2 years after diagnosis. Patients with metastatic sarcoma often feel well at the time that a radiograph or CT reveals metastases and may remain free of symptoms for months, or even years. Thus, alleviation of symptoms is not an immediate concern in many patients, although progressive sarcoma is inevitable.

Surgical resection can provide selected patients with prolonged periods of freedom from disease, and radiation therapy provides palliation for individual patients who have localized symptomatic metastases. Optimal treatment of patients with unresectable or metastatic soft tissue sarcoma requires an appreciation for the natural history of the disease, close attention to the individual patient, and an understanding of the benefits and limitations of the therapeutic options.

RESECTION OF METASTATIC DISEASE

Approximately 20% of patients with a soft tissue sarcoma of an extremity or the trunk develop pulmonary metastases, and in the majority, the lung remains the only clinically evident site of metastasis. In retrospective series, 20% to 30% of patients who undergo metastasectomy are alive 5 years later.

Of 716 patients with primary extremity sarcoma who were treated at Memorial over a period of 6 years, pulmonary-only metastases occurred in 19%, or 135. Of these 135 patients, 58% underwent thoracotomy and 83% of those had a complete resection of their tumor. In the 65 patients who had a complete resection of their tumor, 69% recurred with pulmonary metastases as their only site of disease. Median survival from complete resection was 19 months, and 3-year survival was only 23% of those resected and 11% of those presenting with lung metastasis only. Patients who did not undergo thoracotomy all died within 3 years. Chemotherapy had no obvious effect on survival in either the resected or unresected patients. Incomplete resection was no better than no operation ( Fig. 39.1-25 ). At M. D. Anderson, in contrast to the experience with primary sarcoma, response to chemotherapy administered before pulmonary resection did not predict for improved outcome. Again, there is a glaring need for effective approaches to reducing systemic recurrence in patients rendered free of disease by surgical resection.

FIGURE 39.1-25. Pulmonary resection of soft tissue sarcoma metastases from the extremity. Comparison of no resection, versus incomplete resection versus complete gross resection of all known metastases. (From ref. 528, with permission.)

In patients who have pulmonary only metastatic disease that is not amenable to resection, an innovative approach under study is isolated lung perfusion. This technique or direct lung infusion can be used to administer chemotherapeutic drugs or biologic agents in a way that results in a high concentration of the agent in the lung, with no systemic exposure.

SYSTEMIC THERAPY FOR ADVANCED DISEASE

The activity of individual commercially available chemotherapeutic agents in patients with soft tissue sarcoma is summarized in Table 39.1-12. Doxorubicin has been the mainstay of chemotherapy for advanced sarcoma. Whereas early studies suggested overall response rates of 30%, in more recent trials the response rate was closer to 20%. Subset analysis of patients with soft tissue sarcoma from a large randomized phase II trial of different doses of doxorubicin demonstrated a dose-response relationship in patients with sarcoma. These data have been confirmed in other trials of single-agent doxorubicin and trials with doxorubicin-containing combination therapy. Some studies have begun to examine liposomal forms of doxorubicin, which may have fewer side effects than doxorubicin itself; response rates have been low, however.

Table 39.1-12. Selected Studies of Single-Agent Chemotherapy for Advanced Disease

I fosfamide has approximately the same efficacy as doxorubicin. In the past, ifosfamide dosing was limited by severe urothelial toxicity (hemorrhagic cystitis). The uroprotective agent mesna has markedly changed the ability to give both ifosfamide and cyclophosphamide, and ifosfamide doses as large as 14 to 18 g/m² over several days are given in some studies. There has been a debate as to the relative efficacy of cyclophosphamide versus ifosfamide, in particular whether ifosfamide is truly a different drug or whether differences in dosing of the two drugs accounts for the difference in response. The best study addressing this question came from the EORTC, which performed a randomized phase II trial examining the response rates of ifosfamide, 5 g/m², to cyclophosphamide, 1.5 g/m². There was greater myelosuppression with cyclophosphamide, but response rates were 7.5% for cyclophosphamide and 18% with ifosfamide; although suggestive, this difference did not
achieve statistical significance. Additionally, there is some evidence to suggest a dose-response relationship for ifosfamide. This is also borne out by the large number of phase II trials examining high-dose ifosfamide in metastatic soft tissue sarcoma (Table 39.1-12); responses to higher doses of ifosfamide are occasionally seen in patients failing lower doses of alkylating agents. The similar response rates of ifosfamide and doxorubicin, even in doxorubicin-resistant patients, suggested a lack of cross-resistance in combination chemotherapy. It should be noted that synovial sarcoma appears relatively responsive to ifosfamide.

The third drug with modest activity in sarcoma is dacarbazine. Its activity was recognized over 20 years ago, and later confirmed. Dacarbazine has frequently been used in combination chemotherapy with doxorubicin (Combination Chemotherapy for Advanced Soft Tissue Sarcoma, later in this chapter). Dacarbazine is given in a variety of schedules, from intravenous continuous infusion as part of the mesna, doxorubicin, ifosfamide, and dacarbazine (MAID) protocol (see Table 39.1-10), to one large bolus. The major side effect of dacarbazine is nausea and vomiting, which is abrogated to some extent by dividing the dose over 2 to 4 days. In general, nausea and vomiting from dacarbazine have been substantially reduced with the use of serotonin antagonist antiemetics.

As for other single agents, cisplatin and carboplatin have given occasional responses in phase II trials. However, in contrast to pediatric sarcomas such as Ewing’s sarcoma and rhabdomyosarcoma, other agents such as single-agent vincristine, etoposide, and actinomycin D appear to be inactive. The taxanes also show little activity; however, there are data that vinorelbine and gemcitabine have modest activity in at least some subtypes of soft tissue sarcoma.

The response rates of other largely investigational agents in soft tissue sarcomas are shown in Table 39.1-13. Few of these drugs have demonstrated meaningful activity in soft tissue sarcoma.

TABLE 39.1-13. Selected Studies of Investigational Agents in Sarcoma Therapy

Used in some of the earliest studies in sarcoma adjuvant chemotherapy, immunotherapy for sarcoma treatment is seeing renewed interest, without significant success to date. Cytokines alone appear to be ineffective in sarcoma (Table 39.1-14), as does nonspecific immunotherapy with bacterial cell wall components. A study underway at the NCI is examining vaccination of patients with peptides representing the fusion proteins observed in specific subtypes of sarcoma. Lymphocyte activated killer cell and other T-cell immunotherapy with cytokines was investigated in a small number of patients at the NCI without any observed responses. Dendritic cell vaccines as well as other forms of tumor-specific immunotherapy are undergoing investigation and may be of relevance to patients with soft tissue sarcoma.


Angiogenesis inhibition has emerged as a potential new therapy for solid tumors of all types, including sarcoma. To date, weak angiogenesis inhibitors such as the interferons have shown no efficacy in sarcoma. The antiangiogenic drug thalidomide binds to the receptor PPAR-g (peroxisome proliferator-activated receptor-g). This receptor is present on the cell surface of some liposarcomas. When PPAR-g binds a ligand, it can induce differentiation of the liposarcoma toward an adipocyte, with abundant fat droplet accumulation and decreased S-phase fraction. This laboratory finding led to an ongoing trial of troglitazone in patients with advanced liposarcoma. Interferons have shown no efficacy in sarcoma. Stronger angiogenesis inhibitors such as TNP-470 (AGM-1470), or vascular endothelial growth factor (VEGF)-pathway inhibitor SU5416 have been examined in phase I trials, but there have been only a handful of sarcoma patients treated with these more potent antiangiogenic agents.

Newer biologic agents are beginning to be assessed, based on the biology of specific sarcoma subsets, in particular liposarcoma. The antidiabetic drug troglitazone binds to the receptor PPAR-g (peroxisome proliferator-activated receptor-g). This receptor is present on the cell surface of some liposarcomas. When PPAR-g binds a ligand, it can induce differentiation of the liposarcoma toward an adipocyte, with abundant fat droplet accumulation and decreased S-phase fraction. This laboratory finding led to an ongoing trial of troglitazone in patients with advanced liposarcoma. A subset of patients with liposarcoma demonstrates similar lipid accumulation in vivo to that noted in vitro. To date, there are no data on relapse-free or overall survival of these patients.

COMBINATION CHEMOTHERAPY FOR ADVANCED SOFT TISSUE SARCOMA

A variety of combinations of chemotherapy have been developed and examined in phase II trials. The typical backbone of a combination regimen is doxorubicin (or its analogue epirubicin) with an alkylating agent, with or without other agents (see Table 39.1-10). One of the earliest combinations used was doxorubicin and dacarbazine, which has been well studied by the Southwest Oncology Group. Although initial responses noted a 41% major response rate, subsequent study of either a bolus or continuous infusion of the same regimen yielded a 17% response rate.

CyVADIC has been widely used for sarcoma therapy in the United States and Europe. Although single arm studies showed response rates as high as 71%, a randomized trial showed no significant difference in overall survival between CyVADIC and doxorubicin as a single agent. The two drug combinations of doxorubicin and ifosfamide or epirubicin and ifosfamide have consistently given response rates above 25%. Current studies are investigating higher doses of ifosfamide with fixed doxorubicin dose and growth factor support.

MAID was proven effective in metastatic soft tissue sarcoma in a large phase II trial from the Dana-Farber Cancer Institute. This randomized trial took place before the routine use of growth factors for aggressive chemotherapy regimens and examined doxorubicin and dacarbazine versus MAID. The study showed an increased response rate in the MAID arm (32% vs. 17%, P < 0.002). Underscoring the increased toxicity of aggressive chemotherapy regimens, there were eight toxic deaths on the study, seven in the 170 patients treated with the 7.5 g/m^2 total dose of ifosfamide per cycle. This dose was decreased to 6 g/m^2 during the course of the study. All treatment deaths occurred in patients older than 50 years of age. In a univariate analysis, there was a survival advantage for the two-drug arm (13 months vs. 12 months for MAID); however, this difference was not significant in a multivariate analysis. As noted in the later section on Dose Intensity, with the introduction of
growth factors, the dose intensity of this regimen has become better tolerated.

The response rates of metastatic sarcoma to cisplatin are low, and response rate to mitomycin C is zero in one small study. However, the combination of the two drugs with doxorubicin (called MAP) yielded a 43% response rate in a study from the Mayo Clinic. The activity of the MAP regimen has been confirmed in an independent ECOG trial.

A recent metaanalysis of all of the data from seven large EORTC provided a useful resource to assess response rates to combination chemotherapy in a multinational setting. The 2185 patients with follow-up in this study were subjected to a univariate and multivariate analysis of survival based on a number of factors, including age, sex, performance status before chemotherapy, presence and site of metastatic disease, histologic subtype, histologic grade, and disease-free interval (time since initial diagnosis of sarcoma). The overall median survival time was 51 weeks. The predictors of overall survival included good performance status, lack of liver involvement, low histopathologic grade, long disease-free interval, and young age (P < .005 for all these factors in a multivariate analysis). Although absence of liver involvement, young age, and high histopathologic grade also predicted for response to chemotherapy, so did liposarcoma histology (P < .01 for all these factors in a multivariate analysis). Leiomysarcoma histology did not qualify as a factor for response to chemotherapy independent of liver metastasis. Although not stratified by site, these data provide some of the best evidence that response rate does not necessarily correlate with overall survival.

Is combination chemotherapy better than single-agent doxorubicin for overall survival? Again, the concept arises of response rates differing from rates of overall survival. There have been several phase III trials examining the issue of combination chemotherapy versus single agents for patients with metastatic disease. The Table 39.1-15: two such trials examined this question in uterine sarcoma. There were improved response rates in several of the trials with combination chemotherapy, but there was no survival advantage over single-agent doxorubicin. Complete responses were rare during these studies and were not durable. These data argue that single agents are as effective as combination chemotherapy for patients with metastatic disease, in terms of overall survival. However, some patients may be eligible for palliative resection of metastatic disease. In these situations in which such aggressive therapy is contemplated, combination chemotherapy, which gives better response rates than single agents, can be considered.

**TABLE 39.1-15. Selected Randomized Trials in Advanced Disease**

**DOSE INTENSITY**

It is a central tenet of oncology that response to chemotherapy is a function of dose and dose intensity. A dose-response effect for doxorubicin and ifosfamide has been suggested in a variety of studies. However, toxicity limits the amount of chemotherapy that can be given in any one cycle, as illustrated by the phase III trial of the MAID combination chemotherapy noted previously. It is argued that if dose could be increased, better responses might be seen. Better supportive care can help increase dose intensity as outlined in this section.

The use of hematopoietic growth factors has allowed for the study of higher doses of chemotherapy in sarcoma. Some of the aggressive regimens for therapy of metastatic sarcoma satisfy the American Society of Clinical Oncology guidelines for use of growth factors given their high rate of febrile neutropenia. Granulocyte-macrophage colony-stimulating factor (sargramostim), the first granulocyte growth factor used, decreased the myelosuppression seen with CyADIC and MAID chemotherapy, and allowed for increased dose intensity of high-dose ifosfamide. Granulocyte-macrophage colony-stimulating factor allowed for escalation of the dose of doxorubicin when given in combination with 5 g/m^2^ of ifosfamide, with improvement in response rate. Granulocyte-macrophage colony-stimulating factor has also been shown to allow increased dose intensity of the MAP combination of chemotherapy, allowing addition of ifosfamide.

Similarly, granulocyte colony-stimulating factor (filgrastim) has been widely used to increase dose intensity and decrease myelotoxicity of aggressive chemotherapeutic regimens such as MAID or dose-escalated doxorubicin and ifosfamide. However, with escalated doses (25% increase) in the MAID regimen, there appears to be no significant increased response rate despite use of growth factors. There may be other ways to achieve dose intensity. A study of low-dose, long-term (approximately 2-week) ifosfamide showed responses in patients who failed other forms of chemotherapy for their sarcomas. As was seen with previous studies, it may well be that responsiveness to a particular regimen may not translate into increased survival.

Unfortunately, the cardiac toxicity of doxorubicin and nephrotoxicity and central nervous system toxicity of ifosfamide prevent much greater dose escalation than performed in some studies today. The next logical step is to proceed to high-dose therapy with stem cell support, which is currently under study with pediatric sarcomas. Such studies show long-term disease-free survival for a handful of patients with Ewing's sarcoma, osteosarcoma, or rhabdomyosarcoma. Even in these relatively chemotherapy-sensitive sarcomas, the majority of patients have relapsed rapidly. Given that complete responses (and therefore chemotherapy sensitivity) are rare in the metastatic setting of adult soft tissue sarcoma, it is not surprising that the few patients with soft tissue sarcoma who undergo high-dose therapy with stem cell rescue relapse quickly. High-dose therapy with stem cell rescue should not be considered for patients with metastatic sarcoma outside the setting of a clinical trial. With poor results from high-dose therapy, the pursuit of agents with better activity against soft tissue sarcoma will remain a primary focus for therapy of relapsed disease.

**RESPONSE BY HISTOLOGIC SUBTYPE AND SITE**

A major focus in critical reading of the literature concerning responses of soft tissue sarcoma to chemotherapy is the variety of patient sarcoma histology. Pediatric sarcomas are known for their relative sensitivity to chemotherapy (Ewing's sarcoma, osteosarcoma, and rhabdomyosarcoma). As for adult sarcomas, synovial sarcomas and fibrosarcomas are generally sensitive to chemotherapy. GISTs, alveolar sarcoma of soft parts, and low- to intermediate-grade chondrosarcomas are notorious for their resistance to chemotherapy. An imbalance in the subtypes of sarcomas in various groups of patients can markedly affect overall outcome for the study in question.

Site of disease is another important factor in determination of outcome for patients with soft tissue sarcoma. For example, patients with large low-grade liposarcoma of the extremity show lower relapse rates than patients with low-grade liposarcomas of the retroperitoneum; the latter are more difficult to control locally. Similarly, formerly called leiomyosarcomas of the gastrointestinal tract, both true leiomyosarcomas and gastrointestinal stromal tumors (GISTs), are less responsive to chemotherapy than leiomyosarcoma of other sites (see Leiomysarcoma, later in this chapter). The site of disease or metastasis pattern may at least in part account for the different responses noted in randomized trials of chemotherapy for soft tissue sarcoma.

It is clear that specific subtypes of soft tissue sarcomas demonstrate unique biologic behavior. As diagnosis and classification of sarcomas improve, these unique features may become more evident. Examples of specific sites or subtypes of sarcoma and their characteristics are presented here.
LEIOMYOSARCOMA

Leiomyosarcomas are one of the most common forms of soft tissue sarcoma. They are also relatively uniform in histologic appearance, and thus there is greater concordance of pathologists in the diagnosis of leiomyosarcoma than other forms of soft tissue sarcoma. Given their relative frequency and the consistency of diagnosis of leiomyosarcoma, it is useful to examine the sensitivity of this subset of sarcomas to standard chemotherapy.

The response rate of leiomyosarcoma in subset analysis of randomized trials is shown in Table 39.1-16. Subset analyses cannot substitute for primary trials of chemotherapy, but still can be useful in generating hypotheses for further studies. Doxorubicin appears to be active in leiomyosarcomas, but ifosfamide appears to add little to the response rate of this subset of tumors. In one small study of uterine leiomyosarcomas, a modest response to ifosfamide was observed. Ifosfamide, in contrast, appears to be effective in other subtypes of sarcoma.

<table>
<thead>
<tr>
<th>Chemotherapy Regimen</th>
<th>Response Rate (% of Patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ifosfamide (5 g/m²)</td>
<td>100 (13 patients)</td>
</tr>
<tr>
<td>Etoposide (14–18 g/m²)</td>
<td>30 (2 patients)</td>
</tr>
</tbody>
</table>

The primary site of leiomyosarcoma can have an equally important effect on survival. The difference in response rates for different sites of leiomyosarcoma is highlighted in the trials from ECOG and Southwest Oncology Group. Although only 20% to 25% of uterine leiomyosarcomas responded to chemotherapy, uterine leiomyosarcoma was approximately twice as responsive to chemotherapy compared with leiomyosarcomas arising from the gastrointestinal tract (GISTs). These diseases differ from typical adult sarcomas in that they are considered systemic diseases despite their initial presentation. Ewing's sarcoma and osteosarcoma of bone should receive neoadjuvant or adjuvant chemotherapy in addition to therapy for local control of their tumor. However, in extraskeletal osteosarcoma, the use of chemotherapy as an adjuvant to surgical control of the primary disease remains controversial, largely due to the low response rates to chemotherapy seen in patients with metastatic soft tissue osteosarcoma.

SYNOVIAL SARCOMA

Synovial sarcoma demonstrates two histologies, a monophasic form and a biphasic form. Specific translocations in this subset of sarcoma between the SSX and SYT genes on chromosomes X and 18 may be prognostic factors for this subtype of sarcoma. Patients with biphasic histology demonstrated SYT-SSX1 gene fusions. These patients fared more poorly than patients with SYT-SSX2 positive tumors that were associated with the monophasic phenotype, such molecular phenotyping represents an attractive method of predicting outcome to therapy and need for more or less intensive therapy.

Patients with synovial sarcoma tend to be younger than patients with other subtypes of soft tissue sarcoma. Patients with synovial sarcoma are therefore likely to have a better performance status than patients with other subtypes of sarcoma, a positive predictor for response to chemotherapy in the EORTC database. The higher response rates in such patients may therefore be in part due to patient selection factors, not just histologic diagnosis.

In patients with advanced synovial sarcoma, ifosfamide (at a high dose of 14 to 18 g/m²) appears to be an active agent with a 100% response rate in one study of 13 patients. The EORTC metaanalysis of 2185 sarcoma patients included 115 synovial sarcomas evaluable for response to chemotherapy; the response rate was 31%, not significantly different than the overall response rate of 26%. The conflict between these results may be due to dose intensity, as well as the use of an inappropriate group for comparison; the EORTC data examined the response of metastatic sarcoma to anthracyclines and only a portion of patients received ifosfamide (at a maximum dose of 5 g/m², a low dose by today's standards).

PEDICULAR SARCOMAS IN ADULT POPULATIONS

A number of pediatric sarcomas occur in the adults, including Ewing's sarcoma (in soft tissue or bone), rhabdomyosarcoma (usually embryonal), and osteosarcoma. These diseases differ from typical adult sarcomas in that they are considered systemic diseases despite their initial presentation. Ewing's sarcoma and rhabdomyosarcoma are typically much more sensitive to chemotherapy than adult soft tissue sarcomas. In osteosarcoma, long-term survival has been achieved in pediatric patients with the use of adjuvant chemotherapy. Unfortunately, adults with osteosarcoma are generally more resistant to chemotherapy than children.

Adjuvant (or neoadjuvant) chemotherapy is the standard of care for adults with a diagnosis of rhabdomyosarcoma or Ewing's sarcoma. In addition, adults with a typical osteosarcoma of bone should receive neoadjuvant or adjuvant chemotherapy in addition to therapy for local control of their tumor. However, in extraskeletal osteosarcoma, the use of chemotherapy as an adjuvant to surgical control of the primary disease remains controversial, largely due to the low response rates to chemotherapy seen in patients with metastatic soft tissue osteosarcoma.

Typical regimens for small cell pediatric sarcomas, specifically rhabdomyosarcoma and Ewing's sarcoma, include the combination of vincristine, doxorubicin, and cyclophosphamide (occasionally with actinomycin D), and the combination of ifosfamide and etoposide. The MAID regimen also shows activity in pediatric sarcomas. There is debate as to whether adults do worse than pediatric patients with the same stage of disease. Adults are less likely than children to tolerate the aggressive regimens of chemotherapy used in these diseases. In addition, adults may present with advanced stage disease relative to children or adolescents. One retrospective study showed older patients with rhabdomyosarcoma tolerated chemotherapy as well as the pediatric population, but fared worse overall; tumor size, site, and response to chemotherapy predicted outcome in another series. In Ewing's sarcoma, the role of age in predicting outcome is controversial. A high percentage of patients with pediatric sarcomas are enrolled on protocols examining new therapy in the setting of randomized trials. Adults with diagnosis of sarcoma usually seen in pediatric populations should be included on pediatric protocols whenever feasible to help determine appropriate care for patients with these rare diagnoses.

UTERINE SARCOMAS

Uterine sarcomas are rare, accounting for 3% to 7% of all uterine malignancies. The uterus is a unique site in that at least three different sarcomatous entities may arise from this organ, including leiomyosarcoma, endometrial stromal sarcoma, and carcinosarcoma (also known as malignant mixed Mullerian tumor). The most common histopathologic type is Mullerian tumor.

For localized disease surgery is the main treatment. Whether adjuvant radiation is needed remains a controversial topic. Most studies showed some improvement in local control but not survival. More recently, however, Ferrer et al. reviewed the experience of the Grup Oncologic Catala-Occla and found that the addition of radiation to surgery improved local control as well as survival in 103 patients with stage I to IVa. It is hoped that the ongoing EORTC-55874 randomized trial will determine the exact effect of adjuvant radiation in this malignancy.

The Gynecologic Oncology Group performed a prospective randomized trial comparing adjuvant chemotherapy with no further therapy in patients with stage I to II...
In advanced disease, the Gynecologic Oncology Group also compared doxorubicin alone with doxorubicin and dacarbazine in a randomized trial. Response rates and overall survival did not differ between the two arms; the response rate to doxorubicin of 28 women with leiomyosarcoma was 25%. Thereafter, doxorubicin was compared with doxorubicin plus cyclophosphamide; response rates in both arms were 19%, with a 13% response rate to doxorubicin for patients with leiomyosarcoma. Uterine sarcoma overall showed a 22% to 25% response rate to chemotherapy as noted previously.

A number of phase II studies have examined responses to various agents for various subtypes of uterine sarcoma. Patients with carcinosarcoma (one form of mixed Müllerian tumor) have been treated with cisplatin, or with doxorubicin; there were no responses in the small cohort of patients given doxorubicin. When patients develop metastatic disease from carcinosarcoma, it is usually of the carcinomatous elements, indicating this is the more important characteristic of the tumor to treat. This may explain the responses of this sarcoma to therapy effective for epithelial tumors. Leiomyosarcoma is responsive to doxorubicin as noted previously, less sensitive to ifosfamide (see Leiomyosarcoma, earlier in this chapter), and also relatively unresponsive to cisplatin.

Endometrial stromal sarcomas express estrogen and progesterone receptors, and anecdotal responses to progestins have been noted. However, it is clear that frequency of positive estrogen or progesterone receptor staining is substantially greater than the response rate to hormonal therapy such as tamoxifen. In a prospective trial of tamoxifen in uterine sarcomas, only one patient (with a mixed Müllerian tumor) responded, out of a total 29 patients treated (19 with leiomyosarcoma).

**DESIMIDS (AGGRESSIVE FIBROMATOSES)**

Desmoid tumors belong to a family of myofibroblastic fibromatoses that are unusual in their bland histology and slow progression. Surgery remains the treatment of choice for these lesions, which cannot truly be called sarcomas because of their lack of metastatic potential.

The role of adjuvant radiation for completely resected primary desmoid tumor is controversial. Most authors agree that for patients with negative resection margins, postoperative radiation is not recommended. However, for patients with positive microscopic margins the role of adjuvant radiation is more debatable. Spear et al. from Massachusetts General Hospital reported a local control rate of 61% for patients with primary tumors with positive microscopic margins treated with surgery alone. Others, however, have reported lower local control rates. The conclusion from these studies is that failure does not invariably occur if residual microscopic tumor from a primary lesion is left in situ as long as local progression would not cause significant morbidity. When adjuvant radiation is indicated for some primary lesion or in most recurrent tumors, the usual dose is approximately 50 Gy.

In advanced cases desmoids can still cause significant morbidity in proximal extremities and can be fatal if they arise in the retroperitoneum, since such sites are difficult to resect completely.

Although the use of adjuvant radiation is becoming more restricted, the role of definitive radiation is emerging as a reasonable alternative to radical surgery. Ballo et al. reported a 5-year local control rate of 69% for patients treated with radiation for gross disease. Others have shown similar findings. The recommended dose for definitive radiation is usually 56 Gy in 2 Gy fraction to 60 Gy given at 1.8 Gy per fraction.

Desmoids classically arise in pregnancy as an abdominal mass independent of the uterus. Desmoids have been examined for hormone receptors and have binding sites for estrogens and antiestrogens in some cases. There are anecdotes of responses to hormonal manipulation such as tamoxifen, testolactone, toremifene, goserelin, and progestins. There are well-documented responses of desmoids to sulindac and other nonsteroidal antiinflammatory drugs, and reports of responses to vitamin K, vitamin C, and warfarin. Responses can take months and continue for years.

Responses have been reported to single-agent doxorubicin chemotherapy as well as to combination chemotherapy at either standard or relatively low doses. As noted previously, responses can be slow, and therapy should not be abandoned for stable disease.

In summary, for easily resectable disease, surgery alone would appear to be the optimal approach especially in patients with negative microscopic margin. In advanced cases, a trial of nonsteroidal antiinflammatory drugs or hormonal therapy can be considered in most patients. A period of close observation is also reasonable, because some patients demonstrate regression without any therapy. However, if a patient is symptomatic and not a candidate for surgery, consideration should be given to radiation or chemotherapy to increase the chance of a response.

**RECOMMENDATIONS FOR PATIENTS WITH ADVANCED DISEASE**

Low-grade tumors grow slowly and may be less responsive to chemotherapy than higher grade lesions. Accordingly, an asymptomatic patient with stable or only slowly progressive disease can be observed only. Resection of metastastic disease, in particular lung metastases, provides some patients with long-term survival and can be considered if the lungs are the only site of remaining disease.

Randomized studies have shown that combination chemotherapy can provide a better probability of a response than single-agent doxorubicin. However, overall survival for any combination chemotherapy has not been proven superior to doxorubicin alone as a single agent. When a clinical response is needed, e.g., before potential surgery for metastases, combinations of agents such as doxorubicin and ifosfamide should be considered, especially for patients with good performance status. For patients with poor performance status, single-agent doxorubicin remains the standard of care, since no other therapy or combination of treatments has proven superior to it for overall survival. Single-agent ifosfamide or dacarbazine can be used as a second-line agent. Dacarbazine demonstrates modest activity in soft tissue sarcoma, and with doxorubicin is a well-studied and well-tolerated combination in metastatic disease. Patients with advanced disease are candidates for phase I and phase II studies of new therapy for sarcoma, since we have but few tools with which to treat such patients presently.

**FUTURE DIRECTIONS**

Metastatic sarcoma, whether at time of disease presentation, or after local control of primary disease, remains an extremely difficult problem. The search for effective chemotherapeutic and biologic agents will be the focus of continuing research for patients with advanced disease. In the near future, results should be forthcoming of the study of the differentiation agent tretinoin for patients with metastatic or recurrent liposarcoma. Even more potent antagonists of the PPAR-γ receptor such as rosiglitazone and pioglitazone will be examined in the metastatic and adjuvant setting for patients with liposarcoma. The study of angiongenesis inhibition is just beginning. The examination of antagonists of the VEGF and other pathways of angiogenesis, inhibition of angiongenesis in this class of tumors, using agents such as SU5416, angiostatin, and endostatin. In terms of novel chemotherapeutic agents, eteclinascidin 743 has demonstrated some promise in phase I studies and may provide the first new effective antisarcoma agent since ifosfamide.

In the longer term, it is hoped that new biologic agents for sarcoma therapy can be found that are as potent as TNF in murine models of sarcoma. Responses have been reported to single-agent doxorubicin chemotherapy as well as to combination chemotherapy at either standard or relatively low doses. As noted previously, responses can be slow, and therapy should not be abandoned for stable disease.

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INTRODUCTION

Malignant tumors arising from the skeletal system are rare, representing only 0.2% of all new cancers. Approximately 2600 new cases occur in the United States each year. Osteosarcoma and Ewing's sarcoma, the two most common bone tumors, occur mainly during childhood and adolescence. Other mesenchymal (spindle cell) neoplasms that characteristically arise after skeletal maturity—fibrosarcoma, chondrosarcoma, and malignant fibrous histiocytoma (MFH)—are less common. The vast majority of experience reported in the management of bone neoplasms has been obtained in patients with osteosarcoma. As a result, the surgical, chemotherapeutic, and radiotherapeutic principles developed for treatment of osteosarcoma form the basis of the management strategy for most of the spindle cell neoplasms.

Since the late 1970s, an explosion of clinical knowledge and experience in the management of bone neoplasms has been seen. The development of centers of specific interest in these tumors has played an important role in the advancement of biologic understanding and surgical management of these lesions and the development of multimodality treatment regimens. A surgical staging system that permits standardized preoperative evaluation, analysis, and end-result reporting has been developed. Amputation has been the standard method of treatment for most bone sarcomas, but the 1990s was witness to the development of limb-sparing surgery for most
malignant bone tumors. \textsuperscript{52,} 53, 54, 55, 56, 57, 58, 59, 60, and 61 Advances in orthopedics, bioengineering, radiographic imaging, radiotherapy, and chemotherapy have contributed to safer, more reliable surgical procedures. \textsuperscript{62,} 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, and 83 Today, limb-sparing surgery is considered safe and routine for approximately 90% of patients with extremity osteosarcomas. An evaluation system has been developed to determine a patient's functional status. \textsuperscript{84} This system, for the first time, permits evaluation and comparison of the various limb-sparing procedures and types of surgical reconstructions.

Paralleling these advances has been the demonstrated effectiveness of adjuvant chemotherapy in dramatically increasing overall survival; specifically, the bleak 15% to 20% survival rate associated with surgery alone before the 1970s rose to 55% to 80% with various adjuvant treatment regimens by the 1980s. \textsuperscript{85,} 86, 87, 88 and 89 Multiple-drug regimens are now considered essential treatment. The timing, mode of delivery, and different combinations of these agents are being investigated at many centers. Preoperative chemotherapy regimens (termed neoadjuvant or induction chemotherapy) and postoperative regimens are being evaluated to determine their effect on the tumor and their impact on the choice of operative procedure and on overall survival. \textsuperscript{90,} 91, 92, 93, 94, 95, and 96

This chapter focuses only on malignant spindle cell tumors. Ewing's sarcoma is presented in detail in Chapter 39.1. Benign tumors are described briefly, and their significance for the oncologist is described. \textsuperscript{97} Emphasis is placed on natural history, surgical staging, tumor imaging, criteria of patient selection for amputation versus limb-sparing surgery, and technique of limb-sparing procedures. The development, role, timing, and mode of delivery of adjuvant chemotherapy and its relationship to stage of disease are discussed. The role of radiotherapy in specific clinical situations is presented.

CLASSIFICATION AND TYPES OF BONE TUMORS

Bone consists of cartilaginous, osteoid, and fibrous tissue and bone marrow elements. Each tissue can give rise to benign or malignant spindle cell tumors. \textsuperscript{98} and 99

Bone tumors are classified on the basis of cell type and recognized products of proliferating cells. The classification system, described by Lichtenstein \textsuperscript{100} and modified by Dahlin,\textsuperscript{1} is presented in Table 39.2-1. Jaffe\textsuperscript{2} recommends that each tumor be considered a separate clinicopathologic entity. Radiographic, histologic, and clinical data are necessary to form an accurate diagnosis and to determine the degree of activity and malignancy of each lesion.

TABLE 39.2-1. General Classification of Bone Tumors

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cartilaginous</td>
<td>Lesions are cartilaginous, may be benign, or malignant. Benign forms are osteoid osteoma and osteoblastoma. Osteoid osteomas are benign. Malignant forms are osteosarcoma and chondrosarcoma.</td>
</tr>
<tr>
<td>Osteoid</td>
<td>Lesions are osteoid osteoma and osteoblastoma. Osteoid osteomas are benign. Malignant forms are osteosarcoma and chondrosarcoma.</td>
</tr>
<tr>
<td>Fibrous</td>
<td>Lesions are fibrous tumors and osteosarcoma of bone. Benign forms are osteoid osteoma and osteoblastoma. Malignant forms are osteosarcoma and chondrosarcoma.</td>
</tr>
</tbody>
</table>

Cartilage tumors are lesions in which cartilage is produced. They are the most common bone tumors. Osteochondroma is the most common benign cartilage tumor; some 1% to 2% of solitary osteochondromas become malignant. \textsuperscript{101} and 102 Enchondroma is a benign cartilage tumor that occurs centrilobally; in adults, malignant transformation may occur. Chondrosarcoma, the most common malignant cartilage tumor, is either intramedullary or peripheral. Ten percent are secondary, arising from an underlying benign lesion. Most chondrosarcomas are low grade, although 10% desdifferentiate into high-grade spindle cell sarcomas or, rarely, a mesenchymal chondrosarcoma. \textsuperscript{103}

Osteoid tumors are lesions in which the stroma produce osteoid. The benign forms are osteoid osteoma and osteoblastoma. Osteoid osteomas are benign. Osteoblastomas rarely metastasize; when they do, it is only after multiple local recurrences. \textsuperscript{104} Osteosarcomas are the most common primary malignant tumors of the bone. Histologically, they are composed of malignant spindle cells and osteoblasts that produce osteoid or immature bone. Several variants are now recognized. \textsuperscript{105} Parosteal, periosteal, and low-grade intraosseous osteosarcoma are histologically and radiographically distinct from the "classic" central medullary osteosarcomas and have a more favorable prognosis. \textsuperscript{106}

Fibrous tumors of bone are rare. Desmoplastic fibroma is a locally aggressive, nonmetastasizing tumor, analogous to fibromatosis of soft tissue. \textsuperscript{107} Fibrosarcoma of bone appears histologically as its soft tissue counterpart. Multiple sections must be obtained to demonstrate the lack of osteoid production. If osteoid is present, the lesion is classified as an osteosarcoma. MFH, a rare lesion and the counterpart of soft tissue MFH, has been described in bone. \textsuperscript{108} and 109 The pathophysiologic behavior of bone and soft tissue MFH is similar, consisting of a storiform pattern with a histiocytic component. Giant cell tumors of unknown origin were originally called benign bone tumors but are now considered low-grade sarcomas. They have high rates of local recurrence and malignant transformation. \textsuperscript{110}

Tumors presumably arising from bone marrow elements are the round cell sarcomas. The two most common are Ewing's sarcoma and the rarer non-Hodgkin's lymphoma.

RADIOGRAPHIC EVALUATION AND DIAGNOSIS

Radiographic evaluation combined with the clinical history and histologic examination is necessary for accurate diagnosis. Bone scans, angiography, CT, and MRI are generally not helpful in determining a diagnosis but are important in delineating the extent of local involvement. A systematic approach to the radiographic evaluation of skeletal lesions has been described by Madewell and colleagues. \textsuperscript{111} who studied and correlated several hundred radiographic and pathologic specimens. They considered the radiograph as the gross specimen from which a detailed histologic interpretation could be made and biologic activity accurately diagnosed. According to their system, a bone tumor is evaluated by five radiographic parameters:

1. Anatomic site. Specific anatomic sites of the bone give rise to specific groups of lesions. Johnson \textsuperscript{112} explained this by a "field" theory, which hypothesizes that the most active cells of certain areas of bone give rise to tumors that are characteristic of that area. In general, spindle cell sarcomas are metaphyseal, whereas round cell sarcomas tend to be diaphyseal.

2. Borders. The border reflects the growth rate and the response of the adjacent normal bone to the tumor. Most tumors have a characteristic border. Benign lesions (e.g., nonossifying fibromas and unicameral bone cysts) have well-defined borders and a narrow transition area that is often associated with a reactive sclerosis. Aggressive or benign tumors (e.g., chondroblastoma and giant cell tumors [GCTs]) tend to have faint borders and wide zones of transition with very little sclerosis, reflecting a faster-growing lesion. Poorly delineated or absent margins indicate an aggressive or malignant lesion.

3. Bone destruction. Bone destruction is the hallmark of a bone tumor. Three patterns of bone destruction are described: \textsuperscript{113} geographic, moth-eaten, and permeative. In general, these patterns are found in the tubular bone rather than in the flat bone and represent a combination of cortical and cancellous destruction. These patterns reflect a progressively increasing growth rate of the underlying tumor.

4. Matrix formation. Calcification of the matrix, or new bone formation, may produce an area of increased density within the lesion. Calcification typically appears as floculent or stippled rings or clusters. The appearance of the new bone varies from dense sclerosis that obliterates all evidence of normal trabeculae, to small, irregular, circumscribed masses described as "wool" or "clouds." Calcification and ossification may appear in the same lesion. Neither type of matrix formation per se is diagnostic of malignancy.

5. Periosteal reaction. Periosteal reaction is indicative of malignancy but not pathognomonic of a particular tumor. A combination of periosteal changes is often noted. In malignant tumors, periosteal reaction is noncontinuous and thin, with multiple laminations. A parallel or a perpendicular pattern may be present.
The radiographic parameters of benign and malignant tumors are quite different. Benign tumors have round, smooth, well-circumscribed borders. No cortical destruction and, generally, no periosteal reaction are found. Malignant lesions have irregular, poorly defined margins. Evidence of bone destruction and a wide area of transition with periosteal reaction are noted. Soft tissue extension is common.

**NATURAL HISTORY**

Tumors arising in bone have characteristic patterns of behavior and growth that distinguish them from other malignant lesions. These patterns form the basis of a staging system and current treatment strategies. These principles and their relationship to management, as formulated by Enneking and colleagues, are described here.

**BIOLOGY AND GROWTH**

Spindle cell sarcomas form a solid lesion that grows centrifugally. The periphery is the least mature part of this lesion. In contradistinction to a true capsule, which surrounds a benign lesion and is composed of compressed normal cells, a malignant tumor is generally enclosed by a pseudocapsule and consists of compressed tumor cells and a fibrovascular zone of reactive tissue with an inflammatory component that interdigitates with the normal tissue adjacent to and beyond the lesion. The thickness of the reactive zone varies with the degree of malignancy and histiogenic type. The histologic hallmark of sarcomas is their potential to break through the pseudocapsule to form satellite lesions of tumor cells. This characteristic distinguishes a nonmalignant mesenchymal tumor from a malignant one.

High-grade sarcomas have a poorly defined reactive zone that may be invaded and destroyed by the tumor. In addition, tumor nodules in tissue may appear to be normal and not continuous with the main tumor. These are termed skip metastases. Although low-grade sarcomas regularly demonstrate tumor interdigitation into the reactive zone, they rarely form tumor nodules beyond this area.

The three mechanisms of growth and extension of bone tumors are: (1) compression of normal tissue, (2) resorption of bone by reactive osteoclasts, and (3) direct destruction of normal tissue. Benign tumors grow and expand by the first two mechanisms, whereas direct tissue destruction is characteristic of malignant bone tumors. Sarcomas respect anatomic borders and remain within one compartment. Local anatomy influences tumor growth by setting the natural barriers to extension. In general, bone sarcomas take the path of least resistance. Most benign bone tumors are unicompartmental; they remain confined and may expand the bone in which they arose. Malignant bone tumors are bicompartamental; they destroy the overlying cortex and go directly into the adjacent soft tissue. The determination of anatomic compartment involvement has become more important with the advent of limb-preservation surgery.

On the basis of biologic considerations and natural history, Enneking and colleagues classified bone tumors into five categories, each of which shares certain clinical characteristics and radiographic patterns and requires similar surgical procedures.

1. Benign/latent: lesions whose natural history is to grow slowly during normal growth of the individual and then to stop, with a tendency to heal spontaneously. They never become malignant and, if treated by simple curettage, heal rapidly. Surgery is not indicated unless they become symptomatic.
2. Benign/active: lesions whose natural history is one of progressive growth. Simple curettage leaves a reactive rim with some tumor. Curettage is associated with a high recurrence rate. Wide excision through normal bone results in local control in approximately 95% of all cases.
3. Benign/aggressive: lesions that are locally aggressive but do not metastasize. The tumor extends through the capsule into the reactive zone. Local control can be obtained only by removing the lesion with a margin of normal bone beyond the reactive zone.
4. Malignant/low grade: lesions that have a low potential to metastasize. Histologically, a pseudocapsule rather than a true capsule is found. Tumor nodules exist within the reactive zone but rarely beyond. Local control can be accomplished only by removal of all tumor and reactive tissue with a margin of normal bone. These lesions can be treated successfully by surgery alone.
5. Malignant/high grade: lesions whose natural history is to grow rapidly and metastasize early. Tumor nodules are often found within and beyond the reactive zone and at some distance in the normal tissue. Surgery is necessary for local control, and systemic therapy is warranted to prevent metastasis.

**METASTASIS**

Bone tumors, unlike carcinomas, disseminate almost exclusively through the blood; bones lack a lymphatic system. Early lymphatic spread to regional nodes has only rarely been reported. Lympathic involvement, which has been noted in 10% of cases at autopsy, is a poor prognostic sign. McKenna and associates noted that 6 of 194 patients (3%) with osteosarcoma who underwent amputation demonstrated lymph node involvement. None of these patients survived 5 years. Hematogenous spread is manifested by pulmonary involvement in its early stage and secondarily by bone involvement. Bone metastasis is occasionally the first sign of dissemination. With the use of adjuvant chemotherapy, the skeletal system has become a more common site of initial relapse.

**SKIP METASTASIS**

A skip metastasis, as previously defined, is a tumor nodule that is located within the same bone as the main tumor but not in continuity with it. Transarticular skip metastases are located in the joint adjacent to the main tumor. Skip metastases are most often seen with high-grade sarcomas. A skip lesion develops by the embolization of tumor cells within the marrow sinuses; in effect, they are local micrometastases that have not passed through the circulation. Transarticular skips are believed to occur via the periarticular venous anastomosis. The clinical incidence of skip metastases is less than 1%. These lesions are a prognosticator of poor survival.

**LOCAL RECURRENCE**

Local recurrence of a benign or malignant lesion is due to inadequate removal. The aggressiveness of the tumor determines which surgical procedure is required for local control. Ninety-five percent of all local recurrences, regardless of histology, develop within 24 months of attempted removal. Local recurrence of a high-grade sarcoma decreases overall survival prospects substantially. Local recurrence in patients who have undergone therapy is associated with an even poorer prognosis (Fig. 39.2-1).

**STAGING BONE TUMORS**

**MUSCULOSKELETAL TUMOR SOCIETY CLASSIFICATION**
In 1980, the Musculoskeletal Tumor Society (MSTS) adopted a surgical staging system for bone sarcomas (Table 39.2-2). The system is based on the fact that mesenchymal sarcomas of bone behave similarly, regardless of histiogenic type. The surgical staging system, as described by Enneking and colleagues, is based on the GTM classification: grade (G), location (T), and lymph node involvement and metastases (M).

<table>
<thead>
<tr>
<th>Stage</th>
<th>Grade</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>G1</td>
<td>T1</td>
</tr>
<tr>
<td>IB</td>
<td>G1</td>
<td>T2</td>
</tr>
<tr>
<td>IIA</td>
<td>G2</td>
<td>T1</td>
</tr>
<tr>
<td>IIB</td>
<td>G2</td>
<td>T2</td>
</tr>
<tr>
<td>IIIA</td>
<td>G1 or G2</td>
<td>M1</td>
</tr>
<tr>
<td>IIIB</td>
<td>G1 or G2</td>
<td>M1</td>
</tr>
</tbody>
</table>

G represents the histologic grade of a lesion and other clinical data. Grade is further divided into two categories: G1 is low grade, and G2 is high grade.

T represents the site of the lesion, which may be intracompartmental (T1) or extracompartmental (T2). Compartment is defined as "an anatomic structure or space bounded by natural barriers or tumor extension." The significance of T1 lesions is easier to define clinically, surgically, and radiographically than that of T2 lesions, and the chance is better for adequate removal of the former without amputation. In general, low-grade bone sarcomas are intracompartmental (T1), whereas high-grade ones are extracompartmental (T2).

Lymphatic spread is a sign of widespread dissemination. Regional lymphatic involvement is equated with distal metastases (M1). Absence of any metastasis is designated as M0.

The surgical staging system developed by Enneking and colleagues for surgical planning and assessment of bone sarcomas is summarized thus:

Stage IA (G1,T1,M0): low-grade intracompartmental lesion, without metastasis
Stage IB (G1,T2,M0): low-grade extracompartmental lesion, without metastasis
Stage IIA (G2,T1,M0): high-grade intracompartmental lesion, without metastasis
Stage IIB (G2,T2,M0): high-grade extracompartmental lesion, without metastasis
Stage IIIA (G1 or G2,T1,M1): intracompartmental lesion, any grade, with metastasis
Stage IIIB (G1 or G2,T2,M1): extracompartmental lesion, any grade, with metastasis

AMERICAN JOINT COMMITTEE ON CANCER BONE TUMOR CLASSIFICATION

In 1983, the American Joint Committee on Cancer Bone Tumor Classification (AJCC) recommended a staging system for the malignant tumors of bone. This system has undergone minimal changes and remains unchanged in the fifth edition of the AJCC Cancer Staging Manual. This system is based on two indications: TNM designation [extent of the tumor (T), nodal status (N), and distant metastases (M)] and grade (G). This system is similar to the MSTS classification; however, the AJCC uses four stages instead of three. The four stages are designated I to IV and may be further modified by A or B. Stages I and II are defined by the histologic grade (grade I and II) and modified by tumor extent (i.e., cortical involvement: designated E1 to E6) (Table 39.2-3). T(I) indicates that the tumor is confined within the cortex (similar to the MSTS classification A), and T(II) indicates that the tumor extends beyond the cortex (similar to the MSTS classification B). In the AJCC, stage III has remained undefined and stage IV is defined as the presence of metastases. Stage IV tumors are modified by A, which is equivalent to III M1 in the MSTS system (i.e., indicates a nodal metastasis), and B, which is equivalent to III M1 in the MSTS system (i.e., indicates distant metastases).

<table>
<thead>
<tr>
<th>Stage</th>
<th>Grade</th>
<th>Extent</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>G1</td>
<td>T(I)</td>
</tr>
<tr>
<td>IB</td>
<td>G1</td>
<td>T(II)</td>
</tr>
<tr>
<td>IIA</td>
<td>G2</td>
<td>T(I)</td>
</tr>
<tr>
<td>IIB</td>
<td>G2</td>
<td>T(II)</td>
</tr>
<tr>
<td>IIIA</td>
<td>G1 or G2</td>
<td>M1</td>
</tr>
<tr>
<td>IIIB</td>
<td>G1 or G2</td>
<td>M1</td>
</tr>
</tbody>
</table>

TABLE 39.2-3. Definitions of AnatomicExtent for Stage IIIB Tumors

PREOPERATIVE EVALUATION

If the plain radiographs suggest an aggressive or malignant tumor, staging studies should be performed before biopsy. All radiographic studies are influenced by surgical manipulation of the lesion, making interpretation more difficult. More important, the biopsy site may be in a location that is not optimal for subsequent en bloc removal or radiotherapy. Bone scintigraphy, MRI, CT, angiography, or a combination of these is required to delineate local tumor extent, vascular displacement, and compartmental localization.

BONE SCANS

Bone scintigraphy helps determine polyostotic involvement, metastatic disease, and intraosseous extension of tumor. Malignant bone tumors, although solitary, may in rare cases present with skeletal metastasis. Skip metastases are rarely detected by bone scan, because they are small and localized to the fatty marrow and do not excite cortical response.

 Appreciation of the intraosseous extension of a bone tumor is important in surgical planning. Removal of bone 3 to 4 cm beyond the area of scintigraphic abnormality...
has been accepted as a safe margin for limb-sparing procedures after induction chemotherapy.

**COMPUTED TOMOGRAPHY**

CT allows accurate determination of intra- and extracortical extent of skeletal neoplasms. It accurately depicts the transverse relationship of a tumor. By varying window settings, one can study cortical bone, intramedullary space, adjacent muscles, and extracortical soft tissue extension. CT should include the entire bone and the adjacent joint. Infusion of intravenous contrast material permits identification of the adjacent large vascular structures. CT evaluation must be individualized. To obtain the maximum benefit and from image reconstruction, the surgeon should discuss with the radiologist what information is desired. Three-dimensional reconstruction may be useful. Today, CT and MRI are considered complementary studies for bone sarcomas. Both studies are recommended for most patients.

**MAGNETIC RESONANCE IMAGING AND STAGING**

MRI has several advantages in the diagnoses of bone sarcomas. It has better contrast discrimination than any other modality; furthermore, imaging can be performed in any plane. MRI is ideal for imaging the medullary marrow and thus for detection of tumor as well as the extracortical component. It has proved especially helpful in several heretofore difficult clinical situations, such as detecting small lesions, evaluating a positive bone scan when the corresponding plain radiograph is negative, determining the extent of infiltrative tumors, and detecting skip metastases.

Dynamic MRI is currently being evaluated as a more accurate method of determining intracortical extent of tumor than conventional MR. Iwasawa et al. performed a microscopic evaluation of six macroscopics after tumor resection and chemotherapy. They concluded that the calculation of the slope value of dynamic MRI discriminated regions of microscopic invasion from tumor-free marrow in patients with osteosarcoma after chemotherapy. The slope value of dynamic MRI was greater in the region of microscopic invasion than in the tumor-free marrow and less than in the area showing macroscopic tumor invasion. This technique may provide more accurate determination of intracortical bony extent than traditional MRI.

**ANGIOGRAPHY**

The technique of arteriography for bone lesions differs from that used for arterial disease. At least two views (biplane) are necessary to determine the relation of the major vessels to the tumor. Because experience with limb-sparing procedures has increased, it has become essential to determine individual vascular patterns before resection. This is especially crucial for tumors of the proximal tibia, where vascular anomalies are common. Angiography is the most reliable means of determining vascular anatomy and displacement, whereas MRI and CT better demonstrate extracortical extension. Presently, magnetic resonance angiography is being evaluated in the treatment of bone sarcomas.

**THALLIUM SCANS**

Thallium 201 scintigraphy has been shown to accumulate in musculoskeletal neoplasms; however, it cannot distinguish benign from malignant tumors. Thallium scintigraphy is helpful in following the response to neoadjuvant treatment and detecting local recurrence when MRI cannot be used.

**CHOOSING A METHOD OF RADILOGIC EVALUATION**

All of the above studies are required in the preoperative evaluation of a bone sarcoma. Each study has unique benefits. Bloem et al. performed a prospective study comparing results of CT, MRI, scintigraphy, and angiography with 56 resected specimens to determine the appropriate choice of procedures. MRI, the single best study, was most accurate for determining intracortical extent of tumor; scintigraphy and CT were often misleading. Angiography was performed only if the primary tumor was in the vicinity of the major vascular structures. They also reported that CT and MRI were equally accurate in evaluating cortical changes. MRI was superior to CT for detecting muscle involvement in the knee, pelvis, and shoulder.

MRI and CT (transverse data), combined with bone scans and angiography, allow the physician to develop a three-dimensional construct of the local tumor area before surgery and thereby formulate a detailed surgical approach.

**BIOPSY TECHNIQUE AND TIMING**

The biopsy of a suspected bone tumor must be performed with great care and skill. This principle cannot be overemphasized. The consequences of a poorly executed biopsy are often the deciding factor in the choice between a limb-salvage procedure and amputation. Murray and coworkers from the M. D. Anderson Cancer Center judged that only 19% of patients referred to that institution for treatment of primary bone sarcomas had properly placed biopsies. All of these patients had open (incisional) biopsies, whereas 92% of such procedures performed at the M. D. Anderson Cancer Center over the same period were needle biopsies.

Similarly, Mankin et al. compared the results of biopsies performed at the referring institution with those performed at the treatment center. In this study, which involved 329 patients, a major error in diagnosis occurred in 60% of patients from referring hospitals. Importantly, 18.2% of the referred patients had to have less than optimal treatment owing to problems related to the biopsy, and for 8.5% of the total, the prognosis and outcome were thought to have been adversely affected by the biopsy. It is recommended that the biopsy be performed by the surgeon who will make the ultimate decision about the operative procedure. This entails referring some patients who are strongly suspected of having primary bone malignancies to a regional cancer center for biopsy.

Trehpene or core biopsy is recommended and often obtains an adequate specimen for diagnosis. Multiple samples can be obtained from the same puncture site by slightly changing the angle of approach. Radiographs should be obtained to document the position of the trocar. Core biopsy is preferred if a limb-sparing option exists, because it entails less local contamination than does open biopsy. Core biopsy is especially helpful in difficult areas, such as the spine, pelvis, and hips. If a core biopsy proves to be inadequate, a small incisional biopsy is performed.

Every precaution should be taken to avoid contamination when performing an open biopsy. A tourniquet is used if feasible. If a soft tissue component is present, there is no need to biopsy the underlying bone. To decrease subsequent hemorrhage, polymethylmethacrylate (PMMA) is used to plug a cortical window. Gelfoam is used for hemostasis in the soft tissue. The overlaying pseudocapsule is carefully closed to ensure maximum hemostasis. If it is necessary to biopsy the underlying bone, it is essential to use a small, rounded cortical window, especially if the tumor requires primary radiotherapy. Large segments will not reossify, and they often fracture and require late amputations. Regardless of the technique used, tumor cells contaminate all tissue planes and compartments transversed. All biopsy sites must therefore be removed en bloc when the tumor is resected or irradiated.

**RESTAGING AFTER PREOPERATIVE CHEMOTHERAPY**

With the advent of preoperative chemotherapy for osteosarcoma, a need has developed for serial evaluation of the clinical and radiographic response of the tumor before surgery. The staging and preoperative clinical studies previously described are used to evaluate tumor response. These studies have been summarized. Complete restaging studies should be obtained after the completion of induction chemotherapy. MRI, CT, thallium scans, and angiography should be evaluated before making a final surgical decision.

**CLINICAL EVALUATION**

Pain often decreases after induction chemotherapy. Alkaline phosphatase (AP) levels likewise decrease. The tumor shrinks, especially if significant matrix is not present. Conversely, increase of pain, elevated AP values, and increasing tumor size are signs of tumor progression.

**PLAIN RADIOGRAPHY**

There is a good correlation between radiographic response and the amount of necrosis. Smith and colleagues described the radiographic responses seen on serial radiographs: increased ossification of tumor osteoid, marked thickening and new bone formation of the periosteum and tumor border (giving the tumor a more...
"benign" appearance, and decreased soft tissue mass. The healing ossification is usually solid, homogeneous, and regular and is easily differentiated from tumor osteoid. Less significant changes take place within the intramedullary component, which may include both increased sclerosis and lysis, presumably caused by necrosis and hemorrhage.

**ANGIOGRAPHY**

After chemotherapy, vascularity decreases markedly. Chuang et al. evaluated 53 patients and reported that those with a complete angiographic response had more than 90% necrosis; among those with a partial response, necrosis ranged from 40% to 78%. They concluded that angiographic evaluation was as reliable as pathologic evaluation and that the angiographic features were the best clinical criteria for the evaluation of tumor response.

Carrasco and coworkers from the M. D. Anderson Cancer Center reported on their extensive experience with intraarterial chemotherapy for osteosarcoma (81 patients) and evaluated the angiographic appearance and changes after two and four cycles of preoperative chemotherapy. They developed a simple radiographic system for angiographic changes. They evaluated the midarterial (tumor vascularity) and parenchymal (capillary) phases. They described three types of responses:

1. Angiographic response: complete disappearance of tumor vascularity and stain.
2. Total disappearance of tumor vascularity, with slight persistence of tumor stain (capillary phase).
3. No response: persistence of tumor vascularity and capillary stain.

They reported that 40% of the histologic responders (more than 90% tumor necrosis) and 91% of nonresponders were identified after two cycles. The number of courses was no different between the responders and nonresponders. They concluded that the disappearance of tumor vascularity after two courses of chemotherapy was highly suggestive of a good histologic response and was unlikely to occur in the histologic nonresponders.

**COMPUTED TOMOGRAPHY**

The most consistent finding in patients who respond to therapy is a decrease in soft tissue mass and the development of a rim-like calcification similar to that seen on plain radiographs. Changes in marrow are not helpful in evaluating response.

**BONE SCINTIGRAPHY**

Bone scan changes are difficult to evaluate. A decrease in activity generally indicates a favorable response; however, reparative bone formation, signaled by increased activity, may be misleading. Dynamic (quantitative) bone scans, which are based on tumor blood flow and regional plasma clearance by bone and soft tissue, may allow more valid evaluations. Regions that show a greater than 20% decrease in technetium 99m methylene diphosphonate plasma clearance are reported to be associated with necrotic tumor. To quantify bone scans, a tumor to nontumor ratio is obtained after bone scintigraphy. This ratio is then determined preoperatively and after induction chemotherapy on serial scans. A decrease in this ratio is an indication of a good response to chemotherapy.

**MAGNETIC RESONANCE IMAGING**

Monitoring of neoadjuvant chemotherapy by MRI has become the focus of many studies. Holscher and colleagues evaluated 57 patients at the University Hospital of Leiden. T1- and T2-weighted images were obtained in longitudinal, coronal or sagittal, and axial planes. Factors evaluated were margins, homogeneity, hematoma, fibrosis, calcification liquefaction, edema, joint effusion, and fracture. The authors concluded that increased tumor volume or increased or unchanged peritumoral edema and inflammation indicated a poor response. Subjective criteria, such as improved tumor demarcation or an increase in size of area of low signal intensity (presumably necrotic tumor), were independent of tumor response. They concluded that subjective criteria could not predict the good responders.

Conventional MRI is not specific enough to distinguish viable tumor from chemotherapy-related inflammation. On routine T2-weighted images, the signals for tumor, hemorrhage, necrosis, and edema are similar. Tumor cannot be differentiated from inflammation on T1-weighted gadolinium-enhanced images.

**THALLIUM SCINTIGRAPHY**

Several studies have demonstrated that serial thallium 201 scintigraphy is an accurate way to follow the response of osteosarcoma during the course of neoadjuvant treatment and to predict tumor responses. Rosen and associates used this technique to evaluate tumor necrosis after preoperative chemotherapy in 27 patients. They concluded that serial thallium scans can accurately predict a good histologic response and good prognosis. Furthermore, thallium scintigraphy can identify poor responders within the first 2 weeks after the initiation of treatment. They described a simple classification of response: type I, no response; type II, discemible lesion still present; type III, no detectable lesion. All patients with a type III classification and 67% of those with a type II classification were rated as good responders (types II and III constituted a total of nine patients).

**POSITRON EMISSION TOMOGRAPHY**

Positron emission tomographic scans are nuclear medicine scintigraphy techniques that use $^{18}$F-fluoro-2-deoxy-D-glucose as the radiopharmaceutical. This technique is under investigation. It is hoped that it will be able to dynamically evaluate the tumor and the percentage of tumor necrosis after chemotherapy.

**SURGICAL MANAGEMENT OF SKELETAL TUMORS**

Surgical removal, including curettage, resection, and amputation, is the traditional method of managing skeletal neoplasms. Limb-sparing techniques were developed during the early 1970s. Enneking and colleagues have described cryosurgery for some bony tumors. Enneking and colleagues have formulated means of classifying surgical procedures based on the surgical plane of dissection in relationship to the tumor (Table 39.2-1) and the method of accomplishing the removal (Table 39.2-3) and the various operative procedures and gives surgeons a common language.
TABLE 39.2-5. Surgical Procedure, Plane of Dissection, and Residual Disease for Musculoskeletal Tumors

<table>
<thead>
<tr>
<th>Type</th>
<th>Plane of Dissection</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intralesional</td>
<td>Curettage, direct into lesion, pseudocapsule</td>
<td>Lesion macroscopically remains, entire operative field potentially cont.</td>
</tr>
<tr>
<td>Marginal</td>
<td>Resection through pseudocapsule or reactive tissue</td>
<td>Macroscopic tumor remains, reactive zone removed, potential contamination</td>
</tr>
<tr>
<td>Wide</td>
<td>Resection through pseudocapsule or reactive tissue</td>
<td>Macroscopic tumor remains, reactive zone removed, potential contamination</td>
</tr>
<tr>
<td>Radical</td>
<td>Resection through pseudocapsule or entire tumor</td>
<td>No residual disease</td>
</tr>
</tbody>
</table>

Intralesional: An intralesional procedure passes through the pseudocapsule of the neoplasm directly into the lesion. Macroscopic tumor remains, and the entire operative field is potentially contaminated. Curettage is an intralesional procedure.

Marginal: A marginal procedure is one in which the entire lesion is removed in a single piece. The plane of dissection passes through the pseudocapsule or reactive zone around the lesion. When performed for a sarcoma, it leaves macroscopic disease.

Wide (intracompartmental): A wide excision, commonly termed *en bloc* resection, includes the entire tumor, the reactive zone, and a cuff of normal tissue. The entire structure of origin of the tumor is not removed. In patients with high-grade sarcomas, this procedure may leave skip nodules.

Radical (extracompartmental): A radical procedure involves removal of the entire tumor and the structure of origin of the lesion. The plane of dissection is beyond the limiting fascial or bony borders.

It is important to note that any of these procedures may be accomplished either by a local (i.e., limb-sparing) procedure or by amputation. Thus, amputation may entail a marginal, wide, or radical excision, depending on the plane through which it passes. Amputation does not necessarily remove all cancer, but it can achieve a specific margin. The local anatomy determines how such a margin can be obtained. Therefore, the aim of preoperative staging is to assess local tumor extent and important local anatomy to enable the surgeon to decide how to achieve a desired margin (i.e., to evaluate the feasibility of one surgical procedure over another). This system allows meaningful comparisons of surgical procedures, end-result reporting, and analysis of combined data. In general, benign bone tumors may be treated adequately by an intralesional procedure (curettage) or a marginal excision. Malignant tumors require either a wide (intracompartmental) or radical (extracompartmental) removal, by an amputation or an *en bloc* procedure. Today, wide excision combined with adjuvant chemotherapy is the treatment for most high-grade bone sarcomas. Radical resections are rare.

**PRINCIPLES AND TECHNIQUES OF LIMB-SPARING SURGERY**

Limb-salvage surgery is a safe operation for selected cases. This technique may be used for all spindle cell sarcomas, regardless of histogenesis. Approximately 90% of osteosarcomas can be treated successfully with this technique. Successful management of localized osteosarcomas and other sarcomas requires careful coordination and timing of staging studies, biopsy, surgery, and preoperative and postoperative chemotherapy or radiation therapy.

**FIGURE 39.2-2.** Patient survival after three different types of surgical procedures for osteosarcoma of the distal femur.

**PHASES OF OPERATION**

Successful limb-sparing procedures consist of three surgical phases:

1. Resection of tumor: Tumor resection follows strictly the principles of oncologic surgery. Avoiding local recurrence is the criterion of success and the main determinant of how much bone and soft tissue are to be removed.
2. Skeletal reconstruction: The average skeletal defect following adequate bone tumor resection measures 15 to 20 cm. Techniques of reconstruction vary and are independent of the resection, although the degree of resection may favor one technique over another.
3. Soft tissue and muscle transfers: Muscle transfers are performed to cover and close the resection site and to restore motor power. Adequate skin and muscle coverage is mandatory. Distal tissue transfers are not used because of the possibility of contamination.

**GUIDELINES FOR LIMB-SPARING RESECTION**

The surgical guidelines and technique of limb-sparing surgery used by the senior author (MM) are as follows:

1. No major neurovascular tumor involvement
2. Wide resection of the affected bone, with a normal muscle cuff in all directions
3. *En bloc* removal of all previous biopsy sites and potentially contaminated tissue
4. Resection of bone 3 to 4 cm beyond abnormal uptake, as determined by CT or MRI and bone scan
5. Resection of the adjacent joint and capsule
6. Adequate motor reconstruction, accomplished by regional muscle transfers
7. Adequate soft tissue coverage

**TYPES OF SKELETAL RECONSTRUCTION**

Large skeletal defects are reconstructed after tumor resection by several different modalities. Osteoarticular defects are most often reconstructed by segmental, custom prostheses that are fixed to the remaining intramedullary bone by PMMA. The newer knee prostheses allow some rotation as well as flexion and extension, this mobility decreases the forces on the bone-cement interface and thus reduces the risk of loosening.
Pain was usually minimal, but when present, was associated only with lower extremity amputation. The pain pattern suggested deafferentation syndromes. No fertility was a problem. Twenty-three normal progeny were born after chemotherapy to eight women and the wives of five men. Only two women were among patients who did not do well, multiple symptoms, family problems, and socioeconomic problems were more common than among patients who fared well.

The reported rates of psychopathology among amputees and those undergoing limb-sparing surgery did not differ significantly. The benefit of attention to the management of depression, treatment of substance abuse, and help with financial difficulties could contribute to the quality of life of patients who underwent limb-sparing surgery or amputation. Pain management, physical and vocational rehabilitation, and sexual counseling may also be of benefit, as may psychotherapeutic counseling when required.

CONTRAINDICATIONS TO LIMB-SPARING SURGERY

Major Neurovascular Involvement

Although vascular grafts may be used, the adjacent nerves are usually at risk, making successful resection less likely. In addition, the magnitude of resection in combination with vascular reconstruction is often prohibitive.

Pathologic Fractures

A fracture through a bone affected by a tumor spreads tumor cells via the hematoma beyond accurately determined limits. The risk of local recurrence increases under such circumstances. If a pathologic fracture heals after neoadjuvant chemotherapy, a limb-salvage procedure may be performed successfully.

Inappropriate Biopsy Sites

An inappropriate or poorly planned biopsy jeopardizes local tumor control by contaminating normal tissue planes and compartments.

Infection

The risk of infection after implantation of a metallic device or an allograft in an infected area is prohibitive. Sepsis jeopardizes the effectiveness of adjuvant chemotherapy.

Skeletal Immaturity

The predicted leg-length discrepancy should not be greater than 6 to 8 cm, although expandable prostheses have been used with success in this situation. Upper extremity reconstruction is independent of skeletal maturity.

Extensive Muscle Involvement

Enough muscle must remain to reconstruct a functional extremity.

RELATIONSHIP OF VARIOUS ASPECTS OF SURGICAL MANAGEMENT TO PROGNOSIS

Makley and coworkers from the Children's Cancer Study Group reported a randomized study of 166 patients that examined the relationship of various aspects of surgical management to prognosis for disease-free survival. They found no advantage to the various aspects of surgical management, specifically, interval from first symptom to definitive surgery, interval from biopsy to definitive surgery, surgical sequence, type of surgery, or site of primary tumor.

QUALITY-OF-LIFE CONSIDERATIONS: LIMB-SPARING SURGERY VERSUS AMPUTATION

During the 1990s, as the techniques of limb-sparing surgery were being developed, it had been assumed that such surgery was superior to amputation. Nonetheless, when complications occurred, many surgeons thought that an amputation might have been preferable. Despite the extensive literature on the various chemotherapy regimens, surgical techniques, and limb-sparing surgery, few studies have focused on the patients' evaluation of their overall quality of life. Two studies that have been published are described here.

1. The reported rates of psychopathology among amputees and those undergoing limb-sparing surgery did not differ significantly.
2. Fertility was not a problem. Twenty-three normal progeny were born after chemotherapy to eight women and the wives of five men. Only two women were considered infertile; both had undergone radiation therapy associated with other childhood cancers.
3. All responders who had undergone limb-sparing surgery believed the effort to save their limb was worthwhile. Twenty patients rated the effort of limb-salvage very worthwhile, (mean 4.5 out of 5). Those whom the attempt at limb-salvage failed rated the effort as 4.0 (not significantly different than the successful group). Those patients who were less satisfied with surgery had secondary amputations.
4. Pain was usually minimal, but when present, was associated only with lower extremity amputation. The pain pattern suggested deafferentation syndromes. No patients undergoing upper extremity limb-sparing procedures had pain as a sequela.
5. Among patients who did not do well, multiple symptoms, family problems, and socioeconomic problems were more common than among patients who fared well.

The authors concluded that attention to the management of depression, treatment of substance abuse, and help with financial difficulties could contribute to the quality of life of patients who underwent limb-sparing surgery or amputation. Pain management, physical and vocational rehabilitation, and sexual counseling may also be of benefit, as may psychotherapeutic counseling when required.
Christ and coworkers evaluated the long-term psychosocial effects of limb-sparing surgery and primary amputation for coping capacity and the degree of psychopathology. The overall incidence of emotional disturbance in the entire osteosarcoma group was no different than the general population. Unlike patients in other studies, those in the group with initial amputations had substantially difficult maintaining an optimal functional level. Their difficulty was even greater than that of limb-salvage patients with a compromised outcome, including those with late amputation. Specifically:

1. An amputee was significantly less likely to have married than a limb-spared patient.
2. Coping mechanisms of those with primary amputations were less effective than those patients in the limb-salvage group. This deficit was still evident several years after surgery.
3. Patients who had limb-salvage without later complications were very pleased with their outcome.
4. Good work experience was an important compensation for physical loss.
5. Male dependency needs were often underestimated. Some men were left to manage their own adaptation tasks, whereas for females the opposite was true. Female patients tended to become excessively dependent.
6. Patients reported no difficulty in enjoying sexual activity. The first post-surgical sexual experience was described as no more traumatic than the first experience that required showing the leg (e.g., swimming).

Despite good social support scores, the amputees had higher psychopathology scores than patients who had undergone limb-sparing procedures. The authors concluded that patients undergoing primary amputation need more intensive support than those whose limbs are spared. They recommend an overall approach similar to that for posttraumatic stress disorder.

**AMPUTATIONS**

An amputation provides definitive surgical treatment in patients in whom a limb-sparing resection is not a prudent option. A significant number of patients still require amputation, despite the advent of limb-sparing surgery. In contrast to amputations performed for noncancer causes, those for cancer tend to be at a more proximal anatomic level, to occur in younger persons (reflecting the incidence of bone sarcomas), and to be technically more difficult. The resultant psychological and cosmetic losses are also more substantial. The amputation experience of the National Cancer Institute since the 1960s has been reviewed; 89% of these procedures were done for sarcomas. Fifty-five percent of the lower extremity amputations were either hip disarticulations or hemipelvectomies. One-half of the upper extremity amputations were interscapulothoracic (forequarter) resections. Osteosarcoma accounted for one-third of all amputations. Large lesions around the pelvis or proximal femur still generally require an amputation, whereas most sarcomas of the shoulder girdle and knee can now be resected. Amputation techniques are well described in the literature.

**CRYOSURGERY**

Cryosurgery is the use of liquid nitrogen (temperature, –196°C) after curettage of a tumor cavity to kill the remaining tumor cells. Necrosis has been shown to occur between –20° and –40°C. In general, a double freeze-thaw cycle is required. The aim of this technique is to enhance local tumor control after a careful curettage and thus avoid resection of the involved bone. Cryosurgery was initially developed by Marceau and colleagues at Memorial Hospital for treatment of metastatic bone tumors. They have applied this technique to the treatment of aggressive benign tumors, specifically GCTs, and more recently to low-grade sarcomas as well as chordomas. The local recurrence rate after cryosurgery for these aggressive benign tumors has decreased from more than 30% to 40% to between 5% and 10%. This technique is not used for high-grade sarcomas.

**CHEMOTHERAPY FOR BONE SARCOMAS**

Before the advent of effective adjuvant chemotherapy, the outlook for patients with osteosarcoma was dismal. The overwhelming majority of patients who presented without evidence of metastases and were treated with surgery ultimately developed metastases and died. Results of these trials confirm that the natural history of osteosarcoma has not changed since the 1970s; fewer patients with nonmetastatic osteosarcoma remain alive, and more recent trials that include presurgical chemotherapy, suggest that life tables of event-free survival have stable plateaus beyond 4 years and that relapses after 3 years are infrequent. The majority of patients surviving 3 years without evidence of recurrence are probably cured.

The rationale for adjuvant chemotherapy of osteosarcoma is derived from experimental evidence that microscopic metastatic disease can be eradicated if the primary tumor has been applied successfully in the management of other childhood tumors. However, osteosarcoma is a relatively drug-resistant neoplasm, and efforts to improve local tumor control after surgery have included combinations of various agents that require showing the leg (e.g., swimming). Female patients tended to become excessively dependent.

The hopelessness for patients with osteosarcoma led to the enthusiastic application of the available agents, singly or in combination, as adjuvant therapy for patients with nonmetastatic osteosarcoma. An apparent improvement in outcome compared with the historical experience before 1970. Results of these trials confirm that the natural history of osteosarcoma has not changed since the 1970s; fewer than 20% of patients treated only with surgery ultimately developed metastases and died. The local recurrence rate after cryosurgery for these aggressive benign tumors has decreased from more than 30% to 40% to between 5% and 10%. This technique is not used for high-grade sarcomas.

Two randomized, controlled trials were conducted in the mid-1980s by investigators of the Multi-Institutional Osteosarcoma Study and from the University of California, Los Angeles to resolve the controversy over the role of adjuvant chemotherapy in osteosarcoma. Both studies included a control group treated only with surgery of the primary tumor and no post-surgical adjuvant chemotherapy. Preliminary and mature results of these studies confirm the favorable impact of adjuvant chemotherapy in the treatment of osteosarcoma. Furthermore, life tables of event-free survival for patients in the control groups of these studies recapitulated the historical experience before 1970. Results of these trials confirm that the natural history of osteosarcoma has not changed since the 1970s; fewer than 20% of patients treated only with surgery of the primary tumor can be expected to survive relapse-free. The bleak historical experience that served as the background for many uncontrolled adjuvant trials in the 1970s appears to be equally valid as a control for studies in the 1980s, 1990s, and beyond. Microscopic, subclinical metastatic disease can be presumed to exist in virtually all patients at the time of diagnosis. Although the more favorable results from the Mayo Clinic for patients treated without adjuvant chemotherapy remain unexplained, it is apparent from the Multi-Institutional Osteosarcoma Study and University of California, Los Angeles studies that adjuvant chemotherapy has a significant favorable influence on outcome and should, therefore, be recommended for all patients with osteosarcoma.

**ADJUVANT CHEMOTHERAPY**

The rationale for adjuvant chemotherapy of osteosarcoma is derived from experimental evidence that microscopic metastatic disease can be eradicated if the primary tumor has been applied successfully in the management of other childhood tumors. However, osteosarcoma is a relatively drug-resistant neoplasm, and results of studies of the activity of single agents and drugs in combination against macroscopic osteosarcoma have been disappointing. Few drugs have produced responses in more than 15% of patients, and most responses are partial. Notable exceptions are the responses observed in trials of doxorubicin, cisplatin, ifosfamide, and high-dose methotrexate (HDMTX) with leucovorin rescue. Logic dictates that the application of agents with only modest activity against macroscopic osteosarcoma should not influence the natural history of this disease. Experimental evidence, however, suggests that eradication of microscopic metastases is possible, even with drugs that are marginally effective or even ineffective against gross macroscopic tumors.
The optimal chemotherapy regimen for treatment of osteosarcoma continues to be the subject of investigation and heated debate. Although most investigators use intensive, multiagent regimens, the superiority of such regimens as compared to simpler, shorter, less intensive multiagent regimens has been questioned. A large, randomized study conducted by the European Osteosarcoma Intergroup compared the combination of doxorubicin and cisplatin alone, or doxorubicin and cisplatin alternating with HDMTX as pre- and postsurgical chemotherapy for patients with osteosarcoma. The disease-free survival for patients receiving the two-drug regimen (without HDMTX) was significantly superior to that of patients treated with all three drugs. However, the intensity of administration of HDMTX was compromised by the design of the study, and the overall outcome of patients in this report is inferior to that observed in other studies.

The role of HDMTX in chemotherapy of osteosarcoma requires further investigation. The effectiveness of this drug may be dose-dependent, and few modern regimens incorporate it. Carboplatin is an attractive agent to use in place of cisplatin because of possible reduced renal and ototoxicity. However, this analogue may be considerably less active against osteosarcoma than cisplatin, and it cannot yet be recommended.

The optimal chemotherapy regimen for treatment of osteosarcoma continues to be the subject of investigation and heated debate. Although most investigators use intensive, multiagent regimens, the superiority of such regimens as compared to simpler, shorter, less intensive multiagent regimens has been questioned. A large, randomized study conducted by the European Osteosarcoma Intergroup compared the efficacy of six cycles of doxorubicin and cisplatin with the more complicated, multiagent T-10 regimen pioneered at the Memorial Sloan-Kettering Cancer Center (Fig. 39.2-6). No differences in progression-free (47% at 3 years and 44% at 5 years) and overall survival (85% at 3 years and 55% at 5 years) were detected between the treatment groups, although these results are unsatisfactory when compared with the outcomes achieved on other studies conducted in North America and Europe. Thus, whether any regimen is superior to six cycles of doxorubicin and cisplatin remains an open question.

Further improvements in outcomes for patients with osteosarcoma will likely result from the development of new active agents. The activity of ifosfamide against macroscopic disease has been demonstrated, and this drug has been incorporated into newer regimens under study with promising results. The role of ifosfamide in the presurgical and adjuvant settings was addressed specifically in a randomized trial conducted by the American Pediatric Cooperative Oncology Groups. Overall, the projected event-free survival at 3 years is 66% (P. Meyers, personal communication, 1999), but the data are immature, and results pertaining to
the contribution of ifosfamide have not yet been analyzed.

**PRESURGICAL CHEMOTHERAPY**

Presurgical chemotherapy has been used with increasing frequency in the management of osteosarcoma. This strategy evolved concurrently with limb-sparing procedures. Initial attempts at limb salvage at the Memorial Sloan-Kettering Cancer Center in 1973 involved the fabrication of customized endoprostheses for select patients undergoing *en bloc* resection. While the prosthesis was being made (a process requiring up to 3 months), chemotherapy was administered to prevent tumor progression. Retrospectively, it appeared that patients treated with presurgical chemotherapy fared better than did patients treated during the same period with immediate surgery and postoperative adjuvant therapy.

In studies from the Memorial Sloan-Kettering Cancer Center, responsiveness of the primary tumor to preoperative chemotherapy, assessed by histologic evaluation, was found to be a powerful prognostic factor; unfavorable responders were likely to develop distant metastases despite continued use of chemotherapy with the same agents after surgery. The prognostic significance of tumor response to preoperative chemotherapy has been confirmed in multiple studies. An analysis from the Memorial Sloan-Kettering Cancer Center, responsiveness of the primary tumor to preoperative chemotherapy, assessed by histologic evaluation, was found to be a powerful prognostic factor; unfavorable responders were likely to develop distant metastases despite continued use of chemotherapy with the same agents after surgery. The prognostic significance of tumor response to preoperative chemotherapy has been confirmed in multiple studies.

Although the initial impetus for presurgical chemotherapy was limb salvage, several theoretical advantages of presurgical chemotherapy apply to all patients with osteosarcoma. Because chemotherapy is administered very soon after biopsy and diagnosis, treatment of the micrometastases known to be present in the majority of patients can be instituted early. This offers a substantial advantage over the traditional adjuvant approach, in which the administration of systemic chemotherapy is delayed by 1 month or more for surgery and wound healing. Earlier administration of systemic treatment may reduce the emergence of drug-resistant cells in the micrometastases.

For the surgeon, presurgical chemotherapy offers some advantages, because it allows time for fabrication of prostheses and may effect a reduction of bulky tumors, thereby increasing the feasibility of limb-salvage surgery in selected patients.

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**TABLE 39.2-8. Considerations for Presurgical and Postsurgical Chemotherapy**

**ASSESSMENT OF TUMOR RESPONSE**

Assessment of the response of primary tumors has been based on clinical and radiographic data (see Restaging after Preoperative Chemotherapy, earlier in this chapter); however, the histologic appearance of the resected tumor specimen after presurgical chemotherapy has emerged as the standard for measuring response.

Several systems for grading the effect of preoperative chemotherapy have been proposed, all of which are based on the degree of cellularity and necrosis in the resected specimen. Grading systems are necessarily imprecise and subject to sampling errors; however, with scrupulous attention to adequate sectioning from many sites of the surgical specimen, the degree of response can be reliably and reproducibly assessed. The grading system designed at Memorial Sloan-Kettering Cancer Center by Huvos and colleagues has been used widely. Grade III and IV responses, indicating extensive to complete response in the primary tumor, are considered favorable. Grade I and II responses, indicating minimal destruction of the tumor, are unfavorable. In studies using the Huvos grading system, patients with favorable response (grade III or IV) are likely to develop distant metastases. Thus, patients at high risk for recurrent disease can apparently be identified early in treatment on the basis of poor response to presurgical chemotherapy. The Huvos grading system has served as a model for other systems for grading tumor response.

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**TABLE 39.2-9. Histologic Grading of the Effect of Preoperative Chemotherapy on Primary Osteosarcoma**

Although the predictive value of tumor response to presurgical chemotherapy is now indisputable, a number of problems have surfaced in the application of such response grading to patient management. Different criteria for the definition of favorable and unfavorable response are used in different grading systems, making comparisons among studies difficult. The grading system formerly used by the German Society of Pediatric Oncology (GPO) identifies six categories of response. In the Germany-Austria-Swiss Cooperative Osteosarcoma Study (COSS 80) study conducted by the GPO, favorable response was defined as more than 50% tumor destruction after presurgical chemotherapy; however, in more recent GPO studies, 90% destruction is required. The grading system favored by investigators at the M. D. Anderson Cancer Center divides response into three categories: (1) no effect or doubtful effect with less than 40% tumor destruction; (2) partial effect with 40% to 60% tumor destruction; and (3) definite effect, in which more than 60% of the tumor is destroyed and fibrovascular regeneration is present. Of particular concern is that an update of the Memorial Sloan-Kettering experience with presurgical chemotherapy suggests that a modification of the Huvos system has been used widely. (Table 39.2-9). Grade III and IV responses, indicating extensive to complete response in the primary tumor, are considered favorable. Grade I and II responses, indicating minimal destruction of the tumor, are unfavorable. In studies using the Huvos grading system, patients with favorable response (grade III or IV) are likely to develop distant metastases. Thus, patients at high risk for recurrent disease can apparently be identified early in treatment on the basis of poor response to presurgical chemotherapy. The Huvos grading system has served as a model for other systems for grading tumor response.

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Of particular concern is that an update of the Memorial Sloan-Kettering experience with presurgical chemotherapy suggests that a modification of the Huvos system is in order because the implications of “favorable” and “unfavorable” response to presurgical chemotherapy have changed somewhat. It is apparent that grade IV response is predictive of favorable outcome; however, the outcome of patients with grade III response is not significantly superior to that of patients with grade II response. Thus, only patients who experience a grade IV response to presurgical chemotherapy might be considered as being in the most favorable prognostic group.

Perhaps most problematic are the differences among studies conducted to date in the timing of surgery relative to the initiation of chemotherapy, and especially the variable duration of exposure to chemotherapy before definitive surgery and histologic evaluation of the response of the primary tumor. It appears that presurgical chemotherapy regimens of longer duration are associated with a higher proportion of “favorable” responders. However, as the duration of presurgical chemotherapy increases, the predictive value of response for outcome may be lost; longer, more intensive presurgical regimens may achieve a greater proportion of favorable responders, but the favorable responses achieved with such regimens may not translate into more favorable outcomes. An analysis from the Memorial Sloan-Kettering Cancer Center suggests that this is indeed the case.
TAILORING THERAPY

One of the most compelling rationales for presurgical chemotherapy is its use as an *in vivo* drug trial to determine the sensitivity of an individual tumor and to customize postoperative chemotherapy. As noted above, results of studies from the Memorial Sloan-Kettering Cancer Center and elsewhere suggest that patients who respond favorably to presurgical therapy can be treated postoperatively. Patients whose tumors are unresponsive to the presurgical regimen have a much lower favorable outcome and might benefit from a change in chemotherapeutic agents. This strategy was pioneered at Memorial Sloan-Kettering in the T-10 protocol [128] (see Fig. 39.2-4A). Patients were treated preoperatively with HDMTX, the BCD combination, and doxorubicin. Those with favorable (grades III and IV) histologic responses continued to receive the same agents postoperatively (T-10B regimen). Patients demonstrating unfavorable (grades I and II) histologic responses were treated on regimen T-10A, consisting of doxorubicin and cisplatin along with the BCD combination (without HDMTX) postoperatively (see Fig. 39.2-4B). Although only 39% of patients achieved a favorable histologic response to presurgical chemotherapy (51% if only patients younger than 21 years were analyzed), virtually all of the favorable responders were projected to survive free of recurrence. [206] The patients whose primary tumors demonstrated an unfavorable histologic response were switched to the cisplatin-containing regimen and almost 50% were initially projected to remain relapse-free at 3 years. Overall, in preliminary reports, 90% of patients treated on the T-10 regimen with tailored therapy were projected to remain disease-free at 3 years. Moreover, a significant difference in outcome could no longer be detected between those who did and did not respond to presurgical chemotherapy, supporting the contention that poor responders were “salvaged” by the administration of alternative chemotherapy postoperatively. Because of these very favorable preliminary results, the T-10 protocol served as a model for many of the osteosarcoma treatment studies launched in the 1980s and 1990s, virtually all of which featured presurgical chemotherapy and tailoring of treatment on the basis of responsiveness of the primary tumor.

NEOADJUVANT CHEMOTHERAPY

Results reported from representative trials using presurgical chemotherapy are summarized in Table 39.2-7. Responses in the primary tumor have been variable, with favorable responses observed in 30% to 85% of patients. The overall results are excellent but are comparable to adjuvant studies that used regimens of equal intensity without any preoperative chemotherapy (see Table 39.2-6). Furthermore, the importance of custom tailoring of therapy in this strategy remains to be defined. Several trials are pertinent in this regard. The CCG attempted to duplicate the T-10 regimen in a multimodality setting (CCG 782). [160] Results were not as favorable as those initially reported from Memorial Sloan-Kettering Cancer Center; only 28% of the patients demonstrated favorable responses in the primary tumor. These patients fared extremely well (projected 5-year event-free survival, 87%). The remaining poor-responding patients did not benefit from a change in therapy postoperatively and had a less favorable outcome (projected 5-year event-free survival, 49%). Overall, only 58% of patients in the CCG study were projected to remain free of recurrent disease at 5 years—a disappointing result when compared with the initial results reported from Memorial Sloan-Kettering. The COSS 82 trial of the GPO also tested the strategy of tailoring treatment. As in the CCG trial, results suggest that patients demonstrating poor response of the primary tumor are destined to do poorly and that treatment of poor responders with “salvage regimens” (as in the T-10 protocol) does not improve their prognosis. Investigators of the GPO concluded that active agents should not be withheld from the initial therapy of newly diagnosed patients. At the Rizzoli Institute, [217,218] overall results have improved over time, concurrent with the adoption of the strategy of presurgical chemotherapy. However, the Rizzoli investigators conclude that the improvement in prognosis more likely reflects increased effectiveness of the agents used rather than the use of presurgical chemotherapy per se, because a group of patients treated concurrently at the same institution without the benefits of presurgical chemotherapy fared just as well as patients treated with presurgical chemotherapy. [218] As in most trials of presurgical chemotherapy, an early trial of presurgical chemotherapy reported from the Rizzoli Institute demonstrated that favorable responders had a better overall outcome; change in the postoperative chemotherapy for poor responders did not alter their unfavorable prognosis. However, in a more recent Rizzoli trial conducted between 1986 and 1990, patients were treated initially with HDMTX, doxorubicin, and intraarterial cisplatin preoperatively. Favorable responders (more than 90% necrosis in their primary tumors) in their treated postoperational weeks of the same agents, were projected to receive 30 weeks of chemotherapy, including ifosfamide and etoposide in addition to doxorubicin, cisplatin, and HDMTX. Seventy-one percent of patients in this study achieved a favorable response to presurgical chemotherapy, and 71% of these patients were projected to be disease-free survivors at 5 years. Of note, the poor responding patients had a projected disease-free survival equal to that of good responders if only patients receiving adequate therapy were considered. This is one of the few studies in which the strategy of salvage chemotherapy for poorly responding patients has been shown to be of benefit.

Perhaps of greatest significance, an update of results of the Memorial Sloan-Kettering Cancer Center studies [219,220] indicates that the very promising preliminary results have eroded with further follow-up. Moreover, no difference in overall disease-free survival is apparent, regardless of whether patients received presurgical chemotherapy. Although histologic response to presurgical chemotherapy strongly predicted subsequent disease-free survival and overall survival, with longer follow-up the Memorial Sloan-Kettering investigators were unable to demonstrate an improvement in disease-free survival for poor responders who received a modification of their postoperative chemotherapy compared with a similar group of patients treated without such tailoring of treatment. [221] In support of these findings, members of the Pediatric Oncology Group reported preliminary results of a randomized trial designed to test the impact of presurgical chemotherapy on outcome of patients with extremity osteosarcoma. [222] The overall event-free survival was identical whether patients were treated with chemotherapy before definitive surgery of the primary tumor. Moreover, the overall results of this study were identical to those achieved in a predecessor study (Multi-Institutional Osteosarcoma Study) in which all patients were treated with immediate surgery followed by conventional adjuvant chemotherapy. Thus, it does not appear that the administration of presurgical chemotherapy (with or without individualizing of therapy based on tumor response) per se has led to an improvement in the outcome of children with osteosarcoma, at least in terms of rate of cure. Rather, improvements in outcome probably reflect the increasing intensity of the chemotherapy regimens used.

Although reponsiveness of the primary tumor to presurgical chemotherapy is a powerful predictor of outcome, the likelihood that an individual patient will respond cannot be predicted at the time of diagnosis. Because a majority of poor responders relapse and modifications of postoperative chemotherapy do not have an impact on this unfavorable outcome, strategies are needed to predict favorably and poorly responding patients. [223] Because a majority of poor responders relapse and modifications of postsurgical chemotherapy do not have an impact on this unfavorable outcome, strategies are needed to predict favorably and poorly responding patients. [223] Because of these findings, [223] overall results have been inconclusive. Tumor expression of high levels of HER2/neuB2 has been associated with unfavorable histologic response to chemotherapy and inferior event-free survival. [224,225] If confirmed, these findings suggest a possible intervention with anti-HER2 monoclonal antibodies (Herceptin) for patients whose tumors express high levels of this unfavorable molecular marker.

INTRAARTERIAL CHEMOTHERAPY

Presurgical chemotherapy may be administered directly into the arterial supply of the tumor to maximize drug delivery to the tumor vasculature ([Fig. 39.2-6]). Several agents, in particular, have been delivered by prolonged intraarterial infusion to the tumor. High local drug concentrations have been achieved. [226] However, the rationale for the use of intraarterial therapy is not self-evident for several reasons. Even in the presurgical era, control of the primary tumor in patients with extremity primaries was rarely a problem. Rather, micrometastatic disease present in the lung ultimately killed patients. Improvements in the outcome of patients with osteosarcoma have resulted directly from improvements of systemic chemotherapy for micrometastatic disease rather than from better local control measures. Thus, strategies that improve drug delivery to the primary tumor at the expense of drug delivery to micrometastatic disease are counterintuitive. Little evidence suggests that responses to intraarterial administration of chemotherapy are superior to those seen with systemic intravenous administration of the same agents, nor has intraarterial chemotherapy improved the proportion of patients suitable for limb-sparing surgery. Finally, the administration of intraarterial chemotherapy in resectable osteosarcoma has waned, and the strategy cannot be recommended for most patients.
Osteochondroma is the most common benign bone tumor. The tumors characteristically are sessile or pedunculated, arising from the cortex of a long tubular bone.

**TREATMENT PLANNING**

Optimal radiotherapy of bone tumors requires careful planning (Table 39.2-10). Such planning begins with tumor localization and accurate definition of the clinical and radiographic extent of tumor as well as of all tissue at risk for microscopic involvement. Precise, three-dimensional definition is required. This evaluation is identical to that done for surgical evaluation (see Preoperative Evaluation, earlier in this chapter). Using these composite studies, the maximal tumor dimensions are established.

**TABLE 39.2-10. Guidelines for Optimal Radiation Therapy in the Treatment of Bone Sarcomas**

With the clinical physicist, decisions are then made concerning the optimal choice of radiation beam (e.g., photon, electron), technique (external beam, brachytherapy, intraoperative therapy), beam modifiers (compensators, wedge filters), and immobilization system. All patients should undergo simulation and be treated with megavoltage therapy units. No role for orthovoltage (low-kilovoltage x-ray) exists in the management of primary tumors of bone.

Patient immobilization is essential to optimal radiotherapy. The patient should be placed in a comfortable position on the treatment table. The precise patient set-up should be planned using three points for reproducibility. Immobilization devices, such as casts, shells, vacuum pillows, and sandbags, are frequently necessary. Molding techniques that require a cast of the anatomic site to be treated are generally preferred when treatment fields are complex and the radiation course is lengthy.

**DOSE AND VOLUME CONSIDERATIONS**

Large treatment volumes that include the entire clinical and radiographic extent of tumor plus a generous margin for microscopic or subclinical extension of disease are needed. For tumors that tend to spread along the medullary canal (lymphoma, Ewing’s sarcoma), the standard radiation field in the past included the entire bone, with a boost of radiation to the area of bulky disease. However, current practice suggests that radiation confined to the involved area may be sufficient for small round cell bone tumors that have responded to induction chemotherapy. If large fields are needed, it is desirable to use an extended source-to-skin distance to enable the entire radiation field to fit into one portal. If extended distances are not possible and two radiation fields must abut, the abutment must pass through areas of the nonirradiated strip should overlie the lymphatic drainage, which is located medially in the extremity.

Because large doses often are necessary for treatment of malignant bone tumors, a shrinking field technique is recommended, which allows treatment to a large volume of tissue involved by subclinical disease with a moderate radiation dosage, whereas the area of gross tumor is treated with a larger, sterilizing dose.

**COMPLICATIONS OF RADIATION**

The complications of radiation are related directly to treatment dose and volume. Reactions that occur during the early stages of treatment usually are reversible and not of major significance. These include erythema, dry desquamation of the skin, and epilation. More serious late reactions may include fibrosis, contracture, atrophy, impaired growth, secondary fracture, and radiation-induced neoplasm. When pelvic treatment is necessary in young women, it is important to consider ovarian transposition whenever possible. Techniques to move the small bowel out of the pelvis are useful, as is avoiding treatment of the entire bladder if cyclophosphamide or fotemustine is also being used. Fibrosis and contracture can be minimized—or possibly avoided—by embarking on an active physical therapy program during radiation therapy; such a program should be continued in the postradiation therapy follow-up period. Whenever possible, treating across a joint space and treating an area with radiation sensitizers to normal tissue.

**RADIOThERAPY FOR BONE TUMORS**

In keeping with the multidisciplinary, multimodality approach to the treatment of bone tumors, all patients should be evaluated by a radiation oncologist and by an orthopedic and medical (or pediatric) oncologist before decisions are made concerning therapy. Close communication between members of the care team is crucial. Tumors of the axial skeleton and facial bones are treated by a combination of limited surgery and radiotherapy. Ewing’s sarcoma and peripheral primitive neuroectodermal tumors of bone may be managed by definitive radiation treatment, complete surgical excision, or combined surgical and radiotherapy approaches and are discussed in Chapter 39.1. In general, radiation therapy is not used in the primary treatment of osteosarcoma. Radiation therapy is used for patients who have refused definitive surgery, require palliation, or have lesions in axial locations.

**SOLITARY AND MULTIPLE OSTEOCHRONOMAS (EXOSTOSIS)**

Osteochondroma is the most common benign bone tumor. The tumors characteristically are sessile or pedunculated, arising from the cortex of a long tubular bone adjacent to the epiyphal plate. Osteochondromas are usually solitary, except in multiple hereditary exostosis. Plain radiographs are usually diagnostic, and no
Further tests are required. Sessile osteochondromas are difficult to diagnose, especially when they occur in unusual sites, such as the distal posterior femur, where they must be differentiated from a parosteal osteosarcoma. Bone scintigraphy and CT are helpful in distinguishing between the two.

Osteochondromas grow with the individual until skeletal maturity is reached. Growth of an osteochondroma during adolescence does not, therefore, signify malignancy. Pain is not a sign of malignancy in childhood or adolescence, although in adulthood it is a significant warning sign. Pain in a child may be due to local bursitis, mechanical irritation of adjacent muscles, or pathologic fracture.

Between 1% and 2% of solitary osteochondromas undergo malignant transformation; patients with multiple hereditary exostoses are at higher risk. \(^4\) Malignant tumors arising from a benign osteochondroma are usually low-grade chondrosarcomas. Proximal osteochondromas are more likely than distal ones to undergo malignant transformation. In general, surgical removal is recommended only for symptomatic osteochondromas and for those arising along the axial skeleton or pelvic or shoulder girdle.

**SOLITARY AND MULTIPLE ENCHONDROMAS**

Enhondromas are composed of mature hyaline cartilage that arises within a bone. They may be solitary or multiple (Ollier's disease) and have been reported in most bones.\(^4\) Their biologic potential is often over- or underestimated. In general, pathologic interpretation of cartilage tumors is more difficult than that of other bone tumors; it is particularly difficult to differentiate a benign enchondroma from a grade 1 chondrosarcoma.\(^5\) Malignant transformations do occur, but the rate is difficult to determine.\(^4\) Lesions of the pelvis, femur, and ribs are generally at higher risk for malignant transformation than are lesions at more distal sites.

Pain is a sign of local aggressiveness and possible malignancy. Enchondromas of the hands and feet are benign, irrespective of pathology,\(^4\) whereas cartilage tumors of the pelvic or shoulder girdle are often malignant, even though the histology appearance is benign. Plain radiographs may be helpful in making this distinction. Radiographic scalloping is a sign of local aggressiveness. Bone scintigraphy is not helpful in differentiating a low-grade chondrosarcoma from an active enchondroma. Patient age is an important indicator of possible malignancy; enchondromas rarely undergo malignant transformation before skeletal maturity. Painful, histologically benign-looking proximal enchondromas in adults are often malignant, despite their histology. Thus, correlation of symptoms, plain radiographic findings, and histology is crucial.

**CHONDROBLASTOMA, OSTEOSTROBLASTOMA, AND OSTEOID OSTEOMA**

Chondroblastoma and osteoblastoma are characterized by immature but benign chondroid or osteoid production, respectively. Both may undergo malignant transformation in rare cases.\(^6\)\(^7\)\(^8\) Osteoid osteomas are smaller than 1 cm, painful, bone-forming tumors that are always benign. It is essential that the oncologist be aware of these entities and be able to differentiate them from their malignant counterparts, chondrosarcoma and osteosarcoma. Chondroblastomas appear radiographically in the epiphysis of a child; conversely, primary chondrosarcomas are rarely epiphyseal and occur in adults. Although osteoblastomas may be found in any bone, one-half of them are in the spine and skull. Osteoblastomas must be differentiated from osteosarcomas and osteoid osteoma.

Both chondroblastomas and osteoblastomas are considered aggressive, benign lesions with a high recurrence rate after simple curettage.\(^9\)\(^10\)\(^11\) Local control can be achieved by primary resection; however, routine resection cannot be recommended for tumors adjacent to a joint. Marcove et al.\(^12\) report a 5% to 10% local recurrence rate when curettage is combined with cryosurgery. This method has obviated resection and extensive reconstruction in select patients. Osteoid osteoma is treated by simple excision. In a few cases, nonsteroidal antiinflammatory drugs have proven curative when continued for a minimum of 1 year. Because surgical removal is the treatment of choice for these benign bone lesions, the role of radiotherapy is limited. For nonresectable tumors, radiotherapy has been associated with long-term control (Table 39.2-11), but most radiation oncologists do not believe that radiation plays a role in the management of these conditions.\(^13\)\(^14\)\(^15\)

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<th>Table 39.2-11. Radiation Guidelines for Benign Bone Lesions</th>
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**ANEURYSMAL BONE CYSTS**

Aneurysmal bone cysts (ABCs) are benign tumors of childhood, occurring typically before skeletal maturity.\(^3\)\(^4\)\(^5\)\(^6\) They never become malignant. They often involve the metaphyseal regions of the long bones or the vertebrae. Radiographically, ABCs are eccentric, lytic, and expansile, characterized by cortical destruction and periosteal elevation. They can grow rapidly and appear extremely aggressive, and distinguishing them from a primary malignancy may be difficult. Differential diagnosis includes Ollier's disease and malignant osteosarcoma. ABCs contain some osteoid; however, careful examination reveals this to be reactive and not neoplastic. Approximately one-third arise in conjunction with another bony neoplasm.\(^3\)\(^4\)\(^5\)\(^6\)\(^7\) The classic treatment is simple curettage and bone graft, which has a recurrence rate of 20% to 35%.\(^4\)\(^5\)\(^6\)\(^7\)\(^8\)\(^9\) Wide curetage may decrease the recurrence rate to approximately 10%. Marcove and colleagues\(^10\)\(^11\)\(^12\) recommend curettage and cryosurgery as the primary treatment. Primary resection of tumors involving weight-bearing bones is not warranted. Expandable bones, especially the ribs and fibula, may be treated by primary resection. The Mayo Clinic reviewed its experience of 238 patients with ABCs.\(^10\) Eighty percent of those lesions involved long bones. The investigators noted that CT and MRI may show characteristic septations or fluid-fluid levels. Of 153 patients treated, 19% had recurrence after curettage. The long-term control (Table 39.2-11) but most radiation oncologists do not believe that radiation plays a role in the management of these conditions.\(^5\)\(^6\)\(^7\)

**DESMOPLASTIC FIBROMA**

Desmoplastic fibroma is an extremely rare bone tumor; only 80 cases have been reported.\(^26\) It is characterized by abundant collagen formation and a fibrous stroma without evidence of mitosis or pleomorphism. It presents radiographically as an osteolytic lesion with well-defined margins. Most important in differential diagnosis is primary fibrosarcoma of bone. Treatment is en bloc resection; curettage has a significant rate of local recurrence. Radiation therapy has been suggested when surgery is not a reasonable option, but dose-response data are not available.\(^26\)

**LANGERHANS' CELL HISTIOCYTOSIS**

Langerhans' cell histiocytosis is a more descriptive and recently accepted term to describe the disease commonly referred to as histiocytosis X. The solitary or multifocal osseous lesions (Greenberger stage IA and B) were formerly referred to as eosinophilic granuloma.\(^27\) This condition can be difficult to diagnose and may mimic radiographically a primary bone malignancy.

Almost any bone can be involved. Radiographically, the lesions appear as lytic, destructive defects, with ill-defined margins. Periosteal elevation occurs in one-half of
all cases. This combination of characteristics strongly resembles that of Ewing’s sarcoma or osteomyelitis. When the disease arises in a flat bone, specifically the pelvis, there may be a large soft tissue component. Solitary lesions are treated by surgical curettage.

**MALIGNANT BONE TUMORS**

**CLASSIC OSTEOSARCOMA**

Osteosarcoma is a high-grade, malignant spindle cell tumor that arises within a bone. Its distinguishing characteristic is the production of “tumor” osteoid or immature bone directly from a malignant spindle cell stroma. 3,14,22

**Clinical Characteristics**

Osteosarcoma typically occurs during childhood and adolescence. An epidemiologic study from the Swedish Cancer Institute documented that the mean and median age of patients with osteosarcoma has increased since 1971. 22 Investigators evaluated 227 patients from 1971 to 1984 and reported the peak incidence to be between 10 and 19 years of age but noted the mean and median values to be 29 and 20 years, respectively. The overall incidence—21 cases per million people per year—has not changed. When osteosarcoma occurs in patients older than 40 years, it is usually associated with a preexisting condition, such as Paget’s disease, irradiated bones, multiple hereditary exostosis, or polyostotic fibrous dysplasia. 3,23,24-26,27,28 Bones of knee joint and the proximal humerus are the most common sites, accounting for 50% and 25%, respectively, of all osteosarcomas. 3,21 In general, 80% to 90% of osteosarcomas occur in the long tubular bones. 46,72,73,74,75,76,77,78,79 The axial skeleton is rarely affected. Fewer than 1% are found in the hands and feet. 82

With the exception of serum AP levels, which are elevated in 45% to 50% of patients, laboratory findings are usually not helpful. 83 Furthermore, elevated AP per se is not diagnostic, because it is also found in association with other skeletal disease. Pain is the most common complaint. Physical examination demonstrates a firm, soft tissue mass fixed to the underlying bone with slight tenderness. No effusion is noted in the adjacent joint, and motion is normal. Incidence of pathologic fracture is less than 1%. Systemic symptoms are rare.

**Radiographic Characteristics**

Typical findings are increased intramedullary radiodensity (due to tumor bone or calcified cartilage), an area of radiolucency (due to nonossified tumor), and an area of permeative destruction with poorly defined borders, cortical destruction, periosteal elevation, and extraskeletal extension with soft tissue ossification. 3,22,24,25 This combination of characteristics is not seen in any other lesion. Wilner classified 600 radiographs of osteosarcoma seen at the Memorial Sloan-Kettering Cancer Center into three broad categories 22: sclerotic (32%), osteolytic (22%), and mixed (46%). Although no statistically significant difference was found in overall survival rates among these types, the patterns are important to recognize. The sclerotic and mixed types offer few diagnostic problems. Errors of diagnosis most often occur with pure osteolytic tumors. The differential diagnosis of osteolytic osteosarcoma includes GCT, ABC, fibrosarcoma, and MFH. 84 In a series of 305 osteosarcoma cases, DeSantos and Edemken 85 reported that 42 (13.5%) were purely lytic. Most commonly, they presented as ill-defined lesions with a moderate to large soft tissue component. Nine of the lesions had benign radiographic features.

**Clinical and Prognostic Considerations**

Before the era of adjuvant chemotherapy, treatment consisted of amputation. Metastasis to lungs and other bones generally occurred within 24 months. A large number of series shows an overall survival of 5% to 20% at 2 years. 12,22,73,74 (Fig. 39.2-4). This pattern has been altered by adjuvant chemotherapy and aggressive thoracotomy for pulmonary disease. 46,72,73,74 Metastases may now appear at less common sites, and disease-free intervals are longer. 22 In 1968, Lockshin and Higgins 86 reviewed the experience of 100 authors over 50 years and concluded that there was no significant difference between survival rates of patients with the three histiogenetic subtypes (osteoblastic, chondroblastic, and fibroblastic) or between patients whose lesions had a different radiographic appearance (sclerotic, osteolytic, or mixed). 22 Likewise, tumor size, patient age, and degree of malignancy did not correlate with survival. The most significant variable was anatomic site. Patients with pelvic and axial lesions had a lower survival rate than those with tumors of the extremities, probably due to surgical inaccessibility and incomplete removal. Patients with tumors of the tibia had a significantly higher survival rate than those with tumors of the distal femur (35% vs. 16%). Larsson and colleagues, 227 using a multifactorial analysis of all patients from the Swedish Cancer Registry between 1958 and 1968, similarly concluded that patients with tibial lesions had a better survival rate than those with femoral lesions (38.1% vs. 15.1%), due to the fact that the former were less advanced at the time of treatment.

**FIGURE 39.2-6.** The historical survival curve for 145 patients with osteosarcoma treated by surgery alone at Memorial Sloan-Kettering Cancer Center as reported by Marcove and associates. (From Marcove RC, Mike V, Hajek JV, et al. Osteogenic sarcoma under the age of 21. J Bone Joint Surg Am 1966;48:1, with permission.)

Marcore et al., 2 reviewing 145 patients younger than 21 years of age who underwent surgery without adjuvant chemotherapy at Memorial Sloan-Kettering, noted no statistically significant differences with regard to race, gender, or duration of symptoms (see Fig. 39.2-6). Younger patients developed metastases sooner, but this made no difference in overall survival. Location had no impact on the 5-year survival rate. Brostrom and coworkers 85 evaluated 52 patients treated by surgery alone. They studied tumor size and site and reported that patients with distal lesions measuring smaller than 10 cm had a significantly higher survival (P < .01) than those with proximal lesions larger than 10 cm (43% vs. 12%, respectively). More recently, Hudson and associates 88 reported on 88 patients treated at the M. D. Anderson Cancer Center with three different protocols. Tumor size (P = .04) and the percentage of tumor necrosis induced by induction therapy (P = .01) were the most important prognostic factors.

Baldini et al., 20 from the Rizzoli Institute have reviewed the prognostic factors of osteosarcoma patients treated with preoperative chemotherapy. This is one of the more recent studies that attempts to determine prognostic factors when chemotherapy is administered, in contrast to older studies, which evaluated prognostic factors before chemotherapy. Baldini et al. evaluated 160 patients with stage II high-grade osteosarcomas at a single institution. One hundred forty-two patients were treated by a limb-sparing procedure, and 18 underwent amputation. Tumor size was not found to be associated with a histologic response to chemotherapy. One-hundred fifteen patients had a good response (more than 90% necrosis), and 40 had a poor response. Larger tumors were not found to be associated with a lower likelihood of response to chemotherapy. No association was found between the size of the tumor and the event-free survival of the patients, as determined by univariate and multivariate analysis.

**Changing Pattern of Metastasis**

The classic pattern and time frame of metastatic dissemination of osteosarcoma has been somewhat modified by the use of adjuvant chemotherapy and thoracotomy. Bacci and coworkers, 1 evaluated the pattern of metastatic spread of osteosarcoma in 193 patients at the Rizzoli Institute. Thirty patients who were treated with surgery alone were compared to 163 patients who underwent adjuvant chemotherapy. No difference was found in sites of first relapse; approximately 90% of cases in both groups occurred in the lungs. After chemotherapy, extrapulmonary spread occurred in 10% of cases, usually to bony sites. Simultaneous bone and lung
metastases occurred in approximately 2%. The time to metastases differed (surgery alone was 13 months vs. adjuvant chemotherapy at 8 months), and the number of metastatic nodules were reduced. In general, lung metastases appeared later and were fewer in number after adjuvant chemotherapy but with variable difference on extrapulmonary or bony spread. The authors of this study concluded that the alteration of metastatic spread permitted surgical resection of pulmonary metastases in a larger number of patients (51% vs. 29%).

**Alkaline Phosphatase**

Serum AP level is an important biologic marker of tumor activity in patients with osteosarcoma. The early studies of the relationship of AP activity and survival were evaluated in several studies before the introduction of adjuvant chemotherapy (i.e., in patients treated with surgery alone).

The prognostic significance of AP has more recently been evaluated in conjunction with neoadjuvant chemotherapy. Bacci and coworkers evaluated patients treated for osteosarcoma between 1972 and 1989. The study demonstrated that for patients with osteosarcoma of the extremities, presurgical serum AP levels are useful prognostic markers in patients treated with adjuvant or neoadjuvant chemotherapy. Specifically, the study demonstrated that patients presenting with nonmetastatic osteosarcoma and an elevated serum AP level had a worse prognosis than those with normal values (55% of relapses versus 26%). Among those patients determined to have elevated pretreatment serum AP levels, there was a correlation showing that the higher the serum levels of AP, the greater the risk was for relapse. Patients with elevated pretreatment serum AP who experienced relapse or recurrence had a poorer disease-free survival when compared with individuals who relapsed and had normal pretreatment serum AP levels.

**Surgical Resection of Localized Extremity Osteosarcoma**

Before the early 1980s, treatment for localized osteosarcoma was amputation one joint above the tumor-containing bone or, occasionally, transmedullary amputation. Since the early 1980s, parallel developments in radiology, orthopedics, and oncology have made limb-sparing procedures an option in 50% to 80% of patients. A significant impetus for these developments was the introduction of effective chemotherapeutic agents in the early 1970s.

Springfield and coworkers from the University of Florida compared limb-sparing surgery with amputation in 53 patients with stage IIB osteosarcoma. For ethical reasons, the patients were not randomized. No difference in survival was found between amputation and resection or between radical resection and a wide surgical margin. Three local recurrences were reported. The investigators concluded that a wide surgical resection was adequate for local control. In general, they recommended amputation if the major neurovascular bundle was involved. They concluded that local recurrence was due to an extremely aggressive tumor or to skip metastases.

Rougraff and colleagues updated a combined study from the Musculoskeletal Tumor Society of 227 patients from 26 institutions treated for osteosarcoma of the distal femur. One hundred nine patients (48%) were alive at an average of 11 years after surgery. No differences in local recurrence, overall survival, or duration of disease-free survival were noted between amputation and limb-sparing groups. The local recurrence rate (10%) was identical for above-knee amputation and limb-sparing surgery. The most common causes of failure were local recurrence procedures were infection and local recurrence. Rougraff et al. concluded that the type of surgery did not affect outcomes. No difference was noted among patients treated with endoprostheses, allografts, composites, rotationplasties, and arthrodesis; however, the numbers of patients in those categories were small.

**Local Recurrence, Tumor Necrosis, and Surgical Margins**

During the 1990s, many surgeons intuitively believed that a patient with a good response to neoadjuvant chemotherapy was more likely to undergo a limb-sparing procedure safely than a patient with a poor response. A relationship appears to exist between the safety of limb-sparing resection and the surgical margins achieved with neoadjuvant chemotherapy. Patients whose lesions respond well to chemotherapy are less likely to develop local recurrence than those whose lesions respond poorly. Picci and coworkers from the Rizzoli Institute analyzed the relationship between local recurrence after neoadjuvant chemotherapy, surgical margin obtained, and tumor response as demonstrated by percentage of tumor necrosis. Of 355 patients, 7% developed local recurrences. The mean time to local recurrence was 13 months from diagnosis (range, 2 to 56 months). Eighty-nine percent of the local recurrences developed within 18 months of the diagnosis. Of 237 patients in the group who had undergone a limb-sparing procedure, 23 (10%) developed a local recurrence. The types of surgical margins obtained and their respective local recurrence rates were as follows: wide margin, 3%; marginal margin, 29%; intraligamental margin, 36%; contaminated margin, 15%.

When the type of surgical margin and the response to chemotherapy were analyzed together, differences in outcome were dramatic. The patients with poor necrosis had very high local recurrence rates (48%); wide margins, 3%; marginal margin, 36%.

**Treatment by Anatomic Site**

The unique features of evaluation, management, and resection of tumors of the most common anatomic areas, the shoulder and knee, are described and illustrated in this section.

**SHOULDER GIRDLE.** A surgical classification for shoulder girdle resections has been described and is shown schematically in Figure 39.2-7. This classification is useful for all limb-sparing procedures of the shoulder girdle. It is recommended that osteosarcomas arising from the proximal humerus be treated by a type VB resection (see Fig. 39.2-7). Figure 39.2-8 illustrates the various means by which a sarcoma may involve the shoulder joint.

**FIGURE 39.2-7.** Schematic of proposed surgical classification of shoulder girdle resections. In general, types I to III are for benign or low-grade tumors, and types IV to VI are for high-grade tumors. A and B denote the status of the abductor mechanism: A is intact, and B is partially or completely excised. Types I to III and types IV to VI are intraarticular and extraarticular resections, respectively.
is dismal. Only 1 of 25 patients remained disease-free. The five patients that lived the longest were all treated with chemotherapy. Innovative treatment strategies are

The high incidence of venous invasion requires that the iliac vessels be evaluated preoperatively and intraoperatively. Radiographic staging studies should include a

patients, the inferior vena cava in three patients, and unnamed veins in four patients.

margins, and only two of the eight limb-sparing patients obtained negative margins. Major intraoperative complications occurred in 11 patients. Intraoperative blood

of tumor in otherwise normal tissue, and extension into adjacent (and other) pelvic structures. They noted marked differences in obtaining tumor-free margins with

anatomic and surgical considerations are discussed in the section on chondrosarcomas (see

Osteosarcomas of the pelvis and proximal femur are less common than those occurring at other anatomic areas. They account for 10% and 5%, respectively, of all

functional deficit is footdrop, which is treated by an orthosis. Knee function is normal.

Contraindications to resection are direct tibial involvement, necessity of ligation of the anterior and peroneal arteries, sacrifice of the peroneal nerve, and tumor infiltration of the tibiofibular joint capsule.

contributes to the anatomic constraints: minimal adjacent soft tissue and the normal subcutaneous location of the medial tibial border. It is extremely important that the biopsy be small and that it avoid the knee joint. A core biopsy of medial flare is preferred to avoid contamination of the anterior musculature and peroneal nerve.

Today, limb-sparing procedures often are feasible for tumors of the proximal tibia after induction chemotherapy. It is more difficult to obtain an adequate margin of

resection and a good functional result with lesions of the proximal tibia, which tend to have a higher incidence of local complications than do distal femoral tumors. These problems are directly related to the anatomic constraints: minimal adjacent soft tissue and the normal subcutaneous location of the medial tibial border. It is extremely important that the biopsy be small and that it avoid the knee joint. A core biopsy of medial flare is preferred to avoid contamination of the anterior musculature and peroneal nerve.

The popliteus muscle adjacent to the posterior aspect of the tibia prevents direct tumor involvement of the neurovascular bundle. Lateral angiography is crucial to determine popliteal vessel involvement. Biopsy must avoid the sartorial canal and the knee joint. Contraindications to resection are popliteal vessel involvement, massive soft tissue contamination from previous biopsy, and fracture. Large tumors requiring removal of the entire quadriceps or hamstrings can be adequately reconstructed by an arthrodesis.

PROXIMAL TIBIA.

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PROXIMAL FIBULA.

Tumors of the proximal fibula require the same evaluation as do proximal tibia lesions. Unique considerations are early soft tissue extension, proximity to the lateral tibial condyle, necessity of ligation of the anterior and peroneal arteries, sacrifice of the peroneal nerve, and tumor infiltration of the tibiofibular joint capsule. Contraindications to resection are direct tibial involvement, an anomalously absent posterior tibial artery, and intraarticular knee joint extension. Adequate resection includes the fibula, the tibiofibular joint, the anterior and lateral muscle compartments, and a portion of the lateral gastrocnemius muscle. After surgery, the only functional deficit is footdrop, which is treated by an orthosis. Knee function is normal.

OSTEOSARCOMA OF THE PELVIS AND PROXIMAL FEMUR

Osteosarcomas of the pelvis and proximal femur are less common than those occurring at other anatomic areas. They account for 10% and 5%, respectively, of all osteosarcomas. Tumors arising from these structures are often large, involve important structures, and are difficult to resect. Hemipelvectomy often is required for pelvic tumors, whereas modified hemipelvectomy is used for tumors of the proximal femur. The limb-sparing options, when feasible, are all functionally superior to amputation at this level. A poorly planned biopsy often contaminates the extrapelvic structures, typically making a hemipelvectomy the only safe option. Detailed anatomic and surgical considerations are discussed in the section on chondrosarcomas (see Chondrosarcoma, later in this chapter), which often arise in these sites.

Fahey and Spanier reviewed 25 patients with osteosarcoma of the pelvis treated at the University of Florida between 1967 and 1990 and described their biologic behavior, growth, and histologic and vascular findings. Common problems included delay in diagnosis, widespread invasion into major pelvic veins, microscopic foci of tumor in otherwise normal tissue, and extension into adjacent (and other) pelvic structures. They noted marked differences in obtaining tumor-free margins with surgery. Eighteen patients underwent surgery (ten hemipelvectomy and eight limb-sparing resections). Only two of ten hemipelvectomy patients obtained wide margins, and only two of the eight limb-sparing patients obtained negative margins. Major intraoperative complications occurred in 11 patients. Intraoperative blood loss exceeded 10 L in six patients. An unexpected intraoperative finding was obvious tumor invasion into the large veins in nine patients: the iliac veins in two patients, the inferior vena cava in three patients, and unnamed veins in four patients.

The high incidence of venous invasion requires that the iliac vessels be evaluated preoperatively and intraoperatively. Radiographic staging studies should include a thorough evaluation of the iliac vessels. This can best be performed by CT, MRI with contrast, and pelvic venography. Survival for patients with pelvic osteosarcoma is dismal. Only 1 of 25 patients remained disease-free. The five patients that lived the longest were all treated with chemotherapy. Innovative treatment strategies are
needed for pelvic osteosarcomas.

Clinical Analysis of Limb-Sparing Surgery

The most recent comparison of the results of limb-sparing surgery and amputation were reported by Stauga and colleagues. They evaluated 130 consecutive patients younger than 21 years of age treated for osteosarcoma of the extremity. Ninety percent (116 patients) were treated by a limb-sparing procedure. Fourteen amputations, 32 rotationplasties, and 84 resections with subsequent reconstruction were performed. The 5-year metastasis-free survival rate was 60% for patients treated by amputation or rotationplasty and 71% for patients treated by limb-sparing surgery. The surgical margins were classified as wide in 109 cases and radical in ten cases. The overall local recurrence rate was 2.3%. 4.3% for amputation and/or rotationplasty and 1.2% for limb-sparing surgery. The overall survival rate was significantly influenced by tumor volume \(P = .0018\), response to chemotherapy \(P = .039\), and presence of metastases at the time of diagnosis \(P = .001\). The authors emphasize that there was no selection bias by tumor volume for the type of surgical procedure performed. The authors warn that limb-sparing is not suitable for every patient, patients with large tumors and close margins may require amputation. They emphasize the importance of wide margins to a successful limb-sparing procedure. This study, as well as previous studies, showed no difference in patient survival or local recurrence in patients treated by a limb-sparing procedure and those undergoing an amputation.

Rougoff and colleagues evaluated 227 patients with nonmetastatic osteosarcoma of the distal femur treated at 26 institutions. They reported eight (11%) local recurrences in 73 patients with a limb salvage procedure, and nine (6%) local recurrences in 115 patients who had an above-knee amputation. No local recurrences were reported in the 39 patients who had a hip disarticulation.

Bacci et al. retrospectively evaluated 540 patients treated over 10 years in three multicenter studies with 63 participating institutions. The rate of local recurrence was 8% for patients with a poor histologic response and 3% for those with a good histologic response. A limb-sparing procedure was performed on 84% of the 540 cases evaluated, with a local recurrence rate of 6%. The most important determinant of local recurrence was the type of surgical margin and the response to chemotherapy. Of the 540 patients, 31 had a local recurrence. The overall outcome of this group was extremely poor. All local recurrences were accompanied by metastases, and despite treatment, only one patient remains alive (3%). Local recurrence did not correlate with patient age, gender, histologic type, site and volume, pathologic fracture incidence, chemotherapy, or type of surgical procedure.

It appears, in summary, that the safety and efficacy of limb-sparing procedures for high-grade bone sarcomas have been well answered during the 1990s. The senior author (M. M.) would like to emphasize that these procedures are demanding and must be performed by surgeons experienced in limb-sparing procedures.

Allograft Replacement

Allograft (cadaver bone) replacement was popular in the 1970s and mid-1980s, which were the early days of limb-sparing surgery. Allograft was used for replacement of large bony segments after limb-sparing surgery. When used in patients in conjunction with chemotherapy, allografts have a significant complication rate, including infection, fracture, necrosis, and local recurrence, which may lead to secondary amputation.

The most recent authors to evaluate the use of allografts for reconstruction of the distal femur (the most common site for osteosarcoma) were Powell et al. They evaluated their experience over a 13-year period. A total of 37 osteoarticular allografts were used to reconstruct the distal femur of 34 patients who underwent tumor resection. Twenty-one patients with sarcoma received chemotherapy. Average follow-up was 86 months. Eighty-five percent of patients had postoperative complications, and 21 of 33 patients (75%) required further surgery. The most common complications were joint instability (55%), degenerative joint disease (44%), nonunion (36%), allograft fracture (28%), and infection (13%). Only 13 of the 36 of the allografts (36%) remained intact. A steady decline in actuarial survivorship of the reconstruction was noted over time: 83.2% at 2 years, 42.3% at 5 years, and 14.3% at 10 years.

Allograft replacement remains popular at some institutions but is reserved for low-grade tumors that do not require chemotherapy. The use of allografts has become less common with the development of reliable prosthetic replacements, especially the modular replacement systems.

Prosthesis Survival and Complications

Prosthetic replacement is commonly used for reconstruction after resection of the proximal humerus, proximal femur, distal femur (Fig. 39.2-10), and proximal tibia. Several studies have evaluated the long-term results, prosthetic survivorship, and complications associated with prosthetic replacement.

Campanna and colleagues reported on 133 cases of nonmetastatic osteosarcoma of the extremities treated with neoadjuvant chemotherapy and limb-sparing surgery. Sixty-three percent of the patients had one or more complications. Twenty-eight complications were considered minor (i.e., no surgery was required), and 77 complications were major. The infection rate was 6.2%. Mechanical problems occurred in seven patients (5%). The average number of complications per patient was 1.3. The authors thought that the most serious problems resulting from a complication were those that required the delay of chemotherapy or deviation from the recommended dose, either of which could jeopardize survival. Such consequences were not, however, demonstrable statistically.

In 1999, Henshaw et al. reported the long-term prosthetic survival analysis of the 100 patients treated with the American-designed modular replacement system (Howmedica and Osteonics, Inc., Allendale, N.J.). The minimum follow-up period was 2 years. Prosthetic failure was defined as removal of the implant for any reason. Kaplan-Meier survival analysis was performed for all implants and for each site of reconstruction. The authors reported no mechanical failures of the stem, body, or taper components. No clinically significant prosthetic loosening was reported. The infection rate was 8% (four in distal femurs, three in proximal tibias, and one in proximal humerus), leading to six amputations and one prosthetic removal. The amputation rate was 7% (six infections and one local recurrence). The Kaplan-Meier
Management of osteosarcoma requires the expertise of a multidisciplinary team familiar with the various management options. For presurgical chemotherapy; those with a good response may then become suitable candidates for limb-sparing operations. The management of these patients requires a consideration of subsequent definitive surgery. A poorly conceived and poorly placed biopsy may jeopardize the subsequent treatment, especially a limb-sparing procedure. Whenever possible, this individual should be the surgeon who will ultimately perform the definitive surgical procedure, because the biopsy must be planned carefully with a consideration of subsequent definitive surgery. A poorly conceived and poorly placed biopsy may jeopardize the subsequent treatment, especially a limb-sparing procedure.

The patient with a primary tumor of the extremity without evidence of metastases requires surgery to control the primary tumor and chemotherapy to control the tumor location, size, or extramedullary extent; the presence or absence of distant metastatic disease; and patient factors such as age, skeletal development, and lifestyle preference. Routine amputations are no longer performed; all patients should be evaluated for limb-sparing options. Intensive, multiagent chemotherapeutic regimens have provided the best results to date (see Table 39.2-6 and Table 39.2-7). Patients who are judged unsuitable for limb-sparing options may be candidates for presurgical chemotherapy; those with a good response may then become suitable candidates for limb-sparing operations. The management of these patients.

Revision of Limb-Sparing Surgery (Prosthesis)

The growing popularity of limb-sparing surgery has led to a need for revision of a limb-sparing endoprosthesis. The early causes of prosthetic failure were postoperative infection, secondary infection due to transient bacteremia during postoperative chemotherapy, and local recurrence. These events usually occur within the first 2 years after surgery. Long-term survival of the prostheses depends on the mechanical properties of the prosthesis and on the host response to the polyethylene, methylmethacrylate, and metallic components. The most common causes of late failure of a prosthesis necessitating revision (i.e., removal and replacement of the prosthesis) are aseptic loosening of the prosthesis, mechanical breakage, or polyethylene component failure.

Renard et al. evaluated 26 revision procedures. The most common reasons for a revision were polyethylene wear (nine cases) and aseptic loosening (eight cases). The follow-up after the last revision ranged from 6 months to 12 years, with a median of 3 years. All patients retained their extremity, and approximately 75% incurred no functional loss after prosthetic revision.

Cost of Limb-Sparing Surgery versus Amputation

The question of the cost effectiveness of limb-salvage surgery for bone tumors has arisen in the face of managed care, especially within the United States. The only published report on this subject is by Grimer et al., who compared the cost of a limb-sparing procedure in lieu of an amputation. They developed a formula for the cost of the limb-salvage procedure versus an above-knee amputation with subsequent prosthetic replacement over the predicted life of the patient. This was calculated for patients around the knee. They excluded tumors of the proximal humerus and of the proximal femur, because, whatever difference in cost there might be, there was a tremendous advantage of replacing the proximal femur rather than performing a hemipelvectomy or hip disarticulation. Similarly, there is a tremendous advantage in preserving the upper extremity and a functioning hand in lieu of a forequarter amputation for a proximal humeral sarcoma. Their study is based on large experience of amputations and limb-salvaging procedures at the Royal Orthopedic Hospital in Birmingham, England. The formula is $E = 2F + S + R$ to $3F + R$, where $E$ is the cost of the original procedure, $y$ is the number of years since the original operation, $F$ is the cost of follow-up attendance, $s$ is the risk of a service procedure in any year, $S$ is the cost of a servicing procedure in any year, $r$ is the risk of a revision procedure being needed, and $R$ is the cost of revision procedure.

They concluded the savings for an average patient undergoing a limb-sparing surgery over a 20-year period to be approximately 70,000 British pounds (at 1977 prices), which is approximately six times the cost of the original limb-salvage procedure. They concluded that the equation can be used for any method of limb-salvage procedure. This study was performed with distal femoral resections that used a simple hinge prosthesis, which is now out of date. The modern rotating hinged-knee prosthesis, with an improved surface and a collar coated with porous beads, provides a much longer rate of survival. These features should provide a significantly lower rate of wear and failure, thus increasing cost-effectiveness.

The surprising feature of these findings is the considerable cost of amputation. Most active young people would demand and use a sophisticated artificial limb. These individuals frequently have stump problems and require multiple replacements of the socket and prosthesis. They often require a spare prosthesis as well. Many request and use a sports limb and a limb designed for swimming. A new prosthesis is required at regular intervals. With the increasing complexity of artificial limbs, it is likely that the maintenance cost of the amputated extremity will increase.

Limbsaving Surgery and Pathologic Fracture

Traditionally, a fracture through an osteosarcoma was treated by amputation. As experience with induction chemotherapy and limb-sparing surgery has increased, however, several centers have attempted limb-sparing surgery in this high-risk patient population. The assumption has been that if the fracture can be immobilized during the induction period and the tumor shows clear signs of necrosis and secondary fracture healing, an amputation may be avoided. The earlier strategy, immediate amputation, was based on the presumed high risk of local recurrence after a limb-sparing procedure. A limb-sparing procedure may now be safely performed if the response to induction chemotherapy is good, as evidenced by fracture healing. Steadman et al. evaluated their experience with patients with osteosarcoma-induced pathologic fractures between 1970 and 1995. Nine primary instances of limb salvage in patients with preoperative chemotherapy and eight primary cases of amputation with postoperative chemotherapy were studied. No significant difference in survival was found. One local recurrence occurred in the limb-salvage group, and none in the amputation group. This retrospective analysis, combined with other reported results, makes a convincing case that a pathologic fracture does not indicate the need for an immediate amputation. The strategy today is to immobilize the extremity and proceed with induction chemotherapy. If the fracture heals and the tumor appears to respond to chemotherapy, a limb-sparing operation is warranted. Repeat staging studies after induction chemotherapy and close serial observation during the induction period are essential.

CLINICAL PRESENTATIONS OF OSTEOSARCOMA AND TREATMENT CONSIDERATIONS

Treatment Considerations

LOCALIZED EXTREMITY DISEASE. Management of osteosarcoma requires the expertise of a multidisciplinary team familiar with the various management options. Patients with a suspected diagnosis of osteosarcoma (based on radiographic findings) should be referred to centers with treatment programs before biopsy. The biopsy should be performed by an orthopedic surgeon familiar with the management of malignant bone tumors and experienced in the required techniques. Whenever possible, this individual should be the surgeon who will ultimately perform the definitive surgical procedure, because the biopsy must be planned carefully with a consideration of subsequent definitive surgery. A poorly conceived and poorly placed biopsy may jeopardize the subsequent treatment, especially a limb-salvage procedure.

The patient with a primary tumor of the extremity without evidence of metastases requires surgery to control the primary tumor and chemotherapy to control micrometastatic disease. The choice between amputation and limb-sparing resection must be made by an experienced orthopedic oncologist, taking into account tumor location, size, or extramedullary extent; the presence or absence of distant metastatic disease; and patient factors such as age, skeletal development, and lifestyle preference. Routine amputations are no longer performed; all patients should be evaluated for limb-sparing options. Intensive, multiagent chemotherapeutic regimens have provided the best results to date (see Table 39.2-6 and Table 39.2-7). Patients who are judged unsuitable for limb-sparing options may be candidates for presurgical chemotherapy; those with a good response may then become suitable candidates for limb-sparing operations. The management of these patients...
Historically, patients developing recurrent disease had a poor prognosis and were treated palliatively; most died. Metastatic disease detected at initial diagnosis does not preclude a curative treatment strategy, although the presence of extrathoracic metastases makes cure extremely unlikely. In general, the surgical principles outlined for the treatment of relapsing patients apply equally to the patient presenting with macroscopic metastases. Newly diagnosed patients have not been exposed to chemotherapy and are, thus, less likely to have drug-resistant tumors. Therefore, several options are available to them.

For the patient presenting with resectable disease (i.e., usually fewer than 15 pulmonary nodules and a primary tumor of the extremity), the traditional approach has been resection of all evidence of macroscopic disease by median sternotomy and limb amputation or resection, followed by intensive adjuvant chemotherapy. The tumor burden is thereby reduced to a minimum before the application of adjuvant therapy. Some investigators have favored treatment with chemotherapy, followed weeks or months later by definitive surgery for residual macroscopic disease in primary and metastatic sites. Arguments advanced to justify this approach are similar to those used to support preoperative chemotherapy in general, and the theoretical advantages and disadvantages of this strategy as discussed for patients with metastatic osteosarcoma apply here as well. The risk for the patient with metastases is that growth of tumor nodules in the face of chemotherapy may render small, operable metastases unresectable and prevent cure. Although the timing of the surgery of the primary tumor and metastatic sites has been variable, most modern approaches entail alternating chemotherapy and surgery. The initial treatment is usually a course of chemotherapy, followed by surgical resection of the primary tumor, followed by a second course of chemotherapy and surgical ablation of metastatic sites, followed by the remaining courses of chemotherapy. Patients with tumors that respond to presurgical chemotherapy are more likely to be cured. In patients with inoperable metastases, primary treatment with chemotherapy is probably appropriate; metastases may respond sufficiently to allow complete resection. Because these patients may usually require surgery for the primary tumor as a palliative procedure, early surgery may be recommended, despite unresectable pulmonary disease. Although improving, the outlook for patients presenting with metastatic disease remains poor.

RECURRENT DISEASE AFTER CURATIVE ATTEMPT. Historically, patients developing recurrent disease had a poor prognosis and were treated palliatively, most died within 1 year of the development of metastatic disease. Because more than 85% of metastases occur in the lung, surgical resection of tumor nodules can be readily accomplished. With the advent of thoracic CT scanning, metastatic nodules can be detected when quite small and more easily resectable, although in most cases the surgeon discovers more lesions at thoracotomy than anticipated on the basis of the CT scan. In many patients, the lungs are likely to be the only site of metastasis, especially in cases in which recurrences appear more than 1 year after diagnosis and in which the metastatic lesion is solitary. In such cases, the recurrent tumors are likely to behave more indolently and may not further metastasize. These patients have been cured by thoracotomy alone.

Surgical resection of all overt metastatic disease is a prerequisite for long-term salvage after relapse. Patients not treated by thoracotomy have little hope for cure, because complete responses of macroscopic metastases to chemotherapy are rare. The completeness of surgical resection is an important determinant of outcome, because patients left with measurable or microscopic disease at the resection margins are unlikely to be cured. Many investigators have recommended adjuvant chemotherapy after thoracotomy for the management of metastatic osteosarcoma to destroy residual microscopic tumor deposits. For patients who develop recurrent disease within 1 year of initial surgery, the possibility of additional microscopic metastatic disease is quite high, and further chemotherapy is indicated. Long-term survival has been reported for some patients with recurrent osteosarcoma who were treated only with surgery. These survivors were more likely to be patients experiencing late relapses with solitary pulmonary nodules.

If overt metastatic disease is discovered, a thorough search for all metastatic lesions is essential. The discovery of unresectable extrathoracic metastases or unresectable pulmonary disease is a contraindication to aggressive thoracotomy, and the patient should be treated palliatively. Radiotherapy may be particularly useful in this context. In some patients with unresectable disease, an aggressive approach with curative intent may still be indicated. Chemotherapy, with or without radiotherapy, rarely eradicates all metastatic disease; nonetheless, some patients with inoperable metastases may respond sufficiently to allow for complete resection of disease at a later date. Occasionally, patients with unresectable pulmonary metastases are cured with chemotherapy or high-dose radiotherapy alone.

Patients with resectable lung disease should undergo thoracotomy to remove all evidence of disease. Bilateral disease may be approached by staged bilateral thoracotomies or a median sternotomy. The role of adjuvant chemotherapy after thoracotomy should be studied; it is probably indicated for patients with more than three lesions appearing 6 months to 1 year after initial surgery, for patients whose metastatic disease has not been completely resected, or for those with evidence of pleural disruption by tumor. Repeat thoracotomies may be required for subsequent recurrence and should be performed if all disease can be resected.

Survival after relapse has undoubtedly been enhanced by approaches designed with curative intent that incorporate repeated aggressive surgery to remove overt disease. With such treatment, 30% to 40% of patients have been reported to survive beyond 5 years after relapse, although not all of these patients are ultimately cured. Such considerations emphasize the value of close follow-up, with frequent chest radiographs and thoracic CT scans, to detect recurrent disease when it is still resectable. Thus, for the patient with osteosarcoma, the development of metastases is not a hopeless situation; aggressive systematic treatment offers prolonged survival for many patients and the possibility of cure for a significant fraction. Ironically, as adjuvant regimens used in front-line therapy of patients are intensified and the number of patients surviving without ever developing recurrence increases, the proportion who are likely to be salvageable after relapse may decrease, because relapsing patients are more likely to have drug-resistant recurrences.

**Radiation Therapy in the Treatment of Osteosarcoma**

**BACKGROUND.** Significant experience with primary radiotherapy for osteosarcomas was obtained in the 1950s and early 1960s. Primary radiotherapy with delayed amputation gained acceptance in 1955, when Cade advocated initial therapy with radiation and delayed amputation for patients in whom there was no evidence of metastasis 4 to 6 months after radiotherapy. This approach was designed to circumvent amputation in the majority of patients who were destined to develop an early relapse. The usual doses were 7000 to 8000 cGy administered over 7 to 9 weeks at 1000 cGy/week. A few patients in Cade’s series who were not subjected to delayed amputation were controlled with irradiation alone, and amputation was eventually performed. The 5-year survival rate was 21.8%. Other investigators followed a similar regime, using various radiotherapy doses and schemes (Table 39-2). Subsequent surgical specimens of many of the patients managed in this fashion were found to have no histologic evidence of tumor. The ability of high radiation doses to sterilize some tumors, however, was associated with significant necrosis of normal tissue.

**PELVIC TUMORS AND UNRESECTABLE DISEASE.** In some pelvic and most vertebral primary tumors, complete resection often is not possible. Most pelvic osteosarcomas can be treated by hemipelvectomy; more centrally located pelvic tumors, especially those involving the sacrum, are unresectable. Only a few pelvic osteosarcomas can be treated by limb-sparing resection (internal hemipelvectomy). Contraindications to resection are unusually large extracapsular extensions with sacral plexus or major vascular involvement. On rare occasions, vertebral and sacral resections have been attempted. In general, these tumors cannot be resected with negative margins and are best treated by radiotherapy and chemotherapy. Some success has been achieved with systemic or intraarterial chemotherapy, which is administered to convert apparently inoperable tumors into lesions that can be ablated surgically. Patients with primary tumors of the axial skeleton have a poor outcome, because local control was rare. The prognosis for these patients may improve with a more aggressive surgical approach and more effective chemotherapy. Patients whose tumors can be completely resected should be approached with curative intent; radiotherapy provides significant palliation in patients with unresectable primary tumors.

**METASTATIC PULMONARY DISEASE AT DIAGNOSIS.** Metastatic disease detected at initial diagnosis does not preclude a curative treatment strategy, although the presence of extrathoracic metastases makes cure extremely unlikely. In general, the surgical principles outlined for the treatment of relapsing patients apply equally to the patient presenting with macroscopic metastases. Newly diagnosed patients have not been exposed to chemotherapy and are, thus, less likely to have drug-resistant tumors. Therefore, several options are available to them.
Results of preoperative radiation were subsequently evaluated. Overall success with preoperative radiation followed by ablative surgery was, in general, suboptimal; most patients relapsed shortly after treatment. This led Jenkin et al. at Princess Margaret Hospital to recommend limiting radiation to patients who had unresectable tumors or who were being treated for palliation only. Beck et al. observed no survival advantage for preoperative radiation followed by surgery over surgery alone; furthermore, only 43% of their patients obtained any palliative benefit from radiotherapy.

Radiotherapy has, however, been shown to be successful in several distinct clinical situations—facial lesions, palliation and, possibly, as a postoperative adjuvant. High-dose combination photon and proton radiation using three-dimensional treatment planning may improve long-term local control. Guidelines for the use of radiotherapy for osteosarcoma and other malignant bone tumors are shown in Table 39.2-12 and Table 39.2-13.

| TABLE 39.2-12. Series of Primary Radiation Followed by Delayed Surgery for Osteosarcoma |

| TABLE 39.2-13. Radiation Guidelines for Malignant Bone Lesions |

PALLIATION. Radiotherapy is extremely beneficial in patients requiring palliation of metastatic bony sarcomas; tumors at axial sites, which are unrespectable; and advanced, inoperable lesions of the pelvis or extremities. A novel approach using high-dose-per-fraction radiation and intratraherial 5'-bromodeoxyuridine (BUDr) as a radiosensitizer was undertaken by the Stanford Group. Pulsed 48-hour BUDr infusions were performed before each 600-cGy radiation fraction, with a total radiation dose to the primary site of 4200 to 4800 cGy in 5 weeks (seven to eight fractions). Infusions of methotrexate-leucovorin were administered simultaneously. Local control was achieved in seven of the nine patients (78%) treated. However, local tissue toxicity was excessive and included subcutaneous fibrosis, nonhealing traumatic fractures, peroneal neuropathy, and atrophy. Because the patients were treated with an unusual fractionation scheme using large fractions as well as intravenous chemotherapy, the specific role of the BUDr in both the local control and the excessive toxicity was not established.

Kinsella and Glattstein have used intravenous radiosensizers of BUDr, iododeoxyuridine, or misonidazole with high-dose radiotherapy, with various fractionation schemes and usually with chemotherapy, in patients with large, unrespectable primary or metastatic sarcomas. Twenty-one of 29 patients (75%) achieved local control, which was defined as freedom from symptoms and absence of growth. These studies demonstrated the efficacy of radiation therapy in obtaining long-term local control and palliation. They lend support to further clinical investigations using radiation sensitizers with high-dose radiotherapy.

VARIANTS OF CLASSIC OSTEOSARCOMA

Dahlin and Unni have identified 11 variants of the classic osteosarcoma. These accounted for 268 of 1021 (28%) cases reviewed at the Mayo Clinic. Osteosarcoma arising in the jawbone, the most common variant, is characterized by well-differentiated cells with a low metastatic potential. Excluding tumors arising secondary to Paget's disease, irradiation, or dedifferentiation of a chondrosarcoma, parosteal and periosteal osteosarcomas are the most common variants of classic osteosarcoma arising in the extremities. In contrast to classic osteosarcoma, which arises within a bone, both parosteal and periosteal osteosarcomas arise on the surface of the bone (juxtacortical).

The three types of surface osteosarcomas are parosteal osteosarcoma, periosteal osteosarcoma, and high-grade surface osteosarcoma. The Mayo Clinic reported 518 surface osteosarcomas seen between 1926 and 1996. The incidence was 335 parosteal osteosarcomas (64.7%), 137 periosteal osteosarcomas (26.4%), and 46 high-grade surface osteosarcomas (8.9%). These 518 surface osteosarcomas were from a pool of 4365 osteosarcoma tumors (i.e., a ratio of 1:8.4 cases).

Parosteal Osteosarcoma

Parosteal osteosarcoma is a distinct variant of conventional osteosarcoma that accounts for 4% of all osteosarcomas. It arises from the cortex of a bone and generally occurs in older individuals. It has a better prognosis than classical osteosarcoma.

CLINICAL CHARACTERISTICS. There is a slight predominance of parosteal osteosarcoma in women. The distal posterior femur is involved in 72% of all cases; the proximal humerus and proximal tibia are the next most frequent sites. Parosteal osteosarcoma metastasizes slowly and has an overall survival rate of 75% to 85%. Unni and colleagues noted that all patients who died of tumor lived longer than 5 years. The natural history of parosteal osteosarcoma is progressive enlargement and late metastasis. Parosteal osteosarcoma presents a mass and occasionally is associated with pain. In contrast to conventional osteosarcoma, duration of symptoms varies from months to years. Unni et al. reported that 50 of 79 patients had complaints of longer than 1 year, and one-third of this group had pain for more than 5 years. Tumor size, location, and duration of symptoms did not correlate with survival.

RADILOGIC FINDINGS. Roentgenograms characteristically show a large, dense, lobulated mass broadly attached to the underlying bone without involvement of the medullary canal. If old enough, the tumor may encircle the entire bone. The periphery of the lesion is characteristically less mature than the base. Ahuja and coworkers emphasized that intramedullary extension is difficult to determine from plain radiographs. Unni et al. emphasized that high-grade foci did not usually alter the roentgenographic appearance of these tumors.

PATHOLOGY AND GRADING. Parosteal osteosarcoma is characterized by well-formed lamellar or woven bone with a mature spindle cell stroma with few signs of malignancy. The cellularity of the spindle cell components varies; generally, it is not anaplastic, with few mitoses. The differential diagnosis is osteochondroma, myositis ossificans, and conventional osteosarcoma. Cortical tumors of the posterior femur should always be suspected of malignancy; this is a rare location for a benign osteochondroma. In contrast to sarcoma, myositis ossificans is rarely attached to the underlying bone. In addition, the periphery is more mature, both radiographically and histologically. Ahuja and colleagues reviewed all cases of parosteal osteosarcoma at Memorial Sloan-Kettering Cancer Center from 1934 to 1975 and described three grades: grade I (low grade), grade II (intermediate), and grade III (high grade). They emphasized the importance of evaluating the fibroblastic, cartilaginous, and osseous components independently. Of 24 patients, eight were grade I, ten grade II, and six grade III. Unni et al. reviewed 79 patients and reported that 18 were grade II (23%), and seven had high-grade foci (9%). Neither group of researchers could distinguish the three grades on plain radiographs. The survival rate of patients with grade III tumors is similar to that of patients with conventional osteosarcoma.

Jelinek et al. reviewed the records of the Armed Forces Institute of Pathology and evaluated 60 patients with parosteal osteosarcomas for tumor size, location, and presence of cleavage plane; intramedullary extension; soft tissue mass; and the presence and pattern of ossification. Tumors were classified as low grade or high grade. The average maximal length for low- and high-grade tumors was 7.7 and 15.0 cm, respectively. A cleavage plane was present in 20 low-grade (62%) and 19
high-grade (68%) lesions. On cross-sectional imaging, intramedullary extension was present in 13 low-grade (41%) and 14 high-grade (50%) lesions. They concluded that a poorly defined soft tissue component distinct from the osseous matrix is the most distinctive feature of high-grade parosteal osteosarcoma and may be the optimal site to perform a biopsy.

Intramedullary involvement does not necessarily imply a worse prognosis, although this may be the case in patients with high-grade lesions. Eleven of 24 patients (46%) reviewed by Ahuja had medullary involvement; moreover, the patients with medullary involvement who had a local resection all had a local recurrence.

Okada and associates updated the experience of the Mayo Clinic. They reviewed the records of 226 patients. Dedifferentiation was more common (16% of patients) than previously reported and emphasized the usefulness of cross-sectional imaging in planning surgical resection. The tumor often had extensive intramedullary, extraskeletal, and adjacent soft tissue components. Medullary involvement was present in 22% of the patients, and extraskeletal, unmineralized soft tissue peripheral to the mineralized cortical mass was noted in 51% of the patients. Adjacent soft tissue extension occurred in 46% of patients. In contrast to their previous studies, intramedullary involvement was not a poor prognostic factor. The authors stressed the need for long-term follow-up. Eleven of the 67 patients managed at their institution died at an average of 14 years (range, 2 to 41 years). Ten of the 11 patients died from a dedifferentiated tumor.

One of the largest reported series was by Okada et al. from the Mayo Clinic. They evaluated 46 patients and described their radiographic, clinical, and pathologic evaluation. All the tumors were broad based and attached to the underlying cortex. Nineteen of the 46 tumors (41%) showed infiltration into the cortex of the underlying bone. Medullary involvement was documented on gross or radiologic examination in 13 tumors and by microscopic examination only in six tumors. They attempted to evaluate the effectiveness of chemotherapy in this very rare subtype of osteosarcoma. Fifteen of the 21 patients receiving systemic treatment showed no response to chemotherapy. Among these 15 patients, only one patient remains alive. All six patients who showed a good response to chemotherapy are alive. Medullary involvement did not affect prognosis. The survival rate was 57.5% at 3 years and 46.1% at 5 years.

Treatment is similar to that of other high-grade lesions. En bloc resection should be performed when feasible; amputation is rarely indicated. Table 39.2-12 compares the significant characteristics of periosteal tumors with those of conventional osteosarcoma.

Paget's Sarcoma

Approximately 1% of patients with Paget's disease will develop a primary bone sarcoma. Greditzer and colleagues reported 41 sarcomas among 4415 patients with Paget's disease followed at the Mayo Clinic; 35 were osteosarcomas and six were fibrosarcomas. The average patient age was 64 years old, and the most common sites were the pelvis, femur, and humerus. One-half of these lesions were osteolytic; the remainder had a mixed pattern. Cortical destruction and a soft tissue component were the most common signs noted; periosteal elevation was rare. Most patients with this condition present with pain; thus, a patient with known Paget's disease who complains of increasing pain, especially when it is well localized, should be evaluated radiographically. The diagnosis is usually made by plain radiography and confirmed by biopsy. Traditionally, fewer than 8% of patients survive, and most deaths occur within 2 years. Treatment is similar to that recommended for adolescent patients with osteosarcoma without metastatic disease.

High-Grade Surface Osteosarcoma

High-grade surface osteosarcoma (peripheral conventional osteosarcoma) is the rarest variant of surface osteosarcoma. The parosteal and perosteal osteosarcomas have a better prognosis, whereas the parosteal surface variant has the same prognosis as the conventional, intramedullary lesion. This variant was previously called type III parosteal osteosarcoma. Schajowicz and coworkers studied the different surface osteosarcomas. They reported that only 7 of 80 surface osteosarcomas (9%) were considered to be the high-grade variant. Clinically, the median age was 13.5 years (younger than that of patients with other soft tissue lesions), and almost all were located in the diaphyseal region of the bone. The femur was the most common site. These tumors may show extensive intramedullary involvement. Radiographically, it appears as a small or moderate-size lesion with slight to heavy calcification. The broad base of the lesion abuts the cortex. The radiographic features often are misleading and may suggest the periosteal variant; thus, the preoperative diagnosis may be difficult. But the young age, diaphyseal location and, most important, the highly malignant histologic features indicate the correct diagnosis. Wide excision with limb preservation has been reported. Adjuvant chemotherapy is warranted due to the high rate of metastases.

Small cell Osteosarcoma

The small cell osteosarcoma, a rare variant of osteosarcomas, resembles an Ewing's sarcoma and is often classified as an "atypical" Ewing's sarcoma. Characteristically, areas of osteoid and, on occasion, chondroid formation are present. The differential diagnosis includes Ewing's sarcoma, atypical Ewing's sarcoma, primitive neuroectodermal tumor, mesenchymal chondrosarcoma, lymphoma, and Askin's tumor. Differentiation from Ewing's sarcoma and the typical osteosarcoma is important, because the response of small cell osteosarcoma to treatment is poorly defined.
Devaney and colleagues\textsuperscript{273} from the Bone Branch of the Armed Forces Institute of Pathology evaluated 79 round cell tumors of bone with immunohistochmistry in an attempt to distinguish small cell osteosarcoma from the other round cell tumors of bone. They noted that none reacted with cytokeratin, epithelial membrane antigen, factor VIII–related antigen, synaptophysins, or Leu-M1-positive. Thus, a strong positivity of any of these studies should rule out small cell osteosarcoma. Vimentin was seen in the majority of the various tumor types. They concluded that immunohistochemical stains alone could not make the diagnosis.

Sim et al.\textsuperscript{345} recommend surgery, whereas at the Pediatric Branch of the National Cancer Institute, these tumors, like other pediatric round cell tumors, are treated by a combination of radiation therapy and chemotherapy.

**Radiation-Induced Osteosarcoma**

Radiation-induced osteosarcomas arise in a previously irradiated field and meet the general criteria of a radiation-induced sarcoma [i.e., they appear after a latent period of 5 to 20 years, are documented to be secondary (different from the original one), and occur in a documented irradiated field]. Amendola and coworkers\textsuperscript{282} from the University of Michigan reviewed 22,306 patients treated with radiation between 1934 and 1983 and reported 23 patients with radiation-associated sarcoma (prevalence, 0.1%). The median latent period was 13 years (range, 3 to 34 years). The radiation doses ranged from 25 to 72 Gy. The data suggest that intensive chemotherapy may have shortened the latency period.

In two nested case-control studies of 3-year cancer survivors from France and the United Kingdom, the risk of osteosarcoma was found to be a linear function of radiation dose and alkylating agent chemotherapy.\textsuperscript{282,345} The 20-year risk of osteosarcoma among survivors of retinoblastoma (7.2%), Ewing's sarcoma (5.4%), and other bone tumors (2.2%) suggests a genetic influence in the induction of secondary osteosarcoma. However, the risk of developing bone sarcoma within 20 years for the majority of survivors of childhood cancer is less than 0.9%.

The treatment of radiation-associated osteosarcoma is whole resection, when possible, combined with adjuvant chemotherapy.\textsuperscript{345} A previously irradiated field presents a unique challenge for the surgeon—choosing the best local option. The likelihood of local complications is greater in such cases.

**CHONDROSARCOMA**

Chondrosarcoma is the second most common primary malignant spindle cell tumor of bone.\textsuperscript{2} Chondrosarcomas form a heterogeneous group of tumors whose basic neoplastic tissue is cartilaginous without evidence of direct osteoid formation.\textsuperscript{274} Occasionally, bone formation occurs from differentiation of cartilage. If evidence is found of direct cartilage to bone production, the lesion is classified as an osteosarcoma. The five types of chondrosarcomas are central, peripheral, mesenchymal, differentiated, and clear cell.\textsuperscript{2} and\textsuperscript{25} The classic chondrosarcomas are central (arising within a bone) or peripheral (arising from the surface of a bone). The other three are variants and have distinct histologic and clinical characteristics.

Both central and peripheral chondrosarcomas can arise as primary tumors or secondary to underlying neoplasms. Seventy-six percent of primary chondrosarcomas occur centrally.\textsuperscript{3,24} Secondary chondrosarcomas most often arise from benign cartilage tumors. The multiple forms of benign osteochondromas or enchondromas have a higher rate of malignant transformation than the corresponding solitary lesions.\textsuperscript{11,215,273}

**Central and Peripheral Chondrosarcomas**

**CLINICAL CHARACTERISTICS.** One-half of all chondrosarcomas occur in persons older than 40 years of age.\textsuperscript{2} Only 3.8% occur in those younger than 20 years.\textsuperscript{273} The most common sites are the pelvis (31%), femur (21%), and shoulder girdle (13%).\textsuperscript{11,16,215} Chondrosarcomas are the most common malignant tumors of the sternum and scapula. The clinical presentation varies. Peripheral chondrosarcomas may become large without causing pain, and local symptoms develop only because of mechanical irritation. Pelvic chondrosarcomas are often large and present with referred pain to the back or thigh, sciatica secondary to sacral plexus irritation, urinary symptoms from bladder neck involvement, unilateral edema due to iliac vein obstruction, or as a painless abdominal mass. Conversely, central chondrosarcoma present with dull pain; a mass is rare. Pain, which indicates active growth, is an ominous sign of a central cartilage lesion. This cannot be overemphasized. An adult with a plain radiograph suggestive of a “benign” cartilage tumor but associated with pain most likely has a chondrosarcoma.

**HISTOLOGY AND GRADING.** Chondrosarcomas are categorized as grade I, II, or III. The majority of chondrosarcomas are either grade I or II.\textsuperscript{11,16,215} Grade III lesions have the same metastatic potential as osteosarcomas.\textsuperscript{273}

Because cartilage tumors are difficult to grade histologically,\textsuperscript{275,276} some investigators have attempted to apply cyologic, histochemical, and biochemical analysis to evaluate these tumors.\textsuperscript{303,277} Sanerkin\textsuperscript{326} described a combination of cyologic and histologic criteria. He emphasized that cyologic analysis evaluates nuclear abnormalities better than conventional histologic sections, whereas histologic evaluation of bone-tumor interface is the best predictor of local aggressiveness. Krocsberg and colleagues\textsuperscript{16} performed a retrospective study of DNA content of 45 chondrosarcomas as an indicator of malignancy by evaluating diploid (normal DNA content) and hypodiplod (abnormal increase in DNA) cells and correlating the findings to 10-year survival. Regardless of tumor grade, size, and location, patients with diploid cells had a better prognosis than those with hyperdiploid cells. A preliminary report assessing the malignancy of cartilage tumor by flow cytometry to determine the percentage of diploid, tetraploid, and aneuploid cells indicates that it may be a promising method of grading chondrosarcomas.\textsuperscript{275}

**RADIOGRAPHIC DIAGNOSIS AND EVALUATION.** Central chondrosarcomas have two distinct radiologic patterns.\textsuperscript{12} One is a small, well-defined lytic lesion with a narrow zone of transition and surrounding sclerosis with faint calcification. This is the most common malignant bone tumor that may appear radiographically benign. The second type has no sclerotic border and is difficult to localize. The key sign of malignancy is endosteal scalloping. It is difficult to diagnose on plain radiographs and may go undetected for a long period. In contrast, peripheral chondrosarcoma is recognized easily as a large, calcified mass protruding from a bone. Its differential diagnosis includes large benign osteochondroma, parosteal osteosarcoma, and juxtacortical myositis ossificans. Correlation of clinical, radiographic, and histologic data is essential for accurate diagnosis and evaluation of the aggressiveness of cartilage tumor. Proximal or axial location, skeletal maturity, and pain point toward malignancy, even though the cartilage may appear benign.

**prognosis.** Metastatic potential tends to correlate with the histologic grade of the lesions.\textsuperscript{275,276,278} Marcove et al.\textsuperscript{287} reported on long-term follow up of 113 chondrosarcomas of the proximal femur and the pelvis. The survival rates in patients with grade I, II, or III lesions were 47%, 38%, and 15%, respectively; the overall survival rate was 52%. No significant difference was noted between grades I and II; however, the mortality rate for grade III was significantly higher (P <0.02) than for the other two. Eleven of 59 deaths occurred after 5 years. The authors emphasized that the meaningful survival interval should be considered 10 or 15 years. No relationship between grade, age, gender, or location was found, and there was no statistical difference between primary and secondary chondrosarcomas. Adequacy of surgical removal was the main determinant of recurrence. In general, chondrosarcomas occurring during childhood have a worse prognosis than those of adult onset.\textsuperscript{12}

In a review of 125 chondrosarcomas at the Rizzoli Institute, Gitelleis and colleagues\textsuperscript{12} reported that adequacy of treatment was the main determinant of local recurrence, length of survival, and length of disease-free interval. Patients adequately treated had a 6% local recurrence rate, whereas the recurrence rate among those inadequately treated was 69%. The 10-year survival rates were 78% (adequately treated) versus 61% (inadequately treated). No relation between local recurrence and grade was determined.

In the largest reported series of chondrosarcomas from one institution, Bjorsson et al.\textsuperscript{334} from the Mayo Clinic reported the experience and the clinical pathologic profiles of 344 patients with chondrosarcomas over 80 years. They analyzed the anatomic site, clinical history, and overall survival. Survival analysis was limited to 233 patients whose primary tumors were treated at the Mayo Clinic. The minimum follow-up period was 5 years. The overall 5-year survival rate was 77%. Local recurrence developed in 19.7% of patients, and metastatic lesions in 13.7%. The recurrence rate was higher for tumors of the shoulder and pelvis than for tumors of long bones. Histologic tumor grade was an important predictor of local recurrence and metastases.

In general, peripheral chondrosarcomas have a lower grade than central lesions. Gitelleis et al.\textsuperscript{12} reported that 43% of peripheral lesions, compared with 13% of central lesions, were grade I. The 10-year survival rate among those with peripheral lesions was 77%, and among those with central lesions was 32%.
TREATMENT. The treatment of chondrosarcomas is surgical removal. No reports of effective adjuvant chemotherapy have been published. Resection guidelines for high-grade chondrosarcomas are similar to those for osteosarcoma. The shoulder and pelvic girdle are the most common sites for chondrosarcomas. This, combined with the fact that chondrosarcomas tend to be low grade, make them amenable to limb-sparing procedures. Lesions of the ribs and sternum are treated by wide excision. Cryosurgery, a technique using liquid nitrogen after thorough curettage of the lesion, has been used for central, low-grade chondrosarcomas. There have been a few reports of effective radiation therapy for axial chondrosarcomas and, more recently, encouraging reports using fractionated proton radiation therapy for the low-grade chondrosarcomas arising at the base of the skull. The Massachusetts General Hospital group report a 5-year local control rate of 82% and a 10-year local control rate of 58% among 28 patients with low-grade base-of-skull chondrosarcomas treated to approximately 69 CGE (cobalt Gy equivalent) using the proton beam. High-grade chondrosarcomas warrant consideration of adjuvant chemotherapy.

Limb-Sparing Procedures: Specific Anatomic Sites

The four most common sites of chondrosarcomas are the pelvis, proximal femur, shoulder girdle, and diaphyseal portions of long bones. The unique characteristics of each are described in the following sections.

PELVIS. The pelvis consists of three areas: ilium, periacetabulum, and pubic rami (Fig. 39.2-13). Each site may be resected independent of the others. Resections are classified as type I (iliac wing), type II (acetabulum), or type III (pubic rami, pelvic floor). Bone scan most accurately determines specific bony involvement, whereas CT and MRI delineate the extraosseous component. Contraindications to resection are vascular (iliac artery and vein), peritoneal, and sacroiliac joint and/or sarcroplexus involvement.


The retroperitoneal space is explored first to determine resectability. Type I resection is performed by a supraacetabular osteotomy and disarticulation of the sacroiliac joint. Type II resection may require removal of the femoral head; intraarticular involvement of the hip joint by tumor is evaluated by arthrotomy before finalizing the surgical plan. Type II and III resections require mobilization of the iliac vessels and femoral nerve. Care must be taken to protect these structures. Type III procedure requires mobilization of the bladder and urethra before resection. Bilateral pelvic floor resection may be used for chondrosarcomas arising from the midline of the symphysis pubis, in which case urethral resection and reconstruction may be required. Partial cystectomy may be necessary.

Long-term results of these procedures have been published by Enneking and Dunham, who reported that local recurrence was only 4% if adequate margins were obtained. Function was nearly normal if the hip joint was preserved. If the hip joint was removed and fusion was obtained, results were good. A saddle prosthesis (Fig. 39.2-14) has been developed, permitting reconstruction after periacetabular resections with minimal morbidity.

FIGURE 39.2-14. Limb-sparing resection for a large periacetabular chondrosarcoma involving the pelvic floor. A: Computed tomography shows acetabular destruction by a large tumor mass (arrows) with involvement of the pubic rami. B: The patient was treated by an internal hemipelvectomy (type II and III resection). C: A custom-made saddle prosthesis was used for the reconstruction. This is a new type of pelvic prosthesis that has made pelvic reconstruction more reliable with less morbidity than other techniques.

Treatment of malignant tumors of the pelvis is one of the greatest challenges in musculoskeletal oncology. Kawai and coworkers pioneered the technique of cryosurgery for bone tumors. This method involves thorough curettage and cryotherapy of the cavity with liquid nitrogen. With increasing experience, the indications were expanded to low-grade intramedullary cartilage tumors as well as to some high-grade lesions. With these indications, they have treated 30 chondrosarcomas with only one local recurrence. The major advantages of cryosurgery are preservation of bone
stock and the avoidance of resection.

Schreuder et al. reported the experience of 26 benign and low-grade intramedullary chondrosarcomas treated with curettage and cryosurgery. Fourteen enchondromas and nine grade I chondrosarcomas were treated with curettage, cryosurgery, and bone grafting. After a follow-up of 26 months, no recurrences were observed. The most common complication was postoperative fracture (two cases). All bone grafts had incorporated, resulting in full weight-bearing capacity and excellent functional results. These authors emphasized that the preoperative assessment of these lesions is essential and that only low-grade cartilage tumors should be treated with a cryosurgical technique.

**Variants of Chondrosarcoma**

CLEAR CELL CHONDROSARCOMA. Clear cell chondrosarcoma, the rarest form of chondrosarcoma, is a slow-growing, locally recurrent tumor resembling a chondroblastoma but with some malignant potential. It generally occurs in adults. The most difficult clinical problem of this entity is early recognition. It is often confused with chondroblastoma. Metastases occur only after multiple local recurrences. Primary treatment is wide excision. Systemic therapy is not required.

MESENCHYMAL CHONDROSARCOMA. Mesenchymal chondrosarcoma is a rare, aggressive variant of chondrosarcoma characterized by a biphasic histologic pattern (i.e., small, compact cells intermixed with islands of cartilaginous matrix). It has a predilection for flat bones; long, tubular bones are rarely affected. It tends to occur in younger individuals and has high rates of metastatic potential. Harwood and colleagues reported that 8 of 17 patients died within 1 year of diagnosis. The 10-year survival rate is 28%. This entity responds favorably to radiotherapy. It is hypothesized that the round cell component, similar to other round cell sarcomas, is relatively radiosensitive. Treatment is surgical removal combined with adjuvant chemotherapy. Radiotherapy is recommended if the tumor cannot be completely removed.

Approximately 10% of chondrosarcomas may be dedifferentiated into a fibrosarcoma or osteosarcoma. This occurs in older individuals and is highly fatal. Surgical treatment is similar to that described for other high-grade sarcomas. Adjuvant therapy is warranted.

**Radiation Therapy in the Treatment of Chondrosarcoma**

Unresectable or inoperable chondrosarcomas arising within the axial skeleton and pelvic or shoulder girdle can be controlled, and in some cases cured, by radiation therapy. A unique situation is chondrosarcomas of the facial bones and skull, in which a combination of radiotherapy and surgery has been shown to be successful.

Although chondrosarcomas have generally been considered radioresistant, data exist to show that some are radioresponsive. Among 38 patients undergoing radical irradiation, with or without concurrent chemotherapy, at the Princess Margaret Hospital, 5- and 10-year actuarial survival rates of 41% and 36%, respectively, were achieved. Median survival was 46 months. The best results, a 48% 5-year actuarial survival rate, were obtained in the group with favorable (well and moderately differentiated) histology. Conversely, for those with unfavorable (mesenchymal and poorly differentiated) histology, the 5-year survival rate was only 22%. Radical radiotherapy was defined as a minimum of 40 Gy in 4 or more weeks of megavoltage therapy. Of the 38 patients treated, 17 developed local recurrence. The authors recommend 50 Gy in 4 weeks with treatment to the whole bone if possible and, if not, at least a 5-cm margin of normal bone. These authors noted tumor regression continued slowly for 2 to 3 years after therapy.

McNaney et al. from the M. D. Anderson Cancer Center, reported 20 patients with chondrosarcoma treated with photons and/or neutrons, with or without chemotherapy. The doses of radiation administered ranged from 4000 to 7000 cGy. Thirteen of 20 (65%) were surviving at 30 months' median follow-up. Among the 11 patients treated with radiotherapy alone, six survived (54%). Six patients, all of whom had received photon therapy alone, developed local failure. No local failures were reported among the four patients treated with a mixed beam of photons and neutrons. Similarly, Hug et al. reported 100% local control and disease-free status for patients with axial skeleton chondrosarcoma treated with a mean target dose of 73.9 CGE delivered using a 160 MeV proton beam and 23 MV megavoltage beam.

After radical irradiation, clinical regression of tumor is slow and may take months to complete. Radiographically, the affected bone never returns to normal. The combination of extremely slow regression of tumor with a persistent radiologic defect makes follow-up and assessment of response difficult. No biopsy data are available to document long-term sterilization of these tumors. Radiotherapy for chondrosarcoma can provide palliation. In such cases, high doses (in the range of 5000 cGy in 4 to 5 weeks, or its equivalent) are necessary; low doses for symptomatic relief are ineffective.

Ryall et al. used radiation and the radiosensitizer raxazane (ICRF 159) in eight patients with 12 chondrosarcomas. Seven tumors in five patients achieved complete or partial remission after 4500 to 6000 cGy. Two of the responders were disease-free 2.5 years after treatment.

**GIANT CELL TUMOR OF BONE**

GCT is an aggressive, locally recurrent tumor with a low metastatic potential. Between 8.6% and 22% of known GCTs become malignant after local recurrence. The best results, a 48% 5-year actuarial survival rate, were obtained in the group with favorable (well and moderately differentiated) histology. Conversely, for those with unfavorable (mesenchymal and poorly differentiated) histology, the 5-year survival rate was only 22%. Radical radiotherapy was defined as a minimum of 40 Gy in 4 or more weeks of megavoltage therapy. Of the 38 patients treated, 17 developed local recurrence. The authors recommend 50 Gy in 4 weeks with treatment to the whole bone if possible and, if not, at least a 5-cm margin of normal bone. These authors noted tumor regression continued slowly for 2 to 3 years after therapy.

Giant cell tumors are eccentric lytic lesions without matrix production. They have poorly defined borders with a wide area of transition. They are juxtaepiphyseal with a metaphysal component. Although the cortex is expanded and appears destroyed at surgery, it is usually found to be attenuated but intact. Periosteal elevation is rare; soft tissue extension is common.
Treatment

Treatment of GCT of bone is surgical removal. Resection is curative in 90% of these tumors, whereas curettage, with or without bone grafts, has a recurrence rate of 40% to 75%. Johnson and Dahlin reported a recurrence rate of 29% within 1 year of curettage and of 54.1% within 5 years. O'Donnell and colleagues reviewed the literature from 1970 to 1990 and reported an overall recurrence rate of approximately 40%.

Although en bloc excision offers a reliable cure, routine resection is not recommended. Primary resection of a joint has a significant morbidity. It is recommended for GCT of the proximal radius and fibula, distal ulna, tubular bones of the hand and foot, coccyx, sacrum, and pelvic bones. Under certain situations, a curettage is reasonable. If the lesion heals, resection is avoided. In general, curettage does not rule out a later curative resection. Today, the technique of curettage is more extensive than previously performed. Curettage is accomplished through a large cortical window, perforated to the length of the bony defect, using both mechanical curettage and a mechanical burr. This extensive technique has been termed curettage/resection and has decreased the rate of local recurrence to approximately 15% to 25%. Bone graft and PMMA are used to reconstruct the surgical defect.

O'Donnell et al. reviewed the experience at the Massachusetts General Hospital of 60 patients with GCTs treated by curettage and packing with PMMA. The overall rate of local recurrence was 25% (15 of 60 patients) occurring at an average of 4 years. Risk factors for local recurrence were pathologic fracture, stage III disease, anatomic site, and the use of adjuvant treatment. The distal radius and the proximal tibia had the highest rate of local recurrence: 50% (five of ten patients) and 28% (7 of 25 patients), respectively. These authors emphasized that adjuvant treatment with a high-speed burr or PMMA, or both, after curettage decreased the local recurrence rate from 42% (8 of 19 patients) to 17% (7 of 41 patients). They concluded that PMMA alone did not reduce the rate of local recurrence, but that the use of a wide curettage combined with additional curettage with a high-speed burr is necessary.

Malawer et al. in a multicenter study of 100 cases of GCTs of the extremities (treated with wide curettage, high-speed burr, and either a single or double cycle of cryosurgery with liquid nitrogen), reported a local recurrence rate of 9% (9 of 100 patients). They used the direct-pour technique as described by Marcove. Reconstruction of the surgical defect was performed with PMMA (combined with internal fixation in most cases). The secondary fracture rate was 5%. Only two patients required a secondary resection and prosthetic replacement. These authors recommend liquid nitrogen adjuvant after curettage in the treatment of GCTs.

Amputation is reserved for massive recurrence, malignant transformation, or infection. Because of the biologic propensity for malignant transformation, radiation is reserved for specific lesions, usually lesions of the spine, that cause bone destruction in a confined area and can lead to spinal cord compression and severe deformity. Thus, treatment of GCT of the vertebrae and sacrum must be individualized. A combination of surgical excision and cryosurgery or radiotherapy is required to eradicate the tumor and prevent neurologic impairment.

Cryosurgery

Cryosurgery has been used more successfully for GCTs than for any other type of bone tumor. Marcove and colleagues developed the technique of cryosurgery because of the high recurrence rates after curettage and the significant risk of sarcomatous degeneration in GCTs treated by irradiation. He found cryosurgery effective in eradicating the tumor while preserving joint motion and avoiding resection or amputation. He reported a 17-year experience of 100 GCTs treated by thorough curettage and cryosurgery. He noted a recurrence rate of 16% in the first 50 cases and 2% in the following 50 cases. The major complications of cryosurgery are necrosis of the adjacent bones, which are liable to develop a late pathologic fracture, and delayed union. The rate of secondary pathologic fracture has been decreased by a combination of PMMA, augmentation, bone graft, internal fixation of the cavity, and postoperative use of a long-leg brace with a quadrilateral socket. Persson and Wouters have reported curettage with PMMA augmentation of the bony defect with bony necrosis due to the heat of polymerization. This technique may provide better local control than curettage alone.

Bickels and colleagues reported 102 patients treated by curettage and cryosurgery at two institutions between 1983 and 1993. The surgical stage was I in 15 cases, II in 47 cases, and III in 40 cases. Sixteen percent of the patients had presented with local recurrences. The local recurrence rate among 86 treated patients was 2.3%. There were six local recurrences among 16 patients who were referred with recurrent disease. The overall recurrence rate was 7.9%. The most common complication was pathologic fracture (5.9%). No pathologic fractures occurred when internal fixation was used along with PMMA. This study emphasized that the overall function was good to excellent in 92% of the patients. All 102 patients were free of disease at final follow-up.

Cryosurgery is a powerful physical adjunct to curettage in the treatment of GCTs of bone. Bickels and colleagues recommend routine use of cryosurgery for all GCTs of long bones.

Giant Cell Tumors of the Sacrum

Giant cell tumors of the sacrum are difficult to treat. Patients often present with back pain, neurologic deficits, and rectal symptoms. The diagnosis is often delayed. CT, MRI, and bone scintigraphy are required for accurate local anatomic staging. Turcotte et al. reviewed the treatment of 26 patients treated at the Mayo Clinic between 1960 and 1986 with an average follow-up of 7.8 years. Neurologic deficit was present in 88%. The local recurrence rate for patients treated by curettage was 33%. Twenty-one patients had radiation therapy; malignant transformation occurred in three. They suggested initial treatment is complete curettage. Radiation therapy is recommended for incomplete resection and local recurrence. Resection of the sacrum should be reserved for extensive recurrences. The technique of surgical resection of the sacrum is similar to the combined anterior and posterior approach described for chordomas.

RADIATION THERAPY.

The specific indications for radiation include inoperable and incompletely resected lesions, and lesions that occur locally despite definitive surgery. These situations are most likely to occur in the spine. Doses of 35 to 50 Gy in 4 to 5.5 weeks using megavoltage equipment is recommended. Although concern has been raised about malignant transformation after radiotherapy.

Marcove and colleagues reviewed the treatment of 26 patients treated at the Mayo Clinic with a recurrence rate of 29% within 1 year of curettage and of 54.1% within 5 years. O'Donnell and colleagues reviewed the literature from 1970 to 1990 and reported an overall recurrence rate of approximately 40%.

The extent of the operation is guided by the extent of the disease. Local control of GCT treated with surgery alone ranges from 75% to 85% in recent series. The Princess Margaret Hospital group has reported that local control was achieved in 13 of 14 patients with GCT treated with one course of megavoltage radiation. The disease in 12 patients was controlled for longer than 5 years. The researchers observed no instance of malignant transformation. Larsson and colleagues reported three patients with GCT of the spine and sacrum treated by moderate doses of radiotherapy; all have done well. Similarly, the Gainesville group reports 12 of 16 tumors (75%) controlled locally with 35 to 54 Gy, with no untoward complications or secondary sarcomas. Several authors now suggest curettage, followed by planned megavoltage radiation, as a good alternative to complex and difficult surgery.

MALIGNANT FIBROUS HISTIOCYTOMA

Clinical Characteristics

MFH is a high-grade bone tumor histologically similar to its soft tissue counterpart. It is a disease of adulthood. The most common sites are the metaphyseal ends of long bones, especially around the knee. AP values are normal. Pathologic fracture is common. Huvos emphasized that a lytic metaphyseal lesion with a pathologic fracture in an adult with a normal serum AP level suggests a primary MFH rather than an osteosarcoma or fibrosarcoma. MFH disseminates rapidly. Spanier and colleagues reported that 9 of 11 patients died of the tumor. The average disease-free survival was 6 months. One-third of patients (three of nine) with pulmonary metastasis had lymph node dissemination. The author hypothesized that lymphatic spread was due to the histiocytic component of the tumor.

Radiographic Characteristics

MFH is an osteolytic lesion associated with marked cortical disruption, minimal cortical or periosteal reaction, and no evidence of matrix formation. The extent of the tumor routinely exceeds plain radiographic signs. McCarthy et al., reporting on 35 patients with MFH, noted that four tumors were multicentric and four were...
associated with bone infarcts.

**Treatment**

Today, MFH and osteosarcoma of bone are treated in much the same way. Data demonstrate that results of limb-sparing surgery for MFH of bone, as well as responses to chemotherapy among MFH patients, are very similar to those of patients with primary osteosarcoma. Pici et al., 232,234 in the largest review to date, evaluated the effects of neoadjuvant chemotherapy of MFH of bone and extremity osteosarcomas. They reported 51 patients treated with high-grade MFH of bone and 390 patients with high-grade osteosarcoma treated with identical regimens of neoadjuvant chemotherapy at the Rizzoli Institute between 1982 and 1994. All tumors were located in the bone. Preoperative chemotherapy was performed according to three successively preoperated regimens consisting of methotrexate and cis-diaminedichloroplatinum II (CDP): MTX/CDP intraarterially, MTX/CDP plus Adriamycin, and MTX/CDP plus Adriamycin and ifosfamide). Rates of limb salvage were approximately the same for MFH (92%) and osteosarcoma (85%). Although MFH showed a statistically significantly lower rate of good histologic response, the rate of tumor necrosis for MFH was 90% or more [27% vs. 67% for osteosarcoma (P < 001)] for all three regimens. Despite this low chemosensitivity, the disease-free survival rates for the two neoplasms were similar (67% vs. 65%). Nevertheless, the two tumors had similar prognoses when treated with chemotherapy regimens based on methotrexate, cisplatinum, Adriamycin, and ifosfamide. The surgical procedures were both similar limb-sparing procedures. This study emphasized that induction chemotherapy, followed by limb-sparing surgery and subsequent postoperative chemotherapy, was just as effective for MFH of bone as for the osteosarcomas. 232

Bacci et al., 235,236 also from the Rizzoli Institute, reported on 65 patients treated with MFH of bone in the extremities with neoadjuvant chemotherapy. The limb-salvage rate was 89% (58 patients) and amputation rate was 11% in seven patients. The histologic response to preoperative chemotherapy was good (90% or more tumor necrosis) in 16 patients (25%) and poor in 49 patients (75%). At a median follow-up of 7 years, 40 patients (69%) remained free of disease and 20 patients experienced relapse (19 metastases and two local recurrences followed by metastases). The rate of disease-free survival was significantly higher for patients who had a good response than for those who had a poor response (94% vs. 61%). Similarly, these authors concluded that a high percentage of patients with MFH of the extremities can be cured with neoadjuvant chemotherapy and that it is usually possible to avoid amputation. Similarly, Nashida and colleagues 237 from the Mayo Clinic reviewed their experience with MFH of the extremities and reported that the overall prognosis for patients with MFH was not significantly different from that of patients with osteosarcoma. The primary approach to the treatment of MFH of bone is similar to that of osteosarcoma—wide surgical resection (usually limb-sparing surgery) combined with pre- and postoperative chemotherapy. Similar chemotherapy regimens are recommended.

**FIBROSARCOMA OF BONE**

**Clinical Characteristics**

Fibrosarcoma of bone is a rare entity characterized by interlacing bundles of collagen fibers (herringbone pattern) without any evidence of tumor bone or osteoid formation. 238 Fibrosarcoma occurs in middle age. The long bones are most affected. Fifteen percent of tumors are found in the bones of the head and neck. 239 Fibrosarcomas occasionally arise in conjunction with an underlying disease, such as fibrous dysplasia, Paget's disease, bone infarcts, osteomyelitis, and postirradiation bone and GCT. 238 Fibrosarcoma may be either central or cortical (periosteal). The histologic grade is a good prognosticator of metastatic potential. Huvos and Higinbotham 240 reported overall survival rates of 27% and 52% for central and peripheral lesions, respectively. Late metastases do occur, and 10- and 15-year survival rates vary. In general, periosteal tumors have a better prognosis than central lesions.

**Radiographic Features**

Fibrosarcoma is a radiolucent lesion that shows minimal perosteal and cortical reaction. The radiographic appearance closely correlates with the histologic grade of the tumor. 238 Low-grade tumors are well-defined, whereas high-grade lesions demonstrate indistinct margins and bone destruction similar to that of osteolytic osteosarcoma. In general, plain radiographs underestimate the extent of the lesion. Pathologic fracture is common (30%) owing to the lack of matrix formation. Differential diagnosis includes GCT, ABC, MFH, and osteolytic osteosarcoma. 238

Fibrosarcoma of bone is primarily managed surgically. Irradiation is recommended for inoperable tumors, for patients with postsurgical residual disease, and for palliation.

**MALIGNANT HEMANGIOENDOTHELIOMA OF BONE**

Malignant hemangioendothelioma of bone (also referred to as epithelioid hemangioendothelioma or histiocytoid hemangiomia) comprises only 0.5% to 1.0% of primary malignant bone tumors. 241,242,243,244 More than one-third of these lesions arise in the long, tubular bones, especially those of the lower extremity. 241 Incidence peaks in the third decade of life, but the tumor can present at any age. Multicentric lesions are common. The treatment of choice has been surgery, often in combination with radiotherapy. 245 In rare cases, radiotherapy has been the sole modality of treatment. 246,247,248 Radiation doses in the range of 50 to 60 Gy are associated with long-term local control. Chemotherapy plays no significant role in treatment.

**CHORDOMA**

Chordoma is a rare neoplasm arising from notochordal remnants in the midline of the neural axis and involving the adjacent bone. The ends of the spine are the most common sites. The sacrococcyx and the base of skull (35%) near the spheno-occipital area are most commonly involved, accounting for 50% and 35%, respectively, of all chordomas. 249 Histologically, the physaliferous cell is pathognomonic. Large areas of spongylous strands of cells lying in a mass of mucus are typically present. Myxoid chordosarcoma and metastatic carcinoma must be differentiated. This tumor is highly fatal because of the high rate of local recurrence and local complications. 250,251,252,253 Death is most commonly due to local disease. 250,251,252,253 Gray and colleagues 250 reviewed 222 cases from the literature and noted that only two patients were disease-free at 10 years. Average survival was 5.7 years. Mindell 255 emphasized that the main malignant potential of chordomas resides in their critical locations adjacent to important structures, their locally aggressive nature, and their extremely high rate of recurrence. Chordomas at the base of the skull are often described as chordoid chordomas. Patients with these lesions at this site tend to survive longer than those with the sacrococcygeal tumors.

The most common complaint of patients with sacrococcygeal chordomas is dull pain; constipation is an occasional symptom. Bladder and sensory loss are late complaints. Clinical suspicion is the key to early diagnosis. Rectal examination characteristically reveals a large presacral mass. Spheno-occipital tumors present with signs of cranial nerve or pituitary dysfunction, or both. CT and MRI are essential for accurate evaluation. Myelography is used to determine intraspinal extension. A transrectal biopsy should not be performed because of potential contamination. A small midline posterior incision or trocar biopsy is recommended.

**Treatment**

The first surgical procedure has the best chance of cure. 256,257 Inadequate surgery results in local recurrence, with little chance of subsequent surgical removal. Sacrococcygeal tumors are best removed by a combined abdominopelvic approach, as described by Lococo and colleagues. 258,259 They emphasized wide excision of the sacrum if necessary. The last position is used. The retroperitoneum may be removed with the sacrum if necessary. Guterberg et al. 260 reported that if only one-half of the first sacral vertebra remains bilaterally, the pelvic girdle is still stable enough to allow immediate mobilization. DeVries and associates 261 reported two long-term survivors (7 years and 10 years) after cryosurgery of sacral chordomas.

**Radiation Therapy**

Because local recurrence is common with chordomas, radiation therapy is an integral treatment modality, particularly for tumors of the base of skull and spheno-occipital region. Results of conventional radiation therapy have been disappointing. Heffelfinger et al. 262 reported on 36 patients with nonchondroid varieties of chordoma. Five years without evidence of disease by surgery, radiation, or a combination thereof. However, the chordoid variant is more sensitive; of 19 patients with chordoid chordomas, seven were alive and six were disease-free.

Amendola et al. 263 reported on 21 patients with a 5-year survival rate of 50% but a disappointing 10-year survival rate of only 20%. This is not surprising, because chordomas are relatively slow-growing. In fact, long-term survival free of tumor regrowth over 10 years is relatively rare. Amendola et al. emphasized the importance
of using CT in planning the radiation field, administration of high radiation doses (i.e., 5500 to 7000 cGy with megavoltage equipment), and use of irradiation immediately after surgery to prevent local control, rather than reserving it until recurrence. The Massachusetts General Hospital experience of 48 patients is similar to that reported by others; 50% of the patients survived years or more. Radiation doses varied from 4500 to 8040 cGy, but even with high doses, a 45% incidence of local recurrence was reported. The Princess Margaret Hospital group investigated various fraction schedules in an effort to impact local control. They used conventional fractionation at a median dose of 50 Gy in 25 fractions over 5 weeks, and a hyperfractionated radiation schedule at a median dose of 1 Gy over 4 hours four times per day, with a median dose of 40 Gy in 44 fractions over 14 days. No difference was found between the conventional or hyperfractionated regimes with respect to symptomatic response or progression-free interval. With a median survival of 65 months, the authors concluded that external-beam radiation provided useful palliation but was rarely curative.Investigators now advocate using precision heavy-charged particle irradiation, particularly for chordoma of the basiphenoid region and cervical spine. The Massachusetts General Hospital experience includes 68 patients, 40 with chordomas and 28 with low-grade chondrosarcomas of the basiphenoid region and cervical spine, who have been treated with proton-beam radiation therapy at a median tumor dose of 68 CGE. The actuarial 5-year disease-free survival rate is 76%, whereas the local control rate is 82%. No difference was found in local control between those patients with low-grade chondrosarcoma and those with either chondroid or nonchondroid chordoma. Hug and the Massachusetts General Hospital investigators reported axial skeleton chordoma treated with a myxoid proton and photon beam (mean dose of 73.9 CGE). Five of 14 patients (36%) had local recurrence, and two of the five developed distant metastases. The 5-year actuarial local control and overall survival rates were 53% and 50%, respectively, for the chordoma patients. Other groups also report local control and reversal of neurologic symptoms and signs using 75.5 Gy proton therapy for chordoma of the clivus.22 Proton therapy should be considered after initial surgical removal for inoperable clivus chordoma.

Stereotactic radiosurgery has been tried for skull-based tumors and is a potential means to provide symptomatic relief for small-volume (4 cm or smaller) tumors.23,24

**SMALL ROUND CELL SARCOMAS OF BONE**

Round cell sarcomas of bone behave differently than spindle cell sarcomas and require different therapeutic management.25-27 These tumors consist of poorly differentiated small cells without maturation defect. They present radiographically as osteolytic lesions. These lesions are best treated with chemotherapy and surgery; surgery is reserved for special situations. Non-Hodgkin's lymphoma and Ewing's sarcoma are the two most common small cell sarcomas. The differential diagnosis of all round cell sarcomas includes metastatic neuroblastoma, metastatic undifferentiated carcinoma, histiocytosis, small cell osteosarcoma, osteomegaly, and multiple myeloma.

**LYMPHOMAS OF BONE (DIFFUSE LARGE CELL LYMPHOMA)**

Lymphoma of bone (previously called reticulum cell sarcoma of bone) accounts for only 5% of the primary bone tumors. In general, lymphoma presenting in bone is a stage IV disease (Table IV). Histopathologically, diffuse large cell lymphoma may be either of the “immunoblastic type” (stage IE) or “pleomorphic type” (stage IIIE). Reimer and coworkers29 at the National Cancer Institute reported that only 1 of 12 patients presenting with bone lymphomas had a true solitary lesion. Sweet and colleagues30 from the University of Chicago reported that 50% of so-called “solitary” lesions were associated with disease elsewhere. Sweet et al. presented a useful algorithm for the evaluation and treatment of bone lymphomas. They emphasized that all patients with a presumed solitary lymphoma of bone should undergo a thorough evaluation for other involvement.31

Treatment is based on extent of disease. Stage IE lesions have traditionally been treated with radiotherapy, with a reported 90% cure rate.32 The role of surgery is limited to obtaining adequate tissue for diagnosis and treatment of pathologic fracture. The technique of biopsy is important to avoid secondary fracture through potentially irradiated bone. Biopsy for a suspected bone lesion and cell tumor should always include a frozen section and additional material for electron microscopy, tissue culture, and immunophenotyping. Patients presenting with pathologic fractures require fixation. To prevent late fractures, all patients treated with radiotherapy should be protected with a brace until ossification occurs.

**Radiation Therapy**

Local control of the primary tumor with retention of good function of the affected part is commonly achieved after radiation therapy. Radiation therapy is administered to the entire bone and soft tissue extent with a dose of 4000 cGy and a boost to the optimal tumor area of 500 cGy. Regional lymph node sites should be included in the radiation field if they are adjacent to the area treated or if clinically involved. Mendenhall et al.33 from the University of Florida achieved local and regional control in all irradiated sites among 21 patients with primary bone lymphomas. Two patients relapsed in apparently uninvolved regional lymph node sites that had not been included in the primary treatment portal.

Patients with lymphoma of the bone should be considered to have systemic disease; accordingly, they require chemotherapy. Patients treated with radiation and Adriamycin-based chemotherapy have long-term survival in the 90% to 100% range. The Dana Farber Cancer Center reported 90% lymphoma-free survival at 8 years, with radiation and the Adriamycin, prednisone, and Oncovin combination regimen.36 Similarly, the Bone Tumor Center in Bologna, Italy, reports 88% disease-free survival at 7.5 years with radiation and Adriamycin, vincristine, and cyclophosphamide.37 Patients presenting with monostotic disease have a better overall survival than polyostotic disease.38 Although a randomized controlled clinical trial testing radiotherapy and chemotherapy versus radiation therapy alone has not been performed, combined modality is commonly used in adults with primary and non-Hodgkin's lymphoma of the bone.39 The international index of age 60 years or younger, normal lactate dehydrogenase, and Eastern Cooperative Oncology Group performance status of 0 are prognostic factors for good outcome.39 The Dana Farber investigators reported second bone tumors 5 and 7.5 years after combined modality therapy. Because of this concern and the success of following patients, the Dana Farber group has begun to question the need for primary chemotherapy therapy among children regarding the risk of second malignancies.37 The Pediatric Oncology Study Group reported the impact of localized bone radiotherapy in children with early-stage primary non-Hodgkin's lymphoma, all of whom received multigland chemotherapy. Thirty of 31 disease-free and all survived, thus leading these investigators to recommend a 9-week chemotherapy regimen of modest intensity without radiation therapy as definitive treatment of children with localized primary lymphoma of bone.

**CHAPTER REFERENCES**


SECTION 40.1
Molecular Biology of Mesothelioma

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INTRODUCTION

Malignant mesotheliomas (MMs) are highly aggressive neoplasms that arise primarily from the surface serosal cells of the pleural, peritoneal, and pericardial cavities. Epidemiologic studies have established that exposure to asbestos fibers is the primary cause of MM, and more recent investigations have implicated simian virus 40 (SV40) in the etiology of some MMs. Characterization of this tumor by cytogenetic studies of MM have been mapped at the molecular genetic level by loss of heterozygosity (LOH) analysis using polymorphic DNA markers.

The recurrent genomic losses just described are consistent with a recessive mechanism of oncogenesis and can be viewed as indicators of the locations of putative tumor suppressor genes (TSGs) important in the development and progression of MM. As a prelude to the isolation of these genes, the critically deleted regions in 1p, 3p, 6q, 9p, and 15q were mapped to this region.

The meiotic role of asbestos and SV40 in this malignancy.

MECHANISM OF ASBESTOS-INDUCED ONCOGENESIS

Presently, it is not known whether asbestos fibers act directly on mesothelial cells or if they act indirectly via formation of reactive oxygen species (ROS) and growth factors. In tissue culture, asbestos can physically interact with the mitotic spindle apparatus, which can result in aneuploidy and other forms of chromosome damage. In vivo, iron-rich crocidolite asbestos fibers may lead to the release of ROS when hydrogen peroxide and superoxide react to form hydroxyl radicals.

Asbestos has been shown to induce the expression and enzymatic activity of the mammalian DNA repair enzyme, apurinic/apyrimidinic (AP) endonuclease, suggesting that ROS generated by asbestos may induce DNA damage. Furthermore, the inflammatory response to asbestos leads to the generation of several cytokines that are responsible for the well-known local and systemic immunosuppressive activity of asbestos. Asbestos can also induce autophosphorylation of the epidermal growth factor (EGF) receptor, leading to increased expression of the protooncogenes c-fos and c-jun, which encode transcription factors that activate various genes critical in the initiation of DNA synthesis. Persistent induction of these transcription activators by asbestos may enhance cellular proliferation and could render cells more susceptible to subsequent mutations in TSGs. Such enhanced expression of protooncogenes and inactivation of TSGs may cooperate in a multistep process that leads to MM.

CYTOGENETIC ASSESSMENT OF MALIGNANT MESOTHELIOMAS

Chromosome banding analyses have revealed that most MMs have complex karyotypes. Among 20 MM karyotyped by one of us (J. R. T.), all but one displayed more than ten clonal chromosome alterations. Deletions of specific regions in the short (p) arm of chromosomes 1, 3, and 9 and long (q) arm of 6 were repeatedly observed in these tumors. Loss of a copy of chromosome 22 is the single most consistent numerical change seen in MMs. In the series by Taguchi et al., deletions and unbalanced rearrangements accounted for overlapping losses from the chromosome region 1p21-22 in 17 of 20 cases (85%). Thirteen of 20 MMs (65%) had interstitial deletions or other rearrangements that resulted in losses from 3p21. Ten cases (50%) showed losses from 6q, with a shortest region of overlap (SRO) at 6q15-21. Losses involving 9p were observed in 16 cases (80%), with the SRO being 9p11-22. Monosomy 22 was documented in 13 cases (65%). These recurrent losses of 1p, 3p, 6q, 9p, and 22q frequently occurred in combination in a given tumor. All five of these aberrations were found in 5 of our 20 MMs. Losses of 1p, 3p, 9p, and 22q coexisted in another three cases, and various combinations of three of these four abnormalities were seen in seven other cases. It is not known if this multistep cascade evolves slowly during the course of tumor formation or in rapid succession at some critical stage of the disease. In any case, the accumulated loss of DNA sequences from chromosomes 1p, 3p, 6q, 9p, and 22q appears to play a critical role in the pathogenesis of MM.

More recent molecular cytogenetic studies, using comparative genomic hybridization (CGH), also have documented recurrent genomic imbalances in MM. CGH is a fluorescence in situ hybridization technique that permits the identification of chromosome gains and losses in the entire tumor genome in a single experiment. Balsara et al. performed CGH analyses on 24 MM cell lines derived from patients seen in the United States; each of these cell lines exhibited multiple (6 to 25) genomic imbalances. Losses involving 22q, documented in 14 of 24 cell lines (58%), was the most prominent alteration. Also in agreement with earlier karyologic findings, losses of 1p, 3p, 6q, and 9p were common, with each being observed in approximately 30% to 40% of cell lines. In addition, CGH analysis uncovered other recurrent chromosome losses not highlighted in previous karyotypic studies. In particular, 13 of 24 MMs (54%) showed losses of part or all of 15q, with the SRO being 15q11-21. In addition, losses involving 14q24.2-qter and 13q12-14 were each observed in 42% of the cell lines. The most frequently overrepresented chromosome arm was 5p (54% of cases), suggesting the involvement of a putative oncogene(s) at this location.

Many of the recurrent genomic imbalances identified in U.S. cases were also detected in MM specimens examined by Finnish investigators. However, three prominent imbalances in the series from the United States (i.e., losses of 15q11.1-21.1, 8p21-pter, and 3p21) were each observed in only 1 of 42 cases from Finland. Discrepancies between the data from Finland and the United States could reflect dissimilarities in the type of asbestos exposure or genetic differences in the study populations. Alternatively, they may be related to the presence of SV40 in MMs from the United States and the absence of SV40 in MMs from Finland.

DELETION MAPPING

The recurrent genomic losses just described are consistent with a recessive mechanism of oncogenesis and can be viewed as indicators of the locations of putative TSGs important in the development and progression of MM. As a prelude to the isolation of these genes, the critically deleted regions in 1p, 3p, 6q, 9p, and 15q defined by cytogenetic studies of MM have been mapped to the molecular genetic level by loss of heterozygosity (LOH) analysis using polymorphic DNA markers. Results of these investigations have been reviewed in detail elsewhere, but are briefly summarized here.

CHROMOSOME 1p22

To map the critically deleted region of 1p, Lee et al. performed LOH analyses of 50 MMs using a large panel of DNA markers located throughout the entire short arm of chromosome 1. Allelic losses at 1p21-22 were observed in 36 cases (72%), and we were able to localize the SRO of deletions to a 4-centimorgan segment within 1p22. Currently, candidate TSGs mapped to this region are being assayed for possible mutations and altered expression in MMs.
ALTERATIONS OF TUMOR SUPPRESSOR GENES IN MESOTHELIOMA

One of the protein products of the CDKN2A locus, p16, is capable of binding to the cyclin-dependent kinase CDK4, thereby inhibiting the catalytic activity of the CDK4/cyclin D enzymes. Several months after its initial cloning, the p16 gene was identified as the 9p21 putative TSG by using a positional cloning approach, and homozygous deletions of p16 were detected at high frequencies in cell lines derived from many different kinds of cancer.

Because of its location within the region we previously determined as the SRO of 9p deletions in MM and because of its involvement in many other cancer types, p16 emerged as the prime candidate for the 9p TSG in MM. Among 40 MM cell lines studied by Chen et al., 34 (85%) had homozygous deletions of one or more p16 exons and another had a point mutation in p16. Down-regulation of p16 was observed in four of the remaining cell lines. Homozygous deletions of p16 were identified in 5 of 23 MM specimens (22%). The finding of a much higher incidence of p16 alterations in MM cell lines than in tumor tissues may be associated with a selective growth advantage provided by p16 deletion during the culture process. On the other hand, MM samples often contain a significant amount of contaminating normal stroma, which can mask the existence of a homozygous deletion in the malignant cell population. Down-regulation of p16 in MM cells may result from 5 CpG island hypermethylation, as has been demonstrated in other types of cancer. At the protein level, Kratze et al. reported abnormal expression of p16 in 16 of 12 MM specimens and 15 of 15 MM-derived cell lines examined by immunohistochemistry. Moreover, in xenograft experiments, repression of p16 in MM cells resulted in cell-cycle arrest and cell death, as well as inhibition of tumor formation or diminished tumor size.

It is important to note that homozygous deletions of the CDKN2A locus would in many cases also lead to the inactivation of another putative TSG, p14ARF (the mouse homologue of p19ARF), because if p16 and p14ARF share exons 2 and 3, although their reading frames differ, p14ARF is essential for the activation of p53 in response to the action of oncoproteins such as Ras. On the other hand, p16 induces a G1 cell-cycle arrest by inhibiting the phosphorylation of the retinoblastoma protein, pRb. Thus, homozygous loss of p14ARF and p16 would collectively affect both p53- and pRb-dependent growth regulatory pathways. However, there is evidence that retention of exon 1b, which encodes the active domain of p14ARF, may produce a peptide containing a functional, or partly functional, protein. Moreover, unlike the response to oncogenic Ras, p14ARF is not required for activation of p53 in response to DNA damage by agents such as asbestos, suggesting that p16 could be the critical TSG targeted by p51 deletions in MM.

Extensive LOH analysis of chromosome 22 losses in MM has not been performed because an entire copy of chromosome 22 is lost in most cases. Although the neurofibromatosis type 2 TSG, NF2, predisposes affected individuals primarily to tumors of neuroectodermal origin, somatic mutations of NF2 have occasionally been identified in seemingly unrelated malignancies. Thus, two groups independently embarked on unrelated studies of NF2 in MM. Bianchi et al. identified nucleotide mutations in 8 of 15 MM cell lines (53%). The mutations, which included deletions and insertions and one nonsense mutation, predicted truncated forms of the NF2 protein, known as merlin or schwannomin. Similar results were also reported by Sekido et al., who detected somatic mutations in one MM specimen and in 7 of 17 MM cell lines (41). In the study by Bianchi et al., the mutations observed in complementary DNAs from MM cell lines were confirmed in genomic DNA from six melanoma and one mesothelioma specimens. It is intriguing that the two complementary DNA alterations that could not be confirmed by genomic analysis were both splicing-related—that is, deletion of exon 10 in one cell line and a 43-base-pair insertion between exons 13 and 14 in the other. This finding suggests that aberrant splicing, either by mutations of cis elements or by changes in the splicing machinery regulating the processing of NF2 transcripts, may constitute an additional mechanism for NF2 inactivation in MM.

In a subsequent report, mutations in the NF2 coding region were detected in 12 of 23 new MM cell lines. Western blot analyses revealed high levels of NF2 in 11 MM cell lines lacking NF2 mutations, whereas NF2 protein was not detectable in the 12 cell lines that exhibited alterations of the NF2 gene. In addition, two cell lines with NF2 mutations reported in an earlier study were also examined, and both of these cell lines showed no NF2 expression. LOH analyses were performed on the entire 25 MM cell lines using two polymorphic DNA markers residing at or near the NF2 locus in chromosome 22q12. Eighteen of the 25 cell lines (72%) showed losses at one or both of these loci. All cases exhibiting mutation or aberrant expression of NF2 showed altered signals, implying that inactivation of NF2 in MM occurs via a two-hit mechanism.

SIMIAN VIRUS 40

SV40 is a DNA tumor virus that has been associated with MM. Although SV40 is endogenous to the rhesus monkey, the virus infected the human population through contaminated polio- and adenovaccines, both attenuated and killed, between 1955 and 1963. Polioviruses were prepared in cell cultures grown as monolayers of infected rhesus monkey kidney cells. Because the virus produces no cytopathic effects in these cells, their infection went unrecognized until 1960, when high titers of the virus were found in some lots of the vaccine. As a result of this contamination, it is estimated that up to 96 million adults and children in the United States alone may have been infected with polioviruses containing SV40. After 1963, slow-replicating strains of SV40, which are difficult to detect using cytopathic tests, may have infected humans exposed to products produced with monkey cells. This hypothesis is supported by the observation that individuals born after 1962 with minimal risk of exposure to contaminated vaccines had an approximately 10% positive rate for SV40-neutralizing antibodies. In addition, horizontal transmission is also possible because SV40 sequences have been detected in sperm, in circulating mononuclear phagocytes, and in cells obtained from the milk of a healthy woman. Regardless of its method of introduction into humans, SV40 appears to be presently transmitted among humans similarly to other papovaviruses.

A link between SV40 and tumor development was first recognized in hamsters, when, in 1960, Bernice Eddy found that subcutaneous injection of rhesus monkey kidney cells into newborn hamsters resulted in the formation of sarcomas at the injection site. In 1991, it was found that 60% of hamsters injected intracardially with SV40 developed MM. The first MM developed 16 weeks after injection, but the majority of MM developed in 3 to 6 months. Interestingly, in hamsters, SV40 is a much more potent carcinogen in the induction of MMs than asbestos. For example, in a study by Smith and Hubert, hamsters were injected intraperitoneally with varying doses of chrysotile, amosite, and tremolite. Of 50 hamsters, 13 developed MMs on injection with chrysotile. In a separate group of 50 animals, four developed MMs when injected with amosite. No tumors were observed in those injected with tremolite. Among all tumors that developed, the earliest was observed after 151 days in a hamster injected intraperitoneally with 25 mg of chrysotile. In contrast, MMs developed in 100% of hamsters injected intraperitoneally with...
The discovery that SV40 produced MM in hamsters subsequently led to the polymerase chain reaction analysis of human MM specimens for the presence of the virus. It is widely accepted that 29 of 48 human MM (60%) contained and expressed SV40 DNA. Sequence analysis revealed that these DNA sequences were homologous to SV40. These results were confirmed by many laboratories and by an independent multilaboratory study organized by the International Mesothelioma Interest Group. This study found that 83% of MM tested positive for SV40 DNA sequences. More recently, using a microdissection technique, Schivapurkar et al. demonstrated that SV40 is specifically present in neoplastic MM cells and not in the surrounding reactive stromal cells or in lung cancer cells. It should be noted, however, that Finnish MM specimens consistently tested negative for SV40. This finding, together with the observation of a different incidence of SV40 in bone tumors from different regions of the world, suggest geographic differences for SV40 in human tumors. It has been hypothesized that these differences may be related either to the use of contaminated poliovaccines (because Finnish poliovaccines were not contaminated by SV40) or to other factors presently unknown.

The ability of SV40 to transform human cells in vitro is well established. The SV40 genome is a double-stranded circular DNA molecule containing 5243 base pairs, which can be divided into two regions, early and late, according to the order in which they are transcribed. The early region encodes three proteins—large T antigen (Tag), small t antigen (tag), and 17K—and is responsible for the transforming ability of the virus. The late region encodes viral coat proteins. Only the early region is necessary for transformation to occur, so immortalization experiments have been done with both the whole viral genome and the early-region DNA alone. Tag binds to viral and cellular DNA, inducing their replication, and has mutagenic and clastogenic function, as it can cause chromosome rearrangements, point mutations, and aneuploidy. Tag is also capable of binding and inactivating the products of several TSGs, including p53, pRB, p21, p107, p105, and p300, which are necessary to prevent cells with DNA damage from cycling. In addition, inhibition of p53, Tag inactivates an essential cell checkpoint at which DNA alterations are repaired before the cell is allowed to continue into the S phase of the cell cycle. If the cell does not repair the mutations, normally apoptosis occurs. Tag inhibition of p53 allows the cell to undergo mitosis even in the presence of mutations. Whether continuous expression of Tag is necessary to maintain the transformed phenotype is currently unclear. Experiments in hamsters indicate that continuous expression of Tag is necessary to induce and maintain transformation. In contrast, more recent experiments in SV40 transgenic mice and human cells in vitro and in rats suggest that continuous expression of Tag is not always needed for maintenance of the transformed phenotype.

A 19-kD protein, tag, is found predominantly in the cytoplasm of infected cells and performs several functions to increase the transforming potential of Tag. It increases production of Tag, causes mislocalization of p53 through stimulation of mitogen-activated protein (MAP) kinase and AP-1, and contributes to the complete inactivation of p53 by stimulating cellular phosphatase 2A (PP2A) to indirectly alter the phosphorylation state of p53.

After infection with SV40, some human cells die and others are transformed. Many of the transformed cells eventually reach crisis and die, but a few become immortal. Although human cells immortalized by SV40 do not produce tumors in nude mice, these same cells may become oncogenic if they are transplanted with an oncogene, mutated by carcinogens, or if they are passed enough times to allow a significant number of mutations to accrue. Through the actions of Tag and tag, human mesothelial cells, fibroblasts, bronchial epithelium, and breast epithelium have been transformed in vitro. Human cells transformed by SV40 in tissue culture, when injected into human volunteers, have induced subcutaneous tumors. Analysis of p53 and retinoblastoma family members demonstrated that Tag complexes and inactivates these gene products in human MM. p53, pRB, p107, and pRB2/p130 are present in detectable quantities in human mesothelial cells, and their expression is also significantly associated with Tag expression. Their absence of mutations, their unusually high level of expression in human MM cells, and the ability of Tag to co-precipitate with each of these tumor suppressors supports the assertion that SV40 Tag binds, stabilizes, and inactivates p53 and retinoblastoma proteins, which may allow for MM development. This hypothesis has been supported by experiments in which transfection of antisense SV40 inhibited Tag expression, restored the p53-p21 pathway, and caused growth arrest and apoptosis of SV40-positive human MM cell lines. These findings suggest that antisense SV40 strategies may be useful in the treatment of SV40-positive MM patients.

CONCLUSIONS

Multiple genetic alterations are involved in the development of most malignancies. Many MM patients who expressed SV40-Tag contained asbestos in their lungs. Both SV40 and asbestos cause genetic damage. Thus, SV40 may act with asbestos to cause MM. Cells of patients with preexisting genetic alterations have been found to be more susceptible to SV40 transformation than normal control cells. For instance, the transformation frequency by SV40 of fibroblasts from a lung cancer patient with Klinefelter's syndrome was three to ten times higher than that of fibroblasts from normal individuals with no history of cancer. Furthermore, fibroblasts from individuals with Down syndrome and Fanconi's anemia also have increased susceptibility to transformation by SV40 in vitro. Thus, it is possible that because cells with preexisting genetic alterations are more easily transformed by SV40, cell harboring DNA alterations caused by asbestos would also be more prone to SV40 transformation.

In normal conditions, DNA is controlled through a delicate balance of phosphorylation and dephosphorylation events. Increased levels of AP-1 are ultimately responsible for cell growth and viability of AP-1 is normally regulated through phosphorylation and dephosphorylation events (Fig. 40.1.1). Autophosphorylation of the EGF receptor, or activation of ras and others, leads to phosphorylation of MEK1 kinase, which in turn phosphorylates the MAP kinases, also known as extracellular-regulated kinases (ERK). The activation of these kinases causes activation of other intermediaries, such as elk-1, and this in turn stimulates c-fos and c-jun and other members of the AP-1 family, inducing cell division. Down-regulation of AP-1 activity is achieved through PP2A, which dephosphorylates MAP kinases. Asbestos and SV40 Tag, working through this mechanism, may actually induce tumor formation. Asbestos is capable of inducing both DNA damage and autophosphorylation of the EGF-receptor, which eventually leads to increased c-fos and c-jun expression, AP-1 expression, and cell division. When Tag is concurrently expressed, it binds and inhibits p53 and pRB and causes DNA alterations. In addition, tag can bind and inactivate PP2A, allowing increased activity of MAP kinases, AP-1 and, ultimately, cell division. Tag inactivation of p53 does not allow repair of the mutations caused by asbestos and/or Tag at the G2/M checkpoint mediated by p53 through p21. Thus, these carcinogens would allow the cell to divide unchecked and accumulate further somatic genetic changes. Whereas DNA alterations are either of no significance or lead to cell death in the majority of the cases, a few cells could potentially develop perturbations of key cell-cycle regulatory genes and become immortalized, transformed, and tumorigenic. Therefore, we propose that the combined effects of asbestos and SV40 overwhelm cell-cycle regulatory mechanisms, result in unchecked cell division, and occasionally allow transformation and MM development. Evidence in support of this assertion comes from experiments with p53-deficient mice. These studies demonstrate that p53-deficient animals are more the induction of MM on exposure to asbestos. Similarly, human mesothelial cells positive for SV40 have Tag-mediated inhibition of p53 and may be more susceptible to asbestos carcinogenicity. The finding that, in MM cells, restoration of the p53 pathway with antisense Tag causes growth arrest and apoptosis supports this scenario. It should be noted that SV40 is a very strong immunogen and that cells expressing SV40 viral antigens are usually efficiently recognized and killed by the host immune system. In other words, SV40 is a very potent carcinogen, capable of fully transforming human cells in tissue culture. At the same time, SV40 is a strong immunogen; therefore, SV40-transformed cells should be killed by the immune system. It is possible that the local and systemic immunosuppressive activity of asbestos may favor the growth of cells expressing SV40 antigens and may partly explain the strong association of SV40 with MM.
SUMMARY

A large body of experimental and epidemiologic data support the notion that asbestos, or at least amphibole asbestos, causes MM. The same data also support the notion that exposure to asbestos is usually not sufficient for MM development and that other factors, including radiation, genetic predisposition, and SV40, can render some individuals more susceptible to asbestos carcinogenicity. At this time, the involvement of radiation and genetic predisposition in MM development is speculative. On the other hand, SV40 is present in most human IMMs. In these neoplasms, SV40 interferes with key cell-cycle regulatory genes and may contribute to asbestos- or alone (or non–asbestos-associated tumors) to the development of molecular genetic alterations that ultimately lead to a malignant phenotype. The local and systemic immunosuppressive activity of asbestos may also interfere with the ability of the immune system to eliminate cells expressing SV40 antigens and thus favor tumor progression.

Acknowledgments

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23. Frizelle SP, Grim J, Zhou J, et al. Re-expression of p16INK4a in mesothelioma cells results in cell cycle arrest, cell death but occasionally may result in immortalization, which may be followed by transformation and tumor development. Therefore, the combined effects of asbestos and SV40 may overwhelm the cell-cycle regulatory mechanisms and result in cell division and occasionally in cellular transformation, which may lead to mesothelioma development. Because asbestos interferes with both the local and systemic immune responses, asbestos may help mesothelial cells expressing SV40 antigens to escape immune surveillance. Arrowheads indicate a stimulatory effect, and crossed bars indicate an inhibitory effect. The circle indicates nonintegrated SV40; in some tumors, however, SV40 has been found integrated in the host DNA. NF2, neurofibromatosis type 2; TSG, tumor suppressor genes.


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SECTION 40.2
Management of Mesothelioma

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Epidemiology

Asbestos-Associated Mesothelioma

Mesotheliomas without a History of Asbestos Exposure

Radiation-Induced Mesothelioma/Peritoneal Studies

Diagnosis of Mesotheliomas

Pulmonary Exudates

Pathology

Malignant Pleural Mesothelioma

Staging

Natural History

Surgical Treatment

Radiation Therapy

Chemotherapy

Multimodality Treatment

Combined Radiotherapy and Chemotherapy

Surgery with Postoperative Advanced Therapy

Pleurocopy, Intrathoracic Chemotherapy, with or Without Postoperative Chemotherapy

Extrapleural Pneumonectomy, Intravenous Chemotherapy, and Postoperative Radiotherapy

Novel Multimodal Approaches

Malignant Peritoneal Mesothelioma

Presentation

Malignant Mesotheliomas of the Tunica Vaginalis Testis

Malignant Mesotheliomas of the Pericardium

Biphasic Mesotheliomas

Recent Advances in the Treatment

Recent Fibrous Mesotheliomas of the Genital Tract

Benign Mesothelioma of the Cardiac Atrioventricular Node

Chapter References

EPIEMIOLOGY

Asbestos is the predominant cause of pleural, peritoneal, and probably epididymal mesothelioma in humans. The resistance of asbestos to heat and combustion was recognized by ancient civilizations. Although Pliny had observed that asbestos miners were less healthy than other slaves, the health hazards of asbestos exposure were generally not recognized until this century. 1

The Industrial Revolution greatly expanded demand for asbestos as insulating and packing material for machines and power generators. In 1898, pulmonary scarring and eventual death from respiratory failure was noted in asbestos workers from French and English asbestos textile mills. 2 However, the cause of the pulmonary fibrosis remained uncertain because tuberculosis and other respiratory infections were often epidemic among poor laborers. The two World Wars further increased the use of asbestos in ships and other equipment of combat and transport. The availability, durability, and low cost of asbestos additionally expanded its range of uses in industrial and consumer products. In 1930, the causal association between asbestos and asbestosis was firmly established by Merewether and Price at the London Chest Hospital. 3 When limits were set on allowable industrial levels of asbestos exposure in England, many thought the asbestos problem had been solved. 4 However, case reports of lung cancer in patients with asbestosis appeared as early as 1935. 5

In 1955, Doll 6 reported a case-control study that established the association between asbestos and lung cancer. The attitudes and opinions of scientists between 1935 and 1965 reveal early agreement on the carcinogenesis of asbestos by 1943 in Germany, but rejection of German scientific thought during and after World War II and the lack of epidemiologic and experimental evidence delayed a consensus elsewhere. 7

Up to 8 million living persons in the United States have been occupationally exposed to asbestos over the last five decades during mining and milling of asbestos and in diverse manufacturing processes that use the material. Today, many public and private buildings contain asbestos, including 10% to 15% of schools in the United States that were insulated or sprayed on interior surfaces with asbestos between 1946 and 1972. The public health significance of exposure in such buildings and the cost-effectiveness of asbestos removal are controversial. However, one study suggested risk from such incidental exposures. For 9 of 12 schoolteachers with mesothelioma, the only potential asbestos exposure was that derived from asbestos-containing building materials in schools. 8

ASBESTOS-ASSOCIATED MESOTHELIOMA

The existence of mesothelioma as a distinct pathologic entity was debated by pathologists before 1960. 9 In the late 1940s, case reports of mesotheliomas in patients with asbestosis began to appear. In 1960, Wagner et al. 10 in South Africa reported 33 cases of mesothelioma diagnosed between ages 31 and 68 years in a South African crocidolite mining community. An additional 14 cases were added in an addendum to the paper. A substantial proportion of these patients were exposed in childhood through living in the vicinity of asbestos mills and mines; a few had occupational exposure. This study was followed by reports of mesotheliomas in asbestos workers in other parts of the world.

Mechanisms of Asbestos Carcinogenicity

Two major forms of asbestos exist: curly pliable serpentine asbestos (chrysotile) and rod-like amphiboles (crocidolite, amosite, anthophyllite, tremolite, and actinolite). The first three of these are mined for their commercial utility; the latter three are usually contaminants. Asbestos fibers tend to separate readily and form numerous individual strands, which often are less than 1 μm in diameter.

Carcinogenic effects of asbestos appear to result from its physical properties, rather than chemical structure. In one animal experiment, other fiber types produced mesothelioma more efficiently than amosite asbestos. Long rod-like fibers of narrow diameter are more likely to induce tumors in laboratory animals. Although serpentine asbestos (chrysotile) is generally considered less carcinogenic than the rod-like amphiboles (crocidolite, amosite, anthophyllite, tremolite, and actinolite), debate continues over whether cases associated with chrysotile asbestos are actually caused by amphibole contamination, or are caused by chrysotile itself. Long, needle-like amphibole fibers lodge more readily in the distal respiratory area, where they persist longer and are transported to the pleura and peritoneum.

After inhalation most asbestos is expectorated or swallowed and subsequently excreted in the feces. The remainder can be cleared from the tracheal and bronchial tree via multiple mechanisms, including ciliary action in the trachea, ingestion by macrophages, or penetration through the endothelial lining into interstitial tissues. Short fibers are cleared more readily than long fibers. Fibers that remain preferentially accumulate in the lower third of the lungs adjacent to the visceral pleura. Fibers can be counted visually or using electron microscopy and correlate with asbestos exposure, although visual counting provides substantially lower estimates of fibers per gram of lung.
Asbestos results in an inflammatory and fibrotic process, mediated in part by cytokines released by activated alveolar macrophages. At a molecular level, protooncogenes such as c-sis (platelet-derived growth factor-b chain) are up-regulated in alveolar macrophages from fibrotic lungs, a factor that enhances mesothelial cell proliferation. In addition, asbestos can transfect DNA into cells. Epidermal growth factor–positive cells have been found in 68% of mesotheliomas examined and correlate with improved survival. Chrysotile fiber has been shown to be a strong mutagen in mammalian cells. Asbestos fibers can cause persistent expression of early- or late-oncogenes, such as c-fos and c-jun in tissue culture. The oxidative stress response gene product, heme oxygenase, can be induced by asbestos fibers. These findings suggest that reactive oxygen species produced by asbestos fibers are responsible for the expression of cytotoxicity, DNA damage, mutation, gene expression, or carcinogenesis. Asbestos fibers have also been shown to enhance gamma ray–induced oncogenicity in mammalian cells.

**Risk Rates**

The annual incidence of mesothelioma is not known with certainty. The neoplasm can be difficult to diagnose, even by expert pathologists. Data from death certificates are unreliable for estimating disease frequency despite the usually rapidly fatal outcome of malignant mesothelioma. Cancer deaths are not coded by morphology (mesothelioma). Rather, the cause of mortality is assigned by primary site of the neoplasm (primary neoplasms of pleura and peritoneum). In a study of the Surveillance, Epidemiology, and End Results program of the National Cancer Institute, only 274 of 1130 white decedents with mesothelioma (approximately 95% diagnosed by microscopy) were recorded as having died of a primary neoplasm of pleura or peritoneum. The majority of these mesothelioma cases were coded as having malignant neoplasm of the lung or unknown site.

A reasonable estimate is that 2200 new cases of mesothelioma occur annually in the United States (range, 1000 to more than 3000 cases) or approximately 12.1 per million white men. In the United States, mesothelioma is approximately threefold more common in men than in women. Incidence rises steadily with age and is approximately tenfold higher in men aged 60 to 64 years as compared with those aged 30 to 34.

Because of local asbestos industries, some locations in the United States have incidences as high as 636 male cases and 96 female cases per year per million population. Whether risk in such communities extends to the population at large who are not employed in the asbestos industry remains controversial. The standardized incidence of mesothelioma in Wittenoom, Australia, was 260 per million for both men and women once residents employed in the crocidolite industry were excluded. Purely residential exposure accounted for only 3% of incident cases in Yorkshire, England, but at least 18% of the cases in South Africa.

The incidence of mesothelioma appears to be increasing perhaps by as much as 50% in the last decade. Projections of future incidence for the United States suggest that the numbers of cases will peak at the turn of the twenty-first century or rise moderately in the twenty-first century, and then decline as a result of lifetime exposure and asbestos exposure in the environment. In the Netherlands, the peak in annual male mesothelioma deaths is expected later, in approximately the year 2018. Pleural mesothelioma may account for 0.87% of all deaths in the 1943 to 1947 birth cohort of Dutch men. Peto et al. project that the risk of dying of mesothelioma in Western Europe will double over the next 20 years, with the highest risk of approximately 1 in 150 men in the 1945 to 1950 birth cohort.

**High-Risk Individuals**

Persons at high risk of mesothelioma can be identified by tracing the processing and commercial uses of asbestos. The mineral is mined, milled, and incorporated into a wide range of industrial and commercial products, including insulation, textiles, heat protectors, filters, and construction materials (sparking, roofing, siding, and floor and ceiling tiles). Workers with high levels of asbestos exposure, therefore, are miners, millers, producers of asbestos products, and laborers who install plumbing, boilers, and heating equipment in ships, factories, and homes. The risk extends to workers who may not handle asbestos directly but are in proximity to the material, such as carpenters, electricians, and welders in shipyards.

The risk of mesothelioma associated with occupational exposure to asbestos has been examined in case-control studies and cohort studies. In case-control studies, up to 75% of cases had asbestos exposure, as compared with a small fraction of controls. In cohort studies, up to 10% of asbestos workers have died of mesothelioma. However, mesothelioma risk is difficult to quantitate for several reasons. First, ambient levels of asbestos in most workplaces have not been measured. A high level in one study might be called moderate or low in another. Duration of employment has been used as another surrogate measure of exposure. Second, the time from exposure to the development of mesothelioma is long, usually three to four decades in most reported studies. Mathematical modeling suggests that risk of mesothelioma increases exponentially by the third to fourth power of time from first exposure, but few cohorts have been followed to the end of life. Third, the composition of the inspired asbestos differed among exposed workers.

Despite the obstacles to quantifying risk of mesothelioma, several consistent observations have emerged from studies worldwide. Crocidolite is associated with high risk of mesothelioma in miners, manufacturers, and workers who install asbestos products. Another amphibole, amosite, appears to carry an intermediate risk. Chrysotile, currently the major form of asbestos in production, shows the weakest association with mesothelioma. Occupations with highest risk appear to be insulators, asbestos producers and manufacturers, and heating and construction tradespeople. The projected lifetime risk among these workers exposed from early adulthood ranges up to 20%. Working in proximity to these occupational groups in construction sites confers a relatively lower risk. In addition, some patients with mesothelioma have reported only isolated or brief occupational exposures to asbestos.

In a cohort study of 248 insulation workers in Sweden who exposed to asbestos had almost ended in the mid-1970s, 84 deaths occurred between 1970 and 1994 compared with 46 expected mainly due to an increased cancer mortality (approximately 50%). The morbidity was increased for lung cancer (11.0 cases vs. 2.5 expected), peritoneal mesothelioma (7 vs. 0), and cancer in pancreas (5.0 vs. 0.7). No pleural mesotheliomas were found. The risk of lung cancer did not reach normal levels despite decreased asbestos exposure. Mesothelioma in insulation workers seems to be peritoneal more often than pleural.

Malignant mesothelioma is rarely curable at present, so screening of asbestos workers for mesothelioma is inappropriate. However, smoking greatly increases the risk of lung cancer (but not mesothelioma) in asbestos workers and smoking cessation efforts are needed in this high-risk group. Clinicians considering the diagnosis of malignant mesothelioma should take a detailed exposure history emphasizing the period 20 to 50 years before diagnosis and including possible household contact exposure. Brief exposures may be long forgotten.

**Exposure in the Home**

Mesothelioma in wives and children of asbestos workers has prompted studies that show increased asbestos levels in their homes. Presumably, asbestos was brought into the home on hair and on clothing to be washed in the family laundry. Asbestos workers have been required to shower and change clothing before leaving the workplace only since 1972. Asbestos-related neoplasms have been reported in multiple members of some families, but genetic predisposition to the neoplasm remains to be shown. The risk of mesothelioma in household contacts of asbestos workers has been estimated to be as high as 0.4 to 1.0%, but clearly varies with the level of household contamination, and may be overestimated in the reported data. More than one-half of women with mesothelioma in one series were household contacts of asbestos workers.

A high incidence of mesothelioma (22 per 10,000 persons of age greater than 25) observed in the Anatoli region of Turkey has been attributed to zeolite, a silicate material, such as carpenters, electricians, and welders in shipyards. In a cohort of 162 Karain immigrants to Sweden, 18 cases of mesothelioma had occurred, accounting for 14 of the 18 deaths (78%). Although human herpes virus (HHV) is associated with body cavity lymphomas, HHV-8 amplification products were absent by polymerase chain reaction in 13 diffuse malignant mesotheliomas.

**MESOTHELIOMAS WITHOUT A HISTORY OF ASBESTOS EXPOSURE**

No asbestos exposure can be documented in approximately 30% to 50% of cases of mesothelioma. Quantification of asbestos fibers in some of these patients has documented background pulmonary fiber levels consistent with the absence of a substantial asbestos exposure. Two cases of peritoneal mesothelioma were associated with familial Mediterranean fever.
Approximately 25 published cases of pleural and peritoneal mesothelioma have developed following therapeutic radiation or in two patients, arising adjacent to deposits of thorium dioxide (thorotrast) still visible on chest radiographs after extravasation during diagnostic procedures years earlier. Patients with a history of Hodgkin’s disease may have an increased risk of developing mesothelioma. All five of the mesotheliomas in one series occurred in the field of prior radiation therapy with an average interval between radiation treatment and diagnosis of mesothelioma of 15 years. Three of the five patients also received chemotherapy. No patients recalled exposure to asbestos or had evidence of asbestosis on chest radiography. In reported cases a median of 16 years (range, 7 to 38 years) had elapsed between radiation and detection of mesothelioma.

**BIOLOGY OF MESOTHELIOMA: PLOYDI STUDES**

Ploidy status and the percentage of cells actively synthesizing DNA have been analyzed by flow cytometry in almost 200 malignant mesotheliomas. Ploidy and S-phase fraction seem to be consistent in different sections from the same tumor and were not associated with histologic subtype. In the various studies, 60% to 78% were diploid and 27% were near diploid. In contrast, 85% to 88% of lung cancer are aneuploid. Significantly shorter survival is associated with a high percentage of S-phase cells (but not aneuploidy).

**DIAGNOSIS OF MESOTHELIOMA**

Initial misdiagnosis is common. Pathologic opinion appears particularly diverse when litigation is involved. Because a substantial percentage of mesotheliomas develops in patients with no known asbestos exposure and other malignancies are common in asbestos workers, asbestos exposure should not influence the diagnosis of mesothelioma. Because of the poor current prognosis of pleural mesothelioma, a major role of establishing the diagnosis is to exclude the possibility of a more treatable illness. Accurate diagnosis is also important in the event of subsequent litigation and for epidemiologic and therapeutic studies.

**HUMORAL FACTORS**

Hyaluronic acid has been reported to be useful in diagnosis or for following response but is relatively nonspecific. The level of hyaluronic acid was studied in the pleural fluid of 19 patients with malignant mesothelioma, 27 with lung cancer, 1 with breast cancer, 1 with mediastinal tumor, and 51 with benign diseases. The pleural fluid concentration of hyaluronic acid was greater than 100 µg/mL in 37% of (7 of 19) mesotheliomas and 1.3% of (1 of 80) lung cancers and other malignant and benign diseases. A markedly elevated serum or pleural fluid carcinoembryonic antigen, however, suggests a diagnosis other than mesothelioma.

Hematopoietic growth factors and blood group antigens have been produced by normal and malignant mesothelial cell lines. Serum levels of interleukin-6 (IL-6), C-reactive protein, a -acid glycoprotein, and fibrinogen were significantly higher in 25 mesothelioma patients than in patients with lung adenocarcinoma with cytology-positive pleural effusions. Serum IL-6 levels correlated with the levels of the acute-phase proteins and significantly with platelet counts. The level of IL-6 in the pleural fluid of patients with mesothelioma was approximately 60 to 1400 times higher than in the serum. Even higher levels of IL-6 in the pleural fluid and of thrombocytosis were found in patients with tuberculous pleurisy. High cytokine levels were not specific to mesothelioma (similar profiles were found in patients with tuberculous pleurisy). However, the detection of a markedly increased level of IL-6 in pleural fluid argues against a diagnosis of adenocarcinoma.

**PATHOLOGY**

Benign inflammatory and reactive processes producing mesothelial hyperplasia or other malignant tumors may mimic mesothelioma but do not invade normal tissues and lack cytologic atypia and hyperchromatism. Repeated cytologic examination or biopsy results may be negative despite active tumor. When tumor tissue is obtained, light microscopy often provides documentation of malignancy, but usually does not distinguish adenocarcinoma from mesothelioma. Electron microscopy of either needle biopsy or cytospin specimens from pleural fluid may establish the mesothelial origin of the malignant tumor. Spumus cytology and bronchoscopy may be helpful in documenting an occult bronchogenic adenocarcinoma. The Cancer Committee of the College of American Pathologists has established a checklist protocol for the examination of specimens from patients with malignant pleural mesothelioma.

Adenocarcinomas from primary lung, breast, ovary, stomach, kidney, or prostate cancer frequently metastasize to the pleura and can be extremely difficult to distinguish from epithelial mesothelioma cytologically or histologically. Metastatic adenocarcinoma with extensive pleural involvement may grossly resemble mesothelioma and has been called pseudomesothelioma.

**Cytopathology**

Mesothelial cells must be distinguished from fibrosarcoma, malignant fibrous histiocytoma, malignant schwannoma, and hemangiopericytoma. Synovial sarcoma and carcinosarcomas, which may also have mixed sarcomatous and epithelial components, usually present as a localized mass in the lung. Autopsy requires skilled performance and experienced interpretation to reliably exclude other occult primary carcinomas. Advanced malignant mesothelioma tends to form peripheral visceral masses mimicking primary carcinomas. Asbestos counts and postmortem examinations may have legal as well as epidemiologic value.

**Cytology**

In one study of 21 cases of epithelial malignant mesothelioma (15 pleural, 6 peritoneal) diagnosed by effusion cytology, 13 were of the cohesive cell type and 8 were of the noncohesive cell type. Because of its resemblance to florid reactive mesothelial hyperplasia and the general lack of awareness of the existence of the single-cell pattern of mesothelioma, the noncohesive cell type can often be missed. For 29 patients with at least one cytologic pleural fluid examination, cytology was positive for mesothelioma in 32%. The median time from initial symptoms to the time from presentation to diagnosis was greater than 1 year all had negative cytologic results followed by long periods without further workup, despite a history of exposure to asbestos. Because the sensitivity of cytologic examination for mesothelioma is so low, patients in whom mesothelioma is suspected should undergo immediate pleural biopsy if the pleural fluid cytology result is negative.

**Fine-Needle Aspirations**

Cytomorphologic features (amount of cytoplasm and the degree of nuclear pleomorphism and cellular cohesion) on fine-needle aspiration of primary mesothelioma and of metastatic lesions varies greatly among individual cases. However, numerous distinct, uniformly small intracytoplasmic vacuoles, believed to represent intracellular fat and glycogen, were consistently present in metastatic lesions.

**GROSS DESCRIPTION**

Discrete nodules and plaques of firm, grayish tumor coalesce, eventually obliterating the parietal and visceral surfaces. A rim of up to 5 cm in thickness may encase and constrict the lung with only superficial invasion. The chest wall, pericardium, and diaphragm as well as the interlobar fissures are involved relatively early. At autopsy, tumor invades thoracic lymph nodes in up to 70% of patients with occasional extension to cervical nodes. Small hematogenous metastases are documented to liver and lung and less commonly to kidney, adrenal, and bone in 33% to 67% of cases. Without careful postmortem examination, hematogenous metastases may be missed.

**MICROSCOPIC DESCRIPTION**

Extensive sampling of biopsy, laparotomy, pleurectomy, or pneumonectomy specimens is required. A small piece should be fixed in glutaraldehyde for electron microscopy and the remainder promptly fixed in neutral buffered formalin. There are three histologic variants: epithelial, sarcomatoid, and mixed. Fifty percent to 90% are epithelial, characterized by tubular, papillary, solid, or vacuolated patterns. The sarcomatoid variant is composed of ovoid to spindle-shaped cells with cellularity and hyperchromatism similar to that of a fibrosarcoma. A biphasic pattern with mixed epithelial and sarcomatoid elements is virtually pathognomonic of malignant mesothelioma although extensive sampling may be required to demonstrate the minor component.

**Histochonometric Methods**
Three methods are in common use to distinguish metastatic adenocarcinomas from epithelial mesotheliomas. The periodic acid–Schiff stain used before and after diastase digestion, is the single most reliable histochemical method generally available. Neutral mucopolysaccharides that are strongly positive for periodic acid–Schiff diastase are found in intracellular secretory vacuoles and in intracellular vacuoles in most adenocarcinomas, but are rarely found in mesotheliomas. Their presence is strong but not unequivocal evidence for a diagnosis of adenocarcinoma. Appropriate controls for diastase activity and to distinguish staining of vacuoles from stroma and other structures are essential. Alcian blue at pH 2.5 and colloidal iron stain acid mucopolysaccharides are present in mesothelioma and many adenocarcinomas. Disappearance after digestion with hyaluronidase, which removes hyaluronic acid in intracellular and secretory vacuoles and intercellular lumens, is characteristic of mesothelioma. Stroma hyaluronic acid is a nonspecific finding in many tumors, however. Under most staining conditions, Mayer's mucicarmine method (which stains neutral and weakly acidic mucopolysaccharides in intracellular and intercellular secretory vacuoles pink or red) is strongly positive in many adenocarcinomas. Mesotheliomas are usually negative but occasionally may stain strongly in some laboratories possibly due to fixation or technical conditions. Thus, the method is not completely reliable.

**Immunohistochemistry**

Immunoperoxidase stains using various antibodies may be effectively applied to paraffin-embedded tumor tissue. Monoclonal antibodies against keratin proteins are strongly reactive in mesothelioma with diffuse cytoplasmic staining, and perinuclear accentuation with ring formation. Both epithelial and spindle-shaped tumor cells of mixed and sarcomatoid variants are often stained, reflecting transitional patterns of differentiation also observed on electron microscopy. This reactivity is helpful in distinguishing mesothelioma from fibrosarcoma, malignant fibrous histiocytoma (MFH), and schwannoma; however, carcinomas and synovial sarcomas, which also have biphasic histology, also express keratin proteins. Adenocarcinomas also stain positively, usually with localization to the periphery of the tumor cell. Immunoperoxidase staining for Leu M1 is usually absent in mesotheliomas but positive in most adenocarcinomas. Staining for carcinoembryonic antigen is moderate to strong in most adenocarcinomas, but often weak or absent in renal, prostate, and some ovarian and endometrial carcinomas as well as mesotheliomas.

**Electron Microscopy**

The epithelial variant is composed of polygonal cells with numerous long, slender branching surface microvilli, desmosomes, abundant tonofilaments, and intracellular lumen formation. Primary lung, breast, and upper gastrointestinal tract adenocarcinomas have short stubby surface microvilli, fewer tonofilaments, and microvilli/rootlets or lamellar bodies. Ovarian and endometrial carcinomas lack intracytoplasmic lumens, but have few tonofilaments and may express features of intestinal metaplasia (abundant mucus droplets, numerous cilia, and dense core granules). Elongated nuclei, and abundant rough endoplasmic reticulin are found in the sarcomatoid variant. Stromal cells separated by matrix containing collagen fibers appear spindle or ovoid with both sarcomatoid and epithelial features, characteristic of the biphasic nature of mesothelioma.

**Prognostic Correlations**

Serum concentrations of two cytokeratin markers, CYFRA 21-1 and tissue polypeptide antigen, were elevated in 26 (50%) and 30 (58%) of 52 patients, respectively, and were highly correlated ($r = .98$). Univariate analysis of data from 51 patients showed a relationship with survival for performance status ($P = .010$), thoracic pain ($P = .014$), platelet count ($P = .027$), CYFRA 21-1 ($P = .002$), and tissue polypeptide antigen ($P = .003$). Multivariate analysis identified independent prognostic significance for performance status, platelet count, and CYFRA 21-1. In addition to performance status, the cytokeratin markers identified patients with good prognosis in a log rank test.

Micrvascular quantification by staining for the antigens CD34 and CD31 in 25 mesotheliomas counted manually or on a computerized image analysis system significantly correlated with each other and with shorter survival independent of patient age and histologic type or grade of mesothelioma. No association was noted with p53 immunoperoxidase

**MALIGNANT PLEURAL MESOTHELIOMA**

**PRESENTATION**

Malignant pleural mesothelioma most commonly develops in the fifth to seventh decade (median age, 60 years), typically 20 to 50 or more years since first documented asbestos exposure. The risk has been estimated to be linearly proportional to the intensity and duration of exposure, and to the time since first exposure to a power of between 3 and 4. Latency periods between first exposure to asbestos and a diagnosis of mesothelioma may vary by occupation, with shorter latencies for insulators and dock workers and longer intervals for shipyard and maritime workers, as well as domestic exposures. A significant proportion of patients with mesothelioma diagnosed between the ages of 20 and 40 report household or maritime exposure during childhood. Children who present with the disease generally have no apparent asbestos exposure.

A ratio of five men to one woman is affected. Dyspnea, nonpleuritic chest wall pain, or both bring 90% of patients to medical attention. Examination is generally remarkable for dullness at one base, and chest radiography reveals a large freely movable unilateral pleural effusion. Occasional patients are asymptomatic, an effusion found incidentally on chest radiography. Five patients in one series presented with spontaneous pneumothorax with the unsuspected diagnosis of mesothelioma at pleurectomy Sexti percent have right-sided lesions, and less than 5% have bilateral involvement at the time of diagnosis. Pulmonary function test results may document restrictive lung disease resulting from encasement of the lung and assess the potential tolerance for pneumonectomy. Obstructive spirometric changes are unrelated to mesothelioma or asbestosis. Laboratory evaluation is otherwise generally unremarkable except for an elevated platelet count and erythrocyte sedimentation rate.

**STAGING**

As described by Rusch and Venkatraman, the five staging systems before the International Mesothelioma Interest Group (IMIG) Staging System have been “to some extent imprecise and incompletely validated.” The Butchart classification (Table 40.2-1) suffers from an absence of tumor, node, metastasis (TNM) descriptors and vague statements regarding lymph node involvement and degrees of chest wall invasion. Mattson’s classification recognizes contralateral involvement as stage II rather than stage III and has largely been abandoned. Chahinian was the first to devise a TNM-based mesothelioma staging system, with an attempt to qualify the influence of such parameters as locoregional lymph node involvement as well as specific sites and extent of invasion.

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<th>Table 40.2-1. Two of the Five Published Staging Systems for Pleural Malignant Mesothelioma</th>
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The Union International Contra le Cancrum proposed a TNM staging system that evolved into the presently described International Mesothelioma Interest Group Staging System. The IMIG staging system has only been available for a short time, but it has been validated in two large surgical series of mesothelioma. Sugabaker et al. have proposed the alternative but complementary Brigham Staging System based on tumor, resectability, and nodal status. In any evaluation for the patient with mesothelioma, careful attention must be paid to the diaphragmatic extent of the tumor with suspicious scans confirmed by laparoscopic evaluation for transdiaphragmatic extension.

The most important preoperative prognostic indicator may be tumor status of the patients. Tumor volumes associated with malignant pleural mesothelioma patients who have no spread to lymph nodes are significantly smaller than in those patients with positive nodes. Moreover, progressively higher IMIG stage is associated with higher median preoperative total volume of tumor. Further studies verifying that presection tumor volume is representative of tumor status in malignant pleural mesothelioma and can predict overall and progression-free survival, as well as postoperative IMIG stage, are needed to complement metabolic imaging studies.

Noninvasive Studies to Determine Stage

The major role of noninvasive procedures is to determine isolated hemithorax disease. Despite a history of asbestos contact in 50% to 70% of patients, pleural plaques or interstitial fibrosis are apparent on chest radiography in only approximately 20%, but pleural calcifications are evident on almost one-half of computed tomographic (CT) scans and in up to 67% at autopsy. Scolliosis with contracture of the ipsilateral hemithorax is visible even on chest radiography with advanced disease.

A CT scan or magnetic resonance imaging (MRI) of the primary tumor to assess the extent of disease is indicated if treatment is contemplated. Characteristic CT findings in almost 100 patients are pleural thickening in 92% (and of the intralobal fissures in 86%), effusions in 74%, and pleural calcifications in 20% to 50%. CT scan is helpful in differentiating benign from malignant pleural thickening, but does not reliably distinguish primary from metastatic malignancy.

Coronal MRI is particularly helpful to evaluate the diaphragm. In a study of 26 mesothelioma patients evaluated with sequential paired CT and MRI scans, MRI showed tumor spread into the interlobar fissures, tumor invasion of and through the diaphragm, and invasion of bony structures better than CT. Invasion of the chest wall and mediastinal soft tissue and tumor growth into the lung parenchyma were equally well seen on both imaging methods. CT was better for detecting pleural calcifications.

Twenty-eight consecutive patients referred for the evaluation of suspected malignant mesothelioma were evaluated by positron emission tomography (PET) with 2-fluoro-2-deoxy-d-glucose (FDG) imaging. Video-assisted thorascopy or surgical biopsies provided a malignant diagnosis in 24 patients (22 with mesothelioma) and benign processes in the remaining four. The uptake of FDG was significantly higher in malignant than in benign lesions (P = .001). FDG-PET images identified active tumor sites. Hypermetabolic lymph nodes were noted on FDG-PET images in 12 patients, 9 of which appeared normal on CT scans. Histologic examination in six patients confirmed malignant nodal disease in five cases and granulomatous lymphadenitis in one. Standardized uptake values were inversely correlated with duration of survival after the PET study (P = .05). These important data require verification in larger numbers of patients but could be useful in deciding which patient may be a candidate for an aggressive approach since a high FDG uptake in these tumors may indicate a shorter patient survival.

Mesotheliomas are reported to take up gallium 67. Gallium 67 scans in seven cases obtained before resection were compared with pathology. When the involved pleural thickness was over 6 mm, gallium 67 uptake correlated with the macroscopic thickness of mesothelioma in resected specimens. Thickness of the pleura on CT images was only reliable for thick involvement. No definite correlation was found between gallium 67 uptake and the histologic type, extent of tumor parenchyma, interstitial volume, and tumor vascularity.

Planar TI-201 scintigraphy in a single mesothelioma patient revealed diffuse pleural tumor accumulation. Single photon emission CT demonstrated exact tumor location.

Brain, bone, and liver metastases or extension into other serosal surfaces, although present in more than one-half of patients at autopsy, are sufficiently uncommon at presentation to obviate the need for extensive baseline studies in the absence of symptoms or laboratory abnormalities. However, such studies may identify an occult adenocarcinoma of the lung, a pattern of widespread metastases, or a markedly elevated serum or pleural fluid carcinoembryonic antigen suggesting a diagnosis other than mesothelioma.

Although there are no definitive biomarkers for mesothelioma, future studies investigating serial serum levels of tissue polypeptide antigen or thrombomodulin may be of interest.

Diagnostic Surgery

Although obtaining an accurate histologic confirmation of mesothelioma from pleural fluid cytology or needle biopsy specimens is often difficult, the diagnosis of mesothelioma has such a poor prognosis that an unequivocal tissue diagnosis is mandatory. Surgical intervention is usually required, either a thorascopy or thoracotomy, despite the risk of seeding the biopsy site or surgical scar with tumor. For patients who are not candidates for radical surgery, thorascopy or thoracotomy usually revealed benign tumor with the macroscopic thickness of mesothelioma in resected specimens. Thickness of the pleura on CT images was only reliable for thick involvement. No definite correlation was found between gallium 67 uptake and the histologic type, extent of tumor parenchyma, interstitial volume, and tumor vascularity.

If preoperative studies suggest stage I mesothelioma in good-risk patients with asbestos exposure, most surgeons combine the diagnostic and therapeutic surgical interventions in one stage. Generous biopsies can be performed at the inception of the exploration, using frozen sections to differentiate mesothelioma from adenocarcinoma. A sample of uninvolved lung should be obtained for counting asbestos fibers.

Bronchoscopy should be performed in all patients suspected of mesothelioma to rule out endobronchial disease, rare in mesothelioma. The role of mediastinoscopy in patients with suspected mesothelioma is undefined. Some surgeons believe it is unnecessary because nodes can be removed with the lung. Other surgeons believe that, because positive nodes indicate stage III disease, surgery would be contraindicated. Nevertheless, if radical extrapleural pneumonectomy (EPP) is contemplated, mediastinoscopy is recommended, because 20% of patients with mesothelioma have mediastinal lymph node involvement.

NATURAL HISTORY

Shortness of breath and chest pain can be controlled initially by repeated thoracenteses and minor narcotics. Although chest tube drainage and sclerosis is generally unsuccessful, pleural fluid eventually becomes loculated as the tumor obliterates the pleural space. With advanced disease, fatigue and dyspnea increase out of proportion to radiographic findings or pulmonary function values. Because hypoxia results from shunting of desaturated blood through a poorly aerated lung, therapeutic oxygen provides little symptomatic relief.

Mesothelioma tends to be locally invasive. Chest wall masses develop in approximately 10% of patients, generally over thoracentesis, chest tube drainage, or thoracotomy tracts. Direct involvement of esophagus, ribs, vertebrae, nerves, and the superior vena cava cause dysphagia, pain, cord compression, brachial plexopathy, Horner’s syndrome, or superior vena cava syndromes, respectively. Fevers and sweats with no documented source of infection are common and often accompanied by significant weight loss, poor performance status, and an early death. Tumors of mesothelioma can prevent normal lymphatic drainage, resulting in pleural effusions, ascites, and pleural plaques or interstitial fibrosis are apparent on chest radiography in only approximately 20%, but pleural calcifications are evident on almost one-half of computed tomographic (CT) scans and in up to 67% at autopsy. Scolliosis with contracture of the ipsilateral hemithorax is visible even on chest radiography with advanced disease.

The median survival is 4 to 16 months in various series (range, weeks to 16 years). Patients generally die of respiratory failure or pneumonia. Small bowel obstruction from direct extension through the diaphragm develops in approximately one-third, and 10% die of pericardial or myocardial involvement.

Prognostic variables at presentation are shown in Table 40.2-2. Poor prognostic variables in 180 patients in one single institution series included chest pain, older
In the European Organization for Research and Treatment of Cancer experience in 204 adults with malignant pleural mesothelioma on five consecutive phase II clinical trials, the median survival was 13 months from diagnosis and 8 months from trial entry. In the multivariate analysis, poor prognosis was associated with a poor performance status, a high white blood cell count, male gender, and the sarcomatous histologic subtype.\textsuperscript{117}

Factors predictive of poorer survival among 337 patients with mesothelioma on Cancer and Leukemia Group B studies included poor performance status, chest pain, dyspnea, platelet count greater than 400,000/\(\mu\)L, weight loss, serum lactate dehydrogenase level greater than 500 IU/L, pleural involvement, low hemoglobin level, high white blood cell count, and increasing age over 75 years.

With decreasing risk ratio, a multivariate Cox analysis showed that pleural involvement, lactate dehydrogenase greater than 500 IU/L, poor performance, chest pain, platelets greater than 400,000/\(\mu\)L, nonepithelial histology, and increasing age older than 75 years jointly predict poor survival. Performance was the most important prognostic split in the regression tree.\textsuperscript{118}

Localized malignant fibrous tumors of the pleura that may resemble sarcomatous mesotheliomas histologically have also been described. Of 82 malignant localized tumors, 45% were cured by simple excision.\textsuperscript{119} If the nature of the lesion is ambiguous, involvement of the pleura on random biopsy would establish a diagnosis of diffuse (malignant) disease.

**SURGICAL TREATMENT**

The role of surgery in managing diffuse pleural mesothelioma remains controversial, but there are an increasing number of thoracic oncologic surgeons who are operating for this disease. Nevertheless, overwhelming pessimism for curative surgical options continues in most centers that do not routinely deal with the disease since the combination of effective disease and bulky tumor renders surgical eradication virtually impossible. The disappointing long-term overall survival results, the historically high morbidity and mortality, as well as the propensity for local recurrences have forced many centers to abandon radical operations except for the rare localized situation. The arguments regarding appropriate management of mesothelioma can have geographic differences. In a United Kingdom poll of chest physicians, only 46% of the physicians surveyed would consider referral to a thoracic surgeon for radical resection (E. G. Butchart, personal communication). The French approach to the disease has been a concentration on detection of early stage I disease that is treated with intrapleural therapy, including interferon-\(\gamma\) with or without cisplatin.\textsuperscript{120} Surgery is performed after this therapy only to improve local control, either by pleurectomy or EPP. In patients with stage II or III mesothelioma, Boutin et al. recommend surgery and postoperative radiation therapy. In the United States a cohort of specialized cancer centers have evolved that have maintained an interest in the surgical management of the disease. As a new cohort of aggressively trained, specialized thoracic oncologists enters practice, the necessity for such referrals may be diminished. At the present time, however, the evolution of the use of surgery with or without intraoperative, postoperative innovative adjuvant therapies is being defined by these centers. In general, innovative, multimodality protocols that incorporate surgery as part of the package are being explored in larger numbers of patients.

**History of Surgical Management**

Eiselberg\textsuperscript{121} is credited with the earliest resection of mesothelioma in a 46-year-old man in whom he removed chest wall and a portion of lung. Much of the original interest in en bloc resection for diffuse malignant mesothelioma originated in Germany between 1920 and 1960. With advances both in surgery and anesthetic management, a more extensive resection that included lung, pleura, and diaphragm became technically feasible.

**Rationale**

Diffuse pleural mesotheliomas are rarely amenable to en bloc removal. A small proportion of tumors called mesotheliomas may present as an encapsulated mass, not associated with pleural effusion, and these may be amenable to surgical extirpation with negative margins of resection. The majority of diffuse malignant mesotheliomas, however, cannot be surgically removed en bloc with truly negative histologic margins because many of the patients have had a previous biopsy and there is invasion of the endothoracic fascia and intercostal muscles at that site, or pleural effusion, which, although cytologically negative, may be breached, or both leading to local permeation of tumor cells either into the residual cavity or into the abdomen. Nevertheless, in the largest series of EPP performed for mesothelioma from the Boston group, 66 of 183 patients were defined as having negative resection margins after EPP. Patients with this finding who had epithelial mesothelioma were found to have 2- and 5-year survival rates of 68% and 46%, if the node dissection did not reveal tumor.\textsuperscript{122} The operation of choice, especially for early pleural mesothelioma, has yet to be defined. There is no doubt that EPP is a more extensive dissection and may serve to remove more bulk disease than a pleurectomy, chiefly in the diaphragmatic and visceral pleural surfaces. Some surgeons, however, include diaphragmatic resection and pericardial resection with their pleuromectomies to accomplish removal of "all gross disease." For EPP, it is almost a necessity to include pericardiectomy with or without resection, for the maneuver aids in the exposure of the vessels and allows intrapericardial control to prevent a surgical catastrophe. There are no real guidelines preoperatively that one can use to assure the patient which operation will accomplish tumor removal. The presence of irregular, bulky disease that on the CT scan appears to fill the fissures probably dictates the necessity for EPP; a large effusion with minimal bulk disease may call for pleurectomy decortication. Moreover, the philosophy of the surgeon regarding the operation may affect his or her choice, because some surgeons reserve EPP for those patients with bulk disease that presents simple pleurectomy, whereas others believe that the greatest chance for complete gross excision is via EPP performed in the patient with minimal disease. This important factor, preoperative quantitative bulk of disease, may not only influence the choice of resection, but may be an important preoperative prognostic factor in any patient with malignant pleural mesothelioma.\textsuperscript{123}

**Indications for Surgical Management**

Surgery is involved in the management of pleural mesothelioma either for diagnosis, palliative therapy, or as part of a multimodal therapeutic plan. The operations involved in this management include thoracoscopy, pleurectomy and decortication, or EPP. The indications for each of these operations depend on the extent of disease, performance and functional status of the patient, and the philosophy of the treating institution. Basically, operative intervention in mesothelioma is for primary effusion control, cytoreduction before multimodal therapy, or to deliver and monitor innovative intrapleural therapies.

**Functional Evaluation of the Patient Being Considered for Surgical Intervention**

The majority of patients seeking treatment for mesothelioma are middle-aged to older individuals with a long latency period between asbestos exposure and tumor development. If surgical intervention is to be considered, a detailed physiologic and functional workup directed chiefly at the cardiopulmonary axis must be performed.

### TABLE 40.2-2. Poor Prognostic Variables at Presentation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Risk Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>≥75 years</td>
</tr>
<tr>
<td>Pleural involvement</td>
<td>Yes</td>
</tr>
<tr>
<td>Serum lactate dehydrogenase level</td>
<td>&gt;500 IU/L</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>Yes</td>
</tr>
<tr>
<td>Low hemoglobin level</td>
<td>≤10 g/dL</td>
</tr>
<tr>
<td>Male gender</td>
<td>Yes</td>
</tr>
<tr>
<td>Poor performance status</td>
<td>Yes</td>
</tr>
<tr>
<td>Chest pain at diagnosis</td>
<td>Yes</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>Yes</td>
</tr>
<tr>
<td>Low hemoglobin level</td>
<td>≤10 g/dL</td>
</tr>
<tr>
<td>Male gender</td>
<td>Yes</td>
</tr>
<tr>
<td>Poor performance status</td>
<td>Yes</td>
</tr>
<tr>
<td>Prior biopsy</td>
<td>No</td>
</tr>
</tbody>
</table>

Factors predictive of poorer survival among 337 patients with mesothelioma on Cancer and Leukemia Group B studies included poor performance status, chest pain, dyspnea, platelet count greater than 400,000/\(\mu\)L, weight loss, serum lactate dehydrogenase level greater than 500 IU/L, pleural involvement, low hemoglobin level, high white blood cell count, and increasing age over 75 years.

With decreasing risk ratio, a multivariate Cox analysis showed that pleural involvement, lactate dehydrogenase greater than 500 IU/L, poor performance, chest pain, platelets greater than 400,000/\(\mu\)L, nonepithelial histology, and increasing age older than 75 years jointly predict poor survival. Performance was the most important prognostic split in the regression tree.\textsuperscript{118}
PULMONARY EVALUATION. Poor underlying pulmonary function in patients with malignant mesothelioma usually reflects the burden of asbestos exposure, concomitant smoking history (up to 70% of the patients have had a heavy tobacco intake), degree of lung trapped by tumor or fluid, and patient age. Decreases in the forced vital capacity correlate with the degree of costophrenic angle involvement, width, and length of pleural fibrosis, and the presence of either circumscribed plaque or diffuse pleural thickening. The extent of fibrosis correlates with the amount of dyspnea on exertion, and the diffusion capacity of carbon dioxide is reduced in these patients. There is restriction of chest wall motion resulting in reduced lung volumes. Such changes may be bilateral and thus the extent of surgical therapy is influenced by the patient's respiratory functional reserve. Generally accepted criteria for tolerance of an EPP can be assessed by pulmonary function testing including the patients’ response to bronchodilators. Patients with a forced expiratory volume in 1 second (FEV₁) of greater than 2 L/sec usually are able to withstand a pneumonectomy. In general, an FEV₁ of less than 1 L/sec, a PO₂ less than 55, or a pCO₂ greater than 45 are relative contraindications to performance of EPP. If the patient presents with an FEV₁ of less than 2 L/sec, or if the predicted FEV₁ is less than 1.2 L/minute after pneumonectomy, quantitative ventilation-perfusion scanning should be performed.

CARDIAC EVALUATION. Operations for malignant pleural mesothelioma are associated with profound blood loss and potentially significant cardiac demands. The patient should be carefully screened for a history of hypertension, angina, and previous myocardial infarction, and routine electrocardiography should reveal no signs of previous injury. Any patient sustaining a myocardial infarction within the past 3 months or having an arrhythmia requiring medication should not be considered for EPP. Patients without objective evidence of cardiac injury who have a history of chest pain compatible with angina or remote myocardial infarction should have dobutamine thallium screening to investigate reversible perfusion defects indicative of myocardial at risk. In general, patients with an ejection fraction of less than 45% are not considered to be candidates for EPP. This may also affect their enrollment in innovative multimodality programs using potentially cardiotoxic drugs. These patients may then be considered for angioplasty before operative intervention for their disease, and indeed, may be better candidates if a multimodality approach is being contemplated.

Other Preoperative Evaluation

Preoperative medications must be carefully scrutinized, specifically any nonsteroidal antiinflammatory drugs that could affect platelet function. Patients should have complete extrathoracic staging evaluation including bone scan, abdominal CT, and head CT to rule out systemic involvement. If patients are to participate in multimodality programs that use drugs with potential renal toxicity (i.e., cisplatin), a preoperative creatinine clearance should be performed.

Effusion Control

In general, the indications for palliative surgery include the control or prevention of effusion that results in disabling dyspnea. The most efficacious and least invasive of the surgical procedures to accomplish effusion control is thoracoscopy with talc pleurodesis. Two to 5 g of asbestos-free, sterile talc can be insufflated over the lung and the parietal surfaces. Success rates in effusion control with talc, used either via thoracoscopy or via slurry, approach 90%. Failure of these techniques are usually associated with mesothelioma with entrapped lung, a large solid tumor mass, a long history of effusion with multiple thoracenteses leading to loculations, or age older than 70 years. This technique is widely used once the diagnosis of mesothelioma is made. Primary care physicians, however, should carefully deliberate before using sclerosants and consider the extent of visceral and parietal pleural disease. The use of talc or other sclerosants could affect the suitability for patients to enter innovative trials that incorporate either pleurodesis or EPP and could jeopardize the ability of the surgeon to spare a lung that may not have visceral pleural implants. Table 40.2-3 reviews the results of videothoracoscopic talc pleurodesis specifically for mesothelioma. Patients who were able to have a successful pleurodesis had a significantly longer survival than those who did not, and success depended on presence of trapped lung or degree of invasion of the pleura.

TABLE 40.2-3. Videothoracoscopic Talc Pleurodesis for Malignant Pleural Mesothelioma

<table>
<thead>
<tr>
<th>Infect</th>
<th>N.</th>
<th>Success (%)</th>
<th>Death Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vagal</td>
<td>84</td>
<td>81</td>
<td>9</td>
</tr>
<tr>
<td>Gastro</td>
<td>66</td>
<td>59</td>
<td>11</td>
</tr>
<tr>
<td>Carcin</td>
<td>33</td>
<td>20</td>
<td>5</td>
</tr>
</tbody>
</table>

Success defined as no further need for surgery or chest tube placed after 6 months.

Effusion control via palliative surgery is occasionally attempted after lesser procedures (including sclerotherapy) have failed because of the inability of the lung to expand. Generally, the procedure of choice for such palliation is a pleurectomy with or without decortication of the underlying lung. The use of EPP for palliative intent is only rarely described in the literature and because of its morbidity and mortality some surgeons state that EPP should never be used for palliative purposes.

Pleurectomy

MORBIDITY AND MORTALITY. When performed routinely pleurectomy for mesothelioma can be associated with few major complications. In the series that specify postoperative morbidity, the most common complication was prolonged air leak (i.e., greater than 7 days), occurring in 10% of the patients. On average the chest tubes can be removed in approximately 5.5 days with greater than 50% of the patients having the chest tube removed within 4 days. Pneumonia and respiratory insufficiency may occur and are usually related to the burden of disease and preoperative functional status. Empyema is a rare occurrence (2%) and is managed by prolonged chest tube drainage and antibiotics. Hemorrhage requiring reexploration is rare (i.e., less than 1%).

FIGURE 40.2-1. Pleurectomy for diffuse pleural mesothelioma. Preoperative tomograms demonstrate thickened pleura and fluid. The operative photograph and specimen are depicted.

Earlier studies in patients requiring pleurectomy (but not having mesothelioma) had an in hospital or operative mortality of 10% to 18% in the 1960s. The modern-day mortality from pleurectomy has decreased and is generally considered to be 1.5% to 2.0%, with death either from respiratory insufficiency or hemorrhage. Most recently, total pleurectomy in 50 patients performed for mesothelioma had a 30-day mortality of 2%. In a series of 39 pleurectomies, the hospital mortality was...
**SHORT- AND LONG-TERM RESULTS**

Pleurectomy and decortication are effective in controlling malignant pleural effusion. Law et al. report effusion control in 88% of patients having decortication for mesothelioma. In 63 patients having partial decortication and pleurectomy Ruffie et al. reported 86% control of effusion, and Brancatisano et al. reported a 98% control of effusion after pleurectomy in 50 cases of pleural mesothelioma.

Many of the published series using pleurectomy for palliative management have added therapies postoperatively in an uncontrolled, institution-related fashion (Table 40.2-4). The majority have no sampling of the mediastinal nodes, little less a mediastinal dissection. Nevertheless, the overall median survival for patients having pleurectomy alone is approximately 13 months. The patients who receive pleurectomy and decortication alone usually have early effusive disease with minimal bulk tumor. If these patients have epithelial mesothelioma and are not found to have nodal involvement, survival rates can be significantly longer than that quoted previously.

**TABLE 40.2-4. Results of Pleurectomy Alone for Mesothelioma**

<table>
<thead>
<tr>
<th>Author</th>
<th>Sex</th>
<th>No. of Patients</th>
<th>Pleuronecrosis</th>
<th>Median Effusion (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Babcock</td>
<td>M</td>
<td>16</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Cluiter</td>
<td>F</td>
<td>15</td>
<td>0</td>
<td>15</td>
</tr>
<tr>
<td>Lee</td>
<td>M</td>
<td>43</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>Belkile</td>
<td>M</td>
<td>26</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Oldham</td>
<td>M</td>
<td>50</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Ruffie</td>
<td>M</td>
<td>30</td>
<td>2</td>
<td>15</td>
</tr>
<tr>
<td>Bronzol</td>
<td>M</td>
<td>26</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>207</td>
<td>5</td>
<td>15</td>
</tr>
</tbody>
</table>

**Radical Curative Surgery: Extrapleural Pneumonectomy**

**INDICATIONS.** Radical EPP classically has been described for pure epithelial tumor, stage I that is technically resectable and encapsulated by the parietal pleura (Fig. 40.2-2). Due to sampling error it is impossible to clarify with 100% certainty whether the tumor is a pure epithelial type or mixed tumor based on the preoperative or intraoperative biopsy.

**FIGURE 40.2-2.** Left-sided diffuse mesothelioma. Two computed tomographic cuts show chest wall, fissure involvement, and aortic arch abutment. The surgical photograph demonstrates the skeletonized aorta, partial pericardiectomy, and partial diaphragmatic removal via a counterincision. The surgical specimen is demonstrated in the lower right.

The centers that are able to attract large numbers of mesothelioma patients due to ongoing prospective trials may be relaxing the so-called classic indications based on stage, age, and histology. Surgeons at these institutions are chiefly concerned with the patients’ functional ability to tolerate the operation, and the ability to accomplish maximal tumor debulking. If, indeed, higher stage patients can undergo the operation with risks equal to pleurectomy and decortication, enthusiasm for its general incorporation in more aggressive adjunctive trials would be justified.

There are few patients who actually qualify for exploration outside the research setting. In Butchart’s review, 29 of 46 or 63% of patients were eligible for EPP. The only other series that reveals this percentage is DaValle’s in which 33 of 56 patients over a 27-year period had EPP (59%). Sugarbaker reported 50% of the patients seen at his institution are not eligible for EPP and adjuvant therapy. Unfortunately, these series really do not define why one patient may have a pleurectomy while another would have EPP, and it is obvious, however, that some institutions have simply never adopted the operation as feasible for treatment of the disease.

Probably the most enlightening study on eligibility was the Lung Cancer Study Group malignant mesothelioma pilot study from 1985 through 1988. To be eligible for entry into the study the patient was required to have disease limited to the hemithorax by roentgenographic evaluation, a residual FEV₁ after resection of at least 1 L/second, and no significant cardiovascular illness, clearly more lenient criteria than those that limited eligibility due to age, histologic type, or presumed stage. Even with these relaxed criteria only 20 of the 83 evaluated patients were resected with an EPP. The reasons that EPP could not be performed were chiefly extent of disease not allowing complete gross resection (54%), inadequate respiratory reserve (33%), stage IV disease (11%), and concurrent medical illness (10%) (Table 40.2-5).

**TABLE 40.2-5. Extrapleural Pneumonectomy: Results**

<table>
<thead>
<tr>
<th>Author</th>
<th>Sex</th>
<th>No. of Patients</th>
<th>Pleuronecrosis</th>
<th>Median Effusion (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Walde</td>
<td>F</td>
<td>17</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>Babcock</td>
<td>M</td>
<td>30</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>Belkile</td>
<td>M</td>
<td>29</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>Oldham</td>
<td>M</td>
<td>50</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Ruffie</td>
<td>M</td>
<td>30</td>
<td>2</td>
<td>15</td>
</tr>
<tr>
<td>Bronzol</td>
<td>M</td>
<td>26</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>207</td>
<td>5</td>
<td>15</td>
</tr>
</tbody>
</table>

**COMPLICATIONS.** Due to its magnitude, EPP has significantly greater morbidity than pleurectomy. The major complication rate ranges from 20% to 40%, and arrhythmia requiring medical management is the most common complication. In the most recent report of Sugarbaker et al., major morbidity occurred in 24% of the...
patients having EPP and minor morbidity in 41%. The rate for bronchopleural fistula is greater with right-sided EPPs with an overall fistula rate of 3% to 20%. The bronchopleural fistula can be handled for the most part with open thoracostomy drainage with or without muscle flap interposition.

MORTALITY. The mortality following EPP was unacceptably high in the 1970s, with 31% reported by Butchart et al. Since then, however, there has been a steady decline in the operative mortality for the operation to consistent rates less than 10% in series of 20 or more patients. Mortality occurs chiefly in older patients from respiratory failure, myocardial infarction, or pulmonary embolus. Rusch and Venkatraman reported a perioperative mortality of 6% (3 of 50) after EPP and Sugabaker et al. reported a perioperative mortality of 3.8% from myocardial infarction and presumed pulmonary emboli.

Recurrence after Extrapleural Pneumonectomy

Rusch et al. described sites of recurrence after EPP to be distant areas compared with biopsy only or pleurectomy and decortication, and the local control was superior to that of the other modalities. Pass et al. also found a higher proportion of first sites of local recurrence seen in the pleurectomy population compared with the patients having EPP. In the series of patients reported by Sugabaker et al., Baldini et al. have reported that the sites of first recurrence were local in 35% of patients, abdominal in 26%, the contralateral thorax in 17%, and other distant sites in 8%.

survival. Long-term survival rates after EPP remain disappointing, with the median survivals ranging from 9.3 to 17.0 months for the majority series. Rusch and Venkatraman reported a median survival of 10 months in their series of 50 EPP, and the median survival of malignant pleural mesothelioma patients having EPP (all histologies) in the National Cancer Institute series is 9.4 months. The majority of patients were pathologic stage II or III in these two series. Most recently, Sugabaker et al. reported a 17-month median survival in a series heavily weighted with stage I, epithelial patients (52 of 183), using a multimodality approach (see Combined Modality Approaches, later in this chapter) whose 2- and 5-year survivals were 68% and 46%. In the series by Rusch and Venkatraman, the 2- and 5-year survivals of stage I patients (16 of 131) were 65% and 30%, respectively.

RADIATION THERAPY

The efficacy of irradiation, like that of other treatment modalities, remains uncertain in the definitive treatment of patients with pleural mesothelioma. While there are no prospective randomized clinical trials that define a role for radiation therapy, several studies suggest benefit. However, the variable clinical course of the disease and the frequent use of radiation in conjunction with either surgery or chemotherapy make assessment of its contribution to an overall treatment program difficult. One report suggests prolonged patient survival among patients with malignant pleural mesothelioma receiving combined modality treatment versus supportive care alone or single modality therapy.

Mesothelioma cell lines seem to be more sensitive to radiation (as assessed by the surviving fraction after 2 Gy) than non–small cell lung cancer cell lines, but less sensitive than small cell lung cancer cells. The results of a more recent study suggest that mesothelioma cell lines from different patients exhibit remarkable differences in radiosensitivity. The use of radiation for mesothelioma, however, often consists of its use in lung cancer because of the extensive pleural involvement seen in mesothelioma. If radiation is to be used for definitive treatment of malignant mesothelioma, treatment of the entire ipsilateral pleura is indicated. This target volume is extremely difficult to radiate to tumoricidal doses without exposing patients to a risk of normal tissue injury to adjacent lung, heart, spinal cord, and liver.

Most reports from the literature document occasional regressions of gross disease with modest doses of radiation, but do not indicate that survival is significantly altered by irradiation compared with supportive care. Between 1971 and 1980, 116 patients with good performance status and without evidence of extrathoracic disease were evaluated at the Brompton and Royal Marsden Hospitals in London. Fifty-two patients underwent active treatment, whereas the other 64 received supportive care. No difference in survival was seen between the two groups at 2 (33%) and 4 years (0% to 11%). Active treatment consisted of nonoperative parietal pleurectomy and decortication of the lung in 28 patients, radiation therapy in 12 patients (following surgery in 8), and chemotherapy in the remaining 12 patients (8 of whom also underwent operation). Radiation therapy consisted of 50 to 55 Gy using rotating arc fields designed to treat the pleura and spare underlying lung. One patient showed a dramatic response to radiotherapy, with resolution of effusion, pain, and dyspnea. She was doing well 4 years after completion of treatment. Two other patients experienced sustained regression of recurrent pleural effusions after radiation therapy. Thus, although the treatment volume and adjuvant normal tissue limit radiation dose, radiation therapy to bulky tumors occasionally produces significant regression and palliation.

TABLE 40.2-6. Radiation Series

Because of the variable course of the disease, different radiation treatment techniques used (anteroposterior and posteroanterior, rotational arc, combined photon electron), and normal tissue constraints on radiation dose, the relationship between treatment response and radiation dose is not well established. The series from the Joint Center for Radiation Therapy in Boston included 29 treatment courses for palliation between 1968 and 1980. Relief of dyspnea, pain, and other symptoms was seen in four of six patients treated with doses of greater than or equal to 40 Gy, whereas only 1 of 23 treatment courses at lower doses of radiation achieved palliation of symptoms. Doses of 15 to 20 Gy (the normal tissue tolerance dose of whole lung irradiation) did not control disease in patients with diffuse involvement of the visceral pleura with 1- to 2-mm nodules.

A series from the Peter MacCallum Cancer Institute in Australia described good palliation in 17 of 26 (65%) evaluable palliative radiation courses. Short-course treatment for palliation with 20 Gy in five fractions appeared to give similar results with more protracted courses (30 to 40 Gy in 10 to 15 fractions). Fifteen patients were given high-dose radiotherapy with radical intent. Twelve completed treatment to 50 Gy. The median survival of the 12 patients completing treatment was 17 months, with an estimated 2-year survival of 17%. A more recent report from the Peter MacCallum Cancer Institute on 111 patients showed that 60% of the patients obtained successful palliation, with a median survival of 5 months. No dose-response curve for palliation could be identified.

In a series from Thomas Jefferson Medical School in Philadelphia, two of nine patients had local control at 20 and 40 months after 60 Gy to the entire ipsilateral pleura, mediastinum, and involved areas of lung. Radiation was delivered in three courses of 20 Gy over a total of 10 weeks by a split-course technique.

While the volume of disease can influence radiotherapeutic outcome in many other tumors, its effect on the radiation response of pleural mesothelioma is not well characterized. The combination of radiation therapy with debulking surgery can be rationalized if only microscopic disease on the majority of the pleural surfaces remains after surgery. Radiation is more effective at a given dose level when treating microscopic compared with gross disease. Higher doses of boost irradiation with either a shrinking-field technique or brachytherapy can be used on sites of residual gross disease. Such a strategy likely maximizes local control while minimizing the normal tissue complications from irradiation.

Radiation therapy can be used to prevent seeding of biopsy tracts and surgical wounds. In a series from Marseilles, France, radiation treatment of 21 Gy in three fractions prevented wound seeding after thoracoscopy or thoracotomy in 24 patients. Before initiation of an adjuvant irradiation policy in this setting, wound seeding occurred in 17 of 33 (61%) patients. None of the patients who developed growth of nodules in an incision site responded to subsequent irradiation.
When considering the use of radical radiation therapy in this disease, the potential complications of high-dose irradiation to a large volume should also be weighed in the treatment decision. The frequency, type, and severity of radiation complications depends on volume, dose, fractionation, technique, and normal tissue in the field, as well as type and timing of any other treatment, such as chemotherapy. Remarkably, some earlier series reported no acute or chronic complications from the use of radiotherapy alone. This may have been the result of limited volume treatment or short survival. One series noted few complications with radiotherapy when 50 to 55 Gy were delivered with an off-axis rotational technique. Among 12 patients, complications included nausea and malaise in six, transient radiation hepatitis in one, and mild esophagitis in another. No case of radiation pneumonitis was noted. However, in cases in which no attempt has been made to shield lung or when the organ tolerance of other tissues such as the liver has been exceeded, significant complications have been seen. Ball and Cruickshank reported a case of fatal radiation hepatitis in a patient treated for a right pleural mesothelioma and one case of radiation myelitis (after 40 Gy) in their series of 12 patients treated with radical irradiation. Maasila et al. reported deterioration in lung function after high-dose irradiation (56 to 71 Gy) given with chemotherapy. Indeed, forced vital capacity and diffusing capacity showed a significant decline at 1.5 to 2.0 months following radiotherapy and continued to decline over the year following the end of radiation. By radiologic assessment, treatment essentially obliterated lung function on the affected side. Of note, hypoxemia and pathologic and physiologic shunting increased in two of six patients monitored. Hence, lung function should be evaluated to assess potential tolerance before undertaking hemithorax irradiation. Liver position and volume should be determined, and adequate hepatic shielding should be used. Maasila and Hallman et al. have reported the association of bronchoalveolar lavage plasmacytosis and surfactant in mesothelioma patients with radiation pulmonary injury.

The use of radioactive colloids such as 198Au or chronic phosphate-32P instilled into the pleural space has also been studied. Pleural effusions have been reported to disappear for up to 3.5 years. The exact response rate and duration to this approach is not known. In a series from Hahnemann Medical College, all six patients were alive at 12 months or longer after instillation of isotopes. The extent of other treatment and exact length of survival, however, was not reported. Because of the physical characteristics of these isotopes, their effect on gross disease is limited. 32P is a pure beta (electron) emitter with maximum tissue penetration of 8 mm, and the bulk of energy deposited in the first 2 mm. 198Au emits 90% of its energy as beta particles (electrons) with an energy of 0.86 MeV. These have tissue penetration of less than 5 mm, although the emitted photons have energies of 0.412 to 1.099 MeV and would penetrate several centimeters. An equally important limitation on the use of radiocolloids is the problem of obtaining optimal distribution of isotope throughout the pleural space. Gordon and colleagues reported an attempt at radiosotope instillation in three patients, but fluoroscopy or gamma camera measurements indicated that the distribution was suboptimal. Hence, both agents may have a limited role in patients with low-volume disease or in conjunction with surgery in patients with an adequate pleural distribution. The distribution of a radioisotope or contrast material should be tested before a therapeutic administration of these agents is considered.

**Radiation Therapy Techniques**

Different radiotherapy techniques have been used to irradiate the pleura to high doses. Because of the extensive pleural involvement, the target volume is large and includes the pleural surface, diaphragm, and mediastinum. Attempts at radical radiotherapy should be limited to those patients with disease confined to one hemithorax. Field borders must extend above the first rib superiorly, below the diaphragmatic reflection of the pleura inferiorly, which is usually at about the lower border of the twelfth thoracic vertebra, laterally to clear the bony rib cage, and include the full width of the mediastinum. The field size can be increased to include masses extending into the chest wall or diaphragm, or to include the whole heart when the pericardium is involved. The identification of sites of residual gross disease with surgical clips at thoracotomy greatly facilitates radiation planning by allowing accurate, well-defined high-dose boost volumes and lessens the likelihood of normal tissue injury. CT scanning can also help delineate sites of gross disease, but may miss invasion of tumor into the mediastinum or through the diaphragm, as well as areas of miliary seeding of the pleura.

**Radical Irradiation**

Radical irradiation commonly delivers 40 to 55 Gy to the entire pleural surface (with the exception of the reflections extending into the fissures in the lung) and the mediastinum. Other structures, such as the heart, are included as clinically indicated. This has been followed by boosts to focal areas of gross disease through reduced portals to doses of 55 to 71 Gy. While some have chosen to irradiate the entire hemithorax with opposed anterior and posterior photon fields to doses of 40 to 50 Gy without lung shielding followed by a cone-down to smaller fields, such techniques are associated with irreversible pulmonary injury. Hence, techniques have been developed to spare the lung. One involves the use of an off-axis beam rotational technique to irradiate the pleural space to high dose while shielding underlying lung. Several others involve matching photon and electron beams. These involve the use of large, opposed anterior and posterior external-beam portals with central lung blocking. The pleural areas underneath the blocks are treated with electron beams of appropriate energy (generally 10 to 15 MeV). CT scans are used to define the thickness of the chest wall, delineate patient contour, and plan treatment. Tissue compensators may improve dose distribution. None of these techniques are ideal. Even careful photon and electron techniques deliver substantial doses to the lung because of the penetrating ability of the electron beams in the lung and contribution from side-scattered electrons set in motion during photon irradiation.

Advances in sophisticated conformal radiotherapy may improve the available dose distribution. A single report using fast neutrons describes a complete regression of bulk disease without evidence of recurrence 78 months after treatment. However, a portion of the disease was treated with cobalt 60 irradiation with similar response. Because of the poor depth dose characteristics of the available neutron beams, only thin patients could be treated with a pure neutron technique. However, these or other particles may have a role in selected patients in delivering boost treatment to sites of gross disease. Other particles, such as protons, may have a role in selected patients in delivering boost treatment to sites of gross disease.

Intensity modulated radiation therapy techniques permit higher doses of radiation to be delivered to target tissue while limiting radiation dose to the lung and other normal tissues (Fig. 40.2-3). When conventional fractions of 1.8 to 2.0 Gy are given daily five times per week, reasonable treatment precautions would limit the spinal cord dose to 40 Gy, the esophagus to 45 to 50 Gy, the whole lung to 20 Gy, a functional portion of the liver to 30 Gy, and 50% of the heart to 40 Gy. Radiation tolerances may be lowered when radiation is given in conjunction with chemotherapy, especially doxorubicin, despite temporal separation of the two modalities by weeks or even months.

**CHEMOTHERAPY**

**Single-Agent Studies**

Before the wide availability of CT scans, most mesotheliomas were not strictly measurable. Measurable masses on chest radiography were frequently obscured by effusions that are totally unreliable in determining response to therapy. Response rates to standard agents remain difficult to define. Relatively small positive studies are reported promptly, whereas larger series with lower response rates may never be published. Nevertheless, data from single-agent studies are shown in Table.
Response rates are included in the table when the number of evaluable patients exceeds ten.

### TABLE 40.2-7. Single-Agent Response Rates in Malignant Mesothelioma from Series with More Than Five Patients

Doxorubicin appears to have some activity against mesothelioma although response rates vary considerably. Methotrexate with rescue, 5-azacitidine, and 5-fluorouracil may also have single-agent activity. Neither cisplatin nor paclitaxel as single agents appear to be significantly active.

#### Intrapleural Cytokine Therapy

Interferon-γ has had intriguing results by the intrapleural route as documented by Boutin et al. Interferon was administered at a dose of 40 million U twice a week for 8 weeks intrapleurally via a catheter or an implantable port for 89 patients over 46 months. Thoracoscopic or surgical biopsy was performed if CT scan 2 weeks after the end of treatment demonstrated a reduction in tumor size. Eight histologically confirmed complete responses and nine partial responses with at least a 50% reduction in tumor size were obtained. The overall response rate was 20%. The response rate for patients with stage I disease was 45, with the main side effects being hyperthermia, liver toxicity, neutropenia, and catheter-related infection.

IL-2–based regimens have also been exploited in mesothelioma. The largest experience to date with intrapleural IL-2–based therapy has been reported by Astoul et al. Of 22 patients with mesothelioma (19 epithelial, 2 mixed, 1 sarcomatous) treated with intrapleural IL-2 ($21 \times 10^6$ IU/day for 5 days) 11 responded partially and 1 completely. The median survival was 18 months. The 24- and 36-month survival rates for responders were 58% and 41%, respectively.

#### Combination Chemotherapy

Response rates for combination regimens range from 0% to 48% (Table 40.2-8). The highest response rate reported is for cisplatin and gemcitabine (48% in 21 patients). Nine of ten responders and three of nine with stable disease has symptomatic improvement, and three responders had improved vital capacity on functional testing.

#### Randomized Trials in Mesothelioma

Doxorubicin and cyclophosphamide with or without dacarbazine yielded response rates of 7% in both arms of a large randomized trial that accrued advanced patients concurrently with a second study for stage I and II mesothelioma. Thus, the response rates may be artificially low in this study because better prognosis patients were treated on a competing study.

The Cancer and Leukemia Group B randomized 79 patients with measurable mesothelioma to cisplatin and doxorubicin versus cisplatin and mitomycin C. The objective response rates in patients with measurable disease (24%) were similar but time to treatment failure (4.8 vs. 3.6 months) and survival (8.8 vs. 7.7 months) were slightly longer for the doxorubicin and cisplatin combination compared with mitomycin and cisplatin.

#### Intrapleural Chemotherapy

Based on the activity of intraperitoneal cisplatin (see Intrapleural Chemotherapy, below), the Lung Cancer Study Group completed a trial of 47 patients treated with intrapleural cisplatin and cytarabine. Of the 37 patients evaluated, 49% had at least 75% decrease in the size of their effusion.

Pharmacokinetic data in 12 patients treated with intrapleural cisplatin and mitomycin showed three- to fivefold higher pleural to plasma levels of both drugs. In an Italian pharmacokinetic study of four patients treated with 90 mg/m² intrapleurally compared with seven patients treated with the same dose intravenously, the mean area under the concentration versus time curve was 50 times greater than that detected in plasma. Intrapleural cisplatin resulted in significantly lower plasma mean area under the concentration versus time curve and prolonged plasma levels of filterable platinum compared with intravenous administration.

The use of an implantable port facilitates repetitive intrapleural administration and probably decreases the risk of infection.

#### MULTIMODALITY TREATMENT

**COMBINED RADIOTHERAPY AND CHEMOTHERAPY**

Theoretically, cisplatin or doxorubicin could be used as a radiosensitizer and may be more effective than radiotherapy or chemotherapy alone. A small group of South African patients treated with doxorubicin and radiation of 10 Gy every 6 weeks for four courses survived a median of 23 months. Paclitaxel has been described as a radiation sensitizer. A phase I report from the National Cancer Institute combining a 120-hour (5-day) continuous infusion of paclitaxel every 3 weeks during thoracic radiation therapy (57.6 to 63.0 Gy) has been shown to be safe in 27 patients with malignant pleural mesothelioma. Many patients achieved local control; however, only four patients were alive with a median follow-up of 15 months. One of these patients is without evidence of disease at 14 months.
A nonrandomized phase II study from University Hospital in Lund, Sweden, compared the effect of hemithorax radiation (40 Gy) alone or combined with doxorubicin and cyclophosphamide in 47 patients with biopsy only. No significant difference was detected between the two groups of patients with regard to tumor response, survival, or palliation of tumor-related pain.

**SURGERY WITH POSTOPERATIVE ADJUVANT THERAPY**

The majority of patients with mesothelioma, independent of staging, cannot be rendered free of disease with surgical therapy alone. In a Memorial Sloan-Kettering Cancer Center report of 41 patients who underwent parietal pleurectomy between 1970 and 1982, disease at the completion of surgery remained on the diaphragm (49%), parietal pleura (51%), mediastinum (49%), chest wall (27%), and lung (5%). Seventy-eight percent had residual disease after surgery. Radical pleuropneumonectomy can remove more disease in selected patients, but many still have residual microscopic or gross tumor after even the most aggressive surgical resection.

Alberts et al., in a series of 26 selected patients (10% of a total of 262 patients), reported an 11-month median survival after maximal pleural cytoreduction, 4500 cGy postoperative radiation therapy, and doxorubicin, cyclophosphamide, and procarbazine. The results, however, may reflect a generally poor risk group as the duration of symptoms was usually less than 6 months.

A nonrandomized prospective study from Helsinki University Central Hospital reported on 100 patients treated between 1977 and 1989 with debulking surgery, chemotherapy, and hemithorax irradiation. The median survival time was increased from 8 to 12 months for those patients who completed one of five protocols. The first protocol (1977 to 1981, 16 patients) was 20-Gy hemithorax irradiation in ten fractions over 2 weeks and a variable number of courses of cyclophosphamide, vincristine, doxorubicin, and dacarbazine. The second study (1982 to 1984, 26 patients) was a split-course radiation therapy program consisting of 55 Gy in 25 fractions over 7 weeks with a midway 2-week rest. Major tumor areas were boosted with 15 Gy in six fractions. Chemotherapy was as described for the first protocol. The third protocol (1985 to 1986, 15 patients) was hemithorax irradiation using a hyperfractionation schedule to 70 Gy (1.25 Gy twice daily) over 7 weeks with a 10-day rest halfway through. Radiation was preceded by single-agent chemotherapy with mitoxantrone for a maximum of six cycles. The fourth protocol (1988 to 1988, 28 patients) included 35-Gy hyperfractionated into 28 fractions over 3 weeks and hypofractionation of 36 Gy into nine fractions every other day over 3 weeks. This schedule was preceded with 4-epirubicin for a maximum of six cycles. The fifth and final protocol (1988 to 1989, 19 patients) included hemithorax irradiation using 38.5 Gy in 11 fractions over 15 days. A maximum of six cycles of etoposide preceded the radiation therapy. None of the protocols prevented progression of local disease or spread of tumor outside the hemithorax. Significant lung injury (radiation pneumonitis and fibrosis) occurred in regimens 2, 3, 4, and 5.

**Pleurectomy, Intraoperative Brachytherapy, and Postoperative Radiation**

Memorial Sloan-Kettering Cancer Center has been the leading proponent of this technique, which includes as complete as a parietal pleurectomy as possible to remove the bulk of the tumor followed by permanent or temporary implantation to deliver 3000 rads in 3 days to a 1-cm distance from the implant plane. Radioactive iodine (BP) is selectively instilled intrapleurally to 7 days after thoracotomy, followed by external-beam radiation therapy commencing 4 to 6 weeks postoperatively using electrons and photons to deliver 4500 rads in 4.5 weeks. They report minimum morbidity in the 41 patients discussed, and the median survival was 21 months at the time of their report. The majority of patients had recurrences at distant sites (54%) with or without local recurrence. Unfortunately, there has been little follow-up information with regard to the ongoing status of these patients, as the median follow-up in 40% of the patients was 12 months or less at the time of the first report in 1984.

**PLEURECTOMY, INTRAPLEURAL CHEMOTHERAPY, WITH OR WITHOUT POSTOPERATIVE CHEMOTHERAPY**

Few studies of combining debulking surgery with intracavitary treatment of pleural mesothelioma have appeared since the first reports of intrapleural chemotherapy alone for malignant mesothelioma. In a report describing intrapleural chemotherapy without surgery for malignant pleural mesothelioma in 1987, 21 patients received 290 mg/m² of doxorubicin weekly for 4 weeks and then monthly. The average survival was 21 months, but the indications for the therapy and the monitoring of responses and recurrence data were difficult to extract from the report. Kirman et al. treated 17 patients with intrapleural cisplatin (90 to 100 mg/m²) weekly for 3 weeks followed by a 3-week rest. Only 2 of 12 evaluable patients with pleural mesothelioma responded, with a median survival of 4 months. The 2 responders survived 9 months.

Rusch et al. combined the elements of intrapleural chemotherapy with cisplatin and cytarabine after surgical debulking followed by systemic chemotherapy in ten patients. One patient died postoperatively, but the chemotherapy complications were reversible, making such an approach feasible. They followed this regimen with an even more aggressive regimen of pleurectomy, immediate intracavitary cisplatin and mitomycin C, followed by two cycles of cisplatin and mitomycin C systemically. Toxicity was acceptable. The overall survival rate of the 27 patients was 68% at 1 year and 44% at 2 years, with a median survival of 17 months. Recurrences, however, were chiefly locoregional.

A similar regimen combining cisplatin and mitomycin C has been attempted at the Cleveland Clinic Foundation of 14 patients. The projected 18-month survival was 31%, yet patients' tolerance permitted delivery of only 50% of the chemotherapy treatments adjuvantly.

In an Italian study, pleurectomy and diaphragmatic or pericardial resection was combined with intrapleural cisplatin and cytarabine for 4 hours immediately after pleurectomy and systemic epirubicin and mitomycin C. The median time to disease progression was 7.4 months, and median survival was 11.5 months in 20 patients. Recurrences, however, were chiefly locoregional.

Pleurectomy with intrapleural chemotherapy with or without radiation therapy remains an intriguing strategy, but its efficacy is not established. Further investigation should include standard debulking with definition of the extent of residual disease, a tolerable but effective intrapleural regimen, and compulsive follow-up to document recurrence patterns.

**EXTRAPELURAL PNEUMONECTOMY, INTRAVENOUS CHEMOTHERAPY, AND POSTOPERATIVE RADIOTHERAPY**

An ongoing interest in a multimodal approach to malignant mesothelioma was developed at the Dana Farber Cancer Institute beginning in 1980. The program has evolved with regard to the chemotherapy, and presently consists of EPP, followed by two cycles of paclitaxel and carboplatin. Concurrent radiation to a dose of 40.5 Gy is given with weekly paclitaxel. Over a 19-year period, 183 patients were treated, with a perioperative mortality of 3.8%. The median survival in this group of patients is approximately 17 months, which is a significant improvement over other trials. Favorable subgroups include those with no mediastinal nodal involvement and epithelial histology.

A series of 93 patients from Hamburg who chose either multimodal treatment or best supportive care has also shown some prolongation of life expectancy with systemic chemotherapy alone for malignant mesothelioma. In a report describing intrapleural chemotherapy without surgery for malignant pleural mesothelioma in 1987, 21 patients received 290 mg/m² of doxorubicin weekly for 4 weeks and then monthly. The second study (1982 to 1984, 26 patients) was a split-course radiation therapy program consisting of 55 Gy in 25 fractions over 7 weeks with a midway 2-week rest. Major tumor areas were boosted with 15 Gy in six fractions. Chemotherapy was as described for the first protocol. The third protocol (1985 to 1986, 15 patients) was hemithorax irradiation using a hyperfractionation schedule to 70 Gy (1.25 Gy twice daily) over 7 weeks with a 10-day rest halfway through. Radiation was preceded by single-agent chemotherapy with mitoxantrone for a maximum of six cycles. The fourth protocol (1988 to 1988, 28 patients) included 35-Gy hyperfractionated into 28 fractions over 3 weeks and hypofractionation of 36 Gy into nine fractions every other day over 3 weeks. This schedule was preceded with 4-epirubicin for a maximum of six cycles. The fifth and final protocol (1988 to 1989, 19 patients) included hemithorax irradiation using 38.5 Gy in 11 fractions over 15 days. A maximum of six cycles of etoposide preceded the radiation therapy. None of the protocols prevented progression of local disease or spread of tumor outside the hemithorax. Significant lung injury (radiation pneumonitis and fibrosis) occurred in regimens 2, 3, 4, and 5.

**NOVEL MULTIMODAL APPROACHES**

**Intrapleural Photodynamic Therapy**

Photodynamic therapy (PDT) involves the light-activated sensitization of malignant cells. Photofrin II, the sensitizer, is retained by malignant tissue in vivo in comparison with normal tissue. The sensitizer is activated by 630-nm light and then interacts with molecular oxygen to produce an excited reactive oxygen species. Singlet oxygen forms the basis of PDT cytotoxicity. The potential for minimal normal tissue toxicity due to the selective retention of the sensitizer within tumors has prompted an interest in studying PDT for the treatment of a variety of tumors including skin, bladder, lung, head and neck, brain, and esophagus. From July 1993 to June 1996, 63 patients at the National Cancer Institute, National Institutes of Health, with localized malignant pleural mesothelioma were randomized to surgery, with or without intraoperative PDT. All patients received postoperative immunochemotherapy with cisplatin, tamoxifen, and interferon. Median survival (14.4 vs. 14.1 months) was longer in patients receiving intraoperative PDT. A nonrandomized phase II study from University Hospital in Lund, Sweden, compared the effect of hemithorax radiation (40 Gy) alone or combined with doxorubicin and cyclophosphamide in 47 patients with biopsy only. No significant difference was detected between the two groups of patients with regard to tumor response, survival, or palliation of tumor-related pain.
months, median progression-free time (8.5 vs. 7.7 months), and sites of first recurrence were similar. Thus, aggressive multimodal therapy incorporating PDT can be delivered for patients with higher stage malignant pleural mesothelioma, but first-generation PDT does not prolong survival or increase local control for malignant pleural mesothelioma.

**Pleural Perfusion**

There has been a resurgence of interest in the delivery of intrapleural cytotoxic chemotherapy at the time of operation for pleural mesothelioma. Using hyperthermic pleural space perfusion, Ratto et al. delivered cisplatin to the pleural space after pleurectomy or EPP in 10 patients. This study has recorded the pharmacokinetics, but has no data as of yet on survival or recurrences.

**Gene Therapy**

A tumor cell infected with an adenovirus construct TK gene (AdHSVtk) containing the herpes simplex thymidine kinase (TK) gene can be killed with ganciclovir. The goals of phase I trial at the University of Pennsylvania were to assess the safety, toxicity, and maximally tolerated dose of intrapleural AdHSVtk, to examine patient inflammatory response to the viral vector, and to evaluate the efficiency of intratumoral gene transfer. Twenty-one previously untreated patients were enrolled in this viral liter dose-escalation study. A replication-incompetent recombinant adenoviral vector containing the HSVtk gene under control of the Rous sarcoma virus promoter-enhancer was introduced into the pleural cavity of patients with malignant mesothelioma followed by 2 weeks of systemic therapy with 5 mg/kg twice a day of ganciclovir. The initial 15 patients underwent thoracoscopic pleural biopsy before and 3 days after vector delivery. The last six patients underwent only the postvector instillation biopsy. Dose-limiting toxicity was not reached. Side effects were minimal and included fever, anemia, transient liver enzyme elevations, and bullous skin eruptions. In addition, a temporary systemic inflammatory response in those receiving the highest dose. Strong intrapleural and intratumoral immune responses were generated. Using RNA polymerase chain reaction, in situ hybridization, immunohistochemistry, and immunoblotting, HSVtk gene transfer was documented in 11 of 20 evaluable patients in a dose-related fashion.

A similar approach is under investigation by the group at Louisiana State University. In vitro mixing experiments, gene-modified tumor ovarian tumor cells killed both mouse and human mesothelioma cells in a dose-dependent manner. Use of the ovarian HSVtk ovarian cells also prolonged survival of mice with mesothelioma in a dose-dependent fashion. These data have served as the basis for an ongoing phase I clinical gene therapy trial to determine the maximal tolerated dose of an HSVtk-transduced ovarian cancer cells infused into the pleural cavities of mesothelioma patients followed by systemic administration of ganciclovir.

**MALIGNANT PERITONEAL MESOTHELIOMA**

**PRESENTATION**

Patients usually present with symptoms and signs of advanced disease including pain, ascites, weight loss, or an abdominal mass. A cake of tumor in the omentum may be palpable as an epigastric mass. No satisfactory staging system has been proposed for peritoneal mesotheliomas, which are usually confined to the abdomen at diagnosis. Chest radiography reveals pleural plaques in approximately 50% of patients with peritoneal primaries, compared with 20% in patients with pleural mesothelioma, reflecting the higher level of asbestos exposure. Final diagnosis may be difficult and requires the evaluation of other abdominal diseases before the diagnosis is considered. Peritoneal fluid from malignant ascites may be a watery transudate or a viscous fluid rich in mucopolysaccharides. No diagnostic significance has been attached to changes in the character of the fluid, although a viscous ascites (with high fluid hyaluronidase levels) may suggest the diagnosis. Massive ascites may result in confusion of mesothelioma with peritoneal cirrhosis. Cytology establishes the diagnosis in only 5% to 10% of cases. Ultimately, definitive diagnosis requires adequate tissue sampling, preferably from peritoneoscopy or an open directed biopsy. A generous biopsy specimen is required to perform immunohistochemical stains, as well as electron microscopy. Open biopsy also permits inspection of the abdominal cavity for extent of disease with particular attention to the bowel and ovaries to distinguish mesothelioma from more common causes of peritoneal carcinomatosis. Peritoneal mesotheliomas can be confused with adenocarcinomas arising from an abdominal organ, but the pattern of spread and tendency to accumulate in the pelvis readily leads to confusion with adenocarcinoma of the ovary or carcinoma arising from Müllerian duct remnants in the peritoneum. The tumor generally remains confined to the abdomen until late in the course and even then is more likely to spread to one or both pleural cavities than to disseminate hematogenously. Thrombocytosis is common and associated with high levels of IL-6 and a poor prognosis. Other common clotting abnormalities include platelet, emboli, hemolytic anemia, and disseminated intravascular coagulation. Most patients die without metastases or involvement of the chest.

**WELL-DIFFERENTIATED PAPILLARY MESOTHELIOMA OR CYSTIC MESOTHELIOMAS OF THE PERITONEUM**

Rare, well-differentiated papillary variants of a syndrome of recurrent peritoneal mesothelial cysts have both been found predominantly in younger women associated with a prolonged survival despite bulky disease. Rarely, the disease progresses over time to a typical malignant mesothelioma. Approximately 130 cases of multicystic peritoneal inclusion cysts (also called benign cystic peritoneal mesotheliomas) have been described, mainly in the pathologic and surgical literature. Some authors have advocated classifying this lesion as reactive proliferation rather than as malignant. The radiologic differential diagnosis has been reviewed. Frequently associated with prior surgery, endometriosis, or pelvic inflammatory disease, they occur predominantly in women, but can occur in men. Treatment should be provided for palliation of symptoms or for clearly documented progression. Despite initial surgical resection, approximately one-half recur locally. Neither lesion size nor proliferation correlates with outcome. Tamoxifen resulted in a prolonged response in a 19-year-old woman. Permanent transvaginal catheter drainage in a patient with recurrent cysts resulted in infection and obliteration of the cyst. The potassium tita niy phosphate laser has also been used in treatment of benign multicystic peritoneal mesothelioma.

**THERAPY**

**Surgery**

Surgical and autopsy series have shown that peritoneal mesothelioma involves all peritoneal surfaces, often with masses of 5 cm or more. Sites of local invasion included the liver, abdominal wall, diaphragm, retroperitoneum, gastrointestinal tract, and bladder. Seeding of laparotomy scars and biopsy tracts has also been observed. The tumor is most often confined to the peritoneal cavity at the time of initial diagnosis and remains there for much or all of the subsequent clinical course. Hence, effective local therapy may have a substantial effect on the survival of patients with this disease. Complete surgical resection is rarely, if ever, feasible, and has not been shown to afford survival benefit in the absence of additional therapy. Nevertheless, surgical intervention can provide palliation for small bowel obstruction and relief of massive ascites by peritoneovenous shunting or paracentesis via Tenckhoff's catheter.

**Radiation**

Despite its use in the few reported survivors in this disease, the role of radiation therapy remains unclear. Megavoltage external radiotherapy can deliver a homogenous dose to the entire abdominal cavity and its contents, although critical organ tolerance limits dose in several areas. Several techniques have been described and used predominately for the therapy of ovarian carcinoma. The first report was the moving slit technique, which was necessary because of limited field size and dose rate in patients requiring full body irradiation. The technique used open fields with a 67% transmission block to attenuate the dose given to the abdomen superior to the L-5 to S-1 interspace. The
superior border of the field is placed above the maximum excision of the diaphragm by 1 to 2 cm as observed by fluoroscopy. The inferior border is placed at the ischial tuberosities. Lateral, the field extends 1 to 2 cm beyond the propionetral fat stripe. Daily fractions of 1.2 Gy in the upper abdomen and 1.8 Gy in the pelvis are given five times weekly to opposed anterior and posterior fields, with both fields treated daily. Doses are prescribed to midplane of the heart and the inferior pelvis lateral to the abdominal cavity to protect the femoral heads and soft tissue. Treatment breaks are given when the total leukocyte count drops to 1500 to 2000/µL or the platelet count drops below 75,000/µL.

Intrapерitoneal instillation of radioactive colloidal gold (198Au) was first reported to improve the symptoms of peritoneal mesothelioma in 1955.32 Nine other patients treated by the administration of colloidal 198Au have been reported.33 Two of nine were free of disease for 3.5 and 5.0 years, respectively. Four other patients were reported to have clinical improvement of symptoms. The concentration of radiocolloid is generally greatest in the peritoneal cavity and decreased systemic toxicity. In addition, substantial intravenous drug concentrations are obtained from peritoneal absorption of some drugs such as cisplatin. Thus, the combination of free surface diffusion and intracapsular drug flow may be potentially more efficacious than intravenous treatment alone.

Intrapерitoneal cisplatin and intravenous thiosulfate protection have resulted in a 59% complete response rate. However, many patients in this study have relapsed quickly after treatment, implying incomplete eradication of tumor using cisplatin alone.34 Mitomycin C, doxorubicin, and epidoxorubicin have also been used intrapерitoneally.35

Intrapерitoneal cisplatin in 19 patients (with mitomycin in as well in 18) resulted in 2 (10%) disease free more than 5 years from therapy.36 Cisplatin and etoposide resulted in one complete response in five patients with measurable disease.37

Of four patients receiving cisplatin-based intrapерitoneal therapy in a Dutch study, two responded, one completely. At 2 years he developed intestinal obstruction. Laparotomy revealed only adhesions.38 A case report noted continuing complete response at 53 months in a patient treated with intrapерitoneal cisplatin and cytarabine.39

Combined Modality Approaches

Because surgery or radiotherapy alone has resulted in only a few anecdotal long-term mesothelioma survivors, integrated combined modality approaches are being studied at several institutions. One of four patients treated at Seattle with surgery, radiotherapy, and chemotherapy had no tumor by follow-up CT scan at the time of publication.

In a retrospective review of 15 women with peritoneal mesothelioma, clinical features included abdominal or pelvic masses in 93%, abdominal distention in 73%, ascites in 60%, abdominal pain in 40%, thrombocytosis in 27%, thromboembolic manifestations in 20%, and elevated CA-125 in 40 of four. The response rate to first-line chemotherapy regimens was 30% overall, but 67% to pemetrexed plus cisplatin. The median survival of all patients was 12 months. The median survival was longer for patients who underwent cytoreductive surgery versus biopsy only (14 vs. 6 months, P = .04), and chemotherapy versus none (29 vs. 1 month, P = .03).40

In three sequential studies by Antman and colleagues of patients with peritoneal mesothelioma treated with surgery, radiotherapy, and chemotherapy, one of three patients treated in the first trial with surgery, whole abdominal radiotherapy, and cyclophosphamide, doxorubicin, and dacarbazine remains alive more than 15 years from diagnosis.41 Of seven patients treated on a second phase I trial between 1982 and 1985 with debulking of all lesions greater than 1 cm, and intraperitoneal doxorubicin (20 to 50 mg) alternating every 2 weeks with intraperitoneal cisplatin (20 to 100 mg/m²) for a total of 8 to 12 treatments. At the time of second laparotomy for removal of the access device, all six patients had at least an objective 50% decrease in the size of the tumor. Chemotherapy was followed by whole abdominal irradiation in four patients. (One patient refused and a second had prior irradiation for Hodgkin’s disease.) Four of the six patients (including three of the four who received irradiation) remain disease free more than 14 years after diagnosis.42 One patient requires chronic intravenous hydration, caused by malabsorption; the remaining three patients have normal performance status. In the third (phase II) trial begun in 1986,43 20 patients have completed debulking, intraperitoneal doxorubicin, and cisplatin and radiation as above. The median survival for the entire treated group was 16.4 months. Thus, intensive multimodality therapy produces a high response rate and may ultimately prolong survival for this otherwise rapidly fatal disease.

Of 18 patients with primary peritoneal mesothelioma who underwent tumor debulking followed by a 90-minute continuous hyperthermic peritoneal perfusion with cisplatin as part of three consecutive phase I trials conducted at the National Cancer Institute, 13 had associated ascites. One patient had a symptomatic, multiply recurrent, benign, cystic peritoneal mesothelioma. Three patients who had a recurrence after a progression-free interval of more than 6 months after continuous hyperthermic peritoneal perfusion underwent reoperation. Two patients had superficial wound infections, and one patient each had atrial fibrillation, pancreatitis, fascial dehiscence, ileus, line sepsis, and Clostridium difficile colitis, but no toxic deaths occurred. Renal toxicity occurred at cisplatin doses above the recommended phase II dose. Nine of ten patients had resolution of their ascites postoperatively. Three patients with recurrent ascites at 10, 22, and 27 months after initial treatment had resolution of their ascites with ongoing responses at 4, 6, and 24 months after the second perfusion. The median progression-free survival is 26 months, and the overall 2-year survival is 80%.44

MALIGNANT MESOTHELIOMA OF THE TUNICA VASALIS TESTIS

Approximately 75 cases have been reported in the literature,45 most often in patients between ages 55 and 75 years, although approximately 10% of the patients were younger than 25 years and occasional children are affected.46

Asbestos exposure was documented in approximately one-half of the more recently reported cases.47

Patients generally present with a hydrocele or hernia. An accurate preoperative diagnosis was reported in only two cases.48 Diffuse peritoneal or abdominal lymph node involvement may be present at the time of diagnosis.

Mesotheliomas arising in the tunica vasalis testes appear to have a more indolent disease course.49 The overall recurrence rate (local and disseminated) was 52%, and 38% died of disease progression.49 Local recurrence occurred in 36% of patients who underwent local resection of the hydrocele wall, 10% after scrotal orchectomy, and 12% after inguinal orchectomy.50 More than 60% of recurrences developed within the first 2 years of the follow-up. The median survival of the patients was 23 months, but was 14 months after recurrence. In some cases of disseminated mesothelioma, adjuvant chemotherapy or radiotherapy was given. Survival correlated significantly with younger patient’s age (P = .01), and with localized as opposed to disseminated disease (P = .05) in univariate analysis. A multivariate Cox regression model of prognostic parameters concerning survival did not yield statistically significant results.51

MALIGNANT MESOTHELIOMA OF THE PERICARDIUM
Benign tumors involving mesothelium arise with some frequency in the pleura and peritoneum, the tunica vaginalis testis, the atrioventricular node of the heart, and rarely in the mediastinum, liver, and adrenal. Those of peritoneum, including tunica vaginalis testis and adrenal, are mesothelial derived, but the others are of disputed histogenesis (atrioventricular node) or appear to arise from submesothelial mesenchymal cells that do not exhibit mesothelial differentiation.

Benign fibrous tumors of the pleura are generally classified as one of two types: benign mesotheliomas, or solitary fibrous tumor of the pleura.

Benign mesotheliomas are approximately one-third as common as diffuse malignant mesotheliomas and are most common from age 40 to 70 years. Because they appear to arise from subperitoneal fibrous tissue, rather than from the mesothelial lining, they have also been called submesothelial fibromas, localizations when the pleura may be involved. They are diagnosed by examination of the pleural fluid or peelings of the pleural surface. Other tumors that may require a limited chest wall resection. Oftentimes, when completely resected, recurrences are not found after several decades. Localized malignant fibrous tumors of the pleura have also been described. Of 82 malignant localized tumors, 45% were cured by simple excision. The nature of the lesion is ambiguous, involvement of the pleura on random biopsy would establish a diagnosis of diffuse (i.e., malignant) disease.

Benign fibrous tumors of the pleura. These neoplasms are probably more accurately designated adenomatoid tumors. They generally arise in the scrotum and epididymis. Similar tumors histologically also are occasionally described in women. Talc granulomas have been described in proximity to the tumor in one case.

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Chalk River, Ontario; Chalk River Laboratories, 1967.


SECTION 41.1
Molecular Biology of Skin Cancer

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INTRODUCTION

In skin cancer, the interaction between genes and the environment figures prominently. At the molecular level, skin tumors appear to result from a succession of genetic alterations; many of these changes are caused by carcinogens, such as sunlight. At the cellular level, one of the mutant genes, p53, causes a deficiency in the programmed cell death of damaged keratinocytes. Without such apoptosis, large numbers of precancerous cells accumulate in the sun-exposed skin of normal individuals. A second gene, PTCH, affects skin development and is mutated in basal cell carcinomas (BCC). Various aspects of these advances have been reviewed.

SKIN CARCINOGENS

Nonmelanoma skin cancer is associated with exposure to chimney soot in chimney sweeps, burn scars, arsenic ingestion, and exposure to sunlight. Sunlight is the principal skin carcinogen in humans and the human carcinogen whose mechanism is clearest. Basal and squamous cell carcinomas are most frequent at low latitudes, in outdoor workers, on exposed regions of the body, and in light-skinned individuals with blonde or red hair who have a tendency to burn rather than tan. Many BCCs that occur on body sites not chronically exposed to sunlight, such as the trunk and legs, seem related to intermittent sun exposure. In experimental animals, the most effective wavelengths are the ultraviolet B (UVB) region of the solar spectrum; the UVA used in tanning parlors can cause skin tumors as well. UVB's effectiveness is due to its ability to partially penetrate the ozone layer and stratum corneum and then be absorbed by DNA. Nonmelanoma skin cancers exceed the incidence of all other cancers combined in the southern United States, Hawaii, and Australia.

The first molecular step in sunlight-induced carcinogenesis is the induction of DNA photoproducts by UVB photons. The most frequent photoproducts involve adjacent pyrimidines. UV photons tend to be absorbed at the 5-6 double bond of pyrimidines, allowing the bond to open. The result is either the cyclobutane dimer or a pyrimidine-pyrimidone (6-4) photoproduct. Both lead to abnormal DNA structures. When DNA is copied during subsequent DNA replication, the DNA polymerase often incorrectly inserts an adenine opposite a damaged cytosine. At the next round of replication, the adenine correctly codes for thymine opposite. After UV, these C®T mutations occur only where a cytosine lies next to a thymine or another cytosine, reflecting the specificity of the sites at which UV photoproducts occur. If two adjacent cytosines mutate, the result is CC®TT. These distinctive patterns of mutation are pathognomonic for UV radiation.

FIGURE 41.1-1. Ultraviolet light photoproducts. TT cyclobutane pyrimidine dimer (left) and TC pyrimidine-pyrimidone (6-4) photoprodut (right).

Mutations are prevented by DNA repair systems that excise UV photoproducts from DNA. A transcription-coupled repair system rapidly removes lesions from the transcribed strand of active genes, whereas a slower global excision system removes lesions from inactive genes and from the nontranscribed strand of active ones.

GENETIC EVENTS

PTCH

Two genes normally prevent cancers but are inactivated in skin tumors. PTCH, a component of a cellular signaling pathway, is mutated in perhaps 90% of BCCs. p53, which encodes a regulator of the cell cycle and cell death, is mutated in half of BCCs and more than 90% of squamous cell carcinomas (SCC).

PTCH was discovered as the gene mutated in nevoid basal cell carcinoma syndrome, an autosomal dominant disorder characterized by multiple BCCs, jaw cysts, and pits of the palms and soles. It is a human homologue of the Drosophila gene patched, and most sporadic BCCs have inactivating PTCH mutations, and almost all tumors without PTCH mutations have activating mutations in its partner, smoothened.

Patched is important in establishing anterior-posterior relationships of the segments of developing Drosophila embryos. It encodes a large transmembrane protein that, in a complex with smoothened, another transmembrane molecule, is believed to serve as the receptor for the secreted molecule hedgehog. In hedgehog's absence, smoothened and patched form an inactive complex. On hedgehog binding, smoothened is released from inhibitory effects of patched and transduces a signal (Fig. 41.1-2). Mutations that inactivate patched switch on the hedgehog pathway without hedgehog. Smoothened functions as an oncogene when switched on in mouse skin, and some BCCs result from activating mutations of smoothened instead of inactivating mutations of patched. GLI1, a downstream transcription factor in the hedgehog pathway, is an oncogene in brain tumors, and its overexpression causes epidermal proliferation in frogs. Activating GLI turns on transcription of WNT7, which is known to act as an oncogene in mammary tumors in mice, as well as members of the tumor growth factor-b family. The latter genes have complex roles in regulating differentiation and cell growth.
Mutating the hedgehog pathway is an early step in tumor development because minute BCCs are as likely as large tumors to have patched mutations, and all histologic subtypes have a high frequency of loss of patched. A congenital lesion that can progress to BCC, the sebaceous nevus, has allelic loss in the PTCH region in 40% of cases. No tumors have loss on other chromosomes without involvement of the PTCH locus; so PTCH appears to function as a "gatekeeper gene" in basal cell carcinogenesis. Inactivating this function seems to be necessary before clonal expansion and accumulation of other genetic hits can lead to BCC formation.

Nearly all hereditary BCCs have allelic loss as their second, somatic hit. This allelic loss is usually related to sunlight, since nevoid BCC syndrome tumors are most frequent on sun-exposed skin and are rare in African Americans. However, UBV causes this type of gross rearrangement of genetic material only rarely, so other wavelengths, such as UVA, may be important. Sporadic BCCs from XP group A patients contain PTCH mutations that are UBV-like, with CC®TT mutations predominating. However, in typical patients, approximately one-third of BCCs have mutations that are clearly not UBV-induced. These may reflect factors such as UVA, oxidative damage, or arsenicals. Sunscreens may need to block both UBV and UVA to be completely protective against BCC.

p53

The distinctive mutations caused by UBV radiation identify a tumor suppressor gene critical for both BCC and SCC: p53. More than 90% of SCC of the skin in U.S. patients contain mutations in p53. These are predominantly C®T and CC®TT base substitutions at sites of adjacent pyrimidines, directly implicating cytosine-containing cyclobutane dimers or (6-4) photoproducts and sunlight UBV as the mutagen. Each p53 mutation changes the amino acid, indicating that the mutation was selected for and contributed to tumor development, rather than being solely an indicator of sun exposure. p53 is a transcription factor that turns on or off the expression of other genes involved in the cell cycle, programmed cell death, and DNA repair. Most mutations inactivate p53's transcriptional activator function. The gene is mutated in approximately one-half of all human cancers and is considered a tumor suppressor gene because these mutations inactivate the gene's ability to suppress growth of tumor cells in culture.

BCCs, though usually diploid and nonmetastasizing, also contain UV-induced p53 mutations. Approximately one-third of BCCs occur on body sites that are relatively sun shielded; p53 mutations from these tumors resemble those seen with UVA, ionizing radiation, or oxidative damage, rather than UBV. UBV-induced p53 mutations are frequent in skin cancers from XP patients, with CC®TT mutations being prominent, and in carcinoma in situ. Aggressive tumors from patients with exposure to both sun and tobacco or agricultural chemicals contain multiple unrelated p53 mutations, as if multiple tumors arising in an abnormal field had merged. In Taiwanese arsenic-induced BCC and SCC, p53 mutations are not UV-like. Non-UV p53 mutations are common in keloids, results of dysregulated wound healing.

The p53 mutations in skin cancers tend to cluster at nine mutation hot spots. DNA photoproductions are not particularly frequent at these sites, but excision of UV photoproductions is slower than at surrounding nucleotides. Excision repair of UV photoproductions is reduced in T lymphocytes from patients with SCC or a family history of skin cancer.

Sunlight mutates p53 quite early. UBV-induced mutations are found in actinic keratoses, which occasionally progress to SCC; each lesion has a different p53 mutation. Strikingly, some 60,000 tiny clones of p53-mutant cells are found in sun-exposed skin from normal individuals (Fig. 41.1-3). Thus, precancerous cells are not only made early in life but begin to proliferate early. The molecular evidence supports migration studies indicating that sunlight exposure critical for skin cancer occurs before age 15 to 20.

CELLULAR EVENTS

The contribution of a p53 mutation to tumorigenesis is partially understood. The p53 protein is not required for normal development but is elevated in cells treated with DNA-damaging agents and in cells with cell-cycle abnormalities. The signal for UV induction of p53 originates from active genes whose transcription has been blocked. Elevated p53 protein has two effects on cells. In the "guardian of the genome" pathway, DNA damage induces the p53 protein. p53 then leads to cell-cycle arrest at a G2®phase checkpoint by inducing p21, an inhibitor of cell-cycle-dependent protein kinases. In keratinocytes, however, UBV induces p21 without p53. p53 facilitates DNA repair by transcriptionally activating the p48 protein, which is required for global excision repair and is defective in XPE. In the "cellular proofreading" pathway, inducing p53 in an aberrant cell leads to apoptosis, a form of programmed cell death.

In the epidermis, cellular proofreading is operative after DNA damage. UBV and UVA induce p53 by reducing its degradation rate. p53 then causes irradiated keratinocytes to become the apoptotic "sunburn cells" familiar to dermatologists. Inactivating the p53 gene prevents sunburn cell formation. Some point mutations in p53 do not block apoptosis, so different p53 mutations may have different effects on tumor development. Mice inactivated for the p53 gene develop more and earlier skin cancers after UBV. Cells defective in p53, or mice defective in UV-induced apoptosis due to a defect in the fas ligand, accumulate mutations at a rapid rate faster than wild-type mice.
The situation can grow worse, due to a second consequence of death—resistance. Because the cancer-prone cell's normal neighbors undergo apoptosis when damaged, their death provides an opportunity for the p53-mutated cell to clonally expand. Sunlight exposure can thus act as a selection pressure favoring the clonal expansion of p53-mutated cells (Fig. 3). Indeed, transgenic mice carrying a p53 point mutation that does not affect apoptosis have more tumors after UVB but no shortening of tumor latency. Solar UV can thus act several times in skin carcinogenesis: first to mutate the p53 or PTCH gene and then afterward to select for clonal expansion of a p53-mutated cell. These two actions correspond to tumor initiation and tumor promotion. UVB is known to have tumor-promoting activity in mouse skin.

**FIGURE 7.14.1-5.** A model for genetic and cellular events in the onset of human skin cancer. Mutation of the p53 tumor suppressor gene and selection for apoptosis-resistant p53-mutant cells by repeated sunlight exposure are described in the text. SBC, sunburn cells; UV, ultraviolet; UVB, ultraviolet B. (From ref. 41, with permission.)

Progression of a single mutant cell to a clone of precancerous or cancerous cells can be traced long after the fact. Taking advantage of p53 mutations as lineage markers, it has been found that when an SCC is adjacent to carcinoma in situ, the two lesions carry the identical mutation. Similarly, microdissecting BCCs into regions of 50 to 100 cells reveals that a BCC contains a dominant cell clone accompanied by subclones containing a second or even a third mutation.

**THERAPEUTICS**

The foregoing molecular findings are beginning to impact the clinic, first in the realm of diagnostics. Sunscreens of SPF 15 reduce cyclobutane dimers, p53 protein induction, sunburn cells, and p53 gene mutations nearly tenfold.5,16 Tumors in mice are reduced up to 50-fold,21 consistent with simultaneous protection of several genes. This is reassuring, since some common sunscreens ingredients are mutagenic,21 and protection against actinic keratoses in humans is only twofold.21

Molecular therapeutics is in its infancy. A gene therapy strategy is to restore p53 to render cells more sensitive to radiotherapy- or chemotherapy-induced apoptosis. Obtaining a useful therapeutic index depends on apoptosis being greater in the tumor cells than in normal tissue. In fact, many treatments leading to apoptosis in transformed fibroblasts only growth-arrest rather than kill cells.27,29 Since p53 is also essential to cell-cycle aberrations or other aberrations of tumor cells,23 an alternative therapeutic strategy introduces p53 without adjutant treatment to induce apoptosis in transformed but not normal cells.27 In vivo intraperitoneal delivery of a retroviral p53 vector leads to a 75% reduction in peritoneal metastatic cells from murine pancreatic cancer.3 Pharmacologic approaches include activation of latent normal p53 protein with small peptides and desmutating mutant p53 using modifiers of its interaction with heat-shock protein. Several chemoprevention regimens increase apoptosis of premalignant cells, including dietary antioxidants23,27 and calorie restriction.23

**CHAPTER REFERENCES**


SECTION 41.2
Management of Skin Cancer

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JOHN A. CARUCCI

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Punch Biopsy
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Mohs Micrographic Surgery
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Nonmelanoma Skin Cancer and Precancerous Lesions
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Basal Cell Carcinoma
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Merkel Cell Carcinoma
Microcystic Adnexal Carcinoma
Sebaceous Carcinoma
Atypical Fibroxanthoma
Malignant Fibrous Histiocytoma
Dermatofibrosarcoma Protuberans
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INTRODUCTION

In 1999, approximately 1 million nonmelanoma skin cancers (NMSCs) were diagnosed in the United States. One in five Americans will develop skin cancer during life, and more than 97% of these will be NMSCs. Some studies suggest that development of NMSC, including basal cell (BCC) and squamous cell carcinoma (SCC), may indicate increased risk for internal malignancy. However, the precise relationship between skin cancer and the risk of internal malignancy is not yet completely defined. The approach to diagnosis and management of common skin cancers, including BCC and SCC and other, less common tumors of follicular, neuroendocrine, and fibrohistiocytic origin, is discussed in this chapter.

DIAGNOSIS

Although many NMSCs present with classic clinical findings such as nodularity and erythema, definitive diagnosis can be made only by biopsy. Adequate tissue obtained in a nontraumatic fashion is critical to histopathologic diagnosis.

Skin biopsies may be performed by shave, punch, or fusiform excision. The type of biopsy performed should be based on the morphology of the primary lesion. A shave biopsy usually is adequate for raised lesions such as nodular BCC, SCC, or tumors of follicular origin. Punch biopsy is effective for sampling flat, broad lesions for which shave or fusiform excision would be technically inappropriate. An excisional biopsy may be used to sample deep dermal and subcutaneous tissue. Excision is appropriate when it is necessary to distinguish between a benign lesion such as a dermatofibroma and a malignant tumor such as a dermatofibrosarcoma protuberans.

SHAVE BIOPSY

The basic techniques involved in performing skin biopsies are demonstrated in Figure 41.2-1. A shave biopsy is performed under clean conditions. Local anesthetic (lidocaine 1% with epinephrine 1:100,000, unless contraindicated) is injected with a 30-gauge needle. The use of a sterilized razor blade, which can be precisely manipulated by the operator to adjust the depth of the biopsy, often is superior to the use of a No. 15 scalpel. After the procedure, adequate hemostasis is achieved with topical application of aqueous aluminum chloride (20%) or electrocautery.

PUNCH BIOPSY

A punch biopsy is performed under local anesthesia, using a trephine or biopsy punch. The operator makes a circular incision to the level of the superficial fat using a rotating motion of the trephine. Traction applied perpendicularly to the relaxed skin tension lines minimizes redundancy at closure. Hemostasis is achieved by placement of sutures.

FIGURE 41.2-1. Biopsy techniques. A: Shave biopsy. A scalpel blade is precisely manipulated by the operator to adjust the depth of the biopsy, and hemostasis is achieved with topical application of aqueous aluminum chloride (20%), ferric chloride (25%), or electrocautery. B: Punch biopsy. The operator makes a circular incision to the level of the superficial fat using a rotating motion of the trephine. Traction applied perpendicularly to the relaxed skin tension lines minimizes redundancy at closure. Hemostasis is achieved by placement of sutures.

PUNCH BIOPSY

A punch biopsy is performed under local anesthesia, using a trephine or biopsy punch. The operator makes a circular incision to the level of the superficial fat, using a rotating motion of the trephine. Traction applied perpendicularly to the relaxed skin tension lines minimizes redundancy at closure. Hemostasis is achieved by placement of simple, nonabsorbable sutures that can be removed in 7 to 14 days depending on anatomic site. If the punch biopsy is small and not in a cosmetically important area, the wound will likely heal very well by second intention.

EXCISIONAL BIOPSY
After local anesthesia has been achieved under sterile conditions, a scalpel is used to incise a fusiform ellipse to the level of deep fat. Hemostasis is obtained with cautery as needed, and the wound is closed in a layered fashion using absorbable and nonabsorbable sutures. In most cases, postoperative care involves daily cleansing with mild soap and water followed by application of antibiotic ointment and a nonstick dressing. Though popular in the past, it is now known that hydrogen peroxide may not have a favorable effect on wound healing. The toxicity of hydrogen peroxide to keratinocytes has been well described, and its use as an adjuvant to wound care is, in our opinion, contraindicated.

GENERAL APPROACH TO MANAGEMENT OF SKIN CANCER

The management of skin cancer depends on the histologic nature of the tumor, the anatomic site, the underlying medical status of the patient, and whether the tumor is primary or recurrent. Because specific management varies with histologic diagnosis, an accurate interpretation of biopsy specimens is essential. Though the majority of BCCs and SCCs are straightforward, identification of the histologic subtypes is important because it can guide proper treatment. Depending on the aggressiveness of the tumor, cancers of the skin may be excised or, in some cases of superficial tumors or precancerous lesions, destroyed in a nonexcisional fashion. Electrodesication and curettage is the most common nonexcisional approach. If a cancer requires excision, the two options are conventional excisional surgery or extirpation by Mohs micrographic surgery (MMS).

EXCISION

Excisional surgery involves removal of the cancer and a margin of clinically uninvolved tissue, followed by layered closure or second-intention healing, as indicated. Frozen or permanent sections interpreted by the pathologist determine adequacy of margins. Margins are assessed from representative sections of the specimen in “breadloaf” fashion, allowing for examination of approximately 3% of the excisional margin of the specimen. This degree of examination may occasionally result in a false-negative assessment of clear margins in cases of infiltrating or aggressive-growth cancers. Similar misdiagnosis may result when one relies on vertically cut frozen specimens for intraoperative margin control. Excision, especially that performed in a physician’s office rather than a hospital operating room, is effective and cost-efficient when the cancer is small (<1 cm), nonrecurrent, or noninfiltrative.

MOHS MICROGRAPHIC SURGERY

MMS facilitates optimal margin control and conservation of normal tissue in the management of NMSC. Individuals specially trained in the technique perform MMS in an office setting under local anesthesia. Briefly, after gentle curettage, a tangential specimen of tumor with a minimal margin of clinically normal-appearing tissue is obtained, precisely mapped, and processed immediately by frozen section for microscopical examination. Optimal margin control is obtained by examination of the entire perimeter of the specimen and contiguous deep margin. Meticulous mapping allows for directed extirpation of any remaining tumor. A key defining feature of MMS is that the surgeon excises, maps, and reviews the excised tissue functionally, minimizing the chance of error in tissue interpretation and orientation. MMS has gained acceptance as the treatment of choice for recurrent skin cancers as well as for primary skin cancers located on anatomic sites that require maximal tissue conservation for preservation of function and cosmesis.

CURETTAGE AND ELECTRODESSICATION

Common methods of skin cancer destruction include curettage and electrodesiccation (C&D) and cryotherapy using liquid nitrogen. C&D is performed under clean conditions with local anesthesia. Visible tumor is first removed by curettage. Curettage is extended for a margin of 2 to 4 mm beyond the clinical borders of the cancer. Electrodesiccation then is performed to destroy another 1 mm of tissue at the lateral and deep margins. Salasche recommended that C&D be performed for three cycles. Others report satisfactory results after a single cycle of C&D for tumors smaller than 1 cm. Although this leads to decreased scarring, it may lead to higher rates of recurrence, as suggested by Robins and Albom, who attributed to insufficiently aggressive treatment the higher rates of recurrence observed in young women with BCC. Tangential shave excision followed by gentle curettage and cautery as needed, and the wound is closed in a layered fashion using absorbable and nonabsorbable sutures. In most cases, postoperative care involves daily cleansing with mild soap and water followed by application of antibiotic ointment and a nonstick dressing. Though popular in the past, it is now known that hydrogen peroxide may not have a favorable effect on wound healing. The toxicity of hydrogen peroxide to keratinocytes has been well described, and its use as an adjuvant to wound care is, in our opinion, contraindicated.

CRYOSURGERY

Cryosurgery exposes skin cancers to subzero temperatures, which causes tissue destruction (Fig. 41.2-3). Heat transfer occurs from the skin, which acts as a heat sink. Tissue damage is caused by direct effects initially and, subsequently, by vascular stasis, ice crystal formation, cell membrane disruption, pH changes, and thermal shock. Successful cryosurgery requires that temperatures reach –50° to –60°C, including deep and lateral margins. The subsequent thaw leads to vascular stasis and failure of local microcirculation. The open-spray technique is used most often and requires liquid nitrogen spray delivery from a distance of 1 to 3 cm. With the confinespray technique, liquid nitrogen is delivered through a cone that is open at both ends. With the closed-cone technique, one end of the cone is closed and the confined-spray technique, liquid nitrogen is delivered through a cone that is open at both ends. With the closed-cone technique, one end of the cone is closed and the confined-spray technique, liquid nitrogen is delivered through a cone that is open at both ends. With the open-spray technique, a prechilled metal probe is applied to the tumor. Delivery time is determined via a depth-dose estimation, which takes into account freezing time, lateral spread, and halothaw time. Immediately after cryosurgery, local erythema and edema are apparent. An exudative phase ensues in 24 to 72 hours, which is followed by sloughing at approximately day 7. Complete healing usually is seen with facial lesions at 4 to 6 weeks and in nearly 12 to 14 weeks in lesions on the trunk and extremities.
Temporary complications may include extensive drainage, edema, bulla formation, and hypertrophic scarring. Rarely, delayed hemorrhage can occur suddenly approximately 2 weeks after the procedure, most commonly after treatment on the nose, temple, and forehead. Paresthesia may occur if superficial nerves are frozen. Other less common side effects may include headache, syncope, febrile reaction, cold urticaria, pyogenic granuloma, milia formation, or hyperpigmentation. Permanent complications may include tissue contraction, hypopigmentation, and scarring. Other less frequently reported complications are neuropathy, ulceration, tendon rupture, alopecia, and ectropion. Cryosurgery is not considered the standard of care for recurrent NMSC or any tumor other than very small, superficial BCC or SCC.

Cryosurgery and C&D both are limited by the inability to evaluate thoroughness of tumor eradication. The absence of margin control and the development of dense scar, which might obscure recurrence, make these methods valuable primarily in the care of histologically superficial NMSC. Close follow-up of the patient is necessary.

Acknowledgments

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Nonmelanoma Skin Cancer and Precancerous Lesions

Actinic Keratosis

Actinic keratoses (AKs) are very common lesions that tend to occur on sun-exposed areas in blond or red-haired, fair-skinned, individuals with green or blue eyes. Although not invasive, AKs are considered by some dermatopathologists to be SCC in situ.

AKs are caused by exposure to ultraviolet B light (UVB), and the possibility for progression to invasive SCC exists. The risk for transformation of a single AK has been estimated to be as low as 1 per 1000 per year. However, the long-term risk of the development of invasive SCC in patients with multiple AKs has been estimated to be as high as 10%. In one study, AK was histologically present or adjacent to invasive SCC in 82% of cases. Molecular characterization of the role of the p53 tumor suppressor gene in AK, and its similar finding in SCC and BCC, suggests that the AKs represent an early stage in the molecular carcinogenesis of NMSC. It has recently been suggested that the term actinic keratosis be replaced by another term, such as solar keratotic intraepidermal SCC.

Clinical Features

AKs are red, pink, or brown papules with a scaly to hyperkeratotic surface. They occur on sun-exposed areas and are especially common on the balding scalp, forehead, face, and dorsal hands. A hypertrophic, indurated variant [hyperplastic AK (HAK)] exists and may be difficult to distinguish from SCC.

Treatment

Due to their potential to develop into invasive SCC, AKs usually should be treated. Numerous destructive options are available for the treatment of AKs, including cryosurgery, C&D, topical 5-fluorouracil (5-FU), chemical cauternization using trichloroacetic acid, or excision (Fig. 41.2-6). Treatment of solitary lesions is straightforward. However, management of patients with hundreds of lesions can become complicated. In this situation, we initially treat the largest lesions by tangential excision followed by C&D. Raised lesions of smaller size are treated by destructive methods, especially the open-spray cryosurgery technique. When flat lesions are extensive, topical application of 5-FU with or without topical retinoids can be effective. The clinical effects of erythema, crusting, or discomfort associated with 5-FU therapy may limit compliance with its use. Alternative specialized deepithelializing techniques, such as laser and chemical exfoliation, may be helpful in the patient with severe solar damage and extensive AKs. Regardless of the treatment used, because AK is a clonal disease that results from exposure to UVB, the chance for developing new lesions over time is clinically significant.
FIGURE 41.2-5. Management of a solitary actinic keratosis does not present a therapeutic challenge, whereas management of multiple actinic keratoses is likely to require combination therapy. 5-FU, 5-fluorouracil.

FIGURE 41.2-6. Erythema, crusting, and discomfort secondary to the use of topical 5-fluorouracil limit compliance with its use.

BASAL CELL CARCINOMA

BCC is a neoplasm of nonkeratinizing cells originating in the basal cell layer of the epidermis. BCC is the most common human cancer, accounting for approximately 75% of all NMSCs and almost one-fourth of all cancers diagnosed in the United States. Characteristically, BCC develops on sun-exposed areas of lighter-skinned individuals, with 30% of lesions occurring on the nose. Men are affected only slightly more often than are women and, although once rare before the age of 50, BCCs are becoming more common in younger individuals.

The pathogenesis of BCC most commonly involves exposure to ultraviolet light (UVL), particularly rays in the UVB spectrum (290 to 320 nm), which triggers mutations in tumor suppressor genes. Other factors that appear to be involved in the pathogenesis include mutations in regulatory genes, exposure to ionizing radiation, and alterations in immune surveillance.

BCC is a feature of inherited conditions. Included among these are the nevoid basal cell carcinoma syndrome (NBCCS), Bazex syndrome, Rombo syndrome, and unilateral basal cell nevus syndrome. Patients with NBCCS may exhibit a broad nasal root, borderline intelligence, jaw cysts, palmar pits, and multiple skeletal abnormalities in addition to hundreds of BCCs. In one case, bilateral cystic adrenal lymphangiomas have been reported in association with NBCCS. Recently, studies have indicated an association with mutations in the PTCH regulatory gene. In addition, mutations in the PTCH gene have been identified in sporadic nonfamilial BCC.

Bazex syndrome is transmitted in an X-linked dominant fashion. Patients present with multiple BCCs, follicular atrophoderma, dilated follicular ostia with ice-pick scars, hypotrichosis, and hypohidrosis.

In contrast, Rombo syndrome is transmitted in an autosomal dominant fashion. Patients present with verruculate atrophoderma, milia, hypertrichosis, trichoepitheliomas, BCCs, and peripheral vasodilatation. Hypohidrosis is not a feature of Rombo syndrome. Patients with unilateral basal cell nevus syndrome present with a congenital, unilateral lesion of comedones and epidermoid cysts, with basal cell proliferations that are thought to be basaloid follicular hamartomas.

The role of the immune system in the pathogenesis of skin cancer that is not completely understood. Immunosuppressed patients with lymphoma or leukemia and patients who have undergone transplants experience a marked increase in the incidence of SCC but only a slight increase in BCC development. A potential link between UVL and immune surveillance has been suggested by Gutierrez-Steil et al., who demonstrated that UVL-induced BCC tumor cells express Fas ligand (CD95L) and further showed that these cells were associated with CD95-bearing T cells undergoing apoptosis. This represents a potential mechanism by which UVL might mediate the tumor cells’ avoidance of cytotoxic T lymphocytes. Patients with depressed cellular immunity secondary to human immunodeficiency virus (HIV) infection show a higher frequency of infiltrative BCC.

Clinical Behavior of Basal Cell Cancer

BCC is associated with extremely low metastatic potential, but it does invade locally. This biologic behavior depends upon angiogenic factors, stromal conditions, and the propensity for the cancer to follow anatomic paths of least resistance. BCCs can elicit angiogenic factors that account for the telangiectatic vessels characteristically seen on the tumor’s surface. Necrosis occurs in tumors that have outgrown their blood supply. Recently, tumor microcirculation was examined in vivo in 12 BCCs from the head and neck by Bedlow et al. Mean blood vessel size, density, and length per unit area were increased in BCC in comparison to normal tissue. An earlier study showed that mean vessel counts were increased in SCCs versus BCCs, suggesting that angiogenesis may be linked to biologic
aggressiveness and that antiangiogenic factors may play a potential therapeutic role in the treatment of aggressive BCCs.

Tumor stroma is critical for both initiating and maintaining the development of BCC. Transplants of neoplasms devoid of stroma usually are unsuccessful. In one study, Hernandez et al. demonstrated that cultured BCC tumor cells stimulated collagenase production by fibroblasts. The concept of stromal dependence is supported by the low incidence of metastatic BCC.

BCC has a tendency to grow along the path of least resistance. Invasive BCC can migrate along the perichondrium, periosseum, fascia, or tarsal plate. This type of spread accounts for higher recurrence rates noted in tumors involving the eyelid, nose, and scalp not treated by MMS. Embryonic fusion planes offer little resistance and can lead to deep invasion and tumor spread, with very high rates of recurrence, if complete tumor extirpation is not achieved (Fig. 41.2-8). The most susceptible areas include the inner canthus, philtrum, middle to lower chin, nasolabial groove, preauricular area, and the retroauricular sulcus.

Perineural spread is uncommon and occurs most often in recurrent, aggressive lesions. In one series, Niazi and Lambert noted perineural invasion in 0.178% of BCC. In all cases, perineural extension was associated with recurrent tumors that were most often located in the periauricular and malar areas. Perineural invasion may present with paresthesia, pain, and weakness or, in some cases, paralysis. Involvement of the cranial nerves and, in one case, thoracic spine has been reported. Metastatic BCC is rare, with incidence rates varying from 0.0028% to 0.1%. Metastases, when reported, have involved lung, lymph nodes, esophagus, oral cavity, and skin. Although long-term survival has been reported, the prognosis for metastatic BCC is generally poor, survival of 9 to 10 months after diagnosis being the norm. Platinum-based chemotherapy appears to have some effect in the treatment of metastatic BCC.

**Basal Cell Carcinoma Subtypes**

Clinical variants of BCC include nodular, superficial, morpheaform (also termed aggressive-growth BCC or infiltrative BCC), pigmented, and cystic BCC, and fibroepithelioma of Pinkus (FEP) (Fig. 41.2-9, Fig. 41.2-10, Fig. 41.2-11, Fig. 41.2-12, Fig. 41.2-13, Fig. 41.2-14, and Fig. 41.2-15). Nodular BCC presents as a raised, translucent papule or nodule, with telangiectasia, and has a propensity for involving sun-exposed areas of the face. Superficial BCC commonly presents as an erythematous scaly or eroded macule on the trunk and may be difficult to differentiate clinically from AK, SCC in situ, or a benign inflammatory lesion. Not uncommonly, superficial BCC may be mistaken for perineural invasion of the cranial nerves and, in one case, thoracic spine has been reported. Metastatic BCC is rare, with incidence rates varying from 0.0028% to 0.1%. Metastases, when reported, have involved lung, lymph nodes, esophagus, oral cavity, and skin. Although long-term survival has been reported, the prognosis for metastatic BCC is generally poor, survival of 9 to 10 months after diagnosis being the norm. Platinum-based chemotherapy appears to have some effect in the treatment of metastatic BCC.

**FIGURE 41.2-9.** Superficial basal cell carcinoma presents as an erythematous patch and may be difficult to distinguish from dermatitis.

**FIGURE 41.2-10.** Nodular basal cell carcinoma. A: A red, translucent nodule with rolled border, as seen here, is a classic presentation of nodular basal cell carcinoma. B: Nodular basal cell carcinoma demonstrating ulceration.
FIGURE 41.2-11. Morpheaform or aggressive-growth basal cell carcinoma (BCC). A: Morpheaform BCC may be difficult to differentiate from scar. B: Microscopical examination reveals strands of basaloid cells aggressively infiltrating dense collagen. C: BCC may recur without an obvious clinical lesion. D: Recurrent BCC after extirpation by Mohs micrographic surgery in the patient depicted in C.

FIGURE 41.2-12. If neglected, basal cell carcinoma invades locally with devastating results. (Courtesy Neil A. Swanson, M.D.)

FIGURE 41.2-13. Pigmented basal cell carcinoma may be difficult to differentiate clinically from melanoma.

FIGURE 41.2-14. Nodular basal cell carcinoma (BCC). Microscopical examination of nodular BCC reveals islands of basophilic cells exhibiting typical BCC morphology.

FIGURE 41.2-15. Cystic basal cell carcinoma. This variant may resemble an epidermal inclusion cyst.

Histologic subtypes of BCC include superficial, nodular, and infiltrative BCC. All BCC subtypes tend to share certain histologic characteristics. These include peripheral palisading of large, basophilic cells, nuclear atypia, and retraction from surrounding stroma. Nodular BCC accounts for approximately 50% of BCCs and is characterized by the presence of tumor cells in rounded masses within the dermis (see Fig. 41.2-14). Peripheral palisading of nuclei is prominent, and surrounding retraction artifact may be present. Groups of cells may be solid, or there may be dermal necrosis or degradation, with formation of cysts or microcysts. The stroma is characteristically coarse and myxoid. If nodules measure less than 15 µm, the tumor may be called micronodular. Infiltrative histology is seen in 15% to 20% of BCCs and represents that subclass of BCCs referred to as aggressive-growth tumors. Tumor cells manifest irregular outlines with a spiky appearance. Palisading is characteristically absent. The stroma is less myxoid than in the nodular form. In the morpheaform variant, which accounts for approximately 5% of BCCs, small groups or cords of tumor cells infiltrate a dense, collagenous stroma parallel to the skin surface (see Fig. 41.2-11B). Superficial multifocal BCC accounts for approximately
15% of BCCs and is characterized by basophilic buds extending from the epidermis. Retraction artifact is present, as is peripheral palisading within the buds. FEP, which accounts for 1% of BCCs, is characterized by a polypoid lesion in which basoid cells grow downward from the surface in a network of anastomoses of cords of cells in loose connective tissue. Mixed histology is apparent in approximately 15% of BCCs.

The significance of histologic subtype lies in the correlation with biologic aggressiveness. The infiltrative and micronodular types are the most likely to be incompletely removed by conventional excision. Rates of incomplete excision vary from 5% to 17%. Incompletely excised infiltrative and micronodular BCCs may recur at rates of 33% to 39%. Recurrences after RT show a tendency toward infiltrative histology and evidence of squamous differentiation, and even recurrent BCC after excision or C&D may become metatypical. In general, recurrences are more frequent in BCCs with infiltrative and micronodular histology, when clear margins are less than 0.38 mm, and in the presence of squamous differentiation. Although historical reports in the literature suggested that 60% of incompletely excised BCCs will not recur, none of these studies provided an appraisal of recurrence rates as a function of histologic subtype. In general, incompletely excised BCCs should be removed completely, preferably by MMS, especially if they occur in anatomically critical areas such as the central zone of the face, retroauricular sulcus, or perioral area.

Adequate treatment of BCC requires appreciation of the histopathologic pattern of the neoplasm. Though some BCCs are small and superficial and behave in essentially a "biologically benign" manner as long as they are conservatively removed, others behave more aggressively and thus require more aggressive treatment. Examples of the latter include clinical BCCs that ulcerate and those located in the central face or on the ear. Furthermore, BCCs that show an aggressive growth pattern histologically require definitive treatment with confirmation of histologically negative margins.

Occasionally, it may appear that a BCC has been adequately removed by biopsy alone, leading to the question of whether to render further treatment. In one study, 41 consecutive patients with 42 BCCs apparently removed by biopsy were treated by MMS, and blocks of tissue, sectioned consecutively until exhausted, were examined for the presence of residual tumor. In 28 of 42 cases (66%), residual cancer was identified. The presence of residual cancer was not related to age, site, histologic subtype, or extent of surrounding inflammation. The results indicate that patients with small BCCs that appear to be completely removed by initial biopsy may be at risk for recurrence if not treated further.

**Characteristics Related to Anatomic Site**

BCCs may demonstrate unique characteristics based on anatomic site. The nose is the most common site for cutaneous malignancies (30%), and BCCs involving the nose may be aggressive. A study of 193 cases of infiltrative BCC involving the nose confirmed that the majority of infiltrating and recurrent BCCs affect the ala. Analysis of the recurrences' aggressive local behavior indicated that recurrent lesions were subject to inadequate therapy initially. In one study, 26 recurrences were identified in 71 nasal skin cancers at an average of 36 months after non-MMS excision. This suggests that MMS may be the treatment of choice for all BCCs involving the nose, especially those exhibiting aggressive growth characteristics.

Perioral BCC represents a significant therapeutic challenge. In one study, perioral BCC accounted for 7.3% of 3192 BCCs treated over a 10-year period. Of these, 48.5% involved the medial canthus, 22.35% involved the lower eyelid, 10.7% involved the upper eyelid, and 5.6% involved the lateral canthus. BCC is the most common tumor affecting the eyelid. In a series of 97 cases of BCC involving the eyelid, 69% were nodular, 13% were infiltrative, 1% were ulcerated, and 12% were mixed (defined as having a significant nodular or ulcerative component in addition to an infiltrative component). Follow-up of 8 of 12 patients with mixed tumors revealed three recurrences. In one patient, orbital exenteration was required. This suggests that mixed tumors of the eyelid with aggressive growth history warrant thorough treatment with complete margin control.

In a review of 24 eyelid tumors treated by MMS, high clearance rates were shown (100%), although follow-up was short (14 months). In addition, 50% of patients were left with intact posterior lamellae, highlighting conservation of normal tissue. The results suggest that MMS followed by ocuoplastic reconstruction, if necessary, is the preferred strategy in the management of perioral BCC.

Approximately 6% of BCCs involve the ear, a site notable for high rates of recurrence. In a recent study, nine patients with BCC involving the conchal bowl were treated by an interdisciplinary approach. In each case, tumor extirpation was accomplished by MMS, and an otorhinolaryngologist was available in the event of temporal bone involvement. There were no cases of recurrence at mean follow-up of 1 year.

It must be stressed that BCC can occur anywhere, even in non–sun-exposed areas, and has been reported to occur on the vulva, penis, scrotum, and perianal area. In one series of vulvar BCC, mean age at presentation was 74 years. Patients have been seen with a history of local irritation that had been present for a few months to several years.

**Treatment**

Excisional surgery, C&D, and cryosurgery have been used to treat circumscribed, noninfiltrating BCCs. In 28 of 42 cases (66%), residual cancer was identified. The presence of residual cancer was not related to age, site, histologic subtype, or extent of surrounding inflammation. The results indicate that patients with small BCCs that appear to be completely removed by initial biopsy may be at risk for recurrence if not treated further.

Surgical excision offers the advantage of histologic evaluation of the excised specimen. Although appropriate for management of most BCCs, cure rates for traditional excisional surgery are inferior to those for tumors treated by MMS in cases of recurrent BCC, infiltrative BCC, and BCC in high-risk anatomic sites. It has been demonstrated that 4-mm margins are adequate for removal of BCC in 98% of cases of nonmorpheform BCC of less than 2 cm in diameter. Extending the excision into fat generally is adequate for a small primary BCC. It should be noted that the majority of BCCs are well treated with conventional excision or C&D. However, in the circumstances just outlined, MMS is especially helpful.

MMS permits superior histologic verification of complete removal, allows maximum conservation of tissue, and remains cost-effective as compared to traditional excisional surgery for NMSCs. In a large study of treatment of primary BCC by Rowe et al., MMS demonstrated a recurrence rate of 1% over 5 years. This was superior to all other modalities including excision (10%), C&D (7.7%), RT (8.7%), and cryotherapy (7.5%). In a similar study of treatment of recurrent BCC, treatment with MMS demonstrated a long-term recurrence rate of 5.6%. Once again, this was superior to all other modalities including excision (17.4%), RT (9.8%), and C&D (40%). MMS is the preferred treatment for morpheaform recurrent BCC, recurrent poorly delineated, high-risk, and incompletely removed BCC, and for those sites in which tissue conservation is imperative.

C&D is the method most frequently used by dermatologists in the treatment of BCC. Knox et al. noted cure rates as high as 98.3%, whereas Kopf et al. in an earlier study, cited a significant difference in the cure rates obtained between patients treated by private practitioners (94.3%) and those treated by trainees in the...
New York University Skin and Cancer Unit (81.2%). This supports the premise that though C&D is simple and cost-effective, it is dependent on operator skill. In a series of 233 patients treated by Spiller et al., an overall cure rate of 97% was reported. The highest cure rate was obtained in lesions that measured less than 1 cm (98.6%), with recurrences observed in 2 of 165 patients treated. Recurrences were noted in 2 of 45 patients with lesions that measured between 1 and 2 cm, for an overall cure rate of 95.5%. Recurrences were significantly higher in patients with lesions larger than 2 cm, for whom the overall cure rate was 84%. In this series, as in others, recurrences were most commonly noted on the forehead, temple, ears, nose, and shoulders. Some practitioners advocate that the procedure be repeated for three cycles, but we believe that the histology, location, and behavior of the tumor should dictate the number of cycles.

When surgery is contraindicated, RT is an option for treating primary BCC. RT may be indicated postoperatively if margins are ambiguous. Advantages of RT include minimal to no discomfort for the patient and avoidance of an invasive procedure in a patient who may not be able to tolerate or is unwilling to undergo surgery. Disadvantages include lack of margin control, poor cosmesis over time, a drawn-out course of therapy, and possible increased risk of future skin cancers. In one series, control rates of 95% were achieved in BCC involving the eyelid treated with RT. The recurrence rate for primary BCC treated by RT approaches 5% to 10% over 5 years. In one study by Wilder et al., local control rates among 85 patients with 115 biopsy-proven BCCs were compared. The local control rates varied significantly, a 95% control rate being achieved in primary BCC and a 56% control rate in recurrent BCC at 5 years. From the standpoint of cosmesis, scars from RT tend to worsen over time (Fig. 41.2-17), as contrasted to surgical scars, which improve over time.

Cryosurgery has been used to treat BCC. Two freeze-thaw cycles with a tissue temperature of \(-50^\circ\)C are required to destroy the tumor sufficiently. A margin of normal skin also should be frozen to ensure eradication of subclinical disease. Complications include hypertrophic scarring and postinflammatory pigmentary changes. Fractional cryotherapy has been used with success in treating eyelid lesions. The method has been described as quick and cost-effective. A serious potential adverse outcome is recurrent BCC that can become extensive because of concealment by the fibrous scar created when aggressive cryosurgery is used.

Ablation by the CO\(_2\) laser has been used in the treatment of BCC. In a recent study, Humphreys et al. reported ablation of primary superficial BCC with the high-energy, pulsed CO\(_2\) laser. Because of the absence of margin control and lack of large series studies, physicians familiar with laser and tumor biology should use this method only in unique circumstances.

Management of BCC must be directed by the histologic nature of the tumor and the clinical context in which it presents. We recommend MMS for BCC showing aggressive growth patterns and for BCCs occurring in high-risk anatomic sites or sites that require maximum conservation of normal tissue. For non-aggressive-growth BCCs on the trunk and extremities, fusiform excision with margins of 4 mm or C&D are appropriate. For patients with numerous BCCs, including patients with NBCCs, tangential excision followed by gentle curettage and cautery for smaller, superficial lesions is effective. Cryosurgery can be helpful in the management of multiple, small BCCs of NBCCs.

It is imperative that patients with a history of BCC receive annual full-body skin examinations. Although most recurrences appear within 1 to 5 years, they can develop later. Rowe et al. found that 30% of recurrences developed within the first year after therapy, 50% within 2 years, and 66% within 3 years. Subsequent new primary BCC can present at rates of approximately 40%, with 20% to 30% of these developing within 1 year of treatment of the original lesion.

SQUAMOUS CELL CARCINOMA

SCC is a neoplasm of keratinizing cells that shows malignant characteristics, including anaplasia, rapid growth, local invasion, and metastatic potential. Approximately 100,000 cases of SCC are diagnosed in the United States each year, making it the second most common human cancer after BCC. As with BCC, affected men tend to outnumber affected women. People of Celtic descent, individuals with fair complexions, and those with poor tanning ability and a predisposition to sunburn are at increased risk for developing SCC (Fig. 41.2-18). Patients taking immunosuppressive medications after organ transplantation are also at increased risk. Another high-risk group includes patients treated with psoralens and ultraviolet A light (PUVA) for psoriasis. Patients exposed to arsenic are at increased risk for SCC, particularly Bowen's disease.

Pathogenesis

Factors involved in the pathogenesis of SCC are similar to those for BCC and include exposure to UVL, genetic mutations, immunosuppression, and viral infection. The evidence for an association with UVL is even stronger for SCC than for BCC. UVL may mediate development of SCC through several mechanisms. Exposure to UVL appears to interfere with the density and antigen-processing capability of Langerhans' cells and may suppress production of the Th1 cytokines interferon-\(\gamma\) and interleukin-2. Recent studies have demonstrated that UVL may introduce mutations into the tumor suppressor gene p53. This allows UVL to act as both tumor initiator and promoter. Development of SCC has been associated with radiation exposure, burn scars, chronic inflammatory dermatoses, ulcers, osteomyelitis, and arsenic ingestion. Heritable conditions associated with SCC include xeroderma pigmentosum and ocularcuteaneous albinism. Immunosuppression also may play a role in pathogenesis. Skin cancers in immunosuppressed patients appear primarily on sun-exposed sites. This correlation suggests that immunosuppression and UVL act as cofactors in the development of SCC. HIV patients tend to have a higher incidence of SCC than the general population. However, the exact nature of the relationship between HIV and SCC has not yet been determined. The role of
human papillomavirus (HPV) in the development of SCC has been studied. Eliezri et al. found a direct correlation between the venereal spread of HPV-16 and the initiation of SCC, and others have demonstrated an association of HPV-16 with periungual SCC.

**Biologic Behavior**

The biologic behavior of SCC is determined by a number of variables. The overall invasiveness and depth of the neoplasm is significant when determining the risk of recurrence. SCCs that invade the reticular dermis and subcutis tend to recur if not properly treated. Immerman et al. observed a 20% incidence of recurrence in 86 patients with invasive SCC. Degree of cellular differentiation is an important factor in recurrence also, with poorly differentiated neoplasms showing increased rates of recurrence.

SCC *in situ* tends to arise in association with preexisting AK. Arsenical keratoses are rarely seen nowadays but are associated with SCC. These lesions are considered to be at low risk for metastasis. While SCC *in situ* carries no risk of metastasis, invasive SCC can metastasize and can originate in neglected SCC *in situ* (Fig. 41.2-19). The most common type arises on sun-damaged skin. The incidence of metastasis of such lesions is 3% to 5%. A higher incidence (10% to 30%) is associated with SCC arising on a mucosal surface (lip, genitalia) and in sites of prior injury (scars, chronic ulcers).

**FIGURE 41.2-19.** Metastatic squamous cell carcinoma (SCC). A: In this patient, primary cutaneous SCC metastasized to the parotid gland and draining lymph nodes. B: Metastatic SCC after multiple excisions.

The tendency for regional lymph node metastasis is variable. Tumors arising in areas of chronic inflammation have a 10% to 30% rate of metastasis, whereas the incidence of metastasis from SCC that is not due to preexisting inflammatory or degenerative conditions varies from 0.05% to 16%. Although tumors that arise on sun-damaged skin may behave less aggressively than de novo SCC, all lesions have the potential to become invasive locally and to metastasize to draining lymph nodes. The large number of sun-mediated SCCs makes this clinical potential a concern. Friedman et al. demonstrated that all trunk and extremity primary SCCs that later developed local or nodal recurrence were at least 4 mm deep and penetrated into the reticular dermis or subcutis. The extent of cellular differentiation also influences the metastatic potential in that tumors that invade regional lymph nodes tend to be more anaplastic than those that have not metastasized. Tumors are more likely to disseminate to regional lymph nodes than to distant sites, although intravascular metastases to viscera have appeared in as many as 5% to 10% of SCCs metastatic from skin.

Invasive SCC has the potential to involve nerves. Regional lymph node and distant metastases may increase with perineural involvement. SCCs on the skin of the head and neck may metastasize to cervical lymph nodes and distantly to the central nervous system, the latter either hematogenously or via the perineural space, which directly connects to the subarachnoid space. SCCs on the midface and lip are prone to neural involvement. These patients show a lower 10-year survival (23% vs. 88%) and a higher local recurrence rate (47% vs 7.3%) than do those without neural involvement.

**Clinical Features**

On the skin, SCC appears as a slightly raised, red, hyperkeratotic macule or papule on sun-exposed sites but may occur anywhere (Fig. 41.2-20, Fig. 41.2-21, Fig. 41.2-22, Fig. 41.2-23, Fig. 41.2-24). It can be difficult to clinically distinguish an invasive SCC from a HAK, a benign seborrheic keratosis, or a benign inflammatory lesion. Appropriate biopsy should be performed on any lesion suspicious for SCC, considering the potential for invasive disease. Shave biopsy is sufficient and will not lead to spread of the cancer. Verrucous carcinoma, a variant of SCC, includes oral florid papillomatosis, giant condyoma of Buschke-Löwenstein, and epithelioma cuniculatum. A biopsy should be performed on an atypical wart or one that is unresponsive to therapy to rule out the presence of verrucous carcinoma.

**FIGURE 41.2-20.** Recurrent squamous cell carcinoma, keratoacanthoma type, successfully treated by Mohs micrographic surgery.

**FIGURE 41.2-21.** Squamous cell carcinoma can arise within a cutaneous horn.
Periungual squamous cell carcinoma treated by Mohs micrographic surgery can result in sparing of a digit that otherwise may have been amputated.

Squamous cell carcinoma, keratoacanthoma type. This variant of squamous cell carcinoma presents as a rapidly growing nodule.

Bowen's disease presents as an erythematous macule or patch and can be difficult to differentiate from a benign inflammatory process. Bowen's disease is characterized by proliferation of atypical cells arranged in such a way as to suggest a windblown appearance. Bowen's disease represents SCC in situ with a distinctive microscopical appearance (see Fig. 41.2-24). Erythroplasia of Queyrat is simply Bowen's disease occurring on the penis. Bowenoid papulosis classically presents as a reddish brown verrucous papule and is associated with HPV-16. Bowenoid papulosis usually involves the genitals but may present elsewhere.

A grading system was devised to classify SCC with respect to percentage of differentiated cells. Grade 1 tumors are described as having more than 75% well-differentiated cells, whereas in grade 2 SCC, 50% to 75% of cells are described as well-differentiated and, in grade 3 SCC, 25% to 50% of cells are described this way. Primary cutaneous SCC with fewer than 25% well-differentiated cells is termed grade 4 SCC. Prognosis worsens with decreased degree of differentiation.

Recurrence and Metastatic Risk

In a review of studies of SCCs from 1940 to 1992, Rowe et al. correlated risk for local recurrence and metastasis with treatment modality, prior treatment, location, size, depth, histologic differentiation, evidence of perineural involvement, precipitating factors other than UVL, and immunosuppression. They found that with tumors greater than 2 cm in diameter, recurrence rates double from 7.4% to 15.2%. In addition, they demonstrated that tumors less than 4 mm deep were at low risk for metastasis (6.7%) as compared with tumors deeper than 4 mm (45.7%). Locally recurrent SCCs showed an overall metastatic rate of 30%, with high rates of metastasis in the context of local recurrence in skin (25%), lip (31.5%), and ear (45%). Immunosuppressed patients showed a 5- to 20-fold increase in the incidence of SCCs, with a reversal of the SCC/BCC ratio from 0.25:1 to 3:1. The number of SCCs per patient was increased, and the age at initial presentation was decreased. In immunosuppressed patients, SCCs metastasized at a rate of 12.9%. Poorly differentiated SCC metastasized more frequently (32.9%) than did well-differentiated SCC (9.2%). SCC arising on sun-exposed skin recurred at a rate of 7.9% and metastasized at a rate of 5.2%. Recurrence rates were increased in SCC on the lip (10.5%) and ear (18.7%), as were metastatic rates from the lip (13.7%) and ear (11%). SCCs with perineural invasion recurred in almost one-half of cases (47.2%) and
showed a similar rate of metastasis (47.3%).

**Treatment**

Many of the treatments for BCC are appropriate for SCC (Fig. 41.2-26). The type of therapy should be selected on the basis of size of the lesion, anatomic location, depth of invasion, degree of cellular differentiation, and history of previous treatment. There are three general approaches to treatment of SCC: (1) destruction by C&D or cryosurgery, (2) removal by traditional excisional surgery or MMS, and (3) RT.

C&D can be used for small lesions arising on sun-damaged skin. Well-differentiated, primary SCCs measuring less than 1 cm in diameter are amenable to this form of therapy. Honeck and Jansen reported a 99% cure rate for 281 SCCs after a 4-year follow-up. In this study, two recurrences were noted in lesions less than 2 cm in diameter.

SCC in situ may be treated by cryotherapy. As with BCC, two freeze-thaw cycles with a tissue temperature of –50°C are required to destroy the tumor sufficiently. A margin of normal skin should be frozen to ensure eradication of subclinical disease. Complications include hypertrophic scarring and postinflammatory pigmentation changes. Concealment of recurrence within dense scar tissue presents a danger.

Surgical excision is another well-accepted treatment modality for SCC. Brodland et al. demonstrated that lesions of less than 2 cm in diameter are best treated by excision, with margins of 4 mm, whereas high-risk SCC requires 6-mm margins. These investigators found that certain characteristics were associated with a greater risk of subclinical tumor extension, thus qualifying such tumors as high-risk. These included size of 2 cm or larger, histologic grade higher than 2, invasion of the subcutaneous tissue, and location in high-risk areas. Carcinomas of the penis, vulva, and anus usually are treated by excision because of the poor tolerance of these areas to irradiation. Surgical excision is the treatment of choice for verrucous carcinoma.

MMS is indicated in cases of large primary or recurrent SCC, as this modality allows conservation of normal tissue with preservation of function and enhanced cosmesis. MMS is also superior to other forms of treatment with regard to local recurrence. Recurrence rates with Mohs surgery are superior to those obtained with traditional excisional surgery in primary SCC of the ear (3.1% vs. 10.9%), primary SCC of the lip (5.8% vs. 18.7%), recurrent SCC (10% vs. 23.3%), SCC with perineural invasion (0% vs. 47%), SCC larger than 2 cm (25.2 vs. 41.7%), and poorly differentiated SCC (32.6% vs. 53.6%). MMS has proven useful in SCC involving the nail unit and has been used as a limb-sparing procedure in cases of SCC arising in osteomyelitis.

RT may be used for head and neck cutaneous SCC in which there is no spread to bone or cartilage and there is no evidence of metastasis. As with BCC, RT may be indicated for elderly patients with SCC who are unwilling or unable to undergo surgery. In one series, 108 patients with SCC of the lower vermilion lip were stratified into stage T1 (82.4%), T2 (15.7%), or T3 (1.9%) disease and were treated with RT. Recurrences occurred in 12.4% of patients with T1 disease and 6.7% of patients with T2 disease. Radiation therapy often is used as an adjuvant modality after treatment of SCC in which perineural involvement is identified, although no controlled studies have proven its usefulness.

MMS is indicated for invasive lesions, poorly differentiated lesions, and lesions occurring in high-risk anatomic sites or sites in which conservation of normal tissue is essential for preservation of function or cosmesis.

Invasive SCC can be a potentially lethal neoplasm and warrants close follow-up. In one study, approximately 30% of patients with SCC developed a subsequent SCC, with more than one-half of these occurring within the first year of follow-up. In another study, the median time to recurrence was 15 months. Thus, it is recommended that patients with SCC be examined every 3 months during the first year following treatment, every 6 months during the second year after treatment, and annually thereafter. Evaluation should include total body cutaneous examination and palpation of draining lymph nodes. Currently, roentgenography, magnetic resonance imaging, and CT play no role in the routine workup of uncomplicated cutaneous SCC.

**MERKEL CELL CARCINOMA**

Merkel cell carcinoma (MCC) is a potentially aggressive tumor of neuroendocrine cell origin. Though it primarily affects the head and neck, other areas may be involved. MCC affects more men than women and most often occurs between the seventh and ninth decades of life.

The pathogenesis of MCC is incompletely characterized. UVL has been indirectly implicated in its development, as 36% of such cancers arise on the face. More than 50% of tumors occur on the head and neck, while 35% develop on the extremities. Mixed MCC/SCC and, recently, MCC/BCC have been reported, thus supporting the role of UVL exposure as a risk factor. Immunosuppression may play a role in the development of MCC, as rapid progression has been reported in the setting of immunosuppressive therapy after organ transplantation. An association with arsenic-induced Bowen's disease has been reported, implicating arsenic exposure as a risk factor for development of MCC.

Lymph node metastases have been identified in up to 20% of cases of MCC at initial presentation. Approximately 50% of patients experience nodal disease at some point in the disease course. Distant metastases have been reported in up to 30% of patients at presentation. Metastases have been noted in skin, lymph nodes, lung, liver, brain, intestine, bladder, and abdominal wall. Although MCC is a highly aggressive and potentially lethal cancer, spontaneous regression has been reported. The significance of this phenomenon is unknown.

MCC usually appears as a red, violaceous, dome-shaped papule or plaque on sun-exposed skin (Fig. 41.2-27). It may develop on the extremities and can involve the trunk. Clinical differential diagnosis includes leukemia cutis, amelanotic melanoma, metastatic carcinoma, pyogenic granuloma, and SCC.
Microscopical examination reveals sheets and cords of atypical cells in the dermis, extending to the subcutaneous layer, that sometimes form an interlacing trabecular or pseudoglandular pattern. A grenz zone often is present, separating tumor from epidermis. Cell membranes often are indistinct, giving a syncytiatal appearance. Cells are round to oval and generally noncohesive. Cytoplasm tends to be scant, with round to oval nuclei containing two to three nucleoli. Foci of squamous differentiation resembling SCC have occasionally been noted. Special stains may prove useful in the histlogic diagnosis of MCC. Cytokeratin-20 (CK-20) staining gives a characteristic paranuclear dot pattern. Histologic differential diagnosis includes lymphoma, BCC, metastatic oat cell carcinoma, or noncutaneous neuroendocrine tumors. Lymphoma cells are differentiated in that they are CD45-positive and CK-20-negative. Melanoma can be differentiated in that melanocytes are strongly S-100-positive. In addition to CK-20, MCC stains positively for chromogranin neuron-specific enolase and may be weakly positive for S-100 protein.

MCC warrants aggressive therapy (Fig. 41.2-28). Evaluation of a patient with histologically confirmed MCC must include full-body skin examination and lymph node evaluation. A complete blood count and liver function tests should be performed as well. CT scanning of the chest, pelvis, and abdomen may be indicated to rule out the presence of small cell carcinoma of the lung. CT scanning of the head and neck may prove valuable in detection of nodal disease. MCC tends to spread in a cascade pattern, first affecting local, then regional lymph nodes and finally progressing to fatal distant metastatic disease.

FIGURE 41.2-27. Merkel cell carcinoma presenting as a red to violaceous, dome-shaped papule or plaque on the sun-exposed skin of an elderly person.

MCC warrants aggressive therapy (Fig. 41.2-28). Evaluation of a patient with histologically confirmed MCC must include full-body skin examination and lymph node evaluation. A complete blood count and liver function tests should be performed as well. CT scanning of the chest, pelvis, and abdomen may be indicated to rule out the presence of small cell carcinoma of the lung. CT scanning of the head and neck may prove valuable in detection of nodal disease. MCC tends to spread in a cascade pattern, first affecting local, then regional lymph nodes and finally progressing to fatal distant metastatic disease.

Management of MCC follows staging of patients according to local, regional, or metastatic disease. Current recommendations support wide local excision (WLE) with lymph node dissection and adjuvant RT, if indicated. In cases of local disease, sentinel lymph node dissection may be advisable, if available. In a recent study, 18 patients with stage I MCC underwent sentinel lymph node dissection. In two patients, involvement of the sentinel node was identified, resulting in complete lymph node dissection. Sentinel node–negative patients received no therapy other than wide and deep excision. All patients remained free of recurrence at 7 months. Patients with negative sentinel nodes may be treated by WLE with margins of up to 3 cm and, possibly, adjunctive RT. Patients with positive sentinel nodes should be treated as patients with regional disease. The combination of WLE, therapeutic lymph node dissection, and RT has been suggested for treatment of regional disease. Metastatic disease is treated with chemotherapy. The most common regimens used in the treatment of metastatic MCC include cytoxan, doxorubicin, and vincristine, and cisplatin and etoposide. However, brief responses were reported recently in a small series of patients treated with carboplatin and etoposide. In a review by Voog et al., overall response to first-line chemotherapy for MCC was 61%, with a 57% response in metastatic disease and a 69% response in locally advanced disease. The 3-year survival rate was 17% in metastatic disease and 35% in locally advanced disease. In a recent series of nine patients with neuroendocrine tumors, complete response in a patient with inoperable MCC was reported using 5-FU, dacarbazine, and epirubicin. Patients with MCC must be followed up aggressively for potential local recurrence and development of metastatic disease.

FIGURE 41.2-28. Merkel cell carcinoma should be treated by wide local excision followed by sentinel or complete lymph node dissection (SLND, CLND), radiation therapy (XRT), or chemotherapy, depending on stage.

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MICROCYSTIC ADNEXAL CARCINOMA

Microcystic adnexal carcinoma (MAC) was first described as a distinct entity in 1982 by Goldstein et al. In this study, six cases of MAC were described. In each case, the tumor was originally misdiagnosed on initial biopsy as benign. MAC originates from pluripotent adnexal cells capable of eccrine and follicular differentiation. Synonyms for MAC include sclerosing sweat duct carcinoma, sweat duct carcinoma with syringomatous features, and combined adnexal tumor of the skin.

MAC is a tumor that primarily affects middle-aged individuals, though it has been reported in an 11-year-old boy. Unlike the other primary cutaneous malignancies considered thus far, affected women outnumber affected men. The pathogenesis of MAC is not completely understood but may involve exposure to ionizing radiation. In many cases, patients with MAC have received RT. In general, these patients were treated with RT for conditions ranging from tinea capitis to thyroid carcinoma. Treatment may precede development of MAC by as long as 40 years.

MAC is a locally aggressive tumor with low metastatic potential. It has been demonstrated that the increased stromal collagen observed in MAC is not due to soluble factors excreted by MAC cells. Perineural invasion is common with MAC, as are involvement of muscle, perichondrium, and vascular adventitia. Birkby et al. reported MAC on the face of a 51-year-old man that invaded the bone marrow of the mandible and spread along the inferior alveolar and mental nerves. Recently, the first case of MAC metastatic to lymph node was reported.

MAC classically presents as a sclerotic or indurated plaque with intact epidermis and yellow hue (Fig. 41.2-29A). The tumor usually involves the central face and lip but is not limited to those anatomic sites. MAC involvement of the eyelid, scalp, tongue, and eyebrow have been reported.
FIGURE 41.2-29. Microcystic adnexal carcinoma. A: Classic presentation is as an indurated plaque with intact epidermis and yellow hue. B: On microscopical examination, the dermis shows numerous basaloid cells forming cords, nests, small ducts, and horn micocysts.

On microscopical examination, MAC may be misdiagnosed as a benign adnexal process. The epidermis is normal, although mild hyperkeratosis may be present. The tumor is composed of large basaloid cells forming cords, nests, and individual cells superficially, containing laminated keratin and, occasionally, small vellus hairs. Cysts may be calcified. Small ducts, either empty or filled with eosinophilic material composed of sialomucin, are commonly present. Ducts may be well-differentiated, with two rows of cuboidal cells, or less differentiated, with single strands without lumina. A dense sclerotic stroma is present. Immunohistochemical analysis may be useful in differentiating MAC from desmoplastic trichoepithelioma (DTE). Wick et al. reported that MACs were reactive to hard keratin subclasses AE13 and AE14, epithelial membrane antigen, carcinoembryonic antigen, and LeuM1. DTEs were positive for AE14, epithelial membrane antigen, and LeuM1 only focally and were, in contrast, negative for carcinoembryonic antigen. Correct diagnosis of MAC is imperative, as the tumor can be highly invasive and may involve adipose, muscle, perichondrium, or bone.

MAC has been treated by WLE as well as MMS. In a recent series, 11 cases of MAC treated by MMS remained free of tumor for a median of 5 years. This suggests that extirpation by Mohs technique may prove beneficial in the management of MAC. However, these findings must be interpreted cautiously, as recurrences have been reported up to 30 years after surgical excision. Non-Mohs surgical excision is associated with recurrence rates of 47% to 59%. It appears that the tumor is resistant to RT, thus presenting difficulties in the management of MAC with perineural invasion.

After surgery for MAC, patients must be evaluated regularly for recurrence and for development of other skin cancers. Evaluation should include examination of skin and lymph nodes and, due to the potential for recurrence long after treatment, continue indefinitely.

SEBACEOUS CARCINOMA

Sebaceous carcinoma (SC) is a malignant adnexal tumor with variable sites of origin, histologic growth patterns, and clinical presentations. Ocular SC is more common and may arise from meibomian glands and, less frequently, from the glands of Zeis. The upper eyelids are most frequently involved. Approximately 50% of SCs are initially incorrectly diagnosed histologically and, in some series, all have been initially misdiagnosed clinically. SC is the second most common eyelid malignancy after BCC and is the second most lethal after melanoma.

In SC, women are affected more commonly than men, at a ratio of approximately 2:1. SC classically presents in the seventh to ninth decade. SC is associated with sebaceous adenomas, radiation exposure, Bowen's disease, and Multi-Torner syndrome. In Multi-Torner syndrome, an autosomal dominant heritable condition, SC and (more commonly) sebaceous adenoma (or sebaceous epithelioma) are associated with a second internal malignancy, usually a carcinoma of the colon or urogenital tract. SC may be associated with a history of RT. SC has been reported after RT for retinoblastoma, eczema, and cosmetic epilation. In one study, SC was associated with thiazide diuretic use. In addition, recent studies have identified HPV DNA and overexpression of p53 protein in some SCs.

Commonly, SC presents as a slowly growing, deeply seated nodule of the eyelid and may present as chronic diffuse blepharocconjunctivitis or keratoconjunctivitis. Upper eyelid involvement is more common. Approximately 25% of cases involve extraocular sites, which may include head and neck, trunk, and external genitalia. In a case of SC has occurred within a benign dermoid cyst of the ovary.

SC can spread by lymphatic or hematogenous routes or by direct extension. Distant metastases are reported in up to 20% of cases and may involve the lungs, liver, brain, bones, and lymph nodes. The parotid gland may be involved secondarily. Ocular SC may spread via the lacrimal secretory and excretory systems.

On microscopical examination, SC shows nonencapsulated tumors within the dermis. Sebaceous cells exhibiting varying degrees of differentiation, nuclear pleomorphism, hyperchromatism, and locally infiltrating surrounding tissues and neurovascular spaces are observed. Poor prognostic indicators in SC have been reviewed. These include multicentric origin, poor differentiation, infiltrative pattern, pagetoid changes, vascular invasion, lymphatic channel involvement, and orbital spread.

Treatment options for SC include traditional excisional surgery and extirpation by MMS. In one study of 14 cases of SC excised with frozen-section margin control, 5 recurrences were observed in cases with surgical margins of 1 to 3 mm, whereas no recurrences were seen with margins of 5 mm. Potential difficulties arise because tumors are often multicentric, and pagetoid spread is difficult to determine even on high-quality, paraffin-embedded sections. Extirpation of SC by Mohs has thus far yielded varying results. Folberg et al. reported recurrences in two of three patients treated by the Mohs technique, with tumor noted at reconstruction in one of the three patients. Dzubow reported two patients with recurrent SC who underwent MMS. One patient who underwent MMS followed by occlusal repair was tumor-free at 6 months. In the other patient, tumor distal to the Mohs defect was noted at reconstruction. A case of poorly differentiated SC successfully treated with RT has been reported.

Patients with SC should be evaluated by an internist, and routine screening for internal malignancy (stool for occult blood, analysis of urine, colonoscopy) should be performed. A family history for internal malignancy should be sought and family members screened, if indicated, to rule out Multi-Torner syndrome. After treatment for SC, patients should be followed up for recurrence or progression through regular examination of skin and lymph nodes.

ATYPICAL FIBROXANTHOMA

Atypical fibroxanthoma (AFX) is a spindle cell tumor that occurs on the head and neck of sun-exposed individuals and on the trunk and extremities of younger patients. Tumors of the head and neck characteristically present during the eighth decade, whereas tumors involving the extremities often present during the fourth decade. The ratio of affected men to affected women appears to be equal.

The pathogenesis of AFX may involve exposure to UVL, ionizing radiation, or aberrant host response. In one study of ten cases of AFX, seven cases showed mutation in p53. Of the seven, all showed abnormal single-strand conformation polymorphism, with four of those showing CBT mutations characteristically induced by UVL. Exposure to ionizing radiation may play a role in the development of the tumor, as AFX after RT has been demonstrated. An increased incidence of AFX was shown in a study of 642 renal transplant patients, and invasive AFX has been reported in a heart transplant patient. Finally, metastatic AFX has been reported in a patient with null cell variant chronic lymphocytic leukemia.

AFX usually presents as an asymptomatic papule or nodule. There may be hyperpigmentation or ulceration. The clinical appearance is not distinctive, and the lesion may be confused with pyogenic granuloma, SCC, or BCC. The tumor characteristically presents on the head and neck of the elderly or the trunk or extremities of younger individuals but is not limited to these sites. Occurrences on the eyelid are and within the ethmoid sinus and oral cavity have been reported. Although AFX rarely metastasizes, it is a locally aggressive tumor with metastatic potential. Metastases to parotid gland, lymph nodes, and lung have been reported. In a series of eight cases of metastatic AFX, poor prognostic indicators included vascular invasion, recurrence, deep tissue penetration, necrosis, and impaired host resistance.

On microscopical examination, there is a dermal nodule with a dense infiltrate of bizarre spindled cells arranged in haphazard fashion. Often, bizarre giant cells are present, and there is no connection to the epidermis. Special stains for vimentin are positive and for CD68 are weakly positive, while stains for HMB-45 and S-100 are negative, distinguishing this lesion from spindle cell melanoma. Differentiation from malignant fibrous histiocytoma (MFH) may be aided by special stains, as AFX stains negatively for LN-2, a marker present on B cells, Reed-Sternberg cells, and macrophages, and MFH cells are positive for LN-2 in...
FIGURE 41.2-30. Atypical fibroxanthoma. On microscopical examination, there is a dermal nodule with a dense infiltrate of atypical spindle cells arranged in a haphazard fashion and associated with bizarre giant cells.

Treatment options for AFX include WLE and MMS. In one large series comparing WLE with MMS, recurrences were observed during a mean follow-up period of 73.6 months in 12% of 25 cases treated by WLE. Metastatic involvement of the parotid gland occurred in one of these patients, for an overall regional metastatic rate of 4%. In contrast, no recurrences or metastases were observed over a mean follow-up period of 29.6 months in any patient treated by MMS. Others have reported similarly favorable outcomes after treatment of AFX by MMS, albeit with smaller numbers of cases. The authors favor the use of MMS for AFX because of the superior margin control and conservation of normal tissue.

MALIGNANT FIBROUS HISTIOCYTOMA

MFH is an aggressive spindle cell carcinoma and is the most common soft tissue tumor in the elderly, primarily affecting the extremities. Peak incidence is during the seventh decade.

Though the pathogenesis of MFH is incompletely understood, there appears to be a predilection for development in scar tissue. Inoshita et al. report development of MFH in an amputation site in one patient and in a hemioplasty scar in another. In both patients, the initial clinical diagnosis was subcutaneous abscess. MFH in a burn scar has also been reported. A case of MFH associated with discoid lupus erythematosus has also been described. Decreased immune surveillance may play a role in the development of MFH. A significant increase in the incidence of MFH (158 per 100,000) has been reported in a large series of renal transplant patients.

MFH is aggressive, with high metastatic potential. In one series, a higher percentage of histologically infiltrative tumors (83% vs. 24%) were observed in subcutaneous MFH as opposed to intramuscular MFH. An increased percentage of local recurrences (17% vs. 0%) were observed in the subcutaneous variant. However, infiltrative growth pattern was not predictive of metastatic potential. In one large series, the local recurrence rate was 44%, and the rate of metastasis was 42%. Metastasis, in this series, occurred most commonly in lung (82%) and lymph nodes (32%). Factors that appeared to influence metastasis included depth and size of tumor and inflammatory response. Small, superficially located tumors and tumors with a prominent inflammatory component metastasized less frequently.

Clinically, MFH may present as a subcutaneous mass or ulcerative nodule. In one large series, MFH occurred principally as a mass on an extremity (lower extremity, 49%; upper extremity, 19%) or in the abdominal cavity or retroperitoneum (16%) of adults. Deep fascial involvement was typical (19%), as was involvement of skeletal muscle (59%). Fascial involvement was absent in only a small percentage of cases (7%).

On microscopical examination, morphologic features vary, and MFH may show transitions from areas with a highly ordered, storiform pattern to less differentiated areas with a pleomorphic appearance. Differentiation from AFX may be aided by staining with LN-2, a marker present in 90% of MFHs in one series but absent or only weakly present in AFX.

Treatment options for MFH include WLE, although recurrence rates of up to 40% have been reported with this approach. Some authors have reported successful treatment of subcutaneous MFH with MMS. Brown and Swanson reported no recurrences over a 3-year follow-up period among 17 patients with 20 tumors treated by MMS. Halfner et al. reported successful treatment of MFH by MMS with margin control achieved using paraffin-embedded tissue sections. After treatment for MFH, patients should be followed up aggressively for development of recurrent and metastatic disease.

DERMATOFIBROSARCOMA PROTUBERANS

Dermatofibrosarcoma protuberans (DFSP) is a low-grade cutaneous sarcoma with well-characterized clinical and histopathologic features. The lesion frequently appears as a plaque on the trunk and, less commonly, on the extremities of middle-aged adults. Gender distribution of DFSP tends to vary in published series.

The pathogenesis of DFSP is incompletely understood but may involve factors as diverse as aberrant tumor suppressor genes or history of local trauma. In one study, increased p53 protein immunoreactivity was found in DFSP but not in dermatofibrosarcoma, suggesting that expression of the protein may be important in the pathogenesis of DFSP. In addition, DFSP has been reported to occur at previously traumatized sites.

DFSP has a tendency to recur locally, with an overall rate of 50%. However, metastases are rare. In one series of 19 cases of DFSP, there were 20 local recurrences in 8 patients. Recurrences in this series followed narrow excision. No recurrences were noted during a mean follow-up period of 13.2 years after WLE with margins greater than 2 cm. Lymph node metastases occur in approximately 1% of cases and distant metastases, principally to lung, occur in approximately 4% of DFSP cases. A fibrosarcomatous variant, FS-DFSP, represents an uncommon form of DFSP. In a series of 41 patients with FS-DFSP, follow-up in 34 patients for a mean period of 90 months revealed a local recurrence rate of 58%. Metastases were observed at a rate of 14.7%. Thus, fibrosarcomatous change in DFSP is indicative of a more aggressive clinical course. A case of acral DFSP with fibrosarcomatous change and pulmonary parenchymal metastases was reported recently.

DFSP classically presents as a plaque on the trunk and, less frequently, on the extremities but may occur anywhere. The tumor may be difficult to differentiate clinically from a dermatofibroma or a keloid. The tumor most commonly presents during early or middle adulthood, though it can occur during childhood.

The Bednar tumor is a rare pigmented variant of DFSP.

Microscopically, the tumor is composed of monomorphous spindle cells arranged in a storiform pattern and embedded in a sparse to moderately dense fibrous stroma. The distinction between deep penetrating dermatofibroma (DPDF), which involves the subcutis, and DFSP may be challenging. In most instances, attention to the cytologic constituency of the lesions and the overall architecture is sufficient for differentiation. DPDF is typified by cellular heterogeneity. DPDF includes giant cells and lipidized histiocytes and extends deeply, using the interlobular subcuticular fibrous septa as scaffolds, or in the form of broad fronts. In contrast, DFSP tends to be monomorphous, surrounding adipocytes diffusely or extending in stratified horizontal plates. Immunostaining for factor XIIIa and CD34 may be helpful in distinguishing DPDF from DFSP. Characteristically, DPDF is diffusely factor XIIIa-positive and CD34-negative, whereas DFSP is factor XIIIa-negative and CD34-positive.

Treatment options for DFSP include WLE and MMS. Some authors advocate surgical excision with a minimal margin of 2 to 3 cm of surrounding skin, including the underlying fascia, without elective lymph node dissection. Although WLE has been the standard treatment of DFSP, recurrence rates approach 50%. In one series, 58 patients with DFSP treated by MMS at three institutions showed a local recurrence rate of 2%. There were no cases of regional or distant metastases. Other
Kaposi's sarcoma (KS) is an indolent vascular tumor that has been subdivided into epidemiologic variants including classic KS, African endemic KS, iatrogenic KS, and epidemic, acquired immunodeficiency syndrome–associated (AIDS-associated) KS. Although these variants differ in presentation, they share key features, including clinical appearance of primary lesions, a biologically aggressive nature and, ultimately, poor outcome.

Cutaneous KS of the head and scalp usually affects the elderly, with men being affected more often than women. Although no predisposing factors have been identified, exposure to UVL has been suggested as a risk factor due to the propensity for the tumor to affect sun-exposed sites of the scalp and face. Other researchers have questioned this connection because, in several series, KS has presented on scalps protected by hair as frequently as on bald scalps. Others have demonstrated that patients with KS show no significant increase in numbers of BCCs and SCCs, thus arguing against increased UVL exposure.

KS, for the most part, behaves in an indolent fashion, with some variance according to epidemiologic subtype. Patients with long-standing classic KS may show human herpesvirus-8 (HHV-8). Epidemic KS presents with violaceous macules involving the face, chest, and oral mucosa. The hard palate and ocular conjunctiva nodules. Cutaneous and mucous membrane involvement are rare in lymphadenopathic endemic KS.

AS presents as a violaceous to red ill-defined plaque, often initially resembling a bruise (Fig. 41.2-31). The differential diagnosis may include benign vascular tumors, hematoma secondary to trauma, or an inflammatory dermatosis. Unexplained facial edema may be a presenting sign as well. As AS progresses, lesions increase in size, become indurated, and may eventually ulcerate. Satellite lesions are common.

On microscopical examination, it becomes evident that AS extends far beyond clinical margins. In well-differentiated lesions, histology shows irregularly dilated vascular channels lined by flattened endothelial cells. Less differentiated tumors show proliferation of polygonal or spindle-shaped, pleomorphic endothelial cells and anastomosing vascular channels. The state of cellular differentiation has not been shown to correlate with prognosis. Special stains may be of value in histologic diagnosis of AS, as cells stain positively for Ulex europeaus I lectin and factor VIII–related antigen. Ulex I is considered to be more sensitive for AS. In addition, AS cells express stem cell antigen CD34 and endothelial cell surface antigen CD31.

AS is a biologically aggressive tumor with high metastatic potential. Metastases to lymph nodes, lung, and brain are common. Prognosis for metastatic disease is poor. Although prognosis does not correlate with degree of cellular differentiation, there appears to be a correlation with lesion size at presentation: Increased survival has been demonstrated in lesions smaller than 5 cm at time of presentation.

Owing to the aggressiveness and poor prognosis of AS, treatment options are limited. Radical excision is currently the treatment of choice and may be difficult to accomplish in tumors involving the face. Amputation with shoulder disarticulation or hemipelvectomy are recommended for tumors involving the extremities. As stated, AS tends to extend far beyond clinically appreciated margins, thus complicating excision. Several cases of AS have been treated by MMS in an attempt to control margins; however, the difference between AS and normal vasculature may be difficult to interpret on frozen sections, even with the use of immunohistochemical stains. Prognosis of AS is poor, with a mortality rate of 50% at 15 months after diagnosis. The 5-year survival rate is approximately 12%.

Lymphedema-associated AS (LAS) was first reported by Stewart and Treves in patients with mastectomy lymphedema. In each case, AS developed in the ipsilateral arm and occurred several years after mastectomy. Subsequently, LAS was reported after axillary node dissection for melanoma and in the context of congenital lymphedema, filarial lymphedema, and chronic idiopathic lymphedema. The risk for developing LAS 5 years after mastectomy is approximately 5%. The most common site is the medial aspect of the upper arm.

LAS presents as a violaceous plaque or nodule superimposed on brawny, nonpitting edema. Ulceration may develop rapidly. The pathogenesis of LAS is incompletely understood and may be related to imbalances in local immune regulation or angiogenesis, leading to proliferation of neoplastic cells. The prognosis is poor, and survival rates are comparable to AS involving the scalp and face. Long-term survival has been reported after amputation of the affected limb.

Radiation-induced AS may occur from 4 to 40 years after RT for benign or malignant conditions. AS may occur from 4 to 40 years after RT for benign conditions, including acne and eczema, or from 4 to 25 years after RT for malignancies. Lesions appear at sites treated with radiation and are clinically and histologically similar to AS involving the scalp and face. Prognosis is poor and comparable to that observed in other forms of AS.

Epitheliod AS (EAS) is a rare, recently described variant of AS. It tends to involve the lower extremities. On microscopical examination, the tumor may mimic an epithelial neoplasm, with sheets of rounded, epitheliod cells intermingled with irregularly lined vascular channels. Epitheliod AS results in widespread metastases within 1 year of presentation. Prognosis, as in other forms of AS, is poor.

Angiosarcoma (AS) is an aggressive, usually fatal neoplasm of vascular cells. Four variants of cutaneous AS currently are recognized, including AS of the scalp and face, AS in the context of lymphedema (Stewart-Treves syndrome), radiation-induced AS, and epitheliod AS. Although these variants differ in presentation, they share key features, including clinical appearance of primary lesions, a biologically aggressive nature and, ultimately, poor outcome.

On microscopical examination, it becomes evident that AS extends far beyond clinical margins. In well-differentiated lesions, histology shows irregularly dilated vascular channels lined by flattened endothelial cells. Less differentiated tumors show proliferation of polygonal or spindle-shaped, pleomorphic endothelial cells and anastomosing vascular channels. The state of cellular differentiation has not been shown to correlate with prognosis. Special stains may be of value in histologic diagnosis of AS, as cells stain positively for Ulex europeaus I lectin and factor VIII–related antigen. Ulex I is considered to be more sensitive for AS. In addition, AS cells express stem cell antigen CD34 and endothelial cell surface antigen CD31.

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Kaposi's sarcoma (KS) is an indolent vascular tumor that has been subdivided into epidemiologic variants including classic KS, African endemic KS, iatrogenic KS, and epidemic, acquired immunodeficiency syndrome–associated (AIDS-associated) KS. Classic KS affects elderly men, with increased incidence in Ashkenazi Jews and in persons of Mediterranean descent. Classic KS typically presents with violaceous macules on the lower extremities. Slow progression with coalescence to plaques is observed. Eventually, the disease enters a nodular phase and may ultimately progress to a hyperkeratotic or even ulcerative phase.

Although no predisposing factors have been identified, exposure to UVL has been suggested as a risk factor due to the propensity for the tumor to affect sun-exposed sites of the scalp and face. Other researchers have questioned this connection because, in several series, KS has presented on scalps protected by hair as frequently as on bald scalps. Others have demonstrated that patients with KS show no significant increase in numbers of BCCs and SCCs, thus arguing against increased UVL exposure.

KS, for the most part, behaves in an indolent fashion, with some variance according to epidemiologic subtype. Patients with long-standing classic KS may show
visceral involvement, but this is usually asymptomatic. The adult variant of endemic KS tends to follow an indolent course as well. In contrast, lypmphadenopathic endemic KS progresses to fulminant, fatal disease. Iatrogenic KS is somewhat more aggressive than classic KS; however, lesions usually regress on discontinuation of immunosuppressive therapy. In epidemic KS, extracutaneous involvement is commonly encountered in lymph nodes, gastrointestinal tract, and lungs. Disseminated disease accounts for death in 10% to 20% of patients with epidemic KS.

On microscopic examination, KS varies according to patch, plaque, and nodular subtypes. The histologic changes in early patch-stage KS are inconspicuous, leading to misdiagnosis of a benign inflammatory process. A superficial and deep perivascular infiltrate with increased numbers of jagged vascular spaces is observed in the dermis. The thin-walled vessels surround normal vessels and adnexal structures, resulting in the so-called promontory sign. Plasma cells may be seen surrounding the newly formed vessels. In plaque-stage KS, the entire dermis and superficial fat may be involved, with an increase in the number of spindle cells arranged in small fascicles between collagen bundles centered around proliferating vascular channels. The spindle cells outline irregular slit-like vascular spaces that contain erythrocytes. In nodular KS, the number of spindle cells increases. They are arranged in interwoven fascicles with erythrocytes scattered in the interstices. Although nuclear atypia, mitotic figures, and pleomorphism may be observed in these, they are not prominent. Cells that stain positively for factor VIII–related antigen and spindle cells that stain positively for Ulex europeaus I lectin line well-formed vessels within KS lesions.

Both local and systemic therapies have been used in the management of KS, depending on epidemiologic context, extent of disease, and concomitant disease. Kaposi's sarcoma has been treated successfully using cryosurgery, RT, laser ablation, and intralesional injection of cytolytic agents. Local infiltration with vincristine has been particularly effective in the treatment of oral lesions in epidemic AIDS-associated KS. Other, more aggressive approaches have included systemic therapy with interferon and with single- or multiagent chemotherapy. Tur and Brenner treated 11 classic KS patients with low-dose subcutaneous interferon-α for 6 months. Initial response, defined as reduction of lesion size and fading of color, was noted in 9 of the 11 patients after 3 to 13 weeks of treatment. Maximum response was noted in 4 to 6 months, with remission lasting from 4 to 72 months. Experimental therapies including antiangiogenesis agents TNP-470 and thalidomide, 9-cis retinoic acid, and human choriconic gonadotropin may prove useful in management of KS in the future.

FIGURE 41.2-32. The scalp is a common site for cutaneous metastatic disease.

![Image](72x520 to 272x661)

FIGURE 41.2-33. The appropriate management of less common skin cancers may include wide local excision (WLE), Mohs micrographic surgery (MMS), cryosurgery, or intralesional or systemic chemotherapy. AFx, atypical fibroxanthoma; DFSP, dermatofibrosarcoma protuberans; MAC, microcystic adnexal carcinoma; MFH, malignant fibrous histiocytoma.

CONCLUSION

The discovery of an atypical skin lesion should result in consultation with a dermatologist for evaluation. It is necessary that skin biopsy specimens be sent to a dermatopathologist for interpretation to minimize misdiagnosis and delayed treatment of skin cancers. Management of skin cancer is based on histopathologic analysis of a given lesion; hence, accurate interpretation of skin biopsy specimens is essential. After treatment for skin cancer, patients should be followed up regularly, through full-body skin examinations performed by a dermatologist, for the development of recurrences as well as new primary skin cancers.

CHAPTER REFERENCES

Basal cell cancer, the most common cancer among humans, can present with a variety of clinical lesions. Familiarity with the spectrum of basal cell cancer permits early diagnosis, when treatment is most easily accomplished.

**FIGURE 41.3-1.** Nodular basal cell carcinoma on nasal tip. Note pearly, translucent appearance with telangiectasias.

**FIGURE 41.3-2.** Nodular basal cell carcinoma on right cheek. Note confluence of multiple nodular lesions with telangiectasias.

**FIGURE 41.3-3.** Nodular basal cell carcinoma of the left glabella with central depression. Note classic rolled borders and pearly appearance. There is also a large violaceous nodule in the left medial canthus. This long-standing lesion is an eccrine acrospiroma.

**FIGURE 41.3-4.** Large nodular basal cell carcinoma of the forehead with classic rolled border.
FIGURE 41.3-5. A: Nodular basal cell carcinoma of the forehead at the site of a previous automobile injury. The patient states that she had multiple fragments of glass removed over a long period of time. Basal cell carcinoma and squamous cell carcinoma are known to develop at the site of chronic scar. B: Microscopical example of nodular basal cell carcinoma demonstrating peripheral palisading of basal cells, retraction of tumor masses from dermis, and hyperchromatic cells. C: Defect following Mohs micrographic excision, demonstrating extension of cancer to the periosteum. The patient subsequently underwent skin flap repair.

FIGURE 41.3-6. Superficial basal cell cancer on the left upper lip of a 27-year-old woman. The patient, an aspiring actress, did not want treatment with surgery or radiation therapy. A course of intralesional interferon was successful at eliminating the cancer. It should be noted that this approach should only be used in superficial, easy to monitor basal cell cancer and has a recurrence rate of 20%.

FIGURE 41.3-7. Superficial basal cell cancer on an extremity. This lesion had been treated for many years as eczema and psoriasis. Topical corticosteroids provided no benefit. Any persistent rash that does not respond to topical treatment or is not otherwise diagnosed should be promptly biopsied.

FIGURE 41.3-8. Superficial basal cell carcinoma on trunk.

FIGURE 41.3-9. Pigmented basal cell carcinoma with nodular morphology.
FIGURE 41.3-10. Large pigmented basal cell carcinoma. The differential diagnosis includes melanoma.

FIGURE 41.3-11. Ulcerating basal cell carcinoma of the angle of the jaw.

FIGURE 41.3-12. Extensive basal cell carcinoma of the medial eyebrow and nasal root. Proximity to the supraorbital nerve raises the possibility of perineural extension of cancer in this long-standing carcinoma.

FIGURE 41.3-13. A: Large nodular basal cell carcinoma in the medial canthus. Deep extension of the cancer in this area can involve the lacrimal duct.  B: Defect following Mohs micrographic surgery indicates complete elimination of cancer. The lacrimal duct was not involved.

FIGURE 41.3-14. Extensive basal cell carcinoma of the right medial canthus, nasal sidewall, and distal nose. Basal cell cancer is typically a slow-growing tumor, but neglect can result in extensive destruction sometimes requiring removal of the orbital contents.

FIGURE 41.3-15. Cystic basal cell carcinoma of the glabella. This tumor was misdiagnosed as a cyst until a biopsy confirmed that it was a basal cell carcinoma, cystic type.
FIGURE 41.3-16. Morpheaform basal cell carcinoma of the left chin. Note light coloration and smooth texture. Although it appears to be well demarcated, the infiltrative histologic nature of this cancer can be expected to result in a larger defect upon complete extirpation.

FIGURE 41.3-17. Long-standing morpheaform basal cell carcinoma of the left cheek. Note smooth, white appearance, slightly elevated from the surrounding tissue. Crust in the center is an indication of tumor necrosis. Patients who have this type of cancer diagnosed histologically must be prepared for the large extent of the defect.

FIGURE 41.3-18. Morpheaform basal cell carcinoma, a form of aggressive growth basal cell cancer, is noted on the right cheek of a 30-year-old woman. It had been long-standing and was noted to grow very slowly. Especially in young patients, the true extent of the cancer must be discussed in advance and proper preparation must be made so that optimal reconstruction results in the best aesthetic outcome. This cancer, located in the embryonic fusion plain, must be removed with Mohs micrographic surgery to minimize the chance of recurrence. Recurrent basal cell cancer, especially in this region, is at high risk for extension deep in the facial planes.

FIGURE 41.3-19. Poorly defined morpheaform basal cell carcinoma of the right upper eyebrow in a 55-year-old woman. The patient had this lesion for some time before noting that it had changed. The extent of the cancer is larger than it appears clinically. It is best treated with the Mohs micrographic surgery method.

FIGURE 41.3-20. Morpheaform basal cell carcinoma of the right upper eyebrow. The patient believed that she had a scar at the site for many years but could not identify an episode of related trauma. This is the classic appearance of a morpheaform basal cell cancer, the true extent of which is significantly greater than appears clinically.
FIGURE 41.3-21. Large basal cell cancer of the left upper outer arm. The cancer had been present for approximately three years before the patient sought treatment.

FIGURE 41.3-22. Extensive basal cell carcinoma of the left face. Although this is an extreme example, it highlights the potentially aggressive nature of basal cell carcinoma. Despite the very low risk of metastasis, the cancer can be extremely locally destructive and, if present near vital organs, lethal.

FIGURE 41.3-23. Young patient with a nevus sebaceous on the left cheek. This is a benign tumor of sebaceous glands but is associated with basal cell carcinoma. Current recommendations are that a nevus sebaceous be removed in young adulthood to minimize the risk of basal cell cancer.

FIGURE 41.3-24. A: Multiple small papules in the periorbital region. Patients may present concerned that these represent cancer. In fact, they are syringomas, or benign tumors of the sweat glands. No treatment is necessary. B: This patient was referred because of concern that the red patch on the cheek, of long-standing duration, represented basal cell cancer. This is the classic appearance of rosacea, an adult form of acne. The condition responds promptly to topical therapy.

FIGURE 41.3-25. Severe solar damage of left face. This is the classic setting for the development of non-melanoma skin cancer. Note fair skin, mottled pigmentation, and telangiectasias.
FIGURE 41.3-26. Close-up of patient in Fig. 41.3-25. This patient has skin type I. When exposed to ultraviolet radiation from the sun, he always burns and never tans. The absence of the tanning response probably increases the risk for epidermal mutations from solar radiation. Actinic keratoses, hypopigmentation from previous cryotherapy, and telangiectasias are noted.

FIGURE 41.3-27. This patient has had lifelong problems with basal cell carcinoma. Some patients who received radiation therapy for acne later developed multiple basal cell cancers. Despite multiple surgeries, topical chemotherapy, and cryotherapy, the patient continues to develop new basal cell carcinomas.

FIGURE 41.3-28. A: This patient worked for many years in his youth as a lifeguard. Evidence of basal cell cancer and solar damage, as well as scar related to previous surgery, are noted. B: The same patient 10 years later with progressive basal cell cancer and areas of scar associated with basal cell cancer recurrence. Although we refer to these lesions as recurrences, histologic evaluation of the patient's facial skin indicates widespread basaloid budding in the epidermis, consistent with a field defect.

FIGURE 41.3-29. Elderly patient with multiple basal cell cancers. This patient has a history of arsenic exposure, which is associated with the development of basal cell carcinomas.

FIGURE 41.3-30. Nodular basal cell carcinoma on the nasal sidewall of a 40-year-old woman. Although most likely to be basal cell carcinoma, all such lesions must be biopsied. Melanoma and other forms of non-melanoma skin cancer are in the differential diagnosis, although they are less likely.

FIGURE 41.3-31. Ulcerated nodular basal cell carcinoma of the nose.
FIGURE 41.3-32. Nodular basal cell carcinoma of the left upper lip and alar groove. Basal cell cancer is thought to double in size over approximately 1 year. The size of this lesion suggests it has been present for many years. It is at risk for deep infiltration into the nasolabial groove.

FIGURE 41.3-33. Basal cell carcinoma of the tip of the nose. Because of the ill-defined margins of this cancer and its technically challenging location, Mohs micrographic surgery is indicated.

FIGURE 41.3-34. Basal cell carcinoma of the right nose. Patients must be advised of the likely size of the cancer, which is often larger than appears clinically. The final wound and reconstruction may be unsettling to the patient if he or she has not been properly prepared.

FIGURE 41.3-35. Small basal cell carcinoma of the left upper lip.

FIGURE 41.3-36. Basal cell carcinoma of the nose. Note the extensive nodularity under the surface of the skin. This cancer is likely to be at least 50% larger than it appears on the surface.

FIGURE 41.3-37. Nodular basal cell carcinoma of the left ala. This lesion is easily treated by Mohs micrographic surgery. Because of its presence in the alar groove,
healing by second intention is often an acceptable alternative plastic reconstruction.

FIGURE 41.3-38. A: Recurrent basal cell carcinoma on the left nose of an individual who works outdoors. Although very little scar tissue is noted on clinical exam, the cancer proved to be approximately twice the clinical size because of the extension of cancer cells within and under scar tissue. B: The defect following Mohs micrographic surgery. C: Immediately after Mohs micrographic surgery, the defect was repaired in a linear fashion, which will result in a fine-line scar. Patients must be advised that the complete healing process takes approximately 12 months. Maturation and fading of the scar continues during this whole period.

FIGURE 41.3-39. Ulcerating nodular basal cell carcinoma of the left alar rim. Because of its proximity to the alar rim as well as to the embryonic fusion plain, Mohs micrographic excision is indicated. A shallow defect in this area can be allowed to heal by second intention with excellent results. Alternatively, plastic reconstruction may be required to preserve normal anatomic and functional relationships.

FIGURE 41.3-40. Linear erosions on the right alar rim of a patient with a history of squamous cell cancer of the cheek. The patient also has a history of prurigo. The area was biopsied and failed to reveal any cancer. The patient admits to scratching. If topical treatment with corticosteroids fails to resolve the problem, a deeper biopsy may be indicated.

FIGURE 41.3-41. Nodular basal cell carcinoma on the left ala, similar to Fig. 41.3-39.

FIGURE 41.3-42. Extensive basal cell carcinoma of the left nose. Mohs micrographic treatment surgery is the treatment of choice. The reconstruction technique depends on the final defect.
FIGURE 41.3-43. Large eroding basal cell carcinoma of the nasal bridge. This patient, of northern European ancestry, had worked outdoors his whole life. Several other basal cell carcinomas are noted on the cheek and lip.

FIGURE 41.3-44. A: Large basal cell carcinoma of the left ala. Note elevation and retraction of the alar rim. This is an indication of extensive deep infiltration by basal cell carcinoma. B: Defect following Mohs micrographic surgery. The patient was referred for complex flap reconstruction.

FIGURE 41.3-45. A: Large nodular basal cell carcinoma of the left upper lip and left nostril. B: Defect following Mohs micrographic surgery. It is essential to minimize the recurrence of cancer in this location, as recurrent tumor is likely to invade deeply. The patient was referred for plastic reconstruction. Recurrence of cancer under complex flaps may be concealed, so careful examination including bimanual palpation of the region is necessary.

FIGURE 41.3-46. A: Extensive basal cell carcinoma of the left upper lip. Excision with conventional margins would not have adequately removed the cancer. Mohs micrographic surgery was performed. B: Following Mohs micrographic excision with preservation of the orbicularis oris. C: After reconstruction using an Abbe flap. (Fig. 41.3-46C courtesy of Dr. Stephan Ariyan.)

FIGURE 41.3-47. Nodular basal cell carcinoma of the right upper lip.
FIGURE 41.3-48. A: Morpheaform basal cell carcinoma of the left cheek with indistinct margins. Excision by the Mohs micrographic surgery technique resulted in a 5-cm defect. The wound was repaired under local anesthesia at the time of Mohs surgery. B: Three months following reconstruction with cheek advancement flap.

FIGURE 41.3-49. A: Long-standing basal cell carcinoma of the left cheek. Note areas of nodularity, hypopigmentation, and crusting resulting from bleeding from the surface of the cancer. B: Extensive defect following Mohs micrographic excision demonstrates histologic extent of cancer. Incomplete excision of cancer is an important cause of recurrence. Proper preparation of the patient for the extent of this defect was essential. Repair was performed without complication.

FIGURE 41.3-50. Ill-defined extensive basal cell carcinoma of the left temporal region.

FIGURE 41.3-51. A: Neglected basal cell carcinoma of the right temporal region and ear. Cancer in this area, especially when long-standing, has the potential for deep invasion. B: Defect following Mohs micrographic surgery reveals temporalis muscle. C: Despite the very high cure rates associated with Mohs micrographic surgery, risk of recurrence is proportional to the size of the cancer. Because of concern about concealing any recurrence, the wound was allowed to heal by second intention. The wound is pictured here at approximately 4 weeks status post excision. D: Completely healed wound at 3 months. The patient did not wish to have reconstructive surgery done on the helix of the ear.

FIGURE 41.3-52. Basal cell cancer within the triangular fossa of the ear. Basal cell cancer on the antihelix is not uncommon, and the recommended treatment is Mohs micrographic excision.

FIGURE 41.3-53. Ill-defined nodular basal cell carcinoma of the forehead.
FIGURE 41.3-54. Large basal cell carcinoma of the right lower eyelid. Retraction of surrounding tissue indicates deeply infiltrative nature of the cancer. The patient was treated with Mohs micrographic surgery and referred for reconstruction to minimize the risk of ectropion.

FIGURE 41.3-55. Very large ulcerated basal cell carcinoma of the glabella.

FIGURE 41.3-56. Basal cell carcinoma of right lower eyelid in an African American. Although basal cell carcinoma is most common in light-skinned people, it can occur in more darkly pigmented individuals.

FIGURE 41.3-57. Ulcerated basal cell carcinoma on the root of the nose. The majority of facial basal cell carcinomas occur on the nose.

FIGURE 41.3-58. Extensive basal cell carcinoma of the left nose extending into the medial canthus and along the lower eyelid. Treatment of this cancer requires an interdisciplinary approach. Following Mohs micrographic surgery, the patient was referred for plastic reconstruction. Because of the large size of the lesion, the patient must be monitored for recurrence.

FIGURE 41.3-59. A: Extensive basal cell carcinoma in a young man. The location in the medial canthus, the long-standing nature of the cancer, and its size create a
high risk that if the lesion recurs it will extend into the orbit. The patient was treated with Mohs micrographic surgery. B: Defect following Mohs micrographic surgery demonstrating the canthal ligament.

FIGURE 41.3-60. Basal cell cancer of the nasal root extending into the medial canthus.

FIGURE 41.3-61. Large nodular basal cell cancer of the lower eyelid. Mohs micrographic excision was performed followed by plastic reconstruction. Based on its size, this lesion had been present for many years.

FIGURE 41.3-62. Extensive basal cell carcinoma with retraction of the medial canthus. This clinical appearance suggests that the cancer likely extends deeply and may be at risk for involving the infraorbital nerve.

FIGURE 41.3-63. Recurrent nodular basal cell carcinoma of the post-auricular sulcus. Basal cell cancer in this region can extend widely along the cartilage and posterior scalp before it is diagnosed. Mohs micrographic excision is indicated.

FIGURE 41.3-64. Nodular basal cell carcinoma within an area of previous excision consistent with recurrent cancer.
FIGURE 41.3-65. Extensive basal cell carcinoma of the ear and temple. Because of the extensive nature of this cancer, radiation therapy was used with a good result. The therapeutic plan was to use Mohs micrographic surgery if the cancer recurred.

FIGURE 41.3-66. Multiple nodular and papular lesions on the scalp in an individual with severe solar damage. Although the clinical diagnosis of the large lesion on the right is basal cell cancer, the red nodular lesions are concerning and require biopsy as well to obtain a definitive diagnosis.

FIGURE 41.3-67. Large superficial basal cell carcinoma on the right breast. This was successfully treated with radiation therapy, although Mohs micrographic surgery and reconstruction would have been an equally acceptable alternative.

FIGURE 41.3-68. Large nodular basal cell carcinoma on the chest. The differential diagnosis includes squamous cell carcinoma.

FIGURE 41.3-69. Basal cell carcinoma on the shin of a 60-year-old woman. Basal cell carcinoma on the lower extremity is more common in women than in men. This highlights the likely association between solar exposure, secondary to clothing styles, and basal cell cancer.
FIGURE 41.3-70. Additional basal cell cancer on the lower extremity in the same patient as in Fig. 41.3-69.

FIGURE 41.3-71. Multiple basal cell carcinomas of the lower extremity with evidence of venous stasis changes. Treatment of cancer in this area is extremely difficult because of the dependent location and the resultant slow healing in older patients. Treatment by Mohs micrographic excision with healing by second intention provides excellent results. While skin grafting creates secondary wounds in the patient that require additional healing, new biologic dressings and allograft permit excellent healing while minimizing limitations on activity.

FIGURE 41.3-72. Large nodular basal cell carcinoma on the upper extremity.

FIGURE 41.3-73. Nodular basal cell carcinoma on the upper extremity, side view, indicating the exophytic nature. The differential diagnosis includes squamous cell cancer and melanoma.

FIGURE 41.3-74. Superficial basal cell carcinoma on the shoulder of a 45-year-old male. This lesion can be treated easily with electrosiccation and curettage.

FIGURE 41.3-75. Basal cell carcinoma on the instep of an elderly woman.
FIGURE 41.3-76. A: Basal cell carcinoma with ill-defined clinical margins on the nasal tip of a 50-year-old man. The lesion had been treated for several years as rosacea. Biopsy confirmed the presence of rosacea but also revealed a few foci of superficial basal cell carcinomas. B: Defect following Mohs micrographic surgery.

FIGURE 41.3-77. Basal cell carcinoma on the philtrum complicated by an outbreak of herpes labialis. Surgery was deferred until the lesion resolved. Prophylactic antiviral medication was used. This case highlights the occasional misdiagnosis of basal cell carcinoma for herpes labialis. The chronic, recurring nature of both, in certain circumstances, may be responsible for the confusion. Basal cell cancer is not associated with a prodrome.

FIGURE 41.3-78. A: Basal cell carcinoma of the right medial canthus. This red, scaling lesion had been treated for many years as a form of eczema. Biopsy was eventually performed when the patient was seen by his dermatologist, and it revealed basal cell cancer. B: Defect following Mohs micrographic surgery. C: Two weeks after placement of a full-thickness skin graft. D: After complete healing of skin graft. E: Recurrent basal cell carcinoma at upper edge of graft 10 years after original surgery.

FIGURE 41.3-79. Multiple basal cell carcinomas in a severely sun-damaged patient. Compare this clinical presentation with that in Fig. 41.3-25, Fig. 41.3-26, Fig. 41.3-27, Fig. 41.3-28, and Fig. 41.3-29. Surgery and radiation therapy are generally the only treatments currently available. Photodynamic therapy, incorporating the use of topical aminolevulinic acid, which avoids systemic adverse effects, holds promise for treatment of large numbers of lesions. The long-term benefit of this approach remains to be determined.

FIGURE 41.3-80. Multiple basal cell carcinomas in a patient who received radiation therapy for acne 50 years earlier. Any new therapeutic modality that is practiced on the skin today may yield unanticipated complications decades later. In most cases, it is difficult to anticipate what those effects might be, and the need for effective current management typically outweighs unknown delayed risks.

NEVOID BASAL CELL CARCINOMA SYNDROME

Neviod basal cell carcinoma syndrome is relatively rare and accounts for less than 0.5% of basal cell cancer cases. It is extremely important, however, because patients with this condition represent a management challenge. It is also important because the basal cell cancer gene was first identified in this group of patients.
The PTC gene has since been shown to be mutated in sporadic cases of basal cell cancer as well.

**FIGURE 41.3-81.** Multiple 2- to 4-mm, slightly pigmented papules are noted on the cheek of this individual with nevoid basal cell carcinoma syndrome (Gorlin’s syndrome). It is now known that this syndrome, associated with a range of developmental defects, is caused by mutations in the PTC gene. Management of these tumors is often a challenge. Because of the multiple lesions, patients become frustrated with ongoing surgery. A comprehensive approach using a combination of electrodesication and curettage, cryosurgery, Mohs surgery in critical locations, and, in the future, photodynamic therapy permits control of the lesions. Intralesional interferon was also used in this patient with some success but has not proven routinely successful. Suppression of new cancers may be achieved with oral isotretinoin or related compounds, but side effects limit its use, and the cancer incidence returns to pre-treatment levels when medication is discontinued.

**FIGURE 41.3-82.** This patient has nevoid basal cell carcinoma syndrome and presented with multiple extensive basal cell cancers of the scalp, face, and trunk. She received radiation therapy as a child for medulloblastoma, and this may have increased the incidence of basal cell cancers of the scalp. After a persistent effort at removing individual lesions, it was determined that the continued growth rate necessitated complete removal of the scalp tissue. Whole-scalp skin grafting was performed.

**FIGURE 41.3-83.** Multiple basal cell carcinomas of the trunk are noted in the patient depicted in Fig. 41.3-82. These can be treated with electrodesication and curettage or with cryosurgery. Excision is sometimes needed. On the back, the risk of recurrence must be considered, because the thickness of the dermis invites deep penetration of recurrent basal cell cancer.

**FIGURE 41.3-84.** A small basal cell carcinoma of the tip of the nose in a 14-year-old boy with nevoid basal cell carcinoma syndrome. When these lesions are small, simple electrodesication and curettage or excision with Mohs micrographic surgery followed by second intention healing often provides excellent results. Nonetheless, the tendency in this syndrome is to develop numerous skin cancers that eventually can make surgery impractical. The search for nonsurgical treatment options continues.

**FIGURE 41.3-85.** Nevus sebaceous on the left cheek of a 14-year-old girl. This benign congenital lesion has a well-documented tendency to transform into basal cell cancer. It is currently recommended that the lesion be considered for excision at or around puberty.
SQUAMOUS CELL CARCINOMA

Squamous cell cancer of the skin is most commonly caused by ultraviolet radiation from the sun. Its clinical distribution is the same as that of basal cell cancer, but this cancer does have the potential for metastasis. Identification of precursor lesions, known as actinic keratoses, is important, as is close management of patients who are immunosuppressed. The incidence of squamous cell cancer in these patients is increased compared with the general population. Approximately 2000 people per year die from metastatic cutaneous squamous cell cancer.
noted on the dorsal hand include hypertrophic actinic keratoses, squamous cell carcinoma, and actinic keratoses. Squamous cell carcinoma in this area, as in other skin sites such as the temple and lip, can metastasize. Aggressive management of these lesions with monthly visits may help minimize the development of infiltrative squamous cell cancer. B: Multiple actinic keratoses on the lower extremity of a 60-year-old woman. Close monitoring is necessary to treat any squamous cell carcinoma that develops. Because of healing problems related to the lower extremities, extensive excision is often problematic. The tissue-preserving benefits of Mohs micrographic surgery as well as conservative tangential excision with cautery of the wound base contribute to successful management of the cancers in these patients.

**FIGURE 41.3-91.** Hypertrophic actinic keratosis in the digital web space. This lesion may be treated by cryosurgery, excision, or electrodesication and curettage.

**FIGURE 41.3-92.** Squamous cell carcinoma. This 4-mm lesion appeared clinically similar to an actinic keratosis. Because it persisted, a shave biopsy was performed, which confirmed the presence of squamous cell carcinoma.

**FIGURE 41.3-93. A:** Cutaneous horn on the helix of the right ear. This horn consists of keratin produced by well-differentiated squamous cell carcinoma and is best treated by Mohs micrographic surgery. Note previous scar superior to the site where a skin cancer was previously treated. Proximity of the horn to scar raises the possibility that it is a recurrent lesion. B: Cutaneous horn of the left helix. Note extension of squamous cell carcinoma beyond the immediate area of the protruding horn. One treatment option for this lesion is Mohs micrographic surgery. In this situation, the tissue-sparing method will likely permit preservation of underlying cartilage and optimum healing.

**FIGURE 41.3-94.** Extensive actinic keratosis of the right infraorbital area. This lesion is marked by a broad plaque of erythema and hyperkeratosis. Biopsy of the most atypical area is indicated. It would not be surprising for the biopsy to reveal squamous cell carcinoma in association with hypertrophic actinic keratosis. Excision is indicated because of the proximity to the eye and the likelihood of progression to invasion. Recurrence can be minimized by Mohs micrographic surgery.

**FIGURE 41.3-95.** Concretion of keratin and debris on the scalp of an individual with skin type I (which always burns and never tans in response to exposure to sunlight). The lesion had been present for many years. Removal of the debris, which was accomplished by pre-moistening with water, revealed the underlying
squamous cell carcinoma.

FIGURE 41.3-96. Similar to the patient depicted in Fig. 41.3-95, hyperkeratosis in multiple areas is associated with severe solar damage and squamous cell carcinoma. Neglected squamous cell carcinoma in the temple and scalp may metastasize.

FIGURE 41.3-97. A: Similar to the patient in Fig. 41.3-94, this patient has multiple areas of actinic keratoses and possible squamous cell carcinoma. The area was previously treated by cryosurgery. Note hypopigmented atrophic scarring. Treatment by electrodesiccation and curettage was performed in this case. B: Hypertrophic actinic keratosis of the nose in a 50-year-old woman. This lesion requires biopsy to rule out squamous cell carcinoma.

FIGURE 41.3-98. A: Extensive squamous cell carcinoma in situ (Bowen's disease) of the neck and jaw area. This region was previously treated by topical 5-fluorouracil but recurred. Mohs micrographic excision is an option, but the surgical defect would be extensive. A trial of imiquimod, an immunomodulator shown to have some effect on superficial skin cancer, was attempted. Alternatively, treatment by ultrapulse carbon dioxide laser may be palliative. Extension of Bowen's disease down the hair follicles, which may not be destroyed by laser or topical treatments, raises the possibility of recurrence and even the development of invasive squamous cell carcinoma. B: Microscopical example of squamous cell carcinoma in situ (Bowen's disease). Note thickened epidermis and large atypical squamous epithelial cells with a wind-blown appearance.

FIGURE 41.3-99. Multiple actinic keratoses associated with areas of Bowen's disease. The spectrum of sun-induced atypical epithelial lesions extends from actinic keratosis to Bowen's disease to invasive squamous cell carcinoma.

FIGURE 41.3-100. Small eroded nodule on the anti-helix of an elderly man. The differential diagnosis includes chondrodermatitis nodularis helicis, which is usually painful, and squamous cell cancer, which may bleed but is usually not tender.
FIGURE 41.3-101. Ulcerated painful lesion on right ear. Biopsy is necessary to rule out squamous cell carcinoma. If chondrodermatitis is suspected because of pain on pressure, a trial of intralesional corticosteroid is a reasonable first approach.

FIGURE 41.3-102. Bowen’s disease of the lower extremity demonstrating that squamous cell carcinoma in situ can develop in individuals with a range of cutaneous pigmentation.

FIGURE 41.3-103. Hypertrophic Bowen’s disease of the lower extremity. Note hyperkeratosis, erythematous background, and extensive size of lesion. Bowen’s disease may rarely be associated with arsenic exposure, but the most common cause is solar radiation.

FIGURE 41.3-104. Same patient as depicted in Fig. 41.3-103 after treatment with emollients to remove hyperkeratosis. This was done in preparation for surgery.

FIGURE 41.3-105. Mohs micrographic surgery. After the cancerous area was prepared with local anesthesia, it was scored in accordance with the Mohs micrographic technique in preparation for removal and mapping of all margins. Because of healing issues related to the lower extremity, the tissue preserving method of the Mohs technique is the treatment of choice for this large lesion.
FIGURE 41.3-106. Squamous cell carcinoma in situ of the left ear in an immunocompromised patient. During complete extirpation by Mohs surgery, invasive squamous cell carcinoma was detected and removed. This highlights the fact that invasive squamous cell cancer can develop in long-standing lesions of Bowen's disease.

FIGURE 41.3-107. Recurrence of squamous cell carcinoma in situ within a scar line of a previous Mohs micrographic surgery excision. The small area recurred approximately one year after the initial treatment.

FIGURE 41.3-108. A 1.3-cm hypertrophic nodule in the center forehead on a patient with skin type I. The differential diagnosis includes squamous cell carcinoma, hypertrophic actinic keratosis, and inflamed seborrheic keratosis. Biopsy is indicated.

FIGURE 41.3-109. Infiltrating squamous cell carcinoma of the right cheek. The location of this lesion over the infraorbital nerve is a special concern. Careful questioning regarding symptoms referable to the infraorbital nerve is important prior to treatment. Imaging studies have not proved especially helpful, but new magnetic resonance imaging methods may help determine whether perineural invasion is present.

FIGURE 41.3-110. Squamous cell carcinoma in situ of the upper eyelid in a 70-year-old woman. This lesion had been present for approximately 20 years. The patient's physician advised her that it was eczema and treated it with a variety of topical medications. Despite the persistence of the lesion, a biopsy was not done until the patient consulted a dermatologist. Removal of the eyelid and orbital contents was recommended. The patient was referred for Mohs surgery, and the squamous cell carcinoma was removed in its entirety, preserving the upper eyelid for reconstruction. Upon removal of the cancer, invasive squamous cell carcinoma and perineural invasion was noted. The use of adjuvant radiation therapy in the management of perineural involvement by squamous cell cancer should be considered if the draining lymph node group is known. Six months after removal of the cancer, the patient developed metastases to the parotid gland and neck nodes.

FIGURE 41.3-111. A: Hyperkeratotic lesion of the chest present for several years in an elderly woman. B: Hyperkeratotic debris was removed with a moist gauze revealing friable, nodular squamous cell carcinoma.
FIGURE 41.3-112. Squamous cell carcinoma on the lower extremity. This patient had received ultraviolet A therapy with psoralens [psoralen plus ultraviolet A (PUVA)] for treatment of psoriasis. Note the extensive freckling and solar damage. Development of multiple squamous cell carcinomas is a known complication of long-term PUVA therapy.

FIGURE 41.3-113. A: Deeply infiltrative squamous cell carcinoma of the left jaw. B: Defect following Mohs excision demonstrating depth of cancer and thus risk of injury to facial artery and marginal mandibular nerve. C: Repair of defect under local anesthesia at time of Mohs surgery. Minimal undermining is performed to prevent the risk of extension of cancer in tissue planes should it recur.

FIGURE 41.3-114. Extensive squamous cell carcinoma of the chin in a middle-aged woman. This lesion had been present for some time. It demonstrates multiple keratin cysts resulting from the atypical epithelial cells of the well-differentiated squamous cell carcinoma. Despite the well-differentiated nature of the cancer, it was deeply infiltrative and involved the underlying muscle. After excision by Mohs micrographic surgery, adjuvant radiation therapy was performed.

FIGURE 41.3-115. Large squamous cell carcinoma of left forehead present for approximately 1 year. The lesion was removed by Mohs micrographic surgery and revealed presence of basal cell carcinoma as well.

FIGURE 41.3-116. Large cutaneous horn of the right jaw. This squamous cell carcinoma developed in a patient who previously underwent orbital exenteration for multiply recurrent basal cell carcinoma of the forehead and eye region.
FIGURE 41.3-117. Squamous cell carcinoma of the dorsal nose in a 75-year-old woman. Note the nodularity of this lesion.

FIGURE 41.3-118. Squamous cell carcinoma, keratoacanthoma type, at the oral commissure of a 55-year-old woman. This small lesion may be excised with margins or removed using Mohs micrographic surgery technique. Although keratoacanthoma has been considered a relatively benign self-regressing lesion, on the central face it can behave aggressively. It must be treated as a squamous cell cancer.

FIGURE 41.3-119. A: Squamous cell carcinoma, keratoacanthoma type, of the left temple. This lesion developed rapidly over a short period, which is the classic history for a lesion of this sort. Excision by Mohs micrographic surgery, conventional excision, radiation therapy, and intralesional methotrexate are options. The preferred treatment in this location is excision by Mohs micrographic surgery followed by immediate reconstruction if indicated. B: Recurrent squamous cell carcinoma, keratoacanthoma type, of the right lateral canthus. Note scar from previous surgery and retraction of lower eyelid indicating depth of penetration of this lesion. Although keratoacanthoma has previously been considered to behave in a benign fashion, it is now recognized as a form of squamous cell cancer and must be managed accordingly. Recurrent behavior highlights the potentially aggressive nature of this cancer. Mohs micrographic surgery was indicated to ensure complete removal. No recurrence has developed.

FIGURE 41.3-120. A: Large squamous cell carcinoma, keratoacanthoma type, of the left upper lip. Squamous cell carcinoma of this size and in this region is at risk for metastasis. B: Microscopical example of keratoacanthoma revealing squamous cell carcinoma in an eruptive cup-like formation.

FIGURE 41.3-121. A: Hyperkeratotic lesion on the right nose consistent with keratoacanthoma. Note that this does not have the typical appearance of the lesions depicted in Figs. 41.3-118, 41.3-119, and 41.3-120. This patient elected not to undergo treatment. B: Same patient after lesion regressed on its own. Observation is not recommended as keratoacanthoma is a squamous cell carcinoma. Certain forms of intralesional chemotherapy may be considered depending on the clinical circumstances.
FIGURE 41.3-122. Large squamous cell carcinoma on the upper extremity of a 76-year-old woman. Excision is indicated, although this cancer would also likely respond to radiation therapy.

FIGURE 41.3-123. A: Eroded lesion in the nasolabial fold of a 50-year-old woman. This lesion was previously diagnosed as keratoacanthoma and treated with a variety of topical medications and cryosurgery. It failed to respond to treatment. The patient declined surgery and elected radiation therapy instead. B: The final cosmetic result after a course of radiation therapy. No recurrence has been reported.

FIGURE 41.3-124. Large infiltrative squamous cell carcinoma of the forehead. This lesion is at risk for perineural extension to the supraorbital and supratrochlear nerves. Sensory changes in the forehead may be an indication of nerve involvement by the cancer.

FIGURE 41.3-125. Microscopical example of perineural invasion by squamous cell carcinoma. The skip-like nature of perineural invasion makes it difficult to be certain that negative margins indeed reflect complete eradication of the cancer. Many recommend adjuvant radiation therapy as an additional means of preventing recurrence and extension. Use of radiation therapy in these situations must be determined by the overall clinical circumstances.

FIGURE 41.3-126. Recurrent squamous cell carcinoma in a previous surgical scar. The rapidly recurrent nature of the squamous cell carcinoma in this case suggests an aggressive behavior. Mohs surgery is indicated. Follow-up radiation therapy may be indicated as well.
FIGURE 41.3-127. Subcutaneous nodule above right eyebrow contiguous with an old scar. The clinical presentation was that of an epidermoid cyst. Despite the mobile nature of the lesion, because of the patient's history of previous squamous cell carcinoma and immune suppression, the lesion was excised and proved to be a squamous cell carcinoma. A high index of suspicion is necessary in any patient who is immunocompromised, as this group of patients is at high risk for the development of nonmelanoma skin cancer.

FIGURE 41.3-128. Multiple scalp nodules consistent with internal malignancy metastatic to the scalp. Absence of histologic connection with the epidermis confirms noncutaneous origin of cancer. Lung, breast, and colon cancer are among the most common internal malignancies that metastasize to the skin.


FIGURE 41.3-130. A: Squamous cell carcinoma adjacent to left lower lip. This large lesion is at risk for metastasis. Treatment by Mohs micrographic surgery may be followed by radiation therapy if indicated. B: Microscopical example of squamous cell carcinoma. Note large eosinophilic epithelial cells with enlarged hyperchromatic nuclei.

FIGURE 41.3-131. Small hyperkeratotic lesion on sun-damaged lower lip. The biopsy revealed squamous cell carcinoma. The lesion had been present for some time, and its early stage was clinically consistent with actinic cheilitis. Actinic cheilitis is equivalent to the precancerous condition noted elsewhere on sun-damaged skin referred to as actinic keratosis. Treatment of actinic cheilitis depends on the severity of the lesion, whether it is symptomatic, and whether the patient is considered at special risk for developing squamous cell carcinoma.

FIGURE 41.3-132. Squamous cell carcinoma on the lower lip of a man in his 30s. This individual works in a marina and has extensive sun damage. In addition, severe actinic cheilitis is present on the lower lip, which is more exposed to solar radiation than is the upper lip. The squamous cell carcinoma was treated by Mohs...
micrographic surgery and proved extensive.

FIGURE 41.3-133. A: Squamous cell carcinoma of the left lower lip in an elderly gentleman. B: Defect following Mohs surgery indicating true extent of cancer. Because the cancer was not especially deep, it was allowed to heal by second intention with an excellent result. In addition, absence of flap reconstruction permitted monitoring for evidence of recurrence.

FIGURE 41.3-134. Long-standing extensive squamous cell carcinoma on the lower lip of a 65-year-old woman. This lesion was treated by Mohs micrographic surgery on three occasions. Each time the lesion recurred the cancer appeared more poorly differentiated. Eventually the cancer metastasized to the jaw. This highlights the potentially aggressive nature of squamous cell carcinoma of the lip and its risk for metastasis.

FIGURE 41.3-135. Large squamous cell carcinoma of the lower lip. This large, aggressive lesion was treated by Mohs micrographic surgery. Following excision, radiation therapy to the surgical site and draining lymph nodes must be considered and pursued based on the clinical circumstances.

FIGURE 41.3-136. Periungual wart. Long-standing periungual wart may be associated with carcinogenic subtypes of human papilloma virus. Biopsy is indicated to rule out squamous cell carcinoma in situ.

FIGURE 41.3-137. Squamous cell carcinoma in situ of the thumb. Mohs micrographic surgery is indicated to preserve tissue and obtain the highest cure rate. Even with the Mohs technique, because of the viral origin of this cancer and the presence of carcinogenic virus in normal-appearing adjacent skin, there is a risk of recurrence.
FIGURE 41.3-138. Squamous cell carcinoma of the distal finger. The patient was advised to have an amputation but elected to undergo Mohs micrographic surgery instead. The defect was allowed to heal by second intention, and the distal phalanx was preserved.

FIGURE 41.3-139. A: Squamous cell carcinoma in situ of the glans penis, also referred to as Erythroplasia of Queat. The patient did not want to undergo a recommended penectomy, so Mohs micrographic surgery was performed. B: Defect following Mohs micrographic surgery. This was allowed to heal by second intention without any compromise of function.

FIGURE 41.3-140. Erythema and scale of the glans penis consistent with ill-defined squamous cell carcinoma in situ.

FIGURE 41.3-141. A: Multiple scars of the left temple indicating previous surgery in an elderly Mediterranean man. Small nodules are noted as well, representing recurrent squamous cell carcinoma and metastatic in transit squamous cell carcinoma. B: Defect following Mohs micrographic surgery. Surgery in this region is at risk for injury to the temporal branch of the facial nerve, which can result in brow and eyelid ptosis. This patient developed metastases to regional lymph nodes and died from his skin cancer.

FIGURE 41.3-142. A: A preauricular nodule present for several years. Biopsy revealed squamous cell carcinoma, and the lesion was removed by Mohs micrographic surgery. The cancer was deep-seated but did not extend to the parotid gland. B: Large nodule of the preauricular region. Clinically this was consistent with a basal cell carcinoma or squamous cell carcinoma. Biopsy is indicated to confirm the precise nature of the cancer prior to treatment. Because of its location, extension of the cancer into the retroauricular sulcus and metastasis to the parotid gland is a distinct possibility.
A 70-year-old man with extensive squamous cell carcinoma of the forehead. Note hypopigmentation from previous treatments with cryosurgery. B: Defect in the same patient following Mohs micrographic surgery. At the time of Mohs micrographic surgery, squamous cell carcinoma was found in a perineural distribution and infiltrating muscle. The decision was made to discontinue surgery and consider radiation therapy. Because of his age and the likely slow progression of this disease, the patient elected not to pursue further therapy. Management of complicated skin cancer must be based on the clinical setting and knowledge of the biologic behavior of the cancer.

Erythema, hyperkeratosis, previous skin graft, and irregular pigmentation are all consistent with severe solar damage of the scalp in this 69-year-old man. He previously underwent excision of squamous cell carcinoma of the scalp with grafting but continued to develop new squamous cell cancers. In an attempt to minimize the development of the cancers, the patient underwent carbon dioxide laser resurfacing to destroy the abnormal clones of epidermal cells thought to give rise to the actinic keratoses that can evolve into squamous cell cancer. He did relatively well after treatment with a decreased number of new lesions. This approach must be considered only in special circumstances in which close follow-up is possible. There is a theoretical possibility that the laser-treated site may conceal the development of invasive squamous cell carcinoma beneath the surface of otherwise well-healed skin.

Metastatic squamous cell carcinoma on the scalp of a 90-year-old man. The patient underwent multiple excisions of squamous cell carcinoma of the scalp but continued to develop new lesions within several months following each excision. B: The patient was referred for Mohs micrographic surgery. The post-surgical defect demonstrates the depth of the cancer invasion. This treatment was unsuccessful, as the patient continued to develop new in-transit metastases.

Extensive squamous cell carcinoma of the scalp of a kidney transplant patient. Squamous cell carcinoma in renal transplant patients is very common and can behave aggressively. Close monitoring of these patients is essential to diagnose and treat cutaneous cancers at the earliest possible stage.

Extensive squamous cell carcinoma of the scalp in an elderly man. This lesion started as a small tumor, similar to the lesion noted in Fig. 41.3-98. Despite aggressive treatment by Mohs micrographic surgery and radiation, the lesion continued to recur. The patient died from extension of the cancer through the calvarium and into the dura.
Extensive squamous cell carcinoma of the forehead with associated satellite lesions representing in transit metastasis.

Recurrent squamous cell carcinoma of the nose following radiation therapy. When seen at the time of his initial consultation, the patient complained of severe chronic pain in the nose. No clearly defined lesion was noted on palpation, but the bridge of the nose was distinctly firm and tender throughout. Biopsy on the left lateral nose revealed highly infiltrative squamous cell carcinoma. Complete rhinectomy resulted from Mohs micrographic surgery. Although margins were negative, the infiltrative nature of this cancer represented a high risk of recurrence. Following healing by second intention the patient continued to complain of pain in the upper maxilla. In order to monitor for recurrence, reconstruction was not performed. Instead a prosthesis was developed with which the patient was satisfied. Identification of cancer within the maxilla explained his ongoing pain and was treated by maxillectomy.

Extensive squamous cell carcinoma in situ of the left parietal scalp and ear. Because of the extensive nature of this lesion and the patient's desire to avoid surgery, radiation therapy was performed in multiple fractionated doses. He obtained an excellent result.

Nonsurgical Management of Nonmelanoma Skin Cancer

There is a variety of nonsurgical treatments that can be used in the management of skin cancer. Most are beneficial in the control of premalignant lesions such as actinic keratoses. Side effects of these treatments must be understood because they can limit compliance with the treatment regimen. In addition to the therapeutic approaches demonstrated here, photodynamic therapy may become a more realistic treatment possibility for a range of cutaneous cancers. Recent refinement of target compounds and the potential for topical administration, which minimizes side effects, have renewed interest in photodynamic treatment of skin cancer and pre–skin cancers.

An actinic keratosis on the forehead consisting of erythema and scale. This lesion is at risk for development into squamous cell carcinoma. Although the precise rate of malignant transformation is difficult to calculate, the molecular hallmarks of malignancy, such as mutation in the p53 tumor suppressor gene, occur in actinic keratoses as well as squamous cell cancers. Treatment of actinic keratoses must be based on the clinical circumstances. Single lesions may be treated by cryosurgery. Multiple lesions require management by topical chemotherapy.

The most effective way of treating an isolated actinic keratosis is cryosurgery. Here, a cotton-tipped applicator soaked in liquid nitrogen is applied to the actinic keratosis. The frosting of the actinic keratosis is the clinical end point of treatment. Overtreatment can result in hypopigmentation and scarring. If the
lesion recurs multiple times, biopsy is needed to rule out squamous cell cancer.

**FIGURE 41.3-153.** Erythema, crusting, and swelling secondary to treatment with 5-fluorouracil. This therapy, which has been in use for at least 30 years, can cause significant side effects that may limit patient compliance. The proper treatment course requires application for 4 weeks, although dermatologists customize treatment to patient needs. Combination regimens that include topical tretinoin and other compounds have been shown to provide some additional benefit.

**FIGURE 41.3-154.** This patient self-treated with 5-fluorouracil and developed culture-proven impetigo. The 5-fluorouracil was discontinued and the infection resolved with antibiotic therapy. No scarring is noted. Rare cases of cribriform scarring have developed with the extensive use of 5-fluorouracil. Patients who are initiated on this therapy should be seen after the initiation of therapy to evaluate the progress and determine the extent of reaction. Topical corticosteroids may be used to control the aggressiveness of the reaction.

**FIGURE 41.3-155.** This patient has a squamous cell carcinoma in situ of the glabella and declined surgery. 5-Fluorouracil was applied twice a day for 4 weeks. The patient developed this crust, as expected. After discontinuation of the treatment, complete resolution of the crust occurred. Close monitoring and rebiopsy to confirm the absence of any deeper tumor may be indicated based on the clinical exam.

**FIGURE 41.3-156.** This patient with extensive solar damage treated his scalp with 5-fluorouracil. He had a history of multiple hypertrophic actinic keratoses and squamous cell cancers. However, he was also anticoagulated with coumadin and developed hemorrhagic bleeding at the sites of erosion caused by the 5-fluorouracil.

**FIGURE 41.3-157.** Slightly pink, smooth skin appearance immediately after complete resolution of 5-fluorouracil treatment course. Although many patients obtain a sustained benefit from this treatment, it is not unusual to see the redevelopment of actinic keratoses in 6 to 8 months. In addition, 5-fluorouracil may eliminate superficial actinic keratoses but conceal the development of basal cell cancer or squamous cell cancer under the skin surface. Although this is not a very common occurrence, one must be alert to the possibility.
FIGURE 41.3-158. This patient had a large squamous cell carcinoma of the left cheek. After complete removal by Mohs micrographic surgery, it was decided to perform adjuvant radiation therapy. The erythema and swelling is typical at this stage in the radiation therapy course. Discomfort can be controlled with emollients and topical corticosteroids.

FIGURE 41.3-159. Large scar on the back of a 70-year-old woman. Previously this patient underwent radiation therapy for a basal cell carcinoma. Note the hypopigmentation, atrophy, scarring, and telangiectasias. This is a common result after radiation therapy. An erosion at ten o'clock required multiple biopsies because of the suspicion that recurrent basal cell carcinoma was present within and under the scar. Biopsies were negative indicating that the erosion was secondary to radiation tissue effects.

FIGURE 41.3-160. This patient underwent radiation therapy for a basal cell carcinoma of the left infraorbital cheek. He presented because of a small erosion and retraction five years after treatment. The nodule was present on palpation, but aggressive biopsy failed to reveal the presence of cancer. The scarring, retraction, and pigmentation change are not uncommonly seen after radiation therapy and can complicate the diagnosis of recurrent cancer.

FIGURE 41.3-161. This patient underwent Mohs micrographic surgery excision of a large basal cell carcinoma of the nose with subsequent reconstruction using a full-thickness skin graft. The erythema consisting of multiple telangiectasias secondary to new vascular growth is very common and makes the graft more prominent than it otherwise should be.

FIGURE 41.3-162. The patient underwent treatment with the pulsed dye laser, a technique used to treat telangiectasias, port wine stains, and other vascular tumors. This simple procedure effectively eliminated the blood vessels and improved the cosmetic result.

MOHS MICROGRAPHIC SURGERY
Mohs micrographic surgery is a technique designed to provide maximal cure rate and optimal tissue preservation. In the first stage of Mohs surgery the tumor is debulked with a curette. A thin layer of tissue surrounding the curetted area is then excised in a horizontal fashion. The tumor is then divided into sections and mapped, denoting margins with different colored ink. B: The tumor specimen is then prepared for frozen section in the adjacent laboratory specifically designed for this procedure. Using a cryotome, the tumor is then sectioned across the inferior margin including the complete peripheral epidermal margin. Sectioning of the epidermal edge and dermis is made possible by the unique way in which the Mohs specimen is obtained, using a 45-degree beveled incision. C: Specimens are then evaluated microscopically and areas of residual tumor are noted on a map by the Mohs surgeon. Residual cancer is then excised according to denoted areas of cancer positivity. D: The specimens are then studied again and additional Mohs micrographic surgery stages are excised until the complete tumor has been extirpated. The final defect is then reconstructed or permitted to heal by second intention. (Figs. 41.3-163 A–D courtesy of Neil A. Swanson, M.D.)

4-mm nodular basal cell carcinoma on the right lower eyelid margin. Basal cell cancer in this area is at risk for spread along the tarsal plate, resulting in a cancer that is larger than appears on clinical exam. To preserve important structures and obtain the highest cure rate, Mohs micrographic surgery was performed. B: Lower eyelid site after excision by the Mohs technique. C: The wound was allowed to heal by second intention, yielding an excellent cosmetic and functional result. Note that reconstruction is often not necessary with defects of this size because of the tissue preservation feature of Mohs micrographic surgery.

An infiltrative basal cell carcinoma of the right ala in a young woman. The area is curetted and then a Mohs micrographic stage is taken under local anesthesia. B: Defect following Mohs micrographic surgery indicating the true extent of the basal cell carcinoma. In this region the tissue preservation technique permits minimal destruction of tissue in an area that is challenging to reconstruct. C: A full-thickness skin graft is placed to yield the best cosmetic result. D: Final result after complete healing of the skin graft.

A large superficial multifocal basal cell carcinoma of the right upper ear. The patient was concerned that he might lose the upper half of his ear. He pursued Mohs micrographic surgery as an alternative. B: Defect following Mohs micrographic surgery indicating preservation of cartilage and ear anatomy. C: A full-thickness skin graft is placed at the time of Mohs surgery. D: A full-thickness skin graft 4 weeks after surgery indicating complete graft take with preservation of the ear anatomy.

An infiltrative basal cell carcinoma of the right nose in a 30-year-old woman. B: Defect following Mohs surgery resulting in preservation of normal anatomic and functional relationships. C: Linear repair of Mohs defect. Complex reconstruction is often not required in smaller lesions excised with Mohs micrographic surgery. D: Final result after plastic reconstruction provides a minimally noticeable scar with preservation of anatomic relationships.
**FIGURE 41.3-168.** A: Clinically ill-defined skin cancer on the dorsal nose. Mohs surgery is indicated because of the need to achieve the highest cure rate while preserving normal tissue in this cosmetically important area. B: Defect following Mohs surgery. C: Dorsonasal flap is used to repair the defect with adjacent tissue to provide the best cosmetic result.

**FIGURE 41.3-169.** A: Ill-defined infiltrative basal cell carcinoma on the nasal tip of a 33-year-old woman. B: Defect following excision indicating true histologic extent of cancer, which is greater than could be appreciated clinically. The tendency of basal cell carcinoma of this type to extend beyond the clinical margins highlights the value of the Mohs technique. C: The patient was referred to a plastic surgeon for forehead flap reconstruction of defect. Repair shown is 2 months status post reconstruction. The repair will continue to mature over time, and patients must be reassured of the fact that with time the cosmetic result will improve. The patient underwent several scar revisions. D: Several years status post final scar revision demonstrates excellent result. There was no evidence of recurrence.

**FIGURE 41.3-170.** A: An ill-defined morpheaform basal cell carcinoma of the left nasal tip and ala. Because of the inability to be certain of the extent of the basal cell cancer, Mohs surgery is indicated. B: Defect following Mohs micrographic surgery. The resulting shallow depth of the wound permits a variety of reconstructive options, including healing by second intention, skin graft, and flap. Because of the potential for elevation of the nasal tip, a full-thickness skin graft is performed. C: The full-thickness skin graft in place. D: Final result after healing of full-thickness skin graft. Note preservation of normal anatomic relationships of the aesthetically complex nasal tip unit.

**FIGURE 41.3-171.** A: Morpheaform basal cell carcinoma of the right infraorbital cheek. Repair of defects in this area has the potential for resulting in ectropion. B: Defect following excision. Note extent of defect is larger than would have been anticipated from the clinical appearance of the cancer but smaller than would have resulted with standard excisional margins. C: Linear repair oriented to minimize inferior traction on lower eyelid.

**FIGURE 41.3-172.** A: Recurrent basal cell carcinoma of the right cheek, below the eye. Note contracture resulting from residual scar tissue from previous treatment. In this situation one should anticipate a relatively large extent of cancer unpredictable from clinical exam. B: Defect following Mohs excision revealing extension of cancer into subcutis. C: Linear repair of defect is designed to conceal the final scar within natural skin tension lines and minimize ectropion. D: The final result at 3 months indicating well-healed scar with no ectropion.
FIGURE 41.3-173. A: Infiltrative basal cell carcinoma of the right ala. Careful clinical examination of the site failed to reveal significant clinical extension.  B: Histologic specimen. Infiltrative basal cell carcinoma noted during Mohs excision. C: Defect following Mohs micrographic excision of infiltrative basal cell carcinoma of the right nose. Note that cancer extended onto the cheek. The patient was referred for plastic reconstruction.

FIGURE 41.3-174. A: Classic morpheaform basal cell carcinoma featuring a scar-like, smooth white appearance. Morpheaform basal cell carcinoma typically extends significantly beyond the clinical margins of the cancer. Its histologic behavior is characterized as aggressive growth.  B: Defect following Mohs micrographic excision. This defect can be repaired in a simple fashion similar to the procedure used on the patient depicted in Fig. 41.3-167.

FIGURE 41.3-175. A: Basal cell carcinoma previously untreated noted in the right nasolabial groove extending under the right ala. Basal cell cancer in this embryonic fusion plane can be expected to be significantly larger than the clinical appearance of the cancer suggests. In addition, extension through the plane, which represents the course of least resistance is thought by some cutaneous oncologists to result in the potential for deeply invasive cancer.  B: Defect following Mohs micrographic surgery revealing extent of cancer to the vermillion border, and extending superiorly into and under the ala. The patient was referred for plastic reconstruction, and after several scar revisions, underwent laser resurfacing to optimize the appearance of the reconstructed site.

FIGURE 41.3-176. A: A long-standing basal cell carcinoma at the angle of the nasolabial fold and the left ala in a woman in her 30s. Palpation of the tumor indicated nodular extension beneath the surface.  B: Defect following Mohs micrographic surgery revealing extension into the orbicularis oris and into the subcutis of the cheek. C: Infiltrative nests of basal cell cancer are noted adjacent to salivary tissue. The patient underwent plastic reconstruction but requires close observation for recurrence of cancer in this region.

FIGURE 41.3-177. A: Patient with surgical excision ulcer on right cheek. This patient was referred for Mohs micrographic surgery after intraoperative conventional excision with frozen sections revealed extensive positive margins.  B: Infiltrating basal cell cancer noted on Mohs micrographic tissue section. C: Extensive defect is noted following complete extirpation of cancer by Mohs micrographic surgery.
Recurrent basal cell carcinoma of right temple. Recurrent cancer often involves extension of cancer cells throughout pre-existing scar tissue. It appears that the scar tissue planes permit broader extension of cancer than would otherwise occur.

Defect following excision revealing the extent of cancer. Injury to the temporal branch of the facial nerve is a significant risk in this region but is unavoidable if cancer involves the nerve.

This patient had a lesion on the nose and cheek for at least 15 years. Because of the long-standing nature of the lesion and the likelihood of extensive disease, Mohs micrographic surgery was indicated. Complete cancer extirpation, as well as tissue preservation, is especially important when cancer is present in the central facial area. In addition, proximity to the embryonic fusion plane is another indication for controlled microscopic excision.

Extensive defect following Mohs micrographic surgery. Although repair with complex flaps and other forms of tissue rearrangement may result in a good cosmetic result, despite the very high cure rate associated with the Mohs technique, there is a risk of recurrence. Minimizing complex repairs can permit recognition of recurrence at the earliest stages. The patient developed recurrent skin cancer under a forehead flap several years after the original surgery.

FIGURE 41.3-180. A: Long-standing basal cell carcinoma of the nasal tip. Following Mohs micrographic surgery, the complete nasal tip, including cartilage, was removed. Basal cell cancer infiltrated between the nasal cartilages.

B: Forehead flap repair 2 months after reconstruction. The patient was referred to plastic surgery for reconstruction. The forehead flap option permitted repair of cosmetic unit with full-thickness tissue to compensate for extent of nasal loss due to cancer. Further revision of the flap under local anesthesia will achieve an improved cosmetic result.

WOUND MANAGEMENT AND RECONSTRUCTION AFTER MOHS MICROGRAPHIC SURGERY

Following excision of skin cancer, whether using the Mohs micrographic surgery technique or conventional frozen section methods, reconstruction of the defect must be addressed. Options usually include plastic reconstruction ranging from simple linear closure to skin grafts and skin flaps. This series demonstrates a range of procedures that represent reconstructive options for defects resulting from relatively large skin cancer excisions. In most cases reconstruction can be performed in the office setting under local anesthesia. Key guidelines to follow include reconstruction within cosmetic units, minimization of repair, and an understanding of the long-term management implications of a particular solution with respect to the possibility of recurrent cancer. In general, the simplest approach that yields the best aesthetic results is preferred. Healing by second intention may often result in a cosmetic result superior to that of plastic reconstruction depending on the location, depth, and breadth of the defect. In cases in which the cancer has been removed using Mohs micrographic surgery, reconstruction is usually performed at the same time as a separate and distinct procedure. Alternatively the wound may be allowed to heal by second intention. In another strategy, the team approach is employed. Mohs micrographic surgery can be performed on one day, and reconstruction can be performed by a reconstructive surgeon at any point thereafter, including the same day. If adjuvant radiation therapy is anticipated, it is usually not initiated until the wound or plastic reconstruction has healed completely, most commonly at 6 weeks.

FIGURE 41.3-181. A: This nasal tip defect resulting from excision of a basal cell carcinoma is especially difficult to reconstruct, because it involves the soft triangle of the nose. Of the many available options, reconstruction using a bilobed transposition flap is chosen. B: Immediately after transposition of the flap into the wound, there is evidence of excellent blood flow ensuring the likelihood of flap viability. This procedure takes approximately 30 minutes under local anesthesia. Patients who smoke, diabetics, and others with compromised blood supply are at a greater risk of flap failure. C: Side view of the original defect site at 4 weeks, demonstrating healing flap and preservation of alar rim. D: Frontal view of repair indicating matching texture of flap tissue with that of adjacent skin. Patients must be advised that the healing process takes approximately 12 months, and fullness and bulkiness of any flap will resolve with time. Early scar revision is usually not indicated. The alar rim is contiguous, and there has been successful reconstitution of the soft triangle of the nose.
FIGURE 41.3-182. A: Large defect involving part of the nasal ala, upper lip, nasolabial fold, and cheek. This defect can be repaired in a variety of ways, but there must be special attention paid to the fact that it traverses several cosmetic units. In general the simplest approach that yields the best cosmetic result is preferable. B: An island pedicle advancement flap was incised inferior to the defect and advanced superiorly. It survives on a vascular pedicle including muscle and subcutis. Once advanced into the defect, the flap is sutured in place. C: Reconstruction as it appears at 3 months postoperatively. Note preservation of natural facial skin lines. This will continue to improve over time and, because of the simplicity of the repair, permit identification of any recurrence of skin cancer in this critical embryonic fusion plane.

FIGURE 41.3-183. A: Large nasal defect on the side of the nose. This would heal well by second intention. The process would take approximately 4 weeks until the wound filled with granulation tissue and closed with epidermal resurfacing. Further wound contraction would result in a final scar approximately one-third of the original defect. Because of the desire to obtain the best cosmetic result, reconstruction was selected. B: A transposition flap was created borrowing skin from the nasolabial fold and transposing it into the defect. Lateral cheek skin was advanced into the nasolabial fold to close the secondary defect. Sutures will be removed in approximately 1 week, and continued improvement can be expected.

FIGURE 41.3-184. A: A very large defect of the nasal bridge involving the nasal cartilages. The reconstructive options include a delayed pedicle forehead flap, skin graft, and healing by second intention. The patient did not want to undergo the extensive surgery involved in a forehead flap. A skin graft would have resulted in an unsatisfactory cosmetic appearance. Healing by second intention would have been similarly unsatisfactory. A further option was explored. B: A bilateral transposition flap was performed borrowing skin from the cheek on each side of the nose. This procedure, performed under local anesthesia, permitted positioning of adjacent tissue, which closely matched nasal skin in color and texture. C: The appearance of the repair 4 months following surgery. Note minimal appearance of scar lines and preservation of natural contours of the nose. It should be noted that patients with fair skin and good facial blood supply tend to heal extremely well. This simple repair is an excellent alternative to more complicated reconstructive procedures when the patient prefers a simple approach.

FIGURE 41.3-185. A: This large defect involved removal of much of the left nasal ala and extended into the cheek and nasolabial fold. The patient had a history of cardiac disease and was not considered a candidate for surgery under general anesthesia. Allowing the wound to heal by second intention might have resulted in deformity and possible closure of the nostril with limited airflow. The decision was made to reconstruct the defect with local tissue. B: A combined repair involving a nasolabial transposition flap and island pedicle flap to re-create the lining and floor of the nose was performed. C: Final result at 6 months. Although the ala does not match that of the other side, it is functional and cosmetically acceptable to the patient. No evidence of recurrence is noted.

FIGURE 41.3-186. A: Large defect of right temple following excision of a large basal cell cancer by Mohs micrographic surgery. Reconstructive options included full-thickness skin graft, split-thickness skin graft, and healing by second intention. Because of the relative extent of the cancer and the patient’s lack of desire to
undergo further surgery, the wound was allowed to heal by second intention. B: Granulation tissue has completely filled the wound by 4 weeks. In another 2 weeks, the wound will heal over with epidermis. In the subsequent 6 to 12 months, contraction of the wound will result in a final scar that will be approximately 30% of the original wound diameter. Wound contraction is an impressive feature of healing by second intention and must be anticipated when considering allowing a wound to heal in this fashion. For example, certain defects surrounding the eye can result in ectropion if allowed to heal by second intention.

FIGURE 41.3-187. A: A large defect of the scalp extending into the periosteum. This patient had multiple medical problems and elected not to undergo flap reconstruction. Moreover, flap reconstruction may be problematic if recurrence develops and cancer spreads under the galea. Healing by second intention was not an option because of exposure of the outer table. Human skin allograft was placed as illustrated here. B: The same patient at 10 to 14 days postoperatively demonstrating vascularization of human skin allograft. This approach minimizes wound care and stimulates normal healing. In the vast majority of circumstances, the human skin allograft will be rejected at 2 to 4 weeks, revealing well-granulated base that subsequently heals by second intention. C: Final wound result after sloughing of human skin allograft and complete healing by second intention. This scar will continue to improve in texture and color over many months. In addition any recurrence of cancer should be easily noted.

RECURRENT SKIN CANCER

While most nonmelanoma skin cancers are easily managed with a range of approaches, if recurrence develops the tumor can behave in an aggressive fashion. This series depicts the clinical behavior of recurrent nonmelanoma skin cancer and highlights the advantages of achieving the highest cure rate when the cancer presents as a primary lesion. Recurrence of skin cancer relates not only to the thoroughness of the original treatment but also to the intrinsic biologic behavior of the cancer. Often, second cancers will develop near the site of previous treatment and in fact do not represent recurrent tumor. A patient who has had one basal cell cancer has a 40% chance of developing a second new skin cancer.

FIGURE 41.3-188. A: Recurrent basal cell carcinoma on the tip of the nose. B: Defect following Mohs micrographic surgery reveals extension onto columella and into the soft triangle of the nose. A wound such as this can heal by second intention or with a skin graft. Extension of the cancer beyond the clinical margins is typical for recurrent basal cell cancer.

FIGURE 41.3-189. Recurrent basal cell carcinoma developing within the scar line of a previous skin cancer excision. The presence of basal cell cancer within the scar line is an indication of recurrent cancer probably resulting from incomplete removal at the time of the original excision. Although the literature suggests that incomplete basal cell carcinoma will frequently not recur, these studies do not take into account the histologic subtype of the basal cell cancer.

FIGURE 41.3-190. A: Multiply recurrent basal cell carcinoma of the left forehead. Of note are a depressed skin graft and an area that appears shiny and white. The patient was referred for Mohs micrographic surgery because of the recurrent nature of the cancer. B: Defect following Mohs micrographic excision with extension of the wound down to periosteum. C: Following reconstruction with a full-thickness skin graft. Although not cosmetically optimal, this repair permits monitoring for recurrence in this large infiltrative basal cell carcinoma.
FIGURE 41.3-191. A: Recurrent basal cell carcinoma of the forehead. This patient underwent multiple previous procedures for removal of the basal cell carcinoma. B: Defect following Mohs micrographic surgery demonstrating extension of cancer into the upper eyelids. In many cases, recurrent basal cell cancer may develop squamoid features and demonstrate more aggressive behavior with recurrence. C: Full-thickness skin graft in place. This cancer is at a very high risk for recurrence despite the Mohs technique. Recurrence will result in extension of cancer along the medial canthus. D: Wound is healing well with complete take of graft at 6 weeks. Central crust will resolve with normal grafted skin underneath. Close monitoring, including palpation in the periorbital area, is essential.

FIGURE 41.3-192. A: Multiple scars indicating previous adjacent tissue transfers. The patient had undergone multiple excisions for basal cell carcinoma in the past, and each time residual cancer was noted. The patient was advised by his physician that basal cell carcinoma is not serious and there is no need to re-excite. The patient presented for evaluation because of the crust located in the scalp area. B: Defect following Mohs micrographic surgery performed under local anesthesia in the office setting. C: Infiltrating basal cell carcinoma noted tracking along the galea. D: Full-thickness skin graft in place at 1 year. E: The patient continued to traumatize the scalp and developed erosions on a regular basis. Clinically, the distinction had to be made whether this represents a recurrent basal cell cancer or simply poor healing due to trauma in a full-thickness skin graft.

FIGURE 41.3-193. A: Eighty-year-old woman with multiple basal cell carcinomas of the forehead. Previously, the patient had superficial basal cell carcinomas, which were treated with dermabrasion. Because of our current knowledge of the biology of basal cell cancer, this approach would not be considered optimum. B: Microscopical example of superficial basal cell carcinoma demonstrating extension into dermis. Elimination of this cancer by dermabrasion is not feasible and can result in the creation of multiple bands of scar in which recurrent skin cancer can develop. C: Defect following Mohs excision of recurrent basal cell carcinoma. Note extension of cancer down to periosteum. The patient was referred for reconstruction.

FIGURE 41.3-194. Recurrent basal cell carcinoma of the left upper lip. This cancer developed at the site of previous cryotherapy. The scar created by previous treatment provided sanctuary for cancer cells to extend. The defect can be expected to be larger than the clinical lesion.

FIGURE 41.3-195. A: Recurrent basal cell carcinoma on the right cheek surrounding previous site of electrodesiccation and curettage. Electrodesiccation and curettage are appropriate for small superficial skin cancers but are not as effective as excision at removing basal cell carcinoma that is infiltrative, nodular, or large. B: Defect following Mohs micrographic surgery reveals extensive nature of cancer that spread through scar tissue bands. In this region, extension into the parotid gland and injury to CVII are risks.
FIGURE 41.3-196. A: Recurrent basal cell cancer in right preauricular region. B: Extensive defect similar to that in Figure 41.3-195 but extending onto the ear and towards the ear canal.

FIGURE 41.3-197. Marginal recurrence of basal cell carcinoma at site of previous excision of basal cell cancer. The patient underwent multiple previous conventional excisions of the skin cancer, each time developing marginal recurrence. It is conceivable that the Mohs micrographic surgery may have limited the number of recurrences in this situation. Alternatively it appears that certain basal cell carcinomas have an aggressive behavior and may recur independent of the surgical technique used.

FIGURE 41.3-198. Recurrent basal cell carcinoma on the chest. Note the white scar indicating the previous site of electrodesiccation and curettage.

FIGURE 41.3-199. Recurrent basal cell carcinoma on the neck. This widespread multifocal superficial basal cell carcinoma on the neck surrounds a site of previous electrodesiccation and curettage. Excision by Mohs micrographic surgery is indicated.

FIGURE 41.3-200. Multiple recurrent areas of basal cell carcinoma surrounding a cryosurgery scar. Excision is indicated because of the tendency of the cancer cells to extend beneath the scar tissue and the clinical difficulty in determining the true extent of the cancer.
FIGURE 41.3-201. Recurrent basal cell carcinoma on the upper extremity of a young woman. Note the previous electrodesiccation and curettage scar and the recurrence of basal cell carcinoma at the margin. Recurrence of basal cell carcinoma at the margin in this as in Fig. 41.3-198, Fig. 41.3-199, and Fig. 41.3-200 suggests the incomplete nature of electrodesiccation and curettage at the peripheral edges.

FIGURE 41.3-202. Recurrent basal cell carcinoma at the right lateral canthus. Note retraction of the lower eyelid and the large nodule. This cancer is very large and requires Mohs micrographic surgery for adequate excision.

FIGURE 41.3-203. Recurrence of basal cell carcinoma in the right nasolabial fold had been treated multiple times by conventional excision and recurred each time despite the report of negative margins.

FIGURE 41.3-204. Defect following Mohs micrographic surgery indicates deep extension into the nasolabial fold. It is believed that this embryonic fusion plane provides low resistance to deep tracking of the tumor.

FIGURE 41.3-205. Histologic features of infiltrative basal cell carcinoma as noted in the patient of Fig. 41.3-204.
FIGURE 41.3-206. A: Multiply recurrent basal cell carcinoma on the nose and medial canthus of a 68-year-old man. B: Following Mohs micrographic surgery, the defect extends into the medial canthus, onto the cheek, and over the midline of the nose. Over the subsequent 8 years, the patient underwent repeat excisions because of recurrence, despite the use of Mohs micrographic surgery. The tumor had an infiltrative histology. Eventually cancer tracked under the floor of the orbit and an orbital exenteration was performed. C: The patient 1-year status post exenteration of the orbital contents and contiguous facial soft tissue. D: The orbital prosthesis is in place. E: Orbital prosthesis. The technology is available now to create very acceptable prostheses. Reconstruction in this patient would have been unacceptable because of the high risk of recurrence and the need to monitor for the development of new cancer, which, in this case, could be life threatening because of extension into the brain.

FIGURE 41.3-207. A: This patient underwent multiple excisions of basal cell carcinoma in the left nasolabial fold over the course of 10 years. Repair with a forehead flap had been done most recently. B: She presented with recurrence of skin cancer on the left upper lip. Mohs micrographic surgery combined with intraoperative conventional excision resulted in complete removal of the nose and medial canthus. The cancer extended into the glabella and tracked under the base of the flap and its origin on the forehead. This highlights the tendency of recurrent cancer to track under flap reconstruction without evidence of recurrence until there has been widespread cancer growth. C: Same patient with nasal prosthesis in place.

FIGURE 41.3-208. A: Recurrent basal cell carcinoma of the left upper lateral eyebrow. Previously, the patient underwent radiation therapy to this site and developed recurrence at multiple foci. B: Defect following Mohs micrographic surgery with removal of cancer in its entirety.

FIGURE 41.3-209. A: Basal cell carcinoma of the nasal tip. Previously this patient underwent radiation therapy for a basal cell carcinoma in this area and received treatment to the whole nose. Note cutaneous changes of telangiectasias, hypopigmentation, and atrophy. B: Defect following Mohs micrographic surgery. Extensive cancer invaded the cartilage and extended onto the cheeks. The patient underwent reconstruction.

FIGURE 41.3-210. Basal cell carcinoma at the site of a previous scar. The patient was unaware of any previous trauma or skin cancer treatment at this site. Basal cell carcinoma is known to develop at the site of long-standing scar.

FIGURE 41.3-211. A: This patient had multiple recurrences of basal cell carcinoma of the back starting many years earlier with treatment by electrodesiccation and curettage. Each time the cancer recurred, it appeared to invade more deeply and become more aggressive. He underwent Mohs micrographic surgery. B: Defect
following Mohs micrographic surgery indicating extension deep into muscle of the back. C: Histologic specimen indicating deep infiltration of basal cell carcinoma. D: Despite successful healing by second intention, the patient developed recurrent basal cell carcinoma, and the decision was made to perform radiation therapy. This treatment failed as well. Long-standing, aggressive, large basal cell carcinomas that undergo squamous differentiation have the potential to metastasize, but this is extremely rare. When it does occur, treatment options are limited.

RARE SKIN TUMORS

While the vast majority of skin cancers are basal cell carcinoma and squamous cell carcinoma, other nonmelanoma skin cancers do occur and, because they present on the skin, can be diagnosed by biopsy at presentation.

**FIGURE 41.3-212.** Dermatofibrosarcoma protuberans (DFSP) noted on the dorsum of the left hand of a 35-year-old woman. The patient first noted the lesion around the time that she received an intravenous infusion at that site. It grew slowly over time. DFSP is a slow-growing sarcoma of skin that may initially be confused with a benign dermatofibroma. Complete excision is indicated, and Mohs micrographic surgery is now considered the treatment choice. Because of the irregular growth pattern, conventional excision with standard wide margins may not completely remove the tumor. Metastasis is rare and usually occurs in circumstances where the cancer has recurred multiple times.

**FIGURE 41.3-213.** Recurrent DFSP in a skin graft adjacent to the clavicle in a 30-year-old man. This cancer had been present for some time prior to initial excision. At that time the cancer extended into the region of the brachial plexus and further surgery was deferred because of the risk. Margins remained positive at the time of the completion of the initial surgery. A skin graft was placed, and this small nodule was noted several years later. Mohs micrographic surgery was performed, and the cancer was removed in its entirety. Close monitoring is essential, because the lesion, with a history of deep positive margins, is at risk for recurrence.

**FIGURE 41.3-214.** Dermatofibrosarcoma protuberans on the nose of a young child. This lesion had been excised with the clinical diagnosis of a cyst. The pathology revealed dermatofibrosarcoma protuberans, and further excision was indicated. This cancer does occur in children, although it is not as common as in older patients.

**FIGURE 41.3-215.** Two lesions are noted. On the left there is a linear scar from the excision of a lesion that was considered to be a dermatofibroma. There are forms of dermatofibroma that may be hard to distinguish histologically from dermatofibrosarcoma protuberans. In this case evaluation by a skilled pathologist is necessary. The use of special stains such as CD-34 is usually helpful. Inferior and to the right of this lesion is a classic dermatofibroma which is represented by an 8-mm, dome-shaped tan nodule. A complete biopsy was performed of this lesion because of the patient's history, but there is nothing about the clinical appearance of this lesion that is concerning, nor is biopsy normally indicated for dermatofibroma.
FIGURE 41.3-216. Leiomyosarcoma is noted on the right outer arm of a 50-year-old man. This patient presented because of continued growth of the lesion, which he had been told was scar tissue. Several years earlier a similar lesion was excised, and the patient was advised that it was not malignant. Review of the original's lines confirmed that it was not possible to make a diagnosis of malignant tumor at that time. However, excision of this lesion down to fascia and careful examination of the pathology revealed that it was a leiomyosarcoma.

FIGURE 41.3-217. Merkel cell carcinoma on the leg of an elderly man. This large cancer can behave much like a melanoma, with potential for metastatic spread. Wide local excision and radiation therapy are indicated. Mohs surgery is advocated by some.

FIGURE 41.3-218. Microcystic adnexal carcinoma of the cheek on a 45-year-old man. The lesion had been present for many years prior to seeking treatment. A microcystic adnexal carcinoma is believed to originate from the sweat gland apparatus. Although it tends not to metastasize, it can behave aggressively and demonstrate perineural invasion. If this occurs, cure rate is diminished.

FIGURE 41.3-219. Microscopical example of microcystic adnexal carcinoma indicating structures similar to sweat glands and the infiltrative nature of the cancer.

FIGURE 41.3-220. A: A microcystic adnexal carcinoma of the nose demonstrating infiltration of the nasal bridge, distortion the soft triangle of the nose, and erosion in that region as well. This had been a long-standing lesion. B: Following Mohs micrographic surgery, which is the treatment choice for this condition, partial rhinectomy resulted. Cancer infiltrated between the nasal cartilages. Reconstruction was performed using a forehead flap.
FIGURE 41.3-221. Microcystic adnexal carcinoma of the chin highlighted by a small area of white papules on the right lateral inferior chin area. Surrounding erythema is identifiable and approximates the true extent of the cancer, which involved most of the lower chin area.

FIGURE 41.3-222. Angiosarcoma of the scalp. The cancer appears as a hemorrhagic patch that does not blanch on compression. This patient progressed to develop nodules and erosions requiring extensive surgery. Angiosarcoma is extremely difficult to treat with chemotherapy, and radiation therapy does not provide consistent results. In addition, the histologic nature of the cancer is such that there are often skip lesions, and negative histologic margins are no indication of complete eradication of the cancer.

FIGURE 41.3-223. A: This patient has multiple small papules, noted for several years. A biopsy was done to rule out basal cell carcinoma. Histology revealed angiosarcoma. The patient underwent Mohs micrographic surgery and reconstruction. Subsequently, and not surprisingly, the cancer recurred in noncontiguous areas. The patient received radiation and several cycles of chemotherapy. B: Same patient after multiple excisions and reconstruction. In addition the patient received radiation therapy to the central facial area, which resulted in breathing complications. Because of the metastatic potential of this cancer, routine monitoring with CT scan and full physical examination is necessary. C: Patient developed a new nodule of angiosarcoma in the glabellar area. He had already completed multiple courses of chemotherapy, and the decision was made to treat this lesion symptomatically. It was excised with margins down to the periosteum, which was involved by angiosarcoma. Overall this patient has done well during the 7-year course of his disease without any evidence of metastatic disease.

FIGURE 41.3-224. Purplish nodule on the nose of a 30-year-old woman. This lesion was an angiosarcoma. Wide excision was successful in eliminating the lesion.

FIGURE 41.3-225. The violaceous plaque with erosion on the scalp of a woman in her 60s. This patient had this lesion for several years before it became darker and thicker. Physicians had treated it with laser, assuming it was a benign vascular tumor. When biopsy was performed, angiosarcoma was identified. In this case the changes of angiosarcoma were very subtle and required consultation with multiple dermatopathologists. Excision was performed initially with Mohs micrographic surgery, but eventually multiple areas of recurrence required complete removal of the scalp tissue with full-thickness skin grafting. The patient did well for approximately 5 years until she presented with a lytic lesion of the posterior parietal scalp. Imaging studies revealed a large infiltrating mass compressing the dura and infiltration of the calvarium by angiosarcoma.
FIGURE 41.3-226. Atypical fibroxanthoma of the arm. This sun-induced tumor is normally seen in elderly men. It has a low potential for metastasis but can behave aggressively and requires excision. Mohs micrographic surgery is the treatment choice.

FIGURE 41.3-227. A: A young patient demonstrating a tumor of the right lower eyelid. B: The same patient many years later demonstrating the effect of neglecting basal cell carcinoma. This cancer must be considered incurable. (Photograph courtesy of Israel Dvoretzky, M.D.)

FIGURE 41.3-228. Long-standing infiltrative basal cell carcinoma of the right cheek in a 95-year-old man. The patient was unable to undergo surgery, and the family declined radiation therapy. A course of intralesional interferon was unsuccessful. This cancer is at high risk for extension into the parotid gland and involvement of the facial nerve.

PIGMENTED LESIONS

Pigmented lesions include benign moles or nevi, atypical nevi, melanoma, and a range of benign epithelial tumors. This series depicts a range of pigmented lesions, highlighting those that should arouse a high index of suspicion for malignancy. Melanoma is most curable when it is diagnosed in its earliest stages. A melanoma that is up to 1 mm in depth has a 96% cure rate with simple local excision. Any lesion that is suspicious for melanoma or an atypical nevus should be promptly biopsied. The clinical photographs represent the spectrum of pigmented lesions with which patients present to their dermatologist.

FIGURE 41.3-229. A: Seborrheic keratosis of right cheek. This very common pigmented lesion has a rough, greasy surface and may often be confused with a melanoma by the patient because of the pigmentation. The visit to the doctor provides an opportunity to perform a full body skin examination. B: Multiple seborrheic keratoses of the trunk. These lesions are very common and accumulate with age. They are benign proliferations of epidermis and do not transform into malignancy.

FIGURE 41.3-230. Compound nevus. This normal mole is slightly darker than the surrounding skin color. The papillated surface is not uncommon. Note the regular border.
FIGURE 41.3-231. Several nevi are noted in this picture. The central lesion is slightly irregular with darker pigmentation in the center surrounded by a rim of tan coloration. These features suggest that this mole may be atypical, especially in comparison to the surrounding nevi. Biopsy of the central lesion is indicated.

FIGURE 41.3-232. A: Two nevi are noted. The one on the right is approximately 2 mm in diameter and is regular in coloration. There is no indication of atypicality. The larger lesion is approximately 5 mm in its longest diameter and has irregular pigmentation. These atypical features are concerning, and biopsy is indicated. A tangential biopsy is sufficient to determine whether further excision is needed due to the degree of atypicality of the nevus. B: This large nevus has irregular pigmentation, a notched border, and a relative lack of symmetry. It is difficult to identify from the photograph, but one must be concerned about the possibility of an atypical nevus at the least and melanoma at the worst. Biopsy is required.

FIGURE 41.3-233. Congenital nevus of the right neck. This lesion has been present since birth. It has slightly irregular pigmentation that has been unchanged during the life of the patient. Close monitoring is indicated, but biopsy at the earliest sign of any change is necessary.

FIGURE 41.3-234. Slightly irregular dark nevus. Note how the dark pigmentation is different from surrounding pigmented lesions in this fair-skinned individual. Biopsy is indicated to rule out melanoma.

FIGURE 41.3-235. Nevus of the left lateral dorsal foot. Nevi on the extremities can occur. If there is any suspicion of melanoma or atypical nevus, biopsy is required.
FIGURE 41.3-236. Multiple nevi on a patient who is being followed for a history of atypical moles. Note the central irregular mole that has a notched border and irregular pigmentation. Careful monitoring of patients with multiple moles may be accomplished with serial photography. Biopsy should be performed on any lesion that demonstrates a change when compared to photographs, or in the opinion of the patient or physician.

FIGURE 41.3-237. A congenital mole characterized by large size, brown pigmentation, regular border, and normal skin surface markings. Opinion varies about whether congenital nevi smaller than 1 cm need to be removed. In general any congenital mole smaller than 1 cm may be monitored.

FIGURE 41.3-238. A: Large congenital nevus on the anterior shin of a patient with a history of melanoma. Because of this history it is judicious to ensure that the congenital nevus is removed in its entirety. Therapeutic options include excision with skin grafting or staged excision. The author prefers the latter in this situation, as it causes minimal discomfort and provides a superior cosmetic result. In the first excision the majority of the lesion is excised in an elliptical fashion to permit linear approximation of wound edges. B: Healed nevus after first stage of excision. C: Final result after second excision of residual nevus. This was performed approximately 3 months after the first excision. Note well-healed scar with no evidence of residual nevus.

FIGURE 41.3-239. Large congenital nevus of the trunk with areas of irregular pigmentation. The risk of transformation to melanoma over time increases with the size of the congenital nevus. Excision in this situation would help minimize the need to monitor for malignant transformation.

FIGURE 41.3-240. Labial lentigo in an 18-year-old with a history of sun exposure. This lentigo has regular pigmentation and a well-circumscribed border. The risk that this represents a malignant lesion is very low, but biopsy may be performed without complication. When multiple lesions of this sort are noted, Peutz-Jeghers syndrome must be considered.

FIGURE 41.3-241. Blue nevus is noted on the cheek of a middle-aged woman. The blue nevus represents pigment cells located within the dermis. The blue coloration is due to the Tyndall effect, light reflecting off pigment deep within the dermis. The differential diagnosis must include melanoma. Common blue nevi are benign, although cellular blue nevi have the potential for malignant transformation.
Lentigo maligna, also called melanoma in situ, noted on the right cheek of a man with severe solar damage. Lentigo maligna can transform over many years into invasive melanoma. Treatment is often complicated by its large size. Atypical melanocytes are confined to the epidermis, and there is no risk of metastasis as long as the lesion has not transformed into invasive lentigo maligna melanoma. Lentigo maligna was historically referred to as Hutchinson's melanotic freckle. The treatment of choice is excision with 5-mm margins. This approach can be complicated by the fact that at the periphery of the lesion, it is sometimes difficult to distinguish sun-damaged melanocytes from truly malignant cells. In addition, the occurrence of these lesions on the face sometimes limits the margin of tissue that may be taken.

Recurrent lentigo maligna on the nose of a 75-year-old woman. This patient underwent excision of extensive lentigo maligna on the nose with skin graft placement. Note recurrent lentigo maligna resulting from migration of malignant cells from marginal skin.

Lentigo maligna, which is most commonly seen in elderly patients, can be extensive. Often, the broad extent of the malignancy precludes surgical excision. This patient was not a surgical candidate but had extensive long-standing lentigo maligna. On an experimental basis, the Q-switched ruby laser was used to treat the lesion with the concern that although the pigment may be removed, amelanotic malignant cells may persist. This presents a theoretical risk of developing invasive melanoma that might not be identified because of the absence of pigmentation. This approach is considered experimental and necessitated by the unique clinical challenge presented by this case. The patient underwent several treatments with the Q-switched ruby laser, and clinical elimination of lesion was achieved. Most notable was the complete elimination of labial lentigo maligna. Follow-up biopsy failed to reveal any malignant cells. Further rigorous studies are needed to determine the role of laser in the management of inoperable lentigo maligna.

This patient presented for laser treatment of this liver spot because of cosmetic concerns. Because of the size of the lesion, biopsy was performed, which confirmed the presence of lentigo maligna. In this case surgical excision is feasible, and laser was not indicated.

Tan, slightly irregular pigmented lesion of the shin in a patient with extensive solar damage. Although this lesion has the appearance of a melanoma in situ, the scale that is noted confirms that clinically this is most likely a seborrheic keratosis.
FIGURE 41.3-247. A: Long-standing irregularly pigmented patch on the cheek of a 65-year-old woman. The patient presented for cosmetic treatment of this lesion. Biopsy revealed lentigo maligna. B: The extent of the lesion was identified using ultraviolet light, which highlights areas of epidermal pigmentation. Those margins were marked as shown, and excision was performed with 3 to 5 mm beyond the identified area. Rush permanent histologic sections permit identification of residual areas of lentigo maligna that require further excision. Once all of the lentigo maligna is removed, the patient may undergo reconstruction. Careful monitoring is required because of the tendency of this type of lesion to recur in sun-damaged skin.

FIGURE 41.3-248. Irregularly pigmented nodular lesion. Note asymmetry, irregular border, variegated color, and diameter greater than 5 mm. This is a melanoma until proven otherwise by biopsy.

FIGURE 41.3-249. A regularly pigmented dark nodule. The differential diagnosis includes melanoma and seborrheic keratosis.

FIGURE 41.3-250. Superficial spreading melanoma in the radial growth phase. Neglect of this lesion or aggressive behavior will result in transformation into the vertical growth phase, thus increasing the risk of metastasis. Early diagnosis of melanoma is the single best approach to obtaining the highest cure rate. The role of sentinel node biopsy is currently under study but is increasingly recommended for intermediate- and some early-stage melanomas.

FIGURE 41.3-251. Nodular malignant melanoma. The dark coloration, size, and nodularity make the diagnoses obvious.
FIGURE 41.3-252. Microscopical example of nodular melanoma with atypical melanocytes extending into the dermis.

FIGURE 41.3-253. Irregular pigmentation under the nail. The differential diagnosis includes hemorrhage and melanoma. Often a clear history of trauma is helpful in clarifying the diagnosis. If the lesion is not obvious hemorrhage, biopsy is necessary to rule out melanoma.

FIGURE 41.3-254. Pigmented band in the thumbnail of a 70-year-old man. The lesion had been present for many months. The diagnosis in this fair-skinned individual is melanoma until proven otherwise. A biopsy was performed following avulsion of the nail under local anesthesia, and the histology revealed a simple lentigo.

FIGURE 41.3-255. Lightly pigmented band extending from the proximal nail fold to the distal toe at the medial edge of the nail plate. This long-standing lesion had begun to change in color. After the nail was avulsed, a biopsy was performed of the nail matrix, and melanoma in situ was identified. Further excision with margins was performed and the wound was allowed to heal by second intention.

FIGURE 41.3-256. A: Irregular growth of the nail plate associated with a nodule under the medial aspect of the great toenail raised the suspicion of an amelanotic melanoma. B: After avulsion of the nail, a digital fibroma was identified and removed. Biopsy confirmed the benign nature of this growth.

FIGURE 41.3-257. Irregular black pigmented lesion on the sole of an African American. This represents an acral lentiginous melanoma. The development of melanoma on the sole is the reason why full body skin examination must include a careful examination of that area, including the interdigital web spaces.
INTRODUCTION

The normal human melanocyte adheres singly to the basement membrane of the epidermis with five to six keratinocytes between each cell. Despite normally resting, melanocytes maintain a lifelong proliferation potential. With their dendrites, they reach to keratinocytes in the upper layers of the epidermis to distribute the pigment melanin. Melanin is packaged in melanosomes and provides protective coloration against the damaging effects of ultraviolet (UV) irradiation. Developmentally, melanocytes arise from pluripotent cells of the neural crest. Their survival, migration to the skin, and differentiation is related to spatial and temporal expression of molecules, not only on the migrating cells, but also on juxtaposed other cell types and the extracellular matrix. Defects during development in genes associated with melanocyte migration lead to complete or partial loss of pigment-producing cells in the skin, whereas defects in genes of the pigmentation pathways lead to presence of melanosomes but absence of pigmentation.1 Genes specific for either melanocyte development or pigmentation are potentially important determinants for melanoma, but a causal relationship has not yet been established. Growth factor receptor genes such as c-kit or endothelin receptor-B (ENDRB) could have a potential role in the pathogenesis of melanoma. Stem cell factor, the ligand for c-kit, is a strong mitogen for normal melanocytes, but has little effect on melanoma cells because expression of c-kit is down-regulated through as yet unknown mechanisms.

The type of pigment, eumelanin versus phaeomelanin, present in the melanosomes appears to be related to susceptibility for development of melanoma.2 Those individuals who produce phaeomelanin instead of eumelanin are at higher risk for developing melanoma. Preliminary investigations have revealed mutations in the gene for the receptor for melanocyte-stimulating hormone (MC1R). Apparently specific point mutations in the MC1R gene correlate with high susceptibility for melanoma, but not all studies came to the same conclusions.3-5

The incidence of melanoma has increased in the United States from 3 cases per 100,000 in 1950 to 13 cases in 2000 with annual increases of 2.5%. This yearly increase is among the highest of all human cancers. In 1999, 44,000 new cases are expected in the United States, with approximately 9000 deaths from the disease. There are no indications that the rate of increase will be slowing in the near future. Fortunately, diagnosis of melanoma in more recent years occurs at an earlier stage, resulting in higher cure rates than two decades ago. Thus, mortality has not increased as steeply as incidence rates.

ETIOLOGY OF MELANOMA

Knowledge of the etiology of melanoma comes predominantly from epidemiologic, less from genetic, studies. UV exposure at the ultraviolet B (UVB) (290 to 320 nm) and ultraviolet A (UVA) (320 to 400 nm) range is the most important, if not the only, causative agent for sporadic melanoma development. Predisposition for poor tanning in combination with high sun exposure provides the largest accumulative risk factor for melanoma development. Risk factors for melanoma development over a lifetime are, in decreasing order from less than tenfold to less than twofold: presence of over ten dysplastic nevi, presence of over 100 common acquired nevi, fair skin (types I and II), red hair, and high intermittent sun exposure (i.e., blistering sunburns as a child).6-8 Excessive intermittent sun exposure is more prevalent in individuals from higher socioeconomic classes.

The melanoma-inducing effects of UV light have been demonstrated in experimental animal systems. Irradiation with UV light sources in the B range induced melanomas in Xiphophorus fish and Monodelphus domestica.9-10 UVA could also transform melanocytes in the highly susceptible Xiphophorus fish.11 Preliminary experimental evidence of melanoma induction by UVB comes also from a human skin/mouse chimera model, in which the human skin was grafted to severe combined immunodeficient (SCID) or recombinase activating gene (RAG) knockout mice and then treated with the carcinogen 7,12-dimethylbenz[a]anthracene followed by chronic UVB irradiation over 9 months.12 In this model, which comes closest to the conditions in humans, melanocytic hyperplasia is seen after 4 to 5 months, followed 2 to 3 months later by atypia in lentiginous lesions. Human melanomas have developed but rarely.

GENETICS OF MELANOMA

Cyto genetic analyses over the last two decades have identified in melanoma cells at least six different chromosomes with loci showing nonrandom deletions, translocations (rarely), or amplifications (rarely). Extensive research efforts in the late 1980s and early 1990s focused on chromosomes 1, 6, 7, 9, 10, and 11 (Figure 42.1-1). The severe aneuploidy of melanoma cells has made it difficult to identify specific regions because each chromosome showed several affected regions. Whereas few laboratories have continued their efforts on the cytogenetic analysis of melanoma cells, most are currently concentrating on screening specific loci or on genome-wide scans. Cytogenetic studies have helped to identify the 9p21 locus, which is frequently affected in melanoma. Intensive research efforts have identified mutations in the p16INK4a gene, which localizes in this region. The p16INK4a gene is affected through germline mutations or deletions in patients with familial melanoma, which represent 8% to 10% of all melanoma cases. Approximately 50% of familial melanoma patients have germline abnormalities at chromosome 9p21, making this the most frequently abnormal locus. Of these, approximately 50% have mutations or deletions in the p16INK4a gene. Thus, p16INK4a abnormalities represent approximately 5% of all melanomas. They are also significant in sporadic melanomas, in which 25% to 40% of all lesions have mutations or deletions or in which the gene is functionally silenced.3 Besides p16INK4a, only the cyclin-dependent kinase (CDK4) gene has been found mutated in familial melanoma, but only two families have been identified to date.14

Figure 42.1-1. Identification of regions in human chromosomes with melanoma-specific abnormalities.
Among sporadic melanomas, mutations have been found in ras genes with the frequency ranging between 5% and 25%. The wide range is due to differences in the site of the lesions among the studied patients' cohorts. Melanomas in the sun-exposed face have relatively higher proportions of ras mutation than those in sun-protected areas.\textsuperscript{22} p53, phosphatase and tensin homologue deleted on chromosome 10 (PTEN) and b-catenin mutations are each around 5% of melanoma cases.\textsuperscript{24,28,29,31,32,33} Further studies are needed to determine for each lesion the relative frequency of each of the six major genes listed in Table 42.1-1. Some lesions may accumulate several abnormalities to account for a lower overall percentage of melanomas with defined genetic aberrations. Little is also known about the sequence of gene defect accumulations in melanomas. With the exception of ras mutations, all abnormalities appear to occur in late stages of progression. Nevertheless, the aberrations have important biologic implications for melanoma progression.

FUNCTIONAL SIGNIFICANCE OF SPECIFIC GENE MUTATIONS IN MELANOMA

CELL-CYCLE–REGULATING GENES IN MELANOMA

Proliferation in melanocytes is tightly controlled in the late G\textsubscript{1} phase of the cell cycle through a number of checkpoint-modulating proteins. These include cyclins (cyclins A, B, D, and E),\textsuperscript{2,3} CDKs such as CDK2, CDK4, CDK6, CDCC2, CDK8,\textsuperscript{2,3} CDK inhibitors such as p16\textsuperscript{INK4a}, p15\textsuperscript{INK4b}, p21\textsuperscript{WAF1/CIP1}, p27\textsuperscript{KIP1},\textsuperscript{34,35} and\textsuperscript{36} pocket proteins of the retinoblastoma (Rb) family (p107, p130, p105),\textsuperscript{37} EZF transcription factors (E2F 1 through 6),\textsuperscript{38} and other regulatory proteins (Figure 42.1-2). A clear definition of the restriction point in the cell cycle has enabled further characterization of each protein in relation to its effects on the cell cycle. Separation of pre–S phase G\textsubscript{1} cells from postmitotic G\textsubscript{0} phase by the restriction point relays the mitogenic signals from growth factors to cell-cycle regulatory proteins. In melanoma, growth factors such as basic fibroblast growth factor (bFGF) and insulin-like growth factor–1 (IGF–1) can stimulate the cells to progress from the restriction point interface to the pre–S phase. Combined with their ability to act as survival and maintenance factors, growth factors can stimulate the expression of positive regulators such as cyclins and CDKs or suppress CDK inhibitors and pocket proteins.

\textbf{TABLE 42.1-1.} Gene Abnormalities in Lesions of Patients with Sporadic Melanomas

<table>
<thead>
<tr>
<th>Gene</th>
<th>Abnormality</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>p53</td>
<td>Deletion</td>
<td>5%–25%</td>
</tr>
<tr>
<td>Ras</td>
<td>Mutations</td>
<td></td>
</tr>
<tr>
<td>PTEN</td>
<td>Mutations</td>
<td></td>
</tr>
<tr>
<td>p53</td>
<td>Mutations</td>
<td></td>
</tr>
<tr>
<td>b-Catenin</td>
<td>Mutations</td>
<td></td>
</tr>
<tr>
<td>Rb</td>
<td>Mutations</td>
<td></td>
</tr>
</tbody>
</table>

The CDK inhibitors belong to two classes: the Cip/Kip and INK4 families. The most prominent protein among Cip/Kip family proteins is p21\textsuperscript{WAF1/CIP1}; others include p27\textsuperscript{KIP1} and p21\textsuperscript{WAF1/CIP1} that are able to associate primarily with CDK2. In addition to other CDKs, and can interact with proteins involved in DNA repair and replication. It has also been identified as a protein induced by the p53 tumor suppressor protein. On DNA damage, p53 is stabilized and acts as a transcription factor, which, in turn, stimulates expression of p21\textsuperscript{WAF1/CIP1}. This induction of p21\textsuperscript{WAF1/CIP1} inhibits cell-cycle progression by inhibiting cyclin-CDK complexes and by inhibiting DNA synthesis through proliferating cell nuclear antigen.\textsuperscript{23} The INK4 family members consist of p16\textsuperscript{INK4a}, p15\textsuperscript{INK4b}, p18\textsuperscript{INK4c}, and p19\textsuperscript{INK4d}. The hallmark of this group of proteins is that they are able to inhibit specifically the assembled cyclin D/CDK4/6 activity, and expression directly correlates with the Rb phosphorylation status.\textsuperscript{24}\textsuperscript{25} The CDK inhibitors belong to two classes: the Cip/Kip and INK4 families. The most prominent protein among Cip/Kip family proteins is p21\textsuperscript{WAF1/CIP1}; others include p27\textsuperscript{KIP1} and p21\textsuperscript{WAF1/CIP1} that are able to associate primarily with CDK2. In addition to other CDKs, and can interact with proteins involved in DNA repair and replication. It has also been identified as a protein induced by the p53 tumor suppressor protein. On DNA damage, p53 is stabilized and acts as a transcription factor, which, in turn, stimulates expression of p21\textsuperscript{WAF1/CIP1}. This induction of p21\textsuperscript{WAF1/CIP1} inhibits cell-cycle progression by inhibiting cyclin-CDK complexes and by inhibiting DNA synthesis through proliferating cell nuclear antigen.\textsuperscript{23} The INK4 family members consist of p16\textsuperscript{INK4a}, p15\textsuperscript{INK4b}, p18\textsuperscript{INK4c}, and p19\textsuperscript{INK4d}. The hallmark of this group of proteins is that they are able to inhibit specifically the assembled cyclin D/CDK4/6 activity, and expression directly correlates with the Rb phosphorylation status.\textsuperscript{24} The b-Catenin pathway is activated by ligand binding to frizzled receptors, GSK3\textsubscript{b} function is inhibited. b-Catenin then accumulates, interacts with TCF/LEF-1 (T-cell factor/lymphoid enhancer factor–1) transcription factors, and activates transcription of promoters of genes containing TCF/LEF-1 binding sites.\textsuperscript{30} Posttranscriptionally, b-catenin's fate is regulated by at least two proteins that control GSK3\textsubscript{b}. Akt/protein kinase B (PKB), which is activated by growth factor receptors and integrins through phosphoinositide 3 kinase (PI3), phosphorylates GSK3\textsubscript{b}, thereby inhibiting its ability to phosphorylate b-catenin, leading to its degradation.\textsuperscript{32,33} Dishevelled, which is a predominantly cytoplasmic protein, is regulated by frizzled.\textsuperscript{44,45} Dishevelled contains an axin–like domain, a PDZ (three proteins) domain (involved in protein interactions), and the DEP domain ( implicated in G protein regulation)\textsuperscript{46} and it interacts with axin to regulate GSK3\textsubscript{b}, thereby influencing b-catenin. In addition, overexpression of axin can suppress the effect of b-catenin in...
cells. Mutations in the b-catenin gene in melanoma would lead to an endogenous activation without degradation.

**FIGURE 42.1-3.** b-Catenin pathways in melanoma. Differences between normal and transformed melanocytes for cadherin signaling. APC, adenomatous polyposis coli; mut.b-cat., b-catenin mutation.

**PHOSPHATASE AND TENSIN HOMOLOGUE DELETED ON CHROMOSOME 10 PATHWAY**

PTEN has emerged as a major component in regulating survival of tumor cells through its involvement in intricate cascading pathways for growth and adhesion signaling. Both the growth factor and the adhesion receptor (integrin) signaling pathways work in tandem, and signaling is initiated from PI3 kinase, which acts as a relay station (**Fig. 42.1-4**). PI3 kinase activity is associated with the transformation ability of oncoproteins and stimulation by growth factors. Akt/PKB, an oncogene initially discovered in retroviruses, binds to phosphatidylinositol 3,4-diphosphate (PtdIns-3,4-P$_2$), and phosphatidylinositol 3,4,5-triphosphate (PtdIns-3,4,5-P$_3$), and is then transported to the membrane where it activates PI3 kinase. Activation of Akt/PKB in melanoma cells by IGF-1 provides survival signal by phosphorylating Bad and caspase 9. PTEN dephosphorylates PtdIns phosphates, thereby depriving the PI3 kinase of its substrate. Thus, a mutated PTEN can constitutively activate Akt/PKB to influence downstream genes. Cells accumulate in the G$_1$ phase of the cell cycle through up-regulation of p27. However, it is unknown whether the phosphatase activity is involved in this process and whether it is necessary for dephosphorylation of FAK leading to inhibition of integrin-mediated signaling of cell spreading.

**FIGURE 42.1-4.** PTEN (phosphatase and tensin homologue deleted on chromosome 10) pathways in melanoma. Schematic representation of PTEN as a central molecule influencing PI3 kinase-dependent Ras and Akt signaling.

It is not yet clear how the PTEN may signal to regulate the ras pathway. One evidence is the involvement of Shc phosphorylation, which affects its association with Grb2. Shc and Grb2 interactions are necessary for subsequent activation of the ras/raf/MEK1/MAPK pathways, providing a central role for PTEN in controlling cellular responses to growth factor– and integrin-mediated signaling.

**BIOLOGY OF MELANOMA DEVELOPMENT AND PROGRESSION**

**PROGRESSION MODEL**

Clinical and histologic studies have resulted in defining distinct steps of melanoma development and progression (**Fig. 42.1-5**): step 0, melanocytes; step 1, common acquired and congenital nevi with structurally normal melanocytes; step 2, dysplastic nevi with structural and architectural atypia; step 3, radial growth phase (RGP), nontumorigenic primary melanomas without metastatic competence; step 4, vertical growth phase (VGP), tumorigenic primary melanomas with competence for metastasis; and step 5, metastatic melanoma. A refinement by Elder et al. of this classification of nevi and primary melanomas divides lesions into three classes: class I represents precursor nevi; class II lesions are intermediates, confined to the epidermis or with microinvasion into the dermis and represented by in situ and microinvasive RGP melanomas; class III are VGP tumorigenic melanomas. As in any neoplastic system, individual melanomas can skip steps in their development, appearing without identifiable intermediate lesions. It remains to be experimentally verified that melanoma cells can develop from a melanocyte precursor cell, which appears to be present not only in murine but also in human skin.

**FIGURE 42.1-5.** Melanoma development and progression. The model implies that melanomas develop and progress in a sequence of steps. However, malignancy can also develop de novo. RGP, radial growth phase; VGP, vertical growth phase.

The progression from each stage to the next is associated with specific biologic changes, which are based on experimental models and clinical and histopathologic observations (**Fig. 42.1-5**). The transition from the mature melanocyte to the formation of a nevus is characterized by a disruption of cell-cell cross-talk between melanocytes and keratinocytes, which leads to an escape of the melanocyte from the regulatory control of keratinocytes. Nevus cells show limited proliferation because common acquired nevi have no apparent chromosomal aberrations. Thus, nevi can develop not just through a stimulatory event, but also through loss of
control of keratinocytes over melanocytes.

Progression from the melanocyte or common acquired nevus cell to a dysplastic nevus or RGP melanoma most likely involves the beginning of genetic aberrations. The cells show cytologic atypia, they can separate from the basement membrane without undergoing apoptosis, and the entire lesion shows architectural atypia. Cells from RGP lesions have biologic properties in vitro that are intermediate between benign and malignant. They require several growth factors for proliferation, do not grow anchorage independently in soft agar and are nontumorigenic in mice. At this time, a local immune response is observed, which could be critical for long-term disease outcome. Specificity and nature of infiltrating lymphocytes in dysplastic nevi or RGP melanoma have not yet been determined. Surgical excision of dysplastic nevi and RGP melanomas leads to a cure from the disease. For example, in the diagnosis of 37 lesions by eight pathologists, disagreements in diagnosis were noted in 40% of the cases.

VGP primary melanomas are characterized as expanding nodules that invade deep into the dermis. Lesions show increased blood vessel infiltration and a decreased host response. Approximately 35% of VGP lesions have already disseminated at the time of surgical excision of the primary lesion. Besides the classical criteria of Clark’s level of invasion and Breslow’s measure of tumor thickness, several additional attributes have been defined that determine disease outcome: (1) mitotic activity (i.e., the higher the number of mitoses, the lower the survival rate); (2) lymphocyte infiltration (i.e., the higher the better for survival); and (3) minor attributes such as sex (i.e., male worse than female subjects), site (i.e., trunk worse than extremity), and regression (i.e., presence worse than absence).

Metastatic melanoma cells grow independently of exogenous growth factors with the exception of IGF-1. They readily grow anchorage independently in soft agar and all form tumors when injected into immunodeficient mice. VGP primary melanomas are highly aneuploid, which has hampered their cytogenetic and molecular genetic characterization. Biologically, the cells are relatively plastic, and selective pressure over a few weeks can render cells independent of all exogenous growth factors or they become highly invasive. Some also acquire metastatic competence.

The metastatic phenotype of melanoma cells isolated from metastatic lesions of patients is unstable. Injection of these cells into an immunodeficient host rarely produces metastases. Metastatic cells also show a high level of phenotypic plasticity, depending on the environment and any selective pressure placed on the cells.

BIOLOGIC BASIS OF MELANOMA PROGRESSION

Monoclonal antibodies have been used for the last 20 years to characterize molecules expressed by melanoma cells (Fig. 42.1-7). They have particularly aided in biologic and biochemical analyses of melanoma-associated antigens. Each group of molecules is represented by 5 to 20 members. Thus, melanoma cells are among the best studied of all human tumors. Most intensely studied are adhesion receptors and their ligands, and growth factors with their receptors. In the following discussion, we focus on the biologic significance of adhesion receptors and growth factors for melanoma survival, growth, motility, and invasion.

ADHESION RECEPTORS

Melanoma cells express all major groups of adhesion receptors: integrins, cadherins, and cellular adhesion molecules of the immunoglobulin supergene family. Expression of most adhesion receptors increases with progression (Fig. 42.1-8). There is a dynamic shift as others decrease. Only few remain unchanged. This shift in adhesion receptor expression between normal and malignant cells is most obvious among the cadherins. Melanocytes express E-cadherin, whereas melanoma cells express N-cadherin. The expression of E-cadherin by melanocytes allows them to adhere to keratinocytes and develop gap junctions through connexin 43 (Fig. 42.1-9). Melanoma cells cannot establish gap junctions with keratinocytes. Instead, melanoma cells, which all express N-cadherin, adhere to either fibroblasts or endothelial cells, which both express N-cadherin. Neither fibroblasts nor endothelial cells can establish gap junctions to keratinocytes. The biologic consequences of gap junction formation are not clear.
Dynamic shifts in the expression of adhesion receptors and their matrix proteins by melanoma cells. The increase or decrease in expression may already start in nevi or only in vertical growth phase melanomas.

Melanocyte and melanoma cell interactions with juxtaposed cells in their environment. Adhesions occur through either E-cadherin (E-cad) or N-cadherin (N-cad) and gap junctional communication is mediated through connexin 43 hexamers.

Keratinocytes can control the phenotype of normal melanocytes but not melanoma cells. They can regulate melanocyte growth and the expression of cell surface adhesion receptors. Figure 42.1-10 illustrates that melanocytes in culture in the absence of any other cell (monoculture) express melanoma-associated antigens. However, the expression of these molecules disappears within 3 to 4 days when the cells are cocultured with normal keratinocytes to allow cell-cell contact.

Melanoma cells are refractory to keratinocytes. However, if the melanoma cells are transduced with E-cadherin, they can adhere to keratinocytes and establish gap junctions. At this time, cell surface molecules are down-regulated, gap junctions are established with keratinocytes, and growth of cells is controlled by keratinocytes. Highly metastatic melanoma cells are no longer invasive. Little is currently known about the signaling mechanisms between keratinocytes and E-cadherin-expressing melanoma cells.

Besides N-cadherin-mediated interactions, melanoma cells can adhere through other adhesion receptor systems (see Fig. 42.1-10). Most notable is adhesion through Mel–cellular adhesion molecules and a yet unidentified ligand, also found on melanoma cells. Melanoma cells and activated endothelial cells share a number of growth molecules that allow heterophilic adhesion between these two cell types in a similar manner as homophilic adhesion between the malignant cells. The similarities in adhesion receptor expression could have functional consequences (Fig. 42.1-11). Maniotis and coworkers demonstrated that melanoma cells could establish tubule-like structures for blood flow, which can connect to bona fide blood vessels.

Expression of tumor-associated antigens on melanocytes and melanoma cells is dependent on the presence of E-cadherin (E-cad) and adhesion to keratinocytes. Keratinocytes can regulate antigen expression on melanoma cells only when E-cadherin is expressed by melanoma cells.

Melanoma-melanoma and melanoma-endothelial cell adhesion. Both cell types use similar molecules for cell-cell adhesion.

b3 is present on almost all VGP primary and metastatic melanomas, but not on cells of earlier stages of progression. One of the most specific markers that characterizes VGP and metastatic cells is the b3 subunit of the vitronectin receptor a_v b3 (Fig. 42.1-12). When the b3 gene was transduced to RGP melanoma cells, there were no changes in growth properties in vitro. On the other hand, the cells became highly invasive in a skin reconstruction model and were now tumorigenic in mice, two attributes of VGP melanoma cells. Apparently, b3 integrin expression triggers the up-regulation of a variety of genes associated with invasion and tumor growth. The b3 integrin subunit is also up-regulated by tumor-infiltrating endothelial cells, and several clinical studies have been initiated to target b3 on endothelial cells, melanoma cells, or both for therapy.
FIGURE 42.1-12. Expression of the integrin subunit b1 of the α,β3 vitronectin receptor in melanocytic cells from different stages of tumor progression. Expression was tested with monoclonal antibodies on both frozen and fixed tissue sections. RGP, radial growth phase; VGP, vertical growth phase.

GROWTH FACTORS

With progression, melanoma cells show an increase in production of growth factors and cytokines (Fig. 42.1-13). Normal melanocytes are relatively inactive in growth factor production, even after stimulation. Nevus cells may produce bFGF and chemoattractive cytokines such as interleukin-8 or MCP-1 (monocyte chemoattractant protein-1). The strongest increase in growth factor expression, most notably a further increase in production of bFGF, and of expression of platelet-derived growth factor (PDGF) and transforming growth factor-b, can be found in VGP melanomas. Vascular endothelial growth factor (VEGF) can be triggered in VGP and metastatic cells by hypoxic growth conditions or by chemokines and growth factors. bFGF, PDGF, and VEGF act in concert with each other (see Fig. 42.1-13). bFGF is the most significant autocrine growth factor in melanoma. Blocking of bFGF production with antisense oligonucleotides stops melanoma cell proliferation. Despite its lack of a signal sequence, it can be released from cells through yet unknown mechanisms. When released from cells, bFGF binds to matrix proteins such as heparan sulfate proteoglycan, and it can then stimulate both fibroblasts and endothelial cells. bFGF is not only a survival factor and a growth stimulator for melanoma cells but also a motility factor. Its role in invasion comes from up-regulation of serine proteinases (urokinase and plasminogen activator), and metalloproteinases (gelatinase A and B). Potentially, a variety of other genes are activated as well, which still need to be identified.

FIGURE 42.1-13. Dynamic up-regulation of expression of growth factors and cytokines during melanoma progression. Whereas initial increases occur after the transition from normal melanocyte to nevus cells, most changes occur between the radial growth phase (RGP) and vertical growth phase (VGP) of primary melanomas. Metastatic cells generally show the highest production levels. bFGF, basic fibroblast growth factor; IL-8, interleukin-8; PDGF A + B, platelet-derived growth factor-a and-b; TGF-b, transforming growth factor-b; VEGF, vascular endothelial growth factor.

The biologically most significant stimulating growth factor for tumor-infiltrating fibroblasts is PDGF (Fig. 42.1-14). Melanoma cells produce both A and B isoforms. PDGF is not only mitogenic for fibroblasts, but it also induces the production of matrix proteins such as fibronectin and collagen, which provide the melanoma cells a scaffolding to which to adhere. Activated fibroblasts produce IGF-1, one of the most significant exogenous growth factors for melanoma cells because they do not produce it on their own. IGF-1 is highly mitogenic for melanoma cells but is also a motility factor and stimulates survival by stabilization of b-catenin. Melanoma cells are strong producers of chemoattractant proteins such as interleukin-8 (neutrophil attractant) or MCP-1 (monocyte attractant). In early malignant lesions, infiltrating neutrophils and monocytes may have a stimulatory role for tumors by producing angiogenic cytokines such as tumor necrosis factor-α or by inducing stroma formation. High production of these chemokines can lead to a strong infiltration of the inflammatory cells, which then kills the malignant cells. Thus, tumor cells must maintain a fine balance of chemokine production for biggest growth advantage. Inflammatory cell infiltrates diminish with metastasis apparently due to a breakdown of the gradient when the chemokine levels are increased to be elevated in serum.

FIGURE 42.1-14. Melanoma to stroma cross-talk. Production of growth factors and cytokines by melanoma cells that affect normal host cells in the environment. A positive feedback may also occur, when the stromal cells produce stimuli for the malignant cells. bFGF, basic fibroblast growth factor; IGF-1, insulin-like growth factor 1; IL-8, interleukin-8; MCP-1, monocyte chemoattractant protein-1; PDGF, platelet-derived growth factor; SF, scatter factor; TGF-b, transforming growth factor-b; TNF-a, tumor necrosis factor-a; VEGF, vascular endothelial growth factor.

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SECTION 42.2
Cutaneous Melanoma

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JOHN M. KIRKWOOD
JOHN C. Flickinger

INTRODUCTION

Cutaneous melanoma is a readily curable neoplasm, with 85% of diagnosed patients enjoying long-term survival following simple surgical excision. In its disseminated state, however, it is a devastating illness with limited effective treatment options prompting the evolution of efforts designed to identify metastatic disease early and to develop novel biologic therapies. The application of immunotherapy has so far provided benefit to only a small percentage of patients. In the majority of patients with metastatic disease, many in their youth, treatment with chemotherapy or biologic therapy is unsuccessful, and they ultimately succumb to their disease. In the United States, melanoma is diagnosed in at least 47,000 people a year, more than double the reported incidence in 1970. There has been a steady increase in melanoma incidence over the last century. In 1935, for example, the incidence of melanoma in the United States was approximately 1 in 100,000. Now, the incidence approaches 15 in 100,000. Although the basis for this increase is incompletely understood, the localized degradation of the ozone layer, the increase in solar exposure as a recreational activity, and the immigration of fair-skinned populations into equatorial latitudes each appears to play some causative role. Because of the effectiveness of early surgical treatment, the international community has focused extensively on preventive measures and screening efforts with some success. The diagnosis of melanoma occurs at thin and easily cured depths of invasion.

Large prospective, randomized, multicenter trials have answered some basic management questions, improved the care of melanoma patients, and expanded our understanding of the disease. However, many aspects of the treatment of melanoma, such as the therapeutic role of sentinel node dissection, isolated limb perfusion (ILP), and cytotoxic, biologic, or both therapies remain controversial and inconclusive. The field of melanoma is rapidly evolving with new techniques and therapeutics becoming standard care, even before substantial evidence of benefit exists. Not surprisingly, many physicians still find the enormous amount of conflicting data confusing. The changing framework of surgical, radiologic, and even pathologic assessment demands additional randomized, prospective, controlled trials to arrive at meaningful conclusions to serve as the foundation for future progress. Many of these are currently ongoing without results available at the time of preparation of this chapter.

Melanoma has been one of the most successful targets for immunotherapy, especially as biologic therapies. Interleukin-2 (IL-2) and interferon (IFN) therapy have now become routine and new peptide or protein vaccines as well as cellular and genetic therapies are being aggressively developed. Melanoma has attracted the attention of immunotherapists for many reasons. Spontaneous regression of melanoma associated with evidence supporting a specific cellular immune response occurs more frequently in patients with melanoma than with other solid tumors. The lack of effective alternatives has allowed the implementation and evolution of new treatments since, as yet, no systemic therapy has been shown to prolong survival significantly for treated cohorts in properly randomized studies. The identification of tumor rejection antigens recognized by CD4 and CD8 T cells as well as prognostically significant roles of antibody response to melanoma antigens has spawned a renaissance of immunotherapy. Occasional patients with advanced disease have been apparently cured by immunotherapy, surviving as long as 15 years without disease, something essentially unheard of for systemic therapy of metastases of any other major solid tumor.

The advances made in melanoma treatment have moved into other areas of oncology. Sentinel node biopsies are increasingly applied in the treatment of breast and...
colon cancer. The rapid advances in understanding melanocyte biology and the immunologic community’s interest in studying the disease has propelled the development of novel biologic therapies for other tumors. Melanoma trials have demonstrated the importance of multidisciplinary approaches in confronting the difficult problems faced in the treatment of cancer patients.

**EPIDEMIOLOGY**

In 1956, Lancaster observed an association between sun exposure and the development of melanoma. He described the relationship between disease incidence and latitude among people of European background. The closer to the equator, the greater the rate of melanoma mortality and incidence of melanoma in whites. 

Since 1973, the Surveillance, Epidemiology and End Results (SEER) program has sampled hospital-based cancer registries in 11 different regions accounting for a total of 10% of the U.S. population. Even with this surveillance system, underreporting is common as numerous thin melanomas are treated in an office setting and not reported in this hospital-based system. For example up to 19% of melanomas were not reported in the Massachusetts Cancer Registry. Using national surveys of community practices, some believe the incidence of melanoma in the United States to be 2.5 times SEER estimates.

In 2000, an estimated 7700 Americans will die of malignant melanoma. The incidence of melanoma in the white U.S. population has increased alarmingly from 1 per 100,000 in 1935 to 15 per 100,000 in 1996 (Fig. 42.2-1). In 2000, at least 47,000 cases are expected. However, the overall melanoma mortality has not increased nearly as dramatically over the last several decades (Fig. 42.2-2). Since 1973 the mortality only increased from 1.6 to 2.3 per 100,000 individuals in the 1996 survey (Fig. 42.2-3). During the same time period, overall 5-year survival in patients with melanoma has increased significantly, possibly due to the thinner depth at diagnosis of lesions and the adoption of improved surgical techniques (Fig. 42.2-4). The increase in melanoma mortality over the last 50 years has only recently shown signs of slowing. Some argue that the increased incidence of melanoma may be secondary to the detection of neoplasms that never would have acquired metastatic potential and were destined for regression. Others question whether a lead-time bias may account for the relative differences in rates of mortality and incidence changes. However, one analysis demonstrates rather clearly that the increase in incidence is only partly associated with earlier detection.

**FIGURE 42.2-1.** Age-adjusted incidence of melanoma in the United States from 1973 to 1996. The incidence has increased for the white population substantially and is rising faster in male than female subjects. This increase in melanoma incidence has not discernibly affected the black population. (Data from the Surveillance, Epidemiology and End Results program, 2000.)

**FIGURE 42.2-2.** The incidence of melanoma has increased disproportionately faster than mortality. This is at least in part due to the increase in superficial lesions diagnosed relative to thicker ones. (Data from the Surveillance, Epidemiology and End Results program, 2000.)

**FIGURE 42.2-3.** Age-adjusted U.S. mortality from melanoma from 1973 to 1996. Note the increasing mortality among white male subjects. (Data from the Surveillance, Epidemiology and End Results program, 2000.)

**FIGURE 42.2-4.** Five-year survival rates after the diagnosis of melanoma in the United States. These have improved from 1960, the earliest time period for which reliable data are available. The difference between the earliest and latest time periods are statistically significant. This increase in survival may be due to the increase in thinner melanomas compared with thicker ones. (Data from the Surveillance, Epidemiology and End Results program, 2000.)
Currently, melanoma is the sixth and seventh most common cancer in American men and women, respectively. The lifetime risk for developing melanoma among white Americans is 1 in 85. The risk of melanoma increases with age and the median age at diagnosis ranges between 45 and 55 years, but people of all ages are at risk. Melanoma commonly afflicts young, productive members of society. One-fourth of melanoma cases identified in the United States occurs in individuals before the age of 40. In women 20 to 35 years old, it is the second most common tumor after cervical cancer and in women aged 25 to 30 it is the leading source of cancer death. The years of productive life lost to melanoma exceed those of all other solid tumors. In the United States, melanoma is more common among higher socioeconomic classes, but the case fatality is highest among lower socioeconomic groups. The highest mortality from melanoma occurs in the state of Vermont and the lowest in Washington, DC. Although there is some increased distribution of melanoma mortality by latitude, other factors such as race are additionally important.

Racial differences in susceptibility are apparent, and melanoma is most prevalent among white, European populations. For example, the incidence of cutaneous melanoma among African Americans is approximately 1/20 that of the U.S. white population and behaves differently at presentation. Among African Americans, melanoma occurs predominantly in acral sites rather than in areas of pigmented integument. The worldwide incidence of melanoma varies considerably as well. Rates of 0.2 per 100,000 in parts of Japan to nearly 40 per 100,000 in Queensland have been reported. Despite these wide variations, the increase in overall melanoma incidence has increased globally. Worldwide, race is the predominant risk factor for the development of melanoma, with white populations having the highest risk and Asian the lowest risk.

In the United Kingdom, trends have been similar to those in the United States. The incidence and mortality of melanoma has increased 50% during the last decade. In Australia, where the incidence rates are the highest in the world, the increase in mortality is only now showing signs of slowing. However, mortality is increasing in many countries that had not previously reported increases such as France, Italy, Spain, and Hungary.

**RISK FACTORS, PREVENTION, AND SCREENING**

With the increase in melanoma incidence over the last 40 years, effective screening strategies have become increasingly important. The biologic and clinical behavior of melanoma supports the broad pursuit of screening programs. Effective screening for melanoma can be accomplished using noninvasive skin examinations since 93% of all primary melanomas are grossly visible. The remaining balance arises in mucosal, ocular, and unknown primary sites. Many primary cutaneous lesions have a distinct radial growth phase that may persist for months to years, giving physicians, family, and patients ample opportunity for early recognition and appropriate excision before progressive vertical tumor invasion. As melanomas less than 0.76 mm deep have a 10-year survival rate of more than 95%, the goal of screening is to identify lesions before the development of the so-called vertical growth phase associated with a worsened prognosis. Furthermore, screening for melanoma can be accomplished in just minutes by trained physicians, and diagnostic biopsies are relatively inexpensive and simple to perform in the office setting.

**RISK FACTORS FOR THE DEVELOPMENT OF MELANOMA IN POPULATIONS AT HIGHEST RISK FOR DEVELOPING MELANOMA**

Education and screening programs should especially focus on populations that are at high risk for the development of melanoma. Many known risk factors can be used by physicians to improve the efficiency of screening programs. Typical risk factors associated with carcinogenesis such as use of tobacco, alcohol, and estrogens do not affect the risk of melanoma. Instead, factors such as patient phenotype (hair, skin, and eye color), sun exposure, family history, and genetics play key roles.

**TABLE 42.2-1. Known Risk Factors for the Development of Melanoma**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Description</th>
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<tr>
<td>Education</td>
<td>Particularly focuses on populations that are at high risk for the development of melanoma. Many known risk factors can be used by physicians to improve the efficiency of screening programs. Typical risk factors associated with carcinogenesis such as use of tobacco, alcohol, and estrogens do not affect the risk of melanoma. Instead, factors such as patient phenotype (hair, skin, and eye color), sun exposure, family history, and genetics play key roles.</td>
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Common Nevi

The role of moles or melanocytic nevi in the genesis of melanoma has been suspected since Norris' first description of melanoma in the English language in 1857. Small, common nevi are pigmented lesions that are often raised, symmetric in outline, and delimited with discrete regular borders. Clearly, the number of moles is an important predictor of melanoma risk and is surprisingly genetically determined, with monozygous twins having almost identical mole counts in contrast with dizygotic twins. A threefold increase in melanoma risk is associated with the presence of five nevi more than 5 mm in diameter, or for those patients with more than 50 nevi greater than 2 mm in diameter. Atypical Nevi

Atypical melanocytic nevi that exhibit histopathologic features of dysplasia were initially described by Reimer et al. in the setting of familial melanoma. These lesions when clinically defined but not pathologically examined are classified as atypical nevi, and lesions defined histologically with specific architectural and cytologic features are called dysplastic nevus. An atypical nevus is defined clinically as a flat macule greater than 5 mm. At least two of the following features are also necessary to distinguish atypical nevi from banal nevi: variable pigmentation; irregular, asymmetric outline; and indistinct borders. Atypical lesions in patients without familial syndromes are more commonly found on sun-exposed areas.

The majority of melanoma is sporadic, and in this setting, the role of atypical nevi has become more clearly apparent. Atypical nevi among patients with sporadic melanoma are clinically indistinguishable from those of patients with familial melanoma. Atypical nevi occur in 2% to 7% of the white population and can be identified in 25% to 40% of patients with melanoma. Atypical nevi are a significant risk factor for the development of melanoma. Their presence may indicate a general instability in melanocyte growth. Estimating the risk incurred by the presence of atypical nevi has been difficult and ranges widely in the literature. The risk of new primary melanoma among individuals with atypical nevi was calculated according to the presence of a family or personal history of prior melanoma by Kraemer et al. This risk relates both to the presence of atypical nevi, melanoma, or both in the balance of the family of a given individual. In cases in which atypical nevi are isolated in an individual, the risk is lowest (27 times population risk). When atypical nevi are found in multiple members of a family or there is a history of melanoma in additional members of the family, the risk rises. Those patients with multiple family members exhibiting atypical nevi and a having a history of melanoma have the highest risk (148 times population risk). Unfortunately, the history of atypical nevi and of melanoma itself is often difficult to elicit. Crjnjs et al. reported that more than one-half of patients without an elicited history of melanoma or atypical nevi on initial family history are later found to have familial patterns of atypical nevi, melanoma, or both. Still the identification of atypical nevi even among skilled clinicians and pathologists is problematic, and some find the distinction from conventional nevi unconvincing.

The risk incurred by the presence of atypical nevi has been difficult to accurately establish. In one series, 716 patients with melanoma were compared with a group of matched controls. In the absence of atypical nevi, increased numbers of small nevi were associated with an approximately twofold elevated risk of melanoma, and increased numbers of both small and large nonatypical nevi were associated with a fourfold greater risk. The presence of a single clinically atypical nevus was associated with a twofold greater risk, while ten or more conferred a 12-fold greater risk of developing primary melanoma. Another smaller series suggested the risk of developing melanoma might be as high as 37 times greater in those individuals who have atypical nevi.

Congenital Nevi

Childhood melanomas are rare, but even infants have been reported with the disease, especially in association with giant congenital nevi. Patients with large congenital melanocytic nevi, those that appear at birth or during early childhood, are at high risk for developing melanomas. Large congenital nevi occur in 1 in 1000 to 1 in 20,000 newborns, and giant nevi involving large body surfaces (i.e., the entire trunk) occur in 1 in 500,000 newborns. Large congenital nevi that cover more than 5% of their total body surface area had a risk of developing melanoma 100-fold higher than the general population. No patients with congenital nevi that involved less than 4% of their total body surface area developed melanomas, but the study size could not exclude a small increase in risk. In another series of 46 patients with large congenital nevi, two individuals developed three melanomas arising from nevi after a mean of 7.3 years of routine screening. Although the study was small, it confirms that these patients are a high-risk population. Furthermore, detecting early melanoma in these lesions is difficult since malignant transformation usually evolves in the deeper layers of the nevus, and visible surface alterations are late manifestations.

Spitz Nevi

Spitz nevi are benign lesions that occur in children, and their importance stems from the difficulty in distinguishing them from melanoma. Whereas Spitz nevi are usually under 1 cm in diameter and may resemble verrucae or small hemangiomas, melanomas in children tend to be larger and quite striking clinically. All children diagnosed with melanoma or Spitz nevi should have the lesions reviewed by experienced pathologists. Parameters suggesting malignancy are age of diagnosis greater than 10 years, presence of ulceration, diameter greater than 1 cm, involvement of subcutaneous fat, and a mitotic activity of at least 6/mm.

Familial Atypical Nevus Syndromes

Melanoma is divisible into familial and sporadic patterns. Our understanding of the role of melanocytic precursor lesions in the genesis of melanoma has been clarified over the past 30 years based on pioneering studies involving familial clusters of patients with melanoma, many of whom are observed to have nevi exhibiting atypical features.

Patients with the dysplastic nevus syndrome, a disease of autosomal dominant inheritance with incomplete penetrance, are at increased risk for developing melanoma. In familial syndromes, the atypical moles of patients with the familial atypical mole-melanoma syndrome were named according to the initials of the probands (B-K nevus syndrome). These atypical nevi were also notable for their location on the skin of the trunk that was not necessarily sun-exposed. The presence of atypical neви identifies patients with a high risk of melanoma among family members with this syndrome. The risk conferred by the presence of multiple atypical nevi in such individuals approaches 100% by age 70. This risk is more complex than that of a discrete precursor lesion that progresses stepwise into malignancy. Although many melanomas have been identified to arise within atypical nevi, most occur in areas of skin that show neither gross nor histologic...
evidence of an antecedent atypical nevus lesion. This observation suggests that removal of atypical lesions is not akin to the reduction in carcinoma risk after resection of adenomatous polyps of the colon as most melanomas arise de novo. In patients with familial melanomas, it is clear that atypical nevi may serve as nonobligate precursors and markers of melanocyte dyscrasia.

Careful molecular, genetic, and pathologic studies in patients with familial atypical mole-melanoma syndrome may define the molecular basis of progression and identify markers for adequate surveillance and ultimate disease prevention. A few apparently important genetic mutations have already been identified in the cyclin-dependent kinase genes, some of which serve as inhibitors of cell-cycle progression. An enhanced incidence of melanoma is associated with a single mutation in CDK4 (12p14) as well as mutations in the CDKNA2 (9p21) and CDKN2B genes. There is a correlation between CDKNA2 mutations in family members with atypical nevus syndromes. Clinical findings associated with this germline mutation involve nevi in abnormal locations and abnormal numbers. These include nevi on the buttocks, nevi on the feet, total nevi greater than 100, and two or more atypical nevi. Germ line mutations of CDKNA2 have been identified in approximately 20% of melanoma-prone families, and CDK4 has been described in three families. Polymorphisms occurring in the melanocyte-stimulating hormone receptor predict skin coloration, risk of developing nevi, and independently and synergistically with p16 mutations, ultimately the development of melanoma. Although familial melanoma provides important insights into the disease, the number of cases of familial melanoma is limited. They represent an estimated 10% of patients with melanoma.

History of Previous Melanoma

A significant number of patients with a past history of melanoma develop a second, metastatic one. A study of 3310 patients from a prospective database with stage I and II melanoma showed that 3.4% developed a second primary melanoma. The 5- and 10-year risk of developing a second primary melanoma was 2.8% and 3.6%, respectively. Patients with a past history of melanoma should undergo frequent cutaneous examinations to screen for such metachronous lesions. Patients who are at especially high risk for metachronous lesions are those with atypical nevi or family history.

Transplant and Other Immunosuppressed Patients

Patients who have had a solid organ transplant are at increased risk for developing melanoma, and the risk is directly related to the degree of immunosuppression. Although the risk for nonmelanomatous cutaneous cancer is estimated at approximately 65-fold that of the general population, the risk for developing melanoma is increased by a more modest threefold. Children who have had a renal transplantation demonstrate higher benign nevus counts than controls, and the duration and degree of immunosuppression correlates positively with these counts. Such nevi are found most commonly on the back and acral sites. Interestingly, in normal adults, nevus counts increase in number, peaking in the early 20s and then progressively decreasing with time. Children with genetically determined immunodeficiencies and who have a three- to sixfold risk of developing melanoma. Of the few patients reported to have melano melanoma and human immunodeficiency virus in the literature, approximately one-third had metastatic disease at the time of initial examination, and systemic symptoms correlate with decreased CD4+ cell counts. Melanomas among patients with human immunodeficiency virus infection are often atypical in appearance, multiple, and metastatic. The number of nevi less than 5 mm in diameter was found to be greater in patients with human immunodeficiency virus than in the general population. Immunodeficiency may promote or permit the development of nevi and raises the question of whether sun-induced immunosuppression plays a role in the development of nevi. The development of melanoma may relate directly to the suppression of cellular immunity. Melanoma in immunosuppressed patients may evolve from precursor nevi that are unable to elicit cellular immune recognition. The detection of dysplastic nevi offers an opportunity to identify those immunosuppressed patients who are at greatest risk of melanoma.

Phenotypic, Solar, and Other Risk Factors

Risk factors for melanoma apart from the presence of acquired and congenital melanocytic nevi include easily identifiable phenotypic characteristics of pigmentation such as pale skin, poor tanning ability, light hair and eyes, and the presence of freckles. Compared with individuals with brown and black hair, the relative risk for developing melanoma for those with blonde and red hair is 1.8 and 2.4, respectively. Individuals with blue eyes have a risk 1.2 times that of individuals with brown eyes. Episodic exposure to intense sunlight and a history of blistering sunburns, especially in childhood (ages 10 to 19), is strongly associated with the development of melanoma. Childhood sunburn with blistering is also associated with increased numbers of atypical nevi. Unlike other nonmelanoma skin cancers, recreational intermittent exposure to sunlight is more strongly associated with risk of melanoma than lifetime continuous exposure.

One might expect a much higher incidence of melanoma in patients with albinism since they have minimal natural solar protection and the development of melanoma is dependent on the presence of melanocytes, not on melanin. However, only 23 cases of melanoma have been documented in the literature in patients with oculocutaneous albinism. They were all, of course, amelanotic. Patients with xeroderma pigmentosum are another group that have little natural solar protection; however, 5% of patients develop melanoma at a median age of 19 years. They are a rare high-risk subgroup that needs close screening for cutaneous malignancies.

Role of Pregnancy and Estrogens in Melanoma

As pregnancy is associated with an increase in melanocyte-stimulating hormone levels and an increase in pigmentation in some patients, the theoretical concern for stimulation of melanoma has prompted concern. Although various case reports initially suggested an adverse outcome in pregnant patients with melanoma, six well-controlled studies have evaluated the effect pregnancy has on survival. No difference in survival between patients diagnosed during pregnancy and controls has been substantiated. Interestingly, one study implied that prior pregnancy was in fact protective by demonstrating improved survival in women under 50 who had more than five children before the diagnosis of melanoma. Nether is there evidence that pregnancy occurring after the diagnosis of melanoma worsens prognosis. In women with a history of melanoma, it may be reasonable to suggest waiting 2 years after initial diagnosis before becoming pregnant since two-thirds of recurrences occur within this time period. However, the stage and depth at diagnosis and the age and desires of the mother factor heavily into these decisions. There is no evidence that estrogen use increases the risk of melanoma. Much of the confusion concerning estrogens results from the expression of estrogen receptors on some melanomas. The presence or absence of these receptors neither predicts prognosis nor hormone responsiveness. Tamoxifen has been suggested to have effects on melanoma; however, its actions may be indirect, through the potentiation of the cytotoxic chemotherapy or enhancing natural killer (NK) function, rather than directly affecting melanoma. More recent randomized controlled trials failed to corroborate a significant benefit of tamoxifen with dacarbazine or multidrug therapy. Well-designed epidemiologic studies have not shown an increased rate of melanoma in patients who have used exogenous estrogens. No studies have specifically examined the risks of hormonal replacement therapy in postmenopausal women with melanoma, but no data exist to suggest that hormonal replacement therapy is harmful. The well-characterized beneficial effects of hormonal replacement therapy likely outweigh any theoretical, unsubstantiated risks of estrogens.

DIAGNOSIS: CHARACTERISTICS OF MELANOMA

Identification of features that may mark lesions suspicious for melanoma can be simply recalled using the mnemonic ABCDE. A stands for asymmetry, B for borders that are irregular or diffuse, C for color variegation, D for diameter more than 5 mm, and E signifies enlargement or evolution. Bleeding and ulceration occurs in 10% of localized melanomas and 54% of late melanomas and is a poor prognostic finding.

Morphotypes

Although specific morphotypes of melanoma have been used for prognostic information, the Breslow depth of the lesion and presence or absence of ulceration are the most significant predictors of biologic behavior of the primary lesion. Morphology does not predict prognosis independently of these well-defined risk factors. The classic morphotypes now serve as descriptive tools that aid in the recognition of these lesions and as historic references (Fig. 42.2-8, Fig. 42.2-9 Fig. 42.2-10 Fig. 42.2-11, and Fig. 42.2-12). Physicians should recognize that many less dangerous (and more common) skin lesions may exhibit features similar to melanoma such as...
seborrheic keratosis, pigmented basal cell cancer, solar lentigines, and atypical nevi.

FIGURE 42.2-8. Lentigo maligna melanoma. These lesions commonly occur on the face in older patients. These lesions may require considerable planning for reconstruction.

FIGURE 42.2-9. Nodular melanoma. The second most common melanoma morphotype. It is associated with the so-called vertical growth phase, manifesting a more aggressive biologic phenotype and worsened prognosis.

FIGURE 42.2-10. Superficial spreading melanoma. This typical example exemplifies the most common melanoma morphotype. Note the irregular borders, large size, color variegation, and asymmetry. Radial growth at the dermal-epidermal junction for prolonged periods is associated with a better prognosis.

FIGURE 42.2-11. Subungual melanoma. All nail bed lesions that have grown or remained unchanged over 4 to 6 weeks should undergo an incisional biopsy and removal of the nail.

FIGURE 42.2-12. Acral lentiginous melanoma. These lesions, located in the extremity, are more common in Asians and African Americans.

Superficial spreading melanoma presents as an asymptomatic, flat macule or barely raised plaque with color variations that may include shades of black and brown. Areas of regression (depigmentation) are common. It is the most common growth pattern and accounts for 60% to 70% of all melanomas. These lesions may exist for years before a rapid growth phase is identified. Notching and scalloping are common, with enlargement during the radial growth phase of melanoma. They can
occur at any site, although they most commonly can be seen on the lower extremities of women and on the trunk of men.²⁷

Nodular melanoma typically presents as a uniform lesion that is dark black-blue or bluish-red, although 5% are amelanotic.²⁷ This is the second most common morphtype, occurring in 15% to 30% of patients, and usually exhibits a more rapid onset.²⁷ Nodular melanomas are associated with deeper Breslow depths because they quickly establish a vertical growth phase. Most commonly, nodular melanomas are located on the trunk or head and neck and are observed in men more frequently than women.

Lentigo maligna melanomas (LMM) are typically located on the face and are generally large, flat lesions that are tan colored, with differing shades of brown. Rarely, LMM can be amelanotic. Up to one-half of lentigo maligna (LM), a precursor lesion that is characterized by atypical melanocytic proliferation, degenerate into melanoma over a period of many years. The diagnosis requires the presence of sun-related changes in both the epidermis and dermis. They are found in approximately 5% of patients with melanoma.²⁷

Acral lentigious melanomas are uncommon and typically occur on the palms, soles, or beneath the nail (subungual). However, not all lesions in these locations are acral lentigious melanomas. Melanoma in the hands or feet account for less than 5% of all melanomas, but they are much more common in dark-complexioned individuals.²⁷ These lesions tend to present late and thus are associated with a poorer prognosis. They represent up to 70% of melanomas in African Americans and up to 46% in Asians.²⁷ They are usually tan, brown to black macular lesions with variegation in color and an irregular border.²⁷ In a Japanese series of 62 plantar melanomas, 62% were acral lentigious, 3% were superficial spreading, and 14% were nodular. The lesions most commonly affected the heel. Acral melanomas are strongly associated with high total body nevus counts [relative risk (RR) = 6.3] and with nevi on the soles. There is also an association with penetrating injuries to the feet or hands (RR = 5.0) and heavy exposure to agricultural chemicals (RR = 3.6).²⁷ Subungual melanomas account for only 1% to 3% of all melanomas. They commonly are diagnosed late because of their close resemblance to many benign lesions of the nail. If a nail bed lesion has not changed significantly in 4 to 6 weeks, a biopsy should be performed, accompanied by removal of the nail. Some clinical parameters that should arouse suspicion of subungual melanoma are lesions occurring in patients greater than 50 years old, a width greater than 3 mm with variegated borders, extension of pigment into the lateral or proximal nail fold, and lesions occurring in individuals of African American, Asian, or Native American ancestry.²⁷ Seventy percent occur on the great toe or thumb. These tumors are associated with a 5-, 10-, and 20-year median survival of 59%, 44%, and 29%, respectively. One-half have associated nail destruction and 70% ulcerate. Twenty-five percent present with metastases and 74% are greater than 1.5 mm thick.²⁷

Desmoplastic melanoma is a rare and locally aggressive variant of malignant melanoma that is difficult to diagnose clinically and microscopically. It represents approximately 1.7% of melanomas. The majority of these tumors occur on the head and neck of elderly patients and one-half are amelanotic.²⁷ Desmoplastic tumors are aggressive locally and behave more like mesenchymal neoplasms. These tumors stain intensely with S-100. The most reliable and characteristic histologic features of an early lesion of desmoplastic melanoma are aggregates of lymphocytes, tumor cell cytologic atypia, stromal myxoid change, and poor circumscription of the dermal infiltrate.²⁷ The risk of local recurrence increases when neurotropism is present.²⁷

PREVENTION

With the assumption that the prime modifiable risk factor in the development of melanoma is UV radiation, prevention strategies focus on reducing the public's excessive exposure to sunlight. The American Cancer Society and the Skin Cancer Foundation recommend that the general population employ "sun-smart" practices. This includes the avoidance of direct midday sun exposure between the hours of 10 a.m. and 4 p.m. and the use of sunscreens, protective clothing, and appropriate shade (e.g., sun umbrellas). The increased risk of melanoma incurred through sun exposure is strongly associated with blistering sunburns between the ages of 10 and 19; thus, special attention should be focused on teaching children these sun-smart practices. While the use of sunscreens of sun protection factor (SPF) of at least 15 is recommended, sunscreens have been largely shown to reduce the nonmelanoma skin cancer incidence. There is much controversy regarding the effectiveness of sunscreen for prevention of melanoma, with the epidemiologic data inconclusive at present.²⁷

Sunscreens and Sunlight

Claims of a reduction in melanoma risk from the use of sunscreens have been controversial and difficult to substantiate. In fact, most studies show an increased risk for the development of melanoma with the use of sunscreens, probably because of their ability to delay or avoid sunburn episodes, which may allow prolonged exposure to unfiltered UV radiation [Table 42.2-2]. Many criticize these epidemiologic studies, for many confounding factors may contribute to these negative results. Individuals who sunbathe frequently are more likely to use sunscreens. In addition, many studies had focused on older preparations that were either less effective at blocking UVB light (low SPF) or contained psoralens, potent tanning activators. People with a poor tanning ability who have used psoralen sunscreen in the past have a risk of developing melanoma 4.5 times that of regular sunscreen users.²⁷ The risk reduction from newer, high SPF sunscreens is difficult to assess due to the long latency from sun exposure to the development of melanoma.²⁷ However, increases in benign nevus counts are clearly associated with the use of sunscreens. In a large, randomized, placebo-controlled study of more than 600 European children, the number of nevi increased in those who used sunscreens even when controlling for factors such as skin type and eye color.²⁷ A theoretical basis exists for the lack of efficacy of sunscreens. Most sunscreens offer greater protection from UVB (290 nm) than UVA (375 nm) radiation, thereby reducing the risk of sunburn while not blocking UVA radiation, which efficiently induces tanning. However, UVA penetrates more deeply and causes more DNA damage than UVB. Although the ozone layer filters UVA more effectively than UVB light, approximately 1000 times more UVA than UVB bathes the earth's surface.²⁷ Thus, the depletion of the ozone layer may significantly affect the incidence of melanoma. An estimated 1% increase in melanoma incidence occurs with each percentage decrease in the ozone layer.²⁷

Several studies show that the excessive use of tanning salons is associated with an increased risk of developing melanoma. No study demonstrates that tanning is protective against subsequent sunburns or melanoma.²⁷²⁸²⁹ Long-term use of tanning salons is associated with premature skin aging, cataract development, and nonmelanoma skin cancers. Prevention strategies should discourage the use of tanning salons.

Self-Examination

Patients at increased risk of melanoma should be informed how to perform regular self-examinations of their skin. Most patients who develop melanoma would have alerted their physicians much earlier if they had used a simple checklist that helps identify high-risk lesions.²⁷ Self-examination is currently underused even in high-risk populations. Only one in five patients with melanoma practices self-screening and only 6% of patients follow recommendations for self-examination, sun protection, and yearly professional examinations.²⁷²⁸ Screening by trained physicians currently cannot be replaced by self-screening until national efforts at public education are more broadly undertaken.

Excision of Nevi

### TABLE 42.2-2. Relationship between Melanoma and Sunscreen Use: Case-Controlled Studies

<table>
<thead>
<tr>
<th>Sunscreen Use</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regular</td>
<td>0.9</td>
</tr>
<tr>
<td>Infrequent</td>
<td>1.3</td>
</tr>
<tr>
<td>Never</td>
<td>1.5</td>
</tr>
<tr>
<td>High SPF</td>
<td>0.6</td>
</tr>
<tr>
<td>SPF &lt; 15</td>
<td>1.1</td>
</tr>
<tr>
<td>SPF &gt; 15</td>
<td>1.2</td>
</tr>
</tbody>
</table>

- Regular: sunscreens used regularly with SPF > 15
- Infrequent: sunscreens used occasionally with SPF ≤ 15
- Never: no sunscreen use
- High SPF: sunscreen use with SPF > 30
- SPF < 15: sunscreen use with SPF ≤ 30
- SPF > 15: sunscreen use with SPF > 30

- Italics indicate statistically significant results.

This table shows the relationship between sunscreen use and the risk of melanoma incidence.
Evidence supports the removal of atypical nevi in patients with a prior history of melanoma as a preventative strategy. The excision of atypical lesions decreases the expected incidence of melanomas in high-risk cohorts, but it is unclear whether a broader population-based strategy supporting the excision of these nevi can be extrapolated. Wholesale removal of unsuspicous nevi should be condemned as a surgical practice. Indiscriminant excisions are associated with unnecessary scarring and little effect on the development of melanoma. Most melanomas, even in patients with familial atypical mole-melanoma syndrome, arise de novo; thus, the excision of all atypical lesions may not eliminate the risk of developing melanoma. Large congenital nevi should be excised if feasible, and frequent screening should be performed in these patients until excision is performed. If the lesion is too large for excision, surgery may be limited to biopsies of the most worrisome sites in combination with observation and photographic documentation. Dermabrasion and other superficial excisions may not decrease the risk of developing melanoma and are not recommended.

SCREENING

Prevention and screening for melanoma are reasonable objectives to restrain the rising incidence of this silent epidemic. Cancer screening for melanoma fulfills many of the requirements necessary for effectiveness. First, early detection appears to result in improved outcomes. Second, the screening process is easy to perform by primary care physicians, and third, the screening is cost effective.

Efficacy

Randomized trials to determine efficacy and cost effectiveness of screening programs would require thousands of people and prolonged (greater than 10-year) follow-up; however, there is sufficient evidence to assume the validity and efficacy of current screening programs, especially in high-risk populations. Although the true effectiveness of screening programs can only be determined by noting an increased survival in screened populations, many reports demonstrate that thinner lesions are found in screened compared with unscreened cohorts. Since the thickness of the melanoma correlates linearly with survival in stage I and II patients, screening programs can measure their effectiveness through this intermediate end-point instead of waiting 10 years (or more) for survival data. Numerous studies have been published from Australia, Europe, and the United States demonstrating the effectiveness of screening programs. Many have focused on high-risk populations in order to attain a high number of events with much fewer patients.

Many of the published screening studies tested high-risk populations with either a strong family history of melanoma, a previous personal history of melanoma, or a diagnosis of the dysplastic nevus syndrome. In one series of 555 high-risk patients, screening reduced the average thickness of diagnosed melanomas to 0.52 mm compared with an average tumor thickness of 1.44 mm before the screening program was instituted. None of the 138 patients diagnosed with melanoma on screening developed metastatic disease. In another series from the Netherlands, in which high-risk patients were screened, the thickness of primary lesions decreased from 1.75 mm before the screening process to 0.6 mm at the start of the screening process and then to 0.54 mm during routine follow-up.

In Australia, the incidence of melanoma is the highest in the world due to an equatorial climate, a fair-skinned immigrant population, and localized depletion of the ozone layer. The decrease in average tumor Breslow depth in Australia has been attributed to extensive screening. In 1960 the average thickness of melanoma was greater than 2.5 mm. By 1986, after the establishment of a comprehensive screening program in the 1960s, the mean tumor thickness dropped to 0.80 mm. In France, a unique situation exists as occupational medicine specialists examine the entire working population yearly. In a study involving 65,000 people, 273 patients examined by occupational medicine specialists were thought to have suspicious lesions. Of these patients only 172 followed up with their primary care physicians and five melanomas were found. This translates to an incidence of 7.7 per 100,000, close to the 9 per 100,000 found in the general French population.

The American Academy of Dermatology has provided more than 1 million free skin cancer screenings from 1985 to 1997. Of all the biopsies performed for suspicious lesions, 17% were found to be melanomas on histology. More than 90% of histologically confirmed melanomas were less than 1.5 mm thick, and the median thickness of all melanomas was 0.30 mm. The 8.3% of cases with advanced melanoma is a lower proportion than that reported by the 1990 SEER registry. The rate of thickest lesions (greater than 4 mm) and late-stage melanomas among all participants was 2.83 per 100,000 population. Thirty-nine percent of screened patients who had melanoma claimed they would not have sought examination otherwise and more than 30% of these melanomas were located on areas not readily visible on self-examination.

Examination

Although dermatologists have superior accuracy compared with nondermatologists in the diagnosis of melanoma and dysplastic nevi, there are too few dermatologists for all routine screening. Dermatologists are generally more qualified in identifying these lesions. Screening for melanoma by a dermatologist has a sensitivity and positive predictive value of 89% to 97% and 17% to 75%, respectively. The use of epiluminescence microscopy by an experienced dermatologist can greatly increase the sensitivity and specificity of the examination. Further, only 12% of nondermatologists were able to correctly identify five out of six melanomas, whereas 69% of dermatologists did. A viable health strategy for reducing the mortality of melanoma involves educating primary care providers to incorporate skin examinations as part of their routine physical examinations. With education, primary care physicians should successfully incorporate skin screenings in their physical examinations as they have with breast examinations, digital examinations, and fecal occult blood testing.

Screening examinations are quick, painless, inexpensive and readily accepted by patients. Complete examination of the skin should be performed systematically, with the patient fully undressed. Care should be taken not to ignore the scalp, nails, palms, soles, ears, and beneath the breasts. Since most melanomas occur on the trunk and lower extremities in women and on the trunk and proximal upper extremities in men, these areas should be carefully examined. Lesions of the perineum are uncommon and may be excluded unless the patient has a specific lesion in question. Problems do exist with screening protocols as some melanomas may have an uncharacteristically benign appearance and a radial growth phase shorter than the screening interval.

Cost-Effectiveness

The cost of screening includes practitioner time spent with patients and the cost of biopsy and pathology. Since the ratio of positive to negative biopsy results ranges from 1:70 to 1:250, the number of biopsies subsequent to mass screenings may be considerable. In a cost-effectiveness model of screening high-risk patients, $29,000 would be spent per year of life saved. This is less than what is currently spent on prostate-specific antigen testing, Pap smears, or annual mammography.

STAGING OF MELANOMA

The staging of cutaneous melanoma involves segregation by local, regional, or distant disease and strongly correlates with survival (Fig. 42.2-13). The vast majority of patients who present with primary melanoma have localized tumors, and for this reason stage I and II have been used to designate early (low-risk) and later (intermediate-risk) tumors, even though both represent localized disease. The features of melanoma that influence the risk of relapse are encapsulated in current and proposed staging systems of the American Joint Committee on Cancer (AJCC) (Table 42.2-3 and Table 42.2-4). The last formal edition of this system (1992) is currently in revision, so the features of the prior system will be contrasted to those of the proposed new system of 2000. In both systems, distant metastases (M1) define stage IV disease, whereas regional lymph node metastases (N1 to N3) define stage III disease and are cardinal prognostic variables for patients with melanoma of the skin. Most patients present with neither distant nor regional disease apparent, so the features of local prognostic significance assume a predominant role in defining the prospect for relapse-free survival and overall survival in patients with melanoma.
FIGURE 42.2-13. Melanoma survival correlates strongly with stage. Fifteen-year survival results are shown for over 4000 melanoma patients. (From Kelcham AS, Balch CM. Classification and staging systems. In: Balch CM, Milton GW, eds. Cutaneous melanoma: clinical management and treatment results worldwide. Philadelphia: JB Lippincott, 1985:55, with permission.)

TABLE 42.2-3. American Joint Committee on Cancer Tumor (T), Node (N), Metastasis (M) Classification System for Melanoma

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>II</td>
<td>T1</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>III</td>
<td>T1</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td>IV</td>
<td>T1</td>
<td>N3</td>
<td>M0</td>
</tr>
</tbody>
</table>

TABLE 42.2-4. American Joint Committee on Cancer Tumor (T), Node (N), Metastasis (M) Stage Grouping for Cutaneous Melanoma

STAGE I MELANOMA

The microstage or Breslow depth and presence or absence of ulceration are the most important variables in those without regional or distant metastases. Patients with localized disease apparent only at the primary site make up by far the largest category of those presenting with melanoma. The division between stages I and II has been arbitrary, in part reflecting an effort to separate low-risk from intermediate-risk disease. The staging system adopted by the AJCC in 1992 moved from a dependence on prognostic assessment based on the levels of skin through which a tumor had penetrated, to a duality of thickness measured in millimeters according to Breslow, and levels according to Clark. The role of the Breslow thickness has been recognized as more predictive of prognosis. A secondary importance of the Clark level, especially in thinner tumors, has been identified. The Breslow depth is the primary predictor of prognosis, even when it predicts a more favorable prognosis than the level of invasion. Although the AJCC 1992 system allowed for either thickness or level (whichever was worse) to be taken as the basis for risk assessment, thickness appears to be considerably more reproducible in predicting prognosis than the Clark level. Thus, in the proposed new classification system, stage I and II melanoma prognostic assessment will be based on Breslow thickness and ulceration. The Clark level of the primary lesion enters multivariate analyses only as a secondary feature when the Breslow depth is less than 1 mm. Patients with T1 lesions and a Clark stage of IV or more have a 10% chance of nodal disease compared with only a 2% risk in those with T1 lesions and Clark stages less than IV. Because of the importance of Clark stage in thin tumors, lesions less than 1 mm in Breslow depth that are level IV or V are designated as T1b lesions.

Breslow Depth

The Breslow depth of a primary melanoma is the cardinal prognostic factor for clinically localized disease (stages I and II). The risk of relapse and death due to melanoma rises incrementally with each millimeter of depth (Breslow thickness) for primary melanoma, and the relationship between primary tumor thickness and the relapse rate is linear between 1 and 6 mm (Fig. 42.2-14). Beyond 6 mm of depth, the incremental risk of relapse and death for each millimeter of invasion is less than for lesions below that thickness.

FIGURE 42.2-14. The relationship between primary melanoma thickness and survival is nearly a linear function. The American Joint Committee on Cancer breakpoints between T stages is not based on defined biologic mortality differences, but for convenience and general prognostic grouping.
Melanoma thickness is therefore a continuous variable, in which there are no natural breakpoints, so the choice of dichotomization between stages I and II (and within stage I between substage A and substage B, or in stage II between substages A and B) is somewhat arbitrary. The designation of T1/stage IA (less than 0.76 mm), T2/stage IB (from 0.77 to 1.50 mm), T3/stage IIA (1.51 to 4.00 mm), and T4/stage IIB (greater than 4.0 mm) has been based in part on data from early series in which it appeared that the regional lymph node dissemination is increased by 10% compared with nonulcerated cases. Adding back the depth of an ulcer crater does not correct for the decrease in survival associated with ulceration, and the width of ulceration is more significant than the depth in predicting prognosis. The AJCC revision of melanoma staging for 2000 proposes the incorporation of ulceration as the major independent factor for prognostic assessment of stage I and II melanomas after the Breslow depth. The suffix a will indicate nonulcerated and b ulcerated primary melanoma.

Morphotype

The morphotype of the primary melanoma was used to predict prognosis. Nodular melanomas have a higher risk and shorter latency than superficial spreading melanomas because of their tendency toward a vertical growth pattern. The less frequent acral lentiginous melanoma similarly has been associated with increased risk compared with that of LMM. The latter morphotype is distinctive in its occurrence at a median age of more than decade later than that of the more common superficial spreading and nodular, as well as acral lentigious, morphotypes. The site of origin is also distinctive for LMM, which is typically found on the chronically sun-exposed areas of the head and neck, and for acral lentigious melanoma. These descriptive terms, although helpful in pattern recognition for clinicians, are less frequently used based on more modern staging systems.

Lymphoid and Dendritic Cell Host Response

Infiltration of the primary melanoma site by lymphocytes has been correlated with an improved outcome in studies performed over the past several decades. The Boston Collaborative Melanoma Study has demonstrated a more favorable prognosis of melanomas infiltrated densely with lymphocytes. The immunologic target of the lymphocyte response frequently observed in primary melanomas, and less often in metastatic sites of disease, has led to intense efforts with each of the emerging therapeutic tools of immunology. There has also been a correlation with the infiltration of other immune mediators and prognosis. Dendritic cells (DC), potent antigen-presenting cells, are also found in melanoma specimens, and DC infiltrate is inversely related to tumor thickness in melanoma. DCs mediate several biologic roles including regulation of angiogenesis and the active uptake of apoptotic tumor, processing of nominal antigens and migration to local nodal basins where a specific T-cell response is capable of being stimulated.

Regression

Historically, lesion regression characterized by the histologic presence of fibrosis and centralzation depigmentation has been suggested as an ominous sign. Many interpret regression as an invalidation of the Breslow depth because the tumor may have once extended deeper than measured at the time of excision. Thus, actual prognosis would be worse than predicted since the patient would be understaged. The studies of the University of Alabama and Sydney Melanoma Unit have not borne this out; in fact, complete regression of primary as well as metastatic lesions has been well documented, and rarely, spontaneous cures occur. Melanomas with undetermined primary sites presumably originate from regressed lesions. These patients have the same if not a slightly better prognosis than equally matched patients whose primary is known. Other evidence suggests that melanoma regression is not a negative prognostic factor. The use of a model that incorporated four variables (i.e., site of origin, gender, age, and Breslow thickness) has been reported; the prognostic variables increased prediction of survival by up to 50%. In patients with positive regional lymph nodes, the site of origin, gender of the patient, and age become unimportant in predicting prognosis.

Site of Origin

Patients with melanoma of acral, subungual, and head and neck sites have a worse prognosis than those with melanoma arising on the extremities. Multivariate analysis from one mature series from the University of Pennsylvania (n = 488) and a multicenter German database (n = 5246) have shown that the site of tumor origin is an independent and significant prognostic variable. In general, patients with primary lesions of the extremities have a significantly better prognosis than those with primary lesions of the trunk and head. Lesions of the upper and lower extremities do not differ in prognosis, but those found distally on the hands and feet fare worse than those with more proximal lesions. The use of a model that incorporated four variables (i.e., site of origin, gender, age, and Breslow thickness) has been reported, the prognostic variables increased prediction of survival by up to 50%. In patients with positive regional lymph nodes, the site of origin, gender, and age become unimportant in predicting prognosis.

STAGE II

A large and relatively heterogeneous population is the group previously designated as stage II, composed of stage IIA (T3) melanomas between 1.5 and 4.0 mm in depth, and stage IIB (T4) melanomas of more than 4 mm in depth. Relapse risk for this group lies between 10% and 40% and is directly related to the primary Breslow depth. Beyond the Breslow depth in this category, the most consistent and powerful prognostic factor identified over the past 20 years has been the presence or absence of ulceration. The presence of ulceration is significantly associated with an increase in the likelihood of nodal metastasis and reduces the prognosis for relapse-free survival by nearly 10% for any given Breslow depth.

Elective lymph node dissection (ELND) has previously been the only available means to demonstrate the presence of regional lymph node involvement and proved to be positive in 20% of these patients with lesions greater than 1 mm in depth. The development of more precise techniques of lymph node mapping has significantly affected the ability to predict prognoses for this group of patients. Many large adjuvant trials have been conducted in patients for whom the pathologic status of the regional draining lymph nodes has either not been assessed at all, or in whom this has only been assessed using anatomically guided elective regional lymphadenectomy, not isotope- or dye-guided sentinel lymph node (SLN) mapping. Thus, the surgical and pathologic assessment of melanoma at the primary site has now been coupled with techniques that have demonstrated improved precision at the regional lymph node basin(s). Consequently, the assessment of relapse and mortality risk for primary melanoma patients with intermediate risk is in substantial flux. In patients for whom SLN mapping is not feasible, the previously defined risk algorithms and factors are still of use. For those in whom SLN mapping is appropriately performed and whose results are negative, the prognosis appears to be substantially improved. The series of patients that have been assessed by SLN mapping have to date less than 5 years of median follow-up. The limited follow-up in these series qualifies interpretation of the data at this time, since it is possible that the identification of nodal disease using refined pathologic, immunohistochemical, and in some cases, molecular [reverse transcriptase-polymerase chain reaction (RT-PCR)] assays for melanosomal antigens such as tyrosinase may simply have improved lead time for the diagnosis of metastatic disease.

STAGE III

In patients with nodal disease, only three variables independently affect overall prognosis: the number of lymph nodes, the presence of ulceration of the primary tumor, and whether the nodal disease is macroscopic or microscopic. In patients with macroscopic disease, more than one positive lymph node, and an ulcerated primary lesion, the 5-year survival is only 16%. In patients with only one microscopically positive node and without ulceration in the primary tumor, the overall 5-year survival is 71%. This large difference in survival demonstrates the inadequacies of previous staging systems and the heterogeneity of supposedly matched patients in previous clinical trials.
Sentinel Lymph Node Mapping

The detection of lymph node metastases previously relied on crude clinical or regional ELND, which has not improved survival in several large randomized controlled trials. Currently, SLN mapping and selective lymphadenectomy directed by isotopic lymphoscintigraphy or blue dye lymphography has been shown to identify lymph node metastases more precisely and with less surgical morbidity, hospitalization time, and cost than elective dissection. All of the observations reported from series attempting to refine the prognostic assessment of patients based on Breslow depth and Clark’s level, with or without ulceration, has been in many ways supplanted by the availability of pathologic assessment of SLNs mapped using isotopic and dye techniques. A study of 580 patients whose sentinel draining lymph nodes localized using dye and scintigraphic techniques (e.g., SLN), and found to be pathologically negative has demonstrated that the status of the SLN is the single most powerful prognostic factor after Breslow depth (P < 0.0001 for each). Sentinel node status remains a significant prognostic factor in multivariate analyses of disease-specific survival in this model after adjustment for other previously identified prognostic factors. Once SLN status is accounted for, a number of factors that have previously been considered as independent prognostic factors lose their significance. The primary site of origin, age of the patient, and sex of the patient are all nonsignificant after incorporation of SLN status in a prognostic model for outcome of stage I and II patients. The multidisciplinary procedure of SLN evaluation requires attention to radiology and meticulous pathology as well as expert surgery for optimal outcome. Whether the information attained from SLN biopsy allows treatment decisions that alter outcome remains a question currently being addressed in a number of prospective trials. Even though it has been widely adopted by most centers in the United States, it is less widely applied elsewhere and the results of seminal prospective studies should be available within the next few years to assess its utility in improving patient outcome. It is conceivable that strategies to quantitatively identify tumor in the peripheral blood using molecular analysis or serologic assays may supplant this surgical staging procedure.

Number of Nodes

Regional lymph node involvement defined stage III in the AJCC system in 1992 as it does currently. The size of involved lymph nodes has previously served as the basis for characterization of patients within stage III (TNN1, N2, N3). Multiple studies have been performed using Cox regression analysis to identify the most important predictors of outcome for patients with stage III disease. In all of these studies, the number of lymph nodes found to be involved with tumor (whether microscopic or macroscopic) has been the cardinal factor identified (Fig. 42.2-15). The advent of sentinel node mapping has increased the precision with which regional lymph node dissemination can be identified, but even in studies that have patients evaluated by SLN mapping, the number of involved lymph nodes has been a significant prognostic factor. The prognosis for patients with one involved regional lymph node is significantly better than for patients with two or more involved regional lymph nodes. The recommended AJCC 2000 staging system will adopt the number of nodes involved with tumor as the principal basis for prognostic assessment of patients with regional disease. N1 will signify one node involved, N2 will signify two to three nodes involved, and N3 will signify four or more nodes involved with tumor. N3 includes matted nodes and ulcerated melanoma with any number of metastatic lymph nodes. A secondary criterion for classification of patients with nodal metastatic disease is that of nodal bulk of disease (microscopic versus macroscopic). The former is invisible to the gross surgical or pathologic evaluation, nonpalpable, and designated (a). The N1(a)/N2(a)/N3(a) category of microscopic involvement represent a significant and increasing fraction of patients identified through sentinel node mapping procedures, for whom the prognosis appears to be improved. Previous data suggested that this subgroup has a more favorable prognosis than patients with microscopic disease identified at ELND as compared with those with clinically manifest recurrence subjected to therapeutic node dissection. Although the sentinel node is meticulously examined using immunohistochemistry and fine sections, for practical reasons, nodes from the completion lymphadenectomy specimen are not. The prognostic importance of rigorously characterizing the number of sub-micrometastatic positive nodes after completion lymphadenectomy using thin sections and immunohistochemical staining is unclear.

Sentilis and In-Transit Disease

The stage III category has also been designated for patients with forms of regional extranodal disease. Satellite involvement, satellitosis, is a form of tumor extension that may be manifested by deep or aggressive primary melanomas, often with intervening areas of apparently tumor-free skin. Satellite involvement signifies a poor prognosis for patient outcomes; prognosis has been shown to resemble that of patients with regional lymph node involvement. A second category of metastatic melanoma that has long been recognized to have a more ominous prognostic significance than localized primary disease is known as in-transit disease. In-transit melanoma does not differ from more typical nodal metastatic disease. The more indolent course of in-transit melanoma, particularly when associated with para-neoplastic hypopigmentation, has led to substantial immunologic interest in this form of melanoma, and its location has lent itself to regional isolated perfusion chemotherapy and biologic therapy. The AJCC staging system encompasses both satellite and in-transit disease. These processes are exemplified by regional nodal disease and the presence of satellite and in-transit disease. Sentinel node status remains a significant prognostic factor in multivariate analyses of disease-specific survival in this model after adjustment for other previously identified prognostic factors. Once SLN status is accounted for, a number of factors that have previously been considered as independent prognostic factors lose their significance. The primary site of origin, age of the patient, and sex of the patient are all nonsignificant after incorporation of SLN status in a prognostic model for outcome of stage I and II patients. The multidisciplinary procedure of SLN evaluation requires attention to radiology and meticulous pathology as well as expert surgery for optimal outcome. Whether the information attained from SLN biopsy allows treatment decisions that alter outcome remains a question currently being addressed in a number of prospective trials. Even though it has been widely adopted by most centers in the United States, it is less widely applied elsewhere and the results of seminal prospective studies should be available within the next few years to assess its utility in improving patient outcome. It is conceivable that strategies to quantitatively identify tumor in the peripheral blood using molecular analysis or serologic assays may supplant this surgical staging procedure.

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Stage IV: M1

Distant disease that has spread beyond the regional draining lymph nodes is generally denoted as M1 in the TNM system and stage IV in the AJCC and Union International Contra le Cancrum systems. The prognosis of patients with stage IV M1 disease is poor, with median survival of less than 1 year. The AJCC Subcommittee on Melanoma has reviewed criteria for this disease category, which represents the smallest fraction of patients of any stage at presentation, but a significant fraction of patients with melanoma who will die each year. For these patients, the identification of important prognostic factors may guide treatment selection or decisions whether to pursue therapy. An analysis of the clinical factors associated with a favorable prognosis in patients with stage IV disease entering therapeutic trials of the Eastern Cooperative Oncology Group (ECOG) has demonstrated that patient factors including a normal appetite, absence of nausea and vomiting or fever, unimpaired performance status, and female gender are all significant. Disease-related factors of prognostic importance include the limited number of sites of disease, disease limited to soft tissues and lymph nodes, a time interval more than 1 year to therapy for metastasis, and the occurrence of a clinical response to treatment. A current reassessment of important factors in 1325 patients with stage IV melanoma treated in eight clinical trials over 25 years in ECOG has identified many of the same factors to be significant, including the number of metastatic sites, unimpaired performance status, and female gender. A number of studies have evaluated the risk of survival in stage IV patients using Cox regression analysis to identify the most powerful prognostic factors associated with outcome. In all of these studies, the number of lymph nodes found to be involved with tumor (whether microscopic or macroscopic) has been the cardinal factor identified (Fig. 42.2-15). The advent of sentinel node mapping has increased the precision with which regional lymph node dissemination can be identified, but even in studies that have patients evaluated by SLN mapping, the number of involved lymph nodes has been a significant prognostic factor. The prognosis for patients with one involved regional lymph node is significantly better than for patients with two or more involved regional lymph nodes. The recommended AJCC 2000 staging system will adopt the number of nodes involved with tumor as the principal basis for prognostic assessment of patients with regional disease. N1 will signify one node involved, N2 will signify two to three nodes involved, and N3 will signify four or more nodes involved with tumor. N3 includes matted nodes and ulcerated melanoma with any number of metastatic lymph nodes. A secondary criterion for classification of patients with nodal metastatic disease is that of nodal bulk of disease (microscopic versus macroscopic). The former is invisible to the gross surgical or pathologic evaluation, nonpalpable, and designated (a). The N1(a)/N2(a)/N3(a) category of microscopic involvement represent a significant and increasing fraction of patients identified through sentinel node mapping procedures, for whom the prognosis appears to be improved. Previous data suggested that this subgroup has a more favorable prognosis than patients with microscopic disease identified at ELND as compared with those with clinically manifest recurrence subjected to therapeutic node dissection. Although the sentinel node is meticulously examined using immunohistochemistry and fine sections, for practical reasons, nodes from the completion lymphadenectomy specimen are not. The prognostic importance of rigorously characterizing the number of sub-micrometastatic positive nodes after completion lymphadenectomy using thin sections and immunohistochemical staining is unclear.

![Figure 42.2-15. Survival for stage III patients according to the number of nodal metastases. Survival correlates strongly with increasing numbers of positive lymph nodes.](From ref. 222, with permission.)
involving the lung but no other viscera has a prognosis that is intermediate between that of nonvisceral distant metastasis and other visceral sites of metastasis. The proposed reformulation of the AJCC for 2000 proposes classification of nonvisceral metastatic disease limited to skin, soft tissue, and nodes designated as M1a, and that involvement of lung sites be considered as M1b, with the M1c category left to designate all other visceral sites of disease.

### Biochemical and Serologic Markers

Many studies have evaluated biochemical, immunologic, or other quantitative blood assays that might reflect the prognosis of patients with melanoma. One of the earliest was that of the enzyme lactic dehydrogenase (LDH), assessed as a marker of metastatic disease, particularly within the liver. Several multivariable proportional hazards models have evaluated the importance of an elevated LDH level (either elevated above the mean value for a laboratory or above the upper limit of normal for the test) in each case as a predictor of survival. The addition of several markers included melanoma inhibitory activity (MIA) and the level of the polypeptide 99mTc-S-100b. The AJCC Subcommittee for Melanoma has taken a significant step in a new direction in the proposed 2000 revision of the melanoma staging system by including LDH measurement as a factor to be employed to define a more ominous prognosis and to downstage patients with known melanoma metastasis to an elevated LDH value, assigning these patients with stage IV disease to stage IV M1c.

A number of studies have proposed the prognostic utility of S-100b measured by radioimmunoassay or a more recent luminometric immunoassay. A prospective, observational study evaluated the clinical and prognostic value of S-100b protein in patients with metastasis-free disease versus patients with newly occurring lymph node, visceral, brain metastases, or all three. In this series that included 570 patients and 52 normal controls, the sensitivity and specificity of S-100 measured by an immunoradiometric assay was 84% and 91%. False-negative results occurred in those with amelanotic melanoma. The negative predictive value was 99%, but the positive predictive value was only 65%.

S-100b was examined prospectively in the peripheral blood of patients undergoing surgical procedures for resection of high-risk primaries or lymph node metastases. Of the patients who were S-100b positive by luminometric immunoassay, 47% developed metastatic disease after at least 2 years of follow-up. Kaplan Meier analysis showed that patients who were S-100b positive had approximately 2.7 times shorter disease-free survival than patients negative for S-100b. This difference was statistically significant, and multivariate analysis showed that S-100b was an independent prognostic determinant of disease-free survival.

RT-PCR has also been used to gain prognostic information by attempting to detect small numbers of blood-borne melanoma cells. The technique is generally limited by its extreme sensitivity. The use of tyrosinase has been somewhat problematic because tyrosinase is also present in nonmalignant cells including melanocytes in the dermis picked up by phlebotomy. Up to 10% of healthy people may have blood tyrosinase-positive cells in this assay. However, tyrosinase has been used to detect circulating melanoma cells in patients with melanoma with intriguing results. Positive tyrosinase results are seen in stage I, II, III, and IV melanoma patients at a frequency of 11%, 18%, 31%, and 67%, respectively. In stage IV patients, median overall survival was 8 months compared with 12 months in those patients with a negative test result. Tyrosinase is present in a proportion of long-term clinically disease-free melanoma patients, and the late presence of circulating melanoma cells predicts a subsequent high risk of relapse and death. Some studies have correlated tyrosinase positivity with increasing stage, survival, presence of visceral involvement, higher LDH levels, and higher Ki-67 proliferation. In another study, survival was 87% for the tyrosinase-negative patients versus 72% for the tyrosinase-positive patients. The use of true real-time quantitative PCR (TaBrman) may improve on the prognostic utility of these melanoma assays.

MIA, a novel molecular marker, has been examined as a potential prognostic marker. One hundred sixty-six patients with melanoma were examined for expression of MIA. A correlation between positive blood sample results and tumor burden in stage III and IV patients was detected and 73% of stage I and II patients were negative for the MIA RNA. Five of 24 patients who were RT-PCR positive progressed to systemic disease within the follow-up period of 6 months. The predictive values were low and the study was too small to deduce prognostic significance. MIA, as currently examined, is limited in its utility as a prognostic marker.

Immunosorting of melanoma cells using magnetic cell separation has been used to isolate, in a specific fashion, viable melanocytes from patient's blood. This technique does not have suitable sensitivity for early detection of metastasis, but may prove a valuable tool in the isolation and identification of circulating autologous melanoma cells. No patients with stage I primary melanoma were found to have circulating melanoma cells, whereas 13.6% and 15.2% of patients with stage III and IV disease were found to have them. The prognostic significance of these circulating cells is unknown.

### Imaging of Malignant Melanoma

Conventional evaluation of the patient with primary melanoma involves chest radiography for all patients with primary lesions deeper than 1 mm. In the setting of established stage I or II disease, radiologic evaluation may be indicated with the use of magnetic resonance imaging of the brain and computed tomography (CT) of the chest, abdomen, and pelvis. In the setting of known metastatic disease, thorough evaluation may be required to allow the participation in clinical trials and in planning therapy. Advances in imaging techniques have improved the ability to identify and localize primary and metastatic melanoma. The most notable advances have been positron emission tomography (PET), radionuclide agents with affinity for melanoma, and the resurgence of lymphoscintigraphy. Lymphoscintigraphy can provide valuable assistance in localizing SLNs for biopsy. It is particularly helpful for tumor locations with variable lymphatic drainage and has identified previously unsuspected drainage patterns for some regions.

Improvements in PET have made it a valuable staging study for melanoma. Rinne et al. prospectively compared whole body 18F-fluorodeoxyglucose PET with conventional imaging (CT, magnetic resonance imaging, and so forth) in 100 consecutive patients (52 at diagnosis, 48 at follow-up). At initial staging, PET was 100% sensitive and 94% specific, whereas conventional imaging did not identify any of the nine lymph node metastases and was 84% specific. In the 48 follow-up patients, the sensitivity, specificity, and accuracy of PET per metastasis was 92%, 94%, and 92%, respectively, compared with 58%, 45%, and 56% with conventional imaging. While PET was better at detecting cervical lymph node metastases (100% vs. 67%) and abdominal metastases (100% vs. 27%), CT was better for small lung metastases (87% vs. 70%). With the exception of brain imaging, where magnetic resonance imaging is superior, these authors suggested that a single whole body PET scan could replace all other imaging performed in melanoma patients. This will need to be evaluated in other series.

Other imaging techniques that show promise in melanoma are technetium 99mTc-sestamibi (MIBI), 99Tc-tetrofosmin, and iodine 123 iodo benzamidine (for melanotic tumors). If these, 99mTc-MIBI has undergone the most thorough evaluation and appears to be a reasonably inexpensive substitute for whole body PET scans in staging melanoma patients.

### Radiobiology of Melanoma

Early experiences with conventional radiotherapy of melanoma led some clinicians to believe that this tumor was so radiosensitive that radiotherapy was of little use. This erroneous deduction was based on experience with treating melanomas with conventional low-dose fractions (approximately 2 Gy per fraction) and moderate to high total dose. Radiobiologic studies of melanoma have subsequently altered the clinical approach to treating melanoma. Some investigators identified wide shoulders for in vivo cell survival curves for melanoma, suggesting a large capacity for repair of sublethal damage that prompted a number of investigators to treat patients with malignant melanoma with large-dose fractions. There is some intrinsic variability within various melanoma cell cultures, and these models differ in many respects from tumors found in patients. Analyses of clinical experiences with various radiotherapy treatment schedules provided important data. Melanoma can be responsive to radiotherapy when large-dose fractions are used.

An important study of the clinical radiobiology of melanoma is the analysis by Bentzen et al. of tumor control in 121 patients with 239 histologically proven recurrent or metastatic malignant melanomas. They identified an alpha to beta ratio of 0.57 (95% confidence interval, –1.07 to 2.5 Gy). The rationale for standard fractionation is that small-dose fractions preferentially spare late reacting normal tissues with lower alpha to beta ratios (1.8 for subcutaneous) than malignant tumors, which usually have alpha to beta ratios closer to 10. With melanoma, these clinical data indicate the reverse situation. In cases in which the larger individual dose fraction is used, more normal tissue is spared the effects of radiation compared with tumor. There is little treatment time effect (negligible repopulation during a treatment schedule) indicating that treatment may be administered with large-dose fractions twice a week rather than conventional application five times per week schedule. The subsequent protraction of the overall treatment time allows normal cell populations that determine acute radiation reactions (such as moist skin erythema and mucositis) to repopulate to a greater degree between fractions to minimize acute side effects. The dose response is markedly influenced by tumor size and the level of the polypeptide S-100b. The AJCC Subcommittee for Melanoma has taken a significant step in a new direction in the proposed 2000 revision of the melanoma staging system by including LDH measurement as a factor to be employed to define a more ominous prognosis and to downstage patients with known melanoma metastasis to an elevated LDH value, assigning these patients with stage IV disease to stage IV M1c.

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Several factors have been postulated to contribute to the relative radioresistance of melanoma including tumor hypoxia, loss or dysfunction of the p16 DNA locus, and decreased cell membrane gangliosides. A number of different innovative techniques are being investigated to improve radiotherapy of malignant melanoma. Hypoxic cell sensitizers such as tirapazamine and gadolinium texaphyrin show promise in preferentially killing radioresistant hypoxic cells within melanoma tumors. Hyperthermia combined with radiotherapy is another approach to optimize killing of hypoxic tumor cells. Approaches that combine radiotherapy with radiosensitizing chemotherapy such as topoisomerase I targeting drugs (topotecan, camptothecin) or taxanes, which arrest cells in the most radiosensitive phase (G2/S), also could improve radiore sponsiveness. Boron neutron capture therapy, which depends on selective drug uptake in tumor (as does gadolinium texaphyrin), also holds potential in treatment of melanoma. Gene therapy including application of N-Ras or Myc transfection is another promising approach to increase radiosensitivity. The specific use of radiotherapy on primary tumors, in-transit disease, recurrences, and metastatic disease are discussed in the following sections.

STAGE I AND II DISEASE: MANAGEMENT OF PRIMARY MELANOMA

All lesions with characteristics suggestive of melanoma should be biopsied. Suspicious lesions may have irregular raised surfaces; ulceration, bleeding, or both; variegations; or recent changes in color or size. As sampling error may occur with incisional biopsies, a full-thickness excisional biopsy is the preferred diagnostic technique since the depth of the lesion determines the extent of resection. Shave biopsies are contraindicated since they may not encompass the full depth of the lesion and make pathologic interpretation of Breslow depth impossible.

PREOPERATIVE WORKUP

The most important staging information obtained from patients with melanoma is the Breslow depth, presence of ulceration, and nodal status. The 1992 National Institutes of Health Consensus conference indicated that asymptomatic patients with T1 lesions do not appear to benefit from any diagnostic staging including computed tomography, magnetic resonance imaging, or nuclear scans. A chest radiograph is performed in patients with stage IB disease or greater.

EXCISIONAL BIOPSY

Performing an excisional biopsy is preferable over an incisional biopsy. Sampling error may limit the reliability of assessing the Breslow depth of incisional biopsies. In most instances, a biopsy can be done in an office setting under local anesthesia with minimal morbidity. An excisional biopsy removes the lesion en toto. No effort is made to obtain a wide margin, but a small margin (1 to 2 mm) of normal skin is taken with the elliptical specimen and primary closure performed on most lesions. The specimen is sent to pathology for permanent section. Some surgeons suggest that a single-stage procedure is possible using frozen sections to characterize tumor depth, but this has not been validated.

INCISIONAL BIOPSY

Wide excision after incisional biopsy was initially thought to be associated with a higher recurrence rate. Those studies were poorly designed and retrospective, and no evidence in the recent literature suggests a worse outcome from incisional biopsy. However, incisional biopsy has a higher rate of inaccurate microstaging and should be reserved for large or subungual lesions to confirm diagnosis. Incisional biopsies may be used in areas where cosmesis and skin coverage are an issue. The biopsy should be a wedge of tissue including normal skin, the center of the lesion, and subcutaneous fat.

SURGICAL MARGINS OF RESECTION

The depth of melanoma resection does not require inclusion of the underlying muscular fascia, although this was initially suggested. Biopsies should go down to, but not include the fascia. For years, no clear standard existed that guided the amount of margin to resect around the primary tumor. The margin is defined as the radial distance from the visible edge of the lesion or scar. Only relatively recently have randomized trials examined the width of surgical margin in relation to local recurrence and overall survival. Pathologists have long observed malignant cells separated by some distance from the primary lesion. Wide excisions minimize the risk of leaving behind these cells that may locally recur or metastasize. Rests of malignant cells can be found distances of 1 cm from the visible edge of the tumor, and their presence outside 1 cm is directly proportional to the depth of the primary lesion. Some histopathologic data show morphologically bizarre melanocytes in normal skin upward of 5 cm from the primary site. The extent of excision necessary should depend of the thickness of the primary tumor. Since large resections risk functional deficits, disfigurements, and increased cost, determining the minimal excision margin has been extensively studied. Appropriate initial resection remains crucial in the management of primary melanoma since almost all patients with a local recurrence die of metastatic disease. Locally recurrent disease may be a just surrogate for more aggressive biologic behavior, but an adequate surgical resection should never be compromised.

Local recurrence, defined as tumor relapse within 3 to 5 cm of the primary closure or skin graft, is a relatively rare event, making the design of trials difficult. In a retrospective series of 3569 patients, local recurrences were found in only 3.2% of patients. Some factors have been identified that are associated with the probability of local recurrence. One large study found that the probability of local recurrence depends on only ulceration of the primary tumor (1.5% without ulceration vs. 19.6% with ulceration) and tumor thickness (2.3%, 4.2%, 11.7% for 1 to 2 mm, 2 to 3 mm, 3 to 4 mm lesions, respectively). Another large prospective series found that the site of primary tumor also predicted recurrence. In the 10-year reassessment of the Intergroup trial, multivariate analysis showed that the only variables that predicted local recurrence were ulceration and a head and neck primary site. The proximal extremity was least likely to have a local recurrence, followed by the distal extremity, and head and neck. When ulceration was present, the relative risk of local recurrence was 6.3 compared with nonulcerated melanomas. In patients with head and neck primaries, the relative risk for local recurrence was 9.4 compared with all sites. Both of these risks were highly significant.

Although the risk of recurrence increases with more narrow margins, wide incisions can be quite morbid. A more radical excision is associated with the morbidity of cosmetic defects, functional losses, and the need for skin grafting. Wide excisions for melanoma were first popularized by Handley in 1907 who described a 1-inch skin margin with further undermining of 2 more inches laterally. In 1947 Urteaga and Pack compared radiation therapy to surgical excision with an 8-cm margin and found resection to have a superior 5-year survival. Others proposed routine amputations or huge 15-cm margins with en bloc lymphadenectomy. Until more recent randomized trials, a 3- to 5-cm excision, which frequently required skin grafting, was the standard treatment. Even as late as the 1980s, there were no national guidelines for the extent of excision necessary and much variation between surgeons existed. Although the rate of recurrence was known to depend on tumor depth, there was no correlation between the extent of operation and tumor thickness. Three well-designed, randomized prospective trials and various retrospective trials...
supports the use of a 1-cm margin for melanomas less than 1 mm thick and a 2-cm margin for deeper lesions deeper (Table 42.2-5).

<table>
<thead>
<tr>
<th>Stage</th>
<th>Margin</th>
</tr>
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<tbody>
<tr>
<td>stage Ia</td>
<td>0.5 cm</td>
</tr>
<tr>
<td>stage Ib</td>
<td>1 cm</td>
</tr>
<tr>
<td>stage II (all)</td>
<td>1 cm</td>
</tr>
<tr>
<td>stage III (T4a) or greater</td>
<td>2 cm</td>
</tr>
</tbody>
</table>

Subungual amelanotic melanoma patients do not require a 1-cm margin greater than 2 cm since patient outcome is dictated more by the presence of regional and systemic disease. Currently, a prospective trial is accruing patients with melanomas greater than 2 mm thick and randomizing them to 1-cm versus a 2-cm margin. Outside of this trial, resection margins of 2 cm are recommended for all lesions greater than 1 mm deep.

Technique

The surgeon should mark the appropriate resection margin from the visible edge of the tumor or scar. If primary closure is desired, an elliptical incision should be performed. The minor axis of the ellipse should encompass the resection margins and the major axis should be approximately three times the minor axis. The long axis of the ellipse should be parallel to the axis of the extremity, or, if on the trunk, along Langer's lines. Care must be taken not to bevel the dissection inward, and the excision should not include the fascia. Generous undermining of the lateral flaps allows for a tension-free closure. Rotational flaps may be required for large lesions or lesions on the face.

SPECIAL SITES

Subungual Tumors

If a nail bed lesion has not changed significantly in 4 to 6 weeks, a biopsy should be performed accompanied by removal of the nail. An incisional biopsy, taking a representative wedge that includes the middle of the lesion, is recommended to establish a diagnosis and prevent needless amputation. The biopsy should include the nail plate and should be oriented longitudinally. The level of amputation does not seem to affect the incidence of recurrence or patient survival, so especially in lesions of the thumb, maintenance of function is important. For disease confined to the nail bed, amputation through the distal interphalangeal joint is recommended, and for bulky disease, a more proximal amputation through the base of the phalanx may be required. Toe amputations should be performed more proximally as the loss of a toe at the metatarsal-phalangeal joint does not result in decreased function. Some surgeons advocate ILP, sentinel node biopsy, or both in patients with these high-risk lesions. There are few data showing a survival benefit in any patient with melanoma using adjuvant ILP.

Acrail and Lentigious Melanoma

Due to functional concerns, there is a tendency to use smaller margins, perhaps accounting for the two- to fivefold higher incidence of local recurrence in this area. Excisions often require split-thickness skin grafting for closure or tissue transfer, especially in wounds involving weight-bearing areas such as the heel of the foot that may require flap transfer. In most instances, skin grafts may be applied successfully to weight-bearing areas. A Wood's lamp examination often helps to define the extent of pigmentation better than room light.

Head and Neck

Melanoma of the face and scalp represent sites where local recurrence, nodal, and in-transit disease occur more frequently perhaps due to the extensive lymphatic drainage. Melanoma of the head and neck usually occurs in an age group 10 years older than truncal and extremity melanoma. The lesions most commonly involve the face (Table 42.2-6). LMM, a common morphotype of head and neck melanomas, is historically associated with an improved prognosis. However, appropriate excision margins for Breslow depth should not be compromised solely on cosmetic bases. LMM, a benign precursor lesion, can be treated through a number of techniques that do not require a wide margin of resection. Since up to one-half degenerate into malignancy, the treatment of these lesions is warranted. Multiple techniques have successfully been used to treat these lesions including excision, micrographic Moh's surgery, cryosurgery, radiotherapy, electrodesiccation and curettage, 5-fluorouracil, azelaic acid, and retinoic acid. A Wood's lamp examination often helps to define the extent of pigmentation better than room light.
MOHS MICROGRAPHIC SURGERY

MMs have been used for some time by dermatologists for nonmelanomatous lesions. The technique reduces scarring and may spare normal tissues by shaving involved tissues until a histologically negative margin. MMS employs repeated shallow (3-mm) resections, each examined histologically by frozen section. Some specialized centers have proposed the use of Mohs surgery in melanoma to minimize loss of normal tissue, especially in areas where the face, hands, and feet. Margins are generally taken somewhat less than the WHO and Intergroup trials found appropriate, which has generated much criticism from most melanoma experts. There have been no randomized trials comparing the standard surgical excision with MMs, but in some uncontrolled centers, rates of local recurrence and overall survival have not been found to be inferior to matched historic controls. Differences exist between traditional surgical resection and micrographic surgery. For instance, the diameter and location of the primary tumor are prime determinants of the expected extent of excision in the MMS literature. Proponents of Mohs surgery claim that repeated frozen sectioning is accurate and saves normal tissues. Opponents cite the fact that satellite lesions may be missed using the Mohs technique and that pathologists do not generally examine the specimens. Critics also claim that frozen section is notoriously inaccurate for identification of melanoma. Appropriate controlled multicenter trials are essential before this technique can be accepted by the surgical community for the treatment of melanoma.

RADIOTHERAPY OF PRIMARY SKIN TUMORS

Radiotherapy is rarely indicated in the management of primary invasive melanoma except in patients who refuse surgical excision or who are poor medical candidates. Treatment is usually administered with 6- to 9-MeV electron beams or 100- to 280-kilovolt (peak) x-rays using wide margins. Seegenschmiedt et al. reported tumor control in all 11 patients with residual (n = 6) or recurrent (n = 4) stage IIB melanoma (one patient with primary disease refused surgical excision). They found better tumor control in these patients compared with control achieved through radiotherapy in patients with skin and lymph node metastases. Radiotherapy is a noninvasive alternative to surgical resection in the management of LM. This therapy may be appropriate for patients who cannot undergo or refuse surgery. Harwood reported 40 cases of LM and LMM managed with radiotherapy alone at Princess Margaret Hospital. They found better tumor control in these patients compared with control achieved through radiotherapy in patients with skin and lymph node metastases. Radiotherapy doses were 45 to 50 Gy in 10 to 15 fractions with orthovoltage beams. Fourteen of 17 patients with LM and 34 of 37 with LMM were alive without tumor progression after 1 month to 7 years. Four patients with local recurrent or persistent tumor (two LM and two LMM) were salvaged by surgery (one LM, two LMM) or further radiotherapy (one LM). One LM patient died of intercurrent illness. Lesions can take up to 2 years to disappear after radiotherapy and the follow-up of available series remains short.

STAGE I AND II DISEASE: EXAMINATION OF THE LYMPH NODE BASIN

Although prophylactic nodal dissection has never clearly been demonstrated to be of survival value in any other tumor, the Halstedian belief of radical lymphadenectomy has, and still dominates the treatment of melanoma. Physicians have believed that a survival benefit exists after the early removal of nodes that are subclinically involved with tumor compared with removal once obvious nodal disease develops because the longer melanoma grows in the lymphatics, the more likely it is to metastasize systemically. This concept was tested in numerous trials by comparing ELND, a complete lymphadenectomy (LND) in those at risk for nodal disease but without clinical evidence, with therapeutic lymph node dissection (TLND), LND in those with clinically positive nodes. Although no clear survival benefits have yet been demonstrated by ELND, many confounding factors may have contributed to the generally negative results. After years of controversy surrounding the potential benefit of elective nodal dissection and numerous trials, it is ironic that, regardless of the conclusions reached, the new technique of sentinel node mapping, has cast a shadow on all the answers recently obtained. The complexity of nodal drainage, the relatively low frequency of nodal disease, inadequate staging, and slight, if any, therapeutic benefit are clear obstacles in attempting any benefit of elective nodal dissection for melanoma. In previous texts, a detailed discussion of ELND was mandatory. Now the wholesale removal of entire nodal basins that may harbor metastatic disease based on inadequate descriptions of drainage patterns, and insensitive pathologic techniques should no longer be performed. With the advent of sentinel node mapping, ELND is only discussed as an historic reference. Regardless of possible therapeutic benefit, sentinel node biopsies efficiently predict prognosis with low morbidity. Current trials are assessing therapeutic benefit of selective nodal dissection. Unlike in breast cancer, there is no clearly beneficial adjuvant therapy available for high-risk patients, but as various new melanoma therapies are being developed, risk stratification by nodal status will become increasingly important. In the future sophisticated assays such as quantitative PCR (Taqman), which can measure melanoma antigens in the peripheral blood, may prove more important than nodal status for predicting prognosis and obviate the need for invasive procedures.

ELECTIVE LYMPH NODE DISSECTION

ELND has been an extremely controversial subject and its theoretical value hinges on the biology of melanoma metastasis. Does melanoma spread stepwise through the draining lymph nodes before reaching other more distant sites, or, as in breast cancer, does a Fisherian theory of nodal disease exist in which positive nodes are only a marker for systemic disease? Selecting patients who may be candidates for ELND has been based on the depth of the primary tumor. Patients with tumor less than 1 mm deep have a 98% cure rate and would not benefit from a relatively morbid operation. Patients with thick lesions (greater than 4 mm) at the time of diagnosis did not undergo ELND. Initial studies of ELND in this group of patients could not show any benefit and data erroneously suggested that this was due to a high percent (70%) of patients with occult metastatic disease. Numerous trials have tried to understand the role of nodal dissection for intermediate-thickness lesions, but, unfortunately, many of the data are conflicting. Although sentinel node mapping has not yet proven therapeutic, the knowledge gained has helped elucidate the reasons for failure in multiple ELND trials and given much insight to the biology of nodal disease in melanoma.

Proponents of ELND advocate the use of ELND for its prognostic information since, in patients with regional disease, the actual number of nodes involved is the most important predictor of overall survival. Advocates also cite retrospective studies that demonstrate a 5-year survival rate increase of up to 10% to 27% when patients...
with clinically occult disease have their nodal basins resected compared with delayed resection of gross disease. As well, regional node disease may determine candidacy for adjuvant treatment such as IFN-a.

Opponents point out the morbidity of the operation, the lack of clear therapeutic benefit of ELND, and a controversial advantage to IFN-a treatment. One of the most important criticisms was that up to 80% of patients had negative nodes on pathology. This large percentage of patients received no benefit from the procedure. Many believe that lymph node metastases are a manifestation rather than a predecessor of distant spread. In a retrospective review of 4682 patients, only 16% of patients had positive nodes at ELND. Ten percent of metastases were positive in the contralateral node, and 6% were positive in nodal basins not classically predicted. At Breslow depths of less than 0.76 mm, 0.76 to 1.5 mm, 1.5 to 2.5 mm, 2.5 to 4.0 mm, and greater than 4 mm, the regional nodal basin was positive in 0%, 5%, 16%, 24%, and 36% of cases, respectively. LND has substantial potential morbidity that includes chronic lymphedema, pain, paresthesias, cosmetic deformity, and, especially in the groin, wound complications. Lesions of the head and neck are especially problematic. As is true for squamous cell cancers of the head and neck, evidence arising from randomized prospective trials is not available to confirm the value of prophylactic nodal dissection for melanoma arising in the head and neck.

The usefulness of ELND has been debated for decades because of conflicting trials of various quality (Table 42.2-7). Multiple trials suggest that TLND does not jeopardize the probability of cure and prevents the need for difficult toilet operations. Most trials are retrospective and mixed in conclusions. In one from Duke University and another from the Sydney Melanoma Unit, initial analysis showed a survival advantage in patients with intermediate-thickness lesions, but both, after 10 years of further data accrual, showed no advantage to ELND. This demonstrated the lack of reliability of retrospective trials and the length of time needed for adequate data accrual.

<table>
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<th>TABLE 42.2-7. Results of Elective Lymph Node Dissection Trials</th>
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Two prospective trials from the WHO in 1977 and Mayo Clinic in 1986 showed no benefit of ELND. Both these trials included what we now recognize as many low-risk patients and their negative results have been criticized. Both the Intergroup and WHO trunk trials are contemporary prospective randomized trials that were developed to address much of the conflicting information. Although long-term data are still accruing, results have been published.

In 1998, the WHO published a series of 252 patients randomized to immediate or delayed node dissection. All patients had truncal melanoma of at least 1.5 mm thickness. The 5-year survival observed in patients who had delayed node dissection was 51.3% compared with 61.7% in patients who had had immediate resection (P = .09). Multivariate analysis showed that routine use of immediate node dissection had no effect on survival. The WHO study, in contrast to the Intergroup Melanoma trial, was much smaller in patient accrual, assessed patients who generally had thicker melanomas, and did not use lymphoscintigraphy to determine the appropriate drainage basins to resect.

In 1996, initial results of the Intergroup Melanoma trial were reported. The trial randomized 740 patients with intermediate-thickness lesions to ELND, and, although there was no difference in survival for the entire group, an apparent survival benefit was seen in a post hoc analysis of a subgroup of patients. Male patients younger than the age of 60, with tumors 1.1 to 2.0 mm thick, and without ulceration had a significant improvement in 5-year survival of 96% versus 84% (P = .007) which was confirmed in multivariate analysis. The subgroup of patients with tumor thickness 1.1 to 2.0 mm of any age who underwent an ELND also had a significantly better 5-year survival compared with the observation group (92 vs. 84%, P = .05).

Cascinelli et al. suggest a role of prophylactic dissection in a randomized study of patients with trunk melanoma comparing elective versus delayed dissection, noting that only patients with positive lymph nodes benefited from lymphadenectomy. These data become important with the advent of sentinel node biopsy and subsequent selective nodal dissection. Now a large percentage (80%) of patients who may not benefit from LND may be spared the procedure while identifying patients who may most benefit. SLN biopsy followed by dissection in patients with positive nodes eliminates the indications for prophylactic dissection, and future studies can focus on a homogenous group of patients in order to establish the true therapeutic role of lymphadenectomy.

**SENTINEL NODE BIOPSY**

Even before the results of the WHO and Intergroup Melanoma trials, the use of sentinel node biopsy was widely adopted as a means to minimize procedural morbidity of LND. The sentinel node is the most likely lymph node to contain metastatic disease. The concept of sentinel node biopsy is based on the presumption of an orderly progression of disease through the lymphatic system. A negative SLN would suggest more upstream metastatic disease has not occurred, whereas a positive SLN would indicate potential involvement of other nodes in the same basin. A lymphadenectomy after intraoperative lymphatic mapping and sentinel node biopsy has been termed a completion lymph node dissection. The importance of a positive sentinel node is underscored by multivariate analyses, which show that the SLN status is the most important prognostic factor influencing disease-free and distant disease-free survival in patients with stage I and II melanoma.

SLN biopsies have clarified the natural progression of melanoma metastasis. The data from initial trials using sentinel node mapping demonstrate an apparent orderly progression of disease with failure to observe lymph node metastases in nodes adjacent to a negative sentinel node. Cabanas was the first to describe the technique of sentinel node biopsy for penile cancer as a means to prevent the morbidity of bilateral inguinal LND. This concept is that discrete areas of skin drain initially to specific node(s) within lymph node basin(s) that may or may not be proximate anatomic basins. The identification of such initially draining nodes allows for pathologic assessment in far greater detail than is possible otherwise.

Although many surgeons believe SLN biopsy is the current standard of care, the true role and benefit of sentinel node mapping is still to be determined. Undoubtedly, sentinel node status is extremely valuable in staging. Clinical trials of melanoma have been hampered by the heterogeneity of patient populations due to suboptimal staging. Accurate knowledge of the lymph node status (macroscopic, microscopic, immunohistochemical, and molecular) enables appropriate comparisons to be made between treatment groups. There is still debate whether a positive sentinel node biopsy with subsequent lymphadenectomy of clinically negative basins and adjuvant therapy is efficacious. Data suggest that the early removal of positive lymph nodes may improve survival. The Intergroup trial suggests that the benefit of elective LND may be meaningful in patients whose tumors are nonulcerated, extremity primaries, of thickness between 1 and 2 mm, and whose age is less than 60 years. Current trials are attempting to determine the efficacy of early LND guided by sentinel node mapping. Although the efficacy of adjuvant treatment for melanoma is less than desired, the ongoing studies of IFNs, chemotherapy, vaccines, and combinations will be improved by a greater precision in prognostic assessment.

**Lymphoscintigraphy**

In 1977 Robinson et al. described the use of cutaneous lymphoscintigraphy in the nodal basin for truncal melanomas using colloidal gold scanning. In 1985, Morton began the first clinical trials using both lymphoscintigraphy and vital dye injection for the identification of sentinel nodes in melanoma patients. In 1993, Alex introduced the use of technetium 99m sulfur colloid, a radioactive tracer, injected intradermally around a primary melanoma site, followed by imaging and subsequent intraoperative use of a gamma probe to localize the sentinel node.

The day before the operation, lymphoscintigraphy is performed using Tc (0.5 to 0.8 mCi), which is injected around the tumor site (Fig. 42.2-18 and Fig. 42.2-19).
The colloidal isopes are phagocytosed by macrophages within the lymph node. This keeps tracer in the draining node and prevents further passage through the nodal basin. Immediately afterward, dynamic images are obtained, and after 2 hours static scintigrams are taken. Dynamic imaging helps differentiate between multiple sentinel nodes and spillover to nonsentinel node. The choice of tracer is also important. The \textsuperscript{99m}Tc sulfur colloid has a particle size in the micrometer range, and transport may be too slow to be suitable for dynamic imaging. \textsuperscript{99m}Tc colloidal albumin and technetium \textsuperscript{99m} human serum albumin appear to be the most favorable as the sentinel node becomes positive within 20 minutes in 97% of patients and is retained for up to 24 hours without an increase in the number of sentinel nodes. \textsuperscript{99m}Tc human serum albumin demonstrated faster washout rates from injection sites and better definition of lymph channels than other particulate agent, whereas particulate agents were retained longer in nodes and demonstrated more nodes in delayed images than in early images. Early dynamic imaging is important, as sentinel nodes cannot be distinguished reliably from nonsentinel nodes in delayed images alone. The radiologist should mark the position of the sentinel node on the skin, although the surgeon must be wary that relaxation during surgery and positioning may change the position of the lymph node relative to the skin marker.

FIGURE 42.2-18. Lymphoscintigram. This patient had a biopsy-proven melanoma on the right hand (note the high area of radioactive tracer around the injection site) and was noted to have an epitrochlear sentinel node. Five percent of patients with distal extremity lesions have popliteal or epitrochlear nodes. Using classical guidelines for lymphadenectomy, a potential positive lymph node may be overlooked, which may result in incorrect staging.

FIGURE 42.2-19. Lymphoscintigram. This patient had a primary tumor on the nose. Sentinel node mapping in the head and neck can be difficult secondary to the increased number of nodes (3.6 vs. 1.3), the overshadowing of pertinent lymph nodes by the primary injection site, the difficult dissections, and cosmetic concerns. Note, the multiple sentinel nodes suggested during early imaging. In this patient, no sentinel nodes in the parotid gland were identified. (Courtesy of H. Edington, M.D., University of Pittsburgh Cancer Institute.)

The surgeon should reexamine the SLN in the operating room with the hand-held gamma counter and make the skin incision directly over the most radioactive point. As only 1% of the injected dose of radioactive colloid reaches the SLN, a primary site close to the nodal basin may preclude effective use of the gamma probe, even if the primary site is excised initially. This shadowing becomes especially important in head and neck melanomas where nodes and the primary site overlap. After the sentinel node is removed, the wound is explored with the gamma probe for additional hot, blue nodes.

Sappey had originally injected mercury into the skin of cadavers and showed that a line drawn just above the umbilicus would differentiate inguinal versus axillary drainage. Lesions within 2 cm of this line had bidirectional drainage. With the use of these techniques, lymphatic drainage not predicted by Sappey’s original description of the cutaneous watershed of lymph drainage has been frequently observed. Only more recently, with the use of lymphoscintigraphy, has Sappey’s guide to lymphatic flow been modified by modern means of assessment.

Discordance from classical drainage patterns is especially common in the head, neck, and trunk. Sixty percent of head and neck and 32% of the trunk tumors drain in unpredicted sites. Operative intervention is changed in almost one-half of patients when lymphoscintigraphy is used. Lymphoscintigraphy may also identify patients with lymphatic drainage in two separate basins. Patients who have positive nodes in two basins have a worse prognosis when compared with patients with nodal disease in one basin, even when controlling for the total number of positive nodes. Even in distal extremity lesions in which lymphatic drainage is seemingly obvious, lymphoscintigraphy may identify popliteal or epitrochlear nodes.

The unpredictability of lymphatic drainage based on anatomic guidelines basins, especially in the head, neck, and trunk, make the use of routine ELND based on classic anatomy inappropriate without preoperative lymphoscintigraphy. The examination of incorrect lymphatic basins, the lack of appropriate immunohistochemical techniques, and the inclusion of patients with a relatively low likelihood of nodal involvement accounts for the difficulty in interpreting the various results of prior trials studying the role of ELND.

**Vital Dye**

After induction of anesthesia, vital blue dye (1.0 mL of isosulfan blue or patent blue V) is injected intradermally around the primary tumor or scar. The gamma counter is more accurate than vital dyes in locating sentinel nodes, especially in the axilla or in deep fatty tissue. Techniques using dye alone require a longer learning curve to achieve success rates of only 80%. The blue dye is still helpful in visual confirmation of a hot node, but up to 15% of radiolabeled sentinel nodes lack any blue dye. Conversely, 8% of blue nodes are not hot, and some of these nodes will be the only site of metastasis. Complications of the technique are infrequent and minor including dye-stained urine and prolonged tattooing of the skin lasting several months.

FIGURE 42.2-20. Vital blue dye injected around a primary melanoma. The patient had undergone lymphoscintigraphy before injection of the vital blue dye. (Courtesy...
Results of Sentinel Lymph Node Biopsy

After nodal mapping, regional recurrence rates are acceptably low and the sensitivity and specificity are quite high. Reintgen, in 1997, reported that after 600 mappings and 5 years of follow-up, no patient developed a recurrence in any basins not predicted at risk by lymphoscintigraphy. In another series, the sensitivity of lymphatic mapping and SLN biopsy for extremity melanoma was 100% and the specificity was 97%. Only 3% of patients with histologically negative SLNs developed inguinal nodal metastases during a mean 2-year follow-up. Lenisa et al. described their series of 580 sentinel node biopsies, 15% of which had nodes involved with tumor. Positive cases were distributed according to thickness as shown in Table 42.2-8. In 77% of the patients, only a single positive node was identified after completion LND. Only eight patients (1%) had a local relapse after a negative sentinel node biopsy. Using multivariate analysis, the probability of a positive sentinel node depends only on tumor thickness, ulceration, and truncal location. Although tumor thickness and ulceration influenced survival in SLN-negative patients, they provided no additional prognostic information in SLN-positive patients. Sentinel nodes are positive in 15% to 26% of patients in various series. Of patients with positive sentinel nodes, 24% to 33% demonstrate lymph nodes to be involved at completion lymphadenectomy. A single SLN is found in 59% of patients, two SLNs in 37%, and three SLN in 3%. The median number of sentinel nodes found in several series ranges from 1.3 to 1.8.

<table>
<thead>
<tr>
<th>Thickness (mm)</th>
<th>No. Percentage Positive Sentinel Lymph Node</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0-1.9</td>
<td>52  98%</td>
</tr>
<tr>
<td>2.0-2.9</td>
<td>59  95%</td>
</tr>
<tr>
<td>≥3.0</td>
<td>27  93%</td>
</tr>
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*The probability of a sentinel node demonstrating metastatic disease depends on tumor thickness. Caution: injection immediately before the start of a sentinel node mapping in patients with TI melanoma. First in patients with node at risk, and then in patients with node at higher risk. A positive sentinel node is a multivariate analysis of the most important variables in determining survival on survival analysis.*

TABLE 42.2-8. Thickness of Melanoma and Sentinel Lymph Node Positivity

Essner et al. were the first to show that sentinel node biopsy followed by completion lymphadenectomy did not decrease survival compared with patients undergoing ELND. They described a series of 534 matched patients with clinical stage I melanoma; one-half of the patients were treated with lymphatic mapping and sentinel lymphadenectomy and the other half were treated with ELND. Because the overall incidences of nodal metastases and survival were no different between the sentinel node and ELND groups, but the incidence of occult nodal disease was significantly higher among patients with intermediate-thickness primary tumors who underwent sentinel node mapping instead of ELND. Essner et al. showed that sentinel node mapping is therapeutically equivalent but prognostically more accurate than ELND. Whether previous wide excision affects the ability to map the sentinel node by changing local lymphatic drainage has been debated. The likelihood of appropriate dye uptake is decreased by one-half if a wide excision has been previously done. Most surgeons strongly recommend the use of lymphoscintigraphy before wide local excision to avoid disruption, artificial drainage of the lymphatic drainage, or both. Morton et al. retrospectively examined 47 patients who had SLN mapping after wide local excision and concluded that SLN biopsy can be cautiously performed in patients who have undergone previous wide local excision if the primary resection margin was no greater than 2.0 cm and the primary was not in a region of ambiguous drainage. Another retrospective review of 142 patients concluded that previous wide excision does not affect the reliability of sentinel node biopsy unless a rotational flap has been used. Further study is needed before firm conclusions can be made on the timing of SLN biopsy.

SLNs of the head and neck behave somewhat differently. Sentinel node biopsy has been less consistently successful in the head and neck due to the frequent alterations in lymphatic draining; likewise, prophylactic nodal dissection has not proven useful. Series reports between a 90% and a 95% success rate in identifying the sentinel node, somewhat less than the success rate for sentinel nodes at other sites. Many differences in head and neck lesions make sentinel node biopsy more difficult. Whereas most patients with extremity melanomas have a median of 1.3 to 1.8 SLNs, a median of 3.8 sentinel nodes is found in patients with intermediate-thickness head and neck lesions. Difficulties in mapping strategies are seen in nonclassical and especially parotid nodes, which may be shadowed by the radioisotope injected in the primary site. Furthermore, only 67% of lesions stain with vital dyes. One-half of sentinel nodes are located in nonadjacent nodal basins. One-fourth are in nonclassical sites and one-half in the parotid gland. Often, a functional node dissection with ex vivo dissection using the gamma probe is...
necessary to find small sentinel nodes. Furthermore, the patients must be warned that prolonged tattooing may occur from injected dyes in cosmetically sensitive areas of the face.

In 1994, the Multicenter Selective Lymphadenectomy Trial was begun to evaluate the therapeutic role of lymphatic mapping and SLN biopsy with and without wide excision in patients with localized melanoma. This trial has just closed with 1800 patients accrued, and long-term results are awaited. The Multicenter Selective Lymphadenectomy Trial has a 99.1% success rate in obtaining sentinel node(s) using both dye and radiolabeling. In centers participating in the Multicenter Selective Lymphadenectomy Trial, a minimum of 30 procedures must be performed before patients can be entered. After performing 30 cases, there was no difference in success of sentinel node biopsies between any of the centers.

**Pathologic Interpretation**

Frozen sections do not have a place in sentinel node mapping because micrometastatic disease cannot be determined, and thus permanent pathologic interpretation is crucial to success of sentinel node staging. Hematoxylin-eosin (H&E) staining is performed with negative samples undergoing immunohistochemical staining with the antibodies reactive with melanoma including S-100 and HMB-45. Ninety percent of melanomas are positive for S-100, HMB-45 is more specific but less sensitive than S-100, which also stains neurons, melanocytes, and DCs. The importance of immunostaining is exemplified in a study by Gershenwald. Of 243 patients with a histologically negative SLN on routine H&E staining, 27 (11%) developed local, in-transit, regional nodal, distant, or both nodal and distant metastases after a median follow-up of 35 months. Ten patients (4.1%) developed a nodal recurrence in the previously mapped basin. Reexamination of the original cassettes using S-100 and HMB-45 demonstrated that 80% of these patients had evidence of occult metastases by serial sectioning or immunohistochemical staining. In another large series of 357 patients and 838 sentinel nodes, 45% of positive nodes were only positive by S-100 staining, again confirming the importance of immunostaining for H&E-negative nodes. At a minimum, all negative SLNs should undergo immunohistochemical staining for melanoma markers.

The Multicenter Selective Lymphadenectomy Trial uses strict guidelines in handling nodal tissue. The Trial recommends cutting the lymph node in two halves through its longest diameter and fixing the specimen. Ten serial 8- to 10-µm sections are then made. Sections 1, 3, 5, and 10 are used for H&E staining, section 2 for S-100, section 4 for HMB-45, and sections 6 and 7 are negative controls for immunoperoxidase studies. Sections 8 and 9 are used to repeat any needed studies.

The use of RT-PCR, or potentially in the future, Taqman analysis to examine nodes for mRNA of melanosomal proteins may be valuable as this could reduce sampling error and improve sensitivity. Its extreme sensitivity, however, may result in the inappropriate upstaging of patients and overtreatment of patients falsely termed positive. In one study of RT-PCR of 124 patients, 58% of patients with histologically negative nodes were upstaged. This group of patients had a worse overall prognosis than those who were RT-PCR negative and histologically negative. Twenty percent of these patients developed either locoregional or systemic disease whereas only 5% of the PCR-negative patients developed signs of disease. One melanoma cell in 1 million background cells can be detected. Since approximately 80% of sentinel nodes will be negative, a quick screening of H&E-negative nodes using PCR may identify patients in whom the more labor-intensive immunostaining may be performed. One aim of the current Sunbelt trial is to examine the importance of PCR-positive lymph node and the effect of adjuvant therapy in patients with histologically negative nodes. The introduction of Taqman analysis may allow more accurate antigen quantitation and further insight into the details of sentinel lymph node biopsies in these patients with thin lesions.

No trial has shown benefit for elective nodal dissection in patients with tumors greater than 4 mm, and, in fact, ELNDs were not performed in this group of patients. However, many centers perform sentinel node mapping in this group of patients. Perhaps the subgroup of patients that have deep lesions and negative sentinel nodes may have improved survival compared with stage III patients and would be spared adjuvant therapy.

**SENTINEL LYMPH NODE RESULTS IN THIN AND THICK MELANOMAS**

Only rarely are sentinel nodes found positive in patients with thin melanomas (T1). The use of sentinel node biopsy is controversial in this group of patients, and many have looked for risk factors that may predict a higher incidence of nodal metastases. Less than 2% of patients with nonulcerated primary lesions less than 1 mm (T1) and less than Clark level IV have positive sentinel nodes. No lymph node involvement has been reported in lesions less than 0.73 mm. Thus, there is no role for sentinel node mapping in these patients. The two most significant risk factors for positive sentinel node in thin primary lesions are ulceration and Clark level greater or equal to IV. Even in patients with T1b lesions, the risk for nodal disease is less than 10%. Patients with T1b tumors have the same risk for nodal disease as T2a patients. In a series of 254 patients reported by Gershenwald, no patient with T1 lesions and a positive sentinel node had positive nodes on completion lymphadenectomy. Regression by itself was not found a risk factor for nodal disease in thin lesions. Careful selection and patient education is necessary before the employment of SLN biopsies in these patients with thin lesions.

There is some suggestion that the probability of a groin recurrence decreased with the introduction of a deep iliac dissection. In a retrospective review of 362 therapeutic groin dissections, 20% had positive deep inguinal nodes. The 5- and 10-year survival for those patients was 24% and 20%, respectively, with the number of positive iliac nodes an independent prognostic factor. The authors suggest that deep lymph node dissection may be of benefit as up to 20% of patients are long-term survivors who would otherwise would have had residual disease if treated only by a superficial dissection. A prospective trial is currently testing the value of deep iliac dissection in patients who will have superficial dissection.

**STAGE III DISEASE: MANAGEMENT OF THE CLINICALLY POSITIVE NODAL BASIN**

**THERAPEUTIC NODE DISSECTION**

The development of clinically palpable nodes in the draining basins of a primary melanoma requires TLND to control local disease. Although there are no randomized trials clearly demonstrating a survival difference after TLND, a significant number of patients attain 5-year survival. Furthermore, the palliative benefits of TLND are considered in patients who are RT-PCR negative and histologically negative. Twenty percent of these patients developed either locoregional or systemic disease whereas only 5% of the PCR-negative patients developed signs of disease. One melanoma cell in 1 million background cells can be detected. Since approximately 80% of sentinel nodes will be negative, a quick screening of H&E-negative nodes using PCR may identify patients in whom the more labor-intensive immunostaining may be performed. One aim of the current Sunbelt trial is to examine the importance of PCR-positive lymph node and the effect of adjuvant therapy in patients with histologically negative nodes. The introduction of Taqman analysis may allow more accurate antigen quantitation and further insight into the details of sentinel lymph node biopsies in these patients with thin lesions.

In patients with a prior history of melanoma but without evidence of infection, 90% of lymphadenopathy is associated with tumor. Tumor-involved nodes tend to be firm and spherical. Five-year survival rates following TLND range from 19% to 38% in retrospective series. In one series of 133 patients undergoing iliac and inguinal nodal dissection, those with one, two, three, or four lymph nodes positive for tumor had median survivals of 90, 78, 49, and 15 months, respectively. The median survival was significantly worse for those with deep nodes positive with survival of 53, 42, 14, and 9 months, respectively.

**Inguinal Dissection**

The extent of surgical management in patients with clinically palpable inguinal nodes is a controversial topic in the treatment of melanoma. An inguinal groin dissection can be either superficial, including all nodes below the inguinal ligament, or complete, including the deep iliac and obturator nodes accessed through retroperitoneal exposure. The superficial dissection is carried out through a longitudinal incision with the removal of subcutaneous tissues, lymphatics, and the anterior portion of the femoral sheath. A sartorius muscle flap is used in closure to protect the femoral vessels and decrease wound complications.

Of patients with palpable inguinal nodes, up to 37% have histologically positive deep iliac nodes. Some believe that the routine removal of all deep nodes in patients with palpable inguinal disease is indicted, whereas others believe patients with radiologically positive pelvic nodes should not undergo TLND given the likelihood of distant disease. There are currently no randomized data comparing complete and superficial LND. Case series suggest that performing a deep inguinal dissection increases the mortality of the operation and does not to offer an obvious survival advantage in a radiologically negative pelvis. In comparing patients who undergo deep TLND for known positive iliac disease with those who have no apparent pelvic disease and only positive inguinal disease, overall survival is equivalent. For some, this is evidence that pelvic dissections are beneficial. They argue that those with grossly positive pelvic nodes should have a predictably worse prognosis since those patients had significantly more positive lymph nodes of generally larger size. There is some suggestion that the probability of a groin recurrence decreased with the inclusion of a deep iliac dissection. In a retrospective review of 362 therapeutic groin dissections, 20% had positive deep inguinal nodes. The 5- and 10-year survival for those patients was 24% and 20%, respectively, with the number of positive iliac nodes an independent prognostic factor. The authors suggest that deep lymph node dissection may be of benefit as up to 20% of patients are long-term survivors who would otherwise would have had residual disease if treated only by a superficial dissection. A prospective trial is currently testing the value of deep iliac dissection in patients who will have superficial dissection.

**Axillary Dissections**

Therapeutic axillary nodal dissection for melanoma involves the complete removal of levels I and II nodes, and some advocate the removal of level III nodes including subsection IVb. This dissection has just closed with 1800 patients accrued, and long-term results are awaited. The Multicenter Selective Lymphadenectomy Trial uses strict guidelines in handling nodal tissue. The Trial recommends cutting the lymph node in two halves through its longest diameter and fixing the specimen. Ten serial 8- to 10-µm sections are then made. Sections 1, 3, 5, and 10 are used for H&E staining, section 2 for S-100, section 4 for HMB-45, and sections 6 and 7 are negative controls for immunoperoxidase studies. Sections 8 and 9 are used to repeat any needed studies.

The use of RT-PCR, or potentially in the future, Taqman analysis to examine nodes for mRNA of melanosomal proteins may be valuable as this could reduce sampling error and improve sensitivity. Its extreme sensitivity, however, may result in the inappropriate upstaging of patients and overtreatment of patients falsely termed positive. In one study of RT-PCR of 124 patients, 58% of patients with histologically negative nodes were upstaged. This group of patients had a worse overall prognosis than those who were RT-PCR negative and histologically negative. Twenty percent of these patients developed either locoregional or systemic disease whereas only 5% of the PCR-negative patients developed signs of disease. One melanoma cell in 1 million background cells can be detected. Since approximately 80% of sentinel nodes will be negative, a quick screening of H&E-negative nodes using PCR may identify patients in whom the more labor-intensive immunostaining may be performed. One aim of the current Sunbelt trial is to examine the importance of PCR-positive lymph node and the effect of adjuvant therapy in patients with histologically negative nodes. The introduction of Taqman analysis may allow more accurate antigen quantitation and further insight into the details of sentinel lymph node biopsies in these patients with thin lesions.

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considered if the limb is nonfunctional or hygiene cannot be maintained. When amputations are necessary, they should be performed as either a hip disarticulation or

Resection is indicated for small, easily excised recurrent tumors and patients with a limited number of in-transit lesions. Simple resection may delay or even eliminate

SURGICAL EXCISION

FIGURE 42.2-23. In-transit disease most often is found between the primary lesion and the draining lymph nodes but in advanced instances is able to track beyond these sites, presumably through lymphatic connections.

SURGICAL EXCISION

Resection is indicated for small, easily excised recurrent tumors and patients with a limited number of in-transit lesions. Simple resection may delay or even eliminate the need for ILP. Wide excisions are unnecessary and excessively morbid in patients whose lymphatics are already contaminated. Amputation should only be considered if the limb is nonfunctional or hygiene cannot be maintained. When amputations are necessary, they should be performed as either a hip disarticulation or
hemipelvectomy as distal amputations usually fail locally. The 5-year disease-free survival after amputation in older series is approximately 20% to 35%.

**ISOLATED LIMB PERFUSION**

ILP for the introduction of chemotherapeutic agents to control regional malignant disease was first described in 1958 by Winblad. Approximately 50% of primary melanomas occur in the extremities, and approximately 10% of those patients have a recurrence as in-transit disease. As only rare patients respond to systemic therapy, ILP was developed as a means of limb salvage that would enable the delivery of cytotoxic drugs locoregionally at doses many-fold higher than would be tolerable systemically. No clear agreement exists on which patients benefit most from ILP and which regimens are most active. Prospective randomized trials that examine regimen, toxicity, dosage, and response are in development. Currently, melphalan is the gold standard reagent for use in ILP. Melphalan can be safely delivered locally at doses ten times higher than systemically tolerated. One-half of patients exhibit a complete response and 75% at least have a partial response to melphalan. Melphalan delivered at maximal systemic doses has negligible activity against melanoma. The use of hyperthermia has also become standard during ILP since Stehlin, in 1969, described improved response rates using perfusate at temperatures of 38.8 to 40°C. Current randomized studies seek to demonstrate that combination therapy using melphalan and TNF is superior to melphalan alone in treatment of patients with in-transit disease and the combination has been reported to have a 100% response rate.

**Indications**

ILP is useful in two groups of patients. Those with locoregionally advanced melanoma such as satellitosis and in-transit metastasis and those in need of palliation who have bulky regional disease and limited systemic metastasis. Prophylactic ILP for use as an adjunct to wide local excision in patients with a high-risk primary or recurrent melanoma cannot be recommended since no improvement in survival can be shown in prospective trials.

**Prophylactic (Adjuvant) Isolated Limb Perfusion**

A well-designed multiinstitutional prospective trial of ILP with melphalan was conducted by the consortium of the EORTC, the WHO, and the North American Perfusion Group. In 1998, the results of this multicenter randomized phase III trial of ILP in patients with primary cutaneous melanoma greater than 1.5 mm in thickness were published. A total of 832 patients were randomized to have wide local excision or wide local excision plus ILP with melphalan and hyperthermia. Median follow-up was 6.4 years. There was no difference in survival. Patients who had not undergone ELND had a nonsignificant trend for a longer disease-free interval. In a subset of patients with melanoma of 1.5 to 2.99 mm thickness, in-transit metastasis was reduced from 6.6% to 3.3% and regional lymph node metastasis was reduced from 16.7% to 12.6%. In thicker lesions, patients succumbed to distant disease. Other retrospective series demonstrate the lack of benefit for prophylactic ILP. A series of 111 patients compared with 111 historical controls with subungual melanoma demonstrated no difference in survival after ILP with melphalan alone. Prophylactic ILP with melphalan cannot be recommended as an adjunct to standard surgical therapy in high-risk melanoma patients.

**Therapeutic Isolated Limb Perfusion**

The role of ILP in prolonging overall survival has some support in the literature. Multiple randomized studies suggest improved survival in a subgroup of patients that undergoes ILP. ILP also is quite effective at ameliorating symptoms from bulky disease such as pain, edema, decreased mobility, and skin breakdown. Numerous nonrandomized series claim survival advantages with melphalan-based ILP, but only two prospective randomized trials, with unfortunately conflicting and criticized results, exist in the literature (Table 42.2-9, Table 42.2-10, and Table 42.2-11).

| Table 42.2-9. Five-Year Survival after Isolated Limb Perfusion Compared with Historic Controls |
|---|---|
| Author | Complete (%) | Partial (%) |
| Subin, 1989 | 54 | 8 |
| Santarelli, 1989 | 60 | 4 |
| Di Pasquale, 1990 | 50 | 5 |
| Kralovecz, 1991 | 59 | 4 |

| Table 42.2-10. Prospective Therapeutic Trials of Isolated Limb Perfusion |
|---|---|
| Author | Complete (%) | Partial (%) |
| Suman | 54 | 8 |
| Santarelli | 60 | 4 |
| Di Pasquale | 50 | 5 |
| Kralovecz | 59 | 4 |

| Table 42.2-11. Tumor Response after Isolated Limb Perfusion with Melphalan Alone |
|---|---|
| Author | Complete (%) | Partial (%) |
| Suman | 54 | 8 |
| Santarelli | 60 | 4 |
| Di Pasquale | 50 | 5 |
| Kralovecz | 59 | 4 |
Ghussen et al. reported results in 107 patients in which wide excision and regional lymph nodes dissection were compared with hyperthermic (42°C) perfusion with melphalan at a mean follow-up period of 554 days. The recurrence rate in the control group was 27.8% in stage I, 31.6% in stage II, and 58.8% in stage III compared with 5.6% in stage I, 5.5% in stage II, and 12.5% in stage III, suggesting improved survival for stage II and III patients. However, there has been wide skepticism regarding the results of this small study. Hafstrom et al. reported a prospective randomized trial in 69 patients testing application of regional hyperthermic perfusion with melphalan after surgery to one-half of patients following excision. Median disease-free survival was 17 months in the perfusion group and 10 months in the control group. There were 15 locoregional recurrences in the perfusion group and 24 in the control group. The disease-free survival was better for the perfusion group than for the control group, but no significant difference in overall survival was noted. Of note, Hafstrom et al. used a lower dose of melphalan than currently standard. Patients developing recurrence after ILP may undergo repeat ILP, but there is a high limb recurrence rate and diminished response and disease control interval with increased toxicity.

Patient factors that have been associated with therapeutic benefits include minimal total tumor surface area, absence of regional node involvement, number of lesions, and lack of previous recurrence.

**Technique and Dosing**

ILP of the lower extremity is performed via cannulation of the external iliac artery and vein through a suprainguinal retroperitoneal dissection. All venous and arterial branches including the hypogastriac artery are ligated to prevent systemic leak syndrome. Cannulation of the upper extremity is similarly performed through the axillary vessels. A proximal tourniquet aids in limiting systemic exposure to the perfusate. The extracorporeal perfusion circuit is primed with 700 mL saline, 1 U of packed red blood cells, and 1500 U of heparin, and flow is maintained in the range of 50 mL/L limb volume per minute (Fig. 42.2-24). The amount of systemic leak is measured using 111In radiolabeled albumin or 99mTc-labeled red blood cells with the gamma counter over the precordium.

**Figure 42.2-24.** Operating room setup of isolated limb perfusion. Note the cumbersome apparatus. If clinical trials are performed demonstrating similar efficacy using isolated limb infusion, the simplification of the treatment of regional disease may enable a more widespread treatment.

**Other Agents**

Melphalan is an alkylating agent that is the mustard derived from phenylalanine, an essential precursor used in melanin synthesis by melanocytes. Weiberdink developed a regional toxicity scoring system to grade the reaction based on actual measurement of limb volume (Table 42.2-12). Based on this dosing regimen, a dose of 10 mg/L for the lower extremity and a dose of 13 mg/L for the upper extremities were developed to limit severe toxicities and optimize response.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Vascular changes</th>
<th>Stromal changes</th>
<th>Other symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>No evidence of necrosis</td>
<td>No evidence of changes</td>
<td>No evidence of changes</td>
</tr>
<tr>
<td>II</td>
<td>Nodular necrosis, acute ischemia</td>
<td>Minimal stromal changes</td>
<td>Minimal systemic symptoms</td>
</tr>
<tr>
<td>III</td>
<td>Concentrated necrosis, ischemia, or lack of flow</td>
<td>Severe stromal changes</td>
<td>Severe systemic symptoms</td>
</tr>
<tr>
<td>IV</td>
<td>Extensive necrosis, severe damage in the deep tissues</td>
<td>Complete destruction of tissue damage</td>
<td>Complete systemic symptoms</td>
</tr>
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</table>

**Table 42.2-12.** Weiberdink Grading System for Regional Tissue Toxicity after Isolated Limb Perfusion

The use of hyperthermia has become standard with the use of ILP, as it seems to augment tissue concentrations of melphalan. True hyperthermia is defined as greater than 41.5°C, mild hyperthermia as 38.5° to 41.5°C and controlled normothermia as 36° to 38°C. Temperatures above 42°C are directly cytotoxic to tumor but result in excessive adverse effects. Stehlin suggested an improvement in the 5-year survival rate from 22% to 76% after introduction of hyperthermia to ILP, but others have demonstrated conflicting data. In one series of 136 patients with recurrent extremity melanoma, a minimum temperature of 41.5°C was an independent factor predictive of complete response. By contrast, hyperthermia was not a significant factor related to complete response in an equally large series (n = 120). The optimal duration of therapy, which has ranged from 45 minutes to 2 hours, is unknown.

**Other Agents**

A number of other agents in addition to melphalan have been administered by ILP including cisplatin, etoposide, actinomycin D, dacarbazine, thiopeta, mitoxantrone, IL-2, IFN-g, TNF-a, and lymphokine-activated killer (LAK) cells alone or in various combinations. Although dacarbazine requires systemic hepatic conversion to its active metabolite, it has been shown, when administered by ILP, to generate an overall response rate of 76%. Cisplatin has an overall response rate of over 50%, but the median response duration is only 5 months. ILP using drugs other than melphalan and TNF is less effective and often associated with increased toxicity.

In murine systems, TNF is capable of significant antitumor effects with a single intravenous injection, but effective doses cannot be achieved systemically in patients because of hemodynamic collapse. Immunohistochemical analysis of biopsies from patients treated with ILP with TNF demonstrates intravascular platelet aggregation, endothelial activation, and neutrophil invasion. Specific tumor vasculature destruction with sparing of the normal vessels is also seen.

The initial study of regional administration of high-dose TNF in conjunction with melphalan and low doses of IFN-g was reported in 1992, demonstrating a complete response rate of 90%. Many other case series corroborate the apparently enhanced activity of combination therapy. IFN-g induces the up-regulation of TNF receptors on tumor cells and has in vitro synergism with TNF in antitumor activity. A randomized trial comparing TNF and melphalan alone or in combination with IFN-g has shown no benefit with the addition of IFN-g.
A dose of 4 mg of TNF, more than ten times the maximal tolerable systemic dosage, is well tolerated during perfusion, and adverse effects are reportedly no greater than with melphalan alone. Subsequent clinical trials demonstrate no benefit for doses above 4 mg. The melphalan and TNF regimen has been successfully applied in patients who historically do not respond to melphalan ILP treatment alone. Patients with bulky disease, who historically are less likely to respond to melphalan alone, may have an improved outcome with the addition of TNF. In addition, those who have failed treatment or had recurrences after prior ILP with melphalan or other chemotherapeutics are candidates for TNF therapy. Phase III randomized studies evaluating ILP and melphalan with or without TNF in patients with localized, advanced, extremity involvement are currently underway.

**Toxicity**

Perioperative toxicity is common but generally tolerable and reversible. Acute regional toxicity after ILP includes pain within the first 48 hours and edema that usually resolves within 14 days. Erythema associated with the procedure fades over a period of 3 to 6 months. Melanomatous lesions soften and flatten, and biopsies show melanin pigment within macrophages without evidence of melanoma cells. Patient age is not an absolute contraindication for perfusion as adverse effects do not appear to be significantly greater in patients greater than 70 years of age. Vrouenraets et al. evaluated 425 patients for treatment-related toxicities after ILP, finding grade I and II toxicities in 85%, grade III and IV toxicities in 15%, and grade V toxicities in 0.5% (Table 42.2-14). The degree of limb toxicity, since it has no correlation with tumor response, should be avoided. Creatinine kinase levels greater than 1000 U after the first postoperative day and temperatures higher than 40°C are both strongly associated with development of severe toxicities. Although some centers recommend prophylactic fasciotomies during ILP, many surgeons simply monitor compartment pressures postoperatively. Renal failure secondary to myoglobinuria can be prevented by maintaining adequate urine output (greater than 4 L/d) and alkalization (pH greater than 7.5) during the first 2 to 3 postoperative days. Serious long-term sequelae of ILP are uncommon. Mild neuropathies are noted in up to 20% to 40% of patients (possibly from the tourniquet) after perfusion (Table 42.2-15). Some advocate the use of drugs other than melphalan to prevent wound complications and edema. The use of dacarbazine, cisplatin, or carboplatin may have less adverse effects but no trial has directly compared the therapeutic and toxic effects of these various regimens. Some evidence suggests that nonmelphalan regimens have more rapid recurrence rates. The incidence of wound complications increases significantly in patients who undergo concurrent lymphadenectomy. Some surgeons opt to perform a lymphadenectomy as a staged procedure after 6 to 8 weeks, whereas others routinely perform them in order to avoid a difficult operation in a previously explored site.

### TABLE 42.2-13. Tumor Response after Isolated Limb Perfusion with Tumor Necrosis Factor and Melphalan

<table>
<thead>
<tr>
<th>Author</th>
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<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Leithead, 1999</td>
</tr>
<tr>
<td>Klee, 1996</td>
</tr>
<tr>
<td>Van Cutsem, 1999</td>
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<tr>
<td>Kentelath, 1999</td>
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### TABLE 42.2-14. Regional Toxicity of Isolated Limb Perfusion

<table>
<thead>
<tr>
<th>Side Effects</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edema</td>
<td>28</td>
</tr>
<tr>
<td>Nausea</td>
<td>9</td>
</tr>
<tr>
<td>Decreased mobility</td>
<td>28-40</td>
</tr>
<tr>
<td>Pain</td>
<td>8</td>
</tr>
</tbody>
</table>

### TABLE 42.2-15. Late Morbidity of Isolated Limb Perfusion

Almost all patients develop hypotension and tachycardia during ILP with TNF. Furthermore, patients undergoing ILP with a TNF with measured leaks of greater than 1% develop mild and transient postoperative hypotension. Prevention of systemic leak and fluid loading before tourniquet release may help prevent the need for vasopressors. The use of a perioperative Swan-Ganz catheter is strongly recommended. Disturbances in pulmonary function are common with TNF but resolve to baseline in 8 weeks. Fever, nausea, and reversible hepatic toxicity are also common with TNF protocols. Acute vascular complications are rare (2.1%) and consist mainly of arterial thrombosis for which urgent embolectomy is required.

### ISOLATED LIMB INFUSION

Thompson et al. have reported an alternative approach called isolated limb infusion with the percutaneous insertion of venous and arterial catheters in the axial vessels followed by proximal tourniquet limb vessel occlusion. The procedure is performed under normothermic and hypoxic conditions for 30 minutes without an oxygenator, thus avoiding much of the cost and complexity of ILP. Long-term survival results are still pending, but complete response rates comparable with ILP are reported. More investigation of this technique is necessary before wide acceptance.

### INTRAARTERIAL THERAPY

Intraarterial cisplatin combined with systemic therapy has been used with only modest success. Fifteen patients treated with systemic vincristine and dacarbazine and intraarterial cisplatin were observed to have a 67% response rate. Only 45% were complete responses and one was pathologically positive at subsequent biopsy.
LOCAL ABLATION

Hill and Thomas reported the use of the ablation of multiple melanoma nodules using a CO₂ laser. Their initial series had a surprising recurrence rate of only 2%. Another small series treated 19 patients with laser ablation. After a median follow-up of 15 months, five patients died of the disease. Among the 14 survivors, 8 had no limb recurrence and the remaining required further treatments to control disease. In larger European trials, higher recurrence rates with this technique are reported. The use of electrical pulses directly applied to cutaneous metastases after administration of local or systemic bleomycin may have activity against melanoma. In one series, a 91% response rate was noted without any significant reported side effects. The use of photodynamic therapy may have some use in the treatment of patients with in-transit disease. Photodynamic therapy can specifically ablate malignant cells at depths up to 1 cm. There are yet no series of melanoma patients using this technique. These treatments may offer reasonable local control using a minimally invasive approach of nonbulky regional disease.

LOCAL IMMUNOTHERAPY

Local injection of bacille Calmette-Guérin (BCG), IFN-a, and other agents has been occasionally locally effective, but has not shown systemic effect on noninjected metastases and has been occasionally associated with significant toxicity (e.g., Pott's disease with systemic BCG infection). For those reasons, BCG is little used at present for local therapy.

RADIOThERAPY

Radiotherapy can be useful in managing in-transit metastases that are too extensive for surgical resection and as an adjuvant therapy after resection of recurrent in-transient disease. Treatment techniques and outcome are similar to those for management of lymph node metastases and remote subcutaneous metastases and are discussed in the sections Stage III Disease: Management of the Clinically Positive Nodal Basin; and Stage I and II Disease: Management of Primary Melanoma.

SYSTEMIC THERAPY

The use of dacarbazine and other systemic chemotherapy, biologic agents, or both benefit patients with in-transit disease at rates equivalent to patients with systemic disease. Immunotherapies including IFN and IL-2 have shown benefit in a small number of patients. Patients with in-transit disease may be ideal candidates for immunobiologic intervention because of their low tumor burden. The use of IL-2 and other novel immunotherapies such as IL-12, IL-18, peptide, or DC-based vaccines may prove effective in the future to control in-transit disease. Morton from the John Wayne Cancer Institute has used the CancerVax vaccine for patients with in-transit disease, and in nonrandomized patients suggests an approximate 50% 5-year survival.

ADJUVANT MEDICAL THERAPY

The prognosis of melanoma predicted from staging information allows the designation of low-, intermediate-, high-, and very high-risk groups that serve as guideposts for the potential consideration of adjuvant therapy. Patients previously enrolled in trials of adjuvant therapy have been those at high risk, in whom relapse and mortality risk exceed 50% at 5 years. The entry criteria for patients in high-risk trials has previously included both locally advanced, surgically curable (AJCC stage IIB), and regionally metastatic node-positive melanoma.

The adjuvant therapy of melanoma using IFN and other related agents is here considered separately under the previously defined categories of high-risk for recurrence melanoma (AJCC stage IIB and III), and with intermediate-risk melanoma (AJCC stage IIA). Patients with AJCC stage I disease have a low relapse risk and an excellent overall and relapse-free survival. For this reason, stage I patients are unlikely to benefit from such therapy and have not been the focus of any adjuvant therapy trials.

IMMUNOSTIMULANTS

A number of approaches for postsurgical adjuvant therapy have been tested since 1970. These have included systemic chemotherapy, immunostimulation with crude microbial agents such as BCG, Corynebacterium parvum, and picibanil, derived from Streptococcus pyogenes. The anthrhemithic chemical immunomodulator levamisole has undergone extensive evaluation. Unfortunately, randomized controlled trials have not demonstrated reproducible increases in relapse-free or overall survival with any of these modalities.

INTERFERONS

More recently, the use of individual cytokines obtained and partially purified from human cells or synthesized by recombinant DNA technology have shown an effect on the natural history of this disease. The IFNs have been the most intensely studied agents for the adjuvant therapy of intermediate- and high-risk melanoma. Results of randomized controlled clinical trials in the United States National Cooperative Groups have now yielded both positive and negative results using high- and low-dose IFN-α. A summary of IFN trials for the adjuvant treatment of melanomas is shown in Table 42.2-16.
Adjuvant Therapy for High-Risk (American Joint Committee on Cancer Stage IIB and III) Melanoma

IFN-α has been widely tested for the adjuvant therapy of melanoma, and the most extensively evaluated IFN-α subspecies has been IFN-α2a. Other agents currently undergoing evaluation in randomized trials include the chemically defined ganglioside vaccines: GM2, keyhole limpet hemocyanin, plus QS 21 (Progenics) and allogeneic whole tumor–derived vaccines for which trials are incomplete or inconclusive [Melacine (Corixa) and CancerVax (John Wayne Cancer Institute)]. Regimens using IFN-α2a for high-risk melanoma can be divided into high-dose regimens given for 1 year, high-dose regimens given for periods of shorter duration (3 months), and low-dose regimens given for longer intervals (of 2 to 3 years). Results of adjuvant IFN trials are shown in Table 42.2-17.

High-Dose Regimens of IFN-α of Intermediate Duration

The ECOG initiated a trial in 1984 (1684) for patients with melanoma at high risk for relapse following surgical resection of primary tumor, regional lymph node metastasis, or both. Twenty-nine centers contributed 287 (280 evaluable) patients who were randomized to treatment with IFN-α2a or observation. Eligibility criteria included the presence of a T4 primary lesion with or without regional lymph node involvement or primary lesions of any depth with pathologically proven regional lymph node involvement. Patients with cutaneous melanoma of any thickness, but with the regional lymph nodes as the site of initial and only relapse were also eligible. All patients underwent regional lymph node dissection and were stratified with respect to clinical and pathologic stage of disease. Maximal tolerable doses of IFN-α2a were used: an initial induction phase of 20 MU/m² intravenously daily for 5 to 7 days for 4 weeks followed by a maintenance phase at 10 MU/m² subcutaneously, three times a week for 48 weeks (total treatment duration of 52 weeks). The rationale for the initial high-dose intravenous treatment phase was to provide maximum dose intensity and minimize the incidence of antibodies. At a median follow-up of 7 years, a significant improvement in both median relapse-free survival (1.72 vs. 0.98 years) and overall survival (OS) (3.82 vs. 2.78 years) was noted in an intent-to-treat analysis. Patients with established lymph node involvement, de novo or recurrent, appeared to derive the greatest benefit from treatment. Only a limited number of patients (31) who were clinically and pathologically node-negative (T4 N0) entered the study, and an imbalance in the distribution of the important prognostic variable, ulceration, made it difficult to draw firm conclusions for this subset. At five years the 40% improvement in relapse-free survival (26% vs. 37%) and 25% improvement in overall survival (37% vs. 45%) led the Food and Drug Administration to approve the use of IFN-α2a given for 1 year by this intravenous and subcutaneous schedule for patients with stage IIB/T4-N0 and stage III node-positive disease in 1995.

As expected, this regimen was associated with substantial toxicity, and grade 3 and 4 (ECOG toxicity scale) events were noted in the majority of recipients. Dose-modification or delays were required at least once in 50% of patients during the intravenous induction phase and in 48% of patients during the subcutaneous maintenance phase. Most treatment delays occurred in the first 4 months of the regimen. A retrospective quality-of-life (Q-TWiST) analysis revealed a mean gain of 8.9 months without relapse (P = .03) and 7 months of overall survival time (P = .02) for the IFN-treated patients after 84 months of follow-up as compared with the observation group. The treated group experienced severe treatment-related toxicity for an average of 5.8 months. The net result was that the IFN-treated group had more quality-of-life-adjusted survival time than the observation group, regardless of the relative valuations placed on time with toxicity and time with relapse. An economic analysis of the E1684 regimen was also published. The incremental cost of IFN per life-year gained ranged from $31,700 to $32,600 at 7 years (the median follow-up of E1684). The benefits of IFN projected over a lifetime yielded incremental cost per life-year or quality-adjusted life-year that are less than $16,000. This compares favorably with the rigorous Canadian benchmark of $20,000 per quality-of-life-year gained and is comparable with other accepted adjuvant therapies of breast and colorectal cancer.

To evaluate the observations regarding the results of trial E1684 and to evaluate concurrently the high-dose regimen and a low-dose IFN-α2a regimen against observation, Intergroup trial E1690 was initiated in 1991. This trial was designed and implemented before the availability of mature data from the E1684 trial. Eligibility criteria for E1690 were similar to those for E1684 but dropped the requirement for regional lymphadenectomy for patients with deep (T4; greater than 4 mm) primary lesions. Six hundred forty-two (95% eligible) patients were randomized to either high-dose IFN-α2a as in E1684, low-dose IFN-α2a for 2 years (IFN-α2a 3 MU subcutaneously, T=TIW), or observation. At a median follow-up of 52 months, the 5-year estimated relapse-free survival for high-dose IFN-α2a, low-dose IFN-α2a, and observation were 44%, 40%, and 35%, respectively. High-dose IFN-α2a showed a significant effect on relapse-free survival as compared with observation in a Cox analysis (P = .03), prolonging median time to relapse by 10 months. There was no significant effect of low-dose IFN-α2a on relapse-free survival, and neither high-dose IFN-α2a nor low-dose IFN-α2a demonstrated a benefit in overall survival.

Of note, the median overall survival for patients assigned to observation in E1690 was 6 years as compared with only 2.8 years for observed patients on E1684. The question has arisen whether the use of systemic IFN-α2a among one-third of patients who relapsed (n = 38), who were originally assigned to observation, may have been in part responsible for the large gain in postrelapse survival seen in E1684. The postrelapse survival for patients originally assigned to observation who subsequent to relapse received IFN, versus those who never received IFN, was significantly prolonged (median 2.2 years vs. 0.8 years; P = .0024). Other factors that could potentially account for the improved outcome on this trial randomized to observation include the use of more accurate staging techniques or more modern surgical intervention at initial treatment, subsequent relapse, or both.

Low-Dose Interferon-α2a for 2 to 3 Years

The use of lower, nontoxic doses of IFN-α2a for high-risk melanoma has been studied both in the United States and in Europe. Between 1990 and 1993, the WHO Melanoma Program entered 444 patients to a randomized trial comparing 3 years of treatment with IFN-α2a (3 MU subcutaneously, TIW) or observation. This trial differed from the ECOG and NCCTG trials in regard to eligibility: Only patients with regional lymph node metastases were eligible for randomization after lymphadenectomy. One-half of the patients studied had extracapsular extension with lymph node involvement, a feature that was excluded from ECOG studies 1684, 1690, and the NCCTG B37052 trials. A preliminary report at 22 months median follow-up suggested prolongation of recurrence-free survival among women younger
than 50 years and men older than 50 years, while a somewhat more mature interim report at 39 months median follow-up revealed no durable benefit in terms of either relapse-free interval or overall survival; a final publication is pending. The negative results of the low-dose arm of the Intergroup trial E1690 discussed previously confirm the results of WHO 16, both in terms of recurrence rates and overall survival for patients with high-risk melanoma.

The EORTC Trial 18952 is currently testing two intermediate doses of IFN-α2b in high-risk melanoma patients. The study design incorporates two 12-week arms and an observation arm. Treatment comprises a modified induction phase of IFN-α2b 10 MU subcutaneously injected, five times per week, followed either by 10 MU subcutaneously injected three times per week, for 1 year or 5 MU subcutaneously injected, TIW for 2 years. This study will accrue 1200 patients with high-risk resected melanoma, including patients with nodal disease with or without extracapsular extension, of whom 200 will be randomized to observation and 400 to each of the IFN arms (1:2:2 unbalanced assignment) to evaluate the role of dose intensity. The Nordic Melanoma Trial group are investigating the efficacy of two intermediate doses of IFN-α2b administered for 2 years, using a similar subcutaneous dosage schedule. While the induction phase and the maintenance phase are modeled on the pivotal E1684 trial, it is important to note that the peak levels of IFN-α2b attained by the intravenous administration of 20 MUI/m2 are orders of magnitude higher than the levels that can be detected following the administration of 10 MU/d, especially when given by the subcutaneous route (10,000 µM/mL vs. less than 100 µM/mL peak).

**Vaccines in the Adjuvant Therapy of Stage IIB and III Melanoma**

A number of vaccine approaches are being evaluated in the adjuvant treatment of patients with melanoma. Biochemical analysis has shown the presence of glycoproteins and melanomas, among others. In general, the purified gangliosides have not been shown to be immunogenic, and it has been difficult to induce antibody responses to these molecules with the exception of the ganglioside GM2, to which antibody responses have been detected spontaneously in up to 5% of patients with melanoma. Two studies have demonstrated that the presence of anti-GM2 antibodies confers a relapse-free survival advantage for patients with melanoma. This led to the conduct of a randomized controlled trial of GM2 plus BCG versus BCG alone (both with cyclophosphamide pretreatment) in 122 patients with AJCC stage III melanoma, at the Memorial Sloan-Kettering Cancer Center in New York. GM2 antibody was detected in 50 of 58 patients treated with GM2/BCG and in only 7 of 64 patients treated with BCG alone. Patients with anti-GM2 antibodies, either preexisting or induced by treatment, had a significantly longer relapse-free survival than antibody-negative patients. A nonsignificant increase in disease-free interval (18%) and overall survival (11%) was found for the GM2/BCG-treated group as a whole. However, exclusion of patients with preexisting anti-GM2 antibodies from the analysis suggested a benefit in terms of disease-free interval for those who developed an antibody response to GM2.

A range of efforts to improve the immunogenicity of the GM2 molecule were tested, including conjugation to immunogenic carrier molecules, and adjuvants with potent new immunologic adjuvant agents. These have subsequently been found to induce more frequent and higher titer antibody responses to the GM2 molecule. The most potent combination tested uses the GM2 molecule coupled with a carrier protein derived from the keyhole limpet hemocyanin with an immunoadjuvant, QS21, a potent immunologic adjuvant of the saponin class. This vaccine induces qualitatively improved antibody responses of the IgG as well as IgM isotype, of higher titer than that obtained by GM2 plus BCG. The GM2, keyhole limpet hemocyanin, plus QS21 vaccine has been developed for clinical evaluation (Progencis, New York, NY: Bristol Myers Squibb) and is currently being compared with high-dose IFN-α2b in the Intergroup U.S. Trial E1694 for patients with AJCC stage IIB and III melanoma. This trial initiated in 1996 completed accrual of 1999, and all its results have recently been unblinded due to the significant relapse-free interval and overall survival advantage of HDI, substantially confirming both RFS ($P = 0.07$) and OS ($P = 0.09$) benefits of HDI observed in E1684.

The John Wayne Cancer Institute has performed a series of phase II trials employing cultured tumor cell–derived vaccines (CancerVax) administered with the immunostimulatory agent for patients with metastatic disease as well as intermediate- and high-risk resected melanoma. Encouraging phase II results have led to the initiation of two ongoing phase III randomized trials of adjuvant therapy for high-risk melanoma and resected metastatic disease patients believed to be at very high risk of recurrence. The first of these is comparing CancerVax plus BCG to BCG alone for the postsurvival treatment of AJCC stage III melanoma. The second is a randomized trial of CancerVax versus placebo for patients with stage IV melanoma rendered clinically disease free with surgery. Firm conclusions will only be possible regarding the therapeutic benefit of these vaccines as their randomized controlled trials are completed and mature.

On the basis of evidence that cellular immune responses to melanosomal antigens may be of therapeutic value, peptide antigens that represent the immunodominant and subdominant melanosomal antigens have been brought into multicenter adjuvant trials for patients with resectable stage IV (M1) or advanced stage III melanoma in an ECOG study E4697. E4697 will investigate treatment with a multipeptide three-epitope vaccine composed of Melan-A/MART-1, gp100, and tyrosinase antigens that have been studied previously in the National Cancer Institute Surgery Branch and the University of Pittsburgh melanoma Center/Biologic Programs. Adjuvant Therapy for Intermediate-Risk Melanoma

Patients with T3, Breslow depth 1.5 to 4.0 mm (S1992 AJCC stage IIA) melanoma account for a substantial fraction of patients at presentation and represent a heterogeneous group with 5-year survival greater than 72%. This category is historically twice as frequent as the stage III category, representing 31% of new melanomas. With 47,000 new cases of melanoma in the United States, approximately 19,000 represent stage II melanoma and from this group 5400 deaths are anticipated. This group of patients has been the focus of several completed European and newly initiated North American cooperative group studies.

**Low-Dose Interferon-a for 18 Months**

Adjuvant therapy trials for high-risk melanoma have generally excluded patients with stage IIA melanoma, although a subset of patients in the NCTCG trial 83-7052 (100 patients) had stage II disease. Austrian, French, and Scottish trial groups have evaluated the low-dosage regimen tested in E1680 and WHO 16 in regimens of IFN-α administered for shorter periods of 12 to 18 months for patients with stage II melanoma (defined by clinical examination alone). The results of these trials are therefore difficult to apply to patients for whom more precise staging, by means of sentinel node mapping, is available.

The French Cooperative Group on Melanoma randomized 499 patients with AJCC stage II melanoma to IFN-α2b 3 MU subcutaneous TIW injections for 18 months, or observation. After a median follow-up of 5 years, a significant improvement in relapse-free survival (P = 0.038) but not in overall survival (P = 0.59) was noted. The Austrian Malignant Melanoma Cooperative Group has reported a smaller trial that is somewhat less mature, at a mean follow-up of only 41 months. Three hundred eleven patients were randomized to observation or treatment with IFN-α2b 3 MU subcutaneous daily injections for 3 weeks, followed by 3 MU subcutaneous TIW injections for 1 year. The prolongation of relapse-free survival noted in this trial (P = 0.02) must be qualified given the short follow-up period; and the absence as yet of any overall survival data for this trial.

Patients entering these trials included those with stage IIA and stage IIB, but neither elective lymph node staging (as in E1684) nor sentinel node mapping were pursued in any participants. This stage grouping therefore represents a heterogeneous population for which multicenter sentinel lymphadenectomy trials suggest that SLNs would be positive in 20% to 28% of patients with T3, T4 melanomas, respectively. The sentinel node mapping technique has had its greatest effect in refining the prognosis for these nominal stage II patients, of whom 50% to 60% have node-negative subgroups at lower risk. These results of the reported studies of low-dose IFN-α2b show prolonged relapse-free interval for patients with intermediate-risk melanoma during treatment, with loss of this benefit over time following discontinuation of therapy. These results differ from the results of the high-dose regimens described previously in showing no durable effect on continuous relapse-free survival. Indeed, one of the conclusions that may be drawn from the Austrian and French experience, is that adjuvant therapy may be more effective against high-risk stage IIA melanoma.

**High-Dose Interferon-a for 4 Weeks**

The high-dose IFN regimens used in E1684 and E1690 were unique in their incorporation of an induction phase of intravenous therapy for the initial 4 weeks, at maximal tolerable doses. The rationale for the induction phase was to provide peak levels of IFN-α2b sufficient to inhibit tumor growth directly, as well as antivascular, and immunomodulatory effects on antigen-presenting and T-cell responses against melanoma antigens while avoiding the potential for induction of anti-IFN antibodies. The relative importance of the induction-phase is suggested by the early effect of E1684 and E1690 regimens, in which hazard functions for relapse-free survival indicated early suppression of relapse risk with high-dose IFN-α2b that is sustained for years after discontinuation of treatment. This has led to the hypothesis that peak dose exposure during induction may represent the critical component of the E1684/1690 regimens. Patient acceptance and tolerance for the induction phase is excellent. Dose modifications were required in one-half of patients during this phase (a fraction equivalent to the portion requiring dose modification during the subsequent maintenance phase). Removal from treatment was rarely necessary during this interval.
To help clarify the role of high-dose induction intravenous therapy, the ECOG and National Cancer Institute of Canada are currently conducting a randomized trial of intravenous therapy for 4 weeks alone, for patients with intermediate-risk stage IIA and IIB or microscopic nodal stage III N1A disease. Pathologic staging with SLN mapping and biopsy (or ELND) is not called for but mandatory, and patients are stratified according to the method of staging. Patients are randomized to receive either the intravenous induction therapy administered as in the first month of E1854 (IFN-a 20 MU/m²/week) or observation. To demonstrate a 7.5% improvement in relapse-free survival for the treated population with 80% power will require 1420 patients in this trial.

Sunbelt Trial
A multicenter adjuvant trial that has been designated the Sunbelt Trial tests the role of high-dose IFN-a 20b in patients who are staged by SLN mapping procedures and in which both routine (H&E and immunohistochemical) and molecular assays (RT-PCR for multiple markers including tyrosinase, MAGE, and gp100) are conducted. One goal is to assess the significance of molecular markers in contrast to immunohistochemistry and standard H&E. This study will require 3000 patients to have a power to assess its multiple goals.

Vaccine Trial for Intermediate-Risk Melanoma
A commercial vaccine preparation from cultured tumor cell lines (Melacine, Corixa) given together with the proprietary adjuvant agent Detox (monophosphoryl lipid A) has also been shown to induce antitumor responses in patients with metastatic melanoma. A pilot experience suggests improved responses in recipients who have been administered IFN-a 20b. The Melacine-cultured melanoma tumor cell vaccine administered with the monophosphoryl lipid A adjuvant Detox has been tested by the Southwest Oncology Group for the adjuvant therapy of patients with T3 melanoma (SWOG 9035). This trial was conducted between 1990 and 1996, with 700 patients having received either the vaccine with Detox, or observation, after primary melanoma resection. Results of this trial have been preliminarily reported, showing no significant prolongation of relapse-free and overall survival in a primary efficacy analysis, but a significant effect in an intention-to-treat analysis that has yet to be clarified.

TREATMENT OF STAGE IV DISEASE
Metastatic melanoma has a median survival of only 6 to 9 months and current systemic therapy has been shown to induce complete durable responses in only a small minority of patients. Most common sites of initial presentation with metastatic disease are the skin, lungs, liver, brain, and bone. Chemotherapy agents, biologic agents individually and in various combinations, and surgery have been used in the treatment of these patients. retrospective studies on 261 malignant melanoma patients with resected local (greater than or equal to 1.69 mm) and regional nodal disease. Follow-up consisted of physical examination, complete blood cell count, blood chemistry panel, and chest radiography and was performed every 2 and 4 months for the first 1 and 2 years, respectively, followed by every 6 months for the subsequent 3 years. Out of 145 evaluable patients with recurrent disease, 32% were asymptomatic. Physical examination detected 37 of 45 (82%) of the asymptomatic recurrences. Chest radiography detected the other 9 of 45 (22%) recurrences, while no recurrences were detected by blood tests alone. Rouet et al. studied 115 relapses in follow-up of 528 stage I melanoma patients. History and physical examination detected 90% of relapses, with chest radiography and abdominal ultrasound detecting the rest. Only two recurrences were resectable. Roth et al. evaluated bone, brain, and liver scans in the follow-up of 58 patients with node-positive melanoma. Only one patient with a true positive bone scan was found, thus calling into question its utility in patients with melanoma.

METASTASECTOMY AND RADIOTHERAPY
Surgical treatment of asymptomatic, distant metastatic lesions remains controversial because of the likelihood of widespread disease at other sites. However, a subgroup of patients exists that may benefit from surgical resection of metastatic lesions, and some surgeons have advocated the more widespread application of surgery in stage IV disease. Unfortunately, no randomized trials exist to support the use of metastasectomy. Retrospective reviews, largely from single institutions, have reported a survival difference in selected operated melanoma patients compared with historic controls. Although, metastatic melanoma has a worse prognosis (by a factor of two) after resection than other carcinomas, prolonged 5-year survival in some patients has been reported following complete resection of melanoma metastases of the lung, soft tissue, and even gastrointestinal tract. Metastasectomy in melanoma has also been advocated because of the absence of a demonstrable survival effect with currently available systemic therapies in more rigorous randomized controlled trials. However, the rigor with which systemic therapy has been tested is far greater than that with which surgical approaches have been evaluated to date. Although numerous series show survival benefits for metastasectomy compared with historic controls, selection bias may account for these differences. Unfortunately, randomized trials to determine the efficacy of surgery in this setting are not likely.

Metastasectomy should be considered in the absence of locoregional disease and when metastatic disease is confined to a single site that is amenable to complete resection. Before the application of metastasectomy with therapeutic intent, patients must be able to tolerate the operation and have appropriate staging studies demonstrating limited disease. The paradigm for optimal staging includes the use of brain magnetic resonance imaging, whole body CT, and PET scanning. The use of immunotherapy following metastasectomy may afford a more suitable setting for demonstration of the potential benefits of vaccine immunotherapy, as researchers at the John Wayne Cancer Institute are attempting to demonstrate.

Nonvisceral Metastasis
More than one-half of patients who have recurrent melanoma manifest disease initially at nonvisceral sites, and one-half of these lesions may be solitary. Adequate data predicting prognosis in patients with nonvisceral metastases range from an assessment of metastasectomy’s efficacy difficult. Following complete resection, median survivals of 8 to 50 months have been reported with 5-year survival between 10% and 61% of patients.

Radiotherapy is an alternative to surgery for managing symptomatic skin metastases not responding to systemic therapy. Impending skin breakdown and pain at the tumor site are relative indications for local ablative therapy. Lesions may respond to radiotherapy using high-dose fractions and high total doses. Commonly used fractionation schemes are 20 Gy/5 fractions and 30 Gy/10 fractions given in conventional daily fractions, or by means of hypofractionated schedules such as 21 Gy/3 fractions and 30 to 36 Gy/5 to 6 fractions.

Pulmonary Metastasis
The lung is the sole site of initial recurrence in 7% to 21% of melanoma patients and is the most common initial visceral site of metastatic disease. Lung metastases are usually detected as asymptomatic lesions on screening chest radiographs. Up to one-third of these are benign or represent a new primary neoplasm, suggesting the importance of biopsy and pathologic confirmation. There is conflicting information concerning prognostic factors such as rapidity of tumor growth, the disease-free interval, the number of lesions, and survival after metastasectomy. One factor that clearly correlates with median survival after resection is the ability to completely remove all metastatic disease.

The rapidity of tumor growth may affect survival after metastasectomy. The average melanoma has a tumor-doubling time of 30 days. Patients with a tumor-doubling time of greater than 60 days have a median survival of 23 months with a 5-year survival rate of 16%. Patients with a tumor doubling time less than 60 days had a median survival of 16 months and no 5-year survivors were reported. In a multivariate analysis, the number of pulmonary lesions, bilateral location, disease-free interval before diagnosis of pulmonary metastases, and size of the nodules did not significantly affect survival.

Five-year survival after pulmonary metastasectomy is 20% to 27%. Historic data suggest a median survival of 10 months in patients with disease confined to the lungs alone who were treated with dacarbazine, and the 1-year survival rate for patients receiving nonsurgical treatment was reported to be 36%.

In a retrospective analysis, improved survival was found when a second resection was performed after localized recurrence from a previous metastasectomy. Twenty percent of patients who had a second complete metastasectomy for melanoma were alive at 5 years.
Although no randomized trials exist, the resection of pulmonary metastases has been suggested in patients with melanoma whose preoperative radiographic workup showed no evidence of extrapulmonary disease. Almost all of these resections can be done using minimally invasive techniques, and even bilateral procedures can be undertaken with low morbidity. Following patients’ chest radiographs serially for a sufficient period may be a reasonable option in order to measure tumor-doubling time and reassess tumor burden when such therapy is considered. The rationale for such heroic surgical approaches may increase if adjuvant trials with IFNs, vaccines, or combinations are found to have a benefit in operable stage IV disease. These resected patients are ideal candidates for adjuvant immunotherapy trials as patients with limited tumor burden may respond better.

**Gastrointestinal Metastasis**

Only 5% of all patients who die of melanoma develop symptoms from gastrointestinal disease. Most have multiple lesions and the goal of surgery has been palliation of obstruction, perforation, or bleeding. Median survival after palliative surgery is only 10 months. The diagnosis of a solitary gastrointestinal lesion is quite uncommon; nonetheless, after resection of solitary gastrointestinal lesions, 5-year survival rates have been reported to be as high as 28% to 41% from some centers.

There is no evidence that invasive procedures for the treatment of hepatic metastasis benefits patients. There are occasional case reports of long-term survival after resections of isolated hepatic melanoma metastasis, but no substantial series exists in the literature. Hepatic metastasectomy cannot be recommended outside an investigational protocol setting. A series examining the use of isolated hepatic perfusion for hepatic melanoma metastasis has also only reported limited response rates in a small number of patients. At the University of Pittsburgh, hepatic metastasis from ocular melanoma demonstrates no advantage for cisplatin via hepatic artery administration and embolic occlusion of the hepatic artery over systemic administration, even with doses beyond the limits of systemic tolerance.

**Adrenal Metastasis**

Isolated adrenal metastases are uncommon; however, a large retrospective series of 83 patients suggested a benefit for surgical excision. Twenty-seven patients underwent surgical exploration and 18 were rendered clinically free of disease at surgery. There was a median survival of 25.7 months for patients rendered disease free compared with only 9.2 months after a palliative resection. Removal of resectable lesions is a reasonable option if other approaches are unavailable, although there is a substantial likelihood of selection bias rather than surgery per se accounting for the suggested benefits.

**Bone Metastasis**

Melanoma metastasizes to the bone relatively late in the disease course. Median survival is just 4 months after diagnosis. Truncal melanomas have a higher percentage of bony metastases compared with melanomas found at other sites. Of those with bone metastases, 67% responded to palliative radiotherapy or decompression with good pain relief. Bone metastases from melanoma respond in a similar fashion to bone metastases from other tumors, with doses of 8 Gy/1 fraction, 20 Gy/5 fractions, or 30 Gy/10 fractions.

**Brain Metastasis**

Brain metastases are detected clinically in 8% to 46% of patients and at autopsy in 55% to 75% of melanoma patients. Brain metastases usually require treatment to relieve symptoms, and available options depend on the number and location of lesions. Corticosteroid treatment often reduces symptoms by ameliorating swelling in many patients and may provide palliation. Melanoma metastatic to the brain is reasonably treated by gamma knife irradiation or surgically, if the lesion is solitary, symptomatic, and can be treated without major neurologic injury.

A series of patients with symptomatic, solitary, intracranial lesions showed a median survival after craniotomy of only 10 months. Patients who responded to previous immunotherapy and subsequently relapsed with intracranial disease seem to enjoy more significant benefit after craniotomy. Forty patients with melanoma or renal cell cancer metastasis involving the brain were reported in a study by the NCI. Thirty-six were rendered free of disease after resection of a single metastasis. The median survival after craniotomy for patients exhibiting complete response, partial response, and no response to previous immunotherapy was 23, 17, and 7 months, respectively. Of the ten patients who had achieved a prior complete response, eight remained disease free in the brain at last follow-up and some have had long-term survival. Twenty-five patients experienced neurologic symptoms before craniotomy, and all had complete resolution of their symptoms after surgical excision. The benefits of resection include palliation of symptoms and the potential for a prolonged disease-free interval in the brain.

The role of conventional radiation for multiple lesions or unresectable disease is controversial. Possibly, because of the sensitivity of the brain to large-dose fractions, studies of whole brain radiotherapy with high-dose fractions have shown little survival improvement. Whole brain radiotherapy (30 Gy/10 fractions) is standard therapy for multiple brain metastases with initial radiosurgery beneficial for cases with two to four metastases. Radiosurgery alone is recommended for patients with solitary brain metastases less than 3 cm in diameter (Fig. 42.2-25 and Fig. 42.2-26). Resection followed by whole brain irradiation is recommended for larger lesions with significant mass effect unrelied by corticosteroids. The local control rates with stereotactic radiosurgery employing single-fraction minimum tumor doses of 16 to 20 Gy are excellent. Mori reported the University of Pittsburgh experience with gamma knife radiosurgery (median marginal dose, 16 Gy; range, 10 to 20 Gy) in 118 brain melanoma brain metastases (median volume, 2.96 mL; range, 0.1 to 25.5 mL) in 60 patients. Median survival was 7 months after radiosurgery and 10 months after the initial diagnosis of brain metastasis, with a 90% local control rate. Local tumor progression developed in seven patients and subsequent remote brain metastases developed in 14 patients. Multivariate analysis demonstrated improved survival was associated with solitary brain metastases and for patients with no other active systemic disease.

![FIGURE 42.2-25. Actuarial survival curves for 60 patients with malignant melanoma treated by gamma knife radiosurgery. Survival is compared for patients with solitary brain metastasis and no active systemic disease (solitary/no systemic) at radiosurgery (n = 11), multiple brain metastases and active systemic disease (multiple/systemic) at radiosurgery (n = 11), and the remaining patients with either solitary brain metastasis and active systemic disease (single/systemic) or multiple brain metastases without active systemic disease (multiple/no systemic) at radiosurgery (n = 38). Some patients with limited brain disease and no systemic disease are able to enjoy prolonged survival. (From ref. 409, with permission.)](image-url)
Chemotherapeutic agents that have been most widely applied in metastatic disease are dacarbazine, the platinum analogs, nitrosoureas, and microtubular toxins (Table 42.2-18). Dacarbazine is considered the reference agent for melanoma, with a response rate of 14% to 20% in multiple series and a median response durations of 4 to 6 months. Long-term follow-up of patients treated with dacarbazine alone indicates that less than 2% of patients survive 6 years. Although early limited phase II and III trials suggested a benefit of tamoxifen, IFN-α, or cisplatin when added to dacarbazine for patients with metastatic disease, these benefits have not been confirmed in large-scale multicenter phase III trials. More recently completed phase III trials using dacarbazine-based combinations are summarized in Table 42.2-19.

The role of dacarbazine combinations involving either tamoxifen or IFN-α has been carefully evaluated. In 1992, a prospective randomized trial of dacarbazine and tamoxifen versus dacarbazine alone indicated that the combination therapy might be more effective. A 28% response rate and 41-week median survival was reported for patients receiving dacarbazine plus tamoxifen versus only a 12% response rate and 23-week median survival for patients treated with dacarbazine alone. The benefit of tamoxifen in this setting was attributed to the potentiation of the cytotoxic chemotherapy rather than to direct antitumor hormonal (antiestrogenic) effects. In a small, randomized trial that compared dacarbazine with dacarbazine and high-dose IFN-α, the combination therapy produced 12 complete and four partial responses in 30 patients compared with only two complete and four partial responses among 30 patients treated with dacarbazine alone. Median response duration and survival were significantly prolonged when dacarbazine was combined with IFN-α. Unfortunately, a large-scale four-arm two-by-two factorial phase III ECOG trial has reexamined the benefit of both tamoxifen and IFN-α using the same protocol and failed to confirm the initial encouraging observations. The overall response rate in this trial (ECOG 3690) was 18% (range, 12% to 21% for the four arms), and median time to treatment failure was 2.6 months. Median survival was identical for all four arms tested at 9.1 months. There was no advantage in terms of response or survival attributable to the addition of IFN-α, tamoxifen, or both agents, to dacarbazine. There is no evidence, based on this trial and the cumulative observations from prior studies to support the use of IFN-α or tamoxifen in combination with dacarbazine in metastatic melanoma. Unfortunately, we also have no clear indication that dacarbazine itself provides any substantial survival benefit, although it represents conventional therapy at this time.

Many chemotherapy combinations have produced response rates ranging from 30% to 50% in single-institution phase II trials for metastatic melanoma. Two of the most active combinations reported are the three-drug combination of cisplatin/vinblastine/dacarbazine (CVD) developed by Legha and the group at M. D. Anderson and the four-drug combination of cisplatin/dacarbazine/carmustine and tamoxifen (CDBT) developed by Del Prete at Dartmouth and known commonly as the Dartmouth combination. The CVD regimen produced responses in 40% of 50 patients with 4% complete response and a median response duration of 9 months. In a randomized multicenter trial comparing CVD with dacarbazine alone encompassing approximately 150 patients, the CVD arm produced a 19% response rate compared with 14% for dacarbazine alone with no differences in either response duration or survival.

The four-drug CDBT or Dartmouth regimen produced responses in 46% of 141 patients (16 complete response and 49 partial responses). Median response duration for this large population was more than 7 months. The inclusion of tamoxifen was suggested to be essential with response rates of 10% when tamoxifen was omitted. However, a randomized phase III NCI Canada Melanoma Trial comparing CDBT with CDB alone showed a response rate of 30% for the CDBT arm and no added value resulting from tamoxifen. In 1999, a randomized phase III trial performed by a consortium including ECOG and Memorial Sloan-Kettering Cancer Center showed no benefit for the CDBT combination relative to dacarbazine alone. This trial involved 240 patients, and the response rate with dacarbazine was 10.2% compared with 18.5% for the CDBT regimen (P = .09). The median survival time from randomization was 7 months, with no difference between the two treatment arms. Toxicity was substantially greater, with bone marrow suppression, nausea, vomiting, and fatigue significantly more frequent with the CDBT treatment regimen than with dacarbazine. Taken together, current controlled trials to date have shown no compelling evidence to support the value of combination chemotherapy.
Temozolomide is a nonclassical prodrug of MTIC (5-/3-N-methyltriazen-l-yl)-imidazole-4-carboxamide), the alkylating agent that is the active metabolite of dacarbazine. Temozolomide spontaneously converts into its active metabolite and in several trials has shown antitumor activity against melanoma that is at least equivalent to that of dacarbazine. A randomized phase III study of temozolomide versus dacarbazine was published in which patients with advanced melanoma were randomly assigned to receive either oral temozolomide at a starting dose of 200 mg/m²/d for 5 days every 21 days. Median survival was 7.7 months for patients treated with temozolomide and 6.4 months for those treated with dacarbazine. No major differences in toxicity were seen. Systemic levels of the active metabolite MTIC were higher than with the intravenous dosing of dacarbazine, and overall quality of life was improved with temozolomide. Temozolomide also has been examined in phase I trials for use in conjunction with cisplatin and has been shown to be safe at the studied dosages. The most attractive advantage of temozolomide is the well-documented penetration of third spaces such as the central nervous system (CNS) and ascites fluid. Approximately one-half of the circulating levels in the blood has been documented in the CNS, and temozolomide has been shown to be an active agent against CNS melanoma, as well as glioblastoma multiforme. Failure to demonstrate improvements in survival has led to denial of licensure for melanoma, although this agent has been licensed by the U.S. Food and Drug Administration for glioblastoma multiforme.

IMMUNOTHERAPY OF METASTATIC DISEASE

Although immunotherapy currently is effective in only a small percentage of patients, the results can be quite dramatic. Six percent of patients have a complete response to IL-2, but two-thirds of patients with complete responses are disease-free survivors at a median follow-up of more than 5 years (Fig. 42.2-27 and Fig. 42.2-28). These infrequent responses suggest that with a better understanding of the immune mechanisms of IL-2, a greater proportion of patients might be benefited and perhaps serve as a more effective model for developing therapies for patients with other neoplasms.

| Table 42.2-20. Clinical Trials Using Interleukin-2 as Monotherapy for Melanoma |
|------------------------|----------|--------|-----------------|-----------------|
| Study                  | Response | Rate (%)| Duration (mo)   | Study Comment |
| Brandenburg, 1990(39)  | 47       | 74     | 2 to 141        |                 |
| Geller, 1990(40)       | 61       | 55     | NR              |                 |
| Pollheimer, 1991(41)   | 66       | 57     | 4 to 59         |                 |
| Whitehead, 1990(42)    | 45       | 55     | NR              |                 |
| DeSanctis, 1991(43)    | 27       | 39     | 4 to 115        |                 |
| Sporn, 1992(44)        | 94       | 3      | 10 to 15        |                 |
| Lygren, 1997(45)       | 59       | 39     | NR              |                 |
| Atkins, 1998(46)       | 283      | 17     | 1 to 102        |                 |

*Study comments*
- *These studies have demonstrated objective response rates and duration of response in patients with melanoma. The response rate is defined as the number of patients with objective response divided by the total number of patients treated. Objective response is defined as a greater than 50% reduction in tumor size.*
- *Complete response is defined as the disappearance of all measurable disease.*
- *Partial response is defined as at least a 30% decrease in the sum of the products of the perpendicular diameters of the measurable lesions.*
Relapse after IL-2 usually occurs within 1 to 2 years (97%) in partial responders but much less frequently (41%) in complete responders. In patients who relapse, repeat administration of IL-2 is rarely effective following IL-2 treatment. Surgical resection following recurrence following IL-2 therapy is associated with a rapid relapse with a median time of 5 months before progression, and resection in such patients should be used only as palliative therapy.

Considerable toxicity from IL-2 administration is observed since IL-2 is given in each patient to maximally tolerated doses on the basis of evidence that efficacy is directly related to dose intensity. Capillary leak syndrome resulting in pulmonary edema as well as renal and cardiac dysfunction, hypotension, fever, and malaise are all common side effects of administration. In these early studies, a 1% mortality was reported, although more recent reports, with careful selection of patients, suggests mortality of less than 0.1%. There has been considerable debate concerning the dosage and regimen of IL-2 necessary to optimize response and minimize toxicity. A large experience supports the application of three daily IL-2 doses of 720,000 IU/kg or as more commonly applied outside of the NCI, 600,000 IU/kg of IL-2. Low-dose IL-2 appears to be markedly less effective. Identification of patients most likely to respond to IL-2 therapy has generally not been effective, although good performance status, low pretreatment serum IL-6 levels, postinfusion thrombocytopenia, and expression of certain HLA antigens have been suggested to be helpful.

IL-2 has been used in numerous trials alone, in combination with other cytokines, with the infusion of autologous immune effector cells, with other chemotherapeutic agents, and with radiation therapy (Table 42.2-21 and Table 42.2-22). None of these combinations has been associated with enhanced survival. The enhanced toxicity and absence of long-term survival advantage compared with IL-2 alone has led to their discontinuation. The Extratumoral IL-2 Working Group also failed to demonstrate improved response rates of high-dose IL-2 and IFN-a over IL-2 alone in patients with melanoma in which the response rates were 10% and 5%, respectively. The EORTC evaluated IFN-a and IL-2 with or without cisplatin in 138 patients with advanced metastatic melanoma. The overall response rate was 18% for patients receiving IFN-a and IL-2 and increased to 35% with the addition of cisplatin. In a subset analysis considering patients with normal pretherapy LDH levels, the response rate was 23%, and with cisplatin improved to 38%. Overall survival was 9 months without any significant differences between the various groups. Although results are still early to determine the true effect IL-2 has on survival, a 5-year survival rate of 13% has been shown in patients receiving IL-2 and IFN-a regardless of the inclusion of chemotherapy. Efforts to reduce toxicity associated with IL-2 administration, including the use of corticosteroids and anti-TNF antibodies, have generally been ineffective or limited the antitumor effects of IL-2.

A prospective randomized trial in patients with metastatic melanoma, comparing treatment with chemotherapy in relation to chemotherapy was carried out at the NCI. One hundred two patients with metastatic melanoma were prospectively randomized to receive chemotherapy consisting of tamoxifen, cisplatin, and dacarbazine or this same chemotherapy followed by IFN-a, and IL-2 using a schedule that has not been explored by others. No increase in survival was seen with the addition of immunotherapy and toxicity was increased. From previous patients treated with immunotherapy alone it was suggested that the chemotherapy might have negatively affected the efficacy of the immunotherapy component of the regimen.

The addition of immune effectors such as LAK cells, tumor-infiltrating lymphocytes (TILs), or activated T cells combined with IL-2 has not improved response or survival rates substantially over IL-2 alone and greatly increases cost and complexity. TILs can be demonstrated to contain some cells that are specific for known melanocarcinoma lineage antigens of melanoma, as well as the patient's own autologous tumor. It has been suggested that the major targets of T cells in melanoma patients may be unique to each individual. Concomitant infusion of IL-2 may act as a survival factor for the infused TILs, may enhance the recruitment of T cells into the tumor site, and augment the specific cytotoxic T-cell response. In one study, 86 consecutive patients were treated with a combination of TILs and IL-2. An objective response was observed in 34% of patients, including some patients who had previously failed treatment with high-dose IL-2 alone. These T cells were also demonstrated to localize to the site following radiolabeling. From both TILs as well as T cells derived from the peripheral blood and sensitized in vitro, genes encoding target antigens as well as the major histocompatibility complex (MHC)-specific peptide epitopes derived from them have been identified. These peptides are being used as vaccine antigens to enhance T-cell response and function against melanoma. Numerous clinical protocols have been initiated based on these new findings.

Other therapies applying cytokines that have been tested in this disease including IL-1, IL-4, IL-12, TNF, IFN-γ, and FLT3L have not been successful. In the future, they may play a role in combination with IL-2 or IFN-a.

MANAGEMENT OF MELANOMA IN THE PREGNANT PATIENT

Appropriate surgical management should not be delayed in a pregnant patient with melanoma. The cornerstone of fetal viability is maternal health, and a delay in surgery only jeopardizes the lives of both the mother and the child. Adjuvant treatment such as high-dose IFN-a, an abortifacient, should be delayed until after delivery. Patients who have been treated with IFNs while pregnant also have had babies of low birth weight. Only rarely do situations arise in which a woman with melanoma should be advised to terminate pregnancy. In patients with stage IV disease, fetal termination should only be considered for the use of chemotherapeutic or biologic agents with the understanding that only a few percent may experience a survival benefit. Managing a pregnant patient with disseminated melanoma can be difficult, but because the prognosis is so poor in these patients and treatment options are lacking, the patient may reasonably decide to attempt a full-term gestation without therapy. Cases of women receiving chemotherapy and focused spinal radiation without subsequent harm to the fetus have been reported. Uncommonly, melanoma can pass through the placenta, but usually in only far-advanced disease. Melanomas account for only 6% of the cancers that affect pregnant women but for 46% of fetal tumors acquired transplacentally. In a gestational patient with melanoma, the placenta should be specifically examined histologically for occult melanoma metastasis.
FUTURE PROSPECTS FOR THE BIOLOGIC THERAPY OF PATIENTS WITH MELANOMA

Some of the goals of the tumor immunologist are (1) the development of a specific T cell response to tumor, (2) delivery of T cells across the endothelial barrier to the tumor, (3) maintenance of the T-cell survival within the tumor microenvironment, (4) the induction of long-lasting immune memory to an individual’s tumor, and (5) regulation of the local angiogenic response mediated by development of a T-cell response in concert with tumor-resident DCs. Future directions in immunotherapy promise more directed stimulation of a specific immune response using vaccines derived from autologous tumor, DCs, and application of known tumor antigens.

ANTIGENS OF MELANOMA

Specific cellular immune responses to melanoma antigens classically occur through the recognition of a foreign peptide on a self-MHC molecule by the T-cell receptor. These peptides, generated through the processing of either exogenous (extracellular) or endogenous (intracellular) antigens, are presented by DCs to specific T cells in regional lymph nodes. Proteins are cleaved to short amino acid sequences of 8 to 10 aa for MHC class I molecules and 13 to 18 aa for MHC class II molecules. MHC class I molecules interact with CD8 cells to stimulate a cytotoxic T-cell response to melanoma, whereas MHC class II molecules activate appropriate helper CD4 cells to induce a humoral immune response. Single amino acid differences in these small peptides have enormous effects on this interaction as alterations in the anchoring of the peptide in the MHC groove may occur and recognition by the T-cell receptor of the MHC peptide complex may no longer occur with minor changes in peptide conformation and charge. Escape from immune recognition can occur in a variety of ways, but evidence for defective transport into the endoplasmic reticulum, loss of expression of individual melanoma antigens, and loss of class I molecules (limited to single alleles or globally, often due to loss of β2-microglobulin expression) has been associated with progression of this tumor. DCs are uniquely required for priming naïve T and B cells and probably play a major role in driving the effector phase of the immune response. DCs, which express high levels of costimulatory molecules and efficiently secrete Th1 cytokines, select, activate, and expand specific T cells. Through positive and negative selection of T cells during maturation, autoimmunity should be minimized. Proteins produced from tumor cells that induce a specific T-cell response are called tumor-associated antigens. Those that are sufficiently potent at stimulating reactivity, demonstrated by a clinical rejection of tumor, are called tumor-rejection antigens. As cancer is a genetic disease, the production of mutated proteins occurs, and these proteins were thought to be prime candidates for the development of peptide vaccines. Of course, this concept is much more complicated as T cells are, in fact, quite capable of recognizing self, and, conversely, are able to develop tolerance or anergy to foreign peptides. In fact, although some mutated self-proteins have been identified in patients that can stimulate an antitumor T-cell response, most peptides thus far identified derive from normal proteins either overexpressed in melanoma or restricted to cells of melanocytic lineage. Understanding the mechanisms of tolerance and the means to stimulate enhanced self-reactivity has been a goal of the tumor immunologist. By identifying antigens present in tumors (the processed epitopes expressed in concert with MHC class I and II molecules, which can bind with sufficient affinity to the T-cell receptor), therapeutic vaccines may be developed that induce a long-lived antitumor response.

Unique Tumor Antigens

Unique antigens, those expressed usually as a result of mutation, only occur in a single patient’s melanoma and not in other patients; those may be the most important target. Techniques to sample the antigenic repertoire of autologous tumors and to express them on autologous DCs have been developed. Several sources of antigen have been applied to DCs, including the use of synthetic peptides, peptides stripped from the surface of the tumor cell by means of acid elution, and cDNA or cRNA preparations encoding genes expressed by the tumor. The creation of antigen-presenting cells by fusing autologous DCs with tumor, incubating with tumor lysates or apoptotic bodies, also has been shown to elicit an antitumor response in murine and some human studies.

Shared Tumor Antigens

A number of proteins providing a source of peptide epitopes, some of them synthetically altered to improve MHC binding, have been identified and used in clinical trials. These epitopes bind either to class I (Table 42.2-23) or class II (Table 42.2-24) MHC molecules. One technique that enabled the rapid detection and identification of antigens of cancer was the technique known as serologic expression cloning. This has been now shown to detect both antibody-recognized and T-cell–recognized antigens of melanoma.

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**Table 42.2-23. Major Histocompatibility Class I–Restricted Human Melanoma Peptide Antigens Used in Clinical Trials**

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Major Histocompatibility Class</th>
<th>CD8+ Reactivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAGE-1</td>
<td>HLA-A2</td>
<td>++</td>
</tr>
<tr>
<td>MAGE-3</td>
<td>HLA-A2</td>
<td>++</td>
</tr>
<tr>
<td>MART-1</td>
<td>HLA-A1</td>
<td>++</td>
</tr>
<tr>
<td>Tyrosinase</td>
<td>HLA-A2</td>
<td>++</td>
</tr>
<tr>
<td>Melan-A</td>
<td>HLA-A3</td>
<td>++</td>
</tr>
</tbody>
</table>

**Table 42.2-24. Major Histocompatibility Class II Human Melanoma Peptides Used in Clinical Trials**

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Major Histocompatibility Class</th>
<th>CD4+ Reactivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>MART-1</td>
<td>HLA-DP</td>
<td>++</td>
</tr>
<tr>
<td>Tyrosinase</td>
<td>HLA-DP</td>
<td>++</td>
</tr>
<tr>
<td>Melan-A</td>
<td>HLA-DQ</td>
<td>++</td>
</tr>
</tbody>
</table>

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Differentiation Antigens

A broad group of antigens is known as the cancer testis group was initially identified in melanoma as MAGE 1, 2, and 3. These antigens are now known to be expressed in cancers of different histologic types, but also in only normal testis and occasionally ovary of adults. The cells in the testis expressing these antigens are immunologically privileged by their anatomic localization and their frequent lack of HLA class I molecules. Thus, cancer testis antigens are restricted to malignant cells in the adult. The identification in melanoma and melanocytes of the cancer testes MAGE genes, which occur naturally in several human cancers, were the first identifiable tumor antigen in human solid tumors. Many more such antigens have been subsequently described.

Melanocyte and Melanoma Tumor Antigens

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The predominant melanocytic antigens include Melan-A/MART-1, tyrosinase, and gp100. These gene products are expressed in both normal and malignant melanocytes, and immune responses against these targets have been associated with the development of autoimmune reactions against normal melanocytes. However, these genes are not expressed in tumors derived from other cell types. Therefore, vaccination against these targets should allow a relatively tissue-specific response to be elicited.

**CLINICAL APPLICATIONS**

### Active Immunotherapy

**CELLULAR ADJUVANTS.** DCs are specialized APC that have the unique ability to stimulate naïve T cells. They are also capable of presenting exogenous antigens either by the MHC class I or II pathways, and DCs can per se mediate antitumor effects; however, current trials use DCs that have been manipulated through various techniques to express tumor antigen on self-restricted MHC molecules (Table 42.2-25). For example, animal studies using synthetic or stripped peptides pulsed onto DCs have shown potent inhibition of tumor growth. DCs can be generated easily from peripheral blood monocytes, or by direct purification from blood or by differentiation of progenitors, or by direct purification from blood or by direct purification from blood and have entered clinical trials in a variety of malignant diseases including melanoma.

<table>
<thead>
<tr>
<th>Table 42.2-25. Uses of Dendritic Cells in Immunotherapy*</th>
</tr>
</thead>
</table>
| Nestle et al. performed a clinical trial involving 30 patients with melanoma in which DCs were used to mediate vaccination. Patients of HLA A1 were treated with peptides derived from the MAGE-1 and MAGE-3 antigens; those who were HLA-A2+ were treated with peptides from Melan-A/MART-1, gp100, and tyrosinase; and those who expressed HLA-B44 received treatment with peptides derived from MAGE-3 and tyrosinase. Clinical responses were noted in 27% (8 of 30) of patients, including three complete remissions and five partial remissions. This study is the most mature of current DC and peptide studies in melanoma and has indicated the feasibility, safety, as well as the tolerability of such therapy. The meaningful clinical responses induced in a group of patients with poor prognosis disease is encouraging but needs further evaluation. A University of Pittsburgh Cancer Institute trial initiated in 1996 has also shown encouraging evidence of activity in 23 patients. The first patient treated exhibited a relapsing and remitting course of her melanoma over several years and multiple trials. After DC vaccination, this patient developed a complete remission and has remained free of disease for more than 20 months. Another patient on this study attained a complete remission sustained for over 3 years, and a third has had a partial remission. New adjuvants are also becoming available. Cytokines of great potential interest are FLT3L and CD40L, which preferentially expands or activates DC in the peripheral blood and many tissues. A major difficulty in conducting trials of cancer immunotherapy is the selection of appropriate end points. Most patients on such studies are heavily pretreated and immunosuppressed. It is logical to apply these treatments to patients with a much lower burden of disease such as in the adjuvant setting, where all obvious disease is removed, but there is a high chance of relapse due to microscopic residual or metastatic disease. Performing such studies using the clinical end points of time to tumor progression or survival involves studying large numbers of patients over a long period. This is justifiable if phase II studies in patients with advanced disease indicate that there is significant clinical activity, but for most strategies, this has not yet been shown to be the case. **CYTOKINE ADJUVANTS.** Granulocyte-macrophage colony-stimulating factor (GM-CSF) is an important cytokine promoting survival and expansion of DCs. In gene transfer models, GM-CSF gene transfer into poorly immunogenic tumors leads to rejection of those tumors in animal models or to clinical and immunologic responses in humans. Direct injection of GM-CSF into subcutaneous melanoma metastases may also lead to regression of injected and noninjected tumor deposits. A study using GM-CSF together with peptides derived from Melan-A/MART-1, tyrosinase, and gp100 in HLA-A2 melanoma patients was reported in 1996. Immune responses were observed, consisting of development of skin reactions to intradermal injections of peptide, infiltration of injection site by CD4 and CD8 lymphocytes, and detectable cytotoxic T lymphocytes in peripheral blood without apparent toxicity. Three patients were reported in whom tumor regressions were seen despite having progressive melanoma at the time of entry into the study: One patient showed complete regression of tumor and the others displayed partial regressions. In a study using modified gp100 HLA-A2 peptides, 13 of 31 patients receiving the peptide plus systemic IL-2 showed regression of metastatic melanoma, with an additional four patients showing minor or mixed responses. Immunologic responses could be generated in 91% of patients using blood lymphocytes stimulated in vitro before assay.

Another approach to the enhancement of immune response to tumor cells consists of introducing genes encoding costimulatory molecules or alloantigens. In human clinical trials, tumor cells (autologous or allogeneic) or normal cells such as fibroblasts, have been transfected with individual cytokine gene(s) and have been used to induce tumor immunity. So far, only early toxicity results from phase I trials have been reported using this approach in advanced disease patients. Current efforts are underway involving the evaluation of IL-4 or IL-12 gene therapy in patients with melanomas. A human clinical trial using this approach was reported using IFN-g gene modified and irradiated autologous melanoma cells. The preparation was given every 2 weeks for a total of six doses. Twenty stage III and IV melanoma patients were treated. Two complete responses were observed and two patients had a decrease in the size and number of their subcutaneous nodules. The vaccinated population showed an increased IgG response dominated by IgG-2, suggesting the development of an effective T-helper cell response. Palmer et al. reported on 12 patients who were treated with autologous irradiated tumor engineered to secrete IL-2 by infection with recombinant retrovirus. No clinical responses were seen, but three patients had stable disease for 7 to 15 months.

Arieti et al. reported the vaccination of 12 patients with metastatic melanoma with an allogeneic human melanoma line genetically modified to release IL-4. Only two mixed responses were recorded, without objective clinical responses by conventional criteria. However, induction of a specific immune response was demonstrated by in vitro studies. Antibodies to allogeneic antigens could be detected in 2 of 11 patients tested. A significant increase in IFN-g release was detected in 7 of 11 cases when postvaccination lymphocytes were stimulated by the untransduced allogeneic melanoma cells. However, induction of a specific recognition of autologous melanoma cells by peripheral blood lymphocytes was obtained after vaccination in only one of six cases studied. This response involved the melanoma peptide Melan-A/MART-1 that was recognized in an HLA-A2–restricted fashion. These results, although modest, show that the induction of a specific immune response is possible in a few patients through novel vaccination strategies.

The feasibility of using melanosomal proteins for the immunotherapy of patients with melanoma is now being addressed. Immunization using peptides or recombinant viruses containing genes encoding the melanosomal antigens MART-1 or gp100, with or without coadministration of cytokines such as IL-2, IL-12, or GM-CSF, are ongoing at the National Institutes of Health, as well as in the ECOG.

PEPTIDES ALONE. Initial studies using melanoma peptides were performed using peptides alone. One of the first involved the use of a MAGE-3 HLA-A1–restricted peptide without of any immunologic adjuvant. In this study, 6 of 19 patients with melanoma displayed peptide regression, and toxicity was minimal. In one patient, tumor regression occurred several months after completing peptide vaccination, although the tumor had progressed while on treatment, leading to the initiation of vaccination. Eventually four of five lung metastases in this patient disappeared entirely. This initial study demonstrated that synthetic peptides derived from
self-tumor antigens were safe and that clinical responses could be obtained in some individuals in the absence of any other adjuvant. Cytotoxic T-lymphocyte
responses against melanoma differentiation antigens correlate inversely with expression of the antigen in melanoma tissues: Patients with progressing disease have
been shown in several experiences to displayed antigen-loss variants, implying in vivo immunoselection under the pressure of peptide vaccination. 513a,513b
A series of studies was performed at the NCI involving peptides derived from the melanoma differentiation antigen gp100. 501,506,507 Initially, HLA-A2+ patients were
treated with the native peptide, and subsequent patients were treated with a version of this peptide containing a single modified amino acid. 507 This substituted
peptide has a higher binding affinity for HLA-A*0201 than the native peptide and has been pursued in the hopes that there will be correspondingly greater induction of
in vivo, as well as in vitro cytotoxic T lymphocytes.507 Patients treated with the substituted peptide developed cytotoxic T lymphocytes recognizing both native and
modified peptide-pulsed target cells, as well as HLA-A2+ tumor cell lines expressing gp100 in almost all cases. Following administration of IL-2 many of these T cells
were not found in the peripheral blood, but a substantial number of patients were observed to respond. Presumably, reactive T cells migrated to the site of antigen.
Considerable work has been done in relation to several HLA class I subtypes to map binding pockets and to determine preferential anchor residues for binding
peptides.509 To improve the stability of the class I complex, some investigators have produced modified class I peptides with amino acid variations designed to
introduce residues that improve the binding to individual class I molecules. This has enhanced the generation of cytotoxic T lymphocytes with specificity not only for
the modified peptide-pulsed target cells, but also for unmodified peptide and for naturally processed peptide. 507,510 Vaccination using modified peptides has now
entered evaluation in clinical trials, and cytotoxic T lymphocytes have clearly been demonstrated in patients vaccinated in these studies. 501
Allogeneic tumor vaccines are based on the presumption that same cell type tumors from different individuals share several common antigens that are capable of
inducing an immunologic response. One vaccine based on this approach, CancerVax, has been developed at John Wayne Cancer Institute. CancerVax is a whole cell
irradiated vaccine developed from three allogeneic melanoma cell lines that were subsequently demonstrated to express several known immunogenic
tumor-associated antigens. Phase II nonrandomized trials have shown impressive results in a select group of patients. Stage IV patients received CancerVax after
resection of all evident metastatic disease and were compared with a matched set of controls. The 5-year overall survival and median survival for patients who
received the vaccine appears to be improved, but it is well recognized that historic controls have great liabilities. Forty-two percent of patients who received the
vaccine were alive at 5 years and the median survival was 42 months. The historic reference had a 19% 5-year survival and an 18-month median survival. After
multivariate analysis, CancerVax therapy was suggested to be a significant predictor of survival. 360 It is believed that prior surgery enabled success of the vaccine by
reducing tumor load and identifying a better group of patients. Prospective randomized studies are now needed, and underway, to appropriately evaluate this therapy
in patients with resected stage III and stage IV melanoma. 514 Use of peptides fused to heat-shock protein hsp70 has been shown to be rapidly taken up by DCs and to
bypass the need for T-cell help in murine models. 515In vivo immunization with these hybrid peptides caused rejection of tumors expressing antigen and may represent
important strategies to be taken into clinical trials.
Lysate vaccines are produced by mechanical disruption of whole tumor cells. Vaccine preparations have been evaluated in which nonpathogenic viruses such as
vaccinia virus and Newcastle disease virus, are used to lyse cells to enhance their immunogenicity (viral melanoma oncolysate). They contain multiple
tumor-associated antigens and are capable of stimulating a polyvalent immune response. Wallack et al. compared a vaccinia melanoma oncolysate with vaccinia virus
alone in AJCC stage III melanoma patients. This phase III, randomized, multicenter trial demonstrated no significant difference in either disease-free or overall
survival at a median follow-up of 46 months. 516 Similar studies by Hersey from Australia have also failed to show either relapse-free survival or overall survival
benefit. 517
CELLULAR ADJUVANTS
Passive Immunotherapy
Passive immunotherapy is a term generally applied to agents that are thought to have direct antitumor activity themselves. Most specifically, this would include the
adoptive transfer of cells or antibodies. Application of the adoptive transfer of T cells and LAK cells has been discussed previously (see Immunotherapy of Metastatic
Disease, earlier in this chapter). Although responses have been observed in conjunction with delivery of IL-2, the general sense is that these responses are inferior in
quality and duration to those of IL-2 alone and provide no long-term benefit. With an improved understanding of the so-called central (CCR7+ vs. CCR7–) memory T
cells that could provide long-term benefit, it would be worthwhile to reevaluate these approaches with these cells as opposed to the effector memory T cells (CCR7+),
which are most likely to provide only short-term responses. 518,519 Application of gene therapies using gene-marked TILs, IL-4, or IL-12 may also enhance induction of
a melanoma-specific immune response.520,521 and 522
The application of antibodies in melanoma was first evaluated with the notion that such antibodies could confer complement or antibody-dependent cellular
cytotoxicity on tumor cells. 523,524 The subsequent genetic engineering of monoclonal antibodies (MAB), resulting in human molecules, and successes with antibodies
targeting breast cancer and lymphoma in clinical trials has led to a reevaluation of these reagents alone or in combination with molecularly defined cytokines and
growth factors for the immunotherapy of melanoma. The development of a human IgG anti-mouse antibody (HAMA) has been observed in virtually every patient and
limited the effectiveness of these early approaches in treated patients. However, first-generation murine MABs have been developed that have been used to
effectively map melanosomal, melanocyte, and melanoma antigens.525 One of these antibodies, R24, an IgG3 murine monoclonal antibody that recognizes GD3, a
ganglioside present on melanoma cells and a subset of T cells, was reported initially to mediate 3 of 12 responses in patients with melanoma. 526 Evidence of immune
reactivity with inflammatory reactions (urticaria, pruritus, erythema, subcutaneous ecchymoses) were observed at tumor sites in some patients treated at doses
greater than or equal to 80 mg/m2. Tumor biopsies during and after treatment showed lymphocyte and mast cell infiltration, mast cell degranulation, and complement
deposition. Subsequent studies with this antibody have failed to confirm this level of response. 527 As a single agent, R24 induced responses in 10 of 103 patients two
of which were complete. Combining R24 with cytotoxic drugs or cytokines did not increase the response rate. An alternative approach was to develop strategies to
immunize with the antiidiotype (so-called Ab2) to induce a host immune response to the original antigen (Ab3). 528,529 BEC2, an antiidiotypic MAB mimics GD3 has
been tested with two immunologic adjuvants, BCG and QS21, administered with BEC2 in melanoma patients free of disease after surgical resection. All patients
developed high-titer IgG antibodies against BEC2. Anti-GD3 antibodies were induced in 3 of 14 patients immunized with BEC2/BCG; no patient immunized with
BEC2/QS21 developed such antibodies. Conjugation of BEC2 to keyhole limpet hemocyanin did not increase the immunogenicity of BEC2 when administered with
BCG. Prolonged disease-free intervals were noted in a majority of treated patients in these adjuvant studies. Two clinical trials with the mouse antiidiotypic MAB
MF11-30, which is an Ab2 of human high-molecular-weight melanoma-associated antigen was administered subcutaneously to patients with advanced
melanoma.530,531 In the first phase I trial in 16 patients, minor responses were observed in three patients. In a second clinical trial MAB MF11-30 was administered to
21; 17 of 19 evaluable patients had increased levels of anti-mouse Ig antibodies and 16 developed antibodies that inhibit the binding of antiidiotypic MAB MF11-30 to
the immunizing anti–high-molecular-weight melanoma-associated antigen MAB 225.28. One patient had increased levels of anti–high-molecular-weight
melanoma-associated antigen antibodies. One patient achieved a complete remission with disappearance of multiple abdominal lymph nodes for a duration of 95
weeks. Minor responses were observed in three patients. These collective results suggest that such antiidiotype antibodies may be useful in patients with melanoma.
Additional antibodies including those directed against the cell surface high-molecular-weight antigen or a transferrin-like molecule have been used in experimental
studies of imaging or therapy with cytokines including IL-2. 527,532,533,534 and 535 MABs with tumor specificity are able to enhance the immunologic specificity of
IL-2–activated LAK cells. MAB 3F8 and 14.G2a, which are specific for neuroblastoma and melanoma and recognize ganglioside GD2, were able to mediate
antibody-dependent cell-mediated cytotoxicity with fresh effector cells and antibody-binding targets. Use of cross-linked antibodies or humanized antibodies has yet to
be clinically explored in this disease but may represent promising approaches. 536
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INTRODUCTION

Melanomas are the most common primary intraocular malignant in whites. They arise from uveal melanocytes (i.e., mature melanin-producing and melanin-containing cells) residing in the uveal stroma and originating from the neural crest. Whereas reactive or neoplastic proliferations of pigmented cells can occur in the epithelia of the iris, ciliary body, and retina, forming adenomas or adenocarcinomas, this chapter deals exclusively with uveal melanomas. A particular emphasis is given to the current therapeutic concerns and issues since (1) the appropriate treatment of the primary tumor remains in many instances controversial and (2) management of metastatic disease is essentially palliative.

EPIDEMIOLOGY

The annual age-adjusted incidence of nonglaucomatous ocular melanomas as reported in the Surveillance, Epidemiology, and End Results program during 1973 to 1977 was 0.7 per 100,000 population in the United States. Similar figures were reported from epidemiologic studies conducted in New England (0.65 per 100,000 residents from 1984 to 1985), the Swedish west coast (0.72 per 100,000 over the period 1956 to 1975), and Iceland (0.7 per 100,000 in male patients and 0.5 per 100,000 in female patients over the period 1955 to 1979). In the Third National Cancer Survey, conducted from 1969 to 1971, the annual age-adjusted incidence in the United States was estimated at 0.6 per 100,000. The precise anatomic origin of ocular melanomas was unspecified in approximately 25% of cases. Seventy-three percent of the tumors arose within the globe (mainly from the choroid), and 2% developed from the conjunctiva. Melanoma accounted for 70% of all primary ocular malignancies, followed in frequency by the childhood tumor retinoblastoma (13%). In persons older than 20, melanoma was the reported diagnosis for 80% of all primary ocular cancers. Data from the Missouri Department of Health; China; the Surveillance, Epidemiology, and End Results program; New England; Iceland; Finland; and the Danish study of patients with uveal melanoma, very few reports are complete enough to be informative. Diener-West et al., respectively. In the Danish study, survival rates were similar; at the end of the 25-year period, 51% patients had died from metastasis. A French study of survival of patients with uveal melanomas treated by enucleation with a long-term follow-up reported similar figures. Rates of survival after radiation therapy appear comparable in the short term and mean term. Yet, as the following discussion shows, both the validity of these data and the long-term predictability of prognosis after conservative treatment remain a matter of controversy. The median survival of patients with metastatic disease is reportedly very short: 2 to 5 months.
ETIOLOGY AND HISTOGENESIS OF OCULAR MELANOMAS

As is the case for most human cancers, the specific causes of uveal melanomas are unknown. However, epidemiologic, electron-microscopic, and experimental data allow characterization of risk factors, predisposing conditions, and hypothetical genetic or oncogenic causes.

GENETICS AND IMMUNOHISTOCHEMISTRY

There is now considerable evidence that, like many cancers, a subset of uveal melanomas is caused by an inherited predisposition. The familial occurrence of uveal melanoma was first mentioned by Silen et al. in 1952 and reported several times. Despite the rare occurrence of uveal melanoma in a family and the presence of many skips in these pedigrees, the occurrence of familial uveal melanoma is not caused by fortuitous familial aggregation of sporadic cases. Because of an insufficient number of families with more than two affected individuals, it is impossible to distinguish between polygenic inheritance, single-gene inheritance with reduced penetrance, and the role of environmental factors as causes of this familial aggregation. A few cytogenetic studies argue for the putative role of a recessive oncogene on chromosome 2, 3, or 8q22-23 and showed abnormality again on chromosomes 6 and 8q22-23. Other studies emphasize the possible relationship of monosomy 3 and multiplication of chromosome 8q to uveal melanoma, suggesting monosomy 3 as an early, if not primary, event and supporting a role for chromosome 8q multiplication in the proliferation of clonally related cells in vitro. A role for the c- myc oncogene, located in the region 8q2.1-ter, in uveal melanoma formation and progression, likely connected to the regulation of cell proliferation, has been hypothesized. This is partly supported by cytogenetic as well as immunohistochemical studies. Abnormalities of the p53 gene have also been demonstrated. The coexistence of ocular and cutaneous melanoma in some patients suggests a predisposition to both types and may imply mutations in the CDKN2A gene on chromosome 9 in a proportion of these cases. An association between ocular melanoma and breast or ovarian cancer (or both) has also been reported, and BRC2A on chromosome 13 may also be involved.

Additional molecular genetic studies are necessary to understand the pathogenesis of familial uveal melanoma. In several studies, investigators have demonstrated a close link between oncogenesis and the cell-cycle machinery. Progression through the cell cycle is orchestrated by sequential activation of a series of cyclin-dependent kinases (CDKs). The CDKs’ activity is primarily dependent on the association with their activating cyclin subunits (Ds, E, G). CDK activity is counterbalanced by a variety of CDK-inhibitory proteins (CKIs), such as p21, p27, p16, and the like. Deregulated expression of G1 cyclins p21, p27, p16 CKIs, and alteration in the interaction of CKIs with CDKs may be implicated in the neoplastic transformation of human ocular melanocytes to malignant melanoma cells.

MDR1 gene and its gene product, Pglycoprotein, which are known to cause drug resistance in cancer cells, are expressed in ocular melanoma. Dunne et al. reported a statistically significant association between MDR1 expression by tumor cells and shorter survival times, which was most striking at grade III. Whether P glycoprotein is a marker for tumor aggressiveness, for clinical chemotherapy resistance, or perhaps for both remains to be clarified.

PREDISPOSING CONDITIONS

Ocular and ocudermal melanocytosis (i.e., nevus of Ota) predispose to the development of uveal melanomas. In 4.6% of reported cases of nevus of Ota, malignant transformation was reported and, except for a single anecdotical case, the melanoma occurred in the pigmented eye. In the vast majority (90%) of patients with ocular and ocudermal melanocytosis, the uveal melanoma was diagnosed between the ages of 31 years and 80 years. Rare cases of uveal melanomas have been reported in patients with type I neurofibromatosis. The tumor cells in neurofibromatosis have their origin in the neural crest, in common with melanocytes.

Evidence that nevi are the origin of most choroidal melanomas has been provided by Yanoff and Zimmerman. Yet a nevus-like configuration associated with choroidal melanoma may, in some cases, be explained by other mechanisms, such as (1) flattening of normal uveal melanocytes or of tumor cells, (2) a secondary proliferative effect of the malignant, or (3) common oncogenic stimuli. The last two mechanisms have been postulated in a few cases of bilateral diffuse metastatic melanomas of the uvea in patients with systemic carcinoma.

In some instances (as discussed), a familial increased occurrence of uveal melanoma has been recorded. Data on the occurrence of uveal melanocytic tumors in patients with the dysplastic nevus syndrome are controversial but generally support the value of periodic ophthalmoscopic examination of patients with atypical nevi. A recent case-control study by Bataille et al. demonstrated that (1) numerous common nevi (i.e., 100) were present in 10% of cases versus 3% of controls; (2) four or more atypical nevi were present in 7% of cases versus 0.4% controls; (3) pigmented iris nevi were significantly more common in cases than in controls (odds ratio, 3.1); and (4) the atypical mole syndrome was a strong risk factor (odds ratio, 7.3). The association between uveal melanomas and other cancers is still a matter of controversy. Turner et al. showed that the overall prevalence of non–basal cell cancers in uveal melanoma patients was twice the expected prevalence based on an age- and gender-matched population. Anecdotal cases of uveal melanomas associated with breast cancer, uterine cancers, and lymphomas exist. A link between cutaneous and uveal melanoma was suspected on the basis of the association, in three cases (among 333 patients), of primary uveal and cutaneous melanomas. A family history of cutaneous or uveal melanoma was present in 14 of the 333 patients. A role for the c-erbB-2 oncogene on chromosome 2, 3, or 6q15 has been suggested in several cases and studies. Bataille et al. reported five cases of primary ocular and cutaneous melanoma occurring in the same individual. Lischko et al. conducted a case-control study among 197 New England cases with 385 matched controls and 337 cases (from the United States) with 700 controls. They concluded that the association of prior malignancies with uveal melanomas is weak. Holy et al., in a similar study of 407 uveal melanoma patients from the western United States with 870 control subjects, found no excess prior cancer.

ONCOGENIC STIMULI

Certain electron-microscopic and biomolecular studies of ocular melanomas suggest an etiologic role of viruses. Viruses such as the feline sarcoma have been used successfully in the induction of animal ocular melanoma models.

In a study of a single population of chemical workers, a statistically significant and higher-than-expected incidence of ocular melanomas was found. Nicotine has been implicated in the unusual incidence of uveal melanoma in male patients but does not appear to increase the risk for metastasis. Various chemicals, including nickel bisulfamide, platinum, methylcholanthrene, ethionine, N-2-fluorenylethamide, radium, and N-methyl-N-nitrosourea have been reported to induce ocular melanocytic tumors in animals. An exploratory study of various occupational associations provided elevated odds ratios for agriculture and farming work, several industrial operations, and exposure to inks, insecticides, gases, radioactive substances, polymethylphenyl, and chemical solvents. A possible connection between Parkinson’s disease, levodopa therapy, and malignant melanoma has been mentioned. The role of hormonal factors and pregnancy has been suggested in some reports. Hartge et al. reported a case-control study comparing 238 women with uveal melanoma with 223 matched control women. They showed that women with a history of pregnancy or hormonal substitutive treatment with estrogens had an increased risk, whereas a history of oophorectomy had a decreasing influence on risk. Seddon et al. and Shields et al. have documented the role of pregnancy in the growth of uveal melanomas. Whether the growth observed clinically is secondary to cellular growth or other factors (e.g., fluid retention or vascular engorgement) is unclear. Foss et al. failed to detect any estrogen or progesterone receptors in 27 choroidal melanomas and questioned the role of these hormones in the development or progression of these tumors.

A case-control study lends support to the etiologic role of sunlight exposure. A study of host factors (Northern ancestry, light skin color, 10 or more cutaneous nevi), ultraviolet radiation, and risk of uveal melanoma indicated that personal attributes are strong independent risk factors. Holy et al. showed that light skin color and easily sunburned skin increase by twofold the risk of uveal melanoma, while ultraviolet exposure increases this risk by fourfold, and sevenfold if intensive. These data, contradicting previous studies, confirm the high association between light iris color and the presence of melanocytic lesions. More recent evidence of an association between light iris color and melanocytic lesions comes from cases of melanomas associated with xeroderma pigmentosum as well as a case-control study of patients with uveal melanoma. It has been suggested that cutaneous freckles (25 or more) or iris freckles and nevi may be risk factors for uveal melanomas. Also, a relationship has been suggested between cutaneous or iris nevi and ocular melanomas. Paraneoplastic uveal melanocytic proliferations have been observed in association with various systemic malignancies, such as ovary and lung. These appear as diffuse multifocal infiltration of the uveal tract by predominantly diploid neovascular cells as well as more anaplastic cells; in addition, an association between bilateral uveal melanoma and a proliferation associated antigen (K667) has been described. The pathogenesis of paraneoplastic uveal melanocytic proliferation remains speculative. Hamartomatous paraneoplastic...
HISTOPATHOLOGY, PROGNOSTIC PARAMETERS, AND NATURAL HISTORY

CYTOLOGIC AND HISTOLOGIC CLASSIFICATION

Experienced pathologists generally make the accurate microscopic diagnosis of uveal melanoma easily, but it is still occasionally difficult to differentiate between primary and metastatic choroidal melanomas. In rare cases, differentiation from metastatic carcinoma may be facilitated by immunohistochemical labeling with monoclonal antibodies to S-100 protein. This technique is not helpful in differentiating other neural crest–derived tumors (schwannomas, neurofibromas, and leiomomas). The S-100 immunophenotypes of uveal melanomas differ considerably from cutaneous melanomas. S-100 is not helpful for distinguishing between primary and metastatic choroidal melanoma. HMB-45 immunostaining appears to be a useful adjunct in the differentiation between nonmelanocytic and melanocytic tumors but serves as a marker of melanocytic activation rather than a tool to differentiate uveal melanomas from nevi. Studies of the immunocytochemistry of uveal melanomas using antibodies against cutaneous melanomas or anti-HLA antibodies have not yet provided a clinically useful characterization of the ocular tumors. Cytometry can phenotype cells in suspension from ocular melanoma tissue. Lawry et al. described antibody binding for MHC antigens, the adhesion molecule ICAM-1, and the oncoproteins c-erb B-2, c-myc, and bcl-2. Further studies should be undertaken to question whether there are any relationships between traditional clinical and pathologic parameters (tumor cell type, volume, location, the tissue origin) and the flow cytometric measurement of cell surface protein or cytoplasmic-nuclear oncoprotein expression in cells taken from samples of primary uveal melanomas.

In 1931, Callender recognized major cell types in the spectrum of cells composing uveal melanomas, and this provided a cytologic classification clearly correlated with prognosis after enucleation. The different cell types are based on cell size and shape, cytoplasmic features, nuclear and nucleolar characteristics, evidence of loss of cohesion, and relative number of various cell types as outlined in Table 42.3-1.

### Table 42.3-1. Designation of the Cell Type Based on the Armed Forces Institute of Pathology Modification of the Callender Classification

According to Callender's cytologic characterization, uveal melanomas are divided into three categories:

- **Spindle cell melanomas** type A, B, or both, accounting for 30% of intraocular tumors, composed of spindle cells
- **Mixed cell melanomas**, when fewer than one-half of the tumor sections examined are composed of epithelioid cells
- **Epithelioid cell melanomas** (accounting for 5% of intraocular tumors), when greater than one-half is composed of epithelioid cells

Based on Callender classification, spindle cell tumors carry the best prognosis and epithelioid cell tumors the worst. In the Collaborative Ocular Melanoma Study (COMS) series, large tumors contain more epithelioid cells than small tumors do; small tumors contain a higher percentage of spindle cell types. In their series, a more malignant cell type was observed more commonly in tumors with large size and anterior location.

Paul et al. reviewed 2652 cases accessioned at the AFIP by 1959 and found that 95% of patients with spindle A tumors, 85% of those with spindle B tumors, 60% of those with mixed tumors, and 83% of those with epithelioid tumors were alive 5 years after enucleation. At 15 years after enucleation, the survival rates were 85% for spindle A, 80% for spindle B, 46% for mixed, and 34% for epithelioid. McLean et al. in a review of 3432 cases from the AFIP, found that the overall mortality from metastasis 15 years after enucleation was 46%. The mortality of patients with mixed cell melanomas was three times that of patients with pure spindle cell lesions.

In Jensen's series of 302 cases reported from Denmark that had been observed for 25 years, 150 patients (50%) died of metastatic melanoma. Fewer than 1% of patients with spindle A tumors died of metastatic disease; 63% with mixed tumors died of this cause, and the cause of death in 71% with epithelioid tumors was metastatic melanoma.

Works by Sorenson et al. and Gamel et al. and others have corroborated the well-documented prognostic value of Callender's classification, especially as to the pejorative significance of a high epithelioid cell content. Yet, the major cell types described by Callender are part of a continuous spectrum, and the pathologist's identification of a particular cell type involves subjective judgment.

In the COMS report number 6, balloon cells were associated with epithelioid tumors but not with tumor size. Metastases containing balloon cells have been reported. These lipid-laden cells are thought to be metabolically less active than spindle or epithelioid cells.

This issue was addressed by Sorenson et al. and Gamel et al. who described a more objective method of assessing uveal melanomas histopathologically. This technique uses computed cytomorphometry and entails evaluating the inverse of the standard deviation of the nucleolar area with measurements made of the mean of the 10 largest nucleoli and stereologic estimates produced of the volume-weighted mean nucleolar volume. This, in conjunction with tumor size as estimated by largest tumor diameter, is among the best objective cytologic measures of a tumor's malignant potential (P > .001). Marcus et al. counting nucleolar organizing regions, reached similar figures.

Folberg et al., Pe'er et al., and Rummelt et al. using sections stained with periodic acid–Schiff, described nine vascular patterns that they observed in ×10 objective fields of uveal malignant melanomas:

- Normal vessels
- Silent-avascular zones
- Straight with randomly distributed vessels
- Parallel-oriented straight vessels without cross-linking
- Parallel with cross-linking between vessels
- Arcs that are incomplete loops
- Arcs with branching
- Loops that represent fibrovascular septa that completely surround lobules of tumor
- Networks that are composed of at least three back-to-back loops

The detection of these patterns in histologic sections is highly reproducible between observers, and more than one pattern can exist in a tumor. Foss et al. showed that the avascular zones contain large numbers of small blood vessels as demonstrated by factor VIII staining.

Two of these microvascularization patterns (networks, parallel with cross-linking) showed a very strong correlation with metastatic disease; two other
microvascularization patterns (silent, parallel without cross-linking) were correlated with a more favorable outcome for the patient. The survival rate was 80% at 20 years in the absence of loops, networks, or parallel with cross-linking vascular patterns and only 40% when these patterns were present. The presence of epithelioid cells is associated with the presence of networks, and the absence of epithelioid cells is associated with avascular zones. These microcirculatory patterns of primary uveal melanomas appear also in foci of metastasis, regardless of the site of dissemination.

The Callender classification of cell typing is highly subjective because it is based on multiple cytoplasmic, nuclear, and nuclear features. Loops and mean of the largest nuclei (MLN) should be less subjective than cell type, because these variables are based on only one feature and MLN is measured objectively.

Several attempts to evaluate the growth and malignant potential of uveal melanomas have been made recently using DNA cell-cycle studies (e.g., bromodeoxyuridine uptake or Ki-67 antibody as a marker of cycling cells, proliferating cell nuclear antigen, DNA or RNA content by flow cytometry). Several reports of DNA ploidy analysis in uveal melanomas showed a progressive predominance of diploid over aneuploid tumors moving from spindle to epithelioid cell type and worsening prognosis. The value of this technique as a diagnostic and prognostic tool in combination with fine-needle aspiration biopsy needs further confirmation.

After the works of Rosenberg et al. on the prognostic and therapeutic value of tumor-infiltrating lymphocytes (TIL), a reappraisal of the lymphocytic infiltration of some uveal melanomas has been undertaken. Wheelch et al. and other authors unexpectedly showed that T lymphocytic infiltration is associated with death from metastasis. T cells appear predominant among TIL. Attempts to generate TIL cytotoxic for ocular melanoma cells showed that after interleukin-2 addition, cells expressing natural killer (NK) cells, lymphokine-activated killer cells, and tumor-specific cytotoxic properties were obtained. Moreover, allogeneic melanomas could substitute for autologous tumors in active specific immunotherapy with CD8+ cytotoxic T lymphocytes. A few studies suggest a link between host-immune responses to the tumor and gangliosides profile (e.g., GM3 vs. GD2 and 3). The role of infiltrating lymphocytes in the regression of animal models of tumors was shown in nude mice for NK cell-mediated lysis and for CD8+ cytotoxic T lymphocytes in the rejection of tumors from transgenic mice.

**Tissue Culture and Animal Models of Uveal Melanomas**

Several cell lines of human ocular melanomas have been established and characterized. These vary greatly regarding doubling times or morphology and are mostly used for genetic studies and the development of animal models.

The most commonly used model of uveal melanoma is the Greene melanoma, which represents a transplantable hamster amelanotic melanoma. When injected into a rabbit eye, this tumor grows rapidly with marked spontaneous necrosis and is, therefore, not reflective of the clinical situation. Other models of either induced or spontaneous pigmented intraocular tumors are available arising from the retinal pigment epithelium or representing atypical nevi. Yet, to date, the most clinically relevant model to the human situation appears to be the heterotransplantation of human uveal melanomas into the choroid of rabbits, and the newer transgenic mouse models.

These transgenic models are based on using the promoter region of the tyrosinase gene to target the expression of oncogenes to pigment-producing cells of different origins. Most of the models have been successful in producing intraocular pigmented tumors, including retinal pigment epithelium tumors, carcinomas, and ocular melanosis. These models might provide better understanding of uveal malignant melanoma pathology.

**Histopathological Effects of Radiation**

The histopathology of radiation-treated globes is of value in understanding the therapeutic mode of action. The aim of treatment is to kill all tumor cells or to render them incapable of sustained proliferation. It is postulated that this result can be achieved through indirect tumor necrosis and hypoxia secondary to blood supply damage. Most studies are biased by the small size of the sample and by the complicated nature of cases examined in the pathology laboratory. Changes in eyes enucleated for radiation-induced complications or poor tumor control may not reflect the radiation response of most treated cases. Using conventional light-microscopy methods, it was difficult in most studies to characterize histopathologically the radiation response aside from radiation-induced damage (radiation retinopathy, uveitis iridis, cataract, vitreous hemorrhage). In the COMS, preenucleation radiation significantly reduced, but did not eliminate, mitotic activity. Not surprisingly, tumor regrowth is correlated with significant mitotic activity, whereas good tumor response is linked with fewer mitotic figures and tumor and blood vessel damage. It seems likely that loss of replicative capacity through DNA damage is a major mode of action of this method. Other significant features of irradiated tumors include necrosis, fibrosis, and balloon cell formation.

Further studies of the sequence of changes after proton beam treatment of uveal melanomas indicates progressive changes with decreased inflammation and increased fibrosis. In successfully treated tumors, mitotic figures persist only for the first 30 months after treatment.

**Natural History**

**Doubling Time**

Little is known about the natural history of uveal melanomas. Until recent decades, all patients underwent enucleation immediately after the diagnosis. Data on the growth pattern of small melanomas from series of patients observed by Gass and others have contributed to our knowledge of the rate of intraocular tumor growth prior to treatment. These findings and other selected reports suggest a gompertzian (exponential) growth curve, as postulated by Manschot et al. The treatment of uveal melanomas involves radiocurability and radiodurability. These vary greatly regarding doubling times or morphology.

**Intraocular Spread**

Small melanomas grow from a discoid to a hemispheric shape. They progressively obliterate the choriocapillaris and displace Bruch's membrane and the retina inward. When Bruch's membrane is disrupted, the tumor usually grows in the subretinal space in a mushroom configuration. The retinal pigment epithelium overlying the tumors undergoes early changes called tumor-associated retinal pigment epitheliopathy, which includes drusen formation and orange pigment (lipofuscin) accumulation.

**Extracocular Extension**

Although uveal melanomas are not particularly sensitive to radiation, they do spread diffusely beyond the eye. Extravascular spread requires an increased blood supply. Because intraocular untreated tumors are carried to the systemic circulation, they may reach distant sites. Intraocular tumors may be disseminated throughout the body, but the most frequent site for distant metastasis is the liver, followed by the lung. In a study by Shahmas and Bodi, approximately 5% of large melanomas in a series reported by Shahmas and Bodi. Approximately 5% of melanomas grow diffusely in the plane of the uvea or circumferentially along the root of the iris. They induce a slight thickening of the uvea (approximately 3 to 5 mm) and are often unsuspected or diagnosed late when secondary glaucoma or extracellular spread occurs. Extracellular spread may occur adjacent to or within the optic nerve or can occur anteriorly about the limbus.

**Metastases**

Although extracranial extension may be observed with small tumors, it is more likely to occur when the tumor has reached a larger size. In a study by Shahmas and Bodi, extracranial extension was observed in 18% of tumors exceeding 10 mm in diameter. The overall incidence of transocular extension was determined to be approximately 13% among 1942 malignant melanomas studied by Starr and Zimmerman. Other series report similar findings. Starr and Zimmerman noted a tenfold increase in the incidence of postoperative recurrence if the tumor extended to the surgical margin. The depth of scleral extension may have a prognostic significance. Otherwise common path of extracellular spread include the optic nerve and the lumen of the vortex veins.
Lympathic spread has not been demonstrated, as would be expected from the absence of lymphatics in the eye. This is in contrast to cutaneous melanomas. Hematogenous dissemination to the liver is a frequent form of metastatic spread. The respective roles of nonspecific trapping and of cell surface antigens in the invasiveness and dissemination of uveal melanomas are not yet fully established. Plasminogen activator function and the epidermal growth factor receptor may play a role in the occurrence and progression of metastases. Metastases to other sites (lung, heart, gastrointestinal tract, lymph nodes, pancreas, skin, central nervous system, bones, spleen, adrenal, kidneys, ovaries, thyroid) generally occur in association with liver metastases. In a survey of metastases from proton beam–treated melanomas, liver involvement was documented in almost all patients (136 of 145); the overall 1-year survival was 13%.

In a series of studies, McLean et al. found that most deaths from metastatic disease occurred in the first 5 years after enucleation, with a peak mortality in the second and third years (approximately 8% per year). They compared these data with the natural course of untreated melanomas and reached a conclusion that remains controversial: McLean et al. incriminated enucleation as a risk factor and suggested two principal mechanisms: (1) dissemination of tumor cells during traumatic operations, as demonstrated experimentally by Braunfelder et al. and (2) decreased host resistance to disseminated tumor cells. This latter mechanism has been called by Niederkorn et al. the "loss of intraocular induced concomitant immunity" mediated by cytotoxic T lymphocytes. Zimmerman and McLean's assumptions have been challenged by several investigators. Seigel et al. concluded that the statistical data can be interpreted differently and that no evidence suggested that the existing pattern of treatment be altered. Manschot and Van Peperzeel, Kersten and Blodi, and Davidoff pointed out that most melanomas are diagnosed only when they have reached a relatively large size and concomitantly given rise to metastases, and only then are enucleated. The clinical consequences of these controversies are the use of less traumatic techniques for enucleation and new impetus to the search for alternative treatments.

### Multiple Choroidal Malignant Melanoma

It has been estimated that only one person will develop bilateral choroidal melanomas in a population of 50 million. There is no clinical evidence of an inherited genetic predisposition for bilateral primary uveal melanoma, and it may be associated with ocular melanocytosis. Unilateral multifocal intraocular malignant melanoma appears to be even rarer than bilateral intraocular melanoma. To eliminate the possibility of a multinodular tumor, serial sections of the enucleated eye are useful to exclude continuity between the two tumors. Intraocular multifocal melanoma has been associated with ocular melanocytosis, iris melanoma with invasion of the ciliary body, iris or choroidal nevus (or both), and with systemic malignant neoplasm. However, other cases of double melanoma do not show any such associations. It is also unknown whether the prognosis for life differs in patients with multiple versus unilateral primary uveal melanoma.

### DIAGNOSIS OF UVEAL MELANOMAS: CHOROIDAL AND CILIARY BODY MELANOMAS

The diagnosis of choroidal and ciliary body melanomas has reached a high degree of accuracy at eye centers where experienced clinicians and modern ancillary testing facilities are available. This is well illustrated by a comparison of the misdiagnosis rates among the eyes on file at the AFIP: 19% (of 529 eyes) until 1962; 20% (of 208 eyes) between 1963 and 1970; and 6.4% (of 744 eyes) between 1970 and 1980. During the 11-year period of the last study, the rate of misdiagnosis declined from 12.5% to 1.4%. Between 1954 and 1977, the misdiagnosis rate was 2.6% (of 224 eyes) at the Mayo Clinic. In the Mayo series, in addition, six clinically unsuspected melanomas were found.

This high rate of correct clinical diagnosis is particularly impressive because only outpatient procedures (including clinical examination, ultrasonography, and fluorescein angiography) were used. No biopsies were performed, as is used for many other tumors. A review of 395 eyes enucleated during a 50-year period, drawn from the pathology files of Ohio State University, revealed a misdiagnosis rate of 10.9% in the period 1931 to 1950 that decreased to 1.7% in the period 1969 to 1981. Nine percent of choroidal melanomas were unsuspected preoperatively: all were in eyes with opaque media. In a series of 400 consecutive patients referred to the ophthalmology unit of the Wills Eye Hospital with an incorrect diagnosis of melanoma (i.e., patients who proved to have a so-called pseudomelanoma), the correct diagnosis was reached through clinical evaluation in 397 cases (99%). In that series, the most commonly encountered conditions mimicking a melanoma included choroidal nevi (26.5%), peripheral disciform degeneration (11%), congenital hypertrophy of the retinal pigment epithelium (9.5%), and choroidal hemangioma (8%). Most metastatic carcinomas had been correctly diagnosed by the referring ophthalmologists. The diagnostic accuracy of 99.7% in the COMS exceeds previously documented rates. It reflects the value of rigorous and standardized ophthalmic and systemic evaluations.

The cornerstone of diagnosis of posterior uveal melanoma remains clinical examination and, in particular, indirect ophthalmoscopy through a dilated pupil. Fundus contact lens examination and the use of a three-mirror lens can be extremely helpful. Scieral transillumination as advocated by Reese is also a useful aid. Pigmented conjunctival lesions, such as conjunctival melanoma, staphylomas, scleral ectasia, hematomata, cellular blue nevi, and ocular melanocytosis, may mimic extracocular extension of uveal melanomas. Visual field studies are of little help, especially in distinguishing melanomas from choroidal nevi. Although clinical examination by an experienced observer remains the most important test in establishing the presence of an ocular melanoma, ancillary diagnostic testing can be extremely valuable.

Fluorescein angiography and monochromatic photography have proved useful in differentiating subretinal or choroidal hemorrhage and hemangioma from melanoma. Although no angiographic pattern is pathognomonic, features of value include early mottling fluorescence, orange pigment over the margin of the tumor, progressive fluorescence of the lesion with late staining, and multiple pinpoint leaks that increase in size. Breaks in Bruch's membrane and retinal invasion can be emphasized the differences between low tumor autofluorescence and bright retinal pigment epithelium autofluorescence due to lipofuscin deposits.

**FIGURE 42.3.1.** Fluorescein angiogram showing characteristic pattern of choroidal melanoma.

Indocyanine green angiography was formerly used as a tool to differentiate melanomas from nevi, but early photographs had a rather poor resolution. Since the introduction of videocangiography and high-resolution fundus digital imaging systems, this technique has proven useful in documenting retinal vascular and choroidal diseases. It can also be used to further differentiate amelanotic choroidal tumors, such as some nevi or melanomas from hemangiomata or metastases, the latter appearing almost invariably hyperfluorescent on early or late frames (or both). This imaging system might also help patients with endogenous fluorescence emphasize the differences between low tumor autofluorescence and bright retinal pigment epithelium autofluorescence due to lipofuscin deposits.
Three-dimensional ultrasonography is a promising imaging technique for evaluating the accurate position of radioactive plaques secured beneath intraocular tumors. It can also be used to observe extrascleral extension of a choroidal melanoma, to quantify the tumor volume, and for posttreatment follow-up.

Direct observation by indirect ophthalmoscopy or the use of a three-mirror lens is useful to display the anterior border of these tumors. Clinical transillumination is helpful but is dependent on tumor characteristics and can be more complicated in those patients with amelanotic tumors, with ocular melanocytosis, and with dark pigmentation, or tumors complicated with paramacular hemorrhage. Transillumination may provide an inaccurate assessment of the anterior tumor margins of the peripheral choroid. Anatomic features evident on ultrasonographic biomicroscopy before enucleation were correlated with pathologic examination: supraciliary choroidal effusions, ciliary body rotation, anterior tumor margin position, and angle involvement.

The clinical need to define the anterior borders of peripheral choroidal melanomas clearly is related mainly to decisions regarding treatment options. Secondarily, the pattern of ciliary body involvement can help differentiate tumors of ciliary origin from those of choroidal origin.

Recent reports on the usefulness of color-coded Doppler imaging in the characterization and follow-up of melanomas are promising, particularly for detection of pulsatile ocular blood flow (POBF) at the tumor base. The tumor blood flow can also be quantified indirectly by ocular blood flow tonography. The higher POBF values observed in eyes with choroidal melanoma indicate that the pulsatile component of choroidal blood flow is increased. At present, these techniques must be interpreted with caution. Fundamental studies to validate the theoretically derived POBF values and clinical studies to determine reference ranges are required before any meaningful interpretation of these parameters can be made.

The usefulness of radioactive phosphorus (32P) in determining malignancy remains controversial, and this is little used at present. It has limited indications for use in routine cases in which adequate support for a diagnosis of choroidal melanoma can be obtained with less complicated procedures.

Radiologic examination, including computed tomography (CT), is useful in evaluating the presence and size of extracocular extension of tumor. It does not, however, add significant information to ultrasonography and implies low doses of radiation.

Images of uveal melanoma have been obtained by magnetic resonance imaging (MRI). This imaging modality has become more useful with employment of thin-section imaging, surface coils, and contrast material (gadolinium). Typically, due to the postulated paramagnetic properties of melanin, pigmented melanomas are hyperintense on T1-weighted images with enhancement by gadolinium and hypointense on T2-weighted images when compared to the brightness of the vitreous. This method is, therefore, promising in the detection and characterization of tumors in difficult cases as well as in the differentiation of associated serous retinal detachments. Magnetic resonance spectroscopy may be helpful in this respect in the near future. Nevertheless, to this date, ultrasonography is by far the main diagnostic modality in intracocular melanomas. Ocular ultrasonography is also more sensitive than MRI or CT for the detection of extracocular extension of choroidal malignant melanomas. Ultrasonography and fluorescein angiography are together very useful in patients’ follow-up (Fig. 42.3-3).

In a review of 51 consecutive patients who had undergone enucleation for a choroidal melanoma and 50 patients with simulating lesions, Char et al. found that the ophthalmoscopic examination was the most accurate diagnostic modality, allowing correct diagnosis of choroidal melanomas in all patients with clear media. Subretinal fluid, orange pigmentation, and collar-button configuration occurred more often with melanomas than with other lesions. In 63% of melanoma patients, fluorescein angiography was diagnostic; in 82%, A- and B-mode ultrasonography was diagnostic.

In some problematic cases, fine-needle aspiration biopsy has been proposed. However, the interpretation of aspirates may be difficult even in the hands of an experienced pathologist, and subsequent tumor cell seeding in the needle track has been reported. Nonetheless, in selected cases, this technique has proven useful in differentiating benign lesions or lymphoid infiltrates from melanoma. Such biopsies obtained through a transocular approach with a 22-gauge needle provided informative specimens in almost 90% of cases, with an accuracy of approximately 98%. It should be emphasized that the lack of histologic data prior to conservative treatment of most uveal melanomas represents a major limitation to our understanding of tumor response to radiation, accurate adaptation of conservative approaches, and establishment of prognosis.

Despite ancillary examinations, the differential diagnosis of small tumors may be difficult. Careful follow-up of such patients at short intervals with photography,
fluorescein angiography, and ultrasonography is advocated to demonstrate tumor growth. 321,358 Butler et al. 358 showed that the presence of symptoms, tumor thickness, orange pigment, acoustic hollowness, and hot spots on fluorescein angiography was a significant predictor of growth.

Patients with suspected intraocular melanoma should undergo a physical examination and metastatic workup. Clinical laboratory studies should include routine blood work, chest radiography, and liver enzyme measurements. CT should be performed if other tests suggest liver involvement. 359,406,90,91 Detection of circulating melanocytes using reverse transcriptase-polymerase chain reaction amplification of the tyrosinase gene is a promising approach. 90,91 Nevertheless, even though it is known that the detection of melanoma cells in blood cannot automatically be taken as a definitive sign for the presence of metastatic disease, polymerase chain reaction might help in interpreting the result of conventional markers for metastasis in the near feature. Haynie et al. 91 noted significant differences in the peripheral blood lymphocytes in two subgroups of patients with clinically less favorable choroidal melanoma; ciliary body involvement was related to reduction in NK cells and, in patients with extrascleral extension, an increased number of activated T cells was noted. Liver ultrasonography, liver-spleen scans, CT of the head, and MRI appear useful in the initial workup and follow-up. 359

MANAGEMENT

PROGNOSTIC ASSESSMENT OF CHOROIDAL AND CILIARY BODY MELANOMAS

The number of epithelioid cells in conjunction with the largest tumor dimension 123,124 and the microvascularization patterns 125,126,127,128 are the most important histologic prognostic parameters. Despite an early study by Flocke et al., 125 a larger study of small melanomas by Char et al. 126 showed that the largest tumor diameter was the best prognostic parameter for such tumors. The location of the anterior margin of the tumor, invasion of the line of transsection, and the degree of pigmentation follow this, according to Seddon et al. 173. Other features that have been associated with prognosis include tumor size, location of the anterior margin of the tumor, and degree of ciliary body involvement. 173 Sharnas and Bliod, 174 in a study of 253 choroidal and ciliary body melanomas for which a follow-up of 5 years or more was available, identified nine factors that significantly influenced prognosis: age of the patient enucleation; location of the tumor; location of its anterior border; largest tumor diameter in contact with the sclera, or largest tumor dimension; height of the tumor; integrity of Bruch's membrane; cell type; pigmentation; and scleral infiltration by tumor cells. 173,174

Char et al. 126 using a multivariate analysis, reached similar conclusions for small melanomas. Parameters that significantly influenced prognosis were cell type, largest dimension, scleral extension, and mitotic activity. A single-factor analysis identified three additional factors of significance: degree of scleral invasion, optic nerve invasion, and pigmentation. In most studies, increased pigmentation has been associated with increased mortality. 124 However, in a multivariate analysis, these last three parameters appear statistically related to cell type and tumor size. 171 Regan et al. 172 described iris color as a prognostic factor in ocular melanoma and concluded that patients with blue or gray irises show light to moderate tumor pigmentation and appear to be at increased risk of metastatic death from choroidal melanoma, independent of other risk factors. Maximum tumor size is believed to be an important predictor of outcome. 174 In the COMS report number 6, 122 anterior location was observed more commonly with large tumor size and more malignant cell type. In many studies, tumors involving the ciliary body have a worse prognosis than those located entirely in the choroid. 174 Microvascular networks tend to develop more commonly in the ciliary body relative to the choroid. 172 This observation is important, because deletion of chromosome 3 may be characteristic of ciliary body melanomas and has been associated with their aggressive behavior. 173

A matter of concern in the present classification of posterior uveal melanomas is the lack of an accurate, consistent, and clinically pertinent size classification. 172 This question is not purely theoretic, since size classification is most often the only available prognostic parameter; a clinically relevant size classification should assign tumors to currently accepted elective treatment modality, or at least to groups of significantly different life prognosis; and a comparison of results using various therapeutic approaches is required. The current TNM staging by the American Joint Committee on Cancer 141 draws boundary lines for small, medium, and large tumors. According to this classification, many tumors considered medium in the current management would belong to the large-tumor category. Whereas a classification according to the largest tumor dimension would appear best suited to predict patient survival, a size classification taking into account tumor thickness and basal diameter is currently in use in most centers and in the COM study (Table 42.3-2). Data from retrospective reports, as well as recommendations from the COM Study group, 175 tend to classify tumors as in Table 42.3-2. In COMS report number 6, 122 larger tumor size was related more commonly with anterior location and more malignant cell type. Large tumors invaded the retina, the vitreous, and vortex veins and ruptured Bruch's membrane more often than medium tumors. 122

TABLE 42.3-2. Classification of Tumor Size According to Boundary Lines

<table>
<thead>
<tr>
<th>Type</th>
<th>Apical Height</th>
<th>Basal Diameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small</td>
<td>1.42-3.5 mm</td>
<td>5 mm</td>
</tr>
<tr>
<td>Medium</td>
<td>3.5-10.5 mm</td>
<td>5-16 mm</td>
</tr>
<tr>
<td>Large</td>
<td>&gt;10.5 mm</td>
<td>&gt;16 mm</td>
</tr>
<tr>
<td>(Adjusted form %)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

It has been shown that certain histologically identified microvascularization patterns are an independent risk factor for the growth and metastatic behavior of choroidal melanomas. The microvascularization patterns that are networked and parallel with cross-linking indicate a high probability for metastatic disease, whereas the presence of microvascular patterns that are silent and parallel without cross-linking indicates a better prognosis. 124,128,136,137,138,139 A Cox proportional hazards model was generated with the conventional prognostic factors (including the largest tumor dimension in contact with the sclera, cell type, tumor-infiltrating lymphocytes, mitotic figures, gender, and location of the tumor within the eye) and the presence or absence of each of the nine microcirculatory patterns. The most important variable in the model was the largest dimension (back-to-back loops). In decreasing order of importance (largest tumor dimension, mitoses, parallel with cross-linking vascular patterns, age, the presence of tumor-infiltrating lymphocytes, and male gender), 141,142 However, in the Foss et al. series, 86 the parallel with cross-linking pattern did not carry a poor prognosis; in this series, a poor prognosis was associated with absence of the normal pattern and the presence of arca, arcs with branches, loops, and networks. Foss et al. 141 suggested that the periodic acid–Schiff patterns are based on three underlying factors that have biological significance: (1) presence of disordered growth, (2) presence of rapidly growing subclones, and (3) sectioning orientation. The first two of these factors carried prognostic significance in a multivariate Cox model that included tumor size and microvessel density. 142

Mehaffey et al. 321 observed that larger areas of these microcirculatory patterns (tumors with >2% occupied) imply a worse prognosis than small isolated foci (tumors with <5% occupied). This study also observed that it is possible to separate choroidal melanomas into three prognostic groups by cross-sectional area measured from histologic sections: small (tumor area <16.0 mm²); medium (tumor area >16.0 mm² but <61.4 mm²); and large (>61.4 mm²).

The estimation of tumor volume was related to outcome, but the relation between estimated volume and outcome did not hold for relatively small tumors (measuring <1.544 mm³). In a series of 217 small tumors (measuring <1.400 mm³), the largest tumor dimension in contact with the sclera was more strongly associated with outcome than the estimated volume, possibly because diffuse melanomas may have a relatively small volume but follow an aggressive clinical course. 323

Technologic advances have implemented the assessment of nucleolar area, nucleolar organized regions, tumor vascular patterns, and tumor vascular density as potential prognostic factors. Cell type, however, remains the most potent single predictor of outcome. 175,176

Seregard et al. have shown that the MLN and PC10 immunostaining counts retain a prognostic value in uveal melanomas when adjusting for the effect of the mean of the diverse vascular patterns. 177 In recent studies, 178 high expression of HLA-A (and, to a lesser extent, of HLA-B) antigens on the primary uveal melanoma was
strongly correlated with poor patient survival. High HLA-B expression was significantly correlated with the presence of epithelioid cells in the tumor. 172 The primary uveal melanomas showed a high expression of monomorphic and polymorphic HLA-A antigens, while metastases showed a high expression of monomorphic and a lower expression of polymorphic antigens. 173

In summary, all studies show that the prognosis of a patient with a choroidal or ciliary body melanoma is adversely affected by the following factors:

- Tumor containing loops, networks, or parallel with cross–linking vascular patterns 87,172,177
- Largest tumor dimension exceeding 10 mm
- Presence of numerous mitotic figures (mean count per 40 high-power field)
- Patient age older than 56
- Presence of tumor-infiltrating lymphocytes 42
- Male gender 42
- Tumor containing epithelioid cells (or related cytologic features, such as nuclear parameters and vascular architecture, as discussed earlier in Histologic Classification)
- Anterior tumor border anterior to equator 174
- Tumor extending to the scleral surface

In the COMS report number 4, 174 older patients with a history of diabetes and patients with more anteriorly located tumors were at increased risk for death. Yet a close interval-by-interval analysis of the prognostic value of size and cell type in a series of 3680 patients shows a decline over time after tumor excision. 175 Gamel et al. 176 applying the log-normal survival model 173 to 2892 patients treated by enucleation, demonstrated that the probability that the patient is cured by tumor resection is not modulated by the same biologic factors as those determining survival time among patients. Their analysis showed that mixed cell type and advanced patient age are associated only with a short median survival time. In contrast, pleomorphic nuclei and large tumor size were independently associated with both a low probability of curative resection and short median survival time. Many of these prognostic parameters are lacking in patients treated conservatively. Furthermore, due to a shorter follow-up, bias in patient selection and size of samples, and the use of different survival analysis models, comparison of survival rates between conservative approaches or between conservative approaches and enucleation remains a subject of intense controversy. 151,156,158,159 To date, the survival rates in large series after 5 years do not differ significantly. The reported tumor-related mortality 5 years after radiation therapy ranges from 11% to 25%, 141,144 whereas preliminary assumptions based on a log-normal model may indicate a poorer life prognosis after 10 years for patients treated conservatively. The COMS, a prospective multicenter study, should provide answers to this most crucial and controversial issue. 152

Several studies have established a correlation between rapid tumor regression after radiation therapy and a poorer life prognosis. 177 Rapid regression of tumor height after radiation therapy appears as a risk factor for metastasis. Rapid regression can possibly be correlated with a less differentiated cell type of fast-regressing tumors. However, such a hypothesis is difficult to ascertain for several reasons: (1) Cytologic study of melanomas is rarely performed before radiation therapy; (2) when needle biopsy is obtained, it often does not provide a reliable characterization of the cell type; and (3) study of enucleated eyes after radiation therapy for any reason may not accurately reflect the features of the tumor prior to radiation therapy, particularly in mixed or epithelioid tumors.

PRETREATMENT CLINICAL STAGING

In light of current knowledge, it is useful to discuss the treatment of choroidal and ciliary body melanomas in terms of tumor size, following the size classification discussed previously in Management. In contrast with the Reese-Ellsworth classification 135 of retinoblastoma, the current classifications are of marginal help in predicting the visual outcome of conservative approaches, since such factors as the distance to the optic nerve and macula are important in estimating final visual acuity.

Another problem is related to the rarity of detectable metastases, particularly lymphatic, at the time of diagnosis. Attempts to detect and treat subclinical metastases should develop in the near future to address appropriately this major clinical problem. Moreover, the lack of histopathologic data in most cases managed conservatively has given emphasis to clinical patterns of tumor growth prior to treatment and histologic analysis of tumor regression after radiation therapy based on enucleated eyes. The results of comparisons of data from retrospective studies have been a source of confusion and controversy.

TREATMENT OF CHOROIDAL AND CILIARY BODY MELANOMAS

In the late nineteenth century, enucleation became the standard and almost universally accepted treatment for all choroidal or ciliary body melanomas. Even today, early enucleation continues to have its ardent advocates. 181 However, in the last two decades, enucleation has been reassessed as the standard means of treating malignant melanomas of the choroid and ciliary body. This reassessment has resulted from (1) the development of newer and more precise diagnostic tests for recognizing malignant melanomas and the serial documentation of their size; (2) more information about clinical and pathologic features that determine survival; (3) additional observations about the natural course of untreated ciliary body and choroidal melanomas; (4) therapeutic developments other than enucleation to treat these tumors without destroying the eye; and (5) disagreements as to the value and risks of enucleation. 182

Most authors today agree that the goals of an ophthalmologist treating a uveal melanoma should be to destroy or inactivate the neoplasm, to maintain useful vision in the involved eye, to employ a treatment with as few side effects as possible, but most important, to provide the patient with the best prognosis for life possible. 137,139 Regarding which treatment can best achieve these goals, controversies will continue until results from prospective randomized treatment trials are collected. 131 In the absence of these data, the selection of treatment is based on the specific findings in each case with regard to tumor size, location, and growth rate; the preferences of the ophthalmologist, and the desires of the patient. Recently, Crucickshanks et al. showed that treatment choice does not seem to be associated with large differences in quality of life (as assessed by the Medical Outcome Study Short Form 36 and the National Eye Institute Visual Function Questionnaire). 134

Small Melanomas

The choices open to the physician treating a small choroidal or ciliary body melanoma include (1) observation; (2) some method of local treatment, such as radiation therapy, photoradiation, cryotherapy, ultrasonic hyperthermia, or local resection; and (3) enucleation.

OBSERVATION. An accumulating body of evidence indicates that the risks in observing most melanomas are generally low. 133,141,183 Serial examination every 3 months without intervention seems appropriate if the tumor is asymptomatic and appears dormant; the diagnosis is equivocal, and no growth is seen on serial ophthalmoscopic, photographic, and ultrasonographic examinations. Observation is also indicated for elderly or seriously ill patients or for tumors in the patient's only useful eye, particularly where the tumor is growing slowly. If the tumor shows progression, especially rapid growth or an increase in size beyond 10 mm in diameter and 3 mm in elevation, or if the lesion results in significant impairment of vision, treatment is indicated.

PHOTOCOAGULATION. In the photocoagulation method, the xenon arc, the argon laser, photoradiation with red light after photosensitization with hematoporphyrin derivatives, or dye laser after phthalocyanine photosensitization can be used. 133 Some success with photocoagulation has been documented histologically in small series. 133,134,135,136 The following criteria 133,134,135 for selecting patients with melanoma for photocoagulation treatment were suggested by Meyer-Schwickerath 136 and Vogel 137 and adapted by Shields 138.

1. The diagnosis of melanoma and evidence of growth should be documented thoroughly.
2. The tumor should not be greater than 5 diopters in elevation and 6 disc diameters at its greatest diameter.
3. The tumor must be surrounded completely without damaging the fovea or the optic disc.
4. The patient must have clear ocular media and a sufficient mydriasis to enable photocoagulation to be performed.
5. The tumor surface should not have large retinal vessels.

Photocoagulation requires several outpatient treatment sessions and is carried out after mydriasis and, in the case of xenon photocoagulation, use of retrobulbar anesthesia. A double confluent row of heavy coagulation is repeated three times at monthly intervals to encircle the tumor and to obliterate the choroidal vasculature supplying the lesion. The tumor subsequently becomes necrotic, with gray discoloration and a surrounding chorioapatric scar.
Long-term complications of photocoagulation include retinal vascular obstruction, visual field defect, macular pucker, cystoid macular edema, choroid neovascularization, vitreous hemorrhage, and retinal detachment. Recurrences may appear, usually within 2 years of treatment. In a 20-year follow-up of 54 patients with uveal melanoma, Vogel reported that 63% are alive, although only 46% were considered cured by photocoagulation. Twenty percent of patients subsequently underwent enucleation. Of the 20 patients (37%) who died, 8 did so as a result of metastatic disease, 3 died of other causes and, in 9 patients, the cause of death was undetermined. Shield reported that among 35 patients treated between 1976 and 1979, 25 retained useful vision, 5 had poor vision, and 5 subsequently underwent enucleation. There were no tumor-related deaths. Effects of laser phototherapy are strongly correlated with tumor pigmentation. Comparison of xenon arc and argon laser photocoagulation in 38 consecutive patients with a minimal follow-up of 58 months showed that recurrences were less frequent and appeared later after xenon radiation therapy. Moreover, primary photocoagulation of small posterior choroidal melanoma with argon laser is not recommended in view of a risk of immediate visual loss.

Photocoagulation seems best suited for small posterior melanomas located within 3 mm of the optic disc or fovea. In such lesions, radiation-induced retinopathy may cause visual loss. The patient's wish to avoid radiation therapy or enucleation may be the deciding factor. Photocoagulation can be helpful in the treatment of secondary serious macular detachments. Reports on hematoporphyrin, benzophenol, monacrid and phthalocyanine, and indocyanine green–enhanced phototherapy are still preliminary.

Transpupillary thermotherapy is a technique that employs infrared light (diode laser, 810 mm) delivered as heat to induce necrosis in tumor tissues. Transpupillary thermotherapy offers promising results in small choroidal melanomas, it may be an effective alternative to external beam radiotherapy for small choroidal melanomas, theoretically reducing radiation-induced complications. In a 14-month follow-up of 100 patients with posterior choroidal melanomas, Shields et al. reported tumor control in 94% of the cases but worsening of visual acuity in 42%. A longer follow-up is necessary to assess the actual rate of local recurrence, survival, and visual outcome.

OTHER LOCAL NONSURGICAL TECHNIQUES. Lincoff et al. obtained discouraging results with cryotherapy of uveal melanomas in four patients. Anecdotal reports of successful treatments for small peripheral melanomas exist. Even more than with radiation therapy, the efficacy of these alternative approaches lacks unequivocal evidence.

LOCAL RESECTION. Peyman et al. developed a technique of local sclerochoriocentral resection for choroidal melanomas. After a series of photocoagulation treatments around the tumor to create a firm chorioretinal adhesion or an area of bare sclera, the tumor is surgically removed, along with the adjacent sclera and retina. The defect is replaced by a scleral graft. Peyman has suggested that surgical candidates should exhibit the following criteria: (1) no evidence of metastatic disease; (2) the ability to tolerate general anesthesia; (3) a tumor base no larger than 12 mm and tumor location at least 3 disc diameters from the optic disc; (4) exudative retinal detachment no larger than one-third of the fundus; and (5) clear media.

After local resection, one-third of the eyes required enucleation because of complications, including vitreous hemorrhage and retinal detachment. Shields et al. advocate, in selected cases, the use of partial lamellar sclerectomy. Damato et al. reported the large experience of a skilled team, concluded that with a technique combining lamellar scleral flap for eye closure, hypotenotic anesthesia for homeostasis and, more recently, ocular decompression by pars plana vitrectomy, visual results can be obtained in nasal tumors and for tumors located more than 1 disc diameter from the optic nerve and fovea. Yet, most authors note that patients treated by local resection are also amenable to radiation therapy and that early visual loss is far more frequent after surgical resection than with radiation. The risk of leaving some viable tumor cells after treatment is also a major concern. Local resection has not been widely accepted. Recently Damato et al. recommended to adjunct systematically Rubrachytherapy to prevent tumor recurrence after local resection.

Iridocyclectomy has proven useful in the treatment of ciliary melanomas in several series. In the report by Forrest et al. of 107 iridocyclectomies for ciliary body melanoma, 6% of the patients had subsequent enucleation. The majority of problems related to surgical management occurred within 4 years of surgery. Damato et al. have promoted and employed this method for many years with good results. A surprising feature is the low incidence of recurrence even when tumor extends to the margins of the resection. In contrast to resection of choroidal melanomas, iridocyclectomy is widely accepted for the treatment of ciliary body melanomas. Endoresection of choroidal melanoma is technically challenging but may bear some interest for the conservation of central vision after removal of juxtapapillary tumors. Preliminary results are encouraging in terms of visual outcome despite a high rate of complication, including retinal detachment (40%), and cataract (65%). The risk of tumor cell release during surgery warrants long-term assessment of this procedure.

ENCELEATION. In the case of patients with a healthy second eye, enucleation is advised if the tumor shows evidence of rapid progression and invasion of the optic nerve or extraocular extension is suspected. Other considerations, including loss of central vision, failure of previous conservative treatment, and the patient's desire for complete surgical removal of the tumor, may make enucleation a reasonable choice.

Large Melanomas

There is at present general agreement that it would be inadvisable to treat cases of large melanoma by methods other than enucleation. Possible exceptions include patients with only one sighted eye, rare patients in whom vision can be salvaged, and patients who refuse enucleation. Abramson et al. recommended local radiation therapy in these latter difficult cases. Some authors recommend external radiation therapy prior to enucleation. Only experimental evidence in animal models exists for the usefulness of this therapy. This method is currently being evaluated in the COMS. This randomized trial reported initial mortality findings that showed no survival difference in the preenucleation irradiated group. Zimmerman et al. have suggested that when enucleation is carried out, the "no-touch" technique of Fraunfelder should be considered. This method was designed to minimize the possibility of seeding of tumor cells into the blood vessels during enucleation. The authors claim that this technique avoids intraocular pressure elevations above 15 mm before complete freezing occurs around the tumor. Cytoreduction is used to minimize the flow of fluid and blood to or from the tumor during the manipulation necessary for enucleation. Although most surgeons do not use the no-touch technique, it is increasingly recognized that enucleation should be carried out by a person skilled and experienced in the procedure and that surgery should be done with a minimum of manipulation.

Medium-Sized Melanomas

Treatment of medium-sized tumors is the subject of current controversy. Although general agreement exists that the observation of small melanomas carries little risk and that large melanomas should be treated by enucleation, there is less consensus regarding the treatment of medium-sized melanomas.

Nonsurgical Techniques

RADIATION THERAPY FOR OCULAR MELANOMA. Ocular melanomas have been successfully treated by a variety of radiotherapeutic modalities, including external-beam techniques using photons or charged particles (protons and helium ions); stereotactic radiosurgery with modified linear accelerators and multisource cobalt units; brachytherapy (plaque) techniques using a wide variety of isotopes; hyperthermia in combination with brachytherapy; and, at least experimentally, boron neutron techniques using photons or charged particles (protons and helium ions); stereotactic radiosurgery with modified linear accelerators and multisource cobalt units; brachytherapy (plaque) techniques using a wide variety of isotopes; hyperthermia in combination with brachytherapy, and, at least experimentally, boron neutron capture therapy (BNCT). Techniques with the most widely reported clinical experience to date include charged-particle beam therapy and plaque therapy.

CHARGED-PARTICLE BEAM THERAPY. Charged-particle beams (protons or helium ions) have specific dosimetric advantages in the delivery of high radiation dose to very precisely localized targets. Treatment of ocular melanoma requires pinpoint accuracy to limit dose to the adjacent retina, optic nerve, lens, and brain. Charged-particle beams are produced by a cyclotron or synchrotron available at only a few sites around the world. High-energy charged particles travel a fixed distance in tissue that varies with the energy of the particle and the nature of the tissue. Near the end of their path, they deposit the bulk of their energy within a well-defined volume, referred to as the Bragg peak. A high and relatively uniform dose can be achieved within a small volume, thereby sparing adjacent normal tissues. Proton beam therapy is available at only 16 facilities in nine countries and helium and other ion beams at even fewer sites. Charged-particle beam therapy is generally delivered in four or five treatment sessions over 1 to 2 weeks. The treatment requires sophisticated planning techniques, precise tumor mapping, immobilization of the head, and fixation of the eye at a reproducible and verifiable gaze angle. Surgical placement of inert radiaopaque rings on the sclera assists in identifying the target volume. Patients are treated in a seated position, with a face mask and bite block to immobilize the head. The correct gaze angle, chosen so that the beam enters the sclera and minimizes radiation therapy of the anterior chamber, is verified by an infrared camera with the patient's vision focused on a fixation point.
light. The treatment portal (beam diameter) ranges from 1 to 4 cm. Daily setup of the patient is accomplished in 10 minutes, and the duration of radiation therapy is only 1 to 2 minutes. Long-term data on the experience with helium ion therapy for ocular melanoma have recently been updated. Three hundred forty-seven patients were reported, with local tumor control achieved in 96%. Although rare cases of tumor regrowth were identified as late as 5 years after treatment, 85% of local regrowth was detected within 3 years. The total enucleation rate was 19% (3% for local regrowth and 16% for complications of radiation therapy, including neovascular glaucoma). The 10-year overall survival is 76%, with 24% of patients manifesting distant metastasis. Risk of metastasis was related to previously known negative prognostic factors, such as large tumor size or unfavorable location.

Proton beam treatment centers report similar local control rate of 90% to 95%. Risk of distant metastasis also appears comparable to the helium ion–treated patients, approximately 20% at 5 years. Randomized studies comparing proton beam therapy and enucleation have not been reported, and retrospective comparisons are difficult because of the need to balance the known prognostic factors (tumor size, tumor location and ocular structures involved, patient age) between the treatment groups. A large and statistically well-balanced comparison of proton-treated patients with enucleated patients from the same institution has shown no apparent difference in long-term survival.

Visual preservation is one of the goals of eye-conserving therapies for ocular melanoma. Radiation maculopathy and papillopathy are major causes of visual loss after successful treatment of melanoma with charged-particle beams. Although preservation of peripheral vision and ambulatory vision has been satisfactory, visual acuity of 20/100 or better was observed in only 32% of patients treated at one major center for proton radiation therapy and was 20/200 or better in only 36% of patients treated with helium ion therapy. These studies concur in the finding that posttreatment visual acuity is greatly affected by tumor location (in relation to optic disc and fovea), tumor size, pretreatment visual acuity, and treatment parameters. In proton beam–treated patients with tumor edge more than 3 mm from the optic disc and fovea, 67% retained useful vision (20/200 or better); with tumors located within 3 mm of these structures, only 39% maintained useful vision.

EPISCLERAL PLAQUE RADIATION THERAPY. Episcleral plaque therapy, a highly specialized multidisciplinary treatment approach, is more widely available than charged-particle beam therapy for ocular melanoma. A concave plaque is constructed to house several small radioactive sources based on preoperative tumor measurements. This requires integration of data from clinical examination, ultrasonography, CT, or MRI scan. The specially designed plaque containing multiple radioactive sources is temporarily sutured to the sclera overlying the tumor under general or retrobulbar anesthesia. Operative localization of the plaque placement is guided by transillumination, ophthalmoscopic observation, or ultrasonography. The plaque remains in place for 2 to 5 days, depending on the type and activity of the radioactive source, and is then removed under similar operative conditions.

Iodine 125 is the most commonly used radioisotope in the United States and is the only isotope permitted in the COMS trial. Ruthenium 106 is frequently used in Europe; other isotopes include cobalt 60 and palladium 103. Isotopes with lower photon and electron radiation (125I, 106Ru, 103Pd) are more easily shielded to reduce the exposure to adjacent normal tissues in the patient and the potential exposure to medical personnel. The choice of radioisotope has been based historically on availability and experience. Newer isotopes have been used after detailed dosimetric study and computer modeling. 103Pd has dosimetric advantages based on its lower photon energy as compared to 125I. Phase I trials of 103Pd have been favorable. A nonrandomized comparison of 125I and 106Ru plaques showed better tumor control with the 125I.

The COMS group recently completed accrual to a randomized trial comparing standardized 125I plaque therapy to enucleation for medium-sized melanomas. A review of factors considered in selecting the 125I plaque therapy for this trial has been published. In comparison to 103Co plaque, 125I results in a significantly reduced exposure of normal tissue to high radiation dose. Each plaque consists of a flexible inner plastic plaque and a rigid outer gold plaque that is sutured in place. Six different plaque sizes are available, and the size selected covers a 2- to 3-mm margin around the base of the tumor. 125I seeds are sandwiched between the gold and plastic plaques. The activity and number of seeds are selected to achieve an apical dose rate between 42 and 105 cGy/h. Treatment duration for the plaque therapy is calculated to deliver a total dose of 85 Gy to the prescription point.

Study end points include survival, freedom from melanoma metastasis, as well as useful vision retained. The accrual objective was reached in July 1998, when 43 clinical centers enrolled a total of 1,517 patients. Published data will be available when reliable 5-year survival estimates are known. The COMS data will have a major influence on the choice of treatments. No other randomized trial has been published comparing enucleation with any radiotherapeutic approach. As with proton beam therapy, retrospective comparisons between plaque therapy and enucleation require careful analysis and balancing of prognostic factors. A large retrospective series comparing 103Co plaque therapy to enucleation identified no significant difference in long-term survival.

Table 42.3 summarizes some of the retrospective data available for a variety of plaque therapies. Survival rates at 5 years range from 80% to 88%. The rate of metastatic disease is approximately 10% at 5 years but appears to increase to close to 20% for studies reporting 10-year data. Enucleation has been required for either tumor progression or severe radiation complication (neovascular glaucoma, vitreous hemorrhage) in 10% to 17% of patients. In Table 42.3, clinical outcomes for charged-particle beam treatments and plaque therapy are compared, with no apparent significant differences between any of the modalities.

Table 42.3-3 summarizes some of the retrospective data available for a variety of plaque therapies. Survival rates at 5 years range from 80% to 88%. The rate of metastatic disease is approximately 10% at 5 years but appears to increase to close to 20% for studies reporting 10-year data. Enucleation has been required for either tumor progression or severe radiation complication (neovascular glaucoma, vitreous hemorrhage) in 10% to 17% of patients. In Table 42.3-4, clinical outcomes for charged-particle beam treatments and plaque therapy are compared, with no apparent significant differences between any of the modalities.

Table 42.3-3. Retrospective Data on Radioactive Episcleral Plaque Therapy

Table 42.3-4. Clinical Outcomes from Three Different Radiation Therapy Techniques

Preservation of useful vision is one of the anticipated benefits of plaque therapy. However, the documentation and analysis of visual outcomes after eye-conserving therapies have been limited by a number of factors. Acuity may decrease with time after radiation therapy, and follow-up data may be incomplete for patients referred to distant tertiary eye care centers. Data from the various retrospective series are not always directly comparable. Visual acuity has been expressed as useful vision, reading vision, ambulatory vision, Snellen chart line decrement, and other measures. As noted with particle beam treatment, loss of acuity is a complex interaction of tumor size, location, and treatment effects. In the recently updated report by Gunduz et al., final visual acuity was better than 20/200 for 44% of patients, but visual
FUTURE DIRECTIONS FOR RESEARCH

The use of BNCT in humans with melanoma, for the treatment of skin nodules, has been reported. This technique has been marked by significant adverse radiation reactions, including retinopathy, optic neuropathy, and glaucoma after treatment with 50 to 70 Gy in a single fraction. Optimal dose and technique have not yet been defined for this approach.

Linear accelerator (photon) fractionated stereotactic radiosurgery has been studied to use the radiobiologic advantage of multiple- rather than single-fraction treatment. Reproducible immobilization of the head and eye is required, and active optical fixation systems, similar to proton beam techniques, have been described. In these studies, 35 to 70 Gy has been delivered in 2 to 8 fractions. Outcome data and toxicity reports will require additional follow-up time, and further refinement of treatment technique will be necessary. The preliminary data indicate a risk of significant adverse treatment effects with the techniques and radiation doses reported to date. The use of these techniques outside of the investigational setting is not recommended, except for patients who cannot be treated with proton beam or plaque therapy.

Hyperthermia and Episcleral Plaque Radiation Therapy. Hyperthermia has been investigated in conjunction with radiation therapy to treat a variety of tumors. Preclinical studies have demonstrated that neoplastic cell lethality is proportional to temperature increase in the target tissue and that the combination of hyperthermia and radiation produces enhanced antitumor effects. Ocular tumor heating has been achieved by a variety of techniques, including microwave applicators, ultrasonic applicators, or ferromagnetic seeds.

One of the primary objectives for combining hyperthermia and radiation is to reduce the radiation dose, which is expected to result in fewer visual complications with a comparable rate of tumor control. An initial report of combined hyperthermia and episcleral plaque therapy employed a 30% reduction in radiation dose (72 Gy, as compared to the prior standard dose of 100 Gy). In this phase I study of 25 patients, 22 showed decrease in tumor height, and ambulatory vision (>5/200) was maintained in 20 patients. Two patients had severe complications (hemorrhagic retinal detachment and vitreous hemorrhage). Evaluation of long-term efficacy and late effects will require additional follow-up.

The administration of boron-containing compounds and neutron radiation therapy has shown efficacy in the Greene melanoma-rabbit model. Boronated compounds have been administered experimentally to human subjects with ocular melanoma prior to enucleation. Increased uptake of boron within the melanoma cells, compared to vitreous body, retina, and sclera was observed. The use of BNCT in humans with melanoma, for the treatment of skin nodules, has been reported. This approach for the treatment of ocular melanoma is at an early experimental stage, and further technical refinement will be required before clinical trials can be considered.

PREENUCLEATION ORBITAL RADIATION THERAPY. For the treatment of larger melanomas, where enucleation is the accepted standard treatment, COMS has reported initial results of a randomized comparison of preoperative orbital radiation therapy (20 Gy in 5 fractions) followed immediately by enucleation versus enucleation alone. The hypothesis tested was that preoperative orbital radiation might reduce the risk of seeding of viable tumor cells during surgery and thereby improve survival through the reduction in the incidence of distant metastasis.

With the sponsorship of the National Eye Institute of the National Institutes of Health, the COMS Group enrolled 1003 patients from 1986 through closure in December 1994. Five-year outcome data on the first 800 patients have been published.

As shown in Table 42.3-5, no advantage in overall survival or prevention of melanoma metastasis was seen with the use of preenucleation orbital radiation therapy at the dose and fractionation studied. The trial had the statistical power of 90% to detect a 20% relative difference in survival between the two arms. Acute complications (occurring 1 to 6 weeks after enucleation) were slightly more common in irradiated patients, but all complications were minor. For late complications (>6 months after enucleation), no increase in cosmetic or functional complications was seen after radiation therapy. In fact, severe piosis was observed less frequently in patients receiving radiation therapy (5% vs. 10%).

Table 42.3-5. Collaborative Ocular Melanoma Study Randomized Trial of Preenucleation Radiation Therapy for Large Choroidal Melanomas

Preoperative radiation did appear to lower the risk of orbital recurrence, although this was a rarely noted event (<1% of the total study population developed local relapse). No recurrences were noted in the preenucleation radiation therapy arm, and five biopsy-proven recurrences were documented in the enucleation-only arm. The five patients with orbital recurrence had metastatic melanoma diagnosed prior to diagnosis of the orbital recurrence and died less than 1 year after presentation of the local recurrence.

With no survival benefit noted from the COMS trial, routine preoperative orbital radiation therapy, as administered in this trial, would not be considered standard therapy. The COMS patients will continue to have follow-up assessments, but any late difference in survival is unlikely, as 46% of patients on study have died at time of this analysis. Preoperative or postoperative orbital radiation therapy may still be considered for selected patients who are at high risk for incomplete tumor excision or perioperative tumor seeding.

INVESTIGATIONAL RADIOTHERAPEUTIC TECHNIQUES.

Radiosurgery and Fractionated Stereotactic Radiation Therapy. High-dose, highly focused radiation therapy for small target lesions (<2 cm) can be accomplished by either gamma knife radiosurgery (multiple fixed, precisely aimed cobalt teletherapy beams) or stereotactic radiation therapy (multiple rotational arcs of photon beams from a linear accelerator). Both techniques are similar in their use of standard energy proton beams for treatment and rely on meticulous patient immobilization to deliver treatment to a precisely localized target within a coordinate mapping system. These techniques have been widely used and well described for the treatment of intracranial neoplasms (meningiomas, acoustic neuromas, and metastatic tumors) and for the ablation of arteriovenous malformations. Several recent retrospective series have examined the application of these techniques for the treatment of ocular melanomas.

The use of high-dose single-fraction Leksell gamma knife radiosurgery has been reported in a few small retrospective series. This technique has been marked by significant adverse radiation reactions, including retinopathy, optic neuropathy, and glaucoma after treatment with 50 to 70 Gy in a single fraction. Optimal dose and technique have not yet been defined for this approach.

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Boron Neutron Capture Radiation Therapy. BNCT is a specialized form of radiation therapy in which a neutron beam is targeted against a tumor that has been pretreated with a boron-containing compound. The boron nucleus is 10,000 times more likely than a hydrogen atom to capture a thermal neutron; therefore, preferential localization of boron in the tumor would result in precise and focal radiation delivery. The capture of the slow neutron by the boron nucleus leads to an energetic fission reaction with the formation of a lithium ion and an alpha particle (helium ion), accompanied by 2.4 MV of energy. The lithium and helium ions travel a distance of only 10 mm, limiting the lethal effect of the radiation to a radius approximately the diameter of one cell.

The administration of boron-containing compounds and neutron radiation therapy has shown efficacy in the Greene melanoma-rabbit model. Boronated compounds have been administered experimentally to human subjects with ocular melanoma prior to enucleation. Increased uptake of boron within the melanoma cells, compared to vitreous body, retina, and sclera was observed. The use of BNCT in humans with melanoma, for the treatment of skin nodules, has been reported. This approach for the treatment of ocular melanoma is at an early experimental stage, and further technical refinement will be required before clinical trials can be considered.
Uveal melanoma, like retinitis pigmentosa, may not constitute a single disease; it may instead consist of an assortment of maladies with multiple genetic origins that simply culminate in a limited phenotype. In the case of retinitis pigmentosa, varying proportions of rod and cone photoreceptor cells degenerate owing to a variety of genetic mutations within the same or different genes. In contrast to a phenotype associated with cell death, uveal melanoma is characterized by uncontrolled proliferation. Fundamentally different mechanisms can lead to unwarranted cell growth, supported in the case of uveal melanoma by cyrogeneric alterations and biochemical findings that disparate genetic events likely initiate the transformation of normal uveal melanocytes.

Cancer, as a multistage process, has an impact on a large number of genes and their related cellular pathways. Recent advances in both biochemical and molecular methods render it possible to study the cellular pathways that comprise this multistage process, endowing tumor cells with properties related to their malignant and metastatic capabilities. Such studies can provide significant information about the course of the disease and about effective treatments, independent of knowing the genetic mutations that cause the disease. It may, in fact, be more prudent to study the common cellular pathways that define the properties of these cells and to develop treatments based on these findings rather than attempting to "fix" a diverse array of genetic mutations.

Many features of ocular melanoma can be studied initially using established cell lines derived from biopsies of human tissues. Normal uveal melanocytes also can be passaged in culture. They are nonmalignant, neither growing in soft agar or athymic nude mice and, therefore, differ from uveal melanomas that can grow in either circumstance as well as alter the structure of the uvea and metastasize to other sites. Comparisons between uveal melanocytes and uveal melanomas can reveal the biochemical pathways that promote malignancy and metastatic disease. It is important to note, however, that the results obtained from in vitro studies need to be confirmed using primary tumor tissue.

In addition, although several properties associated with transformation can be studied in vitro, animal models are essential, since the most general and accepted definition of malignancy requires demonstrating the formation of invasive or metastasizing tumors in vivo. Cells derived from human uveal melanomas, for example, have been shown to grow in athymic nude mice after intraocular or subcutaneous inoculation; migration to the liver ensues, resulting in metastatic lesions and death. An animal model, therefore, can be used to grade the malignant and metastatic properties of different cell lines; these cell lines then can be modified to alter the expression of a gene suspected of being involved in tumor progression, and the consequences for growth and dissemination of the tumor then can be measured in the animal.

As a first step, how can in vitro comparisons be made between uveal melanocytes and uveal melanomas? Genes and their products (proteins) that are uniquely expressed in one cell type can be identified by one of several new approaches, including differential display, suppression subtractive hybridization, two-dimensional gel electrophoresis–mass spectrometry and, most recently, by using cDNA chip arrays. As an example, subtractive cDNA hybridization recently was used to identify differences in mRNA species obtained from normal uveal melanocytes and an epithelioid melanoma cell line. Tissue Factor was among the genes identified and suspected of elevated expression in the melanoma cell line. Tissue Factor has angiogenic properties, contributing to the formation of new vessels associated with solid tumors, perhaps including uveal melanoma. The expression of angiogenic factors is an example of one of the cellular events contributing to the cancer phenotype but which has little to do with the initial genetic mutation underlying transformation. Also, treatments based on antiangiogenic strategies are a prime example of how studying cellular pathways can be beneficial.

The differential expression of Tissue Factor was confirmed by Western blot analysis (detecting levels of protein) and by RNase protection assay (measuring levels of mRNA), as illustrated in Figure 42.3-4A and Figure 42.3-4B. Thus, multiple techniques support in vitro findings that Tissue Factor is expressed at elevated levels in a uveal melanoma cell line compared to normal uveal melanocytes.

To avoid in vitro artifacts stemming from culture conditions, however, differential expression must be confirmed in primary ocular tissues. Biopsies from primary uveal melanomas and normal tissues derived from human donor eyes can be compared by Western blot analysis and by immunohistochimistry using specific antibodies. The expression of the corresponding genes also can be compared by Northern blot hybridization using the same ocular tissues. In addition, archival specimens can be used for case-correlative purposes by employing such techniques as in situ hybridization, immunohistochimistry, and reverse transcriptase-polymerase chain reaction. As illustrated in Figure 42.3-4C, RNA isolated from a 6-mm paraffin section of an enucleated eye with a uveal melanoma was used for reverse transcriptase-polymerase chain reaction with primers specific for Tissue Factor. Tissue Factor was detected in the primary tumor tissue, thus corroborating in vitro studies. In the near future, it will be especially informative to compare these sorts of detailed molecular findings with outcome data for patients made available through the collection of archival specimens.

Further correlations can be established between specific biochemical events and the malignant properties of an ocular tumor by genetic manipulation using established cell lines. Transfection experiments can be conducted to alter the level of expression of interesting genes (e.g., Tissue Factor); the consequences of altered expression on division, growth, and progression of the transfected cells then can be determined both in vitro and in vivo. In some cases, the biochemical function of the protein can be ascertained, and this provides further clues about additional portions of a cellular pathway that might be useful for targeted intervention. The promoters for melanocyte-specific genes also may be useful for targeting oncogenic expression in a transgenic animal, thereby creating an important model of uveal melanoma.

Oncogenes, such as the SV40 transgene producing the large T and small t antigens, can be used to generate pigmented tumors of the eye. To obtain models more representative of uveal melanoma, however, the transgene apparently needs to be driven by a promoter specific for uveal melanocytes rather than one common to multiple cell types. Again, this can be accomplished by comparing normal uveal melanocytes with related ocular tissues and skin. Once the identification has been successful and an appropriate model of uveal melanoma available, the efficacy of different treatments can be evaluated more fully.

However, there is a general misconception that ocular melanoma and cutaneous melanoma are essentially the same disease and that research of the more prevalent skin disorder will satisfy needs within the ophthalmology community. This is not the case. The two diseases differ in their systemic symptoms, metastatic patterns, and susceptibility to treatments. Clearly, the study of ocular melanoma remains within the purview of the vision scientist. Further, the advent of new molecular and biochemical techniques coupled with the availability of tissue specimens and established cell lines now renders it possible to advance our understanding and treatment of ocular tumors. Additionally, as has often been the case, studies of ocular tissues have enhanced our understanding of other tissue types and associated pathologies; delineating the cellular pathways contributing to cancer phenotypes in the eye should be no exception.

Acknowledgments...


250. White VA, Chambers JD, Courtright PD, Chang WY, Horman DE. Correlation of cytogenetic abnormalities with the outcome of patients with uveal melanoma. Cancer 1998;83:354.


SECTION 43.1
Molecular Biology of Central Nervous System Neoplasms

Introduction
Diffuse Fibrillary Astrocytomas
Progression to Anaplastic Astrocytoma
Formation of Low-Grade Astrocytoma

Diffuse, fibrillary astrocytomas are the most common type of primary brain tumor in adults. These tumors are divided histopathologically into three grades of malignancy: World Health Organization (WHO) grade II astrocytoma, WHO grade III anaplastic astrocytoma, and WHO grade IV glioblastoma multiforme (GBM).

The transition from WHO grade II astrocytoma to WHO grade III anaplastic astrocytoma is accompanied by a marked increase in malignant behavior. Although many patients with grade II astrocytomas survive for 5 or more years, patients with anaplastic astrocytomas often die within 2 or 3 years and frequently show transformation to GBM. Historically, the major differences between grade II and grade III tumors are increased cellularity and the presence of mitotic activity, implying that higher proliferative activity is the hallmark of the progression to anaplastic astrocytoma.

A number of molecular abnormalities have been associated with anaplastic astrocytoma, and some studies have suggested that most of these abnormalities converge on one critical cell-cycle regulatory complex that includes the p16, cyclin-dependent kinase-4 (cdk4), cdk6, cyclin D1, and retinoblastoma (RB) proteins. The simplest schema suggests that p16 inhibits the cdk6/cyclin D1 or cdk4/cyclin D1 complex, preventing these complexes from phosphorylating pRB, and so ensuring that pRB maintains its brake on the cell cycle. Individual components in this pathway are altered in up to 50% of anaplastic astrocytomas and in the majority of GBM.

Other abnormalities include increased expression of vascular endothelial growth factor (VEGF). PDGF ligands and receptors are expressed approximately equally in all grades of astrocytoma, suggesting that such overexpression is also important in the initial stages of astrocytoma formation. Tumors often overexpress cognate PDGF ligands and receptors in an autocrine stimulatory fashion. The mechanisms for PDGF overexpression in most cases have not been elucidated, although rare astrocytomas display amplification of the PDGF-a receptor gene. Significantly, loss of chromosome 17p in the region of the TP53 gene is closely correlated with PDGF-a receptor overexpression, in that 17p loss is most often seen in those astrocytomas that have PDGF-a receptor overexpression. These observations may imply that TP53 mutations have an oncogenic effect only in the presence of PDGF-a receptor overexpression. This interdependence is highlighted by observations that mouse astrocytes without functional p53 become transformed only in the presence of specific growth factors.

Astrocytomas display a remarkable tendency to infiltrate the surrounding brain, confounding therapeutic attempts at local control. These invasive abilities are often apparent in low-grade as well as high-grade tumors, implying that the invasive phenotype is acquired early in tumorigenesis. Investigations into astrocytoma invasion have highlighted the complex nature of cell-cell and cell-extracellular matrix interactions. A variety of cell surface and extracellular matrix molecules such as CD44, glycoproteins, gangliosides, and integrins are differentially expressed in astrocytomas. Many of the growth factors expressed in astrocytomas, such as fibroblast growth factor, epidermal growth factor (EGF), and VEGF, also stimulate migration. Such growth factors, cell surface receptors, and extracellular molecules most likely reflect a dynamic interplay between cell-cell adhesion, remodeling of the extracellular matrix, and cell motility.

Less common molecular changes also occur in grade II astrocytomas. Loss of chromosome 22q, for instance, suggests the presence of a chromosome 22q glioma suppressor gene. Comparative genomic hybridization studies have also demonstrated common gains of chromosome 7q in low-grade astrocytomas. Finally, methylation of critical growth regulatory genes has been noted in some astrocytomas and may be another mechanism for gene alteration (W. Cavenee, unpublished data).

PROGRESSION TO ANAPLASTIC ASTROCYTOMA

The mechanisms for PDGF overexpression in most cases have not been elucidated, although rare astrocytomas display amplification of the PDGF-a receptor gene. Significantly, loss of chromosome 17p in the region of the TP53 gene is closely correlated with PDGF-a receptor overexpression, in that 17p loss is most often seen in those astrocytomas that have PDGF-a receptor overexpression. These observations may imply that TP53 mutations have an oncogenic effect only in the presence of PDGF-a receptor overexpression. This interdependence is highlighted by observations that mouse astrocytes without functional p53 become transformed only in the presence of specific growth factors.

Chromosome 9p loss occurs in approximately 50% of anaplastic astrocytomas and GBMs, with 9p deletions primarily affecting the region of the CDKN2A gene.
which encodes the p16 protein and the p14ARF protein. The CDKN2A gene is inactivated either by homozygous deletion or, less commonly, by point mutations or hypermethylation, thereby affecting p16 and p14ARF expression. Moreover, replacement of CDKN2A/p16 into GBM cell lines lacking the gene results in growth suppression.

Loss of chromosome 13q occurs in one-third to one-half of high-grade astrocytomas, with the RB gene preferentially targeted by losses and inactivating mutations. Overall, analysis of chromosome 13q loss, RB gene mutations and RB protein expression suggests that the RB gene is inactivated in approximately 20% of anaplastic astrocytomas and 35% of GBM. Interestingly, RB and CDKN2A/p16 alterations in primary gliomas are inversely correlated, rarely occurring together in the same tumor.

Amplification of the CDK4 gene provides an alternative to subvert cell-cycle control and facilitate progression to GBM. CDK4, located on chromosome 12q13-14, is amplified in 15% of malignant gliomas, although this frequency may be higher among cases without CDKN2A/p16 loss, perhaps reaching 50% of GBMs without CDKN2A/p16 loss. CDK4 amplification and CDKN2A/p16 deletions do not occur together in GBM cell lines and some GBM cell lines overexpress cyclin D1. On the other hand, in some GBMs and GBM cell lines, CDK4 amplification and cyclin D1 overexpression appear to represent alternative events to CDKN2A/p16 deletions, because these genetic changes only rarely occur in the same tumors. CDK4 amplification also occurs, although not as commonly as CDK4 amplification.

Alteic losses on 19q have been observed in up to 40% of anaplastic astrocytomas and GBMs, indicating a progression-associated glial tumor suppressor gene on chromosome 19q. This tumor suppressor gene may be unique to glial tumors and is involved in all three major types of diffuse cerebral gliomas (astrocytomas, oligodendrogliomas, and oligoastrocytomas). This gene maps to a region of chromosome 19q13.3, telomeric to the marker D19S412 and centromeric to the STD locus gene, but is yet to be identified.

PROGRESSION TO GlioBlastoma Multiforme

GBM is the most malignant stage of astrocytoma, with survival times of less than 2 years for most patients. Histologically, these tumors are characterized by dense cellularity, high proliferation indices, microvascular proliferation, and focal necrosis. The highly proliferative nature of these lesions is no doubt the result of multiple mitogenic effects. As mentioned previously, at least one such effect is deregulation of the p16-cdk4-cyclin D1-pRB pathway of cell-cycle control. The vast majority, if not all, GBMs have alterations of this system, whether it be inactivation of p16 or pRB or overexpression of cdk4.

Chromosome 10 loss is a frequent finding in GBM, occurring in 60% to 95% of GBMs but far less commonly in anaplastic astrocytomas. At least two tumor suppressor loci are present on the long arm of chromosome 10, and there may be a third locus on the short arm. The PTEN/MMAC1/TEP-1 gene at 10q23.3 has been implicated as one of these genes, with PTEN mutations identified in approximately 20% of GBM. PTEN functions as a protein tyrosine phosphatase and has 3’ phospholipid phosphatase activity; in addition, PTEN has an amino-terminal domain with homology to tensin and auxin. PTEN may regulate cell migration via affecting focal adhesion kinase and may regulate cell proliferation via control of the AKT serine/threonine kinase. Indeed, introduction of wild-type PTEN into glioma cells with mutant PTEN leads to growth suppression. Nonetheless, given the remarkably high frequency of chromosome 10 loss in GBM, it is likely that other glioma tumor suppressors reside on this chromosome; one candidate is the DBMT1 gene.

EGFR is a transmembrane receptor tyrosine kinase, whose ligands include EGF and transforming growth factor-a. The EGFR gene is the most frequently amplified oncogene in astrocytic tumors, being amplified in approximately 40% of all GBMs but in few anaplastic astrocytomas. Those GBMs that exhibit EGFR gene amplification have almost always genetic material on chromosome 10q and often have CDKN2A deletions. GBMs with EGFR gene amplification display overexpression of EGFR at both the mRNA and protein levels, suggesting that activation of this growth signal pathway is integral to malignant progression to GBM. A proportion one-third of those GBM with EGFR gene amplification also have specific EGFR gene rearrangements, which produce truncated molecules similar to the v-erbB oncogene. These truncated receptors are capable of conferring dramatically enhanced tumorigenicity to GBM cells. The downstream targets of EGFR activation in GBMs include the Shc-CGrb2-ras pathway, involving EGFR in a cascade that facilitates mitogenesis and decreases apoptosis in tumor cells.

Less commonly amplified oncogenes include N-myc, gli, PDGF-a receptor, c-myc, myb, K-ras, CDK4, and MDM2.

As mentioned previously, one of the hallmarks of GBM is microvascular proliferation. A host of angiogenic growth factors and their receptors are found in GBMs. For example, VEGF and PDGF are expressed by tumor cells while their tyrosine kinase receptors, VEGF receptors 1 and 2 for VEGF and the PDGF-b receptor for PDGF, are expressed on endothelial cells. VEGF and its receptors, in particular, appear to play a major role in GBM angiogenesis. A paracrine mechanism has been suggested in which VEGF is secreted by tumor cells and bound by the VEGF receptors on endothelial cells. Interestingly, VEGF is preferentially up-regulated by tumor cells surrounding regions of necrosis, perhaps as a result of necrosis-induced hypoxia, since hypoxia can up-regulate VEGF. In addition, PDGF may up-regulate VEGF expression by endothelial cells, thereby providing an early stimulus for angiogenesis. A link between p53 and tumor angiogenesis has been suggested by the observations that some mutant p53 molecules can enhance VEGF expression and that wild-type p53 regulates the secretion of a glioma-derived angiogenesis inhibitory factor. Related mechanisms may also be responsible for tumor cell edema in GBM, because some of these angiogenic molecules, such as VEGF, may also cause vascular permeability and hence tumor cell edema.

SUB SETS OF GLIOBLASTOMA MULTIFORME

The assumption that all astrocytomas progress through distinct genetic stages in a linear fashion is most likely an oversimplification. Indeed, it appears as if there are biologic subsets of astrocytomas that may reflect the clinical heterogeneity observed in these tumors. For instance, approximately one-third of GBM have TP53/chromosome 17p alterations, one-third have EGFR gene amplification, and one-third have neither change (i.e., TP53 mutations and EGFR amplification are mutually exclusive). Experimental data also support this distinction by showing that p53-deficient cells are not transformed when cultured in the presence of EGF, whereas they are transformed in the presence of other growth factors. Primary GBMs with TP53 mutations may therefore not be expected to acquire EGFR gene amplification, if activation of the EGF-EGFR system does not produce a growth advantage in such cells.

FIGURE 43.1-1. Molecular alterations characteristic of different stages of astrocytoma progression. EGFR, epidermal growth factor receptor; PDGFa(R), platelet-derived growth factor-a (receptor).
Differences may be obscured by the universally grim prognosis of these tumors (see Oligodendrogliomas and Oligoastrocytomas, later in this chapter).

Other Gliomas

Other Astrocytomas

Pilocytic astrocytoma is the most common astrocytic tumor of childhood and differs clinically and histopathologically from the diffuse, fibrillary astrocytoma that affects adults. Pilocytic astrocytomas do not have the same genomic alterations as diffuse astrocytomas. Because pilocytic astrocytomas frequently affect patients with neurofibromatosis type 1 (NF1), it would not be surprising if the NF1 gene on chromosome 17q were altered in pilocytic astrocytomas; in fact, allelic loss occurs on chromosome 17q in one-fourth of cases. Unfortunately, detailed mutational analysis of the NF1 gene in pilocytic tumors has not yet been performed, because of the large size of the gene.

Other pediatric astrocytic tumors are histologically similar to the astrocytomas, anaplastic astrocytomas, and GBMs that occur in adults. Some of these are associated with similar genetic alterations, such as TP53 mutations. For instance, brain stem gliomas have frequent TP53 gene and chromosome 17p alterations without EGFR gene amplification, 2 as do those diffuse cerebral astrocytic tumors that occur in children older than 4 years of age. Desmoplastic cerebral astrocytoma of infancy and desmoplastic infantile gangliocytoma are large, superficial, usually cystic, benign astrocytomas that affect children in the first year or two of life. Allelic loss of chromosomes 10 or 17 have not been detected in these lesions. 3 In adult gangliogliomas, another benign form of astrocytic glioma, EGFR gene amplification or allelic loss on chromosomes 10, 13q, 17p, 19q, and 22q have not been detected (A. von Deimling and D. N. Louis, unpublished data).

Pleomorphic xanthoastrocytoma (PXA) is a superficial, low-grade astrocytic tumor that predominantly affects young adults. While these tumors have a bizarre histologic appearance, they are typically slow-growing tumors that may be amenable to surgical cure. Some PXAs, however, may recur as GBM. Nonetheless, the genetic events that underlie PXA formation and progression differ from those involved in diffuse astrocytoma tumorogenesis. PXAs may have TP53 mutations, but the few documented mutations have been somewhat different from those usually found in diffuse, fibrillary astrocytomas. EGFR gene amplification does not occur in PXAs, but GBMs that arise from PXAs may display EGFR gene amplification. On the other hand, allelic losses of chromosomes 9, 10, and 19q are not observed in PXA.

Subependymal giant cell astrocytoma (SEGAs) are periventricular, low-grade astrocytic tumors that are usually associated with tuberous sclerosis (TS) and are histologically identical to the so-called candle-gutters that line the ventricles of TS patients. Similar to the other tumorous lesions in TS, these are slowly growing and may be more akin to hamartomas than true neoplasms. The association of SEGAs with TS leads to the prediction that the TS genes, TSC1 on chromosome 9q and TSC2 on chromosome 16p (see Neurologic Syndromes, later in this chapter), are involved in SEGAs formation. Loss of heterozygosity studies have shown allelic loss of chromosome 9q and 16p loci in some SEGAs, particularly of the TSC2 locus on 16p, suggesting that the TS genes act as tumor suppressors. 22,56 and 60

Oligodendrogliomas and Oligoastrocytomas

Oligodendrogliomas and oligoastrocytomas (mixed gliomas) are diffuse, usually cerebral, tumors that are clinically and biologically most closely related to the diffuse, fibrillary astrocytomas. The tumors, however, are less common than astrocytomas and have generally better prognoses than the diffuse astrocytomas; patients with WHO grade II oligodendrogliomas, for instance, may have mean survival times of 10 years. In addition, oligodendrogliomas appear to be differentially chemosensitive, 2 when compared with the diffuse astrocytomas.

Allelic losses in oligodendrogliomas and oligoastrocytomas occur preferentially on chromosomes 1p and 19q, affecting 40% to 80% of these tumor types. 25,52 Because of the frequent loss of these loci in low-grade as well as anaplastic oligodendrogliomas and oligoastrocytomas, the 1p and 19q tumor suppressors are probably important early in oligodendroglial tumorigenesis. Mapping of the chromosome 19q locus has demonstrated that the gene resides in the same vicinity as the astrocytoma gene and is likely the same gene. 25 Similar mapping of chromosome 1p has implicated the telomeric region of 1p. 25 Interestingly, chromosome 1p and 19q losses are closely associated; oligodendroglial tumors with 1p loss typically also have loss of 19q, suggesting that these two putative tumor suppressor genes may be involved in biologically distinct pathways. 56 58 In fact, microdissection of the oligodendroglial and astrocytic components in oligoastrocytomas has shown that, despite the histologic differences, the molecular changes are identical in these two components. 52 Oligoastrocytomas may also suffer allelic losses of chromosome 17p, although these losses are not often associated with TP53 mutations. 52 perhaps implying a second chromosome 17p glioma oncogene. Oncogene amplification has only rarely been noted in oligodendroglial tumors. 52

Oligodendrogliomas and oligoastrocytomas may progress, either to WHO grade III anaplastic oligodendroglioma or anaplastic oligoastrocytoma, and sometimes to higher-grade tumors with histologic features similar to GBM (Fig. 43.1-1). Anaplastic oligodendrogliomas and oligoastrocytomas may display allelic losses of chromosomes 9p to include the CDKN2A gene and chromosome 10. 52 However, allelic loss of chromosome 10 may be a common finding in high-grade malignant gliomas, whether they are astrocytic or oligodendroglial in origin. 22


Anaplastic oligodendrogliomas have proven to be the first brain tumor for which molecular genetic analysis has had practical clinical ramifications: Anaplastic oligodendrogliomas that have allelic losses of chromosomes 1p and 19q follow different clinical courses from those tumors that do not have these genetic changes. Anaplastic oligodendrogliomas that have 1p and 19q loss are essentially always sensitive to procarbazine, temozolomide, and vincristine chemotherapy, with nearly 50% of such tumors demonstrating complete neuroradiologic responses; correspondingly, patients whose tumors have 1p and 19q loss have median survivals of approximately 10 years. On the other hand, anaplastic oligodendrogliomas that lack 1p and 19q loss are only chemosensitive approximately 25% of the time and only rarely have complete neuroradiologic responses; as a result, patients whose anaplastic oligodendrogliomas lack 1p and 19q loss have median survivals of approximately 2 years. Thus, molecular genetic analysis of 1p/19q allelic status has already become a clinically useful test in neurooncology and is most likely an indication of the utility of molecular diagnostic approaches in neurooncology.

Ependymomas and choroid plexus tumors

Ependymomas are a clinically diverse group of gliomas that vary from aggressive intraventricular tumors of children to benign spinal cord tumors in adults. Chromosome 22q loss is common in ependymomas. A candidate glialoma tumor suppressor gene on chromosome 22q is the NF2 gene, because NF2 patients have a higher incidence of gliomas, particularly spinal ependymomas, in addition to schwannomas and meningiomas. Analysis of the NF2 gene in spinal ependymomas has revealed mutations and deletions, confirming the role of the NF2 gene alterations in the genesis of spinal ependymomas. For cerebral ependymomas, the paucity of NF2 mutations suggests that another, as yet unidentified, chromosome 22q gene will probably be a more integral ependymoma locus. The TP53 gene is not mutated in ependymomas or in the malignant transformation of ependymomas to anaplastic ependymoma (S. Cortez and D. N. Louis, unpublished data).
Choroid plexus tumors are also a varied group of tumors that preferentially occur in the ventricular system, ranging from aggressive supratentorial intraventricular tumors of children to benign cerebellopontine angle tumors of adults. Choroid plexus tumors have been reported occasionally in patients with Li-Fraumeni syndrome and von Hippel-Lindau (VHL) disease (as well as in Aicardi’s syndrome, which does not predispose to cancer), raising the possibility that the TP53 gene on chromosome 17p is involved in Li-Fraumeni syndrome. 1p and 17p deletions are frequent in choroid plexus neoplasms. Studies of human choroid plexus tumors have not shown TP53 mutations, but choroid plexus neoplasms may be induced in transgenic mice by disrupting p53 and pRB function. 65 VHL mutations have also not been documented in choroid plexus tumors in VHL patients, but some reported choroid plexus tumors in VHL patients may instead reflect papillary tumors of the middle ear (endolympathic sac tumors), which occur in higher frequency in VHL patients and which histologically resemble choroid plexus neoplasms.

Oncogenic viruses may cause human cancer, particularly those viruses whose products interfere with tumor suppressor gene functions, such as the human papillomaviruses implicated in cervical carcinoma. One study has identified sequences similar to SV40 virus, an oncogenic virus that has the ability to inactivate both the RB and p53 proteins in human ependymomas and choroid plexus papillomas. This observation raised considerable excitement since SV40 has been implicated as an oncogenic factor in transgenic models of choroid plexus neoplasia. 66 However, SV40-like sequences have not been found in other choroid plexus papillomas or ependymomas and the role of oncogenic viruses in these tumors remains undefined.

### MEDULLOBLASTOMAS

Medulloblastomas are highly malignant, primitive tumors that arise in the posterior fossa, primarily in children. One-third to one-half of all medulloblastomas have an isochromosome 17q on cytogenetic analysis, 2 and corresponding allelic loss of chromosome 17p has been noted on molecular genetic analysis. 27 TP53 mutations, however, are rare in medulloblastomas. 57 Allelic losses occur preferentially at regions of chromosome 17p that are telomeric to the TP53 locus, 57 implying the presence of a second, more distal chromosome 17p tumor suppressor gene. Allelic losses of chromosome 6q, 11, and 16q have also been noted frequently in these tumors, 2 as have genomic losses on chromosomes 10q, 11q, 16p, 17p, and 8p. 67 But deletions of the CDKN2A gene, which are common in many tumors, do not occur in medulloblastomas. 67 Oncogene amplification has not been found frequently in medulloblastomas; only c-myc is amplified in significant numbers of cases and this change appears more common in medulloblastoma cell lines than in primary tumors. 2 Comparative genomic hybridization studies have demonstrated amplification of chromosome bands 5p15.3 and 11q22.3 and gains of chromosomes 17q and 7. 7

The discovery of genes underlying two hereditary medulloblastoma syndromes has directed attention to two pathways involved in medulloblastoma tumorigenesis. Gorlin syndrome, a condition characterized by multiple basal cell carcinomas (also termed basal cell nevoid syndrome), bone cysts, dysomorphic features, and medulloblastomas arises from defects in the PTCH gene on the long arm of chromosome 9, a homologue of the Drosophila patched gene. Medulloblastomas, particularly the nodular desmoplastic variants that are characteristic of Gorlin syndrome, can show allelic loss of chromosome 9q and PTCH mutations. 28,29,30 The protein encoded by PTCH functions in the pathway regulated by the Sonic hedgehog protein; other molecules in this pathway include smoothened, and rare/smoothed mutations have been documented in medulloblastoma cell lines. 31 Turcot syndrome, a condition characterized by colonic tumors and brain tumors, is also linked to medulloblastoma; patients with the adenomatous polyposis phenotype may develop medulloblastomas, and these patients often have mutations of the APC gene on chromosome 5q. 32 Curiously, APC gene mutations and loss of chromosome 9q are rare in sporadic medulloblastomas. 32 The APC protein operates in a molecular pathway that includes the b-catenin protein, and rare mutations of b-catenin have now been noted in sporadic medulloblastomas. 68 It is likely that other components of these two pathways will also be implicated in medulloblastoma tumorigenesis.

The question of whether molecular analyses can provide ancillary information for the management of medulloblastoma patients remains open. Some papers have suggested that patients whose tumors have loss of chromosome 17p may follow a more aggressive course, 33 but this has not been a universal finding. Others have provided intriguing evidence that the level of expression of the trkC receptor may relate to prognosis, with those tumors showing high trkC expression following a more favorable course. 69

### MENINGIOMAS

Meningiomas are common intracranial tumors that arise in the meninges and compress the underlying brain. Meningiomas are usually benign, but some atypical meningiomas may recur locally, and some meningiomas are frankly malignant. Monosomy 22 is common in meningiomas, with the NF2 gene on chromosome 22q frequently mutated in meningiomas, clearly implicating it in meningothelial tumorigenesis. 34,35,36 In sporadic meningiomas, both chromosome 22q allelic loss and NF2 gene mutations are more common in fibroblastic and transitional subtypes than in meningothelial forms. 37 As in schwannomas (see Peripheral Nerve Tumors, later in this chapter), NF2 gene alterations result predominantly in immediate truncation, splicing abnormalities, or altered reading frames, producing grossly truncated proteins.

Approximately 40% of meningiomas have neither NF2 gene mutations nor allelic loss of chromosome 22q. For these tumors, it is likely that a second meningioma tumor suppressor gene is involved. This putative second gene may be located on chromosome 10q, 14q, 16q, or 17p, suggesting the possibility of a second meningioma locus on chromosome 22. 37 Furthermore, a family with multiple meningiomas but without vestibular schwannomas does not show linkage to the NF2 locus on chromosome 22q, suggesting yet another meningioma predisposition gene. 38 One study has suggested that alternative meningioma genes may reside on chromosomes 1p and 3p. 39 Allelic losses in meningiomas have been noted on a variety of other chromosomes, including 1p, 3p, 5q, 11, 13, and 17p. 40

Atypical and malignant meningiomas are not as common as benign meningiomas. Atypical meningiomas often show allelic losses of chromosomal arms 1p, 6q, 9q, 10q, 14q, 17p, and 18q, suggesting that progression-associated genes may lie at these loci. 41,42,43 More frequent losses of chromosomes 6q, 9p, 10, and 14q also occur in anaplastic meningiomas. 41 Chromosomal gains have also been noted in higher-grade meningiomas, with gains of chromosomes 20q, 12q, 15q, 1q, 9q, and 17q most commonly observed. 44 Chromosome 10 loss, in particular, has been associated with those meningiomas with morphologic features of malignancy, rather than those meningiomas that are designated as malignant on the basis of brain invasion alone. 44 Interestingly, brain invasion used to be considered a histologic indicator of malignancy in meningiomas; molecular genetic studies have, however, shown that histologically benign meningiomas that invade the brain do not have the molecular hallmarks of higher-grade meningiomas. 45 These observations provide another example of how molecular genetic investigations have clarified grading issues in neurooncology.

### PERIPHERAL NERVE TUMORS

Schwannomas are benign tumors that arise on peripheral nerves. Schwannomas may arise on cranial nerves, particularly the vestibular portion of the eighth cranial nerve (vestibular schwannomas, acoustic neoplasms) where they present as cerebellopontine angle masses. NF2 patients are defined by the presence of bilateral vestibular schwannomas, 46 although unilateral vestibular schwannomas are common in the general population as well. Therefore, like meningiomas, schwannomas occur frequently in NF2 patients, have frequent loss of chromosome 22q, and harbor NF2 gene mutations in at least 50% of cases, in vestibular tumors as well as schwannomas from other sites. 47 The majority of the somatic changes are small deletions or insertions that create either framematches or premature stop codons or altered splicing. Inactivating mutations are relatively evenly distributed across the first 15 exons with no outstanding hot spots. Furthermore, loss of the NF2 gene-encoded merlin protein occurs in all schwannomas, consistent with an integral and universal role for NF2 gene inactivation in schwanna formation. 48 Thus, inactivation of NF2 is a common feature underlying both inherited and sporadic forms of schwannoma.

Neurofibromas are also benign tumors of peripheral nerve that most often appear on distal, superficial nerves. Multiple neurofibromas are associated with NF1, suggesting that the NF1 gene on chromosome 17q is involved in the genesis of these benign nerve sheath lesions. Unfortunately, the large size of the NF1 gene has precluded extensive mutation analysis in these lesions. Neurofibromas, particularly the plexiform variants associated with NF1, have the potential for malignant progression to malignant peripheral nerve sheath tumors, a transition that is associated with inactivation of the NF1, TP53, and CDKN2A genes. 50,51

### MISCELLANEOUS TUMORS

HEMANGIOBLASTOMAS
Hemangioblastomas are tumors of uncertain origin that are composed of endothelial cells, pericytes, and so-called stromal cells. These benign tumors most frequently occur in the cerebellum and spinal cord of young adults. Multiple hemangioblastomas are characteristic of VHL, an inherited tumor syndrome in which patients have a tendency to develop tumors, particularly hemangioblastomas, retinal angiomas, renal cell carcinoma, and pheochromocytomas. Allelic loss occurs in hemangioblastomas in the region of the VHL gene on chromosome 3p.

These observations suggest that the VHL gene acts as a classical tumor suppressor gene. Mutations in the VHL gene most commonly occur as inactivation of both alleles. Inactivation of either allele appears to be sufficient for tumor development. The VHL gene codes for a guanosine triphosphatase–activating protein termed von Hippel-Lindau tumor suppressor protein (pVHL).

SUMMARY

For the less common gliomas and for other primary tumors such as medulloblastomas, molecular genetic studies have defined sets of genetic alterations. For meningiomas and schwannomas, the NF2 gene has been clearly implicated, although other genetic alterations must underlie the formation of some meningiomas as well. For some tumors, such as HPC and brain-invasive meningiomas, molecular investigations have clarified classification and grading issues. For those tumors that are members of distinct tumor syndromes, such as the SEGAs in TS and sporadic meningiomas, the same genes appear responsible for the syndromes when mutated in the germline, and for sporadic tumors when mutated on a somatic basis. At present, however, these molecular data are incomplete. Once the genes associated with these tumor syndromes and have assigned the NF1 gene to chromosome 17q; the NF2 gene to chromosome 22q; the TS genes to chromosomes 5q (APC gene) and to the DNA mismatch repair genes on various chromosomes. The NF1 gene codes for a guanosine triphosphatase–activating protein termed neurofibrin. Neurofibrin interacts with the p21 protein of the ras oncogene and is most likely involved in growth-stimulated signal transduction. The NF2 gene encodes a protein, termed merlin, which most likely functions by facilitating signal transduction from the cell surface via the cytoskeleton. One of the TS genes, TSC2 on chromosome 16p, TSC2 encodes a guanosine triphosphatase activating protein–related protein, tuberin, whereas the TSC1 gene on 9q encodes a protein known as hamartin that has no known homology to other proteins. Nonetheless, tuberin and hamartin appear to bind one another and function in a single cellular pathway, consistent with a similar phenotype for patients with either TSC1 or TSC2 gene mutations. For the Li-Fraumeni syndrome, mutational analyses have implicated the TP53 gene on 17p. For some tumors, such as medulloblastomas, molecular genetic studies have defined sets of genetic alterations. For meningiomas and schwannomas, the NF2 gene has been clearly implicated, although other genetic alterations must underlie the formation of some meningiomas as well. For some tumors, such as HPC and brain-invasive meningiomas, molecular investigations have clarified classification and grading issues. For those tumors that are members of distinct tumor syndromes, such as the SEGAs in TS and sporadic meningiomas, the same genes appear responsible for the syndromes when mutated in the germline, and for sporadic tumors when mutated on a somatic basis. At present, however, these molecular data are incomplete. Once the molecular pathways are completely understood, such knowledge will no doubt contribute to the development of more effective therapies for many of these tumors.

CHAPTER REFERENCES

INCIDENCE AND CLASSIFICATION

Available registry data from Surveillance, Epidemiology, and End Results for 1973 to 1990 indicate that the combined incidence of all recorded primary intracranial and spinal axis tumors is between 2 and 19 in 100,000 per year, depending on age. There is an early peak (3.1 in 100,000) between 0 and 4 years, a trough (1.8 in 100,000) between 15 and 24 years, and then a steady rise in incidence that reaches a plateau (17.9 to 18.7 in 100,000) between 65 and 79 years of age. In general, the incidence of primary brain tumors is more common in whites than blacks and the mortality is higher in male than female subjects.

The diversity in primary intracranial and spinal axis tumors partly results from the diversity of phenotypically distinct cells capable of transformation into tumors. Table 43.2-1 shows the hypothetical 15 cell types that can give rise to these tumors. Because of changes in classification and reporting of these tumors, the tumor registry data are not completely accurate. The relative frequency of 15 families of intracranial tumors is given in Table 43.2-2, and the distribution of spinal tumors is shown in Table 43.2-3. The most common tumors are those that are derived from glial precursors (astrocytes, ependymocytes, and oligodendrocytes). The existence of histologically mixed astrocytoma-oligodendroglioma and the extremely uncommon astrocytoma-ependymoma implies that astrocytomas, oligodendrogliomas, and ependymomas may arise from common stem or progenitor cells. The facts that these tumors arise in different locales within the cranium and the spinal axis and that various types predominate at different ages suggest that differing molecular and genetic mechanisms may underlie tumorigenesis at different times in the life span.

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<tr>
<th>Table 43.2-1. Classification of Primary Intracranial Tumors by Cell of Origin</th>
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<td>TABLE 43.2-2. Frequency of Primary Intracranial Central Nervous System (CNS) Tumors</td>
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<td>TABLE 43.2-3. Distribution of Primary Spinal Tumors</td>
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Central nervous system (CNS) tumors are the most prevalent solid neoplasms of childhood, the second leading cancer-related cause of death in children younger than 15 years of age, and the third leading cancer-related cause of death in adolescents and adults between the ages of 15 and 34 years. However, most intracranial tumors occur in people older than 45 years. Glioblastoma rarely occurs in people younger than 15 years, but dramatically increases after the age of 45. The incidence
of most glial tumors, other than glioblastoma multiforme, actually decreases with increasing age. There is some concern that the incidence of glioblastoma multiforme is increasing in the elderly population, although incorrect ascertainment preceding the widespread availability of computed tomography (CT) scans in the late 1970s and magnetic resonance imaging (MRI) in the 1980s may account for some of the presumed increase in incidence. A similar age-related increase in prevalence occurs with differentiated or benign meningiomas that increase from 0.2% of all primary intracranial tumors in patients younger than 24 years of age to 39% of tumors in patients older than 65 years.

The overall incidence of primary spinal cord tumors is approximately 15% of that of brain tumors. For gliomas, the age-adjusted incidence is 0.11% to 0.14%; for meningiomas, 0.08% to 0.28%, depending on sex (female higher than male subjects); and for nerve sheath tumors, 0.07% to 0.13%. As shown in Table 43.2-3, the frequency of specific spinal cord tumors is strikingly different from that of the brain tumors. Gliomas constitute 46% of primary intracranial tumors while only 23% of spinal tumors. Unlike brain gliomas, most spinal cord gliomas are ependymomas with a predilection for the cauda equina. Schwannomas and meningiomas account for approximately 60% of spinal tumors, with schwannomas being slightly more frequent; both types occur most often in adult life. Other less common spinal tumors are the lipomas, dermoids, and hemangioblastomas.

**GENETIC, MOLECULAR, ENVIRONMENTAL, VIRAL, AND OTHER FACTORS ASSOCIATED WITH CENTRAL NERVOUS SYSTEM NEOPLASIA**

In Chapter 43.1, the contribution of genetics and molecular biology to the understanding of CNS tumorigenesis is covered in detail. Less important associations of CNS neoplasia are those associated with viruses, chemicals, and physical forces.

The epidemiology of primary CNS tumors has provided hints but few definitive observations with respect to environmental or occupational causes. Although brain tumors can be experimentally induced in a high proportion of rodents by the use of certain chemicals, the association of chemical exposure and brain tumors is limited to a few occupations. A higher than expected increase in the incidence of brain tumors has been observed as a result of purported exposure to pesticides, herbicides, and fertilizers, various petrochemical industries, and health professions. Whether these statistical observations are credible is difficult to determine. Aside from a known association between vinyl chloride and gliomas, there are no common chemical or environmental threads among these observations. There has also been concern that electromagnetic fields could account for some glial tumors, although the majority of studies do not support such a conjecture.

Viruses have been implicated directly in the development of gliomas only in rats, dogs, and monkeys. In all cases, direct CNS injection of the virus is required. In rats, the avian sarcoma virus produces gliomas; in dogs, Rous sarcoma virus leads to gliosarcomas; in owl monkeys, a human polyoma virus (JC virus) produces glial neoplasms; and in hamsters, JC virus produces medulloblastomas. Although a direct association between virus exposure and CNS tumors has not been established in humans, patients with primary CNS lymphoma have been observed to have a high incidence of infection with Epstein-Barr virus and evidence of Epstein-Barr virus in their tumor tissue. Common viral exposure could explain the occasional glioma cluster observed in schools and communities. However, it is extremely difficult to pinpoint mutations due to a virus to validate this hypothesis.

CNS neoplasia, like most cancers, appears to be unassociated with prior trauma. It has been suggested that the incidence of meningiomas is higher in patients with a prior history of head trauma, but this hypothesis was not supported by a prospective study. Trauma could be a progression event; however, this theory would be difficult to prove.

The incidence of CNS tumors after treatment for a prior malignancy is small. The literature contains examples of astrocytomas occurring 3 to 7 years after craniospinal axis irradiation and chemotherapy for acute lymphocytic leukemia and cranioopharyngioma; unfortunately, none of the reports contains sufficient information to determine risk assessment. In non-Hodgkin’s lymphoma, 2% of 44 second malignancies were an astrocytoma. As in the cases discussed previously, no measure of risk assessment is possible, although such infrequent reporting would suggest that these are uncommon or rare events. Meningiomas have been reported in association with scalp irradiation for tinea capitis, the risk for meningiomas being as high as 21% in one study.

For unknown reasons, transplant recipients and patients with acquired immunodeficiency syndrome have substantially increased risks for primary CNS lymphoma but not gliomas.

**ANATOMIC AND CLINICAL CONSIDERATIONS**

The clinical presentation of the various tumors is best appreciated by considering the relation of signs and symptoms to anatomy.

**INTRACRANIAL TUMORS**

Intracranial tumors produce symptoms primarily by two mechanisms: mass effect (and increased intracranial pressure), due entirely to the tumor or to the tumor and surrounding edema, or infiltration and destruction of normal tissue.

**General Signs and Symptoms**

Typical infiltrative intracerebral tumors, such as the various grades of astrocytoma and oligodendroglioma and some of the more primitive neuroectodermal tumors, can produce headache, gastrointestinal upset such as nausea and vomiting, personality changes, and slowing of psychomotor function. These may be the only clinical indications of tumor.

Because headache is a common presenting symptom in patients with intracranial tumor, clinical patterns and their localizing value must be appreciated. Brain parenchyma does not have pain-sensitive structures, and tumor pain (headache) has been attributed to local swelling and distortion of pain-sensitive nerve endings associated with blood vessels, primarily in the meninges. Tumors grow at different rates and, therefore, achieve variable size before signs and symptoms occur. But once a tumor has achieved a critical volume causing compression and displacement of brain, the onset and demise of headache seem to correlate with changes in intracranial pressure.

Headaches can vary in severity and quality; they often occur in the early morning hours or on first awakening. Patients sometimes complain of an uncomfortable feeling in the head rather than headache. Although there is not an exact relation between the location of tumor headache and the location of the tumor, some rules are worth remembering. More often than not, frontal and temporal tumors produce headache in frontal, retroorbital, or temporal regions, whereas infratemporal tumors tend to produce occipital and retroauricular headache. Occasionally, however, retroorbital headaches are observed with infratentorial tumors.

Gastrointestinal symptoms are common. Patients complain of loss of appetite, nausea, diarrhea, and, occasionally, vomiting. Vomiting appears more commonly in children and in patients harboring infratentorial rather than supratentorial tumors. Although textbooks discuss projectile vomiting as an infrequent generalized symptom of brain tumors, in these authors’ experience, it is common in children but rare in adults. From reports in the literature and discussions with experienced neurosurgeons, it seems as though there is a lower incidence of vomiting currently compared with past years; this may reflect the fact that patients are diagnosed earlier than in previous years and receive glucocorticoids that can modify dramatically many of the generalized signs and symptoms of brain tumors.

Sometimes the only presenting symptoms are changes in personality, mood, mental capacity, and concentration. Occasionally, merely a slowing of psychomotor activity is the antecedent symptom of intracranial tumor. Patients with brain tumors tend to sleep longer at night and nap during the day. These changes in function and activity often are apparent to the family and the examiner but not to the patient; in other instances, only the patient recognizes the changes in mental function. None of these symptoms are unique to brain tumors; they could easily be confused with depression, neurasthenia, or other psychological problems.

**Focal Cerebral Syndromes**

Although fewer than 10% of patients presenting with seizures have a brain tumor as the cause of the seizure, seizures are a presenting symptom in approximately 20% of patients with supratentorial brain tumors. With rapidly growing infiltrative malignant gliomas, they are likely to take the form of focal motor or sensory seizures, although generalized seizures are also common. In patients with slowly growing astrocytomas, oligodendrogliomas, or meningiomas, generalized seizures may antedate the clinical diagnosis by months to years. The value of the focal seizure as a means of tumor localization is high, sufficiently so that tumor should be
considered causative until proven otherwise.

The distribution of infiltrative parenchymal tumors in the brain is directly related to the mass of the lobe or region. Frontal tumors occur more commonly than parietal tumors, which, in turn, occur more often than temporal lobe tumors, and so forth. Anatomic or regional involvement by tumors, although not completely stereotypic as it is with CNS vascular disease, nonetheless has certain features that distinguish them and help the clinician localize the tumor or, at least, to consider the diagnosis.

The frontal lobe syndrome varies markedly from patient to patient. It can range from personality change to headache and mild slowing of contralateral hand movements and to contralateral spastic hemiplegia, marked elevation in mood, or loss of initiative and dysphasia (if it is the dominant lobe). Assuming the normal pattern of left hemisphere dominance, lesions affecting the right frontal lobe can cause left hemiplegia, slight elevation in mood, difficulty in adapting to new situations, loss of initiative, and even occasional primitive grasp and sucking reflexes. Left frontal lobe tumors can cause right hemiplegia and nonfluent dysphasia with or without some apraxia of lip, tongue, or hand movements.

Bifrontal disease, a condition usually associated with infiltrative gliomas and primary CNS lymphomas, can cause varying degrees of bilateral hemiplegia, spastic bulbar palsy, severe impairment of intellect, liability of mood, dementia, and prominent primitive grasp, suck, and snout reflexes.

Temporal lobe syndromes, like frontal lobe syndromes, can range from symptoms that are detectable only on careful testing of perception and spatial judgment to severe impairment of recent memory. Homonymous quadrantanopsia, auditory hallucinations, and even aggressive behavior can occur as a result of tumors of either temporal lobe. Involvement of the nondominant temporal lobe can also result in minor perceptual problems and spatial disorientation. Dominant temporal lobe involvement can lead to dysnomia, impaired perception of verbal commands, and even a full-blown, fluent Wernicke-like aphasia. Bilateral disease, involving both temporal lobes, is rare in comparison with the bilaterality of frontal lobe tumors that readily cross through the corpus callosum. This is fortunate, because bilateral tumor involvement is devastating. It produces impairment of memory, especially recent memory, and can lead to dementia.

Parietal lobe syndromes affect sensory and perceptual functions more than motor modalities, although mild hemiparesis is sometimes seen with extensive parietal lobe tumors. Tumors impinging on either parietal lobe can produce a decrease in the perception of cortical sensory stimuli that may vary from mild sensory extinction, observable only by testing, to a more severe sensory loss with deep tumors that leads to hemianesthesia or other hemisensory abnormalities. Homonymous hemianopsia or visual inattention also may occur. In addition, involvement of the nondominant parietal lobe can lead to perceptual abnormalities and, in severe cases, to anosognosia and apraxia for self-dressing. Unilateral dominant parietal lobe tumors lead to alexia, dysgraphia, and certain types of apraxia.

Occipital lobe tumors can produce contralateral homonymous hemianopsia or visual aberrations that take the form of imperception of color, object size, or object location. Bilateral occipital disease can produce cortical blindness.

The classic disconnection syndromes associated with corpus callosum lesions are seen rarely in patients with brain tumors. Even though infiltrative gliomas often cross the corpus callosum in the region of the genu or the splenium, the involvement of additional structures complicates neurologic interpretation, obscuring classic disconnection syndromes. With respect to partial lesions, interruption of association fibers in the anterior part of the corpus callosum usually causes a failure of the left hand to carry out spoken commands. Lesions in the splenium of the corpus callosum interrupt visual fibers connecting the right occipital lobe and left angular gyrus, resulting in an inability of patients to read or name colors.

Symptoms related to thalamic tumors vary as a function of tumor size and whether the tumor produces secondary blockage of cerebrospinal fluid (CSF) flow and hydrocephalus. Occasionally, tumors in the thalamus and, less commonly, in the basal ganglia, can reach 3 to 4 cm in diameter before the patient has symptoms severe enough to seek medical attention. Patients typically present with headaches resulting from hydrocephalus and increased intracranial pressure secondary to trapping of the lateral horn of one of the ventricles. In addition or independently, patients can present with a mild sensory abnormality on the contralateral side, which is detected only by testing of sensory extinction or, rarely, severe neuropathic pain syndrome. Patients may complain of intermittent paresthesias on the contralateral side; because they are episodic and seizure-like, anticonvulsant drugs are used sometimes and actually may be beneficial. With more involvement of the basal ganglia, contralateral intention tremor and hemiballistic-like movement disorders can be observed. Thalamic tumors usually do not present in a manner typical of thalamic strokes, unless bleeding into the tumor has occurred.

**Focal Infratentorial Syndromes**

The brain stem, composed of the medulla oblongata and the pons, has both nuclear groups and traversing axons. Tumors invading or compressing the brain stem can produce discrete signs; even a small increase in size (e.g., 1 to 2 mm) may lead to death or devastating signs and symptoms. Tumors can be primarily intrinsic or with exophytic components in the fourth ventricle, peripontine cisterns, or in both locations. Cranial nerve involvement, therefore, can be at the nervous level or of the cranial nerve as it leaves the brain stem.

The most common tumor of the brain stem is an astrocytoma (glioma), the initial clinical manifestations of which are palsies involving cranial nerves VI and VII on one side in 90% of patients. These usually are followed by involvement of long tracts resulting in hemiplegia, unilateral limb ataxia, ataxia of gait, paraplegia, hemisensory syndromes, gaze disorders, and, occasionally, hiccups. Less commonly, long tract signs precede the cranial nerve abnormalities; this is more likely with confined intrinsic brain stem lesions.

The midbrain, juxtaposed between the pons and the cerebral hemispheres, encompasses the tectum, the cerebral peduncles, and the cerebral aqueduct. If the midbrain is involved, obstructive hydrocephalus can occur, producing vomiting, drowsiness, and cerebellar signs. Patients with medullary tumors have a more rapidly progressive course and are more likely to have deficits in cranial nerves VI (usually late), VII, IX, and X, and dysarthria, personality change, and head tilt. Unlike the expansive posterior fossa tumors, headache, vomiting, and papilledema occur late. Fourth ventricular tumors, because of their location, tend to produce obstructive hydrocephalus early in their development. This produces profound headache and vomiting and associated disturbances of gait and balance. With rapidly progressing lesions, cerebellar herniation may develop.

Tumors of the cerebellum have valuable localizing signs and symptoms. In slowly growing tumors, the initial symptoms may be headache and nausea, which are caused by increased intracranial pressure, and mild imbalance in gait or ataxia of a limb. In more rapidly growing cerebellar tumors, there may be prominent morning headache; vomiting, a stumbling gait with frequent falling, nystagmus, and diziness; and visual symptoms caused by papilledema. Abnormal posturing of the head is seen often in children but not in adults. In children, the head is tilted back and away from the side of the tumor. Posturing of the head is curious in that it indicates unilateral cerebellum-foramen magnum herniation. Bilateral sixth cranial nerve palsies are uncommon. Midline lesions in and around the cerebellum vermis lead to truncal and gait ataxia, whereas lesions in a cerebellar hemisphere lead to unilateral appendicular ataxia, most readily observed in upper extremity movements.

Tumors of the base of the skull, although not particularly common, nevertheless are important because many are curable by surgery. Table 43.2.4 summarizes the salient clinical features of seven of the more common clinical syndromes.

| Table 43.2.4. Differential Diagnosis of Tumors at the Base of the Skull |
A classic base of skull tumor presentation is that associated with vestibular schwannomas, the most frequent cause of the cerebellopontine angle syndrome. Almost all such patients have involvement of the auditory or vestibular portions of cranial nerve VIII; fortunately, most patients have little morbidity from surgery. Potential postoperative complications depend on size of tumor and surgical approach used. The morbidity of surgery can be facial weakness, hypoesthesia of cornea, disturbance of taste, sensory loss of the face, ataxia of gait, and unilateral appendicular ataxia. Deafness and vestibular dysfunction due to damage to the auditory and vestibular nerve branches are characteristic of these tumors. Finally, these tumors can attain an extremely large size before they are discovered.

Another group of tumors that present with distinct signs and symptoms is that which occurs in or near the sella turcica. Table 43.2-5 summarizes the location, tumors, and some of the salient features of sellar and parasellar tumors.

<table>
<thead>
<tr>
<th>Location</th>
<th>Tumors</th>
<th>Clinical Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sellar</td>
<td>Pituitary adenomas</td>
<td>Visual field defects, blindness, optic atrophy</td>
</tr>
<tr>
<td>Parasellar</td>
<td>Optic nerve gliomas</td>
<td>Visual field defects, blindness, optic atrophy</td>
</tr>
</tbody>
</table>

Some of the pituitary tumors produce secondary signs and symptoms, because they elaborate hormones that create various syndromes of endocrine hyperactivity (Table 43.2-6). A few pituitary tumors produce no detectable hormones or produce hormones in quantities that assume no clinical significance. Currently, it is uncommon for patients with endocrine-active tumors to present with large tumors; it is more common for patients with endocrine-inactive tumors to seek medical attention because of optic chiasmal compression hypopituitarism as a consequence of a large mass. Compression leads to detectable hyposecretion of specific cells, with production of growth hormone being the most sensitive, followed closely by gonadotropins. Cells producing thyroid-stimulating hormone and corticotrophin are much more resistant, and their function is impaired only at a later stage of growth.

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Clinical Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Growth hormone</td>
<td>Growth hormone deficiency</td>
</tr>
<tr>
<td>Adrenocorticotropic hormone</td>
<td>Cushing's syndrome</td>
</tr>
<tr>
<td>Thyroid-stimulating hormone</td>
<td>Hyperthyroidism</td>
</tr>
</tbody>
</table>

TABLE 43.2-6. Clinical Syndromes Produced by Endocrine-Activity Pituitary Adenomas

Table 43.2-7 summarizes the differential diagnosis of tumors by location in children and adults.

<table>
<thead>
<tr>
<th>Location</th>
<th>Age at Onset of Symptoms</th>
<th>Tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suprasellar</td>
<td>Newborn</td>
<td>Meningiomas, craniopharyngiomas</td>
</tr>
<tr>
<td>Sellar</td>
<td>Childhood</td>
<td>Pituitary adenomas</td>
</tr>
<tr>
<td>Subfrontal</td>
<td>Adolescence</td>
<td>Astrocytomas, gliomas</td>
</tr>
<tr>
<td>Infratentorial</td>
<td>Adults</td>
<td>Meningiomas, craniopharyngiomas</td>
</tr>
</tbody>
</table>

TABLE 43.2-7. Differential Diagnosis of Tumors by Location and Age at Onset of Symptoms

**Acute and Life-Threatening Syndromes Caused by Intracranial Tumors**

Because the brain and the spinal cord are surrounded by a rigid skull and dural membranes, expanding lesions within or abutting the brain or spinal cord can cause displacement of vital structures. This can lead, in the brain, to respiratory arrest and death, and, in the spinal cord, to paraplegia or quadriplegia.

To understand the sequence of events leading to temporal lobe-tentorial (uncal) herniation and cerebellar-foramen magnum herniation, a visual image of intracranial anatomy is needed. The tentorium cerebelli forms a rigid tissue partition between the cerebral hemispheres above and the cerebellum and brain stem below. Through this opening passes the midbrain centrally and cranial nerve III laterolaterally. Immediately lateral to cranial nerve III lies the medial portion of the temporal lobe called the uncus. An expanding mass lesion situated above the tentorium may displace the uncus medially and inferiorly beneath the tentorium. Table 43.2-8 summarizes the neurologic findings and pathologic causes for the events that constitute the temporal lobe-tentorial herniation syndrome.
A rapid increase in the volume of the supratentorial compartment leading to herniation can be caused by many different factors. A rapidly growing glioblastoma can present in this manner, although it is more usual for it to occur as a terminal or near terminal event after ineffective therapy for the tumor. It can also occur when there is a dramatic increase in the amount of edema associated with metastasis to the brain or with hyponatremia and hypoosmolar syndromes. The injudicious use of parenteral hypoosmolar 5% dextrose in water often is sufficient to produce an abrupt increase in brain edema and temporal lobe herniation. The authors of this chapter also have seen temporal lobe herniation follow a group of shortly spaced seizures. Presumably, the seizures, which are associated with hypoventilation, produce local hypoxia around the tumor with a resultant increase in brain edema.

Mass lesions in the infratentorial compartment can displace brain tissue upward through the tentorium, but more commonly force brain tissue downward through the foramen magnum. In this situation, the cerebellar tonsils move caudally through the foramen magnum, and in doing so, wedge against the medulla, causing the findings summarized in Table 43.2-9.

Cerebellar-foramen magnum herniation frequently results from, or is contributed to by, obstructive hydrocephalus. In such instances, emergency removal of fluid from the more cephalad ventricular system may relieve symptoms and be life saving. Surgical intervention is indicated only if the reason for the herniation is treatable. In the instance of cerebellar-foramen magnum herniation aggravated by acute obstructive hydrocephalus, ventriculoperitoneal shunting is often necessary. Care must be taken, however, because too rapid a change in the CSF dynamics can lead to a rapid and damaging movement of the brain, which can lead to occlusion of posterior cerebral arteries and brain stem injury.

These two herniation syndromes lead to death, unless there is prompt intervention. The immediate intravenous administration of hyperosmotic agents, such as mannitol or urea, and large doses of synthetic glucocorticoids, such as dexamethasone or methylprednisolone, should be given promptly to reduce intracranial pressure and to avert impending death.

Hemorrhage into a tumor is not as common as might be expected, although the incidence of intratumor hemorrhage may increase because of iatrogenic thrombocytopenia associated with the current use of chemotherapy in the treatment of brain tumors. Primary tumors that most commonly bleed de novo are glioblastoma and oligodendrogliomas; of the metastatic tumors, those from the lung, melanoma, hypernephroma, and choriocarcinoma are most likely to be associated with intratumoral hemorrhage. Signs and symptoms of intratumoral hemorrhage may be temporized by the use of osmotic agents and glucocorticoids, but if extensive and life-threatening, operation and decompression are indicated. Under no circumstances should a lumbar puncture be performed in any of the acute herniation syndromes. In fact, lumbar puncture should never be done indiscriminately. The indications for lumbar puncture are discussed in another section of this chapter (see Neurodiagnostic Tests, later in this chapter).

### SPINAL AXIS

To understand the clinical presentation of tumors of the spinal axis, the local anatomy (Fig. 43.2-1) and how tumors might present with respect to anatomy must be appreciated. The cranial dura is firmly adherent to the skull (with the exception of dural duplications of the falx and tentorium), and no extradural space normally exists between dura and skull. An entirely different anatomic relation in the spinal canal accounts for a well-defined extradural space containing epidural fat and blood vessels. By way of the intervertebral foramina, this extradural space communicates with adjacent extraspinal compartments (e.g., the mediastinum and the retroperitoneal space). With rare exceptions, extradural tumors are metastatic, reaching the extradural space through intervertebral foramina.

![Cross-section of thoracic spinal cord shows relation of spinal nerves to intraspinal tracts.](image)

Tumors arising inside of the dural tube (intradural tumors) may originate within the spinal cord (intramedullary), or they may take origin outside the spinal cord (extramedullary). The two common extramedullary intradural tumors, neurilemmoma (schwannoma) and meningioma, are attached, respectively, to sensory nerve roots and to dura and involve the spinal cord by compression.
Neurology of Spinal Cord Tumors

A spinal tumor produces two effects: local (focal) and distal (remote). Local effects indicate the tumor's location along the spinal axis, and distal effects reflect involvement of motor and sensory long tracts within the spinal cord. Table 43.2-10 summarizes the clinical findings useful in localizing a spinal cord tumor.

<table>
<thead>
<tr>
<th>Location</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>CT scan in detecting and localizing brain tumors and evaluating edema, hydrocephalus, or hemorrhage. MRI is superior to CT in evaluating hydrocephalus and its causes, because reformations are required to generate alternative views, such as orthogonal and off-axis images, all of which have degradation of both spatial and contrast detail. CT scans can be acquired only in the axial or half-axial planes. Computer-generated reformations are required to generate alternative views, such as orthogonal and off-axis images, all of which have degradation of both spatial and contrast detail. CT and MRI also differ in that MRI data can be acquired in any plane desired, including oblique planes, in a primary fashion such that there is no compromise of spatial or contrast detail. CT scans can be acquired only in the axial or half-axial planes. Computer-generated reformations are required to generate alternative views, such as orthogonal and off-axis images, all of which have degradation of both spatial and contrast detail. Because MRI scanning can generate images in any plane and offers high resolution and contrast without associated bone artifact, it has been shown to be superior to CT scan in detecting and localizing brain tumors and evaluating edema, hydrocephalus, or hemorrhage.</td>
</tr>
<tr>
<td>Spinal Cord</td>
<td>MRI produces an image based on pixels, but unlike CT scanning, MRI pixel intensity is based on proton density, T1 and T2 relaxation times, blood–brain barrier and is seen on the CT scan as relatively low attenuation compared with normal brain. On MRI, edema appears as an area of low-signal intensity on T1-weighted images and high-signal intensity on T2-weighted images. MRI also produces an image based on pixels, but unlike CT scanning, MRI pixel intensity is based on proton density, T1 and T2 relaxation times, blood–brain barrier and is seen on the CT scan as relatively low attenuation compared with normal brain. On MRI, edema appears as an area of low-signal intensity on T1-weighted images and high-signal intensity on T2-weighted images.</td>
</tr>
</tbody>
</table>

TABLE 43.2-10. Clinical Manifestations of Spinal Cord Tumors

Distal effects are common to all spinal tumors sooner or later, and symptoms and signs are confined to structures innervated below the spinal cord level of involvement. Although neurologic manifestations commonly begin unilaterally, a full-blown Brown-Séquard syndrome of cord hemisection can occur but is rare. More characteristic are motor changes: weakness and spasticity, if the tumor lies above the conus medullaris, or weakness and flaccidity, if at or below the conus. Typically, sensory impairment begins distally in the feet. Impairment of bladder function occurs later in tumors above the conus, but may be an early manifestation of tumors in or below the conus. The upper level of impaired long tract function usually is several segments below the actual site of tumor involvement.

Local manifestations may reflect involvement of bone, with pain constituting the cardinal symptom of metastatic tumors. Involvement of spinal roots produces pain, sensory impairment, and weakness with atrophy in the appropriate radicular distribution. Less often, involvement of spinal gray matter produced by extensive pressure from extramedullary tumors or direct damage by intramedullary tumors causes segmental sensory and motor changes.

Historically, tumors at or near the foramen magnum have been diagnosed incorrectly more often than have spinal tumors at any other site, because foramen magnum tumors can mimic such diverse conditions as multiple sclerosis, amyotrophic lateral sclerosis, and cervical disk disease. The frequency of delayed diagnoses of these tumors justifies the dictum that MRI is indicated as a diagnostic measure in any neurologic disease that can be accounted for by a lesion at or below the foramen magnum.

Occasionally, a cervical intramedullary tumor mimics syringomyelia, with dissociated sensory loss, weakness, and wasting in the arms and hands and variable long tract involvement. In most instances, the clinical presentation of a spinal tumor does not indicate if it is extradural or intradural.

The rate at which symptoms develop can be helpful in distinguishing extradural from intradural tumor, with a history of days to a few weeks characterizing metastatic extradural tumors, and a longer course, often many months, reflecting the slower growth of intradural tumors. A history of previously diagnosed cancer or other system involvement also is helpful.

NEURODIAGNOSTIC TESTS

NEUROIMAGING

The diagnosis of intracranial tumor requires radiographic confirmation. Fortunately, the great strides in radiology have yielded technologic advances best adapted for the brain and the spinal cord. Today MRI and CT are the major neuroimaging techniques used to demonstrate intracranial and spinal lesions. Both MRI and CT produce cross-sectional digital images. In both, the depicted anatomy and pathology are based on numeric computerized representations of certain physical properties of the tissue. The CT image is composed of pixels based on the attenuation of x-rays that are, in turn, dependent on the electron density of the tissue being studied. The MRI scan also produces an image based on pixels, but unlike CT scanning, MRI pixel intensity is based on proton density, T1 and T2 relaxation times, and flow (blood flow). The MRI scan, therefore, represents a complex interrelation of four parameters. Data acquisition also can be manipulated by the operator to a greater degree than can be done with CT scans. CT and MRI also differ in that MRI data can be acquired in any plane desired, including oblique planes, in a primary fashion such that there is no compromise of spatial or contrast detail. CT scans can be acquired only in the axial or half-axial planes. Computer-generated reformations are required to generate alternative views, such as orthogonal and off-axis images, all of which have degradation of both spatial and contrast detail. Because MRI scanning can generate images in any plane and offers high resolution and contrast without associated bone artifact, it has been shown to be superior to CT scan in detecting and localizing brain tumors and evaluating edema, hydrocephalus, or hemorrhage.

Intraxial CNS tumors normally produce edema that is partially correlated with the rapidity of tumor growth. An exception is the benign cerebral meningoisma, a slow-growing tumor that can produce profound edema. The so-called vasogenic edema associated with brain tumors is fluid that has leaked through an incompetent blood–brain barrier and is seen on the CT scan as relatively low attenuation compared with normal brain. On MRI, edema appears as an area of low-signal intensity on T1-weighted images and high-signal intensity on T2-weighted images. Mass lesions in the brain can obstruct the ventricular system, resulting in hydrocephalus. MRI is superior to CT in evaluating hydrocephalus and its causes, because more planes of view are available to the radiologist. Dilatation of one or both of the lateral ventricles and not the rest of the ventricular system suggests obstruction at the foramen of Monro as is seen with colloid cysts or gliomas in this region. Dilatation of a temporal horn of the ventricular system suggests a tumor in the ventricular atrium trapping the temporal horn. Dilatation of only the lateral and third ventricles points to a lesion of the aqueduct; when all the ventricles are dilated, communicating hydrocephalus caused by tumor seeding to the meninges or by the reaction to previous therapy should be considered.

Brain tumors occasionally bleed, and this bleeding can be insignificant or can cause dramatic clinical consequences. Metastatic brain tumors that tend to bleed are melanoma, renal cell carcinoma, choriocarcinoma, and thyroid carcinoma. Of the primary CNS tumors, glioblastoma and oligodendrogliomas are more commonly associated with hemorrhage than are other primary tumors. Acute hemorrhage appears as high attenuation on CT, but subacute hemorrhage may be harder to detect by CT. On MRI, acute hemorrhage is of low-signal intensity on T1 and T2, but subacute hemorrhage poorly seen on CT produces a bright signal on both T1- and T2-weighted MRI scans.

Assessment of the disruption of tumor endothelia and the passage of contrast material compared with the intact blood–brain barrier is an important step in radiologic evaluation. The use of contrast agents in CT and MRI scanning provides, in some patients, improved tumor visualization and, in all patients, an improved ability to discern tumors from other pathologic entities, to discern one tumor type from another, and even to discern higher from lower grade malignancies. There are few situations when administration of contrast agents should not be included in the radiologic evaluation of the patient with a brain tumor.

Approximately 50% of patients with low-grade gliomas may present with tumors that do not exhibit contrast enhancement on CT scan. Some may not be detected on CT because they are isodense with brain. It is in these patients that the differential sensitivity of MRI can be seen clearly, even in the absence of a paramagnetic contrast agent. Figure 43.2-2 shows an example of a CT scan in a patient with a seizure disorder that was interpreted prospectively and retrospectively as normal before and after contrast agent administration. The MRI scan is clearly abnormal. Stereoelectrobiopsy demonstrated a well-differentiated astrocytoma.
Newer MRI techniques such as MR spectroscopy, dynamic contrast-enhanced MRI, functional MRI, and diffusion-perfusion MRI can provide additional information. MR spectroscopy can evaluate the regional distribution of chemicals associated with energy metabolism in the tumor. Dynamic contrast-enhanced MRI, by quantitating the uptake of gadolinium contrast agents into the lesion, can distinguish the slow rate of uptake of radiation injury from the rapid rate of uptake commonly seen in highly malignant primary CNS tumors. Functional MRI reflects small localized changes in blood flow that occur in response to cortical localization of various neurologic functions. Thus, for instance, dominance of cerebral function or importance of a supplementary motor area can be quickly determined before surgery to enable the surgeon to better protect normal brain function during a surgical resection of a tumor. Diffusion-perfusion MRI can provide better information regarding free neurologic functions. Thus, for instance, dominance of cerebral function or importance of a supplementary motor area can be quickly determined before surgery to superimposed on radiographic simulator films so that the tumor can be localized accurately for appropriate port design. The use of the MRI scan is now routine in treatment planning of brain and spinal cord tumors.

In the evaluation of intracranial tumors, cerebral angiography is used much less frequently than in the past. For many cases MR angiography suffices. Angiography may be useful to confirm an impression gained by MRI or CT that the lesion in question is a vascular malformation or an aneurysm rather than a neoplasm. In certain situations (e.g., with large meningiomas) angiography may be useful before surgery to determine the blood supply so that it can be embolized during the angiographic procedure or obliterated during the surgical procedure, or both.

In the evaluation of intramedullary and extramedullary spinal cord lesions, high-quality MRI is the diagnostic study of choice. Indications for myelography currently are extremely limited, because multiplanar MRI can provide superb delineation of the spinal cord contour, and the addition of gadolinium-diethylenetriaminepenta-acetic acid provides enhancement and visualization of almost all intrinsic tumors (such as ependymomas, astrocytomas, meningiomas, and schwannomas) and facilitates the diagnosis of leptomeningeal disease. Tumor cysts are readily identified on MRI, and currently spinal cord tumors can be distinguished much more reliably from syringomyelia (Fig. 43.2-4).

FIGURE 43.2-4. A 39-year-old man with a known cerebral glioblastoma multiforme developed spinal cord symptoms. A: A T1-weighted (TR 600, TE 20) sagittal scan of the thoracolumbar spine shows mild heterogeneity of signal near the conus, but is otherwise normal. B: A T2-weighted (TR 2000, SE 35, 70) sagittal scan provides no additional information. C: A T1-weighted (TR 600, SE 20) image after gadolinium-diethylenetriaminepenta-acetic acid administration clearly shows high signal-enhancing tumor (black arrows show some of lesions) immediately caudal to the conus resulting in a high-grade partial block and multiple additional drop metastases. D: A water-soluble contrast myelogram demonstrates the drop metastases (white arrows show some of lesions) and incompletely delineates the mass adjacent to the conus. (Courtesy of Gordon Sze, Department of Radiology, Yale University School of Medicine, New Haven, CT.)
and restricted water diffusion in the brain to help differentiate tumor malignancy and secondary effects of treatment on the tumor.

**TANGENT SCREEN, PERIMETRY, AUDIOMETRY, AND ELECTROENCEPHALOGRAPHY**

Testing for abnormalities of the visual system is part of the neurologic examination. However, the results of confrontation visual field testing need quantitation to provide greater accuracy and to follow the effects of treatment. Formal visual field testing is done using tangent screens, and scotomas and field defects are diagnosed with perimeter. Schematic representation of the common visual field abnormalities and their anatomic localization can be readily found in any neurology text.

Quantitation of deafness is performed by formal audiometric testing. This can be helpful in the diagnosis of acoustic neurinomas.

Electroencephalography once had a place in the diagnosis and follow-up study of intracranial neoplasms. Its major value is in the diagnosis of seizure disorders and in following the rare patient whose neurologic deterioration may be related to subclinical seizures rather than tumor growth. Visual-evoked potentials measured over the visual cortex after visual stimuli are less valuable in the evaluation or follow-up study of patients with brain tumors, but can help distinguish multiple sclerosis from tumor.

**TUMOR AND CEREBROSPINAL FLUID MARKERS**

For patients with intracranial and spinal tumors, examination of peripheral blood and CSF has been found to be helpful for diagnosis and for therapy monitoring. Pituitary tumors often produce endocrinologic abnormalities measurable by sensitive radioimmunoassays. Polyacystinemia associated with a tumor of the posterior fossa (cerebellum) may be useful as presumptive evidence for the diagnosis of hemangioblastoma. Some paraseal and pineal region embryonal tumors secrete unique hormones and proteins; human chorionic gonadotropin-b hormone (b-HCG) and a-fetoprotein (AFP) are examples of hormones associated with trophoblastic tissue and yolk sac, respectively.

**INDICATIONS FOR AND INTERPRETATION OF CEREBROSPINAL FLUID EXAMINATION**

Lumbar puncture in a patient with headache, papilledema, and a presumed diagnosis of tumor is risky, because it increases the possibility of a fatal cerebellum-foramen magnum or temporal lobe-tentorial herniation. Lumbar puncture should follow rather than precede neuroimaging studies, such as MRI and CT scanning.

The examination of CSF is useful in following patients with intracranial tumors that have a propensity to seed the subarachnoid space and spread through the CSF pathways. Typically, medulloblastoma, ependymoma, choroid plexus carcinoma, and some embryonal pineal and suprasellar region tumors have a high enough likelihood of spread to justify CSF examinations. In these patients, it is important to obtain a lumbar puncture for CSF to examine for malignant cells (cytology), protein, and glucose, and specific markers such as b-HCG and AFP. These tests determine if malignant cells are in the CSF and if tumor deposits have reached sufficient size to begin to block CSF subarachnoid pathways. A high protein concentration with normal glucose levels and normal cytology is seen in tumors of the base of the skull, such as acoustic neurinoma, and in spinal cord tumors. The appearance of xanthochromic CSF, due to high protein content, with an absence of erythrocytes is characteristic of spinal cord tumors obstructing the subarachnoid space and producing stasis of the CSF in the caudal lumbar sac.

**Evaluation of Patients with Intracranial Tumors during Therapy**

Critical to the evaluation of the efficacy of any therapy for brain tumors is the reliability of the measurement of tumor growth (deterioration) or tumor regression (response). Today, contrast-enhanced MRI and, to a lesser extent, CT are used as the primary measure of response to treatment. The extreme sensitivity of the MRI to changes in brain water content and small enhancing lesions can be confusing in the evaluation of tumor regrowth and progression, especially following radiotherapy. The use of MR spectroscopy, diffusion-perfusion algorithms, and dynamic contrast-enhanced MRI may improve the ability to assess tumor regrowth in the postirradiation period.

To interpret the results of therapy correctly and to improve patient care, understanding factors other than cell division is important.

**FACTORS THAT MAY PRODUCE CLINICAL DETERIORATION**

The most common causes of neurologic deterioration in brain tumor patients undergoing radiation therapy or chemotherapy, or both, are growth of the tumor or increased peritumoral edema. Both cause increased pressure in the cranial cavity that is transmitted primarily to the adjacent brain; in turn, hydrostatic pressure on the brain can lead to impairment of cerebral blood flow. The clinical result can be progressive impairment of functioning brain with resultant neurologic deficits. These manifestations may include signs and symptoms of increased intracranial pressure and temporal lobe or cerebellar herniation (see Table 43.2-9 and Table 43.2-10).

Neurologic deterioration, without neuroimaging evidence of tumor growth, can occur for any of the following reasons:

- Obstructive hydrocephalus can occur secondary to tumor in the ventricular system at the aqueduct of Sylvius, fourth ventricle, or foramen of Monro or communicating hydrocephalus due to infiltrative tumor (carcinomatosis, CNS leukemia, and arachnoiditis).
- Hemorrhage into a tumor may occur.
- Fluid imbalance, particularly hyponatremia caused by excessive administration of parenteral dextrose in water solutions, may develop.
- Hypertension can accentuate intratumoral and peritumoral edema.
- Reactive peritumoral edema (or demyelination) may develop early in the course of radiation therapy.
- An early delayed syndrome, observed in approximately 15% to 40% of patients completing a course of cranial irradiation, can be distinguished from tumor regrowth only by wakening and finding that the patient’s condition improves without further treatment. This encephalopathy responds to corticosteroids and resolves within several weeks without specific sequela. This syndrome is not unique to patients with brain tumors and is observed in leukemic children after prophylactic cranial irradiation and in those with extracranial tumors who receive incidental radiation to the brain.
- Radiation necrosis can occur within 3 months to 13 years or longer after radiation therapy and can produce neurologic impairment that may be indistinguishable from tumor recurrence.
- Seizures may suggest that the tumor is growing and may result in an increase in the neurologic deficit apart from any direct effect of the tumor. Recovery from any increase in weakness and mental dullness may take several hours to a week in postictal patients who are already brain injured. Even subclinical seizures can cause deterioration, persisting for hours to days, which resolves with control of the seizures. Electroencephalography is usually diagnostic in these patients, and the treatment is better control of seizures. Patients receiving long-term chemotherapy often require higher doses of anticonvulsants or widely fluctuating dosages caused by drug-induced hepatic changes.
- Infection and fever often exacerbate neurologic signs and symptoms, regardless of the site of infection. The more common causes of infection include pneumonia secondary to aspiration or atelectasis and urinary tract infections; meningitis and cerebral abscesses are less common.
- Metabolic disorders, anemia, fatigue, and emotional depression can cause clinical deterioration, including increase in focal deficit on testing, that is difficult to distinguish from tumor progression. Such conditions generally produce no alteration of neuroimages.

In these authors’ experience, at least 10% of patients who eventually respond to therapy become significantly worse at the end of a first course of chemotherapy, and transient deterioration is observed occasionally even during the second year of continuous chemotherapy. Paradoxically, this clinical worsening early in therapy may result from an increase in tumor bulk resulting from effective therapy. Several factors contribute: cell mass may increase when doomed cells form giant cells or undergo one or more successful cell divisions before dying; the CNS also has an inefficient mechanism for disposing of dead cells produced by chemotherapy or irradiation; and edema, probably caused by irritative products of cell lysis, may be present within the tumor mass and in adjacent brain.

**GLUCOCORTICOID USE**

Administration of glucocorticoids is usually begun before surgery for brain tumor. If an adequate surgical decompression is achieved, the corticosteroid dose can be tapered off rapidly and discontinued within the first week or two after the operation. Several patients require corticosteroid maintenance because a large volume of tumor remains, because tumor occupies the brain stem or spinal cord, or because of corticosteroid dependence resulting from long-term prior usage.
Patients who no longer require corticosteroids after surgery may need them during or after radiation therapy. Reactive edema may occur during irradiation, and there may be a transient period of drowsiness and increased deficit for 6 to 16 weeks after treatment. In both instances, signs and symptoms usually resolve within a few weeks; observation of the subsequent clinical course is often the only way to differentiate these reactions from tumor progression.

The lowest dosage of glucocorticoid that maintains patients at their maximum levels of comfort and function should be sought. Ordinarily, this is determined by decreasing the dosage until symptoms increase or become apparent, then increasing the dosage until they subside. If deterioration is secondary to tumor growth or treatment-induced effects, glucocorticoids may have to be increased to keep the patient comfortable. For example, 3 mg/d of dexamethasone may have the desired effect for a patient with stabilized disease; however, a deteriorating patient may require dexamethasone doses of 64 mg/d or more.

The efficacy of chemotherapy and radiation therapy can be affected by glucocorticoid dosage. A decrease in corticosteroid requirement suggests improvement, assuming that the previous dosage was actually required. An increase in dosage suggests deterioration. Because increased glucocorticoid dosage may improve neurologic status and reduce the image size on CT scan, an attempt should be made to document tumor recurrence before increasing glucocorticoid dosage. The ability of glucocorticoids to reduce the size of primary brain tumors as measured by MRI is well established.

SURGERY

GENERAL CONSIDERATIONS

No other modality can reduce tumor bulk as quickly as surgery, and advances in imaging, computerized navigation, pharmacologic agents for brain edema, neuroanesthesia, and surgical magnification, illumination, and instrumentation such as ultrasonic aspirators have made operative approaches to tumors in even the most remote corners of the CNS possible and reasonably safe. The goal of brain tumor surgery is to resect and cure the tumor completely. If surgical cure is not possible, such as in most gliomas, tumor bulk reduction and consequent decompression of the brain is the next goal and, where possible, should be the first therapeutic modality for the tumor.

An extremely important by-product of cytoreductive surgery is the acquisition of adequate tissue for histopathologic examination. Only rarely should brain tumors be treated with radiation or chemotherapy without a definitive tissue diagnosis. In patients with tumors that are believed to be inaccessible by open craniotomy or in patients for whom the craniotomy would not be helpful, a needle biopsy should be performed with guidance from CT, MRI, or ultrasound. CT-guided stereotaxy is the easiest method for obtaining tissue with a needle.

SURGICAL PLANNING

The intrinsic characteristics of a tumor's appearance and its relative position in the brain as shown on a technically adequate MRI scan can most often narrow the diagnostic possibilities to one or two choices, and a view of the tumor in several planes simplifies surgical planning.

For tumors that appear to be located in critical motor or language areas, functional MRI is becoming an important preoperative screening test to determine the feasibility of the surgery. If the surgery is deemed possible, the functional MRI scans are used in conjunction with intraoperative electrophysiologic mapping (see Craniotomy for Supratentorial Tumors, later in this chapter) to plan a safe approach to an intraxial tumor. Cerebral angiography is sometimes useful in surgical planning for tumors that may encircle critical cerebral blood vessels, such as basal meningiomas, or for tumors that can be extremely vascular, such as hemangioblastomas, glomus tumors, and certain meningiomas. Angiography done in temporal proximity (24 to 96 hours) to the planned surgical procedure can be combined with embolization of the tumor's blood supply, in many instances making the surgical procedure technically easier.

The final selection of a surgical approach is made after adequate imaging, after developing a differential diagnosis, and after assessing the patient's general condition. In the era of modern neuroanesthesia, it is rare that a craniotomy must not be done because of poor general medical status. The design of an appropriate scalp incision and bone flap is the final preoperative decision.

PREOPERATIVE AND ANESTHETIC MANAGEMENT

Patients undergoing surgery for supratentorial tumors should be placed on anticonvulsants except in the case of surgery for brain metastasis without prior history of seizures. Corticosteroids (commonly dexamethasone) should be administered for a few days preoperatively, when possible, to reduce cerebral edema and thereby facilitate cerebral retraction for perfect exposure. Blood levels of anticonvulsants should be monitored to ensure that the therapeutic range has been achieved. Anticonvulsants should also be continued for at least 1 year. Corticosteroids should be continued into the postoperative period and then tapered, when possible. The anesthetic agents are selected for their lack of effect on intracranial pressure. In general, the head is held rigidly with pin fixation to minimize movement as the surgeon is looking through the operating microscope, where the slightest movement is dramatically amplified. As the procedure is about to commence, mannitol (1 g/kg body weight) is administered and hyperventilation to a p CO₂ of 25 to 30 mm Hg is accomplished for definitive reduction of the intracranial pressure in preparation for brain retraction.

CRANIOTOMY FOR SUPRATENTORIAL TUMORS

The bony opening is designed so that it is generous enough to facilitate surgery. The bone flap is centered over the tumor or positioned to provide access to the route of approach. In all instances, the scalp flap is designed to accommodate the bone flap fully, and the vascular supply to the scalp is given careful consideration in the design.

After the scalp incision is made and the scalp flap reflected, burr holes are drilled and connected with a power saw. The bone flap can be turned back, attached to the temporal muscle (osteoplastic flap) or its blood supply, or removed completely (free flap). The dura is opened only after the brain has been softened completely by mannitol diuresis and intraoperative hyperventilation. Sometimes a few minutes' wait is necessary to secure maximum decompression, and this brief pause can be critical to the success of the subsequent surgical approach.

The dura is reflected back, and the approach to the tumor is made. The surgeon can be confronted by a field of normal appearing and, in some areas, potentially critical cortical structures when seeking a subcortical lesion. In this situation, mapping of cortical motor and speech function can be carried out intraoperatively using electrical stimulation of the cortex. The preoperative functional MRI scan can serve as a guide. Motor mapping can be done in the anesthetized patient when muscle relaxants are not used during surgery, and an increasing number of glioma resections in the dominant hemisphere are being done under local anesthesia for the purpose of speech mapping. Localization of subcortical tumors can be accomplished using intraoperative ultrasonography, but more recently, frameless image-guided interactive surgical systems have been developed. With these systems, a preoperative MRI scan is done with markers on the patient's scalp, which at the time of surgery allow computer digitization of the images onto the patient's head. Placement of the system's probe at the time of surgery gives immediate feedback as to localization as visualized on the MRI. This sort of guidance is invaluable for the design of the craniotomy flap, the localization of the subcortical tumor, and even determination of the extent of tumor resection.

Tumor removal is usually done with grasping instruments, bipolar coagulation, and suction, but removal of firm, adherent, or calcified tumor tissue can be difficult and is simplified by use of the Cavitron ultrasonic aspirator (CUSA), which ultrasonically disrupts the tumor at its tip and sucks it away. Tumor in locations where access is limited (e.g., the third ventricle) and space to use graspers and other equipment is not available sometimes can be dealt with best by use of the CO₂ laser, which can vaporize tumor tissue with a hands-off technique. Tumor removal with a laser is slow, however, and is reserved for special circumstances.

In the rare situations in which brain swelling is worsome at the time of closure, a catheter is left in the subdural space to measure the intracranial pressure. All patients are monitored in the intensive care unit for at least 1 night after surgery, and an MRI scan is done within 48 hours to evaluate the success of the tumor resection. Serum electrolyte levels and osmolality are measured frequently in the postoperative period to ensure that the patient is relatively dehydrated through the first several days and to detect the possible onset of inappropriate secretion of antidiuretic hormone or diabetes insipidus.
CRANIOTOMY FOR POSTERIOR FOSSA TUMORS

The occiput and, commonly, the dorsal aspects of C-1 and C-2 are exposed. A generous craniotomy is done unilaterally or bilaterally to accommodate an approach through the venous or through, over, or around the cerebellar hemisphere. A laminectomy of C-1 and sometimes C-2 is done in certain midline approaches to improve tumor exposure or extend the decompression. The cisterna magna is opened to drain CSF and decompress the cerebellum before initiating retraction.

STEREOTACTIC TUMOR BIOPSY

For intrinsically small tumors of the deep midline (e.g., pontine or corpus callosum gliomas), for deep tumors of the dominant hemisphere, or for diffuse nonfocal tumors, surgical resection is not practical. In these situations, needle biopsy for diagnosis is essential. There is no longer any reason to perform a full craniotomy for the purpose of biopsy only. Tissue can be obtained through a needle directed by hand through a burr hole under CT or MRI scan guidance or a needle directed by many devices that incorporate ultrasound images. However, in these authors’ opinion, nothing is as simple or accurate as CT- or MRI-directed stereotactic biopsy.

A number of image-guided stereotactic systems are available. Typically, the patient undergoes a CT or MRI scan with a rigid array of bars affixed tightly to the skull to minimize movement. In adults, local anesthesia usually is used; children usually require general anesthesia. The CT scan image demonstrates the lesion in which the biopsy will be performed and also the localizing rods, thereby relating the target to a volume encompassed by the rods. By digitizing the position of the target and the position of the rods, this relation is formalized, and the coordinates for a trajectory to the target are created in a way specific to the individual stereotactic system used.

The target is approached through a burr hole or a (smaller) twist drill hole. The biopsy instrument is guided to the target by use of an adjustable stereotactic arc that is placed on the head in fixed relation to the former position of the localizing rods used for the CT scan. A fragment of tissue is aspirated or grasped for removal, and a frozen section confirms the acquisition of diagnostic material and most often also suggests a working diagnosis. Experienced surgeons obtain diagnostic tissue in more than 95% of patients, and these patients stay only 1 night in the hospital. The principal risk of the surgery, hemorrhage at the biopsy site, occurs in few patients. Occasionally, cerebral edema is exacerbated by the procedure.

RADIATION THERAPY

GENERAL CONSIDERATIONS

Most primary CNS neoplasms are uncommon; however, the more common brain tumors, such as the low-grade and malignant astrocytomas, are infiltrative into surrounding normal brain tissue for a distance of 1 to 3 cm or more. Radiotherapeutic approaches for these brain tumors generally consist of an initial dose to the enhancing lesion (which contains solid tumor tissue) plus surrounding edema (which is comprised of normal brain infiltrated by microscopic tumor) plus a 2-cm margin of normal brain tissue followed by a boost dose to the enhancing tumor plus a 2-cm margin. Because of the penetrating nature of the high-energy radiation beams used in current practice, and the presence of a large amount of normal brain tissue in the edema and margin, substantial amounts of normal tissue are often irradiated in the typical patient receiving high-dose radiation with curative intent. The tolerance of the normal brain (and spinal cord in the case of cord tumors) may then be a limiting factor to achieving local control and cure of a CNS neoplasm.

TOLERANCE OF THE BRAIN

Adverse reactions associated with cranial irradiation differ in their pathogenesis and can be temporally classified into (1) acute reactions that occur during or shortly after radiation therapy; (2) early delayed reactions that appear within a few weeks to 4 months after irradiation; and (3) late delayed injuries that develop several months to years after treatment.

Acute reactions are thought to be caused by radiation-induced edema. Within a few hours after the first fraction of radiation, patients may develop headache, nausea, vomiting, somnolence, fever, and worsening neurologic symptoms. Symptoms occur most commonly after large dose fractions (3.0 to 6.0 Gy) are delivered to a large volume of the brain in patients with increased intracranial pressure from primary or metastatic brain tumors. Thus, if symptoms of increased intracranial pressure are present, patients undergoing cranial irradiation should be protected with corticosteroids, administered for at least 48 to 72 hours before beginning treatment. When larger fractions (7.5 Gy or more) are used, this disorder may culminate in abrupt neurologic deterioration or death. However, with conventional daily fractions of 1.8 to 2.0 Gy, the acute radiation reaction most commonly presents as mild headache and nausea, becoming progressively less severe with each succeeding fraction.

Treatment with hyperfractionated irradiation schedules of 0.9 to 1.2 Gy, two or three times daily and accelerated fractionation programs of 1.6 to 2.0 Gy given two or three times daily delivered to a portion of the brain are also well tolerated.

The early delayed reaction is thought to result from temporary demyelination caused by the effects of radiation on oligodendroglial cells and multiple mechanisms are probably involved. The late delayed reaction presents as a focal or as a diffuse white matter injury that may occur together in the same patient. The clinical presentation depends on the site and volume of the brain exposed. Patients with focal radiation necrosis present with localizing neurologic signs, often accompanied by symptoms of increased intracranial pressure. Focal hypodensity or a contrast-enhancing mass with surrounding vasogenic edema may be seen on CT scan. MRI shows a contrast-enhancing mass with focal and confluent white matter alterations on T2-weighted images. Diffuse white matter injury typically occurs after large doses of whole brain irradiation. Clinical features range from seizure disorders and varying degrees of neuropsychological impairment to incapacitating dementia. Diffuse white matter hypodensity is seen on CT scan, often accompanied by a focal enhancing mass, whereas T2-weighted MRI shows diffuse periventricular white matter hyperintensity. Cerebral cortical atrophy, probably a late finding related to diffuse white matter injury, is observed in 17% to 39% of patients who receive whole brain irradiation with chemotherapy for malignant gliomas. Enlarged cerebral sulci and ventricles are seen in neuroimaging studies. The pathogenesis of this formal radiation damage is uncertain. Rarely, therapeutic irradiation causes an intravascular vessel occlusive vasculopathy or secondary neoplasia.

The tolerance of the brain depends on the size of the dose per fraction, total dose administered, overall treatment time, volume of brain irradiated, host factors, and adjunctive therapies. The probability of injury increases with larger daily doses (2.2 Gy per fraction) and doses in excess of 60 Gy delivered in 30 fractions over approximately 6 weeks. Sheline and associates suggested that the threshold doses for brain injury are approximately 35 Gy for 10 fractions, 60 Gy for 35 fractions, and 76 Gy for 60 fractions. They further demonstrated that the isoeffective dose (termed 

steroids) formula should have an exponent of $N = 0.41$ and an exponent of $T = 0.03$ (where $N$ is the number of fractions and $T$ is the total time in days). This formula may not be applicable to extremely small or large numbers of fractions or to extremely short or long overall treatment times. Based on models such as these, the TD 5/5 (a 5% complication rate in 5 years) for the whole brain is between 40 and 60 Gy, for part of the brain is 50 to 10 Gy, and for a 10-cm segment of spinal cord is 45 to 50 Gy (see discussion of spinal cord tolerance in this section), as shown in Table 43.2-12. Although the TD 50/5 (a 50% complication rate in 5 years) for spinal cord is reportedly lower than that of brain, there are no good data to support this difference. Rather, the sequelae of spinal cord radiation injury are perceived as greater than those of brain injury, therefore tolerance doses have been arbitrarily lowered. In clinical practice, TD 5/5 of 60 Gy for partial brain and 50 Gy for a limited segment of spinal cord are commonly used.
TABLE 43.2-11. Factors Associated with Radiation Tolerance of the Normal Central Nervous System (CNS) Tissues

The TD 5/5's given for brain and spinal cord tolerance assume a standard fraction size of 180 to 200 cGy/d. For primary CNS tumor patients being treated with curative intent, fraction size should rarely exceed 200 cGy daily, and in most situations, should be 150 to 200 cGy. Fraction sizes greater than 200 cGy daily (usually 250 to 300 cGy) are commonly used for palliation of brain metastases and spinal cord compression, but only because such patients are not expected to live long enough to manifest normal tissue injury.

Table 43.2-12 shows the tolerance doses for other normal tissues of the CNS, including the brain stem, eye, ear, optic chiasm, optic nerve, and pituitary gland. The clinical manifestations of severe injury to these structures is listed.

TABLE 43.2-12. Tolerance Doses (TD) for Normal Central Nervous System Tissues at 2 Gy Per Fraction over 5 Days per Week

The TD 5/5's given for brain and spinal cord tolerance assume a standard fraction size of 180 to 200 cGy/d. For primary CNS tumor patients being treated with curative intent, fraction size should rarely exceed 200 cGy daily, and in most situations, should be 150 to 200 cGy. Fraction sizes greater than 200 cGy daily (usually 250 to 300 cGy) are commonly used for palliation of brain metastases and spinal cord compression, but only because such patients are not expected to live long enough to manifest normal tissue injury.

Table 43.2-13 shows the tolerance doses for other normal tissues of the CNS, including the brain stem, eye, ear, optic chiasm, optic nerve, and pituitary gland. The clinical manifestations of severe injury to these structures is listed.

TABLE 43.2-13. Tolerance Doses (TD) for Miscellaneous Normal Tissues of the Cranium

Approximately 4% to 9% of patients treated to 50 to 60 Gy with conventional fractionated radiation for brain tumors develop clinically detectable focal radiation necrosis, but this form of injury may be found in as many as 10% to 22% of patients at autopsy. A review by Marks and colleagues of 139 patients who received irradiation for primary brain tumors with at least 45 Gy in daily dose fractions of 1.8 to 2.0 Gy disclosed 7 patients (5%) with brain necrosis. A recalculation of their data, assuming a daily dose of 1.8 Gy given five times per week, demonstrated that the incidence of necrosis was directly related to dose. Of 51 patients who received total doses of 57.6 Gy or less, there were no cases of necrosis. Two of 60 patients (3%) who received between 57.6 and 64.8 Gy developed necrosis, and 5 of 28 patients (18%) who received 64.8 to 75.6 Gy developed necrosis.

Several additional factors may affect the radiation tolerance of the brain. Children younger than 2 to 3 years of age are thought to be more susceptible to injury than are adults because of incomplete development of the CNS. Vasculopathy associated with endocrine disorders, CNS infection, and cerebral edema also appear to potentiate the effects of radiation.

The risk of injury may be amplified by some chemotherapeutic agents. The most dramatic illustration of the toxicity of combined modality therapy was observed in children with acute lymphoblastic leukemia treated with prophylactic brain irradiation and methotrexate administered intravenously and intrathecally. Two delayed syndromes, necrotizing leukoencephalopathy and mineralizing microangiopathy, have been recognized in children who received 24 Gy in 1.5 to 2.0 Gy daily increments, which without chemotherapy are well below tolerance levels. Although necrotizing leukoencephalopathy has not been reported with a dose of 24 Gy in the absence of chemotherapy and occurs in fewer than 1% to 2% of patients receiving intrathecal and high-dose intravenous methotrexate, the incidence with all three therapies combined is as high as 45%. It is currently recognized that methotrexate is most toxic when given during or after radiation therapy, and attention to this detail has reduced the frequency of this complication significantly.

Radiation and chemotherapy-induced changes are often indistinguishable from tumor recurrence on CT. By MRI the changes are better defined and can be more easily anticipated, nevertheless, at time the radiographic diagnosis of radiation necrosis may be difficult to confirm. Thallium 201 single-photon emission tomography, and dynamic contrast-enhanced MRI studies may help separate patients with radiation and chemotherapy necrosis from those with recurrent tumor. However, because most patients have a mixture of necrosis and tumor, a biopsy may be required to confirm the diagnosis, especially when the injury occurs at or near the tumor site.

Corticosteroids may improve or stabilize the neurologic symptoms associated with the effects of radiation and radiation with chemotherapy injury. Surgical resection is often beneficial to patients with favorably situated, focal radiation-induced lesions who deteriorate neurologically and become dependent on corticosteroids. While anticoagulation has been suggested as a therapeutic alternative when surgery is not feasible, a clinical trial that demonstrates real benefit to the patient is lacking at present. In unpublished trials, we and others have tried vitamin E, pentoxifylline (Trental), aspirin, cis-retinoic acid, heparin, coumadin, and enoxaparin (Lovenox) without conclusive evidence of reproducible benefit. As an anecdote, the occasional patient appears to benefit from anticoagulation, cis-retinoic acid, or both.

Decreased levels of intellectual function have been observed after cranial irradiation in children and adults with acute lymphoblastic leukemia, small cell lung carcinoma, and primary brain tumors. IQ decrements and perceptual and learning disabilities seen after CNS prophylaxis in children with acute lymphoblastic
leukemia have long been attributed to cranial irradiation. However, a study comparing the long-term cognitive outcome of children treated with 18 or 24 Gy and intrathalcal methotrexate or intrathalcal and intravenous methotrexate without cranial irradiation failed to demonstrate an overall decline in verbal, performance, or full-scale IQ in any of the three groups, although 22% to 30% of children in each group showed at least a 15-point decline in IQ during the study period. The authors proposed that ecologic factors or continuation phase chemotherapy rather than radiation therapy might account for the IQ changes.

Neuropsychological deterioration has been recognized in long-term surviving patients with small cell lung carcinoma who receive prophylactic cranial irradiation. These patients are treated with potent chemotherapeutic agents that may enhance the effects of radiation on the CNS. The risk and severity of impairment appear to be related to radiation dose and fraction size and to the type, sequence, and dose intensity of the chemotherapeutic agents used.

Children irradiated for brain tumors have IQ decrements and behavioral disturbances. Most require formal psychological intervention and special education programs. Young age at treatment, supratentorial tumor sites, the use of whole brain irradiation, poorly controlled seizure disorders, the presence of sensorimotor deficits, and the addition of chemotherapy have a negative influence on IQ. The risk and severity of neuropsychological dysfunction are also affected by psychological stress, reduced school attendance, and the adequacy of rehabilitative efforts.

Cranial irradiation also leads to intellectual impairment in adults. Unlike in children, however, only a limited amount of quantitative information is available, especially for patients treated with radiation therapy alone. Patients in whom a substantial portion of the brain is irradiated frequently develop recent memory loss and difficulty with attending to tasks that may prevent their return to gainful employment. Impairment is most pronounced in those patients who have had chemotherapy and whole brain irradiation. We found that approximately 60% of long-term survivors irradiated for gliomas were able to be employed at occupations comparable with those they held before treatment. As expected, patients irradiated with partial brain fields had superior memory function and better employment histories than those treated with whole brain fields. Decrements in tests of new learning ability, recent memory, abstraction, and problem solving have been observed in patients who fail to retain their premorbid social or occupational level of function. Early return to work after treatment may lead to improvement or recovery of neuropsychological function.

Radiation therapy may cause hypothalamic-pituitary dysfunction, and the incidence and degree of hormone suppression appear to be dose related. Growth hormone deficiency, the most frequent endocrine dysfunction observed after radiation therapy, can occur after doses as low as 18 Gy. Deficiencies of gonadotrophins, thyroid-stimulating hormone, and adrenocorticotrophins as well as hyperprolactinemia can be seen with doses in excess of 40 Gy. Patients at risk for neuroendocrinologic sequelae should be evaluated for pituitary function before, and periodically after, irradiation. Early detection of a deficiency permits appropriate hormonal replacement therapy before irreversible damage has occurred.

TOLERANCE OF THE SPINAL CORD

Radiation myelopathy may present as a transient early delayed or as a more ominous late delayed reaction. Transient radiation myelopathy is clinically manifested by momentary, electrical shock-like paresthesias or numbness radiating from the neck to the extremities, precociously pared by neck flexion (Lhermitte's sign). The syndrome develops after an average latent period of 3 to 4 months and gradually resolves over the ensuing 3 to 6 months without the need for specific therapy. These findings have been attributed to transient demyelination caused by radiation-induced inhibition of myelin-producing oligodendroglial cells in the irradiated cord segment. An alternative hypothesis suggests that radiation induces a transient disruption of the blood-spinal cord barrier, resulting in vasogenic edema, which in turn leads to demyelination.

Radiation myelopathy is one of the most feared complications in clinical radiotherapy. In addition to its obvious neurologic sequelae, nearly 50% of patients die from secondary complications. The latent period between the completion of radiation therapy and the onset of symptoms is bimodal in distribution, with the first peak occurring at 12 to 14 months and the second occurring at 24 to 28 months. Demyelination and white matter necrosis due to a direct effect on oligodendroglial cells and intramedullary microvascular injury each play a role in the pathogenesis of radiation myelopathy. In addition, microglia, astrocytes, and the release of cytokines are also involved. It is probable that multiple mechanisms exist and that the relative contribution of each depends on radiation dose and other factors. The signs and symptoms that accompany radiation myelopathy are irreversible. They may be partial in some patients, whereas in others there is progressive functional loss that becomes complete over several months. Less commonly, radiation myelopathy is manifested by the acute onset of paraplegia or quadriplegia that evolves over several hours or a few days, resulting from infarction of the cord. Myelopathy may also be heralded by lower motor neuron dysfunction due to selective injury to anterior horn cells.

The diagnosis of radiation myelopathy requires a history of radiation therapy in doses sufficient to result in injury. The portion of the cord irradiated must be slightly above the dermatome level of expression of the lesion, and the latent period from the completion of treatment to the onset of injury must be consistent with that observed in radiation myelopathy. There are no confirmatory laboratory tests or imaging studies that distinguish radiation myelopathy from other spinal cord lesions. MRI findings include swelling of the cord with decreased intensity in T1-weighted and hyperintensity in T2-weighted images. The diagnosis is often one of exclusion.

The medical and legal consequences of radiation myelopathy are such that treatment with radiation therapy is often compromised to keep the spinal cord dose within a safe level. A dose of 45 Gy in 22 fractions over 5 weeks usually is considered to be safe, the risk of myelopathy being less than 0.2%, well below the steep portion of the dose-response curve. It is estimated that with conventionally fractionated irradiation (1.8 to 2.0 Gy per fraction, five fractions per week), the incidence of myelopathy is 5% for doses in the range of 57 to 81 Gy and 50% for doses of 68 to 73 Gy. There is no convincing evidence that the cervical and thoracic cord differ in their radiosensitivity. The belief that the cervical cord is more tolerant than the thoracic cord probably arose from differences in biologic dose resulting from the practice of treating with one field per day, which was common through the mid-1970s. There appears to be little change in tolerance with variations in the length of cord irradiated.

Various isoeffect formulas have been proposed for the spinal cord. Wara and coworkers, for example, derived a formula with an exponent of N = −0.377 and an exponent of T = −0.058. These formulas suggest that in addition to the total dose given, radiation myelopathy is related to the size of the individual daily dose and predict that spinal cord tolerance will continue to increase with decreasing fraction size. However, data indicate that reducing the fraction size to lower than 2 Gy does not alter the dose response significantly. Furthermore, because radiation damage is not completely repaired between multiple daily fractions, extrapolating from a conventionally fractionated cord dose to an equivalent hyperfractionated cord dose using any biomathematical formula should be approached with caution. A dose of 45 Gy in twice daily fractions of 1.2 Gy with an interfraction interval of 6 hours appears safe. Interestingly, experimental animal studies suggest that the majority of occurrences caused by a dose of 44 Gy in 20 fractions is revealed within 2 years. This may have implications on treatment recommendations for previously treated patients.

CENTRAL NERVOUS SYSTEM RADIONUCLIDE SCORING SYSTEMS

The most commonly used system for scoring radiation-associated acute and chronic CNS toxicity is that of the Radiation Therapy Oncology Group (RTOG) and its European counterpart, the European Organization for the Research and Treatment of Cancer (EORTC), and is shown in Table 43.2-14. Pavy et al. have proposed a more sophisticated system for scoring radiation toxicity, called Late Effects on Normal Tissues (LENT), in which they describe four components for each toxicity, including the subjective, objective, management, and analytical (SOMA) components. The LENT/SOMA system is currently being validated by the RTOG and may eventually replace the RTOG/EORTC system.

| Table 43.2-14 | Central Nervous System (CNS) Toxicity Levels of the Radiation Therapy Oncology Group and the European Organization for the Research and |
TUMOR TARGET VOLUME AND TREATMENT TECHNIQUES

The appropriate volume to encompass within the radiation treatment portal varies according to the specific histopathologic tumor type and, with certain histologies, is a topic of considerable controversy. Because their tendency to infiltrate beyond the lesional borders visualized by neuroimaging studies is limited, certain tumors, such as benign meningiomas, pliability adenomas, or pituitary adenomas, or primitive neuroectodermal tumors, may be treated with narrow margins of surrounding normal tissue. In contrast, the astrocytic gliomas require larger margins for uncertainty because of their tendency to infiltrate beyond the identifiable tumor periphery. Improved imaging techniques and a better understanding of recurrence patterns have fostered the use of limited radiation portals rather than whole brain irradiation for some low-grade gliomas. Comparisons of CT and MRI studies with clinical and pathologic findings have shown that (1) malignant gliomas are localized, and microscopic invasion of the perilesional brain is limited at the time of initial diagnosis; (2) only 1.1% of patients present with multiple lesions; (3) most of these lesions, when they recur, do so at their original location; and (4) isolated tumor cell infiltration may extend to the periphery of T2-weighted MRI abnormalities. Clinical studies have failed to demonstrate that irradiating the whole brain is superior to treating more limited fields, and patients surviving for extended periods after whole brain irradiation, especially in combination with chemotherapy, may experience considerable treatment-related morbidity. Until the primary tumor can be controlled with greater frequency, and the patterns of failure in such patients suggest that local fields are unjustified, there is little rationale for treating the whole brain.

The radiation beam energy and field arrangements are selected after consideration of the location of the tumor within the brain and the geometry of the target volume. The across target volume is defined as a three-dimensional reconstruction of the tumor contour based on operative findings and data from CT and MRI studies. The planning target volume consists of the volume of tissue that must be irradiated to encompass the tumor volume with a margin of surrounding tissue considered to be at risk for microscopic tumor spread and to account for patient movement and daily set-up uncertainties. Depending on tumor size and location, treatment portals may be coaxially opposed or designed in a more complex fashion, using multiple or rotational fields with wedge filters. Three-dimensional conformal radiation therapy and the advanced technique of intensity modulated radiation therapy (see Chapter 29.4) are new methods of treatment planning and delivery designed to enhance the conformation of the dose to the target volume, while maximally restricting the dose delivered to the normal tissue outside the treatment volume. In the future, these techniques may improve the outcome of patients with brain tumors by allowing higher than traditional radiation doses to be administered safely. Megavoltage equipment with energies ranging from cobalt 60 to 15 MV photons is used to administer intracranial therapy. Treatment is generally given in daily fractions of 1.8 to 2.0 Gy five times per week. In this chapter, the total doses referred to assume that a conventional fractionation scheme is used unless otherwise specified.

Certain neoplasms, such as medulloblastomas and other primitive neuroectodermal tumors as well as some ependymomas and germ cell tumors, require treatment to the entire craniospinal axis. Patients are treated prone in an immobilization cast to ensure daily positional reproducibility. The intracranial contents, including the upper one or two segments of the cervical cord, are treated through parallel opposed lateral fields. The spine is treated through one or two posterior fields, depending on the size of the patient. The collimator for the lateral cranial fields is angled to match the divergence of the upper border of the adjacent spinal field, and the treatment couch is angulated so that the inferior border of the cranial field is perpendicular to the superior edge of the spinal field. Individualized focused blocks protect the normal extracranial head and neck tissues from the primary radiation beam. The cranial and posterior spine fields may be abutted, but a gap of 0.5 to 1.0 cm is often left between the fields. When two posterior spinal fields are used, as is usually the case, a gap is calculated so that the 50% isodose lines meet at the level of the spinal cord. All junction lines are moved 0.5 to 1.0 cm daily or at least every 10 Gy to avoid overdosing or underdosing segments of the cord. This is accomplished by expanding the lateral cranial fields and moving the posterior spine fields caudally without changing their dimensions. A fixed block is placed at the inferior margin of the caudal spinal field to keep the lower margin of the irradiated volume at the same location. Several modifications of this approach are used in clinical practice.

Radiosurgery is being used to treat a diverse group of intracranial lesions, including small arteriovenous malformations, pliability adenomas, acoustic neuromas, meningiomas, gliomas, and brain metastases. Radiosurgery is a method of highly focal, closed skull external irradiation that uses an imaging-compatible stereotactic device for precise target localization. The relationship between the stereotactic coordinate system and the radiation source(s) allows accurate delivery of radiation to the target volume. Radiosurgery can be administered by gamma knife units, made up of multiple cobalt beams, and by modified linear accelerators. This technique is designed to deliver a high radiation dose to an intracranial target in a single session without delivering significant radiation to adjacent normal tissues. The dose that can be safely administered in a single fraction is limited by the volume irradiated, and to maintain a steep dose gradient at the edge of the field, the application of radiosurgery is restricted to lesions measuring 4 cm or less in diameter.

Radiosurgery may be delivered in a fractionated dose schedule using stereotactic radiosurgery hardware and software and head frames that can be relocalized daily in a reproducible fashion. This approach is referred to as stereotactic radiotherapy or fractionated radiosurgery. Because fractioning the radiation dose improves the therapeutic ratio, larger tumors and those located within or adjacent to critical intracranial structures are suitable for this treatment technique. This approach is being applied to the treatment of malignant gliomas, cranioangiophygiomas, pliability adenomas, small optic tract tumors, and as a boost for medulloblastomas.

CHEMOTHERAPY

GENERAL PHARMACOLOGIC CONSIDERATIONS

The use of anticancer agents in the treatment of intracranial and spinal tumors is established for many primary tumors. For parenchymal CNS tumors, however, controversy surrounds the concept of limited antitumor efficacy for agents with restricted blood–brain barrier permeability, supporting the concept is the fact that many of these primary CNS tumors (e.g., gliomas) have cellular regions within the brain with apparently intact normal-appearing brain capillaries. In addition, the actual extent of capillary breakdown accounting for the leakage responsible for positive-contrast CT and MRI as well as radionuclide brain scans is small. Many infiltrative primary CNS tumors (e.g., gliomas) have cellular regions within the brain with apparently intact normal-appearing brain capillaries. In addition, the actual extent of capillary breakdown accounting for the leakage responsible for positive-contrast CT and MRI as well as radionuclide brain scans is small. Although drug delivery to portions of any primary tumor would be expected to occur to the same extent as with non-CNS tumors, delivery (by diffusion) to infiltrative regions is limited by the volume of tissue encompassed by the radiation treatment portal. The across target volume is defined as a three-dimensional reconstruction of the tumor contour based on operative findings and data from CT and MRI studies. The planning target volume consists of the volume of tissue that must be irradiated to encompass the tumor volume with a margin of surrounding tissue considered to be at risk for microscopic tumor spread and to account for patient movement and daily set-up uncertainties. Depending on tumor size and location, treatment portals may be coaxially opposed or designed in a more complex fashion, using multiple or rotational fields with wedge filters. Three-dimensional conformal radiation therapy and the advanced technique of intensity modulated radiation therapy (see Chapter 29.4) are new methods of treatment planning and delivery designed to enhance the conformation of the dose to the target volume, while maximally restricting the dose delivered to the normal tissue outside the treatment volume. In the future, these techniques may improve the outcome of patients with brain tumors by allowing higher than traditional radiation doses to be administered safely. Megavoltage equipment with energies ranging from cobalt 60 to 15 MV photons is used to administer intracranial therapy. Treatment is generally given in daily fractions of 1.8 to 2.0 Gy five times per week. In this chapter, the total doses referred to assume that a conventional fractionation scheme is used unless otherwise specified.

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Therapy by the CSF route (usually by ventricular reservoir) is a form of regional drug delivery that is used to treat meningeal neoplasia resulting from primary or secondary tumor invasion of the subarachnoid space and, less commonly, one of the ventricular cavities. It is often, but not always, associated with malignant cells floating in the CSF.

The advantages of intra-CSF therapy are high local drug levels; low systemic toxicity; and the ability to increase the frequency of treatments. However, delivery of drugs through the CSF can be dangerous and is associated with a high morbidity. The drugs commonly used are methotrexate, cytarabine, and thiopeta. All three drugs have been reported to produce CNS damage ranging from fever and chills to leukoencephalopathy and myelitis. Efficacy is limited when gross lesions exist (greater than or equal to 5 mm diameter) or when CSF pathways are blocked and CSF flows are diverted.

Of concern in the use of CSF therapy is that slow clearance of drug can lead to increased neurotoxicity. Normally, these authors find, after injection into a ventricular reservoir and pumping the reservoir five times, the CSF distribution and flow of radionuclide-labeled albumin in the ventricle is well distributed and the half-time from ventricle to cisterna magna is approximately 60 minutes. In many instances, obvious hydrocephalus is not apparent by neuroimaging, but a physiologic slowing of CSF flow (and presumably CSF absorption) is present. This slowing of CSF flow can lead to poor distribution in the subarachnoid CSF for drugs with high capillary clearance, such as cytarabine, and a greater likelihood of serious CNS toxicity for a drug such as methotrexate.

Another form of regional therapy is the intraarterial administration of anticancer drugs through carotid or vertebral arteries. The advantage of this approach is an increased uptake during the first passage of drug through tumor capillaries. Increased efficacy would be expected for patients whose tumors reside within the perfusion territory of the infused artery. Contrary to what may be thought, systemic toxicity is not reduced unless the total administered dose is reduced, because the actual amount of drug taken up into the tumor is a small fraction of the injected dose. On the other hand, focal brain and retinal morbidity is increased, as was demonstrated by the clinical trials with BCNU and cisplatin. Controversial results of clinical trials do not commend this form of treatment, except under controlled experimental conditions.

Intratumoral therapy is regional therapy that is applicable for cystic tumors or postsurgical cavities with a narrow rim of surrounding tumor. Pharmacokinetic considerations implicate problems with maintenance of tumor cavity drug levels if the goal is to maintain a concentration in the cavity as a drug source for diffusion into the surrounding tumor and brain. These problems relate to conservation of mass, diffusion distances from the cavity to the outer margin of tumor, nonspecific biodegradation and binding of drug or drug products, and the need for repeat treatments. Modern clinical trials evaluating this form of regional therapy have not been published.

Another intratumoral approach uses a biodegradable drug-containing polymer that allows zero order release of drug that can diffuse into the surrounding tumor and brain. This approach, using BCNU (the Glialad wafer system) has received approval by the Food and Drug Administration for use in patients with glioblastoma multiforme at recurrence. Patient survival benefit is modest in published clinical trials.

CEREBRAL ASTROCYTOMAS

PATHOLOGY CLASSIFICATION

This section deals primarily with the classification of astrocytomas of varying degrees of aggressiveness, ranging from juvenile pilocytic astrocytoma to glioblastoma multiforme. The slower growing or less aggressive lesions are often referred to as low grade or benign and the more rapidly progressive neoplasms are referred to as high grade or malignant. With the exception of juvenile pilocytic astrocytomas, subependymomas, and the limited number of astrocytomas that can be completely resected, even benign astrocytomas are highly lethal. For instance, median 5-year survival for low-grade infiltrating astrocytomas ranges between 21% and 55% following surgery and the 10-year survival between 10% and 43%. For patients with residual tumor after surgery, irradiation increases survival from an average 30% at 5 years to 49%. Median survival for glioblastoma multiforme, on the other hand, ranges between 42 and 60 weeks (Table 43.2.15, for later studies).

| Table 43.2.15. Survival for Adult Glioblastoma Multiforme Patients with Karnofsky Performance Scores Greater Than or Equal to 60 Treated on Protocols Published Since 1990 |

<table>
<thead>
<tr>
<th>Grade</th>
<th>Survival Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>49%</td>
</tr>
<tr>
<td>II</td>
<td>21%</td>
</tr>
<tr>
<td>III</td>
<td>5%</td>
</tr>
<tr>
<td>IV</td>
<td>1%</td>
</tr>
</tbody>
</table>

Many classification systems for astrocytomas have been advanced that have advocated the presumed cell of origin, the degree of malignancy, or both. Most common classification schemas in use over the past two decades have been modifications of that developed by Ringertz. A slightly different approach was proposed by Daumas-Duport and colleagues. Their grading system assigned a point system to nuclear atypia, mitoses, endothelial proliferation, and necrosis. Grade I tumors had none of these features, grade II had one feature, grade III had two features, and grade IV had three or more features. While in their initial evaluation, this grouping led to distinct and separate median survival curves, a subsequent review of 251 cases at the Massachusetts General Hospital found no statistical difference in survival between grades II and III. Necrosis was found to be a significant predictor of short survival, in agreement with previous studies. The most recent grading system is that proposed by the World Health Organization. For practical purposes, a three-tier system is generally satisfactory for infiltrative adult astrocytomas:

- Astrocytoma (includes fibrillary, protoplasmic, gemistocytic)
- Anist (malignant) astrocytoma
- Glioblastoma multiforme (includes gliosarcoma and giant cell glioblastoma)

RATIONALE FOR SURGERY

Data from animal experiments suggest, and a large clinical experience with tumors at many sites would confirm, that maximal surgical resection improves the results of subsequent radiation therapy and chemotherapy. This principle is transferable to the treatment of astrocytomas. Gross total surgical resection was among the dominant factors favoring longer survival in patients with grade I or II astrocytomas treated at the Mayo Clinic and in patients with the more malignant astrocytomas. If one takes a different perspective and looks at the amount of tumor present on the postoperative CT scan and compares it with survival it can be shown that the two are inversely related even for comparing other variables.

A number of factors might be responsible for the improved clinical outcome when astrocytomas are aggressively resected. An assiduous resection can remove 90% of a typical astrocytoma (1-log cell-kill) and thereby decompress the brain as well as substantially reducing the tumor cell burden. In addition, a large tumor mass left in the brain can serve as a nidus for cerebral edema after radiation therapy because of the indolent removal of dead cells from the brain.

SURGICAL PRINCIPLES FOR CEREBRAL ASTROCYTOMAS

The goal of every craniotomy for a cerebral astrocytoma is gross total resection, and adequate exposure should be accomplished for this purpose, although sometimes aggressive resection proves impossible at the time of the operation. Tumors are approached through an incision in the crest of an overlying gyrus or...
through a sulcus. The selection of the entry site is aided by intraoperative ultrasound images and the frameless image-guided stereotactic system. Self-retaining retractors are placed to retract gently both sides of the cortical incision (generally approximately 3 cm in length), and then the operating microscope is brought in for the approach through the subcortical white matter to the tumor. The tumor is resected with suction, two-point coagulation forceps, grasping instruments, the CO₂ laser, or the CUSA, the resection proceeding from the inside out, so that surrounding normal white matter is disturbed minimally. The glistening peritumoral white matter is separated from the cerebral cortex with the use of a microscope as each of the tumor's margins are reached, and it is at this interface that the resection is stopped. Hemostasis is sometimes difficult but must be perfect. Hemispheric tumor cysts can be drained and, when possible, fenestrated into an adjacent ventricle to prevent reaccumulation. Tumors not amenable to resection because of their location or their diffuseness should be biopsied stereotactically. Again, there is no indication for a craniotomy when the purpose is merely to biopsy (and not resect) a tumor.

The introduction of cortical mapping procedures into brain tumor surgery has made feasible the extensive resection of tumors in functionally critical areas. By use of intraoperative cortical stimulation, motor- and speech-associated cortex can be mapped, and safe routes to deep-lying tumors and safe resection limits determined. A principal disadvantage of surgery that incorporates mapping of speech is that the patient cannot be given general anesthesia, and the surgeon must, therefore, anticipate unexpected patient movement and possibly inferior brain relaxation during the operation.

REOPERATION FOR CEREBRAL ASTROCYTOMAS

Evidence is accumulating that reoperation for resection of cerebral astrocytomas at the time of their recurrence can be efficacious. The rationale cited earlier for the aggressive initial resection of cerebral astrocytomas seems to fit equally well the prospect for resection at recurrence. This is only true, however, if there is some treatment modality (e.g., chemotherapy and brachytherapy) that the patient can receive after the reoperation, and most often there is.

Salzman proposes from experience with reoperation of all patients who were to receive further therapy for recurrence of malignant glioma that a relatively nonselective approach might be rational, given that reoperation is safe and of potential benefit despite the patient's age, performance status, tumor grade, or interval between initial surgery and recurrence. Young and coworkers argue for more rigid selection criteria when choosing candidates for reoperation on recurrent malignant gliomas. They found that patients with a Karnofsky performance score (KPS) higher than 60 and an interval between the initial surgery and recurrence of at least 6 months had the longest survival times after reoperation. Harsh and associates looked at the effect of reoperation on the subsequent high-quality survival (KPS of at least 70) of patients with recurrent malignant gliomas. Age and preoperative KPS have effects on the duration of high-quality survival in this study, with relative youth and high performance scores being advantageous. Because their data suggest that reoperation can significantly enhance the effects of chemotherapy on recurrent brain tumors, Harsh and associates would not suggest confining reoperation to young patients in excellent condition, but would suggest instead simply using these factors as guidelines in the broader therapeutic picture. Barker and his coworkers updated the experience from the same institution [University of California, San Francisco (UCSF) ] and found that while the number of patients with high quality survival after reoperation had increased, the overall survival remained poor.

In this series the KPS was the single most significant determinant for longer survival after reoperation.

RADIATION THERAPY

Astrocytoma

Differentiated or low-grade astrocytomas constitute a heterogenous group of tumors. Median survival times may vary from 1 to 12 years depending on the patient's age, performance status, and the presence or absence of tumor enhancement on neuroimaging studies. The variability in their behavior has led to uncertainties regarding their therapy and prognosis. Fortunately, randomized trials are being performed to clarify many of the issues surrounding the treatment of these tumors.

Approximately 10% to 35% of astrocytomas are amenable to total surgical resection. The local control rate for completely resected cystic cerebellar astrocytomas approaches 100%, and postoperative irradiation is not recommended. Similarly, the 5- and 10-year survival rates for patients with juvenile pilocytic astrocytomas are almost 100% after completely or radical subtotal resection and radiation. Wallner and coworkers reported 10- and 20-year progression-free survival rates of 74% and 41%, respectively, for incompletely resected and irradiated juvenile pilocytic astrocytomas. The authors had no data relative to incompletely resected and nonirradiated children with juvenile pilocytic astrocytomas who underwent subtotal resection or biopsy and irradiation survived longer than nonirradiated patients. However, the number of patients treated with surgery alone was small, and, therefore, the efficacy of radiotherapy for this tumor is uncertain. Based on these data, postoperative irradiation is not indicated for pilocytic astrocytomas when a complete or near complete resection has been performed. After subtotal resection, either immediate irradiation or close follow-up, reserving treatment for those patients with symptomatic, progressive, nonresectable tumors may be recommended.

The 5-year recurrence-free survival rates of patients with infiltrative (nonpilocytic) astrocytomas or mixed oligoastrocytomas who undergo total or radical subtotal tumor resection range from 52% to 95%. The variation in outcome may reflect prognostic differences related to age, the inclusion of patients with radical subtotal resections into retrospective analyses of operative reports to determine the completeness of resection in the era before CT and MRI studies. Because recurrences are infrequent in children with completely resected astrocytomas, postoperative irradiation is generally not recommended. The outcome of adult patients after total or radical subtotal resection, has been found in some series to be similar to that of patients undergoing less extensive surgery. Thus, in adults, postoperative irradiation has been recommended after complete resection by some authors, whereas others advise that radiation therapy be withheld until there is evidence of tumor recurrence.

Retropective reviews published between 1956 and 1990 suggested that postoperative irradiation is beneficial for incompletely resected infiltrative low-grade astrocytomas. For irradiated patients, 5-year survival rates varied from 36% and 55%, and 10-year rates ranged from 26% to 43%. In contrast, 5-year survival rates for subtotally resected, nonirradiated tumors varied from 19% to 32% and 10-year rates were approximately 10%. Most of these data precede the era of modern neuroimaging techniques. The outcome of patients diagnosed and treated in the CT/MRI era is notably better than that reported in the older literature. Median survival times in more recent series are in the range of 7.2 to 10.0 years, raising concerns over the value of the older literature in making treatment decisions today. The improved outcome appears to be related to the earlier diagnosis of tumors in neurologically intact patients who exhibit only seizures at the time of diagnosis. In addition, CT and MRI may assist in operative planning, allowing a greater percentage of patients to undergo complete resections.

The earlier diagnosis of patients with low-grade astrocytomas raised new questions regarding the timing of therapeutic intervention. Is it better to intervene early, or to wait until there is disease progression? Recht and colleagues reported 26 patients with suspected low-grade supratentorial gliomas (based on clinical and radiologic features only) who were monitored without other treatment except anticonvulsants. Of these patients, 58% subsequently required intervention (surgery alone or with radiotherapy) within a median of 28 months (range, 4 to 123 months) because of increased size of the radiographic abnormality, refractory seizures, new symptoms, or malignant transformation. When compared with 20 patients who had similar characteristics but in whom the decision was made for immediate intervention, there was no difference in the outcome of patients who received immediate or deferred treatment and no difference in the time in neoplastic transformation. Arguments for performing immediate biopsy to confirm the diagnosis and to identify patients with nonenhancing anaplastic tumors. Further, complete surgical resection may improve survival, obviate the need for irradiation, and decrease the risk of malignant transformation, the most common cause of death in low-grade astrocytoma patients.

The timing of postoperative irradiation is another area of controversy. Although it is generally agreed that patients with unfavorable astrocytomas with radiographic evidence of tumor growth, intractable seizures, progressive neurologic impairment, or malignant transformation of the tumor should undergo radiotherapy, this treatment is commonly deferred in patients with well-controlled seizures who present with asymptomatic, indolent tumors. Proponents of this approach argue that with CT and MRI, the disease is diagnosed much earlier in its natural history than in the past and that it is unclear whether early irradiation provides an outcome advantage over delayed irradiation, can delay or prevent tumor dedifferentiation, or whether radiation therapy even alters the prognosis.

This issue was clarified in a randomized trial conducted by the EORTC and British Medical Research Council Brain Tumor Working Party. Patients with low-grade astrocytomas (65%), oligodendrogliomas (25%), or mixed tumors (10%) were randomized to receive immediate postoperative irradiation to a dose of 54 Gy or no further treatment until neurologic and CT scan evidence of disease progression. Among those in the control arm, 65% of patients received subsequent radiotherapy, 19% underwent surgery, chemotherapy, or both, and the remainder received only supportive care. A preliminary analysis of the study demonstrated that although...
immediate irradiation improved the 5-year progression-free survival (44% vs. 37%, P = .02), there was no improvement in overall 5-year survival (63% vs. 66%). The outcome of patients with astrocytomas strongly correlates with the proliferative potential of the tumor as measured by bromodeoxyuridine (BUDR) and Ki67. The use of immunohistochemical and molecular markers may provide an opportunity for earlier intervention and improvement in the outcome for the prognostically more unfavorable subsets of patients.\footnote{5}

Because radiotherapy is likely to lead to unacceptable sequelae in children younger than 3 to 5 years of age, treatment in this age group is postponed for as long as possible, provided that no significant neurologic defects and no neuromaging changes indicative of rapid tumor progression are present. Management decisions are also influenced in older children with incompletely resected astrocytomas who, compared with adults, have a better prognosis, a less pronounced survival improvement with postoperative irradiation, and a greater risk of late radiation sequelae.\footnote{5}

Limited radiation fields are used in the treatment of low-grade astrocytomas. The lesion defined by CT scan is encompassed with a 2-cm margin of normal tissue, whereas the T2-weighted MRI abnormality, which tends to be larger than the CT-defined lesion is given a margin of 1 to 2 cm. Complex treatment planning should be used whenever appropriate to minimize the risk of long-term sequelae. The standard dose is 54 Gy, administered using daily fractions of 1.8 to 2.0 Gy. The dose is reduced to 50.4 Gy for children younger than 5 years of age.\footnote{10}

Two studies indicate that higher radiation doses do improve the outcome (at least 5 years) and suggest that lower doses may be preferable. In a trial conducted by the EORTC, patients were randomized to receive 45 Gy in 25 fractions or 59.4 Gy in 33 fractions. No difference in survival was observed between the two dose levels. The 5-year survival rates were 58% for 45 Gy and 59% for 59.4 Gy. Progression-free rates were also similar (47% vs. 50%). Minimal surgery, poor neurologic status, large tumors, advanced age, and unfavorable histologic features were adverse prognostic features.\footnote{7} Similarly, a combined North Central Cancer Treatment Group, RTOG, and Eastern Cooperative Oncology Group trial randomized adult patients with supratentral astrocytomas to receive 50.4 Gy in 28 fractions or 64.8 Gy in 36 fractions. As in the EORTC study, the 5-year survival rates were similar for the two dose levels studied, 73% for 50.4 Gy and 68% for 64.8 Gy (P = .57). Age 40 or older and astrocytoma-dominant histology were poor prognostic features.\footnote{5} An increase in functional sequelae\footnote{5} and radiation necrosis\footnote{5} was observed in patients treated in the high dose arms of these studies.\footnote{5}

There have been few studies evaluating combined chemotherapy and radiation therapy for low-grade astrocytomas. In a Southwest Oncology Group trial, adult patients with incompletely excised low-grade gliomas were randomized to receive radiation therapy alone or radiation therapy and CCNU. The median survival time for patients receiving supportive care alone was 14 weeks, whereas those treated with radiation therapy had a median survival time of 36 weeks (P = .001).\footnote{10} Patients with anaplastic astrocytomas and glioblastoma multiforme were treated to a dose of 60 Gy in single daily fractions of 1.8 to 2.0 Gy, five times per week. With this schedule, 25% of patients with glioblastoma multiforme and 50% of those with anaplastic astrocytoma exhibit a significant radiographic response by the completion of radiation therapy. Only 5% of patients have a complete tumor response, and a delayed response after irradiation is uncommon.\footnote{5}

Partial brain fields (also called limited field), defined by the extent of tumor on neuroradiographic studies, are used for the treatment of malignant gliomas.\footnote{The Brain Tumor Cooperative Group trial demonstrated a significant survival advantage for patients who received radiotherapy alone or with BCNU, as compared with those treated with resection and supportive care or with BCNU alone. The median survival time for patients receiving supportive care alone was 14 weeks, whereas those treated with radiation therapy had a median survival time of 36 weeks (P = .001).\footnote{10} Patients with anaplastic astrocytomas and glioblastoma multiforme were treated to a dose of 60 Gy in single daily fractions of 1.8 to 2.0 Gy, five times per week. With this schedule, 25% of patients with glioblastoma multiforme and 50% of those with anaplastic astrocytoma exhibit a significant radiographic response by the completion of radiation therapy. Only 5% of patients have a complete tumor response, and a delayed response after irradiation is uncommon.\footnote{5} The response of malignant gliomas to standard radiation therapy techniques is limited by their striking inherent radioresistance and the radiosensitivity of the surrounding normal brain tissue. Thus, research in the treatment of malignant gliomas has been directed at improving the efficacy of radiotherapy. In addition to pursuing more effective chemotherapy programs (see Chemotherapy section), areas of investigation have included the use of chemical modifiers of the radiation response, altered fractionation schemes, dose escalation with interstitial brachytherapy, radiosurgery and three-dimensional conformal radiotherapy, and the use of heavy particle irradiation.\footnote{10}

Two different classes of radiation-sensitizing agents have been investigated in malignant gliomas. The combination of the hypoxic cell radiation sensitizer, misonidazole, and radiation was compared with radiation alone in several randomized trials. No survival improvement was observed in any of the dose-fractionation or drug schedules tested.\footnote{10} In addition, two halopurine analogue, BUdR\footnote{10} and iododeoxyuridine,\footnote{10} have been tested. In a phase II study conducted by the Northern California Oncology Group, patients with malignant gliomas received BUdR in six weekly 96-hour infusions during the course of radiation therapy. This was followed by 1 year of PCV chemotherapy. The median survival times for patients with glioblastoma multiforme and anaplastic astrocytoma were 64 and 272 weeks, respectively.\footnote{5} Compared with historical controls, the survival of patients with anaplastic astrocytoma using this regimen was particularly encouraging. Based on these results, a randomized trial comparing radiotherapy alone or with BUdR plus PCV chemotherapy in patients with anaplastic astrocytoma was conducted by the RTOG, North Central Cancer Treatment Group, and Southwest Oncology Group. Enrollment into the study was discontinued before it reached its full accrual when it was estimated that there would be no difference between the two treatment arms.\footnote{10}

With conventional radiation therapy the median survival time for patients with anaplastic astrocytoma is 36 months, and the 3-year survival rate is approximately 55%.\footnote{10} In contrast, the median survival time for patients with glioblastoma multiforme is 10 months, whereas the 3-year survival rate is only 6%.\footnote{10} The response of malignant gliomas to standard radiation therapy techniques is limited by their striking inherent radioresistance and the radiosensitivity of the surrounding normal brain tissue. Thus, research in the treatment of malignant gliomas has been directed at improving the efficacy of radiotherapy. In addition to pursuing more effective chemotherapy programs (see Chemotherapy section), areas of investigation have included the use of chemical modifiers of the radiation response, altered fractionation schemes, dose escalation with interstitial brachytherapy, radiosurgery and three-dimensional conformal radiotherapy, and the use of heavy particle irradiation.\footnote{10}

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Hyperfractionated irradiation is the use of two or more treatments per day with fraction sizes smaller than conventional dose fractions to deliver a higher dose in the same overall treatment time as conventionally fractionated therapy. With hyperfractionation, tumor control probabilities should improve without increasing the risk of late sequelae. Furthermore, with a 6-hour interval between doses, there is greater probability that rapidly proliferating tumor cells will be irradiated during more radiosensitive phases of the cell cycle and become self-sensitized by redistribution. Target cells for late sequelae proliferate slowly, and, therefore, for these tissues little redistribution or self-sensitization occurs.\footnote{10}

The RTOG conducted a randomized phase II dose-escalation study in which patients were given 64.8, 72.0, 76.8, or 81.6 Gy in 1.2-Gy twice-daily fractions. Patients receiving 72 Gy had the longest median survival time, and no further improvement in outcome was observed at the highest dose levels.\footnote{10} A randomized trial comparing 72-Gy hyperfractionated irradiation with conventionally fractionated 60-Gy radiotherapy (BCNU given in both arms) was subsequently conducted by the RTOG.\footnote{10} The median survival time for patients with glioblastoma multiforme were similar (10.2 months with hyperfractionation and 11.2 months with conventional fractionation). Likewise, for patients with anaplastic astrocytoma, the median survival was 44 months with hyperfractionation and 50 months with conventional fractionation (P = .81).\footnote{10}

Another fractionation option, accelerated fractionation, attempts to reduce the overall treatment time by giving conventional sized dose fractions two or three times daily. This treatment schedule may improve the therapeutic ratio by reducing the opportunity for tumor cell repopulation during treatment, thereby increasing the probability of tumor control for a given dose level. Several trials using accelerated regimens have been conducted, but none has shown a survival benefit over conventional irradiation.\footnote{10} These studies indicated that although rapid regeneration does not appear to explain the radioresistance of malignant gliomas, the overall treatment time can be shortened. Altered fractionation schedules provide an opportunity to integrate chemosensitizers and hypoxic cell sensitizers in a novel fashion. Trials applying this approach, however, have yet to demonstrate a benefit.\footnote{10} On the other hand, the use of accelerated fractionation and other short-course fractionation schemes may be especially appropriate in patients with relatively short survival expectations.\footnote{10}

Most gliomas are localized to a single area of the brain,\footnote{5} and they should be controllable if sufficiently high radiation doses can be delivered without damaging the surrounding normal brain tissue. One approach to augmenting the radiation dose is with interstitial brachytherapy. Iodine 125 and iodine 192 sources have been
Several Phase II studies have demonstrated survival improvements in patients with glioblastoma multiforme when external irradiation is combined with brachytherapy. Gutin and coworkers evaluated brachytherapy as an adjunct to external radiation and chemotherapy in patients with newly diagnosed supratentorial malignant gliomas. Patients received involved field external irradiation to 60 Gy with concomitant hydroxyurea (300 mg/m² orally every other day) followed by an iodine 125 implant to deliver an additional minimum tumor dose of 50 to 60 Gy. Following removal of the implants, they were given PCV chemotherapy every 6 to 8 weeks for 1 year. Although the median survival time of patients with glioblastoma multiforme (22 months) compared favorably with that of historical controls, there was no apparent gain observed in performing irradiation at diagnosis in patients with anaplastic gliomas (median survival time, 39 months). Loeffler and associates reported the outcome of 35 patients with glioblastoma multiforme who underwent partial brain external irradiation (58.4 Gy in 33 fractions) followed by an additional 50 Gy given by interstitial implantation. Survival rates at 1 and 2 years were 87% and 57%, respectively, for patients receiving brachytherapy compared with 40% and 12%, respectively, for a control group matched by radiographic and patient characteristics (P > .001). Reoxygenation for brachytherapy-induced symptomatic radiation injury is required in approximately 40% of patients.

The Brain Tumor Cooperative Group compared intrastitial implantation (60 Gy at 10 Gy/d) preceding external irradiation (60.2 Gy at 1.72 Gy per fraction) and BCNU with external irradiation and BCNU alone in a randomized trial. Implanted patients experienced improvement in median survival (16 months vs. 13 months) and 18-month survival (47% vs. 32%) compared with those who did not receive brachytherapy. However, in another randomized trial, Lapierre and colleagues found no difference in outcome in patients randomized to receive external beam irradiation alone to 50 Gy (median survival, 14 months) or external beam irradiation and an iodine 125 implant delivering a minimum tumor dose of 60 Gy (13 months). A randomized trial testing the addition of interstitial microwave hyperthermia to the brachytherapy boost after external irradiation in newly diagnosed patients with glioblastoma multiforme was conducted at the UCSF. Median survival was 85 weeks versus 76 weeks and the 2-year survival was 31% versus 15%, favoring patients receiving hyperthermia compared with those treated with external beam irradiation and brachytherapy alone (P = .045 and P = .02, respectively). Brachytherapy has also been shown to improve the survival and quality of life of patients with recurrent malignant gliomas who meet the criteria of implantation.

Table 43.2-12

<table>
<thead>
<tr>
<th>Drug combination</th>
<th>Median survival</th>
<th>1-year survival</th>
<th>2-year survival</th>
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<tr>
<td>PCV</td>
<td>157 weeks</td>
<td>19%</td>
<td>10%</td>
<td>6%</td>
</tr>
<tr>
<td>BCNU</td>
<td>140 weeks</td>
<td>20%</td>
<td>10%</td>
<td>5%</td>
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</table>

Stereotactic radiosurgery has also been used to augment the dose of external beam irradiation in initial treatment of patients with malignant gliomas. Shrieve and colleagues used radiosurgery as a boost after standard external beam irradiation (54.4 Gy) in 78 patients with newly diagnosed glioblastoma multiforme. Patients with discrete, geometrically spherical lesions measuring 4 cm or less in diameter and a KPS of 70 or higher were selected for radiosurgery. The median minimum tumor dose was 12 Gy. The median survival was 20 months, and the 1- and 2-year survival rates were 88% and 36%, respectively. Similar to brachytherapy, 50% of the patients required reoperation for symptomatic radiation necrosis or recurrent tumor. Based on tumor size, geometry and functional status guidelines proposed for radiosurgery are based on 2% of patients with malignant gliomas met the criteria for radiosurgery. The median survival time for radiosurgery-eligible glioblastoma multiforme patients was 12.5 months, compared with 10.5 months for ineligible patients (P < .07). A comparison of these data with those cited previously suggests that for glioblastoma multiforme a survival advantage of approximately 7 months is conferred when radiosurgery is actually given. Unfortunately, the benefit of radiosurgery diminishes when broader selection criteria are used.

Radiosurgery may also be used to treat patients with small previously irradiated tumors. In one series the median survival time of 86 patients with recurrent glioblastoma multiforme was 10 months from the time of radiosurgery, similar to the published experience for brachytherapy at recurrence.

Three-dimensional conformal photon radiation therapy is a mode of treatment planning and delivery designed to enhance the conformation of the radiation dose to the target volume, while maximally restricting the dose delivered to the normal tissue outside the treatment volume. Conformal treatment planning techniques when applied to cerebral tumors have permitted a 30% to 50% reduction in the volume of normal brain tissue irradiated to high doses. This new approach to treatment planning may not only decrease the risk of normal tissue injury, but also allow higher than traditional radiation doses to be safely administered to patients with malignant gliomas. For instance, in a recent study at the University of Michigan, patients with glioblastoma multiforme were treated with an accelerated fractionation regimen to escalate the tumor dose to 90 cobalt gray equivalent (CGE). Twenty-three patients were treated with this approach. The median survival time was 20 months (t = 11-month improvement compared with patients with comparable risk factors treated with conventional radiotherapy) and the 2- and 3-year actuarial survival rates were 34% and 18%, respectively. Tumor regrowth, demonstrated by histologic tissue examination, occurred most commonly in areas that received 70 CGE or less, whereas tumor was found in the 90 CGE volume in only one case.

CHEMOTHERAPY

The era of controlled clinical trials for malignant astrocytomas began with the inception of the Brain Tumor Study Group in 1967. The European Organization for Research on Treatment of Cancer then established a comparable group. In addition, other national and regional cooperative groups have conducted controlled chemotherapy trials.

Table 43.2-15 summarizes some of the trials of adjuvant chemotherapy for glioblastoma. The data are disappointing in that evidence-based survival gains for adjuvant chemotherapy have not occurred over the past 25 years. Chemotherapy appears to benefit modestly those patients that are in the 25th percentile of survivors. This is reasonable, because in vitro drug-sensitivities assays suggest that approximately 60% of patients are resistant to the cytotoxic anticancer drugs used in these studies. From Table 43.2-15 it would appear that nitrosourea-based drug combinations may be modestly superior to monotherapy in that the 25% survival for BCNU is 71 weeks, whereas it is 91 to 120 weeks for drug combinations.

For anaplastic astrocytoma and other anaplastic gliomas, the benefits of combination chemotherapy appear to be greater and better accepted. The first study to open the field was the MRC study. In this study the survival of positive patients was compared to the survival of negative patients. In the positive group the median survival time was 11 months compared to 4 months in the negative group. For PCV patients with only 82 weeks for BCNU-treated patients (P = .009). Even better was the 25th percentile survival, which was greater than 7.7 years for PCV patients compared with 4.1 years for BCNU patients. Laperriere and colleagues found similar results with their combination of CCNU, procarbazine, and vincristine. The study with bromodeoxuryridine together with irradiation and then followed by PCV appears similar for anaplastic astrocytoma patients in whom the median survival is actually higher (4 years vs. 3 years), although it offers no advantage for glioblastoma patients. An additional nitrosourea-based combination, 6-thioguanine and BCNU, appears to be at least as active against anaplastic astrocytoma (and other anaplastic gliomas) with an anticipated median survival of more than 5 years.

More approaches need to be considered to improve the results cited in Table 43.2-15 and Table 43.2-16. The status of Phase II chemotherapy trials is summarized in Table 43.2-17. These studies are disappointing that response rates (progressive stable disease) do not correlate with durability of response. Table 43.2-17 shows that even though the number of patients benefitting from chemotherapy is high in some studies, nevertheless, among the response and stable tumor patients, the duration of benefit has shown only modest gains during the...
level or of the cranial nerve as it leaves the brain stem. The initial manifestations of a brain stem glioma are unilateral palsies of cranial nerves VI and VII in central, diffuse, and infiltrative or focally infiltrative with or without an exophytic; the latter carry a better prognosis. Cranial nerve involvement can be at the nuclear Tumor involvement of the brain stem is caused by, in order of decreasing frequency, astrocytoma, glioblastoma, and ependymoma. These tumors can be primarily

**CLINICAL AND PATHOLOGIC CONSIDERATIONS**

**BRAIN STEM GLIOMAS**

The use of the combination of polyamine inhibitors for anaplastic astrocytomas was somewhat encouraging, and one of the authors has spent many years in pursuit of better drug combinations with little positive gain to date. Alpha-difluoromethyl ornithine (efornithine; DFMO) has been studied alone, with methyl-bisguanylyhydrazine, with BCNU, and most recently with PCV (glioblastoma multiforme [GBM] study submitted). As a single agent, DFMO appears to have similar activity to the DFMO–methyl-bisguanylyhydrazine combination. In both instances, the median time to progression (MTP) for recurrent anaplastic gliomas achieving response and stable disease was almost 1 year. The difference in response rates (72% vs. 46%) may reflect too lenient entry requirements for the DFMO patients and a subsequent high number of patients who went off therapy before the first evaluation at 8 weeks. It has long been known that some alkylating agents such as the nitrosoureas have their DNA damage repaired by an alkyltransferase. Tumors with high alkyltransferase levels are able to repair nitrosourea-inflicted DNA damage and are thus considered resistant to the chemotherapy. This can reflect itself in decreased survival. We have conducted some uncontrolled phase II studies in an attempt to overcome tumor resistance to nitrosoureas. In one study, 6-thioguanine, dibromodulcitol, and procarbazine were given before CCNU to enhance tumor cell kill by interfering with DNA repair. The results were dramatic for the anaplastic gliomas, when 95% of patients who had failed radiation therapy responded or stabilized for an MTP of 15 months, and 25% did not fail until 33 months; 61% of glioblastoma patients with response or stable disease had an MTP of 9.3 months. Of those who failed earlier nitrosourea therapies, 38% of anaplastic glioma patients and 58% of glioblastoma patients benefited, with MTPs of 10.6 and 5.1 months, respectively. Using a modification of this protocol, we combined 6-thioguanine, procarbazine, CCNU, and hydroxyurea and found that in the anaplastic glioma group, 23% of patients had a partial response and 53% had stable disease. This included 77% of 30 patients who had not received prior chemotherapy and 76% of 17 who had undergone previous chemotherapy. The median time to disease progression was 50 weeks for patients responding who had not undergone previous chemotherapy and 25 weeks for those who had undergone previous chemotherapy. More careful controlled studies with drugs that block alkyltransferase levels are indicated, but expectations should not be too high as these early data remain discouraging.

Intravenous cisplatin and carboplatin have shown only modest activity with respect to TTP, although response and stable rates appear high. This may reflect poor tumor and adjacent brain penetration of these drugs and their inability to kill tumor cells at a distance from the main tumor mass. Compounding this pharmacokinetic disadvantage is recent experimental data in rodent tumors that show that dexamethasone can reduce cisplatin penetration into the brain adjacent to tumor where infiltrative tumor cells reside. Paclitaxel studies have shown acceptable toxicity but only modest antitumor activity in the treatment of recurrent malignant gliomas. Against recurrent anaplastic astrocytoma, Chamberlain and Kormanik found a remarkable 80% response and stabilization rate for a median of 7.5 months. Experience with paclitaxel was summarized in a review article where it was shown to have modest activity. Evaluation of paclitaxel has been complicated by accelerated plasma clearance in patients on anticonvulsants. The newest alkylating agent to be approved by the European and American regulatory authorities is temozolomide. It has been approved for anaplastic astrocytoma in the United States and also for glioblastoma multiforme in Europe. The drug has been shown to be modestly active in glioblastoma and moderately active against anaplastic astrocytoma. Temozolomide is oral, better tolerated than procarbazine by patients, and has a predictable and short nadir period. These features make it a popular choice for drug combination regimens. Currently, trials have been completed or are underway to evaluate temozolomide with interferon-α, cis-retinoic acid, BCNU, and Marinamistat to name a few trials.

Betaseron, an interferon-β, attained 50% response and stable rates in a cooperative study; however, the duration of benefit is low, with MTPs of 16 to 18 weeks. Tamoxifen, an antiestrogen with the ability to reduce protein kinase C levels and possibly interfere with angiogenesis, has taken on almost cult status as a brain tumor agent. Evaluation of paclitaxel has been complicated by accelerated plasma clearance in patients on anticonvulsants.

**Autologous bone marrow transplantation** has had few practitioners, generally because of a low rate of observed complete responses to any form of chemotherapy. Single-agent BCNU was used years ago with no definable gains over conventional dose nitrosourea therapy. Other researchers have used thiopeta and etoposide. Although neither thiopeta nor etoposide alone has shown remarkable activity against gliomas, various combinations of the three agents are being evaluated. It is currently unclear whether autologous bone marrow transplantation has a place in the management of cerebral gliomas.

**TABLE 43.2-17. Chemotherapy of Recurrent and Progressive Supratentorial Astrocytomas**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Activity</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temozolomide</td>
<td>Oral, better tolerated than procarbazine</td>
<td>Modest activity</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>Acceptable toxicity</td>
<td>Only modest antitumor activity</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>Intravenous</td>
<td>Modest activity with respect to TTP</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>Intravenous</td>
<td>Modest activity with respect to TTP</td>
</tr>
<tr>
<td>Temozolomide</td>
<td>Oral</td>
<td>Predictable and short nadir period</td>
</tr>
</tbody>
</table>

**TABLE 43.2-16. Survival for Adult Anaplastic Glioma Patients with Karnofsky Performance Scores Greater Than or Equal to 60 Treated on Protocols Published Since 1990**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Survival Rate</th>
<th>Median Time to Progression (MTP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response or stable</td>
<td>72%</td>
<td>1 year</td>
</tr>
<tr>
<td>Partial response</td>
<td>53%</td>
<td>5 months</td>
</tr>
<tr>
<td>No response</td>
<td>25%</td>
<td>33 months</td>
</tr>
</tbody>
</table>

**TABLE 43.2-17. Chemotherapy of Recurrent and Progressive Supratentorial Astrocytomas**

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**Autologous bone marrow transplantation** has had few practitioners, generally because of a low rate of observed complete responses to any form of chemotherapy. Single-agent BCNU was used years ago with no definable gains over conventional dose nitrosourea therapy. Other researchers have used thiopeta and etoposide. Although neither thiopeta nor etoposide alone has shown remarkable activity against gliomas, various combinations of the three agents are being evaluated. It is currently unclear whether autologous bone marrow transplantation has a place in the management of cerebral gliomas.
approximately 90% of patients. Cranial nerve involvement is usually followed by long tract signs, such as hemiplegia, unilateral limb ataxia, ataxia of gait, paraplegia, hemisensory syndromes, gaze disorders, and, occasionally, hiccups. Less commonly, long tract signs precede the cranial nerve abnormalities; this is more likely with confined central intrinsic lesions.

If the tumor is well differentiated or an anaplastic astrocytoma, it is likely to involve the midbrain and produce hydrocephalus, vomiting, drowsiness, and cerebellar signs; if the tumor is a glioblastoma, it more often involves the medulla. Children with glioblastoma characteristically have a rapidly progressive course and are likely to have deficits in cranial nerves VI, VII, IX, X, and dysarthria, personality change, and head tilt. Unlike expansive posterior fossa tumors, headache, vomiting, and papillodema occur late.

As a group, the prognosis is poor, with 5-year survival rates varying between 0% and 38% and a median survival of less than 1 year in most series. 321,322,323 Certain patients do better than others. For instance, patients with type II tumors do better than those with infiltrative type I tumors. Moderately anaplastic ependymic tumors do better than higher grade anaplastic tumors. Landolfi and others reported a small series of 19 brain stem glioma patients between 17 and 70 years of age with a median survival of 14 months. In their group were 2 tectal, 4 cervicomedullary, and 13 pontine gliomas; three pontine gliomas had an ephpticentric component. Surprisingly, only 12 were treated initially with radiotherapy and 3 were treated at recurrence.

SURGERY

Modern imaging of the CNS with MRI has improved the capability for definitive diagnosis of brain stem tumors. Lesions previously difficult to distinguish from brain stem glioma (e.g., divus tumors, foramen magnum meningiomas, multiple sclerosis, occult arteriovenous malformations, and brain stem abscesses) usually can now be excluded. Still, biopsy of brain stem gliomas for confirmation of the diagnosis and for definite tumor grading should be performed when possible. Biopsy of brain stem gliomas accessible through the floor of the fourth ventricle or presenting on the lateral surface of the pons can be accomplished safely, and associated symptomatic cysts can be drained. Attempt at complete resection of these tumors is contraindicated. Stereotactic needle biopsy of brain stem gliomas using CT and MRI guidance seems to have a low complication rate, so this method is being used increasingly, with the consequence that fewer patients are being treated without a tissue diagnosis. 336

RADIATION THERAPY

Radiation therapy, the primary treatment for brain stem tumors, improves survival and can stabilize or reverse neurologic dysfunction in 75% to 90% of patients. 338 Traditionally, brain stem gliomas have been treated with doses of 54 Gy, administered in daily fractions of 1.8 Gy, through parallel opposed portals with the tumor dose calculated at the midline on the central axis of the beam. According to a multiinstitutional survey by Freeman and Suisca, 339 the 1-, 2-, and 5-year survival rates of children treated with conventional radiation therapy techniques were 50%, 29%, and 23%, respectively.

Because of the relatively poor results obtained with conventional radiation dose-fractionation schedules and the observation that these tumors recur locally, hyperfractionated irradiation, designed to deliver higher tumor doses, was evaluated by several investigators. 340,341,342 Early reports demonstrating consistent, although modest, improvements in outcome have been observed when patients treated with hyperfractionation regimens of up to doses of 70.2 to 72.0 Gy (1.0 to 1.17 Gy twice daily) were compared with historical control patients treated with conventional or low-dose hyperfractionated irradiation. 343,344 There was no outcome improvement when the dose was increased to 75.6 Gy and 78 Gy, 345 but considerable morbidity was observed at these higher dose levels. 346 The Pediatric Oncology Group (POG) conducted a dose-escalation trial of 66.0, 70.2, and 75.6 Gy in twice-daily fractions of 1.1, 1.17, and 1.26 Gy, respectively, in children with diffuse brain stem gliomas. No difference in the median time to progression (7 to 8 months) and median survival time (10 months) between the three dose schedules was found. The highest dose was associated with steroid dependency in 62% of patients and a 45% incidence of intraleseional necrosis. 347 Thus, the 70.2-Gy dose level was considered to have the best therapeutic ratio, and was tested by POG in a randomized trial comparing hyperfractionated radiotherapy with 54 Gy given with conventional fractionation. Children in both treatment arms received cisplatin during radiotherapy. 348 Hyperfractionation did not improve event-free survival (P = .96) or overall survival (P = .85) over that of the conventional dose fractionation regimen. For patients receiving the conventional fractionation regimen, the median time to progression was 6 months, the median survival time was 8.5 months, and the 1- and 2-year survival rates were 30.9% and 7.1%, respectively. For those receiving the hyperfractionated irradiation regimen, the median time to progression was 5 months, the median survival time was 8 months, and the 1- and 2-year survival rates were 27% and 6.7%, respectively. 349

Based on the results of the POG trial, the current standard for the treatment of diffuse intrinsic brain stem gliomas consists of conventionally fractionated radiotherapy given to a dose of 54.0 to 59.4 Gy. The availability of MRI and three-dimensional conformal radiotherapy treatment planning approaches offers improved target definition and allows the high-dose radiation volume to be better tailored to the contour of the lesion. The irradiated volume includes a margin of normal tissue of approximately 2 cm around the tumor. Smaller margins may be used for more focal lesions. 350 Dorsal exophytic and cervicomedullary tumors that are completely resected do not require routine postoperative irradiation. 351

CHEMOTHERAPY

As with cerebral astrocytomas, chemotherapy is primarily nitrosourea based. 352 The use of chemotherapy, adjuvant to irradiation, has been infrequent. The Children's Cancer Group (CCG) randomly compared radiotherapy with radiation therapy followed by CCNU, PCV, and prednisone. 353 The mean survival was 11 months, and there was no difference between the two groups. In another trial, 5-fluorouracil and CCNU before radiation therapy and hydroxyurea and mitoxantrone during radiation therapy were evaluated; in that study, TTP (32 weeks) and survival (44 weeks) were not better than the initial CCG study. A pilot study evaluating oral etoposide during and after radiotherapy was closed to accrual by the CCG; analysis of the data has not yet been reported.

For recurrent or progressive brain stem gliomas, few therapies have been evaluated. 354 Some benefit has been demonstrated, but the extent of benefit has not been well established. In one study, 5-fluorouracil, CCNU, hydroxyurea, and 6-mercaptopurine were used to treat children and adults with recurrent or progressive brain stem gliomas. 355 Sixty-nine percent of 13 patients had response or stabilization, with a relapse-free survival of 26 weeks; the overall survival was 27 weeks. This finding is somewhat worse than would be expected for supratentorial gliomas. These authors conducted a phase II study of recurrent malignant gliomas with a combination of BCNU and DFMO. In that study, three of five patients benefited, with the three continuing to benefit at 1 to 3 years. 356 Although not curative, some of these chemotherapeutic leads should be exploited.

CEREBELLAR ASTROCYTOMAS

CLINICAL AND PATHOLOGIC CONSIDERATIONS

Astrocytomas arising in the cerebellum are considered separately, because their prognosis is consistently better than astrocytomas arising in the cerebrum or brain stem. These tumors, which occur most often during the first two decades of life, arise in the vermis or more laterally in a cerebellar hemisphere. Cerebellar astrocytomas usually are well circumscribed; they can be cystic, solid, or an admixture of polycistic and solid. Histologically, most astrocytomas are low grade and lack features commonly associated with anaplasia; many are pilocytic in appearance and, histologically, some are juvenile pilocytic astrocytomas. In a series on 451 children reported from the Hospital for Sick Children of Toronto, cerebellar astrocytomas accounted for 25% of all posterior fossa tumors; 99 of 111 (89%) of the cerebellar astrocytomas were low grade, with nearly all verminian in origin. 357 Approximately 75% of these tumors are located only in the cerebellum, with the remainder involving the brain stem as well. 358

Because most of these tumors arise in the vermis, the clinical presentation is similar to medulloblastoma, with truncal ataxia, headache, nausea and vomiting, and in the young, split cranial sutures and head enlargement from increased intracranial pressure.

SURGERY

Cystic cerebellar astrocytomas are exposed through a posterior fossa craniectomy. The cyst is located with ultrasound, cannulated, and then exposed by an incision through the cerebellar folia. Self-retaining retractors are placed into the cyst and then, with the aid of the operating microscope, the cyst is examined and the vascular,
firm mural module identified, dissected, and removed. The nonneoplastic cyst wall is not excised.

Solid cerebellar astrocytomas are separated carefully from surrounding cerebellar white matter, again using the improved visualization offered by the operating microscope. The texture and appearance of the tumor are usually distinct and the separation from white matter usually is not difficult, so the only barrier to complete resection becomes deep penetration of the tumor into the dentate nucleus, cerebellar peduncles, or brain stem.

RADIATION THERAPY

See the discussion in the section on Cerebral Astrocytomas: the same principles apply. Completely resected cerebellar astrocytomas do not require postoperative radiation therapy. The remainder receive total doses of 50 to 60 Gy, depending on the histologic features and the age of the patient.

CHEMOTHERAPY

Because surgery alone or surgery and irradiation is often curative, chemotherapy has been limited to cases of recurrence or if the tumor is histologically highly anaplastic. For these tumors, the authors’ approach has been to use nitrosourea-based therapies.

Chemotherapy adjuvant to surgery and radiation has not been commonly advocated for these tumors. The authors’ experience is anecdotal (Table 43.2-18), but appears consistent with chemotherapy results for cerebral gliomas. All patients received a nitrosourea; however, the chemotherapy combinations varied depending on which program was being used at the time for supratentorial gliomas. For patients at recurrence, chemotherapy provided palliation, with a median TTP of 24 weeks and 25% of patients surviving longer than 32 months. As with the adjuvant chemotherapy patients, all were treated on a protocol being used at the time for cerebral gliomas. Among these patients, 5 of 18 (28%) developed metastases to the leptomeninges (three of five) or intracranial extracerebellar parenchymal sites (two of five). All leptomeningeal disseminations occurred in conjunction with locoregional recurrences. In many patients, therefore, combined systemic and intraventricular therapy may be needed for tumor control.

TABLE 43.2-18. Chemotherapy for Recurrent Cerebellar Astrocytomas

Other chemotherapy agents have been used on an ad hoc basis to treat recurrent cerebellar gliomas primarily in children. One report cited the palliative potential of oral etoposide in the treatment of juvenile pilocytic astrocytoma with 50% (6 of 12) of responding and stable patients achieving a median 7 months’ progression-free survival. It is safe to assume that temozolomide will be used alone and in combination for recurrent cerebellar gliomas in the future.

OPTIC, CHIASMAL, AND HYPOTHALAMIC GLIOMAS

CLINICAL AND PATHOLOGIC CONSIDERATIONS

Nearly all gliomas of the optic nerve and chiasm are discovered in patients before the age of 20 years, and most before the age of 10 years. In some patients there is a family kindred of neurofibromatosis. Lewis and colleagues prospectively evaluated 217 patients with neurofibromatosis and found that gliomas along the anterior visual pathway occurred in 15% and were occasionally bilateral. Sixty-seven percent of these tumors were not suspected clinically or obvious on ophthalmologic examination.

With respect to tumor location, Housenpian and associates reported that 25% involved one optic nerve, 73% the chiasm, and 3% the optic tracts. In another series, 25% involved the chiasm alone, 33% the chiasm and hypothalamus, and 42% the chiasm and optic nerves or tracts. Clinically, these tumors produce loss of visual acuity (70%), strabismus and nystagmus (33%), visual field impairment (bitemporal hemianopsia, 8%), developmental delay, macrocephaly, ataxia, hemiparesis, proposis, and precocious puberty. Funduscopic evaluation demonstrates a range of findings from normal optic disks through venous engorgement to disk pallor due to atrophy. Tumors involving the chiasm often grow to involve the hypothalamus, causing a dienecephalic syndrome that is characterized by emaciation (especially in children between 3 months and 2 years of age), motor overactivity, and euphoria.

Pathologically, these tumors range from primarily plioid and stelleate astrocytomes (most common), with or without oligodendroglioma, through the gamut of malignant astrocytomas to glioblastoma multiforme (rare). Typically, optic gliomas appear as fusiform expansions of any part of the nerve; they tend to bridge through the optic foramen and expand as dumbbell-shaped tumors within the skull. The nerve can be infiltrated by tumor originating in the chiasm, the walls of the third ventricle, or the hypothalamus. The tumors found in patients with neurofibromatosis often affect a single optic nerve and are grossly normal in appearance, although infiltrated by tumor and surrounded by a fibrous stroma.

Diagnosis is best made by MRI scan and should use images in the sagittal plane. The CT scan is satisfactory for diagnosis but is not as sensitive or descriptive as the MRI scan. The MRI also shows hypothalamic involvement more clearly.

SURGERY

Unilateral tumors of the optic nerve (as opposed to the chiasm) should be resected, particularly when there is profound vision loss or when proposis is disfiguring. A transcranial approach to the orbit is preferred, permitting complete resection of the tumor-infiltrated nerve from the chiasm to the globe and sparing the globe for an optimal cosmetic effect. The involved nerve is inspected through a unilateral craniotomy, and the nerve is sectioned at the chiasm. The orbit is then unroofed, and the optic nerve’s attachment to the globe is exposed and divided, allowing the tumor to be removed.

Biopsy of smaller tumors of the optic nerve, tumors involving the nerve and chiasm, and tumors of the chiasm alone must sometimes be done when radiographic studies cannot exclude meningioma, cranioopharyngioma, or other diagnoses definitively. Subtotal resection of such tumors, particularly if exophytic, can sometimes be done for decompression before radiation or chemotherapy. Resection of the chiasm with resultant blindness is never indicated.

RADIATION THERAPY

Treatment of optic nerve and chiasmal gliomas is controversial, because some patients with incomplete surgical resections have been followed for 10 to 20 years without progression. The literature suggests, however, that untreated optic gliomas, especially those involving the chiasm or extending into the hypothalamus or optic tracts, progress locally or are fatal in 75% of patients. Tenny and coworkers found that only 21% of patients who were followed after biopsy or exploration survived compared with 64% of those who received radiation therapy. In general, optic nerve gliomas have a better prognosis than those involving the chiasm, and tumors confined to the anterior chiasm have a better outcome than those that involve adjacent structures (posterior chiasmal tumors).
Routine postoperative irradiation is not indicated for most gliomas confined to the optic nerve. In contrast, radiation therapy can prevent tumor progression, improve disease-free survival, and stabilize or improve vision in patients with chiasmal lesions. Wong and colleagues reported that 6 of 27 (22%) chiasmal gliomas that did not receive radiation therapy progressed locally, whereas 9 of 20 (45%) that received radiation therapy failed. Three of these recurrences were seen in the adults with extremely aggressive, nonresponsive tumors. Further, 87% of the irradiated patients who received a dose of 50 to 55 Gy were controlled compared with 55% of those who received 45 Gy or less. Radiation therapy significantly improved the relapse-free survival but not the overall survival. Tao and colleagues concluded that radiotherapy was effective in the majority of patients with progressive chiasmal gliomas. The 10-year progression-free and overall survival rates after radiotherapy were 89% and 100%, respectively. Stabilization or improvement in vision was achieved in 81% of the evaluable treated patients. The authors drew attention to the fact that the median time for a radiographic response of 50% or more was 62 months. Hypothalaminism was common after radiotherapy, underscoring the need for life-long endocrine follow-up with appropriate replacement after treatment. Jenkin and colleagues found that for posterior optic gliomas irradiation was more effective in preventing subsequent relapse than subtotal resection alone. The 10-year relapse-free survival rate was 70% for irradiated patients, compared with 41% for those who did not receive primary radiotherapy (P < 0.03). However, there was no difference in overall survival between these two patient groups due largely to the efficacy of radiation therapy in previously nonirradiated relapsed patients. Erkal and colleagues also reported a progression-free survival rate of 77% in children irradiated for optic nerve and chiasmal hypothalamic gliomas. The prognosis for patients with optic pathway tumors and chiasmal hypothalamic lesions was similar. In a series collected from the literature, local control was achieved in 154 of 189 (81%) irradiated anterior chiasmal tumors, whereas 92 of 145 (64%) posterior tumors were controlled. Vision improved in 61 of 210 (29%) evaluable patients and remained stable in 118 of 210 (56%) patients. For hypothalamic tumors, radiation therapy produced radiographic improvement in 11 of 24 (46%) with a median progression-free survival of 70 months compared with 30 months for those patients who did not receive radiation therapy.

Although some clinicians advocate deferring irradiation in asymptomatic patients or in those with lesser visual disturbance until there are signs of disease progression, others recommend that radiation therapy be given early in the course of the disease to minimize the risk of visual deterioration. The radiotherapy portals are tailored to the tumor volume and designed to avoid irradiation of the lens of the eye. Three-dimensional conformal, intensity-modulated radiotherapy and stereotactic radiotherapy techniques are used to minimize the dose to adjacent structures. A dose of 50 to 54 Gy in daily 1.8-Gy fractions is recommended.

CHEMOTHERAPY

The published chemotherapeutic trials for this group of patients represent small series. Chemotherapy has been used successfully to delay the initiation of radiation therapy in young children. Packer and associates treated 24 children (median age, 1.6 years) with a combination of daunomycin and vincristine. Six of the cases involved the chiasm, eight involved the chiasm and hypothalamus, and ten involved the chiasm and visual pathways. At a median follow-up period of 4.3 years, 38% of patients had disease that progressed.

Petronio and coworkers reported on 19 infants or children with chiasmatropic and hypothalamic gliomas treated with chemotherapy after diagnosis. Of the 12 tumors in which a biopsy was obtained, there were 7 juvenile pilocytic astrocytomas, 2 astrocytomas, 2 anaplastic astrocytomas, and 1 subependymal giant cell astrocytoma. The children were between 3 months and 15 years of age when treated. The chemotherapy included one of three regimens: one with daunomycin and vincristine; one with the combination of BCNU, 5-fluorouracil, hydroxyurea, and 6-mercaptopurine; and 15 with the combination of 6-thioguanine, procarbazine, dibromodulcitol, CCNU, and vincristine (BTMC-422 protocol). Fifteen of 18 initially treated with chemotherapy responded or stabilized; the median follow-up period exceeded 1.5 years (range, 1.4 months to 5.8 years). Rodriguez and colleagues reported a series of 33 patients with hypothalamic gliomas, some of whom were included in the Petronio series. Chemotherapy at presentation or recurrence was beneficial in 10 of 16 (62%) patients.

In another study, Prados and colleagues treated 42 children with low-grade gliomas who had either progressive neurologic symptoms or radiographic tumor enlargement with a combination of 6-thioguanine, procarbazine, dibromodulcitol, CCNU, and vincristine (TPDCCV). In that group were 33 patients with hypothalamic chiasmatropic gliomas. Multivariate analysis demonstrated no difference between this group and those with low-grade gliomas elsewhere; for the entire group of 42 patients the median progression-free survival was 2.5 years and the 5-year median survival was 78%, reflecting the value of secondary chemotherapeutic regimens and radiotherapy.

OLIGODENDROGLIOMAS

CLINICAL AND PATHOLOGIC CONSIDERATIONS

Oligodendrogliomas have a relatively flat peak incidence between 25 and 49 years. Although they are most common (80%) in the cerebral hemispheres, approximately 15% occur in the third or lateral ventricles or protrude into a ventricle from the thalamus. Grossly, these tumors are often well demarcated, and in 20% they are cystic. They have a 10% likelihood of spreading through the CSF pathways. Like astrocytomas, they vary in malignancy. Attempts have been made to grade oligodendrogliomas on an A through D scale; however, grades A through C vary little, and B and C are virtually identical with respect to survival such that these subdivisions seem unnecessary; a designation of differentiated or highly anaplastic may be sufficient. These tumors often have both astrocytic or ependymal elements seen at biopsy; such tumors are called mixed gliomas.

Clinically, these tumors present in the typical fashion of hemispheric astrocytomas. However, two features distinguish them from astrocytomas: the antecedent history, averaging 7 to 8 years, tends to be longer, and seizures are more common, occurring in 70% to 90% of patients by the time of diagnosis. Provisional diagnosis may be made by MRI or CT neuroimaging, but histologic confirmation is necessary and almost always possible. Approximately 50% of oligodendrogliomas have scattered calcification, usually related to intrinsic blood vessels, which are evident by CT scan.

At recurrence or autopsy, approximately 60% of oligodendroglioma and most mixed oligoastrocytoma patients demonstrate histologically an anaplastic astrocytoma or glioblastoma multiforme. This may be a common origin of both types of tumors to the O6A progenitor cell.

SURGERY

The surgical resection of hemispheric oligodendrogliomas follows the same principles as discussed earlier for cerebral astrocytomas, with gross total removal being the goal when this is consistent with good neurologic outcome. The margins of oligodendrogliomas can appear to be more distinct than those of astrocytomas, but generally they are infiltrative. Because of this, surgical cure remains unlikely; but the indolent course of these tumors allows for a long progression-free interval after an aggressive resection in some patients. Oligodendrogliomas often recur in the previous operative site. Under these circumstances, recurrence may be advisable, particularly when followed by chemotherapy.

RADIATION THERAPY

The infrequency of oligodendrogliomas and their variable and often long prediagnosis and posttreatment natural history make it difficult to evaluate the effect of radiation therapy in patients with differentiated oligodendrogliomas. Data from Mirk and colleagues indicate that the behavior of these tumors may be more unpredictable and their prognosis less favorable than previously believed. The problems in evaluating retrospective reports for oligodendrogliomas are similar to those previously discussed for low-grade astrocytomas. Conclusions regarding the value of radiotherapy are contradictory, and the lack of randomized trials precludes the latter conclusions. Five-year survival rates for irradiated patients range from 36% and 83% and 10-year rates vary from 30% to 46%. In contrast, 5-year survival rates for subtotally resected, nonirradiated tumors range from 25% to 55% and 10-year rates vary from 13% to 25%. Some authors recommend immediate postoperative irradiation for patients with incompletely resected lesions, whereas others have been unable to show that postoperative irradiation is of benefit.

It has also been suggested that radiation therapy be deferred until there is evidence of tumor progression or recurrence or that only patients with anaplastic tumors or mixed oligoastrocytomas should receive treatment. Most retrospective studies comparing surgery alone with surgery and radiation therapy do not contain analyses to ensure that the distribution of patients in the two treatment groups are comparable with respect to prognostic variables such as the age, completeness of resection, neurologic signs and symptoms, and histopathologic features. Furthermore, treatment selection criteria are either not stated or unknown. It is likely that many retrospective studies in which the pathology material was not independently reviewed contain patients with both differentiated and anaplastic oligodendrogliomas. This has been considered to be an important distinction because on average patients with low-grade oligodendrogliomas survive 9 years, as compared with 2.2 years for those with high-grade
Ependymomas can be classified in various ways. Ependymomas are either differentiated (ependymoma or myxopapillary ependymoma) and, therefore, low-grade or, parenchymal, arising from ependymal rests. Most of the intraventricular tumors arise in the lateral ventricles, and fewer (25%) occur in the third ventricle. 40% are supratentorial.

For anaplastic oligodendrogliomas, Kyritsis and coworkers found a median 1.3 years relapse-free survival after chemotherapy (mostly PCV therapy). For recurrent oligoastrocytoma, the median relapse-free survival is 1 to 1.2 years. To test the efficacy of this chemotherapy regimen in newly diagnosed patients, the RTOG is coordinating an intergroup randomized trial that compares neoadjuvant intensive PCV chemotherapy followed by radiation therapy with radiation therapy alone.

CLINICAL AND PATHOLOGIC CONSIDERATIONS

Ependymoma tumors arise from cells of ependymal lineage and, therefore, have a propensity for occurring in the obliterated central canal of the spinal cord, the filum terminale, and white matter adjacent to a ventricular surface (usually a highly angulated surface). Sixty percent of intracranial ependymomas are infratentorial, and 40% are supratentorial. Of infratentorial sites, the fourth ventricle is the most common site. Extension into the subarachnoid space occurs in 50% of these cases, and encasement of the medulla and upper cervical cord can occur. Of supratentorial ependymomas, 50% are primarily intraventricular, and the remainder are parenchymal, arising from ependymal rests. Most of the intraventricular tumors arise in the lateral ventricles, and fewer (25%) occur in the third ventricle.

Ependymomas can be classified in various ways. Ependymomas are either differentiated (ependymoma or myxopapillary ependymoma) and, therefore, low-grade or,
less commonly, they are anaplastic and higher grade and more likely to disseminate through the CSF pathways.

Clinical presentations are dependent on the location of tumor. Intraventricular tumors often cause increased intracranial pressure and hydrocephalus. As a result, headache, nausea and vomiting, papilledema, ataxia, and vertigo are found in most patients at presentation. Focal neurologic signs and symptoms are more often seen with extraventricular supratentorial ependymomas.

Either MRI or CT scanning is sufficient to make the anatomic diagnosis before surgery. The presence of calcium in a fourth ventricular tumor is highly suggestive but not diagnostic of an ependymoma. Surgical exploration and biopsy are essential for the selection of appropriate treatment. For anaplastic ependymomas, staging meiography and examination of the CSF for cytologic evidence of malignancy are essential.

The inclusion of ependymoblastomas, which are known for their propensity to disseminate throughout the CNS, tends to overestimate the risk of seeding. In a literature review, Vanuytsel and Brada found that the overall incidence of spinal seeding was 6.9%. It was 1.6% for supratentorial tumors, 9.7% for infratentorial lesions, 5.4% for high-grade tumors, and 4.5% for low-grade lesions. No patient with high-grade supratentorial lesions developed spinal seeding, whereas 15.7% of those with high-grade infratentorial tumors developed spinal dissemination. For low-grade tumors, 2.7% of patients with supratentorial lesions developed seeding compared with 5.5% for those with infratentorial lesions. The incidence of spinal seeding was related directly to local tumor control, regardless of tumor grade. The incidence of spinal dissemination was 3.3% in locally controlled patients and 9.5% in those with uncontrolled primary lesions (P < 0.05).

SURGERY

Approximately one-half of hemispheric ependymomas arise from the wall of the lateral ventricle, and one-half appear to be intraparenchymal, arising perhaps from remote fetal ependymal cell rests. Hemispheric ependymomas tend to be cystic and, even when not, are often well circumscribed from surrounding brain, allowing gross total resection. A wide craniotomy permits a transcortical exposure of the tumor through a cortical incision placed to avoid injury to vital brain tissue. The tumor is removed using the operating microscope, and every effort is made to minimize bleeding into the ventricular cavity. At the end of the resection, the ventricular system is gently irrigated free of blood and blood clots to prevent mechanical obstruction to CSF flow, to prevent the blockage of the CSF absorptive bed (arachnoid granulations), and to reduce the irritation of bloody CSF to the brain.

Ependymomas arising from the floor of the fourth ventricle are approached through a wide bilateral suboccipital craniectomy and laminectomy of C-1. The tumor is exposed by retracting the cerebellar tonsils laterally and splitting the inferior aspect of the vermis, although often a tongue of tumor is visible over the dorsal aspect of the medulla and upper cervical spinal cord before the tonsils are retracted. The dorsal convexity of the tumor comes into view as the cerebellar vermis is divided, and its attachment to the floor of the fourth ventricle can then be exposed progressively and evaluated. Firm attachment precludes a complete resection, as does infiltration of the tumor into the cranial nerves of the cerebellopontine angle through the foramen of Luschka. Tumor is removed to the extent possible using illumination and magnification afforded by the operating microscope.

There would appear to be a relation between residual ependymoma left by the surgeon and a poorer outcome after radiation therapy. In ependymomas, as in most of the gliomas, a maximal surgical resection should be carried out when possible.

RADIATION THERAPY

It is well established that postoperative irradiation improves the survival of patients with intracranial ependymomas, and 5-year survival rates with doses of 45 Gy or more range from 60% to 87%. Tumor grade has been considered to be the most important determinant of tumor behavior and prognosis. The 5-year survival for patients with low-grade tumors ranges from 60% to 80%, whereas for anaplastic ependymomas it is only 10% to 47%. Most series fail to distinguish patients with malignant ependymomas from those with ependymoblastomas that are classified as primitive neuroectodermal tumors and have an especially poor prognosis.

Analysis of these data when these lesions are excluded suggested that tumor grade may have less prognostic value.

The amount of normal CNS tissues to include in the treatment volume and the need for prophyllactic irradiation to the entire craniospinal axis are major areas of controversy. The differences in opinion are based on the potential for ependymomas to spread into the ventricular system and to disseminate into the spinal subarachnoid space. In their literature review, Vanuytsel and Brada found that risk of seeding was independent of whether prophylactic spinal irradiation was given.

For high-grade lesions, spinal dissemination occurred in 9.4% of patients receiving craniospinal irradiation and in 6.7% of those treated with local radiation therapy only. Similarly, for low-grade tumors, spinal seeding occurred in 9.3% after craniospinal irradiation, whereas 2.2% developed seeding without prophylactic treatment.

The treatment volumes recommended for low-grade supratentorial ependymomas vary from generous local fields to fields encompassing the whole brain, whereas for low-grade infratentorial tumors they include local fields, the whole brain with cervical spine extension, and the craniospinal axis. Wallner and coworkers reviewed the outcome of 20 patients with supratentorial and infratentorial low-grade ependymomas treated with partial or whole brain irradiation after surgery; only 1 in 16 patients, who was eventually found to have a local recurrence, developed spinal dissemination. The 5- and 10-year survival rates for those who received more than 45 Gy (approximately 50 Gy in most instances) were 67% and 57%, respectively. As nearly all recurrences were limited to the original primary tumor site, it was concluded that treatment of the whole brain was unnecessary. Based on this series and data from others (P < 0.001), and the greater precision in determining tumor extent currently available through high-quality diagnostic imaging, low-grade supratentorial ependymomas are treated using partial brain fields with a dose of at least 54 Gy. Spinal MRI and CSF evaluation are not obtained unless there is evidence of ventricular involvement or signs of subarachnoid metastases. Low-grade infratentorial ependymomas are also treated with limited fields. The craniospinal axis is irradiated only if pretreatment CSF cytology studies reveal malignant cells or if radiographic studies show evidence of tumor spread.

Many authors recommend inclusion of the entire craniospinal axis in the treatment of anaplastic ependymomas, the entire craniospinal axis should be treated, although some suggest that whole brain irradiation with an additional boost for high-grade supratentorial lesions located away from the CSF pathways, if that is the case with no evidence of leptomeningeal spread. A dose of 54 Gy is given to the primary tumor site and 36 Gy to the remainder of the axis. If spread within the brain is demonstrated, the entire brain receives 54 Gy. Spinal imaging studies are routinely performed, and any area of gross involvement is boosted to 50 Gy. However, despite the apparent superiority of craniospinal irradiation in some series, local recurrence is the primary pattern of failure with high-grade ependymomas, and subarachnoid seeding is uncommon in the absence of local recurrence. Furthermore, the patterns of failure are similar in patients treated with whole brain fields or with craniospinal irradiation. The presence of residual tumor and the potential for metastases, such as in patients with local recurrence, do not preclude additional craniospinal treatment. In a series of 28 patients with anaplastic ependymomas, twelve patients received craniospinal irradiation, 2 were treated to the whole brain, and 14 received limited treatment to limited fields. The actuarial 5- and 10-year survival rates were 56% and 38%, respectively. All 19 patients who failed radiotherapy had relapses at the primary site, and one of these also developed subarachnoid dissemination. A benefit from craniospinal irradiation could not be demonstrated. Based on these data and the cited factors, craniospinal irradiation is generally not recommended for patients with anaplastic (high-grade) ependymomas unless evidence of leptomeningeal spread is pathologically or radiographically documented. Others, however, suggest that prophylactic craniospinal irradiation be reserved for those with infratentorial high-grade lesions.

Because the inability to eradicate the primary tumor remains the single most important factor leading to treatment failure, clinical trials are examining more aggressive local therapies to improve local tumor control, both in low- and high-grade ependymomas. These include the use of boosts with stereotactic radiotherapy or conformal radiotherapy techniques as well as hyperfractionated dose schedules. There is no evidence thus far that the addition of chemotherapy to radiotherapy improves the outcome.

CHEMOTHERAPY

Because ependymomas are uncommon tumors and before MRI these tumors were difficult to assess, there are few chemotherapeutic trials. For instance, the only trial for initial treatment of anaplastic ependymomas is one the authors started in 1984. It combined craniospinal axis irradiation with oral hydroxyurea followed by six courses of polydrug chemotherapy TPCDC. Since 1984 17 consecutive children and adults were treated. At publication 11 of 17 patients had failed with an MTP of 141 weeks; the median follow-up for the eight who had not died was 469 weeks, whereas nine patients who died had a median survival of 183 weeks.
stable disease rates of 75% to 78% and MTP of 13 to 16 months.\textsuperscript{264} Results are somewhat better than those achieved for anaplastic astrocytomas. With a variety of drug combinations the best response plus stable disease rate was 82% with an MTP of 21 months for TPDCV.

### TABLE 43.2-20. Chemotherapy for Recurrent Ependymoma and Anaplastic Ependymomas

Goldwein and colleagues retrospectively analyzed 16 recurrent ependymoma patients treated with a variety of agents alone and in combination (VCR, cisplatin, CCNU, procarbazine, VP-16, and ifosfamide).\textsuperscript{267} Approximately 20% of patient trials led to a partial response or stable disease (more common 7:1), for an approximate median of 6 to 10 months.

Gaynon and associates of the CCG used carboplatin every 4 weeks and found a response and stable disease rate of 28% (4 in 14) with a duration of 6+, 17+, 12, and 15 months.\textsuperscript{266} Those who did not receive prior cisplatin were more likely to respond to carboplatin. Bertolone and coworkers evaluated cisplatin and found 6 of 8 (75%) benefiting, with an MTP of 3.8 months.\textsuperscript{163} Ettinger and colleagues, also of the CCG, used dacarbazine on a 5-day schedule every 3 weeks in 12 children with recurrent or metastatic disease. One response more than 35 months was reported.\textsuperscript{265}

If the 87 patients cited in the studies presented in Table 43.2-20 are weighted for the number of patients in each trial, the mean TTP was 16 months.

### MENINGIOMAS

#### CLINICAL AND PATHOLOGIC CONSIDERATIONS

Meningiomas arise from arachnoidal cells in the meninges, especially in areas of the arachnoid villi. In some series, meningiomas constitute 39% of primary CNS tumors.\textsuperscript{24} The most frequent locations of these tumors are along the sagittal sinus and over the cerebral convexity. Table 43.2-21 summarizes the frequency of these tumors according to location.\textsuperscript{268} Meningiomas are extraaxial, intracranial (and sometimes spinal) tumors that produce symptoms and signs through compression of adjacent brain tissue and cranial nerves. They often also produce hyperostosis. Table 43.2-22 summarizes the symptoms and signs associated with these tumors.

### TABLE 43.2-21. Sites of Predilections of Meningiomas within the Intracranial Regions

<table>
<thead>
<tr>
<th>Site</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meningioma</td>
<td>65</td>
</tr>
<tr>
<td>Glioma</td>
<td>33</td>
</tr>
<tr>
<td>Metastasis</td>
<td>36</td>
</tr>
<tr>
<td>Secondary brain tumor</td>
<td>26</td>
</tr>
<tr>
<td>Cerebral artery</td>
<td>10</td>
</tr>
<tr>
<td>Extremitity</td>
<td>8</td>
</tr>
<tr>
<td>Spinal</td>
<td>4</td>
</tr>
<tr>
<td>Skull</td>
<td>2</td>
</tr>
<tr>
<td>Other tumors</td>
<td>1</td>
</tr>
<tr>
<td>Nerve</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
</tr>
</tbody>
</table>

### TABLE 43.2-22. Neurologic Findings Associated with Meningiomas as a Function of Their Location

<table>
<thead>
<tr>
<th>Site</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meningioma</td>
<td>Numbness, parasthesias, cranial nerve palsies, bone erosion, hemorrhage, \textit{in situ} meningioma</td>
</tr>
<tr>
<td>Glioma</td>
<td>Numbness, parasthesias, cranial nerve palsies, bone erosion, hemorrhage, \textit{in situ} meningioma</td>
</tr>
<tr>
<td>Metastasis</td>
<td>Numbness, parasthesias, cranial nerve palsies, bone erosion, hemorrhage, \textit{in situ} meningioma</td>
</tr>
<tr>
<td>Secondary brain tumor</td>
<td>Numbness, parasthesias, cranial nerve palsies, bone erosion, hemorrhage, \textit{in situ} meningioma</td>
</tr>
<tr>
<td>Cerebral artery</td>
<td>Numbness, parasthesias, cranial nerve palsies, bone erosion, hemorrhage, \textit{in situ} meningioma</td>
</tr>
<tr>
<td>Extremitity</td>
<td>Numbness, parasthesias, cranial nerve palsies, bone erosion, hemorrhage, \textit{in situ} meningioma</td>
</tr>
<tr>
<td>Spinal</td>
<td>Numbness, parasthesias, cranial nerve palsies, bone erosion, hemorrhage, \textit{in situ} meningioma</td>
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<tr>
<td>Extremitity</td>
<td>Numbness, parasthesias, cranial nerve palsies, bone erosion, hemorrhage, \textit{in situ} meningioma</td>
</tr>
</tbody>
</table>

### SURGERY

The perception that meningiomas are surgically resectable gives these tumors an undeserved reputation of benignity. Although meningiomas usually are well circumscribed and do not invade adjacent brain, they can occur virtually anywhere in the CNS, and access is sometimes only by deep retraction. In addition, these tumors may be extremely vascular and can surround important structures such as cranial nerves and major arteries at the skull base. Such characteristics can preclude a smooth operation, and a total removal is commonly not possible. Simpson reported on a large series of surgically resected meningiomas and documented that even when there was a perceived total resection, the recurrence rate was 9%.\textsuperscript{270} A more modern series from Massachusetts General Hospital shows that a total resection is followed by 7% recurrence rate at 5 years, 20% at 10 years, and 32% at 15 years.\textsuperscript{271}

Since many meningiomas are surgically resectable, the neurosurgeon is usually more favorably disposed toward operating on them than another glioma. The neurosurgeon's zeal must be tempered, however, with an understanding of the risks of removing a meningioma in a particular location and an understanding of the
effect of this meningioma on the well-being of the patient, because these tumors are often exceedingly slow growing and the patients are often elderly. When surgery is undertaken in an elderly patient, partial removal is sometimes adequate.

Preoperative Planning

The preoperative preparation of the patient, surgical planning, and intraoperative anesthetic management are as described in the earlier Surgery section. However, the planning of surgery for meningiomas must be extremely assiduous, because a detailed knowledge of surgical anatomy is necessary in these tumors. A preoperative angioagram to assess overall tumor vascularity and to identify arterial feeders is often important. In many instances, the angioagram procedure is combined with embolization of the tumor's blood supply. The angioagram is done within 24 to 96 hours of the operative procedure, so that alternative vascular routes to the tumor do not have time to develop.

Surgical Principles

Those feeding arteries that could not be occluded by embolization are addressed first at the operation, if they are accessible. These arteries are meningeal and cerebral in origin. The tumor is resected from subtracting normal brain progressively as the tumor bulk is reduced by the use of the CUSA or, for extremely vascular tumors, the cutting loop of the electrocoagulation unit or the CO₂ laser. Meningiomas at individual sites pose special surgical problems.

At the cerebral vertex, a large bone flap is made around the tumor, a dural incision circumscribes the tumor, and the dura attached to the tumor is used to retract the tumor from the brain as microdissection frees the adhesions between the tumor and surrounding brain.

Parasagittal meningiomas abut the midline; difficulties in resection are related to critical draining veins, to involvement of the sagittal sinus with tumor, and to the occasionally massive overlying bony erosion or hyperostosis or both. A patent sagittal sinus cannot be transected for a complete tumor removal except in its anterior one-third, so a careful study of the preoperative arteriogram looking for the patency of the sinus and for the position of the draining veins in the region is critical. Some clinicians advocate opening the sagittal sinus for removal of tumor that has grown through its wall, and others advocate resecting and grafting the involved sagittal sinus wall. In the authors' opinion, these dangerous maneuvers are not usually indicated, because recurrence-free survivors after subtotal resection of these lesions are extended, and because the tumor may grow to occlude the sinus completely, thereby making complete resection possible later with a lesser risk to life.

Falx meningiomas do not involve the sagittal sinus but occupy the falx below the sinus, often becoming bilateral. Major complications of resection of falx meningiomas relate to interruption of draining veins and consequent cerebral edema and venous infarction.

Olfactory groove meningiomas grow extremely large before their neurologic sequelae lead to their discovery. Surgery is carried out through a large frontal bone flap based low on the forehead. The broad sylvian base of the tumor is attacked first so that its blood supply can be interrupted. The tumor's bulk is then reduced by internal coring and dissection, with attention to protection of the optic nerves, carotid artery, and anterior cerebral arteries on the tumor's posterior aspect.

Tuberose sellea meningiomas are smaller at presentation because of their proximity to the optic apparatus. Attention to the safety of the optic apparatus and the anterior cerebral and carotid arteries is equally critical.

The approach to sphenoid ridge meningiomas varies according to whether they occupy the outer, middle, or inner third of the sphenoid bone. Outer third tumors can be a problem purely of tumor mass, purely of massive temporal hypopertusos from en plaque tumor invading bone, or a combination of both. When it is present, the tumor mass insinuates itself in the sylvian tissue, and its removal through a frontotemporal craniotomy is complicated by the tumor's adherence (on its medial aspect) to sylvian veins. Surgical cure is not possible. Middle third tumors grow into both the frontal and temporal fossa in a globular fashion. The approach is through a frontotemporal craniotomy, with the base of the tumor approached first to eliminate the blood supply. Surgical cure is likely. Inner third tumors arise from the anterior clinoic process and compress the optic nerve and encase the carotid and middle cerebral arteries. In addition, medial sphenoid ridge meningiomas can grow diffusely into the cavernous sinus and optic canals. Only in those tumors s in which the tumor presents early because of optic nerve compression is total removal feasible, with the surgeon stopping when the risk of the surgery exceeds potential benefits.

Tentorial meningiomas arise from the broad surface or free edge of the tentorium and are approached under the temporal lobe or under the occipital lobe, depending on their placement. In all instances, the principle of removal is incision of the tentorium around the tumor and gradual bulk reduction and separation of the tumor from surrounding brain. Venous sinuses and critical draining veins, particularly the vein of Labbe, must be protected.

Cerebellopontine angle meningiomas arise from the petrous bone and if small and dorsolaterally situated are exposed through a posterior fossa craniectomy by resecting the cerebellum medially. More ventrally situated tumors arising at the junction of the petrous bone and the clivus or from the clivus itself are exposed through a combined approach above and below the tentorium, which allows a better way to medially and more generous exposure with less brain retraction. Posterior fossa meningiomas may engulf critical brain vessels and cranial nerves and may be characterized by extreme adherence to the brain stem, so attempts at complete removal must proceed cautiously. In younger patients, particularly, these tumors should be completely resected during the first attempt if possible as subsequent operations are complicated by scar, with obliteration of surgical planes and increased adherence to the brain stem.

Radiation Therapy

The need for adjunctive radiation therapy is determined by the extent of surgical resection and the histopathologic features of the tumor (benign vs. malignant). The risk of recurrence for completely resected benign meningiomas is small, and postoperative irradiation is not usually recommended. In contrast, the risk of relapse after subtotal resection ranges from 33% to 60% at 5 years to more than 90% at 15 years. Several reports provide evidence that postoperative irradiation prolongs the interval to recurrence, prevents tumor regrowth in some patients, and improves the survival of patients with incompletely resected meningiomas. Barbano and associates compared the outcome of 54 patients who were treated with subtotal resection and radiation therapy with a group of 30 patients who underwent subtotal resection alone. Sixty percent of the nonirradiated patients developed recurrence, whereas 32% of the irradiated patients recurred. The median time to recurrence was 10.4 years for the irradiated patients compared with 5.5 years for the nonirradiated group (P < .05). Irradiated patients had a more favorable outcome than nonirradiated patients, despite the fact that they more frequently had tumors located in surgically unfavorable sites. This series was recently updated by Goldsmith and colleagues, who reported the results of 140 patients (117 benign and 23 malignant) treated at UCSF with subtotal resection and postoperative irradiation. The median tumor dose was 54 Gy. For patients with benign meningiomas, the 5- and 10-year progression-free survival rates were 89% and 77%, respectively. Patients who received at least 52 Gy had a 20-year progression-free survival of more than 90%. The 5-year progression-free survival of patients treated after 1980 was 98%, compared with 77% of those treated before 1980. This improvement was attributed to the availability of CT scanning and MRI for tumor localization and treatment planning.

A multivariate analysis identified that for benign meningiomas, improved progression-free survival was not related to tumor size but was associated with younger age (P = .01) and treatment after 1980 with 1980 with innovative technologies (P = .002). Condra and coworkers found that at 15 years 70% of their patients relapsed after subtotal excision alone, whereas only 13% of those treated with subtotal excision and postoperative irradiation recurred (P = .001). The 15-year cause-specific survival of patients treated with combined therapy compared with 51% for nonirradiated patients (P = .003). For patients undergoing complete resection, 24% relapsed after 15 years, and the 15-year cause-specific survival was 88%. The actuarial 5-, 10-, and 15-year relapse-free survival rates for patients undergoing subtotal resection and irradiation reported by Griswold and colleagues were 78%, 67%, and 56%, respectively. These results and those of Goldsmith and coworkers compare favorably with the relapse-free survival rates of 83%, 45%, and 9% reported by Minnamon and associates for incompletely resected, nonirradiated patients.

The size of the residual meningioma affects the outcome of radiotherapy. Connell and colleagues showed that for tumors of 5 cm or larger, the 5-year progression-free survival rate was 40%, significantly less than the 93% that observed for smaller tumors. Among patients irradiated for unresectable tumors and in those with residual disease, the volume of visible tumor on imaging studies rarely decreases by more than 15% and often only after many years.

It is controversial whether patients should be treated with radiation therapy after their initial subtotal resection or when signs of disease progression appear. Some clinicians have found that patients with benign meningiomas do equally well with either approach; others suggest that initial postoperative irradiation is preferable, because recurrence is more likely to develop on outcome, and many patients who recur after initial subtotal excision alone may not be salvaged by subsequent treatment. Postoperative irradiation often is deferred in elderly patients and in those in poor medical condition until there is evidence of symptomatic
progression. When a surgical resection is not feasible, radiation therapy may relieve symptoms and substantially decrease the rate of tumor progression.

Malignant meningiomas behave in a more aggressive manner than their benign counterparts. Chan and Thompson found that the median survival of six patients treated with surgery alone was only 7.2 months, compared with 5.1 years for 12 patients treated with surgery and postoperative irradiation. Six of the nine patients with malignant histology reported by Graheil and coworkers died within 5 years. Goldsmith and colleagues reported a 5-year progression-free survival of 45% for 23 patients treated by subtotal resection and irradiation. The recurrence rate among 53 patients with malignant meningiomas collected from six series in the literature was 49%. The recurrence rates were 33% for patients treated with complete resection alone, 12% for those undergoing complete resection and radiation therapy, 55% for patients treated by subtotal resection and irradiation, and 100% for those treated by subtotal resection alone. These data support the recommendation that all patients with atypical and malignant meningiomas should be offered postoperative irradiation, regardless of the extent of resection.

For benign meningiomas, the planning target volume consists of the residual tumor with a 1 to 2 cm margin of normal tissue, defined by CT scan or MRI and modified by the neurosurgeon's description of the site of residual disease. Extensive tumors of the base of the skull and malignant meningiomas require more generous margins. The preparative tumor volume is used for planning completely resected malignant lesions. A dose of 54 Gy in daily fractions of 1.8 to 2.0 Gy is recommended for benign meningiomas, whereas the dose is increased to 60 Gy for atypical and malignant tumors. Complex three-dimensional conformal treatment planning and delivery techniques and intensity modulated radiotherapy are used to restrict the dose to normal tissues.

Radiosurgery is another option for the treatment of meningiomas. Kondziolka and colleagues reported that 93% of their patients treated with radiosurgery and followed for 5 to 10 years required no further therapy for their tumors. Nearly 65% of patients treated by Hakim and coworkers were controlled with a median follow-up time of 22.9 months. Complications, including cranial neuropathies, transient neurologic deficits, radiation necrosis, and malignant edema, have been reported 6% to 42% of radiosurgically treated patients. Complications have been observed most frequently in patients with large or deep-seated tumors and those treated with high single doses. These data suggest that treatment with radiosurgery should be limited to small lesions, whereas fractionated radiotherapy may be preferable for other subsets of tumors. Although tumor control rates for small meningiomas appear promising, several more years of patient accrual and follow-up will be required to fully evaluate the efficacy of radiosurgery in comparison with surgery and conventional radiotherapy.

CHEMOTHERAPY

There is currently no defined role for chemotherapy for newly diagnosed and nonirradiated meningiomas. Chemotherapy has been used for the most intransigent recurrences. For patients with histologically malignant meningiomas or recurrent, surgically inaccessible, more differentiated meningiomas, the situation is only slightly different. Because of the potentially lethal consequences of these two situations, the authors have been treating with aggressive surgery, focal irradiation, and chemotherapy.

The authors have evaluated primarily sarcoma regimens such as the combinations of cyclophosphamide, doxorubicin, and vincristine (VCR) (nine patients); dacarbazine (DTIC) and doxorubicin (five patients); and high-dose ifosfamide with mesna (two patients). Little objective activity was noted for the first, one in five responses in the second, and one in two in the third. Grunberg and colleagues reported on the use of mifepristone, an antiprogesterone, in 14 patients with recurrent meningiomas; 5 in 14 showed objective response after 6 to 12 months of daily oral therapy. A randomized trial for incompletely resected meningiomas is active through Southwest Oncology Group to better determine the efficacy of mifepristone (RU-486).

Kaba and colleagues reported on six patients with either a recurrent malignant meningioma or an unrespectable meningioma who were treated with interferon-α at a dosage of 4 μIU/m²/d, 5 days per week. Five of six patients exhibited positive response to treatment with stabilization of the size of the tumor in four patients and slight regression in one for 6 to 14 months. A larger study has been opened at the University of Texas M. D. Anderson Cancer Center.

Lastly, there are preliminary data suggesting that hydroxyurea may provide treatment in patients with recurrent and inrecurrent meningiomas.

PRIMITIVE NEUROEPITHELIAL TUMORS

CLINICAL AND PATHOLOGIC CONSIDERATIONS

The treatment of primitive neuroepithelial tumors is controversial and complex. Much of the controversy is based on the failure to understand that there are multiple entities included within this pathologic diagnosis. Controversy surrounds the classification of these tumors. Primitive cells that remain undifferentiated or exhibit varying degrees of neuronal or glial differentiation, or both, are the hallmark of these tumors. Conceptually, these tumors can be viewed as developmentally aberrant brain cells. Therefore, primitive neuroepithelial tumors can be divided into the following classification schema: medulloepithelioma, neuroblastoma, spongioblastoma, ependymoblastoma, pineoblastoma, and medulloblastoma. With the exception of medulloblastoma, primitive neuroepithelial tumors are rare.

It has been proposed that all neoplasms showing primitive poorly differentiated neuroepithelial cells be called primitive neuroectodermal tumors, regardless of location or cell type. Because of the infrequency of these tumors and the controversy surrounding an all-inclusive classification schema currently, it is best to refer to each histotype separately.

Clinically, however, these tumors share some common and disquieting features. Primarily, they are proliferative and malignant tumors that tend to spread throughout the neuraxis like medulloblastoma. As a result, a complete evaluation of the CNS, including contrast-enhanced CT scans of the entire brain, CSF cytology, and metrizamide myelography, must be performed before the initiation of treatment.

SURGERY

The initial therapy for primitive neuroectodermal tumors is surgical bulk reduction whenever feasible. Surgical principles are the same as those for cerebral astrocytoma described earlier.

RADIATION THERAPY

There is general consensus that patients with primitive neuroectodermal tumors should receive postoperative irradiation. Although radiation therapy appears to improve survival time, the outcome is generally poor, and most patients develop local or regional recurrences. Because of their propensity to spread throughout the subarachnoid space, primitive neuroectodermal tumors are treated with craniospinal axis irradiation. The primary tumor is given 54 to 56 Gy and the remainder of the axis receives 36 Gy. The dose is reduced in very young children. Chemotherapy is usually a part of the treatment program. Primitive neuroectodermal tumors are less radiosensitive than medulloblastomas. Whereas in some series 1-year survival rates are as low as 10%, others report 5-year survival rates of 20% to 25%. The disparity in outcome data reflects the heterogeneity of malignancies that are classified under the term of primitive neuroectodermal tumors. For example, in a series of 14 patients reported by Gaffney and coworkers the 3-year survival rate was 29%. None of the patients with tumors containing more than 90% undifferentiated elements were alive at 3 years, whereas 60% of those with less primitive tumors survived 3 years. In another study, Meikleoff and colleagues reported on 30 patients with CNS primitive neuroectodermal tumors other than medulloblastoma treated with gross tumor resection (16 of 30) who were considered good risk who had a 37% 3-year survival. In a more recent series, Paulino and Melian reported a 5-year survival rate of 47% in a small group of patients treated for supratentorial primitive neuroectodermal tumors.

Cerebral neuroblastomas are biologically distinct from other primitive neuroectodermal tumors. They tend to be less malignant, have a better outcome, and are less likely to disseminate throughout the craniospinal axis. These tumors may present as a cystic lesion with a peripheral nodule or as a solid mass, and their morphologic appearance is related to prognosis. Berger and colleagues found that 7 of the 11 patients treated with local irradiation to an average of 52 Gy were alive with no evidence of tumor progression. Of the six patients with cystic tumors, none had recurrent disease, whereas four of the five patients with solid tumors had recurrences. The only patient with a solid lesion who did not have a recurrence received adjuvant chemotherapy. Although subarachnoid dissemination is found in autopsied cases, this pattern of spread does not represent a significant clinical problem. Thus, localized cerebral neuroblastomas are treated with involved field irradiation to 54 Gy. The craniospinal axis is included only if there is evidence of tumor dissemination beyond the site of origin by imaging studies or CSF cytology.
CHEMOTHERAPY
Because primitive neuroectodermal tumors are an uncommon type of tumor, there are no controlled chemotherapy trials. Reports of isolated cases and small series indicate that drugs active against medulloblastoma have activity in primitive neuroectodermal tumors (see Medulloblastoma Chemotherapy section, later in this chapter).

MEDULLOBLASTOMA

CLINICAL AND PATHOLOGIC CONSIDERATIONS

Medulloblastoma appears more similar to the primitive neuroectodermal tumors of childhood than to the gliomas. Although the cell of origin of these tumors is controversial, it is probable that medulloblastoma takes its origin from germinative neuroepithelial cells in the roof of the fourth ventricle. Consistent with its embryonal nature is the fact that the peak incidence occurs in the first decade of life; 50% to 60% of medulloblastomas occur in the first decade, with a peak between 5 and 9 years. A second but lesser peak occurs between 20 and 30 years. The typical location for childhood medulloblastoma is in the cerebellum, mostly in the midline and posterior vermis (Fig. 43.2-5); many encroach on the cisterna magna and the fourth ventricle. In adolescents and adults, there is an increasing tendency for tumors to be laterally placed in the cerebellar hemispheres. Regardless of where in the cerebellum they occur, the tendency for metastatic spread (within craniospinal intradural axis) of medulloblastoma is relatively high. At presentation, as many as 30% of patients have positive cytology or myelographic evidence of spinal metastasis. Extra-CNS metastasis is less common and occurs in fewer than 5% of patients; most metastases are to long bones. Extra-CNS metastasis is less common and occurs in fewer than 5% of patients; most metastases are to long bones.

The thinned cerebellar vermis is progressively incised in the midline until the dorsum of the tumor is exposed. The tumor is usually soft and moderately vascular and attached to the floor of the fourth ventricle is separated from the tumor by a cottonoid pledget. The pledget is advanced to protect the floor of the fourth ventricle as the tumor is resected. After the dura is opened, the cerebellar tonsils are retracted laterally, and it is in the foramen of Magendie that the purplish-gray tumor usually is first seen. The floor is divided, and the tumor is removed. The occipital burr hole is commonly placed at surgery, before the posterior fossa exposure is done, to allow cannulation of the ventricles for drainage of CSF to lower the intracranial pressure.

The overall disease-free 5-year survival for medulloblastoma is approximately 50%. However, the extent of disease at initial diagnosis defines risk. When risk factors are considered, survival is altered dramatically. Poor risk is defined as less than a 75% resection (probably greater than 1 cm residual); invasion of the brain stem (less clearly established); metastasis to the spinal cord, cerebrum, and leptomeninges or seeding of the cerebellum; positive CSF cytology 2 weeks after surgery; and age younger than 4 years. Of the poor risk factors, two need explanation. Resection of less than 75% is an imprecise measure of remaining tumor; CT and MRI measurement of residual tumor volume would be better. However, in most patients, if the surgeon can remove more than 75% of tumor, the resection is usually a gross total resection. Poor risk associated with age 4 years and younger may relate more to the restricted irradiation to the developing CNS and its negative effect on tumor control. Most radiation therapists do not treat with full doses of craniospinal irradiation at 4 years of age.

The disease-free survival of poor-risk patients with craniospinal irradiation with or without chemotherapy is approximately 25% to 30%. Good-risk patients, on the other hand, have 5-year disease-free survivals of 66% to 70%.

At relapse, the major site of first recurrence is the posterior fossa in more than 50% of patients, the frontal lobe in nearly 20%, bone in 10% to 15%, and other cerebral and suprasellar regions in 10% to 15%.

The incidence of systemic metastasis varies between 10% and 30%, although the 10% incidence is most similar to the authors' experience. Most extra-CNS metastases are to long bones and ribs, with lymph nodes being a distant second site. In the series by Park and associates and Lowery and colleagues, the median time to the development of extra-CNS metastasis was 10 to 12 months; in the authors' more recent study, it was 18 months. In the Park study, 17% of ventriculoperitoneal-shunted patients developed systemic metastases, whereas only 4% in unshunted patients did so. In Lowery's series, 30% of patients developed systemic metastases, and none had been shunted previously. These authors' experience is that, except in patients with rampant disease, they did not find an association between ventriculocisternal or ventriculoperitoneal shunting, with or without an in-line filter, and systemic metastases. Bone metastases can occur as the only evidence of recurrence in unshunted patients years after their initial presentation with CNS disease.

SURGERY

Although hydrocephalus associated with medulloblastoma obstructing the fourth ventricle can be relieved with a presection CSF shunt, it is more usual to defer shunting and control increased intracranial pressure with corticosteroids. In as many as 60% of patients, aggressive resection of the tumor relieves hydrocephalus. An occipital burr hole is commonly placed at surgery, before the posterior fossa exposure is done, to allow cannulation of the ventricles for drainage of CSF to lower the increased intracranial pressure so that the dura can be opened safely.

Surgery for medulloblastoma is carried out in the prone or the sitting position. The prone position is preferred, especially in children. The incision and bony exposure are usually in the midline, but a paramedian incision and unilateral bony removal are done when the tumor is limited to one hemisphere, particularly in adults. The more commonly used midline craniectomy extends down through the foramen magnum, and a laminectomy of C-1 (and rarely, C-2) is performed to decompress the brain stem (less clearly established); metastasis to the spinal cord, cerebrum, and leptomeninges or seeding of the cerebellum; positive CSF cytology 2 weeks after surgery; and age younger than 4 years. Of the poor risk factors, two need explanation. Resection of less than 75% is an imprecise measure of remaining tumor; CT and MRI measurement of residual tumor volume would be better. However, in most patients, if the surgeon can remove more than 75% of tumor, the resection is usually a gross total resection. Poor risk associated with age 4 years and younger may relate more to the restricted irradiation to the developing CNS and its negative effect on tumor control. Most radiation therapists do not treat with full doses of craniospinal irradiation at 4 years of age.

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RADIATION THERAPY

Medulloblastomas commonly infiltrate the subarachnoid space and have a striking propensity to spread throughout the CSF. As many as 25% to 30% of patients have clinically unsuspected cytologic and radiographic evidence of CNS dissemination at the time of diagnosis, and for this reason, radiation therapy is directed to the entire craniospinal axis. Doses of 54 to 59 Gy to the primary tumor site and 35 to 36 Gy to the remainder of the craniospinal axis are generally recommended. These doses usually are reduced by approximately 10 Gy for children younger than 2 or 3 years of age. Five-year survival rates in more recent series range from 50% to 65% or higher. The prognosis is affected by local tumor extent, completeness of surgical resection, presence of CSF dissemination, and age at diagnosis. Survival and patterns of relapse in adults with medulloblastoma are similar to those reported for children. Although medulloblastoma is considered to be one of the most radiosensitive tumors of the CNS, local recurrence remains the primary cause of failure.

Although modern radiation therapy techniques have greatly improved the prognosis for patients with medulloblastoma, the maximum benefit that can be achieved with conventional radiation therapy has probably been reached. Adjunctive chemotherapy programs are being pursued actively to further improve the outcome. Randomized trials have been conducted by the International Society of Pediatric Oncology (SIOP) and the CCG and POG. Each study compared radiation therapy plus chemotherapy with radiation therapy alone. The International Society of Pediatric Oncology study used a regimen of weekly VCR during radiation therapy followed by eight courses of VCR and CCNU, cycled every 6 weeks. Patients in the CCG study received similar chemotherapy plus prednisone. Neither trial demonstrated an overall improvement in outcome with the addition of chemotherapy. The 5-year disease-free survival rates in the CCG and International Society of Pediatric Oncology studies were 59% and 55%, respectively, for radiation therapy plus chemotherapy, and 50% and 43%, respectively, for radiation therapy alone. Chemotherapy did, however, appear to benefit certain patients with more advanced stages of disease, including those having only partial or subtotal tumor excision, those with brainstem involvement, and those with advanced T (T3 and T4) and M (M1 to M3) stages. Based on these findings, patients with medulloblastoma have been separated into low-stage or good-risk and high-stage or poor-risk subgroups, and different study questions are being examined in each group.

Clinical studies in good-risk patients have been directed at decreasing treatment-related morbidity, including neuroprotective dysfunction, impaired growth of the spine, and hypothalamic-pituitary dysfunction, by reducing the dose of prophylactic irradiation to areas remote from the primary tumor site. A randomized trial conducted by CCG and POG, which compared 23.4 Gy with the standard 36 Gy craniospinal prophylactic dose in good-risk patients, demonstrated an excessive number of overall treatment failures and isolated neuraxis recurrences in the low-dose arm. In a pilot study conducted by the CCG, the survival rates of patients treated with a combination of low-dose craniospinal axis irradiation and chemotherapy in the form of VCR, CCNU, and cisplatin were found to compare favorably with those in studies of full-dose radiotherapy alone or conventional radiation therapy and chemotherapy.

Studies are also being directed at improving local tumor control. Wara and colleagues used a hyperfractionation schedule (1.0 Gy twice a day) to treat the craniospinal axis to 30 Gy and to boost the posterior fossa to 72 Gy. Poor-risk patients also received chemotherapy. An excess of failures occurred outside the primary site in good-risk patients, and there was no improvement in survival over that observed with conventional regimens in either risk group.

CMEHOTHERAPY

Medulloblastomas are responsive to a variety of antineoplastic agents, including VCR, nitrosoureas, procarbazine, dibromodulcitol, cyclophosphamide, methotrexate, and various drug combinations. Table 43.2-24 summarizes some of the drug combinations that have been used for recurrent or progressive CNS medulloblastoma. It is not possible to compare the durability of these responses, because some reports pool the primitive neuroectodermal tumor patients with medulloblastoma, whereas others do not provide individual lengths of response, an MTP, or Kaplan-Meier curves. This is unfortunate, because those studies suggest an MTP range of 10 to 19 months among the better single agent and combination chemotherapy programs. It is clear, however, that better treatments are needed for recurrent and progressive disease. Whether well-founded or not, current emphasis appears to be on drug combinations such as cyclophosphamide, teniposide, and cisplatin or CCNU, VCR, and cisplatin. Whether these approaches provide long-standing benefit or short-term gain awaits more careful adjuvant studies. Problems with drug delivery of these agents to the CNS and inherent drug resistance may compromise long-term benefits and ultimate cure.
chemotherapy with vincristine weekly during radiotherapy followed by eight 6-week cycles of cisplatin, lomustine, and vincristine. To be eligible, children had to have a subtotal resection, evidence of metastatic disease, brain stem involvement, or all three. Of the 63 eligible patients, 42 had brain stem involvement, 15 had metastatic disease at the time of diagnosis, and 19 had a subtotal resection. Progression-free survival for the entire group at 5 years was 85%. Progression-free survival was not adversely affected by younger age at diagnosis, brain stem involvement, or subtotal resection. Patients with metastatic disease at the time of diagnosis had a 5-year progression-free survival rate of 67%, as compared with 90% for those children with localized disease at the time of diagnosis (P = .037).

The authors conducted a randomized trial of preradiation procarbazine and hydroxyurea during reduced craniospinal irradiation. In that study they found that after 2 weeks of oral procarbazine and irradiation with hydroxyurea, reducing the craniospinal radiation dose to 25 Gy to the spinal axis and 25 to 35 Gy to the whole brain was not detrimental with respect to disease-free survival or recurrence patterns in good- and poor-risk patients. When this group was compared with historical controls treated with conventional doses, Halberg and associates found no increase in tumor recurrence in the brain or spinal axis. The 5-year disease-free survival rates for good- and poor-risk patients were 77% and 39%, respectively. In both groups, 70% of recurrences were in the posterior fossa only.

A randomized postoperative trial with postirradiation nitrogen mustard, PCV, procarbazine, and prednisone versus radiation therapy alone for newly diagnosed medulloblastoma found that patients treated with irradiation plus nitrogen mustard, PCV, procarbazine, and prednisone had a statistically significant increase in overall survival rate at 5 years compared with patients treated with radiation therapy alone (74% vs. 56%; P = .06).

The authors presented preliminary results of a study that opened in 1984. In that study, they gave combination chemotherapy with TPDCV before and for as many as eight cycles every 6 weeks after radiation therapy in children and adults with high-risk (more than 25% residual tumor, brain stem invasion, positive CSF cytology, positive myelogram) medulloblastoma. Radiation therapy consisted of 54 Gy to the posterior fossa and 24 Gy to the craniospinal axis. Of the 30 patients evaluable (25 children and 5 adults), there were 17 failures, a 5-year disease-free survival of 30%, and an MTP of 4.3 years. Seven pineoblastomas were also treated, with four failures to date, an MTP of 1.6 years, and 38% 5-year disease-free survival.

Hyperfractionated radiation therapy regimens, although potentially less damaging to the CNS, may lead to more bone marrow damage and less tolerance to systemic chemotherapy. One approach that is being evaluated consists of aggressive preradiation therapy chemotherapy. The advantage of this approach is that it unequivocally defines response; the disadvantage is that some drugs may fail to achieve adequate levels in patients with poor risk due to CSF spread of tumor cells.

Eight-in-1-day therapy has also been evaluated before radiation therapy. Of 21 eligible medulloblastoma patients who received at least two courses of chemotherapy, 12 (57%) responded (including three complete responses and three partial responses). The MTP for the combined medulloblastoma primitive neuroectodermal tumor group was 2 years.

In another study, Kovnar and associates treated 11 newly diagnosed children with measurable residual disease and characteristics indicative of poor prognosis with preradiation therapy cisplatin and etoposide. There were 2 of 11 complete responses, 8 partial responses, and 1 stable disease determined radiographically in the series.

For extracranial metastases, the best results appear with aggressive combination chemotherapy. In this situation, issues of CNS drug delivery are not important, and many drugs are active. Initially, these authors evaluated the combination of cyclophosphamide, doxorubicin, and VCR; seven patients treated responded for a median duration of 17 months, and two continue at 34 and 62 months without evidence of disease. Other combinations with good activity are cyclophosphamide and VCR, dacarbazine, and cyclophosphamide; cisplatin, cyclophosphamide, and VP-16; and DTIC and doxorubicin.

PINEAL REGION TUMORS

CLINICAL AND PATHOLOGIC CONSIDERATIONS

The pineal gland is located in the posterior portion of the third ventricle. Tumors in this region are rare, accounting for fewer than 1% of intracranial tumors, although in children they constitute 3% to 8% of intracranial tumors. The peak incidence of germ cell tumors is the second decade, and few present after the third decade. Table 43.2-25 summarizes the types of tumors found in the pineal region and their tumor markers. In all series, germinomas are the most common histology, accounting for 33% to 50% of pineal tumors (the higher frequencies are seen in Japan). Gliomas are the second most common, accounting for approximately 25% of pineal tumors; astrocytomas are the most common of the glial neoplasms arising at this site.

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<th>Classification of Pineal Region Tumors and Tumor Markers</th>
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<td>Neurologic signs and symptoms are caused by obstructive hydrocephalus and involvement of ocular pathways. Major symptoms are headache, nausea and vomiting, lethargy, and diplopia. Signs are primarily ocular but can include ataxia and hemiparesis. The major ocular manifestation is paralysis of conjugate upward gaze (Parinaud’s syndrome), although pupillary and convergence abnormalities are seen, as are skew deviation and papilledema.</td>
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Determination of tumor histology, tumor cell markers, and extent of disease is critical for optimal management of pineal region tumors. Figure 43.2-6 is a schema the authors use to evaluate end-stage patients with pineal region tumors.

Figure 43.2-6. Treatment and evaluation schema for pineal region tumors. AFP, a-fetoprotein; CS, ; CT, computed tomography; MRI, magnetic resonance imaging; RT, radiation therapy. (Modified from Edwards MSB, Hudgins RJ, Wilson CB, et al. Pineal region tumors in children. J Neurosurg 1988;68:689.)
The prognosis for these tumors varies depending on the histology and size of tumor and the extent of disease at presentation. Typically, patients with mature teratomas do well with surgery alone; germimomas do best with radiation, although pre-radiation therapy chemotherapy may increase the cure rate and reduce the total radiation dose; gliomas respond to therapy in a manner discussed in earlier sections; and the remaining tumors respond variably to chemotherapy and radiation therapy, leading to survivals ranging from months to years before recurrence.

SURGERY

Because pineal tumors are near the center of the brain, they are among the most difficult brain tumors to remove, and it is this factor that has created some controversy in their management. However, the application of modern surgical technology, with superb illumination, magnification, surgical guidance, and neuroanesthesia to microsurgical approaches to the pineal region have made this region much more accessible. Surgeons choose from several accepted approaches depending on personal preference and the tumor's position and extent. The current recommendation is to obtain a tissue diagnosis when a diagnosis is not forthcoming with diagnostic stereotactic biopsy. Resection of the tumor is possible, especially for the small group of pineal tumors that are radiosensitive or that do not require radiation therapy, such as teratomas, arachnoid cysts, and meningiomas.

Many surgical approaches to the pineal region have been described: (1) through the dilated lateral ventricle; (2) through the posterior corpus callosum; (3) under the occipital lobe; and (4) through the posterior fossa over the cerebellum. The most commonly used microsurgical approaches are currently the infratentorial supracerebellar approach described first by Horsley, later by Krause, and resuscitated and modernized by Stein, and the supratentorial approach under the occipital lobe described by Poppen and popularized by Clark. Both have been associated with low morbidity and mortality in experienced hands.

The place of image-guided (stereotactic) biopsy in the diagnosis of pineal region tumors is unclear. Although such biopsies have been described as relatively safe, particularly in large tumors, there is a risk that tissue sampling of these heterogeneous tumors may not depict accurately the correct histologic nature of the tumor. Without an accurate histologic diagnosis, treatment planning may be erroneous or inadequate. In its favor is the advantage of rapid tissue diagnosis and shortened hospital stay.

RADIATION THERAPY

With certain exceptions, such as benign teratomas, radiation therapy has an established role in the treatment of pineal and suprasellar tumors of pineal parenchymal or germ cell origin. Because of their location and infiltrative nature, complete surgical extirpation often is not possible. In the past, high morbidity and mortality associated with biopsy or attempted resection, especially with older surgical techniques, often led to the use of radiation therapy without histologic confirmation. In such instances, response to low-dose radiation therapy, measurement of AFP and b-HCG, and CSF cytology were used to provide diagnostic information. There has been a tendency to increase the use of biopsy and attempted resection. Although surgery theoretically might be expected to increase the incidence of CSF seeding, there is no proof that this will occur. A review of older literature suggests that the incidence of spinal seeding increased from 3% for tumors in which biopsy was not obtained to 23% when biopsy was obtained from the tumors. However, Linstadt and associates found no instances of failure in the spinal axis in 13 patients with biopsy-proved germimomas, only one of whom received prophylactic spinal irradiation.

Five-year survival rates with radiation therapy range from 44% to 78% and vary with histology and extent of disease, age, radiation volume, and dose to the primary site. According to a multinstitutional survey by Wara and coworkers, the survival of patients with pineal parenchymal cell tumors or malignant teratomas was 21% (3 of 14) compared with 72% (28 of 36) for those with germinomas. More recently, Wolden and colleagues reported 5-year disease-free survival rates of 91% for germinomas, 63% for unbiopsied tumors and 60% for nongerminoma germ cell tumors irradiated to doses of 50 to 54 Gy to the local tumor site with or without additional treatment to the whole brain or ventricular system. Patients younger than 25 to 30 years of age have survival rates of 65% to 80% with 35% to 40% for older patients. This finding may reflect the increased incidence of true germinomas in younger patients.

Germinomas are infiltrative tumors that tend to spread along the ventricular walls or throughout the leptomeninges. The incidence of CSF seeding ranges from 7% to 12%. Because of these features, the use of fields encompassing the entire ventricular system, the whole brain, and even the entire craniospinal axis has been recommended. In a literature review, Salazar and colleagues found a recurrence-free survival rate of 76% for patients with whole brain irradiation compared with 61% for irradiation to the ventricular system and 51% for smaller volumes. Further analysis of those data showed a 90% survival rate for patients treated with whole brain irradiation and a tumor dose of at least 50 Gy. If smaller fields were used or the dose to the primary tumor site was less than 50 Gy, the survival was 65%. With less than whole brain irradiation, recurrences at the margin of the irradiated volume were reported in the older literature. However, the frequency of such recurrences has been reduced with the availability of CT and MRI for treatment planning. Linstadt and associates concluded that the risk for spinal metastases from germinomas was too small to justify routine prophylactic spinal irradiation, but recommended its use when there is tumor spill at surgery or in those patients with malignant CSF cytology or known subependymal or leptomeningeal metastases.

The paradigm described by Edwards and Levin for management of pineal region tumors differs somewhat from the approach just discussed and is outlined in Figure 43-2. If hydrocephalus is present, patients are placed on corticosteroids. A shunt is placed only if corticosteroids fail to relieve the symptoms of increased intracranial pressure. An open operation with the goal to resect the tumor is preferred to a stereotactic biopsy. Occasionally, in a patient with widely disseminated disease, a stereotactic biopsy may be indicated. The approach (supratentorial vs. infratentorial) is planned on the basis of the MRI scan. At the time of craniotomy, an external ventricular drain with an intracranial pressure monitor is placed in the lateral ventricle and CSF is removed to lower intracranial pressure and measure CSF tumor markers (b-HCG and AFP). A tumor biopsy is obtained, and, based on the findings at operation and the histologic diagnosis, a decision is reached regarding the aggressiveness of tumor resection.

Additional therapy is planned based on the histology, CSF markers, staging CT and MRI, and myelography; localized germinomas are treated with 20 Gy to the ventricles plus an additional 30 Gy to the tumor with a 1.5- to 2.0-cm margin for a total of 50 Gy. Treatment with neoadjuvant chemotherapy and low-dose (30 to 40 Gy) focal irradiation is being studied in some centers. If the germinoma is disseminated or if multiple midline tumors are present, systemic chemotherapy or craniospinal irradiation is administered. Doses of 20 to 35 Gy to the craniospinal axis have been recommended when tumor cells are detected in the CSF. Patients given chemotherapy as their primary treatment but who have an incomplete response or subsequently recur can be successfully treated with radiotherapy.

Nongerminomatous malignant germ cell tumors, whether localized or disseminated, are treated with systemic chemotherapy (for six courses), followed by restaging studies. After restaging, localized tumors receive focal radiation therapy (20 to 24 Gy to the ventricular system with a tumor boost to 54 to 60 Gy), and disseminated tumors receive craniospinal irradiation (54 to 60 Gy to the primary tumor, 45 Gy to the ventricular system, 35 Gy to the spinal cord, and 45 Gy to any localized spinal cord lesions).

Biopsy-verified tumors with little or no tendency to metastasize to the spinal cord, such as teratomas, pineocytomas, and low-grade gliomas, are treated by resection or with local field irradiation. Craniospinal axis irradiation is reserved for tumors that have a strong tendency toward cord involvement (such as pineoblastoma), for those with positive CSF cytology, or for those with radiographic evidence of spinal cord involvement.

CHEMOTHERAPY

Chemotherapy for glial neoplasms is similar to that covered in earlier sections. The chemotherapy for germ cell tumors is in flux but is encouraging. Adjunct multidrug therapy with agents such as cisplatin, etoposide, and bleomycin together with high-dose radiotherapy have produced encouraging disease-free and overall survival rates. Finally and coworkers have used high-dose chemotherapy alone (carboplatin, etoposide, and bleomycin) with deferral of radiotherapy. These results also appear promising.

For germinomas, complete responses before radiation therapy or at recurrence have been observed with cisplatin and bleomycin; carboplatin and cyclophosphamide; the combination of cyclophosphamide, vinblastine, and bleomycin; the combination of cisplatin and etoposide; and dactinomycin, methotrexate, vinblastine, and cisplatin. This has led to attempts to reduce or defer radiotherapy. Following surgical diagnosis of germinoma, two courses of high-dose cyclophosphamide produce complete response in 91%. Because of this, Allen and coworkers reduced the radiation dose and volume. Of the 10 complete response patients treated with reduced radiation, only 10% of patients have failed 5 years later. A comparable approach using carboplatin produced an 88%
response rate and a radiation dose-reduction in five of eight patients.\(^{374}\) More recently, Bouffet and colleagues reported on a Societe Francaise d'OncoLogie Pediatricque study of four courses of alternating etoposide-carboplatin and etoposide-ifosfamide followed by 40 Gy localized radiation therapy for nonmetastatic cases and craniospinal radiation therapy for metastatic cases.\(^{375}\) Of the 57 patients registered, 47 had biopsy proof of germinoma. Median follow-up was 42 months. The estimated 3-year event-free survival was 98%.

For nongerminoma malignant germ cell tumors (e.g., embryonal, endodermal sinus, and mixed tumors), the benefits of chemotherapy are far less impressive, with partial rather than complete responses and recurrence within months to years being the norm. Chemotherapies with activity include combinations of cyclophosphamide, vinblastine, and bleomycin; cisplatin, VCR, and bleomycin; cisplatin and etoposide; and cisplatin, bleomycin, and teniposide.\(^{376}\) Occasional patients with recurrent germ cell tumors who have failed the combination of cisplatin, bleomycin, and vinblastine therapies have responded to chemotherapy with TPDCV.

The results with chemotherapy have appeared paradoxical, because patients with systemic seminoma treated with cisplatin, bleomycin, and vinblastine have developed brain metastases while receiving chemotherapy. Using nonseminomatous testicular germ cell lines, Pera and colleagues found that temozolomide was quite cytotoxic and they predict that temozolomide will be active against intracranial metastases from testicular seminomas as well as primary germ cell tumors in the CNS.\(^{377}\)

Given the rarity of CNS germ cell tumors and the similarity of small trials reported in the literature, it is obvious that cooperative group trials are necessary to determine which of the existing chemotherapy combinations are most active. Second-generation studies could then address modifications based on a reasonable database rather than the few anecdotal studies in the literature. Much study needs to be done to elucidate the best drug combinations and use of chemotherapy in these patients.

### PITUITARY ADENOMAS

#### CLINICAL AND PATHOLOGIC CONSIDERATIONS

Pituitary gland tumors tend to produce neuroendocrine or neurologic symptoms and signs. Anatomically, tumors arising from the pituitary gland can compress the pituitary, grow out of the sella to compress and invade the optic chiasm, and, if growth is unabated, extend into the temporal lobe, third ventricle, and the posterior fossa. The chief finding in most patients is vision loss initially characterized by a bitemporal hemianopia. Headache occurs in approximately 20%. Less frequent are ocular palsies due to compression or invasion of the cavernous sinus.

Neuroendocrine abnormalities can be associated with tumor compression of the pituitary gland or hypersecretion of hormones, or both. Table 43.2-6 summarizes some of the more common syndromes and their endocrine abnormalities. Sexual impotence in men and amenorrhea and galactorrhea in women are commonly associated with hyperprolactinemia. Growth hormone hypersecretion is associated with acromegaly or gigantism, depending on the age of the patient. Corticotropin hypersecretion results in Cushing's disease. Elements of hypothyroidism, adrenal insufficiency, and growth hormone deficiency may follow compression of the pituitary gland by growth of an adenoma.

The diagnosis of a pituitary adenoma is based on sensitive radioimmunoassays, CT scans, and, most recently, MRI. Figure 43.2-3 shows an MRI scan of a pituitary adenoma before surgery. Pituitary adenomas are classified as endocrine inactive or endocrine active. Most secrete one or, occasionally, two hormones. The reported incidence of the various types of pituitary adenomas depends on the institution's referral patterns. Of 800 patients operated on at UCSF between 1970 and 1981, 630 of 800 (79%) were endocrine active; of these, 331 of 630 (52%) were prolactin secreting, 27% growth hormone secreting, 20% corticotropin secreting, and only 0.3% were thyroid-stimulating hormone secreting. Undifferentiated cell adenomas are considered to be nononcocytic (null) or oncocytic (oncocytoma) tumors.

Of prognostic importance are the functional status of the tumor and how large or invasive it is. Table 43.2-6 is the grading and staging system used at UCSF.\(^{383}\)

#### SURGERY

The goal of surgery for the larger (usually, but not always, endocrine inactive) pituitary tumors is to decompress the visual pathways and reduce tumor bulk, whereas the goal for hypersecreting adenomas is normalization of the hypersecretion with preservation of remaining normal pituitary function. For larger nonsecreting pituitary adenomas, surgical cure is often not possible or even necessary, because radiation therapy adjuvant to surgery is usually curative. However, radiation therapy is often withheld until regrowth is suspected on postoperative surveillance scans. In contrast, the hypersecreting adenoma should be resected in its entirety, whenever possible, because the effects of hypersecretion can be devastating, and response to radiation therapy is slow and less predictable.

The operative approach of choice for most pituitary tumors is transtemporal, because it is safer and better tolerated than the alternative transcranial (frontal craniotomy) approach.\(^{384}\) The transphenoidal approach is possible for tumors occupying the sella turcica and even in those with generous suprasellar extension as long as the tumor is soft (the usual case) and can drop into the sella with progressive resection. Touch, woody suprasellar tumors and those with extension laterally into the middle fossa or anteriorly beneath the frontal lobes must be resected by craniotomy.

#### RADIATION THERAPY

Microadenomas of the pituitary, usually diagnosed because of endocrine hypersecretion, may be totally resected. There is no indication for radiation therapy, unless there is persistent hormone elevation. Radiation therapy is also indicated for hormone-secreting adenomas that are refractory to pharmacologic management. Macroadenomas, particularly the endocrine inactive lesions, may invade into adjacent structures, such as the cavernous sinus, the optic chiasm, or the third ventricle. Subtotal resection and postoperative irradiation can relieve mass effect, shrink the remaining tumor, prevent regrowth, and lower hormone levels. Further, radiation therapy alone or medical treatment for patients with hormone-secreting tumors are effective alternatives to resection for patients who are medically inoperable or who refuse surgery.

Breen and colleagues found that for irradiated nonfunctioning adenomas the actuarial tumor control rate was 87.5% at 10 years, 77.6% at 20 years, and 64.7% at 30 years. The oncocytic variant of pituitary adenoma appears to be less sensitive to control by radiotherapy than the nononcocytic form of undifferentiated cell adenoma.\(^{385}\) Sheline demonstrated that patients with large, nonfunctioning adenomas or prolactin-secreting adenomas associated with visual field deficits had a 60% recurrence rate (using visual field changes as an end point) within 5 years after incomplete resection alone.\(^{386}\) The recurrence rate was reduced to approximately 4% by the addition of radiation therapy, whereas 7% treated with radiation therapy alone recurred. Approximately two-thirds of patients who presented with modest visual field defects, involving not more than one quadrant, who were treated by surgery or radiation therapy alone had return of normal vision in the involved eyes. With larger visual field defects, restoration of vision was better in patients who received preradiation therapy and surgical decompression than in those treated by radiation therapy alone. Normal vision was achieved by irradiation alone in approximately two-thirds of patients with acromegaly and visual field defects.

Radiation therapy is less effective in controlling endocrine hypersecretion than in controlling the growth of pituitary adenomas. Radiation therapy decreases serum growth hormone concentrations to normal levels (defined as basal growth hormone levels of less than 2 ng/mL) in 80% to 85% of acromegalic patients.\(^{387}\) Growth hormone levels decrease at a rate of 10% to 30% per year. Thus, several years may be required for the levels to normalize.\(^{388}\) The probability of normalization is related to the pretreatment growth hormone level. Radiation therapy is most effective in tumors with relatively small preradiation therapy growth hormone elevations (30 to 50 ng/mL), whereas the response is less predictable with higher growth hormone levels.\(^{389}\) In contrast, serum insulin-like growth factor-I levels remain elevated after radiotherapy,\(^{390}\) and long-term treatment with somatostatin or its analogues may be required.\(^{391}\) Radiation therapy controls hypercortisolism in 50% to 75% of adults and 80% of children with Cushing's disease. Response occurs within 6 to 9 months of treatment.\(^{392}\)

Data on control of prolactin secretion by conventional radiation therapy are difficult to interpret. When radiation therapy is used as primary treatment or after incomplete surgical resection, the rate of prolactin normalization varies from 30% to 70%.\(^{391}\) The response occurs over several years, and the probability of cure (defined as prolactin less than 25 ng/mL) is inversely related to the baseline prolactin level. In some cases persistent hyperprolactinemia after treatment may be caused by damage to the hypothalamic prolactin inhibitory pathway.\(^{393}\) Dopamine agonist therapy with agents such as cabergoline is often part of the initial
management of prolactinomas. Radiation therapy in such cases is reserved for patients who fail to respond to this treatment.

Pituitary adenomas may be treated using several different techniques. One approach is to use bilateral coronal arcs with moving wedge filters. The usual treatment plan includes two 110-degree arcs with 30-degree wedge filters. The field size is chosen to include the target volume in the 95% isodose line. The neck is placed in the flexed position so that the plane of rotation is behind the eyes. During simulation, markers are placed on the eyelids. Three tattoo marks are placed on the skin and used for alignment with laser beams to ensure daily positional reproducibility. For large tumors, a three-field technique with lateral opposed wedgealed portals and a superior or vertex field may be used. Three-dimensional conformal radiotherapy approaches as well as stereotactic radiosurgery and radiotherapy and charged particle beams have also been advocated. With conventional radiotherapy techniques, the total dose is carried to 45 Gy in 25 fractions of 1.8 Gy, calculated at the 95% isodose line. This combination of fraction size and total dose controls tumor growth in 90% of cases at 10 years, and, therefore, a larger dose is not indicated. Further, radiation-induced injury to optic apparatus or adjacent brain with this dose-fractionation scheme is rare, whereas larger fractions or greater total doses lead to a higher incidence of injury. The optic chiasm appears especially sensitive to radiation injury in patients with acromegaly. Hypopituitarism, however, may develop as a late complication years after completion of radiation therapy. It is more likely to occur in patients who have had surgery and postoperative radiation therapy than in those who have been treated by radiation therapy or surgery alone. Because hypopituitarism is largely correctable by hormone replacement therapy, patients treated for pituitary adenomas should be observed by an endocrinologist for the remainder of their lives. The risk of developing a radiation-induced brain tumor after treatment is 1.3% to 2.7% at 10 years and 2.7% to 30 years.

Reirradiation can be considered for patients with recurrent pituitary adenomas when there has been a long interval after the first course of radiotherapy and when other therapeutic methods have been unsuccessful. Schoenenthaler and colleagues reported the outcome of 15 patients who were retreated (median dose, 42 Gy) after a median of 9 years from their initial course of radiation therapy (median dose, 40.8 Gy). With a median follow-up time of 10 years, 80% of patients were locally controlled. Although no visual complications were observed, all patients developed hypopituitarism and two sustained temporal lobe injury.

CRANIOPHARYNGIOMAS

CLINICAL AND PATHOLOGIC CONSIDERATIONS

Craniopharyngiomas occur primarily in children. These tumors arise from cell rests that are remnants of Rathke's pouch at the juncture of the infundibular stalk and the pituitary gland. Most of these tumors become symptomatic only after they have attained a diameter of approximately 3 cm. They are usually cystic at the time of presentation. They may compress the optic chiasm or pituitary gland and extend up into the third ventricle. The cyst is high in proteinaceous material and calcium and is seen easily by CT scan or MRI. Clinically, craniopharyngiomas produce increased intracranial pressure and hypopituitary-hypothyroidic-chiasmal dysfunction. Symptoms vary and, in children, may include obesity, delayed development, decreased vision and optic atrophy, field defects, and papilledema.

SURGERY

Craniopharyngiomas usually are approached by a microsurgical procedure done through a frontal or frontotemporal craniotomy. Large craniopharyngioma cysts that enter and enlarge the sella turcica can be drained and resected through a transphenoidal procedure. The goal of most surgeries in the surgery of craniopharyngioma is total removal, but some do a more conservative operation and depend on the excellent results with radiotherapy. Aggressive removal nearly guarantees some injury to the pituitary stalk, with subsequent temporary or permanent diabetes insipidus and elements of hypopituitarism. Patients injured in this manner must take replacement hormones and use inhaled desmopressin acetate spray for the control of diabetes insipidus for life. However, patients whose vision was affected by the craniopharyngioma can expect improvement after surgery. The mortality of craniopharyngioma resection should be extremely low.

In Europe, a few centers are treating craniopharyngioma cysts with stereotactic puncture and the instillation of colloidal therapeutic radioisotopes, particularly yttrium 90. Such treatments are being tried in this country also with colloidal phosphorus 32. Intracisternal therapy may be a good treatment for craniopharyngioma cysts recurring after conventional external beam irradiation.

RADIATION THERAPY

Although debate exists regarding the extent to which total excision should be attempted, numerous reports demonstrate that local tumor control and survival after subtotal removal, consisting of extensive resection or of limited biopsy and cyst aspiration and irradiation, is comparable with that achieved by radical excision. The local control rates after complete resection, subtotal resection alone, and incomplete resection and postoperative irradiation are 70%, 26%, and 75%, respectively. Ten-year survival rates range from 24% to 100% for complete resection, 31% to 52% for subtotal resection, 62% to 86% for incomplete resection and irradiation, and 100% after radiotherapy alone. The latter group are comprised of patients with small tumors at presentation. Patients undergoing conservative treatment including biopsy and cyst drainage and irradiation appear to enjoy a better quality of life and demonstrate less psychosocial impairment than those initially treated with more extensive resections. Further, conservative therapy is associated with less hypothalamic and pituitary dysfunction and a lower incidence of persistent diabetes insipidus than when a total or near total excision is attempted. More extensive resections using a subfrontal approach may be associated with frontal lobe and visual perceptual dysfunction.

The radiation therapy target volume is based largely on CT and MRI scanning using relatively small margins around demonstrated tumor. The technique varies according to size and location of residual tumor, but most patients are treated by biconoral arcs with moving wedge filters, similar to the method used for pituitary adenomas. More sophisticated three-dimensional conformal radiotherapy and intensity-modulated radiotherapy approaches and stereotactic radiotherapy techniques using relocatable immobilization devices may further spare surrounding normal tissues. The use of radiosurgery is limited because of the proximity of most lesions to the optic chiasm and brain stem. The total dose is 50 to 55 Gy, given in daily 1.8-Gy increments. In children younger than 3 years of age, it is recommended that, if possible, irradiation be delayed until the child is older.

CEREBELLOPONTINE VESTIBULAR SCHWANNOMAS

CLINICAL AND PATHOLOGIC CONSIDERATIONS

The major tumors occurring in this region are the acoustic nerve tumors and meningiomas. Meningiomas have been discussed previously (see Meningiomas, earlier in this chapter); therefore, the discussion that follows is limited to vestibular schwannomas (acoustic neuromas). These tumors originate on cranial nerve VIII, almost always on the vestibular division, at the point where the nerve acquires its reticulin and Schwann cell investment. Within the skull, this transition zone occurs in the internal auditory foramen and causes local erosion of the internal auditory meatus. Slow growth characterizes these tumors; therefore, they can grow to substantial size before clinical symptoms lead to diagnosis. They often occupy the posterior fossa at the angle between the cerebellum and thepons. By compression, they can affect cranial nerves VII, V, and, less often, IX and X, alone or in various combinations. When large enough, they can compress the medulla and obstruct the CSF, leading to hydrocephalus.

Vestibular schwannomas are most common in the fifth decade and can be associated with familial neurofibromatosis. In the latter instance they occur earlier, in late childhood and adolescence, and may be bilateral.

In a series from the Massachusetts General Hospital, auditory and vestibular branch involvement was found to occur in 98% of patients, facial weakness with disturbances of taste in 56%, sensory loss over the face in 56%, gait abnormality in 41%, and appendicular ataxia in 20%. Diagnosis by skull radiographic examination is suggestive, but definitive diagnosis is most effectively made with MRI or CT scan done in conjunction with the CSF administration of metrizamide contrast.

SURGERY
The transsaccipital approach requires a unilateral posterior fossa craniectomy, after which the dura is opened and the cerebellum is retracted medially to expose the cerebellopontine angle. The lower cranial nerves are protected while tumor is removed, and the pons acusticus is uncovered in an effort to identify the facial nerve, and in smaller tumors, the acoustic nerve as well. Once the facial nerve is identified, the remainder of the tumor is removed in a usually lengthy and involved operation that fully exploits the surgeon's microsurgical skill.

Complete removal of vestibular schwannomas through the posterior fossa can be predicted in almost every instance, and life-threatening complications are rare except in patients with extremely large tumors. While preservation of the acoustic nerve is uncommon in even small tumors, the facial nerve is in continuity at the end of most acoustic tumor resections. Therefore, any postoperative paresis or paralysis tends to be temporary. When the facial nerve is divided during surgery, it is sutured together when possible, or a nerve graft is placed between the stumps. Facial paralysis with no evidence of recovery within a few months is treated with surgical rerouting, wherein another cranial nerve, usually the hypoglossal nerve, is joined to the facial nerve peripherally. Bilateral acoustic tumors are seen with neurofibromatosis type 2 and present difficult problems in surgical decision making. In general, a conservative approach is taken, treating the largest tumor when symptoms absolutely require it. Bilateral aggressive tumor resections lead to complete deafness and confer the possibility of bilateral facial nerve paralysis, a cosmetic and functional problem.

**RADIATION THERAPY**

There have been few reports on the role of conventional radiation therapy for treatment of acoustic neurollemomas. A review by Wallner and colleagues disclosed 62 patients who were thought to have had a total resection and did not receive irradiation. The recurrence rate in this group was only 3% (2 of 62). The 15-year actuarial survival and relapse-free survival rates were 98% and 94%, respectively. Thirty patients underwent subtotal resection, defined as removal of less than 90% of the tumor. Six of the 13 (46%) patients with subtotaly resected lesions recurred, whereas only 1 of 17 (6%) of those treated with subtotal resection and postoperative irradiation did so to a dose higher than 45 Gy. The 15-year tumor control survival rate for patients treated with subtotal resection and radiation therapy (greater than 45 Gy) was 94% compared with 41% for nonirradiated patients (P < .01). The corresponding 15-year survival rates were 100% and 67%, respectively (P = .016). There were no recurrences among three patients in whom biopsy was obtained at the time of surgery that was followed by irradiation. On the other hand, four of seven patients who were irradiated for disease progression after having had resection alone subsequently developed a second recurrence. Based on these data, it was concluded that postoperative irradiation should be given after subtotal resection to reduce the risk of local tumor progression. The target volume includes a narrow margin around the residual tumor. Maire and colleagues reported a local control rate of 88% among 24 patients with large tumors, the majority of whom were irradiated without initial surgical resection. Hearing was maintained in five of five patients with bilateral neurollemomas after contralateral tumor resection. No patient developed facial or trigeminal neuropathy. Treatment is given using a homolateral pair of angled beams with wedge filters in daily increments of 1.8 to 2.0 Gy to a total of 50 to 55 Gy.

Stereotactic radiosurgery and stereotactic radiotherapy have been used as an alternative to surgery in selected patients with small acoustic neurollemomas. In a long-term follow-up study Kondziolka and colleagues reported that 98% of 162 patients treated to a median dose of 16 Gy were controlled. Only four patients required subsequent surgical treatment. Normal facial function was preserved in 79% of patients after 5 years, and normal trigeminal function was preserved in 73%. Patients may develop new incomplete trigeminal and facial cranial neuropathies within a median of 6 to 7 months after radiosurgery. These tend to be mild and usually recover within 6 to 12 months. Occasionally, 45% to 50% of patients with useful hearing before radiosurgery maintain their pretreatment hearing level, whereas patients with hearing deficits before treatment generally do not improve after radiosurgery.

The risk of treatment-induced cranial neuropathy is directly related to the volume of the lesion, the dose administered, and the length of nerve irradiated. Efforts are being directed at decreasing the complication rates while maintaining the high control rates with more sophisticated planning and treatment techniques and reducing dose levels.

**GLOMUS JUGULARE TUMORS**

**CLINICAL AND PATHOLOGIC CONSIDERATIONS**

Glomus jugulare tumors arise from glomus tissue in the adventitia of the jugular bulb (glomus jugulare) or along Jacobson's nerve in the temporal bone, sometimes multifocally. The tumor invades temporal bone diffusely, but growth is characteristically slow. Sometimes they are endocrine active, with a carcinoid or pheochromocytoma-like syndrome. Because glomus jugulare tumors occur in the jugular foramen, they commonly cause lower cranial nerve palsies and early symptoms of hoarseness and difficulty swallowing. Later, facial weakness, hearing loss, and atrophy of the tongue become prominent. Pulsating tinnitus also may be a presenting symptom, and a pulsating mass can sometimes be seen behind the eardrum. A presumptive radiologic diagnosis of glomus tumor can be made by CT or MRI scanning, with jugular neurollemoma being the main differential diagnosis. Because glomus tumors incite a tremendous blood supply, particularly by way of the ascending pharyngeal artery, cerebral angiography provides the definitive diagnosis. Because preoperative tumor embolization is essential to surgical removal of glomus tumors, the diagnostic angiogram should be performed just before surgery when possible.

Histopathologically, numerous vascular channels are distinctive. The background is composed of clear cells clumped in a fibrous matrix. A small percentage of glomus tumors are malignant.

**SURGERY**

The treatment of glomus jugulare tumors is controversial, with advocates for radiation, surgery, and the combination. Most clinicians would agree that a resection should be attempted and that in most instances gross surgical resection, if not a cure, is a realistic goal. Surgery on glomus tumors is most often performed by a neurotologist and a head and neck surgeon to work in concert. The base of the skull in the region of the jugular foramen is first exposed, and neurovascular structures are identified and mobilized through a high transverse cervical incision. When the incision is extended behind the pinna and a mastoidectomy is completed, the facial nerve can be protected, and the entire tumor bulb, jugular bulb, and internal jugular vein can be seen passing through the base of the skull and adjacent soft tissue. Because the internal jugular vein below can be ligated, and the segment between them excised with the attached tumor. Complications of this procedure include CSF leak and cranial nerve (particularly facial) palsy.

**RADIATION THERAPY**

Even though glomus tumors are histologically benign, radiation therapy is effective and has been recommended for symptomatic lesions that cannot be totally resected or as primary treatment. These tumors regress slowly after irradiation, and the success of radiation therapy is measured by the amelioration of symptoms and the absence of disease progression. In their review of the literature, Springate and Weichselbaum found a 94% local control rate for temporal bone glomus tumors treated with radiotherapy alone and a 91% local control rate for glomus tympanicum and jugular tumors treated with radiotherapy alone or with preoperative or postoperative irradiation. The dose required for control is relatively modest. Kim and associates reported a series of 40 patients with such lesions and added a literature survey. The control rate with subtotal resection and postoperative irradiation was 85%. When radiation therapy only was used for inoperable or recurrent tumors, control was achieved in 86%. Their composite data, including cases from the literature, showed a 25% recurrence rate for doses lower than 40 Gy, whereas only 1.4% recurred with doses of 40 Gy or higher.

Based on these data, a dose of 45 Gy in 5 weeks is recommended. Although a dose of 50 Gy has been advocated for more advanced tumors, there is no evidence that such lesions require higher doses. Treatment is usually delivered through a homolateral pair of angled, wedged portals, depending on the precise location of the tumor and the size of the anatomic components involved.
the lesion. More sophisticated three-dimensional conformational techniques may be used to reduce the dose to surrounding normal tissue structures.

CHORDOMAS

CLINICAL AND PATHOLOGIC CONSIDERATIONS

Chordomas occur along the pathway of the primitive notochord, which extends, in human embryos, from the tip of the dorsal sellae to the coccyx. Chordomas are extruded, multilobulated tumors, varying in consistency from extremely soft to woody and cartilaginous. They are pseudoencapsulated and may invade through the basal dura.

The typical chordoma is composed of cord-like rows of distended, vacuolated (physaliferous) cells. A variant, the chordoid chordoma, has distinctly chordoid elements and may be less aggressive. None of the histopathologic characteristics of tumor aggressiveness (cellularity, pleomorphism, and mitoses) seems to be predictive in chordoma.

The diagnosis of clivus chordomas cannot be made without radiologic tests and often is delayed because symptoms are nonspecific and vague. At onset there is usually headache and intermittent diplopia. These vague symptoms often are not reported, allowing the tumor to grow to an enormous size before the diagnosis is made. Gradually, headache (upper clivus tumors) and neck pain (lower clivus tumors) worsen. Superiorly placed tumors proceed to cause diplopia and facial numbness as the cavernous sinus and Meckel's cave are invaded. Lower clivus tumors compress the lower cranial nerves and later the brain stem.

The differential diagnosis of cranial chordoma includes basal meningioma, neurilemmoma (schwannoma), nasopharyngeal carcinoma, pituitary adenoma, and craniopharyngioma. MRI scanning usually results in a working diagnosis of chordoma, but surgical biopsy (and resection) is mandatory.

SURGERY

Surgery for cranial chordomas is obligatory to obtain diagnostic tissue, to enhance the effectiveness of subsequent radiation therapy, and to improve the patient's clinical condition. With an aggressive surgical resection, a favorable effect on the severe headaches and neurologic deficits associated with chordomas can be anticipated.

Intracranial chordomas occur at the base of the skull, a region relatively remote from surgical access. Consequently, a variety of innovative approaches have been developed by neurosurgeons and head and neck surgeons, and these procedures are commonly done with both types of specialist in attendance.

For midline lesions of the upper clivus that extend into the sella or sphenoid sinus, or both, a transseptal, transsphenoidal approach (as for pituitary tumors) is best. Large, compressive, transradial extensions of these upper clivus tumors into the interpeduncular cistern must be removed through a transcranial, supratentorial, intradural approach. For the more lateralized upper clival tumor and some lateralized midclival tumors, an approach through a sphenoorbitomeatocytomy (to which may be added a maxilllectomy) is useful. For midline tumors of the midclivus and lower clivus, a transoral resection is commonly used. A combination of exposures sometimes is necessary for extremely large tumors.

A potentially serious complication of the transsphenoidal, transsphenohemtomid, and transoral approaches is CSF leakage and consequent meningitis. Therefore, every attempt must be made to keep the dura intact during these procedures. Because dural invasion by cranial chordomas may occur 50% of the time, inadvertent entry of the dura during tumor resection is sometimes unavoidable. Careful intraoperative patching of the leak with fat and muscle grafts followed by postoperative spinal CSF drainage is essential.

Cranial chordomas often recur after surgery and radiation therapy. In this situation, reoperation directed toward symptomatic improvement is the only treatment option. Reoperations are complicated by surgical scarring and tissue compromise from irradiation.

RADIATION THERAPY

Chordomas and low-grade chondrosarcomas of the base of skull, clivus, and axial skeleton are not amenable to complete surgical resection. With conventional megavoltage irradiation (median dose of 50 Gy), the local control rate for these lesions is only 27%. Although higher doses appear to improve the local control rate, the proximity of dose-limiting critical structures, such as the optic nerves, chiasm, other cranial nerves, brain stem, temporal lobes, and spinal cord, limit the dose that can be delivered safely to these lesions. Charged particle beams such as protons and helium ions, which feature sharp lateral beam edges and a finite range in tissue, may be used to deliver higher doses than are possible with conventional photon irradiation while keeping the dose to neighboring critical structures at a safe level.

The depth of penetration can be tailored to the clinical situation by varying the energy of the beam or by interposing bolus material in the beam path. Charged particle beams can be made to stop in front of a critical structure, such as the spinal cord, and in combination with other lateral or oblique beams, a target volume may be wrapped around a critical structure. Precise tumor and normal tissue identification and beam delivery techniques, highly reproducible patient positioning, and accurate compensation for tissue inhomogeneities in the beam path are required.

Available data suggest that the higher doses that are achievable with charged particle irradiation result in higher local control rates than have been observed with conventional radiation therapy techniques. Munzenrider and coworkers reported the outcome of 132 patients with nonchondroid and chordoid skull base chordomas treated postoperatively at the Harvard Cyclotron Laboratory at Massachusetts General Hospital with a 160-MeV proton beam. Patients received a median dose of 69 cobalt Gy equivalent (CGE; the dose in proton Gy multiplied by 1.1, the relative biologic effectiveness for protons compared with cobalt 60), with a range of 36 to 79 CGE, and 95% received 67 CGE (70% to 100% of dose given with proton beam). Follow-up ranged from 2 to 158 months (median, 46 months). Local control was achieved in 70% of patients (93 of 132). Local control was more common in men than women (77% vs. 45%) and more frequent in those with chondroid chordomas than in nonchondroid tumors (83% vs. 66%). The 5-year actuarial local control and disease-specific survival rates were 59% and 80%, respectively. Treatment was complicated by functional and anatomic abnormalities in the brain and cranial nerves, visual and auditory deficits, and pituitary insufficiency requiring hormone replacement. Skull base chondrosarcomas treated with proton therapy have a better prognosis than chordomas. Rosenberg and colleagues reported a 5- and 10-year local control rate of 99% and 98%, respectively, whereas the disease-specific survival rates at 5 and 10 years were both 99%.

Berson and colleagues reviewed the results of 45 patients with chordomas and chondrosarcomas of the base of skull and cervical spine treated at the University of California Lawrence Berkeley Laboratory with helium ion or neon beams. Total doses ranged from 59.4 to 80.0 Gy equivalent (the physical dose multiplied by the relative biologic effectiveness; 1.2 to 1.3 for helium and 2.0 to 3.3 for neon). For initial subtotal resection, 23 patients were treated with charged particles alone, and 13 were treated with photons and particles combined. Nine patients were treated for recurrent disease. Similar to the findings of Munzenrider and coworkers, the 5-year actuarial local control and survival rates were 59% and 62%, respectively. The 2-year actuarial local control rate for patients treated at initial diagnosis was 78% compared with 33% for those with recurrent tumors (P <.01). The 2-year local control rate for tumor volumes of less than 20 mL was 80%, whereas it was 33% for larger lesions (P <.05). Complications included unilateral or bilateral blindness in five patients, and four patients developed brain stem injury.

HEMANGIOBLASTOMAS AND HEMANGIOMAS

CLINICAL AND PATHOLOGIC CONSIDERATIONS

Hemangioblastoma accounts for approximately 2% of intracranial tumors, arising most often in the cerebellar hemispheres and vermis. Usually solitary, these tumors can be multiple and may also occur in the brain stem, spinal cord, and supratentorial compartment. Cerebellar hemangioblastoma can be sporadic or occur as a familial disorder as part of the von Hippel-Lindau complex that is transmitted as an autosomal dominant disorder with varying degrees of penetrance. Other entities associated with familial hemangioblastoma are hypernephroma, polycystic kidneys, pancreatic cysts, pheochromocytoma, and erythrocytosis.

Cerebellar hemangioblastomas usually are recognized in the third decade, causing symptoms of increased intracranial pressure and symptoms and signs of cerebellar dysfunction. Gait disturbance and imbalance are particularly common. Clinical progression is slow because these tumors enlarge extremely slowly.

The hemangioblastoma probably arises during embryonic life from primitive endothelial cells around the fourth ventricle. The tumor is composed of numerous capillary and sinusoidal channels lined with endothelial cells. Interspersed are nests of lipid-laden pseudoxanthoma cells. The tumor is usually cystic and contains...
proteinateaceous, xanthochromic fluid. The cyst contains a red (vascular) firm mural nodule, the apparent source of the fluid. The cyst wall is a glial nonneoplastic reaction to the sequestered fluid. Occasional hemangioblastomas (brain stem and spinal cord, particularly) are without cysts.

SURGERY

In most instances, the diagnosis can be made by CT scan or MRI. Angiography, to confirm the diagnosis and map the tumor’s blood supply, is usually done before surgery. Cerebellar hemangioblastomas are readily approached and excised, with the cyst drained and the entire solid portion carefully dissected and removed. Solid hemangioblastomas of the brain stem are exceedingly vascular, and their removal is associated with high mortality. Such tumors are sometimes irradiated with or without a confirmatory biopsy.

RADIATION THERAPY

Radiation therapy is recommended for patients with unresectable, incompletely excised, and recurrent hemangioblastomas and for those patients who are medially inoperable. Smalley and associates reported the outcome of 25 patients treated with radiation therapy for hemangioblastoma. Nineteen patients had gross residual disease after initial surgery or recurrent tumors, whereas six had only microscopic disease. The overall 5-, 10-, and 15-year survival rates were 85%, 58%, and 58%, respectively, and the recurrence-free survival rates were 76%, 52%, and 42%, respectively. Eight of the 19 patients with gross disease were locally controlled. In-field disease control rates were significantly higher in patients who received at least 50 Gy ($P < .001$) than in those who received lower doses. Five of the six patients treated for microscopic disease had the disease controlled. Based on these data, doses of at least 50 to 55 Gy in 5.5 to 6.0 weeks appear to be warranted.

Radiosurgery has also been applied to the treatment of hemangioblastomas. Patrice and colleagues summarized the outcome of 38 lesions in 22 patients (eight patients with multifocal tumors) who received radiosurgery as definitive treatment or in relapsed patients after surgery or surgery and conventional radiotherapy. The median tumor volume was 0.97 cc (range, 0.05 to 12.0 cc), and the median dose was 15.4 Gy (range, 12 to 20 Gy). With a median follow-up time of 24.5 months (range, 6 to 77 months), 31 of 36 evaluable tumors (86%), including all tumors treated definitively with radiosurgery, remained locally controlled. All five lesions that relapsed after radiosurgery were among the tumors that were treated for recurrence after initial surgery. Better control rates were associated with higher doses and smaller tumor volumes. The 3-year actuarial progression-free survival rate was 86%, and the 2-year actuarial survival rate was 88%. Among 29 hemangioblastomas treated by Chang and coworkers, only one (3%) progressed. Five tumors (17%) regressed completely, 16 (55%) partially regressed, and 7 (24%) remained unchanged in size. Radiosurgery should be considered for surgically unresectable hemangioblastomas, as adjuvant treatment for incompletely excised tumors, as definitive treatment of multifocal disease, and for salvage therapy for discrete recurrences after surgical relapse.

CHOROID PLEXUS PAPILLOMA AND CARCINOMA

CLINICAL AND PATHOLOGIC CONSIDERATIONS

Choroid plexus papilloma and carcinoma are rare tumors that occur most often in children younger than 12 years of age, although they can occur at any age. Nearly one-half of these tumors are found in patients younger than 20 years of age. The tumor is an irregularly lobulated reddish mass, which on histopathologic examination is apparently normal choroid plexus. Rarely, these tumors show malignant features and are then classified as choroid plexus carcinoma.

In children, choroid plexus papillomas most often occur in the lateral ventricles. In adults, the fourth ventricular papilloma is most common. Third ventricle tumors are exceedingly rare. Because papillomas tend to grow slowly within ventricles, they expand to fill the ventricle and block CSF flow. In addition, papillomas are thought to secrete CSF. Choroid plexus papillomas (and carcinomas) can produce hydrocephalus secondary to obstruction of the CSF, by CSF overproduction by the tumor, or by damage to the CSF resorptive bed from recurrent hemorrhages. As a result, increased intracranial pressure without focal findings is the most common presentation; fourth ventricular tumors can also be associated with focal findings of ataxia and nystagmus.

Although choroid plexus papillomas and carcinomas extensively seed through the ventricular and subarachnoid spaces, seeding from papillomas is usually subclinical, whereas that from carcinomas is frequent and dramatically symptomatic. These tumors are seen easily by CT scan and MRI. For patients with anaplastic changes, the authors advocate staging by myelography and examination of the CSF.

Therapy for anaplastic tumors should be approached in a manner similar to medulloblastoma and malignant ependymomas. Because of the aggressive nature of the more anaplastic tumors, therapy must be equally aggressive, requiring radiation therapy and, in some instances, intraventricular chemotherapy.

SURGERY

The treatment of choroid plexus papillomas is total surgical excision. Choroid plexus tumors of the lateral ventricle are approached through a high parietal cortical incision and transcortical approach to the ventricular trigone. The predilection of these tumors for the left (often dominant) side makes this approach worrisome. Hydrocephalus is the rule and simplifies the exposure when retraction into the ventricle is established. Tumor arteries and veins are identified by use of the operating microscope and then coagulated, after which smaller tumors are removed intact and larger tumors are removed piecemeal. In one-half of the patients, hydrocephalus is relieved by tumor resection, but persistent hydrocephalus requires shunting.

Choroid plexus papillomas of the third ventricle are exceedingly rare but can be approached through various surgical exposures of the third ventricle. The problems of requiring radiation therapy to prevent the inevitable recurrence and CSF dissemination common to the choroid plexus carcinomas. As with many of the less common tumors discussed, there are no chemotherapeutic guidelines and few reports to guide the therapist.

INITIALLY, the authors used chemotherapy only for recurrent disease. They have used combinations of cyclophosphamide, doxorubicin, and VCR and nitrosourea-based combinations. They have seen transient responses and disease control with both. They have also used intraventricular chemotherapy with low-dose methotrexate (2 to 3 mg/d for 5 days) or cytosine arabinoside (30 mg/d for 3 days), or both, to stave subarachnoid spread. As a result of this experience, the authors currently advocate the use of adjuvant chemotherapy with a nitrosourea-based combination after irradiation and the use of concomitant intraventricular chemotherapy. During
SPINAL AXIS TUMORS

CLINICAL AND PATHOLOGIC CONSIDERATIONS

Some of the clinical features of spinal axis tumor localization and diagnosis have been discussed previously. Most primary spinal axis tumors produce symptoms and signs as a result of spinal cord and nerve root compression rather than because of parenchymal invasion.

The reported frequency of primary spinal cord tumors is between 10% and 19% of all primary CNS tumors. Although most spinal axis tumors are extradural, most primary spinal axis tumors are intradural. Of intradural tumors, the intradural extramedullary neurilemmomas and meningiomas are the most common (see Table 43.2-3). Neurilemmomas and meningiomas are normally intradural, but occasionally they may present as extradural tumors. Other intradural extramedullary tumors are vascular tumors, chordomas, and epidermoids.

Intradural tumors have the same cellular origins as the other CNS tumors discussed previously. In terms of frequency, ependymomas occur in approximately 40% of patients with intradural tumors; next most common are the astrocytomas of low- and mid-anaplasia. These are followed in frequency by less common histologies such as oligodendroglioma, ganglioglioma, medulloblastoma, and various hemangiomas and hemangioblastomas.

Table 43.2-26 classifies spinal axis tumors by location. Although different tumor types exhibit a predilection for certain spinal regions, taken altogether, spinal tumors are distributed almost evenly along the spinal axis. Approximately 50% of spinal tumors involve the thoracic spinal canal, 30% involve the lumbosacral spine, and the remainder involve the cervical spine, including the foramen magnum. Some tumors, such as the neurilemmomas, occur with greatest frequency in the thoracic region, although they can be found throughout the spine and often extend through an intervertebral foramen to acquire a dumbbell configuration.

TABLE 43.2-26. Classification of Spinal Tumors by Their Location in Relation to the Spinal Cord and Dura Mater

Meningiomas are dural based and arise preferentially at the foramen magnum and in the thoracic spine. Astrocytomas are distributed throughout the spinal cord, and most ependymomas involve the conus medullaris and the cauda equina. Spinal chordomas are characteristically sacral.

Clinically, patients with spinal axis tumors present with a sensorimotor spinal tract syndrome, a painful radicular spinal cord syndrome, or a central syringomyelic syndrome. In the sensorimotor presentation, symptoms and signs are in response to compression of the spinal cord. The onset is gradual over weeks to months, initial presentation is asymmetric, and motor weakness predominates. The level of impairment determines the muscle groups involved. Because of external compression, dorsal column involvement occurs with paresthesia and abnormalities of pain and temperature on the side contralateral to the motor weakness.

Radicular spinal cord syndromes occur because of external compression and infiltration of spinal cord roots. The main symptom is sharp, knife-like pain in the distribution of a sensory nerve root. The intense pain is often of short duration, with pain that is more aching in nature persisting for longer periods. The pain typically is exacerbated by coughing and sneezing or other maneuvers that increase intracranial pressure. Local paresthesia and impairment of sensations of pain and touch are common, as are weakness and muscle wasting. These findings commonly antedate cord compression by months.

Spinal tumors, particularly intradural extramedullary tumors, can produce syringomyelic dysfunction by destruction and cavitation within the central gray matter of the cord. This produces lower motor neuron destruction and attendant segmental muscle weakness, wasting, and loss of reflexes. There is also a dissociated sensory loss of pain and temperature sensation with preservation of touch. With extension of the lesion, however, touch, vibration, and position sense are affected.

Finally, many patients with spinal axis tumors or supratentorial tumors that show a tendency toward drop metastases tend to lead to leptomeningeal neoplasia. Choucair and colleagues found that 1.2% of glioblastomas and 1.5% of anaplastic gliomas had metastatic spread of their supratentorial tumors to the spinal cord at some time during the course of their disease.

SURGERY

General Considerations

The use of the operating microscope is as essential for spinal cord tumor surgery as it is for brain tumor surgery. In addition, other surgical adjuncts, such as intraoperative ultrasound, the CO2 laser, and the CUSA, are equally valuable for the resection of spinal cord tumors. The ultrasound is particularly useful for examining the spinal cord through an intact or open dura to assess the level of maximum tumor involvement or to differentiate tumor cysts from solid tumor masses.

Surgical Planning

MRI scanning is invaluable for the diagnosis, localization, and characterization of spinal tumors (see Fig. 43.2-4). In all but vascular tumors (e.g., hemangioblastoma), in which angiography is needed, or tumors that cause extensive bony destruction (e.g., metastasis), where CT scanning might be helpful, a technically excellent MRI scan is most often sufficient for preoperative planning for spinal tumors. Determination of the spinal level of the tumor and its exact relation to the spinal cord is important in localization. Corticosteroids are given before, during, and after spinal cord tumor surgery to help control spinal cord edema.

Removal of Intradural Extramedullary Tumors

Meningiomas and neurollemomas (schwannomas) occur in the intradural extramedullary spinal compartment. Most of these tumors can be completely resected (cured), because through a laminectomy exposure they can be easily separated and rotated away from the spinal cord, which is already displaced, but not invaded, by tumor.

Neurilemmomas arise from spinal rootlets (most often dorsal rootlets), and their removal includes sections of those rootlets involved. Neurilemmomas can grow along the nerve root in a dumbbell fashion through a neural foramen; and although some of these extraspinal tumor extensions can be removed by extending the initial laminectomy exposure laterally, some must be resected at a separate operation through a thoracotomy, a costotransversectomy, or a retroperitoneal approach.

Meningiomas in most patients can be removed through a posterior (laminectomy) approach, because they are commonly lateral or anterolateral, and even the more anteriorly placed tumors cause enough lateral displacement of the spinal cord to allow access for resection without traction on the spinal cord. The uncommon tumor directly anterior to the spinal cord must sometimes be approached anteriorly, anterolaterally, or posterolaterally. Anteriorly situated meningiomas at the foramen
magnesium are sometimes unresectable because of their encasement of the vertebral artery.

**Removal of Intramedullary Tumors**

The most common intramedullary tumors are ependymoma and astrocytoma. Hemangioblastoma is another (infrequent) tumor occurring in the spinal intramedullary compartment. Surgery is the principal treatment for all these tumors, with the exception of anaplastic astrocytomas.

Intramedullary tumors are approached through a laminectomy exposure, and after the dura is opened, a longitudinal myelotomy is made over the widened region of spinal cord and a microscope is used to separate several millimeters around the tumor surface. Dissection planes are kept from the normal cord and lesional tissue is removed at the lower dose levels and malignant tumors to the higher level. For lesions involving only the cauda equina and in situations in which irreversible and complete transverse myelopathy already has occurred, higher doses are permissible. The tumor usually is excised in a margin of 2 cm or two vertebral bodies above and below the lesion. Extension of the portals to include the thecal sac has been suggested for ependymomas that are removed piecemeal and for those arising in the distal spinal canal. Ependymomas of the cord have a longer natural history than astrocytomas. Although most astrocytomas that recur do so within 3 years of treatment, recurrence of ependymomas may be delayed for as long as 12 years.

Adjunctive radiation therapy is not necessary when ependymomas are removed completely in an en bloc fashion. However, 75% of patients (three of four) reported by Wen and associates who had resection limited to the thecal sac alone when the tumor was encased piecemeal. All seven nonirradiated patients with incompletely excised lesions reported by Barone and Elvidge and Schuman and coworkers recurred. In contrast, postoperative radiation therapy appears to improve tumor control and disease-free survival in patients with incompletely resected ependymomas. Stoof and colleagues found their irradiated patients survived nearly twice as long as those who were not irradiated. Five- and 10-year survival rates in irradiated patients with localized ependymomas range from 60% to 100% and 60% to 100% respectively, whereas 10-year relapse-free survival rates vary from 43% to 61%. Malignant astrocytoma has a more substantial effect on outcome. Waldron and colleagues found that for well-differentiated tumors the 5-year cause-specific survival was 97% as compared with 71% for intermediate or poorly differentiated tumors (P = .005). Myxopapillary ependymomas that arise exclusively in the conus medullaris have a better prognosis than the cellular ependymomas that arise in the cord. Local recurrence is the predominant pattern of treatment failure, occurring in 25% of irradiated patients.

The 5- and 10-year survival rates for irradiated patients with low-grade astrocytomas of the spinal cord vary from 60% to 90% and 40% to 90%, respectively, and 5- and 10-year relapse-free survival rates range from 66% to 83% and 53% to 83%, respectively. Approximately 50% to 65% of astrocytomas are controlled locally. Patients with malignant gliomas have a much poorer prognosis; none of the patients with anaplastic astrocytoma or glioblastoma multiforme reported by Linsdale and colleagues survived longer than 8 months.

**CHEMOTHERAPY**

There have been no reports of controlled clinical trials of chemotherapy for primary spinal axis tumors. Drugs active against intracranial astrocytomas, oligodendrogliomas, ependymomas, and hemangioblastoma, and germ cell tumors logically may be assumed to be equally efficacious against these same histologies in the spinal cord. Along with reports of chemotherapy activity against intracranial tumors, anecdotal patient reports have been included. The authors' experience suggests that palliation is possible for astrocytomas using nitrosourea-based chemotherapy regimens. No therapy is clearly superior. For drop metastases from ependymomas, they have used BCNU and dibromodulcitol as single agents and various combinations with some benefit. For metastases from neuroblastoma and other varieties of primary brain tumors, various drugs have been found to be beneficial. Specifically, cyclophosphamide, carboplatin, methylrethoxate, procarbazine, teniposide, and VCR have been used alone or in various combinations. These drugs would be expected to produce palliation for weeks to many months.

Although leptomeningeal spread is a common complication of primary spinal axis tumors, the use of intraventricular and intrathecal chemotherapy is limited to the treatment of microscopic deposits. Redistribution in the subarachnoid CSF can be limited in the face of intradural extramedullary tumors. Adjunctive radiation therapy is not necessary when ependymomas are removed completely in an en bloc fashion. However, 75% of patients (three of four) reported by Wen and associates who had resection limited to the thecal sac alone when the tumor was encased piecemeal. All seven nonirradiated patients with incompletely excised lesions reported by Barone and Elvidge and Schuman and coworkers recurred. In contrast, postoperative radiation therapy appears to improve tumor control and disease-free survival in patients with incompletely resected ependymomas. Stoof and colleagues found their irradiated patients survived nearly twice as long as those who were not irradiated. Five- and 10-year survival rates in irradiated patients with localized ependymomas range from 60% to 100% and 60% to 100% respectively, whereas 10-year relapse-free survival rates vary from 43% to 61%. Malignant astrocytoma has a more substantial effect on outcome. Waldron and colleagues found that for well-differentiated tumors the 5-year cause-specific survival was 97% as compared with 71% for intermediate or poorly differentiated tumors (P = .005). Myxopapillary ependymomas that arise exclusively in the conus medullaris have a better prognosis than the cellular ependymomas that arise in the cord. Local recurrence is the predominant pattern of treatment failure, occurring in 25% of irradiated patients.

The 5- and 10-year survival rates for irradiated patients with low-grade astrocytomas of the spinal cord vary from 60% to 90% and 40% to 90%, respectively, and 5- and 10-year relapse-free survival rates range from 66% to 83% and 53% to 83%, respectively. Approximately 50% to 65% of astrocytomas are controlled locally. Patients with malignant gliomas have a much poorer prognosis; none of the patients with anaplastic astrocytoma or glioblastoma multiforme reported by Linsdale and colleagues survived longer than 8 months.

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Molecular Biology of Childhood Cancers

INTRODUCTION

The biologic nature of tumors of childhood is clinically, histopathologically, and biologically distinct from that of adult-onset malignancies. Childhood cancers tend to have short latency periods, are often rapidly growing and aggressively invasive, are rarely associated with exposure to carcinogens implicated in adult-onset cancers, and are generally more responsive to standard modalities of treatment, in particular chemotherapy. Most childhood tumors occur sporadically in families with at most a weak history of cancer. In approximately 10% to 15% of cases, however, a strong familial association is recognized, or the child has a congenital or genetic disorder that imparts a higher likelihood of specific cancer types. Examples of genetic disorders that render a child at increased risk of tumor development include xeroderma pigmentosa, Bloom’s syndrome, or ataxia-telangiectasia, which predispose to skin cancers, leukemias, or lymphoid malignancies, respectively. In all three cases, constitutional gene alterations that disrupt normal mechanisms of genomic DNA repair are blamed for the propensity to cell transformation. Other hereditary disorders including Beckwith-Wiedemann syndrome (BWS) and the multiple endocrine neoplasias types 1 and 2 are thought to be associated with their respective tumor spectra through constitutional activation of molecular pathways of deregulated cellular growth and proliferation. The cancers that occur in these syndromes are generally secondary phenotypic manifestations of disorders that have distinctive recognizable physical stigmata. On the other hand, some cancer predisposition syndromes are recognized only by their malignant manifestations, with nonmalignant characteristics being virtually absent. These include hereditary retinoblastoma, the Li-Fraumeni syndrome (LFS), familial Wilms’ tumor (WT), and familial adenomatous polyposis coli. Each of these presents with distinct cancer phenotypes, and for each the identified molecular defect is unique (Table 44.1-1).

TABLE 44.1-1. Hereditary Syndromes Associated with Childhood Cancers

The study of pediatric cancer and rare hereditary cancer syndromes and associations has led to the identification of numerous cancer genes including dominant oncogenes and tumor suppressor genes. These have proved to be important not only in hereditary predisposition, but also as major players in the normal growth, differentiation, and proliferation pathways of all cells. Alterations of these genes have been consistently found in numerous sporadic tumors of childhood and led to studies of their functional role in carcinogenesis. The numerous properties of transformed malignant cells in culture or in vivo can be explained by the complex abnormal interaction of numerous positive and negative growth regulatory genes. Pediatric cancers offer unique models in which to study these pathways in that they are less likely to be disrupted by nongenetic factors. The embryonic ontogeny of many childhood cancers suggests that better understanding of the nature of the genetic events leading to these cancers will also augment the understanding of normal embryologic growth and development. This chapter begins with an outline of tumor suppressor genes, the most frequently implicated class of cancer genes in childhood malignancy. This leads into discussion of molecular features of retinoblastoma, the paradigm of cancer genetics, followed by analysis of the molecular understanding of other common pediatric cancers. Evaluation of the importance of molecular alterations in familial cancers, as well as new approaches in molecular therapeutics, are also addressed.

TUMOR SUPPRESSOR GENES

Faulty regulation of cellular growth and differentiation leads to neoplastic transformation and tumor initiation. Many inappropriately activated growth-potentiating genes, or oncogenes, have been identified through the study of RNA tumor viruses and the transforming effects of DNA isolated from malignant cells. However, activated dominant oncogenes themselves do not readily explain a variety of phenomena related to transformation and tumor formation. Among these is the suppression of tumorigenicity by fusion of malignant cells with their normal counterparts. If these malignant cells carried an activated dominant oncogene, it would be expected that such a gene would initiate transformation of the normal cells, likely leading to either embryonic or fetal death. The observation is more readily explained by postulating the existence of a factor in the normal cell that acts to suppress growth of the fused malignant cells. Malignant cells commonly exhibit specific chromosomal deletions (Table 44.1-2). The best example of this occurs in retinoblastoma, a rare pediatric eye tumor in which a small region of the long arm of chromosome 13 is frequently missing. The presumed loss of genes in specific chromosomal regions argues strongly against the concept of a dominantly acting gene being implicated in the development of the tumor. Hereditary forms of cancer are also not readily explained by altered growth-potentiating genes. Comparisons between the frequencies of familial tumors and their sporadic counterparts led Knudson to suggest that the familial forms of some tumors could be explained by constitutional mutations in growth-limiting genes. The resulting inactivation of these genes would facilitate cellular transformation. Such growth-limiting genes were termed tumor suppressor genes.
WT. Since linkage studies have also excluded this locus as the gene for familial WT interacts with the gene product of either of the two WT genes, the gene has been neither cytogenetically localized nor isolated. Whether, of course, the gene for familial WT interacts with the gene product of either of the two WT genes and maps to chromosome 11p15.

Denys-Drash syndrome carry WT1 point mutations in the germline. Denys-Drash syndrome is a rare association of WT, intersex disorders, and progressive renal failure. The second syndrome closely associated with this locus was initially described by Denys in 1967 and recognized as a syndrome by Drash 3 years later. WT1 demonstrated that this gene spans approximately 50 kb of DNA and contains 10 exons. The WT1 protein is a transcription factor.

The WAGR syndrome, the association of WT (W) with congenital aniridia (A), genitourinary malformations (G), and mental retardation (R), has been correlated with constitutional deletions of band q13 of chromosome 11.

Using classic cloning techniques, a 4.7-kb cDNA fragment was isolated from retinal cells. This gene, RB1, consisted of 27 exons and encoded a 105-kD nuclear phosphoprotein. As well as being altered in retinoblastoma, this gene and its protein product have also been found to be altered in osteosarcomas, small cell lung carcinomas, and bladder, breast, and prostate carcinomas.

Although it is clear that RB1 and its protein product play some role in growth regulation, the precise nature of this role remains obscure. In the developing retina, inactivation of the RB1 gene is both necessary and sufficient for tumor formation. Although the RB1 gene is expressed in virtually all mammalian tissues, only in the retina is its inactivation sufficient for tumor initiation. Outside the retina, RB1 inactivation is often a rate-limiting step in tumorigenesis generated by multiple genetic events. The molecular characteristics and potential functional activities of RB1 are outlined in detail elsewhere in this volume.

The patterns of inheritance and presentation of retinoblastoma have been well described, and the responsible gene identified. Although the basic mechanisms by which the gene is inactivated are understood, much still remains to be determined about the biologic function of the gene and its protein product.

WILMS' TUMOR: THREE DISTINCT LOCI

WT, or nephroblastoma, is an embryonal malignancy of the kidney that arises from remnants of immature kidney. It affects approximately 1 in 10,000 children, usually before the age of 6 years (median age at diagnosis, 3.5 years). Some 5% to 10% of children present with either synchronous or metachronous bilateral tumors. A peculiar feature of WT is its association with nephrogenic rests, foci of primitive but nonmalignant cells whose persistence suggests a defect in kidney development. These precursor lesions are found within the normal kidney tissue of 30% to 40% of children with WT. Nephrogenic rests may persist, regress spontaneously, or grow into a large mass that simulates a true WT and presents a difficult diagnostic challenge. Another interesting feature of this neoplasm is its association with specific congenital abnormalities, including genitourinary anomalies, sporadic aniridia, mental retardation, and hemihyperplasty. The WT1 tumor suppressor gene is homozygously deleted, at least in part, in a small but highly informative set of sporadic WTs. In addition, both sporadic and hereditary WTs have been described in which WT1 is specifically altered.

A genetic predisposition to WT is observed in two distinct disease syndromes with urogenital system malformations (the WAGR syndrome and the Denys-Drash syndrome) as well as in an overgrowth syndrome characterized by visceromegaly, macroglossia, and hyperinsulinemic hypoglycemia (BWS). These congenital disorders have now been linked to abnormalities at specific genetic loci implicated in Wilms' tumorigenesis.

The WAGR syndrome, the association of WT (W) with congenital aniridia (A), genitourinary malformations (G), and mental retardation (R), has been correlated with constitutional deletions of band q13 of chromosome 11. Whereas it is now known that the WAGR deletion encompasses a number of contiguous genes, including the aniridia gene Pax6, the cytogenetic observation in patients with WAGR was also important in the cloning of WT1 at chromosome 11p13.

Characterization of WT1 demonstrated that this gene spans approximately 50 kb of DNA and contains 10 exons. The WT1 protein is a transcription factor. However, the identity of the gene(s) targeted by WT1 during normal kidney development is not known.

The second syndrome closely associated with this locus was initially described by Denys in 1967 and recognized as a syndrome by Drash 3 years later. Denys-Drash syndrome is a rare association of WT, intersex disorders, and progressive renal failure. It has been demonstrated that virtually all patients with Denys-Drash syndrome carry WT1 point mutations in the germline.

WT1 is altered in only 10% of WTs. This observation implies the existence of alternative loci in the etiology of this childhood renal malignancy. One such locus also resides on the short arm of chromosome 11, telomeric of WT1, at 11p15. This gene, designated WT2, is associated with BWS. Patients with BWS are at increased risk of developing mesenchymal tumors such as osteosarcoma, fibrosarcomas, and melanomas later in life. It is thought that several genetic mechanisms may be involved in elimination of the second wild-type WT1 allele in an evolving tumor. These include chromosomal duplication or nondisjunction, mitotic recombination, or gene conversion.

The RB1 gene was eventually mapped to chromosome 13q14. Using Southern blot analysis, it was then possible to demonstrate that the second target gene that led to disease was actually the second copy of the RB1 locus. Reduction to homozygosity of the mutant allele [or loss of heterozygosity (LOH) of the wild-type allele] would lead to the loss of functional RB1 and account for tumor development.

The remaining 60% of retinoblastoma cases are sporadic (nonheritable). Both RB1 alleles in a single retinal cell have been inactivated by somatic mutations. As one can imagine, such an event is rare, and these patients usually have only one tumor that presents later than in infants with the heritable form. Fifteen percent of unilateral retinoblastoma is heritable, but by chance develops in only one eye. Survivors of heritable retinoblastoma have a several-hundred-fold increased risk of developing mesenchymal tumors such as osteosarcoma, fibrosarcomas, and melanomas later in life.
At the molecular level, embryonal tumors are characterized by LOH at the 11p15 locus, which is of particular interest since this region harbors the IGF-2 gene. Microarray analysis has identified that certain embryonal tumors express a pattern of developmentally regulated genes found late in the chromaffin lineage and functions in an autocrine growth pathway.

Neurofibromatoses (NF) comprise two similar entities. NF1 is one of the most common autosomal dominantly inherited disorders, affecting approximately 1 in 3500 people, and is thought to arise from new spontaneous mutations. Carrier of mutant NF1 are predisposed to a variety of tumors including optic nerve glioma, neurofibroma and neurofibrosarcoma, malignant schwannoma, astrocytoma, and pheochromocytoma. Occurring with less frequency are leukemias, osteosarcoma, RMS, and WT.

Using standard linkage analysis, the NF1 gene was mapped to chromosomal band 17q11 and subsequently cloned. The NF1 gene is unusual in that it contains three embedded genes, OMGP, EV12A, and EV12B, in a single intron. This gene encodes a 2818 amino acid protein, termed neurofibrin, that is ubiquitously expressed. One region of the gene shows extensive homology to the GTPase activating domain of mammalian guanosine triphosphatase-activating proteins: Loss of the protein's activity results in failure of hydrolysis of guanosine triphosphate to guanosine diphosphate by the ras oncoprotein. Loss of neurofibromin function usually results from mutations in one allele of the gene leading to premature truncation of the protein, followed by absence or mutations of the second allele of the gene.

In addition to this fusion transcript being identified in peripheral primitive neuroectodermal tumor, other variants, notably the chest wall Askin's tumor and soft tissue sarcomas, can be terminally differentiated by nerve growth factor and may demonstrate morphologic changes typical of ganglionic differentiation. Tumors showing ganglionic differentiation and trk gene activation have a favorable prognosis. As noted previously, resistance to multidrug chemotherapeutic regimens (multidrug resistance) is characteristic of aggressive, poorly responsive N-myc amplified neuroblastomas. It is interesting to note that expression of the multidrug-resistance-associated protein, found to confer multidrug resistance in vitro, is increased in neuroblastomas with N-myc amplification and decreased after differentiation of tumor cells in vitro. This observation is considered to be associated with multidrug resistance and may be associated with therapeutic failures. Finally, expression of multidrug resistance protein expression are significantly associated with poor outcome, independent of N-myc amplification. Gain of chromosome segment 17q21-qter has been shown to be the most powerful prognostic factor yet. However, no gene has yet been implicated at this site. Cell lines that express markers corresponding to more immature cells are responsive to IGF-2, but do not produce the mitogen itself. This paracrine growth-modulating effect is consistent with observations of IGF-2 expression in infiltrating tumor specimens and adjacent normal tissues.

Ewing's sarcoma family of tumors

Ewing's sarcoma is one of the first tumors to which the application of molecular diagnostics led to improved tumor classification. Ewing's sarcoma was first described by James Ewing as a bone tumor characterized by small blue round cells and minimal mitotic activity. Investigators subsequently demonstrated a cytogenetically identical t(11;22) in adult neuroblastoma or peripheral primitive neuroectodermal tumor, so named because of its histologic similarity to neuroblastoma. Based on the presence of the identical translocation, it was hypothesized that peripheral primitive neuroectodermal tumor was related to Ewing's sarcoma. This translocation breakpoint has been molecularly characterized as an in-frame fusion between a new Ewing's sarcoma gene, EWS, on chromosome 22 and an ETS transcription family member, FLI-1, on chromosome 22. This observation is considered to be associated with rapid tumor progression. Expression of N-myc is increased in undifferentiated tumor cells compared with much lower (or single copy) levels in differentiated cells (ganglioneuroblastoma and ganglioneuroma). N-myc expression is diminished in association with the in vitro differentiation of neuroblastoma cell lines. This observation is considered to be associated with a survival advantage for patients treated with cis-retinoic acid. Furthermore, a close correlation exists between N-myc amplification and advanced clinical stage.

It is clear that altered expression of N-myc contributes to the development of malignancy, it is not yet apparent which cellular functions are altered. The molecular mechanisms underlying regulation of neuroblastoma differentiation may be explained in part through the contribution of other genes and proteins.

Neuroblastoma cells that express the high-affinity nerve growth factor receptor TrkA can be terminated by nerve growth factor and may demonstrate morphologic changes typical of ganglionic differentiation. Tumors showing ganglionic differentiation and trk gene activation have a favorable prognosis. Expression of the neurofibromin gene, an oncogene with considerable homology to the cellular protooncogene c-myc, is amplified within homogeneous staining regions and double-minute chromosomes. Virtually all neuroblastoma tumor cell lines demonstrate amplified and highly expressed N-myc. N-myc amplification is thought to be associated with rapid tumor progression. Expression of N-myc is increased in undifferentiated tumor cells compared with much lower (or single copy) levels in differentiated cells (ganglioneuroblastoma and ganglioneuroma). N-myc expression is diminished in association with the in vitro differentiation of neuroblastoma cell lines. This observation is considered to be associated with a survival advantage for patients treated with cis-retinoic acid. Furthermore, a close correlation exists between N-myc amplification and advanced clinical stage.

Rhabdomyosarcoma

The two major histologic subtypes of RMS, embryonal and alveolar, have both unique histologic appearance as well as distinctive molecular genetic abnormalities, while sharing a common myogenic lineage. Embryonal tumors make up two-thirds of all RMS and are histologically characterized by a stroma-rich, spindle-cell appearance. Alveolar tumors make up one-third of RMS and are histologically characterized by a stromal-free, highly cellular tumor with a histologic pattern reminiscent of a pulmonary alveolus, giving rise to its name. Both histologic subtypes express muscle-specific proteins including α-actin, myosin, desmin, and MyoD. They virtually always express high levels of IGF-2.

At the molecular level, embryonal tumors are characterized by LOH at the 11p15 locus, which is of particular interest since this region harbors the IGF-2 gene.
The loss of heterozygosity (LOH) at 11p15 occurs by loss of maternal and duplication of paternal chromosomal material. While LOH is normally associated with loss of tumor suppressor gene activity, in this instance LOH with paternal duplication may result in activation of IGF-2. This occurs because IGF-2 is now known to be normally imprinted (i.e., this gene is normally transcriptionally silent at the maternal allele, with only the paternal allele being transcriptionally active). Thus, LOH with paternal duplication potentially leads to a twofold gene-dosage effect of the IGF-2 locus. Furthermore, in alveolar tumors where LOH does not occur, the normally imprinted maternal allele has been shown to be reexpressed. Thus, LOH and loss of imprinting may in this case lead to the same functional result, namely, biallelic expression of the normally mononally expressed IGF-2. However, loss of an as yet unidentified tumor suppressor gene due to LOH also remains a possibility.

Alveolar RMS is characterized by a t(2;13)(q35;q14) chromosomal translocation. Molecular cloning of this translocation has identified the generation of a fusion transcript encoded by fusion of the 5′ DNA-binding region of PAX-3 on chromosome 2 to the 3′ transcriptional domain region of FKHR gene on chromosome 13. A variant t(1;13)(q36;q14) has been identified in a small number of alveolar RMS tumors that fuses the 5′ DNA-binding region of the PAX7 gene on chromosome 1 with the identical 3′ transcriptional domain of the FKHR gene. Fluorescence in situ hybridization or reverse transcriptase polymerase chain reaction can be used to identify these PAX-FKHR fusions in approximately 90% of tumors and are diagnostic of alveolar RMS. As noted previously, the fusion protein generated by the translocations leads to a novel transcription factor. The nature of this transcription factor and its downstream targets are the subject of active investigation. Of particular interest is the association of the PAX3-FKHR fusion with increased expression of c-met. Met is the receptor tyrosine kinase for hepatocyte growth factor/scatter factor and is overexpressed in both embryonal and alveolar RMS. It has also been suggested that, like the Ewing's sarcoma family of tumors, where the specific expressed fusion transcript has prognostic significance, the PAX3-FKHR and the PAX7-FKHR fusions lead to distinct clinicopathologic entities.

Other frequently reported genetic alterations that may be common to both embryonal and alveolar RMS include activated forms of N-RAS and K-RAS, inactivating p53 mutations, as well as amplification and overexpression of MDM2, CDK4, and N-MYC.

HEREDITARY SYNDROMES ASSOCIATED WITH TUMORS OF CHILDHOOD

LI-FRAUMENI SYNDROME

A hereditary cancer syndrome are associated with the occurrence of both childhood and adult-onset neoplasms. The paradigm Li-Fraumeni familial cancer syndrome was originally described in 1969 from an epidemiologic evaluation of more than 600 medical and family history records of childhood sarcoma patients. The original description of kindred with a spectrum of tumors that includes soft tissue sarcomas, osteosarcomas, breast cancer, brain tumors, leukemia, and adrenocortical carcinoma has been overwhelmingly substantiated by numerous subsequent studies, although other cancers are also observed. Germline alterations of the p53 tumor suppressor gene are associated with Li-Fraumeni syndrome. These are primarily missense mutations that yield a stabilized mutant protein. The spectrum of mutations in p53 in the germline are distinct from somatic mutations found in a wide variety of tumors. Carriers are heterogeneous for the mutation, and in tumors derived from these individuals, the second (wild-type) allele is frequently deleted or mutated, leading to functional inactivation. Only 60% to 80% of classic Li-Fraumeni families have detectable alterations of the gene. It is not yet determined whether the remainder are associated with the presence of modifier genes, promoter defects yielding abnormalities of p53 expression, or simply the result of weak genotype-phenotype correlations. Other candidate predisposition genes, such as p16, p15, p16, BRCA1, BRCA2, and PTEN, associated with multisite cancer associations have generally been ruled out as potential targets.

Germline p53 alterations have also been reported in some patients with cancer phenotypes that resemble the classic LFS phenotype. Between 3% and 10% of children with apparently sporadic RMS or osteosarcoma have been shown to carry germline p53 mutations. These patients tend to be younger than those who harbor wild-type p53. It appears as well that more than 75% of children with apparently sporadic adrenocortical carcinoma carry germline p53 mutations, although in some of these cases, a de novo mutation that is not transmitted to the child is the likely explanation. Alterations in allele-specific DNA methylation of IGF-2 and H19 reflect this genetic link cloudy and the likelihood of multiple pathways to tumor formation strong.

BECKWITH-WIEDEMANN SYNDROME

BWS occurs with a frequency of 1 in 16,700 births. More than 450 cases have been documented since the original reports of exomphalos, macrocephaly, gigantism, and other congenital anomalies. With increasing age, phenotypic features of BWS become less pronounced. Laboratory findings may include, at birth, hypoglycemia (extremely common), polythemia, hypocalcemia, hypertriglyceridemia, hypercholesterolemia, and high serum a-fetoprotein levels. With increasing age, phenotypic features of BWS become less pronounced. Laboratory findings may include, at birth, hypoglycemia (extremely common), polythemia, hypocalcemia, hypertriglyceridemia, hypercholesterolemia, and high serum a-fetoprotein levels. Laboratory findings may include, at birth, hypoglycemia (extremely common), polythemia, hypocalcemia, hypertriglyceridemia, hypercholesterolemia, and high serum a-fetoprotein levels. Laboratory findings may include, at birth, hypoglycemia (extremely common), polythemia, hypocalcemia, hypertriglyceridemia, hypercholesterolemia, and high serum a-fetoprotein levels.

The genetic basis of BWS is complex. Various 11p15 chromosomal or molecular alterations have been associated with the BWS phenotype and its tumors. It is unlikely that a single gene is responsible for the BWS phenotype. Because it appears that abnormalities in the region affect imprinting domain, it is more likely that normal gene regulation in this part of chromosome 11p15 occurs in a regional manner and may depend on various interdependent factors or genes. Chromosomal abnormalities associated with BWS are extremely rare, with only 20 cases having been associated with 11p15 translocations or inversions. The chromosomal breakpoints are not always known, with cases involving either paternal or maternal chromosomes. These observations suggest that germline p53 alterations may be associated with early-onset development of the childhood component tumors of the syndrome. It is not clear what clinical significance these findings have in that no studies of prognostic significance or potential impact on anticancer treatment modalities are performed. Nevertheless, in light of the critical role played by p53 in the initiation and progression of cancers initiated by DNA damage repair, studies into the effect of such germline mutations on the potential of tumor development related to therapeutic interventions would be important.

GORLIN SYNDROME

Nevoid basal cell carcinoma syndrome, or Gorlin syndrome, is a rare autosomal dominant disorder characterized by multiple basal cell carcinomas, developmental defects including bifid ribs and other spine and rib abnormalities, palmar and plantar pits, odontogenic keratocysts, as well as generalized overgrowth. This syndrome appears to be caused by germline mutations of the tumor suppressor gene PTCH, a receptor for sonic hedgehog. Approximately 5% of patients with Gorlin syndrome develop medulloblastoma. Furthermore, approximately 10% of patients diagnosed with medulloblastoma by the age of 2 years are found to have Gorlin syndrome. It is not clear what clinical significance these findings have in that no studies of prognostic significance or potential impact on anticancer treatment modalities are performed. Nevertheless, in light of the critical role played by p53 in the initiation and progression of cancers initiated by DNA damage repair, studies into the effect of such germline mutations on the potential of tumor development related to therapeutic interventions would be important.

MALIGNANT RHABDOID TUMORS

These unusual pediatric tumors occur as primary renal tumors, but have also been described in lung, liver, soft tissues, and the CNS, where it is often termed atypical and teratoid rhabdoid tumor. Recurrent chromosomal translocations of chromosome 22 involving a breakpoint at 22q11.2, as well as complete or partial monosomy 22, have been observed, strongly suggesting the presence of a tumor suppressor gene in this area. The hSNF5/INI1 gene has been isolated and shown to be the target for biallelic, recurrent, inactivating mutations. The encoded gene product is thought to be involved in chromatin remodeling. Studies have not only demonstrated the presence of inactivating mutations (renal or extrarenal), but also in chronic myeloid leukemia, as well as in a wide variety of other childhood and adult-onset malignancies. An intriguing feature in some individuals with malignant rhabdoid tumors is the observation of germline mutations, suggesting that this family may occur as a result of a primary inherited defect in one allele of the INI1 gene. Further studies of the function of this gene will be important in determining its role in tumorigenesis of this wide spectrum of neoplasms.
PREDICTIVE TESTING FOR GERMLINE MUTATIONS AND CHILDHOOD CANCERS

Several important issues have arisen as a result of the identification of germline mutations of tumor suppressor genes in cancer-prone individuals and families. These include ethical issues pertaining to testing in such families and in unaffected relatives, and selection of patients to be tested, as well as the development of new testing techniques, the development of protocols, development of clinical applications, and the role of clinical intervention based on test results. This chapter was not meant to discuss these problems in detail, but one would be remiss to ignore their significance.

For several reasons, testing cannot as yet be offered to the general pediatric population, particularly in light of the demonstrably low carrier rate of the abnormal tumor suppressor genes and the general lack of standardized methods of preclinical screening of carriers. Exceptions to these limitations include screening of gene carriers in RB, BWS, multiple endocrine neoplasia, and multiple melanoma families. Whether predictive testing studies are initiated in high-risk families or surveys are carried out in cancer populations likely to harbor germline mutations in tumor suppressor genes, the investigations should be undertaken in a research setting involving expertise in oncology, genetics, psychology, psycho-oncology, counseling, medical ethics, and molecular genetics. The development of screening programs should address aspects of cost, informed consent (particularly where it affects children), socioeconomic impact on the individual tested, and counseling, especially in affected families (see previous discussion). As targets of mutant transcription factors generated are identified, it is hoped that they may represent additional targets for therapeutic intervention.

Finally, fusion proteins derived from tumor-specific translocations may themselves represent potential neoantigens that could be targeted by cytotoxic T cells. It is likely that identification of aberrant signaling pathways and the transcriptional regulation of the genes involved will be critical in the development of more-effective treatment approaches in the near future. It is likely that some of these innovative approaches will at least initially be integrated into standard therapeutic protocols.

CHAPTER REFERENCES

Malignant solid tumors account for 30% of all cases of childhood cancer. Collaborative, multimodality treatment efforts undertaken in the context of pediatric cooperative group clinical trials have produced a remarkable improvement in survival since the 1970s. In addition to improvements in survival and functional outcome, the cooperative group studies have also facilitated a rapid growth in our understanding of cancer genetics and tumor biology. Prospective studies are currently underway to validate new risk group stratification schemes that integrate classical tumor staging information with prognostically significant features of tumor biology detectable with molecular diagnostics. We review the epidemiology, pathology, clinical presentation, evaluation, treatment, and prognosis of the common malignant solid tumors of children and adolescents.

EPIDEMIOLOGY

Approximately 12,400 children and adolescents younger than 20 years of age were diagnosed with cancer in 1998. Malignant neoplasms are a major cause of
mortality in children between 1 and 14 years of age. In 1998, the most recent year for which statistics are available, accidents, congenital anomalies, and homicide were responsible for more deaths in the age group 1 to 4 years, whereas only accidents were a more frequent cause of death in the age group 5 to 14 years.

The most common malignant neoplasms diagnosed in pediatric patients are acute leukemia, non-Hodgkin’s lymphoma, Hodgkin’s disease, and primary tumors of the central nervous system. The most common malignant solid tumors are neuroblastoma, Wilms’ tumor, rhabdomyosarcoma (RMS), and retinoblastoma (Table 44.2-1).

<table>
<thead>
<tr>
<th>Disease</th>
<th>White</th>
<th>African American</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute lymphoblastic leukemia</td>
<td>55.0 (45.9%)</td>
<td>50.0 (41.9%)</td>
</tr>
<tr>
<td>Burkitt’s lymphoma</td>
<td>7.9 (25.2%)</td>
<td>7.2 (23.1%)</td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>14.3 (27.5%)</td>
<td>10.6 (18.1%)</td>
</tr>
<tr>
<td>Neurocystic astrocytoma</td>
<td>4.8 (5.8%)</td>
<td>5.1 (15.0%)</td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma</td>
<td>9.9 (5.3%)</td>
<td>5.5 (5.0%)</td>
</tr>
<tr>
<td>Ewing’s sarcoma</td>
<td>2.3 (7.0%)</td>
<td>2.7 (8.2%)</td>
</tr>
<tr>
<td>Hodgkin’s Disease</td>
<td>5.2 (14.8%)</td>
<td>16.7 (14.8%)</td>
</tr>
<tr>
<td>Germ cell sarcoma</td>
<td>9.4 (23.2%)</td>
<td>9.4 (23.5%)</td>
</tr>
<tr>
<td>Acute lymphocytic leukemia</td>
<td>7.7 (25.2%)</td>
<td>7.7 (25.2%)</td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>6.3 (23.9%)</td>
<td>6.1 (18.1%)</td>
</tr>
<tr>
<td>Wilms’ tumor</td>
<td>4.7 (6.1%)</td>
<td>4.7 (6.1%)</td>
</tr>
<tr>
<td>Neurocystic astrocytoma</td>
<td>4.3 (5.3%)</td>
<td>4.3 (5.3%)</td>
</tr>
<tr>
<td>Ewing’s sarcoma</td>
<td>3.1 (8.5%)</td>
<td>3.1 (8.5%)</td>
</tr>
<tr>
<td>Retinoblastoma</td>
<td>0.4 (0.5%)</td>
<td>0.4 (0.5%)</td>
</tr>
</tbody>
</table>

TABLE 44.2-1. Annual Incidence Rates and Percentage Distribution of Malignant Diseases in U.S. Children

Insights into the etiology of malignant solid tumors of childhood have been suggested by well-designed case-control studies (Table 44.2-2).

TABLE 44.2-2. Risk of Solid Tumors Following Parental Preconception Exposures

Some childhood solid tumors occur in association with well-recognized single gene defects. Examples of these include the association of Wilms’ tumor with Denys-Drash syndrome (Wilms’ tumor suppressor gene (WT1) mutation), bilateral retinoblastoma (retinoblastoma tumor suppressor gene (RB1) mutation), hepatoblastoma and adenomatous polyposis coli (APC gene mutation), RMS or malignant peripheral nerve sheath tumor and neurofibromatosis type 1 (NF1 gene mutation), RMS and Li-Fraumeni syndrome (p53 gene mutation).

The etiology of most childhood tumors is unknown. Knudson proposed the two-event model to explain the pattern of retinoblastoma, in which approximately 10% of patients with sporadic unilateral tumors and all patients with bilateral tumors carry a germline mutation of RB1. This mutation could be either a new germinal mutation transmitted from the father or a mutation transmitted from a carrier or affected parent. The interstitial deletion occurs preferentially in the paternally derived allele of RB1, resulting in the loss of function of one of the alleles of the RB1 gene. This loss occurs via one of several mechanisms (Fig. 44.2-1), recognized by loss of heterozygosity for markers of specific chromosomal regions, all of which result in complete absence of the normal gene product. This mechanism has been demonstrated in tumor tissue derived from embryonal RMS, hepatoblastoma, retinoblastoma, and Wilms’ tumor.

FIGURE 44.2-1. Loss of heterozygosity may occur by a variety of mechanisms. (From Cavenee WK, Dryja TP, Phillips RA, et al. Expression of recessive alleles by chromosomal mechanisms in retinoblastoma. Nature 1983;305:779, with permission.)

The genetics of some childhood solid tumors may be more complex. Analysis of the epidemiologic and clinicopathologic features suggest, for example, some cases of bilateral and multicentric Wilms’ tumor may arise from somatic mosaicism rather than germinal mutation.

MANAGEMENT OF CHILDHOOD CANCER

Childhood malignant solid tumors are unique due to their responsiveness to many chemotherapeutic agents. Effective combination chemotherapy regimens have been identified and evaluated through cooperative group multiinstitutional trials. The cooperative groups’ membership includes multidisciplinary treatment teams consisting of pediatric oncologists, radiologists, surgeons, and surgical subspecialists, as well as pediatric pathologists, pediatric radiation oncologists, and allied pediatric health professionals. The dramatic improvements in survival of pediatric patients with cancer are the result of treatment by such teams with experience in the evaluation, staging, surgical management, radiation treatment, and administration of intensive chemotherapy regimens to these children.

Surgery plays two roles in the management of solid tumors. The first role is establishing a histologic diagnosis and staging the tumor; the second is resection of the primary site of disease. It is increasingly important that the surgeon work in a collaborative fashion with the pediatric oncologist and radiation oncologist, since resection may be best accomplished after initial chemotherapy and radiotherapy. These initial treatments may decrease both the potential risks of resection and the long-term morbidity. Similarly, it is critical that the surgeon be involved from the outset in the care of a child presenting with a solid tumor since an inappropriately performed biopsy of the tumor may complicate later resection efforts. Questions regarding timing and feasibility of resection should only be considered by surgeons who are facile in reconciling the sometimes competing demands of durable local control and optimal functional outcome in a growing child. In light of the exquisite
radiosensitivity of most pediatric solid tumors, all deliberations concerning timing and extent of resection efforts must recognize the importance of radiotherapy as an effective adjunct in efforts to secure local control.

Advances in anesthetic management of infants and children have contributed greatly to the surgical resection of solid tumors. Procedures that were performed in the past with a significant rate of postoperative mortality, such as hepatectomy and extensive retroperitoneal resections, are now accomplished on a routine basis with limited risk. The duration of a procedure with modern anesthetic techniques is also rarely a consideration. Although the length of anesthesia was once a major determinant of operative morbidity and mortality, duration of a procedure is now rarely an issue.

Significant advances have also been achieved in postoperative pain management. Epidural catheters and continuous intravenous infusions of narcotics by mechanical pumps have greatly limited the severity of pain following extensive resections. Improvements in pain management have permitted more rapid mobilization of postoperative patients, with a corresponding decrease in the risk of pneumonia.

These advances in surgical management have been complemented by substantial improvements in radiation planning and delivery. Conformal radiotherapy using three-dimensional treatment planning to spare normal tissues has had a salutary effect on functional outcome. Advances in our knowledge of radiation dosing and planning techniques are discussed separately under each specific tumor type.

**WILMS’ TUMOR**

Wilms’ tumor is the most common primary malignant renal tumor of childhood. The striking success of national cooperative studies in improving survival and decreasing treatment-related morbidity mark this disease as the paradigm for multimodal treatment of a pediatric malignant solid tumor.

**EPIDEMIOLOGY AND GENETICS**

The incidence rate of Wilms’ tumor is 7.9 cases per 1 million in white children younger than 15 years of age. The incidence rate is approximately three times higher for African Americans in the United States and blacks in Africa than for East Asians, with rates for white populations in Europe and North America between these extremes.

Wilms’ tumor in the United States is slightly less frequent in boys than in girls. The tumor presents at an earlier age among boys, with the mean age at diagnosis for those with unilateral tumors being 41.5 months compared with 46.9 months among girls. The mean age at diagnosis for those who present with bilateral tumors is 29.5 months for boys and 32.6 months for girls.

Children with Wilms’ tumor may have associated anomalies, including aniridia, hemihypertrophy (as an isolated abnormality, or as a component of the Beckwith-Wiedemann syndrome), cryptorchidism, and hypospadias. They have suggested that the disease comprises at least two pathogenetic entities that are identifiable on the basis of distinct precursor lesions.

Approximately 1.5% of National Wilms’ Tumor Study Group (NWTSG) cases have one or more family members with the disease. In the absence of a history of parental consanguinity in such families, the mode of inheritance is generally thought to be autosomal dominant, with variable penetrance and expressivity. The rate of synchronous and metachronous bilaterality among NWTSG familial cases is significantly higher than for the NWTSG population as a whole. In addition, the mean age at diagnosis for familial unilateral or familial bilateral cases is significantly lower than the corresponding group of sporadic cases.

Predicting the outcome in multicentric disease is likely to be more complex than previously imagined because of the emerging evidence for genetic heterogeneity. Mechanisms other than an inherited mutation may account for at least some of the bilateral and multicentric cases. Analysis of the epidemiologic and clinicopathologic features of Wilms’ tumor patients led NWTSG investigators to suggest that some bilateral and multicentric tumors may arise from somatic mosaicism rather than germine mutation. They also suggested that the disease comprises at least two pathogenetic entities that are identifiable on the basis of distinct precursor lesions.

**PATHOLOGY**

Wilms’ tumor is characterized by tremendous histologic diversity and is thought to be composed of, or derived from, primitive metanephric blastema. Most Wilms’ tumors are uniconcicentric lesions, although a substantial number arise multifocally in the kidney. Among 1905 NWTSG cases, approximately 5% involved both kidneys either at initial presentation or subsequent to diagnosis. An additional 7% of reported cases were multicentric unilateral tumors. There is no predilection or either side. The tumor may arise anywhere within the kidney, which is usually markedly distorted by the neoplasm.

The most distinctive microscopic feature of Wilms’ tumor is its structural diversity. The classic nephroblastoma is made up of varying proportions of three cell types (i.e., blastemal, stromal, and epithelial), but they are not all present in every case. Anaplasia is marked by the presence of gigantic polyoid nuclei within the tumor sample. The new definition of focal anaplasia emphasizes distribution, requiring that cells with anaplastic nuclear changes be confined to sharply restricted foci within the primary tumor. By definition, focally anaplastic disease must not be identifiable in any site outside the renal parenchyma.

Clear cell sarcoma of the kidney is an important primary renal tumor associated with a significantly higher rate of relapse and death than favorable histology Wilms’ tumor. Clear cell sarcoma of the kidney has a wider distribution of metastases than favorable histology Wilms’ tumor. Most clear cell sarcomas of the kidney specimens have a distinct histologic appearance, although a number of variant patterns, such as epithelioid, spindling, myxoid, and cystic patterns, invite confusion with Wilms’ tumor or other tumor types.

Rhabdoid tumor of the kidney was identified for the first time in 1978 by NWTSG pathologists. The neoplasm, previously confused with Wilms’ tumor, is a monomorphous tumor like clear cell sarcoma of the kidney. The cell of origin for this distinctive tumor remains unknown. Rhabdoid tumor of the kidney tends to metastasize to the lung and brain. Several studies have reported that separate primary neuroectodermal tumors of the brain have apparently developed in children with this neoplasm. Primary rhabdoid tumors of the kidney and brain (atypical teratoid/rhabdoid tumors) share deletions of chromosome band 22q11.2.

The existence of precursor lesions to Wilms’ tumor has been recognized for many years. They take the form of small, usually microscopic clusters of blastemal cells, tubules, or stromal cells that are generally situated at the periphery of the renal lobe. The lesion that occurs within the deeper cortex of medulla has been termed an intralobar nephrogenic rest in contrast with the more commonly encountered perilobar nephrogenic rest. One or both of these variants are encountered in the renal parenchyma of approximately 30% of Wilms’ tumor cases. These nephrogenic rests are present in approximately 1% of random perinatal postmortem examinations.

Congenital mesoblastic nephroma is important to recognize since it is usually curable by nephrectomy alone. These tumors are typically identified in the first months of life, with a median age at diagnosis of 2 months.

**CLINICAL PRESENTATION AND NATURAL HISTORY**

Most children with Wilms’ tumor come to medical attention because of abdominal swelling or the presence of an abdominal mass. This feature is usually noticed by a parent while bathing or dressing the child. Abdominal pain, gross hematuria, and fever may be present at diagnosis. Hypertension, present in approximately 25% of cases, has been attributed to an increase in renin activity.

During the physical examination, it is important to note the location and size of the abdominal mass and its movement with respiration. A varicocelet secondary to...
obstruction of the spermatic vein may be associated with the presence of a tumor thrombus in the renal vein or inferior vena cava. It is also important to note specifically any signs of the Wilms' tumor-associated syndromes marked by the presence of aniridia, partial or complete hemihypertrophy, and genitourinary abnormalities, such as hypospadias and cryptorchidism.

**STAGING**

The staging system currently employed by the NWTSG is shown in Table 44.2-3.

| **TABLE 44.2-3. National Wilms’ Tumor Study Group Staging System for Renal Tumors** |

**EVALUATION**

Laboratory evaluation should include a complete blood cell count, differential white blood cell count, platelet count, liver function tests, renal function tests, serum calcium, and urinalysis. Elevation of the serum calcium may occur in children with rhabdoid tumor of the kidney or congenital mesoblastic nephroma.

**DIAGNOSTIC IMAGING**

Imaging studies initially should be restricted to those necessary to establish the presence of an intrarenal space-occupying lesion. These studies should also be directed at identifying the presence of a contralateral kidney, which must be assessed for possible tumor involvement. In addition, imaging of the affected kidney must look for evidence of tumor thrombus in the renal vein and measure its proximal extent.

The initial radiographic study often selected is an abdominal ultrasound examination. This demonstrates whether the abdominal mass is solid or cystic and may allow identification of the mass’s organ of origin and measurement of the maximum diameter of the mass. Contrast-enhanced computed tomography (CT) of the abdomen, performed to further evaluate the nature and extent of the mass, may suggest apparent extension of the tumor into adjacent structures such as the liver, spleen, and colon (Fig. 44.2-2). However, most children believed to have invasion of the liver on CT are found to have hepatic compression at the time of surgery, rather than hepatic invasion. The examination also may demonstrate small lesions that may be nephrogenic rests or Wilms’ tumor in the opposite kidney. Small superficial or intrarenal lesions are frequently not identified even when CT is employed.

**FIGURE 44.2-2.** Computed tomography scan of abdomen demonstrating bilateral renal tumors (arrows).

The patency of the inferior vena cava may be demonstrated relatively inexpensively using real-time ultrasonography. When tumor is identified within that vessel, the proximal extent of the thrombus must be established before operation. Extension of the thrombus to the right atrium may produce few, if any, clinical signs and may not be suspected preoperatively.

The results of the radiographic studies and real-time ultrasonography provide sufficient information to support proceeding with a laparotomy in most children, although no imaging study unequivocally establishes the histologic diagnosis of Wilms’ tumor.

Plain chest radiographs should be obtained to determine if pulmonary metastases are present. Insufficient data are currently available to firmly establish the need for CT of the chest in the initial evaluation of children with Wilms’ tumor. Substantial interobserver variation exists in the interpretation of chest CT scans of children with Wilms tumor. The available data suggest that, in many cases, nodules identified are not metastatic tumor. Thus, at least one nodule should be biopsied to confirm the stage.

A radionuclide bone scan and skeletal survey should be obtained postoperatively on all children with clear cell sarcoma of the kidney and all children, regardless of histologic type, with pulmonary or hepatic metastases who have suggestive symptomatology. Both studies are necessary due to the potential of clear cell sarcoma of the kidney to cause lytic bony lesions, which may be evident on plain radiographs but undetectable on bone scan.

In light of the association of intracranial metastases with both clear cell sarcoma and rhabdoid tumor of the kidney, children with either of these histologies should undergo brain imaging.

**TREATMENT**

**Surgery**

Resection is the primary means of achieving local control in Wilms’ tumor, with radiotherapy reserved for locally advanced or metastatic disease. Accurate surgical staging is critical as it determines subsequent requirements for chemotherapy and radiotherapy based on penetration of renal capsule by tumor, regional lymph node involvement, and residual tumor. These factors cannot be determined radiographically with sufficient sensitivity for treatment planning. A review of children treated in NWTS-4 demonstrated an increased incidence of local recurrence in those cases in which lymph node biopsies were not obtained. Presumably, these children were understaged and thus, undertreated. The increased incidence of local recurrence in these cases highlights the need for complete surgical staging.
Initial resection of the tumor has been the policy supported by the NWTS through all of its protocols. Despite the presentation of most Wilms' tumors as a large mass, resection is generally feasible. In contrast to neuroblastoma, attempted resections of Wilms' tumors are less likely to be complicated by tumor invasion of surrounding organs. Close surveillance of children undergoing initial nephrectomy in the NWTS-3 cohort demonstrated an operative complication rate of 19.8% in a group that was evaluated. Of these, 28% were serious complications, occurring in 14%, followed by extensive intraoperative hemorrhage in 5.8% of cases. Injuries to other visceral organs (1%) and extensive vascular injuries (1.4%) were much less frequent. Factors that correlated with increased risk of surgical complications included advanced local stage, intravascular extension of the tumor, and resection of other organs. Resected adjacent organs were often found to be merely compressed or distorted by the tumor rather than directly infiltrated. Extensive resection involving removal of other organs or the aorta is expected to carry a high risk of mortality. In such cases of extensive dissection, the first step of initial surgery should be limited to a biopsy, followed by administration of chemotherapy. Resection can be more readily performed after the tumor has regressed.

The International Society of Pediatric Oncology (SIOP) has promoted the use of preoperative treatment of children with Wilms' tumor with radiotherapy or chemotherapy, without histologic confirmation of the diagnosis before therapy is initiated. They report a lower surgical complication rate of 8% by following this policy. This approach has several risks, including (1) the potential for administration of chemotherapy for benign disease; (2) modification of the tumor histology; (3) loss of staging information; and (4) delivering treatment that is inappropriate for a particular histology (e.g., rhabdoid tumor of the kidney). Treatment without an initial diagnosis is difficult to support when NWTS and SIOP studies have both demonstrated a 7.6% to 9.9% rate of benign or other malignant diagnosis in children with a nephrectomy diagnosis of Wilms' tumor. A major driving factor for the use by SIOP of preoperative therapy was the high rate of operative tumor rupture in their early series. This rate decreased from 33% to 4% in the SIOP series when prenephrectomy abdominal radiation was given. However, 33% is an extremely high frequency of this complication. Operative rupture occurred in NWTS-1 and NWTS-2 in 22% and 12% of children, respectively. In NWTS-4, operative rupture occurred in 14% of cases. A subsequent randomized SIOP study reported that the rate of rupture was essentially the same for children receiving abdominal radiation and daunomycin (8%) and those receiving vincristine and daunomycin (6%). In two consecutive nonrandomized studies, the proportion of stage II lymph node–negative children versus stage II lymph node–positive and stage III changed from 45% to 32% and 33% to 19%, suggesting that the preoperative treatments significantly decreased the apparent stage of the children’s disease. Evaluation of NWTS-4 clearly demonstrates that operative rupture, whether localized to the renal fossa or diffuse in the peritoneal cavity, is associated with an increased incidence of local recurrence. This supports the need to avoid rupture by use of an adequate abdominal or thoracoabdominal incision to safely remove the tumor.

Adequate biopsy of lymph nodes in the renal hilum and along the vena cava or aorta is critical for staging. The surgeon must always consider the possibility of stage III disease, and obtain adequate tissue for its diagnosis. While grossly involved lymph nodes are generally resected, this approach should not be extrapolated into a recommendation for an extensive retroperitoneal lymph node dissection since this has not been shown to improve local control. The histologic diagnosis following preoperative treatment of pathologic findings that would determine staging were not altered by preoperative therapy. A SIOP study randomized the use of local radiotherapy (20 Gy) in children treated preoperatively with chemotherapy who had stage II node-negative disease at resection. The study was terminated after randomization of 123 children because of an increased incidence of abdominal recurrence during the first year of follow-up in the children not receiving radiation (six vs. none). This suggests that the difference in outcome suggested that prenephrectomy treatment altered the pathologic findings that would otherwise have led to a diagnosis of stage III disease (i.e., lymph node involvement or capsular penetration) and inclusion of local radiation.

Preoperative treatment of Wilms' tumor is generally accepted in certain circumstances. These include the occurrence of Wilms' tumor in children with a solitary kidney, bilateral renal tumors, tumor in a horseshoe kidney, and resectional distress from extensive puly, and nearby metastases. In most instances, pretreatment biopsy should be obtained. In children with bilateral disease or involvement of a solitary kidney, preoperative chemotherapy is intended to permit maximal conservation of uninvolved renal parenchyma. Studies on pretreatment of children with unilateral tumors have demonstrated that in most instances a complete nephrectomy is still required due to extensive involvement with the kidney at presentation. In the bilateral cases, preservation of normal renal tissue is a more critical issue. In these children the contralateral tumor often is smaller and more amenable to a partial nephrectomy after treatment with chemotherapy. Concerns about long-term renal impairment following removal of more than one-half of the renal parenchyma have resulted in a less radical surgical approach to the treatment of these children.

The goal of therapy in bilateral cases is to eradicate all tumor, and second, to preserve as much renal tissue as possible to minimize the frequency of renal failure. The management presently recommended is initial bilateral renal biopsy and staging. Children then receive combination chemotherapy based on the stage and histology. A reevaluation is performed after 5 weeks to determine if there has been sufficient response of the tumors to allow tumor resection, with performance of an adequate abdominal incision. This approach has the potential of gaining the advantage of preoperative chemotherapy, as well as the potential advantages of both surgery and chemotherapy. Missed tumors at surgery due to incomplete resection or tumor extension into adjoining structures increases the risk of dissemination. Intraoperative extension of a tumor thrombus is an uncommon event, occurring in 4% of children with Wilms' tumor. Identification of vascular extension by preoperative radiographic studies or by palpation early in the surgical exploration is critical to avoid embolization during mobilization of the kidney. Traditionally, vascular extension has been managed by resection following nephrectomy. Cardiopulmonary bypass is used for atrial extension. This approach has been associated with a significant risk of complications. In one NWTS report, 23 children with vascular extension were treated initially with chemotherapy after biopsy of the renal mass. Complete resolution of the tumor thrombus occurred in seven children, and all lesions except one decreased in size. Of the 14 children with tumor initially extending into the atrium, only 4 had residual atrial involvement at resection requiring sternotomy and bypass. Tumor embolism did not occur during chemotherapy. This study suggests that children with atrial or caval involvement generally require less extensive resection after preliminary treatment with combination chemotherapy.

Gross hematuria in children with Wilms’ tumor is infrequent, but should lead to suspicion of extensive involvement of the renal pelvis with possible extension into the ureter. Cystoscopy should be considered in these children to identify extension of the tumor into the bladder and avoid transection of the tumor with division of the ureter. Ureteral extension that is recognized and entirely resected does not increase the stage of the tumor.

Exploration of the contralateral kidney has been recommended by the NWTS based on the 5% occurrence of synchronous lesions. Exploration of the renal fossa by cephalad Gerota's fascia to directly examine the anterior and posterior aspects of the kidney is suggested. A review of children with bilateral tumors treated on NWTS-4 identified 9 of 122 children in whom the diagnosis of bilateral disease was missed by the preoperative imaging studies [CT, ultrasonography, or magnetic resonance imaging (MRI)]. All but one of these lesions were small, with five being less than 1 cm and three being 1 to 3 cm in diameter. CT was found to be more sensitive for diagnosing contralateral disease than ultrasonography. Thus, 7% of the 5% of children presenting with bilateral disease would have been missed if exploration had not been performed, or an incidence of 0.35% among children with Wilms’ tumor. This low frequency explains why more recent studies with smaller
numbers of children have reached other conclusions.

The role of surgery in the treatment of pulmonary relapse has been evaluated by the NWTS in 211 patients. While diagnostic confirmation of relapse may be required, there was no therapeutic benefit identified to resection of a solitary pulmonary metastasis in addition to pulmonary radiotherapy and chemotherapy alone. Four-year survival rates were identical in the two groups.

**Radiation Therapy**

Pioneering radiation oncologists noted that Wilms' tumors were responsive to radiation therapy. This modality then became routine postoperative treatment at Children's Hospital, Boston, where many of the initial observations concerning the management of these children were made. First, the treatment volume was extended across the midline to include the entire circumference of the implicated vertebral bodies. This was done to equalize the growth suppression; irradiation of only one side of a vertebra had been shown to lead to an obligatory scoliosis convex away from the irradiated side.

The original radiation therapy concepts have been modified as the result of the clinical trials conducted by the NWTS. For example, the age-adjusted dosages were shown to be unnecessary in tumors of favorable histology. The advent of effective drugs had a profound effect, not only on the general management of these children, but also on the indications for the administration of postnephrectomy abdominal irradiation. Presumed microscopic residual disease in the tumor bed of children with stage I favorable histology Wilms' tumor can be successfully treated with combination chemotherapy rather than flank irradiation. This was demonstrated in the first two NWTS randomized clinical trials that indicated the overall relapse-free survival rate in all patients, regardless of age, was similar to that of irradiated patients in NWTS-1 who had received chemotherapy with doxorubicin. Retrospective analyses of the data accumulated in NWTS-1 and NWTS-2 were conducted to determine the patterns of relapse and to evaluate the relationship between abdominal radiation therapy dose and intraabdominal tumor recurrence. In NWTS-3, the unirradiated and the irradiated (20 Gy) stage II, favorable histology patients had similar relapse-free survival percentages, as did those with stage III, favorable histology, who received nominal doses of 10 versus 20 Gy. Meanwhile, excellent results continued to be recorded for stage I, favorable histology patients, none of whom received radiation therapy. In summary, NWTS-1, NWTS-2, and NWTS-3 demonstrated that stage I and II patients with favorable histology tumors who receive vincristine and doxorubicin do not require postoperative irradiation. A dose of 1000 Gy is sufficient for local control in stage III, favorable histology patients if they also received chemotherapy with vincristine, doxorubicin, and cyclophosphamide. Whole lung irradiation (12 Gy) is recommended for patients who present with pulmonary metastases visible on plain chest radiography. Chemotherapy doses given immediately after the completion of whole lung irradiation are decreased by 50%.

A pilot study conducted by investigators from SIOP produced results similar to those of the NWTS in stage IV, favorable histology patients following treatment with nephrectomy and chemotherapy only. Patients with persistent or recurrent lung nodules received whole lung radiation therapy or surgical removal of the metastatic lesions or both. Using a similar approach, the United Kingdom Children's Cancer Study Group reported results inferior to those of the NWTS in this group of patients.

The potential adverse effects of whole lung irradiation and chemotherapy (which includes vincristine, doxorubicin, and doxorubicin as employed in the NWTSG treatment regimens) include radiation pneumonitis or Pneumocystis carinii pneumonia, or both. These complications are an important cause of morbidity and mortality in patients with stage IV Wilms' tumor. Patients with pulmonary lesions identified only on CT of the chest should undergo biopsy of one or more lesions to confirm that they are due to metastatic Wilms' tumor if treatment with whole lung irradiation and doxorubicin is planned. A report from St. Jude Children's Research Hospital suggested that such patients have an increased risk of pulmonary recurrence following treatment with chemotherapy only. A review of the experience with such patients treated on NWTS-3 and NWTS-4 did not demonstrate a clear benefit of whole lung irradiation for such patients. The 4-year relapse-free survival rate was 85% among 53 irradiated patients and 80% among 37 unirradiated patients. This improvement in relapse-free survival must be balanced against the increase in potential side effects of therapy, leaving the use of whole lung irradiation as a continued source of debate.

**Chemotherapy**

Wilms' tumor was the first pediatric malignant solid tumor found to be responsive to the systemic chemotherapeutic agent doxorubicin. Other active agents were subsequently identified, including vincristine, doxorubicin, and cyclophosphamide.

### FAVORABLE HISTOLOGY WILMS' TUMOR

#### NATIONAL WILMS' TUMOR STUDY-3

Patients with stage I Wilms' tumor were successfully treated using an 11-week regimen composed of vincristine and doxorubicin without abdominal irradiation. The 4-year relapse-free percentage and overall survival percentage with this regimen were 89.0% and 95.6%, respectively.

Patients with stage II Wilms' tumor were randomized to receive vincristine and doxorubicin or these two drugs and doxorubicin. They were also randomized to receive tumor bed irradiation (20 Gy) or no radiotherapy. The 4-year relapse-free percentage and overall survival percentage for patients who were treated with vincristine and doxorubicin and no abdominal irradiation were 87.4% and 91.1%, respectively. There was no statistically significant difference between these results and those for the remaining three treatment regimens for patients with stage II, favorable histology tumors.

Patients with stage III Wilms' tumor were randomized to treatment with vincristine and doxorubicin or these two drugs and doxorubicin. They were also randomized to receive 10 or 20 Gy of abdominal irradiation. This study demonstrated that these patients benefited from the addition of doxorubicin to the two-drug combination of vincristine and doxorubicin. There was no statistically significant difference in the frequency of intraabdominal relapse among those treated with 10 Gy compared with 20 Gy. Although there was no statistically significant difference in the frequency of intraabdominal relapse in any of the subgroups, there appeared to be a higher frequency among those treated with vincristine and doxorubicin with 10 Gy (7 of 61), compared with those receiving vincristine and doxorubicin with 20 Gy (3 of 68) or vincristine, doxorubicin, and doxorubicin with 10 Gy (3 of 70). The 4-year relapse-free percentage and overall survival percentage of those children treated with vincristine, doxorubicin, doxorubicin, and 10 Gy of abdominal irradiation were 82.0% and 90.9%, respectively.

Patients with stage IV Wilms' tumor were randomized to receive vincristine, doxorubicin, and doxorubicin or these three drugs and cyclophosphamide. All underwent immediate nephrectomy, and all received abdominal irradiation (20 Gy) and whole lung irradiation (12 Gy). The 4-year relapse-free percentage and overall survival percentage for the patients treated with vincristine, doxorubicin, and doxorubicin were 79.0% and 80.9%, respectively. There was no statistically significant improvement in the 4-year relapse-free percentage or overall survival percentage from the addition of cyclophosphamide to the three-drug regimen.

#### NATIONAL WILMS' TUMOR STUDY-4

Previous success in treatment strategies allowed the design of a unique study, NWTS-4, with the primary aims of continuing to improve treatment results while decreasing the cost of therapy through modification of the schedule of drug administration. This study was based on experimental and clinical data demonstrating the safety and efficacy of doxorubicin when administered in a single, moderately high dose.

The design of NWTS-4 (Fig. 44.2-3) allowed the results of pulse-intensive chemotherapy regimens employing single doses of doxorubicin and doxorubicin to be compared with treatment regimens using divided dose regimens of each drug. In addition, treatment durations of 6 and 15 months were compared in patients with stages II to IV, favorable histology tumors.
Toxicity analyses confirmed that the pulse-intensive regimens produce less hematologic toxicity than the standard regimens, and the administered drug dose intensity is greater on the pulse-intensive regimens. Also, an analysis of the cost of chemotherapy treatment suggested that at least $728,000 per year could be saved if all U.S. children with stages I to IV, favorable histology Wilms' tumor were treated using the pulse-intensive regimens. In addition, there were no statistically significant differences in the 2-year or 4-year relapse-free percentages or overall survival percentage of patients treated with pulse-intensive, compared with standard, modes of chemotherapy administration.

TREATMENT

These recommendations are based on the results of the NWTSG, which advocates early surgery without preoperative therapy and modulates therapy according to stage and histology. For stage I, favorable or anaplastic histology, stage II, favorable histology, combination chemotherapy with vincristine and dactinomycin is recommended; no abdominal radiation therapy is necessary. For stage III, favorable histology, combination chemotherapy with vincristine, dactinomycin, and doxorubicin and postnephrectomy abdominal radiation therapy are recommended. For stage IV, favorable histology, combination chemotherapy with vincristine, dactinomycin, and doxorubicin and postnephrectomy abdominal radiation therapy if renal tumor is stage III are recommended; all patients with pulmonary metastases receive whole lung radiation therapy. For stages I through IV, anaplastic histology, combination chemotherapy with dactinomycin, vincristine, doxorubicin, and cyclophosphamide is recommended; all patients receive abdominal radiation therapy; all patients with pulmonary metastases receive whole lung radiation therapy. For stages I through IV, clear cell sarcoma of the kidney, combination chemotherapy with vincristine, dactinomycin, and doxorubicin is recommended; all patients receive abdominal radiation therapy; and all patients with pulmonary metastases receive whole lung radiation therapy.

Prognostic Factors

Tumor size, age of the patient, histology, lymph node metastases, and local features of the tumor, such as capsular or vascular invasion, have been predictive of outcome. Modern treatments have been so successful that some of these factors no longer pertain.

The results of the first three NWTS were evaluated using logistic regression analysis. Children entered on NWTS-1 who were younger than 24 months of age had a significantly better prognosis than those who were older. The relapse rate was 14.8% for those younger than 2 years of age, compared with 34.7% for those between 2 and 4 years old, and 27.6% for those older than 4 years.

The histology of Wilms' tumor was identified as the most important determinant of prognosis. More recent analyses have confirmed the importance of histopathology and lymph node involvement, whereas the prognostic significance of other factors, such as age and tumor size, changes as treatment efficacy improves.

NEUROBLASTOMA

EPIEDEMIOLGY AND GENETICS

Neuroblastoma is the most common malignant intraabdominal tumor in children. Based on the most recent epidemiologic survey compiled in 1995, neuroblastoma (including ganglioneuroblastoma) occurs at an annual rate of 9.1 cases per 1 million U.S. children younger than 15 years of age. Neuroblastoma occurs more frequently in boys than in girls. The median age at diagnosis was 2 years for both boys and girls.

Neuroblastoma has been pathologically documented in additional members of immediate and extended families, including parents, siblings, twins, and cousins.

Mediastinal or cervical neuroblastoma is associated with hypertension and Horner's syndrome.

Patients with neuroblastoma have been diagnosed with several other conditions, including neurofibromatosis, Beckwith-Wiedemann syndrome, and Hirschsprung's disease.

Neuroblastoma in situ was identified in 0.37% to 2.58% of infants younger than 3 months of age who died of other causes and underwent autopsy examination. This finding suggests that the frequency of neuroblastoma may be higher than indicated by figures derived from death certificate diagnoses or clinical (pathologic) diagnoses. Many in situ neuroblastomas may undergo involution or maturation or both.

PATHOLOGY

The microscopic features of a typical neuroblastoma include the presence of nests of tumor cells, separated by fibrovascular septa, with additional areas of hemorrhage, calcification, and necrosis. The tumor cells are uniform round cells with a round hyperchromatic or densely speckled nucleus. Mitoses are not frequent. Homer-Wright rosettes, with a central fibrillar core, may be present. Lymphocytic infiltration may be observed. Neuroblastoma may contain mature elements, including ganglion cells.

Histochemical stains may aid in the differentiation of neuroblastoma from other common pediatric solid tumors. The periodic acid–Schiff stain result is generally negative, and neuron-specific enolase is generally positive.

Shimada and colleagues developed a histologic classification of neuroblastomas based on the separation of tumors into two large groups: stroma-rich and stroma-poor tumors based on the presence or absence of schwannian spindle cell stroma. Stroma-poor tumors were further subdivided into those that were nodular, well-differentiated, or mixed. These histopathologic features were evaluated along with other characteristics, including patient age and the mitotic-karyorhexis index for their importance in predicting prognosis. Patients with nodular, stroma-rich histology and undifferentiated, stroma-poor histology had a poor prognosis. This histologic classification was based on an examination of 295 pathologic specimens from a population of patients, of whom only 25% had stage IV (Evans') disease. This stage distribution is not representative of unselected series of neuroblastoma patients. Several subsequent reports have evaluated the Shimada classification in case series that included patients with advanced disease. There may be a high degree of overlap between classification as a ganglioneuroblastoma and stroma-rich tumors. The International Neuroblastoma Pathology Committee has developed a modification of the Shimada system that was validated in a case-cohort sample of 227 neuroblastic tumors. The International Neuroblastoma Pathology Classification (the Shimada system) is proposed for international use in assessing neuroblastic tumors. Further statistical evaluation of this histopathologic classification and its correlation with other prognostic variables, such as age at diagnosis, stage, primary tumor site, and biologic variables (i.e., N-myc copy number and DNA ploidy), is necessary to establish the importance of histopathologic grading for the management of children with neuroblastoma.

CLINICAL PRESENTATION AND NATURAL HISTORY

FIGURE 44.2-3. Treatment randomization for patients entered on National Wilms' Tumor Study-4. Doxorubicin and radiation therapy (RT) are included in the treatment regimen only for patients with stage III or IV Wilms' tumor. EE, K, and DD are regimen designations; RT, radiotherapy; S, surgery.
Neuroblastoma may originate from any sympathetic nervous system tissue in the body (Fig. 44.2-4). The most common site of origin of neuroblastoma is within the abdomen. The adrenal gland is the primary tumor site in 38% of cases. Other intraabdominal sites include the paravertebral sympathetic ganglia, celiac ganglion, superior mesenteric ganglion, and inferior mesenteric ganglion. The remaining patients with neuroblastoma have tumors that originate in the thorax or neck.

Infants and children with neuroblastoma come to medical attention with a variety of signs and symptoms, most commonly the presence of abdominal swelling or an abdominal mass. Abdominal or thoracic paravertebral tumors frequently cause symptoms referable to the central nervous system. Children with hematogenous metastases may complain of pain in one or more bones or present with periportal swelling or ecchymoses. Fever is present in 23% of patients at diagnosis. Uncommon clinical presentations include hydrops fetalis, chronic diarrhea due to secretion of vasoactive intestinal polypeptide by the tumor, and myoclonus-oppositional. Jones and coworkers reported that 50% (8 of 16) of patients evaluated for acute cerebellar encephalopathy were found to have neuroblastoma. Although the prognosis for complete recovery from the movement disorder is poor, treatment with intravenous gamma globulin has been effective in some patients, supporting an autoimmune etiology for this disorder. Hypertension is an uncommon presenting sign in children with neuroblastoma.

Infants and children with neuroblastoma frequently present with hematogenous metastases. These were identified in 62% of patients. The most frequently involved sites were bones, liver, bone marrow, lung, and skin.

Normal sympathetic tissues secrete the catecholamines epinephrine and norepinephrine. Most patients with neuroblastoma have increased urinary excretion of vanillylmandelic acid, homovanillic acid, dihydroxyphenylalanine, dopamine, and norepinephrine at the time of diagnosis. Mass screening of infants at 4 months of age has been employed in Kyoto, Japan, since 1974, and throughout Japan since 1985. Data from both Kyoto and Sapporo suggest that mass screening has resulted in a decrease in the incidence of neuroblastoma among older children and a decrease in the percentage of patients who have metastatic disease at diagnosis. However, the absence of adequate data have precluded the demonstration that screening in Japan has altered the mortality due to neuroblastoma. Population-based screening of 3-week-old infants has been conducted in Quebec province, Canada. Because excellent population-based data on incidence, survival, and mortality are available, these studies address the questions raised by the studies from Japan. Unfortunately, the Canadian experience has paralleled the outcome of the Japanese efforts. Mass screening in both countries has led to the prudential identification of increased numbers of infants with favorable tumor biology. Most of these infants would have had an excellent prognosis with little, if any, therapy. Neither screening effort has had any effect on the number of children identified with clinically advanced disease and unfavorable tumor biology. To date, newborn screening has had a negligible effect on survival and may have led to overtreatment of children with good prognostic features.

STAGING

Local features of neuroblastoma that can be related to treatment success include the extent of the primary tumor and the presence or absence of lymph node metastases. Dissemination of tumor to the liver, subcutaneous tissue, bone marrow, and bones can also influence prognosis.

Evans and colleagues developed a staging system, first reported in 1971, that considered the extent of the primary tumor, the presence or absence of regional lymph node tumors, and the presence or absence of hematogenous metastases in determining the tumor stage. This system recognized the existence of a unique group of infants with small primary tumors and liver, skin, and bone marrow metastases, but without positive findings in the skeletal survey (stage IVS). This system demonstrated the favorable prognosis of patients with localized primary tumors, but did not consider the possible independent effects of lymph node involvement or surgical excision on prognosis.

A new staging system, the International Neuroblastoma Staging System, was proposed in 1986. Because of ambiguity regarding the classification of tumors originating near the midline and having a favorable prognosis, the staging system was revised in 1993. This staging system, recommended for adoption by the Children's Cancer Group (CCG) and the Pediatric Oncology Group (POG), is shown in Table 44.2-4.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
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<tbody>
<tr>
<td>I</td>
<td>Resected tumor, no evidence of dissemination</td>
</tr>
<tr>
<td>II</td>
<td>Tumor not resectable, no evidence of dissemination</td>
</tr>
<tr>
<td>III</td>
<td>Tumor not resectable, with evidence of dissemination</td>
</tr>
<tr>
<td>IV</td>
<td>Tumor not resectable, with evidence of dissemination</td>
</tr>
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CLINICAL EVALUATION

The evaluation of a child suspected to have neuroblastoma begins with a careful history. The maternal history should be examined for the use of tranquilizers, anticonvulsant medications, and the abuse of alcohol. The review of systems should include careful questioning regarding symptoms such as diarrhea and ataxia. The physical examination should include a careful examination of the skin. Subcutaneous metastases from neuroblastoma are reddish-purple, raised lesions that may be solitary. Periorbital ecchymoses are a frequent finding in children with disseminated tumor. The color of the irises and the location and consistency of the abdominal mass should be noted. A careful neurologic examination should be performed. Occasionally, the tumor mass in a child with paraplegia can be detected only on rectal examination.
The laboratory examination of a child suspected to have a neuroblastoma should include a complete blood cell count, urinalysis, liver and renal function tests, sedimentation rate, serum ferritin, and a urine sample for quantitation of the excretion of vanillylmandelic acid and total catecholamines.

The radiographic evaluation of a child with an abdominal mass suspected to be a neuroblastoma begins with a plain supine examination of the abdomen that may demonstrate the presence of a soft tissue mass frequently having calcification. Abdominal ultrasonography demonstrates the presence of a solid mass that may contain cystic areas. CT provides information regarding the extent of intraperitoneal disease that is not obtained with the plain radiography or abdominal ultrasound. However, there is a substantial difference between findings using CT and surgical findings. Patients with thoracic neuroblastomas typically have a palpable mediastinal mass demonstrated on plain chest radiography. Calcification is present within this mass less frequently than within primary intraabdominal neuroblastomas. Detailed films of the ribs and vertebral bodies may demonstrate erosion of the adjacent ribs, transverse processes, and widening of the intervertebral foramina.

Patients with paraspinal primary tumors may have asymptomatic extension of the tumor through the spinal foramina. Armstrong and coworkers reported symptoms suggestive of spinal cord or nerve root compression by tumor were present in only 55% of patients with paraspinal neuroblastoma subsequently shown to have such compression at myelography. Due to the increased risk of neurologic compromise with paraspinal tumors, patients with tumors in this location should undergo careful evaluation of the spinal canal using MRI with gadolinium.

All patients should have a conventional skeletal survey, including the long bones, spine, ribs, and skull, and a technetium 99m methylene diphosphonate bone scan. Although most bone metastases are identified using the technetium bone scan, occasional lesions, especially in the metaphyses of long bones, are identified only on the conventional skeletal survey.

Bilateral trephine bone marrow biopsies and bone marrow aspirates should be performed. The biopsy is positive in 11% to 30% of children with negative bone marrow aspirate results. Bone marrow replacement by tumor is occasionally so extensive that the microscopic picture resembles acute leukemia.

TREATMENT

Surgery

Surgery plays a major role in the treatment of low-stage neuroblastoma. The surgical approach varies depending on the stage and site of the primary. It is increasingly recognized that the biologic characteristics of the tumor should also contribute to therapeutic decision making. Most thoracic, pelvic, and cervical primaries and limited abdominal lesions that do not extend across the midline to involve the great vessels are resectable at presentation. Surgery alone is curative in many children with low-stage disease. The need for postresection chemotherapy is now frequently determined by the biologic markers of the resected tumor. Reports suggest that even subtotal resection in infants and children with neuroblastoma with favorable biologic features results in a correspondingly favorable outcome and constitutes adequate therapy.

Improved survival has been identified in children with more extensive primary tumors (stage III disease) whose tumors were completely resected at initial exploration or during subsequent surgeries following administration of chemotherapy. This improvement in outcomes may be a reflection of favorable biology than a product of skillful surgery. Children previously treated on CCG protocols were reclassified using the International Neuroblastoma Staging System. This study demonstrated a strong correlation between survival and the extent of residual tumor after resection. Histologically, viable neuroblastoma is found in most tumors resected following preliminary chemotherapy, supporting the important role of resection in achieving local control. No difference in survival was found between those children undergoing resection at presentation versus those receiving preliminary chemotherapy.

Neuroblastoma arising in the posterior mediastinum appears to have a favorable prognosis when compared with other primary sites. This has been correlated with a higher incidence of favorable biologic markers in mediastinal tumors. Large tumors are also more readily resected in the chest than in the abdomen where they may surround the aorta, vena cava, renal vessels, celiac axis, and the superior mesenteric artery.

Regrettably, the majority of infants and children present with metastatic disease. In these cases, the initial role of surgery is obtaining diagnostic tissue. Traditionally, surgical diagnosis has employed either a laparotomy or thoracotomy. Improved methods have been developed for percutaneous biopsy with radiographic imaging or biopsy via laparoscopic or thoracoscopic techniques. If these latter methods are used, it is critical that adequate tissue be obtained for evaluation of biologic markers.

Most children with widely disseminated disease have large primaries. Abdominal primaries arising from adrenal or paravertebral sites often encircle the celiac axis and the superior mesenteric vessels. Several studies have demonstrated that resection of these extensive lesions can be best accomplished after initial treatment with chemotherapy. In addition to reducing tumor volume, preoperative chemotherapy decreases the vascularity and friability of the tumor. This neoadjuvant approach has also contributed to decreased operative morbidity, including a lower complication ratio with nephrectomy.

Postoperative diarrhea may complicate resections of extensive tumors surrounding the superior mesenteric or celiac arteries. This increased stool output is presumably produced by disruption of the autonomic nerve supply to the gut and not related to the timing of surgery. Several studies have demonstrated an apparent decrease in the frequency of local recurrences following resection of the primary in stage IV tumors. Improved survival, however, has not been achieved since the majority of these advanced stage patients ultimately succumb to relapse at distant sites. As systemic therapy improves, local control will become more critical. Use of radiolabeled metaiodobenzylguanidine and a hand-held gamma detector to identify sites of neuroblastoma in extensive or recurrent cases has been described. Whether use of these techniques will result in better outcomes has yet to be established.

Attempts should be made to preserve the ipsilateral kidney during resection of the primary tumor in children with stage IV neuroblastoma. Many of these children receive either a bone marrow transplant or nephrotoxic agents, making maximal preservation of maximum renal function an important goal. Children with adrenal or paravertebral primaries generally have metastatic tumor in lymph nodes that wraps around the renal vessels. These must be dissected free to preserve the kidney. The risk of nephrectomy is greatest in children undergoing resection before the administration of chemotherapy.

Infants with stage IVS disease require exploration or a percutaneous biopsy for diagnosis. In most cases resection is not necessary unless the most readily obtained tissue is suggestive of neuroblastoma. In fact, one review of 110 infants with stage IVS disease treated by members of the POG showed that there was no statistical difference in survival rate for patients with complete resection of their primary tumor compared with those who underwent partial resection or biopsy only. Decreased survival was associated with age less than 2 months, diploid ploidy, amplification of the N-myc protooncogene, or tumors with unfavorable histology. If a mass remains at the primary site after resection of the distant disease, resection is often performed and frequently demonstrates a ganglioneuroma or neuroblastoma with extensive maturation. Surgical techniques have been developed for abdominal expansion for infants presenting with extensive hepatomegaly that impairs respiratory function. The abdominal fascia is divided and prosthetic material is inserted to increase the volume of the abdominal cavity.

Antenatal diagnosis of neuroblastoma appears to identify a particularly good risk population of infants. The biologic markers on these tumors are favorable. In keeping with their less aggressive biology, infants have done well following resection of the primary tumor. It is not known whether spontaneous regression would occur if these infants were observed, but a report of four infants with antenatal diagnosis of adrenal masses (two solid and two cystic) demonstrated resolution of the abnormalities by 2.5 to 8.0 weeks of age.

Radiation Therapy

Radiation therapy has been used in the treatment of patients with neuroblastoma both to decrease the frequency of local tumor recurrence and to eradicate microscopic or macroscopic distant metastases. Wyatt and Farber systematically treated patients with neuroblastoma with local irradiation. They suggested radiation therapy should be instituted in every case once the diagnosis is established.

Rosen and colleagues reported local control in 100% (14 of 14) of patients with stage I to stage III (Evans') neuroblastoma treated with 10 to 20 Gy, and in 87.5% (21
of 24) of patients treated with 20 to 40 Gy. One patient had recurrence in the treatment volume, whereas two others were considered marginal misses, occurring outside of high-dose boost volumes.  

Reports have demonstrated patients with stage I (International Neuroblastoma Staging System) neuroblastoma have a 4-year relapse-free survival percentage of 89% when treated with surgery only.  

Children with stage II (Evans’) neuroblastoma with microscopic residual disease may benefit from local irradiation.  

The POG randomized patients with stage C neuroblastoma to treatment with postoperative chemotherapy or postoperative chemotheraphy and local irradiation (24 to 30 Gy). The 3-year event-free survival percentage was 32% for patients with stage III (Evans’) randomized to treatment with combination chemotherapy, compared with 59% for those randomized to the same chemotherapy and local radiation therapy (P = .009). Thus, in patients with residual disease or positive lymph nodes, the addition of irradiation therapy appears to improve the prognosis. Refinements of these recommendations may be necessary in the future as newer studies that use biologic markers for treatment stratification identify subsets that do or do not benefit from local radiation therapy.  

Chemotherapy  

Although two published studies offer a glimmer of hope for metastatic patients treated with dose-intensive regimens incorporating stem cell support,  

prospects for long-term survival in advanced stage disease remain poor despite increasingly toxic therapies. At the other end of the spectrum, trials conducted in patients without evidence of gross residual disease have not demonstrated a survival advantage for adjuvant chemotherapy. A retrospective analysis of patients with locally unresected disease, however, demonstrated a clear survival advantage for children treated with temozolomide and cisplatin (93%) versus those whose treatment did not include these two drugs (42%; P = .02). The role of chemotherapy in these patients must be addressed in future randomized trials.  

The poor response of patients with metastatic neuroblastoma to aggressive combination chemotherapy programs stimulated clinical trials that incorporated autologous bone marrow transplantation (ABMT) or peripheral blood stem cell rescue. Event-free survival 2 years after ABMT was reported to be 6% to 64%,  

among progressions patients with advanced neuroblastoma who received a bone marrow transplant. The spectrum of results may reflect patient selection. A retrospective analysis by the POG showed no significant prognostic benefit of changing, in remission, from conventional therapy to bone marrow transplant. The CCG reported the results of a randomized trial comparing the outcome following intensive chemotherapy without bone marrow transplant to that following ABMT. The 3-year event-free survival was 34% ± 4% for those randomized to ABMT, compared with 22% ± 4% for those randomized to continuation chemotheraphy (P = .034). However, 32% of patients randomized to ABMT did not receive the randomized therapy, whereas 21% of those randomized to continuation chemotherapy did not receive the randomized treatment. ABMT did not improve overall survival compared with continuation chemotherapy. A secondary randomization involving a 6-month course of 13-cis retinoic acid following completion of treatment produced a 3-year relapse-free survival rate of 46% ± 6% for those who received the drug. This outcome compared favorably with the 29% ± 5% relapse-free survival for patients who were not randomized to treatment with cis-retinoic acid (P = .027). Current treatment protocols employed by the POG and the CCG stratify patients by stage, age, N-myc status, Shimada histology, and DNA ploidy (Table 44.2-5).  

### TABLE 44.2-5. Risk Group and Protocol Assignment Schema: Pediatric Oncology Group and Children’s Cancer Group  

#### Low-Risk Patients  

Children with stage I neuroblastoma have an excellent prognosis following excision of the primary tumor without adjuvant therapy. Children with stage II disease with a single copy of N-myc, regardless of histology, have an excellent prognosis following tumor excision alone. Stage II patients with greater than ten copies of N-myc and favorable Shimada histology also have a good prognosis following tumor resection. Despite the amplification of N-myc in this subset of children with localized disease, the favorable Shimada histology has sufficient predictive power that radiation and chemotherapy are not recommended unless recurrence is documented. Perhaps the most unique cohort of low-risk patients consists of asymptomatic infants with disseminated stage IVS neuroblastoma and hyperdiploidy (DNA index greater than 1.0). Since many of these infants spontaneously improve, they should be observed without treatment.  

#### Intermediate-Risk Patients  

Among children without N-myc amplification, those with stage III (Evans') neuroblastoma who are younger than 12 months of age, stage III patients with favorable Shimada histology who are more than 12 months of age, and those with stage IV neuroblastoma who are less than 12 months of age all have a moderate risk of disease recurrence. Their treatment may include local radiation therapy and combination chemotherapy. As noted previously, infants with stage IVS neuroblastoma require supportive care only. Those younger than 6 weeks of age at diagnosis may have feeding intolerance or respiratory insufficiency due to massive hepatomegaly, mandating a brief course of chemotherapy.  

#### High-Risk Patients  

All children with N-myc amplification, regardless of stage, and all children older than 1 year of age with stage IV neuroblastoma have a substantial risk of disease progression. These children should be treated using study regimens being evaluated by the national or international pediatric clinical trials groups. The role of ABMT is being evaluated in the subgroup of patients who have a favorable response to combination chemotherapy.  

### PROGNOSTIC FACTORS  

Breslow and McCann evaluated the interaction between age at diagnosis, stage (Evans’), and probability of survival. These investigators confirmed the adverse effect of both increasing age at diagnosis and advanced stage on the probability of survival.  

Other clinical investigators have reported lower survival percentages in stage IV (Evans’) patients with a vanillylmandelic acid to homovanillic acid ratio of less than 1.5. A poorer prognosis has also been ascribed to stage III and IV (Evans’) patients with a neuron-specific enolase level greater than 100 ng, and for stage IV patients (Evans’) with serum lactate dehydrogenase greater than 1000 IU.  

Look and coworkers reported that patients with hyperdiploid tumor cells had a more favorable response to combination chemotherapy than did patients with diploid tumor cells. Brookman and colleagues demonstrated the relationship between advanced tumor stage and increased copy number of N-myc, and Nakagawara and associates reported that increased expression of TRK-A was associated with a favorable prognosis. Although several reports have documented the prognostic effect of several of these markers, the retrospective design of the published analyses and the small number of patients with all markers evaluated has prevented an adequate multivariate analysis from being performed. A prospective study in which treatment was not a variable would facilitate this important analysis.  

### RETINOBLASTOMA
EPIDEMIOLOGY AND GENETICS

Retinoblastoma is the most frequent malignant ocular tumor in pediatric patients. The incidence rate per year is 3.8 cases per 1 million U.S. children younger than 15 years of age. Approximately 70% to 75% of all cases are unilateral. Among children with unilateral disease, 10% to 15% have hereditary germline deletions of chromosome 13, band q14, which contains the RB1 tumor suppressor gene locus. Germline mutations of 13q14 uniformly affect the 25% to 30% of children with bilateral disease. Retinoblastoma occurs slightly more frequently in boys than girls, especially among those who have bilateral retinoblastoma. The median age at diagnosis was 2 years for boys and 1 year for girls with unilateral retinoblastoma. In cases of bilateral disease, the median age at diagnosis is less than 12 months for both boys and girls.

Retinoblastoma may occur in children with other anomalies, including congenital cardiovascular defects, cleft palate, Bloch-Sulzberger syndrome, infantile cortical hyperostosis, dentinogenesis imperfecta, incontinencia pigmenti, and familial congenital cataracts. While most children with retinoblastoma have normal intellectual function, some patients have been reported who had mental retardation in addition to a constellation of features associated with the deletion of the more distal portion of 13q. These features include a broad nasal bridge, hypertelorism, microphthalmos, micrognathia, and variable foot and toe anomalies.

While the majority of new cases of retinoblastoma arise spontaneously from new somatic mutations, a significant, and possibly increasing, fraction of retinoblastomas are hereditary. The familial pattern may demonstrate direct transmission of retinoblastoma from parent to child, or the presence of two or more affected offspring from unaffected parents who have affected first-degree relatives. Retinoblastoma is transmitted in each of these situations as a highly penetrant, autosomal dominant trait. An analysis of the offspring of patients with sporadic, bilateral retinoblastoma demonstrated that 49.2% of the offspring developed the disease. This suggests that essentially all patients with sporadic, bilateral retinoblastoma had a germinal mutation that was transmitted in an identical manner as in families with a positive history of retinoblastoma. Approximately 5.5% of the offspring of patients with sporadic, unilateral retinoblastoma developed the disease, suggesting that 9.9% to 12.3% of patients with sporadic, unilateral retinoblastoma actually have a germinal mutation that may be transmitted to their offspring.

A more complex problem in genetic counseling arises when one is asked to estimate the risk of an unaffected member of a sibship with a positive family history for retinoblastoma who carries the retinoblastoma gene. It is also difficult to estimate the risk for recurrence of retinoblastoma in a sibship from unaffected parents with one affected sibling. Nussbaum and Puck have analyzed these situations and developed equations for estimating these various probabilities.

The parents and siblings of all patients with retinoblastoma should have a thorough ophthalmoscopic examination. Retinoblastomas may undergo spontaneous regression, leaving characteristic retinal changes. Margo and associates suggested such lesions were benign at their outset. These lesions indicated the presence of the same mutation found in patients with retinoblastoma, although they occurred in a more mature retinal cell.

PATHOLOGY

The gross appearance of retinoblastoma is that of a chalky white, friable tumor with dense foci of calcification. Those arising from cells in the internal nuclear layer, nerve fiber layer, ganglion cell layer, or external, nuclear layer grow toward the subretinal space, pushing the retina inward and frequently causing retinal detachment. Such tumors are called the endophytic type. Those tumors arising from the inner layers of the retina grow toward the vitreous and are called the exophytic type. Multiple foci of tumor are usually present.

Retinoblastoma is composed of uniform small, round, or polygonal cells, which have scanty, poorly staining cytoplasm. The sparse cytoplasm is located at one side of the cell, suggesting the appearance of an embryonal retinal cell. The nucleus is large and deeply staining. Three types of cellular arrangements may be identified: the Homer-Wright rosette (a radial arrangement of cells surrounding a tangle of fibrils), the Flexner-Wintersteiner rosette (a radial arrangement of cuboidal to short columnar cells about a lumen, with the nuclei displaced basally, away from the lumen), and the fleurette (areas composed of pail-appearing cells, with abundant, pale eosinophilic cytoplasm and small, hyperchromatic nuclei; the cells are arranged in a fleur-de-lis pattern). Calcification and necrosis are often observed in retinoblastomas.

CLINICAL PRESENTATION

Patients with retinoblastoma come to medical attention most frequently because of the presence of leukokoria. Strabismus, conjunctival erythema, or decreased visual acuity are other common presenting complaints. The tumor may be diagnosed during a routine examination performed because of a family history of retinoblastoma or during an examination for an unrelated complaint in patients without a family history of retinoblastoma.

The history obtained during the evaluation of a child with leukokoria should include questions regarding the administration of oxygen following birth, the eating of dirt, or the close association of the patient with a dog. Prolonged administration of oxygen is associated with the occurrence of retrolental fibroplasia. Domestic animals, particularly young puppies, may be infested with Toxocara canis; a parasite that may cause an ocular lesion resembling retinoblastoma in some of its clinical features. The family history should be examined for other cases of eye and bone tumors.

The physical examination reveals the presence of a white pupillary reflex. Tumors located near the macula may be readily apparent with direct ophthalmoscopy, whereas those located at the periphery of the retina may not be detected unless the patient looks in a particular direction. Esotropia or exotropia may be identified. The eye may be red and painful due to uveitis following spontaneous necrosis of a retinal tumor or due to glaucoma. Decreased visual acuity may be due to involvement of the macula by the tumor or the presence of cells and debris in the vitreous.

EVALUATION

The laboratory evaluation of a child suspected of having retinoblastoma should include a complete blood cell count with white blood cell differential, tests of renal and hepatic function, and a urinalysis. An enzyme-linked immunoabsorbent assay for the detection of Toxocara antibody is available. An antibody was detected in the serum of 65% of patients with ocular toxocariasis, indicating this determination may be helpful in differential diagnosis when an antibody is present.

Radiographic evaluation of a child suspected of retinoblastoma may include CT of the orbit or orbital ultrasonography. CT may be used both to define the extent of the intraocular tumor and to determine the presence and extent of extraocular disease. Calcification was identified in orbital CT scans of 48% of patients with retinoblastoma confined to the globe, compared with 13% of patients with tumor extension beyond the globe. Head CT or MRI may identify intracranial extension in patients who have normal plain radiographs of the bones adjacent to the orbits. The tumor may metastasize to the central nervous system, bones, or bone marrow. The risk of such dissemination is related to the extent of the ocular tumor. A diagnostic lumbar puncture with examination of the cerebrospinal fluid following cytocentrifugation should be performed on all patients with involvement of the choroid, ora serrata, ciliary body, or anterior chamber. It should also be performed on patients with involvement of other extracocular structures, including the orbit or optic nerve, or when symptoms, signs, or diagnostic imaging studies suggest involvement of bones, soft tissues, or the central nervous system.

Radionuclide bone scans should be obtained only for patients with extensive ocular involvement, symptoms suggesting the presence of a bone metastasis, and bone marrow involvement by retinoblastoma.

STAGING

Martin and Reese proposed the first staging system for patients with retinoblastoma in 1942. The classification segregated patients into large treatment groups and established four categories: (1) unilateral tumors not extending outside of globe; (2) bilateral tumors; (3) residual tumors in the optic nerve or orbit at the time of enucleation or recurrent tumors following enucleation; and (4) widely disseminated retinoblastoma. These investigators recognized the more favorable prognosis of patients with a small flat tumor and the ominous nature of tumors that extended toward the vitreous or into the choroid. Subsequently, those patients with anteriorly located tumors were shown to have an unfavorable prognosis. These factors were considered in developing a more detailed staging system.
A useful staging system for patients with retinoblastoma must incorporate those features known to influence prognosis, therapy, or both. Simplicity would allow easy adoption of the system by investigators at many treatment centers. The system adopted by the St. Jude Children’s Research Hospital incorporates many of these features (Table 44.2-7).

### TABLE 44.2-6. Staging System for Retinoblastoma (Reese and Ellsworth)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Tumor limited to sensory retina in one eye only.</td>
</tr>
<tr>
<td>2</td>
<td>Tumor limited to sensory retina in both eyes.</td>
</tr>
<tr>
<td>3</td>
<td>Tumor extends beyond the sensory retina, but not into the optic nerve.</td>
</tr>
<tr>
<td>4</td>
<td>Tumor extends into the optic nerve, but not into the orbit.</td>
</tr>
<tr>
<td>5</td>
<td>Tumor extends into the orbit.</td>
</tr>
</tbody>
</table>

The diagnosis of retinoblastoma is based on the clinical history of the patient (including the family history) and the results of an examination of both eyes under general anesthesia. Ellsworth suggested the pupils must be maximally dilated and the examination be performed with the binocular indirect ophthalmoscope. Scleral indentation must be performed around the entire circumference of the ora serrata to ensure detection of all anteriorly located tumors. Using scleral indentation, retinoblastoma may be identified in the periphery of the fundus in approximately 65% of patients. These tumors either originated posterior to the equator (82%) or were of small to moderate size and located anterior to the equator, where they could only be seen with indentation of the sclera. The examination of the retinal surface is not completed when the first tumor is identified. The entire retinal surface of both eyes must be evaluated and the locations of tumors noted on a diagram.

### SURGICAL CONSIDERATIONS

The indications for enucleation include (1) unilateral retinoblastoma that completely fills the globe or that has damaged and disrupted the retina so extensively that restoration of useful vision is not possible; (2) bilateral retinoblastoma in which the previously mentioned conditions exist in only one eye; (3) a tumor present in the anterior chamber; (4) painful glaucoma with loss of vision following rubeosis iridis; (5) extensive bilateral retinoblastoma in which there is no potential for restoration of useful vision; (6) retinoblastoma unresponsive to other forms of local therapy; and (7) cases with permanent visual loss in which intracocular tumor is suspected.

### ADVANCED UNILATERAL DISEASE

Patients with suspected retinoblastoma should be referred to a pediatric ophthalmologist experienced with the treatment of retinoblastoma. The standard surgical technique is modified to allow excision of the longest possible segment of optic nerve in continuity with the globe. The surgeon must be careful not to perforate the globe when the extraocular muscles are divided. The globe and optic nerve are inspected for evidence of extraocular extension of the tumor. Orbital biopsies should be obtained when extracocular extension is suspected to be present. After the globe is enucleated, a plastic implant is placed in the muscle funnel. Although the presence of the ocular prosthesis may prevent early detection of an orbital recurrence of tumor, the cosmetic result and promotion of normal development of the bony orbit are considerably improved with the use of a prosthesis.

The importance of including a sufficient (10 to 15 mm) length of optic nerve in the surgical specimen is emphasized by reports of inferior survival rates among patients with extension of retinoblastoma to the margin of the excised optic nerve.

The survival rate reported for patients with retinoblastoma confined to one or both globes, treated only with enucleation, was 86% for those with unilateral disease and 97% for those with bilateral disease.

### LIMITED UNILATERAL OR LIMITED BILATERAL DISEASE

Patients with limited unilateral or bilateral residual or recurrent disease after radiation therapy may benefit from photocoagulation or cryotherapy. Photocoagulation was reported to have successfully eradicated retinoblastomas in 80% of the patients treated. Hopping and Meyer-Schwickerath stated that suitable cases for this technique included solitary or multiple tumors, less than 4 to 5 disc diameters in size, situated at or posterior to the equator. Tumors located near the macula or papillary area and those with a mushroom shape should not be treated with photocoagulation.

Cryotherapy was first employed for the treatment of a patient with retinoblastoma in 1963. Subsequent reports that included some patients treated sequentially with local irradiation and cryotherapy suggested long-term control of retinoblastoma was possible using this technique. Abramson and colleagues reported long-term control of retinoblastoma with one cryotherapy session in 80% of patients with previously untreated tumors, 59% of new postirradiation tumors, and 56% of recurrent tumors following irradiation. Tumors arising from the vitreous base were not responsive to cryotherapy. These investigators stated that previously untreated patients with tumors located anterior to the equator and those with recurrent or new tumors following irradiation were candidates for cryotherapy. Cryotherapy is generally effective for tumors up to 2.5 mm in diameter and 1.0 mm thick that are confined to the sensory retina.

### BILATERAL DISEASE

Historically, external-beam irradiation was used for the treatment of the less involved eye, following enucleation of the more involved eye of a patient with bilateral retinoblastoma. The decision to irradiate or enucleate the remaining eye was based on consideration of the location of the tumor, the presence of multiple foci of
The development of megavoltage radiation allowed the design of treatment plans that could irradiate the retinal surface to a uniform dose, while relatively sparing the posterior surface of the lens. All current techniques require meticulous attention to daily field placement. Treatment can be administered reproducibly with the use of general anesthesia. Many radiation oncologists prefer to use a single, temporal field, moving the edge of the field anteriorly in patients who are at high risk of anterior recurrence of tumor.

Many new techniques have been proposed for a more conformal dose distribution in retinoblastoma. Proton beam therapy or stereotactic techniques offer significant advantages in sparing normal tissues. For example, even with the conventional small fields used, the posterior field edge frequency encompasses the hypothalamic and pituitary area. This may lead to the late occurrence of endocrine dysfunction. Proton beam techniques avoid such an exit dose to normal structures.

Several patterns of tumor regression following irradiation have been described, including the following patterns. In type I (cottage cheese calcium) the tumor shrinks in size and assumes an irregular, glistening white appearance similar to cottage cheese. In type II, the tumor shrinks in size to one-half to three-fourths of the initial volume and loses the pink color of capillary injection. The surface is gray and homogeneous, and some areas may be markedly translucent. An annulus of pigment disturbance may be exposed at the border of the tumor. In type III, a glistening white nidus of calcium, or DNA, is present in the center of an amorphous, translucent gray mass. The lesion loses its pink, solid appearance. It may be possible to see through the translucent tumor and identify normal choroidal markings. A pigment disturbance is frequently noted at the periphery of this lesion.

Increased awareness of the risk of retinoblastoma among the siblings and offspring of retinoblastoma patients resulted in the diagnosis of tumors when they were small. Abramson and coworkers reported on the treatment of patients with early, bilateral retinoblastoma using bilateral irradiation. The radiation dose used for the treatment of the majority of the cases was 55 Gy. Residual tumors were present in 37% of the eyes when treatment was completed, and additional tumors developed in 16% of the eyes treated. All patients had group I, II, or III tumors. The risk of developing a second, nonocular malignancy in this group of irradiated patients is significant.

Patients presenting with group IV and V bilateral retinoblastoma have been treated with radiation doses of 35 to 60 Gy. Enucleation was subsequently required for persistent or recurrent tumors in 67% of the treated eyes. The survival rate of the combined series of patients treated with bilateral irradiation was 82% compared with a survival rate of 71% among a group of patients treated only with bilateral enucleation. Although the risk of a radiation-related second malignant tumor developing in a patient with bilateral retinoblastoma is considerable, the data available suggest the long-term survival of patients treated with bilateral irradiation is not worse than that of patients treated with bilateral enucleation only. The preservation of some useful vision in these patients is an obvious advantage of such a treatment approach, but prolonged follow-up of patients so treated is necessary to thoroughly evaluate the effect of radiation-related second malignant tumors on long-term survival.

Local irradiation, after enucleation, is recommended for all patients with extension of retinoblastoma into the orbit. Presentation with exophthalmos or a palpable mass through the eyelids suggests the presence of orbital extension of the tumor. The identification of an encapsulated or unencapsulated extracocular mass, enlargement of the cut end of the optic nerve at the time of enucleation, or rupture of the globe during removal are associated with orbital contamination with the tumor. These findings are confirmed histologically by the identification of an episcleral mass of tumor tissue or tumor at the margin of the cut end of the optic nerve. The presence of tumor cells in the choroid and scleral emissaria, in the tissue between the choroid and optic nerve, or the presence of significant scleral necrosis, are highly suggestive of orbital contamination with the tumor. Patients with orbital retinoblastoma should receive irradiation to a volume, including the entire orbit and the optic nerve to the optic chiasm, as indicated. The recommended dose is 44 Gy in 4 weeks to 50 Gy in 4.5 to 5.0 weeks.

**CHEMOTHERAPY**

The role of adjuvant single-agent or combination chemotherapy in the management of patients with retinoblastoma is not well defined. Wolff and associates reported the results of a randomized study of adjuvant chemotherapy with cyclophosphamide (40 mg/kg) and vincristine (0.05 mg/kg) administered every 3 weeks for 57 weeks to patients with unilateral group V retinoblastoma following enucleation. The control patients received no adjuvant chemotherapy. The relapse rates of 7.4% among those randomized to receive adjuvant chemotherapy and 11.1% among those randomized to receive no adjuvant chemotherapy did not differ statistically. Subsequently, Pratt and his colleagues and others reported successful treatment of some patients with advanced or recurrent retinoblastoma using various combinations of etoposide, cisplatinum, doxorubicin, and cyclophosphamide.

The combination of etoposide and carboplatin was evaluated in patients with extracocular retinoblastoma, 85% of whom had partial or complete responses following treatment. These two drugs, in combination with vincristine, doxorubicin, and cyclophosphamide, have been recommended for treatment of children with orbital involvement from retinoblastoma.

The demonstration that combination chemotherapy can produce responses in children with advanced or recurrent tumors has led to pilot studies of combination chemotherapy for reduction of tumor bulk in previously untreated patients. The goal of these trials has been preservation of vision, primarily in children with bilateral disease. Tumor shrinkage may decrease the need for enucleation or external-beam radiation therapy for local control. Unfortunately, the use of different end points, particularly for the definition of treatment failure, has complicated interpretation of the outcomes of these studies. Responses to chemotherapy have been sufficiently provocative, however, that a multicenter, randomized trial of chemotherapy has been undertaken. This trial is intended to assess the therapeutic value of chemotherapy combined with cyclosporin for multidrug resistance reversal in managing advanced stage retinoblastoma.

**RHABDOMYOSARCOMA**

**EPIDEMIOLOGY AND GENETICS**

RMS is the most common malignant tumor of the soft tissues in infants and children. The incidence rate per year is 4.6 cases per 1 million U.S. children younger than 15 years of age. The annual incidence is lower for Asian children than for whites or African American children. RMS occurs slightly more frequently in boys. The median age at diagnosis of children with RMS is approximately 4 years, with girls presenting at slightly older ages than boys.

RMS has been pathologically documented in siblings and cousins of patients and is a frequent tumor in families affected by the Li-Fraumeni syndrome. This syndrome is defined by familial clustering of cancers that include RMS and adrenocortical carcinoma in children and breast cancer in young adults. Affected relatives share germline mutations in the p53 tumor suppressor gene, which maps to chromosome 17p13. In addition to p53 mutations, which have been associated with nearly 50% of RMS cases, mutations in the NF1 gene occurring in children with neurofibromatosis confer an increased risk for developing RMS.

RMS may arise anywhere in the body, although the head and neck region is most frequently involved, accounting for 35% of all cases (Fig. 44.2-5). The most common primary site for RMS is the orbit, accounting for 29% of the RMS in the head and neck, and 13% of all RMS in children. The tumor may develop in a child with retinoblastoma. A melanocytoma of the choroid is an unusual manifestation of RMS and is a frequent tumor in families affected by the Li-Fraumeni syndrome.
The remaining primary tumor sites in the head and neck are divided into parameningeal and nonparameningeal locations. The parameningeal sites, including the nasopharynx, paranasal sinuses, middle ear, mastoid, pterygopalatine fossa, and infratemporal fossa, account for 40% of the RMS that originate in the head and neck. Additional primary tumor sites in the head and neck include the scalp, oral cavity, oropharynx, larynx, parotid gland, and neck. The second most frequently involved regions include the abdomen and genitourinary tract, which account for the location of 29% of primary tumor sites in children with RMS. These tumors originate most frequently from the paratesticular tissues. Other primary tumor sites include the bladder, prostate, vagina, uterus, cervix, and bile ducts. RMS arising in the genitourinary tract tends to affect young children, particularly the vaginal botryoid variant, which commonly presents in infancy.

The third group of tumor sites for RMS originates within the thorax or from the soft tissues of the trunk or extremities. The most common sites involve the lower extremities, with 22% originating in the thigh or groin. RMS arising in the extremities is more likely to be identified in the second decade of life. Almost one-half of these extremity primaries contain alveolar elements that are associated with a more aggressive tumor biology (see Pathology, later in this chapter).

Overall, nearly 25% of all newly diagnosed cases of RMS are metastatic at initial presentation. The most common sites of dissemination include lung, bone marrow, bone, and lymph nodes, in approximate order of frequency.

**PATHOLOGY**

RMS has been traditionally classified into three histologies, consisting of embryonal (including botryoid), alveolar, and pleomorphic subtypes. As noted previously, tumor histology is strongly correlated with the primary tumor site. Alveolar histology is uncommon except in primary tumors of the trunk and extremity, whereas embryonal histology is most common in RMS of the head and neck and those of the genitourinary system. Slightly over one-half of all cases are characterized by favorable embryonal histology, with an additional 6% demonstrating the uniquely favorable botryoid architecture. The prognostically unfavorable alveolar histology constitutes only 21% of all cases of RMS.

Various histologic classification schemes have been proposed since Horn and Enterline first categorized RMS as either embryonal or alveolar in 1958. A revised classification of childhood RMS was proposed in 1995, based on the results of an international collaborative study. This system recognizes six subtypes: botryoid RMS, spindle cell RMS, embryonal RMS, alveolar RMS, undifferentiated sarcoma, and RMS with rhabdoid features. Application of this system has been shown to have greater reproducibility than prior classification schemes, separating patients into prognostically significant groups. Histologic classification of childhood RMS can be difficult, however, since individual tumors may have areas consistent with two or more histologic subtypes. Although immunohistochemical staining for desmin may be useful for the identification of RMS, some tumors lack distinguishing microscopic characteristics and cannot be further categorized.

In light of the limitations of immunohistochemical assessment, molecular diagnostics may prove to be important in identifying biologically less favorable subsets of patients for stratification to more intensive treatment regimens. Embryonal RMS is characterized by loss of heterozygosity at the chromosome 11p15 locus. Although immunohistochemical staining for desmin may be useful for the identification of RMS, some tumors lack distinguishing microscopic characteristics and cannot be further categorized.

**CLINICAL PRESENTATION AND EVALUATION**

Because RMS may originate from so many sites, the radiographic examination of the primary tumor must be individualized. Evaluation of children with RMS requires expert radiographic interpretation, competent pathologic examination of surgical specimens, and knowledge of distant sites to which RMS may spread.

The lungs should be evaluated with plain chest radiography and CT of the chest. Pulmonary nodules identified in children with RMS are frequently benign, suggesting that solitary nodules identified on a chest radiograph of a child with RMS should be examined pathologically. The skeleton may be evaluated using conventional radiography and radionuclide scanning. The bone marrow may be involved by RMS in the absence of bone or pulmonary metastases. Potential bone marrow involvement that may produce hypercalcemia is assessed by bilateral bone marrow aspiration and biopsy. The bone marrow aspirate was positive at the time of diagnosis in approximately 10% of patients and may be the only definite site of identifiable disease.

In addition to the aforementioned sites of hematogenous dissemination, lymph node involvement has been documented in 10% to 20% of cases of RMS. These nodal sites may be evaluated radiographically or pathologically.

**STAGING**

Staging and risk-group stratification of children with RMS is complicated by the many potential sites from which the tumor may originate and the correspondingly different prognoses for affected children depending on site, resectability, and histology. Recognizing these difficulties, an international panel of experts evaluated two staging systems and concluded that the TNM system (Table 44.2-8) best defined the pretreatment extent of the disease, facilitating patient management based on the extent of the disease and comparisons of treatment outcome between studies. Treatment decisions for patients treated using the Intergroup Rhabdomyosarcoma Study Group protocols are based on both TNM stage and clinical outcome, as shown in Table 44.2-9.

**TABLE 44.2-8.** Tumor (T), Node (N), Metastasis (M) Pretreatment Staging for Rhabdomyosarcoma
The addition of doxorubicin to the combination of vincristine and actinomycin improved the relapse-free survival of children with group III RMS (excluding primary tumors of the bladder, prostate, vagina, and uterus). The addition of cisplatin with or without etoposide to the combination of VAC did not improve the relapse-free survival of children with group III RMS (excluding primary tumors of the bladder, prostate, vagina, and uterus).
cavity, larynx, oropharynx, and cheek. The addition of doxorubicin to the combination of VAC did not improve the relapse-free survival of children with group IV RMS. 266 The addition of doxorubicin and cisplatin, with or without etoposide, to the combination of VAC did not improve the relapse-free survival of children with group IV RMS. 266

From 1991 to 1997, 894 patients were enrolled on IRS-IV. This study randomized patients between VAC, VAI (vincristine, actinomycin-D, ifosfamide), and VIE (vincristine, ifosfamide, etoposide). The 3-year failure-free survival for all three groups was approximately 75% for nonmetastatic disease. There were no statistically significant differences in outcome between the randomized treatment groups. In light of the therapeutic parity of the three regimens, VAC remains the gold standard due to the lesser risk of renal damage compared with the two regimens containing ifosfamide. 266

The current IRS-V study, which was first started in 1995, focuses on improving survival in the intermediate- and high-risk subsets of patients. An attempt at dose-escalating cyclophosphamide (Cytotoxan) in one of these pilots was proven to be prohibitively toxic. Since all three agents in the VAC regimen are currently delivered at maximal dose intensity, improvements in survival will require identification of new active agents. Based on encouraging pilot data from treatment of metastatic patients with VAC plus topotecan, a phase III study is now being conducted in intermediate-risk patients. Eligible patients are being randomized to VAC alone versus VAC alternating with vincristine, topotecan, and Cytotoxan.

Survival for metastatic (stage IV) patients has only marginally improved from 20% to 32% since the inception of the IRS in 1972. In an effort to improve survival in this very high-risk subset of children, a series of phase II window studies have been undertaken. Patients with metastatic RMS are now being treated with an induction regimen that combines vincristine with irinotecan. Like topotecan, irinotecan is a camptothecin analogue that exerts its cytotoxic effect by inhibition of topoisomerase I. Irinotecan has demonstrated impressive antitumor activity in preclinical studies with murine xenografts. Subsequent pilot studies for metastatic patients may revisit the therapeutic potential of anthracyclines in the form of Doxil, a liposomally encapsulated analogue of doxorubicin, currently in phase I studies. It is hoped that the liposomal delivery system will minimize cardiotoxicity, permitting more dose-intensive application of anthracyclines to sarcoma therapy.

**SPECIFIC PRIMARY TUMOR SITES**

**Head and Neck**

**ORBIT.** Children with orbital RMS present with proptosis, due to a retrobulbar tumor, or swelling of the eyelid. The radiographic evaluation must demonstrate whether the tumor is confined to the orbit or has extended inferiorly into the maxillary sinus or posteriorly into the ethmoid sinus and cranial cavity. CT provides excellent definition of the soft tissue mass and can demonstrate the presence of bone destruction. 267

Surgery. Biopsy is required before beginning treatment of orbital tumors. Due to the excellent response to radiation and chemotherapy, orbital exenteration is not indicated except for the unusual cases of recurrent disease in this site.

Radiation Therapy. The technique of local irradiation should include treatment of a volume that includes the entire soft tissue mass, demonstrated radiographically, with a margin of normal tissue. The dose given to the macroscopic tumor should be 45 to 50 Gy. These patients should receive combination chemotherapy with VAC. The 5-year progression-free survival percentage for those patients with orbital RMS of the nasopharynx present with signs of upper airway obstruction, which is frequently associated with cranial nerve palsies. On examination, they are found to have a soft tissue mass that is depressing the palate and extending into the retropharyngeal space.

The radiographic evaluation of a patient with a parameningeal RMS must document the presence and extent of bone destruction and identify local or intracranial extension of the tumor. The temporal bone, petrous bone, mastoid, and infratemporal fossa can be adequately evaluated using CT. Coronal sections obtained either by rescanning the patient or reprocessing the data obtained from the axial scan of the head allow identification of tumor extension into the floor of the middle and posterior cranial fossae. 267

Surgery. Surgical resection is infrequently required at this site because of the excellent response to chemotherapy and radiotherapy. In children who have persistent disease after completion of radiotherapy or who have tumor recurrence, surgery should be considered. 271 Modern methods of resection and reconstruction of these sites make surgery much less mutilating than in the past, with improved long-term functional outcomes. Before the initiation of therapy, a lumbar puncture should be performed. A cytocentrifuge preparation of the cerebrospinal fluid should be examined for tumor cells.

Radiation Therapy. Parameningeal RMS progresses locally by destruction of the adjacent bones and by growth along nerves. 272, 273 To achieve local control of this tumor, a generous margin of these tissues must be included within the volume of irradiation. 274, 275 The tumor mass must receive a radiation dose of at least 50 Gy. Meticulous treatment planning is necessary to deliver adequate therapy to the tumor without causing excessive or unnecessary damage to adjacent normal tissues including the brain and eye. 276

RMS of the middle ear may recur as diffuse meningeal disease. This occurred in 17.5% of patients with a parameningeal primary tumor entered on IRS-I. 276 The high rate of primary meningeal relapse in this study may have been related to inadequate radiation technique. Although these investigators recommended the administration of craniospinal irradiation to prevent meningeal recurrence, others reported isolated meningeal relapse in 5.4% to 7.4% of patients with parameningeal RMS. 276, 277, 278

This suggests that the rate of meningeal recurrence is related to the adequacy of the volume and dose of irradiation to the primary tumor. Current guidelines in IRS-V for parameningeal disease do not recommend craniospinal irradiation. Treatment is confined to the tumor volume plus a 2-cm margin for parameningeal tumors without intracranial extension. In cases of documented intracranial extension, the skull is included in the irradiated target volume.

Chemotherapy. Approximately one-half of children with parameningeal primary tumors have group III tumors. These children require treatment with the combination of vincristine, dacarbazine, and doxorubicin. The 5-year progression-free survival percentage for all children with parameningeal primary tumors on IRS-III was 70%, 262 a result similar to that reported for IRS-II. 261 Patients who present with bone erosion of the cranial base, with or without a cranial nerve palsy, have a 3-year disease-free survival percentage of 43%, compared with 65% for those with intracranial extension and 81% for those without any evidence of meningeal involvement. 262 VAC remains the therapy of choice for parameningeal disease.

**Other Head and Neck Sites.**

RMS may originate in several nonorbital and nonparameningeal sites, including the parotid region, larynx, soft and hard palate, tonsil, tongue, cheek, nose, scalp, and neck. Children with a parotid RMS present with unilateral swelling at the angle of the mandible and local pain. Those with RMS of the larynx present with hoarseness or signs of airway obstruction.

Although radical excision of tumor in these sites has been reported in a few cases, local infiltration of the tumor usually precludes gross total excision. Despite the prohibitions of surgical morbidity, local tumor control can be achieved with irradiation. The volume of irradiation should include a margin of normal tissue. Direct tumor extension along the extracranial portions of the adjacent cranial nerves may occur. These areas should be included within the treatment volume. The dose to gross residual disease should be 45 to 50 Gy. These patients should receive combination chemotherapy with VAC. The 5-year progression-free survival percentage for these children was 78% on IRS-III, similar to the result of IRS-II. 262, 266
RMS of the thorax may arise from the soft tissues of the chest wall or within the thoracic cavity. Primary tumors of the chest wall present as a localized swelling.

The radiographic evaluation of a patient with a primary tumor of the chest wall should include plain chest radiography and CT.

SURGERY. Lesions in the trunk, arising in the chest or abdominal wall and paraspinal or retroperitoneal sites, are best resected if possible because of their less favorable response to chemotherapy and radiotherapy. Complete surgical removal is limited by the frequently large size of these lesions at diagnosis as well as their involvement of vital structures within the abdomen or chest. Resections of the chest or abdominal wall often require prosthetic mesh reconstruction. Primary resection should be considered if pathologic examination of the initial specimen demonstrates microscopic residual disease. In a review of IRS studies II and III, there were 84 patients with thoracic sarcomas. Although 71% (60 patients) achieved an initial complete response, 39 suffered a local relapse, whereas an additional 22 patients developed distant relapse. Fifty-eight percent (49 patients) have died, with an average survival of 1.1 years. Survival was significantly associated with clinical group, size, and local or distant recurrence.

RMS arising in the abdominal wall is rare, accounting for only 1% of all cases of this disease. A review of patients with abdominal wall primaries treated on IRS I through IV demonstrated a substantial advantage to complete versus partial resection of localized tumors (100% vs. 62%). Biliary tract primaries appear to be more responsive to chemotherapy than other truncal sites. Affected children typically present with symptoms of biliary tract obstruction. Diagnostic biopsy followed by chemotherapy is appropriate, with resection reserved for those children with persistent disease.

Initial biopsy followed by chemotherapy and radiotherapy has also been standard therapy for bulky tumors of the retroperitoneum and nongenital pelvic sites. These tumors make up approximately 10% of all RMS. The treatment outcome for these tumors on IRS-III and -IV has been reviewed. All of the 138 eligible patients with tumors in these locations were either group III (gross residual) or group IV (metastatic). Nearly one-half of these patients were metastatic at diagnosis. Children with embryonal histology had a 4-year failure-free survival of 56% versus only 33% for children with alveolar or undifferentiated histology. Nearly all of the patients with alveolar tumors underwent biopsy only, followed by chemotherapy and radiation. In contrast, 40% of patients with embryonal tumors underwent extensive debulking at initial surgery. Among the embryonal patients, the failure-free survival at 4 years was 72% for those who underwent debulking versus only 48% for those embryonal patients who underwent biopsy followed by chemotherapy and radiation. The apparent advantage to debulking will be prospectively analyzed in IRS-V.

RADIATION THERAPY. When complete tumor excision is not possible, local control is established with the use of radiation therapy. The volume must include the grossly apparent tumor with a margin of normal tissue. A radiation dose of 40 Gy is adequate for microscopic residual disease, while 50 Gy is required for gross residual disease. The pleural space is considered contaminated if there is a malignant pleural effusion, or if the tumor is cut across and the pleural space is opened at the time of surgery. The entire pleural surface must be irradiated when pleural contamination with tumor cells has occurred. Failure to do so may result in disease recurrence on the pleural surface not included within the volume of irradiation.

CHEMOTHERAPY. Embryonal RMS of the trunk should be treated using the chemotherapy regimens appropriate for the clinical group. Group I tumors are treated with the combination of vincristine and actinomycin, whereas groups II, III, and IV are managed with the combination of VAC. Primary tumors of the trunk frequently consist of alveolar elements. As in other sites, alveolar tumors in the trunk do not respond to chemotherapy as favorably as embryonal disease. Children with intermediate- or high-risk disease arising in these sites are currently being evaluated for response to VAC plus one of the camptothecin analogues.

Extremity

Patients with RMS of an extremity usually present with localized swelling. Occasionally, a child with RMS of an extremity comes to medical attention due to symptoms caused by metastases, such as spinal cord compression secondary to vertebral body metastases, or pain due to other bone metastases. Nearly 25% of extremity primaries are metastatic at the time of diagnosis.

Radiographic evaluation of a patient with an RMS of the extremity should include plain radiographs of the primary tumor site and a bone scan. The presence of increased radionuclide uptake in the adjacent bone, although generally not associated with frank invasion of the bone by tumor, is correlated with the presence of inflammatory adhesions between the tumor and adjacent bone. Local recurrence of the tumor is likely if the tumor is not removed en bloc with the adjacent bone. CT and MRI are useful for defining the extent of the soft tissue mass and the presence of bone destruction. Arteriography may be necessary to evaluate the relationship between the tumor, contiguous muscle compartments, and their vascular supply.

SURGERY. Complete resection of the tumor with negative microscopic margins is the goal in extremity sarcomas. There is no advantage to amputation or muscle group excision compared with local excision with an adequate surrounding rim of normal tissue, provided the resection results in negative microscopic margins. The extent of the resection is often tempered by attempts to minimize functional impairment. In extremity tumors, consideration of the initial biopsy site and the direction of the incision is particularly important, because an inappropriate biopsy can greatly complicate later resection. Extremity lesions should rarely be resected without an initial biopsy because the surgical approach when resecting a malignant lesion will be quite different from the approach for a benign lesion.

Extensive local lesions with invasion of vital structures are often treated first with chemotherapy and subjected to delayed surgical resection. The goal of delayed resection is to render the child free of gross residual disease and then to control microscopic residual disease that can be controlled with a lower dose of radiotherapy than the dose required for gross residual disease (40 vs. 55 Gy). This multidisciplinary approach results in good local control, while minimizing the potential morbidity of an extrease initial resection or amputation.

Lymph node sampling is important in extremity RMS due to the significant risk of lymphatic involvement. Nearly 25% of all extremity tumors demonstrated regional nodal infiltration. A representative sample of lymph nodes from the draining nodal group should be biopsied. A lymph node resection should not be performed because of the risks of producing lymphedema, which complicate radiotherapy and subsequent surgical resection of the primary lesion.

Analysis of data from IRS-III has shown that estimated 5-year survival was directly related to the clinical group, with a 95% survival in group I, versus 67% in group II, 58% in group III, and 33% in group IV. Survival was independent of histology or site. Multivariant analysis of pretreatment factors showed that lymph node metastasis, age over 10 years, and distant metastasis predicted worse survival. The difference between the survival percentage of 51 group I and III patients with lymph node-negative distal extremity lesions who could have been made group I with extensive resection and that of patients with group I distal extremity tumors approached statistical significance in univariate analysis (P < .06). All four group II patients who had resection of margins survived, whereas only 18 of 31 without resection survived. In IRS-IV, the failure-free survival rate was 55%, with an overall survival rate of 70%. Again, the 3-year failure-free survival was closely related to group (group I, 91%; II, 72%; III, 50%; IV, 23%). In this cohort, clinical group and stage were both highly predictive of outcome. None of the other variables were predictors of failure-free survival by multivariate analysis.

RADIATION THERAPY. Postoperative irradiation must be to a volume that includes a generous margin around the tumor. The radiation dose should be 50 Gy to areas of gross residual disease. Patients with histologic confirmation of regional lymph node involvement should receive similar treatment to a volume that includes the involved lymph nodes.

CHEMOTHERAPY. Embryonal RMS of the extremity should be treated using the chemotherapy regimens described earlier for RMS of the trunk. Approximately one-half of extremity RMS have alveolar histology and require chemotherapy appropriate for this histologic subtype with a poorer prognosis.

Genitourinary

Patients with RMS of the paratesticular tissue present with painless enlargement of the testis. The age distribution is bimodal, with peaks at 5 and 16 years of age. Children with RMS of the prostate present most frequently with acute urinary retention or with difficulty in voiding. Hematuria, dysuria, and abdominal swelling are also observed. Those with RMS of the bladder usually present because of hematuria, urinary frequency, or dysuria. The physical examination of children with a prostate tumor is unremarkable except for the presence of a mass between the bladder and rectum that is palpable on rectal examination. Radiographic evaluation should include a voiding cystourethrogram or CT of the abdomen and pelvis. These studies demonstrate displacement of the bladder, in the case of a prostatic primary.
tumor, or the presence of multiple polypoid masses within the bladder, with thickening of the bladder wall in the case of a bladder primary tumor. Children with sarcoma botryoids of the vagina frequently present with a polypoid mass protruding from the vaginal orifice or with vaginal bleeding. These children should have an a-fetoprotein (AFP) level obtained before tumor biopsy or excision, since yolk sac tumor may also present as a vaginal mass.

SURGERY. Anterior pelvic exenteration is rarely required today. Bladder, prostate, and vaginal primaries are first biopsied, and lymph node extension is defined. Chemotherapy and radiotherapy are then used to eradicate residual disease. In the IRS-I and -II studies there were 28 vaginal and 10 uterine lesions. Vaginal lesions generally arise from the anterior vaginal wall in the area of the embryonic vesico vaginal septum. The mean age of children with vaginal tumors was under 2 years. Over the course of the first four IRS studies spanning 25 years, the percentage of children undergoing resections of vaginal tumors has steadily decreased from 90% to 13%. Despite the limitation of surgical intervention to biopsy, survival in this group remains excellent, exceeding 90% with minimal surgical morbidity.

In contrast to vaginal lesions, uterine primary tumors arise in older children demonstrate a greater propensity for local recurrence. As with vaginal lesions, initial surgical intervention is limited to biopsy in most cases. Hysterectomy is reserved for those patients who fail to achieve a complete response to chemotherapy and radiation. Survival in women with uterine disease approaches 90%.

Preservation of the bladder and prostate was one of the primary goals of the IRS-II study in which surgical therapy was shifted from initial resection to primary biopsy with subsequent radiotherapy or surgery. The 5-year survival rate of patients on IRS-II (70%) was similar to that of IRS-I (70%), but the 2-year disease-free survival rate was lower (62% vs. 70%). The percentages of 95 children with bladder and prostate tumors in IRS-II who retained their bladder and were alive at 2 and 3 years of age were 33% and 22%, respectively, compared with 26% and 23% in the 66 children with bladder or prostate tumors in IRS-I. Sequential treatment on this protocol failed to improve bladder salvage. The rate of retention of a functional bladder at 4 years from diagnosis was 60%. Excluding children who presented with disseminated disease, mortality was only 10% among children treated on IRS-III for bladder or prostate tumors.

Successful treatment of paratesticular RMS first requires a transinguinal radical orchectomy. Testicular masses should never be approached through the scrotum due to the risk of inducing spread into the pelvis via the inguinal lymphatics. In addition, the desired high inguinal ligation of the spermatic cord cannot be accomplished by the scrotal approach. A total of 121 boys with paratesticular RMS treated on IRS-III had retroperitoneal lymph node dissection to evaluate metastasis. Lymph node excisions were radiographically negative based on CT in 81% of the boys, 14% of whom had positive nodes when biopsy or retroperitoneal lymph node dissection was performed. Among the boys with abnormal nodes by radiographic criterion, 94% had pathologic confirmation of lymph node involvement. Retroperitoneal relapse occurred in only 2 of the 121 boys, one of whom had pathologically negative lymph nodes and did not receive radiotherapy. While CT was accurate if lymph node abnormalities were identified, it was not extremely sensitive in identifying nodal involvement.

RADIATION THERAPY. The IRS reported that there was no obvious benefit from prophylactic retroperitoneal lymph node irradiation among patients with paratesticular RMS, who had negative pathologic staging of retroperitoneal nodes.

Tumors of the bladder and prostate were initially managed with radical resections including cystectomy. Although excellent survival was achieved with this approach, the extensive surgical morbidity of this strategy prompted subsequent efforts at tissue-sparing treatment designs. Current IRS guidelines now recommend early introduction of radiation in combination with chemotherapy following a minimally invasive biopsy. Employing this multimodal approach on IRS-III produced improved progression-free survival of approximately 75%, while maintaining partial or complete bladder function.

CHEMOTHERAPY. Patients with group II paratesticular primary tumors of embryonal histology have an excellent prognosis when treated with the combination of vincristine and dactinomycin, with a 5-year progression-free survival percentage of 81%. All patients with group III (biopsy only) genitourinary tumors are treated with VAC.

PROGNOSTIC FACTORS

As noted previously, the favorable prognostic factors for children and adolescents with RMS include tumor status (T1, tumor localized in the organ or tissue of origin) and primary tumor site (orbit, genitourinary nonbladder, or prostate). Although alveolar histology predicts a poorer outcome with standard therapy, the difference in survival between alveolar and embryonal cases resolves when more intensive therapy is applied to alveolar tumors. Despite improvements in therapy, however, children with metastatic disease still fare poorly, with a 5-year survival between 20% and 30%.

The rarity of Ewing's family tumors in African American children is only 0.6 per 1 million. The rarity of Ewing's sarcoma in African American and Asian populations has been confirmed by several investigators. Ewing's sarcoma occurs more frequently in boys than girls and has been reported in three pairs of female siblings.

The femur is the most frequent primary site for Ewing's sarcoma, accounting for approximately 20% to 25% of all cases. Lower extremity tumors may also arise in the tibia, fibula, or the bones of the feet. Combining all potential sites of lower extremity disease, these tumors account for 45% of newly diagnosed Ewing's sarcomas. The pelvis is the second most common primary site for Ewing's sarcoma, accounting for an additional 20% of new cases. Pelvic tumors may arise in the ilium, ischium, pubic bone, or sacrum. Upper extremity sites comprise another 12% to 16% of new diagnoses, with the humerus accounting for the majority of these cases. The remainder of Ewing's sarcomas originate from the vertebral, ribs, clavicle, mandible, and skull. These axial lesions account for nearly 13% of all newly diagnosed cases.

PATHOLOGY

Ewing's sarcoma and primary neuroectodermal tumors are counted among the small blue round cell tumors of childhood. Based on readily apparent features noted on light microscopy, this grouping includes neuroblastoma, RMS, and non-Hodgkin's lymphoma. Tumors of the Ewing's sarcoma family are characterized by the presence of highly cellular aggregates of tumor cells compartmentalized by widely separated strands of fibrous tissue. The tumor cells are regular in shape, with round to oval nuclei. The slightly granular cytoplasm is often framed by indistinct cellular outlines. The nuclei contain finely dispersed chromatin, giving the nucleus a ground glass appearance. Inconspicuous nucleoli may be present with occasional mitotic figures.

Within the Ewing's family of tumors, primary neuroectodermal tumors are characterized by significant neuroectodermal differentiation. These tumors typically demonstrate Homer-Wright pseudorosettes on light microscopy and positive immunohistochemical staining for synaptophysin and neuron-specific enolase. In contrast to primary neuroectodermal tumors, Ewing's sarcomas are poorly differentiated tumors that do not form pseudorosettes and do not stain positively for neural markers.

Regardless of the extent of neural differentiation, nearly all tumors within the Ewing's sarcoma family express the MIC2 gene product (CD99) on their cell membranes. Approximately 95% of all Ewing's family tumors contain translocations consisting of either t(11;22) or t(21;22). These gene rearrangements can be seen in one of two ways: either by a chromosome 11 breakpoint (t;11;22) or by a chromosome 22 breakpoint (t;21;22). Regardless of mechanism, the N-terminus of EWS is fused to the C-terminus of FLI1 or ERG, both transcription factors with Ets domain that control cell growth.

The presence of a t(11;22) or t(21;22) is a nearly diagnostic feature for Ewing's sarcoma and peripheral primitive neuroectodermal tumor (PNET). In 1994, the International Union Against Cancer Pathology Committee recommended the term "Ewing's sarcoma/PNET" for these tumors.

EWING'S SARCOMA AND PERIPHERAL PRIMITIVE NEUROECTODERMAL TUMOR

EPIDEMIOLOGY AND GENETICS

Ewing's sarcoma and primitive neuroectodermal tumors are closely related, if not identical, malignancies that may occur as osseous or soft tissue tumors.

The rarity of Ewing's sarcoma in African American and Asian populations has been confirmed by several investigators. Ewing's sarcoma occurs more frequently in boys than girls and has been reported in three pairs of female siblings.

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The sedimentation rate and serum lactate dehydrogenase level are frequently elevated in patients with Ewing's sarcoma.  

**RADIONUCLIDE BONE SCANS**

Radionuclide bone scans demonstrated disease in additional bones in approximately 10% of patients with Ewing's sarcoma.  

**CLINICAL PRESENTATION AND NATURAL HISTORY**

Localized pain is typically the first symptom reported by pediatric patients with bone tumors. The pain progresses from intermittent to more constant, often awakening the patient from sleep. Depending on the location of the tumor, the patient may develop a limp, complain of pain that increases with respiration, or experience pain that is radicular in character. Local swelling is often noticed by the patient. This finding is more readily identified when the tumor is located in an extremity. Paraplegia secondary to vertebral disease is present at the time of diagnosis in approximately 3% of patients.  

The clinical presentation of patients with Ewing's sarcoma is similar to that of patients with osteomyelitis. Fever is present in 28% of patients with Ewing's sarcoma at the time of diagnosis.  

Metastases are present in approximately 26% of patients at initial diagnosis. The most frequent sites of metastases are the lungs and other bones. Patients may seek medical attention because of symptoms related to metastatic disease, rather than the primary tumor. Multiple pulmonary metastases may produce respiratory insufficiency, or paraplegia may develop secondary to a vertebral body metastasis.

Evaluation of a patient suspected of having Ewing's sarcoma includes radiographic examinations of the primary tumor site, documentation of the presence or absence of hematogenous metastases, and additional laboratory studies that correlate with prognosis or exclude the presence of other possible diagnoses.

Lesions that originate in the long bones characteristically involve the diaphysis, with extension toward the metaphyses. A lytic or mixed lytic-sclerotic lesion is identified in the bone. Parallel, lamellated periosteal new bone formation (onion skin) or, less frequently, radiating bone spicules may be present. A soft tissue mass is frequently identified on CT or gadolinium-enhanced MRI.

Plain radiographs of tumors that originate in the pelvic bones frequently demonstrate a mixed lytic and blastic lesion. CT and MRI of the pelvis are required to adequately delineate the presence and extent of any associated soft tissue mass.

Radionuclide bone scans should be obtained, both to define more precisely the extent of disease at the primary site and to determine whether bone metastases are present.

**STAGING**

Ewing's sarcoma can metastasize to the lungs, other bones, and bone marrow. As with other sarcomas, nodules identified on plain chest radiography or CT of the chest in patients with Ewing's sarcoma are not always malignant. Cohen and colleagues reported that 60% (three of five) of nodules identified in such radiographs were benign. A solitary nodule identified only on the CT scan of one patient was shown pathologically to be secondary to histioplasmosis.

Radionuclide bone scans demonstrated disease in additional bones in approximately 10% of patients with Ewing's sarcoma.

Patients with Ewing's sarcoma may have disseminated bone marrow disease in the absence of radiographically detectable bone metastases. Bilateral bone marrow sampling is required to complete the staging of all patients regardless of primary site or tumor size.

**TREATMENT**

**Surgery**

Local control must be achieved by either high-dose radiation therapy or resection. Larger tumor size (more than 8 cm) or volume (more than 100 cm³) has correlated with decreased success in achieving durable local control. No randomized study has been performed to define whether local control is better accomplished with surgical resection or radiotherapy. In nonrandomized trials, the improved survival in the surgical resection group has been attributed to the allocation of larger tumors with correspondingly poorer prognosis to the radiotherapy group. Not all series have reported better survival among patients treated surgically than among those treated with radiation therapy. In the German Cooperative Ewing's Sarcoma Study, survival with resection was better, although this relative advantage of surgery lost statistical significance when tumor size was considered. The 3-year relapse-free survival was 78% for patients whose tumor volume was less than 100 mL, compared with 17% for patients with tumor volumes greater than 100 mL. Extraskeletal extension has also been associated with an increased risk of distant relapse.

The long-term morbidity produced by radiotherapy versus surgery is often the deciding factor when selecting the most appropriate modality for local control. In addition to analyses of resectability and functional outcome, deliberations about local control must also consider the risk of late-onset second malignancies in tissues treated with intensive radiotherapy. Central pelvic or spinal lesions are frequently treated with radiation alone. Extremity lesions amenable to limb-sparing resections are treated predominantly with resection after an initial 12- to 15-week phase of induction chemotherapy. It is critical for the surgeon performing the diagnostic biopsy to place the incision appropriately to avoid complicating future resection.

Chest wall lesions make up 6.5% of primary Ewing's sarcomas, representing the most frequent chest wall tumor in children. They frequently present with large lesions extending into the thoracic cavity. Traditionally, these have been biopsied by open techniques that can be difficult because of the extremely vascular nature of this tumor and the limited surgical exposure. Percutaneous biopsy, which can provide adequate material for histologic and cytogenetic testing, may be a preferable approach in many cases.

Preoperative chemotherapy can greatly reduce the size, vascularity, and friability of the tumor, facilitating resection and decreasing the risk of intraoperative tumor rupture. Analysis of the 53 patients with nonmetastatic chest wall primaries treated on the first intergroup Ewing's Sarcoma Study (POG/CCG) demonstrated a decreased incidence of residual tumor in those patients resected after induction chemotherapy, in contrast to those who underwent resections before treatment with chemotherapy. Current practice mandates the addition of radiotherapy for all patients with microscopic or gross residual disease after resection. Since surgical outcome was improved in patients receiving preoperative chemotherapy, they were less likely to require postoperative chest wall radiotherapy with its well-established risks of cardiac and pulmonary damage. As noted previously, the inclusion of 12 to 15 weeks of systemic chemotherapy before introduction of local control measures has become standard practice, regardless of tumor size, location, or stage.

**Radiation Therapy**

Radiation responsiveness was one of the cardinal diagnostic features of the bone tumor first described by Ewing in 1921. Unfortunately, the long-term survival rate of patients with Ewing's sarcoma following treatment with local radiation alone was only 9%. The vast majority of these patients ultimately succumbed to metastatic disease, suggesting the presence of occult metastatic tumor foci in most affected children. These findings presaged the routine inclusion of systemic chemotherapy.
in the treatment of this disease, leading to a marked improvement in survival over the past three decades.

Local control of Ewing's sarcoma with radiation is dependent on the delivery of a sufficient dose of irradiation to an adequate volume of tissue. Both the requisite minimum dose and the optimal treatment volume continue to be debated. Although dose-response information is limited for modern studies that employ adjuvant chemotherapy, local control rates have been fairly similar, ranging from 75% to 90% at radiation doses varying from 45 to 65 Gy. 2

Local control rates have improved with the introduction of adjuvant chemotherapy. Chan and colleagues 3 reported local tumor recurrence in only 2.8% of patients treated with 60 Gy and adjuvant chemotherapy. Local disease recurrence was identified in 33.3% of patients who received identical local irradiation, but no adjuvant chemotherapy.

The Intergroup Ewing's Sarcoma Study (IESS) examined the relation of primary tumor site, radiation therapy dose, treatment volume, and adjuvant chemotherapy regimen to local tumor control. Local tumor recurrence occurred in 22.6% of patients with primary tumors in the humerus, 15.3% of those with tumors originating in the pelvis, 10.3% of patients with tubal primaries, and 6.7% of those whose tumor originated in the femur. A dose-response relationship was not apparent when local control was evaluated in patients who had received treatment to an adequate volume. 3

The comparable outcome achieved with smaller, tailored fields is most provocative when considered in the context of the late sequelae of radiation therapy. The risk associated with considerable long-term morbidity. Although the available data did not suggest that doses exceeding 40 Gy were essential for adequate local control rate when doses greater than 40 Gy were employed. Radiation doses greater than 60 Gy did not appear to significantly increase the local control rate and were associated with considerable long-term morbidity. Although the available data did not suggest that doses exceeding 40 Gy were essential for adequate local control rates in patients treated with adjuvant chemotherapy, comparisons between this dose and higher doses should be conducted in controlled trials. The current standard for the open POG and CCG trial is 55.8 Gy for gross and 45 Gy for microscopic residual disease.

The comparable outcome achieved with smaller, tailored fields is most provocative when considered in the context of the late sequelae of radiation therapy. The risk of secondary sarcomas arising in irradiated bone is variously reported as ranging from 5% to 10% at 20 years from diagnosis. Although no clear therapeutic advantage can be attributed to radiation dose beyond 60 Gy, analysis of the long-term outcome in patients treated with doses greater than or equal to 60 Gy demonstrated an unacceptable excess risk of secondary bone sarcomas. In marked contrast to the late complications seen in patients receiving very high-dose radiation, the risk of developing a secondary bone tumor in the irradiated field was negligible at doses below 48 Gy. 3

Chemotherapy

The availability of chemotherapeutic agents active against microscopic deposits of Ewing's sarcoma suggested that improved relapse-free survival rates might be achieved with the use of these agents in patients with microscopic residual disease.

In 1973, the IESS initiated a trial (IESS-I) to evaluate the potential additional benefit of adding doxorubicin and prophylactic whole lung irradiation to standard treatment of patients with nonmetastatic Ewing's sarcoma with vincristine, dactinomycin, and cyclophosphamide. The patients treated with the four-drug regimen that included doxorubicin had superior relapse-free survival. 3 Improved event-free survival with the dose-intensified regimen. 3

Studies from the National Cancer Institute confirmed the importance of autopsy examination for the identification of locally recurrent Ewing's sarcoma. Telles and colleagues identified recurrent or persistent tumor at the primary site in 13 of 20 patients at autopsy. Tepper and coworkers reported that local tumor recurrence was clinically apparent in 5 of 20 autopsyed patients, but was identified histologically in an additional 6 of 20 patients. Since many of these patients had widespread metastatic disease, the possibility that the primary tumor site was reseeded with tumor cells derived from metastatic disease cannot be excluded. These results suggest that local failure rates in irradiated patients may be higher than suggested by the clinical determination of locally recurrent tumor.

Improved local control of tumor with irradiation followed the identification of a target volume encompassing the entire medullary cavity to moderately high-dose levels. Suit summarized the experience of the 1950s and 1960s in recommending irradiation to the entire involved bone with a higher dose boost to the primary tumor site, noting few instances of marginal or distant intramedullary recurrence with such treatment. 3

Assessment of the primary tumor volume requires detailed attention to both intraosseous and adjacent soft tissue tumor extent. Prior treatment recommendations included a 3- to 5-cm margin beyond the known soft tissue extension and inclusion of the entire intramedullary cavity. The radiation therapy results of IESS-I demonstrated an overall increase in local recurrence with fields that had not included the opposite epiphysis. Although local failure increased from 7% to 20% with marginal or inadequate treatment fields, the differences were not statistically significant. Subsequent studies have reported comparable irradiation results using treatment techniques that have not included the opposite epiphysis. 3

The results of the German Cooperative Ewing Sarcoma Study indicated an excessive rate of local recurrence attributed to poor quality control for radiation therapy. Protocol modifications, which included central planning for radiation therapy, diminished the frequency of local treatment failure. 3

Local or tailored fields encompassing the primary tumor with a 3- to 5-cm margin, rather than treatment of the entire bone, have been evaluated. Marcus et al. reported excellent local control using tailored fields, noting the ability to spare a component of the long bones in tumors less than 8 cm in diameter, while frequently requiring whole bone irradiation to achieve a 4-cm margin around larger tumors. 3

The POG prospectively evaluated whole bone (conventional) irradiation compared with tailored treatment fields, ultimately collapsing a planned randomized study to a single arm trial using only tailored fields. A published analysis of this trial supports the efficacy of more limited treatment volume as defined by prechemotherapy tumor volume. 3 There was no difference in local control rates between patients receiving whole bone versus involved field irradiation. This more tailored field has become the standard strategy used in the most recent CCG and POG Ewing's sarcoma trials.

The data available in the literature, and those accumulated by the IESS, have not demonstrated a strong relationship between the radiation dose and the local control rate. Although greater than 60 Gy were employed, radiation doses greater than 60 Gy did not appear to significantly increase the local control rate and were associated with considerable long-term morbidity. Although the available data did not suggest that doses exceeding 40 Gy were essential for adequate local control rates in patients treated with adjuvant chemotherapy, comparisons between this dose and higher doses should be conducted in controlled trials. The current standard for the open POG and CCG trial is 55.8 Gy for gross and 45 Gy for microscopic residual disease.

The comparable outcome achieved with smaller, tailored fields is most provocative when considered in the context of the late sequelae of radiation therapy. The risk of secondary sarcomas arising in irradiated bone is variously reported as ranging from 5% to 10% at 20 years from diagnosis. Although no clear therapeutic advantage can be attributed to radiation dose beyond 60 Gy, analysis of the long-term outcome in patients treated with doses greater than or equal to 60 Gy demonstrated an unacceptable excess risk of secondary bone sarcomas. In marked contrast to the late complications seen in patients receiving very high-dose radiation, the risk of developing a secondary bone tumor in the irradiated field was negligible at doses below 48 Gy. 3

Chemotherapy

The availability of chemotherapeutic agents active against microscopic deposits of Ewing's sarcoma suggested that improved relapse-free survival rates might be achieved with the use of these agents in patients with microscopic residual disease.

In 1973, the IESS initiated a trial (IESS-I) to evaluate the potential additional benefit of adding doxorubicin and prophylactic whole lung irradiation to standard treatment of patients with nonmetastatic Ewing's sarcoma with vincristine, dactinomycin, and cyclophosphamide. The patients treated with the four-drug regimen that included doxorubicin had superior relapse-free survival. In a subsequent study (IESS-II), the efficacy of administration of high-dose (1400 mg/m²) cyclophosphamide every 6 weeks was compared with administration of cyclophosphamide (500 mg/m²) weekly for 6 weeks. The regimen that included high-dose cyclophosphamide also included a higher dose of doxorubicin (75 mg/m²) than did the weekly cyclophosphamide schema. The 5-year relapse-free survival was 73% for the high-dose cyclophosphamide, high-dose doxorubicin regimen, compared with 56% for the weekly cyclophosphamide regimen (P = .03). A finding supported by the analysis by Smith and colleagues. 3

The POG and CCG completed an intergroup study comparing the combination of vincristine, doxorubicin, cyclophosphamide, and daunomycin to the combination of these four drugs plus ifosfamide and etoposide. The 5-year event-free survival was 68% for those who received the six-drug regimen, compared with 52% for those who received the four-drug regimen (P = .0005). Similar improvements in survival with the addition of ifosfamide have been reported in studies by the National Cancer Institute and multiple European cooperative groups. 3, 34 and 35

Standard chemotherapy for nonmetastatic disease currently consists of a five-drug regimen including the three-drug combination of vincristine, doxorubicin, and cyclophosphamide, alternating with the two-drug combination of ifosfamide and etoposide for a total of 48 weeks. The intergroup POG/CCG study for nonmetastatic Ewing's sarcoma compared this 48-week five-drug combination with a dose-intensified 30-week schedule employing the same agents at identical cumulative doses. The experimental arm in this study increased the dose intensity of alkylating agents by 25%. Preliminary statistical analysis of this study reveals no evidence of improved event-free survival with the dose-intensified regimen. Although the Kaplan-Meier plots for event-free survival may yet diverge, current data from this
randomized study suggest that new treatment strategies will be required if further improvements in survival are to be achieved.

In contrast to the improvement in survival for nonmetastatic patients treated with the addition of ifosfamide and etoposide, no comparable benefit could be demonstrated for metastatic patients. Previous studies, however, had shown improved survival with the addition of radiation to metastatic sites of disease. Patients with previously untreated metasastases entered on IESS-II were treated with irradiation to the primary tumor, in addition to lung radiation (18 Gy) for patients with pulmonary metastases and local bone irradiation for bone metastases. This strategy yielded a progression-free survival of 39%, demonstrating that some patients with hematogenous metastases can be successfully treated.

Several groups have explored the feasibility and efficacy of maximally dose intensive chemotherapy regimens in combination with total body irradiation and peripheral blood stem cell rescue in an effort to improve the prognosis for high-risk patients. Analysis of these studies is complicated by the nonstandardized inclusion of both metastatic and nonmetastatic patients in some of the high-risk cohorts. One study reported a 3-year relapse-free survival of 43% following megatherapy with chemotherapy, total body irradiation and stem cell rescue. Unfortunately, longer follow-up of this cohort revealed a disappointing decline in event-free survival to 27%. Another study reported a 5-year event-free survival of 34% with similar high-dose chemotherapy and radiation therapy. None of these results is clearly superior to the outcome reported for similar patients treated on IESS-II without intensive chemotherapy or total body irradiation. While the early response data from several of these dose-intensive regimens appears promising, their small size and short follow-up mandate a guarded approach to their therapeutic potential. Further substantial improvements in survival for both metastatic and nonmetastatic patients will require identification of new non–cross-resistant cytotoxic agents and translation of our growing understanding of the unique molecular derangements of this disease into targeted biologic therapies.

**PROGNOSTIC FACTORS**

Historically, the prognosis for children and young adults with Ewing's family tumors has been assessed based on tumor size, location, and extent. Aside from the poor prognosis associated with metastatic disease, large tumor size (greater than 8 cm in diameter) and volume (greater than 100 mL) have correlated with adverse outcome. Children with nonmetastatic pelvic primary sites also have a poorer prognosis than children with extremity primaries, although this difference may be related to the larger size and more difficult resectability of pelvic tumors. High serum lactate dehydrogenase levels at diagnosis have been shown to predict a poorer prognosis in several studies. Although not true prognostic factors assessable at the time of diagnosis, radiographic and histologic response to initial chemotheraphy appear to be strong predictors of treatment outcome. Poor histologic response correlates with a poor prognosis, while complete or near complete tumor necrosis strongly correlates with good outcome, with a 5-year event-free survival of 94% to 95%. Researchers in Vienna and New York have independently identified the type of EWS-FLI1 fusion transcript as a strong predictor of outcome in nonmetastatic patients. Both studies reported remarkably congruent results, with a predicted 5-year event-free survival of approximately 70% for type 1 transcripts versus 20% for all other types of fusion transcripts. Nearly two-thirds of all patients in both studies were found to have type 1 fusion transcripts. Although the prognostic significance of this finding appears to be substantial, these findings must be prospectively validated before they are used to stratify patients for therapeutic purposes. All upcoming north American pediatric cooperative group studies conducted by the Children's Oncology Group (POG/CCG) will require submission of diagnostic tissue for molecular analyses that will include determination of EWS-FLI1 gene rearrangement status.

**PRIMARY HEPATIC TUMORS**

**EPIDEMOLOGY AND GENETICS**

Approximately 60% to 70% of all primary liver tumors in children are malignant, with hepatoblastoma and hepatocellular carcinoma (HCC) representing the vast majority of malignancies arising in this location. Hemangiomatis and hamartomas constitute the majority of nonmalignant liver tumors in the pediatric population. Hepatoblastoma accounts for slightly more than one-half of hepatic malignancies, occurring at an annual rate of 1.3 cases per 1 million children less than 15 years of age. In contrast, HCC occurs less frequently in children, accounting for one-third of all malignant hepatic tumors, with an annual incidence of 0.4 cases per 1 million. The risk of hepatoblastoma is highest in children with Down syndrome, Beckwith-Wiedemann syndrome,帆状静脉囊肿, and neurofibromatosis. Efforts to reduce the incidence of hepatitis B infection with universal hepatitis B vaccination in Taiwan have produced a corresponding decrease in the risk of developing HCC.

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In addition to the association with hepatitis B, HCC has been diagnosed in pediatric patients with several other underlying diseases, including tyrosinemia, galactosemia, biliary atresia, progressive familial cholestatic cirrhosis, giant cell hepatitis of infancy, Fanconi's anemia, type I glycogen storage disease, hepatic glycogenosis with Fanconi's syndrome, Down syndrome, and neurofibromatosis. Hemochromatosis has not been associated with HCC in pediatric patients, although it is frequently associated with this disease in adult populations. Determinations of iron reserves, as estimated by serum iron, unsaturated iron-binding capacity, and serum ferritin, might clarify the relationship between hemochromatosis and HCC in children.

**PATHOLOGY**

Hepatoblastoma may be divided into two broad histologic subsets of uncertain prognostic significance. The pure epithelial type consists of either fetal or embryonal elements or a combination of both cell types. Alternatively, the tumor may consist of a mixture of epithelial cells with mesenchymal elements. Pure fetal histology is prognostically favorable in patients with completely resected hepatoblastoma. Hepatoblastoma tends to occupy a single site within the liver, most commonly arising in the right lobe.

Two types of HCC are frequently recognized in pediatric patients: microtrabecular and fibrolamellar. The fibrolamellar histology is most commonly seen in older children and young adults. In contrast to hepatoblastoma, HCC is often multicentric at diagnosis, substantially limiting the feasibility of complete resection.

**CLINICAL PRESENTATION**

Infants and children with hepatoblastoma are most frequently identified by the discovery of an abdominal mass or abdominal distention. Symptoms such as weight loss, anorexia, or fever may also be present, although jaundice is infrequent. A rare but interesting presentation of patients with hepatoblastoma occurs in young boys with idiopathic precocious puberty due to production of human chorionic gonadotropin (HCG) by the tumor cells. The presenting physical findings in children with HCC are quite similar to the characteristic features of hepatoblastoma. Children with HCC typically present with an...
abdominal mass or abdominal distention. Abdominal pain, anorexia, and weight loss are less frequent complaints. Jaundice is infrequently present at the time of diagnosis, although it is a more common finding in HCC than hepatoblastoma. Occasionally, a patient with HCC presents with acute abdominal pain due to tumor rupture, with intrabdominal hemorrhage. 37

EVALUATION AND STAGING

The history of pediatric patients suspected of having a malignant hepatic tumor should be reviewed for any history of jaundice or hepatitis. Laboratory data obtained in the perinatal period for the evaluation of hyperbilirubinemia should be reviewed. The maternal prenatal history should be evaluated for the use of steroidal hormones. Prior exposures to hepatotoxic agents should be recorded. The family history should be reviewed for prior cases of hepatic or biliary disease in siblings or parents.

The physical examination may reveal a solitary or multiple hepatic nodules. The presence of dilated collateral vessels on the anterior thorax and abdomen should be noted. Hemihyper trophy or stigmata of the Beckwith-Wiedemann syndrome, such as macroglossia or omphalocele, may be present.

Laboratory evaluation should include a complete blood count, white blood cell differential, tests of renal and hepatic function, and a urinalysis. The serum levels of total bilirubin, alkaline phosphatase, and glutamic-oxaloacetic acid transaminase are not generally useful for the differential diagnosis of malignant hepatic tumors in children.

The serum level of AFP is increased in approximately 90% of patients with hepatoblastoma 33,38 and 78% of adult patients with HCC. The increase of AFP in 51% of white and 81% of African American patients with HCC suggests the presence of ethnic variability in the production of this protein by malignant hepatocytes. 39 Once the diagnosis of hepatocellular carcinoma is established, additional studies should include hepatitis B surface antigen, hepatitis B antibody, serum iron, total iron-binding capacity, serum ferritin, and a -antitrypsin phenotyping. The serum level of HCG should be determined if the clinical presentation included precocious puberty. Several authors reported the excretion of increased amounts of cystathionine in the urine of patients with hepatoblastoma. 40 This finding has also been reported in patients with neuroblastoma, decreasing the utility of this determination for the differential diagnosis of hepatomegaly.

Abdominal radiographic examination may demonstrate the presence of a homogeneous density in the upper abdomen. Malignant hepatic tumors are rarely calcified. 39

Abdominal ultrasoundography demonstrates the presence and extent of a solid mass. Sonography assesses both kidneys and the inferior vena cava, providing information useful for differential diagnosis and surgical management. The proximal extent of tumor thrombus within the inferior vena cava may be determined by echocardiography or cardiac angiography.

A radionuclide liver and spleen scan may demonstrate solitary or multiple defects in the liver. Transient, early perfusion of the defect is frequently observed in hepatic adenomas, hepatoblastomas, and HCCs. Persistent perfusion is found in hepatic hemangiom as and hepatic adenomas. 40

Pulmonary metastases are identified on plain chest radiography in approximately 10% of patients with hepatoblastoma 41 and HCC. 42 The additional yield of CT in pediatric patients with hepatoblastoma or HCC has not been evaluated.

The grouping system employed in the therapeutic studies of children with malignant hepatic tumors conducted by the CCG and POG segregates patients according to the resectability of the primary tumor, a criterion that may vary among treatment centers. This staging system also accounts for the presence of lymph node or hematogenous metastases (Table 44.2-10). 43

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>Patient has complete excision of tumor by wedge resection, hemihepatectomy, or extended lobectomy, or the resected specimen is free of tumor.</td>
</tr>
<tr>
<td>Stage II</td>
<td>Patient has resection of hepatic segments.</td>
</tr>
<tr>
<td>Stage III</td>
<td>Cross-sectional lesions or regional (length &lt; 6 cm) hepatic or other tumor involvement. A: Regional (length &lt; 6 cm) involvement by tumor or tumor, tumor, tumor, and tumor, tumor. B: Cross-sectional involvement by tumor or tumor, tumor, tumor, tumor, tumor, and tumor.</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Bilateral metastases are present. A: Portal vein involvement is present. B: Portal vein involvement is not present.</td>
</tr>
</tbody>
</table>

TABLE 44.2-10. Clinical Staging System for Childhood Hepatic Tumors

TREATMENT

Surgery

Resection is the cornerstone of treatment for hepatoblastoma and HCC. Long-term survival is rare for patients who have not undergone a successful resection. 43 Hepatoblastoma is generally unifocal, arising at one site within the liver parenchyma, whereas HCC is frequently multifocal. HCC has an invasive pattern of spread across anatomic planes and is generally unresponsive to current forms of chemotherapy. 43 Complete resection of HCC is frequently difficult due to its multifocality and invasiveness. Approximately one-half of all hepatoblastomas are resectable at initial presentation, whereas only 30% of HCCs can be fully resected at diagnosis. 27

The resectability of a primary liver tumor is determined by its anatomic location within the liver and by its size. Surgical considerations are complex and best addressed by surgeons intimately familiar with hepatic anatomy and resection. For successful resection, perfusion and drainage for an anatomic segment of the liver must be preserved. The liver lobes are perfused by the two divisions of the hepatic artery and the portal vein, with one branch to each lobe. The left and right lobes are divided along a plane between the bed of the gallbladder and the anterior aspect of the vena cava. The liver is drained by three veins into the vena cava at the most superior aspect of the liver. The right hepatic vein drains the major portion of the right lobe (the posterior segment and a portion of the anterior segment of the lobe). 27 The middle hepatic vein, which courses along the anterior portal vein anterior to the vena cava between the right and left lobes, drains one-third of the liver (a large portion of the anterior segment of the right lobe and all of the medial segment of the left lobe). The left hepatic vein, arising from a short common trunk with the middle vein in 50% of cases, travels along the umbilical fissure of the liver and primarily drains the lateral segment of the left lobe. In a right or left lobectomy, the left or right branches of the hepatic artery and portal vein are preserved, along with the left and middle or right and middle hepatic veins. In an extended right or left hepatectomy (also referred to as a trisegmentectomy), the same inflow vessels are removed, along with the middle and left or right hepatic veins. A much greater portion of the hepatic parenchyma is removed in this type of resection (Fig. 44.2-7).
Japan, and Germany. These studies have consistently demonstrated that a substantial number of initially unresectable tumors can be surgically removed after treatment with various combinations of chemotherapy. In a series published by King et al. in 1991, the increased frequency of complications in patients with HCC treated only with surgery. Those patients with completely resected disease (group 1) entered on the first study received no therapy following induction chemotherapy. The distribution between lobectomies and trisegmentectomies was similar for children undergoing primary resections and resections following several course of induction chemotherapy. Hepatic transplantation has been used several centers for children with unresectable tumors, with a survival rate of 50.0% to 87.5% reported for children with hepatoblastoma and HCC. Success with this treatment approach for patients with hepatocellular carcinoma has been extremely limited and is difficult to justify. Disease must be limited to the liver for efforts to be successful. Lymph node involvement is a contraindication for resection and transplantation. Cryoablation or radiofrequency ablation of hepatic malignancies has been increasingly used in adults, particularly for metastatic lesions in the liver. While these techniques have been employed in treatment of recurrent disease, their overall role in treatment of pediatric neoplasms remains to be defined. Long-term evaluation of infants and children following hepatic resection has demonstrated normal synthetic and degradative function of the liver. Liver volumes assessed by MRI are nearly normal, despite prior anatomic lobectomies or trisegmentectomies. Sequential studies have shown that hepatic volumes continue to increase as the children grow following completion of their treatment. Radiation Therapy Radiation therapy has a limited role in the treatment of hepatoblastoma or HCC. Generally, combination chemotherapy is given preoperatively to patients with large, unresectable tumors. Postoperative radiation therapy may be valuable in the treatment of children with residual disease following resection. Generally, doses of 25 to 40 Gy are recommended for treatment of limited volumes. Chemotherapy Following initial biopsy, combination chemotherapy has been administered to children with malignant hepatic tumors to facilitate subsequent surgical excision. In addition to its role in reducing the size of tumors before attempted resections, chemotherapy has been employed as a postoperative adjuvant following complete excision of the primary tumor. Initially reported by single institutions, these results led to the design of much larger cooperative group trials of combination chemotherapy in children with hepatoblastoma and HCC. Evans and coworkers reported the results of sequential studies conducted by two pediatric cooperative groups in patients with malignant hepatic tumors. Patients with hepatoblastoma and HCC were evaluated together. Those patients with completely resected disease (group 1) entered on the first study received no therapy following surgery. Those entered on the second study received adjuvant chemotherapy consisting of doxorubicin, cyclophosphamide, vincristine, and 5-fluorouracil. Comparison of these sequential studies demonstrated a significant survival advantage for those patients who received adjuvant chemotherapy compared with patients treated only with surgery. Based on pilot data that demonstrated the activity of the combination of doxorubicin and cisplatin and of the combination of cisplatin, vincristine, and 5-fluorouracil in patients with malignant liver tumors, the CCG and POG conducted a randomized comparison of these two combinations. The results of this trial demonstrated that the two combinations produced similar relapse-free and overall survival percentages within stages. The combination of cisplatin, vincristine, and 5-fluorouracil produced substantially less severe myelosuppression, less need for prolonged hyperalimentation, and fewer toxic deaths. Event-free survival rates for patients treated with the three-drug regimen were 85% for stage I, 100% for stage II, 62% for stage III, and 23% for stage IV. Similar results have been reported by investigators in Toronto, Japan, and Germany. These studies have consistently demonstrated that a substantial number of initially unresectable tumors can be surgically removed after induction chemotherapy with variations in the selections of agent or drugs used. Despite the remarkable similarity in outcomes between these various studies, there was a significant differences in survival for children who underwent initial complete resection, corresponding to postoperative management. The Toronto group reported a 100% event-free survival for children with complete resections treated with postoperative chemotherapy, versus 72% survival for a similar group of children on the POG/CCG study who received no chemotherapy following definitive surgery. Although the numbers in the comparison groups are small, the more favorable outcome with inclusion of chemotherapy suggests that this approach should be prospectively examined.

Japanese investigators have reported successful application of transarterial chemoembolization using cisplatinum and doxorubicin in combination with iodized oil in treatment of a small number of children with inoperable hepatoblastoma. Although the results of this limited series are provocative, the role of this more invasive technique is uncertain given the efficacy of systemic, intravenous administration of the same chemotherapeutic agents.

PROGNOSIS
For both hepatoblastoma and HCC, resectability of the primary tumor and disease extent at diagnosis remain the strongest predictors of survival. Prospects for long-term survival are extremely poor for both histologies in cases of widely metastatic disease. Despite aggressive efforts at surgical management of HCC, long-term survival remains dismal even for patients with fully resected tumors. A North American Pediatric Cooperative Group study demonstrated only 13% survival for children with totally resected HCC. 52 This outcome sharply contrasts with the good survival documented for children with localized, completely resected hepatoblastoma, as described previously (see Surgery, earlier in this chapter).

Although correlation of survival with histology in hepatoblastoma and HCC remains controversial, there appear to be favorable histologic subsets within both types of hepatic malignancy. Multiple studies have demonstrated that pure fetal histology is prognostically favorable in patients with completely resected hepatoblastoma. 37-39,52 Several studies have shown a better outcome for children with the fibrolamellar variant of HCC. 52 Although this advantage was not apparent in the cooperative studies conducted by the POG and CCG, 52 multivariate analysis of prognostic factors in children with hepatoblastoma by the German Pediatric Liver Tumor Study group has identified AFP level at diagnosis and vascular invasion as important prognostic factors. Children with either very low AFP (less than 100 ng/mL) or very high AFP (greater than 1 million ng/mL) had a poorer prognosis than children with intermediate levels (100 to 1 million ng/mL). Children with venous tumor invasion also fared poorly. 52

GERM CELL TUMORS

Germ cell tumors arising in gonadal or extragonadal sites constitute a remarkably heterogeneous group of tumors that account for approximately 3% of all pediatric malignancies. Although extragonadal germ cell tumors are relatively infrequent in adults, accounting for only 5% to 10% of all cases, extragonadal tumors make up nearly two-thirds of all germ cell tumors in children. 52 The sacrococcygeal region represents the most common site for germ cell tumors in children, constituting 40% of all childhood germ cell tumors. 52 and 79% of all extragonadal disease. 52 Less commonly, extragonadal disease arises in the mediastinum, retroperitoneum, vagina, and pineal region. Biologic behavior among this diverse grouping of tumors varies from the benign mature teratoma to the highly malignant embryonal carcinoma and chorionicarcinoma. Fortunately, the introduction of platinum-based chemotherapy by Einhorn and Donahue in the 1970s has greatly improved survival for most children affected by these highly chemosensitive tumors 52 (Table 44.2-11).

Table 44.2-11. Relative Incidence According to Age and Pathology

EMBRYOLOGY

Primordial germ cells arise in the embryonic yolk sac endoderm. These cells migrate through the wall of the midgut to the genital ridge at 4 to 5 weeks’ gestation. Migration along this paravesical gonadal ridge proceeds in a caudal to cranial direction. Arrested migration of these germ cells along this pathway has been proposed as an explanation for the near midline location of most extragonadal germ cell tumors, including the sacrococcygeal region, retroperitoneum, mediastinum, and intracranial sites, which primarily consist of the pineal and suprasellar regions. 51,60,63

PATHOLOGY

Pediatric germ cell tumors include an enormously diverse array of histologies. The majority of extragonadal tumors arising in infancy are benign teratomas. Similarly, most ovarian germ cell tumors are benign lesions. In contrast, the vast majority of germ cell tumors developing in the testis contain malignant yolk sac elements. While many of these tumors contain a mixture of benign and malignant elements, their clinical behavior and therapeutic management are determined by the most malignant component identified on extensive sectioning. 62 This section reviews the various histopathologic subtypes of germ cell tumors most frequently seen in children.

TERATOMA

Teratomas contain elements derived from more than one of the three primary germ layers (ectoderm, mesoderm, endoderm), frequently arranged in a haphazard manner. The tissues are immature to well differentiated and foreign to the anatomic site. Mature teratomas are either cystic or solid, although the cystic presentation predominates in gonadal sites. Immature teratomas are graded according to the amount of immature tissue present on light microscopic assessment of sampled tissue. Grade 1 immature teratomas have neuroepithelium or other immature elements limited to only one low-power field per slide. Grade 3 immature teratomas contain abundant immature tissue that is identifiable on greater than or equal to four low-power fields per slide. 52 Nearly all mature teratomas are diploid with normal karyotypes. In contrast, chromosomal derangements are frequently identified in immature teratomas. Phoidy may correlate with clinical behavior in immature ovarian teratomas. Grade 1 and 2 immature teratomas are typically diploid, whereas grade 3 tumors are often aneuploid. 52

YOLK SAC TUMOR (ENDODERMAL SINUS TUMOR)

Intracellular and intercellular hyaline droplets are present in typical yolk sac tumors. This material is periodic acid–Schiff-positive and resists digestion with diastase. Several groups of investigators have shown that these droplets contain AFP as well as other proteins. 51,62,63 Teilmann and colleagues suggested that the presence of AFP in these tumors supported the theory that such tumors originated from the yolk sac endoderm. 52

The polyvesicular vitelline tumor is a variant of the yolk sac tumor that is composed predominantly of cystic structures. 64,65 Such evidence of differentiation has been associated with a more favorable prognosis for patients with this histologic subtype of yolk sac tumor.

A cytogenetic study of childhood endodermal sinus tumors employing fluorescent in situ hybridization demonstrated deletions of the distal portion of the short arm of chromosome 1 (1p36) in eight of ten cases. This deletion maps to the same locus identified in neuroblastoma, another embryonal malignancy that typically affects young children. 52 The prognostic importance of this finding remains uncertain. Several putative tumor suppressor genes have been mapped within or adjacent to this locus, however, suggesting a role of this deletion in the pathogenesis of these tumors.

EMBRYONAL CARCINOMA

Embryonal carcinoma is composed of cells that resemble epithelial cells. There is considerable variation in their size, shape, and arrangement. They may be large and pleomorphic without distinct cell borders. The cytoplasm may be homogeneously amorphophilic or vacuolated. The nuclei are irregular, oval, or round, with an irregular and coarse nuclear membrane, and one or more large nucleoli. The cells may occur as solid sheets. Frequently, small or large acinar, tubular, and papillary structures are formed. Hemorrhage and necrosis are frequent. 52

SEMINOMA
Seminomas arising outside the testis are referred to as germinomas or dysgerminomas (ovarian). Typical seminoma is composed of uniform cells supported by a delicate connective tissue stroma. Characteristically, the seminoma cell is large, polyhedral, or round, with a distinct cell border. It has clear or granular cytoplasm and a large, centrally located, spherical hyperchromatic nucleus, an irregular nuclear membrane, distinct and granular chromatin distribution, and one or two basophilic nucleoli. Tumor giant cells may be seen. Lymphocytic infiltration is present in most seminomas, with a granulomatous reaction identifiable in approximately one-half of cases. As is commonly found in adult testicular tumors, isochromosome 12p (two copies of the short arm of chromosome 12) is frequently identified in adolescent testicular germinomas. This chromosomal abnormality is rarely seen in malignant testicular tumors of infancy in which yolk sac tumor is the predominant histology.

CHORIOCARCINOMA

Chorionicarcinoma consists of two distinct cell types: syncytiotrophoblast and cytotrophoblast. The syncytiotrophoblast is a large, multinucleated cell with many hyperchromatic, irregular nuclei and cytoplasm usually eosinophilic or amphophilic. Cytotrophoblast cells are medium sized and closely packed with clear cytoplasm, distinct cell borders, and a single, uniform, moderate-sized vesicular nucleus.

TERATOCARCINOMA

Teratocarcinomas contain derivatives of more than one of the three primary germ cell layers (endoderm, mesoderm, ectoderm) consistent with the diagnosis of teratoma, and areas of embryonal carcinoma. In addition, areas of seminoma, endodermal sinus tumor, and chorionicarcinoma may be identified within the tumor.

LABORATORY MARKERS

AFP and the β subunit of HCG (β-HCG) are oncofetoproteins that are found at elevated serum levels in association with a variety of germ cell tumors. These proteins are clinically useful both as diagnostic tools and in surveillance of children on or off treatment for tumors that secrete these markers. AFP is a glycoprotein that is produced in the liver, gastrointestinal tract, and yolk sac of the human fetus. The serum concentration of AFP reaches a maximum at 13 weeks of gestation. It is readily detectable at birth, when high physiologic levels confound its diagnostic utility in infants with suspected germ cell tumors. Due to its long serum half-life of 7 days, the level of AFP may remain elevated in normal infants as old as 6 months of age. Abelev and colleagues reported in 1967 that patients with testicular tumors that contained elements of embryonal carcinoma had elevated levels of AFP in their serum. Other investigators have reported that children with embryonal carcinomas and malignant teratomas have elevated serum levels of AFP. Most commonly, high serum levels of AFP are identified in pediatric patients with testicular, ovarian, presacral, and vaginal primary yolk sac tumors. HCG is a glycoprotein that is secreted by the placenta. Patients with a pure yolk sac tumor do not have detectable serum levels of HCG. Patients with malignant germ cell tumors of the ovary or embryonal carcinoma of the ovary or testis may have elevated serum HCG levels. HCG has a much shorter serum half-life than AFP, lasting only 24 to 36 hours. Thus, a decline in the serum level of this marker occurs much more rapidly with successful therapeutic intervention than is seen in management of tumors that secrete AFP.

CLINICAL PRESENTATION AND TREATMENT BY ANATOMIC SITE

SACROCOCCYGEAL TUMORS

Presacral and sacrococcygeal teratomas are usually diagnosed at birth or during the first month of life. Four types have been defined on the basis of the extent of pelvic and abdominal extension of the teratoma, and the presence or absence of external extension of the teratoma. Only 2% of presacral and sacrococcygeal teratomas diagnosed before 6 months of age were malignant, compared with 65% of those diagnosed after 6 months of age. Both benign and malignant teratomas are more frequent in girls. Children with presacral or sacrococcygeal teratomas frequently have congenital anomalies of the vertebrae, genitourinary system, or anorectum.

Malignant presacral or sacrococcygeal teratomas may arise de novo or at the site of a previously excised benign teratoma. The frequency of malignancy depends on the type of teratoma, varying from 8% for patients with type I, to 21% for those with type II, 34% for those with type III, and 38% for those with type IV lesions. The much higher rate of malignancy in type IV tumors may reflect inadequate or delayed treatment of infants with foci of endodermal sinus tumor within a mature or immature sacrococcygeal teratoma.

Clinical Presentation and Evaluation of Sacrococcygeal Teratomas

Children with malignant pelvic teratomas present with an abdominal or buttock mass or signs of urinary or fecal obstruction. Rectal examination reveals the presence of a mass between the rectum and the sacrum. The mass may extend through the sciatic notch deep into the gluteal muscles.

Staging of the patient with a sacrococcygeal teratoma requires a radionuclide bone scan, plain radiographs of any positive area on the scan and any symptomatic bone, plain chest radiography and CT of the chest, abdomen, and pelvis.
Yolk sac tumor accounts for the vast majority of malignant presacral and sacrococcygeal teratomas. In marked contrast to the predominance of benign teratomas in neonates with type I tumors, nearly 90% of children with type IV anatomy have tumors consisting of malignant elements. Before the advent of modern, platinum-based chemotherapy in pelvic yolk sac tumors, survival was poor, barely exceeding 10%. Since the advent of modern, platinum-based chemotherapy in the late 1970s, however, more than 80% of patients with malignant sacrococcygeal teratomas are survivors.

Surgery

Before surgical resection, the upper limit of the tumor should be assessed by both rectal examination and either ultrasonography or MRI. In the vast majority of cases, the tumor can be resected by a perineal approach in which an incision is placed around the periphery of the protruding teratoma, preserving the maximum amount of skin. In approximately 10% of infants, a combined perineal and abdominal approach is required. The plane between a benign teratoma and the normal anatomic structures can be readily defined. All normal structures should be preserved, accepting a narrow margin of resection. In light of a much higher recurrence rate when the adjacent coccyx is spared, the coccyx should routinely be removed with the tumor. The sacrum, however, can be preserved. Caution must be taken when resecting the anterior aspect of the teratoma to preserve the anal musculature, which may be directly adherent, and to avoid injury to the rectum that is draped over the anterior aspect of the tumor. If the tumor is identified in an older child or there is suspicion of malignancy, a preliminary biopsy should be performed. Preoperative chemotherapy should be administered if malignancy is confirmed. A complete resection of malignant teratomas can rarely be achieved without prior treatment with combination chemotherapy. This approach allows maximum preservation of normal structures including the rectum, anus, and the sacral plexus, which is critical for bladder and bowel function. If significant abdominal extension of the tumor is present, initial abdominal exploration allows control of the vascular supply to the tumor before the perineal dissection.

Radiation Therapy

Radiation therapy is not necessary for those children who undergo a complete excision or who have a complete response to combination chemotherapy. In patients who have residual disease after treatment with chemotherapy and second-look surgery, local control with irradiation is poor. If irradiation is indicated, the dose required for extragonadal germ cell tumors is 45 to 50 Gy.

Chemotherapy

As noted previously, malignant pelvic yolk sac tumors are highly responsive to chemotherapy regimens that include cisplatinum. Children with pelvic yolk sac tumors should be treated aggressively, with the expectation that such an approach will result in long-term tumor control. Table 44.2-13 contains an algorithm for the inclusion of chemotherapy in the treatment of germ cell tumors based on the risk-group stratification currently employed by North American pediatric cooperative groups (POG/CCG).

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-risk</td>
<td>Surgery and Adriamycin*</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Surgery and PE (cisplatinum)*</td>
</tr>
<tr>
<td>High-risk</td>
<td>Surgery and PE (cisplatinum)*</td>
</tr>
</tbody>
</table>

Children with yolk sac tumors of the testis have been diagnosed with additional anomalies including inguinal hernia, double ureter, ectopic kidney, hypospadias, and renal agenesis.

Clinical Presentation and Evaluation

Most children with primary testicular tumors present with painless testicular enlargement. In the relatively infrequent cases of metastatic disease, patients present with abdominal swelling due to malignant ascites, inguinal lymphadenopathy, or acute abdominal pain.

Physical examination reveals testicular enlargement. Transection is usually negative, but the presence of a hydrocele should not decrease the index of suspicion that a testicular tumor is present. Yolk sac tumor occurs with equal frequency in the right and left testis. Less than 1% of cases had bilateral testicular involvement, occurring in very young children and adolescent boys. Yolk sac tumor, or endodermal sinus tumor, is the most common malignant germ cell tumor of the testis in prepubertal boys, with a median age at diagnosis of 24 months. Testicular tumors in adolescent boys have histologic features similar to those of adults.

Children with yolk sac tumors of the testis have been diagnosed with additional anomalies including inguinal hernia, double ureter, ectopic kidney, hypospadias, and renal agenesis.

Management of the Undescended Testis

Patients with an undescended testis have an increased risk of developing testicular cancer, although most associated tumors are diagnosed well beyond 15 years of age, often arising in the fourth decade. The undescended testis occupies an intrapelvic location in 14.2% of patients. Cryptorchid testes in intrapelvic sites account for 51.5% of the cases of cancer diagnosed in patients with undescended testes, suggesting these patients are at the greatest risk of malignancy.

Orchiopexy has been recommended both to preserve testicular function and to facilitate the identification of malignancy in the abnormally located testis. Several authors have reported the occurrence of testicular cancer in maldescended testes following orchiopexy. Most patients were more than 6 years of age when...
orchiopexy was performed. While orchiopexy permits identification of tumors, it does not uniformly prevent their occurrence. Normal testicular function is unlikely in boys who undergo orchiopexy after 2 years of age. Children with an undescended testis and a normal contralateral testes should undergo orchiectomy if the undescended testis is not recognized until puberty. Orchiopexy is the treatment of choice for younger patients with cryptorchidism. Preservation of normal testicular function is most likely if surgical repair is performed before 2 years of age.

Staging

Once the histologic diagnosis is established, the patient must be staged. Although the majority of pediatric testicular germ cell tumors are nonmetastatic, the tumors may spread to retroperitoneal lymph nodes, liver, lungs, and rarely to bones or brain.

As noted previously, staging must include CT of the chest, abdomen, and pelvis, in addition to a radionuclide bone scan.

The retroperitoneal lymph nodes may be evaluated by CT or MRI. Absence of significant retroperitoneal fat in these young children and the inability of CT to identify normal sized lymph nodes that contain tumor may limit the sensitivity of CT for staging these patients. Since 90% of malignant testicular germ cell tumors in young children elaborate AFP, adjuvant chemotherapy is reserved for advanced stage disease and the small percentage of children with occult metastatic disease whose AFP fails to decline following orchiectomy (Table 44.2-14).

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Limited solely to the tumor site with no evidence of spread. The surgical margins are disease-free.</td>
</tr>
<tr>
<td>II</td>
<td>Limited to any of the following: a) bilateral orchiectomy, b) resection of the testis with a tumor-free margin, or c) any surgical procedure with evidence of disease at the surgical margin.</td>
</tr>
<tr>
<td>III</td>
<td>Limited to any of the following: a) bilateral orchiectomy, b) resection of the testis with a tumor-free margin, or c) any surgical procedure with evidence of disease at the surgical margin.</td>
</tr>
<tr>
<td>IV</td>
<td>Any site outside the testis or retroperitoneum.</td>
</tr>
</tbody>
</table>

TABLE 44.2-14. Pediatric Oncology Group/Children’s Cancer Group Staging System for Testicular Germ Cell Tumors

Treatment Planning

SURGERY. Preoperative diagnostic studies of a scrotal mass may include ultrasonography that can define the solid or cystic nature of the mass and its relationship to the testicle. All scrotal masses should be explored through an inguinal incision. A transscrotal biopsy contaminates the scrotum and its lymphatic drainage to the inguinal lymph nodes and prevents high ligation of the spermatic cord. If the tumor is clearly malignant, high ligation of the spermatic cord should be performed at the internal ring.

Increasingly, effective cisplatin-based chemotherapy for nonseminomatous germ cell tumor has decreased the role of surgical resection of the retroperitoneal lymph nodes as a therapeutic modality. Infants have a predominance of early-stage lesions that are primarily endodermal sinus tumors (yolk sac tumors), in contrast with teenagers who in whom the embryonal carcinoma or mixed germ cell tumors predominate. Teenagers frequently delay seeking medical attention, resulting in a higher proportion of advanced stage disease at initial presentation. In most series, infants with clinical stage I endodermal sinus tumors are treated by radical orchietomy and then close follow-up. In the United Kingdom Children’s Cancer Group Study of malignant germ cell tumors, 87% of the boys presented with stage I testicular tumors that were treated by orchietomy alone. The pathology of these lesions was predominantly yolk sac tumors (57 of 61). In seven boys, a rising serum AFP was the only evidence for incomplete resection. All responded well to chemotherapy. Survival using this protocol was 100%. A smaller series from the Institute Gustave-Roussy reported recurrence in 2 of 12 boys followed without adjuvant chemotherapy or retroperitoneal lymph node dissection. Both were cured by surgery and chemotherapy.

TABLE 44.2-15. Staging System for Yolk Sac Tumor of the Testis

The clinical behavior of testicular embryonal carcinomas is similar in teenagers and adults. Studies have demonstrated that adults with clinical stage I embryonal carcinoma of the testes have positive retroperitoneal lymph nodes in approximately 30% of cases. This earlier finding is supported by reports of a 28% relapse rate in adults with stage I disease who were initially observed after radical orchietomy. A similar approach to localized disease in children was employed at the St. Jude Children’s Research Hospital where relapse with a pulmonary metastasis was seen in one of eight boys. In many current protocols, children with clinical stage I disease (i.e., no radiographically identifiable retroperitoneal tumor and falling serum markers) are followed after radical orchietomy. Children with identifiable retroperitoneal tumor frequently receive initial chemotherapy, with surgery reserved for residual masses or persistently elevated markers. Resection of postchemotherapy residual masses in adults demonstrated that 45.0% had necrosis, 42.5% had teratoma, and 12.5% had viable germ cell tumor. Both the North American and European pediatric cooperative groups currently employ this strategy of surgery alone followed by close surveillance in children with stage I germ cell tumors, regardless of site or histology.

Children with yolk sac tumors of the testis rarely require bilateral retroperitoneal lymph node dissection for adequate staging. The procedure results are usually negative, but the procedure carries a substantial risk of producing impotence and retrograde ejaculation. In one series, only 2 of 49 bilateral retroperitoneal lymph node dissections and 4 of 29 unilateral retroperitoneal lymph node dissections performed in children with yolk sac tumor of the testes were positive. The percentage of positive retroperitoneal lymph node dissections was not influenced by the age of the patient. Since this diagnostic procedure carries substantial potential morbidity and infrequently provides information that will change the stage or influence therapy, retroperitoneal lymphadenectomy should be avoided.

CHEMOTHERAPY. Current therapeutic practice reserves chemotherapy for children with either advanced stage disease, recurrent localized tumors, or children with stage I disease whose tumor markers fail to decline following orchietomy. Inclusion of chemotherapy in the treatment of children with stage I disease has not provided a statistically significant advantage in relapse-free survival.

The application of combination chemotherapy to the treatment of children with advanced stage or recurrent yolk sac tumor has proceeded from the use of similar programs for the management of adults with nonseminomatous germ cell tumors of the testis. The first effective combinations included dacarbazine, chlorambucil,
therapy is given for histologies other than dysgerminoma if surgery and chemotherapy render the child free of disease.

RADIATION THERAPY.

Closely paralleling the chronology and evolution of chemotherapy for testicular germ cell tumors, subsequent clinical trials for ovarian germ cell tumors employed the cisplatin, etoposide, and bleomycin regimen for treatment of primary nonlocalized or recurrent ovarian germ cell tumors. This regimen has resulted in complete response.

Several other investigators have reported activity of the PVB combination against a variety of ovarian germ cell tumor histologies. 545-547 Current pediatric practice uses the cisplatin, etoposide, and bleomycin regimen in view of comparable response rates with and without the addition of doxorubicin. 548-549 In light of the pulmonary toxicity of bleomycin, multiple studies have been conducted to assess the value of continued inclusion of this agent in platinum-based regimens. Although several randomized adult studies suggest that bleomycin may be deleted from the cisplatin, etoposide, and bleomycin combination based on comparable response rates with and without this agent, there were sufficient differences in overall and relapse-free survival to recommend its continued use. 545-547,549,550 In view of impressive responses to alternative regimens using ifosfamide and etoposide and a United Kingdom study that effectively substituted carboplatin for cisplatin, there are now several potentially less toxic chemotherapy options that need to be prospectively tested. 545-547,551,552

The same guidelines for management of young children with yolk sac tumors of the testis should be applied to adolescents with malignant germ cell tumors. Teenagers with stage I nonseminomatous germ cell tumors may be managed with close surveillance. 545 Those with more advanced stage disease should receive platinum-based combination chemotherapy.

OVARY

Ovarian tumors account for approximately 25% of all pediatric germ cell tumors. The majority of these tumors arise later in childhood, with a peak incidence at 10 years of age. Most of these tumors are benign mature cystic teratomas, although nearly one-third contain malignant elements. In contrast to adult ovarian tumors, malignancies of epithelial or stromal cell origin are uncommon in children. The most common pediatric ovarian neoplasias are dysgerminomas and yolk sac tumors. Immature teratomas account for approximately 10% of ovarian masses. 553,554,555,556,557

Clinical Presentation

Patients with ovarian tumors present with abdominal pain or an abdominal mass. The pain may be severe due to torsion of the ovarian pedicle by the ovary and tumor. 558 Fever is present in 24% of patients at the time of diagnosis. Preoperative radiographic evaluation should include studies that localize the mass to the ovary. A plain abdominal radiograph should be obtained and examined for the presence of calcification. Abdominal ultrasonography demonstrates whether the mass is cystic in nature. CT provides more detailed information about the site of origin of the tumor. In patients with suspected ovarian germ cell tumors, serum levels of AFP and HCG should be assayed before diagnostic or therapeutic surgical intervention. Once the tissue diagnosis is established, the potential sites of metastatic disease should be examined. Possible sites of dissemination include peritoneal implants, retroperitoneal lymph node metastases, lung, liver, and bone. There has been considerable controversy regarding the proper risk group stratification and treatment of patients with immature teratomas and glomaitoma peritonei (peritoneal seeding with mature glial tissue). In general, immature teratomas are treated with surgery alone. The controversy resides in questions about the appropriateness of surgery alone for immature teratomas that have extensively seeded the omentum and peritoneal surfaces. In a report by POG/CCG documenting 135 cases of childhood immature teratomas, 22 of 86 cases of ovarian immature teratomas were characterized by glomaitoma peritonei. Investigators on this study found that this feature had no adverse effect on outcome in patients treated with surgery alone. 551 Only the finding of microscopic foci of malignant yolk sac tumor in immature teratomas correlated with poor prognosis, mandating inclusion of adjuvant chemotherapy for this small subset of children. These same authors note that while modest elevations of AFP (less than 60) may be recorded in children with immature teratomas without malignant elements, nearly all patients with AFP greater than 100 have occult foci of malignant yolk sac tumor. 551

Staging

Staging evaluation should include CT of the chest, abdomen, and pelvis, in addition to bone scintigraphy with technetium 99m pertechnetate. Ovarian tumors are staged using the POG/CCG staging system, which represents a simplified derivation of the International Federation of Gynecology and Obstetrics staging system. 552 (Table 44.2-16).

TABLE 44.2-16. Pediatric Oncology Group/Children's Cancer Group Staging System for Pediatric Ovarian Germ Cell Tumors

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Eclipsed ovarian teratoma; peritoneal washings negative for malignant cells; tumor thrombus or angiosarcoma of uterine vein</td>
</tr>
<tr>
<td>II</td>
<td>Micronodular or nodular teratoma (less than 5 cm); peritoneal washings negative for malignant cells; tumor thrombus or angiosarcoma of uterine vein</td>
</tr>
<tr>
<td>III</td>
<td>Lymph node metastasis (0.5 cm or greater) with evidence of invasion of adjacent structures</td>
</tr>
<tr>
<td>IV</td>
<td>Lymph node metastasis (0.5 cm or greater) with evidence of invasion of adjacent structures</td>
</tr>
<tr>
<td></td>
<td>Peritoneal washings positive for malignant cells</td>
</tr>
<tr>
<td></td>
<td>Peritoneal washings positive for malignant cells</td>
</tr>
<tr>
<td>V</td>
<td>Ipsilateral node metastases or ovarian dissemination</td>
</tr>
<tr>
<td></td>
<td>Ipsilateral node metastases or ovarian dissemination</td>
</tr>
</tbody>
</table>

Treatment Planning

SURGERY. Surgical exploration of an ovarian mass must accomplish two goals: resection of the primary tumor and adequate staging. Peritoneal fluid should be aspirated for cytology. If no fluid is present, peritoneal washings should be obtained. Any peritoneal seeding should be biopsied and a partial or complete omentectomy performed. Ipsilateral lymph nodes should be examined and biopsies taken from the iliac, low periaortic, or pericaval nodes and the periaortic or pericaval nodes at the level of the renal vessels. The contralateral ovary should be examined closely, and if nodules are present, particularly in dysgerminomas or teratomas, a biopsy should be obtained. With current techniques available for in vitro fertilization, increasing efforts are taken to preserve the fallopian tube and uterus in cases in which both ovaries must be resected. 550

CHEMOTHERAPY. Combination chemotherapy with VAC was employed in the 1970s in two small series of pediatric patients with ovarian yolk sac tumor. These early studies demonstrated that improved survival could be achieved with inclusion of chemotherapy in treatment of patients with stage I and II disease. 551-552 Results of these pediatric trials were consistent with the outcomes of studies in adults with ovarian yolk sac tumor that documented similar improvements in survival with adjuvant VAC chemotherapy. 551-552 Neither study reported the response rate of women with advanced ovarian yolk sac tumor to VAC.

Closely paralleling the chronology and evolution of chemotherapy for testicular germ cell tumors, subsequent clinical trials for ovarian germ cell tumors employed the combination of PVB in the treatment of women with advanced ovarian germ cell tumors. In one series, the response rate was 91%, with six women achieving a complete response. 553-554 Several other investigators have reported activity of the PVB combination against a variety of ovarian germ cell tumor histologies. 545-547 Current pediatric practice uses the cisplatin, etoposide, and bleomycin regimen for treatment of primary nonlocalized or recurrent ovarian germ cell tumors. This regimen has produced survival rates exceeding 90% for localized and advanced stage ovarian germ cell tumors in children. 551

RADIATION THERAPY. With the advent of such effective chemotherapy for ovarian germ cell tumors, the current role of radiation therapy is uncertain. No radiation therapy is given for histologies other than dygerminoma if surgery and chemotherapy render the child free of disease. 552 In the unusual situation in which there is...
Treatment options for persistent ovarian dysgerminomas are more complex. Dysgerminomas are curable with irradiation, with one small pediatric study documenting a 5-year overall survival of 94%. Unfortunately, this same study described extensive late sequelae to radiation therapy, including infertility, dysmenorrhea, hypogonadism, and pelvic pain. The morbidity of pelvic irradiation, given the morbidity of this site, may be difficult, therapeutic morbidity may be minimized by treating malignant tumors with neoadjuvant chemotherapy followed by delayed resection.

There are insufficient data available to evaluate the relative importance of surgical excision, local irradiation, and combination chemotherapy in the management of patients with yolk sac tumor of the mediastinum. Frequently, therapeutic failure is due to local progression of the tumor. Since achieving complete surgical excision in this site may be difficult, therapeutic morbidity may be minimized by treating malignant tumors with neoadjuvant chemotherapy followed by delayed resection.

Treatment outcomes have improved with the application of cisplatin-containing chemotherapy regimens, with approximately 40% of patients being relapse-free survivors.

**CHAPTER REFERENCES**


**SECTION 45.1**

**Molecular Biology of Lymphomas**

RICCARDO DALLA-FEVARA  
GIANLUCA GAIDANO

**INTRODUCTION**

The term lymphoma identifies two distinct groups of neoplasms: non-Hodgkin’s lymphoma (NHL) and Hodgkin’s lymphoma (HL). Since the late 1970s, significant progress has been made in the elucidation of the pathogenesis of NHL as a clonal malignant expansion of B or T cells. The molecular characterization of the most frequent cytogenetic abnormalities associated with NHL has led to the identification of a number of genes that are altered in B-cell or T-cell NHL. The pathogenicity of these gene alterations has been confirmed by their ability to cause tumors in transgenic animal models. In addition, the advent of single-cell molecular analysis of NHL has been facilitated by the paucity of the neoplastic population within HL biopsies.

This chapter outlines the main types of genetic lesions in lymphomas and their distribution among the various clinicopathologic subtypes of these disorders, with major emphasis on NHL. The last section of the chapter briefly discusses the present and future applications of molecular genetic analysis in the clinical management of lymphomas.

**HISTOGENETIC PATHWAYS OF LYMPHOMA**

The histogenesis of lymphoma can be assessed by identifying the precise cellular subset from which a given lymphoma category derives (Fig. 45.1-1). This is achieved by defining the lineage and the precise differentiation stage of the various types of lymphoma and by comparing them with the features proper of the different maturation stages of normal lymphocytes. To date, the histogenesis of lymphoma has been clarified to a sizable extent in the case of lymphomas derived from B cells, whereas it is still poorly understood in the case of lymphomas originating from T cells.

**FIGURE 45.1-1.** Model of B-cell non-Hodgkin’s lymphoma (NHL) histogenesis and pathogenesis. A lymphoid follicle, constituted by the germinal center (GC) and the mantle zone (MZ), is represented together with the surrounding marginal zone (MargZ). Upon entering the GC, B cells activate into centroblasts, proliferate, and mature into centrocytes. These events are coupled to somatic hypermutation of immunoglobulin (Ig) genes and isotype switch of the Ig produced. Only GC B cells that are positively selected by antigen survive and exit the GC successfully. Cells that have exited the GC (post-GC B cells) have two fates: differentiation into plasma cells or memory B cells. Based on the absence or presence of somatic Ig hypermutation, B-cell NHL may be distinguished into two broad histogenetic categories: (1) B-cell NHL derived from pre-GC B cells and devoid of Ig mutations, represented in this figure by mantle cell lymphoma (MCL), and (2) B-cell NHL derived from BC cells that have transited through the GC and harbor Ig mutations, represented in the figure by follicular lymphoma (FL), lymphoplasmacytoid lymphoma (LPL), mucosa-associated lymphoid tissue lymphoma (MALT), diffuse large cell lymphoma (DLCL), and Burkitt’s lymphoma (BL). For each lymphoma category, the arrow indicating the histogenetic origin is flanked by the genetic lesion associated with the lymphoma. In the case of DLCL, as well as in a subset of DLCL, the relevant cancer related gene has not been identified.

B lymphocytes are generated in the bone marrow as a result of a multistep differentiation process. Precursor B cells usually begin immunoglobulin (Ig) gene rearrangements of the heavy-chain locus followed by rearrangements of the light-chain locus. If precursor B cells express a functional surface antibody acting as antigen receptor, they are positively selected into the peripheral B-cell pool comprising naive B cells. Cells failing to express a functional antigen receptor are eliminated within the bone marrow. For many B cells, the subsequent maturation steps are linked to the histologic structure of the germinal center. The germinal center is constituted by a dark zone, characterized by a dominant growth of rapidly proliferating B cells, and by a light zone, in which nonproliferating B cells are selected and induced to differentiate through interactions with follicular dendritic cells and T helper cells. Within the germinal center, antigen-activated B cells accumulate somatic point mutations within their rearranged heavy- and light-chain genes (a phenomenon known as somatic hypermutation), which modify the affinity of their surface antibody to the antigen. Only B cells that have acquired mutations leading to high-affinity binding are positively selected and differentiate into memory B cells or plasmablasts, whereas the majority of B cells are eliminated by apoptosis within the germinal center.
The use of somatic hypermutation as a specific marker of B-cell transition through the germinal center allows for the definition of two broad histogenetic categories of B-cell lymphomas.

1. Lymphomas devoid of somatic Ig hypermutation, which may derive from either pre-germinal center B cells or from B cells that have achieved maturation without transiting through the germinal center. Lymphomas generally devoid of somatic Ig hypermutation include mantle cell lymphoma and a substantial percentage of B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma.

2. Lymphomas associated with somatic Ig hypermutation and thus putatively derived from germinal center or post-germinal center B cells. Among the NHLs, lymphomas generally associated with somatic Ig hypermutation include follicular lymphoma, lymphoplasmacytoid lymphoma, mucosa-associated lymphoid tissue (MALT) lymphoma, diffuse large cell lymphoma (DLCL), Burkitt’s lymphoma, and primary effusion lymphoma. In addition, a fraction of B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma, approximating 50% of cases, is thought to originate from germinal center–related B cells. Most, if not all, HL cases also are thought to derive from germinal center or post-germinal center B cells. Extranodal lymphomas associated with somatic Ig hypermutation are postulated to originate from B cells that have transited through the germinal center and subsequently migrated to the involved extranodal site.

GENERAL MECHANISMS OF GENETIC LESIONS IN LYMPHOMA

Analogous to most cancer types, the pathogenesis of lymphoma represents a multistep process involving the progressive and clonal accumulation of multiple genetic lesions affecting protooncogenes and tumor suppressor genes. However, several important features distinguish the mechanism and type of genetic alterations associated with lymphoma from those associated with solid tumors. Extensive cytogenetic studies have shown that, during most stages of the disease, the genome of lymphoma cells is relatively stable and is not affected by the generalized random instability typical of many solid tumors, particularly those of epithelial origin. Lymphoma also appears devoid of microsatellite instability, the hallmark of molecular defects in DNA mismatch repair genes observed in some hereditary cancer predisposition syndromes as well as in most sporadic tumor types. Conversely, the genome of lymphoma cells is characterized by few, sometimes single, nonrandom chromosomal abnormalities, commonly represented by chromosomal translocations.

At the molecular level, the genetic lesions identified so far in lymphomas include activation of oncogenes by chromosomal translocations, as well as inactivation of tumor suppressor loci by chromosomal deletion and mutation. In addition, the genome of certain lymphoma subtypes can be altered by the introduction of exogenous genes by various oncogenic viruses.

CHROMOSOMAL TRANSLOCATIONS

Chromosomal translocations represent the genetic hallmark of lymphoid malignancies, including NHL. As in other types of malignancies, NHL-associated translocations represent reciprocal and balanced recombinations between two specific chromosomes that are recurrently associated with a given tumor type and clonally represented in each tumor case.

The precise mechanisms leading to chromosomal translocations in hematopoietic neoplasms are not clearly understood. However, data suggest that the translocation process most likely occurs during Ig gene and T-cell receptor gene rearrangements in B and T cells, respectively, as a consequence of errors of the VDJ recombination machinery or the class switch machinery. This evidence is supported by the following observations:

1. A significant number of translocations involve chromosomal breakpoints within the Ig or T-cell receptor loci.
2. In B-cell NHL, breakpoints within the Ig loci are often located precisely within sequences that normally mediate Ig gene rearrangement in B cells, such as the J and switch sequences. Moreover, N-nucleotides, which are template-independent nucleotide additions generated at the site of VDJ recombination by terminal deoxynucleotidyl transferase, can be detected at certain breakpoint junctions, suggesting the action of the recombinase.
3. Similarity has been shown between the sequences surrounding the breakpoints and recombination targeting motifs, such as the heptamer/nonamers and the bp45 nuclease binding sequence.

Not all chromosomal translocations involve B-cell NHL breakpoints within the Ig or T-cell receptor loci. For example, based on sequence analysis of reciprocal chromosomal breakpoints, the chromosomal translocation t(14;11) seen in acute leukemias of B lineage appears to be initiated by several DNA strand breaks on both participating chromosomes and by subsequent DNA repair by an “error-prone” DNA repair mechanism. Similarly, analysis of the breakpoint junction sequence at TEL in t(12;21)(p13;q22) supports the occurrence of staggered DNA double-strand breaks followed by DNA repair. Therefore, the generation of DNA double-strand breaks by exogenous and endogenous sources (e.g., chemicals and oxygen-free radicals) and faulty DNA repair can lead to chromosomal rearrangements. These models have been validated by mouse models but have yet to be proven in humans.

The suggestion also has been made that some translocations, namely those occurring in lymphoid malignancies derived from germinal center B cells, such as Burkitt’s lymphoma and DLCL, may be a result of somatic hypermutation that takes place in the germinal center B cells. It has been shown that deletions and duplications can be introduced into the rearranged variable (V)_{gamma} genes in a substantial portion of germinal center cells during somatic hypermutation. Because the formation of these deletions and duplications is intrinsically associated with DNA double-strand breaks, they may provide a potential source for chromosomal translocations in germinal center B cells. Somatic hypermutation may be the underlying mechanism of the chromosomal translocations between the Ig_{gamma} locus and c-MYC in the endemic form of Burkitt’s lymphoma, and these translocations are generally believed to be a result of errors of the VDJ recombination machinery. This theory is supported by the observation that the breakpoints at the Ig_{gamma} loci in endemic Burkitt’s lymphoma are not usually directly adjacent to the recombination signal sequence that mediates VDJ recombination, but are located in the J inhibitor or within rearranged VJ genes (i.e., the target region for hypermutation). It remains to be seen if somatic hypermutation also plays a role in the generation of chromosomal translocations at the BCL-6 locus, which also is a target for somatic hypermutation, in B-cell DLCL (see Diffuse Large Cell Lymphoma, later in this chapter).

The common feature of all chromosomal translocations associated with NHL is the presence of protooncogenes in proximity to the chromosomal recombination sites. In most cases, the structure of the protooncogene and, in particular, its coding domain is not affected by the translocation, but the pattern of expression of the gene is altered as a consequence of the juxtaposition of heterologous regulatory sequences derived from the partner chromosome (protooncogene deregulation). Two distinct types of protooncogene deregulation may occur, including homotypic and heterotypic deregulation. Homotypic deregulation occurs when the protooncogene is expressed constitutively in the lymphoma, whereas its expression is tightly regulated in normal lymphoid cells. Conversely, heterotypic deregulation occurs when the protooncogene, which is normally not expressed in lymphoid cells, undergoes ectopic expression in the lymphoma. In most types of NHL-associated translocations, the heterologous regulatory regions responsible for protooncogene deregulation are derived from antigen receptor loci, which are expressed at high levels in the target tissue.

**FIGURE 45.1-2.** Models of chromosomal translocations in non-Hodgkin’s lymphoma (NHL). The two genes involved in the translocation event are represented by their coding sequences (CS), which are represented by the rectangles, and by their regulatory sequences (RS), which are represented by the circles. The two genes are identified by different colors (black or white). **Top:** Germline configuration of the two genes involved in the translocation. The coding sequence of each of the two...
genes is proximal to its physiologic regulatory sequences, which coordinate the normal expression of the gene. **Bottom:** Chromosomal translocations may lead to two different consequences. In the case of transcriptional deregulation, the normal regulatory sequences of the protooncogene are removed and substituted with regulatory sequences derived from the partner chromosome. The protooncogene coding sequence (black rectangle) is thus juxtaposed to heterologous regulatory sequences (white circle). In NHL, most commonly the novel regulatory regions are derived from the immunoglobulin gene loci, which are consistently expressed at high levels in mature B cells. In the case of fusion transcript formation, part of the coding sequence of the two genes involved is fused together, generating a novel fusion protein with biochemical properties distinct from the native proteins.

An alternative mechanism of oncogene activation by chromosomal translocation is the juxtaposition of two genes to form a chimeric gene coding for a novel chimeric protein. This mechanism, which is common in chromosomal translocations associated with acute leukemias, is rarely associated with NHL. Examples are the t(11;18) of MALT lymphoma and the t(2;5) of T-cell anaplastic lymphoma.

The molecular cloning of the genetic loci involved in the translocations most frequently associated with NHL has led to the identification of a number of protooncogenes involved in lymphomagenesis (Table 45.1.1). The majority of these protooncogenes code for nuclear molecules belonging to major families of transcription factors, although regulators of programmed cell death and signal transducers may also be involved. The structural and functional consequences of each chromosomal translocation associated with NHL are described in each section of this chapter dedicated to the molecular pathogenesis of the various NHL subtypes.

### TABLE 45.1.1. Chromosomal Translocations of Non-Hodgkin's Lymphomas

<table>
<thead>
<tr>
<th>Chromosomal Translocation</th>
<th>NHL Subtype</th>
</tr>
</thead>
<tbody>
<tr>
<td>t(11;18)</td>
<td>MALT lymphoma</td>
</tr>
<tr>
<td>t(2;5)</td>
<td>T-cell anaplastic lymphoma</td>
</tr>
<tr>
<td>t(8;14)</td>
<td>Burkitt's lymphoma</td>
</tr>
<tr>
<td>t(14;18)</td>
<td>Follicular lymphoma</td>
</tr>
</tbody>
</table>

## OTHER MECHANISMS OF PROTOONCOGENE ALTERATION

In addition to chromosomal translocations, other mechanisms of protooncogene activation can also occur in NHL. Protooncogene amplification is substantially less common than in epithelial cancers, yet it occurs in some cases of high-grade NHL, as exemplified by the instance of REL amplifications in DCLL. Amplification may involve many other unknown chromosomal sites, which are likely to be revealed by the extensive use of advanced cytogenetic techniques, such as comparative genomic hybridization. Point mutations can alter the coding sequence of the protooncogene, as in the case of c-MYC and BCL-2, and thus alter the biological properties of the protooncogene product. Alternatively, mutations may affect the protooncogene regulatory sequences, as in the case of c-MYC and BCL-6, thus altering their sensitivity to factors normally regulating the expression of the protooncogene through binding to its regulatory sequences. Mutations of the RAS genes, which represent a frequent protooncogene alteration in human neoplasia, are virtually always absent in NHL. Mutations activating unknown oncogenes may be a frequent event in NHL, and the search for these oncogenes is the focus of current investigations.

## INACTIVATION OF TUMOR SUPPRESSOR GENES

Deletions and mutations of the p53 tumor suppressor gene, which are thought to represent the most common genetic alteration in human cancer, are restricted to specific subsets of NHL, including late stages of follicular lymphoma and Burkitt's lymphoma. The mechanisms of p53 inactivation in NHL is similar to that detected in human neoplasia in general and occurs through point mutation of one allele, chromosomal deletion of the second allele, or both.

In addition, NHLs are associated with specific chromosomal deletions, suggesting the loss of presently unknown tumor suppressor genes. The most frequent of these deletions involves the long arm of chromosome 6 (6q). The observations that 6q deletions may occur as the sole cytogenetic abnormality in some NHL cases and are associated with poor prognosis strongly support a pathogenic role for these alterations. Deletions of chromosome 13q14 represent the most frequent lesion in B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma, occurring in more than 50% of cases. Mapping studies have ruled out the involvement of the RAI tumor suppressor gene, which is also located on chromosome 13q14, and have suggested the presence of a distinct tumor suppressor gene in the same region.

## ONCOGENIC VIRUSES

The infection of tumor cells by oncogenic viruses must be considered as a mechanism of genetic lesion because viruses introduce foreign genes into their target cells. Three distinct viruses are associated with the pathogenesis of specific NHL subtypes: Epstein-Barr virus (EBV), human herpesvirus-8 (HHV-8), and human T-cell leukemia virus type 1 (HTLV-I).

EBV was initially identified in cases of endemic Burkitt's lymphoma from Africa; subsequently, EBV also was detected in a fraction of sporadic forms of Burkitt's lymphomas, acquired immunodeficiency syndrome (AIDS)-associated lymphomas, and primary effusion lymphomas. With infection of a B-lymphocyte, the EBV genome is transported into the nucleus, where it exists predominantly as an extrachromosomal circular molecule (episome). The formation of a circular episome is mediated by the cohesive terminal repeats, which are represented by a variable number of tandem repeats sequence. Because of this termini heterogeneity, the number of variable number of tandem repeats sequences enclosed in newly formed episomes may differ considerably, thus representing a constant clonal marker of the episome and, consequently, of a single infected cell. Evidence for a pathogenetic role of the virus in NHL infected by EBV is at least twofold. On one side, it is well recognized that EBV is able to significantly alter the growth of B cells. On the other side, EBV-infected lymphomas usually display a single form of fused EBV termini, suggesting that the lymphoma cell population represents the clonally expanded progeny of a single infected cell.

HHV-8 is a gamma herpesvirus initially identified in tissues of patients with AIDS-related Kaposi's sarcoma, and it subsequently was found to infect a peculiar type of T lymphocytes. Lymphoma cells naturally infected by HHV-8 harbor the viral genome in its episomal configuration and display a marked restriction of viral gene expression, suggesting a pattern of latent infection. HHV-8 carries several genes that may behave as oncogenes, including a gene homologous to the cellular D-type cyclins, a G protein–coupled receptor displaying constitutive activation, and several genes encoding for molecules displaying high homology with cellular cytokines [viral interleukin (IL)-6] and chemokines [viral macrophage inflammatory protein (MIP)-1a, MIP-2]. However, because primary effusion lymphoma cells carry latent HHV-8 infection, only a restricted subset of viral genes are expressed in vivo, including viral cyclin D and viral IL-6.

HTLV-I is a member of the lentivirus group, which can immortalize normal T cells in vitro and can cause adult T-cell leukemia/lymphoma. Unlike acutely transforming retroviruses, the HTLV-I genome does not encode a viral oncogene. Furthermore, this retrovirus does not transform T cells by cis-activation of an adjacent cellular protooncogene, because the provirus appears to integrate randomly within the host genome. Rather, the pathogenetic effect of HTLV-I
MOLECULAR PATHOGENESIS OF B-CELL NON-HODGKIN'S LYMPHOMA

The following section describes the detailed genetic lesions and the molecular pathways presently identified in association with distinct B-cell NHL categories classified according to the World Health Organization (WHO) system of lymphoid neoplasia. B-Cell NHL categories known to associate with specific genetic lesions include B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma, lymphoplasmacytoid lymphoma, mantle cell lymphoma, follicular lymphoma, MALT lymphoma, DCLL, and Burkit's lymphoma among B-cell NHL. The molecular pathogenesis of AIDS-related NHL also is addressed. The precise molecular pathogenesis of all other B-cell NHL types has not yet been elucidated.

B-CELL CHRONIC LYMPHOCYTIC LEUKEMIA/SMALL LYMPHOCYTIC LYMPHOMA

The molecular pathogenesis of B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma is still largely unknown (see Fig. 45.1-1). Mutations of the p53 gene and loss of heterozygosity at 17p, the p53 site, are found in a small number (10% to 15%) of cases. A higher frequency of p53 alterations is observed after transformation of B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma to Richter's syndrome, a highly aggressive lymphoma with a poor clinical outcome. Suggesting that p53 may be involved in the genetic mechanisms underlying B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma progression. Despite initial suggestions, it is now well established that "true" cases of B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma (i.e., CD5+, CD23+, according to the WHO and the Revised European-American Lymphoma classification) are consistently devoid of BCL-1 and BCL-2 rearrangements (Table 45.1-2). Because high levels of bcl-2 expression are consistently seen in B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma, it is conceivable that they result from mechanisms other than chromosomal translocation. A small fraction of B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma harbor mutations of the ataxia-telangiectasia mutated (ATM) gene. Because these mutations may occur in the patient germline, ATM mutations may account, at least in part, for the familial cases of the disease.

Despite the paucity of information regarding the molecular lesions associated with B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma, cytogenetic studies have revealed several recurrent chromosomal abnormalities. Trisomy 12 is found in approximately 35% of B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma cases evaluated by interphase fluorescence in situ hybridization and correlates with a poor survival. Based on karyotypic and deletion mapping studies, it is likely that the 13q14 chromosomal region harbors a novel tumor suppressor gene involved at high frequency in B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma. In fact, deletions of 13q14 occur in approximately 60% of cases when analyzed by sensitive molecular tools, but the relevant gene has not been identified. Deletions of 6q define a subset of B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma cases displaying prolymphocytic features.

Studies of B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma have revealed novel insights into the disease histogenesis. It is now apparent that the clinical heterogeneity of B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma might be related to heterogeneity in the disease histogenesis. Although B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma has been traditionally viewed as a tumor of naive, pre-germinatal center B cells, more recent data have suggested that a fraction of cases derives from germinal center–related B cells. In fact, the malignant cells of approximately 50% of B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma harbor mutations of Ig genes, with or without BCL-6 mutations, which are well-established markers of germinal center transit. The molecular spectrum of Ig and BCL-6 mutations in B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma is superimposable to that of germinal center–derived lymphomas. Intriguingly, the histogenetic heterogeneity of B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma appears to carry prognostic relevance, because cases with mutations of Ig genes are associated with a significantly longer survival.

Lymphoplasmacytoid lymphoma is typically CD5-negative and associated in a large fraction of cases with a monoclonal serum IgM-type paraprotein, causing the clinical syndrome known as Waldenström's macroglobulinemia. Approximately 50% of these lymphomas associate with the t(9;14)(p13;q32) translocation, a recurrent chromosomal abnormality in B-cell NHL (see Table 45.1-1 and Fig. 45.1-1). The chromosomal breakpoints of t(9;14)(p13;q32) involve the Igκ locus on chromosome 14q32 and, on chromosome 9p13, a genomic region containing the paired homeobox-5 (PAHX-5) gene. The PAHX-5 encodes a B-cell–specific transcription factor involved in the control of B-cell proliferation and differentiation. Presumably, the juxtaposition of PAHX-5 to the Igκ locus in NHL carrying t(9;14)(p13;q32) causes the deregulated expression of the gene, thus contributing to tumor development. Apart from t(9;14)(p13;q32), no other genetic lesion has been detected at significant frequencies in lymphoplasmacytoid lymphoma (see Table 45.1-2).

MANTLE CELL LYMPHOMA

Mantle cell lymphoma constitutes 25% of nonfollicular small B-cell lymphomas and is typically associated with t(11;14) (q13;q32) translocation, a recurrent chromosomal abnormality in B-cell NHL (see Table 45.1-1 and Fig. 45.1-1). The t(11;14)(q13;q32) translocation juxtaposes the BCL-1 locus at 11q13 with Igκ, t(11;14) and t(11;14) (q13;q32). The consistent and selective clustering of BCL-1 overexpression with NHLS carrying t(11;14) strongly suggests that this gene is indeed the critical component of t(11;14)(q13;q32), because the t(11;14) consistently leads to homotypic deregulation of BCL-1 (also known as CCND1 or PRLD1), a gene located in proximity to the breakpoint region and encoding for cyclin D1, a member of the D-type G1 cyclins that regulate the early phases of the cell cycle. The precise contribution of cyclin D1 to cell-cycle regulation is still under investigation. As for other D-type cyclins, cyclin D1 is thought to act primarily as a growth factor sensor, integrating extracellular signals with the cell-cycle clock. The pathogenic role of BCL-1 activation in human neoplasia is suggested by the ability of cyclin D1 overexpression to transform cells in vitro and contribute to B-cell lymphomagenesis in transgenic mice. The application of strict phenotypic criteria to the classification of B-cell lymphoproliferations has defined that the distribution of BCL-1 rearrangements and activation are restricted to mantle cell lymphoma (see Table 45.1-1 and Fig. 45.1-1). The frequency and specificity of this genetic lesion provide an excellent marker for diagnosis of mantle cell lymphoma. The precise identification of mantle cell lymphoma among nonfollicular small B-cell lymphomas is clinically relevant because mantle cell lymphoma is a far more aggressive disease and displays a significantly shorter survival than other histologically related forms.

Other genetic alterations may be also involved in mantle cell lymphoma. Inactivation of p53 occurs in approximately 20% of cases and is a marker of poor prognosis. Inactivation of p16 by deletion, mutation, or hypermethylation is detectable in approximately one-half of cases belonging to the aggressive mantle cell lymphoma variant characterized by a blastoid cell morphology.

FOLLICULAR LYMPHOMA

The genetic hallmark of follicular lymphoma is represented by chromosomal breaks at 18q21 and rearrangements of BCL-2, which are detected in 80% to 90% of the cases independent of cytologic subtype. The pathogenic role of BCL-2 activation in human neoplasia is suggested by the ability of cyclin D1 overexpression to transform cells in vitro and contribute to B-cell lymphomagenesis in transgenic mice. Other genetic lesions may also occur, especially in follicular lymphoma cases that have undergone histologic progression to a high-grade NHL.
TABLE 45.1-2. Frequency of Genetic Lesions in B-Cell Non-Hodgkin’s Lymphoma

### Chromosomal Translocations Involving the BCL-2 Gene

The t(14;18)(q32;q21) translocation is the most common translocation in human lymphoid malignancies.\(^{135,136,137}\) (see Table 45.1-1). The rare variant translocations t(2;18)(p11;q21) and t(16;22)(q21;q21) represent biologic equivalents. Virtually all follicular lymphomas and a fraction of DLCLs carry breaks at 18q21.\(^{138,139,140}\)\(^{,}141\) (see Table 45.1-1). In t(14;18), the rearrangement joins the BCL-2 gene at its 3′ untranslated region to an Ig\(_{\gamma}\) J segment (Fig. 45.1-3), resulting in homotypic deregulation of BCL-2 expression.\(^{135,137,138}\)\(^,\)\(^{142}\) The consequence of the translocation is the presence within the cells of constitutively high levels of BCL-2 protein resulting from both enhanced transcription and, possibly, more efficient RNA processing.\(^{137,142}\) Approximately 70% of the chromosome 18 breakpoints cluster within the major breakpoint region, and the remaining cases usually break in the more distant minor cluster region.\(^{135,136,137,140}\)\(^,\)\(^{142}\)

![Schematic representation of BCL-2 translocations](image)

**FIGURE 45.1-3.** Schematic representation of BCL-2 translocations. The germline configuration of the BCL-2 gene, mapping to 18q21, is shown in the upper panel of the figure. Its germline configuration, BCL-2 is composed of three exons with a large intron between exon 2 and exon 3. The coding region of the BCL-2 gene is indicated by black boxes, whereas noncoding exons (or portions of exons) are indicated by white boxes. The BCL-2 promoters within exon 1 are shown by arrows. The location of the major breakpoint region (MBR) and minor cluster region (mcr), where most BCL-2 breakpoints fall, is indicated by an arrow. The germline configuration of Ig\(_{\gamma}\) on chromosome 14q32 is also shown in the upper panel of the figure. Boxes indicate the joining (J), switch (S), and constant (C) regions of Ig\(_{\gamma}\). The 14q32 breakpoint (indicated by an arrow) falls within J\(_{\gamma}\). The bottom panels of the figure depict the molecular consequences of t(14;18)(q32;q21), which causes the juxtaposition of BCL-2 to the Ig\(_{\gamma}\) locus. Both the MBR and mcr type of translocations are shown. Within the Ig\(_{\gamma}\) locus, the breakpoint involves J\(_{\gamma}\) sequences. Notably, the BCL-2 coding sequence of the translocated BCL-2 allele is intact. Because the BCL-2 coding region is preserved, the hybrid BCL-2/Ig\(_{\gamma}\) transcript gives rise to a wild-type and normal-size BCL-2 protein. The reader is referred to the text for a description of the functional consequences of BCL-2 translocations on the transcriptional regulation of BCL-2.

The BCL-2 gene encodes a 26-kD integral membrane protein that has been localized to mitochondria, endoplasmic reticulum, and perinuclear membrane.\(^{144}\) In contrast to most protooncogenes of lymphoid neoplasia, BCL-2 has little or no ability to promote cell-cycle progression or cell proliferation, but rather controls the cellular apoptotic threshold by preventing programmed cell death.\(^{144,145,146}\)\(^,\)\(^{147}\) In normal cells, the topographic restriction of BCL-2 expression to germinal center zones of surviving B cells suggests that BCL-2 drives the emergence of long-surviving memory B cells.\(^{148}\) Indeed, BCL-2–trangenic animals show markedly protracted secondary immune responses and an extended lifetime for memory B cells in the absence of antigen.\(^{149}\)

The precise molecular mechanisms by which BCL-2 regulates cell death stem from the observation that BCL-2 is only one member of a family of apoptotic regulators, which also includes BAX and BCL-X.\(^{150,151}\)\(^,\)\(^{152}\) It is now clear that BCL-2 exists as part of a high-molecular-weight complex generated through heterodimerization with BAX.\(^{153,154}\) The inherent ratio of BCL-2 to BAX determines the functional activity of BCL-2.\(^{155,156}\) When BAX is in excess, BAX homodimers dominate and cell death is accelerated; conversely, when BCL-2 is in excess, as in NHL carrying BCL-2 rearrangements, BCL-2/BAX heterodimers are the prevalent species and cell death is repressed. The biochemistry of the translocated BCL-2 antipapoptotic function has been elucidated to a certain extent and relies on activation of an antioxidant pathway at sites of free radical generation or regulation of endoplasmic reticulum–associated Ca\(^{2+}\) fluxes.\(^{157,158}\)

The precise role of BCL-2 activation in follicular lymphoma pathogenesis is complex. Despite the fact that follicular lymphoma is comprised of mature B cells, the translocation appears to occur earlier in ontogeny at a pre-B cell stage.\(^{159}\) In contrast to other genetic lesions occurring in pre-B cells and leading to B-cell lineage acute lymphoblastic leukemia through a differentiation block of the target cells, BCL-2 rearrangements are permissive of B-cell maturation to the stage of surface sigM/sigD\(^+\) B cells.\(^{160}\) The pathogenic contribution of BCL-2 lesions to follicular lymphoma development is documented by the observation that the growth of human B-cell NHL bearing BCL-2 translocations is specifically and efficiently inhibited in vitro by antisense oligonucleotides targeted against the BCL-2 gene.\(^{161}\) Furthermore, BCL-2 transgenic mice develop a pattern of polyclonal hyperplasia of mature, long-lived B cells resting in G\(_{0}\), which, despite morphologic similarities, contrasts with the consistent monoclonality of human follicular lymphoma.\(^{162}\) Hence the view that BCL-2 activation is not sufficient for follicular lymphoma development and that other genetic lesions or host factors are required. A strong candidate is represented by chronic antigen stimulation and selection that would synergize with BCL-2 in driving follicular lymphoma expansion.\(^{163,164}\) With time, and analogous to the human disease, a fraction of BCL-2 transgenic mice progresses to develop aggressive, clonal large cell lymphomas that have acquired additional genetic lesions.\(^{165}\) (see the following section, Other Genetic Lesions).

**Other Genetic Lesions**

Other cancer-related genes involved in lymphomagenesis, such as c-MYC and p53, do not appear to be involved in follicular lymphoma. Deletions of chromosome 6 are present in 20% of cases.\(^{166}\) Over time, follicular lymphomas tend to convert into an aggressive lymphoma with a diffuse large cell architecture (see Fig. 45.1-1). This histologic shift is generally accompanied by the accumulation of p53 mutations and, in approximately 40% of cases, by mutations of BCL-6 or inactivation of p16 (or both).\(^{166,167}\) Rearrangements of c-MYC may also accompany the histologic transformation of follicular lymphoma in rare cases.\(^{168}\)

**MUCOSA-ASSOCIATED LYMPHOID TISSUE LYMPHOMAS**

The majority of gastric MALT lymphomas are associated with Helicobacter pylori infection.\(^{169}\) It has been suggested that gastric MALT lymphomas may be dependent on antigen stimulation by H pylori because malignant lymphoid cells respond to H pylori antigens and because the lymphoma may regress, at least partially, when the infection is eradicated.\(^{170}\) The potential role of antigen in MALT lymphoma pathogenesis is further supported by the observation that MALT lymphoma cells harbor the gerotypic clone of antigen-experienced B cells (i.e., somatic hypermutation of Ig genes).\(^{171,172}\) Whether the development of MALT lymphoma arising in body sites other
than the stomach is also dependent on antigen stimulation and selection remains an open question. In this respect, it is remarkable that thyroid MALT lymphoma is generally a sequela of Hashimoto thyroiditis, an autoimmune process causing the exposure of B cells to thyroid-derived autoantigens.

Cytogenetic studies have pointed to several abnormalities selectively and recurrently involved in these tumors. The most common of these abnormalities is t(1;18)(q21;q21). The t(1;18)(q21;q21) translocation occurs in approximately 50% of cytogenetically abnormal MALT lymphomas, independent of the site of origin. Recurrent abnormalities are more often seen in DLCL, generally represented by t(1;14)(p22;q32), occur in a small percentage of MALT lymphomas and cause alterations of the BCL-10 gene. BCL-10 is a cellular homologue of the equine herpesvirus-2 E10 gene and encodes an amino-terminal caspase recruitment domain homologous to that found in several apoptotic molecules. The wild-type BCL-10 gene activates the NF-kB signaling cascade and is able to induce apoptosis in different cell types. Two distinct types of BCL-10 alterations are observed in MALT lymphomas carrying t(1;14)(p22;q32). First, BCL-10 is overexpressed. Second, BCL-10 genes from t(1;14)-positive MALT lymphomas harbor truncations either in, or carboxy-terminal to, the caspase recruitment domain. BCL-10 mutants lose the proapoptotic ability of wild-type BCL-10 and, in some cases, also fail to activate NF-kB. Therefore, it is conceivable that overexpression of BCL-10-translocated alleles might have a twofold effect on lymphomagenesis: Loss of BCL-10 proapoptosis may confer a survival advantage to MALT B cells, and constitutive NF-kB activation may provide both antipapoptotic and proliferative signals mediated via its transcriptional targets.

Other genetic alterations commonly involved in other lymphoma types also have been observed in MALT lymphomas, including BCL-6 alterations and p53 mutations. 182,183 and 184

**DIFFUSE LARGE CELL LYMPHOMA**

B-lineage DLCL is a potentially curable disease that accounts for approximately 40% of NHLs of adulthood. The molecular pathogenesis of DLCL is complex and includes both genetic lesions specific for this disease (i.e., rearrangements of BCL-6) and molecular alterations common to other NHL categories (see Fig. 45.1-1).

### Chromosomal Translocations Involving the BCL-6 Gene

Cytogenetic studies of NHL have demonstrated that chromosomal alterations affecting band 3q27 are a frequent recurrent abnormality in B-lineage DLCL. These alterations are predominantly represented by reciprocal translocations between the 3q27 region and several alternative partner chromosomes, including, though not restricted to, the sites of the Ig genes at 14q32 (Igκ), 1p11 (Igλ), and 22q11 (Igδ). (Fig. 45.1-4). The variability of the partner chromosomes juxtaposed to 3q27 in B-lineage DLCL translocations suggests that these abnormalities belong to the group of “promiscuous” translocations, which involve a fixed chromosomal breakpoint on one side and, on the other side, have different chromosomal partners in different cases.

The cloning of the 3q27 chromosomal breakpoints revealed the BCL-6 gene, which is involved in the overwhelming majority of B-lineage DLCL cases harboring 3q27 breaks, irrespective of the partner chromosome participating in the translocation. BCL-6 is a transcriptional repressor belonging to the POZ protein sequence motif containing zinc fingers, a protein sequence motif able to mediate the protein binding to specific DNA sites. The amino-terminal domain of the BCL-6 protein contains a domain, termed POZ, which is homologous to domains found in several other zinc-finger transcription factors. Apparently, the POZ domain acts as a protein-protein interface implicated in homo- and heterodimerization processes. These structural features of the BCL-6 protein are consistent with functional studies indicating that BCL-6 can indeed function as a transcriptional repressor that inhibits the expression of genes carrying its specific DNA-binding motif.

The pattern of BCL-6 protein expression in human tissues is highly specific, and high levels are specifically found in B cells. In particular, BCL-6 expression is topographically restricted to the germinal center, where BCL-6 is expressed by both centroblasts and centrocytes, whereas expression of BCL-6 is absent in pre-germinal center B cells (virgin B cells) and post-germinal center B cells (memory B cells and plasma cells). The observation that BCL-6 is expressed within the germinal center, but not before entrance into or after exit from the germinal center, led to the postulation that BCL-6 may be needed for germinal center development and sustainment, whereas its down-regulation may be necessary for further differentiation of B cells.

The precise role of BCL-6 in physiologic immune processes has been further clarified by knockout animal models carrying biallelically disrupted BCL-6 genes. Mice carrying the BCL-6null phenotype consistently fail to form germinal centers. Consistent with lack of germinal center formation, BCL-6null mice also display impairments in the T-cell-dependent antigen-specific IgG response. Overall, these animal models unequivocally demonstrate that BCL-6 is a key regulator of germinal center formation and B-cell immune response.

Chromosomal translocations involving band 3q27 truncate the BCL-6 gene within its 5' flanking region or within the first exon or intron (Fig. 45.1-5), making these alterations readily detectable as rearrangements by Southern blot hybridization analysis of tumor DNA. By conventional molecular assays, BCL-6 rearrangements are detectable in 35% of B-lineage DLCL cases and in a small fraction of follicular lymphomas. Conversely, BCL-6 rearrangements are virtually absent in all other types of lymphoid neoplasms. The coding domain of the BCL-6 gene is left intact in all cases displaying BCL-6 rearrangements, whereas the 5' regulatory sequences, which contain the BCL-6 promoter, are either truncated or, alternatively, completely removed. In all BCL-6 rearrangements, the entire coding sequence of BCL-6 is juxtaposed downstream to heterologous sequences that, based on cytogenetic data, may originate from different chromosomal sites in different patients (see Fig. 45.1-4 and 45.1-5). The common functional consequence of BCL-6 translocations is the juxtaposition of heterologous promoters to the BCL-6 coding domain, a mechanism called promoter substitution (see Fig. 45.1-5). The substitution of the BCL-6 promoter by heterologous regulatory sequences causes deregulated BCL-6 expression in B-lineage DLCL carrying BCL-6 rearrangements. One feature shared by the heterologous promoters linked to rearranged BCL-6 alleles is that they are physiologically active in normal B cells and are not down-regulated during the late stages of B-cell differentiation. Thus, BCL-6 rearrangements may prevent down-regulation of BCL-6 and, in turn, block the differentiation of germinal center B cells toward the
stage of plasma cells. According to this model, B-lineage DLCL cells carrying BCL-6 rearrangements would thus be “frozen” at the stage of germinal center cells.

**FIGURE 45.1-5.** Schematic representation of BCL-6 translocations. The germline configuration of the BCL-6 gene, mapping to 3q27, is shown in the upper right panel of the figure. In its germline configuration, BCL-6 is composed of ten exons. The coding region of the BCL-6 gene is indicated by block boxes, whereas the noncoding exons (or portions of exons) are indicated by white boxes. The physiologic BCL-6 promoter within exon 1 is shown by an arrow. The frequency of BCL-6 breakpoint locations is also shown. The germline configuration of several BCL-6 translocation partners (TTF, BOB1, Ig�, and other hypothetical genes designated as X) is shown in the upper left panel of the figure. The bottom panel of the figure depicts the molecular configuration of representative translocated BCL-6 alleles. Independent of the partner chromosome involved, all translocated BCL-6 alleles are deprived of their exon 1 and, consequently, of their physiologic promoter. The novel sequences derived from the partner chromosomes are thus juxtaposed 5′ to the intron 1 of BCL-6. These novel sequences provide a heterologous promoter to BCL-6, such as the Ig�, germline transcript promoter (Ig�, or, alternatively, Im) in the case of t(3;14); the TTF promoter in the case of t(3;4); and the BOB1 promoter in the case of t(3;11). The genomic configuration of the BCL-6 gene downstream to the breakpoint site is preserved, thus leaving intact the BCL-6 coding sequence. The transcripts resulting from representative BCL-6 translocations are also shown in the lower part of the bottom panel of the figure. In all cases, the translocation gives rise to a fusion transcript, exemplified by TTF/BCL-6, BOB1/BCL-6, Ig/BCL-6, and X/BCL-6. These transcripts initiate from the heterologous promoter provided by the chromosomal site juxtaposed to BCL-6, and they retain the entire BCL-6 coding domain, which translates into a normal-size BCL-6 protein.

Beside promoter substitution, the BCL-6 gene can also be altered by somatic hypermutation at its 5′ noncoding region. Hypermutation of BCL-6 can be found in normal germinal center cells. It is also found in B-cell NHLs that are also characterized by somatic IgV hypermutation, suggesting a common mechanism of mutation. Functional analysis of BCL-6 mutated alleles indicates that some mutations derived from DLCL but not from normal germinal center cells may deregulate the basal level of BCL-6 transcription (unpublished results). This finding indicates that BCL-6 can also be deregulated by somatic hypermutation of its promoter, which further supports the role of BCL-6 deregulation in the pathogenesis of DLCL.

**Molecular Heterogeneity of Diffuse Large Cell Lymphoma**

The WHO classification has established that, with current knowledge and methods, it is impractical to histologically subclassify DLCL into its morphologic variants (i.e., diffuse centroblastic lymphoma and diffuse immunoblastic lymphoma). However, both clinicians and pathologists reach consensus in suggesting that DLCL is in fact a heterogeneous disease. Most likely, diversity does not depend on cytoplastic features, but rather on the tumor genotype. The biologic diversity of DLCL has been validated by the identification of at least three distinct genetic types of the disease (diffuse centroblastic lymphoma and diffuse immunoblastic lymphoma). The first type, accounting for approximately 40% of cases, is characterized by the absence of known genetic lesions. DLCLs harboring BCL-6 rearrangements are de novo lymphomas, presenting without a previous history of follicular lymphoma. The second genetic type of DLCL involves activation of BCL-2 in combination with p53 mutations. DLCLs harboring BCL-2 rearrangements and p53 mutations derive from the histologic transformation of a previous follicular lymphoma. Finally, the third genetic group of DLCL displays germline BCL-2 and BCL-6 genes. The genotypic configuration of DLCL is thought to be of prognostic relevance. For example, some studies suggested that DLCLs associated with BCL-2 rearrangements display the most favorable prognosis, whereas cases carrying BCL-2 translocations have the poorest outcome. The exact prognostic relevance of BCL-6 rearrangements, however, still remains a controversial issue.

**FIGURE 45.1-6.** Model of molecular pathways in B-lineage diffuse large cell lymphoma (B-DLCL) development. Three main pathogenetic pathways may be recognized in B-DLCL. The first two molecular pathways are designated de novo pathways, because in these instances B-DLCL develops without a preexistent follicular lymphoma. One de novo pathway implicates the BCL-6 gene and occurs in approximately 35% of B-DLCL. The second de novo pathway involves presently unknown genetic lesions (indicated by the question mark), although some cases may harbor alterations of REL. The third pathway, designated as the transformation pathway, implicates the transformation of a preexisting follicular lymphoma to a B-DLCL histology. Cases of B-DLCL belonging to this pathway harbor rearrangements of BCL-2 and mutations of p53. Whereas the BCL-2 rearrangement is already present in the follicular lymphoma phase, p53 mutations are gained during histologic transformation. Other genetic lesions, including p16 inactivation, also associate with transformed B-DLCL.

The application of novel DNA technologies to DLCL is likely to refine the biologic heterogeneity of this disease. One study using DNA microarrays demonstrated diversity in gene expression among DLCL cases, allowing for the distinction between a germinal center–like variant of the disease and a variant resembling peripheral blood B cells activated in vitro. This distinction has been proposed to be of prognostic value, because patients with the germinal center–like variant of the disease display a better overall survival.

**BURKITT’S LYMPHOMA**

Burkitt’s lymphoma includes two clinical variants: sporadic Burkitt’s lymphoma and endemic Burkitt’s lymphoma. Some cases may present as acute leukemias with Burkitt’s tumor cells and are termed acute lymphoblastic leukemia. All Burkitt’s lymphoma cases, including the leukemic variants, share one common genetic lesion (chromosomal translocations involving region 8q24 and one of the Ig loci) and, at variable frequency, other genetic lesions, including inactivation of p53 and p16, deletions of 6q, and infection by EBV. The C-MYC locus tends to be involved in the pathogenesis of Burkitt’s lymphoma. Translocations of region 8q24 involve the C-MYC locus and have provided the first example of the involvement of protooncogenes in tumor-associated chromosomal abnormalities. The C-MYC locus can be involved in three distinct translocations with one of the Ig loci, including Ig�, Ig�, or Ig�, and involve frequent, other genetic lesions, including inactivation of p53 and p16, deletions of 6q, and infection by EBV.
Although fairly homogenous at the microscopic level, these translocations display a high degree of molecular heterogeneity. The t(8;14) breakpoints are located 5' and centromeric to c-MYC, whereas they map 3' to c-MYC in t(2;8) and t(8;22). Further molecular heterogeneity derives from the exact breakpoint sites of chromosomes 8 and 14 of t(8;14) (Fig. 45.1-7). Translocations of endemic Burkitt's lymphoma tend to involve sequences on chromosome 8 at an undefined distance (more than 1000 kilobases) 5' to c-MYC, and sequences on chromosome 14 within or in proximity to the Ig Jδ region. In sporadic Burkitt's lymphoma, t(8;14) preferentially involves sequences within or immediately 5' (fewer than 3 kilobases) to c-MYC on chromosome 8, and sequences on chromosome 14 within the Ig switch regions.

The common feature of t(8;14), t(2;8), and t(8;22) is that c-MYC–translated alleles are expressed constitutively in tumor cells, as opposed to the tight regulation of c-MYC levels in normal B cells. At least two distinct mechanisms may be responsible for c-MYC deregulation. These include (1) juxtaposition of c-MYC to heterologous enhancers derived from Ig loci; and (2) structural alterations in the 5' regulatory regions of c-MYC, putatively altering their responsiveness to cellular factors regulating c-MYC expression. In fact, the c-MYC exon 1–intron 1 border, where c-MYC regulatory sequences are located, is either decapitated by the translocation or undergoes selective and consistent mutations in translocated alleles (see Fig. 45.1-7). In addition to homotypic deregulation, concomitant expression of c-MYC is also thought to be due to amino acid substitutions in c-MYC exons 2 corresponding to the transactivation domain of the c-MYC protein. These mutations would abolish the physiological ability of p107, a nuclear protein related to RBF1, to suppress the transactivation domain of c-MYC.

**FIGURE 45.1-7.** Schematic representation of c-MYC translocations. The germline configuration of the c-MYC gene, mapping to 8q24, is shown in the upper panel of the figure. In its germline configuration, c-MYC is composed of three exons. The coding region of the c-MYC gene is indicated by black boxes, whereas noncoding exons (or portions of exons) are indicated by white boxes. The c-MYC promoters within exon 1 are indicated by arrows. The breakpoints of translocations are shown by arrows in the upper panel of the figure. Boxes indicate the joining (J), switch (S), and constant (C) regions of Igλ, Igμ, and Igα (see Table 45.1-2). The bottom panels of the figure depict the molecular consequences of t(8;14)(q24;q32), which causes the juxtaposition of c-MYC to Igλ locus. Two molecularly distinct types of translocations are recognized, which preferentially associate with either sBL or eBL. In the case of t(8;14) of sBL, the c-MYC breakpoint involves sequences within c-MYC, which is thus decapitated of its exon 1. Because the physiologically active promoters of c-MYC are removed by t(8;14) of sBL, a novel transcriptional initiation site (P3), located within c-MYC intron 1 and otherwise silent in physiologic conditions, is activated in c-MYC alleles involved by t(8;14) of sBL. Within the Igλ locus, the breakpoint falls in the proximity of the switch μ (Sμ) region. Notably, the gross configuration of the coding sequence of the translocated c-MYC allele is left intact. At the nucleotide level, however, translocated c-MYC alleles frequently harbor point mutations within the exon 2 coding sequence, leading to alteration in the amino acid sequence of the c-MYC protein. The complementary DNA (cDNA) resulting from t(8;14) of sBL includes c-MYC exons 2 and 3, which, on their 5' side, are preceded by an abnormally transcribed sequence of intron 1, starting from the novel transcriptional initiation site within c-MYC intron 1. Because the c-MYC coding region is intact, a normal-size c-MYC protein is translated by (8q14)/of sBL. The reader is referred to the text for a description of the functional consequences of t(8;14) of sBL in terms of deregulation of translocated c-MYC. In the case of t(8;14) of eBL, the c-MYC breakpoint involves sequences on chromosome 14q32, which is an undefined distance (more than 1000 kilobases) 5' to c-MYC and sequences on chromosome 14q32 or 5' to IgJδ, and such translocation is either decapitated by the IgJδ region. The internal genomic configuration of the translocated c-MYC allele is thus apparently preserved. However, c-MYC alleles involved by t(8;14) of eBL consistently harbor small mutations clustered around the exon 1–intron 1 border, where c-MYC regulatory regions are located. In addition, and in common with t(8;14) of eBL, point mutations within the exon 2 coding sequence, leading to alteration in the amino acid sequence of the c-MYC protein, also are frequently detected in c-MYC alleles affected by t(8;14) of eBL. The cDNA transcribed by t(8;14) of eBL includes c-MYC exons 1 through 3 and gives rise to a normal-size c-MYC protein. The reader is referred to the text for a description of the functional consequences of t(8;14) of eBL on the transcriptional regulation of c-MYC.

The product of c-MYC is a ubiquitously expressed nuclear phosphoprotein that functions as a transcriptional regulator controlling cell proliferation, differentiation, and apoptosis. In vivo, c-MYC is found mainly in heterodimeric complexes with the related protein MAX, and such interaction is required for c-MYC–induced stimulation of transcription of target genes. c-MYC can form heterodimers with MAX and MAD and MXI1, two novel basic helix-loop-helix/leucine zipper proteins that act as negative regulators of transcription. In NHL carrying c-MYC translocations, it is conceivable that constitutive expression of c-MYC leads to the prevalence of MYC/MAX complexes over MAD/MAX and MAD/MAD heterodimers, thus inducing positive growth regulation. In fact, expression of c-MYC regulates transcription of a subset of target genes that have diverse roles in regulating cell growth by affecting DNA metabolism and dynamics, energy metabolism, and protein synthesis. One of these genes is represented by TERT (for telomerase reverse transcriptase), a specialized type of transcriptase modulating the activity of telomerase. The fact that TERT is directly induced by c-MYC explains the association between c-MYC overexpression and telomerase activity observed in human cells. Because telomerase preserves chromosome integrity by maintaining telomere length, and because telomere length is a limiting factor in determining the replicative lifespan of a cell, the maintenance of chromosomal integrity via stimulation of telomerase activity may be an important component of the role of c-MYC in facilitating cell proliferation.

Substantial experimental evidence documents that the constitutive expression of c-MYC can influence the growth of B cells in vitro and in vivo, consistent with a role in B-cell lymphomagenesis. In vitro, the expression of c-MYC oncogenes transfected into EBV immortalized human B cells, a potential natural target for c-MYC activation in EBV-positive Burkitt's lymphoma, leads to their malignant transformation. In addition, antisense oligonucleotides directed against translocated c-MYC alleles are able to revert tumorigenicity of Burkitt's lymphoma cell lines. In vivo, the targeted expression of c-MYC oncogenes in the B-cell lineage of transgenic mice leads to the development of B-cell malignancy at relatively high frequency.

**Other Genetic Lesions**

In addition to c-MYC activation in 100% of Burkitt's lymphoma cases, disruption of p53 occurs in 30% of sporadic and endemic Burkitt's lymphoma. Deletions of p53 are detected in approximately 30% of the Burkitt's lymphoma cases independent of the clinical variant. Inactivation of p16 also has been reported in a fraction of cases. Another lesion that contributes to the development of this malignancy is monochlonal EBV infection, present in virtually all cases of sporadic and endemic Burkitt's lymphoma. The reader is referred to the text for a description of the functional consequences of t(8;14) of eBL on the transcriptional regulation of c-MYC.

**ACQUIRED IMMUNODEFICIENCY SYNDROME–RELATED NON-HODGKIN'S LYMPHOMA**

The association between an immunodeficiency state and the development of lymphoma has been long since recognized in several clinical conditions, including congenital (e.g., Wiskott-Aldrich syndrome), iatrogenic (e.g., treatment with immunosuppressors agents), and viral-induced (e.g., AIDS) immunodeficiencies. The increasing frequency of human immunodeficiency virus infection has emerged as a major risk factor for lymphomagenesis and has prompted detailed investigations of...
AIDS-related NHLs invariably derive from B cells and are primarily classified into three main clinicopathologic categories: AIDS-related Burkitt's lymphoma, AIDS-related DLCL, and AIDS-related primary effusion lymphoma. Based on the presence or absence of immunoblastic features, AIDS-related DLCL may be further distinguished into large noncleaved cell lymphoma and immunoblastic lymphoma. Based on the site of origin, AIDS-related NHLs are generally grouped into systemic AIDS-related NHL and AIDS-related primary central nervous system lymphoma. Systemic AIDS-related NHLs may be either AIDS-related DLCL or AIDS-related Burkitt's lymphoma. Conversely, AIDS-related primary central nervous system lymphomas display a uniform morphology consistent with a diffuse architecture of large cells.

The different categories of AIDS-related NHL associate with distinct molecular pathways. Cases of AIDS-related Burkitt's lymphoma consistently display activation of c-MYC by chromosomal translocations that show structural similarities to those found in sporadic Burkitt's lymphoma. Rearrangements of BCL-6 are consistently present in up to 60% of cases. Cases of AIDS-related Burkitt's lymphoma also frequently harbor mutations of p53, mutations of BCL-6's noncoding regions (60%) and, in 30% of cases, infection of the tumor clone by EBV. The EBV-encoded antigens LMP-1 and EBNA-2 are not expressed by AIDS-related Burkitt's lymphoma. In addition to genetic lesions and EBV infection, stimulation and selection by antigens, frequently represented by autoantigens, appear to be a prominent feature of AIDS-related Burkitt's lymphoma.

AIDS-related DLCL displays several genotypic differences when compared with AIDS-related Burkitt's lymphoma. First, the most frequent genetic alteration detected in AIDS-related DLCL is infection by EBV, which occurs in approximately 60% to 70% of cases and associates frequently, although not always, with expression of LMP-1 and EBNA-2. Second, AIDS-related DLCL displays rearrangements of BCL-6 in 60% of cases. Mutations of BCL-6's noncoding regions occur in 70% of AIDS-related DLCL cases. AIDS-related DLCL can be segregated into two distinct histogenic categories based on the expression pattern of the BCL-6 protein: the EBV-encoded LMP-1, and the CD138/syndecan-1-antigen, a proteoglycan associated with the terminal phases of B-cell differentiation. AIDS-related DLCL associated with the BCL-6/syndecan-1/LMP-1 phenotype tend to display a large noncleaved cell morphology and closely reflect the phenotype of germinal center B cells. Conversely, BCL-6/syndecan-1/LMP-1 AIDS-related DLCLs are morphologically consistent with immunoblastic lymphoma plasmacytoid and reflect a post-germinal center stage of B-cell differentiation.

All AIDS-related primary central nervous system lymphomas harbor EBV infection. However, only a fraction of AIDS-related primary central nervous system lymphomas, namely those with immunoblastic plasmacytoid morphology, express the LMP-1–transforming protein of EBV. As for systemic AIDS-related DLCL, AIDS-related primary central nervous system lymphomas may be distinguished into two phenotypic categories based on the expression pattern of BCL-6: CD138/syndecan-1 and LMP-1. AIDS-related primary central nervous system lymphomas also carry mutations of BCL-6 in 60% of cases. The association of AIDS with this phenotype of primary central nervous system lymphoma with mutations of BCL-6 as well as Ig genes indicates their origin from germinal center–related B cells. Although some reports have suggested that HHV-8 may be related to primary central nervous system lymphoma pathogenesis in immunocompromised patients, extensive analysis of AIDS-related primary central nervous system lymphoma has unequivocally ruled out this hypothesis.

The last type of AIDS-related NHL that has been characterized at the molecular level is represented by primary effusion lymphoma, also known as body cavity–based lymphoma. This entity is a novel lymphoma characterized by HHV-8 infection and clinically presenting as effusions in the serosal cavities of the body (pleura, pericardium, peritoneum) in the absence of solid tumor masses. Primary effusion lymphoma consistently derive from B cells that reflect a preterminal stage of B-cell differentiation. Infection of the tumor clone by HHV-8 occurs in 100% of cases and is a sine qua non for the diagnosis of the disease. In addition to HHV-8, cases of primary effusion lymphoma frequently carry co-infection of the tumor clone by EBV.

MALIGNANCIES OF T-CELL ORIGIN

Malignancies of mature T cells are a highly heterogeneous group of diseases. These malignancies greatly differ in clinical behavior, immunophenotypic features, and genetic lesions involved in their pathogenesis. In Western countries, mature T-cell malignancies overall represent only 15% to 20% of tumors derived from mature lymphocytes and are relatively uncommon when compared to mature B-cell malignancies. A higher frequency of mature T-cell malignancies is reported in other parts of the world, namely Japan and the Caribbean.

Only a few categories of mature T-cell malignancies have been investigated in detail at the molecular level. These include Ki-1+ (CD30+) anaplastic large cell lymphoma, adult T-cell leukemia/lymphoma, T-cell prolymphocytic leukemia and, to a lesser extent, cutaneous T-cell lymphoma. CD30+ anaplastic large cell lymphoma tends to occur in childhood and young adults. The term adult T-cell leukemia/lymphoma encompasses a spectrum of lymphoproliferative diseases associated with the human retrovirus HTLV-1 and characteristically expressing large amounts of IL-2 receptors (CD25). The geographic distribution of adult T-cell leukemia/lymphoma is mainly restricted to Southern Japan and the Caribbean basin, although cases also have been reported in the United States and Europe in long-term immigrants from the affected geographic areas. T-cell prolymphocytic leukemia represents a rare T-cell malignancy that presents predominantly as a leukemic disease. An intrinsic tropism for the skin is displayed by cutaneous T-cell lymphoma, which includes mycosis fungoides and its leukemic manifestation, known as Sézary syndrome.

ANAPLASTIC LARGE CELL LYMPHOMA

Anaplastic large cell lymphoma is a specific category of T-cell NHL composed of large pleomorphic cells that usually express the CD30 antigen. Anaplastic large cell lymphoma is characterized by frequent cutaneous and extranodal involvement. Conventional karyotyping analysis of anaplastic large cell lymphoma cases has shown a unique translocation involving bands 2p23 and 5q35 in a substantial fraction of cases. The cloning of the t(2;5)(p23;q35) translocation has demonstrated that it involves the fusion of the nucleophosmin/B23 (NPM) gene on 5q35 to a novel anaplastic lymphoma kinase (ALK) on 2p23 (see Table 45.1,1–4). As a consequence of this translocation, the NPM and ALK genes are fused to form a chimeric transcript that encodes a hybrid protein (p80) in which the amino-terminus of NPM is linked to the catalytic domain of ALK. Two distinct oncogenic effects are thought to be caused by the t(2;5) translocation. First, the ALK gene, which is not physiologically expressed in normal T lymphocytes, undergoes heterologous expression in lymphoma cells, conceivably because of its juxtaposition to the promoter sequences of NPM, which are physiologically expressed in T cells. Second, based on the activation model of other tyrosine kinase oncoproteins, one would predict that the truncated ALK constitutively phosphorylates intracellular targets to trigger malignant transformation.

The pathogenetic role of NPM/ALK rearrangements is supported by studies in vitro and in vivo. First, overexpression of the p80 hybrid protein induces neoplastic transformation of target cells in in vitro models, substantiating the notion that the p80 kinase is in fact aberrantly activated. Second, retroviral-mediated gene transfer of NPM/ALK into vivo causes T-cell lymphoid malignancies in mice. In such animal models, NPM/ALK selectively transforms lymphoid cells of T-cell lineage, whereas the growth properties of other hematopoietic cells remain unaffected.

The distribution of NPM/ALK rearrangements throughout the spectrum of NHL is highly selective, being virtually restricted to T-cell lineage anaplastic large cell lymphoma. Within this category, NPM/ALK rearrangements seem to preferentially associate with cases of childhood (more than 85% positivity), although they are also detected in a large fraction of cases of adulthood (60%).

ADULT T-CELL LEUKEMIA/LYMPHOMA

The molecular pathogenesis of adult T-cell leukemia/lymphoma has been elucidated to a wider extent in comparison with other mature T-cell tumors. Adult T-cell leukemia/lymphoma is associated with HTLV-1 infection of the tumor cells in 100% of cases, although the rate of adult T-cell leukemia/lymphoma development among seropositive individuals is relatively low (less than 5% lifetime risk). The period between infection and onset of clinical disease is typically quite long, varying between 10 and 30 years. Unlike acutely transforming animal retroviruses, the HTLV-1 genome does not encode a known oncogene. Furthermore, this retrovirus does not transform T cells by cis-activation of an adjacent protooncogene, because this provirus appears to integrate randomly within the host genome. Rather, the pathogenetic effect of HTLV-1 in adult T-cell leukemia/lymphoma seems to be due to the viral production of a transregulatory protein (HTLV-1 tax) that markedly increases expression of all viral gene products and transcriptionally activates the
expression of certain host genes, including IL-2, a chain of the IL-2 receptor (CD25), c-sis, c-fos, and granulocyte-macrophage colony-stimulating factor. Indeed, a property of adult T-cell leukemia/lymphoma cells is the constitutive high level expression of IL-2 receptors. The central role of these genes in normal T-cell activation and growth, together with the results of in vitro studies, support the notion that tax-mediated activation of these host genes represents an important mechanism by which HTLV-I initiates T-cell transformation. In addition, tax interferes at multiple sites with DNA damage repair functions and with mitotic checkpoints, consistent with the fact that adult T-cell leukemia/lymphoma cells harbor a high frequency of karyotypic abnormalities.

The long period of clinical latency that precedes the development of adult T-cell leukemia/lymphoma, the small percentage of infected patients that develop this malignancy, and the observation that leukemic cells from adult T-cell leukemia/lymphoma are monoclonal suggest that HTLV-I is not sufficient to cause the full malignant phenotype. An attractive model for adult T-cell leukemia/lymphoma would therefore include an early period of tax-induced polyclonal T-cell proliferation that, in turn, would facilitate the occurrence of additional genetic events leading to the monoclonal outgrowth of a fully transformed cell. In this respect, a recurrent genetic lesion in adult T-cell leukemia/lymphoma is represented by the p53 tumor suppressor gene, which is inactivated in 40% of cases.

T-CELL PROLYMPHOCYTIC LEUKEMIA

T-cell prolymphocytic leukemia frequently carries cytogenetic abnormalities of chromosome 11, the most common abnormalities being monosomy 11, partial or terminal deletions of 11q, and unbalanced translocations involving the 11q arm. The gene relevant to these abnormalities has been identified and has been shown to correspond to ATM, a gene that is also responsible for the hereditary disorder ataxia-telangiectasia. Whereas ATM is mutated in the germline of ataxia-telangiectasia patients, it is altered somatically in cases of T-cell prolymphocytic leukemia associated with the deletion of the other allele and shared by the majority of T-cell lymphomas. ATM mutations in T-cell lymphomas include deletion of exons 10 and 11, premature truncation, or alteration of the ATM gene product, consistent with the inactivating model of tumor suppressor genes. Circumstantial evidence suggests that ATM might be involved in cell-cycle regulation and DNA repair, which in fact have been shown to be defective in cells with biallelic ATM inactivation.

CUTANEOUS T-CELL LYMPHOMA

Rearrangements of the lyt-1/NFκB-2 gene at 1q24 have been demonstrated in a sizable fraction of cutaneous T-cell lymphoma tumors. The lyt-10 gene (also called NFκB-2) is a novel member of the NFκB rel family of transcription factors. The normal products of these genes have structural homologies within the DNA-binding rel domain and share the ability to bind to specific (κB) target sequences found in various inducible enhancer and promoter elements. In addition to the DNA-binding domain, the lyt-10/NFκB-2 gene harbors an ankyrin motif, which is thought to regulate the physiologic nuclear/cytoplasm distribution of the lyt-10/NFκB-2 protein. The translocation breaks observed in NHL consistently disrupt the ankyrin domain, separating it from the DNA-binding domain. It is therefore conceivable that an intact DNA-binding domain, once separated from the regulatory ankyrin portion of the gene, might be constitutively activated and act as an oncogene to T cells.

MOLECULAR PATHOGENESIS OF HODGKIN’S LYMPHOMA

HL, also known as Hodgkin’s disease, is characterized by scattered large atypical cells residing in a complex admixture of inflammatory cells. Two different biologic entities have been recognized within HL: nodular lymphocyte predominance HL (NLPHL) and classic HL comprising the nodular sclerosis, mixed cellularity, and lymphocyte depletion variants. Historically, biologic studies of HL have been hampered by the paucity of HL diagnostic cells [i.e., Reed-Sternberg (RS) or Hodgkin’s cells] in HL biopsies. More recently, however, the availability of sophisticated laboratory techniques that enable the isolation and enrichment of HL neoplastic cells has been instrumental in the understanding of HL histogenesis.

The neoplastic cells of both classic HL and NLPHL typically represent clonal populations of B-lineage cells, as documented by the presence of clonal rearrangements of Ig genes. The consistent occurrence of somatic mutations and their pattern within (V) region genes amplified from neoplastic cells of both classic HL and NLPHL indicate that both types of HL are derived from B cells that reside in, or have transited through, the germinal center. NLPHL displays ongoing mutation of Ig genes, suggesting derivation from centroblasts residing in the germinal center. Also, neoplastic cells of NLPHL show the typical clues of antigen selection, indicating a putative pathogenetic role of stimulation by antigen molecules. Conversely, no ongoing mutation of Ig genes is observed in RS cells of classic HL, consistent with selection from centrocytes or post–germinal center B cells. In some cases, RS cells of classic HL harbor stop codons in in-frame Vλ genes rearrangements (crippling mutations). Because IgV crippling mutations prevent antigen selection, it is likely that RS cells of classic HL have escaped apoptosis through a mechanism not linked to antigen stimulation, possibly represented by a transforming event, such as that mediated by the EBV LMP-1. The differences in the histogenesis of NHL and classic HL revealed by molecular studies also have been confirmed at the phenotypic level. In fact, the neoplastic cells of NLPHL consistently display the BCL-6–syndecan-1 profile typical of germinal center B cells, whereas RS cells of classic HL frequently, although not always, display the BCL-6–syndecan-1 phenotype of post–germinal center B cells. Although the overwhelming majority of HL cases derive from the B lineage, occasional cases have been formally proved to be of T-cell origin.

The truly neoplastic nature of RS cells has been debated since the description of HL. The detection of heterogeneous clonal karyotypic changes in HL lymph nodes and in cells identifiable as RS cells suggested that HL may indeed represent a clonal malignancy. Many chromosomal breaks detected in HL are also shared by other lymphoid malignancies, whereas a cytogenetic abnormality specifically associated with HL has yet to be found.

The p53 pathway is thought to be altered in HL. RS cells express abnormal levels of the MDM2 protein, which, in turn, conceals functional domains of the wild-type p53, thus blocking the physiologic activity of the tumor suppressor gene. Despite initial observations, it appears that the p53 gene itself is not affected by mutations in HL.

A number of epidemiologic features of HL suggest that the disease might result also from infectious cofactors. HL lesions express EBV antigens, carry EBV DNA demonstrable by conventional Southern blot or in situ hybridization techniques, and contain EBV-encoded RNA. The latent infection of HL displays ongoing mutation of Ig genes, suggesting derivation from centroblasts residing in the germinal center. Also, neoplastic cells of NLPHL show the typical clues of antigen selection, indicating a putative pathogenetic role of stimulation by antigen molecules. Conversely, no ongoing mutation of Ig genes is observed in RS cells of classic HL, consistent with selection from centrocytes or post–germinal center B cells. In some cases, RS cells of classic HL harbor stop codons in in-frame Vλ genes rearrangements (crippling mutations). Because IgV crippling mutations prevent antigen selection, it is likely that RS cells of classic HL have escaped apoptosis through a mechanism not linked to antigen stimulation, possibly represented by a transforming event, such as that mediated by the EBV LMP-1. The differences in the histogenesis of NHL and classic HL revealed by molecular studies also have been confirmed at the phenotypic level. In fact, the neoplastic cells of NLPHL consistently display the BCL-6–syndecan-1 profile typical of germinal center B cells, whereas RS cells of classic HL frequently, although not always, display the BCL-6–syndecan-1 phenotype of post–germinal center B cells. Although the overwhelming majority of HL cases derive from the B lineage, occasional cases have been formally proved to be of T-cell origin.

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GENETIC LESIONS AS CLINICAL TOOLS IN THE MANAGEMENT OF LYMPHOMA

From a clinical standpoint, NHL genetic lesions represent molecular markers of disease serving four purposes: (1) They assist morphologic diagnosis, (2) they provide a prognostic indicator in some cases, (3) they allow evaluation of minimal residual disease by highly specific and highly sensitive technologies, and (4) they provide targets for molecular therapy.

With respect to diagnosis, the use of genetic lesions as markers for NHL diagnosis is justified by the selective association between a given genetic alteration and a specific NHL category. For example, the detection of BCL-1 alteration in nonfollicular small cell NHL is considered the most specific clue to the diagnosis of mantle cell lymphoma. The growing knowledge of the molecular pathogenesis of lymphoma will progressively refine the way we classify these disorders. Ideally, genetically distinct groups of lymphomas should be considered as distinct diseases requiring distinct therapeutic options.

The prognostic relevance of genetic lesions of lymphoma is a growing field of investigation that may provide significant improvement in the therapeutic stratification of lymphoma. Although several genetic alterations have been proposed to influence the prognosis of specific lymphoma categories, the application of novel DNA technologies, namely, DNA microarrays, is likely to rapidly expand the molecular markers available for prognostic studies. On these grounds, the application of DNA microarrays to DLCL has allowed the recognition of distinct disease variants with different response to therapy and survival.
Genetic lesions of lymphoma also represent the most specific and the most sensitive marker for evaluation of minimal residual disease by polymerase chain reaction (PCR). Examples are the PCR assay for BCL-2 in follicular lymphoma and for BCL-1 in mantle cell lymphoma. Overall, the sensitivity of PCR analysis is several-fold higher than that of standard diagnostic techniques and allows to detect the loss of one tumor cell among 10 normal cells. To date, most studies of minimal residual disease in lymphoma have centered on follicular lymphoma and have demonstrated a survival advantage in cases achieving PCR negativity compared to cases that remained positive for minimal residual disease. Finally, the study of the molecular pathogenesis of lymphoma may provide molecular targets for therapeutic strategies aimed at reversing the very genetic lesions that are responsible for tumor development. Such therapy should, by definition, be largely specific for the lymphoma cells and, hence, devoid of major side effects presented previously encountered with chemotherapy.

CHAPTER REFERENCES


LEUKEMIAS

The development of successful therapy for most children with acute lymphoblastic leukemia (ALL) can be attributed to a series of prospective clinical studies that clarified the pathophysiology of ALL and showed the importance of combination chemotherapy, sanctuary-specific treatment, and supportive care measures. On the other hand, the relative resistance of acute myelogenous leukemia (AML) to chemotherapy led to the development of treatment strategies that include dose-intensified chemotherapy and bone marrow transplantation (BMT). During the 1990s, we have also greatly advanced our knowledge of leukemia cell biology, most notably in the area of molecular pathogenesis. Molecular biologists have developed powerful diagnostic tools, sensitive methods for detecting minimal residual leukemia, and potential new therapeutic targets. The improvement in long-term survival for children with acute leukemia has been gratifying but also has been associated with significant late effects that underscore the need for vigilant follow-up and for designing risk-adapted therapies.

EPIDEMIOLOGY

Leukemia is the most common form of cancer in children. Approximately 2500 new cases of childhood leukemia are diagnosed each year in the United States. ALL and AML are diagnosed in 75% and 20% of the cases, respectively, and chronic myeloid leukemia in fewer than 5%. The well-established peak incidence of childhood leukemia at age 4 years is due to ALL. ALL affects males and whites more often than females and African Americans. Nearly a threefold higher incidence of ALL at 2 to 3 years of age occurs for white children compared to black children. The incidence of AML is constant during childhood, except for a slight peak in infancy and late adolescence.

It is likely that the majority of acute leukemias in children are initiated by acquired mutations within the hematopoietic tissues. Intriguing results of molecular genetic studies using stored neonatal blood spots from children who eventually developed ALL suggest a prenatal origin in some patients. In studies of monzygotic twins who both developed acute leukemia (approximately 5% concordance rate), it appears that the initial chromosome translocation occurred in utero with subsequent transfer of the leukemia clone from one twin to the other via the shared blood supply. Because the concordance rate for leukemia is low in identical twins, it follows that an additional event or environmental exposure is required postnatally.

A small number of children are at increased risk to develop leukemia because of an inherited predisposition. For example, children with Down syndrome have a 10- to 20-fold increased risk of leukemia during the first 10 years of life. The types of leukemia in children with Down syndrome follow the usual distribution of childhood leukemia, except at younger than 3 years of age when AML (mostly FAB M7) is more likely to occur than ALL. Neonates with Down syndrome or trisomy 21 mosaicism may also develop a "transient myeloproliferative disorder" (TMD) that is indistinguishable from congenital AML. This disorder is usually diagnosed within the first 2 weeks of life, and the incidence is unknown. Peripheral blood or bone marrow blasts from infants with TMD have features of the megakaryocytic and erythroid lineages and, in some cases, have been shown to be clonal in origin. In more than 90% of these infants, however, the blasts spontaneously disappear and normal blood counts recover within the first several weeks to months after diagnosis of TMD. One retrospective study reported that up to 30% of infants with TMD eventually developed either a myelodysplastic syndrome or AML before the age of 3 years. Because the majority of these infants appear never to develop leukemia, neonates with Down syndrome and a hematologic picture consistent with AML should be observed for 4 to 10 weeks before cytotoxic therapy is initiated. If therapy is eventually needed, the outcome for these children has been surprisingly favorable.

Children with neurofibromatosis are predisposed to develop myeloid malignancies, especially myelodysplastic and myeloproliferative syndromes. In patients with neurofibromatosis who develop leukemia, evidence indicates loss of both neurofibromatosis (NF-1) alleles in bone marrow cells. These data provide evidence that NF-1 may function as a tumor-suppressor gene in children with NF-1.

Some epidemiologic studies suggest that maternal reproductive history of previous fetal loss and maternal alcohol consumption during pregnancy is associated with an increased risk of AML in infants. In general, most studies have not found a consistent association between common infectious or environmental exposures and an increased risk of childhood leukemia. On the other hand, AML has been observed as a secondary leukemia in both children and adults who were treated with alkylating agents or topoisomerase II inhibitors (e.g., epipodophyllotoxins).

CLONALITY AND CELL OF ORIGIN

Normal blood cell production is polyclonal, whereas leukemia is a clonal disorder. The return of polyclonal hematopoiesis in remission and the reappearance of the original clone at relapse suggests that the leukemia clone was suppressed but not eradicated by chemotherapy. This also implies that normal bone marrow stem cells repopulate the marrow during remission. In rare situations, patients with AML in remission have had persistent clonal hematopoiesis.

Within the hierarchy of hematopoietic development, there are many potential targets for leukemic transformation. Characterization of the leukemic blast population by morphology, genetics, and immunologic methods has helped to establish a revised classification system that may or may not reflect the nature of the leukemic "stem cell." The detection of lymphoid lineage–associated determinants on the surface of lymphoblasts plus an analysis of immunoglobulin (Ig) and T-cell receptor gene rearrangements suggest that ALL derives from either a precursor T or precursor B cell. The cell of origin for AML has been postulated to be either a multipotent or committed myeloid progenitor (e.g., CFU-GEMM or granulocyte-macrophage colony-forming unit), but more recent data indicate that the AML stem cell may be more
primitive than previously postulated.21,22

CLASSIFICATION

Morphology

In the 1970s, a morphologic classification system was developed for the acute leukemias by a French-American-British (FAB) Cooperative Working Group and has since gained wide acceptance.23 The FAB system divides ALL into three morphologic subtypes (L1, L2, and L3). L1 lymphoblasts, the most common FAB type in children, have scanty cytoplasm and inconspicuous nuclei. Blasts in the L2 category account for 10% of cases; they are larger and more pleomorphic in size, with abundant cytoplasm and prominent nuclei, and they may be difficult to distinguish by morphology alone from FAB subtype M0 AML.

L3 is the rarest subtype (1% to 2%) of ALL, and these blasts have very basophilic vacuolated cytoplasm. These L3 blasts have the same immunophenotype as well as karyotype and molecular genetic abnormalities as the tumor cells in small noncleaved or Burkitt lymphomas (see Non-Hodgkin’s Lymphomas, later in this chapter).

The FAB classification recognizes eight subtypes of AML (M0 to M7). Table 45.2-1 presents a distribution of FAB subtypes for 180 cases of AML in children younger than 18 years of age studied at St. Jude Children’s Research Hospital from 1984 to 1992. Most children younger than 2 years of age with AML have either the M4 or M5 subtypes.24 Although the M7 subtype may have several characteristic morphologic features, the diagnosis of M7 AML requires confirmation either by ultrastructural histochemistry (platelet peroxidase granules on electron microscopy) or monoclonal antibody positivity for specific megakaryocyte or platelet glycoproteins (e.g., IIBIIIa or IIB).

The FAB M7 subtype most often is seen in children younger than 3 years of age with Down syndrome.25

| TABLE 45.2-1. French-American-British Classification of Acute Myelogenous Leukemia in Children |
|-------------|-----------|-----------|
| Subtype | Blasts | Progenitors | Adenocytes |
| Acute lymphocytic leukemia | 50% | 30% | 20% |
| T-cell leukemia | 25% | 5% | 10% |
| Natural killer cell leukemia | 5% | 15% | 80% |
| Acute myeloblastic leukemia | 1% | 1% | 98% |
| Acute megakaryoblastic leukemia | 0% | 0% | 100% |

By using a panel of lineage-associated monoclonal antibodies, most cases of ALL can be broadly divided into precursor B- and precursor T-cell subgroups.26 Precursor B-cell ALL is further subdividing into early pre-B and pre-B, and the T-cell cases as immature according to level of thymocyte differentiation (e.g., early, mid-, or late thymocyte).27 The expression of several antigens, such as CD10 (CALLA) and CD34, are not lineage-specific and, in some studies, were of prognostic importance. The CALLA antigen is expressed in most cases of precursor B ALL; hence the derivation of the term common ALL previously used to define this large subgroup of childhood ALL. Most infants with ALL have a CALLA-negative, early pre-B immunophenotype.28 The proportion of children with specific immunophenotypes of ALL is shown in Table 45.2-2 according to age group.

| TABLE 45.2-2. Percentage Distribution of Immunophenotypes of Acute Lymphoblastic Leukemia by Age Group |
|-------------|-----------|-----------|
| Age Group | Early Pre-B | Pre-B | Pre-T |
| 0-2 years | 50% | 30% | 20% |
| 2-5 years | 40% | 40% | 20% |
| 5-10 years | 30% | 35% | 35% |

Compared to early pre-B-cell ALL, the pre-B (cytoplasmic Ig) immunophenotype develops more often in African Americans, is associated with a higher initial leukocyte count and hemoglobin level, and is more likely to have a DNA index lower than 1.16 and a pseudodiploid karyotype.29 The previously known adverse outcome associated with pre-B ALL was due to the subgroup with the t(1;19)(q23;p13). The clinical features of T-cell ALL have long been recognized and include an adolescent male with a high leukocyte count, bulky lymphadenopathy (especially mediastinal), and extramedullary leukemia (central nervous system (CNS), skin, testes).21,22 In the past, these children had a poor prognosis. However, the prognostic distinctions among ALL immunophenotypes have been lost by improvements in therapy with risk-directed protocols.1

B-cell (surface Ig) ALL is associated with L3 morphology, male predominance, and bulky extramedullary disease (e.g., intraabdominal masses).1,20 Many children with B-cell ALL come to medical attention because of a “primary tumor mass,” which on biopsy is a small noncleaved or Burkitt lymphoma and on further staging is found to have extensive replacement of the bone marrow with L3 blasts. If more than 25% marrow blasts are present, these children are considered to have mature B-cell ALL rather than advanced-stage Burkitt’s lymphoma, but they are treated on identical protocols and now enjoy a favorable prognosis.21

There has been limited clinical use for a classification of AML based on immunophenotype.27 The primary value of cell surface antigen analysis in most cases of AML is distinguishing between AML and ALL (L2 versus M0) and diagnosing FAB M7 AML.

Hybrid or Acute Mixed-Lineage Leukemias

Blasts from approximately 5% to 20% of children with acute leukemia have either morphologic, cytochemical, immunophenotypic, or genetic markers suggesting derivation from both myeloid and lymphoid lineages.20 In these biphenotypic, hybrid, or acute mixed lineage leukemias, individual blasts usually co-express markers of more than one lineage, but in rare instances, two distinct populations of blasts are present. Whether these cases represent aberrant gene expression or transformation of a multipotent stem cell is unknown. Hybrid leukemias appear to be more common in patients with prior myelodysplastic syndromes, secondary leukemias, leukemias associated with 11q23 (especially t(4;11)) translocations and the Philadelphia (Ph) chromosome.

Myeloid-antigen expression (blasts reactive with two or more myeloid-specific monoclonal antibodies) is detected in fewer than 10% of cases of childhood ALL, and lymphoid-antigen expression is noted in approximately 15% of AML.30 Mixed-lineage expression in AML lacks prognostic significance, and patients should be treated on AML protocols.21,22 Myeloid-antigen–positive ALL is not associated with a poor prognosis if patients are treated on intensive, risk-adapted ALL protocols.21,22
Leukemias with two distinct leukemic clones (one lymphoid and the other myeloid) are rare. No specific treatment recommendations have been established for these patients, but most oncologists favor a hybrid ALL/AML protocol in this situation.

**CYTOGENETICS AND MOLECULAR GENETICS**

The combination of cytogenetics, fluorescence in situ hybridization, and molecular methods identify chromosomal abnormalities in approximately 80% of cases of childhood acute leukemia. Identification of numerous chromosomal abnormalities in leukemia blasts, including translocations, deletions, and inversions, have enabled molecular geneticists to clone the genes that ultimately have been shown to be important in the malignant transformation of hematopoietic cells. The genetic abnormalities also have been proved valuable as diagnostic and prognostic tools. For example, TEL-AML1, or ETV6-CBF2, is a newly identified fusion gene that is detected in approximately 25% of children with precursor B ALL. The fusion gene results from a cryptic t(12;21) translocation and identifies a group of patients with a favorable prognosis (Fig. 45.2-1).

Many of the chromosomal translocations in ALL involve Ig or T-cell receptor genes and transcription factors. The prototype translocation is the t(8;14) in L3 ALL and Burkitt’s lymphoma (see Small Noncleaved Cell (Burkitt’s Lymphoma), later in this chapter). The t(1;19) is seen in approximately one-fourth of patients with pre-B-cell ALL and fuses the E2A gene on chromosome 19 with the PBX1 gene on chromosome 1. Approximately 2% to 5% of children with ALL have the t(9;22)(q34;q11) or Ph chromosome. In Ph-positive chronic myelogenous leukemia, the translocation results in a bcr-abl gene product of 210-kD, whereas in most cases of Ph-positive ALL, the breakpoint within the bcr region of the Ph chromosome is more centromeric, yielding a smaller fusion protein (185 kD). The presence of the Ph chromosome in ALL usually indicates high-risk leukemia warranting a stem cell transplantation in first remission, except for those children presenting with a low leukocyte count or good early response to prednisone. The genetic abnormalities associated with T-cell ALL are discussed in the section Lymphoblastic Lymphoma, later in this chapter. Genes involved in cell-cycle control (e.g., p53, p16) also have been implicated in the pathogenesis of ALL.

Childhood ALL can also be classified by the number of chromosomes (or DNA content) per leukemia cell. Hyperdiploidy with a DNA index greater than 1.16 (greater than 50 chromosomes) is associated with the precursor B-cell phenotype and a highly favorable prognosis, especially if there are trisomies of chromosomes 4 and 13. It is not known why patients with a DNA index greater than 1.16 respond well to chemotherapy, but it may be related either to a favorable intracellular distribution of methotrexate or the marked propensity for hyperdiploid blasts to undergo apoptosis.

On the other hand, hypodiploidy (less than 45 chromosomes) is associated with a poor prognosis.

Many of the chromosomal abnormalities in AML are associated with specific FAB subtypes. These include t(8;21)(q22;q22) and FAB M2; t(15;17)(q22;q11-21) and acute promyelocytic leukemia (FAB M3); translocations involving chromosome band 11q23 and various partner chromosomes (e.g., t(9;11) and FAB M4 and M5); and inv(16)(p13;q22) and FAB M4eo. The t(8;21) and t(15;17) translocations are extremely rare in patients younger than 2 years of age, whereas translocations involving 11q23 are quite common in this age group. Translocations of 11q23 almost always involve the MLL gene and are also the most frequent karyotypic change in infants with ALL. Infants with t(4;11)(q21;q23) or molecular rearrangements of MLL have an almost fivefold higher risk of relapse compared with other infants. The MLL gene is also rearranged in most cases of secondary AML induced by topoisomerase II inhibitors. In contrast, the t(1;22)(p13;q13), a unique but rare chromosomal translocation, has been detected in infants with FAB M7 AML. Monosomies or partial deletions of chromosomes 5 or 7 are commonly observed in adults with AML and patients with secondary AML (postlayklytation agent therapy or myelodysplastic syndromes) but are unusual in de novo childhood AML. The critical genes involved in leukemia transformation on chromosomes 5 and 7 have not yet been identified.

**CLINICAL AND LABORATORY MANIFESTATIONS AND DIAGNOSIS**

The most common presenting signs and symptoms in children with acute leukemia are fever or infection, fatigue, pallor, and bleeding. These symptoms result from decreased normal hematopoiesis secondary to bone marrow infiltration by leukemic blasts, leading to neutropenia, anemia, and thrombocytopenia. Bone or joint pain (or both) are initial complaints in approximately 25% of children with acute leukemia and are more commonly observed in ALL than AML. Bone pain is usually due to periosteal elevation but may be secondary to microfractures or bone necrosis. The classic radiologic findings in acute leukemia include metaphyseal lucent bands (growth arrest lines), periosteal elevation, and lytic lesions. These changes are best seen in the long bones near the knees, ankles, or wrists.

Moderate to massive lymphadenopathy and hepatosplenomegaly are associated with T-cell ALL and infant acute leukemias. Nonspecific abdominal pain is relatively common and may be secondary to organomegaly, gastrointestinal bleeding or, rarely, leukemic infiltration of the bowel wall. Most of the gastrointestinal lesions encountered in patients with leukemia are secondary to complications of treatment and include oral mucositis, esophagitis, gastritis, typhilitis or neutropenic enterocolitis, lactose malabsorption, and hepatitis or cholestasis.

**Extradendular Leukemia**

Extradendular spread of leukemia at either the time of diagnosis or relapse is important because it can cause local problems, represent a sanctuary site of disease, or herald bone marrow relapse. At diagnosis, clinically detectable extramedullary leukemia of the central nervous system (CNS), skin, and testes is rare, except in infants. Therefore, the major treatment strategies are aimed at eradication of subclinical disease. In the past, the most common sites of extradendular relapse included the CNS and testes.

Symptomatic CNS leukemia (e.g., increased intracranial pressure or cranial nerve palsies) is extremely rare, but between 4% and 10% of children with acute leukemia have blasts present in the cerebrospinal fluid (CSF) at diagnosis. The diagnosis of CNS leukemia is made by examining a cytocentrifuged preparation of CSF. Traditionally, CNS leukemia was defined by the presence of at least five leukocytes per microliter of CSF with blasts. However, more recent data indicates that the presence of blasts in CSF samples with fewer than five leukocytes per microliter may be of prognostic significance. The most common signs of CNS leukemia include headache, nausea and vomiting, lethargy, or cranial nerve palsies (sixth and seventh being most common). Neurologic symptoms in children with acute leukemia may also be due to epidural masses causing cord compression or myeloblastomas of the cerebral cortex or cerebellum, hemorrhage, or leukostasis (plugging of vessels by aggregates of leukemic blasts). Patients with AML and initial leukocyte counts greater than 200,000 cells per microliter are at highest risk for leukostasis.

Leukemia cutis is a rare finding seen most often in AML (FAB M4 and M5) and T-cell ALL. Infants with AML are at particularly high risk for leukemia cutis. The lesions of leukemia cutis are typically subcutaneous nodules that are blue-gray or salmon in color. The skin nodules in babies with AML have been observed to spontaneously regress for short periods before progressive leukemia ensues.
Overt testicular leukemia is extremely unusual at diagnosis, and with current effective chemotherapy regimens, it is rarely encountered as a site of relapse. Clinically it presents as a firm, painless, unilateral or bilateral testicular swelling. The diagnosis should be confirmed by testicular biopsy. Enlarged kidneys from infiltration of leukemia is not uncommon but is usually asymptomatic. The rare cases of renal failure in newly diagnosed children with acute leukemia are either secondary to uric acid nephropathy or ureteral obstruction from retroperitoneal lymphadenopathy.

Leukemic infiltration of the pericardium/myocardium or lungs is also extremely rare at diagnosis or during treatment. Congestive heart failure during therapy is much more likely due to sepsis or anthracycline cardiac toxicity rather than leukemic infiltration. Diffuse pulmonary infiltrates are most often secondary to an infection, but leukemic infiltration, diffuse alveolar hemorrhage, and pulmonary leukostasis should be considered in the differential diagnosis.

The most common ocular findings in patients with acute leukemia include retinal hemorrhages secondary to either thrombocytopenia or vessel infiltration, or papilledema from CNS leukemia. Leukemic involvement of the anterior chamber (hypopyon) or retinal infiltration are both infrequent.

Myeloblastomas are also referred to as chioromas or granulocytic sarcomas and occur in fewer than 5% of children with AML. These solid tumors of myeloid leukemia cells can appear simultaneously with bone marrow infiltration or may be the initial clinical manifestation of leukemia, occurring weeks to months before an increase in bone marrow blasts occurs. Myeloblastomas have a predilection for the CNS (brain or epidural) and the bones and soft tissues of the head and neck (especially the orbits).

**Laboratory Features and Differential Diagnosis**

The peripheral blood findings in patients with acute leukemia often include a normocytic anemia with teardrop or nucleated red blood cells, thrombocytopenia with platelet counts averaging between 20,000 and 50,000 cells per microliter, and leukocyte counts between 5000 and 50,000 cells per microliter. Approximately 20% of patients, however, have leukocyte counts greater than 100,000 cells per microliter. The white blood cell (WBC) differential usually reveals neutropenia (absolute neutrophil count <1000 cells per microliter) and circulating blasts, especially if the leukocyte count is greater than 5000 cells per microliter.

The bone marrow biopsy in most cases of acute leukemia is hypercellular, with blasts accounting for the majority of nucleated cells. The numbers of normal granulocyte-monocyte, erythroid, and megakaryocytic precursors are markedly decreased. To establish the diagnosis of acute leukemia, the bone marrow aspirate or biopsy must have more than 25% and 30% blasts, respectively, in ALL and AML. Most cases of childhood acute leukemia can be readily diagnosed and classified by routine bone marrow morphology and histochemistry. Additional laboratory tests, such as genetics and immunophenotyping, are important for risk assignment and are sometimes necessary for distinguishing ALL from AML.

Other significant laboratory findings at diagnosis may include metabolic derangements [see Small Noncleaved Cell (Burkitt’s) Lymphoma, later in this chapter] and disseminated intravascular coagulation or fibrinolysis. Disseminated intravascular coagulation usually is associated with acute promyelocytic leukemia (FAB M3) or FAB M5 AML, but it may be seen in other children with newly diagnosed acute leukemia.

The diagnostic evaluation in a child suspected of having acute leukemia includes juvenile myelomonocytic leukemia, myelodysplastic syndromes, metastatic tumors with marrow involvement (neuroblastoma and rhabdomyosarcoma), idiopathic thrombocytopenic purpura, juvenile rheumatoid arthritis, aplastic anemia, sepsis and other conditions that might result in neutropenia, infectious diseases associated with lymphocytosis, and the TMD in neonates with Down syndrome.

**TREATMENT**

**Acute Lymphoblastic Leukemia**

Most children with acute leukemia are referred to tertiary care hospitals, where they are treated by pediatric oncologists according to institutional or cooperative group protocols [e.g., Pediatric Oncology Group (POG), Children Cancer Group (CCG), Berlin-Frankfort-Munster (BFM), Medical Research Council]. Therapy for childhood ALL has been based on risk classification systems because it has become clear that outcome of treatment varies substantially among different subsets of children with the disease. The philosophy behind this approach has been to use less toxic therapy for children with a lower risk of relapse and to treat high-risk patients with experimental and potentially more aggressive regimens. Because no single best protocol has been established for either low- or high-risk patients with ALL, enrollment in clinical trials is still encouraged.

**PROGNOSTIC FACTORS.** Numerous prognostic factors (Table 45.2-4) have been identified for children with ALL, and some of these have been incorporated into risk classification systems used to assign treatment. These prognostic factors include combinations of presenting clinical and laboratory parameters, biologic features of the leukemia blast, and early response to chemotherapy. Because prognostic factors are treatment-dependent, improvements in therapy may abrogate a previously accepted prognostic variable. In an effort to compare the results of various clinical trials worldwide, a uniform risk classification for treatment assignment was accepted at a National Cancer Institute workshop. The agreed on standard risk category includes patients 1 to 9 years of age with precursor B ALL and a WBC count at diagnosis of less than 50,000 cells per microliter. The remaining patients are classified as high risk. The event-free survival rate for children in the standard-risk category is approximately 80% at 4 years and approximately 65% for the high-risk patients.

**TABLE 45.2-3. Initial Clinical and Laboratory Features in Children with Acute Lymphoblastic Leukemia According to Major Immunophenotypes**

<table>
<thead>
<tr>
<th>Immunophenotype</th>
<th>Percent (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-ALL</td>
<td>45</td>
</tr>
<tr>
<td>B-ALL</td>
<td>55</td>
</tr>
<tr>
<td>TdT-negative B-ALL</td>
<td>10</td>
</tr>
<tr>
<td>TdT-positive B-ALL</td>
<td>5</td>
</tr>
<tr>
<td>NK-ALL</td>
<td>5</td>
</tr>
<tr>
<td>LGL-ALL</td>
<td>3</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
</tr>
</tbody>
</table>

**TABLE 45.2-4. Acute Leukemia: Adverse Prognostic Factors**

- Age greater than 10 years old
- White blood cell count over 50,000 cells/μl
- Number of leukemic blasts on bone marrow biopsy
- Presence of CNS leukemia
- Presence of extramedullary leukemia or prior work-up for leukemia
Some investigators continue to classify T-ALL as an independent high-risk feature, and others assign risk to these children based on age and WBC criteria. The prognosis for patients with T-cell ALL has significantly improved during the 1990s with the advent of multigene dose-intensified ALL protocols.

In addition to age and WBC count, other important prognostic variables evaluated in the study include hyperdiploidy, cytogenetics, early response to treatment, and CNS status. The prognosis for patients with blasts with additional copies of whole chromosomes (hyperdiploidy) has been very favorable, as reported by several groups. Hyperdiploidy can be measured by DNA content (DNA index) of leukemic cells and by karyotyping. A DNA index of more than 1.6, especially if blasts contain extra copies of chromosomes 4 and 10, is associated with an extremely favorable prognosis. The majority of children with hyperdiploid blasts have standard-risk age and WBC features. In some studies, DNA index and trisomies of chromosomes 4 and 10 are used to change risk assignment independent of age and WBC criteria.

Early response to chemotherapy as measured by bone marrow findings within 7 to 14 days of induction or peripheral blood blast response to corticosteroids on day 8 of treatment is associated with outcome. A more rapid clearing of blasts from either the bone or bone marrow confers a more favorable prognosis. In one study, an augmented postinduction therapy for children with high-risk ALL and a slow response to induction has improved their long-term outcome.

Patients with the Ph chromosome [9(2;22)] and a high initial WBC count or slow early response to prednisone, and infants with t(4;11), continue to be at high risk for treatment failure. Experimental therapies, such as antigenic stem cell transplantation in first remission, are recommended for these very high-risk patients. Studies have shown that the poorer response associated with t(1;19) can be overcome by more intensive therapy.

New genetic abnormalities are continuing to be identified in patients with ALL. For example, the TEL/AML1 fusion gene occurs in approximately 25% to 30% of cases of pediatric precursor B ALL and defines a subgroup with a favorable prognosis. Molecular studies also are identifying genetic changes (e.g., MLL, TAL, TEL/AML1) in leukemic blasts that are undetectable at the routine cytogenetic level.

Other factors that have been shown to independently affect prognosis include race, gender, blast cell morphology, lymphomatous presentations, and serum lactate dehydrogenase. African Americans have a poorer prognosis than whites for reasons that cannot be totally explained based on known prognostic factors. In several studies, males had a higher risk of bone marrow relapse compared to females. Long-term follow-up data also indicate that females have an increased risk for some late effects, especially CNS and cardiac effects.

REMISSION INDUCTION. The achievement of a complete remission is a prerequisite for the long-term survival of patients with acute leukemia. In 1948, Sidney Farber demonstrated the first remissions in ALL using amethopterin, an analogue of methotrexate. Vincristine and prednisone are effective in inducing remissions in 85% to 90% of children with ALL, without unduly suppressing normal bone marrow function. Daunorubicin and L-asparaginase were subsequently identified as active drugs in the treatment of ALL. The addition of either one of these drugs to vincristine and prednisone increased the complete remission rate in childhood ALL to more than 95%. The combination of vincristine, prednisone, and L-asparaginase is one of the standard remission induction regimens in childhood ALL.

The use of additional drugs, such as the anthracyclines (daunorubicin or doxorubicin) or cyclophosphamide, are often reserved for children with high-risk ALL.

Data from both experimental models and human clinical trials indicate that maximum leukemia cell kill during induction decreases the likelihood for the emergence of drug-resistant clones and results in higher cure rates. Therefore, maximum tolerated doses of all active agents are delivered as early as possible during treatment. As previously discussed, a more rapid response to induction chemotherapy as measured by day 8 peripheral blast count or day 14 marrow aspirate is a favorable prognostic sign. New technologies, including polymerase chain reaction and multiparameter flow cytometry, are able to quantitate "minimal residual leukemia" at the end of induction. The results of this type of analysis may be predictive of risk of subsequent relapse, although the best assay and optimal timing for testing are not known.

CONTINUATION THERAPY. It has been estimated that approximately two to three logs of leukemic blasts are killed during the induction phase of therapy, leaving a residual leukemic burden of approximately 100 million cells. Therefore, additional treatment is necessary to prevent relapse. In the past, children with ALL relapsed within a median of 4 to 6 months when treatment was not continued beyond the remission induction phase. In the late 1960s, investigators at St. Jude Children’s Research Hospital developed a "total therapy" approach for treatment of children with ALL. The model included remission induction, continuation chemotherapy with or without intensification, and preventive CNS therapy. The choice of continuation therapy was empiric. The early St. Jude studies evaluated 6-mercaptopurine, methotrexate, cyclophosphamide, and cytarabine in various doses and combinations. The best outcome was achieved in patients who received 2 to 3 years of daily oral 6-mercaptopurine and weekly methotrexate. Long-term follow-up of patients treated with this latter combination show a 42% disease-free survival rate for children with initial WBC counts of fewer than <25,000 cells per microliter, whereas it was only 16% for all other patients.

Before the observation that the intensity of treatment requirement for a successful outcome varied substantially among subsets of patients, investigators in the BFM group, at Memorial Sloan-Kettering Cancer Center and the Dana Farber Cancer Institute treated all children with ALL with up-front intensive multiagent chemotherapy. The Dana Farber Cancer Institute protocols emphasized the intensive use of L-asparaginase and doxorubicin, and the BFM group used 4 months of intensive multidrug therapy (induction, consolidation, and intensification). CNS prophylaxis varied between the groups (see Central Nervous System Prophylaxis, later in this chapter). Children with high-risk ALL benefited most from these protocols. The advantage of these regimens compared to antimitobolite-based protocols for children with lower risk ALL was less obvious. However, more recent BFM and POG randomized trials have shown the importance of intensive reinduction therapy or dose intensified antimitobolite therapy, even for patients with favorable risk features.

Other successful approaches for patients with high-risk ALL have included the use of alternating non–cross-resistant pairs of active agents. For example, investigators at St. Jude Children's Research Hospital reported encouraging results with the combination of VM-26 and cytarabine in refractory ALL and subsequently introduced those drugs into front-line protocols. Most protocols for high-risk patients include the use of four or more drugs during remission induction, followed by intensification therapy for a brief period, CNS prophylaxis, and continuation therapy. With this approach, the cure rates for these very high-risk patients have reached levels of 65% to 75%. The use of bone marrow transplant (BMT) from a related or unrelated histocompatible donor for select groups of very high-risk patients in first remission is being investigated.

Several groups treat infants with ALL and those with T-ALL on separately designed protocols. The results of these studies have been comparable to therapies used to treat a more inclusive group of patients with high-risk ALL. On the other hand, because children with B-ALL (Burkitt’s or L3 type) had such a dismal prognosis after treatment with classic ALL protocols, an entirely different treatment approach was developed. These children were treated according to regimens that were designed for patients with advanced-stage Burkitt’s lymphoma. The protocols for B-ALL and advanced-stage Burkitt’s lymphoma included short but dose-intensive chemotherapy cycles that include cyclophosphamide, methotrexate, and cytarabine plus intensive intrathecal (IT) chemotherapy. The long-term disease-free survival rates increased from less than 10% to more than 60% with this approach. As more is learned about the biologic, pharmacologic, and other factors that distinguish the various "genotypic species" or subtypes of ALL, we will hopefully be able to select our therapies accordingly.

The duration of continuation therapy for children with ALL has been empiric. Chemotherapy has not been given for indefinite periods because of its short- and long-term toxicities. Because of our new techniques for quantifying minimal residual leukemia, we may soon be able to adjust the length of treatment based more on our knowledge of the number of leukemic cells and the duration of the drug-sensitive period. The duration of therapy is now based on more intensive clinical and molecular studies.

The risk of relapse after cessation of therapy is highest in the first year and tapers off to 2% to 3% in the second and third years. Very late relapse, after 5 or more years in remission, is rare but reported. There appears to be an increased risk of relapse off therapy for males compared to females.

PREVENTIVE OR PROPHYLACTIC CENTRAL NERVOUS SYSTEM THERAPY. CNS relapse in children with ALL became clinically apparent as bone marrow remissions became more durable. Before the use of preventive CNS therapy, CNS relapse heralded bone marrow relapse in almost 60% of patients. It was postulated by investigators at St. Jude Children’s Research Hospital that leukemia blasts were already present in the CNS by the time ALL was diagnosed and that the drugs used to treat leukemia did not penetrate the meninges in therapeutic concentrations. The CNS was considered a "sanctuary site," requiring site-specific therapy for subclinical disease. This concept proved to be correct and led to major increments in cure rates for childhood ALL. Clinical trials at St. Jude Children’s Research
Hospital established that the risk for CNS relapse could be reduced to less than 5% by the early use of 24 Gy of craniospinal irradiation (CSI) or 24 Gy of cranial irradiation plus IT methotrexate. Cranial irradiation plus IT methotrexate replaced craniospinal irradiation because of the toxicities of CSI. CSI was myelosuppressive and also caused impaired growth of vertebral bodies.

The target volume for cranial irradiation includes the entire intracranial subarachnoid space. By convention, the caudal margin of the field extends to the bottom of the second cervical vertebra. Standard guidelines for preventive cranial irradiation also include the posterior retina and orbital apex, encompassing the extension of the subarachnoid space along the optic nerves. A subacute somnolence syndrome that follows cranial irradiation has been well described. Approximately 50% of children develop some degree of lethargy, irritability, or low-grade fever at a median onset of 4 to 8 weeks after cranial irradiation.

The neurologic and cognitive sequelae of 24-Gy cranial irradiation led to treatment modifications. The CCG safely reduced the dose of cranial irradiation to 18 Gy. In an effort to further reduce toxicity, the Dana Farber ALL consortium compared 18 Gy given in a single daily fraction with a hyperfractionated schedule (twice daily), and the BFM reduced the dose to 12 Gy. An alternative strategy for preventing CNS relapse has been the use of IT chemotherapy alone, starting during induction and continuing for an extended period throughout therapy. Protocols using repetitive doses of IT chemotherapy also include multiple cycles of intravenous moderate- to high-dose methotrexate. This approach has been successful in preventing CNS relapse in children with standard-risk ALL, as well as intermediate- and high-risk patients in some studies, but it is also associated with neurotoxicity.

IT methotrexate has the same efficacy as triple IT therapy (methotrexate, hydrocortisone, and cytarabine) and may be less neurotoxic. The risk of a CNS event was gender-dependent in the CCG trials. Boys were at greater risk for relapse, whereas girls were more vulnerable than boys to cognitive and growth dysfunction after cranial irradiation and IT chemotherapy. Similar findings have been observed by the Nordic and Dana Farber groups.

In some protocols, subgroups of children with ALL at high risk of CNS relapse (e.g., WBC count higher than 50,000 cells per microliter, T-cell ALL, Ph-positive ALL, and infants) continue to be treated with cranial irradiation (12 to 18 Gy) plus IT chemotherapy. The percentage of children with ALL who currently receive cranial irradiation as part of CNS prophylaxis ranges from 15% to 60% depending on the protocol.

OVERT CENTRAL NERVOUS SYSTEM LEUKEMIA AT DIAGNOSIS. Fewer than 5% of children with ALL have leukemic blasts detected in the CSF at diagnosis. The definition of CNS leukemia has been revised. Three categories have been defined according to CSF findings: CNS-1 (no blasts), CNS-2 (fewer than 5 WBCs per microliter with blasts), and CNS-3 (more than 5 WBCs per microliter with blasts or cranial nerve palsies). Patients with CNS-3 status have a higher frequency of isolated CNS relapse and a lower long-term survival rate than patients with CNS-1 status, but the significance of CNS-2 status is not clear. Some investigators treat patients with CNS-2 status with additional doses of IT chemotherapy but give a risk assignment based on age and WBC criteria.

The management of patients with overt CNS leukemia (CNS-3) is less controversial than is the choice of preventive or prophylactic CNS therapy. After inducing a complete hematologic and CNS remission with IT and systemic chemotherapy, most investigators give CNS irradiation toward the latter part of the first year of treatment. Doses of 24 to 30 Gy of radiation have been given to these children.

THERAPY AFTER RELAPSE. The two most important factors relating to prognosis after relapse are the length of the initial remission and the site of relapse. Children with late relapse have a better prognosis than those with early relapse, but the definition of early and late relapse is variable. An initial remission duration of less than 3 years is considered to represent an early relapse. Relapse in extramedullary sites compared to bone marrow is also more favorable in terms of survival.

The second complete remission rate is more than 80%. The question of whether to perform a BMT or to continue chemotherapy has been one of the most controversial issues in second remission. The likelihood of long-term survival after chemotherapy alone is less than 10% to 15% for patients with early relapse. This finding is in contrast to a 40% to 50% leukemia-free survival rate for children whose first remission was longer than 3 years. These children also require a second course of CNS-directed therapy. BMTs from HLA-identical sibling donors compared with chemotherapy result in fewer relapses and better leukemia-free survival rates for the early-relapse group and, in some studies, for all risk groups.

Some investigators recommend autologous BMT for children with ALL in second remission who lack histocompatible family donors. Various methodologies have been developed to purge or remove contaminating leukemia cells present in the patient's harvested marrow, but the merits of this approach are unknown. The relapse rates are higher after autologous BMT compared to allogeneic BMT because of the lack of a graft-versus-leukemia effect. It remains controversial as to whether autologous BMT is superior to chemotherapy for children with ALL in second remission. The value of matched unrelated stem cell transplantation in the therapy of children with recurrent ALL is under investigation.

Isolated CNS relapse occurs in 5% to 10% of children treated for ALL on current protocols despite CNS-directed therapy. In the past, CNS relapse was associated with a very poor long-term prognosis, and the few survivors had serious long-term neurotoxicity. Salvage therapies included cranial or craniospinal irradiation plus IT or intraventricular chemotherapy. In the early trials, hematologic relapse rather than a subsequent CNS event was the main obstacle to a long-term second remission. Current approaches for these children include intensified reinduction and consolidation chemotherapy, IT chemotherapy, and delayed craniospinal irradiation to 6 months in remission. The delay in craniospinal irradiation allows for intensive chemotherapy to be administered during the early phases of therapy. The 5-year-disease-free survival estimates are approximately 70% with this strategy. However, a very high rate of relapse still occurs in children whose initial duration of remission was less than 6 months. The neurologic toxicity with this type of therapy has been acceptable. BMT should be considered for the very high-risk patients with an isolated CNS relapse.

Reports of ALL treatment in the 1970s indicated that 5% to 16% of boys had a testicular relapse during hematologic remission. Males with T-cell ALL were at highest risk for testicular leukemia. The time of testicular relapse was early for patients with T-cell ALL and usually was after cessation of therapy for most others. These data led to trials of prophylactic testicular irradiation in T-cell ALL and testicular biopsies at completion of chemotherapy for patients with precursor B ALL. Prophylactic testicular irradiation significantly reduced the incidence of testicular relapse but did not influence overall survival. As therapy for children with ALL has improved, testicular relapse has become a rare event. As with other sites of relapse, patients who develop early testicular relapse have a worse prognosis than those with a late relapse. Treatment includes both local radiation (24 Gy to both testes) and systemic chemotherapy. The target volume for radiation therapy includes the entire scrotal region, encompassing both the testes and epididymis bilaterally. Patients with late isolated testicular relapse have a 75% long-term disease-free survival rate. However, hormonal dysfunction usually is seen after these doses of gonadal irradiation.

COMPLICATIONS. The most concerning late complications of leukemia therapy include second cancers, adverse effects on growth and development, cardiotoxicity, and also caused impaired growth of vertebral bodies.
Mechanisms of drug resistance are beginning to be elucidated. For example, increased expression of the multidrug resistance gene (mdr1) or its protein product (P-glycoprotein) has been demonstrated in blasts from 20% to 40% of newly diagnosed patients with AML, and it increases approximately 15-fold at the time of relapse. High in vitro expression of mdr1 correlates with resistance to multiple drugs (e.g., etoposide, anthracyclines, vincristine) by promoting their cellular efflux. A number of chemotherapeutic agents used in the treatment of the acute leukemias have been associated with many acute and chronic toxicities. The prolonged use of corticosteroids may induce osteoporosis and pathologic fractures. Avascular necrosis of long bones and foot bones also has been observed in patients with AML who have received steroid treatment. The antiestrogens (e.g., methotrexate, 6-mercaptopurine, and cytarabine) induce cholestatic and hepatic toxicities in the liver but are associated with few documented long-term toxicities in this population of patients. -Asparaginase is associated with significant acute toxicity. Including allergy, pancreatitis, and deep venous thrombosis, but has not been associated with long-term complications. The anthracyclines, doxorubicin and daunorubicin, have been associated with cardiomyopathy, especially when the cumulative doses administered are more than 300 mg per square meter of body surface area. Studies indicate that a very high percentage of long-term survivors of childhood cancer who received doxorubicin have subclinical echocardiographic abnormalities, including impaired contractility and increased afterload. Risk factors for doxorubicin cardiac toxicity include female gender, young age at treatment, cumulative dose, and dose intensity. The clinical significance of these findings remains to be determined, but late congestive heart failure and death have been reported. AML regimens that do not include alkylating agents appear not to impair reproductive function.

The neurologic and cognitive sequelae of CNS-directed therapy for children with acute leukemia have been a major concern and a highly controversial subject. It was once thought that cranial irradiation produced a greater impairment in cognitive function (e.g., impairment of verbal memory and coding and IQ declines) than did chemotherapy. Because of those concerns, many investigators eliminated cranial radiation from therapeutic protocols. However, studies indicate that prednisone and high doses of intravenous or IT methotrexate are associated with neurotoxicity, and that 18 Gy of cranial irradiation may not be an independent toxic agent for cognitive outcome. High-dose intravenous methotrexate is particularly toxic if it follows cranial irradiation. Acute Myelogenous Leukemia

In contrast to ALL, only a modest improvement has been made in the long-term survival of children with AML since the late 1970s. The complete remission rate has increased from less than 50% to approximately 85%, but only 30% to 50% of patients are long-term survivors. The survival rate is somewhat better for those children with HLA-matched family donors who receive an allogeneic BMT early in first remission. INDUCTION.

The most commonly used remission induction regimen for children with AML, excluding those with Down syndrome and FAB M3, includes a 5- to 7-day course of cytosine arabinoside, plus 2 to 3 days of daunorubicin, or with or without thioguanine or etoposide. The high complete remission rate with all-trans-retinoic acid (ATRA) in patients with acute promyelocytic leukemia (FAB M3) led to prospective randomized trials testing the value of ATRA in the overall treatment plan. Results of these studies clearly show that the combined use of ATRA and chemotherapy is superior to chemotherapy alone for patients with acute promyelocytic leukemia. Therefore, induction therapy for all patients with acute promyelocytic leukemia should include ATRA combined with an anthracycline (daunorubicin or idarubicin) and cytarabine. Children with Down syndrome and AML needs to be less intensive than standard chemotherapy because of the increased risk of toxicity in these patients. Despite dose modifications, the outcome of children with Down syndrome and AML is excellent.

CENTRAL NERVOUS SYSTEM PROPHYLAXIS.

Isolated CNS relapse is frequently observed in both patients with AML. IT chemotherapy in combination with high-dose systemic cytosine arabinoside is effective in lowering the CNS relapse rate. Data from the BFM studies using historical comparisons suggests that cranial irradiation plus IT chemotherapy in children with standard-risk AML improves outcome.

POSTREMISSION THERAPY.

The intensity and duration of postremission chemotherapy and the role of allogeneic and autologous BMT in first remission have been under intense investigation. The improvement in outcome from 40% to 50% in 5 years is a result of more effective remission induction and postremission chemotherapy. There is no proven role for maintenance chemotherapy if it follows several courses of high-dose cytarabine–based consolidation chemotherapy. Most pediatric AML protocols include one to three cycles of high-dose cytarabine after remission is achieved.

BONE MARROW TRANSPLANTATION IN FIRST REMISSION.

Allogeneic BMT was first applied to children and young adults with AML in first remission as an alternative to continued chemotherapy in the mid-1970s. The early results were favorable compared with chemotherapy, but the transplantations were done in a selected group of patients. The CCG initiated the first cooperative group study comparing allogeneic BMT to chemotherapy in children with AML in first remission. Long-term follow-up of this study, plus data from POG and Associazione Italiana Ematologia e Oncologia Pediatrica, all show a survival advantage for allogeneic BMT compared to chemotherapy. However, fewer than one-fourth of children have a fully histocompatible family donor. Because of improving results of chemotherapy and the morbidity and mortality associated with BMT, the German BFM and Medical Research Council cooperative groups are not recommending allogeneic BMT in first remission for patients with favorable prognostic factors. BMTs are reserved for second remission in this group of patients.

For patients who lack histocompatible family donors, autologous BMT became an attractive option in first remission after it was reported to be efficacious (30% to 40% survival) in second remission of AML. The results of the early studies were controversial because they were not prospectively controlled. Beginning in the mid-1980s, both the adult and pediatric AML cooperative groups initiated prospective randomized studies to compare autologous BMT and intensive postremission chemotherapy. In the pediatric trials, no event-free or survival advantage was found for autologous BMT compared with chemotherapy. The majority of failures after autologous BMT are due to recurrent leukemia.

PROGNOSTIC FACTORS.

In contrast to childhood ALL, very few clinical or laboratory factors are consistently related to prognosis. Standard-risk patients included FAB subtypes M1 or M2 with Auer rods, M3 or M4eo, rapid response to initial induction chemotherapy, and the absence of adverse cytogenetic abnormalities. The lower remission rates associated with hyperleukocytosis are only partially accounted for by early deaths secondary to leukostasis. In the German BFM AML studies, two risk groups were identified. Standard-risk patients included FAB subtypes M1 or M2 with Auer rods, M3 or M4eo, rapid response to initial induction chemotherapy, and Down syndrome. The standard-risk group includes patients "with favorable chromosomal abnormalities" (t(8;21), inv(16), and inv 16). All other patients are high risk and include approximately 70% of the entire group. Event-free survival rates for standard-risk versus high-risk patients was 65% and 34%, respectively.

MANAGEMENT OF THE RELAPSED PATIENT.

The prognosis for children with AML who do not enter complete remission or who relapse is poor. BMT offers these patients a chance for long-term survival. A variety of chemotherapy regimens have been evaluated in children with refractory or relapsed AML. The second remission rates range from approximately 30% to 50% and are highest for children whose first remission duration was longer than 1 year. However, the length of chemotherapy-maintained second remissions are very brief. On the other hand, 5-year event-free survival ranges from 30% to 50% for those patients who receive an allogeneic (related or unrelated marrow donor) marrow transplantation. Autologous BMT in second remission for patients who lack suitable marrow donors offers some hope for long-term survival, but it has become a less attractive option because of the expanding unrelated marrow and cord blood banks and the opportunity to find a matched unrelated donor for an allogeneic transplantation.

FUTURE DIRECTIONS.

The major challenge for the future is to develop effective therapy for patients who have a poor prognosis and to minimize toxicity for those children who are successfully treated. Strategies are being developed to target drug doses to achieve predetermined serum or intracellular concentrations to improve the therapeutic index. The use of recombinant human hematopoietic growth factors may reduce the myelosuppressive complications from chemotherapy and allow dose intensification to proceed safely.
The wider availability of stem cell transplants from unrelated marrow or cord blood donors has enabled many more patients to successfully undergo marrow transplantation. Studies are testing nonmyeloablative marrow transplants in an effort to achieve mixed chimerism that will hopefully achieve a more favorable balance of the graft-versus-host and graft-versus-leukemia reactions. Biologic response modifiers, such as interleukin-2 and -12, are under study for their potential to enhance the host response to tumor. It is now possible to target the genetic lesions of leukemia cells, as exemplified by the successful use of ATRA in acute promyelocytic leukemia and a specific bcr-abl tyrosine kinase inhibitor in Ph-positive leukemias.

NON-HODGKIN'S LYMPHOMA

The lymphomas are the third most common childhood malignancy and account for approximately 10% of cancers in children. Approximately two-thirds of the lymphomas diagnosed in children are non-Hodgkin's lymphoma (NHL) and the remainder are Hodgkin's disease. The spectrum of NHL seen in pediatric patients differs significantly from that seen in adults. The three major histologic categories of NHL in children are lymphoblastic, small noncleaved cell (Burkitt's), and large cell lymphoma (Table 45.2-5). In adults, Burkitt's and lymphoblastic lymphoma are rare, but follicular center cell lymphoma, a histologic type exceedingly rare in children, predominates. No sharp age peak (median age, 11 years) occurs in children with NHL, and the male to female ratio approaches 3:1.

The pediatric NHLs in the Revised European-American Lymphoma classification include precursor B and precursor T lymphoblastic lymphoma/leukemia, Burkitt's lymphoma, diffuse large B-cell lymphoma, and anaplastic large cell lymphoma (ALCL) (T- and null cell types). The pediatric NHLs in the Revised European-American Lymphoma classification include precursor B and precursor T lymphoblastic lymphoma/leukemia, Burkitt's lymphoma, diffuse large B-cell lymphoma, and anaplastic large cell lymphoma (ALCL) (T- and null cell types).

RISK FACTORS

Numerous factors have been linked to an increased risk of NHL. Children with severe combined immunodeficiency syndrome, Wiskott-Aldrich syndrome, common variable immunodeficiency, ataxia-telangiectasia, and the X-linked lymphoproliferative syndrome are at increased risk for developing a lymphoma. Acquired immunodeficiency secondary to human immunodeficiency virus infection or immunosuppressive therapy, especially after solid organ transplantation or BMT, also places individuals at greater risk for developing a lymphoproliferative disorder or malignant lymphoma. Most of the lymphomas that occur in these high-risk groups are B-lineage large cell or small noncleaved (Burkitt's). Monoclonal Epstein-Barr virus (EBV) DNA has been identified in tumor tissue from many of these patients, indicating an important and early role for the virus in tumor development. It has been postulated that the immunodeficient host does not generate an adequate T-lymphocyte response (EBV-specific cytotoxic T cells) against B cells that are latently infected with EBV.

EBV has long been associated with endemic Burkitt's lymphoma, and more recently with hairy leukoplakia, nasopharyngeal carcinoma, and leiomysarcomas in children with human immunodeficiency virus. The role of EBV in the pathogenesis of Burkitt's lymphoma and other malignancies is unknown. In the Working Formulation, the major categories of childhood NHL are lymphoblastic, small noncleaved cell (Burkitt's and non-Burkitt's), diffuse large cell, and large cell immunoblastic. The pediatric NHLs in the Revised European-American Lymphoma classification include precursor B and precursor T lymphoblastic lymphoma/leukemia, Burkitt's lymphoma, diffuse large B-cell lymphoma, and anaplastic large cell lymphoma (ALCL) (T- and null cell types).

STAGING

The Ann Arbor staging classification is not well suited for childhood NHL for several reasons. It does not adequately reflect prognosis, because there is early widespread, noncontiguous dissemination of disease despite the limited initial sites of involvement (e.g., mediastinal lymphoblastic lymphoma). In addition, extranodal involvement is common, whereas stage III nodal disease is rare. In view of these deficiencies, an alternative staging system (see Table 45.2-6) was developed at St. Jude Children's Research Hospital. The St. Jude system considers both primary site and extent of tumor in assigning a clinical stage, and it has been widely accepted. Pathologic staging is not helpful in the overall management of children with NHL because the mainstay of treatment is systemic chemotherapy with a very limited role for irradiation of involved sites of disease.

Lymphoblastic lymphomas account for 30% of childhood NHL and share many clinical and biologic features with ALL. The distinction between lymphoblastic lymphoma and ALL is arbitrary (see Table 45.2-3) and has not been based on clinical presentation. If the bone marrow has more than 25% lymphoblasts, the patient is considered to have ALL rather than stage 4 lymphoblastic lymphoma.
The tumor cells of lymphoblastic lymphoma are morphologically indistinguishable from the lymphoblasts of precursor B and precursor T ALL. Lymphoblastic lymphomas in the anterior mediastinum have a precursor T cell immunophenotype that most often correlates with the middle or late stage of thymocyte maturation. The cells express various combinations of the CD1, CD2, CD5, and CD7 antigens and, in many cases, express both CD4 and CD8. The CD3 antigen and associated T-cell receptor molecule are not commonly expressed. The CD10 or CALLA antigen is variably present. Significant overlap of the immunophenotype is found in many cases of lymphoblastic lymphoma and T-cell ALL, suggesting a common cell of origin. The early-stage lymphoblastic lymphomas have the phenotype of an early B-cell precursor, identical to that seen in most children with ALL.

In more than one-half of the cases of T-cell lymphoblastic lymphoma/leukemia, recurrent nonrandom chromosomal translocations involving the a, b, and g chains of the T-cell receptor have been identified. Many of these translocations occur in error during the normal process of rearrangement of the T-cell receptor genes, a situation that is analogous to the Ig rearrangements noted in Burkitt's lymphoma. Several of the partner genes involved in these translocations include the transcription factors TAL1 and HOX11, and the cytokine-rich (LIF) proteins RHOM1 and RHOM2. In the t(1;14)(p32;q11), detected in 3% of patients with T ALL, the TAL1 gene is rearranged in its 5' regulatory sequence by its translocation into the T-cell receptor alpha chain locus. A submicroscopic deletion in the same region of TAL1 is detected in up to 25% of patients with T-cell ALL/lymphoblastic lymphoma, making it the most common genetic change in this disease.

Clinical Presentation and Staging

Most children with lymphoblastic lymphoma present with rapidly enlarging neck and mediastinal lymphadenopathy, although subdiaphragmatic nodal presentations are occasionally seen. The classic presentation is that of an adolescent male with respiratory distress due to a large anterior mediastinal mass with or without pleural effusions. Cough, wheezing, or shortness of breath and facial swelling (evidence of superior vena cava syndrome) are frequent complaints in these patients. Other common presenting sites of disease include cervical nodes, Waldeyer's ring, cutaneous lesions, bone marrow, and single- or multiple-site bone disease. The majority of children have advanced-stage disease (see Table 45.2-5).

Because the pace of the disease is usually rapid, diagnostic studies and institution of therapy should proceed quickly. The least invasive procedure should be used to establish the diagnosis. Because bone marrow is frequently involved and patients with T-cell ALL often present with an anterior mediastinal mass, a close examination of the peripheral blood and bone marrow should be undertaken before proceeding to a more invasive procedure. Pleural effusions should be tapped because they are often positive for malignant cells. If the bone marrow and pleural fluid are nondiagnostic, a lymph node outside of the mediastinum should be biopsied, if possible. Sufficient tissue should be obtained for histopathology, genetic studies, and immunophenotyping. Biopsy under general anesthesia should be avoided if at all possible, especially if there is significant airway narrowing or symptoms of respiratory distress. The prebiopsy use of mediastinal irradiation or steroids for respiratory distress results in rapid disappearance of the mass and jeopardizes the likelihood of establishing a tissue diagnosis. The remainder of the workup should include a lumbar puncture with a cytocentrifuged examination of cerebral spinal fluid, and a computed tomographic (CT) scan or magnetic resonance imaging of the primary site. Bone and liver-spleen scans are not necessary. Routine blood chemistries and liver function tests should be obtained before starting therapy.

TREATMENT

Historically, children with lymphoblastic lymphoma had less than a 10% survival rate after careful pathologic staging followed by extended-field radiotherapy. Despite the favorable outcome, the toxicity of combined modality therapy led to attempts to reduce the intensity and duration of treatment without compromising survival. Several single-institution and cooperative group protocols were successful in maintaining excellent survival rates (85% to 90%) while reducing the morbidity and mortality of therapy. The CCG protocols demonstrated the equal efficacy of 6 and 18 months of cyclophosphamide, Oncovin, methotrexate, and prednisone (COMP) combination. However, all children also received radiotherapy to involved fields. A POG study demonstrated that the omission of radiotherapy from the treatment of localized NHL in children did not jeopardize survival. The POG chemotherapy regimen included three cycles of cyclophosphamide, doxorubicin, Oncovin, and prednisone (CHOP) followed by 24 weeks of 6-mercaptopurine and methotrexate. The CCG and POG protocols included IT methotrexate for patients with primary tumors in the head and neck region. Treatment with either CHOP or COMP results in 65% event-free survival for children with localized lymphoblastic lymphoma, but survival is 90% because of the successful treatment of relapse with salvage chemotherapy.

Fewer than 40% of patients with advanced-stage (stages 3 and 4) lymphoblastic lymphoma were cured with standard-risk ALL regimens (e.g., vincristine, steroid, L-asparaginase, methotrexate, and 6-mercaptopurine) or COMP therapy. The addition of drugs such as the anthracyclines, cyclophosphamide, cytosine arabinoside, or the epipodophyllotoxins to ALL regimens substantially improved the prognosis for these children.

The vincristine, doxorubicin (Adriamycin), and prednisone (APO) and LSA2L2 regimens were two of the early successful protocols for children with high-risk ALL or advanced-stage lymphoblastic lymphoma. LSA2L2 included ten drugs, and the APO protocol featured intensification with doxorubicin and L-asparaginase (Table 45.2-7). Both protocols included preventive CNS therapy. Radiation therapy to the mediastinum was generally limited to emergency situations. These regimens resulted in approximately 65% survival for children with advanced-stage lymphoblastic lymphoma. The use of more intensive ALL chemotherapy regimens appears to further improve the outcome for these children. Although radiotherapy has been omitted from most of the protocols, a small percentage of patients have local tumor failure.

Early preventive CNS therapy is critical in the treatment for children with advanced-stage lymphoblastic lymphoma. IT chemotherapy alone or combined with cranial irradiation has been the mainstay of CNS preventive therapy. Relapse at any site is a significant obstacle to cure in children with advanced-stage lymphoblastic lymphoma. Most of the relapses occur within 2 years from diagnosis, but occasional late relapse is observed. In contrast to relapse for early-stage disease, the outcome after a second course of chemotherapy is poor. However, these patients have a 30% to 50% survival rate after allogeneic BMT from a histocompatible sibling donor.
SMALL NONCLEAVED CELL (BURKITT’S) LYMPHOMA

The small noncleaved cell lymphomas (Burkitt’s type) were initially described by Dennis Burkitt in equatorial Africa where the tumor is endemic. The lymphomas were subsequently recognized worldwide and account for approximately 40% of childhood NHL. The endemic form is common (100 per 1 million children) and is nearly always associated with EBV (95%) and is commonly associated with HIV (15%). In endemic areas, involvement of the jaw and other facial bones is frequent, whereas extensive intraabdominal disease and bone marrow involvement are commonly seen in sporadic cases. Histologically, the small noncleaved cell lymphomas include the Burkitt’s and non-Burkitt’s types. The Burkitt’s type was defined by the World Health Organization in 1969. It is characterized by homogeneous cells with round to oval nuclei with multiple nuclei and intensely basophilic vacuolated cytoplasm that contains neutral fat. The non-Burkitt’s type has a greater degree of nuclear pleomorphism compared to the Burkitt type. The non-Burkitt type may be difficult to distinguish on a morphologic basis from some large-B-cell lymphomas.

Burkitt’s lymphoma is a B-cell tumor based on expression of cell surface Ig heavy chains (usually IgM) and either k or l light chains. Approximately 50% of cases are also associated with EBV. Approximate 75% of cases are B-cell lymphoblastoid leukemia/lymphoma and contain sufficient numbers of tumor cells for cytology and biology studies. Imaging should include a CT scan or magnetic resonance imaging of the primary site and a bone scan. Patients with head and neck primary tumors may have clinically nondetectable disease in the abdomen (especially of the kidneys) and therefore should also have abdominal imaging studies.

Clinical Presentation

The abdomen is the most common presenting site in sporadic cases of Burkitt’s lymphoma (see Table 45.2-5). Approximately one-third of children with an abdominal primary tumor present with a right lower quadrant mass or with signs and symptoms of either acute appendicitis or intestinal obstruction secondary to an ileocecal intussusception. This presentation is typically seen in boys between 5 and 10 years of age. An exploratory laparotomy is indicated for diagnostic purposes. If a tumor is discovered, it is invariably a small noncleaved Burkitt’s lymphoma that is limited in extent to the distal ileum or cecum. Complete surgical resection of the involved segment of gut with its associated mesentery, followed by an end-to-end anastomosis, is the proper treatment. Children with completely resected Burkitt’s lymphoma (stage 2) of the intestinal tract have an excellent prognosis after treatment with a limited course of chemotherapy (discussed later, in the section Treatment). The majority of patients with Burkitt’s lymphoma of the abdomen, however, have unresectable disease that may involve the mesentry, retroperitoneum, kidneys, ovaries, and peritoneal surfaces (often associated with malignant ascites). Surgical debulking is not feasible or appropriate for this latter group of patients.

The head and neck region is the second most common site of disease presentation. Patients in nondemic areas present with tonsilar enlargement, cervical lymphadenopathy and, occasionally, a soft tissue facial mass associated with involvement of the jaw or other facial bones. Less common presenting sites include an epidural mass, skin nodules, bone, and bone marrow.

The least invasive procedure should be used to establish the diagnosis, and the staging evaluation should be expedited because these patients usually have rapidly growing tumors with significant electrolyte imbalance as well as impaired renal function. This is especially true for children with massive abdominal disease. Effusions are usually malignant in these children and contain sufficient numbers of tumor cells for cytology and biology studies. Imaging should include a CT scan or magnetic resonance imaging of the primary site and a bone scan. Patients with head and neck primary tumors may have clinically nondetectable disease in the abdomen (especially of the kidneys) and therefore should also have abdominal imaging studies.

Attention to kidney function, and the serum levels of uric acid, potassium, calcium, and phosphorus, is critical in children with advanced-stage Burkitt’s lymphoma. These patients are at high risk for the “tumor lysis syndrome” and uric acid nephropathy. Measures should be taken to reduce the likelihood of uric acid nephropathy, including vigorous intravenous hydration, alkalinization of urine with either sodium bicarbonate or Diamox, administration of allopurinol, and careful monitoring of serum electrolytes. Hemodialysis is required in a small percentage of cases.

Treatment

Complete remissions were induced in 80% of African children with Burkitt’s lymphoma with cyclophosphamide administered as a single agent. Patients with facial tumors (early stage) had sustained remissions with single- or multiple-dose cyclophosphamide, whereas the majority of children with abdominal tumors relapsed with systemic and CNS disease. Successor protocols used combination chemotherapy and IT methotrexate. The use of cyclophosphamide and vincristine with methotrexate or cytarabine was associated with higher remission rates and more durable remissions compared to single-agent cyclophosphamide. The most important prognostic factor was the extent of tumor at diagnosis.

Clinical trials in the United States demonstrated that the complete response rate, relapse frequency, and survival in American patients were similar to results in Africa. Approximately 85% of patients with early-stage Burkitt’s lymphoma were cured using as little as 9 weeks of CHOP chemotherapy. Similar results were achieved using POG/COMP protocols. A POG study demonstrated that the addition of involved-field radiation therapy did not influence outcome. Treatment for patients with head and neck primary sites of disease also included IT methotrexate.

COMP therapy, however, resulted in only a 40% survival rate for patients with advanced-stage disease, which was similar to the African experience. Relapses occurred in systemic and CNS sites at a median of 3 months from the beginning of therapy. Protocols that were highly effective for children with ALL and lymphoblastic lymphoma (e.g., LSA2L2 and APO) were less effective than COMP for advanced-stage Burkitt’s lymphoma or L3 ALL. These poor results were most likely due to the omission of limited use of cyclophosphamide.

Several groups of investigators began to evaluate dose-intensified systemic and IT chemotherapy for these high-risk patients. Cyclophosphamide, methotrexate, and cytarabine were administered in high doses with or without anthracyclines and the epipodophyllotoxins. Treatment courses were repeated at early signs of bone marrow recovery in an attempt to prevent regrowth of tumor between cycles of chemotherapy. Hematopoietic growth factors were used in some protocols to enhance bone marrow recovery. CNS prophylaxis included systemic chemotherapy that penetrated the CNS (high-dose methotrexate and cytarabine) and intensive prophylactic therapy that used once weekly administration of EBV. In endemic areas, involvement of the jaw and other facial bones is frequent, whereas extensive intraabdominal disease and bone marrow involvement are commonly seen in sporadic cases.
realistic hope of long-term survival for these children. The outcome is more favorable for patients who achieve a second remission before proceeding to BMT. However, second remissions are difficult to induce in these patients, especially for those with advanced-stage disease.

**LARGE CELL LYMPHOMA**

The large cell lymphomas constitute approximately 30% of childhood NHL. Approximately 30% of pediatric large cell lymphomas are classified as ALCCL in the Revised European-American Lymphoma classification. The remainder are diffuse large B-cell lymphoma, primary mediastinal large B-cell lymphoma, and the rare peripheral T-cell lymphoma. ALCCL in children tends to involve lymph nodes and extranodal sites, including the skin, soft tissues, lung, and bone. Lymphomatoid papulosis and the primary cutaneous form of ALCCL are rare in childhood. The majority of cases of ALCCL studied in children have had a T-cell phenotype. The (1;2)(p32;q35) translocation has been associated with Ki-1+ and CD30+ lymphomas in both children and adults. The chromosomal breakpoints involved in the (1;2) translocation have been cloned and involve the gene that encodes nucleophosmin (NPM), a nonribosomal nuclear phosphoprotein on chromosome 5, and a gene that encodes a novel transmembrane tyrosine-specific protein kinase (ALK) located on chromosome 2. The translocation results in the fusion of these genes, producing a chimeric NPM-ALK gene and message. Reverse transcribe-polymerase chain reaction assays for this translocation have been positive in all cases with cytogenetic evidence of the (1;2) and in several cases of ALCCL with a normal karyotype.

**Clinical Presentation**

The clinical presenting features of large cell lymphoma in children are more varied than those for lymphoblastic or Burkitt's lymphoma. Also, a relatively equal distribution is seen between early- and advanced-stage disease. The most common primary sites of disease include the nasopharynx, cervical nodes, skin, soft tissues, mediastinum, bone, and abdomen. The bone marrow and CNS are rarely infiltrated (see Table 45.2-5).

**Evaluation and Treatment**

The workup and staging of the child with large cell lymphoma are similar to that recommended for children with the other histologic subtypes of NHL. The treatment of large cell lymphoma in children has evolved from local radiotherapy to primarily combination chemotherapy. Because of the relative rarity of large cell lymphoma in children, many of the treatment strategies and protocols derive from adult studies.

Children with localized large cell lymphoma have a very favorable prognosis. The COMP and CHOP regimens that are effective in early-stage lymphoblastic and Burkitt's lymphoma also result in 85% survival for these children (see Table 45.2-7). The results of CHOP with or without involved-field irradiation were similar. CHOP has not been systematically evaluated in children with advanced-stage large cell lymphoma. The results of COMP therapy for these children were disappointing (approximately 50% event-free survival). However, the use of the APO and Adriamycin, Cytoxan, Oncovin, and prednisone (ACOP+) regimens resulted in approximately 70% event-free survival for children with stage 3 or 4 large cell lymphoma. These latter protocols include up-front vincristine, prednisone, doxorubicin, and cyclophosphamide (ACOP+ only). Because of the similar incidence after APO and ACOP+ therapy and the concerns of secondary malignancy and gonadal failure after cyclophosphamide, POG investigators prospectively compared APO to ACOP+ in children with advanced-stage large cell lymphoma. The event-free survival rate is approximately 70% in both arms at 5 years, thereby questioning the value of the addition of an alkylating agent to an Adriamycin-containing regimen. Conclusions about the safety of omitting cyclophosphamide await confirmatory studies and a detailed analysis of various subsets of patients.

The most important prognostic factor in children with large cell lymphoma is stage. Children with ALCCL do not have an adverse prognosis compared with other subgroups of patients with large cell lymphoma. In a retrospective POG study, B-cell phenotype was associated with superior survival.

Most protocols for children with advanced-stage large cell lymphoma do not include involved-field radiotherapy, but no controlled trials have addressed this issue. The risk of an isolated CNS relapse is rare, but nevertheless, pediatric protocols include IT chemotherapy for these patients.

**HODGKIN'S DISEASE**

Approximately 10% to 15% of all cases of Hodgkin's disease occur in patients younger than 16 years. The natural history of Hodgkin's disease and outcome of treatment is similar in children and young adults 20 to 45 years of age. Fully grown adolescents generally are evaluated and managed in the same way as adults. Treatment decisions are more complex in young children because of the adverse effects of irradiation on growth of bone and soft tissues and the risk of secondary malignancies. The preceding concerns led to the development in the 1970s of combined modality therapy with reduced doses and volumes of irradiation for children with both early and advanced stages of Hodgkin's disease. The following section focuses on the unique aspects of the treatment of Hodgkin's disease in children.

**Epidemiology**

In industrialized countries, the age of Hodgkin's incidence is bimodal, with a first peak in adults 20 to 30 years of age and a second peak in late adulthood. Hodgkin's is uncommon before age 5 years, and the majority of pediatric cases are in children older than 11 years. Before age 10, the male to female ratio is approximately 3:1; this ratio approaches 1:1 by adolescence. The etiology of Hodgkin's disease remains unknown. An increased risk of Hodgkin's disease is noted in children with inherited immunodeficiency syndromes. Genetic susceptibility and environmental factors probably both play a role in the pathogenesis of Hodgkin's disease (discussed in detail in Chapter 45.1 and Chapter 45.6). Although rare, Hodgkin's can be familial. Evidence is increasing for the role of EBV in some subgroups of patients with Hodgkin's disease, especially children with mixed-cellularity histology.

**CLINICAL PRESENTATION, STAGING, AND WORKUP**

Hodgkin's disease usually presents in supradiaphragmatic lymph nodes, with cervical, anterior mediastinal, and axillary nodes occurring in decreasing frequency. Mediastinal adenopathy may produce symptoms such as dyspnea, cough, or superior vena cava syndrome. Approximately 90% of children present with painless neck adenopathy, and 60% have involvement of anterior mediastinal, paratracheal, or hilar lymph nodes. Isolated infradiaphragmatic Hodgkin's disease is rare. Approximately one-third of children have B symptoms [unexplained fever (exceeding 100°F), drenching night sweats, more than 10% weight loss]. The Ann Arbor staging system is used for all age groups of patients with Hodgkin's disease and is described in detail in Chapter 45.6. Although not included in the staging system, a precise measurement of the size of the anterior mediastinal mass is important. If the ratio of the width of the mediastinal mass over the maximum transhilar diameter is greater than one-third, this is considered large mediastinal adenopathy and is an adverse prognostic variable. The diagnosis of Hodgkin's disease must be established by lymph node or tissue biopsy. The lymphocyte-predominant subtype is closely associated with stage I and II Hodgkin's disease, and lymphocyte depletion is extremely rare in children. Despite the unique biology and natural history of lymphocyte-predominant Hodgkin's disease, most pediatric oncologists recommend the same stage-appropriate treatment as given to other children with Hodgkin's disease. The pathology and immunobiology of Hodgkin's disease is reviewed in detail in Chapter 45.8.

Once the diagnosis is established, the pretherapy evaluation begins with "clinical" staging. Clinical staging should include a history and physical examination with particular emphasis on defining lymphadenopathy by palpating the major lymph node chains. The size of the nodes should be measured and recorded for staging and follow-up. Laboratory studies include complete blood cell count with platelets, erythrocyte sedimentation rate, and kidney and liver function studies. Patients with B symptoms or stage III or IV disease should have bone marrow biopsies from two separate sites. Imaging studies should include a chest radiograph with a posteroanterior and lateral view, and thoracic and abdominal CT scans. Lower extremity lymphangiography is no longer routinely performed in most centers because it does not visualize the upper abdominal nodes and spleen and sometimes require general anesthesia in children. High-dose gallium scanning in children with Hodgkin's disease, similar to the situation in adults, is most helpful for following response to therapy if the tumor
The thoracic CT scan is useful for detecting minimal mediastinal disease, pulmonary parenchymal and hilar disease, pericardial involvement, paracardiac nodes, and chest wall extension. No optimal method has been developed for detecting abdominal involvement of Hodgkin's disease. The false-positive and false-negative rates for abdominal CT scans were 14% and 22%, respectively, in a pediatric series. More than 90% of children who are upstaged by laparotomy have evidence of splenic involvement that is not detected by CT scanning or lymphangiograms. In a POG study, models based on clinical and radiographic findings were developed to predict for splenic involvement and upstaging with laparotomy. Risk factors, such as B symptoms, an erythrocyte sedimentation rate of more than 70, histology other than nodular sclerosis or lymphocyte predominant, more than four sites of involvement, and an enlarged spleen (based on spleen CT index), were predictive for abdominal disease but still were associated with 25% to 30% false-negative and false-positive rates, respectively.

The merits of staging laparotomy remain a source of controversy. Although information provided by a staging laparotomy and splenectomy may be unobtainable by other means, surgical staging is recommended only if the information provided will influence treatment planning. If radiation therapy alone is used for stage I and II disease, pathologic staging will more accurately define appropriate patients and, in certain cases, spare them paraaortic and splenic irradiation. However, staging laparotomy is no longer routinely performed in children because of the increasing use of combined modality therapy for all stages of disease.

In the era of staging laparotomy in children, a concern existed for the risk of overwhelming postsplenectomy sepsis from encapsulated pathogens. With the use of pneumococcal, meningococcal, and Haemophilus influenzae vaccinations before surgery and prophylactic antibiotics, this risk appears to have decreased.

Among 2238 consecutive patients with Hodgkin's disease treated at Stanford University, 4% were 10 years old or younger and 11% were 11 to 16 years old. Stage I and II disease was present in approximately 60% of children. Stage I disease was slightly more common in younger children (18%) than in adolescents (8%); stage II disease occurred in 40% to 50% of all age groups; and stage IV disease was less common in younger children (3%) than in adolescents (15%). B symptoms occurred in 19% of younger children and in 30% of adolescents.

As the treatment of Hodgkin's disease has improved, previously identified prognostic factors have diminished in importance. However, stage, tumor bulk, and constitutional symptoms continue to influence the success and certainty of choice of therapy. Because prognostic factors are similar for adults and children with Hodgkin's disease, the reader is referred to Chapter 45.6 for an in-depth discussion of this topic.

### SELECTION OF THERAPY

The cure rate for children with all stages of Hodgkin's disease is approximately 90%. As the cure rate has increased, an increasing focus has been placed on the late complications of therapy. In the pediatric patient, especially the prepubescent child, treatment decisions must be weighed in view of the toxicities of radiation therapy on growth and development. For example, the use of high-dose (40 Gy) extended-field radiotherapy alone in children and adults with pathologic stage I or II Hodgkin's disease results in 85% to 90% 10-year survival. However, this therapy has serious late effects on musculoskeletal growth in the prepubescent child. In this young age group, the effect on bone and soft tissue is manifest by intracavicular narrowing, shortened sitting height, decreased mandibular growth, and decreased muscle development in the treated volume (Figure 45.2-3). Other well-known late complications of irradiation, including hypothyroidism and second neoplasms, are not unique in patients treated for Hodgkin's disease in childhood (discussed later in the section on Complications).

![Figure 45.2-3](image)

**Figure 45.2-3.** Frontal view of patient several years after mantle irradiation with 4-MeV linear accelerator for Hodgkin's disease. Note the intacavicular narrowing and hypodevelopment of neck musculature.

In an attempt to decrease the late effects of high-dose extended-field irradiation, alternative treatments have been developed. These have included chemotherapy combined with both lower doses and less extensive fields of irradiation and chemotherapy alone (Table 45.2-8).

### TABLE 45.2-8. Representative Combined Modality Trials for Pediatric Hodgkin's Disease

A Stanford study was one of the first to demonstrate that combined modality therapy with Mustargen, Oncovin, procarbazine, and prednisone (MOPP) and low-dose radiation to involved regions was highly effective and associated with fewer adverse effects on musculoskeletal growth and development than had been observed with high-dose radiation alone. In this study, patients were surgically staged and treated with six cycles of MOPP chemotherapy and an age-adjusted radiation dose of 15 to 25 Gy. Boost doses of 10 Gy were used in select patients. The projected 10-year survival rate was 89% for all patients. However, the long-term side effects included a 10-year risk of 6.5% for the development of secondary leukemia, as well as azoospermia in all males tested. The Princess Margaret Hospital team in Toronto used a similar combined modality approach, but avoided staging laparotomy. In an effort to maintain efficacy while decreasing the occurrence of secondary leukemia and male infertility, the Stanford successor study alternated MOPP with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) for six cycles in combination with a 15- to 25-Gy radiation dose to involved fields. The projected 10-year survival rates were 96%, and growth and development have progressed normally. At the time of the report, no patient had developed a second leukemia, but one solid tumor in a radiation field was noted. Approximately one-third of patients had asymptomatic changes noted on pulmonary function tests. Azoospermia is documented in approximately one-third of patients treated with ABVD, but it appears transitory in almost all patients.

Similar treatment strategies with the goal of decreasing the risk of secondary leukemia, solid tumors, and gonadal failure have been reported by other groups. The French Society of Pediatric Oncology randomized patients with clinical stage I and IIA Hodgkin's disease to four cycles of ABVD, or two cycles of MOPP and two cycles of ABVD, plus low-dose (20-Gy) involved-field radiation therapy. Children with advanced disease (stages IB, IIB, III, and IV) were given three cycles of...
MOPP and three cycles of ABVD plus extended-field low-dose radiotherapy. Patients with a poor response to chemotherapy received full doses of irradiation. The
\[\text{\textit{Blood}} 1998;92:1143.\]  

The event-free survival rate was 90% at 6 years, with no difference noted in the two arms of the study (see Table 45.2-8).  

In the past, there had been only limited experience using chemotherapy as the only treatment modality in children with Hodgkin's disease. The early experience was reported by the investigators from the Royal Children's Hospital in Melbourne, Australia.  

After clinical staging, they treated children with stage I to IV Hodgkin's disease with combinations of MOPP or ABVD or chemotherapy and prednisone (CHOP) therapy. The event-free survival rate was 92% at a median follow-up of 45 months. Twenty-eight of 32 patients with stage I or II disease and 14 of 15 patients with stage III or IV were disease-free. Although the outcome was excellent, these children were exposed to multiple cycles of alkylating agents with the high risk of secondary leukemia and infertility in males.  

The POG investigators have completed two large randomized trials in early-stage and advanced-stage Hodgkin's disease. The first POG study compared six cycles of MOPP alternating with ABVD to four cycles of the same chemotherapy followed by involved-field irradiation (25 Gy) in surgically staged children with stage I to IIIA Hodgkin's disease.  

The second randomized study, POG, showed that no benefit existed for low-dose total nodal or subtotal nodal radiation after eight cycles of MOPP alternating with ABVD in children with advanced-stage Hodgkin's disease. Results of CCG study 5942 indicate inferior results in patients with advanced-stage disease or B symptoms who were randomized to receive chemotherapy only (J. Nachman, personal communication). Further investigations are needed before radiation therapy is omitted in the treatment of children with Hodgkin's disease, especially for unfavorable subgroups.

The combined modality approach using limited doses of both radiation (15 to 30 Gy) and alkylating agents for children with all stages of Hodgkin's disease produces an excellent outcome with significant reduction in the risk of serious late effects. As the doses of irradiation are safely lowered in combined modality treatments, future studies will undoubtedly test whether chemotherapy alone can achieve these excellent results. In addition, less toxic and equally effective chemotherapy regimens are being tested.

The cumulative risk of leukemia is highest in patients receiving chemotherapy alone (7.9%) and rose with an increase in the alkylating dose. Based on these data, efforts to lower the doses and volumes of radiation and limit exposure to alkylating agents and anthracyclines are steps in the right direction.

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SECTION 45.3
Non-Hodgkin’s Lymphomas

INTRODUCTION

Neoplasms of lymphoid cells can present clinically as leukemia, lymphoma, and myeloma. Leukemia and myeloma are dealt with in separate chapters in this text (see individual Chapter 46.1, Chapter 46.2, Chapter 46.3.1, Chapter 46.3.2, Chapter 46.4, and Chapter 46.5). Lymphomas (i.e., the solid tumors of lymphoid cells) are typically subdivided into Hodgkin’s disease (see Chapter 45.6) and non-Hodgkin’s lymphomas (NHL), the topic of this chapter.

Our knowledge of the biology of NHLs has increased dramatically over the last decade. This is reflected in an improved system of classification that categorizes patients in a more clinically relevant way. New insights into the immunology and genetics of lymphomas have offered new therapeutic opportunities. Some of these, such as monoclonal antibodies directed against specific proteins on the surface of malignant lymphoma cells, have already become widely applied.

It has been known for more than 30 years that some patients with NHL can be cured using chemotherapy. Those clinical factors that predict curability are now well known. The prognostic effect of clinical variables such as age, stage, performance status, serum lactic dehydrogenase level, and specific sites of involvement must be mediated through expression of certain genes. The next improvement in lymphoma classification, improved prognostic categories, and new opportunities for therapy will come as the patterns of gene expression that underlie clinical variables become increasingly apparent.

EPIDEMIOLOGY

In 2000 it is estimated that there will be 54,900 new cases of NHL diagnosed in the United States, and that 26,100 people will die with this diagnosis. NHL accounts for 5% of new cancers in men and 4% of new cancers in women each year in the United States and is responsible for 5% of deaths. In 1997, NHL was reported to be the leading cause of death from cancer in men between the ages of 20 and 39.

According to the Surveillance, Epidemiology, and End Results program of the National Cancer Institute, the U.S. age-adjusted incidence rate for NHL was 15.5 per 100,000 in 1996. International NHL incidence rates vary as much as fivefold. The highest reported incidence rates are in the United States, and also Europe and Australia, while the lowest rates have generally been reported in Asia.

NHL is more common in male subjects, with a reported incidence of 19.2 per 100,000 as compared with 12.2 per 100,000 for women. In some sites, such as the thyroid, NHL incidence may be higher in women, however. The incidence rate for whites is 15.9 per 100,000 as compared with 12.0 per 100,000 for African Americans. The NHL incidence rate for white male subjects is approximately 54% higher than Japanese Americans and 27% higher than Chinese Americans.

Incidence rates are also lower among Native Americans and Hispanics.

The median age of NHL diagnosis was 65 years in the American College of Surgeons’ National Cancer Data Base. NHL incidence increases with age and peaks in the 80 to 84 age group. In the period between 1992 and 1996, the incidence rate for white men in this age group was 131.5 per 100,000. Incidence rates have tripled for patients older than 65 years of age.
There has been a striking increase in NHL incidence rates over the last four decades that has been referred to as an epidemic of NHL. The lifetime risk of being diagnosed with NHL is 2.0%. The incidence rate for white men and women increased 150% between the late 1940s to the late 1980s. The incidence rate is increasing approximately 3% per year and has increased more than 80% since 1973 (Fig. 45.3-2). An increase in incidence has been observed in all geographic areas of the United States, although the largest increase has been from the San Francisco area. A registry analysis from seven European countries showed that the incidence rate for NHL increased 4.8% each year between 1985 and 1992. Similar increases in NHL incidence have been noted in international cancer registries in addition to well-defined population-based registries.

There has been an increase in all histologic types of NHL except for diffuse small cleaved histology. The decreasing incidence of this histology probably reflects the reclassification of most of these biopsies to a diagnosis of mantle cell histology. The largest increases have occurred in patients with high-grade lymphomas. The incidence of extranodal lymphomas has increased more rapidly than nodal disease in some reports, whereas others have noted similar increases in the incidence of nodal and extranodal disease. The incidence of primary CNS lymphoma in the United States increased more than tenfold between 1973 and 1991 to 1992. This increase is undoubtedly related to the occurrence of primary CNS lymphomas in patients with acquired immunodeficiency syndrome (AIDS). Although the increase in incidence began before the AIDS epidemic, and incidence rates have increased in non-AIDS populations. Furthermore, some studies have failed to show evidence of an increasing incidence of primary CNS lymphoma in non-AIDS populations.

Geographic differences in histologic subtypes of NHL have been noted. Examples include the endemic form of Burkitt’s lymphoma, which is seen most commonly in children in equatorial Africa. Higher rates of gastric lymphoma have been reported to occur in Northern Italy. Other examples include nasal T-cell lymphomas, which are most common in China, certain small intestinal lymphomas, which are most common in the Middle East, and adult T-cell leukemia/lymphoma (ATL), which is most common in southern Japan and the Caribbean. Several reports have shown a lower incidence of follicular lymphomas in Asia and in developing countries. The incidence of follicular lymphomas is lower in Asian immigrants to the United States as compared with later generations, suggesting an environmental influence. Geographic differences in the distribution of mantle cell lymphoma, certain T-cell lymphomas, and in the incidence of primary extranodal lymphomas have also been described.

The mortality for NHL has also increased steadily over the last four decades, although mortality increased more slowly than incidence (see Fig. 45.3-2). Increasing mortality suggests that increased incidence rates cannot be entirely due to artifacts of improved detection. Between 1973 and 1986 the U.S. mortality increased from 4.7 per 100,000 to 6.9 per 100,000. Mortality for NHL is approximately 20% higher in urban areas when compared with rural areas, and rates are higher in counties with higher median education levels among residents.

Several hypotheses have been used to explain the increasing incidence of NHL. Some of the increase may be artifactual. For example, new NHL classification systems and techniques such as gene rearrangement studies have led to a diagnosis of NHL in some patients who would have previously had other diagnoses such as pseudolymphoma or atypical lymphoid hyperplasia. This is especially true for entities such as lymphomas of mucosa-associated lymphoid tissue (MALT) as well as certain T-cell lymphomas that might have previously been given diagnoses such as angioimmunoblastic lymphadenopathy. However, these changes in diagnosis can only account for a small fraction of the increase in incidence. In addition, improved imaging techniques have undoubtedly led to more NHL diagnoses, particularly for primary CNS lymphoma, and less invasive biopsy techniques have led to more vigorous attempts at establishing a diagnosis than before. Finally, some increase in NHL incidence can be attributed to reclassification of cases that would have previously been called Hodgkin’s disease. It has been estimated that this may account for 10% to 15% of cases, although in some series more than 25% of Hodgkin’s disease patients were reclassified as NHL. However, such large discrepancies apply mostly to cases diagnosed before the 1970s and are unlikely to be responsible for much of the later increase in incidence. While these artifacts have undoubtedly led to some increase in the reported incidence of NHL, they can only account for a small fraction of the increase.

The aging U.S. population can account for only a small increase in NHL incidence, although other factors, such as the AIDS epidemic, may be responsible to a greater extent. In 1996 the incidence rate for NHL in men was 44.4 per 100,000 in the San Francisco county and county region as compared with 18.1 per 100,000 for areas exclusive of the San Francisco metropolitan area. The incidence rate was 62.4 per 100,000 men aged 20 to 54 in the San Francisco city and county area. While AIDS can account for some of the increased NHL incidence, the rise in NHL incidence began before the AIDS epidemic, and it has been estimated that only 8% to 27% of NHL cases can be attributable to AIDS. Although studies have demonstrated that in some areas such as San Francisco, as many as 66% of the increased NHL incidence can be attributed to AIDS. In summary, even when factors such as accuracy and completeness of diagnosis, the effect of human immunodeficiency virus, and occupational exposures are considered, the reason for most of the increase in NHL incidence is unexplained. Many investigators have postulated that a ubiquitous environmental or toxic exposure is responsible.

ETIOLOGY

The cause of most cases of NHL is unknown, although several genetic diseases, environmental agents, and infectious agents have been associated with the development of lymphoma. Although the existence of a familial NHL risk is debated, familial aggregations of NHL have been described, and some studies have shown a higher risk of NHL in siblings or first-degree relatives of people with lymphoma or other hematologic malignancies. Three categories of familial aggregations have been described. The first consists of male preadolescents and adolescent siblings who often have extranodal lymphoma. The second category consists of adult siblings with NHL, and the third is represented by adults with NHL from two or more generations. Familial clustering may reflect a true genetic susceptibility or a shared environmental exposure. In some cases, affected individuals in familial clusters have had well-defined or subtle immune deficiencies. In one study, no evidence of germline p53 mutations was noted in unaffected members of lymphoma-prone kindreds.

IMMUNODEFICIENCY
Several rare inherited disorders are associated with as much as a 25% risk of developing lymphoma. These disorders include severe combined immunodeficiency, hypergammaglobulinemia, common variable immunodeficiency, Wiskott-Aldrich syndrome, and ataxia-telangiectasia. Lymphomas associated with these disorders are often associated with Epstein-Barr virus (EBV) and vary in appearance from polyclonal B-cell hyperplasia at one end of the spectrum to monoclonal lymphomas at the other end.

Ataxia-telangiectasia is an autosomal recessive multisystem disorder associated with a risk of lymphoma that is increased more than 250-fold in affected individuals. Both B-cell and T-cell NHL has been described. A mutated ataxia-telangiectasia gene (ATM) has been cloned and localized to chromosome 11. Mutations are thought to inactivate or eliminate a protein involved with control of cell-cycle checkpoints responding to DNA damage. Mutations and deletions of ATM have also been identified in chronic lymphocytic leukemia and mantle cell lymphoma.

The Wiskott-Aldrich syndrome is an X-linked recessive disorder. The relative risk of developing malignancy is more than 100 times that expected in the general population. NHL accounts for most of the increased cancer risk, and the incidence of NHL increases with age. Patients frequently have extranodal and CNS lymphomas. A 30-fold excess of lymphoma has been noted in individuals with common variable immunodeficiency, and a similar increase in risk has been noted in patients with severe combined immunodeficiency syndrome.

The risk of developing NHL in association with Sjögren's syndrome is increased approximately 30- to 40-fold. These lymphomas are usually marginal zone lymphomas that most commonly occur in salivary glands and other extranodal sites such as the stomach and lung. Other condition associated with NHL is Hashimoto's thyroiditis. Most cases of thyroid lymphoma occur in association with thyroiditis. NHL may also be more common in patients with systemic lupus erythematosus. Celiac sprue is associated with poor-prognosis lymphomas that are now classified as enteropathy-type intestinal T-cell lymphomas.

INFECTIOUS AGENTS

EBV was discovered in cell lines from tumors of patients with African (endemic) Burkitt's lymphoma. EBV DNA is associated with 95% of endemic Burkitt's lymphomas, and less commonly with sporadic Burkitt's lymphoma. Both type A and type B EBV strains are observed. Since EBV is not seen in all cases of Burkitt's lymphoma, the actual relationship and the mechanism by which EBV might contribute to the development of Burkitt's lymphoma is unknown. Burkitt's lymphoma is associated with c-myc deregulation, although different chromosome 8 breakpoints are observed in the endemic and sporadic forms, and the presence or absence of EBV DNA is related to the breakpoint location. It is hypothesized that early EBV infection and environmental factors may increase the numbers of EBV-infected precursor cells and the risk of genetic error.

EBV is also linked to posttransplant lymphoproliferative disorders (PTLDs), some AIDS-associated lymphomas, and some lymphomas associated with congenital immunodeficiency. Virtually all AIDS-associated primary CNS lymphomas have EBV in the tumor clone, although EBV is associated with other AIDS-associated lymphomas less frequently. Following EBV infection, normal host immune responses mediated by T lymphocytes suppress EBV-induced proliferation. In patients with depressed T-cell immunity, clones of EBV-transformed B cells can proliferate, leading to the development of lymphoma. The pattern of EBV-associated nuclear proteins in AIDS-associated Burkitt's lymphomas differs from large cell lymphomas. C-myc activation in the absence of EBV infection can occur in AIDS-associated lymphomas. The EBV latent membrane protein 1 is a viral analogue of the tumor necrosis factor receptor. The activity of this protein is similar to activated CD40 and is essential for the transformation of B cells by EBV. EBV-positive AIDS-associated NHL and PTLD, it appears that latent membrane protein 1 binds to members of the tumor necrosis factor receptor-associated factor family and activates the NF-κB transcription factor, leading to cellular proliferation. EBV is also seen in association with human herpesvirus-8 (HHV-8) in primary effusion lymphomas.

The human T-cell lymphotropic virus type I (HTLV-I) was the first human retrovirus associated with a malignancy. HTLV-I is a type C RNA virus that is responsible for ATL in addition to HTLV-I–associated myelopathy/tropical spastic paraparesis and other disorders. HTLV-I is primarily transmitted by means of breast feeding, sexual contact, and blood transfusion. The latent period between infection and development of ATL is several decades. HTLV-I seropositivity and ATL are most prevalent in southern Japan, South America, Africa, and the Caribbean, although ATL is seen in the United States. In endemic areas more than 50% of all NHL cases are ATL, although the risk of developing disease is only approximately 5% in infected patients. The HTLV-I genome contains the regulatory tax gene, whose product is a potent transcriptional activator of several genes and is thought to be responsible for the transforming features of HTLV-I. The risk of ATL may be higher in patients with higher anti-HTLV-I titers and lower reactivity to tax.

A third virus associated with NHL is HHV-8. This virus was originally discovered in Kaposi's sarcoma lesions from AIDS patients and was called Kaposi's sarcoma–associated herpesvirus. The virus is also associated with multicentric Castleman's disease. An analysis of 193 lymphoma specimens from patients with HIV and without AIDS identified the presence of virus in only eight specimens, all of which were from patients with primary effusion lymphomas. The virus was subsequently shown to be a member of the gamma herpesvirus subfamily and was named HHV-8. Subsequent studies have shown that primary effusion lymphomas and Kaposi's sarcoma are associated, lack c-myc gene rearrangements, and have distinct clinical and phenotypic features. The mechanism of HHV-8 growth stimulation is unknown, although several potential mechanisms have been proposed. It has been suggested that HHV-8 may be necessary for EBV-induced transformation in these patients.

Evidence also links hepatitis C virus (HCV) infection with NHL. Infection with HCV is strongly associated with essential mixed cryoglobulinemia, which is itself associated with low-grade NHL. Several analyses have demonstrated significantly higher rates of HCV infection when B-cell NHL patients were compared with controls. The association appears strongest for patients with monocytoid B-cell lymphoma and lymphoplasmacytoid lymphomas. HCV has been identified in NHL cells from a patient with type II mixed cryoglobulinemia. Although HCV is not thought to be oncogenic, chronic antigenic stimulation from circulating HCV RNA may produce clonal expansion leading to development of NHL. Some studies have failed to find an association between HCV infection and NHL.

Several lines of evidence link the bacteria Helicobacter pylori to gastric MALT lymphomas. H pylori can be found in the gastric mucosa of patients with gastric MALT lymphoma. In patients with gastric lymphoma, H pylori is more likely than controls to have serologic evidence of past H pylori infection. It is hypothesized that development of gastric MALT lymphomas is a multi-step process beginning with H pylori colonization. This leads to chronic antigenic stimulation and gastritis and the subsequent development of malignant B-cell clones. Stimulation by H pylori–associated antigens appears to be strain specific and T-cell mediated.

ENVIRONMENTAL AND OCCUPATIONAL EXPOSURES

Studies of occupational and environmental NHL risk are frequently inconsistent and contradictory. Difficulties in estimating risk are often related to sample size and other methodologic difficulties in addition to difficulties in quantifying exposure. The risk of NHL has been reported to be increased in several occupations. Occupations frequently associated with a higher risk include farmers, forestry workers, and agricultural workers. Metaanalysis has shown a slightly increased risk of...
NHL in farmers. Increased risk of NHL in farmers may be related to an infectious agent or chemical exposure.

Several studies have shown an increased risk of NHL in relation to herbicide exposure, especially phenoxy herbicides such as 2,4-dichlorophenoxyacetic acid. Other analyses have found less evidence for an association between 2,4-dichlorophenoxyacetic acid exposure and NHL. The development of NHL has also been linked to hair dyes, especially darker and permanent colors, although some studies have failed to find an association. NHL has also been associated with organic solvents, high levels of nitrites in drinking water have been associated with NHL in some studies, but not others.

**DIET AND OTHER EXPOSURES**

Cohort and case-control studies suggest that the risk of NHL is increased approximately twofold in association with higher intake of meats and dietary fat. Recreational drug use has been associated with increased NHL risk, and tobacco use has been associated with a higher risk in some studies, but not others. The risk of NHL may be increased more than 20-fold after treatment for Hodgkin's disease. Studies examining the relative risk of combined modality treatment have been inconsistent, although the risk of NHL in association with ionizing radiation is minimal. Solar ultraviolet exposure has been associated with NHL in some studies. Although some analyses have shown that the risk of NHL is increased after blood transfusion, other studies have failed to identify a significantly increased risk.

**BIOLOGIC BACKGROUND FOR CLASSIFICATION OF LYMPHOID NEOPLASMS**

Although the normal counterpart of the neoplastic cell is not known for all types of lymphoid neoplasms, it can be postulated for many of them. Understanding the normal counterpart of neoplastic cells can provide a useful framework for understanding the morphology, immunophenotype, and to some extent, the clinical behavior of the neoplasms (Fig. 45.3-3A, Fig. 45.3-3B, and Fig. 45.3-3C).

**Figure 45.3-3.** A: Hypothetical scheme of lymphocyte differentiation, showing anatomic locations of different stages of T- and B-cell differentiation. T cells are shown at top; B cells are at bottom. B: Differentiation scheme, showing nomenclature for various types of T cells (top) and B cells (bottom). C: Differentiation scheme, showing postulated normal counterpart of many of the T- and B-cell neoplasms that can currently be recognized. B-ALL, B-cell acute lymphoblastic leukemia; B-CLL, B-cell chronic lymphocytic leukemia; Ig, immunoglobulin; LBL, lymphoblastic lymphoma; MALT, mucosa-associated lymphoid tissue; SLL, small lymphocytic lymphoma; T-LGL, T-cell large granular lymphocyte; T-PLL, T-cell prolymphocytic leukemia.

**Anatomy and Morphology of Normal Lymphoid Tissues**

Lymphoid tissues can be divided into two major categories: (1) the central or primary lymphoid tissues, which harbor lymphoid precursor cells and provide for their maturation to a stage at which they are capable of performing their function in response to antigen; and (2) the peripheral or secondary lymphoid tissue, in which antigen-specific reactions occur.

**Primary (Central) Lymphoid Tissues**

**Bone Marrow (Bursa Equivalent).** Many of the early experiments that elucidated the basic biology of the lymphoid system used chickens and other avian species as experimental animals; in avians, an organ known as the bursa of Fabricius, located in the region of the cloaca, was proven to be the source of cells capable of producing antibody. Thus, these cells were termed B cells, for bursa-derived cells. In mammals, the bursa does not exist, and experiments have shown that the precursors of antibody-producing cells come from the bone marrow. The bone marrow is also the source of other hematopoietic cells, including T cells (so named because their crucial maturation steps cannot occur in the absence of the thymus).

**Thymus.** The thymus, located in the anterior mediastinum, is the site at which immature T-cell precursors (prethymocytes) that migrate from the bone marrow undergo maturation and selection to become mature, naive T cells, which are capable of responding to antigen. The thymus is divided into a cortex and a medulla, each of which is characterized by specialized epithelium and accessory cells, which provide the milieu for T-cell maturation.

**Secondary (Peripheral) Lymphoid Tissues**

**Lymph Nodes.** Lymph nodes are located at sites throughout the body, strategically placed to process antigens present in lymph drained from most organs via the afferent lymphatics. Lymph nodes have a capsule, a cortex, a medulla, and sinuses (subcapsular, cortical, and medullary). The sinuses contain macrophages, which take up and process antigen, which may then be presented to lymphocytes. The cortex is divided into follicular and diffuse (paracortical) regions, and the medulla into medullary cords and sinuses. The paracortex contains high endothelial venules, through which both T and B lymphocytes enter the node, and specialized antigen-presenting cells (APC), the interdigitating dendritic cells, which may be related to the cutaneous Langerhans’ cell, and which present antigen to T cells. Both T-cell and early B-cell reactions to antigen occur in the paracortex, while the germinal center reaction occurs in the follicular cortex. The follicular cortex also contains a specific type of accessory cell, the follicular dendritic cell (FDC); adhesion to the FDC-antigen complex is important in the differentiation of B cells in response to antigen. Plasma cells and effector T cells generated by immune reactions accumulate in the medullary cords and exit via the medullary sinuses.

**Spleen.** The spleen, located in the left upper abdomen, has two major compartments: the red pulp, which functions as a filter for particulate antigens and for the formed elements of the blood, and the white pulp, which is virtually identical in its compartments to the lymphoid tissue of the lymph node. Follicles and germinal centers are found in the Malpighian corpuscles, whereas T cells and interdigitating dendritic cells are found in the adjacent periarteriolar lymphoid sheath. Plasma cells accumulate in the red pulp.

**Mucosa-Associated Lymphoid Tissue.** Specialized lymphoid tissue is found in association with certain epithelia, in particular the nasopharynx and oropharynx (Waldeyer’s ring: adenoids, tonsils), the gastrointestinal tract (gut-associated lymphoid tissue: Peyer’s patches of the distal ileum, mucosal lymphoid aggregates in the colon and rectum), and lung (bronchus-associated lymphoid tissue). Collectively, this is known as mucosa-associated lymphoid tissue (MALT). These tissues tend to have prominent B-cell follicles, but also may have discrete T-cell zones, similar to the paracortex of lymph nodes. MALT is thought to function in response to intraluminal antigens and the generation of mucosal immunity. Lymphoid cells that respond to antigen in the MALT acquire homing properties that enable them to return to these tissues.

**B- and T-Cell Differentiation**

In both the T- and B-cell systems, there are two major phases of differentiation: antigen-independent and antigen-dependent (see Fig. 45.3-3A and Fig. 45.3-3B). Antigen-independent differentiation occurs in the primary lymphoid organs (bursa equivalent [bone marrow possibly] and thymus) without exposure to antigen and produces a pool of lymphocytes that are capable of responding to antigen (naive or virgin T and B cells). The early stages are stem cells and lymphoid blasts, which
are self-renewing, while the later stages are resting cells with a finite life span ranging from weeks to years. On exposure to antigen, the naive lymphocyte undergoes blast transformation and becomes a large, proliferating cell, which gives rise to progeny that are capable of direct activity against the inciting antigen (antigen-specific effector cells). The earlier stages of antigen-dependent differentiation are proliferating cells, while the fully differentiated effector cells are less mitotically active. Thus, neoplasms that correspond to proliferating stages of either antigen-independent or antigen-dependent differentiation are likely to be aggressive, whereas those that correspond to naive or mature effector stages are likely to be indolent.

**B-Cell Differentiation**

**ANTIGEN-INDEPENDENT B-CELL DIFFERENTIATION.**

Precursor B Cells. The earliest B cells to have rearranged immunoglobulin (Ig) heavy-chain genes, but lack surface immunoglobulin (Slg); the B cells at this stage are called precursor B cells or pre-pre-B cells. At the next stage, pre-B cells make cytoplasmic µ-heavy chain, but no light-chain, and do not express Slg. Both types of cells are derived from cells that are densely packed with nucleoli and contain an intranuclear enzyme, terminal deoxynucleotidyl transferase (TdT), and express CD34, a glycoprotein present on immature cells of both lymphoid and myeloid lineage, HLA-DR [class II histocompatibility complex (MHC) antigens], and the common acute lymphoblastic leukemia (ALL) (CD10). Expression of class II MHC antigens persists throughout the life of the B cell and is important in interactions with T cells. Pan-B-cell antigens are sequentially expressed on precursor B cells: CD19 and cytoplasmic CD22, followed by surface CD22. The leukocyte common antigen (CD45) does not appear until surface CD22; thus, staining for CD45 may not be useful in identifying early B-cell neoplasms. Precursor B cells also express CD79a, a molecule that is associated with Slg and is involved in transduction of signal after engagement of the Slg with antigen, analogous to CD3 and the T-cell receptor (TCR) molecule.

Fetal early B-cell development occurs in the liver, bone marrow, and spleen, whereas in adults it is restricted to the bone marrow. Cells with the morphologic and immunologic features of precursor B cells can be found in normal and regenerating bone marrow, where they correspond to the lymphocyte-like cells known as hematogones. Neoplasms of precursor B cells usually involve bone marrow and peripheral blood and are known as common or precursor B ALL, rarely, they present as solid tumors (precursor B lymphoblastic lymphoma).

Naive B Cells. The end stage of antigen-independent B-cell differentiation is the mature, naive (virgin) B cell, which expresses both complete surface IgM and IgD, lacks TdT and common ALL, antigen, and is capable of responding to antigen. Naive B cells have rearranged but unmutated Ig genes. Each individual B cell is committed to a single light-chain, either k or l, and all of its progeny express the same light-chain. In contrast to precursor B cells, naive B cells lack CD10 and CD34. In addition to Slg, naive B cells express pan-B-cell antigens (CD19, CD20, CD22, CD40, and CD79a), HLA class II molecules, complement receptors (CD21 and CD35), and CD1d, which presents glycolipids. Both naive B and precursor B cells express bcl-6 messenger RNA production and bcl-6 protein expression. The bcl-6 molecule and its ligand on T cells, appears to be important in the generation of memory B cells. In addition, both antigen receptor ligation and CD40 ligation switch off adhesion to vascular endothelium, interaction with APCs, and signal transduction. Slg, CD79a, CD19, and CD20, appear to be involved in signal transduction, CD40 is involved in signaling, and CD40 is involved in interaction with T cells and in further differentiation of B cells. Resting B cells also produce the bcl-2 protein, which promotes survival in the resting state. CD5-positive B cells produce Ig that often has broad specificity (cross-reactive idiotypes) and reactivity with self-antigens (autoantibodies).

Naive B cells are small resting lymphocytes. In fetal tissues, they are the predominant lymphoid cell in the spleen; in adults, they circulate in the blood and also make up a minor fraction of the B cells in primary lymphoid follicles and follicle mantle zones (so-called recirculating B cells). Studies of single cells picked from the mantle zone showed that they are donors of naive and contain activated Ig genes, consistent with naive B cells. Tumors of these cells are usually clinically indolent and histologically low grade. In addition, they are often widespread and leukemic, consistent with the recirculating behavior of the normal naive B cell. Two neoplasms appear to correspond to CD5-positive B cells: B-cell chronic lymphocytic leukemia (B-CLL) and mantle cell (centrocytic/intermediate) lymphoma.

**ANTIGEN-DEPENDENT B-CELL DIFFERENTIATION.**

**Immunoblast and Plasma Cell Reaction.** On encountering antigen, the naive B cell transforms into a proliferating cell, which ultimately matures into an antigen-dependent plasma cell. In T-cell–independent reactions, and in the early primary immune response, naive B cells transform into IgM-positive B blasts (B blasts or immunoblasts) in the T-cell zone, proliferate, and differentiate into IgM-secreting plasma cells, producing the IgM antibody of the primary immune response. These plasma cells have largely unmaturated Ig genes. Surface IgD is lost during blast transformation, as are some other antigens, such as CD21 and CD22. Other antigens associated with activation are up-regulated. With maturation to plasma cells, most surface antigens are lost, including pan-B-cell antigens HLA-DR and the leukocyte common antigen CD45, and secretory cytoplasmic IgM accumulates. The corresponding neoplasms to the IgM-producing plasma cell may be the lymphoplasmacytic lymphoma (lymphoma) or Waldenström's macroglobulinemia.

**Germinal Center Reaction.** Later in the primary response (within 3 to 7 days of antigen challenge in experimental animals) and in secondary responses, the T-cell–dependent germinal center reaction occurs. Each germinal center is formed from between three and ten naive B cells and ultimately contains approximately 10,000 to 15,000 B cells; thus, more than ten generations are required to form a germinal center. Proliferating IgM-positive B blasts formed from naive B cells that have encountered antigen in the T-cell zone (paracortex) migrate into the center of the primary follicle and fill the FDC meshwork by approximately 3 days after antigen exposure. Germinal centers are located centrally in the B zone of lymph nodes and contain large centroblasts, centrocytes, centrocytes, and centroblasts. Centroid cells may be distinguished by the presence of small, round, and mitotic figures. The centroblasts are the first cells to express bcl-6 antigen, which is involved in signaling, and CD40 is involved in interaction with T cells and in further differentiation of B cells. Resting B cells also produce the bcl-2 protein, which promotes survival in the resting state. CD5-positive B cells produce Ig that often has broad specificity (cross-reactive idiotypes) and reactivity with self-antigens (autoantibodies).

In centroblasts, a process of somatic mutation of the Ig gene variable (V) region begins, which alters the affinity for antigen of the antibody that will be produced by the cell. In addition, the cell may also switch from IgM to IgG or IgA production. Through these mechanisms, the germinal center reaction gives rise to the better fitting IgG or IgA antibody of the late primary or secondary immune response. Studies on single centroblasts picked from the dark zone of germinal centers suggest that in the early stages, a germinal center may contain approximately five to ten clones of centroblasts, which show only a moderate amount of Ig gene V region mutation; later, the number of clones diminishes to as few as three, and the degree of somatic mutation increases.

Centroblasts mature to nonproliferating medium-sized cells with irregular nuclei, inconspicuous nucleoli, and scant cytoplasm, called centrocytes (small or large cleaved follicular center cells), which accumulate in the opposite pole of the germinal center, known as the light zone, which also contains a high concentration of FDCs. Centrocytes reexpress Slg, which has the same VDJ rearrangement as the parent naive B cell and the centrodome of the dark zone, but which may have undergone a switch and with the class switch, because of the somatic mutations in the Ig V region. This process of somatic mutation thus results in marked intrachromosomal diversity of antibody-combining sites in a population of cells derived from only a few precursors. Also in the germinal center, centroblasts whose Ig gene mutations have resulted in marked intraclonal diversity of antibody-combining sites in a population of cells derived from only a few precursors. The centroblasts are able to process the antigen and present it to T cells in the light zone of the germinal center. It is thought that this activation of processes of FDCs. The centrocytes are able to process the antigen and present it to T cells in the light zone of the germinal center. It is thought that this activation of T cells may induce them to express CD40 ligand (CD40L), which can engage CD40 on the B cell. Both ligation of the antigen receptor by antigen and ligation of CD40 on the surfaces of germinal center B cells can rescue them from apoptosis. Interaction with surface molecules expressed by FDCs, such as CD23, appears to be important in directing differentiation of the centrocytes into plasma cells, while interaction with the numerous T cells present in the light zone, through the CD40 molecule and its ligand on T cells, appears to be important in the generation of memory B cells. In addition, both antigen receptor ligation and CD40 ligation switch off bcl-6 messenger RNA production and bcl-6 protein expression.

Follicular lymphomas are tumors of germinal center B cells, in which centrocytes fail to undergo apoptosis because they have a chromosomal rearrangement, t(14;18), that prevents the normal switching off of the antiapoptosis gene, bcl-2. Most large B-cell lymphomas are composed of cells that at least in part resemble centroblasts and have mutated Ig V region genes and are therefore thought to derive from the germinal center stage of differentiation. Finally, it is possible that...
Burkit's lymphoma corresponds to the early SlgM-positive B blast found in the early germinal center reaction in experimental animals.

Marginal Zone and Monocytoid (Parafollicular) B Cells. When the germinal center polarizes into a dark and a light zone, the mantle zone becomes better defined and eccentric, with the broader portion surrounding the light zone of the germinal center. Antigen-specific B cells generated in the germinal center reaction leave the follicle, migrate to the outer mantle zone, and form a marginal zone; these are particularly prominent in mesenteric lymph nodes, Peyer's patches, and the spleen. Marginal zone B cells have slightly irregular nuclei, resembling those of centrocytes, but with more abundant, pale cytoplasm. The term centrocyte-like has been applied to similar neoplastic cells. On rechallenge with antigen, splenic marginal zone B cells migrate first into the germinal center and then quickly appear in the T-cell zone as Ig-positive blast cells, which give rise to antigen-specific plasma cells; thus, they are thought to be memory B cells. Memory B cells are also detectable in the peripheral blood, where they may be IgM-positive and even CD25-positive. Studies on single marginal zone B cells from splenic and Peyer's patches show that they have mutated V region genes, may be oligoclonal, and are not clonally related to the adjacent germinal center. Cells that resemble marginal zone B cells, but with even more nuclear indention and abundant cytoplasm, known as monocytoid B lymphocytes, are seen in clusters adjacent to subcapsular and cortical sinuses of some reactive lymph nodes, peripheral to and often continuous with the follicle marginal zone. In contrast to marginal zone B cells, the monocytoid B cells found in reactive lymph nodes appear to have either unmutated Ig V region genes or to show only a small number of randomly distributed mutations that do not suggest selection by antigen. Nodal and splenic tumors resembling normal marginal zone and monocytoid B cells have been described. Analysis of Ig V region genes suggests that most of these have mutations consistent with germinal center exposure and antigen selection.

Bone Marrow Plasma Cells. IgG-producing plasma cells accumulate in the lymph node medulla, but it appears that the immediate precursor of the bone marrow plasma cell leaves the node and migrates to the bone marrow. Plasma cells lose IgM, pan-B-cell antigens, HLA-DR, CD40, and CD45, and cytoplasmic IgG or IgA associated with plasma cells also express CD13 and CD33 antigens, which can also be expressed on some T cells and also express some T-cell–associated antigens (CD2, CD71, and CD38). Antigen-dependent T-cell reactions occur in the paracortex of lymph nodes and the periarteriolar lymphoid sheath of the spleen, as well as at extranodal sites of immunologic reactions.

Cortical Thymocytes. As in the B-cell system, the earliest stages of T-cell differentiation involve characteristic rearrangement of the DNA encoding the antigen receptor molecule. The earliest antigen-independent stages of T-cell differentiation occur in the bone marrow; later stages occur in the thymic cortex. The exact site at which precursor cells become committed to the T lineage is not known, since the thymus contains cells that can differentiate into either T cells or natural killer (NK) cells, but not B cells. Cortical thymocytes are lymphoblasts, which contain the intranuclear enzyme TdT. The earliest committed T-cell precursors are CD34+ and CD34AR+, express the CD13 and CD33 antigens usually associated with myeloid cells, and lack CD4, CD3, CD4, and CD8 (triplet negative cells); within the thymus they sequentially acquire CD1, CD2, CD5, and lymphocytic CD3, and first the CD4 helper and then the CD8 suppressor antigen (double positive). In the thymus, rearrangement of the TCR genes is initiated, beginning with the g and d chains, followed by the b and then the a chain genes; these proteins are then expressed on the cell surface. Surface CD3 expression appears at the same time as expression of the T-cell receptor antigen b chain, with which it is closely associated and participates in signal transduction. Cortical thymocytes express the CD45RO epitope of the leukocyte common antigen, instead of CD45RA, and lack the antiapoptosis protein bcl-2.

In addition to providing a pool of mature T cells through proliferation of precursor cells, the thymus plays a major role in the selection of T cells, so that the resulting pool of mature T cells do not react to self-antigens. Both positive and negative selection occur in the thymus at the double positive (CD4+, CD8+) stage. Thymocytes that have anti–self-specificity bind strongly via their TCR ab complex to self-antigens presented by the MHC on thymic dendritic cells and die by apoptosis. Those that lack anti-self-reactivity undergo positive selection on thymic epithelial cells; they then express increased levels of surface CD3, acquire CD27 and CD69, switch their CD45 isotype from RA back to RO, lose CD1, express bcl-2, and lose either CD4 or CD8 to become mature, naive T cells. The tumor that corresponds to the stages of T-cell differentiation in the thymic cortex is precursor T-lymphoblastic lymphoma and leukemia; the variety of immunophenotypes and antigen receptor gene rearrangements found in precursor T-cell neoplasia corresponds to the variety of stages of intrathymic T-cell differentiation.

Naive T Cells. Mature, naive (virgin) T cells have the morphologic appearance of small lymphocytes, have a low proliferation fraction, lack TdT and CD1, and express either (but not both) CD4 or CD8, as well as surface CD3 and CD45RA, and bcl-2. These cells leave the thymus and can be found in the circulation, in the paracortex of lymph nodes, and in the thymic medulla. Some cases of T-cell prolymphocytic leukemia and peripheral T-cell lymphoma may lack T cells.

Antigen-independent T-cell differentiation. A complex interaction of T-cell surface molecules with molecules on the surface of APCs is required for T-cell activation in response to antigen. On the T cell, the CD4 or CD8 molecules bind to MHC class II or class I molecules, respectively, on the APC. A complex of CD3 and the TCR (which may be described as the T-cell receptor complex or TCR/CD3 complex, which fits the specific antigen under study) binds to the antigen/MHC complex on the APC. The adhesion molecule lymphocyte function-associated-1 on the T cell binds to intercellular adhesion molecule-1 on the APC; the activation-associated molecule CD40L on the T cell binds to CD40; and CD28 and CTLA4 on the T cell bind to B7-1 and B7-2 (CD86) on the APC. The binding of CD40-CD40L provides an activating signal for the T-cell receptor and the CD28-CD86 interaction provides a crucial second signal for the T cell to mature into an effector T cell. In addition, CD28 provides a crucial second signal for the T cell to mature into an effector T cell.

T-Immunoblasts. On encountering antigen, mature T cells transform into immunoblasts, which are large cells with prominent nucleoli and basophilic cytoplasm, that may be indistinguishable from B immunoblasts. T immunoblasts, in contrast to T lymphoblasts (thymocytes), are CD4 and CD8 negative, strongly express pan-T-cell antigens, and continue to express either CD4 or CD8, but not both. Activated or proliferating T cells express HLA-DR, as well as CD25 (interleukin-2 receptor), and both CD71 and CD38. Antigen-dependent T-cell reactions occur in the paracortex of lymph nodes and the perilaminar lymphoid sheath of the spleen, as well as at extranodal sites of immunologic reactions.

Effector T Cells. From the T-immunoblastic reaction come antigen-specific effector cells of either CD4 or CD8 type, as well as memory T cells. Antigen-stimulated T cells switch their CD45 isotype from CD45RA to CD45RO. Effector T cells of the CD4 type typically act as helper cells, and those of the CD8 type as suppressor cells in vivo; however, both types can be cytotoxic. CD4 cells can be cytotoxic to cells that are not only complexed with MHC class II antigen, whereas CD8 cells are cytotoxic to cells that display complexed with MHC class I antigen. In addition to cytotoxicity, effector T cells produce a variety of cytokines that affect the function of B cells and APCs, which modulate the immune response. Fully differentiated T-effector cells are small lymphocytes, morphologically similar to other nonproliferating lymphocytes of either T or B type. In addition to differences in subset antigen (CD4 vs. CD8 or double negative) expression, peripheral T cells may differ in their TCR expression (Vj vs. Vδ). The majority of T cells in the circulation and in lymphoid tissues are Vδ+; ab T cells are rare, express the nongerminal bcl-2 and in the spleen.

Most cases of peripheral T-cell lymphoma are thought to correspond to stages of antigen-dependent T-cell differentiation (e.g., mycosis fungoides corresponds to a mature effector CD4+ cell; hepatosplenic gd T-cell lymphoma to a gd T cell; T-cell large granular lymphocyte leukemia to a mature effector CD8+ cell); however, the relationship between neoplastic and normal T cells is not nearly as well understood as in the B-cell system. The systemic symptoms such as fever, skin rashes, and hemophagocytic syndromes associated with some peripheral T-cell lymphomas may be a consequence of cytokine production by the neoplastic T cells.

Natural Killer Cells. A third line of lymphoid cells, called NK cells since they can kill certain targets without sensitization and without MHC restriction, appears to derive from a common progenitor with T cells. NK cells recognize self class I MHC molecules on the surfaces of cells and kill cells that lack these antigens. Immature NK cells have cytoplasmic CD3, but these cells do not rearrange their T-cell receptor genes or express T-cell receptors or surface CD3. They are characterized by certain NK cell–associated antigens (CD16, CD56, and CD57), which can also be expressed on some T cells and also express some T-cell–associated antigens (CD2, CD25, and CD8). NK cells appear in the peripheral blood as a small proportion of circulating lymphocytes; they are usually slightly larger than most normal T and B cells, with abundant pale cytoplasm containing azurophilic granules (so-called large granular lymphocytes). Angiocentric and nasal T/NK cell lymphoma and some
IMMUNOPHENOTYPING OF LYMPHOID CELLS

Individual B- and T-lymphoid cells as well as accessory cells of the mononuclear phagocyte system can be recognized in cell suspensions or tissue sections by the presence of surface or cytoplasmic molecules (antigens) that can be detected using antibodies labeled with either fluorescence or enzymatic (immunohistochemical) methods. Immunophenotyping with monoclonal antibodies can be done using viable cell suspensions, frozen tissue sections, or paraffin-embedded tissue sections. Using monoclonal antibodies and acetylene-fixed cryostat sections, it has been possible to characterize many types of normal and neoplastic lymphoid cells. A series of international workshops has developed a standardized nomenclature for many of the antigens detected by more than one monoclonal antibody. For cells in body fluids, particularly the peripheral blood, flow cytometry with fluorescent-labeled antibodies is the method of choice; this method can also be applied to fine-needle aspiration biopsy specimens and to cell suspensions prepared from fresh tissue specimens, but sampling problems can occur due to selective loss of fragile neoplastic cells. Acetone-fixed frozen sections are the most reliable method for the pathologist to assess the phenotype of lymphoid cells in tissue sections. However, the technology for detecting lymphocyte-associated antigens in paraffin-embedded tissue has greatly improved, so that most clinically necessary immunophenotyping can be accomplished using only routinely processed tissue. Nonetheless, it is still advisable to prepare fresh frozen tissue in all cases of suspected lymphoma, in case a diagnosis cannot be made with certainty on paraffin tissue section analysis and also for possible molecular genetic analysis.

MOLECULAR GENETIC ANALYSIS OF LYMPHOID CELLS

Lymphocyte differentiation involves rearrangement of the genes involved in antigen recognition. This process is required for development of a functional antigen receptor. Some cancers develop due to rearrangements of these genes that can alter the activity of the receptor or generate a receptor that expresses a new antigen specificity. In B cells, the rearrangements occur during immunoglobulin (Ig) production. In T cells, the rearrangements are involved in the development of the T-cell receptor (TCR) and allow the cells to recognize and respond to a specific subset of antigens. The T-cell receptor undergoes somatic hypermutation and class switching to generate a repertoire large enough to respond to the majority of antigens they may encounter. Analysis of these rearrangements has provided insights into normal T- and B-cell differentiation and can also be useful in the diagnosis and classification of lymphoid neoplasms. In addition to these normal rearrangements, chromosome translocations frequently occur in lymphoid neoplasms, as they do in other tumors. In lymphomas, these translocations often involve hotspot spots in the antigen receptor genes; these translocations can also be useful in the diagnosis and classification of lymphoid neoplasms.

Antigen Receptor Gene Rearrangement

IMMUNOGLOBULIN GENE REARRANGEMENT. B-cell differentiation involves rearrangements of the genes involved in Ig production. The genes that encode the constant and variable regions of the Ig heavy and light-chain molecules are located far apart on the chromosomes in germline cells. To produce RNA for an Ig protein, many thousands of base pairs of DNA must be deleted from the genome to bring the different portions of the Ig gene together. These rearrangements change the position on the DNA of restriction sites (points at which restriction endonucleases cleave the DNA). Thus, fragments produced by digesting B-cell DNA with these enzymes are of a different size than those produced by digesting non-B-cell (germline) DNA and migrate differently in an electrophoresis gel. When radiolabeled DNA probes (cloned segments of DNA produced by bacteria) that are complementary to specific portions of the Ig gene are applied to such a gel, they specifically mark the position of the Ig gene, which can be demonstrated on an autoradiograph. The exact size, and therefore position on the gel (Southern blot), of each Ig gene fragment is unique to an individual B cell; thus, this technique provides not only a specific marker for B cells, but also a true marker for monoclonality.

T-CELL RECEPTOR GENE REARRANGEMENT. A process of gene rearrangement analogous to that seen in B cells also occurs during T-cell differentiation. This process involves the DNA encoding a T-cell–specific surface molecule that serves as the T-cell receptor for antigen, analogous to surface Ig on B cells. As in the B-cell system, the size of restriction fragments of the DNA encoding the T-cell receptor gene is specific for a single clone of T cells. Thus, T-cell receptor gene rearrangement is a specific marker for T cells and also a true marker for monoclonality in T cells.

 Oncogene Rearrangements

In addition to rearrangements of antigen receptor genes, hematologic malignancies frequently have specific chromosomal translocations. Cellular oncogenes (genes that can cause malignant transformation when transfected in activated or altered form into cultured normal cells) have been identified in association with some of the more common chromosome translocations that characterize lymphoid malignancies. These translocations can be detected using DNA probes that hybridize to breakpoints on the chromosome carrying the oncogene. Using a technique for amplifying unique DNA segments [polymerase chain reaction (PCR)], rare cells carrying a given translocation can be detected, using probes that span the breakpoint, or using a reverse transcriptase technique to detect RNA produced by the altered or fused gene (reverse transcriptase-PCR). Numeric abnormalities of chromosomes are also common in lymphoid malignancies; these can be detected by fluorescence in situ hybridization, using probes to specific chromosomes.

To the extent to which specific histologic subtypes, prognostic groups, or both of lymphomas are associated with specific gene rearrangements, detection of these rearrangements may prove useful in the characterization of lymphomas. In addition, this technique can potentially be used to detect disseminated or recurrent lymphoma on small biopsy specimens or in the blood. Finally, study of the function of the translocated oncogene is providing clues to the mechanisms of oncogenesis.

USE OF IMMUNOPHENOTYPING AND GENETIC STUDIES IN THE DIAGNOSIS OF LYMPHOID NEOPLASMS

Each of the lymphoid neoplasms has a characteristic morphology, which may be sufficient in a given case to permit diagnosis and classification on morphologic grounds alone. If well-prepared sections are available; thus, most cases of lymphoma can be diagnosed and classified with reasonable certainty on the basis of routine histologic sections alone. However, there are many pitfalls in the histologic diagnosis of malignant lymphoma, and immunophenotyping or, less often, genetic studies can be useful in resolving major differential diagnostic problems. Problems that can be resolved by these techniques include (1) reactive versus neoplastic lymphoid infiltrates; (2) lymphoid versus nonlymphoid malignancies; and (3) subclassification of lymphoma. In a clinical study of the Revised European-American Classification of Lymphoid Neoplasms (REAL), the interobserver reproducibility of experts using the classification was tested, and the contribution of immunophenotype to reproducibility was assessed. For most of the common entities (follicular lymphoma, MALT lymphoma, B-CLL), immunophenotyping was not necessary; however, in some diseases (mantle cell lymphoma, diffuse large B-cell lymphoma) it was helpful, and in all types of T-cell lymphoma it was essential. In a given case, if the morphology is typical of a given entity but the immunophenotypic or genetic features are unusual, the histologic sections should be reexamined; however, the case may still be accepted as an example of the entity suggested by morphologic features. If the morphology is atypical but the immunophenotype and genetic features are classic for a given entity, these features may override morphology in classification. If both the morphology and the immunophenotype are atypical or unclassifiable, then the case is best regarded as unclassifiable or borderline.
TABLE 45.3-2. Immunohistologic and Genetic Features of Common B-Cell Neoplasms

PRINCIPLES OF CLASSIFICATION OF LYMPHOID NEOPLASMS

Revised European-American Classification of Lymphoid Neoplasms from the International Lymphoma Study Group

The International Lymphoma Study Group (ILSG), an informal group of 19 hematopathologists from the United States, Europe, and Asia, adopted a new approach to lymphoma classification in 1993. In this approach, all available information (i.e., morphology, immunophenotype, genetic features, and clinical features) is used to define a disease entity. The relative importance of each of these features varies among diseases, and there is no one gold standard. Morphology is always important, and some diseases are primarily defined by morphology (e.g., follicular lymphoma, angioimmunoblastic T-cell lymphoma, nodular sclerosis Hodgkin's disease), with immunophenotype as backup in difficult cases. Some diseases have a virtually specific immunophenotype [e.g., mantle cell lymphoma, small lymphocytic lymphoma (SLL), anaplastic large cell lymphoma] such that one would hesitate to make the diagnosis in the absence of the immunophenotype. In some lymphomas a specific genetic abnormality is an important defining criterion [e.g., t(11;14) in mantle cell lymphoma, t(8;14) in Burkitt's lymphoma; t(14;18) in follicular lymphoma], whereas others require knowledge of clinical features as well (e.g., nodal vs. extranodal presentation in marginal zone lymphoma and peripheral T-cell lymphomas, and mediastinal location in mediastinal large B-cell lymphoma). The inclusion of clinical criteria was one of the most novel aspects of the ILSG approach. The emphasis on defining real disease entities, rather than focusing on subtleties of morphology or immunophenotype or primarily on patient survival, represented a new paradigm in lymphoma classification.

The ILSG developed a consensus on a list of diseases that its members recognized in daily practice, using a combination of available morphologic, immunologic, and genetic information, and that appeared to be distinct clinical entities. This consensus approach represented the second major departure from previous classifications, most of which represented the work of one or a few individuals. The ILSG recognized that the complexity of the field in the 1990s made it impossible for a single person or small group to be completely authoritative, and also that broad agreement is necessary if the result is to be used by multiple pathologists, even if it requires compromise. The ILSG consensus list of well-defined, real diseases was published in 1994 (Table 45.3-3). Since it represented a revision of current or prior European and American lymphoma classifications (Table 45.3-4), it was called the Revised European-American Classification of Lymphoid Neoplasms. Although its initial publication incited considerable controversy, experience over the intervening years has shown that it can be used by most pathologists, and that the entities it describes have distinctive clinical features, making it a useful and practical classification, despite its apparent complexity.

TABLE 45.3-3. Revised European-American Classification of Lymphoid Neoplasms (1994)

TABLE 45.3-4. Comparison of the Original Revised European-American Classification of Lymphoid Neoplasms with the Kiel Classification and the Working Formulation

World Health Organization Classification of Hematologic Malignancies

Since 1995, members of the European and American Hematopathology societies have been collaborating on a new World Health Organization (WHO) classification of hematologic malignancies. It will use an updated version of the REAL classification for lymphomas (Table 45.3-5) and will expand the principles of the REAL classification to the classification of myeloid and histiocytic neoplasms. The WHO project includes over 50 pathologists from around the world, as well as a Clinical Advisory Committee of more than 30 international expert hematologists and oncologists. Proponents of current classifications (e.g., Working Formulation, Kiel, REAL and French-American-British) are in agreement that the final WHO consensus will replace existing classifications. Thus, it will represent the first true international consensus on the classification of hematologic malignancies.
TABLE 45.3-5. Proposed Updated Revised European-American Classification of Lymphoid Neoplasms/World Health Organization Classification of Lymphoid Neoplasms

Principles of the Revised European-American Classification of Lymphoid Neoplasms/World Health Organization Classification of Lymphoid Neoplasms

The REAL/WHO classification is a list of distinct disease entities, which are defined by a combination of morphology, immunophenotype, and genetic features, and which have distinct clinical features. It recognizes that all of these criteria are at best approximations, and that continued research and experience will be needed to continue to improve the definition of these diseases. Morphology remains the first and most basic approach and is sufficient for both diagnosis and classification in many typical cases of lymphoma. Immunophenotyping and, particularly, molecular genetic studies are not needed in all cases; however, they are useful in difficult cases and improve interobserver reproducibility. It is the availability of these more objective methods that make a consensus on lymphoma classification possible now, while it was impossible in the 1970s, when classification was based purely on subjective morphologic features.

The classification includes all lymphoid neoplasms (i.e., Hodgkin’s disease, NHLs, lymphoid leukemias, and plasma cell neoplasms). Both lymphomas and lymphoid leukemias are included, since both solid and circulating phases are present in many lymphoid neoplasms, and distinction between them is artificial. Thus, B-CLL and B-SLL are simply different manifestations of the same neoplasm, as are lymphoblastic lymphomas and ALLs. In addition, Hodgkin’s disease and plasma cell myeloma are now recognized as lymphoid neoplasms of B lineage and therefore belong in a compilation of lymphoid neoplasms. Immunodeficiency-associated lymphomas are classified according to the basic lymphoma classification; a separate classification of the posttransplant lymphoid proliferations that do not fulfill criteria for lymphoma is also given (Table 45.3-6). Many of the neoplasms recognized in the classification have morphologic variants, clinical subtypes, or both.

TABLE 45.3-6. Categories of Posttransplant Lymphoproliferative Disorders

Clinical Test of the Revised European-American Classification of Lymphoid Neoplasms

An initial criticism of the REAL was that it had not been tested in a clinical study, although it only included diseases that had been previously published and for which the clinical features were known. To address this issue, an international group of oncologists and pathologists devised a clinical study of the classification, in which five expert pathologists reviewed over 1300 cases of NHL at centers around the world. The aims of the study were to (1) see whether the classification could be used in practice; (2) test its interobserver reproducibility; (3) determine the need for immunophenotyping in diagnosis; (4) determine whether the categories of disease identified in the classification were clinically distinctive either at presentation or in outcome; and (5) determine the relative frequency of these diseases in the populations studied.

This study convincingly demonstrated that the classification could be used by expert hematopathologists: Over 95% of the cases with adequate material could be classified into one or another of the categories. The interobserver reproducibility was substantially better than that for other classifications and was better than 85% for most diseases (Table 45.3-7). Immunophenotyping was helpful in some diseases, such as mantle cell lymphoma and diffuse large B-cell lymphoma, in which it improved accuracy by 10% to 15% and was essential for all types of T-cell lymphoma, improving reproducibility from approximately 50% to over 90%. It was not required for many diseases, such as follicular lymphoma, B-SLL, and MALT lymphoma.

The relative frequency of the different B-cell and T/NK-cell lymphomas in the study population was similar to previous patterns reported in the literature (Table 45.3-8). The most common lymphoma was diffuse large B-cell lymphoma, followed by follicular lymphoma; together, these accounted for 50% of the lymphomas in the study. New entities not specifically recognized in the Working Formulation accounted for 27% of the cases: MALT lymphoma, 8%; mantle cell, 7%; peripheral T-cell, 6%; nodal marginal zone, 2%; mediastinal large B-cell, 2%; and anaplastic large T/null-cell, 2%. These results are reassuring, confirming that the majority of the cases that will be encountered by oncologists and pathologists will be only a few subtypes, with which they are already familiar. However, they also underscore the need for recognizing the more recently described entities, which although less common, have important clinical differences. The study also found differences in geographic distribution of the lymphoma types, with follicular lymphoma being more common in North America and western Europe, T-cell lymphomas more common in Hong
The different entities recognized by the classification had significantly different clinical presentations and survivals. For example, diffuse aggressive lymphomas, which would be lumped as intermediate or high grade in the Working Formulation, include diffuse large B-cell lymphoma, mediastinal large B-cell lymphoma, peripheral T-cell lymphoma, and anaplastic large T/null-cell lymphoma. The clinical features at presentation were strikingly different, with a younger age group for mediastinal large T-cell lymphoma and anaplastic large T/null-cell lymphoma, and striking differences in male to female ratios, suggesting that these are distinctive biologic entities (see Table 45.3-9). When overall survivals were analyzed, entities that would have been lumped together as low grade or intermediate/high grade in the Working Formulation showed marked differences in survival, again confirming that they need to be recognized and treated as distinct entities.

A critical finding in this study was that classification is not the only predictor of clinical outcome. Patients with any of these diseases could be stratified into better and worse prognostic groups according to the International Prognostic Index. For example, although patients with follicular lymphoma typically have International Prognostic Index scores of 1 to 3, those patients with scores of 4 or 5 had a predicted median overall survival of only 18 months. Thus, to plan treatment for an individual patient, the oncologist must know not only the diagnosis, but the clinical prognostic factors that influence that patient’s course.

DIFFERENTIAL DIAGNOSIS OF INDOLENT DISSEMINATED LYMPHOMA

For most of the indolent lymphoid neoplasms, both the clinical and pathologic differential diagnosis includes, first, a benign lymphoid proliferation, and second, another type of indolent lymphoma or leukemia. In distinguishing B-CLL/SLL, immunocytoma, or splenic marginal zone lymphoma (SMZL) with villous lymphocytes from reactive lymphocytosis, cytologic criteria can be difficult, since cytologic atypia may be minimal, the only reliable technique is SIg analysis for clonality, usually by flow cytometry. In lymph node or other tissues, the most important distinguishing features include effacement of the architecture and the presence or absence of pseudofollicles. On frozen sections or flow cytometry, demonstration of monotypic SIg and CDS expression are also useful. On paraffin sections, demonstration of a predominance of interfollicular B cells, often with coexpression of CD43, can provide suggestive evidence of B-cell lymphoma.

B-CLL/SLL, immunocytoma, and SMZL must be distinguished from one another and from MALT type lymphoma (in extranodal sites) and mantle cell lymphoma (which can involve blood, bone marrow, and spleen). The presence of pseudofollicles is diagnostic of CLL/SLL; expression of CD23 (frozen sections) and lack of cyclin D1 (paraffin sections) can exclude mantle cell lymphoma, whereas expression of CD5 argues against a diagnosis of MALT type lymphoma, lymphoplasmacytoid lymphoma, or SMZL. By flow cytometry, SIg in CLL is usually weak, whereas it tends to be stronger in the other lymphomas; CD20 or CD103 are also uncommon in B-CLL and more common in some of the other lymphoid leukemias.

 Clinically and pathologically, the differential diagnosis of SMZL also includes hairy cell leukemia. Although the cells in the peripheral blood may resemble hairy cells, the nuclei are usually smaller, with more condensed chromatin, and the villi are polar and less conspicuous than those of hairy cell leukemia. The marrow infiltrate is usually sparse and nodular, in contrast to hairy cell leukemia. The cells may, however, express CD25, CD103, and even TRAP. In the past, many cases were probably diagnosed as atypical hairy cell leukemia or B-CLL. Distinction from lymphoplasmacytoid lymphoma is more problematic; both are CD5– and both may have an M component and evidence of plasmacloy differentiation. The relationship between SMZL/splenic lymphoma with villous lymphocytes and lymphoplasmacytoid lymphoma needs further study.

DIFFERENTIAL DIAGNOSIS OF INDOLENT EXTRANODAL AND NODAL LYMPHOMAS

The most important clinical and pathologic differential diagnosis in indolent lymphomas in either lymph node or extranodal sites is with benign lymphoid hyperplasias. In this situation, if morphologic criteria are insufficient, staining for Ig light-chains is the most useful test to determine clonality.

In the differential diagnosis of gastric MALT type lymphomas, clinical features favoring lymphoma include evidence of a mass, enlargement of gastric folds, or a multinodular appearance to the mucosa. Histologically, the presence of a dense, diffuse infiltrate of marginal zone B cells, with destruction of glands and prominent lymphoplasmacytoid lesions is required for a confident diagnosis. In borderline cases, paraffin section immunoperoxidase stains for cIg may be helpful in approximately 50% of the cases; frozen section immunophenotyping for detection of monotypic SIg is definitive in the rest. If gastric MALT lymphoma is suspected in a patient with Helicobacter infection, it is important not to treat with antibiotics until the diagnosis is ruled in or out by special studies, including rebiopsy if necessary. Antibiotic therapy often causes the lymphoma to regress, but the long-term outcome of these patients is not known, and therefore it is important to know before treatment, whether the patient has lymphoma or just gastritis.

The major differential diagnosis, both clinically and pathologically, for follicular lymphoma is with reactive follicular hyperplasia. The presence of persistent, nontender lymph nodes in an older adult should raise the suspicion of follicular lymphoma, particularly if more than one site is involved. Histologic criteria for this differential diagnosis are well established; in the minority of cases in which a confident diagnosis is not possible on routine sections, demonstration of monotypic SIg on flow cytometry or frozen section, or of bcl-2 expression within the follicles, can confirm the diagnosis. Molecular genetic studies to confirm Ig gene or bcl-2 rearrangement are rarely necessary but can be helpful.

Follicular lymphoma, mantle cell lymphoma, nodal monocyctoid B-cell lymphoma, and extranodal MALT lymphoma must all be distinguished from one another. Clinically, the first three usually involve generalized lymph nodes; however, when mantle cell lymphoma presents with extranodal involvement in the form of lymphomatous polyposis of the gastrointestinal tract, it may be confused with MALT type lymphoma. The presence of widespread disease involving multiple gastrointestinal sites strongly favors mantle cell lymphoma. In other extranodal sites such as the orbit and breast, follicular lymphoma may be more common than MALTomas and should be considered in the differential diagnosis.

Although most cases of indolent nodal lymphoma can be correctly classified by morphologic criteria if good histologic sections are available, immunophenotyping studies can be helpful and are occasionally necessary for correct subclassification (see Table 45.3-2). Expression of CD5 and CD43 and lack of CD23 and (usually) CD10 are useful in distinguishing mantle cell lymphoma from CLL and follicular center lymphoma, respectively. In extranodal sites, CD5 is useful in distinguishing mantle cell lymphoma from MALTomas. Staining for cyclin D1 is potentially the most specific marker for mantle cell lymphoma; Southern blot or PCR studies can also be used to detect the t(11;14).

DIFFERENTIAL DIAGNOSIS OF MATURE (PERIPHERAL) T-CELL LYMPHOMAS

With most peripheral T-cell lymphomas, the clinical and pathologic differential diagnosis includes an atypical reactive process, such as a viral infection, and one of the more common B-cell lymphomas. Because of the great variety of clinical presentations and morphologic features, establishing a diagnosis can be difficult and may require multiple diagnostic procedures. Since there is no reliable immunophenotypic marker for clonality in T cells, molecular genetic analysis is often necessary when the differential diagnosis includes a reactive process. These studies can often be performed on cells isolated from blood or body fluids or from needle-aspiration biopsies, if the initial diagnostic biopsy has not been processed to obtain fresh tissue. An important caveat is excluding a B-cell lymphoma; many B-cell lymphomas of
both low and high grade contain numerous reactive T cells in biopsy specimens. Therefore, simply demonstrating a predominance of T cells does not establish the diagnosis of a T-cell lymphoma; tissues should always be stained for B-cell–associated antigens and Ig.

PRINCIPLES OF MANAGEMENT OF NON-HODGKIN’S LYMPHOMA

The principles of the management of patients with NHL have steadily evolved. The phases of patient management include obtaining an adequate biopsy for an accurate diagnosis, a careful history and physical examination, appropriate laboratory studies, imaging studies, and possibly, further biopsies to determine an accurate stage and to plan therapy. Finally, taking into account factors related to the patient, type of lymphoma, and stage and pace of disease, a treatment recommendation must be made. Treatment choices include no initial therapy, radiotherapy, cytotoxic chemotherapy, a variety of new biologic therapies, and hematopoietic stem cell transplantation.

HISTORY AND PHYSICAL EXAMINATION

A careful history and physical examination is the basis for subsequent studies to determine the extent of the disease and key factor in the therapeutic decision. The duration of symptoms and the pace of progression of the illness should be documented. The physician should not discount the possibility that waxing and waning lymphadenopathy could be related to the lymphoma. Especially in follicular lymphomas, spontaneous regressions are frequent. The presence of specific symptoms known to have an adverse prognosis in patients with some types of lymphoma should be ascertained. These include fevers, night sweats, and unexplained weight loss. Symptoms referable to a particular organ system such as pain in the chest, abdomen, or bones might lead to identification of specific sites of involvement. History of a concurrent illness such as diabetes or congestive heart failure might modify therapeutic decisions.

A careful physical examination can lead to important observations that will direct subsequent care. Obviously, examination of all lymph node–bearing areas and a search for hepatomegaly or splenomegaly are important. Pharyngeal involvement, a thyroid mass, evidence of pleural effusion, abdominal mass, testicular mass, or cutaneous lesions are all examples of findings that might direct further investigations and subsequent therapy. Certain associations of involvement between two organ sites are worth remembering. For example, patients with involvement of Waldeyer's ring often have gastrointestinal involvement, and the converse is also true. These patients usually have mantle cell lymphoma. Patients with paranasal sinus, testicular involvement, and epidermal lymphoma are especially prone to meningeal spread and deserve a diagnostic lumbar puncture and, probably, prophylactic therapy. Patients with one testicle involved are likely to relapse on the opposite side and radiotherapy should be directed to the entire scrotum with this in mind. Patients with ocular lymphoma almost always have dissemination to other parts of the CNS in the absence of prophylactic therapy.

LABORATORY EVALUATION

Laboratory studies should include complete blood count and screening chemistry studies to include renal and hepatic function studies, serum glucose, calcium, albumin, lactate dehydrogenase (LDH), and b2-microglobulin level. Serum protein electrophoresis is frequently appropriate. The purpose of these studies is to aid in determining the prognosis (e.g., LDH, b2-microglobulin, albumin) and identifying abnormalities in other organ systems that might complicate therapy (e.g., renal or hepatic dysfunction).

In addition to the diagnostic biopsy, almost all patients should have a bone marrow aspirate and biopsy performed. The chances of finding bone marrow involvement varies considerably among different subtypes of lymphoma (Table 45.3-9). It is present in approximately 70% of patients with SLL, lymphomas, and mantle cell lymphoma, and even in diffuse large B-cell lymphoma (see Table 45.3-9).126 Bone marrow involvement in patients with follicular and SLL has little prognostic import except when bone marrow is extensively involved and cytopenias or large numbers of circulating lymphoma cells are present. In patients with diffuse large B-cell lymphoma, bone marrow involvement can occur with the large cells or small B cells. Patients with large cell lymphoma in the marrow have a distinctly adverse prognosis, while marrow involvement by small cells has a much less clear effect on prognosis.126

<table>
<thead>
<tr>
<th>Subtype of Non-Hodgkin's Lymphoma</th>
<th>Bone Marrow</th>
<th>Cytogenetic</th>
<th>Extramedullary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follicular</td>
<td>50</td>
<td>10</td>
<td>50</td>
</tr>
<tr>
<td>Small lymphocytic</td>
<td>72</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>High-grade non-Hodgkin's lymphoma</td>
<td>58</td>
<td>10</td>
<td>38</td>
</tr>
<tr>
<td>Mantle cell</td>
<td>40</td>
<td>9</td>
<td>40</td>
</tr>
<tr>
<td>Diffuse large B-cell</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Burkitt's</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Lymphoblastic</td>
<td>10</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Peripheral T-cell</td>
<td>10</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Angioimmunoblastic T-cell</td>
<td>10</td>
<td>10</td>
<td>0</td>
</tr>
</tbody>
</table>

TABLE 45.3-9. Frequency of Extramedial Involvement by Non-Hodgkin's Lymphomas

IMAGING STUDIES

Chest Radiography and Computed Tomographic Scans

Chest radiography and computed tomographic (CT) scans of the chest, abdomen, and pelvis should be performed at the initial evaluation in almost all patients with NHL. Although the chest radiograph is abnormal in less than 50% of patients, identification of hilar or mediastinal adenopathy, parenchymal lesions, or pleural effusions is important and provides an easy method for reevaluation. CT scanning can identify both nodal and extranodal sites of involvement and provides an important approach to monitoring the response to therapy. This approach has largely replaced lymphangiography for the evaluation of retroperitoneal lymphadenopathy. This is partly because of the difficulty of performing lymphangiography. The abdominal and pelvic CT scan can identify mesenteric and retrocrural nodes and is more accurate than the lymphangiogram in determining the dimension of nodal disease. Involvement of intrabdominal organs such as kidney, ovary, spleen, and liver can be identified on CT scans.

Magnetic Resonance Imaging

The value of magnetic resonance imaging (MRI) in the staging of NHL is limited. This technique can be used in lieu of CT scanning in many patients, but its higher cost makes this impractical. MRI is particularly useful in identifying bone and CNS involvement. MRI can suggest meningeal involvement when gadolinium has been used. MRI can also identify bone marrow involvement and might be more sensitive than bone marrow biopsy in this regard. However, it has not yet been accepted as a substitute for bone marrow biopsy.

Nuclear Medicine Studies

The most common nuclear medicine studies used in staging patients with lymphoma are bone scans and gallium scans. Bone scans are rarely used as part of the initial staging studies. They can sometimes be useful in patients who present with or develop back pain during the course of their lymphoma, looking for vertebral involvement and potential spinal cord compression.

Gallium scans are more often used as part of the staging evaluation. This study, because it provides functional rather than purely anatomic information, has potential value in resolving difficulties in determining the response to therapy. To be maximally valuable, high doses of gallium need to be administered and single photon emission CT needs to be used. Gallium scan results are more likely to be positive in patients with aggressive lymphoma such as diffuse large B-cell lymphomas than more indolent lymphoma such as follicular lymphoma, but can be positive in any subtype. Gallium scans are more accurate in evaluating supradiaphragmatic rather
than infradiaphragmatic sites because of colon uptake of the gallium. Unfortunately, this test is most often needed in determining intraabdominal sites of involvement. On rare occasions, technetium liver spleen scans can be helpful in determining the cause of splenic involvement in the patient in whom lymphoma is suspected. One of the differential diagnoses in such patients is occult liver disease. Technetium liver spleen scans that show more uptake in the spleen than liver suggest occult liver disease, and a liver biopsy should be done before considering splenectomy.

**Positron Emission Tomographic Scans**

Positron emission tomographic (PET) scanning has been increasingly applied in staging patients with lymphoma. The specificity and sensitivity of PET scanning seems to be at least that of gallium scanning. The procedure has been more widely adopted in some countries in Europe than in the United States. Despite enthusiastic reports, more large comparative trials assessing the relative merits of PET scanning, gallium scanning, and CT scanning need to be completed before PET replaces previous tests. Merely adding PET scanning to all the previous studies will only increase the cost of therapy.

**STAGING LAPAROTOMY**

Stage laparatomies became popular in the late 1960s and 1970s for evaluating patients with Hodgkin's disease. The same approach was used in patients with NHL. Studies showed that a large proportion of patients with apparently localized follicular lymphoma would be upstaged using staging laparotomy, but this was a less common event in diffuse large B-cell lymphoma. Because of improvements in imaging studies, and the morbidity and potential mortality associated with staging laparotomy, this procedure is rarely appropriate in the initial evaluation of a patient with NHL. However, some patients with NHL are diagnosed at laparotomy, and if the diagnosis is known during the procedure, careful evaluation of other lymph nodes sites and organs by the surgeon can be valuable.

**POLYMERASE CHAIN REACTION FOR EVALUATING MINIMAL RESIDUAL DISEASE**

The use of PCR to expand small numbers of cells with a particular genetic abnormality can allow identification of cells as frequent as 1 in 10\(^{9}\). This has usually been applied to studying blood and bone marrow, but could be applied in other sites. Studies to date have generally focused on the t(14;18) translocation and the associated bcl-2 gene. Several observations have been made. PCR positivity for bcl-2 gene rearrangements can be found in healthy individuals. However, patients with lymphoma in remission who show positive results for bcl-2 gene rearrangement using PCR in the blood or bone marrow are more likely to relapse than patients who do not have this abnormality discovered. Unfortunately, some patients that are positive do not relapse and some patients that are negative do relapse. At present, this approach is probably better considered a research tool. Planning further therapy based only on this abnormality appears risky, until the test is better standardized and the implications of an abnormal finding are better quantified.

**STAGING AND PROGNOSTIC SYSTEMS**

The goal of the initial evaluation of a patient with lymphoma is to provide information that allows intelligent planning of therapy, imparting the prognosis to the patient, and making possible comparisons between patients in clinical trials. The studies to accomplish these goals can be aimed at identifying sites of involvement, characteristics of the patient (i.e., age, performance status, and so forth), or characteristics of the lymphoma (serum LDH, serum b2-microglobulin, growth fraction, and so forth) that predict treatment outcome.

The Ann Arbor Staging System was developed for patients with Hodgkin's disease. This system identifies anatomic sites of involvement by lymphoma and assigns patients into four categories based on the extent of disease dissemination. Patients are also subcategorized by the presence of unexplained fevers, night sweats, or weight loss. This system has a significant effect on prognosis and is important in treatment planning.

The International Prognostic Index for Diffuse Large Cell Lymphoma was developed for patients with diffuse aggressive lymphoma. This index identifies anatomic sites of involvement, symptoms, performance status, serum LDH, serum b2-microglobulin, tumor size, number of sites of involvement, and bone marrow involvement. The bulk of lymphoma is an important prognostic indicator whenever it has been studied. Unfortunately, there has been no consensus on how to best measure bulk. The diameter of the largest mass has been the most common method used, but diameters of 5, 7, and 10 cm have been used by different investigators, making comparisons difficult. Even so, a greater than 10-cm mass, regardless of anatomic stage, is a serious negative prognostic factor. These patients might benefit from adjuvant radiotherapy even if the disease is disseminated.

PET replaces previous tests. Merely adding PET scanning to all the previous studies will only increase the cost of therapy. The procedure has been more widely adopted in some countries in Europe than in the United States. Despite enthusiastic reports, more large comparative trials assessing the relative merits of PET scanning, gallium scanning, and CT scanning need to be completed before PET replaces previous tests. Merely adding PET scanning to all the previous studies will only increase the cost of therapy.

**STAGING AND PROGNOSTIC SYSTEMS**

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**Ann Arbor Staging System**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>No histological evidence of disease.</td>
</tr>
<tr>
<td>B</td>
<td>Histologically confirmed disease of anatomic stage I, II, or III.</td>
</tr>
<tr>
<td>C</td>
<td>Histologically confirmed disease of anatomic stage IV.</td>
</tr>
</tbody>
</table>

Other staging systems have been identified. These have used anatomic stage as identified by the Ann Arbor System, symptoms, performance status, serum LDH, serum b2-microglobulin, tumor size, number of sites of involvement, and bone marrow involvement. The bulk of lymphoma is an important prognostic indicator whenever it has been studied. Unfortunately, there has been no consensus on how to best measure bulk. The diameter of the largest mass has been the most common method used, but diameters of 5, 7, and 10 cm have been used by different investigators, making comparisons difficult. Even so, a greater than 10-cm mass, regardless of anatomic stage, is a serious negative prognostic factor. These patients might benefit from adjuvant radiotherapy even if the disease is disseminated.

At present, the most valuable and widely used system to stratify patients is the International Prognostic Index. This was developed by investigators throughout the world for use in predicting outcome for patients with diffuse aggressive NHLs treated with an anthracycline-containing combination chemotherapy regimen. Five features were found to have approximately an equal and independent effect on survival. These included age, serum LDH, performance status, anatomic stage, and the number of extranodal sites. Because of the approximately equal effect on outcome, the number of abnormalities were simply summed to develop the prognostic index. Thus, patients might have a score of 0 to 5. For patients under the age of 60, a simplified index can be applied that incorporates only anatomic stage, serum LDH, and performance status. This system was initially developed only for patients with diffuse aggressive lymphoma. However, it is clear that it applies to patients with almost all subtypes of NHL.
RESTAGING

After patients have received three or four cycles of the planned treatment regimen or at the completion of the entire regimen, reevaluation should be done to determine the response to therapy. For patients with diffuse aggressive lymphoma, reevaluation after three or four cycles of therapy can add prognostic information. Patients who have a complete response are more likely to be cured than patients who have only achieved a partial response at this point. Achieving a complete remission to therapy is the most important single prognostic factor in patients with NHL. Documenting complete remission is important. It is particularly true since salvage treatment such as high-dose therapy and autologous or allogeneic bone marrow transplantation can sometimes cure disease in patients who fail to respond to initial therapy.

A restaging evaluation typically involves repeating all previous studies with abnormal results to document their current normal results. However, especially in sites of bulky disease, masses do not always completely regress. This does not necessarily mean that patients will have persisting lymphoma. Rebiopsy under these circumstances can be difficult and is not always accurate. If the patient was known to have a positive gallium scan or PET scan at the outset of treatment, a normal result of that test despite a residual mass raises the possibility that only residual fibrous tissue is present. Gallium avidity midtreatment cycle or at the end of treatment is associated with a much higher relapse rate than seen in patients who have negative results on gallium scanning.

SPECIFIC DISEASE ENTITIES

B-CELL NEOPLASMS

Precursor B-Lymphoblastic Leukemia and Lymphoma (Precursor B-Cell Acute Lymphoblastic Leukemia/ Precursor B-Lymphoblastic Lymphoma)

DEFINITION. The definition is a neoplasm of lymphoblasts committed to the B-cell lineage, typically composed of small to medium-sized blast cells with scant cytoplasm, moderately dispersed to dispersed chromatin and indistinct nuclei, involving bone marrow and blood (ALL), and occasionally presenting with primary involvement of nodal or extranodal sites (lymphoblastic lymphoma).

MORPHOLOGY. On smears, lymphoblasts vary from small cells with scant cytoplasm, condensed nuclear chromatin, and indistinct nuclei to larger cells with a moderate amount of cytoplasm, dispersed chromatin, and multiple nuclei. The morphologic pattern is infiltrative rather than destructive, with partial preservation of the subcapsular sinus and germinal centers. A starry-sky pattern may be present, but this is usually less prominent than in Burkitt's lymphoma.

IMMUNOPHENOTYPE. The lymphoblasts are typically positive for TdT and variably express CD19, CD22, CD20, and CD79a, as well as CD45 and CD10. The constellation of antigens defines stages of differentiation, ranging from early precursor (membrane CD19 and CD79a and cytoplasmic CD22) to common ALL (CD10+) to late pre-B ALL (CD20+, cytoplasmic μ heavy-chain). CD34 is expressed on 40%, and coexpression of myeloid antigens is seen in up to 30%, most commonly CD13 (14%), CD33 (16%), or both. CD38 Expression of CD13 and CD33 is associated with rearrangement of ETV6 [t(12;21)(p12;q22),ETV6-CBF12 or TEL-AML1], while expression of CD68, CD15, and CD33 are seen in cases with 11q23/MLL abnormalities.

GENETIC FEATURES. Rearrangement of antigen receptor genes is variable in lymphoblastic neoplasms and may not be lineage specific; thus, precursor B-cell neoplasms may have either or both heavy-chain and TCR γ or β chain gene rearrangements, or may show no rearrangements. (Refer to T-lymphoblastic lymphoma)

POSTULATED NORMAL COUNTERPART. The postulated normal counterpart is precursor B lymphoblast at varying stages of differentiation.

CLINICAL FEATURES AND THERAPY. Precursor B-ALL/lymphoblastic lymphoma occurs most frequently in childhood, with a second peak in the elderly. The outcome is less favorable in infants than 1 year of age and in adults. In addition to cytogenetic features, risk groups are based on age, leukocyte count, sex, and response to therapy. In infants, many cases have translocations involving the MLL gene at 11q23, which is associated with a poor prognosis at any age, older children more often have hyperdiploidy (t(12;21)), which confers a better prognosis (85% to 90% long-term survival). Adult precursor B-ALL is more often associated with the poor-prognosis t(9;22) or t(11q23), and the survival is much poorer than that for childhood cases. Myeloid antigen expression does not seem to be an independent prognostic factor in ALL. Therapy is the same as described for T-lymphoblastic lymphoma.

B-Cell Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

DEFINITION. The definition of B-CLL/SLL is a neoplasm of monomorphic, small round B lymphocytes in the peripheral blood and lymph nodes, admixed with polyclonal B and T lymphocytes and normal monocytes and granulocytes in lymph nodes, usually expressing CDS and CD23. B-CLL is defined as a tissue infiltrate with the morphology and immunophenotype of B-CLL.

MORPHOLOGY. The lymph node infiltrate of B-CLL/SLL is composed predominantly of small lymphocytes with condensed chromatin, round nuclei, and occasionally a small nucleolus. Larger lymphoid cells (polyclonallymphocytes and paraimmunoblasts) with more prominent nuclei and dispersed chromatin are always present, usually clustered in pseudofollicles. In some cases, the cells show moderate nuclear irregularity, which can lead to a differential diagnosis of mantle cell lymphoma.

IMMUNOPHENOTYPE. The tumor cells of B-CLL have faint SIgM, and most coexpress IgD. The antigen specificity of the SIg in many cases has been shown to be against self-antigens, and these antibodies are often broadly specific, so-called cross-reactive idiotypes. Cytoplasmic Ig is detectable in approximately 5% of the cases. B-cell-associated antigens (CD19, CD20, CD79a) are positive, but particularly CD20 may be weak; tumor cells characteristically express both CD5 and CD23. CD23 is particularly useful in distinguishing B-CLL/SLL from mantle cell lymphoma and should be evaluated in every case, if possible.

GENETIC FEATURES. Ig heavy and light-chain genes are rearranged. Most cases (75%) in early studies did not show somatic mutation of their V regions, suggesting that they corresponded to a cell that has not yet undergone antigen selection in the germinal center. However, more recent studies have found up to 40% of the cases to have V region mutations, consistent with exposure to the germinal center. Cases with mutations are reported to express CD38 and to be associated with a better prognosis than cases without mutations or that are CD38−. Approximately 50% of cases have abnormal karyotypes. Trisomy 12 is reported in one-third of the cases with cytogenetic abnormalities and correlates with atypical histology and an agressive clinical course. Abnormalities of 13q are reported in up to 25% of the cases and are associated with long survival. t(11;14) and bcl-1 gene rearrangement have been reported, but many of these cases may be examples of leukemic mantle cell lymphoma; however, at least two clear-cut cases of B-CLL have been reported with bcl-1 gene rearrangement, cyclin D1 overexpression, or both; in both it was associated with an unusually aggressive clinical course. Abnormalities of 1q23 are found in a subset of small cases and are associated with lymphadenopathy and an aggressive course.

POSTULATED NORMAL COUNTERPART. Many cases of B-CLL are thought to correspond to the recirculating CD5+ CD23+ naive B cells, which are found in the peripheral blood, primary follicle, and follicle mantle zone. It has been suggested that they are an anergic, self-reactive CD5+ B-cell subset. Cases that show V region mutations may correspond to a subset of peripheral blood CD5+ IgM- B cells that appear to be memory B cells.

CLINICAL FEATURES. B-CLL accounts for 90% of chronic lymphoid leukemias in the United States and Europe; nonleukemic B-CLL accounts for less than 5% of NHLs. In the International Non-Hodgkin's Lymphoma Classification Project, 6.7% of 1378 cases were diagnosed as B-CLL/SLL. The median age was 65 years, and 83% had stage IV disease. 73% with bone marrow involvement. Generalized lymphadenopathy, hepatosplenomegaly, and extranodal infiltrates may occur. Sixty-four percent had an International Prognostic Index score of 2/3. The 5-year overall actuarial survival was 51%, with a failure-free survival of 25%; for those patients with an International Prognostic Index of 0/1, the overall actuarial survival was 76%, whereas for those with an International Prognostic Index of 4/5 it was only 38%. Thus, the extent of the disease at the time of diagnosis is the best predictor of survival; however, chromosomal abnormalities and immunophenotype may also have
Patients with SLL can present with hypogammaglobulinemia or develop it over the course of the illness. The presence of hypogammaglobulinemia is associated with an increased incidence of infections and can be managed in some patients with intermittent gamma globulin injections. Polyclonal or monoclonal hypergammaglobulinemia can also be seen. Autoimmune hemolytic anemias can be seen in patients with SLL and are particularly likely to develop in patients treated with fludarabine. Autoimmune thrombocytopenia is not rare. Autoimmune neutropenia and pure red cell aplasia are unusual.

THERAPY. Localized SLL is unusual and was seen in only 4% of patients in a large series. The rare patient who presents in this manner could be treated with local radiotherapy. Such patients should have their slides reviewed to make certain they do not have a MALT lymphoma.

Some patients with disseminated SLL/chronic lymphocytic leukemia have a slowly progressive or stable disorder that does not require therapy. The traditional treatment for this lymphoma has been oral chlorambucil or oral cyclophosphamide. However, it is now clear that fludarabine is the most active single agent. Several randomized trials have been completed. One study with 544 patients randomized received fludarabine, chlorambucil, or a combination of both drugs. Patients who failed to respond to an individual drug were crossed over to the other arm. The overall response rate (70% vs. 43%) and complete response rate (27% vs. 3%) favored fludarabine over chlorambucil. Although progression-free survival also favored fludarabine, there was no difference in overall survival. Another randomized trial studied 695 patients and compared fludarabine with anthracycline-containing combinations. Fludarabine had a superior response rate. It appears that combinations including fludarabine and cyclophosphamide are also active and might be more active than fludarabine alone.

Patients with SLL/chronic lymphocytic leukemia can respond to monoclonal antibody therapy using rituximab (anti-CD20) and Campath-1 (anti-CD52). However, the response rate to rituximab appears to be on the order of 20%, perhaps because of the lower level of expression of CD20 than seen in follicular lymphoma. Combination chemotherapy using CHOP or FND produces significant response rates in SLL, but the patients almost always relapse. High-dose therapy and autologous transplantation have both been used in fairly small numbers of patients. It appears that autologous transplantation can probably be curative. In general, principles of therapy of SLL apply to patients with lymphoplasmacytic lymphoma.

**Lymphoplasmacytic Lymphoma (with or without Waldenström's Macroglobulinemia)**

**DEFINITION.** Lymphoplasmacytic lymphoma is defined as a neoplasm of small B lymphocytes, plasmacytoid lymphocytes, and plasma cells, involving bone marrow, lymph nodes, and spleen, lacking CD5, usually with a serum monoclonal protein with hyperviscosity or cryoglobulinemia. Plasmacytoid variants of other neoplasms are excluded. The name, lymphoplasmacytoid (REAL) has been changed to lymphoplasmacytic (WHO).

**MORPHOLOGY.** The tumor consists of a diffuse proliferation of small lymphocytes, plasmacytoid lymphocytes, and plasma cells, with variable numbers of immunoblasts. In lymph nodes, sinuses are open and may contain histiocytes reacting to secreted periodic acid–Schiff-positive Ig. In the spleen, both red and white pulp is colonized. The bone marrow is usually infiltrated, but in some cases may be colonized by diffuse or nodular and is often interstitial and rather subtle. It is usually less massive than that of B-CLL and contains plasma cells and plasmacytoid cells in addition to small lymphocytes. Peripheral blood involvement is usually less prominent than in CLL, and the cells often have a plasmacytoid appearance.

**IMMUNOPHENOTYPE.** The cells have surface and cytoplasmic (some cells) Ig, usually of IgM type, usually lack IgG, and strongly express B-cell–associated antigens (CD19, CD20, CD22, and CD79a). The cells are CD5–, CD10–, CD23–, CD43–, CD11c–, usually cIg– in addition to small lymphocytes. Peripheral blood involvement is usually less prominent than in CLL, and the cells often have a plasmacytoid appearance.

**GENETIC FEATURES.** Ig heavy- and light-chain genes are rearranged, and V region genes show somatic mutations, suggesting that, in contrast to B-CLL, these cells arise from a population of B cells that have undergone antigen–B-driven selection.

**POSTULATED NORMAL COUNTERPART.** The postulated normal counterpart is a peripheral B lymphocyte stimulated to differentiate to a plasma cell, possibly corresponding to the primary immune response to antigen, or to a post–germinal center cell that has undergone somatic mutation but not heavy-chain class switch.

**CLINICAL FEATURES AND THERAPY.** Lymphoplasmacytic lymphoma made up only 1.2% (16 of 1378) of the cases in the REAL clinical study. Similar to B-CLL/SLL, the median age was 63 years and 53% were women; most (73%) had bone marrow involvement. Sixty-nine percent had an International Prognostic Index of 2/3. Lymph node and splenic involvement are common. A monoclonal serum paraprotein of IgM type, with or without hyperviscosity syndrome (Waldenström's macroglobulinemia), is present in most patients as well as with B-CLL, the paraprotein may have autoantibody or cryoglobulin activity.

Most cases of mixed cryoglobulinemia have been shown to be related to HCV infection, even in patients who have demonstrable B-cell lymphoma in the bone marrow. Treatment of patients with HCV and cryoglobulinemia with interferon to reduce viral load has been associated with regression of the lymphoma. HCV infection has also been documented in patients with B-cell lymphoma without cryoglobulinemia, most commonly in MALT type mononuclear B lymphomas and in lymphomas of the salivary gland and liver (two sites of chronic viral infection). HCV is an RNA virus that cannot integrate into the host genome, but it does infect lymphocytes, and viral proteins have been detected in lymphoid cells in these patients. It is not clear at this point whether HCV has transforming potential, or whether these neoplasms are antigen driven, similar to MALT type lymphomas.

The clinical course of PLP is indolent; in some European series its has been reported to be more aggressive than typical B-CLL. Another study, 5-year overall survival (58%) and failure-free survival (25%) were identical to that of CLL/SLL. The traditional therapy for this disorder has been chlorambucil with or without prednisone. Anthracycline-based combination chemotherapy has not been shown to be more effective. However, fludarabine and cladribine are active as single agents. Combinations of fludarabine and cladribine are now being studied.

**Extranodal Marginal Zone B-Cell Lymphoma (Low-Grade B-Cell Lymphoma of Mucosa-Associated Lymphoid Tissue)**

**DEFINITION.** Extranodal marginal zone B-cell lymphoma is defined as an extranodal lymphoma consisting of heterogeneous small B cells, including marginal zone (centrocyte-like) cells, monocytoid cells, and small lymphocytes in varying proportions, and scattered immunoblastic and centroblast-like cells, with plasma cell differentiation in 40% of the cases. The infiltrate is in the marginal zone of reactive B-cell follicles and extends into the follicular region.

**MORPHOLOGY.** Extranodal marginal zone B-cell (MALT) lymphoma reproduces the morphologic features of normal MALT. It is characterized by a polymorphous infiltrate of small lymphocytes, marginal zone (centrocyte-like) B cells, monocytoid B cells, and plasma cells, as well as rare large basophilic blast cells (centroblast- or immunoblast-like). Reactive follicles are usually present, with the neoplastic marginal zone or monocytoid B cells occupying the marginal zone, the follicular region, or both; occasional follicles may be colonized by marginal zone or monocytoid B cells. In epithelial tissues, the marginal zone B cells typically infiltrate the epithelium, forming so-called lymphoepithelial lesions. While blast cells are typically present, they are by definition in the minority. Clusters or sheets of blasts sufficiently large to warrant a diagnosis of large cell lymphoma are associated with a worse prognosis. In these cases, a separate diagnosis of diffuse large B-cell lymphoma should be made. The term high-grade MALT lymphoma should be avoided for large B-cell lymphomas in MALT sites, since it may lead to inappropriate treatment with antibiotics instead of aggressive antilymphoma therapy.

**IMMUNOPHENOTYPE.** The tumor cells express Ig (M greater than G than greater than A), lack IgD, and 40% to 60% have monotypic plasmacytoid Ig, indicating plasmacytoid differentiation. They express B-cell–associated antigens: CD19, CD20, CD22, and CD79a) and are usually negative for CD5 and CD10. Immunophenotyping studies are useful in confirming malignancy (light-chain restriction) and in excluding B-CLL (CD5+), mantle cell (CD5+), and follicle center (CD10+ CD43–, CD11c–, usually cIg–) lymphomas.

**GENETIC FEATURES.** Ig genes are rearranged, and the variable region has a high degree of somatic mutation, as well as intron-exon diversity consistent with a post–germinal center stage of B-cell development. Ig heavy-chain variable regions in the analyzed cases are those often found in autoantibodies.
The postulated normal counterpart is a post–germinal center B memory cell with capacity to differentiate into marginal zone, Sjögren’s syndrome, or when another low-grade B-cell lymphoma (follicular, mantle cell) is present in the same node.

DEFINITION. MALT lymphomas can also be disseminated and present at an advanced stage in approximately one-third of cases.

The disease known as Mediterranean abdominal lymphoma, a heavy-chain disease, and immunoproliferative small intestinal disease, which occurs in young adults in eastern Mediterranean countries, is another example of a MALT type lymphoma that may respond to antibiotic therapy in its early stages.

THERAPY OF MUCOSA-ASSOCIATED LYMPHOID TISSUE LYMPHOMAS.

Nodal and Extrabdominal Marginal Zone B-Cell Non-Hodgkin’s Lymphoma (Mucosa-Associated Lymphoid Tissue).

One-half or more of patients with gastric MALT have the indolent MALT type. The optimal treatment of gastric MALT lymphoma remains to be determined. Gastric MALT lymphoma is frequently associated with chronic gastritis and Helicobacter pylori infection. Based on clinical observations, it has been postulated that Helicobacter pylori infection leads to the accumulation of MALT in the stomach, and that gastric MALT lymphomas arise within this acquired MALT tissue. This has prompted speculation that eradication of the Helicobacter pylori infection might lead to tumor regression. Promising early results have been seen with the use of antibiotics for gastric MALT NHL. In one study from the German MALT Lymphoma Group, 33 patients with low-grade MALT were treated with antibiotics. At 1-year median follow-up more than 70% of patients remained in complete remission. However, in a follow-up study, 23 of 31 patients in complete continuous remission (median follow-up, 16 months) had a monoclonal B-cell population on PCR analysis, leaving open the question of durability of complete response after antibiotics. Nonetheless, the standard treatment for patients with gastric MALT who are positive for Helicobacter pylori is antibiotics and follow-up endoscopy 3–6 months later. Patients who have a complete response should be followed without further treatment. Patients who have a partial response and remain Helicobacter pylori positive should receive a second course of antibiotics before proceeding to more definitive treatment.

Patients who are negative for Helicobacter pylori may be less likely to respond to antibiotics than Helicobacter pylori-positive patients; initial treatment of Helicobacter pylori-negative patients with antibiotics remains under study. For patients who have persistent disease after antibiotics, local regional irradiation therapy is the treatment of choice. Good results have been obtained with total or partial gastrectomy; however, this approach has been associated with long-term morbidity. Local and regional radiation through the three-field approach (anterior and two lateral fields to minimize radiation to the left kidney) provides local control and relief of symptoms in greater than 90% of patients. Although more information is needed, 30 Gy appears sufficient to control disease in most patients.

More than 80% of patients with pulmonary NHL have indolent histology; nearly 90% of these are MALT. The 5-year survival of patients with pulmonary MALT is greater than 90% in the initial treatment setting. However, for patients with recurrent disease, the response rate to low-dose RT has the potential to provide durable remissions. Gastrointestinal MALT is less common than gastric MALT. Approximately 25% of patients with gastrointestinal NHL have MALT. Few data exist on the success of treatment of these patients. The most common sites are the jejunal and the ileocecal.

Patients with MALT in the salivary glands may have a history of Sjögren’s disease. Because these patients often have symptoms of mild xerostomia and low doses of RT worsen the xerostomia, we recommend that the radiation fields be limited to the ipsilateral salivary gland region and draining nodes to spare as much of the remaining salivary tissue as possible.

Lymphomatous involvement occurs in the orbit and in the conjunctiva with approximately equal frequency, accounting for between 5% and 14% of all extranodal presentations. These locations should be considered individually as they are often histologically distinct and have different natural histories. Conjunctival lymphoma tends to be localized, but may be associated with advanced disease. Due to its infiltrative nature, conjunctival lymphoma recurs with a high frequency following surgical excision alone. Surgery is used for diagnosis, but local RT to the entire conjunctiva is the definitive treatment of choice. Treatment of conjunctival lymphoma can be accomplished with either electrons or with photons. We generally use electrons as the lens can be protected with daily placement of a tungsten eyelid.

Dissemination is usually to lymph nodes but can involve other extranodal nodes. Patients with widespread MALT lymphoma should probably be treated in a manner similar to that described for follicular lymphoma.

Nodal Marginal Zone B-Cell Lymphoma

DEFINITION. Nodal marginal zone B-cell lymphoma is defined as a primary nodal lymphoma with features identical to lymph nodes involved by MALT lymphoma, but without evidence of extranodal disease. Monoclonoid B cells may be prominent. This diagnosis should not be made in patients with MALT lymphoma at other sites, Sjögren’s syndrome, or when another low-grade B-cell lymphoma (follicular, mantle cell) is present in the same node.

MORPHOLOGY. Tumors with morphologic features identical to those described for extranodal marginal zone (MALT type) lymphoma have occasionally been reported...
with isolated or disseminated nodal involvement, in the absence of extranodal disease. Most reported cases of nodal monocytoid B-cell lymphoma have been in patients with Sjögren’s syndrome and thus represent nodal involvement by a MALT type lymphoma of the salivary gland. Others have been reported as composite lymphomas with other historically low-grade lymphomas, chiefly follicular lymphoma. In these cases, however, this phenomenon represents focal differentiation to marginal zone or monocytoid B cells and not a true composite lymphoma; these cases should be classified as follicular lymphoma (see Follicular Lymphoma, later in this chapter). Nonetheless, there are occasional cases that do not appear to be associated with other types of lymphoma. Two morphologic lymph node patterns have been identified: cases that resemble MALT lymphoma and cases that more closely resemble splenic marginal zone lymphoma. Those that resemble MALT lymphoma show aggregates of monocytoid B cells in a parafollicular, perivascular, and perisinusoidal distribution, with preserved germinal centers and mantle zones. Those that resemble SMZL have infiltrates of marginal zone cells surrounding reactive follicles with germinal centers, but with attenuated mantle zones.  

**IMMUNOPHENOTYPE AND GENETIC FEATURES.** The cases that resembled splenic marginal zone lymphoma are reported to express IgD and to lack CD5, CD23, and cyclin D1. Those that resemble MALT lymphoma are IgD– and have an immunophenotype identical to those of extranodal marginal zone B-cell lymphoma (MALT).  

**POSTULATED NORMAL COUNTERPART.** The postulated normal counterpart is nodal monocytoid or marginal zone B cell.  

**CLINICAL FEATURES AND TREATMENT.** This is a rare disorder, accounting for 1% of the cases in the international study of the REAL. The patients presented with isolated or generalized nodal disease; bone marrow was involved in 30%; rarely, peripheral blood may be involved. However, when peripheral and blood involvement appears, it seems to have a poor prognosis. The cases reported by Campo and associates were predominantly localized at the time of the diagnosis. Although elderly women with vocalized disease have been reported much more frequently, the disease appears in both genders, and patients with advanced stage are not infrequent. Transformation to large cell lymphoma occurs and has a poor prognosis. Of those that resembled MALT lymphoma, 44% of those with follow-up had an extranodal lymphoma, whereas those resembling SMZL did not. The overall and failure-free survivals appear to be similar to those of follicular or SLLs. The optimal therapy for patients with monocytoid B-cell lymphoma is not known. Patients are frequently treated with regimens that are used for follicular lymphoma.  

**Splenic Marginal Zone Lymphoma with or without Villous Lymphocytes**  

**DEFINITION.** Splenic marginal zone lymphoma is defined as a neoplasm of small B lymphocytes that surround and replace splenic white pulp germinal centers, merging with an outer marginal zone of larger cells with pale cytoplasm admixed with large transformed blasts; both small and large cells infiltrate red pulp, often with villous lymphocytes in the peripheral blood.  

**MORPHOLOGY.** In the spleen, the neoplastic cells occupy both the mantle and marginal zone of the splenic white pulp, usually with a central residual germinal center, which may be either atrophic or hyperplastic. Both the mantle and marginal zones are expanded. The cells in the mantle zone are small, with slight nuclear irregularity and scant cytoplasm, while those in the marginal zone have more dispersed chromatin and abundant pale cytoplasm, resembling marginal zone cells, and are admixed with centroblasts and immunoblasts. The red pulp is also involved, with both a diffuse and micornodular pattern and sinus infiltration. Epithelioid histiocytes may be present singly or in clusters and, particularly in the bone marrow, may give rise to the differential diagnosis of an infectious process. Splenic hilar lymph nodes are often involved; the neoplastic cells form vague nodules, often without a central germinal center, and a marginal zone pattern may or may not be present. Lymph nodes are often present in the peripheral blood they often have abundant lymphomatoid proliferations with small surface villous projections or may appear plasmacytoid.  

**IMMUNOPHENOTYPE.** The tumor cells are IgM+, IgD+, CD5−, CD10−, CD43−, CD23−, express B-cell antigens (CD19, CD20, CD22) and bcl-2, and lack CD11c and CD25. In the majority of cases, lack of CD5 serves to distinguish this disorder from B-CLL, and lack of CD103 and CD25 are useful in distinguishing it from hairy cell leukemia. The cells are cyclin D1 negative by immunoperoxidase staining.  

**GENETIC FEATURES.** Analysis of the Ig variable region genes indicates a high degree of somatic mutation, consistent with a post–germinal center stage of B-cell development. More recently, ongoing mutations of V region genes, similar to germinal center cells, has been reported. Bcl-2 is germline. Early reports that t(11;14)(q21;q32), bcl-1 rearrangement, and cyclin D1 overexpression were common are now thought to have reflected inclusion of cases of leukemic mantle cell lymphoma. Trisomy 3, found in nodal and extranodal marginal zone lymphoma, is detected in only a small number of cases.  

**POSTULATED NORMAL COUNTERPART.** The postulated normal counterpart is post–germinal center, memory B cell of splenic type.  

**CLINICAL FEATURES AND TREATMENT.** Splenic marginal zone lymphoma accounts for only 1% to 2% of chronic lymphoid leukemia found on bone marrow examination, but up to 25% of low-grade B-cell neoplasms in splenectomy specimens. It may make up the majority of chronic B-cell leukemia and low-grade splenic lymphomas that do not fit the defining criteria of B-CLL, lymphoplasmacytoid lymphoma, mantle cell lymphoma, follicular lymphoma, or hairy cell leukemia. Patients typically present with weakness, fatigue, or symptoms related to splenomegaly. Physical examination revealed splenomegaly in almost all patients, hepatomegaly in up to 40% of patients, but lymphadenopathy is rare. Lymphocytosis is a uniform finding, but extreme lymphocytosis is unusual. Anemia and thrombocytopenia are present in a minority of patients. In some series more than one-half of the patients have been shown to have a monoclonal Ig. Although most commonly seen in elderly men, the disease can be seen in both genders and in young patients. Although the disease is usually confined to the spleen, bone marrow, and blood, unusual sites of involvement such as leukemic meningitis have been described. Most patients have an indolent course and require no immediate therapy or respond to splenectomy. However, transformation to a large cell lymphoma with an aggressive course can be seen in some patients. For patients in whom splenectomy is inappropriate, splenic radiation can be an alternative. Oral alkylating agents appear to be marginally effective. One report described four patients who achieved a complete remission with fludarabine.  

**Follicular Lymphoma**  

**DEFINITION.** Follicular lymphoma is a lymphoma of follicle center B cells (centrocytes and centroblasts), which has at least a partially follicular pattern.  

**MORPHOLOGY.** The tumor is composed of follicle center cells, usually a mixture of centrocytes (cleaved follicle center cells) and centroblasts (large noncleaved follicle center cells). Centrocytes typically predominate; centroblasts are usually in the minority, but by definition are always present. Rare lymphomas with a follicular growth pattern consist almost entirely of centroblasts. Occasional cases may show plasmacytid differentiation or foci of marginal zone or monocytoid B cells. The proportion of centroblasts varies from case to case, and the clinical aggressiveness of the tumor increases with increasing numbers of centroblasts. Numerous criteria have been proposed for grading follicular lymphoma. The WHO Classification is adopting the cell-counting method of Mann and Berard (Table 45.3-12). In addition to typical follicular lymphomas, two variants are recognized whose relationship to follicular lymphoma remains controversial: cutaneous follicle center lymphoma and diffuse follicle center lymphoma.

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**Table 45.3-12. Follicular and Mantle Cell Lymphomas: Grading and Variants**  

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**Follicular Lymphoma**  

**Grades**  

<table>
<thead>
<tr>
<th>Grade</th>
<th>B-5-10-centrocytes per high-power field</th>
<th>Grade</th>
<th>B-5-10-centrocytes per high-power field</th>
<th>Grade</th>
<th>B-5-10-centrocytes per high-power field</th>
<th>Grade</th>
<th>B-5-10-centrocytes per high-power field</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Lymphoid proliferation</td>
<td>2</td>
<td>Intermediate</td>
<td>3</td>
<td>Monocytoid</td>
<td></td>
<td></td>
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</tbody>
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**Mantle Cell Lymphoma**  

**Tumor:** Blastic.
IMMUNOPHENO TYPE. The tumor cells of follicle center lymphoma are usually Stg+; approximately 50% to 60% express IgM; approximately 40% express IgG; and rare cases express IgA. The tumor cells express pan-B-cell–associated antigens, approximately 60% are CD10+, and they are CD5–, CD23–/+, CD23– (most cases), and CD11c–. Tightly organized mesh works of FDCs are present in follicular areas. 281 Most cases are bcl-2+; and, nuclear bcl-6 is expressed by at least some of the neoplastic cells. 282 The Ki-67+ fraction is lower than that of reactive follicles.

GENETICS. Ig heavy and light-chain genes are rearranged, and analysis of the ig variable region genes shows that most cases have extensive somatic mutations and a high frequency of intrachromal diversity, indicating ongoing mutations, similar to normal germinal center cells. 283 Most cases are bcl-2+ and, nuclear bcl-6 is expressed by at least some of the neoplastic cells. 282 The Ki-67+ fraction is lower than that of reactive follicles.

POSTULATED NORMAL COUNTERPART. The postulated normal counterpart is germinal center B cells, both centrocytes (small cleaved follicular center cells) and centroblasts (large noncleaved follicular center cells).

CLINICAL FEATURES. Follicular lymphoma is the second most common lymphoma in the United States and western Europe, accounting for 20% of all NHLs and up to 70% of low-grade lymphomas reported in American and European clinical trials. 284,285 Thus, our understanding of the clinical features and response to treatment of low-grade lymphoma is essentially that of follicular lymphoma. Follicular lymphoma affects predominantly older adults, with a slight female predominance. 286 Most patients have widespread disease at diagnosis, usually predominantly lymph nodes, but also spleen, bone marrow, and occasionally peripheral blood or extranodal sites. Despite the advanced stage, the clinical course is generally indolent, with median survivals in excess of 8 years; however, the disease is not usually curable with available treatment. In the international study of the REAL, the few patients (7%) with International Prognostic Index scores of 4/5 have a much worse prognosis, with a median survival of only 1 year. 287 In that study, cases with monocytoid B-cell differentiation had a worse prognosis than other cases. 288

THERAPY OF LOCALIZED FOLLICULAR LYMPHOMA. There are a number of questions regarding RT and follicular grade 1 and 2 NHL. Is follicular grade 1 and 2 NHL curative with RT alone? (Yes.) What is the frequency of recurrence after 10 years? (Only approximately 10%) Are there prognostic factors for recurrence? (Yes, age is the most influential.) What is the extent and dose of RT needed? What are the late effects of treatment? What is the role of CT in early-stage low-grade NHL? Many published studies have demonstrated the efficacy of RT in the treatment of clinically staged patients with localized follicular small cleaved cell NHL. Patients with early-stage disease are curable with local regional irradiation. The updated series from Stanford University details the results of RT in 177 patients treated from 1961 to 1994. 287 Out of 177 patients, 73 were stage I and 104 had stage II disease. Staging laparotomy was performed in 25% of patients and 20% of patients had extranodal presentations. Total nodal irradiation (TNI) and subtotal nodal irradiation were given to 41 patients, and involved-field or extended-field irradiation was delivered to 133 patients. Staging laparotomy and TNI were used in the early years of the study. Histology was follicular grade 1 in 57% of cases and follicular grade 2 to 3 in 43% of patients. The median follow-up was 7.7 years. The 10-year, 15-year, and 20-year survivals were 64%, 44%, and 35%, respectively. The 10-year, 15-year, and 20-year disease-free survivals were 44%, 40%, and 37%, respectively. Only 5 of 47 patients in remission for 10 years or longer have relapsed at longer intervals. This study demonstrates that a substantial percentage of patients with early-stage follicular small cleaved cell NHL never have recurrence of disease following local regional irradiation.

Several other series using local regional radiation demonstrate similar results and are shown in Table 45.3-13. All the series demonstrate greater than a 40% freedom from treatment failure at 10 years. Median survival ranges from 13 to 16 years in the studies. Prognostic factors for relapse were analyzed. 287–290,292–295 Age in all studies was a significant adverse factor for relapse. Although most studies use age under and over 60, the British National Lymphoma Investigation (BNLI) study found no difference in relapse in patients in their 50s or 60s and only age 70 or greater was an adverse factor. 291 Other significant but less important prognostic factors for increasing recurrence risk include extranodal disease, female gender, and stage II disease. There appears to be little difference in outcome between follicular grade 1 and follicular grade 2 disease.

<table>
<thead>
<tr>
<th>TABLE 45.3-13. Radiation Therapy Alone for Early-Stage, Low-Grade Follicular Non-Hodgkin's Lymphoma</th>
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| The techniques of RT (field arrangement and size and dose) in the treatment of NHL are guided by the histologic subtype, the stage of disease, and the patterns of failure. Early-stage indolent lymphomas treated with RT alone have been shown to relapse in extranodal sites or in nodal sites distant from the radiation fields when involved-field or extended-field RT has been used. This observation led some to recommend TLI for patients with follicular small cleaved cell NHL. Several factors, however, argue against the use of such extensive RT for patients with early-stage indolent disease. On multivarient analysis, for patients with stage I to II disease, there is no evidence that the use of extended-field or TLI provided for a survival advantage compared with involved-field or regional irradiation in the Stanford study. There are concerns for increased toxicity with larger RT fields and the possibility that subsequent treatment, if needed, will be compromised as more than 50% of stage I to II patients eventually develop a recurrence and require more aggressive treatment. In addition, there is a high conversion rate of follicular small cleaved cell NHL to a more aggressive histology over time, requiring treatment with chemotherapy. 288–291 Prior treatment with TLI may compromise marrow reserve and limit subsequent multigagent chemotherapy given either for recurrent indolent NHL or for NHL transformed to a more aggressive histology. Also, there appears to be an increased risk of late complications including large-field irradiation. 292 There are no large prospective or randomized studies evaluating the dose and field size of RT for patients with stage I to II follicular small cleaved cell NHL. However, most centers use radiation doses between 30 and 40 Gy, and either involved-field or regional irradiation. Current recommendations include the use of regional RT fields. This consists of irradiating the involved nodal region plus one additional uninvolved region on each side of the involved nodes. For example, the treatment field for lymphoma of the inguinal nodes would include the ipsilateral femoral, inguinal, and external iliac nodes. The treatment of a stage I lymphoma of the right inguinal nodes would include the ipsilateral axilla, supraclavicular, and cervical nodes. The cervical, supraclavicular, oropharyngeal, and nasopharyngeal nodes would be irradiated in patients with involvement of Waldeyer's ring. The recommended dose for patients with follicular small cleaved cell NHL is 3000 to 3600 cGy, with a boost to areas of initial involvement to 36 to 40 Gy. When there is a possibility of significant morbidity from treatment, such as long-term xerostomia from irradiation of the salivary glands, lower doses to the uninvolved nodal areas are recommended (i.e., 25 to 30 Gy).

The role of combination chemotherapy in the management of early-stage follicular lymphoma is unclear. At least three randomized studies conducted in the 1970s failed to demonstrate that non–adriamycin-containing combination chemotherapy regimens plus RT were superior to RT alone. 289–292,294 A more recent BNLI study randomized 148 patients to receive either RT alone or RT plus chlorambucil chemotherapy. 293 There were no differences in freedom from recurrence or survival between the groups. A single-arm study of 91 stage I and II patients treated at the M. D. Anderson Cancer Center with cyclophosphamide, vincristine, and prednisone (COP) or cyclophosphamide, doxorubicin, vincristine, and prednisone-bleochemotherapy in addition to RT demonstrated an improved freedom from recurrence compared with historic controls but no overall survival differences. 294–296 In part, the choice of therapy may lie in the careful assessment of prognostic factors. Most patients with Ann Arbor clinical stage I or II follicular small cleaved cell and follicular mixed lymphomas should have a good prognosis following local regional RT for patients whose prognosis is less certain, such as patients with stage II disease with multiple sites of involvement or bulky nodes, or patients with follicular large cell histology, chemotherapy followed by involved-field irradiation may provide more durable remissions.
The optimal treatment strategy for patients with advanced-stage follicular lymphoma is controversial. Treatment has followed one of two divergent approaches: an aggressive approach that may include extensive RT, combination chemotherapy, or both; and a conservative approach that consists of initial treatment followed by a palliative single-agent chemotherapy or involved-field radiotherapy when treatment is needed. Although many years of clinical investigation have failed to prove that immediate aggressive therapy improves survival compared with conservative therapy, the median survival from diagnosis in patients with stage III and IV disease has prompted the continuation of aggressive treatment approaches. Despite the indolent nature of the follicular lymphomas, most patients ultimately die of their disease. Of 147 previously untreated patients enrolled at St. Bartholomew's Hospital in various protocols, ranging from no initial therapy to conservative treatment with single alkylating agents, only 53 of 147 patients remain alive; 94 patients have died, and only 18 patients died from causes unrelated to lymphoma.

In the treatment of patients with stage III and IV follicular lymphoma serves two roles, as palliative treatment and as part of a potentially curative approach in clinical trials. RT has much to offer as a palliative approach. For patients with isolated disease that has returned after remission or has not responded as well as other sites to chemotherapy, involved-field irradiation can allow for patients to go significant periods of time without the need for additional combination therapy. In addition, follicular lymphoma can produce troubling symptoms through bone or spine involvement, through pressure on peripheral nerves, by disfigurement via large neck or axillary nodes, by intraorbital involvement, and through many other mechanisms. Follicular lymphoma is sensitive to RT, and often nodes resistant to chemotherapy begin to shrink after four to five radiation treatments. Sometimes even a large volume of lymph nodes can be encompassed because the low doses of radiation needed results in minimal toxicity to normal tissues.

As a curative approach, TLI combined with chemotherapy has been used for the treatment of stage III patients in past studies. McLaughlin and colleagues reported on the use of CHOP chemotherapy and TLI in 74 patients with follicular lymphomas. The relapse-free survival at 5 years was 52%. This study did not provide sufficient evidence to advise in favor of this type of therapy. In an another study with this approach, the National Cancer Institute initiated a pilot randomized controlled trial of intensive versus standard-dose therapy (no initial therapy) with aggressive combined modality therapy with ProMACO/MOPP chemotherapy followed by low-dose (24 Gy) total lymphoid RT. Eighty-nine patients were randomized. The disease-free survival was significantly higher in the combined modality therapy group at 4 years (51% vs. 12%); however, no differences in overall survival were seen. As these studies have failed to show a survival advantage for an initial aggressive approach in the management of patients with advanced-stage indolent lymphomas, new high-dose chemotherapy approaches are being developed that for the most part do not include the use of TLI.

When a decision is made to treat a patient with disseminated follicular lymphoma using cytotoxic chemotherapeutic agents, a wide variety of choices is available. These include single-agent chlorambucil, cyclophosphamide, or fludarabine, or popular combination chemotherapy regimens such as cyclophosphamide, vincristine, and prednisone (CVP), CHOP, and fludarabine, mitoxantrone, and dexamethasone (FND). Each of these approaches produces objective responses in a high proportion of patients with previously untreated follicular lymphoma. In general, complete responses occur more rapidly with combination chemotherapy regimens, but it is unclear that the ultimate treatment result is superior with combinations. Approximately 20% of complete responders remain in remission for longer than 10 years.

Patients with follicular lymphoma who are followed without therapy sometimes have spontaneous regressions that can be complete. Spontaneous regressions appear most frequently in patients with predominantly follicular small cleaved cell lymphoma and least frequently in patients with follicular large cell lymphoma. Interferon-a has long been known to be an active drug in the treatment of patients with follicular lymphoma and has an objective response rate of 30% to 55% when used as a single agent with relapsed disease. The value of adding interferon to standard combination chemotherapy regimens has been tested in a number of clinical trials. The dose and duration of administration of interferon-a varied among these studies. A significant increase in remission duration was observed in several studies, and a prolongation of survival was found in one setting. A metaanalysis of eight of the randomized trials incorporating 1756 patients has been recently reported. This analysis found an improvement in overall survival in patients who received an anthracycline-containing chemotherapy regimen and received a dose of interferon of at least 36 MU/month.

The activity of rituximab in patients with relapsed follicular lymphoma has led to its incorporation into the initial treatment and has produced encouraging results. Use of the monoclonal antibody to rituximab in previously untreated patients has also been reported to produce high complete response rates, and a prolongation of survival was found in one setting. The clinical manifestations of histologic transformation to diffuse large B-cell lymphoma typically include rapidly progressive lymphadenopathy (i.e., often localized); the development of new symptoms such as fevers, night sweats, weight loss, and pain; or both. In general, histologic transformation to diffuse large B-cell lymphoma has a poor prognosis and frequently a rapidly fatal outcome. However, some patients can have complete responses to salvage chemotherapy regimens and achieve durable complete remissions. These patients are typically left with persisting follicular lymphoma.

A wide variety of second-line chemotherapy regimens has been used in patients with follicular lymphoma. In addition to repeating standard front-line regimen, purine analogues such as fludarabine and cladribine are often used. However, even when the initial therapy is repeated, patients with follicular lymphoma often respond. In one series using chlorambucil, the response rate was 68% for the second course of therapy in contrast to 70% in the initial treatment.

A variety of other treatment approaches has been used in patients with relapsed follicular lymphoma. Interferon-a used as a single agent has a 30% to 55% response rate. The monoclonal antibody rituximab produces objective responses in 35% to 50% of patients with relapsed follicular lymphoma. Radiolabeled antibodies also directed against CD20 have even higher response rates in patients with relapsed follicular lymphoma. Other treatments such as use of antitumor molecules and tumor vaccines have also been shown to produce objective responses. Both autologous and allogeneic hematopoietic stem cell transplantations have been used for patients with relapsed follicular lymphoma. Both purged and unpurged autologous stem cell products have been used. The value of purging, particularly when blood stem cell products are used, remains uncertain. Autologous transplantation in patients with relapsed follicular lymphoma produces remissions durable for 5 years in approximately 50% of patients who are transplanted at the time of initial treatment failure. Patients transplanted after multiple treatment failures have a poorer outcome. Use of allogeneic bone marrow transplantation is associated with a much higher treatment-related mortality and a lower relapse rate.

Mantle Cell Lymphoma

DEFINITION. A mantle cell lymphoma is a neoplasm of monomorphic small to medium-sized B cells with irregular nuclei, which resemble the cleaved cells (centrocytes) of germinal centers and overexpress cyclin D1; neoplastic transformed cells (centroblasts or immunoblasts) are absent. Tumor cells are typically CD5+ and tumor vaccines have also been shown to produce objective responses. Both autologous and allogeneic hematopoietic stem cell transplantations have been used for patients with relapsed follicular lymphoma. Both purged and unpurged autologous stem cell products have been used. The value of purging, particularly when blood stem cell products are used, remains uncertain. Autologous transplantation in patients with relapsed follicular lymphoma produces remissions durable for 5 years in approximately 50% of patients who are transplanted at the time of initial treatment failure. Patients transplanted after multiple treatment failures have a poorer outcome. Use of allogeneic bone marrow transplantation is associated with a much higher treatment-related mortality and a lower relapse rate.
MORPHOLOGY. The pattern of mantle cell lymphoma may be either diffuse, nodular, or mantle zone, or a combination of the three. Some reports indicate a better prognosis for cases with a mantle zone pattern. Most cases are composed exclusively of small to medium-sized lymphoid cells, with slightly irregular or cleaved, nuclei; however, the morphology in various cases can range from lymphocyte-like to large cleaved or lymphoblast-like. Despite the small size and bland appearance, there is often more mitotic activity than in other histologically low-grade lymphomas. Single epithelioid histiocytes may be present, but clusters and granulomas are not seen. Transformed cells with basophilic cytoplasm (centroblast- or immunoblast-like cells) are extremely rare or absent.

IMMUNOPHENOTYPE. The tumor cells express strong Sigm and IgD, which is often of I light-chain type, strongly express B-cell-associated antigens, and coexpress CD5, similar to B-CLL/SLL, but are CD23-. Rare cases may be CD5- or CD23+. In contrast to follicle center lymphoma, mantle cell lymphoma are usually CD10- and CD43+. A prominent, irregular mesh work of FDCs is found, even in diffuse cases. The product of the cyclin D1 gene can be detected in the nuclei of neoplastic mantle cells in paraffin-embedded tissue sections with the immunoperoxidase technique and is useful in distinguishing mantle cell lymphoma from other low-grade B-cell lymphomas.

GENETIC FEATURES. Ig heavy and light-chain genes are rearranged. The Ig V region genes lack somatic mutations, indicating a pre--germinal center stage of differentiation, consistent with an origin from the follicle mantle. In the majority of the cases results in overexpression of a gene known as PRAD1 or cyclin D1, which encodes a cell-cycle-associated protein that is not normally expressed in lymphoid cells. The protein is overexpressed even in cases lacking the I(11), suggesting that point mutations may also result in overexpression. Overexpression of this protein may explain the often high mitotic index and aggressive clinical course of this histologically low-grade lymphoma. Studies have shown abnormalities in expression of other genes associated with the cell cycle, including mutations of the cdk inhibitors p16 and p17 in blastoid variants and decreased expression of p27, another cyclin inhibitor, in the majority of the cases. Cases of the blastoid variant have been reported to have a high incidence of tetraploidy and p53 gene mutations. Acquisition of a myc translocation has been reported in some fatal cases.

POSTULATED NORMAL COUNTERPART. Mantle cell lymphoma corresponds to a naive B cell of follicle mantle or germinal center origin that is distinct from both the recirculating B cell of B-CLL/SLL and the later centrocyte of follicle center lymphomas.

Clinical Features. Mantle cell lymphoma accounts for approximately 7% of adult NHLs in the United States and Europe. In a review of 376 cases of disseminated low-grade lymphoma (Working Formulation categories A through E), mantle cell lymphoma made up 10% of the cases. It is a tumor of older adults, with a marked male predominance (75%). The majority (70%) of patients are in stage IV at diagnosis; sites involved include lymph nodes, spleen, Waldeyer's ring, bone marrow (greater than 60%), blood (up to 50%), and extranodal sites, especially the gastrointestinal tract (lymphomatous polyposis). The course is moderately aggressive. The median overall survival in most series is 3 years, with no plateau in the curve, and failure-free survival is around 1 year. The blastoid variant is reported in some studies to be more aggressive.

THERAPY. Since mantle cell lymphoma was widely accepted as an entity in only the last decade, the number of therapeutic trials are not as extensive as for some other types of NHL. Localized mantle cell lymphoma is quite rare, seen in only 13% of unselected patients in one large series. The failure-free survival of patients treated for localized mantle cell lymphoma is quite poor, suggesting that unrecognized dissemination was usually present. The optimal treatment for these patients is not known.

Most patients present with disseminated disease. Single-agent chemotherapy has been used less commonly than in other small cell lymphomas, with chlorambucil, fludarabine, and cladribine being the most commonly used agents. The most frequently used combination regimens have been CVP and CHOP. Overall response rates have ranged between 60% and 80% and complete response rates between 30% and 60%. A randomized trial comparing CVP and CHOP showed no significant difference in overall survival (84% vs. 88%) and failure-free survival (41% vs. 58%). A new chemotherapy regimen that was originally used for patients with leukemia called hyper-CVAD (cyclophosphamide, vincristine, dexamethasone, and doxorubicin) has been used in mantle cell lymphoma and has a high response rate. In an historic control study from M. D. Anderson Cancer Center, hyper-CVAD had a superior 3-year event-free survival to CHOP (72% vs. 28%). Because of the poor long-term outlook, patients with mantle cell lymphoma who are sufficiently young and healthy often undergo autologous or allogeneic bone marrow transplantation at best response. The long-term benefits of autologous and allogeneic transplantation are still uncertain, although long-term survivors with both approaches are reported. Patients who relapse and are not candidates for transplantation or those who relapse can be treated with rituximab and interferon.

Monoclonal antibody therapy for patients with mantle cell lymphoma has been attempted with rituximab. The antibody yielded a response rate of 33% in relapsed patients. Further trials will be necessary to define the place of rituximab in the management of patients with mantle cell lymphoma. Interferon-a has been used in the treatment of mantle cell lymphoma. In one randomized trial including 47 patients with mantle cell lymphoma, 22 patients received interferon and 25 patients did not. The disease-free survival was 47% for the patients receiving interferon and 27% for the patients observed without therapy. However, the number of patients and the period of follow-up were not long enough to reach a firm conclusion.

Diffuse Large B-Cell Lymphoma

DEFINITION. Diffuse large B-cell lymphoma is defined as a neoplasm of large, transformed B cells with prominent nucleoli and basophilic cytoplasm, with a diffuse growth pattern and a high (greater than 40%) proliferation fraction. The cells may resemble centroblasts, immunoblasts, multilobated cells, or anaplastic large cells. Rare cases contain only scattered large cells in a background of small T cells and epitheloid histiocytes (T-cell histiocyte-rich large B-cell lymphoma).

MORPHOLOGY. Diffuse large B-cell lymphomas are probably a heterogeneous group of neoplasms. They are typically composed of large cells that resemble centroblasts or immunoblasts, most often with a mixture of the two. Several morphologic variants can be recognized, but their clinical significance is debated (Table 45.3-14).

TABLE 45.3-14. Morphologic Variants and Subtypes of Diffuse Large B-Cell Lymphoma

Centroblastic Variant. The monomorphic centroblastic (large noncleaved cell) type is composed of medium to large lymphoid cells with oval to round vesicular nuclei with fine chromatin and two to four membrane-bound nucleoli. The cytoplasm is generally scanty and amphophilic to basophilic. The multilobated centroblastic type contains many large lymphoid cells with nuclei having more than three lobes. A polymorphic type shows a mixture of centroblasts and immunoblasts and may contain up to 90% immunoblasts.
In immunoblastic Variant. Approximately 10% of the cases of diffuse large B-cell lymphomas have over 90% immunoblasts with a prominent central nucleolus and abundant, basophilic cytoplasm. Plasmacytoid differentiation may be present. These cases are more common in immunosuppressed patients. In nonimmunosuppressed patients, they have been reported to carry a worse prognosis. Although the proliferation of normal B cells, centroblasts or immunoblasts in most cases. The postulated normal counterpart is proliferating peripheral B cells, centroblasts or immunoblasts in most cases.

In some cases of diffuse large B-cell lymphomas, the cells are identical to those of T/NHL anaplastic large cell lymphoma and strongly express CD30 (Ki-1) as well as T-cell antigens. Although these have been called B-cell anaplastic large cell lymphoma (B-ALCL), they do not have the same distinctive clinical or genetic features of T/NHL-ALCL and are considered a morphologic variant of large B-cell lymphoma in the REAL/WHO classifications. The most significant diagnostic differential problem presented by such cases is classical Hodgkin's disease expressing B-cell antigens.

T-Cell–Rich/Histioctye-Rich Large B-Cell Lymphoma. Some cases of large B-cell lymphoma have a prominent background of reactive T cells and often histiocytes, so-called T-cell or histiocyte-rich large B-cell lymphoma. They may resemble Hodgkin's disease of either lymphocyte predominance or mixed cellularity type. In contrast to those with Hodgkin's disease, patients with T-cell/histiocyte-rich large B-cell lymphoma typically present with disseminated disease involving the liver and spleen and have a poor survival. The relationship of this disease to lymphocyte-predominant classical Hodgkin's disease, or both, remains to be elucidated.

Large B-Cell Lymphoma, Lymphomatoid Granulomatosis Type. The entity described as lymphomatoid granulomatosis, which had been thought to be related to nasal or angioimmunoblastic lymphoma, has been shown in some cases to be a large B-cell lymphoma with a T-cell–like phenotype. Tumor infiltrates show extensive necrosis, often with only a few atypical large B cells in a background of histiocytes; the infiltrate may be both angiocentric and angioinvasive. Patients typically present with extranodal disease, involving lung, brain, kidneys, or all three. Evidence of past or present immunosuppression may be found. Although the infiltrates may resemble those of nasal or angioimmunoblastic lymphoma, there is no biologic and little clinical overlap, since the latter is an NK cell or T-cell neoplasm that involves the upper airway and midfacial region, skin, and sometimes the gastrointestinal tract, and rarely the lung or CNS.

Immunophenotype. Diffuse large B-cell lymphomas express one or more B-cell–associated antigens (CD19, CD20, CD22, CD79a), as well as CD45, and often but not always, surface Ig. They may coexpress CD5 or CD10. Approximately 70% express bcl-6 protein, consistent with a germinal center origin. This expression is independent of bcl-6 gene rearrangement.

Genetic Features. Most cases of diffuse large B-cell lymphomas have somatic mutations in the Ig variable region genes. Both the bcl-2 gene is rearranged in 15% to 30% of diffuse large B-cell lymphomas; it is associated with nodal and disseminated disease, but is not associated with either a worse prognosis or with bcl-2 expression. The bcl-6 gene is rearranged in 25% to 40% of diffuse large B-cell lymphomas. The bcl-2 gene is rearranged in 15% to 30% of diffuse large B-cell lymphomas; it is associated with nodal and disseminated disease, but is not associated with either a worse prognosis or with bcl-2 expression. The bcl-6 gene is rearranged in 25% to 40% of diffuse large B-cell lymphomas. Both the 5' noncoding mutations of the bcl-2 gene and both the Ig variable region gene mutations are found in normal germinal center cells; their presence in diffuse large B-cell lymphomas is consistent with a germinal center origin or post–germinal center stage of differentiation.

Postulated Normal Counterpart. The postulated normal counterpart is proliferating peripheral B cells, centroblasts or immunoblasts in most cases.

Differential Diagnosis. For large B-cell lymphoma, as for most of the aggressive lymphomas, the major differential diagnosis is with a non-Hodgkin lymphoma, including poorly differentiated carcinoma, germ cell tumor, gloma, melanoma, or sarcoma. Clinically, when patients present with lymphadenopathy, lymphoma is often at the top of the differential diagnosis, but in extranodal sites, lymphoma may not be suspected. Clinical features that tend to favor lymphoma in extranodal sites include the presence of multiple, noncontiguous lesions, characteristic radiographic findings (e.g., permeative lesions in bone, ring-enhancing lesions in the CNS), involvement of lymphoid organs, and systemic symptoms such as fever and weight loss.

Histologically, the most important factor in establishing the diagnosis is a high index of suspicion and a recognition of the morphologic spectrum of diffuse large B-cell lymphoma. In this differential diagnosis, immunoperoxidase stains on paraffin sections are usually definitive; however, a panel of several antibodies must be used (e.g., cytokeratin, EMA, CD45, pan-B and pan-T antigens, Ig light-chains, and if relevant, S-100 and HMB-45).

Clinical Features. Diffuse large B-cell lymphoma is the most common lymphoma in the international study of the REAL, accounting for 31% of the cases. Patients typically present with a rapidly enlarging symptomatic mass, with B symptoms in one-third of the cases. Among the patients who had recurrences, 15% to 20% were within the radiation field; the remainder were in distant sites. Early randomized trials, published in the 1980s, compared RT alone with RT followed by CVP or BACOP chemotherapy. These studies demonstrated a disease-free and overall survival advantage for combined CT and RT. This dramatically changed the treatment of localized large cell lymphoma. Staging laparotomy and large-cell RT became obsolete as combination chemotherapy with or without RT produced disease-free and overall survival rates equivalent to or better than those seen even in the most selected studies reporting results with RT alone.

New clinical trials were then initiated to evaluate the role of RT as adjuvant to chemotherapy in patients with stage I or II diffuse large cell lymphoma. Small retrospective studies had advocated chemotherapy alone and combined chemotherapy and RT. Several centers reported excellent results using reduced chemotherapy and involved-field irradiation. At the National Cancer Institute, more than 90% of the 49 stage I or II patients with diffuse large cell lymphoma treated with four cycles of ProMACE-MOPP (cyclophosphamide, etoposide, doxorubicin, nitrogen mustard, vincristine, procarbazine, high-dose methotrexate with leucovorin rescue and prednisone) at reduced-field RT to 40 Gy of remaining disease free. In a similar study from Vancouver 78 patients were treated with three cycles of CHOP chemotherapy followed by involved-field RT to a total dose of 30 to 45 Gy; at 3 years the disease-free survival was 84%. Both studies excluded patients with bulky disease (greater than 10 cm). In a third study, which included some patients with bulky disease, 183 patients treated with four cycles of CHOP and 40 to 44 Gy involved-field RT have 5-year relapse-free and overall survival rates equivalent to or better than those seen even in the most selected studies reporting results with RT alone.

Two prospective randomized trials have further evaluated the role of RT in patients with early-stage diffuse large cell lymphoma. The Eastern Cooperative Oncology Group randomized 365 patients with bulky stage I and patients with stage II diffuse large cell lymphoma to eight cycles of CHOP or with involved-field RT. Patients with complete response were randomized to 30 Gy involved-field RT or no further treatment. Patients with partial response received 40 Gy. The disease-free survival (73% vs. 58%, P = .03; freedom from recurrence (73% vs. 58%, P < .04), and survival (84% vs. 70%, P = .06) all favored the patients who received adjuvant involved-field irradiation. The Southwest Oncology Group Trial randomized 401 stage I and nonbulky stage II patients to receive either three cycles of CHOP and involved-field irradiation (40 to 55 Gy) or eight cycles of CHOP alone. The 5-year progression-free survival (77% vs. 64%, P = .03) and overall survival (82% vs. 72%, P = .02) favored the CHOP and involved-field RT treatment arm. As a result of these trials, combination chemotherapy and adjuvant RT has become the standard of care for patients with stage I and II diffuse large cell lymphoma.

There are no prospective trials evaluating dose of radiation when combined with chemotherapy in patients with early-stage diffuse large cell lymphoma. In general, the dose of RT should be based on the number of cycles of chemotherapy and the bulk of disease. Patients with bulky mediastinal or abdominal disease or with multiple sites of involvement have a somewhat worse prognosis; these patients should receive six cycles of CHOP combined with RT. Prior studies support the use of three to four cycles of CHOP combined with RT in patients with more limited disease. With a complete response after six cycles of CHOP we recommend 30-Gy involved-field RT for patients with favorable presentations, and 35 to 40 Gy for patients with initial bulky disease. Patients with diffuse large cell lymphoma localized to the bone should receive 40 Gy. With a complete response after four cycles of CHOP we recommend 40 Gy. These recommendations are...
THERAPY OF DISSEMINATED DIFFUSE LARGE B-CELL LYMPHOMA. The curability of disseminated diffuse large B-cell lymphoma using chemotherapeutic agents was reported in the early 1970s. In both early reports, the majority of patients who achieved a documented complete remission at the end of planned therapy did not relapse on prolonged follow-up. These reports led to a large number of clinical trials documenting the possibility of cure for patients with disseminated diffuse large B-cell lymphoma. Principles of therapy that have evolved include the administration of highly active drugs given in combination for several cycles and then to reschedule the patient to document complete remission (Table 45.3-15). Two or more further cycles of chemotherapy are usually administered after complete remission is documented. In most series, 50% to 75% of completely responding patients do not relapse. It appears that patients who achieve remission promptly are most likely to be cured.

A great deal of effort has gone into attempts to identify the best treatment regimen for patients with advanced diffuse aggressive lymphoma. Most patients in these studies had large B-cell lymphoma. More than 40 randomized clinical trials have been reported. The majority of these trials have not found a significant treatment advantage for any particular regimen. The most widely quoted trial was carried out in the United States comparing CHOP, m-BACOD, ProMAC/ CytaBOM, and MACOP-B (Table 45.3-15). This trial was carried out because of enthusiasm generated by single-arm trials showing apparent superiority of m-BACOD, ProMAC/CytaBOM, and MACOP-B over the older CHOP regimen. This study of 899 patients showed no improvement in failure-free or overall survival with the newer regimen, but did find increased toxicity with m-BACOD and MACOP-B. The 6-year overall survival for the four regimens were CHOP, 33%; m-BACOD, 36%; ProMAC/CytaBOM, 34%; and MACOP-B, 32%. The conclusion from the study was that the less complicated and less expensive CHOP regimen should be considered the treatment of choice. This has been widely applied, and today most patients with diffuse large B-cell lymphoma or other aggressive lymphomas receive CHOP.

Several randomized trials have identified superiority of one chemotherapy regimen over another for the treatment of patients with diffuse large B-cell lymphoma and the most consistent finding from these studies is the superiority of an anthracycline-containing chemotherapy regimen over regimens that do not contain an anthracycline. This appears to be true in older as well as younger patients. An anthracycline, usually doxorubicin, appears to be a key component in optimizing the chances for the cure of patients with diffuse aggressive lymphoma. Substitution of another anthracycline such as mitoxantrone or epirubicin has been controversial, with some studies finding the drugs equivalent, whereas others have found an advantage for doxorubicin.

The importance of duration of follow-up in interpreting comparative trials is pointed out by a study done by the Australian and New Zealand lymphoma group. Investigators carried out a trial comparing CHOP with MACOP-B. Two hundred thirty-six patients were eligible for analysis and an initial report showed no significant difference in outcome between the two approaches, except for more severe toxicity with MACOP-B. The 4-year overall survival was 56% for MACOP-B and 51% for CHOP, with 3.2-year median follow-up. The authors reported the study again with 6.5-year median follow-up. At that point the failure-free survival (i.e., 42% vs. 30%) and overall survival (54% vs. 41%) favored the MACOP-B regimen.

Currently, there is no one superior regimen for the treatment of patients with disseminated diffuse large B-cell lymphoma. Unfortunately, this is because all the regimens are equally bad, rather than that they are all extremely effective. Patients with advanced-stage diffuse large B-cell lymphoma are cured with chemotherapy less than 50% of the time. New treatment approaches are badly needed. Attempts have been made to improve the response to CHOP by combining it with the monoclonal antibody rituximab. An early study of 33 patients showed a 97% response rate and a 73% complete response rate. The place of combined chemotherapy and monoclonal antibody therapy in the management of patients with diffuse large B-cell lymphoma will be determined by subsequent comparative clinical trials.

One approach to improve treatment results in patients with disseminated diffuse large B-cell lymphoma would be the addition of adjuvant drugs, radiotherapy, high-dose therapy with transplant, immunotherapy, or antibodies after a standard chemotherapy regimen. The addition of levamisole, bacille Calmette-Guérin, or both did not improve treatment outcome. Aviles et al. found an improved disease-free and overall survival with the use of adjuvant interferon-a. A combination of standard chemotherapy regimens and monoclonal antibodies is currently being tested.

The most widely studied adjuvant therapy has involved high-dose therapy and autologous bone marrow transplantation. Attempts to shorten the standard chemotherapy regimens and substitute high-dose therapy and autologous bone marrow transplantation have been disappointing. One study that randomized slowly responding patients to continuing CHOP or to autologous transplantation found a superior overall survival in continuing CHOP (85% vs. 56%). Two studies have found an improved disease-free survival and overall survival in patients who underwent autologous bone marrow transplantation after achieving a remission with a standard chemotherapy regimen. In both cases, benefits were restricted to patients who presented with a high International Prognostic Index score. In a French study, the disease-free survival (59% vs. 39%) and overall survival (65% vs. 52%) both significantly favored adjuvant autologous bone marrow transplantation. In an Italian study, sequential high doses of individual drugs followed by autotransplant yielded a better disease-free survival (76% vs. 49%), but
not overall survival, than MACOP-B. An international consensus conference reached the conclusion that autologous high-dose therapy and autotransplantation in patients with high-risk International Prognostic Index scores seemed to provide benefit.

**SAVAGE THERAPY.** The phrase salvage therapy encompasses subsequent treatment administered to patients who failed to achieve an initial remission and the treatment administered to patients who relapse from complete remission. A major prognostic factor for patients receiving any form of salvage therapy relates to the chemotherapy sensitivity of the lymphoma (i.e., patients who achieve an initial complete remission and then relapse generally have a better prognosis than patients who are primarily resistant to chemotherapy). Patients with lymphoma that progresses on the previous chemotherapy regimen have a poorer outlook than those who have stable or partially responding disease. Patients who have been in complete remission and then relapsed require a rebiopsy before initiating salvage therapy. Some patients who present with diffuse large B-cell lymphoma are found to have a follicular lymphoma at the time of relapse.

The initial step in planning salvage chemotherapy is to determine the goal of treatment. Some patients who fail to achieve an initial remission or relapse from complete remission can be cured. This is less likely in elderly patients, those with extensive disease, and those with a poor performance status. In such patients less intensive, palliative treatments might be better pursued.

Radiotherapy can frequently be used to alleviate the symptoms at a particular site of involvement in patients with relapsed diffuse large B-cell lymphoma. This can frequently be accomplished with minimal morbidity. However, the chance for cure with salvage radiotherapy is extremely small. Most patients receive second- or third-line combination chemotherapy regimens. These regimens usually incorporate drugs such as cisplatin, ifosfamide, etoposide, and cytaraabine. The chances for achieving a complete remission have varied in different studies, but generally fell in the 20% to 40% range.

Other approaches used for salvage therapy in patients with diffuse large B-cell lymphoma include the monoclonal antibody rituximab and interferon-α. In patients with diffuse large B-cell lymphoma treated with rituximab, 11 (37%) had an objective response. Most responses were partial. The median time to progression had not been reached at the time of the report. Responding patients were more likely to have tumors less than 5 cm in maximum diameter, and no patient with a tumor greater than 10 cm in maximum diameter responded. Occasional patients with relapsed diffuse large B-cell lymphoma respond to interferon-α. These responses can be complete and durable for several years.

Because of the poor response to salvage chemotherapy in patients with relapsed refractory diffuse large B-cell lymphoma, autologous bone marrow transplantation with high-dose conditioning is gaining acceptance. In a study of 100 patients with relapsed diffuse aggressive lymphoma, survival free from disease could be predicted by the history of previous response to chemotherapy. Approximately 35% of patients who relapsed from complete remission but remained sensitive to chemotherapy at relapse achieved prolonged disease-free survival and apparent cure, in contrast to approximately 10% of those who were chemotherapy resistant at the time of relapse and no patients who were initially refractory to therapy and failed to achieve a complete remission. This study formed the basis for an international randomized trial referred to as the PARMA study. In this trial, 109 patients who had relapsed from complete remission and responded to two cycles of DHAP (dexamethasone, cytarabine, cisplatin) were randomly allocated to high-dose chemotherapy using BEAC regimen (carmustine, etoposide, cytaraabine, cyclophosphamide) or continued treatment with DHAP. Both groups were to receive involved-field radiotherapy. Bone marrow transplantation was associated with a superior failure-free survival (51% vs. 12% at 5 years) and overall survival (53% vs. 32% at 5 years). At present, high-dose therapy and autologous bone marrow transplantation are the treatments of choice for patients with chemotherapy-sensitive relapse who are young enough and healthy enough to undergo the procedures.

Allogeneic bone marrow transplantation has been used less frequently for patients with diffuse large B-cell lymphoma. While occasional patients failing autologous transplantation can have prolonged survival with allogeneic transplantation, overall results from the North American Bone Marrow Transplant Registry have favored autologous transplantation.

**Primary Mediastinal (Thymic) Large B-Cell Lymphoma**

**MORPHOLOGY.** Primary mediastinal large B-cell lymphoma usually involves the thymus at presentation. The tumor is composed of large cells with variable nuclear features, resembling centroblasts, large centrocytes, or multilobated cells, often with pale or clear cytoplasm. Less often, the tumor cells resemble immunoblasts. Reed-Sternberg-like cells may be present. Many cases have fine, compartmentalizing sclerosis.

**IMMUNOPHENOTYPE.** The tumor cells are often Ig-κ, but express B-cell-associated antigens (CD19, CD20, CD22, CD79a) and CD45.

**GENETIC FEATURES.** Ig heavy and light-chain genes are rearranged; the bcl-2 gene is usually germine. Amplification of the REL oncogene has been described in a minority of the cases.

**POSTULATED NORMAL COUNTERPART.** The postulated normal counterpart is putative thymic (mediastinal) B cell.

**DIFFERENTIAL DIAGNOSIS.** The major differential diagnoses clinically are thymoma, germ cell tumor, and Hodgkin's disease. In female subjects, germ cell tumor can be confidently excluded. Involvement of lymph nodes argues against a diagnosis of thymoma. The presence of superior vena cava syndrome argues against Hodgkin's disease. Histologically, the diagnosis depends on recognition of the characteristic morphology; immunohistochemical stains, as for other diffuse large B-cell lymphomas, are helpful.

**CLINICAL FEATURES AND THERAPY.** Primary diffuse large B-cell lymphoma of the mediastinum is a distinct clinicopathologic entity, requiring knowledge of both morphology, immunophenotype, and presenting site for the diagnosis. It accounted for 7% of diffuse large B-cell lymphomas (2.4% of all NHL) in the international REAL study. There is a female predominance and a median age in the fourth decade; patients present with a locally invasive anterior mediastinal mass originating in the thymus, with frequent airway compromise and superior vena cava syndrome. Relapses tend to be extranodal, including liver, gastrointestinal tract, kidneys, ovaries, and CNS.

Although early studies suggested an unusually aggressive, incurable tumor, others have reported cure rates similar to those for other large cell lymphomas with aggressive therapy, usually combining chemotherapy with mediastinal irradiation. With no evidence to the contrary, we recommend treating these patients similarly to other patients with localized diffuse B-cell lymphoma (i.e., with four to six cycles of CHOP and involved-field RT). The prognosis of patients with localized mediastinal large cell NHL is similar to other patients with poor prognosis early-stage disease; approximately 50% of patients are alive without disease at 5 years. Patients who present with a pleural effusion or who remain gullain positive after CHOP have a worse prognosis. Patients without bulky disease have a better prognosis. Patients with disseminated disease should be treated like other patients with disseminated diffuse large B-cell lymphoma.

**Intravascular Large B-Cell Lymphoma**

Rare cases of large cell lymphoma, usually of B-cell type, present with a disseminated intravascular proliferation of large lymphoid cells, involving small blood vessels, without an obvious extravascular tumor mass or leukemia. This tumor has also been variously known as intravascular lymphomatosis, angiotropic lymphoma, and malignant angioendotheliomatosis. The neoplastic lymphoid cells are mainly lodged in the lumina of small vessels in many organs. The tumor cells are large with vesicular nuclei, prominent nucleoli, and frequent mitotic figures. Malignant cells are rarely seen in cerebrospinal fluid, blood, or bone marrow. The organs most commonly involved are CNS, kidneys, lungs, and skin, but virtually any site may be involved.

Patients present with a bewildering variety of symptoms related to organ dysfunction secondary to vascular occlusion, which may be transient. Patients often present with neurologic dysfunction. Other presentations include pulmonary involvement, syndrome of inappropriate antidiuretic hormone production, skin lesions, lycy bone lesions, endocrine dysfunction, disseminated intravascular coagulation, edema and hypoalbuminemia, and thrombotic thrombocytopenic purpura. Because of the wide variety of presentations, diagnosis is often difficult, and many reported cases were diagnosed by autopsy. If a timely diagnosis is made and combination chemotherapy instituted, patients can attain a complete remission, and long-term survival appears to be possible.
Burkitt's Lymphoma

**DEFINITION.** Burkitt's lymphoma is a B-cell lymphoma composed of monomorphic, medium-sized cells with basophilic cytoplasm and a high proliferation fraction, characterized by translocation and deregulation of the c-myc gene on chromosome 8, which is often extranodal and occurs most often in children (endemic, sporadic) and immunocompromised hosts.

**MORPHOLOGY.** Burkitt's tumor cells are monomorphic, medium-sized cells with round nuclei, multiple nucleoli, and basophilic cytoplasm. Cytoplasmic lipid vacuoles are usually evident on imprints or smears. There is an extremely high rate of proliferation as well as a high rate of spontaneous cell death. A starry-sky pattern is usually present, imparted by numerous benign macrophages that have ingested apoptotic tumor cells. Although most cases present no problem in diagnosis, some cases may have larger cells or an admixture of immunoablative-like cells, and there is morphologic overlap with diffuse large B-cell lymphoma. These borderline cases are often called non-Burkitt or Burkitt-like. In children and human immunodeficiency virus–positive patients, these often have a c-myc translocation and behave similarly to typical Burkitt's lymphoma, whereas in adults, so-called Burkitt-like lymphomas often have bcl-2 gene rearrangement and may represent an aggressive variant of diffuse large B-cell lymphoma. In the international study of the REAL, Burkitt-like lymphoma was a nonreproducible category, in which the pathologists agreed on the diagnosis only 50% of the time: Disagreements were equally split between large B-cell and Burkitt's lymphoma.

The most appropriate way to handle this borderline between Burkitt's lymphoma and diffuse large B-cell lymphoma has been the subject of debate in the WHO classification project. Should it continue to be a separate, nonreproducible category; should it be a subtype of large B-cell lymphoma; or should it be a subtype of Burkitt's lymphoma? From a clinical standpoint, it is important to identify patients who should be treated as though they had Burkitt's lymphoma, since patients with Burkitt's lymphoma do not do well with treatment that would be effective for large cell lymphoma. On the other hand, treatment for Burkitt's lymphoma is considerably more aggressive than that for large B-cell lymphoma and may have significant treatment-related morbidity, so that it should not be used for usual large B-cell lymphomas. The question is how to draw the line between large cell lymphoma and Burkitt's lymphoma so that morphologically borderline cases will be assigned to the correct category?

The defining biologic feature of Burkitt's lymphoma is c-myc deregulation, as a consequence of which the tumor cells remain constantly in cycle. It is this phenomenon that results in both its morphologic homogeneity and its clinical behavior. Unfortunately, detection of c-myc translocation is not practical in all clinical specimens for technical reasons. In addition, some large B-cell lymphomas have t(8;14) and c-myc deregulation, and it is not clear if all such cases should be treated like Burkitt's lymphoma. The best practical surrogate for c-myc deregulation is proliferation fraction: In a tumor with c-myc deregulation, 100% of viable cells should be in cycle and should express Ki-67. Thus, the WHO committees concluded that a diagnosis of Burkitt-like lymphoma should only be made in a tumor with morphologic features intermediate between Burkitt's lymphoma and diffuse large B-cell lymphoma, in which the Ki-67 fraction of viable cells is at least 99%. This tumor will be considered a subtype of Burkitt's lymphoma in the WHO classification. Cases with morphologic features of large cell lymphoma with a high proliferation fraction [or t(8;14)] and cases that are morphologically borderline between Burkitt's lymphoma and large B-cell lymphoma with a lower proliferation fraction, should be classified as usual large B-cell lymphoma.

**IMMUNOPHENOTYPE.** Burkitt's lymphoma cells express SigM and B–cell–associated antigens (CD19, CD20, CD22, CD79a), as well as CD10 and CD43; they lack CD5 and bcl-2 and typically lack CD23. They show nuclear staining for BCL-6 protein, which is independent of bcl-6 gene rearrangement.

**GENETIC FEATURES.** Ig heavy and light-chain genes are rearranged. Studies of the Ig variable region genes show conflicting results: One study reported unmutated genes, whereas others report somatic mutations and intrachromosomal heterogeneity, consistent with ongoing mutations. Most cases have a translocation of c-myc from chromosome 8 to either the Ig heavy-chain region on chromosome 14 [t(8;14) or light-chain loci on 2p23 or 22q11]. In African (endemic) cases, the breakpoint on chromosome 14 involves the heavy-chain joining region, whereas in nond endemic cases, the translocation involves the heavy-chain switch region. Mutations in the 5' noncoding region of the bcl-6 gene, similar to those seen in large B-cell lymphoma, have been reported in 25% to 50% of the cases. Most African cases contain EBV genomes, as do 25% to 40% of the cases associated with AIDS.

**POSTULATED NORMAL COUNTERPART.** The postulated normal counterpart is peripheral B cell of unknown stage: perhaps B blast of early germinal center reaction.

**DIFFERENTIAL DIAGNOSIS.** Burkitt's lymphoma must be distinguished from other primary abdominal malignancies in childhood, including Wilms' tumor, neuroblastoma, and peripheral neuroectodermal tumor. In the bone marrow, it must be distinguished from B- and T-precursor and myeloid leukemias. Morphologic features are usually sufficient for the diagnosis if adequate material is available. The presence of leukocyte-associated antigens and Ig and the lack of TdT are important in distinguishing Burkitt's lymphoma from the other tumors mentioned. Among peripheral B-cell lymphomas, the major differential diagnosis is with diffuse large B-cell lymphoma; although this is usually straightforward on histologic grounds, occasional borderline cases occur, a provisional category of high-grade B-cell lymphoma. Burkitt-like is used for these cases. Burkitt's lymphoma is more likely to express CD10 and to have c-myc rearrangement than is diffuse large B-cell lymphoma.

**CLINICAL FEATURES AND THERAPY.** Three distinct clinical forms of Burkitt's lymphoma can be recognized: endemic, sporadic, and immunodeficiency-associated. Similar to typical Burkitt's lymphoma, Burkitt-like lymphoma is highly aggressive, with rapid dissemination and a poor prognosis associated with chemotherapy resistance. The clinical presentations of immunodeficiency associations are variable. Patients with isolated CNS disease have been treated with low-dose chemotherapy alone or in combination with anti-infective chemotherapy, and cranial radiation; however, in most cases, combination chemotherapy, including salvage chemotherapy, is necessary. The overall survival rate of patients with Burkitt's lymphoma is 80% to 90%. In children with Burkitt's lymphoma, the response to treatment is much better than in adults. In endemic cases, patients may present with abdominal pain, fever, and weight loss. In sporadic cases, patients may present with fever and weight loss. The malignancy is highly aggressive but potentially curable with chemotherapy. Because of the extremely rapid progression of Burkitt's lymphoma, patients with this disease should be approached as a medical emergency. Staging should be completed quickly and therapy initiated at the earliest possible time. Because of the risk of tumor lysis syndrome, patients should be well-hydrated, receive allopurinol, and be observed closely after the initiation of therapy. Death from hyperkalemia has been reported. Some patients require hemodialysis to control hyperkalemia.

Burkitt's lymphoma was one of the first malignancies to be shown to be curable with chemotherapy, and the majority of patients should be curable with aggressive chemotherapy regimens. High-dose regimens of brief duration are used to treat patients with Burkitt's lymphoma. Patients with localized disease are cured in approximately 90% of the cases with these intensive regimens, and cure rates within excess of 50% have been reported in patients with extensive disease. When treated with similar regimens, adults and children have comparable outcomes. Because of the propensity for CNS metastases, treatment regimens for Burkitt's lymphoma always involve prophylactic therapy to the CNS. Salvage therapy for patients with relapsed Burkitt's lymphoma has generally been unsatisfactory. However, occasional patients can be cured with autologous bone marrow transplantation. Patients with isolated CNS relapse can sometimes be cured with bone marrow transplantation or a combination of systemic therapy at traditional doses and intrathecal treatment.

**T-CELL AND NATURAL KILLER–CELL NEOPLASMS**

**Precursor T-Lymphoblastic Lymphoma/Leukemia (Precursor T-Cell Acute Lymphoblastic Lymphoma/ Precursor T-Cell Lymphoblastic Lymphoma)**

**DEFINITION.** A T-cell and NK-cell neoplasm is a neoplasms of lymphoblasts committed to the T-cell lineage, typically composed of small to medium-sized blast cells with scant cytoplasm, moderately condensed to dispersed chromatin and indistinct nucleoli, variably involving bone marrow and blood (precursor T-cell ALL), thymus, lymph nodes, or all (precursor T-cell lymphoblastic lymphoma).

**MORPHOLOGY.** On smears, lymphoblasts vary from small cells with scant cytoplasm, condensed nuclear chromatin, and indistinct nucleoli to larger cells with a moderate amount of cytoplasm, dispersed chromatin, and multiple nucleoli. Azurophilic granules may be present. In tissue sections, the cells are small to medium-sized, with scant cytoplasm, oval or convoluted nuclei, and fine chromatin and indistinct or small nucleoli. Occasional cases have larger cells. The pattern is infiltrative rather than destructive, with partial preservation of the subcapsular sinus and germinal centers. A starry-sky pattern may be present, but is usually less prominent than in Burkitt's lymphoma.
IMMUNOPHENOTYPE. The lymphoblasts are typically positive for TdT and variably express CD2, CD7, CD3, CD5, CD1a, CD4, CD8, or all of these. Only CD3 is considered lineage specific. The constellation of antigens defines stages of differentiation, ranging from early or pro-T (CD2, CD7, and cytoplasmic CD3), to common thymocyte (CD1a, sCD3, CD4, and CD8), to late thymocyte (CD4 or CD8). Although there is some correlation with presentation and differentiation stage (with bone marrow and blood presentation may show earlier differentiation stages than cases with thymic presentation), there is overlap.

GENETIC FEATURES. Rearrangement of antigen receptor genes is variable in lymphoblastic neoplasms and may not be lineage specific; thus, precursor T-cell neoplasms may have either or both TCR b or g chain gene rearrangements and Ig heavy-chain gene rearrangements.

Chromosomal translocations involving the TCR a and d loci at chromosome 14q11 and b and g loci at 7q34 are present in approximately one-third of the cases. The partner genes are variable and include the transcription factors c-MYC (8q24), TAL1/SCL (1p32), RB1 (11p15), RB2 (11p13), and HOX11 (10q24) and the cytoplasmic tyrosine kinase LCK (1p34). In an additional 25%, the TAL1 locus at 1p32 has deletions in the 5’ regulatory region. Deletions of 9p involving deletion of the p16INK4a tumor suppressor gene (cdk4 inhibitor) is also seen in T-lymphoblastic neoplasms.

POSTULATED NORMAL COUNTERPART. The postulated normal counterpart is precursor T lymphoblast at varying stages of differentiation.

CLINICAL FEATURES AND THERAPY. Precursor T-cell neoplasia occurs most frequently in late childhood, adolescence, and young adulthood, with a male predominance; it affects 2-6% of all childhood and 25% of adult ALL. The prognosis is typically worse than that for precursor B-cell neoplasms and is not affected by immunophenotype or genetic abnormalities. Patients typically present with a high leukocyte count and often a mediastinal mass. Clinically, a case is defined as lymphoma if there is a mediastinal or other mass and less than 25% blasts in the bone marrow, and as leukemia if there are greater than 25% bone marrow blasts, or with or without a mass. In children, treatment is generally more aggressive than that for precursor B-ALL and is typically the same for lymphomatous and leukemic presentations.

Adults with lymphoblastic lymphoma seem to have an excellent prognosis when presenting with stage I or II disease. In such patients treatment with CHOP, intrathecal methotrexate, and CNS radiotherapy, and maintenance chemotherapy with methotrexate and mercaptopurine yielded a 94% 5-year freedom from relapse rate for patients with lymph node-based disease and a normal serum LDH level. Patients who presented with bone marrow involvement, CNS involvement, or a high serum LDH had a 5-year freedom from relapse rate of only 19%. Because of the propensity for CNS relapse, all patients with lymphoblastic lymphoma should receive prophylactic treatment to the CNS.

More intensive chemotherapy regimens of the type used to treat ALL appeared to yield better results in patients with lymphoblastic lymphoma. Adjunct autologous bone marrow transplantation in high-risk patients has been reported to improve the long-term disease-free survival rate. These data have been supported by the early results from a randomized trial. There is some evidence that allogeneic bone marrow transplantation might have a superior result to autologous bone marrow transplantation. Some patients who relapse from remission can be cured with autologous or allogeneic bone marrow transplantation, although the overall prognosis in such patients is poor.

Mature T Cell: Mycosis Fungoides

For a discussion of mycosis fungoides, see Chapter 45.4.

Adult T-Cell Lymphoma and Leukemia

DEFINITION. Adult T-cell lymphoma and leukemia is defined as a peripheral T-cell neoplasm caused by HTLV-I.

MORPHOLOGY. Cells with hyperlobated nuclei (flower cells) are common in the peripheral blood in leukemic cases. In addition, there is a small proportion of blast-like cells with a deep basophilic cytoplasm. Bone marrow infiltrates are usually patchy, ranging from sparse to moderate. In lymph nodes, the infiltrates are diffuse with architectural effacement. Neoplastic cells are usually medium to large with nuclear pleomorphism; the cytoplasm is amphophilic, basophilic, or pale. Mitotic activity is variable. Reed-Sternberg–like cells and giant cells with convoluted or cerebriform nuclei may be present. Rare cases may be composed of small atypical lymphocytes with nuclear pleomorphism or may resemble anaplastic large cell lymphoma. In the background there is a mild to moderate proliferation of high endothelial venules.

IMMUNOPHENOTYPE. Tumor cells express T-cell–associated antigens (CD2, CD3, CD5), but usually lack CD7. Most cases are CD4+ and CD8+. Rare cases are CD4–, CD8+, or CD8+ and CD4+. CD25 is expressed in a majority of the cases. Anaplastic large cell types react with CD30, but are ALK (p60) negative.

GENETICS. Clonally integrated HTLV-I genes are found in all cases. The TCR genes are clonally rearranged.

POSSIBLE NORMAL COUNTERPART. The possible normal counterpart is peripheral CD4+ T cells in various stages of transformation.

DIFFERENTIAL DIAGNOSIS. Chronic and smoldering forms must be distinguished from benign lymphocytosis. Cutaneous involvement must be distinguished from mycosis fungoides. Lymphomatous presentations may clinically and histologically resemble large B-cell or other peripheral T-cell lymphomas. The typical acute course is clinically and morphologically distinctive, with leukocytosis and the characteristic flower cells in an Asian or Caribbean patient, often with hypercalcemia. Since the disease may be mimicked by other peripheral T-cell lymphomas, and because of its highly aggressive course, serologic evaluation for HTLV-I infection is recommended in any patient with a newly diagnosed peripheral T-cell lymphoma.

CLINICAL FEATURES. ATL is one manifestation of infection by HTLV-I. Tropical spastic paraparesis and HTLV-I–associated myelopathy appear to be more common manifestations of infection than ATL. The diagnosis is established when a patient with a typical clinical and pathologic syndrome is found to have antibodies to HTLV-I. Most patients are adults, although children are occasionally seen with the disorder when they received transfusions in infancy. The virus can be acquired by vertical transmission from mother to child, sexual transmission, or via blood products. Most cases occur in Japan or the Caribbean, with sporadic cases found elsewhere in the world.

In the United States the diagnosis is frequently difficult because ATL is not considered since many clinicians are not acquainted with the syndrome. Various variants have been described depending on the clinical features: acute, lymphomatous, chronic, and smoldering. The most common acute type presents with neoplastic cells in the blood, skin rashes, generalized lymphadenopathy, hepatosplenomegaly, and hypercalcemia. The lymphomatous type is characterized by prominent lymphadenopathy but no blood involvement. The chronic type shows skin lesions and an increased white blood cell count with absolute lymphocytosis, but no hypercalcemia. The smoldering type shows normal blood lymphocyte counts with 5% circulating neoplastic cells. Patients frequently have skin or pulmonary lesions, but hypercalcemia is not present. Progression from chronic and smoldering to acute types eventually occurs in up to 25% of the cases. Peripheral blood and bone marrow are the most frequent sites of involvement, although essentially any organ can be involved by the disease including gastrointestinal tract, liver, lung, and CNS.

THERAPY. The treatment of ATL has been unsatisfactory. Patients with the chronic or smoldering syndromes can sometimes be followed without therapy for extended periods of time. When the disease becomes asymptomatic, combination chemotherapy regimens have usually been used. Although patients frequently respond to the initial combination chemotherapy regimen, the overall survival remains poor, with less than 10% of the patients surviving 5 years after initiating therapy. A variety of the new treatment approaches has been studied including new chemotherapeutic agents, monoclonal antibodies, and allogeneic bone marrow transplantation. One case of long-term, disease-free survival with allogeneic bone marrow transplantation has been described.

Peripheral T-Cell Lymphoma, Not Otherwise Categorized

DEFINITION. In peripheral T-cell lymphoma, not otherwise categorized, a number of distinct entities have been defined, which correspond to recognizable subtypes of T-cell neoplasia. There remains a large group of predominantly nodal T-cell lymphomas, which make up the largest group of T-cell neoplasms in western countries. Although a variety of morphologic subtypes has been described, no consistent immunophenotypic, genetic, or clinical features have been associated with most of them. Therefore, for the time being, these presumably diverse cases are lumped under the heading peripheral T-cell lymphoma, not otherwise categorized, or
unspecified. This category includes heterogeneous diseases that require further definition.

**MORPHOLOGIC FEATURES.** Peripheral T-cell lymphomas typically contain a mixture of small and large atypical cells and are classified as diffuse small cleaved, mixed, large cell, and immunoblastic in the Working Formulation. Admixed eosinophils or epithelioid histiocytes may be numerous; the term lymphoepithelioid cell (Lehnert's) lymphoma has been used for cases rich in epithelioid cells. Because of their relative rarity and heterogeneity, it has been impossible to arrive at a generally useful classification. For the time being, these tumors are simply designated peripheral T-cell lymphomas, unspecified.

**IMMUNOPHENOTYPE.** T-cell–associated antigens are variably expressed (CD3+, CD2+, CD5+, CD7+, CD7−/−), CD4 is more often expressed than CD8, and tumors may be CD4− and CD8−. B-cell–associated antigens are lacking. No specific cytotogenetic or oncogene abnormality has been reported, although complex karyotypes are common in cases with larger cells.

**POSTULATED NORMAL COUNTERPART.** The postulated normal counterpart is peripheral T cells in various stages of transformation.

**CLINICAL FEATURES.** Peripheral T-cell lymphomas accounted for only 6% of lymphomas in the international study of the REAL, reflecting their rarity in American and European populations. The median age was in the seventh decade, and 65% of the patients had stage IV disease. Blood eosinophilia, pruritus, and hemophagocytic syndromes may occur; lymph nodes, skin, liver, spleen, and other viscera may be involved. The clinical course is aggressive, and relapses are more common than large B-cell lymphoma. In the international REAL study, this group had one of the lowest overall and failure-free survival rates.

**THERAPY.** Treatment regimens used for peripheral T-cell lymphoma are the same as used for diffuse large B-cell lymphoma. Because of the poorer overall survival in peripheral T-cell lymphoma as compared with diffuse large B-cell lymphoma, bone marrow transplantation is more likely to be used as part of the primary therapy. Bone marrow transplantation may be as effective in peripheral T-cell lymphoma as in diffuse large B-cell lymphoma.

**Angioimmunoblastic T-Cell Lymphoma**

**DEFINITION.** Angioimmunoblastic T-cell lymphoma is a T-cell lymphoma characterized by systemic disease, a polymorphous infiltrate involving lymph nodes, and a prominent proliferation of high endothelial venules and FDCs.

**MORPHOLOGY.** The nodal architecture is effaced; peripheral sinuses are typically open and even dilated, but the abnormal infiltrate often extends beyond the capsule into the perinodal fat. There are prominent arborizing high endothelial venules, many of which show thickened or hyalinized periodic acid–Schiff-positive walls. Clusters of epithelioid histiocytes and numerous eosinophils and plasma cells may be present. Expanded aggregates of FDCs, visible on immunostained sections, surround the proliferating blood vessels and may have the appearance of burnt-out germinal centers. The lymphoid cells are a mixture of small lymphocytes, immunoblasts, plasma cells, and medium-sized cells with round nuclei and clear cytoplasm. B immunoblasts may be numerous.

**IMMUNOPHENOTYPE.** Tumor cells express T-cell–associated antigens and usually CD4, but many CD8+ cells are present; expanded FDC clusters (CD21+) are present around proliferated venules. The latter feature is useful in distinguishing this disorder from other T-cell lymphomas. Polyclonal plasma cells and B immunoblasts may be numerous.

**GENETIC FEATURES.** The TCR genes are rearranged in 75%; Igh in 10%, corresponding to expanded B-cell clones. EBV genomes are detected in many cases and may be present in either T or B cells; trisomy 3, 5, or both may occur.

**POSTULATED NORMAL COUNTERPART.** The postulated normal counterpart is peripheral T cell of unknown subset in various stages of transformation.

**CLINICAL FEATURES.** Angioimmunoblastic T-cell lymphoma is one of the more common peripheral T-cell lymphomas encountered in western countries. In the Kiel Registry, it accounted for 20% of all T-cell lymphomas and approximately 4% of all lymphomas. Angioimmunoblastic T-cell lymphoma is clinically distinctive: Patients typically have generalized lymphadenopathy, fever, weight loss, skin rash, and polyclonal hypergammaglobulinemia and are susceptible to infections. The course is moderately aggressive, with occasional spontaneous remissions, and is not reliably predicted by the histologic appearance.

**THERAPY.** Approximately 30% of the patients may have initial remission on corticosteroids alone, but most require some form of cytotoxic chemotherapy. Median survivals range from 15 to 24 months, and curability has not been well established. Some patients develop a secondary EBV+ large B-cell lymphoma. A prospective but nonrandomized trial compared an anthracycline-based combination chemotherapy regimen with prednisone followed by combination chemotherapy only if the disease progressed. Initial chemotherapy yielded a higher complete remission rate (64% vs. 29%) and median survival (19 vs. 11 months).

**Extranodal Natural Killer/T-Cell Lymphoma, Nasal Type (Formerly Angiocentric Lymphoma)**

**DEFINITION.** Extranodal NK/T-cell lymphoma, nasal type, is an extranodal lymphoma, usually with an immature NK-cell phenotype and EBV+, with a broad morphologic spectrum, frequent necrosis and angioinvasion, and most commonly presenting in the midfacial region, but also in other extranodal sites. It is designated NK/T because of uncertainty regarding lineage.

**MORPHOLOGIC FEATURES.** Nasal NK/T-cell lymphoma is typically characterized by a polymorphous infiltrate composed of a mixture of normal appearing small lymphocytes and atypical lymphoid cells of varying size, along with plasma cells and occasionally eosinophils and histiocytes. A characteristic feature is invasion of vascular walls and, usually, occlusion of lumina by lymphoid cells with varying degrees of cytologic atypia; however, this is not seen in all the cases. There is usually prominent ischemic necrosis of both tumor cells and normal tissue. The term angiocentric lymphoma has proven confusing, since angiocentricity is not evident in all cases. Since the most characteristic presentation is midfacial, and the cells have both T and NK features, the term extranodal T/NK-cell lymphoma, nasal type, has been proposed.

Cases of pulmonary lymphomatoid granulomatosis were for a time considered to be part of the spectrum of angiocentric lymphoma. Studies suggest that most pulmonary cases are EBV-associated B-cell proliferations, and therefore a distinct disease category; however, some pulmonary lymphomas with histologic features of lymphomatoid granulomatosis lack CD20+ cells and EBV and may be examples of peripheral T-cell lymphoma. Thus, pulmonary lymphomas with angiocentric growth patterns and necrosis may be heterogeneous.

**IMMUNOPHENOTYPE.** The atypical cells in most cases are CD2+, CD56+, surface CD3−, and cytoplasmic CD3+ (Leu 4− but positive with the polyclonal anti-CD3, which detects the epsilon chain of CD3). They are typically CD4− and CD8−, but may express CD4, CD7, or both. Most cases express cytotoxic granule proteins such as Granzyme B and TIA-1.

**GENETIC FEATURES.** The TCR and Ig genes are usually germline; EBV genomes are usually present and are detectable in the majority of the cells in most cases by in situ hybridization for EBER-1.

**POSTULATED NORMAL COUNTERPART.** The postulated normal counterpart is immature NK cell.

**CLINICAL FEATURES.** Nasal-type T/NK lymphoma is a rare disorder in the United States and Europe, but is more common in Asia and in native populations in Peru. It may affect children or adults. Extranodal sites are invariably involved, including nose, palate, upper airway, gastrointestinal tract, and skin. Hemophagocytic syndromes may occur. Some cases of the aggressive variant of NK-cell leukemia and lymphoma may be related to this disorder.
THERAPY. Patients with localized NK/T-cell lymphoma in the nasal pharynx can be cured with a combination of chemotherapy and local radiotherapy. With radiotherapy alone, treatment failure is frequent. Patients with disseminated NK/T-cell lymphoma have an extremely poor outlook. Occasional long-term survivors are seen using the CHOP regimen. Less aggressive regimens have a uniformly poor outcome.

High-dose chemotherapy and autologous bone marrow transplantation can be curative in some patients after relapse from standard therapy. Because of the poor results with standard chemotherapeutic approaches, incorporation of bone marrow transplantation as a primary management of patients with disseminated NK/T-cell lymphoma might improve treatment outcome.

**Enteropathy Type T-Cell Lymphoma**

**DEFINITION.** Enteropathy type T-cell lymphoma is a tumor of intraepithelial T lymphocytes, usually associated with features of gluten-sensitive enteropathy, showing varying degrees of transformation but usually presenting as a high-grade (blastic) tumor.

**MORPHOLOGY.** This disorder was originally termed *malignant histiocytosis of the intestine*, but has since been conclusively shown to be a T-cell lymphoma. On gross examination, circumferentially oriented jejunal ulcers are present, often multiple, and often with perforation. A mass may or may not be present. The tumors contain a variable admixture of small, medium and large, anaplastic tumor cells, often with a high content of intraepithelial T cells in adjacent mucosa. The adjacent mucosa may or may not show villous atrophy[56], this varies depending on the segment analyzed, since in sprue, villous atrophy is most prominent in the proximal small intestine and may be absent in distal jejunum or ileum. Early lesions may show mucosal ulceration with only scattered atypical cells and numerous reactive histiocytes, without formation of large masses; these lesions are nonetheless clonal. Intraepithelial lymphocytes in apparently nonneoplastic mucosa may also be clonal. Clonal TCR gene rearrangements have been found in cases of celiac disease unresponsive to a gluten-free diet, suggesting that these cases may represent early T-cell lymphomas. The tumor may involve liver, spleen, lymph nodes, and other viscera such as the gallbladder.

**IMMUNOPHENOTYPE.** The tumor cells are T cells expressing pan-T antigens (CD3+, CD7+), usually CD8+ and CD4−, and expressing the mucosal lymphoid antigen CD103. CD30 may be positive in some cells. Expression of cytotoxic T-cell–associated proteins (Granzyyme B, TIA-1, perforin) is seen in many of the cases. 

**GENETIC FEATURES.** The TCRβ gene is clonally rearranged; no specific cytogenetic abnormality has been described.

**POSTULATED NORMAL COUNTERPART.** The postulated normal counterpart is intestinal intraepithelial cytotoxic T cells in various stages of transformation.

**CLINICAL FEATURES AND THERAPY.** This disease occurs in adults, typically with a rather brief history of gluten-sensitive enteropathy, as the initial event in a patient found to have villous atrophy in the resected intestine, or without evidence of enteropathy but with either or both antigliadin antibodies or the typical HLA type (DQA1*0501, DQB1*0201) of patients with celiac disease. It is uncommon in most areas of the United States and Europe, but is seen with increased frequency in areas in which gluten-sensitive enteropathy is common. Treatment of celiac disease with a gluten-free diet effectively prevents the development of lymphoma, so that patients diagnosed with celiac disease early in life usually do not develop lymphoma, and patients with lymphoma rarely have a long history of celiac disease. Patients present with abdominal pain, often associated with jejunal perforation; stomach or colon are affected less often, and other viscera such as the skin, or soft tissues may be involved. The course is aggressive, and death usually occurs from multilocular intestinal perforation due to refractory malignant ulcers. A poor response to therapy has been reported. It is probably related to the severe nutritional and immunologic abnormalities found in patients with uncontrolled celiac disease.

**Hepatosplenic gd T-Cell Lymphoma**

**DEFINITION.** Hepatosplenic gd T-cell lymphoma is a neoplasm of mature gd T cells with sinusoidal infiltration of spleen, liver, and bone marrow.

**MORPHOLOGY.** Hepatosplenic gd T-cell lymphoma produces a sinusoidal infiltrate in liver and spleen, as well as bone marrow, of medium-sized lymphoid cells with round nuclei, moderately condensed chromatin, and moderately abundant, pale cytoplasm. Mitotic activity is generally low. The white pulp is atrophic. Erythrophagocytosis may be prominent in spleen and bone marrow sinuses.

**IMMUNOPHENOTYPE.** The tumor cells are CD2+, CD3+, CD5−, CD4−, CD8+, CD16+, CD56+/-, and lack the ab TCR protein, expressing instead the gd complex. Cytotoxic granule protein TIA-1 is typically expressed, but Granzyme B and perforin are absent, indicating a nonactivated cytotoxic T-cell phenotype.

**GENETIC FEATURES.** The TCR g and d genes are rearranged; the TCR b gene may be rearranged or germline. The tumor cells are EBV−. Isochromosome 7q and trisomy 8 have been reported in many cases.

**POSTULATED NORMAL COUNTERPART.** The postulated normal counterpart is gd T-cell of splenic type.

**CLINICAL FEATURES AND THERAPY.** This is a rare neoplasm, but because it has only relatively recently been characterized, its frequency is not known; cases have probably been classified as T-ALL/prolymphocytic leukemia or peripheral T-cell lymphoma unspecified. The diagnosis is often difficult. These patients frequently present as with a multisystem disease with hepatomegaly, splenomegaly, or both. The absence of lymphadenopathy and the sinusoidal pattern of infiltration of the liver, spleen, and bone marrow make the diagnosis difficult. Frequently, only the demonstration of a T-cell gene rearrangement leads to the correct diagnosis.

Patients have been predominantly adolescent boys and young adult men. Although most patients were previously healthy, the disease has been described in immunosuppressed, solid organ allograft recipients. Unusual sites of involvement such as skin, nasal cavity, gastrointestinal tract, lung, mucosal, and larynx have been described. Although circulating neoplastic cells are usually not prominent, subtle bone marrow involvement may be present.

Despite the relatively bland appearance of the cells, this is an aggressive tumor. Complete remission can occur with combination chemotherapy, but most patients relapse. Long-term survival has been described with autologous bone marrow transplantation.

**Subcutaneous Panniculitis-Like T-Cell Lymphoma**

**DEFINITION.** Subcutaneous panniculitis-like T-cell lymphoma is a T-cell lymphoma that preferentially infiltrates subcutaneous tissue, with atypical cells of varying size, showing prominent tumor necrosis and karyorrhexis.

**MORPHOLOGIC FEATURES.** There is a variable mixture of small, medium, and large atypical cells, often containing irregular, hyperchromatic nuclei and pale cytoplasm. Reactive histiocytes with phagocytosed nuclear debris, lipid, or both are numerous. Granulomas may be present. Individual adipocytes are rimmed by neoplastic cells.

**IMMUNOPHENOTYPE.** Most cases express pan-T antigens and usually CD8, although they may be CD4+, express cytototoxic granule proteins TIA-1 and perforin, and in most cases, the ab TCR. Occasional cases derive from gd T cells.

**GENETIC FEATURES.** TCR g genes are rearranged; usually b but occasionally d chain genes are rearranged. No specific cytogenetic abnormalities have been described.

**POSTULATED NORMAL COUNTERPART.** The postulated normal counterpart is the mature cytotoxic T cell.
long-term outlook with this disorder is poor.

**Anaplastic Large T/Null-Cell Lymphoma, Primary Systemic Type**

**DEFINITION.** Anaplastic large T/null-cell lymphoma, primary systemic type, is a neoplasm of large lymphoid cells with pleomorphic or multiple nuclei and abundant cytoplasm, a cohesive growth pattern, and sinusaloid spread in lymph nodes, expressing CD30 and either T-cell or no lineage-specific antigens, involving lymph nodes or extranodal sites, but not limited to the skin.

**MORPHOLOGIC FEATURES.** The tumor is usually composed of large blastic cells with round or pleomorphic, often horseshoe-shaped or multiple nuclei with multiple or single prominent nuclei, and abundant cytoplasm, which gives the cells an epithelial or histiocyt-like appearance. The so-called hallmark cell has an eccentric nucleus and a prominent, eosinophilic Golgi region. The tumor cells grow in a cohesive pattern and often preferentially involve the lymph node sinuses or paracortex. In some cases, the tumors may be more monomorphic appearance, with round to oval nuclei and no Reed-Sternberg-like cells; these cases have been reported to occur with more anaplastic cases, including a low nuclear-to-cytoplasmic ratio, dense, abundant cytoplasm, and a cohesive, often sinusaloid growth pattern. Lymphohistiocytic and small cell variants have been described, again, more commonly in children. Study of cytogenetic and molecular genetic abnormalities as well as clinical features suggests that these cases belong to the same disease entity as the more anaplastic cases.

A variant of ALCI resembling Hodgkin's disease of nodular sclerosis type has been described, originally called ALCI Hodgkin-like and included as a provisional entity under the name ALCI, Hodgkin-like in the REAL. This subtype is defined as having architectural features of Hodgkin's disease (nodularity and sclerosis), but cytologic features of ALCI (sheets of neoplastic cells and sinusaloid infiltration). Many patients are young adults with mediastinal masses, and the outcome was said to be intermediate between that of typical ALCI and nodular sclerosis Hodgkin's disease. Several studies suggest that these are not true borderline cases. First, most cases of ALCI Hodgkin-like lack the T(2;5) or ALK protein. Second, most cases of Hodgkin's disease are now thought to be B-cell derived, based on single-cell studies showing Ig gene rearrangement, while ALCI is predominantly a T-cell disease; thus, there should be no true biologic borderline. Finally, a randomized study showed that patients with ALCI Hodgkin-like received equally well to the ABVD regimen for Hodgkin's disease as a MACOP-B regimen for aggressive NHL. Study suggesting a closer relationship to Hodgkin's disease than to typical ALCI. The current consensus is that the majority of these cases can be resolved as either Hodgkin's disease (CD15+, CD30+ T-cell antigen, ALK–) or ALCI (CD15–, CD30+ T-cell antigen +/- ALK+) by a combination of morphology and immunophenotype. Thus, this category will be eliminated from the WHO classification.

**IMMUNOPHENOTYPE.** The tumor cells are CD30+ and usually express CD25 and EMA; they are typically CD45+ and CD15–; approximately 60% express one or more T-cell–associated antigens (CD3, CD4, CD5, or CD45RO). Studies have shown cyotogentic granule proteins in many of the cases. The ALK protein can be detected in 40% to 60% of the cases using the ALK1 monoclonal antibody, showing both nuclear and cytoplasmic staining in cases with the T(2;5), since nucleophosmin is a nuclear protein. ALK+ cases are more common in children and have a better prognosis than ALK– cases. Based on current information, T(2;5) and ALK expression are not considered defining features of ALCI, since negative case results exist; however, the positive case results appear clinically relatively homogeneous: young patients with a relatively good prognosis.

**DIFFERENTIAL DIAGNOSIS.** Many cases of ALCI were previously diagnosed as nonlymphoid tumors (malignant histiocytic tumors, regressing atypical histiocytosis, melanoma, metastatic carcinoma, sarcoma) or as lymphocyte-depleted Hodgkin's disease. A high index of suspicion is important in recognizing the tumor as lymphoid, immunophenotyping studies on paraffin sections (CD45, CD30, pan-T antigens, lack of epithelial or melanocyte-associated antigens) usually confirm the diagnosis.

**CLINICAL FEATURES.** Anaplastic large cell lymphoma represents approximately 2% of all lymphomas, but approximately 10% of childhood lymphomas and 50% of large cell pediatric lymphomas. Primary systemic ALCI may involve lymph nodes or extranodal sites, including the skin, but is not localized to the skin. Tumors that present with systemic disease (with or without skin involvement) have a bimodal age distribution in children and adults and are associated with the T(2;5); particularly in children, in 20% to 40% of the cases. Patients may present with isolated lymphadenopathy or extranodal disease in any site, including gastrointestinal tract and bone. Anaplastic large cell lymphoma in children is characterized by frequent high stage but a good response to therapy with overall excellent survival. Cases with the T(2;5) have a significantly better prognosis than cases lacking the T(2;5). THERAPY. Treatment regimens used for anaplastic large T/null-cell lymphoma of the primary systemic type are the same as used in diffuse large B-cell lymphoma. Treatment results have been excellent, with better survival in ALK+ patients (71% to 83%) than in ALK– patients (31% to 37%). Excellent results are seen in adults as well as children. One report using autologous bone marrow transplantation early in the treatment of patients with anaplastic large cell lymphoma reported an excellent treatment outcome.

**SPECIAL CLINICAL SITUATIONS**

**CHILDREN**

See Chapter 45.2 for a discussion of lymphomas and leukemias in children.

**ELDERLY PATIENTS**

The incidence of NHL increases with age and more than 50% of patients are beyond 60 years of age at diagnosis. Some studies have failed to identify age as an important prognostic factor in patients who receive aggressive therapy for NHL, although the vast majority of studies have shown that elderly patients have worse outcomes than younger patients. The International Prognostic Index demonstrated that NHL patients older than 60 years of age had a significantly lower complete remission rate, greater chance of relapsing from remission (relative risk, 1.8), and higher risk of death (relative risk, 1.96).

There are several explanations for the poorer outcome in elderly adults. Some analyses have shown that older patients were more likely to have mortality from chemotherapy-related toxicity than younger patients, despite similar complete remission rates. Other studies have identified higher relapse rates in elderly patients. Other analyses have shown inferior survival in elderly patients to be a result of increased deaths from cardiovascular disease and other nonrelapse causes. A Non-Hodgkin's Lymphoma Classification Project demonstrated that elderly patients were more likely to have a high International Prognostic Index than younger patients. Some studies have shown that older patients are more likely to have poor performance status, advanced-stage disease, and diffuse histology, and are more likely to have extranodal disease. Older patients are also more likely to have comorbid conditions. These factors have often led to arbitrary dose reductions or use of less aggressive therapy, which may reduce the possibility of cure. This is exemplified by Southwest Oncology Group studies that revealed a complete remission rate of 37% in patients 65 years of age and above who received initial 50% dose reductions of cyclophosphamide and doxorubicin. Complete remission rates were 52%, a rate similar to younger patients, when full-dose chemotherapy was used.

Some analyses have shown that less intensive regimens may be associated with diminished mortality and equivalent outcomes when compared with more aggressive...
regimens in elderly NHL patients. These results have led to a multitude of phase II trials of chemotherapy regimens designed specifically for treatment of elderly patients with NHL. In general, these regimens have used anthracyclines with less cardiotoxicity than doxorubicin, have substituted mitoxantrone for doxorubicin, and have used short-duration weekly therapy. Although these regimens may be well-tolerated, selection bias and lack of appropriate comparisons make it difficult to determine whether these novel regimens are superior to standard regimens.

Several prospective randomized trials have examined results of NHL treatments in elderly patients. A Canadian trial compared standard CHOP administered every 3 weeks with a regimen in which CHOP was administered weekly at a one-third dose. Patients were 65 years of age or older and had intermediate-grade NHL. No significant differences in complete response rate or progression-free survival were observed, although 2-year overall survival was 74% in the CHOP group and 51% in patients given weekly therapy (P = .05). A Dutch trial compared CHOP and CNOX (cyclophosphamide, mitoxantrone, vincristine, and prednisone) in patients 60 years of age and older with aggressive NHL. The complete response rate was 49% in CNOX-treated patients and 31% in patients who received CHOP (P = .03). Overall survival at 3 years was 42% and 26%, respectively. A trial from the European Organization for Research and Treatment of Cancer randomized patients older than age 70 with aggressive NHL between treatment with CHOP and a regimen consisting of etoposide, mitoxantrone, and prednimustine. The complete response rate was 77% in the CHOP arm and 50% in the etoposide, mitoxantrone, and prednimustine arm (P < .01). Progression-free survival was also significantly longer in the CHOP arm and overall survival at 2 years was 65% and 30%, respectively (P = .004). A Groupe d'Etude des Lymphomes de l'Adulte randomized patients beyond 69 years of age with aggressive NHL to treatment with cyclophosphamide, teniposide, and prednisolone or to treatment with cyclophosphamide, teniposide, prednisolone, and pirarubicin. The complete remission rate was 47% in patients who received the anthracycline-containing regimen, as compared with 32% in the cyclophosphamide, teniposide, and prednisolone arm. Among patients who received the anthracycline-containing regimen, 5-year overall survival rates were 27% and 19%, respectively (P < .05). A British National Lymphoma Investigation trial studied two treatment regimens in patients older than age 60 with aggressive NHL. Patients were randomized between six-drug regimens that contained either doxorubicin or mitoxantrone. Toxic deaths were significantly less common in patients who received the mitoxantrone-containing regimen, and the complete remission rate was 62%, as compared with 58% in patients who received doxorubicin (P = .07). Overall survival at 4 years was 59% and 35%, respectively (P = .0014).

Another Groupe d'Etude des Lymphomes de l'Adulte prospective randomized trial compared fludarabine versus cyclophosphamide, doxorubicin, teniposide, and prednisolone (CHVP) plus interferon in patients older than age 59 with follicular lymphoma. Higher response rates were noted in patients treated with CHVP and interferon. Two-year failure-free survival was 63% in the CHVP plus interferon arm and 49% in the fludarabine arm (P < .05). Overall survival rates were 77% and 62%, respectively (P < .05).

Elderly patients who participate in clinical trials may be subject to selection bias, although these results suggest that these patients may be able to tolerate aggressive anthracycline-containing regimens. When these diverse characteristics such as poor performance status are excluded, elderly NHL patients may have outcomes similar to younger patients. It seems unreasonable to arbitrarily reduce drug dosages or to withhold aggressive therapy because of chronologic age alone in NHL patients with good performance status and without significant comorbidity. These patients should be treated aggressively with CHOP or similar regimens, which can be reduced in intensity at a later time if not tolerated. Other patients may still be candidates for less aggressive therapy, or even a watch and wait approach, if disease is behaving indolently. The use of colony-stimulating factors (CSFs) may allow elderly patients to receive planned chemotherapy doses, although they may be less effective for the oldest patients and do not entirely prevent neutropenic complications. A randomized trial showed that granulocyte-CSF (G-CSF) was able to reduce the incidence of neutropenia and infection in elderly patients receiving an aggressive NHL regimen, although response rates and survival were not significantly different.

**POSTTRANSPLANT LYMPHOPROLIFERATIVE DISORDERS**

The risk of developing lymphoma is markedly increased following solid organ transplantation. PTLDs occur in 0.8% to 20.0% of transplanted patients. Although mortality of 60% to 80% is frequently reported, more favorable outcomes have been described. Initial disorders are seen after allogeneic bone marrow transplantation, especially in recipients of T-cell–depleted marrow. PTLDs are almost always EBV-related, although cases unrelated to EBV have been described. The development of PTLD results from proliferation of EBV-transformed B-cell clones when patients receive immunosuppressive therapy following transplantation. Occasional cases of Hodgkin's disease and T-cell NHL have been reported. Most PTLDs following solid organ transplants are host derived.

The histologic appearance of PTLD is highly variable. Classification systems with clinical relevance have been proposed. Lesions may be polymorphic or monomorphic. In some cases the appearance may resemble infectious mononucleosis and other cases may be indistinguishable from aggressive NHL or plasmacytomas. Lesions may be polyclonal, oligoclonal, or monoclonal. Clinically, patients may have a syndrome similar to infectious mononucleosis with fevers, lymphadenopathy, tonsilar enlargement, and hepatitis. This presentation is more common in children and is frequently seen in the first year after transplantation. Other patients have nodal or extranodal presentations more typical of NHL. Involvement of the CNS and extranodal sites is common, as is involvement of the transplant organ.

The risk of PTLD is highest in recipients of heart-lung transplants and lowest in kidney transplant recipients, although the incidence rate is still 20 times higher than that seen in recipients of bone marrow transplantation. Disease that occurs more than 1 year after transplantation has been associated with worse outcome in most, although mortality of 60% to 80% is frequently reported, more favorable outcomes have been described. Initial disorders are seen after allogeneic bone marrow transplantation, especially in recipients of T-Cell–depleted marrow. PTLDs are almost always EBV-related, although cases unrelated to EBV have been described. The development of PTLD results from proliferation of EBV-transformed B-cell clones when patients receive immunosuppressive therapy following transplantation. Occasional cases of Hodgkin's disease and T-cell NHL have been reported. Most PTLDs following solid organ transplants are host derived.

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The risk of developing NHL is markedly increased in patients infected with human immunodeficiency virus type 1. Large cell lymphomas, small noncleaved cell NHL, and primary CNS lymphoma are considered AIDS-defining conditions. The risk of developing NHL after another AIDS-defining diagnosis is increased 165-fold in the first 3.5 years.

AIDS-related lymphomas are B-cell neoplasms. Virtually all primary CNS lymphomas and approximately 50% of other AIDS-related NHL are EBV-related. Most cases are classified as small noncleaved cell histology or diffuse large cell lymphoma. The risk of low-grade NHL may also be increased, although these lymphomas are not considered to be diagnostic of AIDS. Small noncleaved cell lymphomas are associated with c-myc activation in virtually all cases and are frequently associated with p53 mutations. Rearrangements of bcl-6 are detected in approximately 40% of diffuse large cell lymphomas. Primary effusion lymphoma is seen in 1% to 3% of AIDS patients and is associated with HHV-8. AIDS-related NHL usually behaves aggressively. Systemic symptoms are common, along with involvement of extranodal sites. Gastrointestinal tract involvement is common, as well as unusual involvements of anus and soft tissues, and heart. Approximately 15% of cases are primary CNS lymphomas. The prognosis for AIDS-associated NHL is poor. Median survival averages approximately 6 months and 2-year survival rates are 10% to 20%. Factors associated with improved survival include higher CD4 counts, EBV-negative lymphomas, higher performance status, younger age, and low stage. Patients with a history of drug abuse have worse outcomes, and outcome is better for patients without an AIDS-defining illness before NHL.
Aggressive lymphomas are associated with significant toxicity, and the use of lower dose chemotherapy regimens have been investigated. A randomized trial comparing m-BACOD with reduced-dose m-BACOD demonstrated median survival rates of 31 weeks and 35 weeks, respectively (P = .25), with less toxicity in the low-dose arm. Similar survival has been noted in a phase II trial of oral lomustine, etoposide, cyclophosphamide, and procarbazine. Median survival was 9.3 months in AIDS-associated NHL patients who received the LNH-84 regimen, which incorporates CNS prophylaxis. Median survival was 18 months using a regimen of combined infusion cyclophosphamide, doxorubicin, and etoposide combined with didanosine, and median survival was 13 months using weekly methotrexate combined with zidovudine.

The lack of randomized trials makes it difficult to reach consensus on management approaches for AIDS patients with NHL. Dose-modified regimens should be considered, although many patients can tolerate full-dose chemotherapy. Other investigators have recommended CHOP or similar regimens for low-risk patients, and dose-attenuated regimens for patients with poor performance status, low CD4 counts, or a prior AIDS-defining condition. The benefits of CSFs are uncertain, and no clear survival advantages have been demonstrated, although routine use may be justified. Antiretroviral therapy and prophylactic antibiotics should be continued during therapy. There are differing opinions on the use of CNS prophylaxis, although patients with small noncleaved histology and those with sinus or testicular involvement should receive prophylactic intrathecal therapy.

The prognosis for AIDS patients with primary CNS lymphoma is also poor. Standard therapy has consisted of whole brain irradiation, although median survival is 3 to 4 months. Patients may respond to high-dose methotrexate, and the role of combined modality therapy is being investigated. No standardized approaches have been developed for primary effusion lymphoma and these patients should probably be treated like other patients with AIDS-related NHL.

EXTRANODAL SITES

Primary Central Nervous System Lymphoma

Primary CNS lymphoma accounts for less than 5% of all primary brain tumors and approximately 1% to 2% of all lymphomas in immunocompetent patients. The incidence of primary CNS lymphoma rises with age and has increased four times as rapidly as extranodal NHL as a whole, although there is controversy as to whether this increase is entirely explained by the AIDS epidemic. Most cases are large cell lymphoma, although other histologic subtypes can be observed. Ocular lymphoma is common and slit-lamp examination should be performed for all patients. Leptomeningeal involvement also occurs commonly. Corticosteroid administration may lead to rapid regression of primary CNS lymphoma and make it difficult to obtain diagnostic tissue. Every effort should be made to perform biopsies before corticosteroids are administered to patients with suspected CNS lymphoma.

The median survival of untreated patients is less than 4 months. Median survival was 16 months and actuarial 5-year survival was 19% in a series of 226 patients treated heterogeneously. Overall survival is not improved after surgical resection, and surgery has little role except for diagnostic purposes. The use of RT improves overall survival, although median survival after whole brain irradiation is only approximately 12 months, a rate similar to glioblastoma multiforme. Most patients progress locally after RT despite high rates of remission.

Conventional regimens such as CHOP have little efficacy in primary CNS lymphoma. Several regimens designed specifically for treatment of primary CNS lymphoma have been developed. These regimens have generally employed drugs that penetrate the CNS, such as methotrexate and cytarabine, combined with intrathecal prophylaxis, and RT. It is thought that RT should be administered after chemotherapy because of evidence that neurotoxicity is enhanced if radiation is administered first. Results from these phase II studies, as well as retrospective analyses, suggest that overall survival rates are improved with the use of chemotherapy regimens containing high-dose methotrexate.

Unfortunately, the use of whole brain radiation results in rates of leukoencephalopathy that may be as high as 25% 5 years after treatment. In other studies, the rate of leukoencephalopathy was estimated to be nearly 80% in patients over the age of 60 who survived at least 1 year after treatment. Few patients return to their former functional status after treatment for primary CNS lymphoma and median survival is less than 12 months for patients who develop neurotoxicity.

Analyses of patient-related prognostic factors have consistently identified age over 60 years and poor performance status as adverse prognostic characteristics for patients with primary CNS lymphoma. It has been suggested that improved results associated with combined modality therapy may be due to patient selection, and some trials have shown that regimens using chemotherapy, without whole brain radiation, may be as good as combined modality therapy. Other investigators have reported high response rates using osmotic blood–brain barrier disruption and intraarterial chemotherapy for patients with primary CNS lymphoma.

We recommend that patients receive initial therapy with a regimen that uses high-dose methotrexate. It is unknown whether this eliminates the need for intrathecal therapy, although some analyses have shown that overall survival was improved using regimens that included intrathecal chemotherapy. The use of radiation as initial therapy should be avoided, except in patients who are unlikely to tolerate chemotherapy. Because of the risk of leukoencephalopathy, withholding radiation after chemotherapy may be considered, especially in older patients who achieve a complete remission with chemotherapy.

Testicle

Primary testicular NHL accounts for approximately 1% to 9% of all testicular neoplasms and is the most common testicular neoplasm in men over the age of 60. Testicular lymphoma is frequently associated with involvement of Waldeyer's ring, skin and subcutaneous tissue, lung, and CNS. Involvement of the contralateral testis is common at diagnosis or later in the course of disease. Most tumors are classified as diffuse large cell histology or immunoblastic lymphoma, although Burkitt's lymphoma is common in children, and follicular lymphomas and other histologic subtypes have been described.

Most series have reported poor outcomes with relatively long-term survivors. Five-year overall survival was 17% in a Danish population-based study. Median survival is less than 12 months in many series, although somewhat better results have been reported in more recent series. Nevertheless long-term disease-free survival is poor, especially for patients with advanced disease, and most series have failed to show a survival plateau. Factors reported to be associated with improved outcome have included localized disease, low International Prognostic Index score, age, presence of sclerosis within biopsies, tumor size, and right-sided tumors. Orchiectomy is universally recommended as initial therapy for patients with localized disease. Although long-term disease-free survival has been described after orchiectomy alone, the vast majority of patients relapse, and this is not adequate therapy, even for patients with IE disease. Furthermore, relapse rates exceeding 50% have been observed in the majority of reports in which adjuvant RT was used following orchiectomy. Relapses often occur in extranodal sites, and this suggests that testicular NHL is usually a systemic disease, even when clinically localized.

These poor results have led to use of chemotherapy following orchiectomy for patients with stage IE and IE disease. The Danish Lymphoma Study Group noted that the relapse rate was 15.4% for stage IE or IIE patients who received combination chemotherapy after orchiectomy, as compared with 63.6% for the remaining patients (P < .05). Median relapse-free survival was 28 months and 14 months, respectively. An analysis of men with stage IE disease at Harvard demonstrated that 5-year relapse-free survival was 75% for men who got adjuvant chemotherapy, as compared with 50% for those who received no adjuvant therapy. However, by 10 years no difference in relapse-free survival was observed. The best results in patients with stage IE and IIE disease have been reported by the Vancouver group. Patients were treated with a brief course of doxorubicin-based chemotherapy followed by scrotal radiation for stage IE patients and additional pelvic and paraaortic radiation for patients with stage IIE disease. The 4-year overall survival and relapse-free survival rates were 93%, as compared with 50% in a historic control group treated with orchiectomy and radiation alone. No relapses in the contralateral testis or CNS were observed, and the routine use of CNS prophylaxis was thought to be unnecessary.

However, other groups have reported CNS relapses and contralateral testis relapse after doxorubicin-based chemotherapy and RT in stage IE patients. The use of adjuvant radiation has been recommended by some groups, whereas others found no apparent advantage when pelvic or paraaortic radiation was...
add to stage IE patients who received chemotherapy. **High rates of CNS relapse with aggressive combination chemotherapy have led some groups to recommend routine CNS prophylaxis** and or to consider this for patients who achieve remission. **Others have questioned the value of this approach.** The high rate of contralateral testis recurrence has led some to recommend prophylactic scrotal radiation.

**Cardiac**

Lymphoma involving the heart is not often recognized clinically. Cardiac involvement can be primary or secondary. Patients with mediastinal involvement by a lymphoma frequently have secondary cardiac involvement, particularly pericardial disease. **In one series, 64% of the patients presenting with mediastinal lymphoma were found to have cardiac involvement, with pericardial infusions or infiltration being the most common finding.** In one series of 150 patients undergoing autopsies after death from lymphoma, cardiac involvement was found in 9%. **Cardiac involvement is most often identified by echocardiography, but MRI and radionuclide studies can be helpful.** Patients with secondary cardiac involvement are most likely to present with symptoms of pericardial disease, although arrhythmias have been described as well as ventricular perforation.

Primary cardiac lymphoma is unusual, but several cases have been described. **Primary cardiac lymphoma is often reported in patients with AIDS,** but is also seen in immunocompetent patients. **Primary cardiac lymphoma is often found at autopsy because of difficulty in diagnosis. However, responses to combination chemotherapy are possible.**

**Thyroid and Adrenal**

Most cases of thyroid NHL arise in a background of Hashimoto's thyroiditis, and evidence of thyroiditis is frequently detected in biopsies. **Most thyroid lymphomas are classified as diffuse large cell lymphomas and most of the remainder are MALT lymphomas.** These lymphomas may be difficult to distinguish from thyroiditis, especially when fine-needle aspirates are performed. Large cell lymphomas frequently have a small cell component, suggesting a MALT origin. Factors reported to be associated with better prognosis have included lack of bulk, stage IE disease, and absence of mediastinal or retrosternal extension.

The role of surgery in the management of thyroid NHL is controversial. Some authors have recommended complete surgical excision whenever possible, while others have argued against the use of extensive resection, particularly for patients with large cell histology, except for rare cases in which disease is confined to the thyroid and resection can be accomplished without morbidity. Results of RT for thyroid lymphoma vary widely, with 5-year relapse-free survival rates of 38% to 64%. A retrospective BNI study showed a 5-year cause-specific survival of 90% following RT of thyroid lymphomas of MALT origin, as compared with 55% for patients without MALT histology (P < 0.1). Radiation therapy alone is usually inadequate for primary large cell lymphoma, and reports have shown better outcomes with the addition of chemotherapy. Patients with localized thyroid large cell lymphoma can be successfully treated with a brief course of anthracycline-based chemotherapy followed by involved-field radiation in the same manner as other localized lymphomas. Patients with disseminated disease should receive a full course of chemotherapy.

Primary adrenal lymphoma is unusual. Most patients have diffuse large B-cell lymphoma, and the disease is sometimes bilateral. The disease might present with adrenal insufficiency, but more commonly the presenting manifestation is an adrenal mass that might be found incidentally on imaging studies.

**Pancreas**

Lymphoma presenting in the pancreas is rare. Lymphomas presenting in the pancreas are usually diffuse large B-cell lymphomas. Although rare, recognizing their presence is extremely important for the patient. Diffuse large B-cell lymphoma has a much better prognosis than adenocarcinoma of the pancreas, and failure to make an accurate histologic diagnosis keeps a patient from appropriate therapy and a chance for cure.

**Breast**

Lymphomas presenting in the breast are rare. Lymphomas in this site can be MALT lymphomas, diffuse large B-cell lymphoma, and Burkitt's lymphoma. Breast involvement and Burkitt's lymphoma have been seen particularly in association with pregnancy.

**Kidney, Ureter, Bladder, and Prostate**

Lymphomas presenting in the kidney, ureter, bladder, and prostate are rare. The most common lymphoma seen involving the kidney is diffuse large B-cell lymphoma. Prostatic involvement by lymphoma is often related to SLL.

**Ovary, Uterus, and Vagina**

Lymphomas presenting in the female genital tract are rare. The most common has been diffuse large B-cell lymphoma, although MALT lymphoma can be seen. An accurate histologic diagnosis is important to avoid inappropriate therapy.

**Eye and Orbit**

Lymphomas presenting in the orbit are most often MALT lymphomas. In the past, these tumors were often called pseudolymphomas. In one series, 80% were MALT lymphomas, 14% were diffuse large B-cell lymphomas, and rare cases of mantle cell lymphoma and lymphoplasmacytic lymphoma were seen. Patients with MALT lymphomas in the orbit most often present with unilateral swelling and most have stage I disease. Treatments used have included observation, radiotherapy, chemotherapy, and combined modality therapy. Radiotherapy alone can produce durable remissions in the majority of patients with localized disease and is probably the treatment of choice. Patients with more aggressive subtypes of lymphoma should be treated with modalities appropriate for that subtype.

Primary ocular lymphoma most often presents with altered vision or uveitis that is refractory to therapy. Patients might also present with photophobia, a red eye, retinal detachment, pain, glaucoma, or the symptoms of lymphoma involving other parts of the CNS. Intraocular lymphoma should be considered one presentation of primary CNS lymphoma. Treatment of these patients should include radiotherapy of the eye along with combined chemotherapy and radiotherapy to treat the entire CNS.

**Lung**

Lymphomas presenting in the lung are unusual and have a wide variety of histologic appearances. These include MALT lymphomas, diffuse large B-cell lymphoma, lymphomatoid granulomatosis (which is usually a manifestation of diffuse large B-cell lymphoma), and intravascular lymphomatosis. MALT lymphomas in the lung and at other extranodal sites have an indolent course. Surgery can sometimes be curative. Patients with diffuse large B-cell lymphoma should receive aggressive combination chemotherapy regimens.

**Bone**

NHL presenting primarily in the bone makes up as many as 5% of extranodal NHLs. Since the report by Parker and Jackson, this has been recognized as a distinct clinical pathologic entity. The vast majority of patients have diffuse large B-cell lymphoma and present with bone pain, a palpable mass, or both. As is always true in diagnosing lymphomas, an adequate biopsy is essential for accurate diagnosis.

Most patients with primary lymphoma of the bone have localized disease, often with extension to adjacent soft tissues. The masses can be quite large. Patients have been treated with radiotherapy, chemotherapy, or combined modality therapy. There is a trend in these reports for better failure-free...
survival in patients treated with combined modality therapy. Patients should be managed in conjunction with an orthopedic surgeon because of the risk of fracture. Delayed follow-up should include observation for avascular necrosis as a consequence of the therapy.

**Pleura**

Pleural involvement in NHL is not rare, with a frequency as high as 20% being reported. Pleural involvement can be seen at presentation of the lymphoma or develop during the course of the disease. Effusions can be seen in any subtype of NHL. Most effusions are exudative, with a few patients having chyloous effusion. Cytologic examination results are often positive. In SLL the diagnosis can be difficult because of the bland nature of the lymphoma cells in the fluid. In these circumstances, demonstration of a B-cell immunophenotype can be helpful, since most reactive pleural effusions have predominantly T lymphocytes. The presence of pleural effusion at the time of diagnosis does not seem to adversely affect prognosis in comparison with other patients with similar stages.

A distinct type of pleural involvement by lymphoma has been referred to as pleural effusion lymphoma. These patients demonstrate Kaposi's sarcoma–associated herpesvirus (also known as HHV-8) in the lymphoma cells. These tumors also have been associated with EBV infection. Patients have diffuse large-B-cell lymphomas, sometimes with immunoblastic or anaplastic appearance. These lymphomas rarely express c-myc, bcl-2, or bcl-6 gene rearrangement. The tumors often remain confined to the pleura. These patients have a poor prognosis, probably in large part because of the frequent occurrence of this lymphoma in patients infected by the human immunodeficiency virus. However, this lymphoma has been reported in patients with negative results for human immunodeficiency virus.

**Skin**

Following the gastrointestinal tract, the skin is the second most common extranodal site primarily involved by NHL. As opposed to lymph nodes and most other extranodal sites of presentation of lymphoma, the skin is unusual in that T-cell lymphomas occur more frequently than B-cell lymphomas. The most common cutaneous T-cell lymphoma, mycosis fungoides, is dealt with in Chapter 45.4. The most common presentation is a new or unusual skin lesion.

Skin lymphomas can be classified using the WHO classification. However, the European Organization for Research on the Treatment of Cancer has also developed a classification that specifically deals with primary cutaneous lymphomas. An important feature interpreting any histologic diagnosis of a cutaneous lymphoma is to remember that the clinical behavior may be different than when the same diagnosis is identified in nodal or other extranodal sites. It is also important to realize that full-thickness biopsies usually are required for diagnosis. The diagnosis of cutaneous lymphomas can be extremely difficult, even with immunohistochemical and molecular genetic studies. Repeat biopsies are sometimes required for a definitive diagnosis. In addition, the clinical history may be important in making the diagnosis. Lymphomatoid papulosis is histologically quite similar to CD30+ Tnull-cell lymphomas in the skin. Often a history of chronic recurrent disease is helpful in making the correct diagnosis by making the distinction among cutaneous CD30+ lymphoproliferative disorders ranging from the benign behavior of lymphomatoid papulosis to an aggressive anaplastic large cell lymphoma. Peripheral T-cell lymphomas that are CD30– can involve the skin and typically follow an aggressive clinical course. Tumors with a high proportion of large cells seem to be more aggressive. Anergic lymphomas can also have cutaneous presentations and are associated with a highly aggressive course.

Primary B-cell lymphomas in the skin are less common, but occur more frequently than previously appreciated. These include marginal zone lymphomas and diffuse large-B-cell lymphomas. Marginal zone lymphomas of the skin are typically of MAL T type. These lymphomas have an excellent survival with local therapy, although local recurrence sometimes occurs. Primary diffuse large-B-cell lymphomas occurring on the trunk tends to behave indolently and can be managed with local therapy, in contrast to those on the legs, which tend to follow a more aggressive course.

**Paranasal Sinuses**

Paranasal sinuses represent an unusual site of presentation of NHL in North America. In North America most of these patients have diffuse large-B-cell lymphoma, in contrast to frequent T-cell or NK-cell lymphoma with angiocentric involvement seen in Asia. Patients typically present with pain, rhinorrhea, airway obstruction, swelling, epistaxis, proptosis, or diplopia. In general, patients with disease confined to the primary site should receive combined modality therapy, with a combination chemotherapy regimen including an anthracycline followed by radiotherapy. In some patients, the radiotherapy might not be given and a longer course of chemotherapy may be used because of concerns about visual toxicity or persistently dry mouth. Because this type of lymphoma has a predilection to spread to the CNS, these patients should receive prophylactic CNS treatment with intrathecal chemotherapy.

**Gastrointestinal Tract**

Gastrointestinal tract represents the most frequent extranodal site of presentation of NHLs. Lymphomas can present in the oral pharynx, oropharynx, esophagus, or small intestine or rectum. In North America, lymphomas in most of these sites are predominantly diffuse large-B-cell lymphomas. In the stomach MALT lymphomas represent a minority of NHLs in the United States, but are more common in other areas in the world. Lymphomas occurring in the small intestine can include enteropathy associated T-cell lymphomas and lymphomas arising in immunoproliferative disease of the small intestine. In addition, Burkitt lymphomas as well as diffuse large-B-cell lymphoma can be seen in the rectum in patients affected with human immunodeficiency virus. Patients presenting with multiple polyps in the colon usually have mantle cell lymphoma.

Symptoms and signs of presentation reflect the site of involvement. The most serious presenting symptoms include perforation and bleeding. These can also be complications of the treatment of the lymphoma because of the necessity of perforation of the colon. Because the administration of systemic therapy is often appropriate, for patients presenting with diffuse large-B-cell lymphoma in other sites, it is now clear that surgery, while associated with a modest chance for cure, is not required for cure, and that chemotherapy with or without radiotherapy seems to yield a higher cure rate. Patients with gastric MALT lymphoma can be treated with eradication of Helicobacter pylori as described in the section on MALT lymphomas (see Infectious Agents, earlier in this chapter). For patients with MALT lymphoma who do not respond to this treatment but have disease confined to the stomach, radiotherapy is usually curative.

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Cutaneous T-cell lymphomas

INTRODUCTION

Cutaneous T-cell lymphoma (CTCL) is a lymphoproliferative disorder of epidermotropic, neoplastic T cells with a wide range of clinical manifestations. Although previously considered as distinct clinical entities, mycosis fungoides (MF), Sézary syndrome (SS), reticulumb cell sarcoma of the skin, and several other cutaneous lymphocytic dyscrasias are now recognized as different clinical presentations of CTCL. All forms of CTCL are neoplasms of T lymphocytes, which home to skin and to the T-cell zones of lymphoid structures but generally not to bone marrow. The clinical value of the umbrella classification of CTCL is twofold. First, it highlights the relationship between distinct clinical presentations that can nevertheless evolve into one another (i.e., the plaque stage of MF can develop into the erythrodermic SS) or coexist (i.e., plaque-stage MF and lymphomatoid papulosis (LP)). Second, the nomenclature emphasizes the clinical relevance of advances in the understanding of the biology of the malignant T cells. Recognition of the malignant clone-specific properties of the T-cell receptor (TCR) for antigen on the CTCL cells in individual patients has provided the most sensitive diagnostic tool for the disease and offered an extraordinary target for selective immunologic attack of CTCL cells in such treatments as photopheresis. Still, it remains fairly useful for the clinician to attach the subtype of CTCL to the name (e.g., CTCL/MF), as the management scheme and prognosis for these subtypes differ.

PATHOBIOLOGY

CTCL is a clonal neoplasm of mature CD4+ helper-inducer T cells, which are capable of stimulating immunoglobulin synthesis by B cells, perhaps by secretion of interleukin-4 (IL-4) or other cytokines. CTCL cells also express BE-2, a molecule related to heat-shock proteins the function of which is yet unknown; the CD45R0 marker characteristic of memory T cells, and cutaneous lymphoid antigen (CLA), a glycoprotein that is expressed on the surface of only a small fraction of normal T cells in cutaneous infiltrates. Both of the last two markers are simultaneously expressed on the surface of virtually all circulating CTCL cells. The deficiency of normal T cells that can accompany the systemic dissemination of lymphoma may reflect the production of IL-10, an inhibitory cytokine produced by those CTCL cells.

CLA is the physiologic ligand of endothelial cell E-selectin, a cell adhesion molecule expressed on the surface of endothelial cells of cutaneous venules during chronic inflammation. Interactions between CLA on the surface of CTCL cells and E-selectin on endothelial cells allow CTCL cells to adhere to the walls of cutaneous venules, leave the circulation, and enter the skin. Once CTCL cells enter into the skin, their most striking trait is their profound epidermotropism.

In addition to producing cytokines, CTCL cells are exposed to a complex paracrine environment composed of many growth factors and cytokines elaborated by keratinocytes and stromal fibroblasts, macrophages, endothelial cells, and normal and neoplastic T lymphocytes. Preformed IL-1 may be released by proliferating keratinocytes to stimulate both keratinocytes and benign or neoplastic T cells to release granulocyte-macrophage colony-stimulating factor (GM-CSF) and macrophage colony-stimulating factor (M-CSF). The latter two cytokines enhance the antigen-presenting capabilities of Langerhans’ cells (LC) and activate restimulating macrophages, which respond by releasing a complex mix of cytokines active on keratinocytes, fibroblasts, and endothelial and lymphohemopoietic cells.

In more advanced stages of disease, CTCL cells lose their dependence on epidermal cell adhesion molecules and cytokines so that their epidermotropism either is diminished (to permit the development of tumor nodules that extend deep into the dermis) or is lost completely (to permit dissemination of the neoplastic T cells to nodal and visceral sites). At this stage, the clinical presentation of CTCL may become indistinguishable from that of a peripheral T-cell lymphoma, although the broad involvement of the skin usually remains a distinguishing feature. Even at this advanced stage, the distinctive tissue distribution of the malignant cells (skin infiltration, preferential localization in interfollicular regions of lymph nodes, and avoidance of bone marrow) remains evident.

EPIEMIOLOGY

CTCL is a relatively rare neoplasm, and the Surveillance, Epidemiology, and End Results program reports that the incidence had increased 3.2-fold between 1973 and 1984. The overall incidence rate is approximately 4 per 1,000,000, according to data from that program. The actual incidence rate may be an order of magnitude higher, given possible underreporting and the difficulty and cost of diagnosing the disease. The incidence of CTCL rises with age such that the majority of patients are between 40 and 60 years old. The disease is 2.2 times more common in male than in female subjects, and incidence rates are somewhat higher in African Americans than in whites.

ETIOLOGY

The inability to propagate CTCL cells in vitro after isolation from skin lesions, even from rapidly growing cutaneous tumors, has rendered molecular biologic studies of...
CTCL far less informative than they have been for many other lymphoid neoplasms; to date, the molecular etiology of CTCL remains unclear. However, at least one study has implicated rearrangements or deletions of the tal-1 and NFIB/Zfy/lyt-10 encoded transcription factors in a subset of CTCL patients with very aggressive disease. In addition, transgenic mice that constitutively synthesize IL-7 develop extensive dermal infiltrates that progress to a cutaneous lymphoma resembling CTCL—results that suggest that overexpression of IL-7 might contribute to the development of CTCLs. Such infiltrates develop even when the transgene is expressed in athymic nude mice, implying that the evolution of IL-7–induced dermal lymphoma may be dependent on the skin rather than on the thymus. Although the phenotypes of the lymphomatous T cells and their distribution in the skin are not identical with those of human CTCL, a refinement of this experimental system may ultimately provide an animal model for the human disorder.

Given the inherent immunologic nature of the neoplastic cells responsible for this disorder, it has been proposed that chronic exposure to occupational chemicals, pesticides, or tobacco may predispose to the development of CTCL; however, none of these potential associations has survived scrutiny. The observations that the disease is more common in African Americans than in whites and that it often presents first in areas normally shielded from the sun (i.e., “bathing trunk” distribution) together suggest that actinic exposure may actually inhibit the evolution of the malignant clone from normal “cutaneous T cells.” It is noteworthy that the epidermotropic collections of CTCL cells, referred to as Pautrier microabscesses, may represent congregation of malignant T cells around LC, the dendritic antigen-presenting cells (DC) of the epidermis, and that LC are fairly sensitive to ultraviolet (UV) damage. This observation has suggested that epidermotropic CTCL cells may receive growth signals from their contact with LC. Therefore, it is possible that UV damage of LC, more significant in whites than in African Americans (whose darker pigment shields the LC), may interrupt this growth signal and inhibit the replication of CTCL cells in UV-exposed skin sites. It is also intriguing that the often profound response of plaque-stage CTCL to UV treatment may reflect this phenomenon as well. The observation that individuals infected with the human T-cell leukemia virus type 1 (HTLV-I) often develop T-cell leukemias with skin involvement indistinguishable from those of CTCL has led some to hypothesize that CTCL may be a consequence of infection with HTLV-I or another unknown retrovirus, a possibility that remains the subject of active investigation.

CLINICAL PRESENTATION

MYCOSIS FUNGOIDES

The classic MF presentation of CTCL progresses through the following four distinct phases:

1. A premycotic phase with an asymptomatic, scaling erythematous macular eruption, often in sun-shielded areas (i.e., bathing trunk distribution), which lasts for months to years during which the diagnosis may be suspected but cannot be confirmed by standard clinical or histopathologic means

2. A patch phase with thin, barely palpable, erythematous and eczematous lesions the histologic features of which are at least “consistent” with the diagnosis of CTCL

3. A plaque phase with more readily palpable erythematous lesions

4. A tumor phase, in which the neoplastic infiltrate extends below the upper dermis

Painful erythroderma may arise de novo or during any of the earlier described phases and is not always associated with frank T-cell leukemia (SS). Infrequently, CTCL presents with cutaneous tumor nodules in the absence of patches or plaques. Patients may also present with involvement of internal organs.

RELATED CONDITIONS

The MF presentation of CTCL often manifests alongside (and can be confused with) several related, more benign cutaneous lymphoid dyscrasias. They include LP, alopecia mucinosa–follicular mucinosis (AM-FM), and pagetoid reticulosis (PR). CTCL also has features in common with two other, clearly malignant disorders: adult T-cell leukemia-lymphoma (ATLL) and CD30+ anaplastic large cell lymphoma.

LP is a dermatologic disorder that resembles pityriasis lichenoides et varioliformis acuta. LP lesions often appear as groups of erythematous brown papules that develop a scale or crust. Resolving LP lesions may leave residual pigment or superficial atrophic scars. Depending on the clinical series, from 5% to 20% of patients with LP eventually develop a non-B-cell lymphoma, most often CTCL. Regressing atypical histiocytosis is thought to be a variant of LP.

AM is an infiltrative, cutaneous T-cell dyscrasia also known as follicular mucinosis (FM). AM-FM is characterized by the accumulation of acid mucopolysaccharides in the sebaceous glands and root sheaths of hair follicles. When the lesions of AM-FM develop in a hair-bearing area, patchy alopecia may be their presenting sign. Overall, 15% to 30% of AM-FM patients either have or will develop CTCL.

PR, or Woringer-Kolopp disease, presents as a solitary cutaneous lesion of long duration and is characterized histologically by significant numbers of abnormal mononuclear cells infiltrating the epidermis. The underlying dermis is involved by a mixed inflammatory cell infiltrate. Clonal T-cell gene rearrangements have been observed in PR, which, in all likelihood, represents an indolent, particularly epidermotropic variant of CTCL.

ADULT T-CELL LEUKEMIA-LYMPHOMA AND CD30+ ANAPLASTIC LARGE CELL LYMPHOMAS

ATLL is a disorder that develops in some HTLV-I-infected individuals. The clinical presentation of ATLL is often acute, with rapidly growing cutaneous lesions, hypercalcemia, marked lymphadenopathy, and infiltration of visceral organs. Patients also present with systemic symptoms, such as drenching night sweats and weight loss, and, in marked contrast to CTCL, the diagnosis of ATLL is usually made soon after presentation. Patients may present with a leukemic form of ATLL with extremely high white cell blood counts or may present a lymphomatous variant. ATLL patients are often severely immunocompromised and are susceptible to a variety of opportunistic pathogens. Peripheral blood and cutaneous lymphocytes often express high levels of IL-2 receptor. Current therapy for ATLL consists of simultaneous antiretroviral therapy (zidovudine) and IFN.

Ki-1 (CD30+) anaplastic large cell lymphoma may occur primarily in the skin or with systemic involvement. Patients may present with tumor-like lesions with central ulceration, which may undergo spontaneous regression. Systemic involvement is unusual, and cutaneous lesions may be treated with radiation therapy alone. However, lesions often relapse, even though the overall clinical course may be indolent. Patients with systemic disease, age older than 60 years, or whose tumors do not spontaneously regress appear to have a less favorable prognosis. Anaplastic (vs. nonanaplastic) cell histology does not imply a poorer prognosis; however, prognosis is poor for those patients whose tumors are CD30–.

APPROACH TO PATIENTS WITH MYCOSIS FUNGOIDES

The most important clinical prognostic variables related to CTCL are the type of lesion and the percentage of the total skin surface involved, nodal involvement, dissemination to visceral sites, and the presence of CTCL cells in the circulation. These parameters have been codified in the modified TNM staging classification proposed by the Cutaneous T-Cell Lymphoma Workshop in 1979. Also, this staging system has yet to be modified to incorporate the many clinical, immunologic, and molecular biologic discoveries relevant to the diagnosis and treatment of CTCL.
TABLE 45.4-1. TNM Classification of Cutaneous T-Cell Lymphomas

SKIN LESIONS

Prognosis in CTCL patients depends on both the type of lesions and the extent of cutaneous involvement. All patients should have the number and distribution of each type of lesion and an estimate of the total skin surface involved by CTCL carefully recorded before initiation of therapy. Patients with patches or plaques that involve less than 10% of the body surface (stage T1) are far more likely to be palliated over the long term or cured than those with the same types of lesions occupying more than 10% of the skin surface (stage T2) (Fig. 45.4-1). Prognosis is significantly worse for patients with cutaneous tumors (T3), although it is better for patients with less than 10% of their skin surface involved by tumors than for those with more extensive involvement (Fig. 45.4-2). 126 Prognosis is poorer still for patients with erythroderma either alone or in addition to patches, plaques, and tumors.

Skin biopsies at multiple sites may be necessary to define T-stage, as lesion morphology varies from patient to patient and for different lesions from the same patient. However, because the histopathologic criteria for the diagnosis of early CTCL are not firmly established and there is significant interobserver variability in the pathologic interpretation of the same specimens, 22 accurate definition of T-stage and diagnostic correlation with pathologic material is far from routine. Such problems are especially evident for early patch or plaque lesions wherein only a small fraction of the infiltrating T lymphocytes (confined exclusively to the epidermis) are actually neoplastic. Most of the cells in the underlying, often much more impressive, dermal infiltrate are nonneoplastic, reactive CD4+ and CD8+ T lymphocytes and represent the host’s immune response to the neoplastic clone. This typical histopathologic pattern can be significantly modified by prior therapy, as even topical steroids can significantly alter the intensity and appearance of both the neoplastic and nonneoplastic lymphoid infiltrates.

CTCL biopsy specimens should be reviewed by dermatopathologists with specific experience and interest in the study and diagnosis of CTCL. Specimens that exhibit epidermal collections of lymphocytes (i.e., Pautrier’s microabscesses) with characteristic hyperchromatic, irregularly shaped nuclei without spongiosis are interpreted as “diagnostic” for CTCL, and those that exhibit at least two of these features (epidermal collections of lymphocytes, atypical nuclei, or absence of spongiosis) are judged “consistent with” CTCL. Histopathologic features of “transformation” to a high-grade lymphoma, such as an enlarged pale nucleus and prominent nucleoli or loss of normal T-cell markers, are all associated with a poorer prognosis.

In an attempt to quantitate more precisely the histopathologic features of CTCL, one group of investigators has attempted to use vertical measurements (analogous to the Breslow level in melanoma) to delineate the depth of the cutaneous infiltrates. 22 126 In their preliminary analysis, a positive correlation with morbidity was noted for the distance from the granular layer of the epidermis to the lower limit of the CTCL infiltrate. Cell density has also been found to correlate with clinical outcomes. Jones et al. 144 have demonstrated that cell density predicted remission and progression-free, overall, and cause-specific survival after total skin electron-beam therapy (TSEBT).

Skin biopsies should also be subjected to immunophenotyping to define better the identity of the benign and neoplastic cell populations present in the cutaneous lesions. Several studies have reported correlations between the immunophenotypes of the cells present in the infiltrates and stage of disease. In general, as disease progresses, fewer CD8+ cells are observed, and the relative ratio of CD4+ to CD8+ cells increases. 144 However, in one rare and clinically very aggressive form of CTCL, the neoplastic T cells are CD8+, CD4–, as they have undergone Gd– but not ab–TCR chain rearrangement. 126

Immunogenotyping of skin biopsies can help to define whether an early lesion suggestive of CTCL actually contains a clonal T-cell population. Such analyses are best performed by polymerase chain reaction–based (PCR-based) techniques, as one rarely obtains sufficient neoplastic cell DNA from skin biopsies for routine Southern blot analyses. PCR analysis is performed with primers designed to amplify TCR G chain rearrangements that occur in all T cells before rearrangement of the a and b chain loci. Such PCR-based assays are able to detect clonal T-cell populations in 90% of skin biopsies that show diagnostic CTCL pathology. The 10% false-negative rate may reflect the fact that the currently available PCR primer pairs amplify only 90% of G chain variable regions. This high degree of sensitivity contrasts with the somewhat lower (79%) sensitivity of standard Southern blot techniques that require significantly more DNA. 22

LYMPH NODES

The incidence of lymphadenopathy increases with T-stage and is associated with a poorer prognosis. Imaging studies (computed tomography scan or magnetic resonance imaging) are recommended at initial evaluation for those with advanced disease and during follow-up to detect enlargement of thoracic, abdominal, or pelvic nodes. In practice, biopsy of uninvolved nodal sites is uncommon; lymph nodes are subjected to biopsy either at initial staging or afterward only if they are found to be obviously enlarged on physical examination or imaging studies.

Flow cytometry, immunophenotyping, and Southern blot (or PCR-based) genotyping for clonality are recommended for all nodal samples and may detect neoplastic T cells even in so-called reactive, dermatopathic (stage N1) nodes not obviously involved by CTCL. In a study of lymph node samples from 17 patients with stage N1...
disease, eight showed evidence of clonal T-cell abnormalities consistent with CTCL on Southern blotting, and these eight patients had a poorer prognosis than those whose nodes were free of CTCL. Another study of lymph node in patients with CTCL revealed that specific histologic factors were predictive of outcome. Those patients with small cell infiltrates had a median survival of 40 months, and those with high-grade immunoblastic features had a median survival of only 9 months.

PERIPHERAL BLOOD

The level of circulating neoplastic cells in CTCL patients correlates adversely with prognosis and is an important parameter to document and quantitate both at presentation and during follow-up. The application of nearly clone-specific, family-specific antibodies against the Vb regions of TCRs has also revealed that morphologic evaluations alone often grossly underestimate the level of circulating CTCL cells.

In normal individuals, none of the more than 50 available anti-Vb monoclonal antibodies (mAbs) react with more than 2% to 5% of the circulating peripheral T cells. As shown in Table 45.4-2, it is possible to use these mAbs to detect and quantify precisely the levels of circulating CTCL cells. Such analyses have revealed a remarkable clinical heterogeneity within patients who present with T4 disease. In most, the level of circulating CTCL cells is actually much higher than estimated by less sensitive techniques. In some, the expansion of the neoplastic T-cell clone is accompanied by depression of normal T cells to levels comparable with those observed in advanced acquired immunodeficiency syndrome. Such a de facto T-cell deficiency may both explain the susceptibility of erythrodermic CTCL patients to infection by bacterial, viral, and fungal pathogens and contribute to the progression of the disease, which is often held in check by host immune mechanisms.

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<th>Peripheral Blood Values of Six Patients with Advanced Cutaneous T-Cell Lymphoma</th>
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In the absence of such specific anti-CTCL mAbs, flow cytometry and Southern blot (or PCR-based) analyses of G chain rearrangements can be used to detect and quantify circulating CTCL more accurately. Flow cytometry should be performed with antibodies to the CD4, CD8, CD3, CD45R0, and CD20 antigens. The ratio of CD4+ to CD8+ cells is normally 0.5:3.5; elevations in this ratio correlate with total leukocyte count and with extent of skin disease in CTCL patients. An elevated ratio of CD4+ to CD8+ cells in excess of 4.5:1 reliably indicates significant levels of circulating CTCL cells, and a routine leukocyte count, manual differential, and smear supplemented by a measurement of the CD4:CD8 ratio represent as a good initial screen for circulating CTCL cells. If flow cytometric analysis reveals a marked elevation of the CD4:CD8 ratio or an elevation in the percentage of CD45R0+ cells, it is worthwhile to perform flow cytometry with anti-Vb mAbs to determine whether a clonal expansion of T cells is present.

If any of the aforementioned studies suggest the presence of circulating CTCL cells, the more laborious and expensive TCR gene rearrangement studies to confirm their presence are also worthwhile. Even standard Southern blot assay for TCR rearrangement can detect a neoplastic clone that represents only 1% of the total lymphocyte population and, thus, is far more sensitive in detecting circulating CTCL cells than any of the previously mentioned techniques, including flow cytometry. Nonetheless, in only approximately 10% of CTCL cases with circulating cells are Southern blots the only laboratory abnormality. In one study of 11 CTCL patients in whom circulating CTCL cells were documented by Southern blotting, ten also had CD4:CD8 ratios greater than 10:1. Only one patient's CD4:CD8 ratio was less than 2:1.

PATIENT EVALUATION

HISTORY

The duration of the eruption and the evolution of its distribution should be carefully noted. The patient should also be asked about cutaneous integrity, temperature imbalance, fissuring, pruritis, and the use of moisturizers.

PHYSICAL EXAMINATION

A complete physical examination should be performed with particular attention to the skin and lymph nodes. Examination of the skin should record the number of lesions, including their type (patch, plaque, tumor, or erythroderma), distribution, and the percentage of skin surface involved by CTCL lesions (i.e., by the "rule of nines" used in the evaluation of burn patients). Evaluation of the abdomen should be performed to detect hepatosplenomegaly, and the site, size, and number of palpable peripheral lymph nodes should be recorded.

DIAGNOSTIC TESTS

Dermatopathology

At least two skin biopsies should be obtained for routine hematoxylin and eosin histopathology. Frozen specimens should be harvested for immunophenotyping for the CD2, CD3, CD4, CD5, CD7, CD8, CD19, CD20, CD25, CD30, CD45R0, CD56, bF1, and d antigens. PCR for G chain rearrangements and, if available, b chain rearrangements should be performed on either the paraffin or frozen section tissue.

Peripheral Blood Evaluation

A complete blood cell count with differential and smear examination supplemented by a flow cytometric analysis of peripheral blood lymphocytes screen for circulating CTCL cells. Flow cytometric analysis can measure peripheral blood involvement by revealing an elevation of the CD4:CD8 ratio, an increase in CD4+CD7− lymphocytes, or an elevation of CD45R0+ lymphocytes. The interpretation of these findings is facilitated by the demonstration of the malignant clone by PCR testing for gene rearrangement in the peripheral blood. The latter, in turn, is facilitated by similar PCR testing on the patient's skin biopsy. If the clone is detectable in skin, the test is useful in the peripheral blood. If the clone is undetectable by PCR, this method is not interpretable when performed on the peripheral blood.

Other Studies

A posteroanterior and a lateral chest radiograph should be performed in all patients. Computed tomography or magnetic resonance scans should be carried out of the chest, abdomen, and pelvis both to evaluate mediastinal, retroperitoneal, and pelvic nodes as well as to supplement physical examination of the axillary and inguinal nodes in patients with T3 and T4 disease. The location of pathologically enlarged nodes should be noted and their size recorded. Such enlarged nodes should undergo biopsy (preferably by excision rather than needle sampling) to document both the presence of neoplastic T cells and the histopathologic pattern of involvement (i.e., dermalatrophic adenopathy vs. more extensive replacement). The latter can be supplemented by immunophenotypic and TCR rearrangement analyses to document the presence of neoplastic T cells. Bone marrow evaluation is not routinely performed unless abnormalities are noted on complete blood cell count or smear.
PRINCIPLES OF THERAPY

The therapy for CTCLs is fairly distinct from that of other lymphomas. Hence, many therapeutic strategies that have proved successful with localized and disseminated B-cell lymphomas have often been found to be inappropriate for CTCL. CTCL is first and foremost a disease of cutaneous lymphocytes. Hence, early-stage disease that is localized to the skin has an excellent chance of cure with therapies directed to the skin alone. However, disease that has disseminated and become established in lymph nodes or visceral sites (liver, lung, central nervous system) can be palliated but rarely cured, even with the most aggressive regimens of systemic chemotherapy. This result contrasts with that seen in B-cell lymphomas in which patients with extensive nodal and visceral disease are often cured by aggressive combination chemotherapy or bone marrow or stem cell transplantation.

Effective therapies for CTCL include both skin-directed and systemic therapies (Table 45.4-3). Skin-directed therapy includes topical chemotherapy with such agents as carmustine (BCNU) and nitrogen mustard (NM), systemically administered psoralens activated in the skin by psoralen and ultraviolet A light (PUVA) therapy, and local and generalized superficial ionizing radiation that includes both electron-beam and x-ray therapy.

Such a schedule of multiple treatments per week must be maintained for a minimum of 2 weeks and continued for another 2 years. Interruptions of maintenance PUVA due to intercurrent illness or injury can be followed by recurrence of disease. Once a CR has been achieved, PUVA is administered once weekly as maintenance therapy for 1 year. If the remission is sustained, the interval between treatments should be extended to 3 weeks and continued for another 2 years. Interruptions of maintenance PUVA due to intercurrent illness or injury can be followed by recurrence of disease.

Effective therapies for CTCL include both skin-directed and systemic therapies (Table 45.4-3). Skin-directed therapy includes topical chemotherapy with such agents as carmustine (BCNU) and nitrogen mustard (NM), systemically administered psoralens activated in the skin by psoralen and ultraviolet A light (PUVA) therapy, and local and generalized superficial ionizing radiation that includes both electron-beam and x-ray therapy.

TABLE 45.4-3. General Management of Cutaneous T-Cell Lymphoma

All skin-directed therapies exert their primary effects on disease confined to the skin. All are capable of destroying CTCL cells directly, probably by triggering T-lymphocyte apoptosis and all interfere with the local production of cytokines by epithelial and stromal cells necessary for neoplastic T-cell survival and proliferation.

Photopheresis, a systemic immunologic therapy, acts both directly by killing T lymphocytes by the cytotoxic actions of UVA light/psoralen and indirectly by eliciting anti–CTCL cell immune responses. Similarly, other systemic agents, such as retinoids and the biologic response modifiers (IFN-α and -G) may exert their therapeutic effects by modifying production by keratinocytes and dermal fibroblasts of cytokines necessary for neoplastic T-cell survival and proliferation. This is in addition to any direct cytotoxic or cysotstatic effects they exert on benign and neoplastic T lymphocytes.

TOPICAL CHEMOTHERAPY

Therapy for T1 and T2 CTCL can be carried out with either topical mechlorethamine (NM) or BCNU, both potent DNA-alkylating agents. Topical NM therapy is generally administered daily with a fresh solution of 10 mg in 50 mL tap water, which is applied to the entire body surface. Because NM is a potent irritant, patients should wear protective plastic gloves while applying the solution. Topical NM therapy results in delayed hypersensitivity reactions in up to 40% of patients, who often require at least temporary cessation of therapy. Such reactions can be circumvented by induction of tolerance to NM by topical desensitization or by PUVA-induced suppression of the hypersensitivity reaction. Ointment-based NM is less likely to induce allergic reactions and, in its typical formulation of 10 mg/dL, NM in Aquaphor is stable at room temperature.

Other side effects of topical NM therapy include induction of second cutaneous malignancies (e.g., squamous cell carcinomas), hyperpigmentation, and hypopigmentation. Between 64% and 90% of NM-treated patients with T1 and T2 CTCL can achieve a complete response (CR) to therapy. In one series of 243 patients, the median survival of treated patients was 8 years, and the response rate was better in those with less extensive disease. Although some patients appear to be cured by topical NM therapy, seven of eight patients experience relapse within 3 years unless a maintenance topical NM regimen has been instituted. Maintenance topical NM can also be used to prevent or delay relapse of cutaneous lesions in patients who have achieved a CR to TSEBT or to treat minimal patch or plaque recurrences after such therapy.

Another topical chemotherapeutic agent useful in the treatment of CTCL is BCNU. Because topical BCNU is not immunologically cross-reactive with NM, this agent can be used in patients who have developed allergies to NM. Topical BCNU can be formulated either as a 10- to 40-mg/dL ointment stable indefinitely at room temperature or as a 25- to 50-mg/dL solution in dilute alcohol, which is stable for at least 3 months when refrigerated.

Cutaneous hypersensitivity reactions to topical BCNU are rare and, in one series, such reactions interfered with continuation of therapy in only 10 of 152 patients. However, significant erythema in the treated areas and posttreatment telangiectasia occur in one of three patients. Also, as a small fraction of the drug is absorbed, marrow suppression can occur but is unusual unless the total dose exceeds 600 mg (in increments of 20 to 25 mg). Therefore, hematologic monitoring is necessary when using BCNU.

PSORALEN AND ULTRAVIOLET A THERAPY

Cutaneous phototherapy with orally administered PUVA irradiation of the skin, or PUVA therapy, kills cutaneous lymphocytes and interferes with antigen presentation and cytokine production in the skin. PUVA therapy is also able to induce complete remissions as reliably as TSEBT therapy in CTCL patients with patches or thin plaques. In patients with thicker plaques or tumors, PUVA therapy alone is unlikely to produce a CR but may be used to maintain the CRs induced by other skin-directed therapies, including TSEBT.

PUVA therapy requires the ingestion of 0.6 mg/kg of 8-methoxypsoralen (8-MOP) 1 to 2 hours before the exposure of the skin surface to UVA light (320 to 400 nm). To induce remission, treatments should begin three times per week at doses that are minimally phototoxic. After most of the lesions have cleared, the frequency of treatments can be decreased to twice weekly until the patient has achieved a CR. Such a schedule of multiple treatments per week must be maintained for a minimum of 3 months and a maximum of 6 months. If a CR has not been achieved by this time, several strategies can be used to supplement or enhance the efficacy of PUVA.

We have often used local spot x-ray or electron-beam therapy to treat lesions refractory to PUVA, particularly in regions anatomically shielded from receiving the full UVA dose. Addition of such “PUVA boosters” as IFNs, retinoids, or oral methotrexate can also be considered.

INTERFERON

IFN-α at doses of 3 to 6 MU can help to clear skin lesions refractory to PUVA alone. However, the systemic side effects of such therapy can be troublesome, although some patients experience no significant toxicity. Retinoids also play a role as adjunctive agents in achieving remission or palliating symptoms. Retinoids for acne and psoriasis have been used in the past. However, the ability of bexarotene to increase CTCL as monotherapy suggests that it will supplant other retinoids in the adjunctive role with PUVA and other therapies. If such boosters are successful, maintenance PUVA therapy alone should be sufficient to maintain disease-free status.

Once a CR has been achieved, PUVA is administered once weekly as maintenance therapy for 1 year. If the remission is sustained, the interval between treatments can be extended to 3 weeks and continued for another 2 years. Interruptions of maintenance PUVA due to intercurrent illness or injury can be followed by recurrence of
Patients may be free of disease at this stage, but studies of patients treated with TSEBT have noted relapses at times more than 5 years later, particularly in those with T2 disease. Whether such late relapses are the consequence of the persistence and regrowth of the original neoplastic clone or are "true" second primary CTCLs has not yet been defined. It is also not known whether such "late" recurrences or second primaries will also be observed in patients who have received 5 years of maintenance PUVA. However, patients should probably not be considered "cured" until they have remained disease-free for at least 5 years after completing therapy. Some reports suggest that PUVA therapy may result in true "cures," because the mortality rate from early disease was decreased after the adoption of PUVA as the standard therapy for CTCL in Scandinavia.

LOCAL EXTERNAL-BEAM IRRADIATION

Local x-ray therapy for CTCL lesions was first reported in 1902 by Scholtz, less than a decade after the discovery of x-rays by Roentgen. The cutaneous lesions of CTCL are extremely radiosensitive, and a dose-response relationship has been demonstrated. Doses between 20 and 36 Gy are effective in fractional sizes of 1 to 2 Gy, depending on the size and location of the lesions. Such therapy is rarely first-line but can be considered for the unusual patient with very localized primary patches, plaques, or tumors. Local x-ray or electron-beam therapy in similar doses is also fairly effective in clearing isolated lesions that fail to respond to PUVA or recur after CR to PUVA or TSEBT.

Local treatment of isolated lesions is very effective, and the CR rate is in excess of 90% for both plaques and tumors. Cotter et al. demonstrated that none of nine patients failed when treated with doses in excess of 30 Gy, with a minimum of 1 year follow-up. Approximately 5% of patients with stage IA disease will present with a solitary cutaneous lesion or several in close proximity. Wilson et al. have found that the rate of clinical remission after local external-beam radiotherapy is 97%. A total of 21 patients were evaluated with a minimum follow-up of 1 year and treated to a median dose of 20 Gy. Seventeen of the 21 patients received 20 Gy or higher. The median follow-up was 36 months. The actuarial disease-free survival (DFS) rates at 5 and 10 years were 75% and 64%, respectively, with a local control rate of 75% at 10 years. Acute and chronic toxicities were minor, and such treatment does not preclude TSEBT in the future. For metastatic disease (e.g., nodes, central nervous system and spine and lung involvement), radiation with 4 to 20 Gy may provide a meaningful palliative response.

TOTAL SKIN ELECTRON-BEAM THERAPY

Principles of Application

Treatment of the entire cutaneous surface with TSEBT is technically much more challenging than local x-ray therapy and should be attempted only in centers with appropriate equipment and in which a close working relationship has been established between dermatologists and radiation oncologists committed to and experienced in the treatment of patients with CTCL. TSEBT is excellent treatment for patients with diffuse involvement with thick plaques or cutaneous tumors and is also suitable for patients with symptomatic erythroderma (T4 disease). TSEBT is also an excellent alternative for patients with extensive patches or thin plaques refractory to PUVA or other skin-directed therapies.

The application of TSEBT for the treatment of CTCL was first reported by Trump et al. in 1953, and since that time, a variety of fractionation schedules and techniques have been implemented. In 1960, Karzmark et al. described the details of the "Stanford technique" for the administration of TSEBT, which was later modified to a six-field array to improve the homogeneity of dose delivered to the total skin surface.

Electrons ranging in energy between 4 and 7 MeV are used to treat the epidermis and dermis homogeneously. Structures below the deep dermis are spared, as most of the dose (80%) is delivered within the first 1.0 cm, and less than 5% beyond 2.0 cm depth. Blood and superficial lymph nodes may receive 20% to 40% of the skin surface dose.

At Yale, treatment is offered via a Varian 6-MeV linear accelerator at a treatment distance of 7 m, with a single incident beam energy of 3.9 MeV at the skin. Therapy is delivered via six fields, and supplemental local boosts to the scalp, perineum, and soles of the feet are administered with 120-kV(p) x-rays. Treatment is delivered to the six fields over a 2-day cycle, with three of six fields (anteroposterior, left posterior oblique, right posterior oblique) treated on the first day and the remaining three (anteroanterior, left anterior oblique, right anterior oblique) on the second. External and internal eye shields are used sequentially throughout, and the hands and feet are shielded for 50% of the treatment course. Patients receive TSEBT 4 days per week for a total of 9 weeks, and the boost fields are treated concurrently.

The dose to the skin surface is 36 Gy, 4 Gy/week and usually fractionated over 4 days and two cycles. Photon contamination to the body is 1.2% of the electron dose. Supplemental boosts to the scalp, perineum, and soles of the feet are 6 Gy (2 Gy/d), 20 Gy, and 20 Gy (1 Gy/d), respectively. Areas "shadowed" from the electron beam by large pendulous breasts, abdominal panniculi, or other deep skin folds receive similar boosts with 15 to 20 Gy (1 to 2 Gy/d) of electron-beam or orthovoltage x-ray therapy. Gross tumor lesions that have not completely regressed by the completion of TSEBT should also be evaluated for supplementary boost via x-ray or electron-beam therapy.

More commonly, a dual-beam six-field arrangement has been used. Although the techniques differ between Yale and Hamilton, for example, the dosimetry is similar, as are the clinical results. Regardless of technique, it should be noted that 4 MeV electron energy and more than 30 Gy to the skin surface are recommended. Jones and Thorson have demonstrated (as have other investigators) that improved progression-free, cause-specific, and overall survival are related to these parameters.

Results

Clinical CR rates for patients with T1 or T2 (patch or plaque) disease range from 71% to 98% and are higher in patients with less extensive disease. Representative data on disease-free and overall survival are presented in Table 45.4-4 and Table 45.4-5. In our institution, patients with T1 and T2 disease treated with TSEBT have disease-free and overall survivals of 50% to 65% and 80% to 90%, respectively, at 5 years, although patients with antecedent or coexisting LP or AM-FM appear to have shorter DFS after TSEBT than those who do not. Patients with more advanced T3 and T4 disease fare significantly worse, with 5-year disease-free and overall survivals of approximately 20% and 50%, respectively. However, those T3 patients with less than 10% of the total skin surface involved by CTCL have significantly better disease-free and overall survival after TSEBT than those with more extensive disease.

| TABLE 45.4-4. Progression-Free Survival and Remission Rates for Mycosis Fungoides Patients after Total Skin Electron-Beam Therapy |
For patients with erythrodermic MF (T4) who are managed with TSEBT alone (32 to 40 Gy), without concomitant or neoadjuvant therapy, the CR rate is 74%. The 5-year progression-free, cause-specific, and overall survivals are 26%, 52%, and 38%, respectively. 

Palliation of adenopathy or visceral involvement in patients with N3 disease can be accomplished by the use of appropriate high-energy orthovoltage or megavoltage photons to doses of 20 to 30 Gy. Even 6 to 8 Gy in 3 fractions is sufficient if added during TSEBT. Combinations of TSEBT with total nodal irradiation have been investigated. Although feasible, such combinations do not appear to prolong survival and may be associated with hematologic toxicities not observed with TSEBT alone. 

TOXICITY. TSEBT is well tolerated by most patients, and acute sequelae either during or within the initial 6 months after treatment may include pruritus, desquamation, epilation, hypohidrosis, xerosis, erythema, lower-extremity edema, bullae of the feet, and onychotrophy. Chronic changes can include atrophy of the skin, telangiectasia, alopecia, hypohidrosis, and xerosis. Because of the superficial penetration of the electron beam, patients do not experience gastrointestinal or hematologic toxicities. Second malignancies, such as squamous and basal cell carcinomas, as well as malignant melanomas have been observed in patients treated with TSEBT, and such risk is likely increased by other mutagenic, skin-directed therapies, such as PUVA or methotrexamine (or both). It is interesting that additional x-ray or electron-beam irradiation after TSEBT does not appear to increase the risk of second cutaneous malignancies. 

**TABLE 45.4-5.** Overall Survival at 5 and 10 Years for Mycosis Fungoides Patients after Total Skin Electron-Beam Therapy

![Image](https://via.placeholder.com/150)

<table>
<thead>
<tr>
<th>Patient Type</th>
<th>5-Year Survival rate</th>
<th>10-Year Survival rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1 disease</td>
<td>74%</td>
<td>52%</td>
</tr>
<tr>
<td>T2 disease</td>
<td>60%</td>
<td>20%</td>
</tr>
<tr>
<td>T3 disease</td>
<td>85%</td>
<td>50%</td>
</tr>
<tr>
<td>T4 disease</td>
<td>74%</td>
<td>38%</td>
</tr>
</tbody>
</table>

We have observed that the adjuvant use of PUVA after TSEBT in patients with T1 and T2 disease significantly decreases cutaneous relapse. Patients treated with adjuvant PUVA after TSEBT had a 5-year DFS of 85%, compared to 50% for those not receiving PUVA (P <0.02). The median DFS for the T1 patients receiving adjuvant PUVA was not reached at 103 months, versus 66 months for the non-PUVA group (P <0.01). For those with T2 disease, the DFS figures were 60 and 20 months, respectively (P <0.03). Adjuvant topical NM also appears able to delay cutaneous recurrence after TSEBT. At Stanford, the median DFS of patients was prolonged from 29 to 37 months by the addition of topical NM therapy after TSEBT. In a study of adjuvant doxorubicin-cyclophosphamide after TSEBT, the DFS was longer for those patients who received adjuvant chemotherapy for the first 2 to 3 years of follow-up. However, this early advantage was no longer apparent after 5 years. 

In contrast, ECP administered during and after TSEBT appears to improve survival (P <0.06) for patients with T3 or T4 disease who have achieved a CR to TSEBT, but the group of treated patients is small, and the data are retrospective. We currently do not administer adjuvant systemic chemotherapy after TSEBT but are developing a randomized clinical trial to evaluate the potential utility of adjuvant ECP in patients with T3 and T4 CTCL. Wilson et al. have found a significant improvement in cause-specific survival for erythrodermic patients treated with the combination of TSEBT and ECP as compared to those not treated with ECP. The 2-year progression-free, cause-specific, and overall survival for those receiving TSEBT/ECP were 66%, 100%, and 88%, respectively, versus 36%, 66%, and 63% for those not managed with the combination. These data should be interpreted with caution, though, as the total number of patients was low and the series was nonrandomized. 

**SYSTEMIC THERAPIES**

Systemic therapy for CTCL initially consisted of single- and multiple-agent cytotoxic chemotherapy regimens, often modeled after those that have been used with great success in the treatment of advanced B-cell lymphomas. In most clinical settings, however, cytotoxic chemotherapy has been supplanted by a variety of immunologically based therapies, including ECP (also known as photopheresis), IFNs, mAbs, and an investigational agent, the diphtheria toxin/IL-2 hybrid, DABIL-2. 

**Basic Principles: Photopheresis**

Given the intrinsic immunologic nature of the cells responsible for CTCL, it is reasonable that agents that either directly or indirectly modulate T-cell function or other aspects of host immune response should be applied to the therapy of CTCL. The efficacy of most chemotherapeutic and topical treatments used to treat CTCL has never been directly evaluated by U.S. Food and Drug Administration advisory committees, but the agency has approved three systemic therapies for the specific indication of CTCL. The earliest, ECP, received approval in 1988 and was the first such sanctioned selective immunotherapy for any malignancy. More recently, Ontak (diphtheria toxin conjugated to IL-2) and Targretin (Bexarotene) have become available. Development of Ontak followed Waldmann’s original investigation of an mAb against IL-2 that had shown efficacy in preliminary studies. Activated T cells may develop avid receptors for this growth factor. By attaching a toxin to a carrier that binds to the IL-2 receptor, targeted malignant T cells can then be destroyed, sparing non-IL-2 receptor-bearing bystander cells. Some limitations to the approach are that usually only a minority of CTCL cells, even in an actively expanding tumor, are...
IL-2 receptor-positive.

ECP, or photopheresis, involves systemic pretreatment with oral or parenteral psoralens, removal of a portion of the patient's blood, pheresis of white blood cells away from red blood cells, and exposure to UVA of the white blood cells that have undergone pheresis in an effort to photoactivate intercalated, DNA-bound psoralen to produce psoralen monoadducts and diadducts in DNA. The irradiated cells are then reinfused back into the patient.

The reinfusion of the killed, irradiated CTCL cells appears to stimulate host immune responses selectively against neoplastic T cells. Evidence that such clone-specific immunization actually occurs has come from several different lines of investigation.

Some observations with Vb-family–specific antibodies have demonstrated that only a minority of infiltrating T cells in patches and plaques are actually neoplastic, and of the benign T cells found in CTCL plaques, approximately 20% are CD8+ cells. When studied in vitro, these reactive, nonneoplastic CD8+ T cells have been shown to produce large amounts of IFN-G and tumor necrosis factor-α. Both of the last two cytokines increase benign and neoplastic T-cell surface expression of major histocompatibility complex (MHC) class I molecules and presentation of bound peptide antigens to other CD8+ cells, including cytotoxic T lymphocytes. In this context, it is interesting to note that the CD8+ T cells of several patients who underwent photopheresis were found to be cytotoxic only for autologous CTCL cells.

Similarly, others have demonstrated that exposure of murine T-cell lymphoma cells to 8-MOP and UVA in an experimental protocol analogous to photopheresis, and restimulation of the tumor cells into syngeneic mice protected against a subsequent challenge with this cell line. In theory, such anti-CTCL cell "immunosurveillance" should occur after any therapy that selectively kills a significant number of neoplastic T cells; however, certain animal studies suggest that ECP may accomplish this by a unique mechanism.

Ex vivo exposure of a lymphocytic murine tumor line to 8-MOP (at the temperature at which photopheresis is conducted) appears to block normal intracellular insertion of cytoplasmic peptides into the peptide antigen-binding groove of MHC class I molecules, resulting in the unusual expression of "empty" class I molecules at the cell surface. In theory, such empty class I molecules are free to bind any extracellular peptides that are recognized by the specific amino acid sequence of the antigen-binding groove.

If such exogenous peptides happen to be derived from protein components of other, neoplastic T cells (i.e., the neoplastic clone's TCR), some MHC class I–peptide antigen presentation should facilitate the expansion of clones of CD8+ "killer" and "suppressor" cells specifically directed against the neoplastic clone and immunize the host against its own CTCL cells. Evidence that such phenomena actually occur in vivo in patients undergoing photopheresis has come from studies of the peptide fractions eluted from the MHC class I molecules of CTCL patients who underwent photopheresis. Such peptide fractions appear to be unique and characteristic only of the patient's neoplastic T cells and are not observed on nonneoplastic T cells or B lymphoblasts.

Currently, ECP is frequently used as monotherapy for CTCL, but its combination with other therapies such as TSEBT is currently under study. ECP is initially administered on a once-a-month schedule, with therapy continued until maximal clearing is established. An additional 6 months of therapy may be administered to consolidate the clinical response. After the patient's disease has stabilized, the interval between ECP treatments is gradually prolonged by 1 week per cycle every three cycles. After the interval between treatments has reached 8 weeks for three cycles, therapy can be discontinued.

Patients may experience transient responses 1 to 2 days after photopheresis but begin to show sustained clinical improvement as early as the second month of therapy. However, some do not clear or achieve their maximal response until 12 months after starting therapy. On the average, after 4 to 6 months of therapy, a sustained decrease in erythema, scaling, and pruritus is observed. Patients often notice more subtle changes, such as the return of body hair, loss of rashes, and return of the ability to sweat.

Previous reports suggest that conventional systemic therapies are ineffective in prolonging the survival of patients with erythrodermic CTCL. A population-based study in one tumor registry showing erythematous skin associated with CTCL yielded a 30-month survival. In contrast, patients in the original cohort of ECP patients were found to have a median survival of 60 months, or twice as long as had been observed with prior conventional systemic therapies. No side effects of ECP that compromise its continued administration have been observed in more than 7 years of follow-up. Patients with CTCL in the original cohort treated with ECP have also been carefully studied to determine whether this therapy exerted any adverse effects on host immune response, but none were found. Lymphocyte and leukocyte counts never decreased to low levels. Lymphocyte stimulation studies showed no evidence of immunosuppression, even after years of therapy. Delayed hypersensitivity tests revealed improvement in recall responses after photopheresis; in fact, most of the patients had to experience significant improvement in their erythroderma to allow the skin testing studies to be performed.

In the treatment of T4 CTCL, particularly in patients with markedly elevated white blood cell counts and immunosuppression, ECP has been combined with a variety of other therapies, including IFNs, methotrexate, etoposide, and TSEBT. TSEBT can be particularly useful in producing prompt remissions of symmetrical erythroderma, and results suggest that T4 patients treated with TSEBT and ECP have longer survival than those treated with either modality alone.

The mechanism of this response to photopheresis appears to involve the simultaneous induction of large numbers of DCs and apoptotic CTCL cells. Passage through the UV exposure apparatus, at a film thickness of only 1 mm, causes blood monocytes to adhere transiently to the plastic surface, thereby activating these cells. Over the next few days, at least one-third of the treated monocytes are stimulated in this way to evolve into fully functional DC, the most efficient antigen-presenting cell. The activated androgens are then cocultivating the young DC with the damaged CTCL cells. The CTCL antigens are processed by the DC through the class I MHC pathway and presented to anti-CTCL cytotoxic T lymphocytes. In this way, target cells are killed by the effector T cells. The mechanism of response to this immunotherapy appears to involve the simultaneous induction of large numbers of DCs and apoptotic CTCL cells. Passage through the UV exposure apparatus, at a film thickness of only 1 mm, causes blood monocytes to adhere transiently to the plastic surface, thereby activating these cells. Over the next few days, at least one-third of the treated monocytes are stimulated in this way to evolve into fully functional DC, the most efficient antigen-presenting cell. The activated androgens are then

\[
\text{\textit{Retinoids (Vitamin A Derivatives)\textit{}}}
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Retinoids have a role in the management of several malignancies, including all- trans-retinoic acid therapy of acute promyelocytic leukemia and topical all-transretinoid in the treatment of Kaposi's sarcoma. Each retinoid has distinct binding patterns with respect to the major classes of retinoid receptors: RAR and RXR. Initial studies in CTCL demonstrated that the retinoids approved for acne and psoriasis (binding both RAR and RXR) could produce responses in CTCL. These nonretinoid retinoids have also been combined with other therapies, such as PUVA, TSEBT, and IFN. Bexarotene is a novel RXR-selective retinoid. In a clinical trial of heavily pretreated, refractory CTCL, oral monotherapy with bexarotene had a 50% response rate in a group of 94 patients with plaque, tumor, or erythrodermic CTCL. The ideal starting dose is 300 mg/m² as a single dose taken with a meal. The most frequent toxicity is hypertriglyceridemia necessitating antilipemic therapy in the majority of patients. Hypothyroidism occurred in approximately one-third of patients, and supplemental thyroid hormone was needed. In one report of nine patients with erythrodermic CTCL treated with bexarotene, rapid palliation and remitting responses induced (within 12 weeks) by monotherapy with oral bexarotene. The nine patients with erythrodermic CTCL included those with SS and those without circulating atypical cells. Two achieved CR, and the other seven showed partial responses. As a treatment of erythroderma, this agent could be considered as monotherapy but, in the management of plaque and tumor disease, bexarotene will most likely be combined with skin-directed therapies, including topical steroids. Given the high rate of partial responses with bexarotene, it is recommended that patients be observed closely for any signs of toxicity, particularly hypertriglyceridemia.
**Monoclonal Antibodies**

Several forms of R-Ab have been used in the treatment of CTCL. Miller and Levy 104 have studied the anti-CD8 antibody, and although preliminary study demonstrated partial responses in most of the patients, subsequent investigations were less promising, with no CRs in 34 patients. 18,20,21 Anti-CD4 therapy has been shown by Knox et al. 22 to be effective in seven of eight patients, with a mean freedom from progression of 25 weeks. Seven of the eight patients had plaque disease, and no patient had visceral or SS involvement. 23 Anti-Tac therapy has been studied by Waldmann 24 and, in an effort to enhance the effect, anti-TAC was used in concert with toxins and a b emitters. Of 17 patients studied, 11 had a partial or CR to such therapy.

**Fusion Therapy**

The efficacy of fusion toxin therapy was established in a trial treating patients with refractory CTCL. Fusion toxins are a family of targeted drugs that are recombinant proteins that have the gene for the targeting factor (with CTCL, the T-cell growth factor IL-2 was used) and the gene for diphtheria toxin. The recombinant peptide is selectively toxic for IL-2 receptor–positive T cells at picomolar to nanomolar concentrations. This specific killing can be blocked by the addition of excess IL-2 or mAb to the p55 portion of the IL-2 receptor. Patients are given intravenous infusions of the fusion toxin over a 30-minute period for 5 consecutive days and repeat dosing at 3-week intervals. Using doses of 9 µg/kg and 18 µg/kg, it was possible to demonstrate the dose responsiveness of the efficacy of IL-2 fusion toxin in treating CTCL. The toxicities were also dose-responsive. A vascular leak syndrome occurred at severe levels in 13% of patients. Pretreatment with systemic corticosteroids appears to minimize this complication. Overall, the response rate in heavily treated patients was 30%. 25 Almost all responses occurred within the first three infusion cycles and were maximal at eight cycles. Tumor and plaque lesions appeared to be the most responsive. Patient selection for fusion toxin therapy traditionally relies on skin biopsy findings. Rose et al. 26 detected proliferation of lymphocytes expressing the high affinity IL-2 receptor (CD25). However, dramatic responses have occurred in CD2S-negative CTCLs. The level for CD25 expression to confer toxicity from the fusion toxin is below the level of detection from immunoperoxidase. Thus, the ultimate screening test for a response to fusion toxin is to monitor the patient over two to three cycles and then continue for a full eight cycles to optimize a response. In those patients with remission, retreatment has recapitulated the response.

**Systemic Chemotherapy**

Chemotherapy has been traditionally associated with increased toxicity in the management of CTCL. Presumably, the immunosuppressive effects of advancing CTCL restrict the patients particularly prone to the suppressive effects of chemotherapy. In addition, central lines in patients with CTCL tend to become infected, owing to the continuous seeding by bacteria from the open skin lesions. Thus, there are two strategies with chemotherapy in the management of CTCL: traditional intravenous chemotherapy and low-dose oral chemotherapy. There have not been any formal studies comparing these two distinct dosing regimes. The oral agents used in managing CTCL patients are methotrexate, etoposide, and chlorambucil. Methotrexate is probably the most commonly used, at doses of 15 to 50 mg/wk. Chlorambucil or etoposide is used, the peripheral blood cell count must be carefully monitored. More intense intravenous regimens with cyclophosphamide, prednisone, or CHOP is palliative with patients with CTCL. Single-agent therapy can yield CRs in approximately 30% of patients, but the response durations are relatively short. 27 Commonly used agents have included cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone.

Several studies have reported that the adenine nucleotide derivatives 2′-deoxycoformycin, 2′-chlorodeoxyadenosine, and fludarabine might be useful in the treatment of CTCL. 28-30,31 The anti-CD4/CD8 strategies and the fusion toxins are likely to be more effective. If fludarabine is used, whereas etoposide was somewhat less effective. The duration of these responses was relatively short, however, and severe myelosuppression was often observed. Combining these agents with IFN has been studied, but preliminary results reveal no significant advantages over either modality alone. 18,20,21

Overall, combination systemic therapy yields CR rates of 35% to 50% in CTCL, but there is no significant advantage in the use of drug combinations over single-agent therapy. Chemotherapy may be helpful for patients who are in need of symptomatic palliation when other modalities have proven ineffective or when visceral disease is symptomatic. The use of chemotherapy in CTCL chemotherapy stem cell or bone marrow rescue is investigational, and preliminary results have been discouraging. 32,33

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**REFERENCES**

SECTION 45.5
Primary Central Nervous System Lymphoma

INTRODUCTION

Primary central nervous system lymphoma (PCNSL) is the term applied to non-Hodgkin's lymphoma (NHL) arising in and confined to the central nervous system (CNS). In the past, this tumor was called microglioma, reticulum cell sarcoma, or perivascular sarcoma, but its lymphocytic origin, usually the B cell, is now well established. How a lymphoma can develop within the CNS, which lacks lymph nodes and lymphatics, remains unanswered; however, lymphocytes do normally traffic in and out of the CNS, and these lymphocytes may be the source of PCNSL.

PCNSL was formerly a rare tumor, accounting for only 0.5% to 1.2% of all intracranial neoplasms, and usually associated with congenital, acquired, or iatrogenic immunodeficiency states such as Wiskott-Aldrich syndrome or renal transplantation. The highest incidence has been reported in patients with the acquired immunodeficiency syndrome (AIDS), in whom it is seen in 1.9% to 6.0%. One autopsy study demonstrated an overall risk of 12%, but only one-half of patients were suspected to harbor CNS disease before death. There is a strong clinical impression among experienced clinicians that widespread use of highly active antiretroviral therapy has reduced the incidence of PCNSL in the AIDS population, but this has yet to be confirmed by formal epidemiologic studies. However, there has been a clear and dramatic increase in the incidence of PCNSL among apparently immunocompetent individuals. An epidemiologic study in the United States revealed a threefold increase in the incidence of PCNSL between 1973 and 1984; a tenfold increase has been observed in southeast England. This increase far exceeds the 3% to 4% per year increase seen in systemic NHLs during the same period. Not all epidemiologic studies indicate an increased incidence, and it is unclear if these geographic variations contain important etiologic clues. Currently, PCNSL has an incidence of 0.31 per 100,000 person years, suggesting that approximately 800 new cases occur in the United States every year. This change in incidence cannot be attributed to new diagnostic techniques or the adoption of a uniform nosology, and the reason for this marked rise in PCNSL is unknown.

CLINICAL FEATURES

GENERAL

PCNSL affects all ages, from the very young to the elderly. Its peak incidence occurs in the sixth and seventh decades in immunocompetent patients and younger in immunosuppressed patients. Among apparently immunocompetent individuals, there is a 3:2 male to female ratio, but in the AIDS population, more than 90% of patients are men.

By definition, PCNSL is limited to the nervous system and has not metastasized there from a systemic site. Metastatic NHL typically involves the leptomeninges, rarely the brain, and usually occurs in the setting of advanced disseminated disease. Systemic staging of PCNSL patients has yielded only a 3% to 4% incidence of systemic disease. In all patients, the systemic site was extranodal and identified by bone marrow biopsy or abdominopelvic computed tomographic scan, suggesting that these are the only tests necessary for a systemic evaluation.

BRAIN

Most PCNSLs present with symptoms of an intracranial mass lesion. The specific presenting symptoms and signs reflect the location of the tumor, with focal cerebral deficits occurring in approximately one-half of patients; however, the presentation of PCNSL has some differences from that of other brain tumors. Because the frontal lobe is the most frequently involved region of the brain and multiple lesions are often seen, changes in personality and level of alertness are common presenting symptoms. Headaches and symptoms of increased intracranial pressure are also seen frequently. Seizures are less common than in patients with other types of brain tumors, occurring in approximately 10% of patients as a presenting sign, because most PCNSLs involve deep brain structures rather than seizure-prone cerebral cortex. PCNSL is a rapidly growing tumor, and symptoms are usually present for only weeks to a few months before a diagnosis is made. Staging for PCNSL should include the following tests:

- Cranial magnetic resonance imaging (MRI) with gadolinium
- Lumbar puncture
- Ophthalmologic examination with slit lamp
- Spinal MRI with gadolinium (when appropriate)
- Abdominal computed tomographic scan
- Bone marrow testing
- Chest radiography
- Human immunodeficiency virus-1 serology

PCNSL is often disseminated within the nervous system at diagnosis. Brain lesions are multifocal in 40% of immunocompetent patients and almost 100% of AIDS patients. Multiple lesions often cause diagnostic confusion with brain metastases, particularly as 13% of PCNSL patients have a history of a prior systemic malignancy. Many lesions are periventricular, allowing tumor cells to easily gain access to the CSF. At least 42% of patients have demonstrable leptomeningeal seeding based on a positive CSF cytologic examination, pathologic leptomeningeal invasion, or unequivocal radiographic evidence of subarachnoid tumor, but patients rarely have symptoms or signs of leptomeningeal lymphoma. At autopsy, 100% of patients have leptomeningeal tumor from either direct invasion into the ventricular system by periventricular tumor or local involvement of the leptomeninges overlying a cortical lesion. In addition, approximately 20% of PCNSL patients have ocular involvement at diagnosis.

EYE

The eye, a direct extension of the brain, is a common site of disease in PCNSL. Lymphoma can originate within the eye, and 50% to 80% of these patients eventually develop cerebral lymphoma, usually after several years of latency. Ocular lymphoma typically involves the vitreous, retina, or choroid, but optic nerve infiltration can also occur. Disease outside of the globe but within the orbit is not a feature of ocular lymphoma; it represents systemic NHL. Ocular lymphoma can
present with blurred vision or floaters, or it may be clinically silent; it may begin unilaterally, but most patients eventually develop bilateral, but asymmetric, disease. A cellular infiltrate of the vitreous can be visualized only by slit-lamp examination, and choroidal or retinal lesions often require indirect ophthalmoscopy. Lymphoma can be identified in vitreoretinal specimens; false-negative biopsy results may occur when patients have too few vitreal lymphocytes for the pathologist to examine or if the patient has been given corticosteroids to treat a presumed uveitis.

**LEPTOMENINGES**

Primary leptomeningeal lymphoma, in the absence of a parenchymal brain mass, is rare, accounting for approximately 7% of PCNSLs. Patients can present with progressive leg weakness, urinary incontinence or retention, cranial neuropathies, increased intracranial pressure, confusion, or a combination of these symptoms. Symptoms are usually present for only 2 to 3 months before diagnosis, but occasionally a patient can have symptoms for 1 to 2 years before being diagnosed. Diagnosis is established by demonstrating malignant lymphocytes in the CSF or on meningeal biopsy. The CSF invariably shows an elevated protein concentration and a lymphocytic pleocytosis often in excess of 100 cells/µL; CSF glucose is low in approximately one-third of patients. A gadolinium MRI scan of the head or spine reveals meningeal enhancement, hydrocephalus, or multiple intradural nodules.

**SPINAL CORD**

Primary spinal cord lymphoma is even less common than primary leptomeningeal lymphoma. Lymphoma in the spinal cord parenchyma can occur in isolation or with brain lymphoma. Patients present with painless bilateral limb weakness, usually involving the legs; sensory symptoms and signs may initially follow a radicular pattern, but eventually a sensory level may be found. CSF may be normal or have a mildly elevated protein concentration with a few lymphocytes. Prognosis has been poor, with patients surviving only a few months from the onset of symptoms, but this is often because the diagnosis was not made until autopsy and no appropriate therapy was administered.

**DIAGNOSTIC TESTS**

**CRANIAL IMAGING**

MRT scanning is the imaging technique for any patient with a cerebral neoplasm. The MRI of PCNSL is usually quite distinctive, and the diagnosis may be suspected on the basis of the radiographic appearance alone. The tumor has an isointense signal on the pregadolinium T1 MRI, and after contrast is administered, there is dense and diffuse enhancement. The lesions often have indistinct borders, and the amount of surrounding edema is variable. Unlike brain metastases or malignant gliomas, ring enhancement is rarely seen.

Prominent contrast enhancement is characteristic of PCNSL, occurring in more than 90% of patients; however, nonenhancing lesions may be seen in 10% or fewer patients, particularly at recurrence. Nonenhancing tumor can occur in the absence of corticosteroid administration, particularly in immunosuppressed patients, although it is also seen in immunocompetent patients. At its extreme, nonenhancing PCNSL can rarely present as lymphomatosis cerebri, with diffuse infiltration of the entire brain, usually presenting as a progressive dementia. Although it is a minor component of disease in most patients, nonenhancing PCNSL has important therapeutic implications, indicating tumor behind a relatively intact blood-brain barrier.

The radiographic features of PCNSL in the immunosuppressed patient differ from the characteristic image seen in immunocompetent individuals. In the AIDS patient, ring enhancement is typical, reflecting the higher incidence of necrosis seen pathologically in this group. Consequently, it is impossible to distinguish PCNSL from more common cerebral infections, such as toxoplasmosis, on the basis of MRI. However, positron emission tomography or single photon emission computed tomographic imaging can reliably differentiate PCNSL from toxoplasmosis in most patients, frequently eliminating the need for histologic confirmation.

**LUMBAR PUNCTURE**

Lumbar puncture should be part of the diagnostic evaluation of every patient with PCNSL. The protein concentration is elevated in 85% of patients, although rarely above 150 mg/dL. The glucose concentration is usually normal, but can be low when florid leptomeningeal tumor is present. A CSF pleocytosis is seen in more than one-half of patients and always consists of lymphocytes, either reactive or malignant. An unequivocally positive CSF cytology eliminates the need for a brain biopsy. This may be particularly important in the immunosuppressed or desperately ill patient at increased risk for a surgical complication. Occasionally, immunohistochemical stains of CSF demonstrate a monoclonal population of cells establishing the neoplastic nature of the pleocytosis even if the cells appear to be cytologically benign. Tumor markers, such as b2-microglobulin, lactic acid dehydrogenase isoenzymes, and b-glucuronidase, when their levels are elevated, provide circumstantial evidence for tumor invasion of the leptomeninges.

Systemic lymphomas in immunocompromised patients are often associated with the Epstein-Barr virus (EBV); the virus is believed to be oncogenic in these patients. Using in situ hybridization and the polymerase chain reaction, EBV has been detected in the tumor tissue of most AIDS-related PCNSLs and some non-AIDS tumors as well. EBV may play an important role in the development of this tumor in immunosuppressed patients, comparable with its presumed role in systemic polyclonal and monoclonal lymphoid proliferations in the immunocompromised host. Regardless of its role in the genesis of the neoplasm, it may serve a useful diagnostic function. With polymerase chain reaction, EBV DNA has been detected in the CSF of AIDS patients with PCNSL, but not in the CSF of AIDS patients without PCNSL; this approach offers a simple, noninvasive diagnostic alternative to brain biopsy in the AIDS population. All tumor specimens for homing should be sent to the institution performing the test; when combined with a positive positron emission tomography or single photon emission computed tomographic scan result, provides 100% specificity for a diagnosis of PCNSL.

**PATHOLOGY**

PCNSL is a NHL, usually of an intermediate malignant subtype. Most are diffuse large cell lymphomas or diffuse large cell immunoblastic lymphomas. Response to treatment or prognosis is not related to pathologic subtype; however, most series contain so few patients in any given category that a relationship may be missed. Further prospective studies with a large number of patients may reveal differences comparable with that seen for systemic lymphomas. At this time, all PCNSLs are treated in the same manner, regardless of subtype or cell of origin.

Macroscopically, PCNSL is usually a brownish space-occupying mass involving the deep white matter. In some cases, only a thickened corpus callosum may occur without discoloration, and in occasional patients the brain is grossly normal, but diffuse infiltration is seen microscopically. Histologically, PCNSL can grow as sheets of cells, but a characteristic vasocentric growth pattern with tumor infiltrating the brain parenchyma between involved blood vessels is found in virtually all cases. Neither necrosis nor hemorrhage is a dominant histologic feature. In autopsy specimens, tumor is always found in multiple regions of the CNS that appeared normal of cells, but a characteristic vasocentric growth pattern with tumor infiltrating the brain parenchyma between involved blood vessels is found in virtually all cases. Histologically, PCNSL can grow as sheets of cells, but a characteristic vasocentric growth pattern with tumor infiltrating the brain parenchyma between involved blood vessels is found in virtually all cases.

Several investigators have demonstrated the B-cell nature of this tumor, with immunohistochemistry showing monoclonal immunoglobulin heavy- or light-chain production or identifying B-cell markers. Immunoglobulin gene rearrangement has also been shown and may be diagnostically useful in some patients. A study of adhesion molecules revealed an identical pattern of expression for PCNSLs and systemic lymphomas. Bo rearrangements have been detected in PCNSL, and no unique molecular marker has been identified to discriminate PCNSL from its systemic counterparts. Rare, T-cell PCNSLs seem to have a predisposition to develop in the leptomeninges. Reports suggest a rising incidence in the number of T-cell PCNSLs. This may be a result of new immunohistochemical techniques, or it may be an artifact of the difficulties interpreting immunohistochemical studies. In both the CSF and the tumor itself, these neoplasms may be accompanied by a reactive lymphocytosis. These reactive cells are T cells and can make interpretation of special stains difficult. For the most part, one can clearly distinguish the cytologically malignant cells, which are usually B cells, from the reactive lymphocytes, which are T cells. In lesions partially treated by corticosteroids, however, the reactive T cells may be all that is apparent on a biopsy specimen, making accurate diagnosis difficult.

**MANAGEMENT**

The appropriate management of a patient with PCNSL requires a correct diagnosis. This may be difficult because the clinical presentation of PCNSL is not distinctive and other primary and secondary brain tumors are much more common; however, the method outlined here can aid in the approach to a patient who harbors this
tumor.

When an MRI scan reveals an intracranial mass, the radiographic appearance may strongly suggest PCNSL: multiple lesions, deep or periventricular location, diffuse and dense contrast enhancement, and poorly defined borders are common imaging characteristics. In addition, the clinical setting in which the tumor arises may point to the diagnosis (e.g., an immunocompromised patient). If PCNSL is a strong diagnostic consideration, corticosteroids should be withheld unless the patient is in imminent danger of herniation, a rare situation. Corticosteroids may alter or even eliminate the ability to establish the diagnosis pathologically. Histologic confirmation is essential, by stereotactic biopsy, lumbar puncture demonstrating leptomeningeal lymphoma, or vitreous biopsy demonstrating lymphomatous cells. If the patient requires the immediate use of corticosteroids, or if PCNSL was not considered originally and the patient was placed on corticosteroids, a repeat MRI scan should be done to evaluate for possible resolution or new development of lesions. Biopsy should still be considered if the lesions are cleared in size but still evident; however, nondiagnostic tissue may be obtained. Corticosteroid-induced resolution of an intracranial mass does not establish the diagnosis of PCNSL, because nonneoplastic contrast-enhancing processes such as multiple sclerosis or sarcoidosis can resolve after corticosteroid administration.

Using the clinical staging criteria developed for systemic lymphomas, PCNSL corresponds to stage IE (i.e., disease confined to a single extranodal site). Systemic stage IE disease has a 100% complete response rate and at least a 70% 10-year survival, or cure, rate with focal radiotherapy. Surprisingly, the prognosis for PCNSL is poor. Despite the highly responsive nature of PCNSL to initial treatment, median survival is only 12 to 18 months with cranial radiotherapy. and the 5-year survival rate is only 3% to 4%. This short survival is a result of recurrence of PCNSL after an initial response to cranial irradiation. Relapse occurs primarily in the brain, often in regions remote from the original site but within the prior radiation port; it also occurs in the leptomeninges and eye. Systemic lymphoma is found in only 7% to 8% of autopsied patients, and the vast majority of these patients have a single focus of clinically silent disease, thought to represent a systemic metastasis from recurrent nervous system tumor.

Because of its poor prognosis, new treatment approaches have been developed. The therapeutic strategies differ, depending on the immunologic status of the patient. Most data regarding effective therapies have been accumulated in immunocompetent patients. The presence of significant immunosuppression may compromise the patient’s ability to tolerate more vigorous forms of treatment. Thus, we divide the descriptions of existing and potential treatment regimens for PCNSL into treatments for the immunologically intact patient and those for patients with diminished immune systems from a preexisting condition.

IMMUNOLOGICALLY NORMAL PATIENTS

Corticosteroids

A unique feature of PCNSL compared with other brain tumors is its exquisite sensitivity to corticosteroids. In at least 40% of patients, tumor masses significantly shrink or disappear on MRI scan after corticosteroids are administered. This apparent remission is a direct result of the cytotoxic effect of corticosteroids, comparable with their effect in systemic lymphoma. Experimentally, corticosteroid receptor-like molecules have been identified on mouse lymphoma cells, and their presence correlates with cell lysis after exposure to corticosteroids. Clinically, disappearance of PCNSL lesions is accompanied by improvement, which may last long after the corticosteroids have been discontinued. There are isolated reports of patients being cured or having prolonged survival after treatment with corticosteroids alone. Regardless of apparent tumor regression, corticosteroid-induced remission is short-lived in most patients and is not definitive treatment. Biopsy after corticosteroid administration often yields normal or nondiagnostic tissue. Occasionally, biopsy results are misleading as the corticosteroids can lyse the malignant B cells, leaving the reactive T cells behind, which may be interpreted as an inflammatory process.

Surgery

Surgery is an important means of confirming the histologic diagnosis, but it has no therapeutic role. Mean survival of patients with PCNSL with supportive care alone is 1.8 to 3.3 months. Surgical resection adds little, prolonging the average survival to only 3.3 to 5.0 months. Unlike malignant glioma, for which extensive resection is an important component of therapy, PCNSL’s multifocal and infiltrative nature makes surgical extirpation difficult. Furthermore, the deep location of many PCNSLs leaves the patient susceptible to severe postoperative deficits if a complete resection is attempted. Therefore, the diagnostic method of choice is stereotactic biopsy, which also allows for biopsy of deep lesions that cannot be approached safely by conventional surgery. If cranial biopsy is performed because the diagnosis of PCNSL is not considered preoperatively, an intraoperative frozen section often establishes the diagnosis of PCNSL; the procedure can then be terminated, because further resection is unnecessary.

Radiotherapy

Whole brain radiotherapy (WBRT), combined with corticosteroids, was the conventional treatment for PCNSL, yielding median survivals of 12 to 18 months. There is no clear radiotherapy dose-response relationship in PCNSL. The Radiation Therapy Oncology Group conducted a prospective study of patients with PCNSL treated with 4000 cGy WBRT plus a 2000-cGy boost to the involved area, to assess whether dose intensification improved outcome. Median survival was only 12.2 months, and most recurrences were in the boosted field. This is comparable with our experience at Memorial Sloan-Kettering Cancer Center, where recurrences occurred with equal frequency in a boosted region receiving a total of 5440 cGy and in other areas of the brain treated with only 4000 cGy. Because the added radiotherapy does not improve local control and can contribute to late neurologic sequelae, we have eliminated the boost and use 4500-cGy WBRT in our current protocol.

The primary treatment of ocular disease is radiotherapy to the globe in PCNSL; 3500 to 4000 cGy over 4 to 5 weeks is the recommended total dose. Because ocular lymphoma is predominately a binocular process, both eyes should be irradiated, even when only monoclonar disease can be detected on slit-lamp examination. Most patients have binocular involvement, automatic improvement resulting in resolution of cells, should radiotherapy be stopped after a presumed complete radiologic response. However, some have vitreal clearing without improved vision, and others may not respond to radiotherapy. The incidence of long-term ocular toxicity from radiotherapy in this disease is unknown, but it may increase with improved survival because many of the complications are delayed. Accelerated cataract formation is almost a certainty after these doses of radiation therapy. Conjunctivitis, dry eyes, retinal atrophy, and vitreous hemorrhage have all been reported in PCNSL patients after ocular radiotherapy. However, most patients tolerate a fractionated dose of 3600 cGy to both eyes without significant acute or permanent delayed complications.

Craniospinal irradiation has been proposed as the initial therapy for PCNSL because of the high incidence of clinically evident meningeal tumor at recurrence and the invariable demonstration of leptomeningeal infiltration at autopsy. Few data exist to evaluate this approach, although results in the few patients treated with neuraxis irradiation suggest improved survival over WBRT alone. However, irradiation of such a large portion of the bone marrow compromises the patient’s ability to tolerate subsequent systemic chemotherapy that is likely to be necessary at relapse. Administration of intrathecal chemotherapy at diagnosis is an effective alternative to neuraxis radiotherapy in treating leptomeningeal lymphoma, and it is associated with less systemic toxicity.

Chemotherapy

No large prospective trials have compared chemotherapy plus radiotherapy with radiotherapy alone, but accumulating data from multiple phase II studies clearly document the chemosensitivity of PCNSL to systemic chemotherapy and superior outcomes with combined modality therapy. It is improbable that a phase III trial will be done to evaluate for possible resolution or new development of lesions. Biopsy should still be considered if the lesions are cleared in size but still evident; however, nondiagnostic tissue may be obtained. Corticosteroid-induced resolution of an intracranial mass does not establish the diagnosis of PCNSL, because nonneoplastic contrast-enhancing processes such as multiple sclerosis or sarcoidosis can resolve after corticosteroid administration.

Several investigators have used chemotherapeutic regimens for PCNSL that were successful in treating systemic NHL. The combinations of preradiation cyclophosphamide, doxorubicin, and vincristine with prednisone (CHOP) or dexamethasone (CHOM) have been studied most extensively. Stewart and associates...
were the first to note responses of brain lesions to CHOP, although patients quickly developed florid leptomeningeal tumor. Lachance and associates noted initial responses, but patients rapidly developed multifocal brain recurrence in sites distant from the original location of disease before chemotherapy could be completed. However, two prospective, multicentered trials clearly established the poor efficacy and high toxicity of CHOP/CHOD for PCNSL. The Radiation Therapy Oncology Group conducted a study in which patients received three cycles of CHOD followed by cranial irradiation. The median survival was only 16.1 months for the 52 patients treated. A separate multinstitutional trial of preradiation CHOP included 46 evaluable patients with an estimated median survival of approximately 9.6 months. Only 54% of patients completed two cycles of CHOP before beginning radiotherapy; in the others disease progression or toxicity occurred, with a 15% mortality. Furthermore, it appears that, when effective, CHOP is associated with a high incidence of delayed neurologic toxicity. In addition to CHOP, Brada and associates studied methotrexate, 400 mg/m², with doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin (MACOP-B) preceding cranial radiotherapy, but median survival was only 14 months.

When added to radiotherapy, neither CHOP nor MACOP-B improved survival over that seen with radiotherapy alone. Although the agents in these regimens should have excellent activity against PCNSL cells, they are unable to penetrate an intact blood–brain barrier. Adequate drug concentrations are likely to be achieved in areas of bulky disease seen on MRI scan where the blood–brain barrier is disrupted by tumor, which accounts for the initial resolution of tumor masses; however, the drugs are unable to reach microscopic disease, which persists behind a relatively preserved blood–brain barrier. Drug delivery issues may only partially explain the difficulty of treating PCNSL, but these data strongly argue for the use of drugs that can permeate the blood–brain barrier (Table 45.5-1).

<table>
<thead>
<tr>
<th>TABLE 45.5-1. Management of Primary Central Nervous System Lymphoma</th>
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| High-dose methotrexate has emerged as the most important drug for the treatment of PCNSL. Two large retrospective studies have convincingly demonstrated that methotrexate is the single most active agent for PCNSL. A number of years ago, we treated PCNSL patients at Memorial Sloan-Kettering Cancer Center with systemic, 1 g/m², and intra-Ommaya methotrexate followed by radiotherapy and high-dose cytarabine. An analysis of this original cohort confirms a cause-specific median survival of 42 months, with a 22% 5-year survival, a significant improvement over radiotherapy alone (Fig. 45.5-1 and Table 45.5-2). Age older than 50 years was a poor prognostic factor for response and survival. Others have confirmed that age and performance status are important prognostic factors, regardless of treatment type. Additional regimens using nitrosoureas, procarbazine, cyclophosphamide, and doxorubicin have all been used in a few patients, with reported success.

![FIGURE 45.5-1. Kaplan-Meier curve demonstrating cause-specific survival for 31 patients treated with chemotherapy plus cranial irradiation. Median survival was 42 months, and the 5-year survival rate was 30%.

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<thead>
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<th>TABLE 45.5-2. Chemotherapy Regimens for Primary Central Nervous System Lymphoma</th>
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<td>The history of treatment for systemic NHL documents the superiority of combination chemotherapy over single agents. Consequently, new regimens for PCNSL are combining multiple agents that can penetrate the blood–brain barrier (Table 45.5-3). An intergroup trial with the Radiation Therapy Oncology Group and the Southwest Oncology Group, using a 10-week preradiation regimen of high-dose methotrexate, 2.5 g/m², procarbazine, and vincristine has just been completed. Preliminary results show a median survival of 30 months (Fig. 45.5-2). This is the first multicentered trial to demonstrate an improved outcome over radiation therapy alone.</td>
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In an effort to circumvent the blood–brain barrier and deliver multiagent treatment, Dahlborg and coworkers used blood–brain barrier disruption followed by intrathecal methotrexate, combined with systemic cyclophosphamide, procarbazine, and dexamethasone without cranial irradiation. Their 39 patients treated at the time of diagnosis had a median survival of 40 months; however, 31%, WBBRt. Neither the rate of relapse nor failure of the regimen was reported.

Although most studies have focused on preradiation chemotherapy, the question of adjuvant chemotherapy in patients who have completed WBRT and not received prior chemotherapy often arises. It is unknown if adjuvant chemotherapy is equivalent to a preradiation drug, but preliminary data suggest it is superior to radiotherapy alone. Chamberlain and Levin followed WBRT with procarbazine, lomustine, and vincristine, achieving a 41-month median survival in 16 patients. Therefore, four to six cycles of procarbazine, lomustine, and vincristine after WBRT is completed seem to be reasonable in patients who have received no prior chemotherapy. We have avoided methotrexate in this setting because of potential CNS toxicity.

The prolonged survival seen with combined modality regimens has led to greater appreciation of treatment-induced late neurologic toxicity. Merchut and associates first reported radiation necrosis in a patient with PCNSL treated with radiotherapy alone. Liang and associates noted a high incidence of late toxicity in survivors treated with CHOP and intrathecal methotrexate plus WBRT. Long-term follow-up of our original cohort of patients reveals that almost 100% of patients older than the age of 60 years at diagnosis experience significant late sequelae within 4 years of treatment, whereas only 30% of younger patients have similar problems after a 7.5-year latency. Mass and associates report no toxicity with intraarterial therapy; however, their own experimental work clearly demonstrates damage of normal brain structures when chemotherapy follows blood–brain barrier disruption. These issues led to an exploration of systemic chemotherapy alone as effective treatment for PCNSL. Glass and associates reported long-term survival in a few patients treated with high-dose methotrexate alone. We, and others, have treated elderly patients with a multiagent chemotherapeutic regimen. The response rate was greater than 90%, with most patients having a complete response. Median survival for patients older than age 60 years was 33 months, superior to a median of 7.1 months for radiation therapy alone in a comparable age group.

Furthermore, no patient developed neurotoxicity. Similar results were observed in 14 patients treated by Sandor et al. with a high-dose methotrexate-based regimen without radiation therapy. These preliminary data suggest that good disease control can be achieved by chemotherapy alone.

There are a few examples of ocular lymphoma being treated with chemotherapy. Barr and associates used cyclophosphamide and then vincristine in one patient with metastatic ocular lymphoma without effect. Sullivan and Dallow reported both systemic and ocular remission in a patient with a systemic histiocytic lymphoma and a ciliary body metastasis, after treatment with procarbazine, CCNU, and vincristine. Baumann and coworkers reported a patient with lymphomatous uveitis who relapsed after ocular irradiation. Treatment with intravenous cytarabine, 500 mg, and methotrexate, 200 mg, had no effect; however, high-dose cytarabine, 3 g/m², produced a complete response that was long lasting. Furthermore, therapeutic cytarabine levels were documented in both aqueous and vitreous humor 90 minutes after infusion was completed. Strohland and others treated six patients with primary ocular lymphoma with high-dose cytarabine, obtaining a response in five. We have observed responses of ocular lymphoma to high-dose methotrexate before ocular radiotherapy. In addition, Valtori and coworkers used our original PCNSL regimen to treat three patients with ocular lymphoma, two of whom had concurrent CNS disease; these patients remained in CNS and ocular remission 30 to 40 months after diagnosis.

The role of chemotherapy in treating ocular involvement in PCNSL remains to be clarified; however, these reports suggest that some agents or combination regimens may prove useful in the future. Intravitreal injection of methotrexate was described as effective treatment for recurrent ocular lymphoma. Although this approach eliminates systemic toxicity from intravenous chemotherapy, it requires frequent intracocular injections.

### IMMUNOCOMPROMISED PATIENTS

The treatment modalities for PCNSL in immunocompetent patients are also used to treat AIDS-related PCNSL, although they are generally less effective and more toxic in immunodeficient patients. The initiation of treatment first requires a histologic diagnosis of PCNSL. In the non-AIDS immunocompromised patient a stereotactic biopsy should be performed when an intracranial mass lesion is first diagnosed. In AIDS patients, a noninvasive diagnosis can often be achieved with the use of positron emission tomography or single photon emission computed tomographic imaging and the detection of EBV DNA in CSF. In the absence of a definitive circumstantial diagnosis, biopsy should be performed. Toxoplasmosis continues to be the most common cause of an intracranial mass in an AIDS patient, but PCNSL is the second most common. However, empiric treatment with 2 to 3 weeks of antitoxoplasmosis therapy is an unacceptable diagnostic trial because most PCNSL patients markedly deteriorate during this time, severely limiting subsequent treatment options.

Corticosteroids and cranial irradiation are the mainstays of treatment for PCNSL in immunosuppressed patients. Use of corticosteroids should be limited because they can contribute to the underlying immunosuppression; however, they are still valuable for short-term control of neurologic symptoms and may be necessary during the course of WBRT. AIDS patients with PCNSL do respond to cranial irradiation, but median survival is only 2 to 5 months because most die of systemic or coexistent CNS infections.

Chemotherapy for PCNSL has been used infrequently in immunodeficient patients. Intrathecal methotrexate for leptomeningeal lymphoma was reported to be effective in a single patient with immunoglobulin A deficiency, although the benefit was of short duration. Potent intravenous chemotherapy programs are often inappropriate for immunosuppressed patients, particularly those with AIDS. However, there is a subset of AIDS patients who benefit from a vigorous approach. Typically, these are patients with a good performance status, no active comorbid conditions, and a relatively high CD4 cell count (200/mL or more). Such patients do have prolonged survival when chemotherapy is added to WBRT, often surviving more than 1 year and occasionally for many years. Again, high-dose methotrexate is the agent of choice. There are isolated reports of patients with AIDS-related PCNSL who have been successfully treated with antiviral and biologic agents or reconstitution of their immune system using highly active antiretroviral therapy. These reports open new therapeutic avenues for what has been a virulent and deadly disease.
complication of human immunodeficiency virus-1 infection. Furthermore, monitoring the level of CSF EBV DNA may prove helpful in assessing treatment response, in addition to suitably designed clinical trials.

CHAPTER REFERENCES

Hodgkin’s Disease

A great deal has been written about the life and accomplishments of Thomas Hodgkin. In his historic paper entitled “On Some Morbid Appearances of the Exorbant Glands and Spleen,” presented to the Medical Chirurgical Society in London on January 10, 1832, Hodgkin described the clinical history and postmortem findings of the massive enlargement of lymph nodes and spleens of six patients studied at Guy’s Hospital in London and of a seventh patient who had been seen by Carswell in 1828. Without a microscope, Hodgkin recognized that these patients had a disease that started in the lymph nodes located along the major vessels in the neck, chest, or abdomen, rather than from an inflammatory condition.

In 1886, Sir Samuel Wilks, a Guy’s Hospital pathologist, described ten postmortem cases that had “a peculiar enlargement of the lymphatic glands frequently associated with disease of the spleen.” By 1886, Dr. Wilks had collected 15 cases, which were published in a second paper entitled “Cases of the Enlargement of the Lymphatic Glands and Spleen (or Hodgkin’s Disease) with Remarks.” Wilks’s initial descriptions gave us some of our earliest understanding of Hodgkin’s disease (HD). He described the disease as a cancer that started and remained in the lymph nodes for a long time, perhaps years, before involving the spleen and then spreading to other organs. He also noted anemia, weight loss, and fevers in some of the patients with HD.

Although other physicians had provided descriptions of the characteristic giant cells present in the lymph nodes and spleens of patients with HD, Dr. W. S. Greenfield in 1878 was the first to contribute drawings of them from a low microscopical magnification of a lymph node specimen. Drs. Carl Sternberg (in 1898) and Dorothy Reed (in 1902) are credited with the first definitive microscopical descriptions of HD. Despite Greenfield’s findings, Dr. Carl Sternberg (in 1898) and Dr. Dorothy Reed (in 1902) are credited with the first definitive microscopical descriptions of HD.

Both Sternberg and Reed, along with many other physicians, believed that HD was caused by an associated infection rather than by a separate malignant process of the lymph nodes. Proponents of the infectious theory cited the frequent association of HD with tuberculosis. Eight of Sternberg’s thirteen cases of HD had coexistent tuberculosis, and he believed HD to be a variant of tuberculosis. Other physicians believed that HD was a cancer of the lymph nodes. Clinical and pathologic studies, available in the early twentieth century, helped to confirm their view. Despite the very strong evidence for the malignant nature of HD over the last century, it has only recently been shown that Hodgkin’s-Reed-Sternberg (H-RS) cells are clonal, confirming their origin from a single malignant cell.

ETIOLOGY AND EPIDEMIOLOGY

Approximately 7500 new cases of HD are diagnosed each year in the United States. Slightly more men than women develop this malignancy (1.4:1). In economically developed countries, there is an age-related bimodal incidence for HD. The first peak occurs in the third decade of life, and a second rise in incidence occurs after the age of 50 years. The incidence of HD by age also differs by histologic subtype.

Mycobacterium tuberculosis was first suspected of being the etiologic organism for HD because of the high coexistence of tuberculosis in these patients. This theory...
was later discounted when it was appreciated that HD was associated with deficits in the immune system that accounted for the increased presence of associated infections. Several studies in the 1970s suggested that HD might be contagious because of reports of clustering of the disease. The first reports, by Vianna and Poln, noted clustering among high school students exposed to HD. However, population-based studies, using cancer registries in Connecticut and California, convincingly made the argument that the reported clusters occurred by chance alone, and a study that repeated the methodology of Vianna and Poln in a different location failed to confirm their findings.

A number of studies have suggested that a genetic predisposition for HD exists. There is an increased incidence in Jews and also among first-degree relatives. Siblings appear to have a two- to fivefold increased risk; in siblings of the same gender, there is as much as a ninefold increased risk. An increased risk among parent-child pairs but not among spouses again suggests a genetic predisposition. Also, HD has been linked with certain HLA.

There is less support for most other potential causes of HD. In contrast to other malignancies, HD rarely is seen as a second malignancy and does not appear to be increased in patients with illness- or treatment-related chronic immunosuppression. Although HD has been noted in patients with the acquired immunodeficiency syndrome (AIDS), evidence for a direct correlation with the immunosuppression associated with AIDS is lacking.

In contrast, increasing evidence suggests a viral etiology for HD. In economically developed countries, studies report an association between HD in younger patients and increased maternal education, decreased numbers of siblings and playmates, early birth order, and single-family dwellings in childhood. This association between HD and childhood factors that decrease exposure to infectious agents at an early age has led investigators to propose that the epidemiologic features of HD appear to mimic those of a viral illness that has an age-related host response to infection.

Epstein-Barr virus (EBV) is the leading viral candidate for HD causation. There is a twofold to threefold excess in the incidence of HD among patients with a history of mononucleosis, a disease caused by EBV. In addition, there appears to be an altered antibody pattern to EBV in patients before presenting clinically with HD, with elevated titers against the viral capsid antigen and against the EBV nuclear antigen (EBNA) as compared to controls. This suggests that such patients may have had more severe initial EBV infections or more frequent viral replication associated with the development of HD.

Patients in nonindustrialized countries and from lower socioeconomic groups, as well as children, who develop HD are more likely to have EBV-positive HD than are patients with high socioeconomic backgrounds in the young adult age group. In these groups, even nodular sclerosis HD (NSHD) has a higher incidence of EBV positivity than it does in the young adult cases.

Some cellular and molecular biology data have provided additional support for the association of EBV and HD. Through the use of sensitive molecular probes, including Southern blot, in situ hybridization, and polymerase chain reaction (PCR) assays, 30% to 50% of HD specimens have been found to contain EBV genome fragments in the diagnostic RS cells. In the United States and Western Europe, the tumor cells of classic HD (CHD) are EBV-positive in approximately 50% of the cases. The positivity rate is lower in NSHD (15% to 30%) and higher in mixed-cellularity HD (MCHD) (60% to 70%) (Table 45.6-1).

**TABLE 45.6-1.** Hodgkin's Disease: Differences in EBV Association (Approximate)

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<thead>
<tr>
<th></th>
<th>EBV-Positive</th>
<th>EBV-Negative</th>
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<tbody>
<tr>
<td>Japan</td>
<td>20%</td>
<td>80%</td>
</tr>
<tr>
<td>United States/Europe</td>
<td>55%</td>
<td>45%</td>
</tr>
<tr>
<td>Mexico</td>
<td>50%</td>
<td>50%</td>
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<td>Other Latin American</td>
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<td>Africa</td>
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<td>Other</td>
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EBV genome status appears to be stable over time when studied in initial biopsies and at relapse. The latent gene products, latent membrane protein (LMP) and EBNA2, have important roles in EBV-induced cell transformation in vitro. EBV genome-positive RS cells express the phenotype LMP1 and LMP2+EBNA1+ EBNA2-, a phenotype found in EBV genome-positive nasopharyngeal carcinoma and in a small portion of T-cell non-Hodgkin's lymphomas (NHLs). LMP1 has transforming activity for B cells, and its expression should give a survival advantage to infected cells. Because EBV is capable of immortalizing B cells, and because all the cells in infected cases carry the same clone of EBV and express the most potent transforming protein (LMP1), the obvious conclusion is that EBV must play some role in the pathogenesis of HD. However, the fact that EBV is not present in all the cases leaves open the question of the pathogenesis of EBV-negative cases and, more important, the question of whether EBV is important even in positive cases.

Patients with autoimmune disease who are treated with rather mild immunosuppression with methotrexate occasionally develop a Hodgkin's-like lesion, which is EBV-positive in nearly 50% of the cases. Taken together, these observations suggest that immunosuppression per se does not predispose to the development of HD but that, when it does develop, it is likely to be of mixed-cellularity (MC) or lymphocyte-depleted (LD) type and EBV-positive.

H-RS cells show a specific expression pattern of the viral latent genes with expression of EBNA1 and LMP. This pattern is identical to that found in nasopharyngeal carcinoma endemic in the southwest of China. It differs from such other EBV-associated neoplasias as endemic Burkitt's lymphoma and immunoblastic B-cell NHLs of immunocompromised patients. Except for EBNA1, all latent viral proteins represent targets for cytotoxic T lymphocytes (CTLs). Thus, EBV-infected cells either express the complete set of latent viral genes in an immunocompromised host (immunoblastic NHL) or they down-regulate these proteins except EBNA1 (Burkitt's lymphoma), possibly to escape the host's immune response. Thus far, it remains unclear how the specific viral gene expression pattern in HD (EBNA2- and LMP-positive) and the pronounced T-cell proliferation in affected lymph nodes relate to each other.

The functional relevance of LMP expression in H-RS cells is not understood. LMP has a transforming potential. Transformation of epithelial cells after transfection of LMP has been described. In lymphocytes, apoptosis can be prevented by LMP via up-regulation of the bcl-2 gene. LMP is also a target for CTLs. In addition, it induces apoptosis in cooperation with EBNA2, numerous cellular genes (e.g., activation-associated antigens [CD23, CD20, CD33]) and adhesion molecules [intracellular adhesion molecule-1 (ICAM-1), lymphocyte function-associated antigen 3 (LFA-3)]. Thus it may render a cell indirectly more susceptible for a T-cell response. Knecht et al. described in some HD cases mutations in the carboxy-terminal part of the LMP1 gene identical to those previously reported in LMP isolates from Chinese nasopharyngeal carcinoma. These authors discussed an association of these mutations with a clinically more aggressive HD phenotype.

At least three hypotheses can be advanced to explain EBV-negative cases of HD. First, another virus could be involved in these cases; however, studies to date have failed to identify another virus. Second, EBV may be involved in all the cases but may remain undetectable in some; this has been called the hit-and-run theory. In this scenario, EBV infects the cell, alters the DNA in some way, and then is eliminated, leaving the cell either transformed or susceptible to transformation. Elimination of EBV, with its immunogenic proteins, might be expected to occur most commonly in patients with active immune systems, such as the young women with NSHD. However, a third possibility, and one the one perhaps best supported by epidemiologic data, is that EBV is not important in the pathogenesis of any of the cases of HD and that its presence in some cases simply reflects the presence of a larger reservoir of latently EBV-infected cells in these individuals.

Examination of the epidemiology of EBV-associated HD reveals several paradoxes, which cast doubt on the causative role of EBV in many cases. First, the group in which EBV had been predicted most likely to be involved—young women from high socioeconomic groups with NSHD—proved to have the lowest incidence of EBV in tumor tissue. Second, there is no correlation between a history of either infectious mononucleosis or unusually high titers of antibodies to EBV and detectable EBV in HD tissues. Thus, in contrast to what one would expect if most HD cases were caused by EBV, populations in which HD is common (young women in affluent societies) have EBV-negative HD and populations in which HD is rare (young children in underdeveloped countries, older individuals, and immunosuppressed patients) have EBV-positive HD. These apparent paradoxes force us to at least consider the possibility that EBV may be merely an epiphenomenon in HD, reflecting...
a high incidence of EBV-infected B cells in the patient, rather than an etiologic factor.

In summary, despite data that suggest an etiologic role for EBV in HD, direct evidence of a causative role is lacking. The lack of an animal model and the difficulties in studying the malignant cells in HD continue to frustrate investigators. Additional epidemiologic, serologic, and molecular data are needed to determine whether EBV is a causative agent.

**Biology and Cell of Origin**

**Lineage, Origin, and Clonality of Hodgkin's-Reed-Sternberg Cells**

### Specific Morphologic Features of Hodgkin's Disease

Lymph nodes affected by HD consist of a heterogeneous mixture of lymphocytes, histiocytes, eosinophils, plasma cells, fibroblasts, and other cells. The mononuclear Hodgkin's cells and their polynucleated counterparts, the RS cells, which have long been considered to represent the malignant substrate of the disease, represent only 0.1% to 1.0% of the entire cell population in CHD (i.e., lymphocyte-rich CHD (LRCHD) and the NS, MC, and LD subtypes). Similarly, in lymphocyte-predominant HD (LPHD, nodular paragranuloma), the pathognomonic lymphocytic and histiocytic (L&H) cells represent only a small minority of the total cell population. This scarcity of the putative tumor cells was one of the major obstacles for understanding the nature of these cells. Whereas in the LP subtype of HD, H-RS cells consistently express B-cell-specific surface antigens (CD19, CD20), in CHD H-RS cells express, in the majority of cases, the activation markers Ki-1 (CD30), the Leu-M1 antigen (CD15), the interleukin-2 receptor (CD25), and the transferrin receptor (CD71), and HLA class II molecules (HLA-DR), but not surface antigens, which helped to determine their physiologic counterpart. Until recently, the application of conventional molecular-genetic methods for a more detailed analysis of H-RS cells was not possible owing to their scarcity. In addition, these cells could not be enriched from tissue affected by HD, presumably due to their fragility. Thus, over decades, the cell of origin of the H-RS cells remained an enigma.

### Cell Lines and Animal Models

The establishment of permanently growing cell lines permitted the biologic and genetic characterization of the tumor cell population in numerous human neoplasias. In contrast, outgrowth of a cell line is extremely rare in HD. The first two permanent cell lines (designated L428 and L540) were established in 1979 from patients with advanced-stage HD (clinical stage (CS) VI). These cell lines grew from a pleural effusion and bone marrow. With few exceptions, all subsequently established cell lines were also obtained from body fluids (bone marrow, pleural effusion, peripheral blood) of advanced-stage patients. This observation may reflect an in vivo adaptation of the cells to the conditions of suspension culture as prerequisite for in vitro outgrowth. Thus far, only 15 cell lines have been established that may be regarded as HD-derived. Analysis of immunophenotype, karyotype, immunoglobulin (Ig), or T-cell receptor gene rearrangements of these cell lines revealed, in analogy to analysis of primary tissue, heterogeneous results, not allowing any conclusion to be drawn on the cell of origin of HD. In addition, their derivation from primary H-RS cells could not be determined unequivocally. A novel EBV-negative cell line (L1236) has been established from the peripheral blood of a patient with advanced HD of the MC subtype. Using H-RS single-cell PCR, it could be shown that the genomic sequences of the Ig gene rearrangements of the H-RS cells in the patient's bone marrow were identical to those detected in L1236 cells. Thus, in this cell line, the H-RS cell origin is definitely proven on the molecular level.

HD-derived cell lines were used successfully for the discovery of HD cell-associated antigens, which include CD30 (Ki-1), CD70, and Ki-7, for cloning the CD30 gene, and for studying the CD30 signal transduction pathway. They also enabled the in vitro testing of new immunotherapeutic modalities such as Ricin A-linked anti-CD30 immunotoxins, Saporin-linked anti-CD30 immunotoxins, and anti-CD16/CD30 bispecific antibodies.

Though none of these HD-derived cell lines could grow reproducibly in thymus-aplastic T-cell-deficient nude mice, the HD-derived cell lines L540, HD-MY2, and L1236 have been shown to disseminate intralymphatically after inoculation into T- and B-cell-deficient severe combined immunodeficient (SCID) mice. The SCID mouse model is used for the preclinical in vivo testing of new experimental therapeutic approaches. However, no reproducible growth of primary H-RS cells has been observed after transplantation of biopsy material.

### Results of Single-Cell Analysis: Hodgkin's-Reed-Sternberg Cells Are Clonal B Cells

A methodologic breakthrough for the biologic analysis of H-RS cells was achieved by the establishment of micromanipulation of immunophenotyped single cells from frozen sections, allowing the amplification and analysis of genes derived from a single cell. Küppers et al. amplified rearranged Ig heavy-chain genes from single HD RS cells micromanipulated from two cases of CHD and one case of LPHD. Sequence analysis revealed the clonal B-cell origin of the H-RS cells in all three cases. In 14 of 15 additional cases of CHD, again clonally rearranged Ig genes were detected in the H-RS cells. Clonal Ig gene rearrangements in H-RS cells of CHD were also found by others using micromanipulation and single-cell PCR. Similarly, using the new method, clonally related Ig gene rearrangements were detected in L&H cells isolated from frozen tissue sections of LPHD. Thus, there is overwhelming evidence that at least a substantial proportion of cases (if not all cases) of CHD and LPHD represent monoclonal B-cell disorders.

### Germinal Center Derivation of H-RS Cells

The site of physiologic contact between a specific antigen and a B lymphocyte is the germinal center (GC) of a lymph node. This contact results in somatic mutations accumulating in the Ig genes and leading to the expression of antibodies with a higher affinity due to amino acid exchanges. However, somatic mutations might also result in a lower affinity of the antibody or even in generation of a stop codon. When B cells lose their ability to express an antibody or when they express an antibody with a lower affinity, they subsequently undergo apoptosis within the GC. All other B cells accumulating favorable mutations are rescued from apoptosis by expressing the bcl-2 gene. These B cells clonally expand and can accumulate further mutations to improve the affinity of their antibody. After leaving the GC, they differentiate into B memory cells or plasma cells. In a substantial proportion of LPHD cases, the clonal L&H cells revealed ongoing mutations, which provides evidence that L&H cells are GC-derived B cells that depend on antigen binding and selection. In this context, L&H cells are comparable with follicular lymphoma (FL) cells. Whereas FL cells frequently harbor the chromosomal translocation t(14;18), resulting in activation of the bcl-2 gene, the transforming event in L&H cells remains unknown. H-RS cells of CHD differ from FL as well as from LPHD in that they accumulate crippling somatic mutations within potentially functional Ig gene rearrangements, which prevent further antibody expression. The expression of Ig genes does not necessarily have to be located within the coding region of Ig genes. One case of MCHD has been described in which a somatic mutation within a regulatory element of the IgH promoter was associated with down-regulation of Ig gene expression. The detection of crippling mutations rendering potential functional Ig gene rearrangements nonfunctional suggests that H-RS cells, as a rule, grow independently from antigen selection and even antibody expression. Indeed, no Ig gene expression in H-RS cells could be demonstrated by several groups. The mechanism preventing apoptosis of the H-RS cells within the GC still is unknown.

### Genetic Alterations in Hodgkin's Disease

Conventional karyotype analysis of Hodgkin's and RS cells is hampered by the low number of obtainable mitoses from lymph node suspensions and their poor chromosome banding qualities. In addition, karyotypes cannot be unequivocally attributed to malignant cells, as the cellular compartment with the highest mitotic index in affected tissue is that of nonmalignant lymphocytes in the neighborhood of the H-RS cells. Thus, proliferating cells with a normal karyotype most probably represent reactive lymphoid cells. Depending on the histologic subtype, between 75% (NS) and 42% (LP) of cases studied yielded evaluable metaphases. In karyotype analyses performed by different groups, the percentage of abnormal karyotypes varied considerably, between 22% and 83%. Although numeric and structural cytogenetic aberrations were observed, a specific chromosomal marker of HD—as, for instance, the Burkitt's lymphoma–specific chromosomal translocations—has not yet been defined. In a study of 60 lymph nodes obtained from untreated patients with HD, numeric or structural aberrations (or both) were found in approximately one-half of the analyzable cases. Among HD-associated chromosomal abnormalities, aneuploidy (100%) with hyperdiploidy (70%) is the most frequent. Chromosomes 1, 2, 5, 12, and 21 are often triplicated. In a few cases, gain of chromosomes 7, 9, 11, 13, and 17 was noted. In several cases, the t(14;18) translocation was found in 0% to 39% of HD cases. Whether the translocation was localized in the H-RS cells remained unproven in these positive cases, however, particularly as the detection of the bcl-2 gene. Thus, over decades, the cell of origin of the H-RS cells remained an enigma.
protein by immunohistochemistry in situ was not congruent with the detection of the translocation itself in all cases. In one report using micromanipulation of single H-RS cells followed by PCR, the t(14:18) was shown to be localized in nonmalignant bystander B cells and not in a single case in the H-RS cells. In the p53 tumor suppressor, which are commonly found in a variety of human cancers, also could not be detected in H-RS cells using single-cell analysis. In view of the derivation of H-RS cells from the GC lymph nodes, putative mechanisms preventing apoptosis of their precursors are of special interest for understanding the transforming events. The nuclear transcription factor NFκB might be involved in prevention of apoptosis. Indeed, constitutive expression of NFκB has been found in HD-derived cell lines as well as in primary H-RS cells in situ. It also has been suggested that defects in the inhibitory molecule IkB might underlie the overexpression of NFκB, at least in some cases of HD. So far, however, the mechanisms preventing apoptosis in H-RS cells are not understood.

### IMMUNOLOGY OF HODGKIN’S DISEASE

#### Cellular Immunodeficiencies

HD is associated with a complex deficiency in cellular immunity, including impairment of delayed cutaneous hypersensitivity, enhanced Ig production, high levels of circulating immune complexes, production of antilymphocyte and anti-la antibodies, decreased natural killer (NK) cell cytotoxicity, enhanced sensitivity to suppressor monocytes and T suppressor cells, and a variety of other disorders of serum factors, including high levels of circulating IL-2 receptors. In vitro, peripheral blood lymphocytes show spontaneous DNA and IgG synthesis and depressed proliferative response to T-cell mitogen stimulation, with impairment of lymphokine production.

Increasing numbers of long-term survivors provided the opportunity to restudy anergy and in vivo lymphocyte responsiveness in patients who have been successfully treated. Studies at the National Cancer Institute (NCI), in a population of uniformly staged and treated patients, showed that anergy did not influence prognosis within a given stage. For successful treatment, anergy to recall antigens was reversible, although response to neocarzinostatin remained suppressed. This defect appears to be disease-related, as patients with other types of lymphomas did not show this defect. Unlike the defects in delayed hypersensitivity, most studies have shown that the antibody response of B cells and the B-cell numbers are normal in HD patients, except in those with advanced disease.

#### Antigen-Presenting Phenotype of Hodgkin’s-Reed-Sternberg Cells

In affected lymph nodes, the rare H-RS cells are surrounded by a majority of nonmalignant bystander cells. The majority of lymphocytes in affected lymphatic tissue are activated T helper cells (CD4+, CD45R0+, CD45RB+). These lymphocytes represent the population with the highest mitotic index in affected lymph nodes. The lymph nodes often grow slowly and show fluctuations in their size in early disease stages. These observations point toward a cellular immune reaction as the primary reason for the lymph node enlargement in HD. In contrast to benign lymphoproliferative lesions (e.g., reactive lymph nodes), the immune reaction in HD is not self-limited. One reason might be the inability of the immune system to eliminate the malignant cells expressing the target antigen. The recently established HD-derived cell line L1236 expresses HLA class I and II molecules, B7.1 and B7.2 (CD80, CD86), and the adhesion molecules ICAM-1 (CD54) and LFA-3 (CD58). All of these molecules are essential for efficient T-cell recruitment (accessory molecules). Expression of HLA antigens and of B7.1 molecules has also been described on H-RS cells in biopsy specimens and on other HD-derived cell lines (L428, L540; unpublished observation). The expression pattern of the surface antigens on H-RS cells thus points toward an antigen-presenting functional phenotype.

Antigen-presenting cells and, in particular, dendritic cells play a major role in the recruitment and activation of antigen-specific T cells, which is mainly attributed to their ability effectively to present antigens and to provide costimulatory signals via CD40, members of the B7 family (CD80, CD86), and adhesion molecules (CD11a, CD11c, LFA-3, ICAM-1). Furthermore, immunoregulatory cytokines such as IL-12, secreted by dendritic cells, promote the development of Th1 T cells, which play a major role in tumor-specific T-cell responses (Fig. 45.6-1).

**FIGURE 45.6-1.** Antigen-presenting cell–like functional phenotype of a B-cell–derived tumor cell. Ag, antigen; H-RS, Hodgkin's-Reed-Sternberg; IL-10, interleukin-10; MHC, major histocompatibility complex; TARC, thymus and activation regulated chemokine; TCR, T-cell receptor; TGF-b, transforming growth factor-b; Th2, T helper cell 2.

#### Hodgkin’s Disease and Immunity against Epstein-Barr Virus

In one study, it was shown that the H-RS cell population was uniformly HLA class I–positive in at least 75% of cases of EBV genome–positive HD, whereas the figure was much lower in EBV genome–negative tumors. More than one-half of the EBV genome–negative tumors had no detectable HLA class I expression in tumor cells. Analyses of transporter associated with antigen processing (TAP) expression in H-RS cells found that almost all HD cases, regardless of EBV status, were positive for TAP1 and for TAP2. Furthermore, it has been shown that in the HD-derived cell line L1236, the LMP2 can be processed and presented through the HLA class I pathway. Although TAP expression in L1236 is not down-regulated, processing of the LMP2-derived target epitope might also have occurred via a TAP-independent route.

#### Nerve Growth Factor Superfamily: Relevant Molecules?

The CD30 antigen, a member of the nerve growth factor superfamily, has been defined by a cluster of antibodies raised first against the HD-derived cell line L428. Initially, the expression of CD30 was seemed to be related exclusively to H-RS cells, thus representing a tumor-specific antigen. Subsequently, the CD30 antigen was also found on activated T and B cells as well as on activated and differentiated macrophages. The highest CD30 expression is seen on HD lymphoma cells, CD30+ large cell lymphomas (LCLs) with T-cell phenotype, and acute lymphocytic leukemia T cells.

The CD30/CD30 ligand (CD30/CD30L) interaction probably plays a central role in the complex interaction between H-RS cells and their microenvironment. A CD30L has been described that exerts pleiotropic effects on different lymphoma subtypes in vitro and is expressed only on the bystander cells (T cells, monocytes, granulocytes) but not on the H-RS cells. In tissue culture experiments, some biologic functions of the CD30/CD30L interaction have been characterized that point toward a cytokine receptor function of the CD30 antigen. It remains to be established whether the pleiotropic effects of CD30/CD30L interaction in different cell types are due to different intracellular signaling or whether they reflect sequence differences in the CD30 gene.

The soluble form of CD30 (sCD30) is detectable in the serum of patients with advanced stages of HD. This has been considered to reflect a prognostic factor for an unfavorable outcome. It has been shown in vitro that CD40/CD40L signaling is able to down-regulate BCL-6 in B cells with a GC phenotype. A similar effect is exerted in vitro also by LMP1, which is functionally homologous to CD40. It thus may be postulated that CD40 ligation is the major determinant of the phenotype of the RS cell. The BCL-6+/-syn-1− profile associates with 100% nodular lymphoid HD (NLPHD), thus corroborating the notion that nodular lymphocytic predominance (NLP) is a relatively homogeneous disorder closely reflecting the GC phenotype. The BCL-6+/syn-1− profile associates with the majority of CHD (NS and MC), indicating that RS cells frequently are represented by post-GC B cells that have undergone preterminal differentiation. Whereas CD40 is consistently expressed by both LH and RS cells, the abundance and distribution of CD40L+ T lymphocytes varies markedly in different HD categories. In CHD, CD40/CD40L signaling between neoplastic and reactive cells seems to be a prominent feature that is associated with RS cells displaying the BCL-6+/syn-1− phenotype.
**Chronic Secretion of Cytokines**

IL-2 receptor levels and other inflammatory cytokines are elevated in the sera of patients. The (deregulated?) expression of cytokines may at least partially explain the complex interaction between H-RS and bystander cells. For instance, eosinophilia in HD is caused by IL-5, and fibrosis may be triggered by IL-1 and transforming growth factor-β (TGF-β). IL-1, IL-6, and IL-8, which are produced by H-RS cells, may act as autocrine growth factors and as paracrine growth stimulators for T cells. Vice versa, the T cells may stimulate H-RS cells via IL-2 and IL-6. Many cytokines, including IL-1, IL-5, IL-6, IL-9, IL-10, and TGF-β, are produced by RS cells, and it is suspected that constitutive nuclear expression of NFκB is responsible for this phenomenon.

IL-10 is a pleiotropic cytokine with potent inhibitory effects toward Th1 cells and is mainly produced by Th2 cells, activated monocytes and macrophages, stimulated B cells, and mast cells. It has been suggested that IL-10 is involved in the pathogenesis of malignant B-cell lymphomas. HD is characterized by an abnormal or unbalanced secretion or production of cytokines, including IL-10, which supports growth of both neoplastic Hodgkin’s and Reed-Sternberg (H-RS) cells and their surrounding reactive bystander cells.

In untreated HD patients, 13% were found to be seropositive for IL-10 before therapy, whereas IL-10 was not detectable in a healthy control population. HD patients whose disease was at an advanced clinical stage (stage III or IV) were found to have higher IL-10 serum levels. A univariate analysis indicated a correlation of elevated IL-10 serum levels with early relapse and reduced long-term survival. The group of IL-10-seropositive HD patients showed a significant correlation of elevated IL-10 serum level with a reduced relapse-free survival. Thus, the increased production of IL-10 in HD could be associated with a poor clinical prognosis and may serve as a prognostic factor.

**PATHOLOGY**

**DEFINITION OF HODGKIN’S DISEASE**

The clinical features and responses to treatment of HD differ dramatically from those of most so-called NHLs, suggesting that a specific immunologic reaction is important not only in the definition but also in the clinical behavior of this disease. Studies in the 1980s showed that in NLPHD, the RS cell variants expressed B-cell–associated antigens, whereas these cells in most cases of NSHD and MCHD lacked these antigens. This difference in immunophenotype, together with the observation that NLPHD follows a more indolent clinical course, led to the suggestion that NLPHD was a low-grade B-cell lymphoma and should be removed from the category of HD and placed with the NHLs. However, both immunophenotypic and, more recently, molecular genetic studies have shown that CHD of the NS and MC types can express B-cell–associated antigens and, similar to NLPHD, have rearranged Ig genes. Furthermore, NLPHD and CHD share the feature of having a small number of neoplastic cells in a reactive background, which distinguishes both from most B-cell NHLs. Thus, although it is now known that the neoplastic cells in most cases of both LPHD and CHD are monoclonal B cells, their distinctive pathologic and clinical features still warrant placing them together in a separate category from other lymphoid neoplasms. It is important for both pathologists and oncologists to recognize that HD is two distinct diseases. Therefore, current classifications include two main categories of HD: CHD (NS, MC, and LD) and NLPHD. In summary, the Hodgkin’s lymphomas are defined as lymphomas containing one of the characteristic types of RS cells in a background of nonneoplastic cells; cases are subclassified according to the morphology and immunophenotype of the RS cells and the composition of the cellular background. The differences in the morphology of the RS cells and the composition of the cellular background have formed the basis for the pathologic subclassification of HD (Table 45.6-2).

**CLASSIFICATIONS OF HODGKIN’S DISEASE**

The early classification by Jackson and Parker recognized three categories of HD: paragranuloma, granuloma, and sarcoma. The distinction among the three categories was based on the ratio of neoplastic to normal cells, which increased from paragranuloma to granuloma to sarcoma, and predicted decreasing survival. In 1966, Lukes et al. recognized that the category of granuloma could be subdivided into two categories—NS and MC—which were characterized by distinctive morphologic and clinical features. Lukes et al. also recognized that there were two variants of what they called lymphocytic or histiocytic predominance type (replacing paragranuloma)—a nodular and a diffuse variant—which they found differed in prognosis. The Lukes and Butler classification was modified and simplified at the Rye conference in 1966. The Rye classification has remained the standard classification since that time.

In 1994, the International Lymphoma Study Group introduced an updated classification, incorporating new immunologic and molecular data, as part of the Revised European-American Lymphoma (REAL) Classification. These concepts have been incorporated into the new World Health Organization (WHO) classification of hematologic malignancies, a joint effort of the Society for Hematopathology and the European Association of Hematopathologists.

Several major differences exist between the REAL/WHO classification of HD and older classifications. Most important is the recognition that there are two distinct diseases that have been called HD: CHD, which consists predominantly of NS and MC, and NLPHD (Table 45.6-3). Simply a predominance of lymphocytes in the background is not sufficient to classify a case as NLPHD; cases that have the RS-cell morphology and immunophenotype of CHD, even if they contain predominantly lymphocytes, are classified as lymphocyte-rich classical Hodgkin’s disease (LRCCHD). A second difference is that, in the Lukes-Butler and Rye classifications, MC was a heterogeneous category, including both typical cases and all other cases that did not fit into one of the other categories. We now recommend that MC be restricted to typical cases and that unclassifiable cases be categorized as HD. Finally, it is now clear that immunophenotype is important in the subclassification of HD, both in distinguishing NLPHD from classic types and in distinguishing HD from NHL; thus, the immunophenotype is included in the definitions of HD in the REAL/WHO classification. Typical freedom-from-treatment-failure (FFTF) and survival curves for the main histologic subtypes are illustrated in Figure 45.6-2 using German Hodgkin’s Lymphoma Study Group data.
A distinctive type of follicular lymphoid hyperplasia, known as a morphologic variant, syncytial NS, has been described, in which, focally, the NS pattern is lost and large sheets of cells resembling lacunar RS-cell variants are seen. These cases have been called the nodular lymphocyte-predominant Hodgkin’s disease (NLPHD) because they are characterized by the presence of large numbers of lymphocytes and a network of follicular dendritic cells (FDCs) within the nodules. The RS-cell variants differ from mononuclear and classic RS cells: They have vesicular, polylobed nuclei and distinct but small, usually peripheral nucleoli, without perinucleolar halos; these have been called L&H cells (after Lukes and Butler) or popcorn cells, because of the resemblance of their nuclei to an exploded kernel of corn. In fact, they resemble “exploded” centroblasts. Although popcorn cells may be very numerous, usually no classic, diagnostic RS cells are found. In occasional cases, however, the RS cells may resemble classic or lacunar types; in such cases, immunophenotyping is helpful in establishing the diagnosis. The background is predominantly lymphocytes; clusters of epithelioid histiocytes may be numerous; plasma cells, eosinophils, and neutrophils rarely are seen and, if present, are not numerous. Occasional sclerosis may cause some cases to resemble NSHD.

**Nodular Lymphocyte-Predominant Hodgkin’s Disease**

**MORPHOLOGIC FEATURES.** NLPHD is defined as having at least a partially nodular growth pattern; diffuse areas are present in a minority of cases, and it is controversial whether purely diffuse cases exist. The RS-cell variants differ from mononuclear and classic RS cells: They have vesicular, polylobed nuclei and distinct but small, usually peripheral nucleoli, without perinucleolar halos; these have been called L&H cells (after Lukes and Butler) or popcorn cells, because of the resemblance of their nuclei to an exploded kernel of corn. In fact, they resemble “exploded” centroblasts. Although popcorn cells may be very numerous, usually no classic, diagnostic RS cells are found. In occasional cases, however, the RS cells may resemble classic or lacunar types; in such cases, immunophenotyping is helpful in establishing the diagnosis. The background is predominantly lymphocytes; clusters of epithelioid histiocytes may be numerous; plasma cells, eosinophils, and neutrophils rarely are seen and, if present, are not numerous. Occasional sclerosis may cause some cases to resemble NSHD.

**PROGRESSIVE TRANSFORMATION OF GERMINAL CENTERS.** A distinctive type of follicular lymphoid hyperplasia, known as progressive transformation of germinal centers (PTGCs), is seen focally in approximately 20% of lymph nodes involved by NLPHD and may be seen in the absence of HD in other lymph nodes in the same patient. PTGCs are enlarged follicles that contain numerous small B cells of mantle zone type; these follicles may closely resemble the nodules of NLPHD. This phenomenon has given rise to speculation that NLPHD may arise from PTGCs. PTGCs usually are seen as single or only a few enlarged follicles in a setting of nonspecific reactive follicular lymphoid hyperplasia; however, on occasion, they may be numerous and associated with prominent lymph node enlargement, particularly in adolescents and young adults.

**NODULAR LYMPHOCYTE-PREDOMINANT HODGKIN’S DISEASE AND LARGE B-CELL LYMPHOMA.** Patients with NLPHD have a slightly higher risk of developing NHL than do patients with other types of HD. Transformation of NLPHD to TCL, usually with a B-cell phenotype and often monoclonal with respect to Ig (both phenotype and genotype), is most common. Hansson et al. reported 2.6% in a series of 537 cases, and the British National Lymphoma Investigation (BNLI) reported a 2% incidence in 182 cases; the range in recent reports is from 0.2% to 6.5%. The LCL does not necessarily consist of typical L&H cells and usually resembles other diffuse, large B-cell lymphomas (DLBCLs). Most cases studied have had a B-cell immunophenotype, with B-lineage antigen expression in the majority and monotypic Ig expression in approximately 30% to 50%. In some cases, a clonal relationship between the LP and the DLBCL has been shown by molecular genetic analysis.

In addition to the cases that progress to DLBCL, NLPHD may be composite with DLBCL in the same lymph node, at the time of either diagnosis or relapse. In reported cases, the prognosis of these patients appears to be significantly better than that for usual DLBCL, and patients who respond to treatment may later relapse with only NLPHD.

**IMMUNOPHENOTYPE.** The immunophenotype is an important part of the definition of NLP. In contrast to CHD, the atypical cells are CD45+, express B-cell-associated antigens (CD19, CD20, CD22, CD79a) and epithelial membrane antigen (EMA), but lack CD15 and CD30. In contrast to typical B-cell lymphomas, however, they are usually Ig-negative by routine techniques. J-chain has been demonstrated in many cases. Studies using in situ hybridization for light-chain messenger RNA (mRNA) have shown clonal expression in the atypical cells. Popcorn cells also express the nuclear protein encoded by the bcl-6 gene, which is associated with normal GC B-cell development, and the activation-associated molecules CD40 and CD86 (B7/BB1), which are involved in B-cell interaction with T cells.

The nodules of LP are actually altered follicles or GCs. The small lymphocytes in the nodules are a mixture of polyclonal B cells with a mantle zone phenotype (IgM and IgD+), and numerous T cells, many of which are CD57+, similar to the T-cell population in normal and progressively transformed GCs. T cells in NLPHD may exhibit significant nuclear enlargement and irregularity, resembling centrocytes. In contrast to the T cells in reactive or progressively transformed follicles, which are scattered singly and often concentrated in the light zone or at the junction with the mantle zone, the T cells in NLPHD form small aggregates, often giving the follicle a broken-up, moth-eaten, or irregular contour. They typically surround the neoplastic B cells, forming rings, rosettes, or collarites. Although several reports suggest that the T cells surrounding popcorn cells are mostly CD57+, this can be difficult to demonstrate in many cases, and absence of CD57+ cells in the rosettes does not argue against the diagnosis. A prominent concentric meshwork of follicular dendritic cells (FDCs) is present within the nodules. The interfollicular region contains predominantly T cells; when there are diffuse areas, the background lymphocytes are also predominantly T cells, and the FDC meshwork is lost.

**CLINICAL FEATURES.** NLPHD accounts for 4% to 5% of the cases of HD in most series. The median age of patients is in the mid 30s, but cases may be seen both in children and the elderly. The male-to-female ratio is 3:1 or greater. NLPHD usually involves peripheral lymph nodes, with sparing of the mediastinum. Nearly 80% of the patients in most series are stage I or II at the time of the diagnosis, but rare patients may present with stage III or IV disease, with a concomitantly worse prognosis. More than 90% of the patients have a complete response to therapy, and 90% are alive at 10 years. The cause of death is often NHL, other cancers, or complications of treatment, rather than HD.

**Classic Hodgkin’s Disease**

CHD is defined by the presence of classic, diagnostic RS cells in a background of NS, MC, or LD, with classic immunophenotype (CD15+, CD30+, T- and B-cell–associated antigens usually negative). CHD includes NS, MC, and LD, as well as the proposed new category of LRCHD. Because the immunophenotype, genetic features, and postulated normal counterpart are the same for all of the classic types, these will be discussed together at the end of this section.

**NODULAR SCLEROSIS HODGKIN’S DISEASE.** NSHD, by definition, has at least a partially nodular pattern, with fibrous bands separating the nodules in most cases; diffuse areas are common, as is necrosis. The characteristic cell is the lacunar type RS cell, which may be very numerous. These cells are characterized by multilobed nuclei and small nucleoli, with abundant, pale cytoplasm that retracts in formalin-fixed sections, producing an empty space, or lacuna. Diagnostic RS cells also are present but may be rare. The background usually contains lymphocytes, histiocytes, plasma cells, eosinophils, and neutrophils. Occasional sclerosis may cause some cases to resemble NSHD.

In some cases with characteristic lacunar cells and a nodular or diffuse pattern, fibrous bands may be absent, and differentiating this type from NLPHD may be difficult. These cases have been called the cellular phase of NSHD; in one series, the clinical course of these cases was slightly worse than that for typical cases. Another morphologic variant, syncytial NS, has been described, in which, focally, the NS pattern is lost and large sheets of cells resembling lacunar RS-cell variants are seen.
The prognosis of this variant was not reported to be different from that of typical NS. However, some studies have suggested that NS with lymphocyte depletion is associated with large mediastinal masses, advanced stage, and poor response to radiotherapy alone.

Grading. The BLNI developed a system for grading NSHD (grade 1 and grade 2), based on the number and atypia of the RS cells in the nodules. Cases of grade 2 NS overlap with the syncytial and LD variants already described. Based on this system, approximately 75% to 85% of the cases in most series are grade 1 and 15% to 25% grade 2. In most series, grade 2 tumors were associated with a worse prognosis than grade 1 tumors, with NS2 tumors having an increased rate of relapse, shorter survival, and worse response to initial therapy (see Fig. 45.6.2). The BLNI studies have been criticized because some series included patients who were not pathologically staged and because, as compared to some other series, their patients had a relatively poor outcome.

Results from American and European centers have conflated, showing either no influence on outcome or a significantly worse outcome for NS2 patients. In general, when a center reports either a relatively high rate of relapse or relatively poor survival, NS2 patients are found to have a significantly worse outcome than NS1 patients; conversely, when overall relapse rates are low and survival high, grade has no impact on outcome. This phenomenon was illustrated most clearly in a study of 195 patients treated in the Netherlands, for patients treated between 1972 and 1980, when overall survival was relatively poor, grade 2 patients had a significantly worse outcome (5-year overall survival for NS1 and NS2, 83% and 43%, respectively), whereas for those treated between 1981 and 1992, grade had no impact on outcome (5-year overall survival for NS1 and NS2, 81% and 82%, respectively).

The impact of NS2 on survival is most evident in patients who; those with NS2 have significantly shorter survival after relapse than do those with NS1. Taken together, these results suggest that more aggressive therapy benefits grade 2 patients; they also suggest the possibility that patients with NS1 could be treated less aggressively and still do as well. It could be argued that in future studies, NS should be consistently graded and that trials of less aggressive initial treatment for NS1 might be appropriate.

Clinical Features. NSHD is the most common subtype of HD in developed countries (60% to 80% in most series). It is most common in adolescents and young adults but can occur at any age; the number of affected female individuals equals or exceeds the number of affected male persons. The mediastinum and other supradiaphragmatic sites are commonly involved.

MIXED-CELLULARITY HODGKIN’S DISEASE. In MCHD, the infiltrate is usually diffuse or, at best, vaguely nodular, without band-forming sclerosis, although fine interstitial fibrosis may be present. RS cells are of the classic, diagnostic type and usually are easily identified. Many mononuclear variants are also usually present; rare lacunar cells may be seen. Diagnostic RS cells are large cells with bloomed, double, or multiple nuclei, with a large, eosinophilic, inclusion-like nucleus in at least two lobes of cytoplasm. The infiltrate typically contains lymphocytes, epithelioid histiocytes, eosinophils, and plasma cells.

Clinical Features. MCHD is accountable for 15% to 30% of HD cases in most series; it may be seen at any age and lacks the early adult peak of NSHD. Involvement of the mediastinum is less common than in NSHD, whereas abdominal lymph node and splenic involvement are more common.

LYMPHOCYTE-DEPLETED HODGKIN’S DISEASE. The infiltrate in lymphocyte-depleted HD (LDHD) is diffuse and often appears hypocellular, due to the presence of diffuse fibrosis and necrosis; there are large numbers of RS cells and bizarre sarcomatous variants, with a paucity of other inflammatory cells. Confluent sheets of RS cells are common and are usually predominantly (reticular variants of Hodgkin’s sarcoma). Before the availability of immunophenotyping, many cases diagnosed as LDHD were, in reality, cases of large B-cell lymphoma or T-cell lymphomas, often of the anaplastic large cell lymphoma (ALCL) type. Cases of the reticular variant of LDHD may be difficult to distinguish from ALCL.

Clinical Features. LDHD is the least common variant of HD, accounting for fewer than 1% of the cases in recent reports. It is most common in older people, in human immunodeficiency virus–positive (HIV-positive) individuals, and in nonindustrialized countries. LDHD frequently presents with abdominal lymphadenopathy and spleen, liver, and bone marrow involvement, without peripheral lymphadenopathy. The stage is usually advanced at diagnosis; however, response to treatment is reported not to differ from that of other subtypes of comparable stage.

IMMUNOPHENOTYPE OF CLASSIC HODGKIN’S DISEASE. In most cases of NSHD, MCHD, and LDHD, the tumor cells are CD15+, CD30+, and CD45–. The frequency with which CD15 and CD30 are detected varies in reported series, probably because of technical problems. With microwave antigen retrieval and use of an anti-Îµ secondary antibody, the German Hodgkin’s Study Group (GHSG) reported 83% of 1751 cases to be positive for CD15, 96% positive for CD30, and 5% positive for CD20. Expression of B-cell antigens has been reported in a varying number of cases, usually only weakly and in a minority of the cells. Thus, expression of B-cell antigens does not exclude a diagnosis of HD if the morphologic features are typical.

The diagnosis of HD still is made on routine sections, and immunophenotyping studies are an adjunct to the diagnosis. In a morphologically typical case, immunophenotyping studies are not absolutely necessary; however, they are becoming more standard practice. Failure to detect CD15 or CD30 or expression of a B-cell–associated antigen does not preclude a diagnosis of HD; however, absence of both CD15 and CD30 and expression of CD20 should prompt reexamination of the slides and consideration of either NLPHD or LRCHD. Expression of T-cell antigens is distinctly unusual, and should prompt both re-review of the slides and molecular genetic analysis of the T-cell receptor gene.

In addition to CD15 and CD30, RS cells express CD25, HLA-DR, ICAM-1, CD95 (apo-1/fas), and both CD40 and CD86 (B7), molecules associated with B-cell activation and interaction with T cells. RS cells are found within the mantle area or at the junction of the mantle and interfollicular regions. The RS cells are found within the mantle area or at the junction of the mantle and interfollicular regions. The RS cells are found within the mantle area or at the junction of the mantle and interfollicular regions.

Clinical Features. Of 1959 cases of HD with background infiltrate that consists predominantly of lymphocytes, with rare or no eosinophils. The term lymphocyte-rich classic Hodgkin’s disease was proposed for cases in this set of real classifications. Immunophenotypic studies are an adjunct to the diagnosis. In a morphologically typical case, immunophenotyping studies are not absolutely necessary; however, they are becoming more standard practice. Failure to detect CD15 or CD30 or expression of a B-cell–associated antigen does not preclude a diagnosis of HD; however, absence of both CD15 and CD30 and expression of CD20 should prompt reexamination of the slides and consideration of either NLPHD or LRCHD. Expression of T-cell antigens is distinctly unusual, and should prompt both re-review of the slides and molecular genetic analysis of the T-cell receptor gene.

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multiple relapses and better survival after relapse, as compared with LRCHD, NSHD, and MCHD patients. In the GHSG study, the overall survival of LRCHD was significantly worse than that of NLPHD. These data do not clearly define LRCHD as a distinct entity but are consistent with either an early phase of MCHD or a novel subtype. It is suggested that this category continue to be recognized within the classification of HD, so that additional data can be collected.

ASSOCIATION OF CLASSIC HODGKIN’S DISEASE WITH OTHER LYMPHOMAS. CHD may be associated with other lymphomas, most often of the B-cell type. These lymphomas may occur before, simultaneously with, or after HD. Patients treated for HD are at risk for development of high-grade B-cell lymphomas (DLBCL or Burkitt’s or Burkitt-like lymphoma), which have been presumed to arise in a setting of immunosuppression secondary to therapy for HD; the estimated risk ranges from 1% to 5%. However, EBV has not been demonstrated in the secondary lymphomas, in contrast to the situation in most immunosuppression-associated NHLs.

Numerous cases of CHD associated with FL or DLBCL have been reported; the HD may precede, follow, or occur simultaneously with the NHL. Two cases of HD occurring with NHL (one case of composite HD and FL and one case of DLBCL followed by HD) have been studied by single-cell PCR; a common clone was found in HD and NHL in both cases. Rare cases of B-cell chronic lymphocytic leukemia (CLL) may contain cells with the morphology and immunophenotype of classic RS cells, whereas other patients with typical CLL may go on to develop HD—a so-called HD variant of Richter’s syndrome. Several such cases have been studied using single-cell PCR; in the majority of the cases, the RS cells were of the same clone as the CLL cells, though in one case, they were clonally unrelated. Finally, cases of mycosis fungoides or lymphomatoid papulosis associated with HD have been reported. Thus, it is clear that patients with HD are at some increased risk for development of NHL. In some patients, a single neoplastic B cell can give rise to both HD and NHL, whereas in other patients, it appears that either immunosuppression or other unknown factors can give rise to two independent malignancies.

DIFFERENTIAL DIAGNOSIS OF CLASSIC HODGKIN’S DISEASE

Two lymphomas have been described that have significant morphologic overlap with HD and may cause problems in differential diagnosis (Fig. 45.6-3): T-cell/histiocyte-rich-large B-cell lymphoma (T/HRLBCL) and T-cell ALCL. In addition, DLBCLs with anaplastic cytology may be difficult to distinguish from HD with LD (Table 45.6-4).

T-Cell/Histiocyte-Rich Large B-Cell Lymphoma

In the late 1990s, several groups reported an unusual type of lymphoma with morphologic features reminiscent of diffuse LPHD or MCHD, with a predominance of small T lymphocytes and scattered large neoplastic cells that express B-cell antigens. Patients typically present with advanced-stage disease and have a poor prognosis. The term histiocytoid-rich or T-cell-rich large B-cell lymphoma has been used for these cases. The cases that resemble HD are different from earlier cases reported as T-cell-rich B-cell lymphoma, many of which are simply B-cell lymphomas of follicle center or large cell type in which T cells compose 50% or more of the infiltrate. Whether T/HRLBCL constitutes a distinct disease or is simply an aggressive variant of LPHD is not clear. However, it is important to distinguish it from either NLPHD or HD because of its aggressive clinical course.

T/HRLBCL is a diffuse lymphoma with a lymphocyte-rich background, with small clusters of epithelioid histiocytes and scattered large mononuclear cells, suggesting either LPHD or HD. The large cells may resemble popcorn cells, immunoblasts, or centroblasts, or all three.

The neoplastic cells express CD20 and other pan-B antigens, may or may not express cytoplasmic light chains, and may or may not have detectable Ig gene rearrangement by Southern blot or whole section PCR. Like LPHD, they are often EMA-positive but are CD15-, CD30-, and EBV-negative. The background lymphocytes are T cells that are CD57-negative, and FDC aggregates are not seen.

The immunophenotype of the large cells is of limited value in the differential diagnosis with LPHD, as it is similar; however, readily detectable Ig light chains would tend to favor a diagnosis of T/HRLBCL. In addition, staining for CD20 may reveal a nodular pattern and a B-cell–rich background, which would favor LPHD. Follicular aggregates of FDC (anti-CD21) also favor NLPHD, as do large numbers of CD57+ cells. In distinguishing T/HRLBCL from CHD, immunophenotyping is essential and helpful. If the large cells express CD20 and lack CD15 and CD30, the diagnosis of T/HRLBCL is strongly favored, whereas expression of either CD15 or CD30 strongly favors a diagnosis of CHD. Furthermore, in cases diagnosed as CHD that express only CD20, the prognosis appears to be significantly worse than for cases expressing CD15 or CD30, with or without CD20.

Anaplastic Large-Cell Lymphoma

ALCL is a T-cell lymphoma characterized by large malignant lymphocytes with prominent nucleoli and abundant cytoplasm, which may resemble mononuclear or multinucleated RS-cell variants. However, the tumor cells grow in cohesive sheets and frequently involve lymph node sinuses, a pattern that is unusual in HD. In addition, the neoplastic cells usually are smaller than RS cells, have less conspicuous nucleoli, without perinucleolar halos, and often have bean-shaped or horseshoe-shaped nuclei, with a prominent paranuclear hof, in contrast to the round nuclei of mononuclear RS cells. ALCL has a bimodal age distribution, with one peak in childhood and another in adulthood.
A subtype of ALCL, called Hodgkin-like-related ALCL, has been described (modified to Hodgkin's-like in the REAL classification; a provisional entity). This variant was characterized by cytologic features similar to common ALCL—confluent sheets of tumor cells, a cohesive growth pattern, and sinusoidal infiltration—but with architectural features that resemble HD of the NS type, with nodular growth of tumor cells and occasional fibrous bands. The immunophenotype of ALCL-HD was reported to be similar to that of common ALCL, but some cases had CD15 expression and EBV infection. There has been an ongoing debate about whether ALCL Hodgkin's-like is a variant of HD, a variant of ALCL, a heterogeneous mixture of the two, or a distinct disease.

Analysis of the t(2;5) associated with ALCL has helped to resolve this problem. Studies of the translocation have shown that it is absent in cases of typical HD. In immunophenotyping studies using antibodies to either the ALK protein or the p80 fusion product of the t(2;5), several groups have found the protein to be present in a subset of ALCL but not in HD. Cases diagnosed as ALCL-HD typically lack the ALK protein. Most hematopathologists now believe that cases reported in the literature as ALCL Hodgkin's-like are heterogeneous. Some represent LD variants of HD—either NASHD (syncytioid, LD, or NS grade 2) type or LD (LHD, Hodgkin's sarcoma)—whereas others are cases of ALCL with a nodular growth pattern. Most cases can be resolved as either HD (CD45−, CD15−, T-cell antigen−, CD20−/+, t(2;5)−, ALK−, EMA+) or ALCL (CD45+, CD15−, T-cell antigen+, CD20−, t(2;5)+, ALK+, EMA−).

In cases that are histologically borderline between HD and T-ALCL, immunophenotyping on paraffin sections with CD45, CD15, CD30, CD20, EMA, pan-T antigens, ALK1, and, if necessary, genetic studies should be undertaken to resolve the differential diagnosis. Expression of CD15 or CD20 tends to exclude a diagnosis of T-ALCL (CD20+ cases may be either HD or DBCL), whereas expression of CD45, T-cell antigens, ALK1, or EMA tend to exclude HD. Southern blot or whole section PCR analysis showing T-cell antigen receptor gene rearrangement would tend to exclude HD and confirm the diagnosis of ALCL. Ig gene rearrangement by these techniques would not usually be detectable in HD and would favor DBCL, but a weak band would not exclude HD. Cases that cannot be resolved by immunophenotype or genetic studies should be considered unclassifiable; clinical judgment should be used in deciding whether to perform another biopsy or to treat for either HD or ALCL. The category of ALCL Hodgkin's-like will be eliminated from the proposed WHO classification.

In summary, the data currently available suggest that there is no true borderline between HD and ALCL of the T-null type as defined in the REAL classification: HD is, in most cases, a B-cell neoplasm, whereas ALCL is a T-cell neoplasm. There is morphologic but not biologic overlap between HD and ALCL. HD may resemble ALCL by having areas of LD—that is, it may be ALCL-like—but this is a morphologic resemblance only, not a true biologic borderline. Similarly, ALCL may resemble HD by having areas of nodularity, sclerosis, or granulocyte infiltration—that is, it may be Hodgkin's-like—but again, this is not a true biologic borderline. In contrast, because HD is a B-cell neoplasm, there may be a true biologic borderline between B-cell lymphomas and HD of any type, between DLBCL and NLPHD, between T/HRLBCL and either MC or LPHD, and between large B-cell lymphoma, anaplastic, CD30+ type and lymphocyte-depleted variants of CHD. It is the latter areas that present the most challenging differential diagnoses currently.

DIAGNOSIS AND STAGING

NATURAL HISTORY AND PATTERNS OF SPREAD

The Swiss radiotherapist Gilbert is credited with first reporting that HD spread by contiguity from one lymph node chain to adjacent chains. His work was extended by Peters, Kaplan, and others, who evaluated the use of prophylactic radiotherapy to lymph nodes adjacent to those involved with disease. The development of new radiographic studies and the routine use of staging laparotomy improved understanding of the presentation and evolution of HD. Although there is strong evidence that HD begins in a single group of lymph nodes and then spreads to contiguous lymph nodes, eventually the malignant cells become more aggressive, may invade blood vessels, and spread to organs in a manner similar to other malignancies. This is more likely to occur in patients with stage I11 than with stage I or II HD.

Most patients with NSHD or MCHD have a central pattern of lymph node involvement (cervical, mediastinal, paraaortic). In contrast, certain nodal chains (mesenteric, hypogastic, presacral, epitrochlear, popliteal) seldom are involved. Occult adenopathy in patients with negative radiographic staging ranges from 6% to 35%. The spleen is involved more frequently in patients with adenopathy below the diaphragm, systemic symptoms, and MC histology. Involvement of the liver in an untreated patient is rare and almost always occurs with concomitant splenic involvement. Infiltration of the bone marrow is usually focal and almost invariably associated with extensive disease, systemic symptoms, and unfavorable histology. In the great majority of patients, the initial pattern of spread occurs nonrandomly and predictably via lymphatic channels to contiguous lymph node chains. This important observation, first made in the 1930s, continues to form the basis for prophylactic irradiation of adjacent lymph node–bearing regions in patients with apparently localized HD treated with radiotherapy alone.

STAGING CLASSIFICATIONS

Prior experience with staging laparotomy, the advent of new imaging modalities, and the frequent use of combined modality treatment have made staging procedures simpler and less invasive. The latest international staging classification was proposed in 1989 during a meeting held in Cotswolds, England.

The Cotswolds classification (Table 45.6-5) is a modification of the Ann Arbor classification using information from staging and treatment over the 1970s and 1980s. Some of the recommended modifications include adding criteria for clinical involvement of the spleen and liver, including evidence of focal defects with two imaging techniques, eliminating consideration of abnormalities of liver function, adding the suffix X to designate bulky disease (larger than 10 cm maximum dimension), adding a new category of response to therapy (i.e., unconfirmed or uncertain complete remission) to accommodate the difficulty of persistent radiologic abnormalities of uncertain significance after primary therapy, and separately classifying certain selected patients with localized extranodal disease (e.g., lung, pleura, chest wall, bone) contiguous to involved nodes as the appropriate lymph node system stage followed by the subscript E. The E designation excludes multiple extranodal deposits or bilateral lung extension, which constitute stage IV disease. Recommended staging procedures are listed in Table 45.6-6. An adequate surgical biopsy, possibly of more than one intact lymph node, is required for histopathologic examination.
Involvement of the liver in a patient with newly diagnosed HD is uncommon and occurs almost always with concomitant splenic involvement. HD limited to the spleen is not uncommonly associated with small amounts of pericardial and pleural fluid, but malignant effusions, diagnosed by thoracentesis or pleural biopsy, are rare. The neck or axillary. Less often, such enlarged nodes are found in the inguinal-femoral region. Tenderness and skin changes are believed to reflect rapid growth with stretching of nodal capsules. In most cases, the nodes are discrete and freely movable. Occult disease who are to receive limited treatment.

In general, HD patients present with peripheral lymphadenopathy. The nodes usually are not tender, and changes in the overlying skin are not the norm. Otherwise, tenderness and skin changes are believed to reflect rapid growth with stretching of nodal capsules. In most cases, the nodes are discrete and freely movable. Occult spread by contiguity from one lymph node chain to adjacent chains was extended by the use of prophylactic radiotherapy to lymph node regions adjacent to those involved with HD. The understanding of the presentation and evolution of HD has been improved by the development of new radiographic studies and the use of staging laparotomy.

Massive mediastinal adenopathy [large mediastinal adenopathy (LMA)] has been arbitrarily defined as the ratio greater than one-third between the largest transverse diameter of the mediastinal mass over the transverse diameter of the thorax at the diaphragm or as measuring greater than 5 to 10 cm in width. Patients with LMA have an increased risk of relapsing in nodal and extranodal sites above the diaphragm after radiotherapy alone. These patients make up 20% to 25% of CS I to II patients, generally present with involvement of multiple supradiaphragmatic nodal chains, and may have extension of tumor into the lung, pericardium, or chest wall. Systemic symptoms frequently are present.

Staging with thoracic computed axial tomographic (CAT) scanning can more precisely identify sites of initial involvement. CAT scanning is especially apt at detecting pulmonary disease, pleural or pericardial involvement, apical cardiac nodal enlargement, and extension into the chest wall, and in defining the extent of involved axillary lymph nodes. Such information has considerable potential to alter clinical management. Detection of the extent of thoracic disease will help to define the use of combination chemotherapy and the dose, extent, and need for radiotherapy.

With improved gamma camera resolution, several investigators have described the ability of 67Ga scanning to detect intrathoracic lymphadenopathy, though the reported sensitivities and specificities are somewhat less than those of CAT scanning. Today, the primary role for 67Ga scanning in the thorax is to answer specific questions that arise after treatment (e.g., whether a residual mass represents viable tumor rather than necrosis or fibrosis). As an alternative to gallium scanning, position emission tomography is being explored in Europe and in the United States. Some investigations suggest that the ability of magnetic resonance imaging (MRI) to detect tumor in mediastinum or hilar lymph nodes is not superior to that of CAT scanning. Although, MRI can probably function as an alternative to CAT scanning in the thorax, particularly at the level of chest wall involvement, its continuing high cost and lack of clinical data prevent this modality from being used routinely.

CAT scanning, lymphangiography (LAG), MRI, and 67Ga scanning all have limitations in the radiologic evaluation of abdominal nodes. No single study is reliable for detecting HD in normal-size nodes, and all studies have a 20% to 25% false-negative rate due to the inability to detect occult HD in the spleen. Ninety percent of patients who are up-staged have splenic involvement either alone or in addition to other infradiaphragmatic nodal sites. Head-to-head comparisons of bipedal LAG and CAT scanning suggests that LAG has a small statistical advantage over CAT, particularly in the presence of small lymphadenopathies, because it provides useful information on lymph node architecture. On the other hand, CAT scanning can better evaluate adenopathy in the celiac axis, splenic hilus, porta hepatitis, and mesentery, relying almost exclusively on increases in the size of the nodes. CAT scanning can also demonstrate foci of HD in the liver and spleen; however, the false-negative results are too numerous to allow one to rely heavily on CAT assessment of these organs.

During the late 1990s, LAG gave way to CAT scanning as the examination of choice. MRI may be more sensitive than CAT scanning in the evaluation of abdominal nodes, but information on its usefulness is still limited. MRI appears to be a potentially valuable tool in investigating bone marrow involvement and can help in directing image-guided biopsies. Gallium scanning can also complement LAG or CAT scanning, but its use in the abdomen may be hampered by normal uptake in the liver, spleen, and bowel. With the infrequent use of staging laparotomy and splenectomy in the staging of HD, the risk of overstaging based on a single radiographic test of abdominal involvement (false-positive outcome) has greater potential consequences. Therefore, we recommend that two separate studies (i.e., CAT scanning and 67Ga scanning) be used to assess abdominal involvement and that positive findings on both tests be required to confirm abdominal involvement for the routine radiographic staging of HD.

Staging laparotomy was extensively used when radiotherapy was the only potentially curative treatment for early-stage HD and when it was mandatory to define the extent of abdominal disease to help determine the extent of radiation needed below the diaphragm. With the increasing use of combination chemotherapy, staging laparotomy gradually evolved into a tool that aids in determining whether radiotherapy or chemotherapy should be selected as definitive treatment. With many groups using prognostic factors to determine treatment for HD, laparotomy has disappeared as a routine staging procedure. Its use now is reserved for patients with limited disease who are to receive limited treatment.

\[\text{Recommended Staging Procedures}\]

**RADIOGRAPHIC STAGING ABOVE THE DIAPHRAGM**

More than 60% of patients with newly diagnosed HD have radiographic evidence of intrathoracic involvement. Frontal and lateral chest radiographs should be routinely ordered and also represent the ideal for subsequent surveillance.

**STAGING LAPAROTOMY**

Staging laparotomy was extensively used when radiotherapy was the only potentially curative treatment for early-stage HD and when it was mandatory to define the extent of abdominal disease to help determine the extent of radiation needed below the diaphragm. With the increasing use of combination chemotherapy, staging laparotomy has disappeared as a routine staging procedure. Its use now is reserved for patients with limited disease who are to receive limited treatment.

**CLINICAL PRESENTATION**

First reports about clinical manifestations of HD and patterns of its course of spreading were conducted by Gilbert and others. Their findings that HD spreads by contiguity from one lymph node chain to adjacent chains was extended by the use of prophylactic radiotherapy to lymph node regions adjacent to those involved with HD. The understanding of the presentation and evolution of HD has been improved by the development of new radiographic studies and the use of staging laparotomy. Although there is evidence that the course of HD is characterized by its onset in a single lymph node or group of lymph nodes, followed by spreading to contiguous lymph nodes, there are indications that the disease can spread to organs similar to other malignancies by invading blood vessels. Most convincing data for contiguous spread in HD were found for NS and MC histology. In NS and MC histologic subtypes, a central pattern of lymph node involvement (cervical, mediastinal, paraaortic) was more common than nodal involvement of mesenteric, hypogastric, presacral, or popliteal regions.

In general, HD patients present with peripheral lymphadenopathy. The nodes usually are not tender, and changes in the overlying skin are not the norm. Otherwise, tenderness and skin changes are believed to reflect rapid growth with stretching of nodal capsules. In most cases, the nodes are discrete and freely movable. Occult presentation with central (chest and abdomen) lymphadenopathy, visceral involvement, or systemic symptoms of the disease is uncommon. The most characteristic clinical presentation of HD is enlarged superficial lymph nodes in young adults, the most frequent locations being cervical and supravacular (60% to 80%), high in the neck or axillary. Less often, such enlarged nodes are found in the inguinal-femoral region.

Mediastinal involvement is discovered often by routine staging chest radiography, and even fairly large masses may occur without producing local symptoms. Otherwise, symptoms of retrosternal chest pain, cough, or shortness of breath may be clinical signs of an intrathoracic disease presentation. A bulky mediastinal mass is not uncommonly associated with small amounts of pericardial and pleural fluid, but malignant effusions, diagnosed by thoracentesis or pleural biopsy, are rare.

Involvement of the liver in a patient with newly diagnosed HD is uncommon and occurs almost always with concomitant splenic involvement. HD limited to the spleen

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**TABLE 45.6-6. Recommended Staging Procedures**

**RADIOGRAPHIC STAGING ABOVE THE DIAPHRAGM**

More than 60% of patients with newly diagnosed HD have radiographic evidence of intrathoracic involvement. Frontal and lateral chest radiographs should be routinely ordered and also represent the ideal for subsequent surveillance.

**STAGING LAPAROTOMY**

Staging laparotomy was extensively used when radiotherapy was the only potentially curative treatment for early-stage HD and when it was mandatory to define the extent of abdominal disease to help determine the extent of radiation needed below the diaphragm. With the increasing use of combination chemotherapy, staging laparotomy gradually evolved into a tool that aids in determining whether radiotherapy or chemotherapy should be selected as definitive treatment. With many groups using prognostic factors to determine treatment for HD, laparotomy has disappeared as a routine staging procedure. Its use now is reserved for patients with limited disease who are to receive limited treatment.

**CLINICAL PRESENTATION**

First reports about clinical manifestations of HD and patterns of its course of spreading were conducted by Gilbert, Peters, and others. Their findings that HD spreads by contiguity from one lymph node chain to adjacent chains was extended by the use of prophylactic radiotherapy to lymph node regions adjacent to those involved with HD. The understanding of the presentation and evolution of HD has been improved by the development of new radiographic studies and the use of staging laparotomy. Although there is evidence that the course of HD is characterized by its onset in a single lymph node or group of lymph nodes, followed by spreading to contiguous lymph nodes, there are indications that the disease can spread to organs similar to other malignancies by invading blood vessels. Most convincing data for contiguous spread in HD were found for NS and MC histology. In NS and MC histologic subtypes, a central pattern of lymph node involvement (cervical, mediastinal, paraaortic) was more common than nodal involvement of mesenteric, hypogastric, presacral, or popliteal regions.

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Involvement of the liver in a patient with newly diagnosed HD is uncommon and occurs almost always with concomitant splenic involvement. HD limited to the spleen
The development of chemotherapeutic programs for HD is a story of success. After the discovery of the cytotoxic effects of nitrogen mustard in the 1940s, a number of

Involvement of the central nervous system is rare, although invasion of the epidural space can occur by nodular extension from the paraaortic region through the

Complaints due to extranodal manifestations of disease may occur, such as cough from pulmonary infiltration, jaundice from hepatic involvement, or abdominal pain from disease adjacent to the bowel. Gastrointestinal involvement is an extremely rare event and might occur as infiltration from mesenteric lymph nodes. Initial symptoms of disease limited to extranodal tissue are much rarer in HD than in NHLs.

TREATMENT METHODS

RADIOTherAPY

Principles

The early treatment of HD with crude x-irradiation in 1901 followed the discoveries by Roentgen, Becquerel, and the Curies at the end of the eighteenth century. The first reports of x-ray treatments that would dramatically shrink enlarged lymph nodes produced great excitement and premature predictions for the successful treatment of HD. During the first two decades of the twentieth century, physicians mainly used two methods to treat HD with radiation. Small doses of radiation were administered to the entire trunk at weekly intervals for many weeks or were given as a single massive dose just to the tumor. Neither method controlled the HD, and both caused severe side effects. Enlarged nodes usually shrank with both techniques, but recurrence and spread to previously uninvolved nodes invariably followed. After several courses of radiotherapy, the HD became more resistant to treatment, and very few patients survived 5 years from diagnosis. These multiple recurrences were not attributed to poor radiotherapeutic techniques but were viewed as inherent to the HD itself. Consequently, by 1920, most physicians had stopped using radiation as a means of curing HD. For the next 40 years, in most centers, treatment was mainly palliative, to shrink large nodes that were painful or interfered with movement, eating, or breathing.

The development of modern radiotherapeutic techniques for the treatment of HD began with the work of Gilbert, a Swiss radiotherapist, in the 1920s. He advocated treatment to apparently uninvolved adjacent lymph node chain that might contain suspected microscopic disease, as well as to the evident sites of lymph node involvement. Peters also adapted this technique at the Princess Margaret Hospital in the late 1930s and early 1940s. In her historic paper published in the American Journal of Roentgenology in 1950, Peters provided evidence that patients with limited HD could be cured with aggressive radiotherapy that treated involved nodal disease, as well as adjacent nodal sites. She did this by identifying a group of patients with limited-stage HD that was cured with high-dose, fractionated radiotherapy. She reported 5-year and 10-year survival rates of 88% and 79%, respectively, for patients with disease limited to a single lymph node region, rates that were notably high for a disease in which virtually no one survived 10 years. Nevertheless, the concept that early-stage HD might be curable with radiotherapy using higher doses and larger fields was slow to be accepted. Before the 1960s, most patients with limited HD were not treated at all or with only small doses of radiation.

No one deserves more credit than Henry Kaplan for the development of successful modern treatment for HD. His accomplishments are many and include pioneering work on developing the linear accelerator, defining radiation field sizes and doses for a curative approach for early HD, refining and improving diagnostic staging techniques, developing models for translating laboratory findings into clinical practice, and promoting early randomized clinical trials in the United States.

TECHNIQUES

Excellent results in the treatment of early-stage HD have been achieved through careful delineation of disease and meticulous attention to technique. Treatment-machine generated verification films should be used to ensure proper alignment. Daily doses of no more than 180 to 200 cGy to the mantle field (unless the treatment field includes the entire heart or entire lung, in which case the dose should be limited to 150 cGy or less) reduces risks to both the heart and lungs. Adjusting treatment on the basis of off-central axis dose calculations can reduce dose inhomogeneity from differences in patient separation within the large mantle field. Extended source-to-skin distances of 110 cm or greater, rather than a source-toskin distance of 100 cm, also reduces tissue inhomogeneity. Proper use of matching will ensure that surrounding normal tissues are not underdosed in the buildup region. A 4- to 6-MeV linear accelerator should be used for mantle and pelvic fields, whereas higher energies (10 to 15 MeV) can be used for treating paraaortic nodes.

The mantle field encompasses the submandibular, cervical, supraclavicular, infracervical, axillary, medialsternal, subcarinal, and hilar lymph nodes. A total dose of 3000 cGy to the entire mantle field is sufficient for patients with supradiaphragmatic HD when radiotherapy alone is used. Areas of initial involvement should receive a total dose of 3600 to 4000 cGy through the addition of a cone-down field. Reduction of the radiation dose to 3000 cGy to areas of initial involvement is recommended for patients receiving combined modality therapy, especially when there has been a good response confirmed by CAT scanning. When at least four cycles of chemotherapy have been given, radiation to initial uninvolved prophylactic sites probably is not needed. Further reduction to 1500 to 2500 cGy may be desirable in prepubertal patients receiving combined modality treatment or, occasionally, in patients with extensive nodal involvement who are receiving treatments to large radiation fields after chemotherapy.

There is an increasing use of involved field irradiation after chemotherapy in the treatment of early-stage HD. Involved field irradiation should encompass the entire involved lymph node region, as defined initially by Stanford University Medical School. For example, the ipsilateral cervical and supraclavicular nodes and the inguinal and femoral nodes constitute single regions.

Mantle paraaortic-splenic irradiation after a negative laparotomy occasionally is used as a radiotherapy-alone approach for early-stage disease patients who have not had a staging laparotomy. The paraaortic field encompasses the paraaortic nodes down to the fourth to fifth lumbar vertebral interspace (L4-5). Without staging laparotomy and splenectomy, the entire spleen must be irradiated. A CAT scan should be used to localize the position of the spleen and enable blocking of as much of the left kidney as is possible. The dose to the paraaortic lymph nodes should be 3000 cGy when there is no known disease, and radiotherapy alone is used. Beam divergence from the mantle and paraaortic fields creates the potential for an overdose at the spinal cord. A number of different matching techniques have been published.

Prophylactic pelvic irradiation is used rarely in the modern-day treatment of supradiaphragmatic HD. However, pelvic irradiation continues to be used for patients presenting with stage I or II infradiaphragmatic HD. Iliac wing blocks to spare bone marrow and a pelvic block to shield the bladder and central pelvic organs should be part of the treatment technique (which includes irradiation of inguinal and femoral nodes). Loss of fertility in both men and women is a risk with the use of pelvic irradiation for subdiaphragmatic HD, and techniques should be used to reduce this risk whenever possible.

CHEMOTHERAPY

The development of chemotherapeutic programs for HD is a story of success. After the discovery of the cytotoxic effects of nitrogen mustard in the 1940s, a number of different drugs—including chlorambucil, cyclophosphamide, procarbazine, vinblastine, and vincristine—were developed and showed efficacy in HD. Response rates
were approximately 50% to 60% with 10% to 30% complete response. However, relapse was seen in almost all cases, and no cure could be achieved.

On the basis of a murine leukemia cell line, Skipper et al. \(^{144}\) postulated a model of tumor cell kill based on the logarithmic cell growth and a logarithmic response to cytotoxic agents. From this model, the authors predicted that response to chemotherapy would depend on tumor burden, drug dose, and kinetics of residual tumor cells. It was further postulated that the simultaneous use of several drugs with different modes of action might yield superior results. The combination of drugs might be tolerated if the toxicities were nonoverlapping. Initial attempts with two-drug combinations revealed the potential of this approach.

However, the relevance of this model was realized in 1967, when DeVita et al. \(^{225}\) reported on a four-drug combination chemotherapy program, MOPP (mechlorethamine, vincristine, Oncovin, procarbazine, and prednisone). This combination established the curability of more than 50% of patients with stage III or IV disease.

The development of MOPP was a milestone in oncology, demonstrating that advanced-stage HD could be cured. The differences in survival between historic controls and MOPP-treated patients were so dramatic that randomized clinical trials were not needed to validate these results. Further information on chemotherapy is provided in Advanced-Stage Disease later in this chapter.

### Combined Modality Chemotherapy

In addition to the many factors that affect either chemotherapy or radiotherapy when used alone, there are several issues that arise specifically because of potential interaction and summation of effects when they are combined. It is important to remember that the purpose of adding a second modality is to overcome resistance to the first and, in the case of adding irradiation to chemotherapy for HD, it seems likely that full-dose irradiation may be needed to overcome primary resistance to chemotherapy. Such a situation might occur in which patients with stage IIA or IIB, and stage IIA diseased with extensive mediastinal or splenic involvement or E lesions were treated with two-course cyclophosphamide, Oncovin, procarbazine, and prednisone (COPP) and doxorubicin (Adriamycin), bleomycin, vinblastine, and dacarbazine (ABVD) followed by irradiation. In the first trial (HD1), responders to chemotherapy were then given extended-field irradiation with a dose to nonbulky sites assigned randomly to be either 20 Gy or 40 Gy. In the second trial (HD3), a similar group of patients received 30 Gy to the nonbulky sites. Bulky sites received 40 Gy in each trial. Failure-free survival was the same in all groups, strongly implying that after optimal chemotherapy, irradiation dose, at least to nonbulky sites, can be reduced without sacrificing efficiency.

The risk of two important late complications of irradiation may be reduced by lowering the dose. Studies of late sequelae of treatment for HD suggest that the risk of second neoplasms, especially breast cancer in women, may be reduced by lower radiation dose. \(^{145}\) The other late toxicity possibly associated with radiation dose is cardiovascular. Stanford University investigators found that a higher dose of irradiation to the mediastinum was associated with increased mortality from cardiac disease. \(^{66}\)

An alternative approach to reduce toxicity from irradiation when used in combined modality treatment is to reduce not the dose but the extent of the field encompassed. Several trials involving patients with limited-stage HD have shown that results comparable to those achieved with irradiation alone to an extended field can be achieved when chemotherapy is combined with involved field irradiation. \(^{123}\) The ability to preserve efficacy while limiting toxicity by reducing the size of the treatment fields is one of the most attractive aspects of using combined modality treatment. The same theoretic considerations that apply to irradiation are relevant when one considers reduction of the dose of chemotherapy used in combined modality treatment. The section Choice of Treatment examines these results in more detail.

In theory, either the chemotherapy or the radiotherapy could come first in the sequence of combined modality treatment. In practice, it is almost always desirable for chemotherapy to precede radiotherapy. The reason for this includes early effective treatment of disseminated disease, delay in induction of irreversible loss of bone marrow function, and the opportunity to use smaller, potentially less toxic radiation treatment fields after chemotherapy has induced tumor regression.

### High-Dose Chemotherapy Plus Stem Cell Support

**PRINCIPLES.** High-dose chemotherapy (HDCT) has been used extensively in patients with relapsed and refractory HD. Implicit in the rationale for this approach is the assumption of a steep dose-response relation for lymphoma patients subjected to chemoradiotherapy. Although care must be exercised in interpreting clinical results, both animal models and clinical studies support the existence of such a relationship. \(^{146}\)

The use of autologous bone marrow or peripheral blood stem cells (PBSCs) to support intensification of chemotherapy as salvage treatment has changed the options available for relapsed patients. Autologous transplantation involves the replacement of hematopoietic stem cells that have been irresponsively injured by HDCT or radiotherapy (or both). This can be accomplished either with bone marrow cells obtained by multiple aspirations from the posterior iliac crest under anesthesia or with PBSCs collected by apheresis. The use of PBSCs has surpassed the use of bone marrow, and PBSCs may be used exclusively in the future. The advantage of using PBSCs includes avoiding general anesthesia and more rapid hematopoietic reconstitution.

**CONDITIONING REGIMENS.** Several conditioning regimens have been used and summarized previously. \(^{147}\) The most commonly used are cyclophosphamide, etoposide (VP-16), and BCNU (CVB) or BCNU, etoposide, cytarabine (arabinoine), and melphalan (BEAM) given in different dose schedules. When BCNU-containing regimens are used, careful clinical monitoring to detect early signs of delayed lung toxicity is important, particularly when BCNU doses of 450 mg/m\(^2\) are given. Mucositis and enterocolitis represent the most significant nonhematologic toxicities associated with high-dose melphalan. Total body irradiation has been used only in a few studies, owing to the fact that many HD patients have already received thoracic irradiation by the time they have reached the transplantation stage and to the high treatment-related mortality of patients prepared by this means. \(^{123}\) Although the toxicity profiles differ with these regimens, there currently is no evidence to support the superiority of any particular regimen in HD.

Sequential HDCT is increasingly being used in the treatment of solid tumors and lymphoma. First results from phase II studies show that this kind of therapy is safe and effective. \(^{148}\) In accordance with the Norton-Simon hypothesis, after initial cytoreduction, a few non-cross-resistant agents are given in short intervals. \(^{149}\) In general, the transplantation of autologous stem cells and the use of growth factors allow application of the most effective drugs in highest doses in intervals of 1 to 3 weeks. Sequential HDCT permits the highest possible dosing in minimum time.

**INCORPORATING RADIOTHERAPY IN HIGH-DOSE CHEMOTHERAPY PROGRAMS.** Radiotherapy is a very effective locoregional treatment modality in HD. The rationale for incorporating radiotherapy into HDCT programs stems from the observation that disease progression after HDCT often occurs in sites of prior involvement. Several investigators showed that in 65% to 95% of cases, the sites of failure are involved immediately before HDCT. \(^{146}\) Retrospective analysis suggests that radiotherapy may be incorporated as cytoreductive treatment before HDCT or as a consolidative therapy after HDCT. \(^{142}\) However, no prospective clinical trial has yet answered the questions regarding the extent of the radiation field, the timing of treatment, and the appropriate dose to use. The complementary role of radiotherapy in salvage HDCT is uncertain and remains to be investigated.

**CHOICE OF TREATMENT**

**PROGNOSTIC FACTORS AND TREATMENT GROUPS**

A prognostic factor is a measurement or classification of an individual patient, performed at or soon after diagnosis, that gives information on the likely outcome of the disease. This information will generally be phrased in terms of probabilities—for instance, the probability of cure for various values of a prognostic factor. It may be used for informing the patient or, in the context of clinical trials, for defining or describing the study population or adjusting the data analysis; however, for the clinician, the most important role of the prognostic factor is to help in selecting an appropriate treatment strategy.

In HD, patients have traditionally been divided into two or three prognostic groups, chiefly according to stage and B-symptoms but also taking various other factors into consideration. Most basically, patients with stage IIIB or IV (advanced-stage) disease have been associated with the poorest prognosis and assigned an intensive chemotherapy protocol, sometimes followed by adjuvant radiotherapy. Further prognostic factors often were used to assign stage II A or stage IIB patients to the advanced-stage group. Among the remaining patients with early-stage disease who had previously continued to receive radiotherapy alone, an "unfavorable"
subgroup often was defined to select patients for combined modality therapy. Each group has thus been associated with a typical standard treatment strategy:

- Early stages, favorable: radiation alone (extended field)
- Early stages, unfavorable: moderate amount of chemotherapy (typically four cycles) plus radiation
- Advanced stages: extensive chemotherapy (typically eight cycles) with or without consolidating (usually local) radiation

These "typical" strategies are not uniformly applied, and the investigation of alternatives (e.g., the use of chemotherapy in favorable early stages) is continuing. In the scheme just listed, two divisions between the three prognostic groups must be noted, each division possibly being defined by a different set of factors. Furthermore, the attempt has been made to identify advanced-stage patients with a particularly high risk of failure for intensified therapy (e.g., early HDCT with stem cell support). The selection of factors and the definition of the prognostic groups vary among institutions, as does the choice of treatment.

Prognostic factors are rarely the subject of specific clinical studies but are discovered and evaluated using data from large cohorts of uniformly treated, well-documented, and reliably followed-up patients, usually from large clinical trials. The diversity of diagnostic and treatment strategies used for the early stages, as well as statistical problems caused by the low rate of treatment failure events, has led to the reporting and use of different prognostic factors by different institutions and trial groups.

In the following few sections, recognized prognostic factors are described for early stages treated with radiotherapy alone, for early stages treated with chemotherapy, and for advanced stages (treated with chemotherapy), respectively. Such factors are required to show independent prognostic value in multivariate analyses of large numbers of patients. This account refers in general to clinically staged patients, because laparotomy is now rarely performed. The use of these factors to define prognostic groups for treatment purposes, as practiced by various institutions and study groups, are described.

**Prognostic Factors for Early-Stage Disease (Clinical Stage I or II) Treated with Radiotherapy Alone**

For those patients with early-stage (CS I or II) disease who are to be treated by radiotherapy alone, recognized adverse factors are (1) advanced age (which correlates with the presence of occult abdominal disease and with poor results of salvage therapy and may also be associated with treatment complications, leading to reduced or delayed treatment); (2) male gender (which has a small effect only); (3) histologic subtype MC (which is associated with the presence of occult abdominal disease); (4) the presence of B-symptoms (which is associated with the presence of occult abdominal disease); (5) presence of a large mediastinal mass (LMM), for which there is some evidence of an increased relapse rate in the fox (although there are few, if any LMM patients were treated with radiotherapy alone); (6) the number of involved nodal regions; (7) an elevated erythrocyte sedimentation rate (ESR); (8) presence of anemia; and (9) a low serum albumin level.

These factors are relevant to the decision as to which early-stage patients should be classed as unfavorable and receive combined modality therapy because their prognosis with radiotherapy alone is relatively poor. Major study groups have used criteria as described next. Favorable patients were generally given radiation only, although the additional application of mild chemotherapy has increased.

The European Organization for the Research and Treatment of Cancer (EORTC) has, since 1982, defined CS I and II (supradiaphragmatic only) patients as unfavorable if any of the following factors applied: age older than 50 years, asymptomatic with ESR in excess of 50, B-symptoms with ESR in excess of 30, and LMM, based on the results of earlier EORTC trials H1 and H2. In previous trials, stage II, MC or LD histology, and number of involved regions also were counted as adverse factors.

The GHSG has, since 1988, assigned combined modality treatment to CS I and II patients with any of the following adverse factors: (1) LMM, (2) number of regions (3), (3) elevated ESR, (4) localized extranodal infiltration (so-called E-lesions), or (5) massive splenic involvement. Owing to the rarity of splenectomy, the last-mentioned factor was seldom considered and was relatively unimportant in the present trial generation. It can be difficult to distinguish consistently between E-lesions and stage IV disease, and varying assessments of the prognostic value of this feature have been obtained by different investigators (Table 45.6.7). Stanford began in 1980 to give combined modality treatment to CS I and II patients with LMM or multiple E-lesions.

**TABLE 45.6.7. Definition of Treatment Groups in Two Large Cooperative Trial Groups**

The EORTC has investigated the use of localized radiotherapy in a "very favorable" subgroup of early-stage patients. Inclusion criteria were a stage IA female patient younger than 40 years, with disease of NS or LP histology, without elevated ESR or LMM. A 30% long-term failure rate was observed, however, and this policy was not continued.

**Prognostic Factors for Early-Stage Disease (Clinical Stage I or II) Treated with Chemotherapy**

Despite the different mode of action of chemotherapy as compared with radiotherapy, similar prognostic factors have emerged from analyses of cohorts treated with radiation and with combined modality therapy. All the factors listed for radiation-treated patients have also been reliably confirmed in cohorts who also received chemotherapy. Either in early or in advanced stages. This similarity of prognostic effects is supported by the observation from a metaanalysis of radiotherapy versus combined modality treatment in early stages that the size of the difference in failure-free survival between these two treatment strategies was essentially constant over different prognostic groups.

As a consequence, the prognostic factors relevant to the division between unfavorable early and advanced-stage cases (i.e., between moderate and extensive chemotherapy) are essentially the same as those listed for the division between favorable and unfavorable disease categories. However, generally only stage IB or III patients are given "advanced-stage" treatment owing to the presence of these factors.

The EORTC includes in its advanced-stage cohorts stages III and IV only, without regard to other factors, as did the U.S. NCI and several U.S. cooperative groups.

In the GHSG, all stage III and IV patients plus stage IIB with LMM or E-lesions are included in the advanced-stage group. Earlier trials included in the unfavorable early-stage category either all stage IIA patients or just those without any of the five GHSG factors listed. This gradual shift to use of more intensive therapy was based on prognostic factor analyses.

Certain other trial groups include further stage I and II patients in the advanced prognostic group (e.g., IB and IIB or bulky stage II disease).

**Prognostic Factors for Advanced-Stage Disease**

The more uniform treatment modality and the greater frequency of treatment failure events has permitted more conclusive and generally applicable results for prognostic factor analyses for the advanced stages, as compared with early stages. The results of the International Prognostic Factors Project, though not...
necessarily including all possible factors, can be taken as reliable (Table 45.6-8).

### Table 45.6-8. Final Cox Regression Model

<table>
<thead>
<tr>
<th>Factor</th>
<th>Log(Hazard) Rate</th>
<th>Y Value</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum albumin (g/dL)</td>
<td>0.48 ± 0.19</td>
<td>&lt;0.01</td>
<td>1.49</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>0.50 ± 0.11</td>
<td>0.06</td>
<td>1.30</td>
</tr>
<tr>
<td>Male gender</td>
<td>0.56 ± 0.08</td>
<td>0.04</td>
<td>1.36</td>
</tr>
<tr>
<td>Stage IV/5 status</td>
<td>0.13 ± 0.08</td>
<td>&lt;0.01</td>
<td>1.00</td>
</tr>
<tr>
<td>Age (10 y)</td>
<td>0.54 ± 0.12</td>
<td>0.01</td>
<td>1.50</td>
</tr>
<tr>
<td>White blood cell count [10^9/L]</td>
<td>0.54 ± 0.11</td>
<td>0.01</td>
<td>1.45</td>
</tr>
<tr>
<td>Lactate dehydrogenase activity level (unit/</td>
<td>0.31 ± 0.19</td>
<td>0.02</td>
<td>1.00</td>
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<tr>
<td>ml)</td>
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(Final set EM with permission.)

All these factors were highly significant in the multivariate analysis of data from 5141 patients treated in 25 centers, and their prognostic power was confirmed in an independent sample. Note that factors 1, 2, 4, and 5 are also prognostic for early-stage patients. All seven factors were associated with similar relative risks of between 1.25 and 1.49. Therefore, Hasenclever and Diehl recommended combining these factors into a single score by simply counting the number of adverse factors, thus giving an integer prognostic score between 0 and 7. However, even patients exhibiting five or more factors (7% of cases) had a 5-year failure-free rate of more than 40%. The test of a lower failure rate was close to 80% for those with, at most, one factor (29% of cases), suggesting that a group of advanced-stage patients with a relatively favorable prognosis could be recognized (1618 patients included in the final analysis for FFTF, according to whether the prognostic score was 0 to 2 or 3 or higher) (Fig. 45.6-4).

A number of other factors have been shown to correlate with prognosis in advanced stages, but their independent importance is not proven due to conflicting results or lack of confirmation in a large data set. These include pathologic grade in NSHD, presence of tissue eosinophilia, elevated inguinal involvement, high serum lactate dehydrogenase level, and b microglobulin.

Factors relevant to advanced-stage patients may be used to identify patients for either treatment intensification or treatment reduction. Reduction can be achieved by creating a modified protocol or by including these patients in the early-stage group. Concerning intensification, various investigators have treated a poor-prognosis subset of advanced-stage patients, who had attained a remission by conventional chemotherapy, with HDCT accompanied by hematologic stem cell support. Proctor et al. constructed a continuous numeric index for this purpose as a weighted sum of the variables age, stage, lymphocyte count, hemoglobin, and presence of bulky disease, and included patients with an index greater than 0.5 in the poor-prognosis subset. Carella et al. included patients with two or more of the following factors: high lactate dehydrogenase level, very large mediastinal mass, two or more extranodal sites, inguinal involvement, low hematocrit, and bone marrow involvement. However, none of these methods could consistently select a subset with a failure rate of less than 40% with conventional therapy. This means that the early high-dose approach is unlikely to show a clinically relevant long-term survival benefit as compared with conventional treatment.

Concerning treatment reduction, the short-duration, reduced-dose Stanford V chemotherapeutic regimen (mechlorethamine, Adriamycin, vinblastine, vincristine, etoposide, bleomycin, and prednisone) with or without radiotherapy is currently being tested in patients with bulky stage II or advanced-stage disease who have, at most, two International Prognostic Factor Project adverse factors. Stanford V is, however, not merely a reduction of therapy but rather a rescheduling with lower total doses but greater dose intensities. No data are available on the results of treatment reduction in a favorable subset of the advanced-stage patients.

In conclusion, the three-level scheme of division into early-stage favorable, early-stage unfavorable, and advanced-stage cases remains valid according to current knowledge (see Table 45.6-7). Separation of very favorable early-stage or poor-risk advanced-stage patients for especially mild or intensive therapy, respectively, does not appear justified. Several prognostic factors, other than clinical stage, are used in the divisions among favorable, unfavorable, and advanced cases, and no universally valid set of factors has been determined. Nevertheless, the list of reliably confirmed, independent prognostic factors just reviewed encompasses most of the factors used by the major institutions and study groups. For early-stage and advanced-stage disease patients receiving radiotherapy or chemotherapy or both, the set of relevant factors is fairly similar.

A number of other factors have been shown to correlate with prognosis in advanced stages, but their independent importance is not proven due to conflicting results or lack of confirmation in a large data set. These include both clinical factors, such as inguinal involvement, and biologic factors, such as pathologic grade in NSHD, presence of tissue eosinophilia, high serum lactate dehydrogenase, and high b microglobulin. The search for biologically specific factors directly related to tumor activity is now an important research goal.

### EARLY-STAGE FAVORABLE DISEASE

#### Reduction of Staging or Treatment: Ongoing and Recently Completed Trials

Increasing concern for the long-term consequences of treatment has prompted many investigators to reexamine the aggressive approaches developed for the staging and treatment of early-stage HD in the 1970s and 1980s. Many of the ongoing and recently completed studies were developed in an attempt to reduce the long-term complications of treatment without increasing mortality from HD. These include studies that look at reduction of radiation dose or reduction of field size in pure radiotherapy; seek an optimal, short, or less toxic chemotherapeutic regimen; explore an optimal radiation volume in combined modality therapy; or evaluate chemotherapy alone.

#### Clinical Trials of Radiotherapy Alone

**RADIATION DOSE REDUCTION.** Although a few studies have comprehensively reviewed dose-response data for HD, only one prospective randomized study is available. This multicenter trial by the GHSG evaluated the tumoricidal doses for subclinical involvement by HD. A total of 376 laparotomy-staged favorable-prognosis IA to IIB HD patients were enrolled. Only patients without risk factors were included in the trial. Any one of the following risk factors was cause for exclusion: presence of LMA, massive splenic involvement, extranodal disease, an ESR of more than 30 and B-symptoms, an ESR of more than 50 and no...
B-symptoms, or more than three regions of involvement. Patients were randomized to receive either 40-Gy extended-field radiotherapy or 30-Gy extended-field radiotherapy followed by an additional 10 Gy to involved lymph node regions.

The 5-year FFTF results favored the 30-Gy extended-field plus 10 Gy arm over the 40-Gy extended-field arm (81% vs. 70%, respectively; \( P = .026 \)). The 5-year FFTF and survival rates were (nonsignificantly) higher in the reduced-dose arm, suggesting that 30 Gy is sufficient for treating subclinical involvement of HD with radiotherapy alone. \( ^{2,16} \)

**RADIATION FIELD SIZE REDUCTION.**

Mantle Irradiation Alone in Clinical Stage IA to IIA Patients. The use of mantle irradiation alone for early-stage HD is attractive because all treatment is completed within 5 weeks, patients avoid the long-term risks of radiation to the upper abdomen, and the potential for salvage with combination chemotherapy is not compromised. Results of prospective and retrospective studies of mantle irradiation alone for unselected CS I and II patients have been disappointing. The EORTC H1 trial, one of the first studies to evaluate the role of chemotherapy in the treatment of early-stage HD, randomized clinically staged and Ia patients to receive mantle irradiation alone or combined with vinblastine chemotherapy. All CS I and II patients were enrolled. Fewer recurrences were seen in patients who received both mantle irradiation and vinblastine chemotherapy. However, relapse rates were high in both groups. The freedom from recurrence was only 38% in the mantle-alone group, whereas the 5-year survival rate was only 58%. This suggests that mantle irradiation alone is not adequate treatment for unselected patients with CS I to II HD and that vinblastine is only partially effective in eliminating recurrences, many of which occurred below the diaphragm. \( ^{16} \) Similarly, the Toronto series reported a 10-year rate of freedom from recurrence of only 54%. \( ^{2} \) These high recurrence rates in unselected patients are not surprising, as more than 20% of CS I to II patients have occult abdominal involvement, and absence of mantle potential abdominal disease (with radiotherapy or chemotherapy) will result in higher recurrence rates than are achieved with more extensive treatment. When mantle irradiation was restricted to clinically staged, asymptomatic patients in whom a single lymph node region was involved (CS IA), better results have been seen, with 10- to 15-year freedom-from-recurrence rates of 58% to 81%. \( ^{2} \)

Clinically Staged Patients with a Very Low Risk of Abdominal Involvement. Clinically staged patients with a very low risk of abdominal involvement include female patients with CS IA NSHD, patients with CS IA LP histology, and CS IA patients with interfollicular HD. \( ^{2} \) A similar subgroup of patients was defined by the EORTC (women <40 years of age with CS IA lymphocytic predominance or NS histology and an ESR <50 mm) and treated with mantle irradiation alone without staging laparotomy in the EORTC HTVF (very favorable) and HBFV trials. In the HTVF trial, 40 patients were treated with mantle irradiation alone; complete remission was achieved in 95%. However, 23% of patients experienced relapse, yielding a 6-year event-free survival rate of 66%, a relapse-free survival rate of 73%, and overall survival of 89%. The relapse rates were thought to be unacceptably high in this selected subgroup of stage IA patients. The very favorable subgroup now is treated according to the EORTC strategy for the favorable subgroup.

Mantle Irradiation Alone in Favorable-Prognosis Stage IA and IIA Patients. To determine the role of prophylactic abdominal irradiation in early-stage HD, the EORTC HS trial (1977 through 1982) compared the use of mantle and paraaortic-splenic pedicle irradiation to mantle irradiation alone in patients with favorable early-stage HD. \( ^{2,15} \) This study included only patients with NS or LP histology, aged 40 years or younger, with prognostically staged (PS) I or II disease with mediastinal adenopathy, and an ESR of less than 70. No differences were seen in disease-free survival or overall survival between the two treatment groups with or without prophylactic irradiation. A 1997 update of this trial shows no statistical difference between the two treatment arms, either for treatment failure probability \( (P = .52) \) or overall survival \( (P = .69) \).

In 1989, a single-arm prospective trial was initiated at the Harvard University Medical School Joint Center for Radiotherapy of mantle irradiation alone in laparotomy-staged Ia to IIA HD patients. The objectives were to identify patients most suitable for mantle irradiation alone, to establish guidelines for follow-up after treatment, to evaluate the requirement for staging laparotomy, and to provide an assessment of risk versus gain for the reduction of treatment in early-stage HD. The eligibility criteria for the study included a negative laparotomy, the absence of LMA and B-symptoms, and NS or LP histology. Thoracic CAT scanning and Ga scanning were required to establish the extent of thoracic involvement, and patients with HD in hilar, subcarinal, or cardiophrenic lymph node regions were not eligible for the trial. Eighty-four patients have been enrolled. The 5-year actuarial rate of freedom from recurrence exceeds 80%. These excellent results with mantle irradiation alone also have been seen in other retrospective studies. \( ^{2} \)

**Clinical Trials of Combined Chemoradiotherapy**

Some randomized trials of combined modality therapy are based on the premise that this approach results in a very high freedom from recurrence in early-stage HD and that efficacy can be maintained when using less toxic chemotherapeutic and radiotherapeutic regimens.

**LESS TOXIC CHEMOTHERAPY WITH RADIATION: COMPARISON WITH RADIATION ALONE.** These trials use chemotherapeutic regimens given for four or six cycles in combination with radiotherapy. The regimens are combined with involved-field or regional (mantle) radiotherapy with the premise that the drugs being tested will be able to control both adjacent prophylactic sites and occult abdominal disease in clinically staged patients without upper abdominal and splenic irradiation. Analysis of patients for overall failure frequency of failure eventually will provide better guides to designing optimal regimens to control occult HD not appreciated on physical examination or radiographic evaluation. If successful, these regimens should reduce treatment-related mortality and morbidity by reducing both the amount and toxicity of chemotherapy and by using smaller radiation volumes.

With the objective of reducing acute toxicity and chronic morbidity (sterility, increased risk of leukemia), Horning et al. \( \) developed a "nontoxic" chemotherapeutic regimen—vinblastine, bleomycin, and methotrexate (VBM)—which was tested in a randomized trial of PS IA to IIB and PS IIA patients. The trial compared subtotal or total nodal irradiation to involved-field irradiation (44 Gy) followed by VBM. \( ^{2} \) Data on freedom from disease progression at 9 years favored involved-field irradiation and VBM (86%) over subtotal or total nodal irradiation (78%) \( (P = .01) \). No differences were seen in overall survival \( (P = .09) \). The EORTC has confirmed the efficacy of VBM with involved-field radiation but, in that group's experience, this approach produced unacceptable pulmonary and hematologic toxicity. \( ^{2} \) Favorable results with VBM and extended-field radiotherapy in CS IA to IIA HD also have been reported by the Gruppo Italiano per lo Studio dei Linfomi. \( ^{2} \) In that study of 50 patients, the 5-year progression-free survival rate was 82%. Sixteen percent of patients in the trial experienced pulmonary toxicity.

Based on the Stanford trial results reported above, \( ^{2} \) a follow-up Stanford University trial has been completed. \( ^{15} \) Patients with CS IA to IIA HD (staging laparotomy and splenectomy were eliminated) were treated either with subtotal nodal and splenic irradiation or two cycles of VBM, followed by regional (mantle) irradiation, followed by four additional cycles of VBM (with a reduced bleomycin dose). No differences in 4-year freedom from disease progression or survival were noted between the two arms of the trial.

Epirubicin, bleomycin, vinblastine, and prednisone (EBVP) and involved-field irradiation \( (n = 168) \) versus mantle and paraaortic-splenic irradiation \( (n = 165) \) for favorable-prognosis CS IA to IIA patients was tested in the EORTC H7F trial (1988 through 1993). The EORTC ESVP II regimen (one dose per cycle) was proposed as a potentially less toxic but similarly effective regimen as compared to ABVD. In the H7F trial for patients with favorable disease, six cycles of EBVP were combined with involved-field radiation and were randomly compared with subtotal nodal and splenic irradiation in favorable CS I and II patients. At 6 years, the relapse survival rate was significantly higher for patients on the combined chemoradiotherapy arm than for those on the radiotherapy-alone arm \( (92\% \text{ vs. } 81\%, \text{ respectively}; \ P = .004) \). The 6-year survival rate was excellent in both treatment arms (98% vs. 96%, respectively; \( P = .156 \)). \( ^{2} \)

In contrast, in the H7U trial for patients with unfavorable disease, EBVP and involved-field radiation was inferior to MOPP and ABV and involved-field radiotherapy, suggesting that the use of prognostic factors is crucial in selecting patients for treatment with reduced chemotherapeutic and radiotherapeutic regimens.

**REDUCED NUMBER OF CHEMOTHERAPY CYCLES.** The trials noted here use combination chemoradiotherapy with fewer than four cycles of chemotherapy. Although the precise radiation regimens to evaluate these new regimens are also listed \( \text{in Table } 45.6-9 \), short-course chemotherapy is not indicated for patients with CS IA to IIA HD. Adria, prednisolone, etoposide, cyclophosphamide, and bleomycin (VAPEC-B). The optimal rate of radiotherapy needed is less certain in the short-course trials. For example, there are at least limited data that four to six cycles of chemotherapy are sufficient to control occult abdominal disease in the majority of CS I to II patients. \( ^{2,16} \) With short-course chemotherapy, very few data are available on the effectiveness of different regimens to control HD outside of the involved regions, as defined by physical examination or radiographic evaluation. This uncertainty is reflected in some of the designs that use subtotal nodal and splenic irradiation rather than involved-field or mantle irradiation in combination with chemotherapy. Ongoing and recently completed short-course trials are listed in Table 45.6-9.

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*Note: The above text is a natural reading of the given document and has been formatted for clarity and readability.*
The GHSG HD7 trial (1994 through 1998) randomized 643 favorable CS IA to II HD patients to subtotal nodal and splenic irradiation alone or to two courses of ABVD and the radiotherapeutic regimen. A preliminary analysis of 365 patients showed an advantage in FFTF in the patients receiving ABVD (96%) as compared to those treated with irradiation alone (87%; P = .05) (see Table 45.6-9). Several questions are raised by this study. First, with an expected long-term FFTF in favorable CS IA to IIA HD of approximately 70% to 75% with radiotherapy alone, is the added benefit in FFTF with two cycles of ABVD worth the extra risk from the doxorubicin and bleomycin? Second, is it more difficult to salvage patients whose disease recurs after subtotal nodal and splenic irradiation and two cycles of ABVD than after subtotal nodal and splenic irradiation alone? These questions are that can be answered only with longer follow-up.

The GHSG HD10 trial (opened in 1998) has essentially the same eligibility criteria as does the GHSG HD7 trial. Patients are to be randomized to four arms, namely the four combinations of two or four cycles of ABVD followed by 20- or 30-Gy involved-field radiotherapy. This study should help to determine the number of cycles of ABVD needed to control occult HD in the abdomen and to prevent recurrence of HD in apparently uninvolved sites adjacent to known HD (adjacent to the irradiated involved site). It should also help to determine the minimal radiation needed to control HD when combined with limited chemotherapy.

In a Manchester pilot study and a BNLJ trial, VAPEC-B chemotherapy is given for 4 weeks, followed by involved-field irradiation or mantle irradiation alone. Preliminary reports from the Manchester pilot study using the relatively brief 4-week VAPEC-B regimen in early-stage HD provide background data for the ongoing BNLJ trial. In the Manchester study, 111 CS IA to IIA patients without mediastinal bulk have been randomized since 1989 to receive either limited radiotherapy alone or VAPEC-B followed by local irradiation only to the involved regions. With a median follow-up time of 3.3 years, there have been only two recurrences in the VAPEC-B–plus–local irradiation arm (progression-free survival rate at 3 years, 91%). The current BNLJ study has a similar design; however, the radiotherapy-alone arm includes full mantle irradiation rather than a more limited field (see Table 45.6-9).

The Southwest Oncology Group–Cancer and Leukemia Group B (SWOG/CALGB) study of three cycles of adjuvant doxorubicin and vinblastine plus subtotal nodal and splenic irradiation versus subtotal nodal and splenic irradiation alone in CS IA to IIA HD patients is ongoing (see Table 45.6-9). As of June 1998, 284 patients have been enrolled in the study (information provided courtesy of Dr. Todd Wasserman, CALGB update, June 1998). Of these, 162 patients have been evaluated for short-term toxicity. The questions raised by this study are similar to those for the GHSG HD7 study, including the potential extra toxicity of the doxorubicin and vinblastine in a group of patients with an expected favorable prognosis with treatment by radiotherapy alone and the overall strategy in trial design of giving enough chemotherapy to eliminate the need for abdominal irradiation.

The EORTC H8F trial (1993 through 1998), which compares three cycles of MOPP/ABV hybrid and involved-field irradiation to mantle and paraaortic-splenic irradiation for favorable-prognosis CS IA to IIA patients, was activated in 1993 (see Table 45.6-9). This trial should answer the following important questions: Are three cycles of standard chemotherapy sufficient to control abdominal HD in favorable-prognosis CS IA to IIA patients? Can patients who experience relapse after three cycles of MOPP/ABV and involved-field radiotherapy be cured with an alternative treatment, short of HDCT and stem cell rescue? The one concern of the trial is the use of the hybrid regimen, which confers some risk of sterilization and leukemogenesis in these favorable-prognosis HD patients. ABVD and EBVP are proposed for the H9 trials.

The modified Stanford V trial for early-stage favorable-prognosis HD involves a relatively short, but intensive, chemotherapeutic regimen given for 12 weeks to patients with poor-prognosis stage I to II disease. A modification of this trial has been opened for favorable-prognosis CS IA to IIA patients using 8 weeks of the Stanford V chemotherapeutic regimen for involved-field irradiation to sites of initial involvement (identified radiographically or as nodal enlargement >1.5 cm). The chemotherapeutic regimen includes mechlorethamine (6 mg/m^2 in weeks 1 and 5), doxorubicin (25 mg/m^2 in weeks 1, 3, 5, and 7), vinblastine (6 mg/m^2 in weeks 1, 3, 5, and 7), prednisone (40 mg/m^2 on days 1 through 36, followed by tapering), vincristine (1.4 mg/m^2 in weeks 2, 4, 6, and 8), and bleomycin (5 mg/m^2 in weeks 2, 4, 6, and 8), and VP-16 (60 mg/m^2 on days 15 and 16 and days 43 and 44). This regimen will evaluate the ability of brief but intense chemotherapy to control HD outside of initially involved sites in favorable-prognosis CS I to II patients.

**Clinical Trials of Chemotherapy Alone**

Probably the first published experience of the use of MOPP chemotherapy alone in early stages of childhood HD comes from Uganda, where no radiotherapy was available. Several small, retrospective studies have also reported treatment with MOPP alone. On the basis of this limited experience, two randomized studies were devised to compare radiotherapy alone to MOPP chemotherapy alone in laparotomy-staged patients; both studies have median follow-up times of 7.5 to 8 years. Although both studies are now dated because of the use of the MOPP regimen and the requirement for staging laparotomy, results from these trials provide valuable information for the design of future protocols.

**CHEMOTHERAPY VERSUS RADIATION.** The NCIC study was initially designed to include patients with intermediate-prognosis HD. Although the trial included patients with favorable-prognosis PS IIA disease, the most favorable patients (PS IA patients with peripheral sites) were not included in the trial and were treated with radiotherapy alone. Patients with unfavorable prognosis (B-symptoms, LMA, and limited stage III disease) were included in the trial. Patients were randomized to 6 months of MOPP chemotherapy alone or to subtotal nodal irradiation alone. After researchers recognized that patients with massive mediastinal involvement and PS IIA disease were not optimal candidates for radiotherapy alone, the randomization criteria were changed while the study was ongoing. No difference in disease-free or overall survival was seen at 10 years.

The Italian prospective study randomized patients with PS IA to IIA HD to receive either 6 months of MOPP alone or subtotal nodal irradiation alone. There were no differences in freedom from progression. However, the survival rate was significantly higher in patients treated with radiotherapy alone (93%) than in those treated with chemotherapy alone (56%). The difference in survival was attributed to the inability to salvage patients who experienced relapse after MOPP chemotherapy; these results are similar to the poor results of salvage ABVD in patients who experienced relapse after MOPP for advanced HD.

Both the NCIC and the Italian studies demonstrated greater acute toxicities in patients who received MOPP chemotherapy. In the Longo study, more than 50% of patients treated with MOPP had at least one hospital admission for fever and neutropenia. The NCIC CTG HD6 study (unpublished data) is a modification of the NCIC and Italian studies, with randomization of clinically staged, rather than pathologically staged, patients and the use of ABVD as the chemotherapeutic regimen. Favorable-prognosis patients (NS or LP histology, age <40 years, ESR <50, one to three sites of involvement) are randomized to subtotal nodal irradiation and splenic irradiation versus four cycles of ABVD alone. This study will test the efficacy of four...
cycles of ABVD alone in favorable-prognosis early-stage HD. The study is open for accrual.

CHEMOTHERAPY VERSUS COMBINED MODALITY THERAPY. In 1977, the Grupo Argentino de Tratamiento de la Leucemia Aguda (GATLA)/Grupo Latinoamericano de Tratamiento de Hematopatías Malignas cooperative groups initiated a randomized study of chemotherapy with cyclophosphamide (600 mg/m² on day 1), vinblastine (6 mg/m² on day 1), procarbazine (100 mg/m² on days 1 through 14), and prednisone (40 mg on days 1 through 14) (CVPP) alone for six cycles versus CVPP plus radiotherapy consisting of 30 Gy to involved areas for patients with CS I to II disease. Overall, the 7-year disease-free survival rate was 71% for chemotherapy as compared to 62% for chemotherapy alone (P = .01); survival rates were 89% and 81%, respectively (P = .3). In a subgroup of patients with favorable-prognosis CS I to II disease, no differences were observed in actuarial rates of disease-free survival (77% vs. 70%) or overall survival (92% vs. 91%), respectively, for CVPP plus involved-field irradiation versus CVPP alone. In comparing these results with other adult studies, one should note that in this study and in the subsequent GATLA study, nearly 50% of the patients were younger than 16 years. It is possible that treatment approaches with chemotherapy alone may be more successful in children than in adult patients.

In the subsequent GATLA study, patients with favorable prognosis were randomized to CVPP for three cycles versus six cycles. At 5 years, the actuarial event-free survival (80% vs. 84%) and overall survival (91% vs. 92%) rates were not significantly different.

The ongoing EORTC three-armed trial (HIF) for favorable-prognosis CS I to II patients who achieve a complete remission after six cycles of EBVP are randomized to 36-Gy involved-field irradiation versus 20-Gy involved-field irradiation versus no radiotherapy.

The Memorial Sloan-Kettering Cancer Center trial randomizes CS I through IIIA patients without LMA or bulky disease, who have achieved a complete remission after six cycles of ABVD, to either mantle irradiation (35 Gy) or no further treatment. This trial has enrolled approximately 120 patients of a planned total of 200 patients.

Recommendations and Future Directions

Standard care currently provides a number of treatment options for patients with early-stage favorable-prognosis HD. These include the use of mantle irradiation alone or followed by involved-field radiation, mantle plus paraaortic and splenic irradiation without laparotomy staging, and combination chemotherapy and radiotherapy, often with a reduced number of cycles of chemotherapy and reduction of radiation field sizes and doses (e.g., ABVD for four cycles followed by involved-field radiation to 20 to 30 Gy).

Current clinical trials are evaluating the use of alternative chemotherapy combinations, shortened courses of chemotherapy, chemotherapy with smaller radiation fields or lower radiation doses, and chemotherapy without radiotherapy. Death from HD in favorable-prognosis early-stage patients is unusual, and mortality from other causes occurs many years later. Therefore, survival is a not a useful parameter for evaluating mid-term results in early-stage HD. Current trials must be judged by freedom-from-first-recurrence rates, acute morbidity, and by new criteria such as quality of life and, perhaps, cost-effectiveness. Trials aiming at high freedom-from-first-recurrence rates may show that the tested regimens do not provide the optimum treatment once long-term (10- to 20-year) data are available; treatment-related mortality may exceed HD mortality in favorable-prognosis early-stage patients. New methods in decision analysis should also help in the design of trials and in the analysis of retrospective data.

Despite the increasing availability of guidelines for the treatment of HD, there must remain room for individualization of treatment. With different treatment options, some of which may result in a higher recurrence risk at the gain of less toxic initial treatment, patient preferences must be assessed. In addition, treatment should be individualized when a particular treatment approach might result in a higher risk of a serious late complication (e.g., risk of late breast cancer in young female patients treated with large radiation fields). This is an exciting time for the development of new strategies in the treatment of early-stage HD. Many of the ongoing trials ask questions that will allow us to optimize treatment for early-stage patients and minimize long-term toxicity.

EARLY-STAGE UNFAVORABLE DISEASE

Numerous studies analyzed clinical prognostic factors for patients with stage I to II HD in the 1970s and 1980s. On the basis of these studies, clinical investigators have defined favorable and unfavorable prognostic groups of patients with stage I to II HD in an effort to refine the design of clinical trials and to tailor treatment in accordance with prognostic factors. Although the definition of favorable- and unfavorable-Prognosis early-stage HD continues to vary among different cooperative groups and institutions, three factors of poor prognostic significance are used as grouping criteria in most clinical trials: LMA or bulky disease, B-symptoms, and advanced age. For each prognostic group, the goal is to define the precise amount of treatment that will both minimize recurrence and mortality from HD and provide the least risk for long-term toxicity. Patients with unfavorable disease require, in general, more aggressive treatment than do those with favorable disease. However, the likelihood of cure of patients with unfavorable stage I to II disease is still high and, therefore, consideration of long-term toxicity remains an important issue in the treatment of these patients.

A number of clinical trials comparing radiotherapy alone to combined modality therapy for unfavorable-prognosis stage I to II HD were conducted in the 1970s and 1980s. The high recurrence rates with radiotherapy alone led to the development of strategies in current trials that use various combinations of chemotherapy and radiotherapy. To illustrate, one large trial conducted by the EORTC (HSU) randomized patients with unfavorable prognostic factors to total nodal irradiation or MOPP chemotherapy (six cycles) and mantle irradiation. Although overall survival did not differ (69% in both arms at 15 years), treatment failure (35% vs. 16%; \( P < .001 \)) strongly favored the chemotherapy arm.

Trials to Identify the Best Chemotherapy Combination

The evolution of studies to identify the best chemotherapy combination for unfavorable early-stage HD paralleled analogous trials for advanced stages. Early trials evaluated MOPP versus MOPP-like combinations, later trials compared these combinations with ABVD and, finally, the most recent trials compare new intense chemotherapy combinations with ABVD.

The first combined modality trial to test MOPP versus ABVD in unfavorable-prognosis patients was the Milan study, conducted between 1974 and 1982, using split-course treatment (three cycles of chemotherapy preceding and following subtotal nodal irradiation), which showed no significant difference in freedom from progression. However, in the EORTC H6U trial (1982 through 1988) comparing split-course MOPP and ABVD, the 10-year survival was equivalent in both arms, but the FFTP rate was significantly higher with ABVD than with MOPP.

The GATLA trial and the EORTC HTU trial (Table 45.6-10) studied modified nonalkylating agent regimens versus standard alkylating agent regimens in unfavorable-prognosis early-stage patients. All patients received combined radiotherapy and chemotherapy. In both trials, the arms using modified chemotherapy were associated with significantly higher recurrence rates.

### TABLE 45.6-10. Randomized Clinical Trials in Unfavorable-Prognosis Stage I–II Hodgkin’s Disease: Trials to Identify the Optimal Chemotherapy Combination
In the EORTC trial, the recurrence rate was high enough to result in early closure of the trial. Although, in favorable-prognosis stage I to II HD, less toxic and less intense chemotherapeutic regimens have been effective in combined modality therapy programs, this does not appear to be the case for patients with unfavorable-prognosis disease. In the BATLA trial, the event-free survival was 66% for doxorubicin, vincristine, prednisone, and etoposide versus 85% for CVP (P = .009). In the EORTC trial, the event-free survival was 68% for EBVP II and involved-field radiotherapy versus 90% for MOPP/ABV (P = .0001).

Several nonrandomized trials also have evaluated alternative chemotherapeutic regimens using a reduced number of cycles of chemotherapy or modified chemotherapeutic regimens. It is worth noting one recent trial: At Stanford, the Stanford V regimen, administered for 3 months, was followed by involved-field irradiation to 36 Gy in 38 patients with large mediastinal disease. No patients have experienced relapse or died (median follow-up, 40 months).

Based mainly on trials in advanced HD, ABVD has become the standard regimen used in patients with CS I to II disease. A number of current trials compare combined modality therapy using ABVD with more intense, novel regimens. Both the EORTC H9U and GHSG HD11 studies of combined modality therapy are comparing four cycles of ABVD with four cycles of BEACOPP. In the Eastern Cooperative Oncology Group (ECOG) 2496 trial of combined modality therapy, six cycles of ABVD are being compared to 3 months of the Stanford V regimen.

**Trials to Identify the Optimal Number of Cycles of Chemotherapy**

Two large, randomized trials are currently evaluating whether four cycles of combination chemotherapy and radiotherapy is sufficient treatment as compared to six cycles of chemotherapy and radiotherapy. The recently closed EORTC H8U study randomized patients to combined modality therapy with four or six cycles of MOPP/ABV, but the results have not yet been reported (see Table 45.6-10). The new EORTC H9U trial randomizes patients to four and six cycles of ABVD. A number of retrospective or prospective single-arm studies have evaluated the role of the number of cycles of chemotherapy in patients with large mediastinal disease. The results vary, and the number of patients studied is small; a more definitive answer will need to come from the large, randomized trials currently under way.

**Trials to Identify the Appropriate Radiotherapy Volume**

Several randomized trials have addressed the question of whether four cycles of chemotherapy and radiotherapy is sufficient treatment as compared to six cycles of chemotherapy and radiotherapy. The French trial reported by Zittoun et al. randomized 218 stage I to II unfavorable-prognosis patients to six cycles of MOPP sandwiched around involved-field (40-Gy) or extended-field (40-Gy) irradiation. The 6-year disease-free survival rates were 87% and 93%, respectively (P = .15). The Milan study reported by Hoppe et al. incorporated only 4 months of chemotherapy (ABVD), followed by involved-field (36-Gy) or subtotal nodal irradiation (30 to 36 Gy). The 5-year freedom-from-progression rates were 96% and 93%, respectively (Table 45.6-11).

**Trials of Chemotherapy Alone versus Combined Modality Therapy**

Only one prospective trial of chemotherapy alone versus combined modality therapy in unfavorable-prognosis stage I to II disease patients has been reported. The BATLA randomized 104 patients with unfavorable disease characteristics to six cycles of CVPP alone or six cycles of CVPP sandwiched around involved-field irradiation (30 Gy). The 7-year survival rates were 66% and 84%, and the freedom-from-relapse rates were 34% and 75% (P < .001), both favoring combined modality treatment.

The ongoing NCI of Canada (NCI-C) HD6 trial evaluates patients with unfavorable disease characteristics but excludes patients with LMA or bulky disease. Patients are randomized to receive combined modality therapy with two cycles of ABVD followed by irradiation (an extended mantle plus splenic irradiation or mantle plus paraaortic and splenic irradiation) or four to six cycles of ABVD alone (depending on the rapidity of response).

**Recommendations and Future Directions**

The outcome for treatment of patients with unfavorable-prognosis stage I to II HD has improved dramatically since the 1970s. Mainly, this is due to the use of combined modality therapy, as historically either radiotherapy alone or chemotherapy alone was associated with recurrence rates of approximately 50%. Current clinical trials are exploring new combinations of radiotherapy and chemotherapy to try to reduce late morbidity and mortality while maintaining a high probability of freedom from first recurrence.

**ADVANCED-STAGE DISEASE**

**Basic Regimens: MOPP and ABVD**

MECHLORETHAMINE, VINCRISTINE (ONCOVIN), PROCARBAZINE, AND PREDNISONE. Initially the four-drug MOPP program was administered with each drug given at full dose over 2 weeks, resulting in a complete remission rate of 81%. Complete remission rates of 73% to 81%, long-term freedom from progression of 36% to 52%, and long-term overall survival of 50% to 64% were observed in major trials of MOPP in advanced-stage HD.

Despite the good initial results with MOPP therapy, several groups investigated alternative regimens to improve the efficacy or reduce toxicities. The CALGB showed that omission of the alkylating agents nitrogen mustard or procarbazine from the MOPP regimen was associated with inferior complete remission rates. Thus, the four-drug principle was considered a standard at that time, to which all alternative combinations had to be compared.

Modifications of the MOPP scheme included the substitution of an alkylating agent such as cyclophosphamide or chlorambucil for mechloretamine (COPP) or a vinca alkaloid such as vinblastine or vincristine for Oncovin (MVPP), as well as alteration of the doses of procarbazine and prednisone.

The ECOG developed a five-drug regimen containing BCNU, cyclophosphamide, vinblastine, procarbazine, and prednisone (BCVP). Their results showed that BCVP had a significantly higher freedom-from-progression rate (50% vs. 33%) and overall survival rate (83% vs. 75%) than did MOPP at 5 years.
However, the interpretation of these results is complicated by the inclusion of previously treated patients. In the United Kingdom, the MVPP combination was used, which revealed comparable results to MOPP, with complete remission rates of 60% to 80% and 5-year overall survival rates of 70% to 80%. Also in the United Kingdom, the chlorambucil, vinblastine, procarbazine, and prednisone (CHVP) regimen was developed and showed similar efficacy with less acute toxicity as compared to MOPP, although a randomized comparison was not performed. The BNLI performed a randomized trial to compare chlorambucil (Leukeran), Oncovin, procarbazine, and prednisone (LOPP) with MOPP. No significant differences were observed in complete remission or overall survival rates. Together, several MOPP-like regimens showed similar efficacy with less acute gastrointestinal and neurologic toxicities.

ADRIMUMCYC, BLEDYMCYC, VINBLASTIN, AND DACTCARBAZINE. MOPP and its derivatives had two limitations: Only approximately 50% of patients could be cured, and the alkylating agent-based combination was associated with an increased risk of sterility and acute leukemia. In an attempt to develop a regimen for patients in whom MOPP had failed, Bonadonna et al. introduced the ABVD regimen. Vinblastine had demonstrated high activity as a single agent and lacked cross-resistance with vincristine in human tumors. Both doxorubicin and bleomycin were very active drugs and showed objective responses in approximately 50% of patients. Dacarbazine was added because it was active as a single agent and also showed synergism with doxorubicin.

The Milan group compared three cycles of MOPP or ABVD followed by extended-field irradiation and three additional cycles of the same chemotherapy. A significant difference in favor of ABVD could be achieved, with freedom-from-progression rates of 63% for MOPP versus 81% for ABVD. Both MOPP and ABVD were highly active regimens and had nonoverlapping toxicities. It was therefore straightforward to test combinations of MOPP and ABVD to further increase treatment results. The Milan group randomized patients with stage IV disease to MOPP or MOPP/ABVD for up to 12 cycles. The results were emphatically in favor of the alternating program, with a statistically significant difference in freedom from progression at 8 years (36% MOPP vs. 65% MOPP/ABVD; P < 0.005). Subsequently, three large cooperative trial groups (ECOG, CALGB, and EORTC) have confirmed these results and demonstrated superior results with the combination of MOPP/ABVD over MOPP or a derivative. ECOG compared the MOPP derivative BCP (BCP/ABVD) with MOPP followed by ABVD. Both complete remission and overall survival rates were superior with the MOPP/ABV combination.

The CALGB tested, in a three-arm trial, six to eight cycles of MOPP, six to eight cycles of ABVD, and 12 cycles of MOPP alternating with ABVD. At 10 years, the failure-free survival rates were 38% for MOPP, 55% for ABVD, and 50% for MOPP/ABVD, with a probability value of .02. Overall survival was not significantly different among the three arms, although there was a trend in favor of MOPP or ABVD/ABVD as compared to MOPP alone. The EORTC compared two courses of MOPP alternating with two courses of ABVD to a total of eight courses. Radiotherapy was given to initial bulk or residual masses after chemotherapy. MOPP/ABVD showed a significantly higher failure-free survival rate at 6 years (43% MOPP vs. 60% MOPP/ABVD).

Thus, ABVD alone and MOPP/ABVD are more effective than MOPP alone. In addition, ABVD alone offers the advantage of less acute and long-term toxicities.

DURATION OF THERAPY. In the original NCI studies of MOPP, two additional monthly cycles were given after a complete remission was achieved; Viviani et al. initially applied up to 12 cycles of MOPP and later, in the alternating program, eight cycles without reduction in efficacy. The CALGB trial demonstrated that eight cycles of ABVD was comparable to 12 cycles of alternating MOPP/ABVD. A total of eight to 12 cycles of chemotherapy was given in the more recent phase III trials. Thus, although the optimal duration is not known precisely, eight cycles of MOPP, ABVD, or a combination appear to be sufficient.

Hybrid Regimens

The theoretic basis for multidrug regimens is the predicted advantage of the early introduction of all active agents to avoid resistant tumor cell clones. This idea is based on a model proposed by Goldie and Coldman, who related the drug sensitivity of tumors to their spontaneous mutation rate. The model formed the basis of “hybrid” schemes, which were tested by several groups in advanced-stage HD.

Groups in Vancouver and Milan independently designed two hybrids of MOPP and ABVD to test the Goldie-Coldman hypothesis prospectively. The NCI-C compared the MOPP-ABV hybrid with alternating MOPP/ABVD in patients with stage IIIb or IV HD. At 5 years, there was no significant difference in the overall survival rates between both arms, although the hybrid regimen was associated with higher hematologic and nonhematologic toxicities.

The Milan group compared their MOPP/ABV hybrid with alternating MOPP/ABVD. Freedom-from-progression and overall survival rates at 10 years revealed no significant difference between the hybrid and alternating arms.

The GHSG compared a new hybrid scheme—COPP, ABV, and ifosfamide, methotrexate, and etoposide (IMEP) with their standard COPP/ABV/AB. Complete remissions, FFTT, and overall survival rates showed no statistically significant difference between the two treatment arms.

A second intergroup trial that compared an MOPP/ABV hybrid with ABVD was performed in the United States, recruiting a total of 856 patients with stage III or IV HD or recurrent disease after radiotherapy. This study was prematurely stopped by the Data and Safety Monitoring Board because an excess of treatment-related deaths and second malignancies with the hybrid regimen was observed. At 3 years, similar failure-free survival rates were observed for ABVD (65%) and MOPP/ABV (67%). From this trial, it was concluded that ABVD and MOPP/ABV are equally effective but that ABVD is less toxic and should remain the standard treatment.

The potential relevance of scheduling was exemplified in a recent BNLI study in which a significant difference was found between a LOPP and etoposide, vincristine, and Adriamycin (EVA) hybrid and LOPP alternating with EVA that contained identical total doses. The complete remission was significantly less in the hybrid arm, and the trial was stopped prematurely.

To summarize, the Goldie-Coldman hypothesis could not be proven in advanced-stage HD, although this could be due to the fact that the optimal hybrid regimen has not been identified thus far. ABVD has emerged as the standard against which newer treatments must be compared. With ABVD, 60% to 70% of patients will be free of disease at 5 years. ABVD is much less likely to cause severe myelotoxicity, acute leukemia, or sterility than are treatment programs that contain significant doses of alkylating agents.

New Chemotherapeutic Regimens

The success of ABVD in the CALGB and in the intergroup trials indicated that alkylating agents are not essential for curative treatment for advanced HD. However, the pulmonary toxicity of bleomycin, which is especially pronounced in children and in combination with mediastinal irradiation, remains a major concern with ABVD. A number of drugs showing high efficacy in refractory HD have become candidates for first-line therapy. The topoisomerase inhibitor etoposide has gained special interest among several groups, as a 20% to 60% response rate in refractory HD was reported with single-agent etoposide. On the basis of these considerations, several etoposide-containing drug regimens have been developed.

At Stanford, the five-drug regimen Stanford V was developed. The program was applied weekly over a total of 12 weeks. Sophisticated consolidative radiotherapy to sites of initial bulky disease was used. In this phase II trial, 126 patients had been recruited. The estimated 5-year freedom-from-progression rate was 89%, and the overall survival was 96% at a median observation time of 4.5 years in this single-center study. Reduced long-term toxicities with preserved fertility was a major goal and could be achieved both in men and women. An intergroup trial of Stanford V versus ABVD has been initiated in selected patients with low-risk advanced HD.

Similarly, the Manchester group developed an abbreviated, 11-week chemotherapeutic program, VAPEC-B. In a randomized trial, VAPEC-B and the hybrid CHVP/EVA were compared with radiotherapy applied to previous bulky disease or residual disease. This study was stopped after 26 months owing to a threefold increase in the rate of progression after VAPEC-B.

The Southampton group developed another abbreviated, weekly chemotherapeutic regimen consisting of PACE-BOM. Radiotherapy was applied to residual disease. A 64% failure-free survival was reported after a median observation time of 5 years. Caution should be exercised when comparing results of different trials; particularly the amount of consolidative radiation, can vary widely. Large, randomized trials...
involvement and provided no reduction in relapse among patients with stage IV disease. There was no survival benefit detected by radiotherapy in any subgroup.

In the additional design, radiotherapy reduced the hazard rate by approximately 40%. The benefit of irradiation was more pronounced among patients with mediastinal involvement and provided no reduction in relapse among patients with stage IV disease. There was no survival benefit detected by radiotherapy in any subgroup.

The GHSG analyzed the role of low-dose (20-Gy) involved-field radiotherapy versus two cycles of additional chemotherapy consolidation in 288 patients in complete remission. No significant differences in remission duration or overall survival were detected. A number of phase III trials investigated the role of consolidative radiotherapy after primary chemotherapy, with divergent results. After MOP-BAP chemotherapy, 61% of patients who achieved complete remission were randomized to low-dose involved-field radiotherapy or to no further treatment in a SWOG study. No interim results of these studies have yet been published.

Role of Radiotherapy

The ability of radiotherapy to provide local control in HD is well established. Furthermore, radiotherapy is non-cross-resistant with standard combination chemotherapy. However, the role of radiotherapy in advanced-stage HD is still controversial. Despite this uncertainty, most large trial groups include some radiotherapy as an integral part of their advanced-stage treatment strategy.

The potential contribution of radiotherapy depends on a variety of factors, including patient parameters (e.g., age, stage of the disease, and tumor mass) and the chemotherapy program. The field and dose influence efficacy and toxicity. Radiotherapy in advanced HD can be considered in three clinical settings. First, radiotherapy may be used as an adjuvant after complete remission with standard chemotherapy. Second, radiotherapy may be an integrated component of a combined modality program, possibly with reduced or brief chemotherapy. Finally, radiotherapy can serve as a non-cross-resistant treatment for patients with partial or uncertain response after chemotherapy.

HDCT is frequently used in patients with first or later relapses of HD. Numerous phase II trials and two randomized trials from the BNL and the GHSG have shown superior results with a high-dose program as compared to conventional treatment. In advanced-stage HD, limited data concerning the role of HDCT are available. The Genua group of Carella et al. conducted a phase II trial of myeloablative therapy and autografting among patients with poor-risk features as described by Straus et al. Subsequently, the European Bone Marrow Transplant Registry (EBMT) initiated a prospective study in poor-risk patients comparing HDCT and autografting with additional chemotherapy after four cycles of ABVD-containing chemotherapy. Proctor et al. have used their previously published model to identify patients at risk for an ongoing study in which patients are randomized to additional chemotherapy or HDCT and autografting after three cycles of a hybrid regimen and radiotherapy to bulky sites. No interim results of these studies have yet been published.

A number of phase III trials investigated the role of consolidative radiotherapy after primary chemotherapy, with divergent results. After MOP-BAP chemotherapy, 61% of patients who achieved complete remission were randomized to low-dose involved-field radiotherapy or to no further treatment in a SWOG study. No significant differences in remission duration or overall survival were detected.

The GHSG analyzed the role of low-dose (20-Gy) involved-field radiotherapy versus two cycles of additional chemotherapy consolidation in 288 patients in complete remission after initial chemotherapy with COPP/ABVD. There was no significant difference in freedom-from-progression or overall survival rates between the treatment arms.

To overcome the insufficient power of the randomized studies with too few patients to detect a relevant difference, Loeffer et al. performed a metaanalysis of 14 studies involving more than 1700 patients in total. Two study designs were compared: In the additional design, the same chemotherapy with and without additional irradiation was compared, whereas in the parallel design, irradiation following chemotherapy was compared with further cycles of chemotherapy.

In the additional design, radiotherapy reduced the hazard rate by approximately 40%. The benefit of irradiation was more pronounced among patients with mediastinal involvement and provided no reduction in relapse among patients with stage IV disease. There was no survival benefit detected by radiotherapy in any subgroup analyzed. In the parallel design, there was no significant difference in disease-free survival. However, overall survival was significantly higher among patients treated.
with chemotherapy alone. In the combined modality group, there were more deaths from causes other than HD, including leukemia. The results of the metaanalysis should be regarded with caution, because the studies were initiated 20 or more years ago and because, in most instances, a MOPP-based chemotherapeutic regimen was used, which is not regarded as standard therapy today.

The most important issue today relates to the added efficacy of radiotherapy as adjuvant treatment to modern anthracycline-containing chemotherapy and the added late toxicity of this combined modality. Prospective, randomized trials, such as the comparison of a MOPP-ABV hybrid with or without consolidative radiotherapy by the EORTC, are needed to address these questions. In this EORTC trial, patients in complete remission after MOPP/ABV receive two further chemotherapy cycles followed by randomization to involved-field radiotherapy or observation. A similar approach with a potentially more active chemotherapeutic regimen, BEACOPP, is currently being taken by the GHSG. In this trial, patients are randomized to eight cycles of escalated BEACOPP or four cycles of escalated BEACOPP plus four cycles of BEACOPP-baseline. Subsequently, patients are randomized to radiotherapy to initial bulky and residual disease or to no further treatment. These two important trials should define the role of radiotherapy applied with highly active chemotherapeutic protocols.

**Conclusions**

After more than 30 years of clinical research, advanced-stage HD became a curable disease in most instances. Adriamycin-containing chemotherapy has emerged as the standard against which modern strategies must be compared. With modern chemotherapy, approximately 60% to 70% of patients will be alive and free of disease at 5 years (Table 45.6-13). ABVD has a favorable toxicity profile and causes less myelotoxicity, acute leukemia, or sterility relative to many previous treatment programs containing alkylating agents. However, 20% to 30% of patients eventually experience relapse and then are frequently treated with high-dose programs.

**TABLE 45.6-13. Results of Polychemotherapy Regimens in Advanced-Stage Disease**

The two major goals in advanced HD are to improve the cure rate and to reduce acute and late toxicities. The definition of prognostic factors identified patients who are at a higher risk for relapse as well as those for whom less toxic approaches might be tested. The optimal approach or program has not been identified yet, although new chemotherapeutic regimens (e.g., Stanford V and BEACOPP) with increased efficacies have been identified. These new drug combinations hold the promise of achieving these goals, but efficacy and toxicity data must mature before their contributions can be assessed with certainty (Table 45.6-14). Although the addition of radiotherapy improved disease control in some trials, a survival benefit was not identified and so the role of radiotherapy remains controversial.

**TABLE 45.6-14. Randomized Clinical Trials in Advanced-Stage Hodgkin's Disease: Major Trials Currently Recruiting or Not Yet Published**

Recommendations for primary treatment of early (favorable und unfavorable group) and advanced stages of disease outside clinical trials are given in Table 45.6-15.

**TABLE 45.6-15. Recommendations for Primary Treatment Outside Clinical Trials**

**PROGRESSIVE AND RELAPSED DISEASE**

**Diagnosis and Staging at Disease Progression or Relapse**

Although late relapses more than 10 years after primary treatment have been reported in HD, relapse generally occurs within 1 to 5 years after primary therapy. At relapse, a new histologic workup should be obtained, as the risk for second tumors—NHL or solid tumors—is increased. Moreover, a proportion of NHL patients initially receive a misdiagnosis, as HD or composite lymphomas are not detected during first diagnosis. Therefore, another biopsy at the time of relapse or disease progression is required.

In all patients with relapsed or primary progressive HD, clinical and radiographic restaging is recommended. Because most patients receive salvage treatment, restaging has prognostic and therapeutic importance. Isolated nodal recurrence is associated with a better prognosis than is disseminated relapse, and salvage treatment strategies vary depending on prior therapy and time of failure. The issue of how to define complete remission, partial remission, no change, or progressive...
disease after salvage treatment is vital, because salvage therapies generally are more intense and more toxic than are first-line regimens. In salvage therapy studies, the response criteria usually are defined as in first-line therapies. In most series reported, however, a minimum duration of response of 4 weeks after the end of a salvage therapy is required.

**Prognostic Factors**

The likelihood of successful salvage therapy is determined by biologic features, which may be linked to certain clinical features. Adverse prognostic factors for patients with treatment failure include the treatment modality used in first-line therapy, patient age, relapse site, quantity of disease at relapse, and presence or absence of systemic symptoms. In addition, the duration of first remission is a major determinant of a second complete response.

It was first noted in 1979 that the length of a remission after first-line chemotherapy had a marked effect on the ability of patients to respond to subsequent salvage treatment. In 1992, the NCI updated their experience with the long-term follow-up of patients who experienced relapse after polychemotherapy. Derived primarily from investigations involving failures after MOPP and MOPP variants, the conclusions are relevant to other chemotherapeutic programs. On this basis, chemotherapy failures can be divided into three subgroups:

- Primary progressive HD (approximately 10% of all cases)—that is, patients who never achieved a complete remission
- Early relapses within 12 months of complete remission (approximately 15% of all cases)
- Late relapses after complete remission lasting longer than 12 months (approximately 15% of all cases)

Using conventional chemotherapeutics for patients with primary progressive disease, virtually no patient survives more than 8 years. In contrast, for patients with early relapse or late relapse, the projected 20-year survival was 11% and 22%, respectively.

Patients in whom treatment with first-line radiotherapy, combination chemotherapy, or combined modality therapy fails can be divided into two groups and their treatment selected accordingly: relapse after irradiation for early-stage disease and relapse after primary chemotherapy.

**RELAPSE AFTER IRRADIATION FOR EARLY-STAGE DISEASE.** Primary radiotherapy alone has been used more extensively in the past than in current practice. The survival of patients treated with conventional chemotherapy after relapse of irradiated early-stage disease is at least equal to that of advanced-stage patients initially treated with chemotherapy. Overall survival and disease-free survival range from 57% to 71%.

Patients who experience relapse after radiotherapy alone for localized HD (stage I and II) have satisfactory results with combination chemotherapy and are not considered candidates for HDCT and autologous stem cell transplantation (ASCT). The relapse rates after radiotherapy varied from 19% to 35%, the highest being in the series that included only clinical rather than laparotomy staging. Most patients in these series had salvage treatment based on MOPP or similar regimens. The range of 10-year survival was 57% to 71%, resembling the results of primary treatment with MOPP in patients with advanced disease. This suggests that prior radiotherapy does not cause drug resistance or a clinically significant compromise of chemotherapy dose intensity.

Stage at relapse is an important prognostic variable in radiotherapy failures. A study from Stanford including more than 100 patients with relapsed HD after subtotal or total nodal irradiation showed that conventional salvage chemotherapy is sufficient in patients with limited-stage disease having no systemic symptoms on recurrence (stage IA and IIA); after 10 years, 90% of these patients remained disease-free. In contrast, the 10-year disease-free survival for those with stage III and IV disease or with B-symptoms (all stages) at the time of relapse was 58% and 34%, respectively. An analysis using the International Database on Hodgkin’s Disease showed a worse prognosis for patients whose relapse included an extranodal site and stage IV at relapse and for those patients older than 40 years.

Patients with LP or NS histology fared better than did those with MC or LD histology: Ten-year freedom from relapse for patients with favorable histologies was 67% versus 47% (P = .04) for patients with unfavorable histologies.

The original experience using systemic therapy for radiation failures was based on the use of MOPP. The likelihood of freedom from second relapse was 57% at 10 years. However, sufficient data from doxorubicin-based regimens indicate that the principles for selecting a salvage regimen for a relapse after radiotherapy are the same as the principles for selecting a primary treatment for advanced disease. On the basis of the available evidence, ABVD has superior effects as compared with MOPP for radiation recurrence. The Milan Cancer Institute observed a disease-free survival rate of 81% with ABVD variants, as compared to 54% with MOPP.

**RELAPSE AFTER PRIMARY CHEMOTHERAPY.** Treating recurrence after primary chemotherapy is a difficult issue. The choices available are salvage radiotherapy, conventional salvage chemotherapy, and HDCT followed by ASCT.

Salvage Radiotherapy. There are relatively few instances in which radiotherapy alone would be considered the standard salvage treatment because the perception is that recurrence indicates disseminated disease. However, salvage radiotherapy offers a potentially curative option with low morbidity for a subset of selected patients. Salvage radiotherapy is a valid treatment alternative in patients without B-symptoms who have not been given radiation previously or who experience relapse locally outside the initial radiation field.

This approach has been reported in series of more than 100 patients. Wirth et al. reported the experience of salvage radiotherapy in 51 patients with relapsed or refractory HD. Twenty-three patients (45%) achieved a complete response after irradiation. Five-year failure-free survival and overall survival rates were 26% and 57%, respectively. Significant prognostic factors for failure-free survival were B-symptoms at the time of salvage radiotherapy, extranodal involvement, and histology. For overall survival, significant factors were B-symptoms, patient age, and number of prior chemotherapeutic regimens. For patients who relapsed in supradiaphragmatic nodal sites without B-symptoms, 5-year failure-free survival and overall survival rates were 36% and 75%, respectively.

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**TABLE 45.6-16. salvage Radiotherapy Alone for Relapse after Chemotherapy**

Conventional Salvage Chemotherapy. Since 1980, a number of new salvage chemotherapeutic regimens have been tested that incorporate drugs not used in the initial combination. Because most first-line management programs use MOPP, ABVD, or combinations of both, new salvage regimens have been designed anticipating resistance to these drugs in patients who have relapsed. Primary progressive disease and early relapse suggest cellular resistance to conventional doses of drugs. Patients with primary refractory HD on treatment with MOPP or alternative regimens usually respond poorly to second or third induction attempts and have a particularly poor prognosis (life expectancy <1.5 years). Fewer
than 50% of patients who experience relapse after a short initial remission achieve a second complete remission, even when treated with non-cross-resistant regimens, with a median survival of 2.5 to 4.0 years. For the vast majority of these patients, second-line chemotherapy followed by HDCT is required. In contrast, more than 80% of patients with late relapse achieve a second complete remission with MOPP or alternative regimens, having a median survival of less than 4 years. The Milan and NCI data suggest that late relapse does not necessarily imply resistance, as retreatment with the initial first-line regimen may result in response. An important goal for any retreatment in late relapse is the achievement of a second complete response, as nearly 50% of second complete responses will result in prolonged progression-free survival.

The largest randomized, multicenter trial was performed by the GHSG/EBMT to determine the benefit of HDCT in relapsed HD. Patients with relapse after conventional-dose level (mini-BEAM) or a high-dose level (BEAM) with autologous bone marrow transplantation. The actuarial 3-year event-free survival was significantly better in patients who received HDCT (53% vs. 10%). Although results with HDCT have generally been better than those observed after conventional-dose salvage therapy, the validity of this comparison has been questioned because of the lack of randomized trials. The most compelling evidence for the superiority of high-dose therapy in relapsed HD comes from two reports from the BNLI and the GHSG together with the EBMT. In the BNLI trial, patients with relapsed or refractory HD were treated with a combination of BEAM at a conventional-dose level (mini-BEAM) or a high-dose level (BEAM) with autologous bone marrow transplantation. The actuarial 3-year event-free survival was significantly better in patients who received HDCT (53% vs. 10%).

The randomized, multicenter trial was performed by the GHSG/EBMT to determine the benefit of HDCT in relapsed HD. Patients with relapse after polychemotherapy were randomized between four cycles of dexamethasone-BEAM and two cycles of the dexamethasone-BEAM regimen followed by HDCT (with BEAM) and ASCT. The interim analysis of 142 evaluable patients revealed that for 115 patients with partial or complete response after two cycles of chemotherapy, the FFTF in the HDCT group was 53%, as opposed to 39% for the patients receiving an additional two cycles of conventional chemotherapy (Table 45.6-18).

**High-Dose Chemotherapy in Primary Progressive Hodgkin's Disease.** Patients with primary progressive disease, defined as progression during induction treatment or within 90 days after the end of treatment, have a particularly poor prognosis. Treatment of patients with primary progressive HD has consisted of salvage chemotherapy, radiotherapy, and HDCT with ASCT. Conventional salvage regimens have given disappointing results in the vast majority of patients: Response to salvage treatment is low, and the duration of response is often short. The 8-year overall survival ranges between 0% and 8%. FFTF in second remission is 0% at 4 to 8 years in small series reported. Extensive disease often limits the use of radiotherapy.

In contrast, the data on HDCT and ASCT in these patients are more promising. The EBMT reported its analysis of 175 patients with primary progressive disease who received HDCT and ASCT. The 5-year actuarial progression-free survival and overall survival rates were 32% and 36%, respectively. The Autologous Blood and Marrow Transplant Registry recently reported a progression-free survival of 38% and an overall survival of 50% at 3 years in 122 patients with primary induction failure. In single-institution series evaluating the efficacy of HDCT exclusively in induction failures, Reece et al. reported a 42% progression-free survival at a median of 3.6 years. Similarly, an updated report from Stanford University showed an event-free survival of 49% at 4 years. Cianni et al. reported an event-free survival of 31% at 4 years. The studies by Yuen et al. and Andrè et al. reported improved outcome after HDCT and ASCT as compared with historical control groups given conventional chemotherapy for induction failures. Thus, HDCT and ASCT should be considered for HD patients with primary induction failure.

The GHSG retrospectively analyzed 206 patients with progressive disease to determine outcome after salvage therapy and to identify prognostic factors. The 5-year freedom-from-secondary-failure and overall survival rates for all patients were 42% and 48%, respectively. As reported from transplantation centers, the 5-year freedom-from-secondary-failure and overall survival rates for patients treated with HDCT were 42% and 48%, respectively, but only 33% of all patients received HDCT. A high proportion of those patients will rapidly succumb to progressive disease. Life-threatening severe toxicity on salvage treatment occurred in 11% of the patients. Insufficient stem cell harvest, poor performance status, and older age had also contributed to ineligibility for HDCT. In a multivariate analysis, the Karnofsky performance score at progression (P = .0001), age (P = .019), and attainment of a temporary remission to first-line chemotherapy (P = .0003) were significant prognostic factors for survival. In conclusion, HDCT is an effective treatment for a proportion of patients with primary progressive HD. Owing to the poor outcome of HD patients with progressive disease, future trials must aim at identifying patients at very high risk for induction failure and modifying primary treatment in this group to avoid progressive disease.

**High-Dose Chemotherapy in Early and Late Relapsed Hodgkin's Disease.** Patients who receive transplantation at first relapse from complete remission can often be cured with HDCT and ASCT. At present, patients with early relapse are good candidates for HDCT followed by ASCT. A report from Stanford in which historical controls were used found a 4-year event-free survival of 56% for patients with early relapse, as compared to 19% in patients who received standard-dose salvage chemotherapy. In addition, the HDR-1 study showed improved FFTF for patients with early relapse after HDCT, as compared with conventional
Several published studies have evaluated the importance of prognostic factors for patients with HD undergoing HDCT with subsequent ASCT. **Adverse** prognostic factors identified by multivariate analysis included age, chemoresistance, disease status, poor performance status, extranodal disease, female gender, elevated lactate dehydrogenase level, and failure of more than two prior regimens. An important variable that affects outcome is the ability of conventional salvage chemotherapy to reduce tumor volume before HDCT. Patients who experience relapse after chemotherapy but respond to subsequent conventional salvage therapy make up most of the long-term survivors in transplantation programs. Nevertheless, the role of conventional salvage chemotherapy before HDCT has not been clearly defined. Several studies have confirmed that a subset of patients with disease resistant to conventional salvage therapy clearly benefit from HDCT, with reported long-term survival of 10% to 31%. The number of patients with chemoresistant disease who benefit from HDCT and ASCT largely depends on the definition of chemoresistance or the number and intensity of courses of chemotherapy administered to reduce the tumor burden. Accordingly, chemoresistant patients should not routinely be excluded from transplantation programs.

Allogeneic stem cell transplantation has clear advantages as compared with autologous transplantation: Donor cells uninvolved by malignancy are used, avoiding the risk of infusing occult lymphoma cells, which, despite purging, may contribute to relapse in patients who undergo autologous transplantation. In addition, donor lymphoid cells can potentially mediate a graft-versus-lymphoma effect. As in all allograft studies, issues of donor availability and age constraints have limited its use. Moreover, in all reports using allogeneic stem cell transplantation, a high treatment-related mortality rate of up to 75% was observed in patients with HD, which casts doubt on the feasibility of this approach in larger series. **In most circumstances,** allogeneic transplantation from HLA-identical siblings is not recommended for patients with HD. The reduced relapse rate associated with a graft-versus-tumor effect is offset by lethal graft-versus-host toxicity.

In conclusion, patients who experience relapse after radiotherapy alone for localized HD have satisfactory results with combination chemotherapy and are not considered candidates for HDCT with ASCT. Current data support the use of HDCT with ASCT for patients with relapse and refractory HD after combination chemotherapy (Table 45.6-19).

### SPECIAL CASES: LYMPHOCYTE-PREDOMINANT HODGKIN’S DISEASE

The early-stage characteristics, indolent course, and relatively good prognosis of LP variants of HD have been recognized since the 1930s. Earlier studies consistently demonstrated that patients with an LP variant of HD enjoyed a better prognosis than did those with other forms of the disease. However, the introduction of clinical staging showed that the extent of disease was a more important prognostic factor than was histology and that the localized nature of LP HD could well account for the good prognosis of this subtype. In addition, modern therapeutic strategies were able to improve survival and cure rates for all types of patients, and prognostic differences due to histology often were no longer evident. The clinical relevance of the recent REAL and WHO classifications, particularly the distinction between LPHD and LRCHD, has been clarified by the international retrospective study of the ETFL. The many smaller studies of LPHD paint a similar picture.

### CLINICAL FEATURES

LPHD patients show a similar age distribution to MC patients and are somewhat older, on average, than NS patients (Table 45.6-20). Approximately 75% of patients are male, again similar to MC and different from NS (approximately 50%). Of LPHD patients, 53% had stage I and only 6% had stage IV disease. Thus, the proportion of early stages is consistently high in comparison with CHD, and stage IV is consistently rare, although not negligible. B-symptoms were present in only 10% of cases, far less than in CHD. LPHD seems to favor the peripheral upper neck and inguinal node sites and to occur relatively seldom in central sites such as the mediastinum and upper abdomen.

### TREATMENT RESULTS

There is some evidence to support the hypothesis that certain LPHD patients do well without any therapy beyond excision. Among the 51 nodular LP cases reported by Miettinen, 31 were given no treatment except possibly surgical removal of the tumor, as malignant disease was not suspected. After 7 years’ median follow-up, only seven of the untreated patients died. These results must be cautiously interpreted, as it is likely that especially mild examples would predominate in this retrospective sample. Most LPHD patients have received first-line therapy similar to that prescribed for CHD patients. LPHD cases appear to relapse just as frequently as other subtypes, but the relapse is less aggressive, resulting in frequent multiple relapses and good survival rates (see Fig. 45.6-2).

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**TABLE 45.6-19.** Recommendations for Treatment of Relapsed and Primary Progressive Hodgkin’s Disease

**TABLE 45.6-20.** Characteristics of 219 Cases Confirmed as LPHD in the European Task Force on Lymphoma Project Compared with Nodular Sclerosis and Mixed-Cellularity Cases in the 1988–1994 Trials of the German Hodgkin’s Study Group
TRANSFORMATION TO NON-HODGKIN'S LYMPHOMA

The possibility of occurrence of an NHL after primary LPHD is clinically important for several reasons. The treatment should be chosen to prevent development or progression of NHL, it should avoid inducing a secondary NHL, and a monitoring and diagnostic strategy should be chosen to detect and correctly identify recurrent and secondary tumors. In an analysis from the International Database on Hodgkin's Disease, a significantly higher risk for secondary NHL, increased by a factor 1.8, was found for LP patients as compared with NS and MC patients. Several smaller LPHD studies report secondary NHL, indicating a rate of 2% to 3% on average. Miettinen et al. reported four secondary NHLs among 31 cases of untreated LPHD, suggesting that some, if not all, such NHLs develop independently of treatment.

CONSEQUENCES FOR FUTURE TREATMENT

Although, the prognosis superiority of LPHD as compared with CHD is scarcely discernible under modern treatment, the relatively good prognosis of LP cases under earlier, less intensive treatment does indicate a potential for treatment reduction. Furthermore, as many LPHD patients died of fatal treatment-related secondary leukemias and lymphomas, it is suggested that current treatment strategies might be too intensive, particularly when other late effects, such as cardiac and pulmonary complications, are taken into account. Disadvantages of treatment reduction could include the greater risk of disease progression or of development of NHL.

Caution is needed in identifying those patients for whom treatment reduction is an option. First, immunostaining is needed for a reliable differential diagnosis among LPHD, CHD, and certain NHL variants. Second, patients with advanced-stage LPHD (20% to 25%) had an overall survival and tumor-free survival that was substantially worse than that of patients with early-stage LPHD and was similar to advanced-stage CHD patients. This implies that thorough staging and, in the case of advanced-stage disease, aggressive treatment are needed irrespective of histologic subtype.

A watch-and-wait treatment strategy, in which patients are monitored without treatment until the disease shows signs of progression, has been advocated for LPHD and for other indolent lymphomas. However, most authors report only anecdotal untreated cases. A prospective study with explicit inclusion criteria is required to assess the feasibility, risks, and benefits of a watch-and-wait strategy. The EORTC is currently adopting a watch-and-wait approach for stage I supradiaphragmatic LP after complete resection of the tumor; the involved field is to be irradiated only if the disease progresses. The GHSG is now treating CS IA LPH with risk factors with involved-field irradiation.

Involved-field radiotherapy has been shown to be more effective than irradiation in early-stage CHD but might be adequate for the very localized, less aggressive LP subtype. Two study groups, the EORTC and the GHSG, are currently treating certain early-stage LPH patients with involved-field irradiation.

A new development potentially relevant to LPH is the use of immunotherapy. The monoclonal antibody Rituximab, in particular, is directed against the B-cell receptor on LP cells. This antigen is expressed by the L&H cells of LPHD but rarely by the H-RS cells of CHD. First experiences with indolent follicular B-cell lymphomas have shown good results, with nearly 55% overall responses even in heavily pretreated patients. This therapy is now being tested by the GHSG in relapsed and refractory LPHD.

HODGKIN’S DISEASE IN THE ELDERLY PATIENT

HD treatment results, reflected in complete remission, relapse, and survival rates, tend to worsen with increasing age of the patient at diagnosis. There is no definite threshold age for the onset of this effect, although many authors report changes appearing at approximately age 60 years and older.

HD rarely occurs in patients older than 60 years. Two basic problems in the management of elderly patients emerge as a recurrent theme: a high rate of toxicities during treatment and frequent early relapses. At least two factors are considered to contribute to this poor prognosis. First, older patients differ from younger patients in disease characteristics: Advanced clinical stage and MC histology are more frequent. Second, the older patient may be more likely to experience treatment complications, which in turn influence the given intensity of therapy.

The patient's physical and mental condition, disease history, and the presence of concurrent disorders influence the treatment strategy. Age, in general, is not a contraindication for aggressive treatment. Biologically young patients in good physical and mental condition should be treated by stage-adapted regimens, analogous to conventional treatment protocols. In this subgroup, complete remission rates and relapse-free and overall survival appear to be as good as in younger cohorts. Combined modality treatment with a mild chemotherapeutic regimen and limited radiation (i.e., two cycles of ABVD plus involved-field radiotherapy) is increasingly considered the standard therapy in favorable early-stage HD. If no chemotherapy can be administered, mantle or inverted-Y fields should be irradiated, possibly at a reduced dose. For the patients with intermediate-stage (unfavorable early-stage) disease, two to four cycles of chemotherapy may be administered before involved-field radiotherapy is undertaken.

In advanced-stage disease, treatment should also be given with curative intent. The well-established ABVD combination (six to eight cycles) represents a safe regimen, whereas protocols with severe hematologic toxicities should be avoided. The time-intensified BEACOPP regimen, which has proved especially effective in advanced-stage HD patients aged up to 65 years, appears to be too toxic for patients older than 65. Support with hematopoietic growth factors (granulocyte colony-stimulating factor) should be given liberally, as infectious complications due to prolonged neutropenia are common. Close monitoring of toxicity (i.e., electrocardiography, echocardiography, pulmonary function tests) and response to treatment are important for adjusting treatment at an early juncture.

Treatment for those patients with impairment of lung, liver, heart, or kidney should be individually adapted. Depending on preexisting impairment of organs, single drugs with organ-specific toxicities (i.e., bleomycin, Adriamycin) may be omitted from the chemotherapeutic regimen, replaced, or modified in dose. Involved-field radiotherapy, oral combination therapy (CCNU, etoposide, prednimustine), or less aggressive drugs, such as gemcitabine in the initial treatment as well as the combination of vinblastine, bleomycin, and methotrexate, present possible treatment alternatives.

HODGKIN’S DISEASE DURING PREGNANCY

The peak incidence of HD occurs at female reproductive age. Therefore, the association with pregnancy is not uncommon. One case of HD has been reported per 1000 to 6000 deliveries, making it the fourth most common cancer diagnosed during pregnancy. The ABVD regimen may be used during pregnancy without increasing the risk for teratogenesis, whereas alkylating agents, Adriamycin, bleomycin, etoposide, and the vinca alkaloids would appear acceptable.

The ABVD regimen may be applied to event-free survivors with HD who are pregnant for a second or third trimester, at least most experts agree that a therapeutic abortion should be encouraged. If the woman wishes to continue her pregnancy, treatment should be deferred until the second trimester at least, because the options for therapy at the beginning of pregnancy are rather limited. If therapy is indicated, supradiaphragmatic irradiation with doses less than 10 Gy or vinblastine chemotherapy for more advanced disease may be commenced.

In the second or third trimester, a stage I to II disease may be closely observed, and treatment should be postponed until an early delivery, usually at approximately 32 to 34 weeks' gestation. If there is any sign of rapid disease progression, in supradiaphragmatic lymphadenopathy radiotherapy alone is recommended. Most studies indicate doses of 10 to 44 Gy to the classic mantle field or the involved field, with abdominal shielding to protect the fetus. In the second and third trimesters, the risk for congenital anomalies for the fetus by supradiaphragmatic lymphadenopathy radiation is low. In supradiaphragmatic lymphadenopathy and in stage III to IV disease, combination chemotherapy will be the choice of treatment. Because most chemotherapy agents freely cross the placenta and enter the fetal circulation, both the patient and the fetus must be closely monitored. Chemotherapy administered in the second and third trimester may increase the risk of intrauterine growth retardation, microcephaly, and mental retardation. Application of cytotoxic drugs shortly before birth may be particularly hazardous, as the placenta is also the primary means of drug elimination, and metabolism and excretion will be delayed in the neonates. The current concept is that antimitabolites, especially methotrexate, confer a high risk of teratogenesis, whereas alkylating agents, Adriamycin, bleomycin, etoposide, and the vinca alkaloids would appear acceptable.
used when chemotherapy is indicated beyond the first trimester. Because chemotherapeutic agents reach significant levels in milk, mothers are best advised not to breastfeed during treatment.

HODGKIN’S DISEASE IN HUMAN IMMUNODEFICIENCY VIRUS–POSITIVE PATIENTS

EPIDEMOLOGY AND CLINICAL PRESENTATION

The majority of recent studies demonstrate a slight increase in the incidence of HD in young adult and middle-aged homosexual men. They also suggest that, with regard to a certain risk behavior, HD associated with HIV infection occurs preferentially in intravenous drug users. An increased incidence of HD among such other risk groups as hemophiliacs or women with an increased risk for AIDS has not been convincingly demonstrated.

Several data support the thesis that EBV probably represents a relevant factor involved in the pathogenesis of HIV-associated HD. First, EBV is found in H-RS cells in nearly 80% to 100% of HD tissue specimens from HIV-infected patients, in contrast to the HIV-negative population with EBV in 50% to 70% of HD cases. Second, a pathogenetic role of EBV in HIV-associated HD is supported by the fact that tumor cells of virtually all cases of HIV-associated HD express EBV-encoded LMP1.

A characteristic of HD in HIV-infected patients is the predominance of unfavorable histologic subtypes. Most studies from Europe and the United States reported IC to be the most frequent histologic subtype among HIV-infected patients (40% to 100%). NS was less frequent (0% to 40%) in the HIV-positive population than in HIV-negative persons. The incidence of the LP subtype was rather low (0% to 4%). In contrast, more than 20% of all cases were classified as LD.

At the time of diagnosis, 70% to 90% of all patients with HIV-associated HD present with advanced disease. Extranodal involvement is frequent (60%), the most common sites being bone marrow, liver, and spleen. In contrast to non–HIV-related HD in the general population, in which the involvement of contiguous lymph node groups is typical and dissemination and infiltration of extranodal sites are late occurrences, in HIV-infected patients noncontiguous spread of lymphoma, such as liver involvement without splenic disease or lung involvement without mediastinal adenopathy, can be observed. Bone marrow involvement occurs in 40% to 50% of patients and may be the first indicator of the presence of HD in nearly 20% of cases. HD tends to develop as an earlier manifestation of HIV infection, presenting in patients with a median CD4+ cell count in a range of 275 to 306 µL. At the time of diagnosis, the majority of patients have persistent generalized lymphadenopathy and, in 50% of cases, lymphoma may be concurrently present with persistent generalized lymphadenopathy in the same lymph node group. Therefore, it is important to be aware of HIV-associated HD as a differential diagnosis.

TREATMENT

Treatment is difficult, considering the underlying immunodeficiency caused by HIV itself, and may increase the risk of opportunistic infections by inducing further immunosuppression. Survival of patients with HIV-associated HD is short, typically 12 to 18 months, and the incidence of opportunistic infections is increased owing to standard therapeutic regimens. Because most patients have advanced HD, they have been treated with combination chemotherapeutic regimens such as MOPP and ABVD, but the response was poor in comparison with HIV-unrelated HD. Retrospective evaluations show a complete response rate far below that of HIV-negative patients with HD, poor tolerance of chemotherapy, and necessity of dose reduction or delay of treatment. Other prospective studies show that tailored chemotherapeutic regimens having moderate bone marrow toxicity (e.g., etoposide, bleomycin, and vincristine) in combination with antiretroviral treatment with zidovudine result in a substantial decrease of opportunistic infection, yet overall survival was not significantly improved. Improvement of response rate and median survival could be achieved by full-dose regimens like BEACOPP or ABVD combined with antiretroviral treatment, prophylaxis of the most common opportunistic infection, Pneumocystis carinii, and the use of granulocyte colony-stimulating factor. Preliminary data with BEACOPP showed promising results regarding complete remission, toxicity, and median survival.

In summary, treatment of HIV-associated HD demands a special approach. Therefore, it will likely be the combination of unconventional chemotherapy, antiretroviral agents, prophylaxis of opportunistic infections, and hematopoietic growth factors that will lead to cure of HIV-associated HD. However, the individual components of the recipe are not yet defined.

SEQUELAE

Long-term complications of mantle irradiation include lung, heart, and thyroid dysfunction, second primary cancers, and Lhermitte’s syndrome (Table 45.6-21). Complications such as transverse myelitis and constrictive pericarditis should not occur with the use of modern radiotherapeutic techniques. Other long-term toxicities are not totally avoidable but can be reduced in severity or frequency.

TABLE 45.6-21. Treatment-Related Complications after Curative Therapy for Hodgkin's Disease

PULMONARY COMPLICATIONS

Radiation pneumonitis typically occurs 1 to 6 months after completion of mantle irradiation. Once it resolves, usually there are no long-term sequelae. A mild, nonproductive cough, low-grade fever, and dyspnea on exertion characterize symptomatic radiation pneumonitis. The overall incidence of symptomatic pneumonitis is less than 5% after mantle irradiation; patients with LMA or who receive combined chemotherapy and radiotherapy have a two- to threefold greater risk (10% to 15%). Radiographically, pneumonitis is characterized by the formation of infiltrates confined to the original radiation fields. Infection rather than pneumonitis is more likely if the infiltrates extend into areas of the lung initially protected from radiation. Severe pneumonitis may require treatment with steroids.

Various cardiac complications, including arrhythmias, myocardial infarction, and coronary artery disease, pericarditis, myocarditis, pericardial effusion, and tamponade have been documented after radiotherapy to the mediastinum. In many early studies, these complications were related to treatment techniques that resulted in a high radiobiologic dose to the anterior mediastinum and heart. Current practice, which limits the dose to the whole heart, blocks the subcarinal region part-way into treatment, delivers treatments equally from front and back, and uses a lower overall radiation dose and smaller treatment volumes by the use of preradiation chemotherapy, has yielded more satisfactory results. Some studies have shown a modest increase in cardiac mortality after mantle irradiation. Boivin and Hutchinson have demonstrated an increased, age-adjusted risk of death from myocardial infarction after mediastinal irradiation. When analyzed by year of diagnosis of HD, the risk was much greater for patients treated in 1966 or earlier (relative risk, 6.33; confidence interval, 1.73 to 23.16) as compared to 1967 or later (relative risk, 1.97; confidence interval, 0.72 to 5.17), suggesting an important role for modern treatment techniques in reducing the risk of complications.

CARDIAC COMPLICATIONS

The risk of chronic cardiomyopathy appears to increase as the cumulative dose of doxorubicin exceeds 400 to 450 mg/m². It is still unknown whether there is an increased risk of cardiomyopathy at lower cumulative doses (as commonly given with ABVD) in patients treated with mediastinal irradiation before or after...
of chemotherapy. Careful cardiac evaluation of patients treated with combined radiotherapy and chemotherapy is recommended because of concerns that mediastinal irradiation may predispose to accelerated coronary arteriosclerosis, and this risk may be further increased by the administration of anthracyclines. Consideration should also be given to using lower doses and blocking the lower portion of the heart whenever possible.

**SECONDARY NEOPLASIA**

The occurrence of second malignancies, including acute leukemia, NHL, and a variety of solid tumors, has become a well-acknowledged reality that adversely affects survival of some patients cured of HD. Some of these cases may represent chance association. However, physicians should be aware that HD patients are at higher risk of developing a secondary neoplasm.

A number of reports have stressed the possibility that the occurrence of acute nonlymphocytic leukemia is closely related to drug combinations containing alkylating agents. The use of ABVD in chemotherapeutic regimens for HD has reduced the risk of the leukemia. In most studies, the use of radiotherapy in combination with chemotherapy does not increase the risk over chemotherapy alone, although there may be an increased risk when chemotherapy is combined with extensive irradiation (i.e., total nodal irradiation). There does not appear to be an increased risk of developing acute nonlymphoblastic leukemia after radiotherapy alone.

The total incidence of acute leukemia, which usually occurs within the first 10 years after initial treatment, is reported in most published series to range from 2% to 6%. Other characteristics now are considered to be as important as survival by both patients and physicians. Among these, treatment burden, treatment-related toxicity, cancer. Although survival and survival without disease have long been used as the sole endpoints in clinical trials, these limits are no longer accepted today because data, quality-of-life investigations should be a mandatory component of the clinical trial design and part of the inclusion criteria.

A major argument against the use of radiotherapy as primary or adjunct therapy in HD has been its potential induction of secondary solid tumors by radiation.

The large study from the BNL1 of 2846 patients included 987 patients who were treated with chemotherapy alone. The BNL1 study showed that the relative risk of developing a secondary solid tumor after chemotherapy alone was 5.7. This was not significantly different from the relative risk after radiotherapy alone (4.8) or after combined modality therapy (5.8). Furthermore, a case-control study from a collaborative group of population-based registries and cancer centers that maintains data on 25,865 cases of HD showed that HD patients treated with chemotherapy alone were at approximately twice the risk of developing lung cancer as those were treated by radiotherapy alone or by both modalities. Most of these data are from cases involving MOPP or MOPP-like regimens; little is known of the use of ABVD and the risk of second solid tumors.

**GONADAL DYSFUNCTION**

Many patients who complete successful treatment for HD go on to raise normal children. However, under some circumstances, gonadal dysfunction is an important iatrogenic toxicity that considerably affects the quality of life of patients after HD. Three to six cycles of MOPP or MOPP-like chemotherapy induces azoospermia in 50% to 100% of male patients. This finding is associated with germinal hyperplasia and increased follicle-stimulating hormone levels, with normal levels of luteinizing hormone and testosterone. Only 10% to 20% of patients will eventually show azoospermia. After MOPP alternated with ABVD, the incidence of permanent azoospermia is approximately 50%. With full-course MOPP chemotherapy, nearly half of women become amenorrheal, with occurrence of age-dependent premature ovarian failure (>30 years, 75% to 85%; <30 years, ~20%).

The Milan Cancer Institute has reported that the administration of ABVD chemotherapy produces only limited and transient germ cell toxicity in men and no drug-induced amenorrhea to circumvent chemotherapy-induced sterility, the use of drug regimens not containing alkylating agents, procarbazine, or nitrosourea derivatives is highly recommended. An alternative for men undergoing MOPP or MOPP/ABVD therapy is sperm storage before chemotherapy. The usefulness of the administration of analogues of gonadotropin-releasing hormone in men or oral contraceptives in premenopausal women remains to be fully defined; however, limited data have been discouraging.

**OTHER COMPLICATIONS**

Minor complications can be summarized as follows: Hypothyroidism is a common event (~30%) after mantle-field irradiation, typically picked up by means of an elevated thyroid-stimulating hormone level. Hormone replacement therapy is required. Herpes zoster is another common complication, self-limited and usually occurring in one to two contiguous dermatomes within the first 2 years after treatment and affecting 15% to 20% of patients treated with radiotherapy or chemotherapy alone. However, the incidence appears higher in patients treated with combined radiotherapy and chemotherapy. Cervical dissemination and visceral involvement from this virus are rare. Early treatment with antiviral agents may limit the intensity and duration of the infection. Acute transient radiation myelopathy or Lhermitte's sign (paresthesias down the dorsal portion of the extremities when the neck is flexed) occurs in approximately 10% to 15% of patients after mantle irradiation. This complication typically occurs within 2 weeks to 3 months after radiotherapy and is self-limited, resolving in weeks to months. Xerostomia is a temporary complication of mantle irradiation; saliva returns to normal usually within 6 months of treatment. However, xerostomia may be prolonged in patients older than 40 years at treatment, or if Waldayer's ring is treated. Fluoride supplementation and careful dental care will minimize the risks of radiation caries. The risk of postplenectomy sepsis can occur particularly in children, but it can be minimized by immunization with pneumococcal vaccine; in more recent years, vaccines have been developed against Haemophilus and Neisseria species, the other microorganisms associated with small but finite risks of overwhelming postplenic sepsis.

**QUALITY OF LIFE**

A review of most randomized clinical trials in HD reveals that quality of life has been neglected as a primary or even a secondary outcome measure. After a review of the literature in pediatric oncology, Bradlyn et al. demonstrated that only 3% of all randomized clinical trial reports reviewed (n = 70) include quality-of-life data. However, mainly retrospective analyses of long-term survivors of HD have been performed. These analyses showed that a substantial subgroup of patients still shows serious sequelae of the disease and its treatment even many years after treatment has ended. In one study, men who have experienced serious illness since treatment and who earn less than $15,000 U.S. annually, are currently unemployed, are single, or are less educated were found to be at high risk for maladaptation years after treatment. Furthermore, 22% of the 273 patients studied met the criteria suggested for psychiatric diagnosis. Currently, it remains unclear at which point in the course of the disease patients with a good coping capacity can be distinguished from those without such a capacity. To characterize phases of readaptation and maladaptation more precisely, quality-of-life assessment has to be implemented in prospective, randomized clinical trials. To obtain completeness of data, quality-of-life investigations should be a mandatory component of the clinical trial design and part of the inclusion criteria. The assessment of quality of life has become an essential tool in clinical trials, in particular in the evaluation of therapies given to patients with chronic illness such as cancer. Although survival and survival without disease have long been used as the sole endpoints in clinical trials, these limits are no longer accepted today because other characteristics now are considered to be as important as survival by both patients and physicians. Among these, these treatment burden, treatment-related toxicity, and the psychological and social impacts of disease and treatment are of great importance.

Obviously, this change originates from the dramatic improvement in the efficacy of cancer treatments, particular in HD. Effective therapies, however, have several drawbacks that might limit their use. Chemotherapy and radiotherapy induce severe acute and late toxicities, which may diminish the long-term benefit of curative treatment. Several studies include a quality-of-life approach have highlighted the difficulties that survivors may experience even long after the treatment, such as...
NEW DRUGS IN HODGKIN’S DISEASE

VINO Rebine

Vino rebine belongs to the family of vinca alkaloids and is a semisynthetic analogue of vinblastine (6’nor-andro- vinblastine). The main side effect of vino rebine is myelosuppression. WHO grade III to IV neutropenia occurs in up to 70% of patients but is of very short duration, with a low incidence of infectious complications.

Vino rebine used as single-agent therapy in HD was administered in all studies in a weekly schedule with 30 mg/m². Devizzi et al. report on 22 patients with HD refractory or resistant to at least two chemotherapeutic regimens, of which 50% (n = 11) showed an objective response (complete remission, n = 3; partial remission, n = 8) with a median duration of 6 months. Benczkou et al. evaluated the response to vino rebine in untreated patients with advanced HD. Thirty-two patients received four weekly doses of vino rebine before MOPP/ABVD chemotherapy, and 90% achieved a partial remission.

IDARUBICIN

Idarubicin is a semisynthetic drug that was first purified in 1976. Idarubicin differs from its parent drug daunorubicin only by the replacement of the C-4 methoxyl group in the D ring with a hydrogen atom. This modification has major consequences for the pharmacokinetic characteristics. Idarubicin is much more lipophilic and can be administered intravenously. Its main metabolite idarubicinol is as active as the parent compound. In addition, idarubicin has shown greater cytotoxicity than daunorubicin or doxorubicin in vitro. Idarubicin exhibits less cardiotoxicity at equi-effective doses as compared with other anthracyclines, whereas hemotoxicity and mucositis appear to be more pronounced. The GHSG is currently conducting a clinical phase II study in which idarubicin (8 mg/m², days 1 and 2) is administered together with etoposide (60 mg/m², days 1 to 4), ifosfamide (1000 mg/m², days 1 to 4 continuous infusion), and dexamethasone (20 mg/m², days 1 to 4) in patients with relapsed or refractory HD.

GEMCITABINE

Gemcitabine is a new pyrimidine antimitabolite with unique metabolic and mechanistic properties among the nucleoside analogues. It is a derivative of deoxycytidine, with fluorine substituted for the two hydrogen atoms in the 2’-position of the deoxyribose sugar. Although structurally similar to cytarabine, gemcitabine differs pharmacokinetically and pharmacologically. It acts as a competitive substrate for incorporation into the DNA, where it leads to chain termination. Based on the impressive results in solid tumors such as non-small cell lung cancer and pancreatic cancer, gemcitabine was given in a multicenter clinical phase II study in patients with multiple relapsed or refractory HD who had received at least two prior chemotherapeutic regimens. Gemicitabine was administered in a weekly schedule of 1250 mg/m² on days 1, 8, and 15 of a 28-day cycle. An interim analysis of this trial showed an overall response of 39%, with 2 of 23 complete remissions and 7 of 23 partial remissions. Another ten patients had stable disease. Myelosuppression was the main toxicity.

IMMUNOTHERAPY

Tumor cells that survive intensive therapy in small quantities are defined as minimal residual disease. These partially dormant, chemoresistant lymphoma cells might be eradicated by new immunotherapeutic strategies with a different mechanism of action. Current approaches comprise passive immunotherapy with antibody-based regimens for specific targeting of malignant cells as well as active immunotherapy with modulation of the cellular immune response using cytokines, tumor vaccines, or gene transfer. The combination of immunotherapeutic strategies with standard chemotherapeutic regimens seems to be most promising: Owing to different mechanisms of action, cross-resistance of malignant cells is expected to be rare. Furthermore, the side effects of these two treatment modalities differ, so that toxicity will not usually be additive.

PASSIVE IMMUNOTHERAPY

Systemically administered chemotherapeutic agents kill rapidly dividing cells, whereas monoclonal antibodies can target tumor cells selectively. Normal cells that lack specific tumor antigens are not harmed. For a variety of reasons, Hodgkin’s lymphoma seems to be an ideal target for antibody-based therapeutic approaches: First, H-RS cells express many different cell surface antigens, such as CD15, CD25, CD30, CD40, and CD80 (B7-1), which are present on only a minority of normal human cells. Due to low cross-reactivity with healthy tissue, side effects are rare. Second, because many different markers can be detected on the surface of Hodgkin’s cells, “cocktails” (i.e., a combination of various antibody conjugates targeting different Hodgkin’s-specific antigens) might be useful for selective immunotherapy. If one malignant antigen-deficient cell clone is resistant to one antibody, cells might still be targeted by the second or third antibody conjugate administered at the same time. Third, the number of malignant cells that must be killed is small, as the majority of cells in the involved lymph nodes are reactive bystander cells. Fourth, lymphomas are well vascularized, so that intravenously administered antibody conjugates can easily reach their target cells. Therefore, chemotherapy or radiotherapy (or both) can be used for treatment of bulky disease, whereas immunotherapeutic agents are applied thereafter to eliminate minimal residual disease and thus prevent relapses.

Native Monoclonal Antibodies

Ideally, the antibody targets with high specificity an antigen present only on the tumor cells and has no cross-reactivity with normal human tissue. The mechanisms of action of native antibodies include complement activation, antibody-dependent cellular toxicity, phagocytosis of antibody-coated target cells, inhibition of cell-cycle progression, and induction of apoptosis. In early phase I and II trials, native antibodies have exhibited moderate adverse effects, such as chills, fever, dyspnea, nausea, diarrhea, and myalgia. Toxicity usually was related to the number of circulating tumor cells and the development of human anti–mouse antibody (HAMA) responses. New chimeric antibodies that consist of human constant and murine variable regions rarely induce human anti–mouse antibody formation.

Engert et al. evaluated more than 40 different monoclonal antibodies against Hodgkin’s-associated antigens that exhibit potency in vitro or in vivo when used in native form. The chimeric monoclonal anti-CD20 antibody Rituximab (IDEC-C2B8) has been approved by the U.S. Food and Drug Administration for treatment of patients with relapsed advanced follicular NHL after a pivotal trial demonstrated response rates up to 50% in 166 patients. Because the CD20 antigen is expressed on all malignant cells in paragranuloma or LPHD, this entity might be a good target for treatment with Rituximab. An international study currently is investigating the safety and efficacy of Rituximab in patients with relapsed or refractory LPHD and other multiple relapsed CD20-positive cases of HD.

Immunotoxins

Immunotoxins generally consist of a binding moiety and a toxin moiety, which are either covalently linked via a chemical linker or generated by recombinant fusion technology. The binding domain is usually a monoclonal antibody, a Fab’ fragment, a single-chain variable fragment, or a cytokine, whereas the toxin is of bacterial or plant origin. Recombinant toxins are constructed by fusing coding regions of toxins such as diphteria toxin or Pseudomonas exotoxin-A to ligand genes.

Immunotoxins can bind selectively to their target cells. After internalization of the construct by endocytosis, the toxin is transferred to the ribosomal subunits, where it interferes with protein synthesis, thus killing the tumor cell.

Another interesting target for selective immunotherapy in HD is the IL-2 receptor (CD25), which is expressed on the majority of H-RS cells. In a phase I study, 15 patients with refractory Hodgkin’s lymphoma were treated with the anti-CD25 immunotoxin RFT5.dgA. All patients in this trial were heavily pretreated with a mean of five prior chemotherapeutic regimens, including autologous bone marrow transplantation. Most side effects were related to vascular leak syndrome. Clinical response included two partial remissions, one minor response, and three stable diseases. Promising approaches include deleting immunodominant epitopes and humanizing the antibody moiety of the immunotoxin.

A variety of monoclonal antibodies have been evaluated for their potential clinical use as ricin A chain immunotoxin against HD. The most potent anti-CD30 immunotoxin, Ki-4.dgA, is currently being investigated in a clinical dose escalation trial. In humans, sequential application of anti-CD30 antibodies linked to distinct ribosome-inactivating proteins might prevent formation of human antibodies against the individual toxins.
Radioimmunoconjugates

Radioimmunoconjugates are constructed by linking a monoclonal antibody to radioisotopes without significantly altering the immunologic specificity of the protein. The most important advantage of these constructs as compared to all other antibody-based therapeutic strategies is that b-particles emitted by radioisotopes can kill adjacent tumor cells through a crossfire effect, regardless of whether cells express the target antigen. As opposed to external-beam radiotherapy, radioimmunoconjugates deliver radiation continuously at a low dose rate to the whole body, including occult micrometastases. Currently, both nonmyeloablative and myeloablative strategies involving radiolabeled antibodies are investigated for imaging and treatment of HD.

Low-energy radioisotopes are coupled to monoclonal antibodies either for diagnostic use (immunoscintigraphy) or for low-dose radioimmunotherapy without severe myeloablation. A phase I trial was initiated to investigate the safety of the 131I-labeled anti-CD30 antibody Ber-H2 for immunoscintigraphy and possible immunotherapy in patients with refractory HD and large cell anaplastic lymphoma. Preliminary results suggest good tolerance of the therapy with no major side effects and satisfactory efficacy for imaging or detecting HD lesions. Future trials involving modern radioisotopes (111In, 125I, 131I) are warranted.

Nuclear cell support for hematopoietic recovery might be necessary in high-dose radioimmunotherapy. A phase I II study with 111In-labeled polyclonal antiferritin antibodies for refractory Hodgkin's lymphoma followed by autologous bone marrow transplantation was performed by Vriesendorp et al. Of 17 patients, seven achieved complete remissions lasting 2 to 3 months, and 9 partial remissions (2 to 9 months). Twelve patients received a reduced dose (20 mCi) due to bone marrow involvement or unsuccessful marrow harvest. Complete remissions were observed in two and partial remissions in five of them. For all doses, response rates were better in patients with small tumor burden. Based on these encouraging results, radioimmunotherapy appears to be a new promising option, either alone or in combination with other chemotherapy or immunotherapy (or both).

Bi-Specific Monoclonal Antibodies

Bi-specific monoclonal antibodies contain two different recognition sites, one for antigens on tumor cells and another for antigens on immunologic effector cells, such as macrophages, T-lymphocytes, or NK cells. For treatment of HD with NK-cell-activating bi-specific antibodies, a CD16/CD30 bi-specific antibody was constructed using hybridoma technology. Heavily pretreated patients with refractory HD received intravenous infusions of the CD16/CD30 (A9/HRS-3) antibody four times every 3 or 4 days. Fifteen patients with refractory HD were treated with escalating doses. Side effects were rare and consisted of short-lasting fever, pain in involved lymph nodes, and a maculopapular rash. A total of one complete and one partial remission (lasting 16 and 3 months, respectively), three minor responses (1 to 11 months), and one mixed response was observed.

ACTIVE IMMUNOTHERAPY

Therapeutic strategies modulating the cellular immune response have been investigated in lymphoma patients for more than 25 years. As immunotherapy with Bacillus Calmette-Guérin has suggested therapeutic effects when combined with chemotherapy in patients with acute myeloid leukemia and breast cancer, several randomized clinical trials were initiated in patients with advanced Hodgkin's lymphoma as well. Because of a documented lack of therapeutic benefit and a higher frequency of unacceptable toxicity, trials investigating Bacillus Calmette-Guérin treatment were discontinued.

IL-2 was one of the first immunotherapeutic agents used for anticancer therapy. Several clinical studies were performed to investigate the efficacy of IL-2 alone or in combination with autologous lymphokine activated killer cells (adoptive immunotherapy) in patients with refractory Hodgkin's lymphoma. Toxicity was mild, mainly comprising fever, rash, hypotension, and anemia. In these clinical pilot trials, several transient partial remissions were achieved in heavily pretreated patients with relapsed or refractory disease. IL-2 is currently under clinical investigation as maintenance therapy alone or in combination with other cytokines after HDCT.

Case reports of a few patients who received interferon for treatment of viral infection noted minor responses of Hodgkin's lymphoma. Therefore, some pilot studies were conducted to investigate the efficacy of interferon in the salvage or maintenance therapy of HD. Preliminary results suggest a limited activity of interferon-a in patients with relapsed or refractory HD.

GENE THERAPY

Modulation of EBV-directed T-cell activity might be another interesting new immunotherapeutic option: Hesp et al. developed EBV-specific CTLs for treatment of EBV-associated lymphoma after bone marrow transplantation. Donor's blood samples were used for generation of EBV-transformed B-cell lines (CLLs) and for production of CLTs. Incubation of activated CTLs with LCLs of the same probe induced formation of EBV-specific CTLs. In three of ten patients, elevated levels of EBV DNA after allelic gene transplantation normalized after infusion of the EBV-specific CTLs. EBV-specific CTLs were isolated for an adoptive transfer in patients with EBV-positive HD. Nine of the patients with active disease after subsequent therapy were treated with autologous EBV-specific CTLs: A 100-fold reduction of EBV DNA was observed in all patients; in two of them, B-symptoms ceased.

CHAPTER REFERENCES


MOLECULAR BIOLOGY OF LEUKEMIAS

Leukemia can be broadly defined as a disease whose malignant cell is derived from the hematopoietic system and manifests its expansion in the bone marrow with or without peripheral blood involvement. The cytogenetic study of these malignant cells has revealed that recurrent chromosomal changes occur in over one-half of all cases of leukemia. Most commonly, these are structural changes classified as translocations, inversions, or deletions. Further, it is usually the disruption or deregulation of specific genes at the chromosome breaks that in turn contributes to the process of leukemogenesis. In many instances, these genes have also been found to be directly or indirectly involved in the normal development or maintenance of the hematopoietic system. Thus, leukemia results, at least in part, from the disruption or deregulation of genes that normally regulate cell development, cell homeostasis, or both. In this sense, the molecular biology of leukemia is consistent with the paradigm established for cancer in general: Genes that predispose to human cancer (i.e., oncogenes and tumor suppressor genes) are altered or inactivated versions of genes normally involved in the regulation of cell growth, cell development, and cell death.

Several generalizations about the molecular biology of leukemia can be made. First, the chromosomal aberrations that result in the disruption or deregulation of genes occur in somatic tissues (i.e., hematopoietic cells) and are not found in nonleukemic cells. The genetic mishap often occurs at a specific point in normal hematopoiesis, giving rise to leukemia of a specific lineage that has arrested at a distinct maturational stage. This strongly suggests that the gene or genes altered in a particular type of leukemia are important in a specific stage of development or homeostasis of its normal cell counterpart. There are, however, some notable exceptions to this, such as the myeloid-lymphoid leukemia (MLL) gene that can be involved in leukemia of different or mixed lineages.

The mechanisms by which disrupted or deregulated genes cause leukemia can be broadly classified into two categories. The first is gene fusion, whereby a distinct protein, usually either a transcription factor or receptor tyrosine kinase, fuses with an unrelated gene to create a unique chimeric protein that then critically contributes to malignant transformation of the cell. This mechanism predominates in the genesis of myeloid leukemia, but is also found in lymphoid leukemia. The second is gene activation, whereby a gene that normally controls transcription within the cell is inappropriately placed under the control of an active promoter/enhancer from another gene, usually the immunoglobulin (Ig) or T-cell receptor (TCR) promoter/enhancer during the process of antigen receptor gene rearrangement. Chromosomal translocations that result in gene activation usually occur in lymphoid tissue and lead to a deregulation in gene expression. As discussed in this chapter, more recently it has been appreciated that other genetic and epigenetic events, such as point mutations, gene deletions, and DNA methylation, usually in tumor suppressor genes, can also contribute to the initiation or progression of leukemia.

The improved techniques for the study of chromosomes and the explosive growth in molecular biology are rapidly facilitating the elucidation of genes involved at chromosomal breakpoints in cases of leukemia, and the list of oncogenes is increasing almost daily in the literature. Table 46.1-1 provides the reader with some examples of genes involved in leukemogenesis by either gene fusion or gene activation, their chromosomal location and name derivation, a general description of their function, if known, and the type of leukemia with which they are associated. However, it should be noted that nearly one-half of all cases of leukemia do not have cytogenetic evidence of recurrent structural chromosomal rearrangements, but instead have changes only in chromosome number (e.g., monosomy 7 or trisomy 8), or completely normal cytogenetics. This severely restricts the molecular biologist's ability to focus in on hot spots in the genome where evidence of gene fusion or gene activation is likely to be found. Advances in a fraction of such cases have revealed that comparable genetic mechanisms of leukemogenesis are operative even in the absence of structural cytogenetic abnormalities.

| TABLE 46.1-1. Selected Examples of Cytogenetic and Molecular Abnormalities in Leukemia |

In this chapter, we review the most common genetic disruptions that result from the recurrent cytogenetic aberrations in acute and chronic leukemia, and where possible, provide an explanation as to how such alterations contribute to the molecular pathogenesis of the disease. In addition, we review instances in which the molecular basis for leukemia has been determined in the absence of structural cytogenetic abnormalities. Finally, we discuss other genetic alterations, mostly in tumor suppressor genes, that are likely to contribute to the genesis or progression of leukemia. We proceed with a molecular description of leukemia that simply follows the list of the more common molecular defects provided in Table 46.1-1. There is little or no attention to the more traditional revised histologic classification of leukemia to put more emphasis on the genetic basis of leukemia. Derivations of abbreviations used for the genes discussed in the text can be found in Table 46.1-1.
An important example of interference with transforming growth factor-β–induced growth-inhibitory signals from the marrow stroma. It appears likely that additional myelodysplastic syndromes (MDS), AML, and blast crisis of chronic myeloid leukemia (CML) results in a fusion of $\text{CBF}+\text{CBF-MYH11}$. There are other examples of fusion with $\text{CBFA2}+\text{CBFA2T1}$, a transcriptional regulator that has been shown to promote transcription via acetylation of histone proteins associated with targeted genes (see Fig. 46.1-1).1

There is the fusion of its carboxyl terminus with almost the entire $\text{CBF}$ gene, the normal partner of $\text{CBF-MYH11}$ fusion protein into high-molecular-weight structures. It may therefore be possible that the $\text{CBF-MYH11}$ homodimers could sequester $\text{CBFA2}$ subunits required for heterodimerization with $\text{CBF}$ (originally described as $\text{CBFb}$), which in turn increases the affinity and stability of $\text{CBF}$ binding to the core enhancer sequence, thereby promoting efficient activation of target gene transcription. Additional factors that act as coactivators of transcription participate in this complex transcriptional activation of hematopoiesis through a dominant-negative mechanism (Fig. 46.1-1B).13

The CBFA2 protein binds to the human homologue of the murine nuclear receptor corepressor (N-COR). N-COR forms a complex with mammalian Sin3A and histone deacetylase 1 (HDAC1) and facilitates repression of transcription by altering chromatin structure via histone deacetylation. It is thus possible that in t(8;21) acute myeloid leukemia (AML), the N-COR/Sin3A/HDAC1 complex is recruited to the CBF complex by the CBFA2-CBFA2T1 protein, thereby inducing repression of transcription by deacetylation of CBFA2-targeted genes (Fig. 46.1-1B). This process may result in the disruption of normal hematopoiesis and may also inactivate tumor suppressor genes and other factors important for neoplastic transformation. In support of such a hypothesis, there are data demonstrating that inhibitors of histone deacetylase can reverse CBFA2T1-mediated transcriptional repression and can induce differentiation of CBFA2-CBFA2T1 leukemia cells.2

At the molecular level, inv(16)(p13;q22) and t(16;16) (p13;q22) both result in the fusion of the CBFA2 gene, the normal partner of CBFA2 shown in Fig. 46.1-1A and located at chromosome 16q22, with the MYH11 gene from chromosome 16p13.15 The MYH11 gene encodes a smooth muscle form of the myosin heavy chain, and it is the fusion of its carboxyl terminus with almost the entire CBFA2 gene, including its CBFA2-binding domain, that appears important for leukemogenesis. The genomic fusion of CBFA2-EVI1 fusion product genes is quite variable, and at least 11 different sized fusion transcripts have been described, the biologic and clinical significance of which are unclear.19 The mechanism whereby the CBFB-MYH11 fusion gene contributes to malignant transformation remains to be fully elucidated. In vitro analyses show that the CBFB-MYH11 chimeric protein can bind to the CBFA2 protein, which in turn can bind its TGT/cGGT core enhancer DNA sequence element, albeit with reduced DNA-binding activity. The carboxyl terminus of MYH11 does contain a functional domain, the myosin long tail, that might mediate homodimerization of the CBFB-MYH11 fusion protein into high-molecular-weight structures. It may therefore be possible that the CBFB-MYH11 homodimers could sequester CBFA2 subunits into a nonfunctional complex, thereby inhibiting the transcriptional activation of genes important for hematopoiesis. Indeed, Aya et al. provided compelling in vivo evidence in support of such a hypothesis, demonstrating that the CBFB-MYH11 homodimers could colocalize with the CBFA2 protein in actin filament outside of the nucleus.20 These data would therefore support a dominant negative mechanism of CBFA2 gene inactivation by the CBFB-MYH11 fusion protein, leading to dysregulated hematopoiesis.

Mice have been generated with CBFB+CBFB-MYH11 embryonic stem cells. The CBFB+CBFB-MYH11 mice are chimeric, in that they have hematopoietic stem cells with and without the knock-in CBFB-MYH11 gene in the marrow. The mice have defective myeloid and lymphoid differentiation; however, they did not develop any malignancies in their first year of life. To test the hypothesis that additional genetic events might be required, the mice were injected with a single sublethal dose of N-ethyl-N-nitrosourea, a potent DNA alkylating mutagen. Within 2 to 6 months after treatment, 84% of the treated CBFB+CBFB-MYH11 chimeric mice developed acute myelomonocytic leukemia, whereas none of the control populations (CBFB+CBFB-MYH11 chimeras without injection or wild-type mice with injection) developed leukemia. Leukemic cells expressed the CBFB-MYH11 fusion gene and, importantly, the mice did not show evidence of malignancy in other tissues where the CBFB-MYH11 fusion gene was not expressed. The data from this elegant experimental model and from others not discussed suggest that alterations in the CBFB complex serve to block hematopoietic differentiation, while a second hit that targets these particular cells may be necessary to induce frank leukemia. The molecular appearance of the platelet disorder/AML (PMDS/AML) previously reviewed (see the first clinical observation in support of the mouse model. Patients with familial platelet disorder/AML have haploinsufficiency of CBFA2, which causes an autosomal dominant congenital platelet defect and may predispose to the acquisition of additional mutations that cause leukemia.21

There are other examples of fusion with CBFA2 that lead to dysregulation of hematopoietic and leukemic differentiation. The i(3)q21(q26;q22) noted in myelodysplastic syndromes (MDS), AML, and blast crisis of chronic myeloid leukemia (CML) results in a fusion of CBFA2 with the EVI1 gene, where the zinc finger DNA-binding domains of EVI1 fuse with the amino terminus (runt homology) domain of CBFA2, similar to that described previously for CBFA2-CBFA2T1.22,23 However, like the CBFA2 fusion partner CBFA2T1, EVI1 also has properties that may contribute to leukemogenesis. Using the first zinc finger domain of EVI1, the CBFA2-EVI1 fusion product has been shown to interact with SMAD3 and block transforming growth factor-mediated growth inhibition of myeloid cells.23 Thus, myeloid hematopoietic cells rendered unable to differentiate because of disrupted CBFB function may be further induced toward malignant transformation by interference with transforming growth factor-β–induced growth-inhibitory signals from the marrow stroma. It appears likely that additional CBFA2 partner genes will be cloned from patients with de novo and secondary AML and MDS.24

An important example of CBFA2's involvement in lymphoid malignancies is the TEL-CBFA2 fusion that is associated with pediatric B-lineage acute lymphoblastic leukemia (ALL). The TEL gene, also known as ETV6, is a member of the ETS family of transcription factors that are defined by their highly conserved, 90-amino acid,
winged helix-turn-helix DNA-binding domain, also known as the ETS domain, that recognizes the consensus motif C/GA G/A/T. A role for the TEL gene in human hematopoiesis appears likely, as mice chimeric with TEL embryonic stem cells were unable to establish hematopoesis in the bone marrow, as opposed to other sites of hematopoietic activity during development. The TEL-CBF2 fusion of childhood B-lineage ALL results from the t(12;21)(p13;q22). However, it is best identified by fluorescence in situ hybridization, because the juxtaposition of bands 12p13 and 21q22 is usually unrecognizable in banded metaphase preparations. The TEL-CBF2 fusion occurs in approximately 25% of cases of pediatric ALL and is therefore the most common gene rearrangement in any childhood cancer. The fusion product contains the helix-loop-helix (HLH) homotypic interaction domain adjacent to an amino-terminal domain, including the full-length CBF2 gene, including both the runt homology domain as well as the oncogenic TEL domain (20). Indeed, this is the only known fusion in human leukemia currently known to incorporate the transactivation domain. It is likely that the TEL-CBF2 fusion contributes to leukemic transformation in normal human TEL-CBF2 fusion. However, in addition, this fusion invariably leads to the loss of the remaining wild-type TEL allele, suggesting that this might be an important contributor to leukemogenesis as well. The mechanism by which such a contribution might occur remains unknown. The disruption of the CBF complex in t(8;21), inv(16), and t(12;21) confers a favorable prognosis in patients whose leukemic blasts harbor the consequent molecular alterations. This does not appear to be the case for the t(3;21). The molecular basis for this clinical observation largely remains obscure, but there is at least preliminary evidence that downstream genes that confer resistance to standard induction chemotherapy might be dysregulated by disruptions in the CBF complex.

**ADDITIONAL GENE FUSIONS WITH TEL**

There are several chromosomal translocations in myeloid leukemia that disrupt the TEL gene, which, unlike the TEL-CBF2 fusion noted in ALL, do not involve the CBF complex. In some cases, the amino terminus of the TEL protein, which includes the HLH oligomerization domain, appears to be required for leukemogenesis, whereas in other cases it is the DNA-binding ETS domain of TEL that appears to be relevant. Further, there is little, if any, homology or functional similarity between most of the TEL fusion partner genes. While TEL gene rearrangements in myeloid malignancy are not frequent, their characterization has revealed a multitude of possible mechanisms whereby TEL may contribute to leukemogenesis.

TEL was first identified when the t(5;12)(q33;p13) associated with chronic myelomonocytic leukemia was cloned. This translocation produces an in-frame fusion of the amino terminus of TEL, which includes the HLH oligomerization domain, with the transmembrane and tyrosine kinase domains of the platelet-derived growth factor receptor-β (PDGFR-β), a receptor tyrosine kinase. The TEL-PDGFR-β fusion results in both constitutive activation of the truncated receptor tyrosine kinase as well as its ectopic expression, and both properties are dependent on TEL and its HLH domain. In model systems it has been demonstrated that at least some of the downstream effector molecules normally induced by PDGF, such as MYC, are induced by the TEL-PDGFR-β protein and are required for transformation.

The t(9;12)(q34;p13) fuses the TEL gene with another tyrosine kinase called ABL, named after its homologue, the Abelson leukemia virus oncogene. ABL is best known as the fusion partner with BCR (breakpoint cluster region) in CML (see Philadelphia-positive chronic myelogenous leukemia and acute lymphoblastic leukemia). Result from a Fusion of BCR with the Tyrosine Kinase ABL, later in this chapter). The TEL-ABL fusion is strikingly similar to the TEL-PDGFR-β fusion, in that the in-frame fusion joins the HLH domain of TEL with the catalytic (kinase) domain of ABL. Once again, the HLH domain serves to oligomerize the ABL kinase activation. The fusion has been characterized in acute undifferentiated myeloid leukemia, atypical CML, and ALL. The similarities between the TEL and ABL in their fusion with PDGFR-β are striking. Both appear to function by primarily inducing ABL oligomerization and consequent activation, i.e., a gain-of-function mechanism. Indeed, comparison of TEL-ABL and BCR-ABL transformation properties and downstream signal transduction events suggests that the fusion proteins are indistinguishable.

The t(12;22)(p13;q11) is found in AML and in MDS. In contrast to the two fusions of TEL with tyrosine kinases noted previously, in which the HLH domain of TEL functions to oligomerize and activate its kinase, this translocation fuses the carboxyl terminus-containing ETS domain of TEL with the MNT1 gene which encodes a nuclear protein whose function is unknown. Two types of MNT-TEL fusion transcripts have been identified, one that includes the TEL HLH domain as well and one that disrupts the TEL HLH domain. This suggests that the oligomerization is not likely important in the process of malignant transformation, but rather that the DNA-binding or ETS domain is, and that MNT-TEL-mediated leukemic transformation occurs via a molecular pathway that normally involves TEL. The reciprocal TEL-MNT fusion products are not known to contain any functional domains, suggesting little or no contribution of this protein to leukemogenesis.

**MLL GENE: FUSIONS WITH MULTIPLE PARTNERS RESULT IN ACUTE LEUKEMIA**

In our discussion of the TEL gene at chromosome band 12p13, we reviewed how TEL can fuse with a variety of partners, in a variety of ways, and participate in the genesis of both lymphoid and myeloid leukemias. However, the best example of a promiscuous partner in leukemia is the MLL gene located at chromosome band 11q23. This gene fuses with an extraordinary number (over 30) of diverse partner genes, examples of which are shown in Table 46.1-1. The fusions manifest in myeloid, lymphoid, or mixed lineage leukemias (defined by markers of more than one hematopoietic lineage) of infants, children, or adults, the clinical details of which are provided in subsequent chapters. Further, the leukemias involving MLL may be de novo or primary, but also account for as many as 80% of secondary leukemias that develop in patients who were successfully treated for other tumors at an earlier time with regimens that included topoisomerase II inhibitors.

Collectively, the clinical and correlative laboratory data support the notion that MLL is important for early pluripotent and lineage-specific hematopoiesis, and that disruption of MLL at 11q23 can give rise to leukemias of mixed or multiple lineages.

**MLL (also known as ALL1, HRX, and HTRX1) was cloned by four independent groups and found to contain at least 36 exons that encode 3968 amino acids with a predicted molecular mass of 431 kD.** The various names for the single gene at 11q23 are derived from its association with MLL, its initial identification in a case of ALL (11q1), and because of its strong homology to the Drosophila trithorax protein (HRX and HTRX1). This trithorax homology includes a highly conserved domain covering the carboxyl terminus as SET, because it also is found in suvar-3-9, enhancer-of-zeste, and trithorax proteins (Fig. 46.1-2A). Collectively, the structural and functional data accumulated thus far strongly suggest that wild-type MLL is a maintenance factor for gene expression. For example, in

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**FIGURE 46.1-2.** A: The MLL protein and its known fusion partners with various motifs identified. Protein motifs are indicated in black. The shaded gray regions in EIN and AF9 indicate known domains of homology. Fusion breakpoints are indicated by arrows. AFT1 is unique in that its fusion breakpoint occurs six nucleotides upstream of its open reading frame, resulting in a fusion protein without functional domains. Protein motifs are indicated in black. AT, AT hooks; bromo, bromodomains; CREB, CREB response element-binding protein site; DH, DBD homology domain; DPF, aspartic acid-proline-phenylalanine repeat; GLGF, glycine-leucine-phenylalanine domain; HAT, histone acetyltransferase activity; LZ, leucine zipper; MCBD, methyl-CpG binding domain; NLS, nuclear localization signal; PDZ, PDZ domain; PH, pleckstrin homology domain; SH3, Src homology domain; TH, trithorax homology (SET domain); ZF, zinc fingers. B: The genomic structures of MLL and MLL with an exon 6–exon 2 partial tandem duplication (PTD) are shown. Exons are indicated by vertical lines and boxes, and introns are indicated by the horizontal line for each structure. Vertical arrow indicates point of unique self-fusion that results from the PTD. The predicted protein structure for MLL with the 6-2 PTD is illustrated below and can be compared with the wild-type protein at the top of the figure (A).
Drosophila, tri/trior (the MLL gene homolog) maintains homeobox gene expression, critical for normal development of the head, thorax, and abdomen. Mammalian Mll genes encode DNA-binding, homeodomain-containing, helix-turn-helix transcription factors that appear critical in both skeletal and blood cell development. The Mll−/− mouse completely lacks Hox expression, has defects in yolk sac hematopoiesis, and is lethal to the embryo, while the Mll+/− mouse has a disruption in Hox gene expression and various consequent defects in skeletal, neural, craniofacial, and hematopoietic development. In vitro, Mll−/− embryonic stem cells fail to undergo hematopoietic differentiation. Structure function studies suggest that the SET domain of MLL is required for proper regulation of Hox gene expression.

Virtually all of the translocations involving MLL at 11q23 in human acute leukemia consistently disrupt the gene within an 8.5-kb region located between exons 5 and 11, joining the amino-terminal half of MLL to the partner gene. The large MLL fusion gene on the derivative 11 chromosome includes the AT hook minor groove DNA binding domain, an MLL (MLL or part of the partner gene) DNA-binding domain, an amino terminal transcriptional repression domain, and a long carboxy terminal domain. Missing are the two protein-binding zinc finger domains in the mid region and the tri/trior homolog located in the SET domain at the carboxy terminus of the protein (see Fig. 46.1-2A). This derivative chromosome 11 (der 11) thus contains the MLL promoter and the amino terminus of MLL fused to the carboxy terminus encoded by the gene at the breakpoint of the partner chromosome and is always the one that is transcribed by the leukemic cell.

In contrast to many of the other common translocations discussed in this chapter, we have thus far learned little about the mechanisms of MLL-associated leukemogenesis from the study of its many fusion partners (see Table 46.1-1 and Fig. 46.1-2A). There is limited similarity in protein structure between the partner genes currently known to fuse with MLL in acute myeloid, lymphoid, or mixed lineage leukemia. To date, 18 MLL fusion partner genes have been cloned and sequenced (see Fig. 46.1-2A), and there is no one structure-function that can unify their role in the malignant transformation of hematopoietic cells. Most of the cloned partners are novel genes and inference about their functions comes from the study of their homologies or in vitro systems. Several partners, such as AF4, ENL, AF9, CBF, and P300 have evidence for transcriptional activation or coactivator domains, suggesting that replacement of the MLL zinc finger and SET domains by these partners could result in uncontrolled expression of MLL target genes, possibly within some lineage-specific, transcriptional context (e.g., MLL-4F4 in lymphoblasts).

However, this alone cannot be the only pathway to malignant transformation, as other partner genes (e.g., AF7q) lack homology to any known protein sequence and contribute a minimal portion of its carboxy terminus to the MLL fusion protein (see Fig. 46.1-2A), suggesting this fusion may only contribute through haploinsufficiency or possibly via a dominant-negative effect.

The multitude of partners that fuse with MLL in acute leukemia led us to hypothesize that the MLL gene might be rearranged without structural cytogenetic evidence of translocations, inversions, or deletions at 11q23. We therefore looked for evidence of MLL rearrangements in cases of AML without cytogenetic abnormalities involving 11q23, including cases with normal cytogenetics. Rearrangement of MLL was initially observed in cases of AML with trisomy 11 (+11) as a sole abnormality and in cases of AML with normal cytogenetics. These rearrangements were subsequently found not to result from cryptic fusions with other partner genes, but rather from a partial tandem duplication (PTD) of MLL spanning exons 2 through 6 or exons 2 through 8 (see Fig. 46.1-2B). The putative partially duplicated protein includes duplication of the AT hooks and MCBD, without loss of the carboxy portion of the protein containing the SET domain. Molecular analysis of the chromosome 11 breakpoints of cases of AML with the MLL PTD revealed that most of the MLL rearrangements are the result of a partial tandem duplication (PTD) of MLL spanning exons 2 through 6 or exons 2 through 8 (see Fig. 46.1-2A). Sequence analysis of the genomic fusion in nine cases of MLL PTD indicated that the rearrangement is most likely the result of Alu-Alu-mediated homologous recombination events within the involved introns. This is the first demonstration of homologous recombination between Alu elements as a consistent mechanism for gene rearrangement in somatic tissue.

The PTD of MLL has been found to be present in the majority of AML patients with +11 as a sole cytogenetic abnormality, as well as in some patients with +11 accompanied by additional cytogenetic abnormalities, and is the first consistent gene rearrangement associated with recurrent trisomy in human cancer. In a study of 98 AML patients with normal cytogenetics, 11% of patients had rearrangement of MLL, and in eight of eight cases in which additional material was available, the MLL PTD was documented. In patients with AML and normal cytogenetics, a rearranged MLL gene was associated with a poorer prognosis compared with the remaining AML patients with normal cytogenetics. These adverse prognostic factors were confirmed in a separate study, but with a lower percentage (6%) of the MLL PTD in AML cases with normal cytogenetics. Thus, the MLL PTD is an example of a novel gene fusion detectable in a significant fraction of AML patients without structural cytogenetic abnormalities.

MLL gene rearrangements are seen in 80% of infant AML cases and in approximately 50% of infant AML cases. There have now been several elegant reports of infant twins developing acute leukemia with 11q23 translocations involving MLL in utero. The concordance rate for the development of 11q23-related acute leukemia in monoyzogenic twins with shared circulation approaches 100%, with the disease manifesting quickly (i.e., 5 to 24 months of age). The concordance rate for monoyzogenic twins with shared circulation who develop childhood common ALL, including those with the TEL-CBFA2 fusion, is estimated to be less than or equal to 5%, with the leukemia often developing 3 to 4 years after birth. These twin studies suggest that proliferating pluripotent progenitor cells in the developing bone marrow are uniquely susceptible to malignant transformation by MLL-associated chimeric fusion proteins. Further, the identical MLL gene rearrangements found within each pair of twins suggests the leukemic clone arose in one infant and spread via the placental circulation to the other twin infant.

Approximately 80% of leukemias that develop secondarily in patients treated with DNA-topoisomerase II inhibitors such as the epipodophyllotoxins (e.g., etoposide) and the anthracyclines are associated with a chimeric gene fusion involving MLL. While the MLL fusions in secondary AML occur within the 8.5-kb breakpoint cluster region, they are more often distributed in the telomic region, compared with the more centromeric region in cases of primary AML. Interestingly, the telomic region has scaffold attachment regions and 11q23 translocations on the X chromosome. The DNA-topoisomerase II inhibitors stabilize DNA topoisomerases II, leading to the accumulation of double-strand DNA breaks that are presumably more susceptible to homologous recombination and 11q23 translocations via nonhomologous recombination events. Acute leukemia then develops within 6 to 24 months after diagnosis of the primary malignancy, and typically without antecedent MDS. This is in distinct contrast to the secondary acute leukemias that develop following exposure to alkylating agents, which lack an association with MLL, have a chromosome 7q- or 5q- karyotype, have a latency period of 5 to 10 years, and are more often associated with an antecedent MDS.

The short latency noted with MLL-associated secondary and secondary acute leukemia suggests that the molecular defect itself might be all that is required for malignant transformation, or might predispose the affected hematopoietic stem cells to rapidly undergo additional secondary mutations. For example, if the fusion with an MLL partner gene protected against apoptosis or promoted enhanced cell growth, the stimulation from marrow stromal factors in the developing fetus or in the patient may lead to transformation, or might predispose the affected hematopoietic stem cells to rapidly undergo additional secondary mutations.

The DNA-topoisomerase II inhibitors stabilize the DNA-topoisomerase II complexes, disrupting the DNA with double-strand breaks that are then presumably more susceptible to homologous recombination and 11q23 translocations via nonhomologous recombination events. Acute leukemia then develops within 6 to 24 months after diagnosis of the primary malignancy, and typically without antecedent MDS. This is in distinct contrast to the secondary acute leukemias that develop following exposure to alkylating agents, which lack an association with MLL, have a chromosome 7q- or 5q- karyotype, have a latency period of 5 to 10 years, and are more often associated with an antecedent MDS.

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transcription of target genes responsible for myeloid differentiation. However, unlike PML, PLZF does not disassociate from the complex exposure to ATRA, thus maintaining a repressed chromatin configuration and consequent inhibition of transcription in the presence of this treatment. 66

GENE FUSIONS IN B-LINEAGE ACUTE LYMPHOBLASTIC LEUKEMIA INVOLVING THE E2A Gene

The E2A gene encodes a basic HLH (bHLH) transcription factor that was originally discovered to regulate Ig kappa gene expression, 67 but was subsequently found to have three differentially spliced products involved in multiple regulatory aspects of B-cell development. 68 The amino terminus of the E2A-encoded protein contains two transcriptional activation domains, 69 and the carboxyl terminus contains the bHLH domain. The latter is responsible for both DNA binding and homodimerization or heterodimerization with other bHLH proteins. The various protein partners normally dimerizing with the E2A gene products determine its DNA-binding specificity and consequently gene activation during development. 69 The E2A homodimer is therefore critically important during normal B-cell development. 69 It is the carboxyl end of E2A that is disrupted by distinct partner genes in two important gene fusions associated with B-lineage ALL (see Table 46.1-1). Both of the fusion proteins invariably contain the two transcriptional activation domains at the amino terminus of E2A. 69

The t(1;19)(q23;p13) occurs in childhood pre-B-cell ALL and fuses the amino terminus of E2A, including the two transactivation domains, to the homeodomain of PBX1, a member of the TALE (three-amino acid extension) family of homeodomain proteins. 70 PBX1 is normally not expressed during B-cell development. The inclusion of the PBX1 homeodomain in the fusion protein is likely critical to leukemogenesis, as it allows complex formation with HOX proteins, substituting for the severe bHLH DNA-binding domain interaction motifs of E2A. Thus, although PBX1 by itself, has no transactivating ability, its fusion with the strong E2A transcriptional activation domains for this property. 71 The importance for activation of genes normally controlled by PBX1-HOX complexes, but with inappropriate expression in the pre-B cell. Indeed, the first of such genes (WNT-16, E8-) have been identified and will likely provide additional insights into the mechanism by which this gene fusion induces malignant transformation of human pre-B cells. 72

E2A also fuses with the hepatic leukemia factor (HLF) gene in the t(17;19)(q22;pl3) in a small subset of ALL patients with the pro-B-cell (CD45R+) phenotype and only partial rearrangement of a functional heavy chain gene. 73,74 HLF is a basic region/leucine zipper (bZIP) transcription factor whose protein product has structural similarity to the proapoptotic gene product of Caenorhabditis elegans, CES-2 (for cell-death specification-2). 75 In vitro studies demonstrate that E2A-HLF fusion protein induces strong antiapoptotic gene expression in pro-B cells, 76 and that amino terminus-containing transactivation domains of E2A are critical for this function, while the DNA-binding and protein dimerization motifs of HLF are not. 76,77 It thus appears that E2A-HLF contributes to leukemogenesis by interfering with an evolutionarily conserved lineage-specific pathway in pro-B cells, leading to prolonged survival and subsequent malignant transformation of genetically altered cells normally programmed for cell death. 76

PHILADELPHIA-POSITIVE CHRONIC MYELOID LEUKEMIA AND ACUTE LYMPHOBLASTIC LEUKEMIA RESULT FROM A FUSION OF BCR WITH THE TYROSINE KINASE ABL

The Philadelphia chromosome is produced by a t(9;22)(q34;q11) that results in a fusion of the phosphoprotein BCR with the truncated ABL tyrosine kinase protooncogene on chromosome 22. 78,79,80 The t(9;22) and subsequently the fusion oncogene were first noted in patients with CML, and then in 30% to 40% of adults and 3% to 5% of children with ALL, 81,82 in CML and in ALL, the ABL gene consistently fuses within its first intron to BCR, thus always contributing its complete tyrosine kinase domain. However, in CML, BCR fuses to ABL within a 5.8-kb region known as the major breakpoint cluster region that spans exons 12 through 16 to produce a chimeric oncoprotein product known as p210bc-abl, while in ALL and a minority of patients with CML, ABL fuses with BCR at various sites within its first intron known as the minor breakpoint region to produce a chimeric oncoprotein product known as p185bc-abl or p190bc-abl. A larger BCR-ABL fusion protein (p230bc-abl) has been found in a subgroup of CML patients with a more indolent clinical course (reviewed in reference 83).

The ability of the BCR-ABL fusion protein to transform cells has been studied in a host of elegant in vitro and in vivo systems by numerous investigators and has provided insight into what regions of the fusion protein are required for transformation of cell lines and which signal transduction pathways are likely involved in mediating this transformed phenotype. 84 A comprehensive review of this work has been carefully undertaken. 85 The first 63 amino acids of BCR are recognized to be the transactivation fusion protein, which is necessary for tyrosine kinase activation and activation of the F-actin binding domain within ABL. Tyrosine 177 in the ABL portion of the fusion protein that is required for transformation is the site of tyrosine kinase activity that is restricted to the cytoplasm. This activation results in phosphorylation of a multitude of cellular and nuclear signaling molecules (some of which are shown) whose pathways ultimately affect cell growth, differentiation, and cell survival. PI3-K, phosphatidylinositol-3 kinase; TK, tyrosine kinase.

FIGURE 46.1-3. Promiscuous cell signaling by the BCR-ABL oncprotein. The t(9;22)(q34;q11) results in the fusion of the phosphoprotein BCR with the truncated ABL tyrosine kinase protooncogene. The first 63 amino acids of BCR are responsible for the fusion protein tetramerization and consequent constitutive and elevated tyrosine kinase activity that is restricted to the cytoplasm. This activation results in phosphorylation of a multitude of cellular and nuclear signaling molecules (some of which are shown) whose pathways ultimately affect cell growth, differentiation, and cell survival. PI3-K, phosphatidylinositol-3 kinase; TK, tyrosine kinase.

GENE FUSIONS INVOLVING THE NUCLEOPORIN FAMILY OF PROTEINS

Nucleoporins (NUP) make up the nuclear pore complex (NPC), which promotes the selective transportation of both RNA and protein between the nucleus and the cytoplasm in a bidirectional fashion. 86 In the past several years, a series of gene fusions involving two NUPs have been described in de novo AML, treatment-related AML, and in T-cell ALL. The first such fusion to be cloned was DEK-NUP214, found in children and young adults with t(8;16)(p11;q21) AML (see Table 46.1-1). DEK-NUP214, also called NUP214, is an NPC protein that contains multiple NUP-specific Phc-Gly (FG) peptide sequence motifs that mediate protein-protein interaction thought to be required for nuclear-cytoplasmic transport, cell cycle control, and cell survival. 87,88 NUP214 fuses with the amino terminus of DEK, a putative DNA-binding transcription factor. NUP214 has also been shown, in a single case of inv(9)(q3434) AML, to fuse with SET, a nuclear protein that is thought to regulate G1/S
transition by modulating the activity of cyclin E–cyclin-dependent kinase-2 activity via p21 Cip1.\(^{2,12}\) SET-NUP214, like DEK-NUP214, is located exclusively in the nucleus, leaves the FG repeat-rich motif intact, and therefore presumably interacts with the same cellular proteins likely to be important in leukemogenesis.\(^{12}\)

The other important NPC gene involved in leukemogenesis is NUP98, located at chromosome 11p15, which, like NUP214, lends it amino terminus FG repeat domains to fuse in frame to a variety of partners in acute leukemia. NUP98 was first identified as part of the t(7;11)(p15;p15), associated primarily with AML.\(^{12}\) In this instance, NUP98 fuses with the carboxyl terminus of HOXA5, located at chromosome 7p15, a homeobox gene that regulates hematopoietic differentiation. Evidence suggests that this fusion transcript requires the HOXA5 domains for DNA binding and interaction with PBX proteins, while the FG repeats of NUP98 act as transactivators of gene transcription and recruit CAMP response element (CREB)–binding protein and p300 as requisite transcriptional coactivators. Thus, the properties of the NUP98-HOXA5 fusion protein collectively result in a deregulation of HOX-responsive genes with consequent induction of AML.\(^{12}\) The other fusion partners of NUP98 have not yet shed additional light on the mechanism of FG-rich NPC protein–mediated leukemogenesis, but do provide supporting evidence that NUP98 is a recurrent target primarily in treatment-related AML/MDS.

**GENE ACTIVATION IN LEUKEMIA**

**GENE ACTIVATION INVOLVING IMMUNOLOGOBULIN GENES IN B-CELL LEUKEMIA AND LYMPHOMA**

In the t(8;14)(q24;q32), the prototypic BHLH/bZIP transcription factor MYC is juxtaposed to a region of strong Ig heavy chain enhancer elements. Two variants have also been described in which regulatory portions of the Igk gene on chromosome 2 or the Ig lambda \(\lambda\) gene on chromosome 22 are juxtaposed to the MYC locus of chromosome 8 (see Table 46.1-1). In each instance, the B cell experiences a deregulation of MYC gene expression because of its inappropriate activation and control by Ig regulatory elements whose expression is B-cell specific. This resultant malignant B-cell transformation takes the form of either Burkitt's lymphoma or AML. The earliest of these studies were the first to demonstrate that rearrangement of specific genes that resulted from chromosomal translocations were actually at the heart of malignant transformation.\(^{12}\)\(^{22}\)

MYC is capable of activating gene transcription by forming a heterodimer with MAX, which normally homodimerizes with itself or heterodimerizes with MAD or Mxi-1 to regulate transcription. Therefore, the overexpression of MYC in B lymphocytes, carrying the t(8;14)(q24;q32) or one of its variants, functions to disrupt the normal equilibrium that MAX shares with its partners, ultimately leading to the inappropriate overexpression of a multitude of downstream genes activated by the MYC-MAX heterodimer. How the activation of these downstream events in turn induces the malignant B-cell transformation is still incompletely understood and an area of intense study (reviewed in references 126 and 127).

**GENE ACTIVATION INVOLVING T-CELL RECEPTOR GENE IN T-CELL LEUKEMIA AND LYMPHOMA**

A comparable group of transcription factors, normally active during early hematopoiesis, but not during more committed T-cell development, are rearranged via chromosome translocation to lie near enhancers within the T-cell receptor TCRD (chromosome 7q34) and TCRA (chromosome 14q11) loci. As a consequence, these regulatory genes become inappropriately expressed, and their protein products contribute to T-cell leukemogenesis. They include the bHLH TAL1/TCF and TAL2/SCL, as well as MYC.\(^{123}\)\(^{124}\)\(^{125}\)\(^{126}\) Each of these specific translocations are listed in Table 46.1-1.

Rearrangements involving TAL account for up to 25% of childhood cases of T-cell ALL and T-cell lymphoma, but are seen infrequently in adults. TAL1 is normally coexpressed with another transcription factor called LM02, and both are part of a larger transcriptional complex that includes the zinc finger transcription factors GATA1 and E2A. The complex is also important for normal hematopoiesis.\(^{123}\) LM02 and LM01 are both rearranged near the regulatory elements of TCR loci in T-cell ALL (see Table 46.1-1).\(^{126}\)\(^{127}\)\(^{128}\)\(^{129}\) The mouse Hox11 gene is a homeobox transcription factor that is likely critical for lymphoid development and survival, in that it prevents apoptosis of splenocytes in the mouse.\(^{130}\) Further, Hox11 interacts with a protein serine-threonine phosphatase, PPP1C, allowing bypass of the G2 checkpoint following injury and progression to the M phase.\(^{131}\) Thus, its juxtaposition within the regulatory regions of the TCRb and TCRa/d loci results in its ectopic expression in T cells, which likely contributes to T-cell ALL via its inhibition of normal cell death and disruption of normal cell cycling, two processes that facilitate tumor progression.

The t(14;19)(q11;q32) is a rare form of mature T-cell leukemia characterized by chromosomal inversions and translocations involving chromosome band 14q11, containing the TCRa/d gene. The inv(14)(q11q32) and the t(14;14)(q11q32) each juxtapose the T-cell leukemia-1 (TCL1) gene at 14q32.1 to TCRa/d, and the rarely seen t(7;14) (q35;q32.1) juxtaposes TCL1 to the TCRb gene.\(^{132}\)\(^{133}\) The t(IX;14) (q28;q11) rearranges another gene, MTCP1, within the TCRa/d locus as well in T-PLL. While the function of TCL1 and MTCP1 remain unknown, they share 40% amino acid identity, and with the elucidation of the three-dimensional structures of MTCP1 showing a compact eight-stranded b-barrel structure, it appears that these two gene products are the first members of a b-barrel family of proteins.\(^{23}\)

**TUMOR SUPPRESSOR GENES IN LEUKEMIA**

**INACTIVATION OF TUMOR SUPPRESSOR BY GENE MUTATION**

Inactivation of tumor suppressor genes that result in functional inactivation likely contribute to the process of malignant transformation by disrupting the signals that normally inhibit cell growth (see Chapter 4). This process normally requires disruption of both copies of relevant tumor suppressor genes, which can occur by such genetic alterations as point mutation, frame-shift mutation, and deletion, or by epigenetic alterations such as hypermethylation.\(^{134}\)\(^{135}\)\(^{136}\) Approximately 10% to 20% of patients with B-cell chronic lymphocytic leukemias have mutations in p53, a tumor suppressor gene, with an increase in frequency as the disease progresses and a correlation with poor clinical outcome.\(^{133}\) p53 can also be inactivated by MDM2, itself an oncoprotein that is up-regulated by p53 and then serves to bind and inactivate it in a negative feedback loop without gene mutation. An increased expression of MDM2 in chronic lymphocytic leukemia has been correlated with progressive disease.\(^{144}\)

**INACTIVATION OF TUMOR SUPPRESSOR BY GENE DELETION**

The frequent deletion of the human chromosome 9p21 region in leukemias and other cancers led to the search and ultimate discovery of two tumor suppressor genes at this locus, p16 and p15. p16 blocks cell-cycle progression by inhibiting cyclin-dependent kinase, as does p15, whose expression can be induced by transforming growth factor-b.\(^{142}\)\(^{143}\)\(^{144}\) A review of the literature on the frequency of p15 and p16 deletions (p15del and p16del, respectively) in leukemia showed they were frequently deleted in T-lineage ALL, ranging between 47% and 64%, as well as in B-lineage ALL, with a frequency between 20% and 27%. Likewise, in CML lymphoid blast crisis, the frequency of p15del was noted to be 27%, while p16del was 35%. There was little difference in frequency between children and adults with ALL, but p15del and p16del were absent from infants with ALL. The frequency of p15del and p16del was noted to be low in chronic T- and B-cell leukemias and is uncommon in AML, MDS, or CML, (i.e., less than or equal to 2%).\(^{20}\)

ATM is a kinase and putative tumor suppressor gene thought to have a role in cell-cycle checkpoint control. Indeed, patients with the genetic disease ataxia-telangiectasia have a loss of ATM, an increased frequency of translocations and inversions involving TCL1, and a clonal excess of mature T cells. This develops years before a significant fraction of these patients progress to T-PLL.\(^{142}\) This finding is consistent with a model by which the deregulation of TCL1 could serve as a tumor initiator, and loss of tumor suppressor genes might function to further promote progression of T-PLL. In strong support of this model and in support of ATM as a tumor suppressor gene, a large fraction of sporadic T-PLL cases, many with rearrangements of TCL1, have been shown to contain inactivating deletions and missense mutations of ATM.\(^{145}\)

**INACTIVATION OF TUMOR SUPPRESSOR BY HYPERMETHYLATION**

Methylation of CpG islands located in the 5' regulatory region of genes can lead to the repression of gene transcription and illustrates an epigenetic mechanism for inactivation of tumor suppressor genes.\(^{142}\) Multiple known tumor suppressor genes have been shown to be inactivated via hypermethylation in leukemia, including p15 and p16. While p16 is often inactivated by hypermethylation in epithelial tumors, it is p15 that is frequently inactivated by hypermethylation in hematologic malignancies, most notably in AML and MDS, but also in ALL. P16 is not inactivated in these cases by either deletion, methylation, or point mutation.\(^{142}\)\(^{143}\)\(^{144}\) In AML, and possibly in MDS, the density of p15 methylation (i.e., the percent of CpG dinucleotides that are methylated on each allele) appears to correlate...
best with the degree of gene silencing and may increase as the disease progresses. 157 Other candidate tumor suppressor genes, such as p73 in ALL, 36 have also been shown to be inactivated by hypermethylation.

While most investigations of aberrant CpG island methylation in human cancer have primarily taken a candidate gene approach, we performed a global analysis of the methylation status of 1184 unsolicited CpG islands in each of 98 primary human tumors including AML using a technique termed restriction landmark genomic scanning (RLGS). The RLGS analysis showed that an average of 65% CpG islands were aberrantly methylated in these tumors (range, 0% to 45%), and it allowed the identification of patterns of CpG island methylation that were shared within each tumor type, together with a pattern that was specific for acute leukemia. Which tumor suppressor genes are systematically silenced by this process has not yet been determined. However, these data suggest that the methylation of particular subsets of CpG islands has specific consequences for leukemogenesis and is likely an important event in disease progression. 160 One of the exciting avenues being pursued by several laboratories is the reversal of methylation status with pharmacologic agents such as 5-azacytidine, which often results in reexpression of the target gene.

MOLeCULAR MoNItoRING OF LEUKEMIA

ASSESSMENT OF MINIMAL RESIDUAL DISEASE

Molecular analysis can not only play a role in the diagnosis and treatment of leukemia, but may also prove to be useful for monitoring a patient's response to therapy. Both the identification of specific localization of small fragments of DNA and RNA by polymerase chain reaction (PCR) and reverse transcription PCR, respectively, and the growing discovery of the unique gene fusions and Ig and TCR gene rearrangements in leukemia, form the basis for our ability to detect the presence of these genetic alterations while a patient is in complete morphologic and clinical remission. There have been at least two important observations made with the advancement of this technology and the exploitation of literature on the subject of minimal residual disease (MRD) in leukemia. First, in some instances (e.g., MLL-PTD, BCR-ABL), the fusion transcripts can be detected in bone marrow, blood samples, or both from normal individuals. 154-157 The reasons for this are not entirely clear, but in some cases the fusions in normal individuals are clearly distinct from the malignant gene fusions and likely occur through entirely different mechanisms. 58 158 159

Second, the persistence of PCR-detectable chimeric or rearranged genes is not at all a guarantee of persistent functional disease or eventual relapse in either CML 160 or some types of AML (e.g., CBFA2-CBFA2T3). 161 The reasons for this are also not known, but likely involve the presence of the fusion transcript in a normal population of progenitors. It is possible that the persistence of the rearrangement or the absence of additional genetic alterations that were required for tumor initiation, progression, or both. 160 There are some striking examples of how the detection of MRD by PCR can predict relapse in AML 160 162 and APL 163 but most of these studies have yet to be confirmed in large prospective trials with standardized criteria for quantitative methodologies and uniform evaluation intervals. The ability to accurately quantify these genes and gene products using more fully automated standardized methods 162-164 might ultimately identify levels of MRD above which relapse is probable and below which relapse is unlikely. This may also increase the ability to detect MRD in early stages of disease and the sensitivity of the test in many cases, a multitude of genetic alterations are required for leukemogenesis, the simultaneous detection of several such alterations may prove to be more predictive of outcome following the achievement of a complete clinical remission. The incorporation of genetic profiling with cDNA microarray technology is likely to have a significant effect on unraveling the molecular complexity of leukemia for the purposes of diagnosis, classification, treatment, and monitoring clinical outcome.

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INTRODUCTION

Leukemias are clonal, neoplastic proliferations of immature cells of the hematopoietic system, which are characterized by aberrant or arrested differentiation. Leukemia cells accumulate in the bone marrow cavity, ultimately replacing most of the normal hematopoietic cells, thus resulting in the signs and symptoms of the disease. These include most prominently, bone marrow failure and its consequences of anemia, hemorrhage, and infection. Leukemia cells circulate into the blood and other tissues throughout the body, with patterns characteristic of the particular type of leukemia. The acute leukemias, which can be broadly grouped as either lymphoblastic or myelogenous, can be identified phenotypically and genetically and are characterized by a rapid clinical course usually necessitating immediate treatment. Acute leukemias are derived from, and biologically resemble, primitive hematopoietic progenitor cells; in contrast, chronic leukemias have the phenotype and biologic character of more mature cells. Chronic myeloid leukemia (CML), however, over time may transform to an acute, blastic phase and thereafter more closely resembles an acute leukemia in its biology, clinical course, and need for therapy.

The acute lymphoblastic leukemias (ALLs) are distinguished generally from the lymphomas because the latter resemble more mature lymphoid cells and typically inhabit the lymph nodes, spleen, or other extramedullary sites before spreading to involve the blood or bone marrow. Certain lymphomas, such as lymphoblastic lymphomas and Burkitt's lymphomas, retain features of both the leukemias and lymphomas, but are derived from immature cells and require therapy similar to that used for ALL. Other lymphomas, and sometimes multiple myelomas, however, may spread widely into the blood and bone marrow, and in such a phase, can be described as leukemic, but are not true leukemias.

Leukemia (meaning white blood) was originally described in 1845 by Virchow. Although acute leukemias are relatively rare cancers, these leukemias are the most carefully studied and best characterized neoplasms. Numerous subtypes have been defined based on morphology, genetics, immunophenotype, and biologic behavior. Oncogenes responsible for leukemogenesis are beginning to be identified, and there is an enlarging body of knowledge regarding the factors regulating leukemia cell growth and function. Multiple drugs capable of killing leukemia cells are now available. Therapeutic strategies that have been developed often result in clinical remissions of adult leukemias and, in a smaller fraction of patients, result in cures. Despite these advances, acute leukemia remains, for most patients, a fulminating and incurable disease, requiring immediate diagnosis and treatment. The course of patients with acute leukemia is often complicated by the severity of the treatments themselves (Fig. 46.2-1).

FIGURE 46.2-1. Overall survival for up to 25 years of follow-up in adults treated on protocols at Memorial Hospital, New York City. Patients older than 60 years of age have a substantially worse prognosis for both acute lymphoblastic leukemias (ALL) and acute myelogenous leukemias (AML). Patients treated on more recent protocols have a similar outcome to those on earlier protocols. (Data accrued by B. D. Clarkson, C. Little, D. Tyson, L. Megharian, and D. A. Scheinberg.)

EPIDEMIOLOGY AND ETIOLOGY
INCIDENCE

The acute leukemias are rare diseases, but have a disproportionately large effect on cancer survival statistics among children and younger adults. Although the acute leukemias account for less than 3% of all cancers, these diseases are the leading cause of death due to cancer in the United States in persons younger than 35 years of age. The incidence rate of acute myelogenous leukemias (AMLs) in the United States is approximately 2.5 per 100,000 persons; for ALL, the rate is approximately 1.3 per 100,000 persons. AML has a slight male predominance (1.5:1.0) and accounts for 25% of both acute and chronic leukemias. AML affects approximately 9000 people a year in the United States. ALL affects approximately 4000 people, with a similar predominance of male subjects. The incidences of acute leukemias in the United States have not changed substantially since the 1980s, although there is a slight trend upward among those diagnosed with ALL and a slight decrease in the number of diagnoses of AML in this time period. Incidence rates for acute leukemia are similar worldwide. In ALL, the incidence rates in African Americans are approximately one-half that seen in whites; in AML, rates are similar between these two groups. Age-specific incidences differ dramatically between ALL, which has a median age at diagnosis of 10 years, and AML, which has a median age of 65 years. AML is rare below the age of 40, but the incidence increases progressively with age from approximately 1 per 100,000 at age 40 to more than 15 per 100,000 at age 75 or older. In contrast, ALL has its peak incidence at less than 10 years and has a second smaller increase in persons older than 70.

SECONDARY LEUKEMIAS

For most patients with acute leukemia, the cause of the disease is unknown. Because leukemias are the result of a genetic alteration in a clonogenic cell, which can often be identified by a chromosomal translocation, deletion, or mutation, known and suspected carcinogens have been explored as causative agents in acute leukemia. A clear cause of leukemia can be found in the minority of patients with a history of prior chemotherapy or radiation therapy. Such secondary leukemias, more than 90% of which are myeloblasts, are notoriously difficult to treat. The chromosomal abnormalities often observed in these secondary leukemias are associated with a poor prognosis, even when observed in patients without a history of prior therapy or toxic exposure.

Secondary myeloid leukemias first became apparent in the early survivors of Hodgkin's disease. Studies initially linked the use of alkylating agents such as nitrogen mustards to the increased risk. Among a large cohort of patients treated with chemotherapy and radiotherapy for Hodgkin's disease, 163 cases of secondary leukemia were found. There were dose-related increases in secondary leukemia. More recent studies have not linked radiotherapy, when used alone, to an increased risk. Methylchlorethamine (nitrogen mustard), procarbazine, cyclophosphamide, lomustine, teniposide, and chlorambucil were all implicated in the increased risk. The risk for secondary AML was greatest between 2 and 9 years after therapy, with 85% of cases occurring before the tenth year.

Curative therapy for childhood ALL has a risk of inducing secondary AML as well. The increased risk of AML occurred within 6 years and was originally associated with a T-cell phenotype of the original ALL and use of an epipodophyllotoxin (etoposide or teniposide) or alkylating agent. The risk from epipodophyllotoxins was proportional to the dose intensity of the drug, rather than the cumulative dose, with the highest risks associated with weekly or twice weekly administration. In contrast, secondary AML was not increased in pediatric ALL protocols in which epipodophyllotoxins were not used.

Several additional studies in both adults and children have confirmed the association between treatment with epipodophyllotoxins and secondary AML, particularly in patients older than 60 years. In particular, monocytic leukemias with abnormalities of chromosome 11q23. Promyelocytic leukemias with t(15;17) have also been associated with etoposide and with other chemotherapeutic agents, such as doxorubicin, that target topoisomerase II.

Dose-dependent risks for secondary AML have also been observed in adults treated with alkylating agents, including platinum-based drugs and radiotherapy for breast cancer and ovarian cancer, and for a variety of neoplasms treated with an autologous bone marrow transplant (BMT) after high-dose radiation and alkylating agent therapy. Among the alkylating agents, cyclophosphamide appears to hold less risk; a study of the incidence of secondary leukemia in patients with breast cancer treated with moderate doses of cyclophosphamide confirms this lower level of risk.

OCCUPATIONAL AND ENVIRONMENTAL EXPOSURES

The clear relationship between the atomic bomb radiation or use of carcinogenic therapies and the development of secondary leukemias has led to the exploration of the possible leukemogenic role of other potential carcinogens in the environment, such as low-dose radiation, chemicals, cigarette smoke, and electromagnetic radiation.

Although electromagnetic fields have received considerable attention as a possible carcinogen, the actual risk of leukemia from exposure to commercial and residential power fields remains controversial. There are a large number of conflicting reports, but there is a lack of clear dose-response relationships, and a causal relationship between leukemia and electromagnetic fields, either as a consequence of occupational exposure or residental power use, has little current support.

Both ALL and AML risks increased as a result of exposure to the atomic bomb. Risks associated with occupational exposure to low-dose radiation are controversial. Early suspicions that paternal exposure at power plants resulted in an increased risk for subsequent children of the exposed workers have been disputed.

Cigarette smoke contains numerous carcinogens and has been linked in a dose-dependent manner to leukemia, particularly in patients older than 60 years and to specific chromosomal alterations known to be associated with chemical mutagens. As much as 20% of AML may be attributable to smoking.

Occupational exposure to benzene has been established as a cause of AML, but low-level exposure in the workplace (e.g., less than 10 parts-per-million) has not been clearly established as a risk. Other occupational exposures to solvents, such as to toluene or butadiene in the shoe and rubber industries, or hair dyes, have not been shown conclusively to increase leukemia risk.

OTHER RISK FACTORS

Viruses, and in particular, RNA retroviruses, have been found to cause many neoplasms in experimental animals, including leukemia of mice and cats; a human retrovirus, human T-cell lymphotropic virus-1, has been identified as the cause of a mature T-cell lymphoma and leukemia in humans. A clear retroviral cause for acute leukemia in humans has not been identified. Epstein-Barr virus, a DNA virus, has been associated with oncogenesis in acute B-cell leukemias. Burkitt's lymphomas, especially those of endemic origin, and human immunodeficiency virus-associated lymphomas. Epstein-Barr virus may function by increasing lymphoid cell transformation.
proliferation in patients; this provides a setting in which a second oncogenic event, possibly myc oncogene activation, can result in the clonal, neoplastic proliferation. 34 It has not been demonstrated, however, that simple infection with either an RNA- or DNA-based virus alone is a cause of acute leukemia.

Although leukemias are acquired disorders, there may be significant genetic and immunologic predispositions that allow their occurrence. Several genetic syndromes are associated with increased risk of leukemias, including Down syndrome, Fanconi’s anemia, Bloom’s syndrome, and ataxia-telangiectasia. 34-36 Down syndrome is associated with 20-fold increased risk of leukemia; this is typically a megakaryoblastic leukemia in children younger than 3 years of age and a pre-B ALL in children who are older. 34 These true leukemias must be differentiated from a transient abnormal myeloproliferative disorder. 34 Patients with transient abnormal myeloproliferative disorder are neonates with hepatosplenomegaly, modest elevations in blasts, and pancytopenia. Although transient abnormal myeloproliferative disorder is a clonal disorder, in two-thirds of cases the disease has a benign course.

An immunologic predisposition for acute leukemia has not been clearly delineated. However, analyses of HLA types with specific cytogenetically defined subgroups of AML have pointed to associations between certain HLA A, B, C, and DR types and common chromosomal translocations or deletions. 34 These correlations may become increasingly important as an understanding of the immune response to these breakpoints becomes clear. 34

**BIOLOGY OF ACUTE LEUKEMIAS**

More is known about the pathobiology of the acute leukemia cell than about any other neoplasm. This is the consequence of a confluence of discoveries regarding hematopoietic growth factors, hematopoietic stem cells and progenitor cells, oncogenes, and transcription factors. These discoveries were made possible by the availability of acute leukemia cell lines capable of immortal growth in culture, reliable assays for hematopoietic cell growth, and sensitive tests for specific gene expression and protein expression. The important concepts about acute leukemia cell growth and function are likely to be useful paradigms that will aid in understanding all cancers.

Cell lines derived from and biologically resembling AML and ALL have been available since the 1980s and have allowed careful study of the growth of leukemia cells under controlled conditions and of the effects of antileukemic agents. 37 Mouse models mimicking human leukemias can be prepared by oncogene transfections. 38 In addition, both cell lines and fresh acute leukemias have been propagated in immunocompromised nude or severe combined immunodeficiency (SCID) mice, thus also allowing controlled studies of new therapies under conditions in vivo. 39 Fresh normal and neoplastic hematopoietic cells can also be grown in intermediate-term cultures or colony-forming assays (over 2 to 8 weeks), in which maturation into specific lineages can be observed and modulated by use of exogenous growth factors, drugs, and differentiating agents. 39-41 This has allowed the elucidation of the sequence and importance of the various growth factors and adhesion molecules during normal and leukemia cell growth and cell death (apoptosis). 39 The identification and isolation of primitive normal stem cells, and the partial reconstitution of normal hematopoiesis ex vivo. 42-44 The growth of myeloid leukemia cells in vitro appears to be dependent on interleukin (IL)-3, granulocyte-macrophage colony-stimulating factor (GM-CSF), granulocyte colony-stimulating factor (G-CSF), or macrophage colony-stimulating factor (M-CSF) and may be regulated by IL-6 and tumor necrosis factor as well. 45,46 Autocrine production of colony-stimulating factors or mutations in their receptors by cells that also express the appropriate receptors on their cell surfaces may allow unregulated proliferation in the absence of exogenous factors. 45,46 Comparable assays in vivo using immunosuppressed mice that allow spleen colony formation or complete bone marrow reconstitution have demonstrated that viable hematopoiesis for an entire animal may require as few as 30 hematopoietic stem cells. 46

Enzyme marker studies using glucose-6-phosphate dehydrogenase have shown that leukemia cells derive from a single clonogenic cell. 47 Depending on the cell of origin, the leukemia clone may involve cells of more than one lineage (e.g., erythroid and myeloid) or only one lineage. Unlike normal hematopoiesis, the clonogenic leukemia cell generally retains only a limited ability to differentiate into different lineages. 48 The cells responsible for leukemia colony growth in vitro represent a more primitive subset of the entire leukemia cell population. 49

There is considerable aberrancy in the differentiation of leukemia cells, as compared with normal cells, when the cell is examined for surface protein phenotype. 49,50 There may also be abnormalities in apoptosis, that leads to persistence of the leukemia clone in vivo or abnormalities in telomerase, which promotes longevity. 51 Apoptotic death may still be induced with appropriate growth factors in vitro, or in the case of promyelocytic leukemia, by clinical use of retinoic acid (see Acute Promyelocytic Leukemia, later in this chapter). It is likely that many leukemogenic translocations or mutations (see Chapter 46.1, and Chapter 45.1) result in dysregulation of the cell cycle. 52

Heterogeneity of the cells that make up the leukemic population is frequently seen. 52-54 Although the leukemia clone may involve multiple lineages, typically leukemia blasts are phenotypically of one lineage; within this lineage, stages of maturation may vary, suggesting incomplete control of differentiation. The phenotypic heterogeneity of the leukemic colony-forming cells also suggests that leukemias may arise at various stages of differentiation. This concept was surmised based on the morphologic and phenotypic characteristics of different leukemias; evidence supporting this concept has been demonstrated in patients with acute promyelocytic leukemia (APL), in which the leukemia clone can be positively identified by use of sensitive polymerase chain reaction (PCR) techniques for the t(15;17). In most cases, the most primitive hematopoietic cells remained normal, whereas more mature progenitors contained the neoplastic translocation. 54

Despite the achievement of a complete clinical remission after therapy of acute leukemia, normal hematopoiesis derived from cells originally involved with the leukemic clone is sometimes present. 55 Apparently normal granulocytes have exhibited persistence of chromosomal markers of the original leukemia. 55 The continued presence of clonal hematopoesis may suggest the existence of a preleukemic clone of cells that has a proliferative advantage to other normal cells. 55 In spite of this, hematopoiesis in patients in remission is usually polyclonal or oligoclonal.

**DIAGNOSIS AND CLASSIFICATION OF ACUTE LEUKEMIAS**

**CLINICAL PRESENTATION**

Although the signs and symptoms are relatively nonspecific, the diagnosis of acute leukemia is usually made easily with the history of the illness, the physical examination, and an examination of the blood smear and bone marrow aspirate smear. Additional laboratory examinations (complete blood counts, coagulation profile, chemistry profile) or diagnostic imaging (chest radiography, abdominal sonography) are important in the management of the disease, but are not usually necessary for diagnosis. Patients with acute leukemia typically present with a 1- to 3-month history of fatigue or malaise, easy bruisability or frank bleeding, dyspnea, minimal to modest weight loss, fever, bone pain, or abdominal pain (Table 46.2-1). Excessive hot loss, fever, minor dental procedure or severe epistaxis may bring the patient to the physician’s attention. In adults with an antecedent myelodysplastic syndrome, symptoms may date back for up to a year or more.

**TABLE 46.2-1. Diagnosis and Evaluation of Acute Leukemia**

The physical examination typically shows pallor, consistent with anemia, and hemorrhage (in the gums, as epistaxis, in the stool, in the skin as petechiae or
MORPHOLOGY AND CYTOCHEMISTRY

The French-American-British (FAB) group has proposed a widely used classification of eight different types of AMLs (M0 to M7) and three types of ALLs (L1 to L3) based on morphology and cytochemistry. Monoclonal antibody-based immunophenotyping is also used in undifferentiated cases in which morphologic and cytochemistry are inconclusive. Because the treatments of ALL and AML may differ significantly, the most important first step in the diagnostic assignment is to distinguish the lymphoid and myeloid lineages to assign therapy. Among the lymphoid neoplasms, the distinction of FAB L3-ALL (Burkitt's type; mature B cell) is a second important step, as treatment strategies and prognosis differ with this subgroup. Among the myeloid leukemias, identification of FAB M3-AML (APL) is necessary because retinoic acid differentiation therapy is instituted instead of, or concurrently with, chemotherapy. Moreover, there is a significant risk of highly morbid coagulopathy associated with APL. Because current therapies for all subtypes of AML except APL, are generally similar, and outcomes are typically poor, the advantages of the FAB classification are limited. In addition, the classification of acute leukemia includes other neoplastic hematopoietic disorders, such as lymphomas, myelodysplastic syndromes, multiple myeloma, aplastic anemia, severe megaloblastic anemia due to folate or B12 deficiency, severe lymphocytosis due to infection, such as with Epstein-Barr virus; severe monocytosis due to tuberculosis; and bone marrow failure with release of early cells, such as in myelophtisis, due to carcinoma. Examination of the bone marrow nearly always excludes the nonhematopoietic conditions because of the presence of increased numbers of blasts. Careful morphologic examination and immunophenotyping of the cells then excludes virtually all the hematopoietic conditions based on lineage and maturation stage; one exception is the myelodysplastic syndromes, which often differ from the acute leukemias only in the percentage of blasts in the marrow. Up to one-third of AMLs in patients older than the age of 60 years have evolved from a prior myelodysplastic syndrome or other hematologic disorder, suggesting that the distinction between refractory anemia with excess blasts or refractory anemia with excess blasts in transformation and true AML after myelodysplasia may be clinically unimportant. These conditions each respond more poorly to chemotherapy than de novo AML, and aggressive leukemia and bone marrow failure leading to death is the typical outcome.

CLASSIFICATION OF ACUTE LEUKEMIA

Modern classifications of acute leukemia must answer three questions to be diagnostically and prognostically useful: (1) What is the lineage? (2) What is the maturation stage? (3) What is the genotype? Although traditional classifications relied primarily on morphology and cytochemistry, these limited characterizations are not always adequate for classifying leukemias into groups that assign the most appropriate therapy or predict outcome. Knowledge of the exact immunophenotype and the genotype, either via cytogenetic analysis or molecular analysis, is critically important before commencing the most appropriate definitive treatment, such as high-dose consolidation chemotherapy, BMT, or prolonged maintenance therapy.

TABLE 46.2-2. Classification of Acute Leukemia

The FAB classification of AML, as modified by the National Cancer Institute, is based on morphologic examination for lineage, confirmation of lineage by cytochemical stains, quantitation of the number of blasts, and estimation of the degree of differentiation of the cells (see Table 46.2-2). Myeloid leukemia blasts are typically large with round or irregular, smoothly grained nuclei, and with moderate cytoplasm often containing granules or Auer rods; the Auer rods are pathognomonic for myeloblasts. In contrast, lymphoid leukemia blasts are not distinguishable from T-lineage leukemia blasts based on morphology alone, except if they are mature B-cell type (Burkitt's type, FAB L3) blasts, which have characteristic voluminous, vacuolated, deeply basophilic cytoplasm. Myeloblasts are graded according to the number of and quality of granules (e.g., a type I blast has no granules; a type II blast has up to 15 delicate granules; a type III blast has numerous azurophilic granules). The blasts associated with chronic myelogenous leukemia in blast crisis cannot be distinguished on morphologic or phagocytic grounds alone.

The most important stains for determining lineage initially include myeloperoxidase, which can be positive (golden brown), even in the absence of visible primary azurophilic granules, and Sudan black B, which stains primary and secondary granule lipids black. Myeloid differentiation is inferred if either of these stains are positive in 3% or more blasts. AS-D chloroacetate esterase is another stain (red or blue) for maturing myeloid granules; a-naphthyl butyrate esterase staining (red/brown) is indicative of monocytic differentiation. Acid phosphatase is generally most useful in T-cell ALL, where it stains as a block or patch.
In the small subset of cases in which lineage cannot be indicated by morphology or cytochemistry, immunophenotyping using specific monoclonal antibodies usually determines lineage to be myeloid. Another subgroup that is difficult to classify due to its pleomorphic morphology and unhelpful cytochemistry is acute megakaryoblastic leukemia (AML-M7). The lineage can sometimes be identified by cytoplasmic blebs; electron microscopy for platelet peroxidase is confirmatory, although this is not a routinely or rapidly available test. Monoclonal antibodies to platelet-specific antigens CD41 and CD61 are usually helpful, but false-positive results are seen often. This disease is often associated with bone marrow fibrosis and pancytopenia that obscures the percentage of blasts in aspirates and necessitates the use of a bone marrow biopsy for morphologic diagnosis.

The FAB classification of ALL into L1 and L2 subtypes is based on an examination of blasts for nuclear cytoplasmic ratio, the number and appearance of nucleoli, the regularity of the nuclear membrane outline, and cell size. In general, L1 has a small size in greater than 50% of cells, a high nuclear cytoplasmic ratio in greater than 75% of cells, up to one small, ill-defined nucleoli in greater than 75% of cells, and a regular nuclear membrane in greater than 75% of cells. L2 generally has the opposite characteristics. L1-type blasts are found more often among children and denote a better prognosis. L2 is more common in adults, but has little prognostic significance in this population. L3-ALL is easily distinguished by its homogeneous large cells and basophilic cytoplasm with prominent vacuolization. L3-ALL cells usually express cell surface immunoglobulin. The ALLs are usually distinguished by the absence of myeloid-specific immunophenotypic markers or cytochemical stains and by the presence of lymphoid immunophenotypic patterns.

Additional diagnostic subgroups not classified by the FAB criteria include mixed lineage (biphrenotypic) leukemias, mast cell leukemias, the histiocytoses, juvenile chronic myelogenous leukemia, and eosinophilic leukemias.

**IMMUNOPHENOTYPING OF ACUTE LEUKEMIAS**

Approximately 160 antigen groups, known as clusters of differentiation (CDs), have been identified on the surface of hematopoietic cells by monoclonal antibodies. These antigens are predominantly cell surface glycoproteins, and rarely carbohydrates or glycolipids. Although no leukemia-specific antigens have been identified, the CD antigen characterization of hematopoietic cells using a panel of antibodies can establish lineage with reasonable certainty and may suggest maturational stages of cells. Expression on a cell population of antigens not usually found together can also provide strong evidence for neoplasia. Currently, immunophenotyping plays an important role in the understanding of hematopoietic biology and in the diagnosis of leukemia. The immunophenotype is used (1) to confirm the diagnosis in cases in which the classification is clear; (2) to make a diagnosis when morphology and cytochemistry are equivocal, as in M0-AML; (3) to identify biphenotypic leukemias; (4) to characterize aberrant antigen expression, which can be used to identify a neoplastic clone, even when found as minimal residual disease, as in clinical remission; and (5) to assist in assigning leukemias into prognostic groups.

The lineage and state of maturation of normal hematopoietic cells may be identified by use of a flow cytometer to determine the cell size, granularity, and the presence or absence of a panel of cell surface or cytoplasmic differentiation antigens (designated by their CD numbers). Such analyses, termed multidimensional or multiparameter flow cytometry, are available at most cancer centers or commercial laboratories. Pathways describing the phenotype of normal B, T, and myeloid cells have been constructed (Fig. 46.2-3). Acute leukemias can also be characterized by a similar panel of markers, and in general, lineage can be assigned by examination of expression of the same antigens as those found in normal cells.

**FIGURE 46.2-3.** Schematic diagram of selected important antigens expressed on normal hematopoietic cells and acute leukemia cells throughout the differentiation and maturation of the normal cells. Acute leukemia cells may express these antigens aberrantly as described in the text. (Adapted from ref. 78.)

Acute lymphoid leukemias of T-cell lineage are characterized by expression of the T-cell markers CD2, CD5, CD7, and sometimes CD1 or dual staining of CD4 and CD8. T-cell ALL or lymphoblastic lymphoma may also express the B-lineage markers CD10 and CD21. Acute lymphoid leukemias of B-cell lineage express CD19, CD10, and, depending on maturational stage, CD20, and surface immunoglobulin. Acute myeloid leukemias express CD13, CD15, CD33, and, more often if monocytic, CD14. Terminal deoxyribonucleotidyl transferase is expressed by most lymphoid blasts and approximately 20% of myeloid blasts. CD34 can be expressed by blasts of all lineages, especially if the cells are primitive. HLA-DR is found on virtually all B-lineage leukemias, most myeloid and monocytic leukemias (except FAB M3), and on a rare T-cell ALL.

The pathways of antigen expression, with regard to maturational stage, however, are often aberrant in leukemias. In some cases, there is also abnormal expression of antigens not expected to be found in the lineage. Although such infidelity of antigen expression may prevent exact assignment of the maturational stage of the leukemia cell, it may distinguish that cell as neoplastic from within a larger population of normal cells. Thus, aberrant antigen expression, which can be an antigen of the wrong lineage, the simultaneous expression of antigens of different stages of maturation, or the lack of an expected antigen, can provide a useful diagnostic marker for the leukemia cells. In addition, such a marker may allow the flow cytometric detection of the leukemia cells at a level of 1 cell in 1000 to 10,000 normal cells, even in patients who have apparently normal bone marrow and blood examination by morphologic criteria. The prognostic significance of this detection is not yet clear, but is likely to predict relapse. Mixed lineage leukemias are being increasingly identified as use of larger numbers of immunophenotypic markers becomes widespread. These leukemias exhibit the phenotype of more than one, and sometimes more than two, lineages. In most cases, this is the result of blasts that coexpress markers of several lineages; in rare cases, blasts of different lineages coexist in the same patient. In the former, more common cases, the blasts may be obviously derived from one lineage, based on morphologic, cytochemical, and immunophenotypic criteria; at the same time, the blasts express apparently aberrant markers from another lineage. Myeloid antigen-positive ALL and lymphoid antigen-positive AML occur frequently. In some cases, assignment of true lineage is more difficult. Scoring systems designed to weigh lineage-specific markers have been developed to assign lineage in these difficult cases (Table 46.2-3).
Although several clinical entities of leukemias with aberrant phenotypes have been described, there is considerable overlap in the immunophenotypes, rendering such proposed subgroupings difficult to interpret. In addition, the aberrant markers found on AML blasts are associated with a variety of karyotypes and FAB subgroups. The prognostic significance of mixed lineage phenotype or the expression of aberrant markers is unclear, but single aberrant antigens appear to hold little prognostic importance.

### CYTOGENETICS AND MOLECULAR GENETICS OF ACUTE LEUKEMIAS

The frequent presence of nonrandom chromosomal translocations, oncogene mutations, and tumor suppressor gene abnormalities in leukemia cells has allowed substantial progress to be made in understanding the pathogenesis of acute leukemias, in diagnosing and developing prognostic models for subtypes of leukemia, and in assessing the effects of therapy or detecting early relapse. The molecular genotypy or karyotype is rapidly becoming the gold standard for diagnosis and prognosis in many subtypes of acute leukemias. A detailed discussion of the molecular biology of hematopoietic cancer is found in Chapter 45.1.

In ALL, the presence of t(9;22), found in up to 30% of adults, t(4;11), –7 or +8, which are more infrequently seen, are poor prognostic signs. Abnormal karyotypes are seen in approximately 80% of patients with AML. In AML, t(15;17), t(8;21), and inv(16) or t(16;16), have a favorable prognosis, whereas +8, –5, del (5q), –7, del (7q), –20, +11, +13, inv (3), and involvement of 11q23, are unfavorable. Distinct pathologic and clinical syndromes, such as APL, are strongly associated with t(15;17), AML-M2 with t(9;21), AML-M5 with inv (16) or del 16p and AML-M7 with t(1;22). Chemotherapeutic agents that interfere with DNA topoisomerase II, such as epipodophyllotoxins or anthracylines, can result in the balanced translocations described previously and often appear 1 to 3 years after chemotherapy. In contrast, alkylating agents more typically yield –5, –7, and complex chromosomal abnormalities, 2 to 9 years later, frequently initiate as myelodysplastic syndromes and have a particularly poor prognosis.

### PRINCIPLES OF THERAPY FOR ACUTE LEUKEMIA

Despite advances, the majority of adult patients with acute leukemia die as a result of the disease (see Fig. 46.2-1). Although most patients initially respond to chemotherapy, relapse is common. The goal of therapy in acute leukemia is the eradication of the leukemic clone with the restoration of normal hematopoiesis. This is usually accomplished by the use of profoundly myelosuppressive chemotherapy, which induces a period of relative bone marrow aplasia with the rapid reduction of leukemia cells. It is during the recovery from aplasia, that a state of clonal competition develops.

Normal stem cells gain a growth advantage and repopulate the bone marrow, establishing the predominance of polyclonal hematopoiesis. Leukemia cells are replaced by normal differentiated progeny, which are capable of providing vital life-sustaining functions. The disease process has been temporarily abated.

The transient nature of the initial clinical response is best understood in the context of the enormous size of the total leukemia burden and the limitations of the effect of modern chemotherapy on this critical mass. Based on data from animal models, it has been estimated that there are approximately 10 leukemia cells in the body at the time of diagnosis. Standard chemotherapy regimens generally result in a 2 to 3 log (99.9% to 99.9%) reduction in the total amount of tumor cells. This places the residual leukemia burden below the level of clinical detection, and based on morphologic criteria, the patient has been placed into a complete remission. Laboratory and clinical evidence, however, would suggest that such a remission is far from complete for the great majority of patients. Although standard morphologic evaluation shows no evidence of residual leukemia, a state of minimal residual disease exists, with estimates for the remaining leukemia burden approaching approximately 10 billion cells. A number of laboratory techniques have been introduced in an effort to increase the resolution of detecting remaining leukemia cells (Table 46.2-4). Although none of the available assays are ideal, current studies of minimal residual disease are attempting to establish the clinical validity of such measures and whether the results from these assays may form the basis for therapeutic decisions in individual patients. The paradigm for this has been provided by the reverse transcriptase-based (RT) PCR assay for the PML/RAR gene rearrangement used in APL (see Acute Promyelocytic Leukemia, later in this chapter). Chemotherapeutic agents that interfere with DNA topoisomerase II, such as epipodophyllotoxins or anthracylines, can result in the balanced translocations described previously and often appear 1 to 3 years after chemotherapy. In contrast, alkylating agents more typically yield –5, –7, and complex chromosomal abnormalities, 2 to 9 years later, frequently initiate as myelodysplastic syndromes and have a particularly poor prognosis.

### TABLE 46.2-3. Assigning Lineage in Mixed Lineage Leukemias

The frequent presence of nonrandom chromosomal translocations, oncogene mutations, and tumor suppressor gene abnormalities in leukemia cells has allowed substantial progress to be made in understanding the pathogenesis of acute leukemias, in diagnosing and developing prognostic models for subtypes of leukemia, and in assessing the effects of therapy or detecting early relapse. The molecular genotypy or karyotype is rapidly becoming the gold standard for diagnosis and prognosis in many subtypes of acute leukemias.

### TABLE 46.2-4. Current Methods Used Frequently for Detection of Minimal Residual Disease

The primary goal of the initial chemotherapy in AML is to achieve a complete response (CR). Despite the limitations of morphologic evaluation, clinical standards have been adopted to define outcomes and establish reference points from which therapies can be compared. CR is defined as less than 5% of blasts in the bone marrow normally regenerated as evidenced by both an acceptable level of cellularity (greater than 20% on bone marrow biopsy) and the restoration of normal hematopoiesis (as reflected by peripheral blood values of at least 1500 neutrophils per μL and 100,000 platelets per μL). Red cell parameters are not usually considered in this definition. The peripheral blood should not contain circulating blasts (in the absence of growth factor use), and there should be no evidence of extramedullary disease. These criteria must be sustained for a period of at least 4 weeks.

CR is the only significant form of clinical response in acute leukemia. The ability to achieve such a response has been directly correlated with survival and is a necessary first step in a curative treatment strategy. Although some research studies have chosen to categorize lesser responses and define partial remission (or PR), the inability to morphologically clear leukemia cells from the bone marrow is a treatment failure with grave implications for the patient.

Current treatment strategies divide therapy into two basic parts: induction and postremission therapy. The purpose of remission induction is to achieve a CR. The goal of postremission therapy is to eradicate minimal residual disease, thus preventing relapse and effecting a cure. Different approaches to postremission therapy have been used and defined by a number of studies. Consolidation therapy is used to describe immediate postremission treatments that are similar to induction therapy. The doses of the drugs are either equivalent or slightly attenuated. Intensification is the application of higher doses of active agents while in CR. Maintenance is defined as therapy given in greatly attenuated doses over extended periods.

Relapse is usually heralded by a change in a previously normal complete blood cell count. Reduction in normal cells or the reappearance of blasts in the peripheral blood occur frequently; isolated extramedullary relapse is infrequent. Examination of the bone marrow confirms the relapse by demonstrating more than 5% blasts. In situations in which there is only a borderline increase in blasts, it may be necessary to repeat the bone marrow examination in 1 to 2 weeks to confirm relapse.
Table 46.2-5

Prognostic importance of cytogenetic abnormalities in AML, making this the single most important predictor of outcome. Changes in the initial antibiotic coverage are based either on the sensitivities of the organisms isolated or persistence of fever. Continued fever, despite 4 to 6 days of antibacterial therapy usually requires empiric antifungal therapy with amphotericin B. Additionally, patients with indwelling central venous catheters or other prosthetic devices may require the early institution of vancomycin. Antimicrobial agents should be continued until the absolute neutrophil count has risen above 500 µL. Patients who have a documented bacterial source of infection should complete at least a 10- to 14-day course of therapy, whereas those patients with evidence of infection secondary to invasive mycoses may require a more protracted course of therapy.

Despite the accepted approach to empiric therapy in patients with leukemia and neutropenic fever, there is considerable controversy regarding infection prophylaxis, use of protected environments, reverse isolation, transfusion of granulocytes, or the use of hematopoietic growth factors to accelerate recovery. Although the duration of neutropenia has consistently been shortened by the use of G-CSF or GM-CSF in a number of studies, the effect on infectious complications and mortality has been variable. Careful attention to oral hygiene with regular use of oral rinsing and cleaning with soft tipped (spoke) devices to prevent gingival trauma may prove useful. Rectal or vaginal manipulations should be avoided.

Immediate access to blood products is critical to sustain the patient; the hemoglobin level should be maintained at 8 g/dL or higher in patients with other medical comorbidities (pulmonary disorders or coronary heart disease). There is a direct relationship between hemorrhage and reductions in the platelet count below 5000 to 10,000 µL. Hence, platelets are not only transfused in response to hemorrhage, but also to prevent hemorrhage. The routine use of platelet transfusions has had a significant effect on the incidence of hemorrhagic death. Patients with uncomplicated thrombocytopenia can be transfused when the platelet count falls below 10,000 µL. Patients who are either febrile or have other complicating medical conditions such as severe mucositis or ongoing coagulopathy, require prophylactic transfusions at higher levels.

Some patients require frequent transfusions of platelets. This may result either from alloimmunization in the patients who have received multiple transfusions or may be secondary to other medical conditions such as persistent fever or disseminated intravascular coagulation. This refractoriness poses a particularly difficult management problem for the clinician. Current strategies to overcome alloimmunization include the prevention of sensitization by the use of single, related donor platelets or HLA-matched platelets as well as the use of leukocyte reduction filters. Platelets from a potential bone marrow donor should be avoided in patients who are eligible for allogeneic BMT. A bleeding diathesis or frank DIC may be present in addition to thrombocytopenia and may result in either hemorrhage or thrombosis. This complication is most frequently associated with APL, but may also be found in other subtypes of acute leukemia either at presentation or after the institution of cytotoxic therapy. The coagulopathy has been attributed to the release of procoagulants from the leukemia cells as they lysis. The contribution of increased fibrinolysis to this hemostatic disorder has come under scrutiny.

The approach to the patient with leukemia-associated coagulopathy remains controversial. Laboratory tests that are useful as indicators of coagulopathy include the platelet count, prothrombin time, activated partial thromboplastin time, fibrinogen, fibrin split products, and d-dimer. Clinical management relies on frequent monitoring of the patient with intervention based on a deteriorating clinical status or worsening trend in a laboratory value such as fibrinogen. The former approach of managing the bleeding diathesis of APL with low-dose heparin (7 to 10 U/kg) has largely been replaced by early treatment with retenoids as well as aggressive blood product support.

Platelets and fresh frozen plasma are transfused multiple times daily to maintain platelet counts above 50,000 µL and fibrinogen levels above 100 mg/dL. The hemostatic abnormalities typically abate after the leukemia burden has been reduced.

Metabolic abnormalities can exist in the leukemia patient at presentation or with the institution of therapy. Patients rarely present with disorders of potassium or calcium, but can develop electrolyte problems during treatment with aminoglycosides, amphotericin, or other agents that affect kidney function. Rapid leukemia cell death releases intracellular metabolites, notably uric acid, potassium, and phosphorus, causing a life-threatening metabolic condition known as the tumor lysis syndrome. Uric acid, a product of purine metabolism, may then deposit in the joints, causing a gouty arthropathy or, more important, in the renal parenchyma or collecting system, resulting in renal failure. Hyperuricemia may be detected. Prevention of these complications is usually accomplished by instituting vigorous hydration (with a brisk urine output [greater than 150 mL/h] and administering allopurinol before beginning cytotoxic therapy. The dose of allopurinol ranges from 300 to 900 mg/d. Alkalization of the urine by adding sodium bicarbonate to the intravenous fluids, administering a carbonic anhydrase inhibitor (such as acetazolamide), or both are recommended in extreme cases, or in patients allergic to allopurinol, to increase the solubility of the uric acid.

Complications, such as cardiac disturbances with hyperkalemia or the precipitation of calcium phosphate resulting in renal failure due to hyperphosphatemia, can be avoided in most cases with early attention to metabolic disturbances. Correction of these abnormalities is best accomplished by aggressive hydration with concomitant diuresis to wash out the toxic by-product of the dying leukemia cells. Additional benefit may be gained by using oral phosphate binders (aluminum hydroxide or calcium acetate) to minimize absorption of additional phosphate from dietary sources. In situations in which hyperkalemia is complicated by renal insufficiency, cation exchange resins (Kayexalate) may be indicated. Extreme circumstances may require renal dialysis to correct multiple abnormalities.

Tumor lysis syndrome most frequently complicates acute lymphoid leukemia (particularly Burkitt's type) and is most problematic in the setting of hyperleukocytosis (peripheral blast counts greater than 100,000/µL). Patients with AML are at a relatively reduced risk of tumor lysis, relative to ALL, but are at an increased risk for complications associated with bone marrow failure: infection or hemorrhage. Most patients seek medical attention for symptoms related to infection or bleeding, and these patients typically require immediate therapeutic intervention. Other patients are not candidates for cytotoxic therapy because of a poor performance status or other active severe medical comorbidities that complicate their care. In such settings, a supportive strategy may be most appropriate. The risks and potential benefits and alternatives should be carefully considered in each case and discussed with the patient and the family.

Several prognostic factors have been identified in AML. The difference in treatment results among various trials using similar chemotherapy may, in part, be explained by the frequency of these negative variables within a study population. Age is inversely associated with the ability to achieve remission. Patients older than the age of 60 years, standard therapy achieves CR in only 30% to 50% of treated individuals. AML that occurs as a consequence of prior cytotoxic therapy, or that has developed from an antecedent hematologic disorder (e.g., myelodysplastic syndrome) has a particularly poor outcome, with a lower incidence of achieving a CR and shorter duration of survival than for patients with de novo AML. Studies have demonstrated the prognostic importance of cytogenetic abnormalities in AML, making this the single most important predictor of outcome. Patients with a good prognosis are those with t(15;17), t(8;21), or inv(16), whereas poor-risk patients have loss of all or part of chromosome 5 or 7, translocations involving 11q23, or trisomy 8.

The care of the patient with acute leukemia requires the ability to support the individual through the expected complications of myelosuppressive therapy, most notably the prediction of pancytopenia, which may last for 2 to 5 weeks. Successful clinical management requires a detailed understanding of likely complications accompanied by early therapeutic intervention designed to minimize life-threatening toxicities. With regard to these principles, much of the improvement seen in the care of leukemia patients in the last few years can be directly attributed to advances in supportive care.

Infection and hemorrhage are the primary cause of death in patients with leukemia. Many patients with acute leukemia initially present to the physician with fever and neutropenia. Virtually all patients develop these complications after treatment with chemotherapy. Untreated, infection in the neutropenic host can be rapidly fatal. Therefore, the early institution of antibiotic therapy is necessary. Initial antibiotics must provide a broad spectrum of antibacterial coverage, with particular attention to the potential for Gram-negative organisms. These neutrophil's flora may be determinantal in determining the particular antibiotics used as first-line therapy. Common regimens include an aminoglycoside or cephalosporin coupled with an aminglycoside. Monotherapy with a third-generation cephalosporin, such as cefazidime, or a carbapenem, such as impenem, is an alternative.

Leukapheresis can be used, but, at best, is only a temporizing measure. Instead, immediate treatment with chemotherapy should be undertaken with careful attention to the expected metabolic abnormalities discussed previously.

TREATMENT OF NEWLY DIAGNOSED ACUTE MYELOGENOUS LEUKEMIA

Untreated, AML is a uniformly fatal disease. Although it is possible to support patients for a period with supportive medical care, they ultimately succumb to the complications associated with bone marrow failure: infection or hemorrhage. Most patients seek medical attention for symptoms related to infection or bleeding, and these patients typically require immediate therapeutic intervention. Other patients are not candidates for cytotoxic therapy because of a poor performance status or other active severe medical comorbidities that complicate their care. In such settings, a supportive strategy may be most appropriate. The risks and potential benefits and alternatives should be carefully considered in each case and discussed with the patient and the family.

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Historically, the diagnosis of acute leukemia has left the physician with few therapeutic options. During the 1940s, Farber established the modern era of chemotherapy by effectively using antimetabolites in pediatric patients with ALL. Subsequently, a number of other single agents were demonstrated to have antileukemic activity at first in the laboratory and then later in the clinic. Many of the drugs initially used to treat adults with AML had been used in pediatric ALL, but they were not active in AML, and the early clinical results were disappointing. The introduction of cytarabine (Ara-C) dramatically changed the therapy of patients with AML. Ara-C is the most important drug in use today for the treatment of AML. Much of the clinical investigation done since the 1970s has focused on increasing the efficacy of this drug by either combining it with other agents, escalating the dose, or changing the schedule of administration. Despite some minor modifications made in treatment in the last few years, Ara-C remains the cornerstone of AML therapy.

INDUCTION

Standard induction therapy is based on the combination of Ara-C with an anthracycline or anthracenedione. CR rates in newly diagnosed AML patients younger than the age of 60 years range from 50% to 75%, depending on the patient population studied (Table 46.2-6). In the 1960s, investigators first demonstrated the ability of Ara-C alone to induce responses in approximately 20% to 30% of patients. Ara-C was then tried in combination, at first with 6-thioguanine and later with daunorubicin, and found to increase the incidence of CR to approximately 40% to 50%. When the dose of the Ara-C and daunorubicin used was increased, the response rates improved. Ara-C given for 7 days at 100 mg/m²/d as a continuous infusion with daunorubicin given at 45 mg/m²/d for 3 days became the standard regimen and is referred to as the 3 + 7 or 7 + 3 regimen. Patients who do not achieve a CR with one course of induction therapy may still be induced into a CR with a second cycle of this therapy. A randomized trial by the Cancer and Leukemia Group B (CALGB) reported a 59% CR rate using 3 + 7 induction therapy and found this response to be superior to a briefer course of similar therapy.

As new drugs with antileukemic activity have been introduced into the clinic, trials have been undertaken in an attempt to improve on 3 + 7 induction (Table 46.2-7). The substitution of doxorubicin for daunorubicin produced no significant benefit, but instead resulted in increased gastrointestinal toxicity. In another study, the addition of etoposide to 3 + 7 produced an improved remission duration in a younger cohort of patients. Mitoxantrone, amsacrine, rubidazone, and aclacinomycin have all been substituted for daunorubicin in induction, but no clinical trial has demonstrated the unequivocal superiority of any of these second-generation regimens.

Despite these findings, the anthracycline of choice in the induction regimens remains controversial. Criticism of the idarubicin studies cited previously has centered on the issue of dose equivalency between the idarubicin dose (12 or 13 mg/m²) and the daunorubicin dose (45 or 50 mg/m²) used for comparison. The CR rate (58%,
58%, and 59%, respectively) in the daunorubicin arm was lower than other studies that used a standard 3 + 7 induction. Several nonrandomized trials have used higher doses of daunorubicin (70 mg/m²) and have described response rates similar to those seen with idarubicin, suggesting that the dose of the anthracycline used may be more important than the choice of anthracycline. In addition, preliminary results of a large Eastern Cooperative Oncology Group (ECOG) trial that randomized elderly patients between induction regimens using daunorubicin, idarubicin, or mitoxantrone failed to show an advantage to using the newer agents. Despite conflicting results, idarubicin has been widely adopted as part of current treatment regimens.

The ability of high doses of Ara-C to overcome drug resistance and induction has remained in relapsed disease. Such an approach has been applied to upfront induction therapy in an effort to improve response. Ara-C doses ranging from 0.5 to 6.0 g/m² for 3 to 8 days have been investigated. The effect of these regimens on treatment outcomes has been variable. A University of California, Los Angeles, study randomized patients between a 3 + 7 induction and an intermediate-dose Ara-C regimen and found that both remission rate and actuarial 4-year disease-free survival were similar in the two cohorts. Two other randomized studies, however, have shown a benefit to high-dose Ara-C–based inductions, demonstrating an advantage not only in the likelihood of achieving a CR but in producing more durable responses and a superior disease-free survival. Toxicity was increased with the high-dose regimens and particularly evident during the postremission when infections were increased and recovery times delayed.

Hematopoietic growth factors have been tested in clinical trials in an attempt to reduce the toxicities seen with dose-intensive treatments. In older patients, significant toxicity with standard therapy has prevented testing more dose-intensive regimens. Treatment-related mortality in patients older than the age of 60 years is higher compared with younger patients treated with similar therapy and remains a primary cause of treatment failure in this group. As the hematopoietic growth factors had been used successfully to speed granulocyte recovery after chemotherapy in other malignancies, this approach was tested in older patients with AML. Initially, there was concern over using a myeloid growth factor in AML; however, a clinical trial conducted in patients with relapsed disease did not demonstrate stimulation of leukemia cells when growth factor was used in support of chemotherapy. A number of small, nonrandomized studies have investigated the use of either G-CSF or GM-CSF in low-risk patients in an attempt at better reducing treatment-related toxicity. Other studies have explored a novel application of using growth factors to modify drug sensitivity in addition to their potential supportive role. Both G-CSF and GM-CSF have been used before chemotherapy (as priming) in an effort to increase leukemia cell proliferation and increase sensitivity to cell-cycle–specific agents. None of these trials have demonstrated any benefit to such a strategy.

Given the conflicting data in the early studies, several large randomized trials were conducted in an attempt to clarify the role of growth factors in AML therapy. Although these studies have generally demonstrated a decrease in the duration of neutropenia, the significance of this effect has remained controversial. A study from the ECOG was able to show a decrease in treatment-related mortality with GM-CSF, while another large randomized study from CALGB was not able to demonstrate any significant clinical benefit from this growth factor. It should be noted that two different forms of the recombinant growth factor were used, which could account for the disparity in outcomes. Moreover, large numbers of patients were not randomized to the treatment in the CALGB study, which may have altered the outcome. Using G-CSF, the French AML Cooperative Study Group demonstrated an increased CR rate but no survival benefit. The Southwest Oncology Group also tested G-CSF in older patients (older than 55 years old) and found a reduction in time of neutrophil recovery and decreased duration of infection, but no difference in either CR rate or overall survival. A separate European and Australian phase III study also showed similar response and survival rates in the G-CSF and control groups, but was able to demonstrate significant reduction in measures of morbidity such as duration of fever, requirements of antimicrobials, and duration of hospitalization. This study was not confined to the older population but included all patients older than the age of 16 years with de novo AML seen during the study period. Hence, despite intensive investigation, there is still no consensus regarding growth factor use in AML therapy other than the observation that their use is safe and reduces the neutropenic period. More recently, cost-to-benefit considerations have been introduced into the equation, and future clinical trials may incorporate economic data when dealing with this question.

**POSTREMISSION THERAPY**

Although the exact form of postremission therapy is controversial, the need for such therapy is widely accepted. Induction therapy fails to provide adequate cell kill, and leukemia cells survive the initial treatment. The benefit of postremission therapy was established by two randomized multicenter trials that showed that maintenance therapy was superior to no further treatment in prolonging remission duration. This concept of continuing low-dose therapy over a prolonged period was further modified by subsequent clinical trials. The CALGB addressed the question of the duration of maintenance in a randomized study that compared 36 months of therapy versus 8 months of therapy. No benefit was found for the more prolonged duration of treatment. Additional studies have suggested that more intensive therapy delivered within a shorter period appeared to offer clinical benefit. One study from ECOG randomized patients younger than than 65 years of age to receive either one course of intensive consolidation versus 2 years of maintenance therapy and found superior survival in patients receiving the more intensive form of therapy. This has led to the concept that state-of-the-art therapy of AML includes induction, intensive consolidations, but no maintenance (Table 46.2-8).

However, this concept has been challenged by the experience reported in APL (see *Acute Promyelocytic Leukemia*, later in this chapter).

**TABLE 46.2-8. State-of-the-Art Treatment Programs for Adult Acute Leukemia**

The logical progression of the experience that established consolidation was to further intensify the chemotherapy used in postremission treatment. The efficacy of high-dose Ara-C in treating patients with relapsed AML led to regimens for postremission therapy. A number of nonrandomized trials using Ara-C doses ranging from 1 to 3 g/m² (typically given every 12 hours for 6 to 12 doses) have reported 4-year disease-free survivals ranging from 30% to 40%. These results appear to be superior to the 10% to 20% survival reported with standard consolidation regimens. The most compelling evidence for intensification, however, has been provided by a large randomized study conducted by the CALGB. After achieving remission with a standard 3 + 7 regimen, patients with de novo AML were randomized to receive four courses of Ara-C at one of three dose levels: 100 mg/m²/d for 5 days by continuous infusion (standard-dose arm); 400 mg/m²/d for 5 days by continuous infusion (intermediate-dose arm); or 3 g/m² twice daily via a 3-hour infusion on days 1, 3, and 5 (high-dose arm). A subsequent analysis of this trial according to cytogenetic data underscored the importance of this prognostic factor, with 84% of the patients who had favorable cytogenetics [defined in this study as (8;21) or inv (16)] able to have prolonged disease-free survival. Although the results from this trial have been used to bolster the argument for single-agent high-dose Ara-C intensification, all patients received four courses of maintenance therapy in the format of attenuated doses Ara-C and daunorubicin in addition to the high-dose Ara-C intensification. The effect of such therapy on outcomes is uncertain, causing some speculation as to whether comparable results can be achieved by administering the high-dose Ara-C intensification alone. Still, the results from this trial compare favorably with studies using allogeneic BMT as postremission therapy and have heightened the debate regarding the standard of care in the postremission setting.

**ALLOGENEIC BONE MARROW TRANSPLANTATION**

The use of bone marrow or stem cell transplantation as postremission therapy represents dose intensification carried to the extreme of myeloablative. High doses of chemotherapy with or without total body radiation are used in an effort to maximize leukemia cell kill. Hematopoiesis is restored by the infusion of stem cells harvested from an HLA-compatible donor, thereby rescuing the patient from the consequences of bone marrow failure. The donor bone marrow and peripheral blood stem cells (graft) may also have a number of immunologic effects. Because of differences in HLA composition, the graft may reject the host, resulting in graft-versus-host disease (GVHD). This complication may increase the risk of infection and represents a major source of morbidity and mortality in patients who undergo this procedure.
immunologic effect may, however, also translate into antileukemic activity as evidenced by the lower relapse rates observed in patients with GVHD. This graft-versus-leukemia effect is an evolving area of investigation and probably accounts for the lower relapse rates seen in allogeneic BMT as compared with syngeneic (or autologous) transplants in which similar conditioning regimens are used. 178

Despite treatment-related complications, allogeneic BMT is effective antileukemic therapy. This was first established in a small number of heavily pretreated refractory AML patients who were successfully treated with allogeneic BMT. The concept that the efficacy of this therapy could be improved and its toxicity lessened if transplants were performed earlier in the course of the disease led to a number of nonrandomized trials from large centers or cooperative groups. These trials showed that allogeneic BMTs in first CR using HLA-compatible related donors resulted in 5-year disease-free survival of approximately 45% to 50%, with relapse rates ranging only from 10% to 20%. 177 A significant number of patients, however, succumbed to such complications as GVHD, infection, or interstitial pneumonitis, affecting the overall survival of the group as a whole.

Therefore, the major criticism of allogeneic BMT in first CR is that although it is effective therapy with a relatively low incidence of relapse, it is quite toxic, expensive, and not necessarily better than other forms of dose-intensive therapy. The complication rate increases with age, and it is not standard practice to offer allogeneic BMT with a conventional graft to patients older than the age of 50 to 55 years. As the median age of patients with AML is approximately 65 years, it is clear that most patients with this disease are not eligible for this form of therapy. Because of entry criteria, BMT trials report results in younger groups of patients who may do well with other forms of dose-intensive therapy, but are generally not representative of the majority of patients with AML. In addition, only approximately 30% of eligible patients have an HLA-compatible donor. Despite meeting the minimum requirements of age and availability of a donor, a significant number of patients still fail to undergo transplantation. 184 Therefore, it has been estimated that allogeneic BMT is only applicable in 2% to 10% of patients with AML. 179 Strategies using unrelated HLA-matched or haplotype-mismatched individuals as alternative donors or using nonmyeloablative transplant regimens with reduced toxicity as part of a minitransplant for older patients have been introduced and are currently undergoing investigation. 185

AUTOLOGOUS BONE MARROW TRANSPLANTATION

Despite efforts to expand the donor pool for autologous BMT, the majority of patients do not have an acceptable HLA-matched donor and cannot undergo allogeneic BMT. In an attempt to allow such patients to undergo high-dose therapy with curative intent, investigators began to explore the use of the patient's own bone marrow, obtained while in CR, as a source of hematopoietic reconstitution. 186 Such an approach was thought to provide the antileukemic benefits associated with high-dose conditioning regimens yet avoid the toxic complications such as GVHD. One major disadvantage, however, is the potential contamination of the autologous graft by residual leukemia cells. The inability of currently available laboratory techniques to reliably detect minimal residual disease and predict outcome based on its presence represents a major problem in leukemia therapy. Hence, there is concern that despite the high-dose conditioning designed to eradicate residual leukemia cells in the body, patients will ultimately relapse because undetectable leukemia cells will be reinfused with the graft. One innovative study from St. Jude Children's Hospital attempted to address this important question. 187 Cells in an autologous bone marrow graft were marked with a neomycin-resistant gene before transplantation into two patients with AML. After clinical relapse of the patients, the neomycin-resistant gene marker was detected in the leukemia blast cells of both patients, implying that the remission marrow that had been reinjected contributed to disease recurrence.

Despite this laboratory evidence and the rationale for attempting to remove minimal residual disease from the stem cell graft, the clinical benefits of purging the graft remain unclear. Clinical trials using unpurged bone marrow as the source for hematopoietic reconstitution in first CR have reported treatment results comparable with studies using a purged graft. Results from these trials have generally reported disease-free survival of approximately 40% to 50%. 188 Relapse rates (50% to 60%) are higher than allogeneic BMT, but, as expected, the toxicities are less. In studies that have used either immunologic or pharmacologic methods to purge bone marrow, there has been a profound suppression of normal bone marrow progenitors, resulting in delayed engraftment and a prolonged period of hematologic recovery. Given the experience in other malignancies using peripheral blood stem cells as the source of hematopoietic reconstitution after high-dose therapy, this approach has been investigated in patients with AML. 189 One potential advantage to this approach is the hypothesis that there is a difference between the normal stem cell and leukemia cell compartments in recovery rates after a priming stimulus such as chemotherapy. The normal cells are thought to have a temporary competitive growth advantage so that the cells that initially repopulate the peripheral blood are more likely to be normal progenitors instead of clonogenic leukemic stem cells. Therefore, collecting stem cells early in the priming process may be thought to provide the graft with a kinetic purge, making it relatively free from contamination by residual leukemia cells. Some evidence to support this hypothesis has been provided by a study that used standard cytogenetic analysis to assay for contamination of residual leukemia cells. 190 Further support for the feasibility of this approach as has been provided by the experience of harvesting pure populations of progenitor cells after chemotherapy in CML and myelodysplastic syndromes. 185 Studies using newer, more sensitive techniques, such as PCR or multiparameter flow cytometry, will continue to address the issue of graft contamination by minimal residual disease. 214

The clinical results using peripheral blood stem cells have generally shown a decrease in the duration of neutropenia and thrombocytopenia. The effect on treatment outcomes, however, has been less clear, with some groups reporting relapse rates comparable with trials using unpurged bone marrow grafts. 188 Other studies have shown superior leukemia-free survival using purged bone marrow grafts. Although no studies have appeared, as yet, using purified peripheral stem cells, there has been great interest in intensifying the chemotherapy before collection of these stem cells and, in effect, achieving a form of in vivo purging. 191 This approach has been applied in both peripheral stem cell and bone marrow grafts, with the most compelling evidence provided by the results from the Medical Research Council (MRC) AML 10 trial (discussed in the following section). 192

ASSESSING THE OPTIONS FOR POSTREMISSION THERAPY IN ACUTE MYELOGENOUS LEUKEMIAS

Currently, the options for postremission therapy in younger patients with AML involve three forms of dose-intensive treatments: allogeneic or autologous transplantation and high-dose chemotherapy. These can be applied either alone or in combination. A number of studies have compared the different approaches in an effort to establish the optimal therapy. Although the initial comparisons reported the superiority of allogeneic BMT over chemotherapy, these studies used standard-dose attenuated consolidation regimens. 193 In the modern era, many would consider this suboptimal postremission therapy for patients younger than 60 years of age. More recent studies, however, have compared outcomes in patients who have undergone allogeneic BMT from HLA-compatible donors with those who have received either dose-intensive chemotherapy or autologous BMT. 194,195 The results from several of these studies are summarized in Table 46.2-9. These trials have consistently reported decreased relapse rates with higher treatment-related morbidity and mortality in the BMT groups, but no significant benefit in survival. In fact, a large U.S. intergroup study showed a marginally better overall survival in the cohort treated with a single course of high-dose Ara-C after a standard Ara-Cidarubicin conditioning. 196 In contrast, the MRC 10 trial found a decreased relapse rate with a survival benefit for patients who received autologous BMT after three cycles of intensive postremission chemotherapy. 185 It should be noted that these two studies differed in the amount of therapy patients received before autologous BMT, as well as the conditioning regimen used for the autologous transplant.

TABLE 46.2-9. Randomized Comparisons of Dose-Intensive Postremission Regimens

The results from these randomized studies have failed to provide a clear answer to the postremission question, but have caused many centers to reevaluate the approach to AML patients in first remission. Although some institutions still recommend allogeneic BMT for suitable candidates with HLA-compatible donors, other
TREATMENT OF RELAPSED ACUTE MYELOGENOUS LEUKEMIAS

The majority of patients with AML relapse and ultimately die from the consequences of resistant disease. Chemotherapy is generally not curative in this setting. The data from multiple trials suggest median survivals of only a few months after a second relapse is obtained. Both autologous and allogeneic BMT have been reported to provide prolonged disease-free survival in 30% to 40% of patients treated in first relapse or second CR. Therefore, suitable patients who have relapsed should undergo BMT as this represents the best chance for cure.

The timing of BMT in relapsed disease is controversial. Previous strategies have relied on the ability of salvage chemotherapy to decrease the leukemia burden and induce a second CR. However, a significant proportion of patients are unable to achieve a second CR, and the ability to proceed to allogeneic BMT may be compromised by the additional morbidity seen with such therapy. This is particularly true as high-dose regimens have been moved up front, limiting the treatments available on relapse. Data from the Fred Hutchinson Cancer Center have suggested that autologous BMT performed early in first relapse yields similar results to those transplants performed after a second CR has been obtained. A number of centers have adopted this strategy. It requires that patients are able to proceed to allogeneic BMT in a timely manner. The feasibility of this approach, however, is often problematic as the readiness of the transplant facility or the availability of the donor may instead require the patient to receive some form of chemotherapy before allogeneic BMT. Further complicating the application of this relapse strategy has been disagreements over the definition of early relapse and concerning the maximal level of leukemia burden that will allow a successful transplantation to take place.

A similar strategy may be used for patients proceeding to autologous BMT. Patients who relapse and previously had stem cells (either peripheral blood or bone marrow) harvested and cryopreserved, may proceed directly to autologous BMT. If no provision has been made for the patient and stem cells have not been collected in first CR, a second remission must be obtained. A number of studies have reported durable disease-free survival of approximately 30% in patients who have received autologous BMT in second CR and approximately 20% in third CR. Results were not dependent on whether purged or unpurged marrow was used as the source of hematopoietic reconstitution.

Most patients, however, are not candidates for either type of BMT. For such patients, the goal in treating relapse is to induce a second remission. The ability to achieve a second remission is primarily dependent on the duration of the first remission. Several groups have found that the response rates to salvage therapies are lower in patients with first remission durations of 6 to 12 months. Patients with an exceptionally short remission duration (less than 6 months) are unlikely to respond to standard therapies and investigational approaches are appropriate. Attention to early, potentially curative BMT in those who relapse after 2 years in remission may achieve a second CR by repeating the original induction regimen. Because of the potential cumulative toxicity of the anthracyclines, patients who receive up to three cycles of such chemotherapy require evaluation of cardiac function before additional re-treatment with these agents.

Because most patients with relapsed disease, however, do not respond to repetition of the original induction regimen, research efforts have sought to define the underlying basis for clinical drug resistance with the ultimate goal of identifying new therapeutic approaches. One suspected mechanism of clinical drug resistance that has received much attention is the multidrug-resistant (MDR) phenotype. This laboratory phenomenon describes the observation that cell lines can become cross-resistant to unrelated, structurally diverse chemotherapeutic agents. The mechanism of resistance is linked to a 170- to 180-kD glycoprotein that functions via decreasing the intracellular accumulation of drugs, resulting in decreased cytotoxicity of these agents. The MDR phenotype has been observed in approximately 70% of patients with relapsed or refractory disease but also in 25% to 30% of patients with untreated disease. The variable correlation of clinical response with expression of MDR phenotypes suggests alternative mechanisms may be active in determining resistance of AML cells to current chemotherapy. In addition, other potential mediators of drug resistance, such as lung resistance protein, have been described, and the relationship of this resistant phenotype to MDR and other resistance mechanisms remains under investigation. The emphasis on the MDR data may be explained by the potential for modulators that alter the phenotype and restore chemotherapy sensitivity. Several trials have been undertaken that attempt to use the cyclophosphamide derivative, PSC-833, in an effort to reverse the MDR phenotype.

These studies are ongoing in both relapsed disease and up front as part of a strategy to increase CR rate and improve outcomes. Although such an approach has been shown to be feasible, efficacy remains to be established. A major criticism of this approach is that resistance to the most important antileukemia agent, Ara-C, is not affected by MDR, and that these studies basically ignore a common yet important mechanism of failure. Several investigators, however, have attempted to modify Ara-C efficacy in several different ways: increasing the intracellular concentration of the drug by giving high-dose Ara-C or combining Ara-C with fludarabine or exploiting to attempt the cytotoxic properties of hematopoietic growth factors to recruit leukemia cells into cell cycle, thereby increasing the sensitivity to the drug.

Among the drugs tested in the relapsed setting, high-dose Ara-C, either alone or in combination, has consistently been found to have the greatest antileukemic activity. Although the dose and schedule of Ara-C has varied somewhat between studies, high-dose Ara-C is usually given at 2 to 3 g/m² every 12 hours for up to 12 doses. Several centers now administer the Ara-C once daily or twice daily on an every other day schedule in an effort to decrease toxicity. Responses to such regimens have ranged from approximately 30% to 50%. Other active agents, such as daunorubicin, mitoxantrone, idarubicin, and etoposide, have been combined with high-dose Ara-C, but the therapeutic advantage of these combinations remain unclear. Substantial differences in treatment results between trials containing similar agents may be explained by patient selection and the small numbers of patients enrolled on these trials.

Patients who fail to achieve CR after receiving two courses of standard dose therapy are considered to have primary refractory disease. The prognosis for such patients is exceptionally poor, and response to salvage regimens is rare. Approximately 20% to 40% of these patients who are able to undergo allogeneic BMT can be rendered free of disease with durable remissions. This ability to salvage primary refractory patients underscores the importance of identifying potential donors early in the therapy of patients who may be eligible for BMT. Patients who are not transplant candidates are best enrolled in investigational studies.

As more patients receive some form of high-dose therapy as their initial treatment, the options at relapse have changed. For some patients relapsing after high-dose Ara-C postremission therapy, studies suggest that either autologous BMT or allogeneic BMT can be curative. Those patients who are not BMT candidates may undergo treatment with agents that are non-cross-resistant to Ara-C. Regimens including daunorubicin or carbolatin, were encouraging, subsequent studies have shown that these regimens are relatively ineffective. The combination of cyclophosphamide and etoposide, given in near myeloblastic doses, has been shown to induce CR in approximately 30% of patients who are refractory to regimens containing high-dose Ara-C. Similar to the experience with other chemotherapy-based salvage regimens, such responses are usually short-lived.

Relapse of AML after autologous BMT poses a difficult and frustrating management problem. Although a median survival of 3 to 4 months. However, results are not significantly improved with current available therapy. Treatment options are determined by the performance status of the patient as well as the interval from transplant to relapse. Although a CR rate of approximately 35% has been reported to standard induction regimens, patients who relapse within the first 100 days after BMT are unlikely to respond and have a high treatment-related mortality. Selected young patients who relapse after 1 year may be candidates for a second autologous BMT, but the survival at 3 years has been reported to be approximately 10%. Therapeutic approaches, including the use of G-CSF, modulation of the graft-versus-leukemia effect by discontinuing immunosuppressives such as cyclosporin, or infusing donor leukocytes have been reported to induce remission in this setting.

Although donor leukocyte infusions have received much attention, most of the data have been generated in patients with CML and the results of such therapies in AML have been disappointing, although investigations continue.

ACUTE PROMYELOCYTIC LEUKEMIA

APL represents a distinct entity among the myeloid leukemias. The unique biology that characterizes the disease also serves to make it the paradigm for targeted antileukemic therapy. Historically, the importance of the prompt recognition of this subtype of AML has been stressed because of the coagulopathy associated with the disease and the potential for lethal hemorrhage with the institution of cytotoxic chemotherapy. The incorporation of all-trans-retinoic acid (ATRA) into up-front therapy further underscores the importance of rapid and accurate diagnosis.

When treated with standard Ara-C/Anthracycline–based chemotherapy, there is a higher rate of periinduction mortality in APL than in the other AML subtypes. A variety of supportive interventions have been introduced in an effort to control the hemorrhagic diathesis of the disease, but these complications remain a source of
significant morbidity and, even with best available therapy, constitute a major reason for induction failures. Despite the early hazards associated with cytotoxic treatment, the long-term survival in APL with this therapy is far superior to the other subtypes of AML. In groups that have emphasized dose intensity of the anthracycline, long-term disease-free survival as high as 60% has been reported.\(^3\)

The clinical use of ATRA changed the emphasis from cytotoxic therapy and established differentiation therapy as an effective modality in the therapy of human cancer. The initial experience with this agent was reported by Huang et al. and subsequently confirmed by other groups.\(^221\) ATRA is not a cytotoxic agent but instead causes a proliferation of the abnormal clone coincident with maturation, eventual terminal differentiation, and ultimately, apoptotic cell death. CR is obtained in 90% to 95% of newly diagnosed cases of APL without inducing aplasia and without the toxic effects associated with standard chemotherapy. Instead of worsening APL-associated coagulopathy, there is stabilization and improvement of the condition within days of the institution of ATRA therapy. The biologic effects of ATRA are not restricted to de novo disease but are also seen in patients who have relapsed after chemotherapy as demonstrated by CR rates between 85% and 90% in this population.\(^221\)

Despite the many advantages of ATRA therapy, it is not without potential complications. Although there is prompt improvement of coagulopathy with ATRA, many trials continue to report a 10% to 15% perinduction mortality due to both thrombosis and hemorrhage as well as the occurrence of a newly recognized toxicity named the retinoic acid syndrome (RAS). Approximately 25% of patients develop symptoms consistent with a capillary leak syndrome with features similar to acute respiratory distress syndrome or endotoxic shock.\(^4\) Therefore, RAS is characterized by fever, dyspnea, peripheral edema with resultant weight gain, pleural and pericardial effusions, hypotension, and occasionally renal failure. Untreated, RAS can lead to rapid clinical deterioration and death.

The pathogenesis of RAS and its relationship to the other biologic effects observed with ATRA remain unclear. The description of a similar symptom complex in patients with APL who have not received ATRA has raised the hypothesis that this syndrome is directly related to the underlying disease process.\(^221\) Leukocytosis, which is seen in patients with ATRA-induced coagulopathy, then is stabilization and improvement of the condition within days of the institution of ATRA therapy. The biologic effects of ATRA are not restricted to de novo disease but are also seen in patients who have relapsed after chemotherapy as demonstrated by CR rates between 85% and 90% in this population.\(^221\)

In an effort to exploit the known sensitivity of APL to anthracyclines, extend the durability of remissions obtained with ATRA chemotherapy-based regimens, and reduce ATRA-related toxicity, the Italian cooperative groups, GIMEMA-AIEPO, moved the chemotherapy up to induction by including idarubicin with ATRA (AIDA).\(^230\)

Ninety-five percent of patients achieved CR with AIDA induction and, when followed by three courses of postremission chemotherapy, the actuarial event-free survival at 2 years was reported to be 79%. Only 2.5% of patients developed RAS. Sequential ATRA chemotherapy was subsequently compared with simultaneous administration during induction in a large randomized study conducted by the European APL study group.\(^231\) Although the actuarial relapse rates at 2 years were marginally better in the ATRA plus chemotherapy group, the estimated 2-year survival was statistically similar. In addition, patients who received maintenance in the form of either chemotherapy or intermittent ATRA had superior overall survival. This is in sharp contrast to the other forms of AML in which maintenance therapy after a dose-intensive course of consolidation is generally without benefit.

The unique disruption of the RAR-a locus results in novel fusion proteins that given the current level of sophistication in the laboratory, are readily detectable and provide a useful tool for the clinician. The PML/RAR-a transcript defines sensitivity to ATRA, and the ability of RT-PCR to readily detect the PML/RAR-a fusion product allows for rapid genetic confirmation of the diagnosis, which given the various morphologic variants can be difficult even for the experienced eye.\(^232\) In addition to helping in the diagnosis and planning an effective treatment strategy, RT-PCR has facilitated the detection of minimal residual disease and has made APL a paradigm for the use of molecular techniques to monitor therapy.\(^232\)

Despite the spectacular CR rates and the equally impressive survival results, approximately 30% of patients treated in the large randomized studies relapse. Similar to the experience in other AML subtypes, such patients are generally incurable with chemotherapy alone and achieving a second remission may be difficult. Many are resistant to rechallenge with the retinoid, particularly if the relapse occurs early (within 6 to 12 months). Arsenic trioxide has been used to achieve CR in heavily pretreated patients.\(^232\) For those patients who are able to obtain a remission, both allogeneic and autologous BMT have been reported to offer a chance for cure. The results with autologous transplantation are dependent on the pretransplant status of minimal residual disease with 75% of patients who were PCR-negative before the autograft in molecular and clinical remission with a median follow-up of 28 months.\(^232\)

The therapy of APL in the modern era is marked by great clinical success accompanied by a new understanding of the fundamental biology of the disease. The promise for future progress in AML may lie in mechanism-based drug design. The observation that arsenic trioxide leads to increased expression of caspases resulting in enhanced apoptosis has prompted investigators to combine this agent with the differentiating effects of ATRA in an attempt to amplify the effect of each agent by exploiting the different mechanisms of action. In vivo, this combination has been found to be synergistic, and the investigation of arsenic and ATRA has been undertaken in animal models.\(^4\) The interaction between PML/RAR-a fusion products, coressor binding proteins, and histone deacetylase have been implicated in the pathogenesis of APL. This has led to interest in a class of drugs, the histone deacetylase inhibitors, that may usher in a new era in the drug therapy of leukemia.

**GENERAL PRINCIPLES FOR THE TREATMENT OF ADULT ACUTE LYMPHOBLASTIC LEUKEMIAS**

Treatment of adults with AML has been modeled on the therapy developed for childhood ALL. The similarity between the childhood and adult forms of this disease allows for inferences to be drawn from experience in the pediatric population. However, adults with ALL have a far poorer outcome when compared with children. Some of this difference can be attributed to differences in ability to tolerate intensive therapy coupled with an increased incidence of unfavorable cytogenetic subgroups [particularly t(9;22) and t(4;11)] and a decreased incidence of favorable cytogenetic subgroups [such as hyperdiploidy or t(12;21)]. Despite these mitigating features, the distinctly different outcomes of therapy have led to questions regarding how advances in pediatrics can be used in adult ALL. A broad review of the St. Jude experience in pediatric ALL demonstrated a dramatic stepwise improvement in treatment results since the 1970s.\(^233\) However, adults with ALL have not shared in this remarkable success story.

Treatment of adult ALL is typically divided into four broad categories: induction, consolidation, maintenance, and CNS prophylaxis. At presentation, many patients are quite ill with active infection, hemorrhage, or both, and induction regimens for adult ALL have typically emphasized related myeloid-sparing cytotoxic agents.

Consolidation therapy is administered at a relatively higher level of intensity to patients already in complete remission. Before beginning this phase of therapy, patients have normal blood counts and generally a good performance status. They are therefore able to tolerate significant myelosuppression with acceptable toxicity.

Maintenance therapy is administered to patients in remission after the more intensive consolidation therapy. It is administered at a low level of intensity, but for a protracted period. Current opinion is that 2 years of maintenance therapy is required for optimal results.

The fourth category of treatment is CNS prophylaxis. This is administered concurrently with systemic chemotherapy. Despite aggressive systemic therapy, the CNS remains a sanctuary site and without specific meningeal-directed therapy approximately 35% of adult patients develop CNS disease.
To understand the natural history of adult ALL and to assign specific therapy, the FAB subclassification (see Morphology and Cytochemistry, earlier in this chapter) is less useful than an immunophenotypic subclassification, which recognizes three major groups: The most common subtype is pre-B-cell ALL, which represents approximately 70% of patients. The term pre-B refers to the fact that these cells are committed to the B-cell lineage, as manifested by immunoglobulin gene rearrangement and expression of early B-cell markers such as CD19 and terminal deoxynucleotidyl transferase, but do not express the hallmark of the mature B cell, surface immunoglobulin. In addition to CD19 and terminal deoxynucleotidyl transferase, the lymphoblasts of patients with pre-B-cell ALL typically express CD10, which was previously known as common ALL antigen (CALLA).

The second type of ALL is T-cell disease. T-cell ALL and lymphoblastic lymphoma are essentially the same disease. This disease typically affects young adults and has a significant male predominance. The malignant process begins as a rapidly growing mediastinal mass with early dissemination to the bone marrow. Patients present with symptoms related to their mediastinal mass (cough, dyspnea, chest pain) or to bone marrow involvement (infection and bleeding). Patients without evident bone marrow involvement at diagnosis are said to have lymphoblastic lymphoma. Those with scant bone marrow involvement are said to have stage I lymphoblastic lymphoma and those with significant (greater than 30%) bone marrow involvement are said to have T-cell ALL. These distinctions are largely semantic and are without important clinical implications. All patients with lymphoblastic lymphoma/T-cell ALL require therapy as for ALL.

The third and least common subtype (approximately 5% of adult ALL) is mature B-cell ALL. As the name implies, these leukemic cells are slightly more mature than their pre-B-cell counterparts and express surface immunoglobulin. The typical patient is a young man who presents with a rapidly growing abdominal mass (initial sites are typically the appendix and the ileocecal valve) and early dissemination to the bone marrow. The most common presentation is with symptoms related to the abdominal mass (pain, bloating, and small bowel obstruction) or to bone marrow involvement (infection and bleeding). Patients who present to medical attention with symptoms related to bone marrow involvement (infection and bleeding) marked by significant bone marrow involvement (greater than 30%) are very uncommon in other adults with ALL. Of the three sanctuary sites, B-cell ALL is typically a disease of young adults. Of T-cell ALL, less frequently in patients with Philadelphia chromosome–positive ALL, and is extremely uncommon in other adults with ALL. The incidence of CNS disease at presentation in adult ALL is typically 5% to 10%. Risk factors for developing CNS disease are increased leukocyte count and an elevated lactate dehydrogenase. CNS disease is thus more common in children with ALL, which is less favorable to induction therapy and has yet to be treated. In these instances, the hallmark of the mature B cell, surface immunoglobulin. In addition to CD19 and terminal deoxynucleotidyl transferase, the lymphoblasts of patients with pre-B-cell ALL typically express CD10, which was previously known as common ALL antigen (CALLA).

PROGNOSTIC FEATURES IN ADULT ACUTE LYMPHOBLASTIC LEUKEMIA

There have been several evaluations of prognostic features in adult ALL. The two most widely accepted multivariate analyses were performed by the German multicenter group and the Memorial Sloan-Kettering group. Other analyses have in general supported these two studies and have led to five widely accepted prognostic features: WBC count, age, leukemia cell immunophenotype, Philadelphia chromosome–positive disease, and time to achieve CR (see Table 46.2–3).

Multivariate analyses indicate that a high WBC count at diagnosis is associated with poor prognosis. There is both a reduced likelihood of achieving a CR as well as shorter duration of CR and overall survival in adult ALL. The increased WBC count probably contributes to the earlier dissemination of the disease, which is a major cause of death in adult ALL. The duration of CR and overall survival were associated with a high WBC count, as well as the degree of immunophenotypic abnormalities (e.g., t(4;11) and t(9;22)). A high WBC count is probably a continuous variable that could be associated with the likelihood of achieving a CR. The incidence of CNS disease at presentation in adult ALL is typically 5% to 10%. Risk factors for developing CNS disease are increased leukocyte count and elevated lactate dehydrogenase. CNS disease is thus more common in children with ALL, which is less favorable to induction therapy and has yet to be treated. In these instances, the hallmark of the mature B cell, surface immunoglobulin. In addition to CD19 and terminal deoxynucleotidyl transferase, the lymphoblasts of patients with pre-B-cell ALL typically express CD10, which was previously known as common ALL antigen (CALLA).

In the Memorial Hospital study, WBC counts greater than 10,000/µL were associated with a lower frequency of achieving a CR, whereas counts greater than 20,000/µL were associated with a shorter duration of CR. The German study indicated that WBC counts greater than 30,000/µL carry an adverse prognosis. Older age is also associated with a worse prognosis. Age is probably a continuous variable (the older the patient, the worse the prognosis). In pediatric series, younger patients typically have the worst prognosis, although in adult series this is almost always the most favorable group. Different studies have defined different ages as having a poor prognosis, the two most important being age 35 years from the German group and age 60 from the Memorial Hospital study.

The immunophenotype of the leukemia cell also carries prognostic implication. T-cell disease has a favorable prognosis, pre-B-cell (common) ALL has an intermediate prognosis, whereas mature B-cell disease has a poor prognosis when treated with standard regimens. It should be noted that modern regimens designed specifically for mature B-cell ALL improve the prognosis for this subtype significantly. Previously, null ALL was considered to have a poor prognosis. Modern immunophenotyping has essentially eliminated this entity. It is possible that in the past some acute leukemias now classified as AML-M0 would have been considered null cell ALL: not surprisingly these would fare poorly with vincristine/prednisone-based therapy.

Philadelphia chromosome–positive disease carries a poor prognosis. Adult patients with this entity are essentially never cured by chemotherapeutic regimens. A minority of patients with this disease may be cured if they undergo autologous transplant in first CR. Other cytogenetic abnormalities also have prognostic implications, but their frequency is not sufficient to be noted in multivariate analysis. Most notable of these is the poor prognosis associated with t(4;11).

Time to achieve a CR during induction therapy carries significant prognostic implications. Patients requiring more than 4 weeks or 5 weeks to achieve a CR have a lower likelihood of being cured. It is not clear if this reflects an innate sensitivity to (and curability by) the chemotherapeutic agents used or rather that rapid cyoreduction of the leukemic cell mass minimizes the opportunity for drug resistance to develop and ultimately allows for cure of the patient.

TREATMENT OF NEWLY DIAGNOSED ADULT PATIENTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA

There are several different regimens for adult ALL that have been developed since the 1970s. These regimens, which borrow heavily from advances made in childhood ALL, have many features in common. Current therapy can induce complete remission in approximately 65% to 85% of adults. However, the majority of these patients subsequently relapse, and overall survival remains at approximately 30% of adults, with, for example, 5-year survival of approximately 35% (see Fig. 46.2–1). Four major studies have shown that induction therapy is necessary for optimal results (see Table 46.2–4). The mainstay of induction therapy for ALL has been the combination of vincristine and prednisone. Vincristine and prednisone achieves a CR in approximately 50% of patients. Addition of an anthracycline to induction therapy was demonstrated in a randomized trial to increase the likelihood of achieving a CR (38% vs. 47%). This increase in incidence of CR did not translate into improved survival for the patients randomized to receive the anthracycline. Although lacking support from randomized clinical trials, further intensification of induction therapy with cyclophosphamide or l-asparaginase is widely accepted as improving remission induction, and one or both of these drugs are therefore included in essentially all induction regimens. Current induction regimens are therefore labeled as four drug (vincristine, prednisone, anthracycline, and cytoporphamide or asparaginase) or five drug (vincristine, prednisone, anthracycline, cytoporphamide, and asparaginase) regimens. There are no data currently available to favor one of these induction regimens over another.

Consolidation therapy has evolved over time to include several drugs given in varying sequence. Though there is no standard consolidation therapy, some generalizations can be made. The drug most prominently used in consolidation of adult ALL is Ara-C. Consolidation regimens include Ara-C combined with other drugs, such as doxorubicin, epidophyllotoxins, or antimetabolites (such as methotrexate or thioguanine). Multiple studies seem to indicate the value of such consolidations. Most of these studies are uncontrolled phase II studies or comparisons with historical controls. The experience at M. D. Anderson is typical in this regard in which implementation of such therapy increased 3-year survival from 15% to 40%. A randomized phase III trial demonstrating the importance of methotrexate-containing consolidations was reported by Fiore et al. In this study, after remission induction, patients were randomized to receive consolidation therapy with cytosine arabinoside, doxorubicin, and asparaginase or an immediate repeat of consolidation therapy. Three-year disease-free survival in the consolidation arm was markedly superior (38%) to the no consolidation arm (0%) (P < .005). Although most authors accept that intensive consolidations are beneficial, there is a report by Ellison et al. of a randomized trial that failed to show significant benefit to cytarabine-based consolidation.

Protracted maintenance therapy is a feature unique to treatment strategies for ALL. All other chemotherapeutically curable human malignancies are typically cured with 3 to 6 months of therapy. In pediatric ALL, maintenance therapy is necessary, and most regimens prescribe 2 to 3 years of such treatment. In adults, the necessity of maintenance therapy has been less clearly addressed. Only a few studies have failed to use maintenance therapy, and the low reported disease-free survival seen in the CALGB study (18% at 3 years) and the ECOG study (13% at 4 years) suggests the importance of maintenance therapy in adult ALL. The two most important drugs in maintenance chemotherapy are a combination of oral methotrexate and mercaptopurine. In pediatric ALL, these two drugs alone can be sufficient for maintenance therapy; in adults, however, most maintenance regimens are intensified by incorporating other active agents such as vincristine, prednisone, anthracyclines, and cytoporphamide.

The CNS, along with the eye and the testis, are viewed as sanctuary sites. These are areas where penetration of systemically administered cytotoxic agents is compromised, leading to the potential of local relapse. In adults, ocular relapse is extremely rare. Testicular disease occurs occasionally in patients with mature B-cell ALL, less frequently in patients with Philadelphia chromosome–positive ALL, and is extremely uncommon in other adults with ALL. Of the three sanctuary sites, CNS disease is by far the most common. The incidence of CNS disease at presentation in adult ALL is typically 5% to 10%. Risk factors for developing CNS disease include high WBC count at diagnosis and mature B-cell immunophenotype. Patients who do not receive prophylactic therapy have a cumulative risk of approximately
35% of developing CNS involvement during the course of their disease. Prophylaxis with intrathecal chemotherapy (with or without whole brain irradiation) effectively reduces the cumulative incidence to approximately 10%. Intrathecal chemotherapy can be delivered by lumbar puncture or intraventricularly via Ommaya reservoir. If whole brain irradiation is used, intrathecal chemotherapy can be delivered by lumbar puncture (and requires fewer treatments) to achieve acceptable results. Patients not receiving whole brain irradiation as part of their prophylaxis require a greater number of intrathecal treatments and should have these treatments administered via an Ommaya reservoir. Patients should achieve a comparable remission rate before having an Ommaya reservoir placed to avoid surgery in the subset of patients who have primary refractory disease or die during induction therapy. Intrathecal chemotherapy does not require adjustments for body surface area, and a typical adult dose is 12 mg of methotrexate (or 60 mg of cytarabine). A variety of administration schedules have been used, but for patients not receiving brain irradiation, we recommend six doses during the first 2 months of treatment, two doses per month during consolidation therapy, and two doses for every 3 months of maintenance therapy. The addition of whole brain radiotherapy to intrathecal chemotherapy can reduce the amount of intrathecal chemotherapy required for adequate CNS prophylaxis (and obviate the need for an Ommaya reservoir); however, concerns of late toxicity, including loss of cognitive function and leukoencephalopathy, have led many investigators to omit whole brain radiotherapy from prophylactic regimens. CNS prophylaxis, although effective at reducing the incidence of CNS relapse, has no demonstrable effect on systemic relapse or overall survival.

Features common to state-of-the-art treatment programs for adult ALL are summarized in Table 46.2.8. Since the 1970s, treatment regimens that incorporate these features have been developed at many centers. Multiple formulations have been tested that vary the drug dose and schedule during induction, the number and intensity of therapy cycles during consolidation, and the sequencing and duration of maintenance. Despite years of experience with multiple variations of this treatment strategy, no single formulation appears to be superior to the others. The wide variation in reported outcomes of clinical trials would superficially suggest the superiority of certain regimens (Table 46.2.10). Closer inspection, however, does not support this view. Interpretation of the literature is complicated primarily by differences in patient mix and duration of follow-up. A classic analysis by Ohno of the relationship between median age and disease-free survival in 18 published studies of adult ALL reveals a tight correlation between the median age of the patients treated and the long-term disease-free survival. This suggests that the apparent differences in results among published studies likely reflect patient mix rather than differences in treatment regimen.

The uniformity of results seen with vincristine/prednisone-based regimens has led to exploration of new induction approaches in adults. A phase II study at Memorial Sloan-Kettering Cancer Center used an induction regimen of cytarabine combined with a high single dose of mitoxantrone (80 mg/m²). Vincristine and prednisone were not used during induction therapy. When compared with historical controls, this regimen demonstrated a higher incidence of CR (P = .056), a lower incidence of failure with resistant disease (P = .028), a significantly reduced time to CR (P = .003), and a trend to improved survival. This regimen appeared to have particularly good activity in patients with Philadelphia chromosome–positive disease. A prospective multicenter randomized trial comparing this regimen to a standard four-drug induction regimen is currently ongoing.

TREATMENT OF RELAPSED OR REFRACTORY ADULT PATIENTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA

Most current induction regimens obtain CRs in 65% to 85% of newly diagnosed patients. Early deaths account for some of the induction failures, but in most studies 10% to 25% of patients have disease resistant to vincristine/prednisone-based regimens. In addition to these primary refractory patients, 60% to 70% of patients achieve a CR relapse. Treatment of relapsed and refractory patients is therefore an important and common problem. Numerous regimens have been reported in the setting of relapsed ALL. The most important regimens can be divided into two main groups: those that repeat the regimens used for newly diagnosed patients (this strategy is obviously not used for primary refractory patients) and those that involve high-dose chemotherapy. High-dose regimens appear to obtain a greater incidence of second CRs when compared with reinduction with vincristine/prednisone-based regimens. The high-dose regimens with the greatest likelihood for inducing a second CR are high-dose cytarabine-based regimens.

High-dose cytarabine has been used alone and in combination with a number of different agents. In combination with L-asparaginase, and doxorubicin, idarubicin, or mitoxantrone, CRs as high as 72% have been reported in relapsed patients with ALL. Issues of patient mix make it difficult to assess if a specific regimen is superior to others, but in general a combination of high-dose cytarabine and an anthracycline has the greatest likelihood of achieving a second CR in relapsed patients (or a first CR in refractory patients). The toxicity of these regimens should be balanced against the benefits of achieving a CR. However, second CRs are difficult to maintain and typically each succeeding response is briefer than the preceding one. Patients with a suitable allogeneic transplant option should probably be referred for such a transplant in second CR. The role of autologous or matched unrelated transplants in relapsed adult ALL has not been clearly established and should be considered investigational.

CENTRAL NERVOUS SYSTEM RELAPSE IN ADULT ACUTE LYMPHOBLASTIC LEUKEMIA

CNS relapse occurs in approximately 10% of patients who have received appropriate prophylaxis. In the majority of patients, simultaneous bone marrow relapse can be documented. In occasional patients, CNS relapse may occur without demonstrable systemic relapse (so-called isolated CNS relapse); however, this event almost always predicts subsequent bone marrow relapse, and patients with isolated CNS relapse should receive reinduction chemotherapy as well. Treatment of established CNS disease requires a combination of radiotherapy and intrathecal chemotherapy. Radiotherapy should consist of 1800 to 2400 cGy (in 150- to 200-cGy fractions) administered as often as two or three times per week until the CSF is cleared of leukemic blasts, then twice a week for 3 weeks, and twice a month for 2 or 3 additional months. Patients who develop CNS disease despite prophylaxis with intrathecal methotrexate, or those who do not clear the blasts from the CSF promptly because the dose of radiotherapy to marrow-bearing areas subsequently limits the ability to administer necessary systemic chemotherapy. Intrathecal therapy with methotrexate (12 mg) for patients with established CNS disease should be administered intraventricularly via an Ommaya reservoir. Intrathecal chemotherapy can be administered as often as two or three times per week until the CSF is cleared of leukemic blasts, then twice a week for 3 weeks, and twice a month for 2 or 3 additional months. Patients who develop CNS disease despite prophylaxis with intrathecal methotrexate, or those who do not clear the blasts from the CSF promptly (within two treatments) with methotrexate, should receive intraventricular therapy with cytarabine at a dose of 60 mg.

BONE MARROW TRANSPLANT FOR ADULT ACUTE LYMPHOBLASTIC LEUKEMIA

HLA identical sibling BMTs have been used in adults with ALL in a variety of settings. This dose-intensive treatment approach has the ability to eradicate leukemia in a subset of patients with disease refractory to conventional chemotherapy. However, the lack of availability of HLA-matched donors and the toxicity and mortality seen
with transplant limits the utility of this approach. There is significant controversy over the use and timing of allogeneic transplant in adult ALL. Analysis of patterns of failure highlight a fundamental difference in the use of this modality for AML compared with ALL. Patients with AML (in first or second CR) treated with allogeneic transplant tend to fail therapy because of treatment-related mortality (infectious complications, GVHD, and so forth). Failure because of relapsed AML after allogeneic transplant (for patients in first or second CR) is relatively uncommon. The results for ALL, however, indicate that even for patients who survive the transplant, there is a significant relapse rate, and overall few patients are long-term disease-free survivors. The ability of allogeneic transplants to cure malignant diseases rests in part on the ability of the transplanted (donor) immune system to eliminate residual leukemic cells; this is known as the graft-versus-leukemia effect. There is evidence to suggest that this effect may be less important in ALL than in either BMT or in CML. Data from the International Bone Marrow Transplant Registry compared identical twin to HLA identical sibling transplants. Presumably, graft-versus-leukemia should be more pronounced in the HLA identical sibling transplants as compared with the identical twin transplants. In this study, there was a significantly higher relapse rate in the identical twin transplants for AML and CML, but not for ALL. This implies that graft-versus-leukemia is less important in ALL. A second indication that graft-versus-leukemia is less active in ALL comes from an analysis of studies of donor T-cell infusions used to treat leukemia that has relapsed after allogeneic BMT. In this study, donor lymphocyte infusions produced CRs in 73% of patients with CML, 29% of patients with AML, and in 0% of patients with ALL. The incidence of long-term disease-free survival after allogeneic transplant for adult ALL.

A review of the published experience of allogeneic BMT in adult ALL reveals that only a small fraction of patients are cured by this modality. The results of 192 adults with ALL treated at the Fred Hutchinson Cancer Center report a 5-year disease-free survival of only 15% for patients transplanted in second CR or beyond. Another study that suggested more favorable results is difficult to interpret because this study presents combined results for pediatric and adult patients or patients in first CR (who may already be cured) with higher risk patients.

The ability to cure a small subset of relapsed patients with allogeneic transplant has led investigators to test this modality in first CR. However, two large comparisons of allogeneic transplant versus standard chemotherapy for patients in first CR have failed to demonstrate an improved survival for the transplant arm. In one of these studies, subset analysis suggests a benefit for certain high-risk patients. This benefit was not confirmed in the other study. Currently, the only group for whom allogeneic transplant in first CR can be routinely recommended is patients with t(9;22) and t(4;11) disease. For other adult patients, allogeneic transplant should be reserved for second CR.

Autologous transplant for adult ALL is even less effective than allogeneic transplant. The extremely poor results for patients in second CR or beyond has led to this modality being tested in first CR. However, both a nonrandomized and randomized trial showed no benefit for autotransplant compared with maintenance chemotherapy. This modality should be considered experimental and not routinely performed in first CR.

**TREATMENT OF MATURE B-CELL ACUTE LYMPHOBLASTIC LEUKEMIA**

Mature B-cell ALL is an uncommon disorder that accounts for approximately 5% of all patients with ALL. This disease has an extremely poor prognosis when treated with traditional ALL regimens such as those described previously. Studies indicate that a majority of patients with mature B-cell ALL can be cured with certain intensive regimens. The important features of regimens for this disease are rapid cycling of drugs, fractionated cyclophosphamide, high-dose methotrexate, and intensive CNS prophylaxis. Maintenance therapy is not used in these regimens. A retrospective review of the French experience with this form of therapy indicates that 12 of 22 (55%) patients older than the age of 18 years were cured in the poor-risk group of patients.

**GRANULOCYTE SARCOMAS, LEUKEMIA CUTIS, AND OTHER EXTRAMEDULLARY LEUKEMIC INVOLVEMENT**

Acute leukemia cells may diffusely infiltrate any organ of the body during the course of disease, or may form collections and large masses known as granulocytic sarcomas or chloromas, due to their green hue from the myeloperoxidase. Diffuse involvement of the skin by acute leukemia cells is referred to as leukemia cutis and should be distinguished from Sweet's syndrome, which is an infiltration of the skin by neutrophils. The initial presentation of acute leukemia at a primary extramedullary site with normal marrow and blood findings is extremely rare. However, if extramedullary leukemia is misdiagnosed as carcinoma or lymphoma and treated without leukemia-specific therapy, the prognosis is poor: overt leukemia usually appears within a year, and death occurs at a median of 3 months later. In contrast, granulocytic sarcomas may occur secondarily in approximately 5% of patients, especially in those with (8;21) or (9;11) translocations or inv(16) chromosome abnormalities, and in patients with other monomyocytic leukemias.

The occurrence of extramedullary disease virtually always heralds systemic relapse and should be treated as such. Specific therapy directed at the extramedullary disease, unless it is located in the CNS, is usually not indicated. Treatment of CNS leukemia is discussed earlier in this chapter (see Central Nervous System Relapse in Adult Acute Lymphoblastic Leukemia). The prognostic significance of extramedullary disease is usually negative even when it is associated with other good prognostic signs (e.g., t(12;21)). Extramedullary disease is treated by systemic therapy of the kind used to consolidate or intensify systemic leukemia. Leukemia cutis has been treated by external electron beam therapy, but this has been associated with fatal dermatitis in patients who had also received anthracyclines commonly used to treat ALL.

Involvement of the CNS is rare at presentation in AML, in contrast to ALL, in which it occurs more frequently; therefore, in the absence of symptoms of neurologic involvement, examination of the CSF in patients with AML is not indicated at presentation. In patients with ALL, the CSF should be examined routinely during the initiation of treatment and prophylactic intrathecal chemotherapy should be administered; more aggressive therapy should be initiated if the CSF is involved (as described previously). In AML, CNS disease is more common in patients with high blast counts in the blood and with monocytic leukemias, especially the M4EO lineage. CNS involvement in acute leukemia is more common in patients with high blast counts in the blood and with monocytic leukemias, especially the M4EO lineage. CNS involvement in acute leukemia is confirmed by the presence of leukemia cells in the CSF. The treatment of CNS leukemia consists of cranial irradiation and the administration of cytotoxic agents directly into the cerebrospinal fluid. In patients with CNS leukemia, cranial irradiation is usually administered first, followed by intrathecal chemotherapy with methotrexate and cytosine arabinoside. The use of cranial irradiation is controversial, and some investigators advocate the use of intrathecal chemotherapy alone. The treatment of patients with CNS leukemia is usually initiated at the time of the initial diagnosis of acute leukemia, and the frequency of CNS involvement is dependent on the leukemia cell type. The risk of CNS involvement is highest in patients with M4EO leukemia, and lowest in patients with M1 acute myeloid leukemia.

**BIOLGY AND IMMUNOLOGIC THERAPIES OF ACUTE LEUKEMIAS**

Modern attempts to treat acute leukemias with agents designed to alter the biology and growth of the leukemic cells or to kill the cells via immunologic means have met with limited success. Early work on nonspecific immunostimulators such as interferon, IL-2, and lymphotoxin in the setting of advanced disease, more recently these agents have been proposed for use after induction therapy to eliminate residual leukemia. Treatment of the CSF in patients with AML is not indicated at presentation. In patients with ALL, the CSF should be examined routinely during the initiation of treatment and prophylactic intrathecal chemotherapy should be administered; more aggressive therapy should be initiated if the CSF is involved (as described previously). In AML, CNS disease is more common in patients with high blast counts in the blood and with monocytic leukemias, especially the M4EO lineage. CNS involvement in acute leukemia is confirmed by the presence of leukemia cells in the CSF. The treatment of CNS leukemia consists of cranial irradiation and the administration of cytotoxic agents directly into the cerebrospinal fluid. In patients with CNS leukemia, cranial irradiation is usually administered first, followed by intrathecal chemotherapy with methotrexate and cytosine arabinoside. The use of cranial irradiation is controversial, and some investigators advocate the use of intrathecal chemotherapy alone. The treatment of patients with CNS leukemia is usually initiated at the time of the initial diagnosis of acute leukemia, and the frequency of CNS involvement is dependent on the leukemia cell type. The risk of CNS involvement is highest in patients with M4EO leukemia, and lowest in patients with M1 acute myeloid leukemia.

IL-2, which promotes the growth of T cells and natural killer cells and activates natural killer cells to become lymphokine-activated killer cells, has demonstrated potent activity in vitro in stimulating autologous effector cells to kill leukemia blasts, and to block leukemia cell growth in culture. In vivo and in mouse models, IL-2 has shown significant antileukemia effects in inverse relationship to the leukemia burden. Clinical trials of IL-2 have shown significant antileukemia effects. Inverse relationship to the leukemia burden. Therefore, studies have focused on the use of IL-2 in patients in remission or posttransplantation. There is some preliminary evidence that relapse rates may be reduced in AML but not in ALL. IL-2 is also under investigation as a means to enhance specific therapy with monoclonal antibodies directed to AML cells, because of its ability to enhance antibody-dependent cellular cytotoxicity. Passive soroetherapy in relapsed ALL and AML has generally not been effective because of the lack of antibody potency, rapid loss of the target antigen from the leukemia cell surface, and development of human antimurine antibody responses. Attempts to use genetically engineered humanized antibodies, which have greater potency and can be repeatedly infused, have begun to show activity in the setting of residual disease, particularly in APL. A new drug-conjugated antibody and an

Specific monoclonal antibody therapy of acute leukemia has been under investigation since 1981 using passively infused murine monoclonal antibodies, radiolabeled monoclonal antibodies, immunotoxins, and, most recently, genetically engineered humanized monoclonal antibodies. Passive soroetherapy in relapsed ALL and AML has generally not been effective because of the lack of antibody potency, rapid loss of the target antigen from the leukemia cell surface, and development of human antimurine antibody responses. Attempts to use genetically engineered humanized antibodies, which have greater potency and can be repeatedly infused, have begun to show activity in the setting of residual disease, particularly in APL. A new drug-conjugated antibody and an
alpha-eflamin receptor expression should have no significant activity in relapsed AML as well. Randomized trials to assess the effectiveness of these approaches are in progress. The application of radiolabeled monoclonal antibodies as an ablative agent before BMT in patients with acute leukemia is also under study. CR rates approaching 100% have been achieved using these combined modalities, without detriment to engraftment or significant worsening of toxicity associated with the transplant; the demonstration of a therapeutic advantage of this approach in survival awaits randomized studies.

Antibody therapy can also be used ex vivo to purge bone marrow of residual leukemia before autologous reinfusion. Though initial clinical results are encouraging, no randomized studies confirming the efficacy of this approach have been reported.

Active specific immunotherapy (vaccine therapy) has been explored for its potential in the treatment of leukemias. In principle, peptide sequences derived from oncoproteins and translocated fusion proteins may serve as leukemia-specific targets for stimulated cytolytic T cells. Such approaches are most likely to be effective in the setting of minimal disease or transplantation.

CONCLUSIONS

Two decades of empiric therapy in leukemia have led to long-term cures in a fraction of adult patients with acute leukemia. Advances in the molecular genetics, immunology, and biology of normal and neoplastic hematopoiesis have produced significant progress in understanding the pathogenesis of acute leukemia. This knowledge is leading to an expansion of new, sensitive molecular assays for minimal disease, new diagnostic and prognostic tests, and to more specific, and less toxic therapies. Further, a large gap exists between patients who ultimately achieve remission and those who are ultimately cured. The appropriate care of patients with leukemia requires specialized resource and remains a difficult and complicated task with significant morbidity and mortality. Patients with acute leukemias should continue to be referred to cancer centers and enrolled in investigational treatment protocols until a greater number of patients achieve long-term survival.

CHAPTER REFERENCES


INTRODUCTION

Chronic myelogenous leukemia (CML) is a clonal myeloproliferative disorder of a pluripotent hematopoietic progenitor cell. It is characterized by excessive proliferation of marrow granulocytes, erythroid precursors, megakaryocytes, and connective tissue–forming cells. Clonal proliferation and transformation of myeloid progenitor cells usually dominate the clinical picture. The CML cells harbor a distinctive cytogenetic abnormality, the Philadelphia chromosome (Ph). It results from a translocation between the long arms of chromosomes 9 and 22. Segments of the \( ABL \) gene on chromosome 9 are fused to segments of \( BCR \) on chromosome 22. The \( BCR-ABL \) fusion genes are translated into chimeric proteins with increased tyrosine kinase activity such as p210. Downstream signaling events, which heavily involve ras pathways, eventually activate genes responsible for the uncontrolled proliferation of the leukemic clone.

CML is divided into three clinical phases. The benign or chronic phase may last for a few years. Transformation through an accelerated phase into a blastic phase typically follows. Whereas outcome in the transformed phases is still unsatisfactory, advances in stem cell transplantation (SCT), interferon-based therapies, and supportive care have had a major effect on prognosis in chronic phase disease. Novel treatments based on immunomodulation and our increasing understanding of signal transduction pathways in the leukemic cells have generated new targets for therapy that are currently being investigated in clinical trials.

Current state-of-the-art therapies result in increasing numbers of patients who achieve complete cytogenetic remissions. However, highly sensitive molecular assays such as fluorescence in situ hybridization (FISH) or polymerase chain reaction (PCR) frequently detect \( BCR-ABL \) rearrangements in these patients. In many cases, these patients stay in remission for many years, raising the question of the significance of molecular cures versus functional cures and the mechanisms that sustain these remissions. Thus, CML has not only become a paradigm for our understanding of leukemogenesis and targeted drug development, but is also an ideal model for the study of minimal residual disease in hematologic malignancies.

EPIDEMIOLOGY

Some 4000 to 5000 patients are diagnosed with CML in the United States annually. The incidence of CML is 1 to 2 per 100,000 population with a male to female ratio of 1.4 to 2.2:1.0. CML accounts for 7% to 15% of leukemias among adults. The median age at presentation is between 45 and 55 years. One-third of the patients are older than 60 years. This incidence used to be higher in earlier studies and the more recently reported decrease may be a consequence of earlier detection, referral of younger patients to large centers, and exclusion of patients with CML-like conditions such as chronic myelomonocytic leukemia, Ph-negative CML, or other myeloproliferative disorders. Nevertheless, the proportion of patients over age 60 is important when considering therapeutic options such as allogeneic SCT, which is associated with a high treatment-related mortality, or interferon-\( \alpha \) (IFN-\( \alpha \)), which has more side effects in older patients. CML is uncommon in children and adolescents in whom it accounts for less than 5% of the leukemias.

ETIOLOGY AND PATHOGENESIS

ETIOLOGY

The etiology of CML is unknown. There is little evidence for genetic factors linked to CML. Lack of concordance in monozygotic twins and the demonstration of Ph in hematopoietic progenitor cells only, suggest that CML is an acquired disorder. Offspring of parents with CML do not have a higher incidence of CML than the general population. The incidence of CML is higher among survivors of the atomic bomb explosions in Hiroshima and Nagasaki. Effects of therapeutic doses of radiation on the development of CML are disputed. No association has been established with infectious agents.

MOLECULAR PATHOGENESIS

More than 90% of patients with the clinical picture of CML demonstrate Ph in 95% to 100% of marrow cell metaphases. Through a reciprocal translocation between the long arms of chromosomes 9 and 22, a large 3' segment of the \( ABL \) gene on chromosome 9q34 is fused to a 5' segment of the \( BCR \) gene on chromosome 22q11, creating a hybrid \( BCR-ABL \) gene on 22q11 and, in two-thirds of patients, a reciprocal \( ABL-BCR \) gene on chromosome 9q34. In most cases, \( ABL \) exons 2 to 11 (also referred to as \( a2 \) to \( a11 \)) are transposed into the major breakpoint cluster region (M-bcr) of \( BCR \) between exons 13 or 14 (also called \( b2 \) or \( b3 \)). The \( BCR-ABL \) fusion mRNA extends over 8.5 kb and contains a \( b2a2 \) or \( b3a2 \) junction. It is translated into a chimeric protein of 210 kDa called p210. In most cases, CML cells express either \( b2a2 \) or \( b3a2 \) transcripts, but in approximately 5% alternative splicing causes expression of both forms. No significant difference exists with respect to response to treatment, prognosis, or clinical features, except for a higher platelet count in patients with \( b3a2 \) transcripts.

In rare cases of CML, but in 50% of adults and up to 80% of children with Ph-positive acute lymphoblastic leukemia, the breakpoint on chromosome 22 is located centromeric to the major breakpoint cluster region (M-bcr). The \( e1a2 \) fusion gene is translated into a protein of 190 kDa termed p190. A third breakpoint location occurs telomeric from M-bcr, creating a fusion transcript with an \( e19a2 \) junction and a protein of 230 kD termed p230 (Fig. 46.3-11). Expression of p190 in CML has been associated with monocytosis, and of p230 with the chronic neutrophilic leukemia variant and with thrombocytosis.
In approximately two-thirds of cases, the reciprocal ABL-BCR rearrangement can be detected on the derivative chromosome 9q+. The 5' remnant of ABL exon 1 is transposed to the 3' tail of BCR exons 14 or 15 (b3 or b4). No pathogenetic role in CML has been documented for this rearrangement. 22

Both in vitro and in vivo animal experiments using transgenic mice and retrovirus-mediated gene transfer into murine hematopoietic cells have demonstrated that expression of BCR-ABL can imitate the clinical manifestations of CML, including the progression from chronic to blastic phase. Thus, the combined data from animal experiments support the role of BCR-ABL and its fusion proteins as central mediators of myeloid proliferation and transformation in CML. 24

Whereas ABL encodes a nonreceptor tyrosine kinase (p145) whose activity is rigorously controlled and which is involved in signal transduction and regulation of cell growth, p210 and p190 show increased and uncontrolled kinase activity. Constitutive activation of the kinases initiates downstream signaling pathways that up-regulate transcription of genes mediating proliferation and transformation of CML hematopoietic progenitor cells. A central element of BCR-ABL signaling is Ras. Activation of Ras is mediated through a series of adapter proteins that in turn also connect p210 to other kinases and signal transduction systems. 22

CELLULAR PATHOGENESIS

CML is dominated by expansion of myeloid progenitor cells at various stages of maturation, their premature release into the circulation, and their tendency to home to extramedullary sites. Clonal expansion may also involve the erythroid, megakaryocytic, and B- as well as occasionally T-lymphoid lineages. The disorderly expansion of leukemic progenitors in chronic phase may reflect both alterations in their proliferative activity and shifts in the balance of self-renewal and differentiation. Although Ph-positive primitive hematopoietic cells (long-term culture-initiating cells) are found in lower frequencies than are colonies of normal progenitor cells and have a longer generation time, they may undergo additional cell divisions. 12 Leukemic progenitor mass is also increased by altered regulation at the stem cell level, shifting the balance between self-renewal and differentiation toward the differentiating cell pool, a process that has been referred to as discordant maturation. 21 Stem cells become part of the proliferating compartment, causing the neoplastic population to expand exponentially in later maturational compartments. At this stage, leukemic progenitor cells may also be less responsive to growth regulatory signals from either cytokines or the bone marrow microenvironment. 22-24 Defective adherence of CML progenitors to bone marrow stromal elements further facilitates their premature release into the peripheral blood. 22 Although differentiation remains relatively unaffected during chronic phase disease, transforming events in accelerated and blastic phase substantially deregulate the delicate balance between normal and leukemic progenitor colonies, leading to maturation arrest similar to events observed in acute leukemias.

DIAGNOSIS AND CLINICAL COURSE

CLINICAL MANIFESTATIONS

CML is a triphasic disease (Table 46.3.1-1). At diagnosis, more than 90% of patients are in chronic phase. Symptoms at presentation reflect the increase in mass and turnover of the CML hematopoietic progenitor cells. Patients may complain of lethargy and weakness, night sweats, and weight loss. Increase in abdominal girth and abdominal discomfort may be due to an enlarged spleen. Less frequently, easy bruising and bleeding are recorded due to platelet dysfunction. Ten percent to 20% of patients from older series and as many as one-half of patients in more recent studies have no symptoms and are diagnosed by routine blood tests. Presentations in accelerated or blastic phases occur in 5% to 10%. Splenomegaly occurs in up to 50% and is the most common finding on physical examination. Generalized lymphadenopathy and fever, rare in chronic phase, may indicate an accelerated disease course. 22,23

TABLE 46.3.1-1. Phases of Chronic Myelogenous Leukemia

LABORATORY TESTS

Peripheral Blood and Bone Marrow

Myeloid hyperplasia in the marrow associated with neutrophilic leukocytosis, thrombocytosis, and basophilia in the peripheral blood are typical chronic phase CML laboratory features. Peripheral blood leukocytosis exceeding 100 × 10^9/L occurs in 70% to 90% of patients. Anemia of varying degrees is frequent. The marrow is markedly hypercellular with a myeloid to erythroid ratio between 9:1 to 15:1. Myeloid cells display all stages of maturation, with a preponderance of myelocytes and promyelocytes. Megakaryocytes are frequently increased, especially in accelerated phase. Marrow fibrosis is focal in early disease stages and may progress to a more diffuse pattern with disease evolution. 22

Cyto genetic Analysis

Cyto genetic analysis is the gold standard for demonstration of the Ph translocation and other abnormalities that occur frequently with disease progression (clonal evolution). 24 Cyto genetic analysis is tedious and time-consuming, and only 20 to 25 metaphases per sample are examined. In approximately 10% of patients with CML, no t(9;22) is detected by cyto genetic analysis. However, in up to one-third of these patients, molecular studies detect BCR-ABL rearrangements. The remaining patients are Ph and BCR-ABL negative. These patients carry a worse prognosis and have to be distinguished from typical CML (Table 46.3.1-2). 24

![FIGURE 46.3.1-1. Probability of survival after human leukocyte antigen--identical sibling stem cell transplantation for chronic myelogenous leukemia in chronic phase by age, 1991 through 1997. (International Bone Marrow Transplant Registry data, with permission.)](image-url)
Molecular Analysis

Molecular assays are used in the diagnosis of CML and the assessment of response to therapeutic modalities. PCR, Southern and Northern blot, and immunoprecipitation can determine the exact breakpoints of the fusion genes, detect BCR-ABL transcripts at the RNA level, and demonstrate the p210 protein using antibodies against the N-terminal region of BCR and the C-terminal region of ABL.

Patients on therapy are frequently monitored by PCR and FISH. FISH allows analysis of metaphase and nondividing interphase cells and is easily quantifiable. Interphase FISH can be performed on peripheral blood specimens. However, it overestimates the degree of cytogenetic responses at high Ph-positive percent values and has a false-positive rate of up to 10%. Hypermetaphase FISH is as time efficient as interphase FISH, does not generate false-positive results, but cannot be done on peripheral blood samples. The use of double color probes for FISH is being investigated and may have superior sensitivity and specificity.

PROGRESSION OF CHRONIC MYELOID LEUKEMIA

When treated with chemotherapeutic agents such as hydroxyurea or busulfan, CML invariably progresses into an accelerated phase that is followed after 3 to 18 months by a blastic transformation. Criteria for the definition of accelerated and blastic phase disease have been proposed (see Table 46.3.1-1).

Whereas Ph predominates throughout chronic phase, up to 80% of patients develop additional cytogenetic abnormalities when they progress (clonal evolution). Common changes during clonal evolution of CML are trisomy 8, isochromosome i(17q), trisomy 19, and an additional Ph. Trisomy 8 and isochromosome i(17q) are common during myeloid transformation. Alterations of molecular markers during clonal evolution include p53, RB1, c-MYC, p16, Ras, and AML/EVI-1, a fusion protein resulting from translocation t(3;21)(q26;q22). Abnormalities of p53 occur in 20% to 30% of patients and are mainly associated with myeloid transformation.

Loss of function of p53 has been associated with suppression of apoptosis and progression into blastic phase. Abnormalities of RB1 have been associated with lymphoid transformation.

TREATMENT

Criteria for assignment of response to therapies are summarized in Table 46.3.1-3. A number of poor prognostic features have been identified, and prognostic systems have been developed in CML (Table 46.3.1-4). These systems allow patients to be categorized into good-, intermediate-, and poor-risk groups with respective median survivals of 6, 3 to 4, and 2 years in patients receiving conventional therapy. These models are useful in evaluating the effect of new strategies within different risk groups (see Table 46.3.1-4).

HISTORICAL AND CONVENTIONAL TREATMENTS FOR CHRONIC MYELOGENOUS LEUKEMIA

The median survival of patients with CML used to be 3 years, and less than 20% of patients were alive 5 years after diagnosis. Nowadays, patients in chronic phase can expect a median survival time of 5 to 7 years, and up to 9 years in good-prognosis patients. Five and 10-year survival rates are 60% to 70% and 30% to 40%, respectively. Earlier diagnosis, better supportive care, and more effective anti-CML therapies account mostly for this change.

The use of arsenicals (Fowler’s solution) was first advocated for the treatment of CML in 1856. In the early 1900s up to approximately 1950, total body or splenic radiation therapy was shown to be effective in controlling the signs and symptoms of CML. Its benefit was, however, short-lived and the overall survival was not affected significantly. It is a rarely used modality today.

In the early 1950s, oral alkylating agents such as busulfan became the new mainstay of treatment. Busulfan is inexpensive and allows long periods of hematologic
control, but may be associated with serious side effects such as delayed myelosuppression and pulmonary toxicities (Table 46.3.1-5). Busulfan was replaced by hydroxyurea in the 1970s. Hydroxyurea is a cell-cycle–specific inhibitor of DNA synthesis that allows rapid hematologic control and is well tolerated (see Table 46.3.1-5). Both hydroxyurea and busulfan cause complete hematologic remissions in up to 80% of patients. Cytogenetic remissions occur, but are rare, and neither agent has any notable effect on the natural course of the disease. In a large randomized study, both median survival (56 vs. 44 months) and median duration of chronic phase (47 vs. 37 months) were significantly longer in patients treated with hydroxyurea compared with busulfan. Busulfan therapy before allogeneic SCT has also an adverse outcome on posttransplant survival (3-year disease-free survival of 61% for patients treated with hydroxyurea vs. 45% for patients on busulfan).

While other agents (dibromomannitol, melphalan, 6-mercaptopurine, 6-thioguanine, cyclophosphamide, chlorambucil) have also been used in the treatment of CML, they have been associated with worse outcome. Uncontrolled thrombocytosis on therapy with hydroxyurea may respond to anagrelide, the addition of IFN-α, or intermittent therapy with thiotepa (75 mg/m² intravenously every 2 to 4 weeks).

Splenectomy may benefit occasional patients with persistent and symptomatic splenomegaly and refractory cytopenias. Splenectomy pretransplant reduces the time to marrow recovery, but does not influence long-term prognosis.

TABLE 46.3.1-5. Dosage and Side Effects of Hydroxyurea and Busulfan in the Management of Patients with Chronic Myelogenous Leukemia

While other agents (dibromomannitol, melphalan, 6-mercaptopurine, 6-thioguanine, cyclophosphamide, chlorambucil) have also been used in the treatment of CML, they have been associated with worse outcome. Uncontrolled thrombocytosis on therapy with hydroxyurea may respond to anagrelide, the addition of IFN-α, or intermittent therapy with thiotepa (75 mg/m² intravenously every 2 to 4 weeks).

STEM CELL TRANSPLANTATION

Matched Related Allogeneic Stem Cell Transplantation

SCT has become an effective treatment for CML and can cure a substantial proportion of carefully selected patients with suitable donors. In most studies of chronic phase CML, projected actuarial 3-year to 5-year survival rates range between 50% and 60%, with values up to 80% in large centers. Relapses occur in 15% to 30%, and plateau at 5 to 7 years after transplantation, suggesting a cure for some patients. Late relapses 10 to 12 years posttransplant can occur. Allogeneic SCT is limited by availability of matched siblings and age restrictions. Less than 30% of patients in Europe and North America receive SCT from matched sibling donors.

Transplant-related mortality ranges between 10% and 40%, but can be as high as 68% in subgroups of patients who receive marrows from mismatched or unrelated donors. Several variables influence transplant outcome:

**AGE.** Younger patients do best (see Fig. 46.3.1-1): Disease-free survival is from 60% to 70%, transplant-related mortality 10%, and probability of relapse 20%. Above age 20, patients appear to have a continuous and inverse relationship between age and survival. Older patients do worse mainly because of an increased treatment-related mortality in this age group; the relapse rates are similar. One center reported favorable outcomes for carefully selected patients above age 50: The 2-year estimated survival rate among 57 such patients was 80%. Results from other transplant centers or registry studies are worse. In the International Bone Marrow Transplant Registry (IBMTR), patients over age 45 had a treatment-related mortality of 47% and a 5-year disease-free survival rate of 25%.

**PHASE OF DISEASE.** The largest effect of treatment is achieved in the chronic phase of CML. Disease free survival rates decrease from 40% to 60% in chronic phase to less than 15% in blastic phase (Fig. 46.3.1-3). Transplantation in transformed CML phases is accompanied by increased rates of leukemia relapse and treatment-related mortality. Posttransplant outcome in accelerated phase is better when clonal evolution is the single criterion for disease acceleration: Disease-free survival up to 60% has been reported in these patients. Timing of transplantation in chronic phase is more controversial. Based on earlier data, most centers propose transplantation in early chronic phase CML (i.e., within 1 year of diagnosis) (Fig. 46.3.1-3). However, updates of these data suggest similar rates for 5-year disease-free survival for transplants performed within 12 to 24 months from diagnosis and a critical prognostic cut-off point at around 2 years from diagnosis is suggested.
PRETRANSPLANT CHEMOTHERAPY. Anti-CML therapy before transplantation influences posttransplant outcome. Disease-free survival at 5 years is significantly higher in chronic phase patients pretreated with hydroxyurea than with busulfan (61% vs. 45%). Prior therapy with IFN-a does not appear to affect outcome of matched related SCT. The influence of IFN-a on matched unrelated donor transplantation is more controversial. 57, 58

PREPARATIVE REGIMENS. Results are conflicting regarding the best preparative regimen. Virtually all regimens produce toxic effects, with severe mucositis of the gastrointestinal tract being most common. The combination of busulfan with cyclophosphamide appears as effective as the combination of cyclophosphamide with total body irradiation, except for the more unfavorable toxicity profile of the latter. 59

GRAFT-VERSUS-HOST DISEASE PROPHYLAXIS. Acute graft-versus-host disease (GVHD) occurs in 8% to 63% of patients and is the cause of death in up to 13%. The rates for chronic GVHD can be as high as 50% with a mortality of up to 10%. The use of methotrexate with cyclosporine has resulted in better outcomes than single methotrexate or methotrexate in other combinations. 60 T-cell depletion pretransplant improves tolerance and reduces treatment-related mortality. However, this advantage is offset by increased leukemia relapse, indicating the importance of immune-mediated effects (e.g., graft-versus-leukemia effect) in maintaining remission in CML. 61-64

The incidence of relapse posttransplant ranges from 10% to 70%. It is lowest in patients transplanted in chronic phase and highest in blastic phase. 65 Second transplants from human leukocyte antigen (HLA)-identical sibling donors can achieve disease-free survival rates up to 30%. Results, however, depend on the time interval between transplant and relapse and are most favorable in the setting of a long first remission duration. 66 IFN-a may induce long-lasting cytogenetic remissions in 20% to 40% of patients with cytogenetic relapse in chronic phase postallogetic SCT. 67 Donor lymphocyte infusions (DLI) have generated cytogenetic and complete hematologic response rates in 60% to 80% of patients. Disease-free survival at 3 years is between 40% and 85%. Responses are considerably less frequent and short-lived in transplanted CML phases. A strong correlation exists between development of GVHD and response to DLI, which supports a role for the graft-versus-leukemia activity generated by infused donor T lymphocytes. DLI toxicity can be substantial and includes myelosuppression and severe GVHD. 68

Matched Unrelated Donor Transplants

It is possible to identify HLA-compatible unrelated donors for approximately half the patients who lack an HLA-matched sibling through the National Marrow Donor Program in the United States and similar transplant registries throughout the world. The median time from donor search to transplant is approximately 6 months. Although encouraging results have been obtained with matched unrelated donor transplants, they are associated with significant treatment-related morbidity and mortality depending on age and degree of matching. 69 Graft failure as well as severe acute and extensive chronic GVHD contribute to a treatment-related mortality above 50% in some groups of patients. Good-risk patients for matched unrelated donor transplants are younger (less than 30 years), in early chronic phase, cytomegalovirus seronegative, and have received non-T-cell–depleted marrow infusions. 70 Molecular matching is emerging as a highly significant parameter of treatment outcome. The EBMT group analyzed the effect of HLA class II matching on results of matched unrelated donor transplants in 368 patients, two-thirds of whom had been transplanted in chronic phase. 71 Matching at the HLA-DRB1 locus was the most significant factor influencing overall survival, disease-free survival, and treatment-related mortality. Patients transplanted in first chronic phase, with non–T-cell–depleted marrows, and a matched HLA-DRB1 locus had a 2-year survival of 51%, a treatment-related mortality of 47%, and a relapse rate of 2%. Treatment-related mortality was 80% for HLA-DRB1 mismatches.

In carefully selected patients, 5-year survival rates may be as high as 70%, relapse rates less than 10%, rates of graft failure below 10%, and rates of severe acute GVHD below 50%. Until experience with matched unrelated donor transplants has matured, it should be offered preferentially to younger patients in chronic phase who are resistant to IFN-a and who have a fully matched donor available. 72

Intensive Chemotherapy and Autologous Transplantation

Autografting with unpurged autologous marrow generates transient cytogenetic responses, but a survival advantage has not been proven. 73 Relapse due to reinfused, Ph-positive cells may occur. 74

To reduce contaminating Ph-positive cells, several purging strategies have been developed. These include in vitro manipulations with cyclophosphamide derivatives and biologic response modifiers (interferon-g, interleukin-2), tyrosine kinase inhibitors, antiretroviral oligonucleotides, ribozymes, positive or negative selections based on phenotype determination or long-term bone marrow cultures, and high-dose combination chemotherapy.

Intensive chemotherapy, to eradicate Ph-positive clones, was patterned after acute leukemia programs. Cytogenetic remissions were induced in 60% to 70% of patients and were complete in 35% to 50%. However, the cytogenetic responses were brief and not improved by maintenance with IFN-a. 75 Intensive chemotherapy has been used preceding autologous SCT as a method for in vivo purging that allows collection of Ph-negative marrow and peripheral blood stem cells during early hematopoietic recovery. 76

INTERFERON-a

IFNs are a complex group of naturally occurring proteins produced by eukaryotic cells in response to various stimuli. They have pleiotropic biologic activities including inhibition of cellular proliferation, regulation of cytokine expression, and modulation of the immune system. IFNs consist of three distinct groups of peptides: IFN-a, IFN-b, and IFN-g. IFN-a and IFN-g are acid stable, bind to the same receptor, and are produced by leukocytes and fibroblasts, respectively. IFN-g is an acid-labile, structurally distinct molecule that binds to a different receptor and is produced mainly by T lymphocytes. 77 IFN-a has been used most commonly in the treatment of solid and hematologic malignancies. The mechanism of action of IFN-a is not known. While antiproliferation is thought to be important, other possible mechanisms include (1) restoration of cytoadhesion of hematopoietic cells to marrow stroma; (2) immunomodulation; and (3) antiangiogenesis.

Single-Arm Studies of Interferon-a in Chronic Myelogenous Leukemia

The clinical activity of interferons in CML was first demonstrated with partially purified IFN-a (Finnish Red Cross, Helsinki), given at doses of 3 to 9 million U/d to early chronic phase patients. Preliminary studies showed that laboratory indices of disease activity (elevated lactate dehydrogenase and B12 levels, increased bone marrow cellularity) normalized among responding patients. Subsequently, cytogenetic responses with various degrees of Ph suppression were found in 41% of the patients. 78

In the original studies at M. D. Anderson Cancer Center, patients received IFN-a at a dose of 5 million U/m2 or the maximally tolerated lower dose daily. 79 Complete hematologic response rates were 80% and cytogenetic response rates 58%. The estimated median survival was 89 months. Achieving a cytogenetic response after 12 months of therapy conferred a significant survival benefit by landmark analysis. 5-year survival rates from 12 months into therapy were 90% with a complete cytogenetic response, 88% with a partial cytogenetic response, 76% with a minor cytogenetic response, and 38% in other response categories (P < .001) (Fig. 46.3.1-4). The benefit of cytogenetic response was identified by multivariate analysis, introducing it as a time-dependent variable. It was also observed within each risk group. The 4-year survival data from the 12-month landmark analysis in good-risk patients was 79% with cytogenetic response versus 62% without cytogenetic response (P < .01). In the intermediate-risk group the rates were 52% versus 35% (P < .01); and in the poor-risk group these rates were 83% versus 39% (P < .01). This study confirmed the independent effect of achieving a cytogenetic response on prolongation of survival, and supported efforts aimed at suppressing Ph-positive clones. Among patients with good-risk disease (50% of patients), the median survival was 102 months, and the major cytogenetic response rate 50%.
Three other trials reported similar results (Table 46.3.1-6). The high hematologic and cytogenetic response rates observed with IFN-a were dose-dependent. Furthermore, survival was significantly influenced by achieving a complete hematologic response at 3 months and a cytogenetic response at 12 months of treatment with IFN-a (see Fig. 46.3.1-4).

Achievement of cytogenetic response was associated with prolonged survival in the Italian and Japanese trials and in an updated report of the Medical Research Council data from the United Kingdom. An updated report from the Italian Cooperative Study Group on CML with prolonged follow-up (range, 95 to 129 months) demonstrated continued significantly better survival for patients on IFN-a versus chemotherapy. Median and 10-year survival of low-risk patients were 104 months versus 64 months and 47% versus 30% (P = .03), and 69 months versus 46 months and 16% versus 5% for intermediate and high-risk patients (P = .006), respectively. The German trial found a survival benefit with both IFN-a and hydroxyurea therapy compared with busulfan, but no difference between IFN-a and hydroxyurea. When the data were updated for patients who were on IFN-a for more than 3 months and when intended versus actually delivered therapy was considered, survival was better with IFN-a than with hydroxyurea.

A metaanalysis compared IFN-a with chemotherapy in CML and suggested better survival with IFN-a (57% at 5 years) than with either hydroxyurea (P = .001) or busulfan (P = .00007) (42% at 5 years).

**Interferon-a in Combination with Cytosine Arabinoside**

IFN-a alone in late chronic and accelerated phases of CML yielded modest results. In a study from M. D. Anderson Cancer Center, 140 patients with Ph-positive early chronic phase CML received IFN-a (5 million U/m²) in combination with low-dose Ara-C, 10 mg subcutaneously daily, or intermittent Ara-C (7 d/mo). With daily IFN-a and daily Ara-C, complete hematologic responses were seen in 92% of patients and cytogenetic responses in 74% (major 50%, complete 31%). The estimated 4-year survival rate was 70%. The median time to achievement of a major cytogenetic response was also significantly shorter with daily Ara-C (P <.01).

In a French trial, 721 patients in early chronic-phase CML received either hydroxyurea (50 mg/kg), and IFN-a (5 million U/m²) alone, or with monthly courses of Ara-C (20 mg/m² × 10 d/mo). The complete hematologic response rate was 66% in the IFN-a plus Ara-C group and 55% in the IFN-a group (P = .003). Patients treated with IFN-a and Ara-C survived significantly longer than did patients treated with IFN-a (3-year survival rate 86% vs. 79%, P = .02). This difference remained independently significant by multivariate analysis. Patients achieving a cytogenetic response with either IFN-a alone (P < .001) or with IFN-a plus Ara-C (P < .001) had a significantly longer survival than those who did not achieve a cytogenetic response.

The Italian Cooperative Study Group on CML randomized 540 patients in chronic phase CML to IFN-a alone (median dose, 3.65 million U/m²) versus IFN-a (median dose, 3.8 million U/m²) with low-dose Ara-C (40 mg/kg/d subcutaneously × 10 d/mo). Cytogenetic responses were observed in 54% of patients on IFN-a plus Ara-C versus 47% in the IFN-a group. The rate of major and complete cytogenetic responses was significantly higher in the combined treatment arm (28% vs. 19%, P = .01). At a median follow-up of 24 months, the study demonstrated a significantly higher survival rate among good-risk patients with IFN-a plus Ara-C versus IFN-a alone (3-year survival rates 85% vs. 80%, P = .03).

**Toxicities of Interferon-a and Clinical Management**
Toxicities are common with IFN-a. Almost all patients experience some constitutional side effects, up to 50% of patients require dose reductions, and discontinuation of treatment due to toxicity is necessary in up to 18%. Early adverse effects consist of flu-like symptoms and include fever, chills, postnasal dripping, and anorexia. These are usually not dose limiting, can be managed symptomatically (Table 46.3.1-8), and abate once tachyphylaxis develops within 1 to 2 weeks. Common chronic side effects are fatigue, depression, insomnia, weight loss, alopecia, reduced libido, and impotence. Neurotoxicity (lack of concentration, depression, psychosis) is more common in patients with psychiatric problems and those 60 years and older. Autoimmune phenomena occur in less than 5% of patients: hemolytic anemia and thrombocytopenia, Raynaud's phenomenon, collagen vascular disorders, hypothyroidism, and nephrotic syndrome. Cardiac arrhythmias and manifestations of congestive heart failure are rare but mandate discontinuation of therapy as do severe autoimmune phenomena, severe neurotoxicity, and refractory depression.

**NEW AGENTS AND APPROACHES**

**TABLE 46.3.1-8. Side Effects and Guidelines for Therapy with Interferon-a in Chronic Myelogenous Leukemia**

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early adverse effects</td>
<td>Consist of flu-like symptoms and include fever, chills, postnasal dripping, and anorexia. These are usually not dose limiting, can be managed symptomatically.</td>
</tr>
<tr>
<td>Toxicity</td>
<td>Necessary in up to 18% of patients.</td>
</tr>
<tr>
<td>Chronic side effects</td>
<td>Fatigue, depression, insomnia, weight loss, alopecia, reduced libido, and impotence.</td>
</tr>
<tr>
<td>Neurotoxicity</td>
<td>Lack of concentration, depression, psychosis.</td>
</tr>
<tr>
<td>Autoimmune phenomena</td>
<td>Occur in less than 5% of patients: hemolytic anemia and thrombocytopenia, Raynaud's phenomenon, collagen vascular disorders, hypothyroidism, and nephrotic syndrome.</td>
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</table>

**FIGURE 46.3.1-5. Clinical decision making in chronic myelogenous leukemia (CML).** For patients in early chronic phase CML, allogeneic stem cell transplantation (SCT) and interferon-a are possible first-line therapies. The decision depends on several factors: (1) availability of a matched sibling; (2) age and performance status of the patient; (3) presence of other comorbid conditions; and (4) socioeconomic situation. For patients who have a matched sibling donor and whose physical condition allows SCT with an acceptable treatment-related morbidity and mortality (less than 20%), allogeneic SCT should be the first choice. For other patients, a trial with interferon-a may be preferred given the manageable side-effect profile with absence of treatment-related mortality. Furthermore, a prospective study on 840 patients below age 56 with chronic phase CML found increased survival with matched sibling allogeneic transplant only in those patients who were younger than 32 years and had intermediate- or high-risk CML. Patients in late chronic phase or accelerated phase should be offered investigational therapies or undergo allogeneic transplantation. Delaying allogeneic SCT in favor of IFN-a has raised concerns including worse transplant outcome in late chronic phase CML, adverse effects of prior IFN-a therapy on SCT, risk of sudden disease transformation while on IFN-a, and the fact that almost all patients treated with IFN-a, even in complete cytogenetic remission, express the BCR-ABL transcript compared with only one-third after successful transplantation. However, studies have shown that postponing allogeneic SCT up to 2 years into chronic phase does not adversely affect outcome. Likewise, prior IFN-a therapy, if discontinued for more than 3 months before transplantation, has no adverse effects on transplantation. The risk of sudden disease transformation is low during the first 3 years. The significance of persisting BCR-ABL transcripts is unknown. Patients in long-term complete cytogenetic remission in whom IFN-a has been discontinued and who are still PCR-positive for BCR-ABL have been reported. This observation is consistent with the situation in many other malignant conditions that are considered to be cured despite persistent expression of molecular markers of disease [translocation (14;18), inv(16), translocation (8;21)]. Moreover, long-term cytogenetic responders on IFN-a may become negative.

**MANAGEMENT OF ACCELERATED AND BLASTIC PHASE CHRONIC MYELOGENOUS LEUKEMIA**

Treatment results in the transformed phases of CML are unsatisfactory. Disease-free survival of selected patients after SCT is less than 15%. IFN-a has no effect on the disease course. Control of elevated white cell counts may be achieved by increasing doses of hydroxyurea and combination with other cytotoxic drugs in the short-term. Symptomatic splenomegaly may be treated with splenectomy. Anemia and thrombocytopenia can be managed with transfusions. New agents and combinations of drugs are being developed and can be offered on investigational protocols.

In one-third of the patients, blastic phase is of lymphoid phenotype with expression of markers such as terminal deoxynucleotidyl transferase (TdT), CD19, CD20, or CD10 common acute lymphoblastic leukemia antigen (CALLA). Most cases with lymphoid blastic phase (80%) coexpress myeloid markers (CD13, CD14, CD33). The remaining two-thirds have an acute myeloblastic or undifferentiated leukemia-like phenotype and form a heterogeneous group. Patients with lymphoid blastic phase respond better to treatment with regimens active against acute lymphoid leukemia. The complete remission rate is 60%, one-half of the patients may have suppression of Ph-positive cells (cytogenetic response), and the remission duration is 9 to 12 months. Patients with myeloid blastic phase have a low objective response rate of 20% to 30%, may respond to high-dose cytosine-arabinoside, other antileukemic agents such as 5'-deoxyazacitidine (decitabine), and to BCR-ABL tyrosine kinase inhibitors.
Tyrosine Kinase Inhibitors

Although many molecules along the signaling cascade can be targeted (blockade of SH3, farnesyl transferase, Ras, further downstream targets), inhibition of phosphotyrosine kinase activity has been studied most extensively. Natural inhibitors of tyrosine kinases (herbimycin A, genistein, erbstatin, lavendustin A), extracted from fungal sources, have only broad specificity for a variety of enzyme substrates. To improve target specificity, synthetic compounds have been modeled after the naturally occurring kinase inhibitors. They have been called tyrophostins, and more than 20 of them are known today. Analysis of some of these compounds (AG1112, AG568) showed a growth-inhibitory effect on CML cell lines in vitro, inhibition of the tyrosine kinase activity of p210, and induction of differentiation and death in a CML blast crisis cell line K562. Identification of the crystal structure of several protein kinases allowed the generation of more specific tyrosine kinase inhibitors. In preclinical studies, signal transduction inhibitor 571 (STI571), formerly known as CGP57148B, was found to (1) inhibit the ABL tyrosine kinase at submicromolar concentrations; (2) inhibit the proliferation of BCR-ABL expressing cell lines; (3) inhibit colony formation of BCR-ABL-positive hematopoietic cell lines; and (4) only minimally inhibit the formation of normal bone marrow colonies. Based on these promising results, phase I clinical studies have been conducted in patients with CML in chronic and in transformed phases. Among 54 patients with chronic phase CML who have failed therapy with IFN-α and received STI571 at doses of 300 mg orally daily and more, 96% achieved a complete hematologic remission and 33% a cytogenetic response. After about 3 months of therapy, the cytogenetic response rate is anticipated to exceed 50%, being complete in over 20% to 30%. Responses in de novo patients treated with STI571 may be even higher. In 46 patients with CML in blast phase (32 myeloid, 14 acute lymphoid leukemia or lymphoid blast crisis), 18 (39%) patients had a complete clearance of bone marrow and bone marrow leukemia cells. The narrow complete response rate for patients with myeloid blast crisis was 29%, but responses were often transient. In accelerated phase, the hematologic response is about 70%, cytogenetic responses have been noted in 20%, and responses appear durable. STI571 was well tolerated and no dose-limiting toxicity has yet been reached except for myelosuppression at doses of 300 to 800 mg orally daily. Side effects included nausea, vomiting, diarrhea, and muscle cramps, mostly mild in nature.

Antisense Oligonucleotides

Antisense oligonucleotides are short DNA sequences modified to bind target RNA sequences within the cell, preventing translation of the RNA message into functional proteins. Effective targets for antisense approaches modify BCR-ABL itself, Ras, PI-3-kinase, c-myc, and c-myc. BCR-ABL antisense oligomolecules alone or in combination with sequences targeted against additional oncogenes reduce the level of p210 bcr-abl in CML cells and slow the rate of growth and proliferation. Antisense sequences directed against BCR-ABL for ex vivo purging in autologous SCT are of interest.

Polyethylene Glycol Interferon

Polyethylene glycol interferon is a modified IFN-α molecule that is covalently attached to polyethylene glycol. Polyethylene glycol interferon has a significantly longer half-life in plasma and can be given in a less painful weekly instead of daily. Early data suggest an improved side-effect profile compared with IFN-α. Complete hematologic remissions and cytogenetic responses have been reported. Results with polyethylene glycol interferon are promising, and further investigations are required to validate its role in the treatment of CML.

Homoharringtonine

Homoharringtonine (HHT) is a plant alkaloid derived from the Cephalotaxus fortunei tree. Used in a low-dose continuous infusion schedule (2.5 mg/m² for 14 days for remission induction followed by a 7-day monthly infusion as maintenance), HHT resulted in complete hematologic remission in two-thirds of patients and cytogenetic response in one-third (one-half of which were major). More than one-half of the patients were resistant to prior therapy with IFN-α. In early chronic phase disease, HHT was given for six cycles as remission induction followed by IFN-α maintenance: Complete hematologic remission was 92% and cytogenetic response rate was 68%. Combinations of HHT with IFN-α and Ara-C in the clinical setting, including early chronic phase CML, are in progress with promising results.

5-Aza-2′-Deoxycytidine

5-Aza-2′-deoxycytidine (decitabine) is a potent hypomethylating agent. Decitabine produced response rates of 25% in blast phase and 53% in accelerated phase. Further clinical trials are in progress including decitabine in combination with busulfan and cyclophosphamide as part of a preparative regimen for allogeneic SCT, and as salvage therapy together with stem cell rescue after relapse from allogeneic SCT.

Adoptive Immunotherapy

That leukemic cell proliferation is under the control of the immune system is based on several observations: (1) there is an increased frequency of disease recurrence with T-cell depleted SCT; (2) GVLs in patients who relapse after an allogeneic transplant reestablish cytogenetic remissions in a high percentage of patients; (3) there is a positive correlation between GVHD and reduced risk of relapse after transplant; and (4) cytogenetic response correlates with IFN-associated autoimmune phenomena. Response to GVLs suggests a pivotal role for graft-versus-leukemia activity generated by infused donor T lymphocytes in suppressing Ph-positive clones.

Research is focusing on identification of (1) specific T-cell clones able to eliminate leukemic progenitors and (2) proteins that can serve as targets, even though only a few tumor express structures unique to them. CML is a good model because p210 is uniquely associated with the Ph translocation. Minor histocompatibility antigens, overexpressed normal antigens, and other leukemia-restricted antigens are studied as further immunologic targets. In one study, cultures of CD34-positive CML progenitor cells incubated with granulocyte-macrophage colony-stimulating factor, interleukin-4, and tumor necrosis factor stimulated the formation in vitro of dendritic cells, leukemic-antigen-presenting cells that are strong inducers of T-cell responses in vitro. Identification of leukemia-specific antigens and stimulation of leukemia-specific T cell responses may allow us to use immunogenicity of CML cells in approaches such as immune gene therapy and peptide vaccination.

Investigational combined modalities using T-cell–depleted allogeneic SCT up front (to reduce GVHD and treatment-related mortality), followed by periodic incremental doses of selected T-cell subsets for DLIs (to eradicate minimal residual disease), may render allogeneic SCT safer and more effective and extend its use to older patients and those with unrelated or mismatched donors.

CONCLUSIONS

CML is one of the most extensively studied human malignancies and a prime example of how advances in our understanding of molecular biology can be translated into novel and effective treatment strategies. The most beneficial treatment for the patient in early chronic phase, transplantation versus IFN–a-based therapy, has to be determined on an individual basis. Numerous patient- and treatment-related factors have to be considered, particularly the acceptable threshold of transplant-related mortality, which may be different for different patients. Socioeconomic and logistic factors may play an increasing role in choosing the most appropriate therapy.

CHAPTER REFERENCES

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**Chapter References**

**INTRODUCTION**

Chronic lymphocytic leukemia (CLL) is the most common form of leukemia affecting adults in Western countries. The current annual incidence estimates vary from approximately 8100 to 12,500 new cases in the United States. An apparent decrease from 3.3 in 100,000 population in 1973 to 2.3 in 100,000 in 1990 may reflect an improved ability to distinguish CLL from other chronic lymphoid leukemias. CLL occurs more often in males, with a relative frequency of 1.3:1 to 2.6:1. The median age at diagnosis of CLL is 62 years; approximately 10% to 15% of patients with CLL present younger than 50 years of age, and 20% are younger than 55 years. A 10-year-old child with CLL has been reported. The increase in younger patients most likely represents the more routine use of automated blood counts and differentials. Although younger patients with stage 0 disease may survive as long as a normal age-matched population, those with more advanced stages of the disease have a median survival comparable to older patients when corrected for non-CLL-related causes of death. CLL occurs more commonly in Jewish people of Russian or Eastern European ancestry, and it is infrequent in Japan, China, and Asian countries.

No clear etiologic factors exist for CLL, although few carefully conducted studies have been performed. CLL is one of the few leukemias that does not appear to be associated with prior exposure to ionizing radiation, chemicals, or drugs, and it was the only leukemia not associated with atomic bomb explosions.

A clear familial incidence of CLL has been established. Approximately 20% of patients with this disease have relatives with CLL or another lymphoid malignancy, although no genetic linkage has yet been identified. Rare sets of twins have been affected. A lack of concordance of oncogene expression was reported in monochromatous twin sisters who both had CLL. Immigrants from Japan to the United States maintain their low incidence of CLL. The occurrence in spouses has been observed.

**CELL OF ORIGIN**

The precise origin of the CLL lymphocyte has not been clearly defined. CLL lymphocytes have been assumed to be the malignant counterpart of normal lymphocytes because of their similar morphology. However, whereas B-CLL cells share some immunologic features with normal B cells, marked molecular and immunologic differences distinguish the two cell populations.

CLL cells express pan-B antigens (e.g., HLA class II, CD19, CD20), as well as activation antigens (e.g., CD5, CD23, CD25, CD71), but terminal differentiation antigens exhibited by plasma cells. This profile supports the hypothesis that the B-CLL cell is an "activated" B lymphocyte, meaning that the cells can be activated without dividing, but it does not suggest that they are in a state of active proliferation. Overexpression of BCL-2 is restricted to the malignant cells. CLL B cells express a restricted repertoire of V_{H} genes, which is distinct from that of normal B cells.

Two major features that distinguish CLL cells from normal B cells is their expression of CDS and the barely detectable amount of surface immunoglobulins. Although CDS was formerly considered to be a restricted T-cell antigen, CDS+ B cells are normally present in the mantle zone of normal lymph nodes, and small numbers can be found in the peripheral blood of normal individuals. CDS+ B cells are found in increased numbers in patients with autoimmune disorders (e.g., rheumatoid arthritis, Sjögren's syndrome, and systemic lupus erythematosus), immune thrombocytopenic purpura, and after allogeneic bone marrow transplantation. These observations have led to the current theory that B-CLL is a monoclonal proliferation of mantle zone–based anergic CD5+ self-reactive B cells devoted to the production of polyreactive autoantibodies. A wide variety of growth factors have been implicated in the disordered proliferation and differentiation of B cells in CLL, including tumor necrosis factor, interferon-2, interleukin-4, IL-6, IL-7, IL-8, IL-10, IL-11, IL-12, IL-13, interferon-g (IFN-g), granulocyte-macrophage colony-stimulating factor, transforming growth factor-β, and others.

**IMMUNE FUNCTION AND AUTOIMMUNITY IN CHRONIC LYMPHOCYTIC LEUKEMIA**

CLL is characterized by an accumulation of immunologically incompetent B cells. These cells produce reduced amounts of normal immunoglobulins in response to antigenic stimuli. Quantitative and qualitative abnormalities of normal B cells, T cells, and natural killer (NK) cells also have been reported, with a reduction in the number and function of normal T cells and the function of NK cells, and impaired complement activation. Elevated levels of circulating IL-2 receptor (IL-2R) may down-regulate helper T-cell function and may play a role in the pathogenesis of the immunodeficiency. B-CLL cells express CD40, which down-modulates CD40 ligand (CD154) on CD4+ T cells. Because CD40 ligand allows B cells to respond to T cells, this effect may contribute to the immune incompetence in CLL.
CYTOGENETICS

Conventional banding techniques detect cytogenetic abnormalities in more than 50% of cases of CLL. More recently, fluorescent in situ hybridization has identified cytogenetic abnormalities in more than 80% of cases. The most common cytogenetic abnormality in CLL appears to be deletion of 13q, which is present in 55% of cases. Patients with 13q14 abnormalities tend to experience a more benign course with a normal lifespan. Whether deletion of the breast cancer gene BRCA2 at 13q12 is involved is controversial. Deletions of 11q23 are detected in 18% of cases and are associated with massive lymphadenopathy that is often out of proportion to the increase in peripheral blood lymphocyte count. Trisomy 12 occurs in 16% of cases and is associated with atypical morphology and a poor outcome. Lymphocytes with trisomy 12 tend to have unmutated immunoglobulin variable (V<sub>H</sub>) genes, whereas those with 13q14 have evidence of somatic mutations. Mutations or deletions of p53 at 17p13.1 have been reported in approximately 15% of patients. Chromosome 17 abnormalities are found more frequently in cases of atypical CLL and are associated with a higher likelihood of Richter’s transformation and a poor prognosis.

BCL-3 translocations, t(14;19)(q32;q13.2), are uncommon and, in approximately one-half of cases, occur in association with trisomy 12. These patients tend to be young and have rapidly progressive disease. Of note is the lack of translocations in patients with CLL.

MOLECULAR BIOLOGY AND GENETICS

Lymphocytes from approximately one-half of patients with CLL contain V<sub>H</sub> genes that are mutated postgerminal center B cells [immunoglobulin D (IgD)–, CD38+], whereas the other half are naive and unmutated (IgD+IgM+, CD38–). These two populations are characterized by markedly different clinical outcomes, with the unmutated group having a significantly shorter survival rate. Studies of gene use in CLL have indicated that there may be nonrandom differential usage of V<sub>H</sub> and V<sub>κ</sub> genes used in the cell of origin, with an apparent increase in the usage of the V<sub>H</sub>8-69 (5p11) gene from the V<sub>H</sub>1 family.

No single oncogene has been implicated in the pathogenesis of CLL. Early reports of cases with the BCL-1 translocation were more likely mantle cell lymphoma (MCL). The translocations associated with BCL-2 [t(14;18)(q32;q21)] and BCL-3 [t(14;19)(q32;q13.1)] have been detected in only 5% to 10% of cases. Overexpression of the BCL-2 gene is present in more than 70% of cases, even in the absence of the chromosome rearrangement. The ratio of the antiapoptotic gene BCL2 to the proapoptotic gene BAX is increased in CLL cells, which favors cell survival. Deletions of 13q have been identified using molecular techniques, even in cases without cytogenetic changes. This abnormality was thought to be at the site of the retinoblastoma (RB) suppressor gene but has since been shown to be telomeric to that region with a novel suppressor gene referred to as DBM (disrupted in B-cell malignancy). An apparent correlation exists between the antiapoptotic protein Mcl-1 and resistance to chemotherapy.

Considerable interest has focused on the ATM gene, which is mutated in patients with ataxia telangiectasia, who are at an increased risk for developing lymphoid neoplasms. The ATM gene is located at chromosome 11q22-23 and encodes for a high-molecular-weight protein that is involved in cell-cycle control, DNA repair, and DNA recombination. However, only a subset of patients with deletions at 11q22-23 show mutations in the coding region of the remaining ATM allele, suggesting a pathogenic role for other genes.

Abnormalities of p53 occur in at least 15% of patients and are associated with a higher percentage of prolymphocytes, advanced stage, chemoresistance, and a poorer outcome.

DIAGNOSIS

Most patients with CLL are asymptomatic at presentation, and the diagnosis is often made when lymphocytosis is noted at the time of a routine complete blood cell count. Physical examination is normal in 20% to 30% of patients at presentation. As the disease progresses, however, generalized adenopathy and splenomegaly become common features of this disease.

The diagnosis of CLL requires more than 5000 per µL of small, mature-appearing lymphocytes circulating in the peripheral blood that are unexplained by other clinical disorders. The bone marrow aspirate and biopsy are infiltrated by at least 30% lymphocytes. A bone marrow aspirate and biopsy are rarely required to make the diagnosis of CLL, but they may provide prognostic information and are valuable for assessing response to therapy.

The immunophenotype of CLL cells readily distinguishes CLL from other disorders associated with increased numbers of circulating atypical lymphoid cells [e.g., prolymphocytic leukemia (PLL), hairy cell leukemia (HCL), and hairy cell variant (HCL)]. From non-Hodgkin’s lymphomas (NHL) in a leukemic phase (e.g., lymphoplasmacytic lymphomas; marginal zone NHL, including splenic lymphoma with villous lymphocytes; mantle cell NHL), and from plasma cell leukemia (Fig. 46.3.2-1). CLL lymphocytes are monoclonal B cells that express CD19, CD20, CD23, and CD5, along with low levels of surface immunoglobulin (Ig). T-cell antigens (e.g., CD2, CD3) are absent. Mouse red blood cell rosettes on peripheral blood lymphocytes are characteristic of CLL, but this test is no longer routinely performed. In an occasional patient, CLL B cells express additional antigens more characteristic of hairy cells, monocytes, or myeloid cells. Immunoglobulin heavy-chain gene rearrangements are invariably present but are not required to make the diagnosis.68 Disorders characterized by CD5– chronic lymphocytosis should not be considered CLL because they differ in immunologic, molecular, and functional features.

![FIGURE 46.3.2-1.](image)

CLINICAL FEATURES

CLINICAL PRESENTATION

Patients with CLL are generally asymptomatic at presentation, and the diagnosis is often made incidentally when a lymphocytosis is noted at the time of a routine evaluation. Physical examination is normal at presentation in 20% to 30% of patients, with lymphadenopathy or hepatosplenomegaly, or both, noted in an additional 40% to 50% of patients. As the disease progresses, however, generalized adenopathy and splenomegaly become common features of this disease (Fig. 46.3.2-2).
INFECTIONS

Hypogammaglobulinemia is common in CLL, especially in patients with advanced disease. The increased susceptibility to infections reflects an inability to produce specific antibodies and abnormal activation of the complement system. Historically, the most common pathogens were those that require opsonization for bacterial killing, such as Streptococcus pneumoniae, Staphylococcus aureus, and Haemophilus influenzae. The increased use of immunosuppressive agents, such as fludarabine, 2-chlorodeoxyadenosine (2-CdA), and 2′-deoxycoformycin (DCF), has markedly altered the spectrum of pathogens encountered in patients with CLL, with an increase in infections seen with opportunistic organisms such as Candida, Listeria, Pneumocystis carinii, Cytomegalovirus, Aspergillus, Herpesvirus infections, and others that were rarely encountered before the widespread use of nucleoside analogues. A febrile patient with CLL receiving one of the new nucleoside analogues can no longer be assumed to have a common bacterial pathogen, and aggressive diagnostic measures may be required. Prophylactic antimicrobial regimens cannot be routinely recommended for all fludarabine-treated patients because the broad spectrum of potential pathogens would require multiple, potentially toxic drugs. However, such regimens should be considered for patients with extensive prior therapy, who have failed fludarabine, who have a history of recurrent infections, or are on corticosteroids.

High-dose intravenous immunoglobulins have been evaluated for their ability to prevent infections in CLL. Although a reduction in the total number of bacterial infections is reported with this treatment, these are primarily of trivial to moderate severity, with no decrease in the total number of major infections, either viral or fungal, or in the number of patients experiencing an infection, and with no improvement in overall survival. The prophylactic use of intravenous immunoglobulins is not cost-effective and should be reserved for select patients with documented, repeated bacterial infections.

Whether myeloid growth factors can protect against chemotherapy-induced myelosuppression has not yet been demonstrated. In one study, the use of granulocyte colony-stimulating factor to support fludarabine therapy reduced the occurrence of pneumonias but not other forms of severe infections.

AGGRESSIVE TRANSFORMATION

Approximately 3% to 15% of CLLs evolve into a more aggressive lymphoid malignancy. The most common of these is Richter's syndrome, which was initially described in 1928 by Maurice Richter. He reported a 46-year-old man with CLL who experienced a rapid clinical deterioration characterized by lymphocytosis, massive and diffuse adenopathy, hepatosplenomegaly, and abdominal discomfort. At autopsy, large abdominal and retroperitoneal lymph nodes were infiltrated not only by small lymphocytes, but with larger cells, which reflected the large cell lymphoma component. Additional cases were subsequently reported by Lortholary et al., who designated the entity as Richter's disease. Richter's syndrome develops in approximately 5% of CLL patients. Patients characteristically present with increasing lymphadenopathy, hepatosplenomegaly, fever, abdominal pain, weight loss, progressive anemia, and thrombocytopenia, with a rapid rise in the peripheral blood lymphocyte count. A lymph node biopsy reveals a large cell lymphoma. This transformation is not clearly related to either the nature or the extent of prior therapy. The large cell lymphoma shares immunologic, cytogenetic, and molecular features with the original CLL clone in one-half of the cases. Nucleic acid sequence analysis of the heavy- and light-chain–variable region supports the theory that Richter's syndrome is derived from the same malignant clone in most patients.

Response of patients with Richter's syndrome to systemic therapy is poor, with a median survival of 4 to 5 months using alkylating agents, but may be longer with nucleoside analogue–based regimens.

CLL may also evolve over the years into PLL. This transformation is associated with progressive anemia and thrombocytopenia, with at least 55% prolymphocytes in the peripheral blood. Clinical features include lymphadenopathy, hepatosplenomegaly with a wasting syndrome, and an increasing resistance to therapy.

Autocrine and paracrine growth factors activate the malignant B cells of PLL, and these factors are present locally in the peripheral blood.

Anecdotal reports have been published of a transformation to acute lymphoblastic leukemia, plasma cell leukemia, multiple myeloma, or Hodgkin's disease.

AUTOIMMUNITY

A positive Coombs' antiglobulin test may be present in 20% to 30% of cases of CLL with clinical hemolysis in 10% to 25% of patients. The frequency of immune thrombocytopenia appears to be approximately 2%. The immune hemolysis is more often related to a warm-reactive than a cold antibody. In most cases, these antibodies are polyclonal and, therefore, not produced by the malignant B cells. This phenomenon probably reflects impaired interactions among the malignant B cells, normal B cells, and T cells. However, two V 
 genes have been shown to be preferentially expressed in cells from CLL patients with warm-reacting antibodies: 51p/DP-10 gene and a DP-50 gene. These observations suggest that, whereas the antibodies that are produced by the CLL are not involved in the red blood cell destruction, they may still be involved in the pathogenesis of the autoimmune hemolytic anemia.

Autoimmune anemia, or thrombocytopenia, generally responds to corticosteroids, such as prednisone, 60 to 100 mg/d, which may be tapered after 1 or 2 weeks after evidence of response. Patients who are unresponsive to corticosteroids may respond to high-dose intravenous immunoglobulins using an initial loading dose daily for 5 days followed by 0.4 g/kg every 3 weeks. Splenectomy may be considered when systemic approaches fail. Splenic irradiation induces only transient responses. Rituximab has been associated with dramatic responses (B. Cheson, unpublished observation).

PURE RED BLOOD CELL APLASIA

Pure red blood cell aplasia has been reported in up to 6% of cases of CLL, although that figure is likely an overestimate. This complication is characterized by severe anemia (hematocrit generally less than 21%) without a reticulocyte response or bone marrow normoblasts and in the absence of neutropenia or thrombocytopenia. Corticosteroids may induce transient responses. Chemotherapy increases the hematocrit in the majority of patients with a response of the CLL. Cyclosporine A, with or without concurrent corticosteroids, may also achieve responses, often within 2 to 3 weeks and without requiring a reduction in tumor mass.

SECOND MALIGNANCIES

Secondary malignancies occur with increased frequency in patients with CLL, related both to the immune defects of the disease as well as the consequences of therapy. The most common tumors are lung cancers and melanomas; others include Hodgkin's disease, essential thrombocytopenia, multiple myeloma, and acute myeloid leukemia. Coincidence of CLL and chronic myeloid leukemia also has been observed (B. Cheson, unpublished observation).

FIGURE 46.3.2-2. Pronounced cervical, supraclavicular, and axillary lymphadenopathy in a patient with chronic lymphocytic leukemia.
STAGING SYSTEMS

CLL patients have markedly differing outcomes and may require different therapeutic approaches. Over the years, a number of classification systems have been developed to organize CLL patients into risk groups. The first widely accepted attempt to identify various prognostic groups of patients was the five-stage Rai classification: Stage 0 includes patients with only lymphocytosis (median survival, more than 12.5 years); stage I patients also have lymphadenopathy (median survival, 8.5 years); stage II is characterized by splenomegaly with or without hepatomegaly (median survival, 6 years); stage III includes anemia (not related to hemolysis) (median survival, 2 to 4 years); and stage IV includes thrombocytopenia (median survival, 2 to 4 years). This system was subsequently simplified to three stages: low risk (stage 0), intermediate risk (stages I–II), and high risk (stages III–IV). In Europe a few years later, Binet described his three-stage stage system: Stage A patients have fewer than three node-bearing areas (median survival, more than 10 years); stage B patients have three or more node-bearing areas (median survival, 5 years); and stage C patients have anemia and/or thrombocytopenia (median survival, 2 years). The Rai classification is the most commonly used in the United States, whereas the Binet system is often applied in Europe. A major difference between the two systems is the failure of the Binet system to identify Rai stage 0 patients, who have a 10-year survival rate of approximately 60%. Binet stage A patients include all Rai 0, two-thirds of Rai I, and one-third of Rai II. Neither system identifies patients with lymphocytosis and splenomegaly without lymphadenopathy. Nevertheless, the two systems have similar prognostic value. Other staging systems do not appear to provide an advantage over the two already in widespread use.

TABLE 46.3.2-1. Modified Rai Staging System for Chronic Lymphocytic Leukemia

<table>
<thead>
<tr>
<th>Stage</th>
<th>Clinical Feature</th>
<th>Median Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No clinical feature</td>
<td>More than 12.5 years</td>
</tr>
<tr>
<td>1</td>
<td>One or more node-bearing areas</td>
<td>8.5 years</td>
</tr>
<tr>
<td>2</td>
<td>Splenomegaly with or without hepatomegaly</td>
<td>6 years</td>
</tr>
<tr>
<td>3</td>
<td>Anemia (not related to hemolysis)</td>
<td>2 to 4 years</td>
</tr>
<tr>
<td>4</td>
<td>Thrombocytopenia</td>
<td>2 to 4 years</td>
</tr>
</tbody>
</table>

FIGURE 46.3.2-3. Simplification of the five-stage Rai classification into three risk groups based on survival. Stage 0, low risk; stages I and II, intermediate risk; stages III and IV, high risk.

TABLE 46.3.2-2. Binet Staging System for Chronic Lymphocytic Leukemia

At diagnosis, approximately 20% to 30% of patients are Rai stage 0, and 70% to 80% of patients are in low- or intermediate-risk groups in both the Rai and Binet classifications.

PROGNOSIS

Clinical features and laboratory studies are used to predict survival in CLL.Montserrat and coworkers were the first to use the term smoldering CLL to distinguish patients with early-stage disease who were unlikely to progress from those who were more likely to require treatment. The laboratory features included a hemoglobin of 12 g% or higher, a lymphocyte count of less than 30,000 cells per µL, a platelet count of more than 150,000 cells per µL, and a nondiffuse pattern of bone marrow involvement with fewer than 80% lymphocytes.

A rapid lymphocyte doubling time appears to be a better predictor of a poor outcome than the absolute number of circulating lymphocytes.

In more than one-half of CLL cases, the bone marrow is diffusely infiltrated by small lymphocytes; in the remaining patients, the pattern of infiltration is nodular, interstitial, or a mixture of the two. The diffuse pattern has been suggested to be a strong independent adverse prognostic factor, although this finding does not clearly add to clinical stage.

Additional features associated with a shorter survival include male gender, black race, poor performance status, abnormal liver chemistries, decreased serum albumin, and vertebral bone marrow involvement detected by magnetic resonance imaging.

Of the numerous immunologic characteristics that have been evaluated, soluble CD23 and serum b2-microglobulin appear to have a particularly strong predictive value. Others include the function of various lymphocyte subpopulations, expression of surface IgM, FMC7, loss of CD23, increased serum levels of soluble CD54, and soluble IL-2 receptors.
A serum or urine paraprotein can be detected in more than 60% of cases of CLL, including the presence of Bence Jones proteinuria, but the level of paraprotein does not appear to have prognostic value. There has been no consistent relationship between hypogammaglobulinemia and survival among series.

Cyogenetic and molecular studies best predict outcome in CLL. Patients with 73q abnormalities experience the longest survival and rarely require therapy, whereas complex abnormalities are associated with the poorest outcome. Deletions of the long arm of chromosome 11 (11q21-25) tend to occur in patients who are younger and have more aggressive disease; peripheral, abdominal, and mediastinal adenopathy; advanced stage; and a shorter survival. Trisomy 12 has a prognosis that is intermediate between the two. Cyogenetic studies are not recommended as part of the routine evaluation of the patient with CLL because they are expensive, difficult to perform, and most important, we do not yet know how to apply the information to treatment decisions.

Although BCL-2 expression has not uniformly correlated with outcome, the ratio of BCL-2 to BAX favors survival in CLL cells with enhanced in vitro cell survival and correlates with clinical resistance to chemotherapy and clinical outcome. PS1 and PS3 deletions predict for poor response to therapy with fludarabine or pentostatin.

Studies have shown a strong independent correlation between V\textsubscript{\textmu} gene mutations, CD38 expression, and survival. The V\textsubscript{\textmu} mutation status distinguishes more primitive from more mature B cells and appears to separate CLL patients into markedly distinct prognostic groups (Fig. 46.3.2-4).

**FIGURE 46.3.2-4.** Patients with chronic lymphocytic leukemia can be separated into survival groups on the basis of the mutational status of the immunoglobulin variable gene (A) and CD38 expression (B). (From ref. 50, with permission.)

**THERAPY**

Patients with low-risk CLL often do not require therapy for many years after diagnosis and eventually die of apparently unrelated causes. Anecdotal reports of transient spontaneous remissions also have been published. Many patients with intermediate-risk disease may remain stable for many years as well, whereas others may die from disease-related complications within a few months of diagnosis, despite appropriate therapy. Most patients with high-risk CLL need treatment at diagnosis.

**INITIAL APPROACH TO THE PATIENT WITH CHRONIC LYMPHOCYTIC LEUKEMIAS**

Currently available therapies do not cure patients with CLL (Fig. 46.3.2-5), yet they may be associated with substantial toxicities. Moreover, early intervention has not been shown to benefit patients with early-stage disease. The French Cooperative Group on CLL conducted two studies in patients with Binet stage A disease. In the first study, patients were randomized to daily oral chlorambucil or observation. In the second trial, patients received either intermittent chlorambucil plus prednisone or no initial treatment. Neither study detected an advantage to early intervention. Moreover, a greater number of fatal, secondary solid tumors were reported in the first study, which was not noted in the study using an intermittent drug schedule. Therefore, therapy should not be initiated in patients with early-stage CLL without specific indications, which include disease-related symptoms (e.g., fevers, chills, weight loss, pronounced fatigue); increasing bone marrow failure with anemia and/or thrombocytopenia, autoimmune anemia, or thrombocytopenia; massive or progressive hepatosplenomegaly or lymphadenopathy; and recurrent infections. An elevated lymphocyte count alone is not sufficient to prompt therapy; however, a lymphocyte doubling time of less than 6 months may support the decision to treat.

**FIGURE 46.3.2-5.** Survival of 741 previously untreated patients seen at the M. D. Anderson Cancer Center over three decades, ending in 1990, demonstrating a lack of any incremental improvement in survival with therapies available during that period. (From ref. 155, with permission.)

**SINGLE-AGENT CHEMOTHERAPY**

The most active classes of chemotherapy drugs in CLL are alkylating agents, such as chlorambucil and cyclophosphamide, and the nucleoside analogues fludarabine, 2-CdA, and DCF (pentostatin). When chlorambucil is administered orally, either at a dose of 4 to 8 mg/m\textsuperscript{2} daily for 4 to 8 weeks, or as pulses of 15 to 30 mg/m\textsuperscript{2} every 2 to 4 weeks, responses are attained in approximately 30% to 70% of previously untreated patients, although few of these are complete responses. The activity of cyclophosphamide appears to be similar to chlorambucil, but it is generally used only when chlorambucil has failed or is poorly tolerated, and in combination regimens.

Corticosteroids are less active than alkylating agents in CLL and should be reserved for patients with autoimmune complications because of the risks of bacterial, viral, and fungal infections; diabetes; and osteoporosis.

**PURINE ANALOGUES**

Fludarabine (2-fluoro-ara-adenosine monophosphate) is the most active agent for the treatment of CLL (Table 46.3.2-3). The currently recommended schedule of administration of fludarabine is as an intravenous bolus of 25 mg/m\textsuperscript{2} daily for 5 consecutive days once a month. Patients failing to respond to two or three courses should be switched to an alternative treatment. Patients who achieve a complete response probably do not warrant additional treatment. For those patients with a partial response, therapy is continued to best response plus two additional courses, not exceeding 1 year of therapy because of concerns of cumulative myelotoxicity.
Other schedules have not been as active. The oral bioavailability of fludarabine is 50% to 60%, and an oral formulation is in clinical trials.

Fludarabine induces complete remissions in approximately 30% of previously untreated patients, with an overall response rate higher than 70%. In a long-term follow-up of a large, single institution series, the median time to progression of responders was 31 months, and the overall median survival was 74 months. Those who achieve an immunophenotypic and molecular complete remission appear to experience a longer survival than those with only a clinical and hematologic remission.

Fludarabine has been compared with an alkylating agent–based regimen in several phase III trials (Table 46.3.2-3).

Table 46.3.2-3. Purine Analogues in Chronic Lymphocytic Leukemia

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Patients</th>
<th>GE/CAP</th>
<th>RFS</th>
<th>CI</th>
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<td>Puriset al.</td>
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<tr>
<td>Ritz et al.</td>
<td>344</td>
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<td>Loguerini et al</td>
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<td>Spinola et al</td>
<td>140</td>
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Significance: *P <.05, **P <.001.

Comparison between fludarabine and alkylating agent regimens as initial therapy of chronic lymphocytic leukemia is shown in Table 46.3.2-4.

Table 46.3.2-4. Comparisons between Fludarabine and Alkylating Agent Regimens as Initial Therapy of Chronic Lymphocytic Leukemia

In a North American Intergroup study, 544 untreated patients with advanced-stage, active disease were randomized to either fludarabine at the standard dose, chlorambucil (40 mg/m² single dose), or a combination of the two agents (fludarabine 20 mg/m² daily for 5 days; chlorambucil 20 mg/m² day 1) every 4 weeks for up to 12 months. Patients who were unsuccessful with one of the single agents were crossed over to receive the alternate drug. The 167 patients in the fludarabine group had an overall response rate of 70%, including 27% complete remissions, which was significantly higher than with chlorambucil (43% responses, 3% complete remissions; P < .0001). The duration of response was 32 months with fludarabine versus 18 months with chlorambucil (P = .0002), with a median progression-free survival of 27 months with fludarabine and 17 months for chlorambucil (P < .0001). However, no apparent prolongation of survival was reported, related in part to the crossover design of the study. The combination arm was prematurely closed because it was more toxic with no likelihood of being more effective than fludarabine alone.

A European collaborative group randomized 196 patients with stage A (2), B (104), or C (89) to either fludarabine or one of two anthracycline-based regimens [cyclophosphamide, doxorubicin, and prednisone (CAP) or cyclophosphamide, vincristine, and prednisone (CHOP)]. A higher response rate was attained with fludarabine in the untreated patients, although the difference was not significant. The advantage for fludarabine was significant for remission duration, with a trend toward a survival advantage (P = .087). In a subsequent trial by the International Working Group on CLL, including 486 stage B and 209 stage C patients, a complete hematologic remission was observed in 37% of the fludarabine group, 28% of the CHOP group, and 13% of the CAP-treated patients. The differences were significant between fludarabine and CHOP and between CHOP and CAP (P < .0001) in response and survival, but not between fludarabine and CHOP (P = .15). Nevertheless, fewer deaths were reported in the fludarabine group, resulting in a significant survival advantage (P = .05).

These results establish fludarabine as the preferred initial treatment for most patients with CLL. However, for patients who are elderly or those who have a reduced performance status or an active infection, chlorambucil may be a reasonable first-line treatment option. Another alternative is a 3-day schedule of fludarabine, which appears to be almost as active but has fewer associated toxicities.

The major toxicities associated with fludarabine at the currently used schedules are moderate myelosuppression and severe immunosuppression, with occasional neurotoxicity, particularly at higher than recommended doses. Lymphocyte counts decrease within weeks, particularly CD4 cells, which do not return to normal for 1 year or longer after treatment has been discontinued. Fludarabine has not been found to be more myelotoxic but has been associated with more opportunistic infections than alkylating agent regimens.

Tumor lysis syndrome is a rare complication of treatment of CLL with alkylating agents, radiation, combination chemotherapy, or fludarabine.

Approximately 55% to 85% of patients who are treated with 2-CdA as their initial therapy respond to this agent, but only 10% to 15% achieve complete remissions, and the duration of response appears to be shorter than reported for fludarabine. Fludarabine has not been found to be more myelotoxic but has been associated with more opportunistic infections than alkylating agent regimens.

COMBINATION REGIMENS

Combination regimens are not clearly superior to single-agent therapy for CLL. The most commonly used multiagent regimens include chlorambucil plus prednisone (CP) or cyclophosphamide, vincristine, and prednisone (CVP). CP and CVP induce responses in fewer than 10% to more than 60% of previously untreated patients, although few of these responses are complete, and the median survival is shorter than 2 years. The French Cooperative Group randomized 151 patients with Binet stage B CLL to indefinite daily oral chlorambucil and 160 patients to cyclophosphamide, Oncovin, and prednisone (COP). No difference was noted in response rate, reduction in clinical stage, or overall survival.

More aggressive regimens that include multiple alkylating agents or anthracyclines also have not shown an advantage over less intensive programs. One small randomized trial suggested a survival advantage for an attenuated CHOP regimen (including doxorubicin at 25 mg/m² every 4 weeks) over COP in a small number of patients with stage C disease. Moreover, data from the same investigators suggest an advantage for CHOP over CAP. However, several other randomized trials and a metaanalysis have not confirmed superiority for anthracycline-containing regimens.
Combinations of fludarabine with chlorambucil, anthracyclines or related compounds, cytarabine, and IFN-a are not clearly better than fludarabine alone. Preliminary encouraging data with combinations of fludarabine and cyclophosphamide have led to phase III studies. DCF has been combined with alkylating agents and steroids with high response rates but considerable toxicity.

SECOND-LINE THERAPY

Treatment decisions for relapsed and refractory patients should be based on criteria similar to those used for initial management. Because therapy is palliative in this setting, treatment should not be initiated unless it is clearly needed. Patients with CLL who relapse after or are refractory to initial treatment should be referred to a clinical trial. For patients who are not eligible for or are unwilling to participate in clinical research, salvage therapy determined by the initial treatment and response to that treatment. Alkylating agents and fludarabine remain the most widely used drugs in this setting. Most other cytotoxic drugs have failed to show activity. Patients who initially respond to an alkylating agent can often be successfully retreated with that agent; however, the quality of the subsequent response and its duration are usually inferior to the initial treatment. Response rates with multiple alkylating agents of anthracycline-containing regimens are significantly lower as second-line therapy, with few complete remissions.

Fludarabine has become the standard agent for treating patients unsuccessful with alkylating agents. Rittgers et al. were the first to report activity for fludarabine in a series of 32 previously treated patients. Although they achieved only 3% complete responses and 9% partial responses, a large number of other patients experienced major clinical improvement. When current response criteria were applied, the overall response rate was 45%. Keating and coworkers reported 57% complete responses and 36% partial responses of 28 relapsed patients, and 26% complete responses and 10% partial responses of 50 refractory patients (63% of complete responses had residual lymphoid nodules in the bone marrow) (see Table 46.3.2-3). The median time to progression was 18 months for patients who were refractory to alkylating agents and 17 months for patients who had relapsed after prior treatment. Lower response rates and durability of response were noted in patients with advanced-stage disease, extensive prior therapy, and poor performance status. When compared with CAP as second-line therapy, fludarabine was associated with a significantly higher response rate as well as a longer remission duration and survival, although these differences were not significant.

Re-treatment with fludarabine is successful in one-half of those patients whose initial response to fludarabine lasted 1 year or longer. On the other hand, few effective therapeutic options are available to patients whose disease is refractory to fludarabine.

2-Chlorodeoxyadenosine

In general, response rates with 2-CdA for relapsed and refractory patients are in the range of 30% to 40%, but with few complete remissions. Saven et al. reported 4% complete responses and 49% partial responses of 50 relapsed and refractory patients with CLL, with a median duration of response of 4 months (see Table 46.3.2-3). Variability in response rates among series reflect differences in drug administration schedule, patient selection, response criteria, and other factors.

2-CdA has limited activity in fludarabine failures.

2'-Deoxycoformycin (Pentostatin)

Almost one-fourth of alkylating agent failures respond to DCF, although few of these responses are complete or durable (see Table 46.3.2-3).

A few reports of combinations of DCF with other cytotoxic or biologic agents in CLL in relapsed patients have been published.

OTHER CHEMOTHERAPY AGENTS

Despite the lack of single-agent data for cisplatin and cytarabine, these drugs have been incorporated into multidrug regimens, although their contribution to those regimens is unclear. Theophylline appears to synergize with chlorambucil in vitro in inducing apoptosis and has shown clinical activity.

Several newer agents are currently under investigation in CLL. Compound GW506U78, a prodrug for ara-G, is a new nucleoside analogue with impressive activity in a variety of hematologic malignancies. Responses have been reported in patients with chronic B-cell and T-cell leukemias, even after failure with fludarabine and alkylating agents. Interest in the use of arsenicals in CLL stems from several preclinical studies suggesting that arsenic induces apoptosis of malignant lymphocytes at clinical achievable doses. The protein kinase C inhibitors bryostatin and UCN-01, the cyclin inhibitor flavopiridol, and the histone deacetylase inhibitor depsipeptide are being evaluated as single agents and in combinations. A variety of in vitro observations suggest a potential role for antiangiogenesis agents.

BIOLOGIC THERAPY

Interferon-a

IFN-a has limited activity in CLL, with transient partial responses in patients with limited-stage disease. Preliminary data suggesting benefit for IFN maintenance after a response to induction chemotherapy with alkylating agents were not confirmed in studies with fludarabine.

Monoclonal Antibodies

Early studies with monoclonal antibodies targeting CD5 did not show adequate activity to pursue in larger trials. However, several newer antibodies have shown considerable promise.

The CAMPATH-1H monoclonal antibody recognizes the CD52 antigen, which is present on B cells as well as T cells. This antibody has shown impressive activity against both in CLL and PLL. Responses occur in approximately one-third of patients who have been unsuccessful with other treatments, including fludarabine. This agent appears to be more active against peripheral blood and bone marrow involvement than nodal disease.

Rituximab (Rituxan) is an anti-CD20 antibody C2B8 with major activity against follicular lymphomas. However, its activity using the recommended dose and schedule has not been impressive in patients with small lymphocytic leukemia or CLL, with response rates in the range of 10% to 15% and no complete remissions. This lack of activity may reflect the dim expression of CD20 on CLL cells. Attempts are being made to improve on this activity by increasing the dose, altering the schedule of administration, or augmenting CD20 expression.

The development of antibodies conjugated to radioisotopes, such as iodine 131 or yttrium 90, will be more difficult because of concerns that antibody localization in the bone marrow results in significant myelotoxicity.
BONE MARROW TRANSPLANTATION

Allogeneic bone marrow transplantation has been performed to a limited extent in patients with CLL, primarily because these patients tend to be older and it has been difficult to eradicate the disease in the patient. Although more than 70% of patients may be induced into a remission with bone marrow transplantation, only approximately one-half of patients are alive and free of disease after long-term follow-up. The best outcome has been reported for patients with no evidence of minimal residual disease by polymerase chain reaction. However, the treatment-related death rate has been approximately 30% to 50%, related to a high rate of graft-versus-host disease. Whereas some patients with advanced disease clearly benefit from bone marrow transplantation, the occurrence of late relapses raises questions as to how many patients are actually cured.

Sublymphoelastic preparative regimens, or “mini-transplants,” have been reported to induce successful engraftment without substantial acute graft-versus-host disease. The necessary immunosuppression is provided by a drug such as fludarabine, with a moderately myelosuppressive dose of cyclophosphamide. This approach permits eligibility to older patients and those with impaired performance status or organ function. Further refinement of this technology is needed before it becomes a standard approach.

Autologous stem cell transplantation as currently performed has a limited role for patients with CLL, with the possible exception of patients who can be induced into a molecular remission.

OTHER THERAPEUTIC MEASURES

Small, unconfirmed series have suggested a role for such treatments as leukopheresis or photochemotherapy in the management of CLL; however, these approaches have not been widely accepted.

Splenectomy

Splenectomy may play an important role in the palliative management of patients with CLL who have failed systemic treatment for autoimmune hemolytic anemia or thrombocytopenia, who have mechanical complications from splenomegaly that is unresponsive to chemotherapy, or in patients with hypersplenism who are tolerating chemotherapy poorly. Splenectomy may also assist in making the diagnosis of a suspected Richter’s transformation. Thrombocytopenia is the most likely cell type to respond after splenectomy. When performed by an experienced surgeon, the mortality of the procedure is less than 10%.

Radiation Therapy

Radiation therapy has a limited role in the current management of patients with CLL. Older studies suggesting therapeutic benefit have not been substantiated, and it adds little benefit but considerable morbidity when combined with chemotherapy. Splenic irradiation to palliate symptoms or in the treatment of autoimmune hemolytic anemia achieves only brief responses.

ASSESSMENT OF RESPONSE TO THERAPY IN CHRONIC LYMPHOCYTIC LEUKEMIAS

Several sets of response criteria for CLL have been published. The recommendations of the National Cancer Institute Sponsored Working Group on CLL, published first in 1988 and updated in 1996, are the most widely used for clinical research protocols. These guidelines standardized eligibility, response, and toxicity criteria; provided dose modifications for drug-related myelosuppression; and provided a grading system for infectious complications.

TABLE 46.3.2-5. Revised National Cancer Institute Working Group Guidelines for Chronic Lymphocytic Leukemia

RELATED B-CELL LEUKEMIAS

PROLYMPHOCYTIC LEUKEMIA

PLL can occur either de novo or, less often, as a transformation from CLL. In contrast to the small, mature-appearing lymphocytes of CLL, PLL cells are large, with a round nucleus and a prominent nucleolus. In de novo PLL, most of the peripheral blood mononuclear cells tend to be prolymphocytes; in PLL that has transformed from CLL, there is a dimorphic population of lymphocytes in the peripheral blood.

Cells from patients with PLL exhibit immunologic differences from B-CLL cells. They may be CD5– and may express CD20 brightly. They lack mouse red blood cell rosettes and more frequently express FMC7.

Patients with de novo PLL tend to be older than those with transformed PLL. They are usually symptomatic and may experience a wasting syndrome. They are generally Rai stage III or IV at presentation, with marked splenomegaly and a higher white blood cell count but less lymphadenopathy. The clinical course tends to be aggressive. Nevertheless, the outcome for those patients who have transformed appears to be even worse. The median survival for de novo PLL has been reported to be 3 years, compared with only 9 months for those who have transformed from CLL to PLL. Patients with PLL tend to respond poorly to either single-agent or combination chemotherapy, with overall response rates of less than 25% and rare complete responses. Small series and anecdotal cases suggest impressive activity for cladribine and pentostatin in refractory PLL, and for cladribine in previously untreated patients.

Hairy Cell Leukemia

HCL was initially described by Bouroncle et al. in 1958 and called leukemic reticuloendotheliosis. This chronic B-cell leukemia is characterized by splenomegaly and panhypoperoxidase and, occasionally, lymphadenopathy.

HCL occurs in approximately 500 new patients each year in the United States, and it makes up 2% of all leukemias. It tends to occur in older persons, with a strong male predominance. Patients generally present with symptoms referable to cytopenias, including infections in 29% and weakness or fatigue in 27%. Less common presentations include left upper quadrant pain related to splenomegaly (5%) or bleeding related to thrombocytopenia (4%). Incidence of second malignancies is increased. The most common findings include palpable splenomegaly (72% to 86%), hepatomegaly (13% to 20%), hairy cells in the peripheral blood (85% to 89%),
thrombocytopenia (fewer than 100,000 cells per µL, 53%), anemia (hemoglobin less than 12 cells per µL, 71% to 77%), and neutropenia (absolute neutrophil count less than 500 cells per µL, 32% to 39%).

The hairy cells generally have an eccentric, spongiform kidney-shaped nucleus, with characteristic filamentous cytoplasmic projections. Bone marrow biopsy is generally required to make the diagnosis, because the aspirate is often not obtainable. The malignant cells are of B-cell origin, expressing CD19, CD20, and the monoclonic antigen CD11c. Perhaps the most specific marker is CD103. It is most difficult to distinguish HCL from HCLv; the latter is often associated with a high circulating white blood cell count, cells containing bilobed nuclei with prominent nucleoli, and a typical bone marrow histology with interstitial infiltration of clumped cells. An important distinguishing, almost diagnostic, feature is the resistance of this disease to treatment with IFN-α, cladribine, and pentostatin. HCL may be an indolent disorder, and 10% of patients may never require treatment. In most patients, however, treatment is eventually warranted because of massive or progressive splenomegaly, worsening blood counts, recurrent infections, more than 20,000 hairy cells per µL of peripheral blood, or bulky lymphadenopathy. Until the early 1980s, splenectomy was the standard treatment for HCL. In most patients, this procedure improves symptoms related to splenomegaly and peripheral blood counts, often for prolonged periods, but it does not affect the disease itself. Splenectomy now plays a minor role in the management of HCL and is reserved for the rare patient who is refractory to treatment and has splenomegaly that is either symptomatic or is resulting in cytopenias.

The first systemic therapy to demonstrate activity in HCL was IFN. At doses of 2 × 10^6 U/m² or 3 × 10^6 U three times per week, IFN produces responses in 80% of patients. However, only 10% of these are complete responses. Although responses generally occur within 3 to 4 months, it may take more than 1 year of therapy to achieve the maximal response. The leukemia invariably recurs after IFN therapy is discontinued, and maintenance therapy is associated with excessive toxicity and expense without any apparent survival benefit. Many patients who recur will again respond when retreated. IFN is associated with flu-like symptoms (fevers, myalgias, malaise) in almost all patients. Other toxicities include rash; application site disorders; and gastrointestinal symptoms, with nausea, vomiting, and anorexia. Reduced doses are associated with less toxicity but lower response rates.

The results with DCF are equivalent to those with 2-CdA. However, the shorter duration of treatment makes 2-CdA somewhat more attractive, although no advantage exists with regard to toxicity.

The peripheral lymphocytes have revolutionized the treatment of patients with HCL. In 1984, Spiers et al. first reported complete responses in patients with HCL treated with pentostatin. DCF at doses of 4 mg/m² intravenously every other week for 4 to 6 months achieves complete responses in 60% to 80% of previously treated or untreated patients, including those who have been unsuccessful with IFN, with overall response rates of 80% to 90%. Moreover, only 25% of patients have relapsed with more than 5 years of follow-up. In an intergroup trial, 350 previously untreated patients with HCL were randomized to IFN or DCF; the complete response rate was approximately 11% for IFN compared with 76% for DCF, with a significant advantage to DCF in the durability of response.

In 1990, Piro et al. reported 11 complete responses of 12 patients with HCL who had received a single 7-day continuous infusion of 2-CdA. Numerous studies have now confirmed that the original schedule or a 2-hour infusion for 5 to 7 days achieves responses in 80% to more than 90% of patients, including 65% to 80% complete remissions. These responses tend to be durable, with 20% to 30% of patients relapsing with prolonged follow-up. Relapse can be predicted by the demonstration of minimal residual disease using sensitive immunohistochemical methods. In many cases, relapse is characterized only by an increase in bone marrow hairy cells, with no indication for treatment. Most patients who require re-treatment achieve a second durable response.

The results with DCF are equivalent to those with 2-CdA. However, the shorter duration of treatment makes 2-CdA somewhat more attractive, although no advantage exists with regard to toxicity.

New monoclonal antibodies have shown promise for patients with HCL who are unsuccessful with purine analogue therapy or for those with HCL.

**NON-HODGGIN'S LYMPHOMA IN A LEUKEMIC PHASE**

Patients with NHL may present with or subsequently develop a leukemic picture, most commonly those with a follicular small-cleaved cell histology, MCL, or marginal zone lymphoma. Although morphologic differences exist among these cells, immunophenotyping is necessary to distinguish among these entities. Follicular NHL in a leukemic phase is characterized by cells that are small, with clefts and little or no visible cytoplasm, called Butch cells. These cells strongly express IgM, are positive for CD20, and are negative for CD5 and CD23. The leukemic manifestation of MCL is characterized by a mixture of small- to medium-size lymphocytes with nuclei that are generally cleaved but may be nearly round, leading to a misdiagnosis of DCLL or PLL and small lymphocytic leukemia. MCL cells also express CD5, but in contrast to CLL cells, they strongly express IgM but not CD23.

Leukemic follicular small-cleaved cell lymphomas and mantle zone lymphomas have a median survival rate of 2.0 to 3.5 years and 2 years, respectively, whereas thrombocytopenia is a common feature. Although NHL is more often seen in women, with a median age of 57 years. Physical examination is notable for splenomegaly. Neutropenia is almost universal. A small concentration of an IgG or IgM monoclonal gammopathy can be detected in either the serum or urine from most cases. Fludarabine is active in lymphocytic lymphoma/leukemia. MCL cells also express CD5, but in contrast to CLL cells, they strongly express IgM but not CD23.

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**CHRONIC T-CELL LEUKEMIAS**

The mature (postthymic) T-cell leukemia disorders consist of large granular lymphocytic leukemia (LGL), T-PLL, adult T-cell leukemia/lymphoma, and the Sézary syndrome. The chronic T-cell leukemias are a heterogeneous group of rare disorders that differ significantly from B-CLL with respect to their immunophenotype, virology, biology, morphology, and response to therapy. The term T-cell CLL is no longer used in current classification systems.

**Large Granular Lymphocytic Leukemia**

LGL is the most common chronic T-cell leukemia. The etiology of this clonal disorder is unknown. It is often diagnosed in the setting of an incidental T-cell lymphocytosis with more than 2000 circulating T cells per µL. The peripheral blood lymphoid cells demonstrate characteristic azurophilic granulation. Monoclonal antibodies directed against the V-gene region of the T-cell receptor gene and the p58 family on NK cells may help make the diagnosis.

Proliferations of LGL may be either CD3+ (T-LGL) or CD3- (NK-LGL). Approximately 90% are CD4-/CD8+, although some cases may be CD4-/CD8−. T-LGL is the most common of these entities and occurs more often in women, with a median age of 57 years. Physical examination is notable for splenomegaly. Neutropenia is common and may be severe, with recurrent infections in 40% of patients. Peripheral blood NK cells are often decreased in numbers. The bone marrow is involved in almost all patients. There is a 30% incidence of rheumatoid arthritis, often with Felty's syndrome. Polyclonal hypergammaglobulinemia, rheumatoid factor, antinuclear antibodies, and circulating immune complexes are often present. Pure red blood cell aplasia also has been reported. More than two-thirds of cases eventually require therapy, primarily because of recurrent infections. Responses may be achieved with alkylating agents, corticosteroids, or cyclosporine A. DCF and 2-CdA have shown activity. Splenectomy is generally not associated with long-term benefit.

Disorders associated with an increase in NK cells form a spectrum, from more indolent NK-cell lymphocytosis to an aggressive NK-LGL leukemia/lymphoma. Chronic NK-cell lymphocytosis is a clonal disorder characterized by a sustained increase in cells with a CD3-/CD16+CD5-/CD8+ phenotype. The bone marrow is usually involved. The median age of patients with NK-LGL is 60 years, and the disease appears to be more common in men. Most patients note constitutional symptoms, but lymphadenopathy or splenomegaly are not common at presentation. Associated diseases include pure red blood cell aplasia and vasculitis syndromes. The outcome is similar to that of T-LGL. However, vasculitis and cytopenias may be life-threatening. Cyclophosphamide may be effective in controlling the vasculitis syndrome. NK-LGL leukemia/lymphoma is an aggressive disease characterized by constitutional symptoms and splenomegaly. Response to therapy is poor, and the median survival rate is only a few months.
T-PLL is characterized by massive splenomegaly, lymphadenopathy in 40% of patients, and skin infiltration in 20%. The presenting white blood cell count often exceeds 100,000 cells per µL. The malignant cells generally express CD3, CD4, CD5, and CD7, but are negative for CD8– and CD25–, although one-third of cases express CD4+CD8+ or CD4–CD8+. There are no apparent clinical differences among these subsets. A consistent abnormality of chromosome 14 has been reported with two breakpoints at 14q11 and 14q32.

The prognosis of T-PLL is poor, with a median survival of 7 months. The purge purpura are active agents; DCF has achieved complete responses in up to 10% of patients, with partial responses in one-third. Response rates of more than 70% have been reported in small series with CAMPATH-1H in T-PLL, including almost 60% complete responses.

Adult T-Cell Leukemia/Lymphoma

Adult T-cell leukemia/lymphoma occurs most commonly in patients from the Caribbean and southwestern islands of Japan. This uncommon lymphoid malignancy is associated with human T-cell leukemia virus type 1. The immunophenotype of the with human T-cell leukemia virus type 1 is often positive for CD4+CD8–, but in some cases, CD4–CD8+ and CD56–. The disease exhibits a clinical spectrum ranging from an indolent disease that may not require treatment for several years to an extremely aggressive disease characterized by anemia, hypercalcemia, bone lesions, splenomegaly, skin infiltration, central nervous system involvement, opportunistic infections, circulating leukemia cells, and a very poor outcome. DCF has been used with modest success.

Sézary Syndrome

One-third of patients with mycosis fungoides will have circulating malignant cells at diagnosis. The peripheral blood of patients with skin patches may reveal circulating cerebrocellular forms in 0% to 22%, in 9% to 30% of patients with patches, and in 25% to 50% with skin tumors, and in 90% to 96% of those with erythroderma. The presence of circulating cells may be an independent prognostic factor. Treatment of this disorder is discussed in Chapter 45.4.


Djuric V, Merle-Belarbi H, Daluix AH. Theophylline-induced B-CLL apoptosis is partly dependent on cyclic AMP production but independent of CD38 expression and endogenous IL-10 production. Leukemia 1999;13:739.


SECTION 46.4
Plasma Cell Neoplasms

INTRODUCTION

Plasma cell neoplasms represent a spectrum of diseases characterized by clonal proliferation and accumulation of immunoglobulin-producing cells that are terminally differentiated B cells. The spectrum includes clinically benign conditions, such as monoclonal gammopathy of unknown significance (MGUS) and rare disorders such as Castleman's disease and a heavy-chain disease; indolent conditions such as Waldenström's macroglobulinemia; the more common malignant entity, plasma cell myeloma, a disseminated B-cell malignancy; and a more aggressive form, plasma cell leukemia, with circulating malignant plasma cells in the blood. All of these disorders share common features in the form of plasma cell morphology, production of immunoglobulin molecules, and immune dysfunction. A plasma cell neoplasm is considered to originate from a single B cell, with resultant monoclonal protein secretion that characterizes its type. Occasional oligoclonal or polyclonal protein abnormalities are observed in conditions such as Castleman's disease. Current laboratory data based on complementarity determining region III (CDRIII) confirm the monoclonal origin of this disease.1

There are five major classes of immunoglobulin synthesized by normal B cells and plasma cells: IgG, IgA, IgM, IgD, and IgE. The dysfunctional plasma cells secrete one of these molecules or, in some instances, produce only k or l light chain molecules.1,2,3,4 Usually, intact immunoglobulin molecules are secreted by the plasma cells; however, there may be a discrepancy in the production of the heavy and light chains leading to an imbalance, with an excess of free light chain that is excreted in the urine (Bence Jones proteinuria). Occasionally, plasma cells do not secrete any paraproteins (nonsecretory type myeloma); however, they usually have cytoplasmic immunoglobulin and produce low levels of immunoglobulins undetectable by current methods. Although myeloma can be associated with any of the immunoglobulin subtypes, the IgM type is predominately associated with other malignant conditions such as Waldenström's macroglobulinemia and chronic lymphocytic leukemia (CLL).

The clinical manifestations of plasma cell dyscrasias range from total absence of any symptoms in subjects with MGUS to formation of tumors, paraproteinemia, hypogammaglobulinemia due to decreased levels of the uninvolved immunoglobulins, bone disease, especially osteolytic lesions, hematopoietic and immune dysfunction, kidney function abnormalities, and infectious problems. These clinical manifestations are the result of a variety of pathogenic mechanisms, including cytokine production by the tumor or by the microenvironment, effect of the tumor mass itself, the deposition of the M protein into various organs, suppression of the T- and B-cell functions, and occasionally autoimmune disorders.

HISTORY

The earliest evidence of myeloma has been reported from the Egyptian mummies; however, the first published clinical description of the disease was reported in 1850 in England. A patient, Thomas Alexander McBean, presented with symptoms of episodes of fatigue, diffuse bone pain, and urinary frequency to Dr. William Macintyre of London in 1845. The urinalysis test results detected a urinary protein with the heat properties often observed for urinary light chains and McIntyre called it "mollities and fragilitas ossium" based on the patient's bony symptoms.5,6 Later that year, Dr. Henry Bence Jones also tested urine specimens provided by Macintyre and corroborated the heat properties of urinary light chains. Bence Jones thought that the protein was the "hydrated deuterioxide of albumin" (now called Bence Jones proteins) and published his findings several years before Macintyre published his case report.7 Bence Jones also emphasized the potential importance of looking for this urinary protein in other cases with mollities ossium. After the patient died in 1846, a surgeon, Dr. John Dalrymple, examined several bones and made gross and microscopic observations.8 His drawings are consistent with morphology of myeloma cells.

The term multiple myeloma was coined by Rustizky in 1873 following his independent observation in a similar patient with multiple bone lesions.9 Kahler in 1889 published a review on this condition and the disease became known, particularly in Europe, as Kahler’s disease.10 Ellinger, in 1899, described the increased serum proteins and sedimentation rate in myeloma.11 In 1900, Wright described the involvement of plasma cells in this neoplasm instead of original belief of its origin from the red marrow and for the first time he used roentgenographic abnormality in myeloma, which to date remains one of the diagnostic tests.12

The development of bone marrow aspiration in 1929,13 electrophoresis to separate serum proteins in 1937,14 and a later report of a specific spike in the g globulin region15 enhanced the diagnosis and understanding of myeloma. Identification of the heavy and light chains in the monoclonal protein by immunoelectrophoresis was described by Grabar in 1953, confirming the monoclonality of immunoglobulin in this disease.16 Other developments from 1960s to 1980s include a staging system,
role of several cytokines such as interleukin-1 (IL-1) and IL-6, and significance of chromosome 13 changes in myeloma.

No effective systemic therapy existed before 1947, when urethan was reported to show initial results in a few patients. However, a subsequent randomized trial indicated that the survival of patients receiving urethan was inferior to that observed with a placebo. The first successful use of chemotherapeutic agent in myeloma was reported in 1958 by Biklin and colleagues with the use of a racemic mixture of α- and L-phenylalanine mustards (Sarcolysine). Subsequently, the α- and L-isomers of phenylalanine mustard were tested separately, and the antilymna activity was found to reside in the L-isomer, melphalan. In 1962, Bergsagel and colleagues of the Southwest Oncology Group reported remissions in approximately one-third of myeloma patients with melphalan. Administration of high doses of the glucocorticoid was first reported to induce remissions in relapsing or refractory myeloma in 1967. The use of melphalan in combination with prednisone was then studied extensively. The role of high-dose therapy was investigated by McElwain and Powles in 1984, and addition of bone marrow transplantation with improved safety and further dose escalation was reported in 1986 by Barlogie et al. Since then, numerous developments have taken place including activity of tandem transplant and the role of bisphosphonates and thalidomide.

**EPIDEMIOLOGY**

According to the most recent data from the Surveillance, Epidemiology, and End Results program, multiple myeloma is a relatively uncommon malignancy in the United States, representing 1.0% of all malignancies in whites and 2.0% in African Americans. Among hematologic malignancies, it constitutes 10% of the tumors and ranks as the second most frequently occurring hematologic cancer in the United States after non-Hodgkin's lymphoma. At any one time, the prevalence of myeloma is around 40,000 and approximately 14,000 new patients are diagnosed each year, with 11,000 people dying each year from myeloma. The disease is more common in men and has average annual age-adjusted (1970 U.S. standard) incidence rates per 100,000 among whites of 4.7 in men and 3.2 in women, whereas for African Americans the incidence is 10.2 in men and 6.7 in women. The increased incidence in African Americans is not explained by factors such as social or economic condition, household size, or family income. The incidence data for other ethnic groups including native Hawaiians, female Hispanics, American Indians from New Mexico, and Alaskan natives also show higher myeloma rates relative to U.S. whites in the same geographic group; however, the Chinese and Japanese populations have a lower incidence than whites. The incidence of multiple myeloma has slowly increased in the U.S. white population since 1970; however, the incidence among African Americans has increased more prominently during the 1970s, 1980s, and 1990s.

The incidence of myeloma and other plasma cell disorders increases with advancing age. The median age of onset is 68 years. The mortality pattern also closely follows the incidence curves for age distribution with median age at death in men of 70 years and women of 71 years. As seen in Figure 46.4-1, fewer than 2% of patients are younger than 40 years, whereas more than 40% of the patients are older than 70 years. A similar age distribution is also observed in other related plasma cell disorders including MGUS and Waldenström's macroglobulinemia.

**FIGURE 46.4-1.** Multiple myeloma average annual age-, sex-, and race-specific incidence per 100,000 in the United States, 1992 to 1996. Increase in incidence is noted with advancing age, and higher incidence is observed in male than female subjects and in African American than white populations.

**ETIOLOGY**

**ENVIRONMENTAL EXPOSURE**

Exposure to ionizing radiation is the strongest single factor linked to an increased risk of multiple myeloma. This has been documented in atomic bomb survivors with a five times greater incidence than the control group and a latent period of approximately 20 years from exposure. People exposed to low levels of radiation also demonstrate an increased incidence of myeloma, including radiologists, people employed in the nuclear industry, or those handling radioactive materials. An increase in myeloma risk with increasing numbers of diagnostic radiographs was demonstrated without an increased risk of leukemia or lymphoma, suggesting that even a low level of radiation is a risk factor for myeloma. An association between exposure to various chemicals and the risk of multiple myeloma remains ill defined. Exposure to metals, especially nickel; agricultural chemicals; benzene and petroleum products; other aromatic hydrocarbons; and silicon have been considered as potential risk factors.

Alcohol and tobacco consumption has not been clearly linked to myeloma. Among medications, only mineral oil used as a laxative has been reported to be associated with an increased risk of multiple myeloma in some patients.

Hereditary and genetic factors may predispose to myeloma development. Among 37 families with at least two family members who had myeloma, occurrence among siblings was reported in 25 of the families. However, direct genetic linkage has not been established. Myeloma risk also appears to be enhanced by the presence of HLA-Cw2 in both African American and white populations.

MGUS has been considered a premalignant condition; however, the rate of conversion to myeloma remains extremely small and often associated with additional genetic changes. Repeated infections or antigenic stimulation of the plasma cell compartment has also been proposed as a possible predisposing condition for myeloma. In one interesting patient report in the literature, a prior therapy with horse antiserum against tetanus lead to subsequent development of MGUS, which was eventually becoming malignant after acquiring additional genetic alterations.

Epidemiologic studies have not been able to conclusively establish an association between multiple myeloma and infectious or autoimmune diseases. The human herpes virus (HHV-8; Kaposi's sarcoma herpes virus) has been shown to be present in the bone marrow dendritic cells of the majority of patients with multiple myeloma. Its association with other lymphoproliferative diseases, such as Castleman's disease, body cavity lymphoma, and Kaposi's sarcoma, has been previously demonstrated. Although this association has been reported by some, others have failed to identify HHV-8 in dendritic cells from various sources including mobilized peripheral blood stem cells.

In the initial report, 100% of myeloma patients demonstrated evidence of ORF26 sequences in dendritic cells, compared with zero in normal controls. However, one study reports that 60% of 30 myeloma samples were positive for ORF26, with 44% of 25 normal controls demonstrating positive results. This study also failed to show positivity for the viral genes ORF72 and 75 in both myeloma and control samples.

Antibodies against HHV-8 have not been observed in multiple myeloma. Since HHV-8 produces unique gene products, including possible growth-promoting factors for myeloma such as IL-6, insulin-like growth factor-1, and an IL-6-like molecule, the possible linkage of HHV-8 to myeloma is intriguing, with infection of the stromal cell elements, part of the tumor microenvironment, exerting cell survival or antiapoptotic signals on the tumor cells.

**PATHOGENESIS**

Myeloma occurs not only in humans, but also in mice, canines, and hamsters. In fact, genetic susceptibility to plasma cell tumors has been demonstrated in an inbred strain of mice. A common factor in various species has been considered to be the prevalence of endogenous retroviruses. Animal models are now providing a basis for understanding the role of various molecular events, including the activation of oncogenes, tumor suppressor genes, and various cytokines, and the role of...
The microenvironment not only in causing bone destruction but sustaining and promoting growth, survival, drug resistance, and genetic instability.

**MURINE MODEL**

C57BL/Ka strains of inbred mice spontaneously develop monoclonal gammapathies without tumor formation in 16% of the mice by 2 years. 2 Other strains, such as BALB/c, have a low spontaneous incidence of monoclonal gammapathies. In BALB/c mouse, however, induction of plasmacytoma or myeloma is easily observed after intraperitoneal injection of mineral oil or its clinically defined component, pristane. 2 Production of such tumors can be blocked by administration of indomethacin and accelerated by subsequent infection of the mice with Abelson's virus. The plasmacytomias develop within the oil or other foreign body–mediated granulomas with lymphoproliferative infiltration. Plasmacytoma progression is associated with dysregulated expression of c-MYC as a result of translocation analogous to t(8;14) in human Burkitt lymphoma. The plasmacytomias produce high levels of IgM immunoglobulin, and a growth factor present in the peritoneal fluid has been confirmed to be IL-6. Interestingly, however, the C57BL/Ka strain with a high incidence of spontaneous monoclonal gammapathies is relatively resistant to induction of plasmacytoma by mineral oil.

An association between antigenic stimulation of normal B cells and development of plasmacytoma has been demonstrated in the pristane oil–treated BALB/c immune system. When animals are raised in a germ-free environment, incidence of myeloma after mineral oil stimulation is markedly reduced, whereas that of other lymphoid neoplasms increases. 2 These studies suggest an important role of immune stimulation toward myeloma development.

Human myeloma cell lines can grow and disseminate in a severe combined immunodeficiency (SCID) mouse model, providing a unique opportunity to study this disease in an immune setting. 29,30 The introduction of fetal human bone in to SCID mice (SCID-Hu) has allowed engraftment and proliferation of primary human myeloma cells in more than 80% of mice with human myeloma-specific immunoglobulin and light chains detected in murine blood samples. 29 In this murine model of primary human disease, the fetal bone undergoes osteoporotic and osteolytic change as a consequence of clonotypic plasma cell proliferation and production of human cytokines. 29 Interestingly, the murine bones remain unininvolved at least in the early stages of the disease. This model provides a unique opportunity to study the importance of stromal cell–myeloma cell interaction and the cytokines, chemokines, and various genetic and molecular mechanisms critical for myeloma growth and dissemination. This model also can provide clues to the origin of the myeloma stem cells, as well as the opportunity to evaluate new treatment approaches, such as antiangiogenesis therapy.

**CYTOGENETIC AND MOLECULAR GENETIC ALTERATIONS**

Myeloma karyotypes are complex, with an average of 11 numeric and structural abnormalities per cell. 29,31,32 The relative incidence of gain or loss of various chromosomes and its p and q arm are shown in [Figure 46.4-2](#). The inherent problem in the low proliferative activity of the tumor cells and possible clonal evolution have been obstacles to identify specific chromosomal and molecular changes in myeloma. However, the newer techniques of multicolor fluorescent in situ hybridization (FISH) and spectral karyotyping along with refined G-banding techniques in a large number of patients have identified many nonrandom changes. 33,34

[FIGURE 46.4-2. Summary karyotypic abnormalities in 158 patients with evaluable abnormal cytogenetics from study of 492 patients demonstrating chromosomal chaos. A: Numeric changes with trisomies (gain) and monosomies (loss). B: Structural changes involving short (p) and long (q) arms. (Courtesy of Jeffrey R. Sawyer.)](#)

Partial or complete deletion chromosome 13 q arm confers a poor prognosis, even with high-dose therapy, and suggests a putative tumor suppressor gene. 35 Using the RB1 gene as a probe, FISH analysis reveals RB1 deletion in more than 40% of these patients. 36 On detailed analysis of the 13q chromosome with a 11 probe panel of FISH probes, more than 80% of 50 patients showed molecular deletions, with 13q14 representing a critical region most frequently involved. 35 Additionally, constitutive phosphorylation of pRB is reported in myeloma cells, which is further enhanced by IL-6. 37 Cycline D, cycline-dependent kinases (CDK) and CDK inhibitors, p15 and p16 (ink), p21 and p27 (cip), and p57 (kip) have also been investigated in myeloma based on their effect on pRB phosphorylation. Abnormalities in p16 in 75% and p15 in 67% of myeloma patients have been reported, suggesting an important defect in the pRB regulatory pathway. 38,39,40

The immunoglobulin heavy-chain gene at 14q32 is involved in translocation in 20% to 30% of myeloma by conventional cytogenetics and higher percentage by molecular techniques. 34,41,42 Demonstration of this abnormality in MGUS may suggest its involvement in the initial step of the transformation. 2 The most common translocation involving 14q32 is t(11;14), resulting in overexpression of cycline D. 34,41,42 Additional interesting partners are 4p, 16q, and chromosome 9. Involved in the 4p16 region are fibroblast growth factor receptor III (FGFR3) and MMSET genes. Mutated FGFR3 has been shown to confer resistance to caspase 3–related apoptosis. 43,44 With the help of spectral karyotyping a nonrandom involvement of t(14;16) (q32;q22.23) has been described. Molecular analysis of the locus at chromosome 16q22 shows fusion of immunoglobulin heavy chain with the sequence near the cMAF oncogene. 45 Additionally, (t(9;14) involving PAX5 gene and t(6;14) involving IRF4 genes have been described. 41,46 In the majority of the cases, however, the translocating partner chromosome locus is not identified. Although, 14q32 is one of the common translocation points, its real significance remains unclear in relation to myelomagenesis because of the variety of partner chromosomes involved and lack of prognostic implications.

One of the commonly altered genes in many malignancies is p53. However, in myeloma, abnormalities in p53 in early disease are detected in only 10% of patients. 29,31,32,41,42 However, it represents an important late event associated with progression to an aggressive form of the disease. A study of frequency of p53 mutation in a series of 52 patients with myeloma in different clinical phases showed 7 of 52 patients with abnormalities, all with an advanced and clinically aggressive acute leukemic form of multiple myeloma (7 of 16, 43%). Three of these cases with mutated p53 have been evaluated earlier during the indolent form of the disease and were negative for p53 mutations. 29 One study showed poor prognosis in patients with p53 gene deletion, as assessed by FISH when treated with standard-dose therapy. 47 The effect of p53 deletion in relation to high-dose therapy has not yet been evaluated. In contrast to primary patient samples, mutations in p53 are more frequently detected in myeloma cell lines, which are usually derived from patients with aggressive myeloma. MM2, an important inhibitor of p53 function, is overexpressed in the majority of myeloma cell lines; however, its abnormality is infrequently observed in primary myeloma cells. 48 Changes in another important cell-cycle regulatory gene, c-myc, are also observed in a majority of patients in the form of either abnormal size transcript or high level of expression. 49

An important antiapoptotic gene, BCL-2, is uniformly overexpressed in low-grade non-Hodgkin's lymphoma. In this family of genes, BCL-2 and BCL-XL are antiapoptotic genes, while BAX, BAD, and BCL-xS are proapoptotic genes. A balance between these genes determines cell survival. The t(14;18) translocation involving the BCL-2 gene is quite rare (2% to 3%) in myeloma. However, numerous myeloma cell lines as well as primary cells express high levels of BCL-2. 29,50 Its relation with development of drug resistance as well as radiation resistance in myeloma cells is also well described. 34,51,52 The relation of BCL-2 expression and prognosis remains controversial as one small study failed to correlate it with short survival. Another study in 63 patients, however, showed a significant correlation between BCL-2 expression and resistance to therapy with interferon but not melphalan and prednisone. 53 BCL-XL is up-regulated in myeloma cells after exposure to IL-6 through activation of STAT-3. 54,55 It confers a drug-resistant phenotype and in conjunction with BCL-2 leads to increased genetic instability. These and other molecular changes involving gp130, NF-kB, and STATs combined lead to the development and progression of myeloma. 109

High telomerase activity has also been demonstrated in myeloma cells compared with normal cells, as well as other malignant cell lines. 110 The clinical implication of
this activity remains under investigation; however, telomerase activity provides an additional target for therapeutic intervention.

**DISEASE EVOLUTION**

Multiple myeloma is a germinal center-derived tumor with mainly a post-switch B-cell phenotype characterized by extensive Ig gene hypermutation in the CDRs, which interacts with the antigen. This is reflected in the exceedingly rare occurrence of IgM myeloma. Somatic mutations of other loci, such as BCL-6, have also been reported in the B cells along with the immunoglobulin gene rearrangement. Similar mechanisms may also be affecting other cell-cycle control genes important for cell proliferation and malignant transformation.

As in most malignancies, pathogenesis of multiple myeloma appears to be associated with dysregulated expression and the function of multiple key cellular genes controlling apoptosis, cell growth, and proliferation. Understanding the evolution of myeloma from MGUS has provided a background for a multistep process involving alterations in various oncogenes and tumor suppressor genes. One report suggests the presence of 14q32 abnormalities in patients with MGUS and an additional chromosome 13 change, with a transformation to overt multiple myeloma. This has lead to a theory that a subset of myeloma may originate from prior MGUS with a high incidence of monosomy 13 and a second group of de novo myeloma in which other genetic abnormalities may be involved.

**CYTOKINES**

IL-6 is an important cytokine originally identified as a B-cell differentiation factor that causes proliferation of plasmablastic cells and induces terminal differentiation of B cells into antibody-producing cells. Several studies have confirmed its activity as an autocrine and paracrine growth factor for myeloma cell lines and primary cells. Evidence supporting this includes in vitro myeloma cell growth in the presence of recombinant IL-6, IL-6 production by some of the myeloma cells themselves, expression of high levels of IL-6 receptors, and suppression of in vitro myeloma cell proliferation by anti-IL-6 antibodies. Close cell–cell contact between myeloma cells and the bone marrow stromal cells triggers a large amount of IL-6 production by stromal cells, which supports the growth of myeloma cells and protects them from apoptosis induced by dexamethasone or other chemotherapeutic agents. Correlation has been reported between serum IL-6 levels or C-reactive protein (CRP) levels, an indirect measurement of IL-6 activity, and disease severity as well as extent of bone marrow plasmacytosis; frequent, tlytic bone lesions; and some tumor-associated symptoms such as fever, fatigue, and weight loss. In addition, indirect evidence of the role of IL-6 in B-cell disorders is provided through the transgenic mice. These animals have a high incidence of polyclonal plasmacytosis. Transduction of the IL-6 gene in hematopoietic cells in mice leads to a disorder resembling Castleman's disease. IL-6, however, is not an absolute requirement for myeloma cell growth as some of the myeloma cells do not proliferate in response to IL-6, nor do they require IL-6 for their continued growth. Therapy with anti-IL-6 antibody has also not provided significant clinical benefit.

Expression by myeloma cells of IL-1β, tumor necrosis factor-β (TNF-β), and hepatocyte growth factor has been described, resulting in development of resistance to therapy, possibly through activation of NF-κB. Myeloma cells express a variety of cytokine receptors that play a significant role in cell–cell interactions as well as autocrine and paracrine growth control. A majority of myeloma cell lines and primary cells express IL-6–related receptors gp180 and gp130. Additionally, receptors are expressed for TNF-α, IL-1, IL-2, IL-7, granulocyte-macrophage colony-stimulating factor (GM-CSF), stem cell factor, leukocyte inhibitory factor, oncostatin-M, and insulin-like growth factor 1 and 2. These findings suggest that in addition to IL-6, interferon-γ, IL-1, IL-2, IL-7, GM-CSF, TNF, and insulin growth factor have at least a direct biologic effect on myeloma cells.

The soluble cytokines can be used in vitro to expand the pre-B cells to mature plasma cell stages with cytoplasmic immunoglobulin expression. An important combination of cytokines in this regard is IL-3. However, secretion of immunoglobulin requires contact between marrow stromal cells and myeloma cells; this occurs through adhesion molecules on the surface of the myeloma cells and their counterparts on the stromal cell or extracellular matrix in the bone marrow.

The role of angiogenesis in myeloma has been investigated, showing that advanced-stage myeloma is associated with high microvessel density in bone marrow compared with indolent myeloma or MGUS. An association between increased bone marrow microvessel density at diagnosis with poor event-free and overall survival has also been reported. Angiogenic factors such as vascular endothelium growth factor-1 (VEGF-1) and fibroblast growth factor are expressed by myeloma cells. This observation has lead to an evaluation of thalidomide as an antiangiogenic therapy in myeloma with encouraging results.

**ADHESION MOLECULES**

Adhesion molecules, especially those expressed by myeloma cells and the bone marrow stromal cells, play an important role in mediating the interaction between the host and tumor cells to regulate tumor growth and migration of these cells in vivo. It is believed that after class switching in lymph nodes, myeloma cells home to the bone marrow through acquisition of a variety of adhesion molecules including syndecan-1 (CD138), CD44, very late antigen-4 (VLA-4) (CD49d) and VLA-5 (CD49e), lymphocyte function–associated antigen-1 (LFA-1), intracellular adhesion molecule-1 (ICAM-1), matrix metalloproteinase (MMP), especially MMP-2 and MMP-9, which have also been implicated in myeloma cell proliferation and spread. Serum syndecan-1 levels are reflective of tumor burden as is hepatocyte growth factor. However, in vitro and in vivo studies have documented a role of syndecan-1 in cell–cell and cell–matrix adhesion and in inducing myeloma cell apoptosis. Syndecan-1 expressed by myeloma cells may also serve to trap the growth regulatory molecules such as fibroblast growth factor and insulin-like growth factor as well as angiogenic molecules, such as VEGF and fibroblast growth factor. Expression of different adhesion and surface molecules on normal plasma cells, myeloma cells, and plasma cell leukemia cells are listed in Table 46.4-1.

**PHENOTYPE**

Myeloma cells display heterogeneous phenotypes with differences in the molecules among different patients expressed on the cell surface as well as differences within the same patient at different disease stages. In general, all myeloma cells express high levels of CD38 with immature plasma cell additionally expressing CD45 and the IL-6 receptor. More mature myeloma cells do not express CD45 and lack the IL-6 receptor expression. A subpopulation of myeloma cells may also express CD10, CD56, or CD49e (VLA-5). CD28 expression is associated with more aggressive disease and CD20 expression is present in 20% of

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**Table 46.4-1.** Adhesion Molecule Expression on Normal Plasma Cells and Multiple Myeloma Cells

<table>
<thead>
<tr>
<th>Adhesion Molecule</th>
<th>Normal Plasma Cells</th>
<th>Multiple Myeloma Cells</th>
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<tbody>
<tr>
<td>ICAM-1</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>VLA-4</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>VLA-5</td>
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<td>Present</td>
</tr>
<tr>
<td>LFA-1</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Syndecan-1</td>
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<td>Present</td>
</tr>
<tr>
<td>MMP-2</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>MMP-9</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>CD10</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>CD56</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>CD49e</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>CD28</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>CD20</td>
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myeloma patients, which can be further up-regulated with interferon-α.183 The phenotypic heterogeneity of myeloma cells in fact describes the differentiation process that is an important part of the disease development. The identity of the myeloma stem cell still remains an enigma. B cells expressing CD19 and CD11b can be induced to mature with the help of stromal cells into monotypic plasma cells, suggesting that this cellular compartment may comprise myeloma cell progenitors.184 Using the allele-specific oligonucleotide PCR and the SCID-hu model, the myeloma stem cell will be better defined in the future.

**IMMUNOSUPPRESSION**

Myeloma patients present with suppressed immune function from a variety of factors. The most significant observation is suppression of uninvolved immunoglobulins (e.g., in patients with IgG myeloma there is suppression of serum IgA and IgM levels).185 The factors causing such suppression include the direct role of mononuclear immunoglobulin, increased soluble Fc-receptor or Fc-expressing cells, suppression of helper cell functions through the effect of monoclonal immunoglobulin, and an ill-defined macrogphage-related factor that affects B-cell maturation to plasma cell.186 Recovery of uninvolved immunoglobulin following effective therapy has been associated with improved survival as well as protection from infectious complications. In regard to T-cell function, deficiency of T helper cell is most pronounced.187 The total T-cell count may be decreased; however, in a substantial number of patients it could be normal with no significant change in CD8 cells.188,189-191 There has been demonstration of a stage-dependent suppression of NK cells.192 Antidiotypeic T-cell response has been demonstrated in the majority of the patients with higher Id-specific T-cell frequency in MGUS and early-stage myeloma compared with advanced disease.193 This has lead to a provocative hypothesis that in the early stage of the disease immunologic response plays an important role in controlling proliferation of the malignant clone, and at some point the system is overwhelmed or fails, leading to an overt or more aggressive form of the disease. This also provides a scientific basis to develop idiotype-specific T-cell response through vaccination or in vitro production of idiotype or myeloma-specific cytotoxic T lymphocytes for therapeutic purpose.194

**CLINICAL MANIFESTATIONS**

Patients with multiple myeloma may be entirely asymptomatic and could be diagnosed on routine blood work or may present with a myriad of symptoms, including hematologic manifestations, bone-related problems, infections, various organ dysfunctions, neurologic complaints, or bleeding tendencies (Table 46.4-2). These signs and symptoms result from direct tumor involvement in the bone marrow or location of various plasmacytomas in the body, the effect of the protein produced by the tumor cells and deposited in various organs, production of cytoxins by the tumor cells or by the bone marrow microenvironment, and the effect on the immune system.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Common Cause</th>
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<tbody>
<tr>
<td>Fatigue</td>
<td>Paraproteinemia</td>
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<tr>
<td>Weight loss</td>
<td>Paraproteinemia</td>
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<tr>
<td>Anorexia</td>
<td>Lymphoma</td>
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<tr>
<td>Malaise</td>
<td>Bone marrow involvement</td>
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<tr>
<td>Pruritus</td>
<td>Bone marrow involvement</td>
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<tr>
<td>Paresthesias</td>
<td>Peripheral neuropathy</td>
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<tr>
<td>Polyuria</td>
<td>Dehydration</td>
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<tr>
<td>Hematuria</td>
<td>Glomerulonephritis</td>
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<tr>
<td>Proteinuria</td>
<td>Light chain deposition</td>
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**ANEMIA**

A normochromic normocytic anemia is usually observed in myeloma patients and it may originate from tumor cell involvement in the marrow as well as inadequate erythropoietin responsiveness. Anemia gives rise to fatigue, weakness, and occasionally shortness of breath. In addition to the decreased production of red cells due to marrow infiltration, the effect of various cytokines on erythropoiesis and the effect of renal dysfunction on erythropoietin production may account for some of these effects. High immunoglobulin levels aggravate the anemia due to dilutional effects. In the Durie-Salmon staging system, the level of anemia is considered as one of the criteria to determine the tumor mass load.

**RENAL FAILURE**

Nephropathy is one of the serious adverse complications that can be observed at the time of clinical presentation. The etiology of renal failure can be multifactorial. However, the most common cause is development of light chain tubular casts leading to interstitial nephritis (myeloma kidney).195 Another common cause of renal dysfunction is development of hypercalcemia and hypercalciuria leading to osmotic diuresis and volume depletion and prerenal azotemia. Other modes of kidney involvement in myeloma are light chain deposition disease, which is more commonly associated with k light chain proteins with impaired glomerular filtration; and AL amyloidosis, which is more frequently associated with l light chain, especially l light chain subtype VI, and may have an initial presentation as nephritic range proteinuria, and renal calcium deposition leading to interstitial nephritis.196,197,198, and 199 The presence of l light chain in the urine is also more commonly associated with myeloma kidney when compared with k light chain. Bence Jones proteins bind to a common peptide segment of Tom-Horsfall glycoprotein to promote heterotypic aggregation.200-202 Tom-Horsfall protein deposition in the kidney and its measurement in the urine may be a sensitive measure to predict renal dysfunction.203 Additional factors complicating the renal failure in myeloma patients includes use of nonsteroidal antiinflammatory drugs for pain control, hyperuricemia, nephotoxic chemotherapeutic agents, intravenous contrast for radiographic studies, and calcium deposition and stones in the kidney.204 The proteinuria observed in patients with amyloidosis is more often nonspecific, which can help differentiate it from typical myeloma-related kidney problems in which patients have excessive light chain excretion.205 A demonstration of the development of pathologic renal changes similar to human myeloma-related nephropathy in an IL-6 transgenic mice expressing IL-6 under metallothionen-1 promoter indicates a relationship between constitutive high IL-6 expression in the liver inducing dysproteinemia and long acute phase response and renal changes.206

**HYPERCALCEMIA AND BONE DISEASE**

The mechanism of bone abnormalities, especially depression, in myeloma is an ultrasound process of increased osteoclast activity and suppressed osteoblast activity. These changes are exerted by an increase in osteoclast-activating factors produced predominantly by the bone marrow microenvironment but additionally contributed by the myeloma cells.207-210 These factors include IL-1β, TNF-β (lymphotoxin), and IL-6.211-213 Newly identified factors such as osteoprotegerin and its ligand TRANCE and RANK ligand, which acts as a decoy receptor for TRANCE, have been implicated in the development of bone changes in myeloma.214-216,217 TRANCE is a member of the TNF family and was originally discovered to be secreted by T cells to induce maturation of dendritic cells. TRANCE is also secreted by stromal cells and osteoblasts and induces differentiation and maturation of osteoclast progenitors. Its production is elicited by factors such as parathyroid hormone, parathyroid hormone–related protein, and osteoclast-activating factors. Radiographic findings of such destruction are shown in Figs. 46.4-3-150. All of these changes lead to the development of osteoporotic changes and subsequent development of lytic bone lesions. These bone changes frequently involve the vertebral column, leading to compression fracture and lytic bone lesions that lead to pain-related complications in this disease. A new onset of back pain or other bone pain is a frequent presenting symptom in myeloma patients. These changes in the cytokine milieu and bone destruction may also lead to development of hypercalcemia, which is observed in approximately 25% of patients at some stage of the disease. It may reflect a high tumor burden and the presence of symptoms related to high calcium, which include mental status changes, lethargy, constipation, and vomiting. High paraprotein levels, low albumin levels, or both, commonly observed in patients with myeloma require measurement of ionized calcium rather than total calcium to reliably diagnose hypercalcemia. Hypercalcemia also contributes to renal failure and should be considered an oncologic emergency requiring prompt intervention.
Table 46.4-3

and indolent myeloma, and multiple myeloma are shown in immunoglobulin levels, urinary protein excretion in 24 hours, and bone marrow aspiration and biopsy (The initial evaluation includes a hemogram, complete skeletal radiographic survey, serum and urine protein electrophoresis and immunofixation, quantitative hyperproteinemia or proteinuria, anemia, hypoalbuminemia, low immunoglobulin levels, or marked elevation of erythrocyte sedimentation rate should prompt a further evaluation for diagnosis of plasma cell myeloma.

As myeloma patients present with a variety of symptoms not specific to the disease, the diagnosis of myeloma is quite often delayed. An older patient with a new onset of unexplained back pain or bone pain, recurrent infection, anemia, or renal insufficiency should be screened for myeloma. Additional finding such as nodes, kidneys, subcutaneous tissues, and brain parenchyma. Such extramedullary involvement may be suspected in patients who have more aggressive features of extramedullary disease manifestations are uncommon in patients with myeloma at presentation. However, with more aggressive therapy and improved survival an increased frequency of such manifestations has been observed. Solitary or multiple extramedullary plasmacytomas have been described in the liver, spleen, lymph nodes, kidneys, subcutaneous tissues, and brain parenchyma. Such extramedullary involvement may be suspected in patients who have more aggressive features of myeloma including high lactate dehydrogenase levels, immunoblastic morphology, high tumor cell labeling index, and complex karyotypic features.

The initial evaluation includes a hemogram, complete skeletal radiographic survey, serum and urine protein electrophoresis and immunofixation, quantitative immunoglobulin levels, urinary protein excretion in 24 hours, and bone marrow aspiration and biopsy (Table 46.4-3). The diagnostic criteria for MGUS, smoldering and indolent myeloma, and multiple myeloma are shown in Table 46.4-4.
TABLE 46.4-3. Patient Evaluation in Multiple Myeloma

TABLE 46.4-4. Diagnostic Criteria for Multiple Myeloma, Myeloma Variants, and Monoclonal Gammapathy of Unknown Significance

STAGING AND RISK ASSESSMENT

Following preliminary investigation, more detailed cellular and molecular studies are required to stage myeloma and evaluate other prognostic variables that determine the patient's probable outcome.

PROTEIN ELECTROPHORESIS

Among patients with myeloma, 70% have IgG, whereas 20% have IgA subtype with an additional 5% to 10% having production of monoclonal light chains only. A small proportion, less than 1%, of patients produce monoclonal IgD, IgE, IgM or have nonsecretory myelomas. Suppression of uninvolved immunoglobulins (e.g., IgM and IgA in IgG myeloma) is present in the majority of the patients at diagnosis. Suppression of all of the three major classes of immunoglobulin should raise the possibility that the patient may have light chain only disease or a nonsecretory disease. When multiple immunoglobulin class suppression is associated with small M peak on serum protein electrophoresis, a less common variety of myeloma involving IgD or IgE may be suspected. Patients producing intact immunoglobulin can also have excess light chain production with excretion in the urine (Fig. 46.4-4). The distribution of k and l light chains in the majority of myeloma cases is similar except in IgD myeloma in which l light chain is more common. Currently, there is no difference in therapeutic approach between the different types of myeloma; however, patients with IgA myeloma, despite a higher initial response rate, have poorer survival outcomes.

FIGURE 46.4-4. Serum (SPE) and urine protein electrophoresis (left) showing abnormal monoclonal protein bands (arrows). Quantitation of the M protein is performed by nephelometric measurement of the band. Identification of serum and urine M component by immunofixation electrophoresis (IFE) (right). The labels indicate the specificity of the antiserum used in developing the immunofixation pattern. The top is immunoglobulin (IgG) A-g in serum and bottom is free g light chain in urine.

Myeloma plasma cells usually produce a single, abnormal, unique, monoclonal antibody with a constant isotype and light chain restriction. Rare occurrences of biclonal and triclonal cases have been reported at the time of diagnosis. Occurrence of isotype switch and appearance of abnormal protein bands have, however, been reported in myeloma patients after therapy, especially high-dose therapy. This appears to be related to recovery of normal immunoglobulin production rather than alteration in disease biology. This change is also associated with improved survival. Occasionally, patients with initially intact immunoglobulin production relapse with only Bence Jones proteinuria (light chain escape), nonsecretory disease, or high lactate dehydrogenase disease, and this change has been correlated with more aggressive disease.

Further analysis of a unique variable region in the myeloma-related idiotype (e.g., CDRIII) provides information on the monoclonal nature of the protein and also provides a tool to investigate minimal residual disease by polymerase chain reaction using allele-specific oligonucleotide, thus allowing determination of molecular complete remissions.

BONE MARROW EXAMINATION

Various degrees of bone marrow infiltration are observed in myeloma, with the majority of the patients having an excess number of plasma cells (more than 5%). The pattern of bone marrow involvement (diffuse vs. nodular) is important, as patients with nodular disease seem to have poorer outcomes (in contrast to CLL). The morphology of the plasma cell seems to be an important factor determining severity of the disease. This is based on histologic examination (Bartl grade) in which grade I suggests a slow-growing disease, whereas grade III represents plasmablastic disease with an aggressive course. There is also an increased incidence of cytogenetic abnormalities in patients with Bartl grade III when compared with grade I. As plasma cells contain cytoplasmic immunoglobulins with a constant heavy and light chain, its frequency can be evaluated by flow cytometric analysis using immunohistochemical staining of the plasma cells. When coupled with DNA staining using propidium iodide, two-parameter analysis can detect changes in DNA content in the myeloma cells (Fig. 46.4-5). DNA aneuploidy is observed in the bone marrow of more than 80% of patients, suggesting the existence of chromosomal abnormalities in the majority of patients. This also provides an objective marker for evaluation of therapy and to distinguish reactive from clonal plasmacytosis, especially in nonsecretory disease. A hypodiploid tumor cell has also been
associated with refractoriness to standard-dose therapy.

FIGURE 46.4-5. A: Bone marrow plasma cells in a patient with immunoglobulin G myeloma showing neoplastic plasma cells at various stages of differentiation. B: Two-parameter flow cytometry of DNA content of bone marrow cells; abscissa (propidium iodide), and cytoplasmic immunoglobulin (ordinate, anti-k or g FITC). At diagnosis approximately 45% hyperdiploid tumor cells with k light chain restriction are seen (left panel); at the time of maximal response no hyperdiploid light chain restricted cells are seen (middle panel); at the time of early relapse reappearance of small hyperdiploid and k light chain–restricted population (<1%) is indicative of reemergence of a small number of clonal cells that may not yet be apparent on cytologic examination of the bone marrow (right panel).

CYTOGENETICS

As the myeloma cell represents a mature differentiated cell with low proliferative activity, cytogenetic abnormalities are not frequently found. Abnormalities are detected in only one-third of the patients at the time of diagnosis; however, repeated analysis improves the yield to almost one-half of the patients. The normal karyotypic pattern observed in the remaining half most likely originates from dividing normal hematopoietic cells.

As described previously, a complex karyotypic pattern is frequently observed and its distribution is shown in Figure 46.4-2. Although a predominant constant cytogenetic abnormality has not been identified, certain recurrent changes have been noted. These include the common B-cell tumor–related changes in the 14q32 region involving the IGH region, chromosome 1q, and chromosome 13–related changes. A longitudinal analysis in patients undergoing high-dose chemotherapy has shown clinical evolution including changes involving chromosome 5 and 7, commonly associated with myelodysplastic syndrome. Acquisition of such changes in the myeloma karyotype appears to portend poor prognosis. Detection of chromosome 13 deletion abnormalities at diagnosis as well as after high-dose chemotherapy has now been reported to carry a poor prognosis. The application of FISH technology has improved our ability to detect genetic changes by using interphase cells. The Rb-1 probe detects an abnormality on the 13q14 region, and its deletion has been reported in 40% of patients by interphase FISH, also suggesting a prognostically poor-risk group of patients treated by standard-dose therapy. Interphase FISH analysis for numeric chromosomal aberrations has identified chromosomes 6, 9, and 17 as also carrying favorable outcomes. Plasma cell leukemia has been reported to frequently contain a t(11;14); however, this translocation has also been detected in patients with MGUS without any prognostic relevance.

LABELING INDEX

The proportion of myeloma cells in the cell cycle is small early in the disease. A study of cycling myeloma cells with bromodeoxyuridine or tritiated thymidine methods shows a median of 1% cycling cells at diagnosis. The labeling index has important prognostic significance as patients with more than 1% cells in S phase in bone marrow have worse outcomes.

RADIOGRAPHIC EVALUATION

The radiographic survey of the bone is a standard diagnostic workup, which shows osteopenia in an early phase of the disease and, with increasing tumor burden, lytic punched-out lesions (Fig. 46.4-6). Osteosclerotic lesions are observed in POEMS syndrome. Due to the predominant osteolytic activity with osteoblastic inactivity, bone scans are seldom positive unless a recent fracture has occurred and not useful in the diagnosis of multiple myeloma.


As demineralization of bone (osteoporosis) is one of the common manifestations of myeloma, measurement of bone mineral density (BMD) by dual-energy x-ray absorptiometry is an important evaluation at diagnosis. In a study of 66 patients at diagnosis, majority of the patients had decreased BMD: lumbar mean BMD value (Z score) –1.24 ± 1.45. Following standard-dose therapy, lumbar BMD increased 0.7%, while in a group treated with high-dose therapy the improvement was 4.6% (P = .02). Similar improvements in BMD have also been noted in patients undergoing high-dose therapy with addition of bisphosphonates and show differential effects of pamidronate on cortical and cancellous bones in patients with myeloma undergoing autotransplants.

Magnetic resonance imaging (MRI) of bone marrow provides a better assessment of tumor burden and is essential in the workup of a patient with solitary plasmacytomas of bone. More than 95% of myeloma patients have MRI abnormalities: one-third have diffuse involvement of the bone marrow, one-third have focal lesions, while the other one-third have heterogenous marrow with both focal and diffused involvement. As myeloma is well recognized as a macrofocal disease, random bone marrow sampling may not be entirely diagnostic or predictive of disease status. MRI short tau inversion recovery images (STIR) provide a better assessment of tumor load in myeloma. A focal marrow plasmacytoma can be further analyzed through computed tomographically (CT)-guided fine-needle aspiration allowing cytologic diagnosis, which can be combined with further risk assessment through evaluation of cytogenetic and FISH analysis as well as labeling index. As therapies become more effective, the MRI pattern may change as seen in Figure 46.4-7A, Figure 46.4-7B, and Figure 46.4-7C; a diffuse involvement of the marrow may unravel into a focal disease. Normalization of MRI abnormalities may provide a better definition of complete responses as the therapy for this disease with autologous or allogenic transplantations aims toward cure. Positron emission tomography scanning has been evaluated in a small number of studies and may provide a better functional definition of the lesions observed on MRI or CT and allow selection of lesions for biopsy.
Factors are related to tumor burden, intrinsic property of the tumor, host and microenvironmental influences, and treatment intervention–related factors. It is important to define therapeutic strategies, permit comparison of clinical trial results, and predict life expectancy after diagnosis. As shown in Table 46.4-4, various characteristics have been identified to predict the possible course of the disease. Evaluation of prognostic factors is important to patients with multiple myeloma, who have variable disease courses with survival ranging from less than 1 year with aggressive disease to more than 10 years with indolent disease.

**DIFFERENTIAL DIAGNOSIS**

In the presence of lytic bone lesions and greater than 30% marrow plasmacytosis, the myeloma diagnosis can be readily established. However, in the absence of lytic bone lesions or diffused osteoporosis, other criteria have to be fulfilled to differentiate overt myeloma from MGUS. These include anemia, high levels of monoclonal protein in serum and urine, and marrow plasmacytosis as described in Table 46.4-4. Distinguishing smoldering myeloma and monoclonal gammopathy may be difficult as this distinction is essentially based on levels of serum monoclonal proteins and marrow plasmacytosis. The differentiating features are shown in Table 46.4-5, and in the majority of the patients with monoclonal gammopathy, anemia, bone lesions, or MRI abnormalities are absent. Conventional cytogenetic results are usually negative in MGUS; however, monoclonal plasma cells in some cases with MGUS may be aneuploid. Patients with nonsecretory myeloma are diagnosed based on marrow plasmacytosis and bone lesion. MRI abnormalities and CT- or MRI-guided fine-needle aspiration biopsy are important for follow-up of the disease.

**TABLE 46.4-5. Major Diagnostic Criteria among Monoclonal Gammopathy of Unknown Significance, Smoldering Multiple Myeloma, and Multiple Myeloma**

Diagnosis of solitary plasmacytoma of bone or soft tissue requires intense investigation to rule out systemic disease. Bone marrow examination in a true solitary lesion is negative with no clonal cell population on DNA cIg examination. MRI evaluation for myelomatous involvement of the bone marrow helps detect early lesions before their detection by standard roentgenographic examination. Detection of such lesions and cytologic confirmation through CT- or MRI-guided fine-needle aspiration biopsy may help confirm solitary plasmacytoma and its genetic makeup. In case of MGUS, such detection may change the diagnosis to solitary or multiple myeloma. It is important to note that patients with MGUS or solitary plasmacytoma seldom have suppression of uninvolved immunoglobulins.

Besides plasma cell neoplasms, various other conditions can present with monoclonal immunoglobulin secretion. These conditions include other B-cell neoplasms such as CLL and B-cell non-Hodgkin’s lymphoma; autoimmune conditions such as cold agglutinin diseases, mixed cryoglobulinemia, hypergammaglobulinemia, and Sjögren’s syndrome; inflammatory or storage diseases such as lichen myxedematous, Gaucher’s disease, sarcoidosis, and cirrhosis; and rarely other malignancies such as chronic myelogenous leukemia, and colon, breast, or prostate cancer.

Protein deposition disease involving various organs requires additional special diagnostic procedures. Deposition of amyloid protein (amyloidosis) can be clinically suspected based on macrocrosis, vascular fragility (raccoon’s eyes, peri orbital subcutaneous hemorrhages), carpal tunnel syndrome, organomegaly, nephropathy, and cardiomegaly with arrhythmia. Detection of Congo red–positive amyloid in perivascular area and in subcutaneous fat, bone marrow, or rectal biopsy and classic apple-green birefringence when visualized under polarized light are diagnostic of AL amyloid. Electrocardiography may reveal a low voltage, and echocardiographic evaluation shows thickening of the interventricular septum or classic spackled pattern in the myocardium. Endomyocardial biopsy may establish the diagnosis of cardiac amyloid. Another manifestation of amyloid deposition includes autonomic dysfunction due to amyloid deposition in the vas motor nerves, leading to postural hypotension. Deposition in adrenal glands leads to hypoaldosteronism. Amyloid deposition in spleen may lead to hypersplenism with observation of thrombocytopenia. Deposition in liver may be suspected based on elevated alkaline phosphatase and g-glutamyl transpeptidase, and deposition in gastrointestinal tract leads to malabsorption syndrome. Renal dysfunction needs to be further investigated with a renal biopsy, as diagnosis of light chain cast nephropathy or light chain deposition disease may be reversible following aggressive therapy while deposition of amyloid would require a different therapeutic approach. As deposition of immunoglobulin and light chain can mimic many manifestations of AL amyloid, immunofluorescence analysis of unfixed tissue is important for diagnosis.

**PROGNOSTIC VARIABLES**

Patients with multiple myeloma have variable disease courses with survival ranging from less than 1 year with aggressive disease to more than 10 years with indolent presentation of sensitive disease. Various characteristics have been identified to predict the possible course of the disease. Evaluation of prognostic factors is important to define therapeutic strategies, permit comparison of clinical trial results, and predict life expectancy after diagnosis. As shown in Table 46.4-6, prognostic factors are related to tumor burden, intrinsic property of the tumor, host and microenvironmental influences, and treatment intervention–related factors.
Studies measuring in vitro immunoglobulin production by patients' myeloma cells have lead to the development of clinically applicable methods to estimate tumor mass. A clinical staging system developed by Durie and Salmon for multiple myeloma using standard laboratory measurements has been applied to predict clinical outcomes after standard-dose chemotherapy. As shown in Table 46.4-7, this system uses monoclonal protein or immunoglobulin levels in serum, light chain excretion in a 24-hour urine sample, presence of hypercalcemia, anemia, extent of bone lesions, and presence or absence of renal failure. In a study by National Cancer Institute Canada, overall survival with standard-dose therapy in patients with low-disease burden (stage I) was 49 months and with high-tumor burden (stage III) was 25 months. Including the renal failure in the staging system, patients with stage IIIa disease had a median survival of 30 months and stage IIIb disease, 15 months. The accuracy and predictive value of the Durie-Salmon system is less pronounced in patients undergoing high-dose chemotherapy. The high-dose chemotherapy is probably able to treat the disease burden more successfully, with the patient's outcome depending more on tumor biology factors. As the Durie-Salmon system considers tumor burden variables and depends on subjective interpretation of lytic bone lesions, additional other variables have been investigated to better assess patients' risk.

### TABLE 46.4-7. Myeloma Staging System

<table>
<thead>
<tr>
<th>Prognostic Variables</th>
<th>Stage I (Low-Tumor Burden)</th>
<th>Stage II (Moderate-Tumor Burden)</th>
<th>Stage III (High-Tumor Burden)</th>
</tr>
</thead>
<tbody>
<tr>
<td>b2-microglobulin (b2m)</td>
<td>0 - 2.5 mg/L</td>
<td>2.6 - 10 mg/L</td>
<td>Greater than 10 mg/L</td>
</tr>
<tr>
<td>Light chain excretion</td>
<td>Normal</td>
<td>Increased</td>
<td>Markedly increased</td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>Normal</td>
<td>10%</td>
<td>20%</td>
</tr>
<tr>
<td>Anemia</td>
<td>Normal</td>
<td>10%</td>
<td>20%</td>
</tr>
<tr>
<td>Bone lesions</td>
<td>Normal</td>
<td>10%</td>
<td>20%</td>
</tr>
<tr>
<td>Renal failure</td>
<td>Absent</td>
<td>Present</td>
<td>Markedly present</td>
</tr>
</tbody>
</table>

The bone marrow plasmacytosis reflects tumor burden and has been considered in prognosticating survival. Peripheral blood monoclonal plasma cell has also been reported as a predictor of survival in myeloma. In a study of 254 patients, blood monoclonal plasma cell count was greater than or equal to 4% in 57% of patients, with median survival of 2.4 years compared with 4.4 years in patients with a count less than 4.

Among the various other disease biology variables, Barlow grading of tumor cells correlates with survival even in patients undergoing high-dose chemotherapy. Flow cytometry of DNA and cytoplasmic immunoglobulin (DNA-cIg) can identify hypodiploid tumor cells, associated with resistance to standard-dose chemotherapy, which can be overcome by high-dose chemotherapy. The plasma cell proliferation rate as measured by the labeling index is a valuable prognostic factor, with an index of greater than 2% predicting inferior survival. One study combining b2m and labeling index identified a low-risk group with both parameters low, intermediate-risk group with one parameter high, and high-risk group with both parameters high, with median survival of 71 months, 40 months, and 15 months, respectively.

Cytogenetic analysis has now been identified as a major prognosticator in plasma cell myeloma. Abnormalities involving chromosome 13 carry a poor prognosis with short survival as well as inferior response to high-dose chemotherapy. Additional tumor-related factors associated with inferior survival include increased soluble IL-6 receptor level, elevated serum lactate dehydrogenase level usually associated with extramedullary disease, and increased mitotic activity (greater than one per high power field).

Among the microenvironment-related factors, bone marrow microvessel density has been identified as an important prognosticator. High microvessel density in the bone marrow (greater than or equal to four per high power field) at the diagnosis confers shorter event-free (2.7 vs. 4.3 years; \( P = .03 \)) and overall survival (7.9+ vs. 4.3 years; \( P = .006 \)) after high-dose chemotherapy. This may be reflective of increased VEGF expression by myeloma cells or other microenvironmental factors.

An increased level of serum syndecan-1 has been described as carrying poor prognosis. Soluble CD16 levels have been correlated with disease activity, with significantly reduced levels of soluble CD16 found in sera from patients with multiple myeloma as compared with MGUS patients and normal controls; a stage-dependent decrease in soluble CD16 was observed in myeloma.

Among therapy- and intervention-related prognostic factors, more than 12 months of prior standard-dose therapy affects survival most significantly in patients undergoing high-dose chemotherapy. Additionally, the tandem transplant and the time between the two transplants are also significantly correlated with superior event-free and overall survival. Age over 65 years has been reported to be associated with inferior survival using standard-dose therapy; however, with high-dose therapy, age does not appear to predict poor survival.

As high-dose therapy is able to overcome the problems related to increased disease burden as well as to some other biologic features associated with drug resistance, some traditional prognostic factors are no longer predictive of survival after high-dose chemotherapy. With this background, in a study of 1000 patients receiving high-dose chemotherapy with melphalan, 200 mg/m², the three most significant adverse variables associated with a shorter survival were the presence of chromosome 13 abnormality, b2m greater than 2.5 mg/L at the time of transplant, and more than 12 months of preceding conventional-dose therapy. When patients are divided into groups with none of the previously mentioned risk factors, presence of one of the risk factors, or presence of both the risk factors, inferior prognosis is associated with an increase in the number of risk factors. As shown in Figure 46.4-8, even among these three groups presence of chromosome 13 abnormality predicts inferior survival, confirming its overriding influence. Additional molecular studies with FISH analysis as well as expression of various proteins such as BCL-family proteins, p53, and activation of STAT and NF-kB pathways in the future may provide new insight into the understanding of predictive factors important for prognostication.
other chemotherapeutic combinations showed that melphalan and prednisone and other chemotherapeutic combinations are equivalent.

marrow stem cell damage, remained the same. A meta-analysis of 18 published studies with 3814 patients randomized to receive melphalan and prednisone or various
cyclophosphamide (C), carmustine (BCNU; B), melphalan (M), doxorubicin (Adriamycin; A), and prednisone (P). Commonly used combinations include VBMCP or
OTHER ALKYLATING AGENT-BASED COMBINATIONS.

incidence of treatment-related myelodysplastic syndrome and acute myeloid leukemia increases and partial resistance even to high-dose chemotherapy develops.
are not being used as induction therapy because the ability to mobilize adequate numbers of stem cells decreases with prolonged use of this combination; the
the development of cytopenia and eventually myelodysplastic changes in the marrow. With successful treatment with high-dose therapy, melphalan and prednisone
The median response duration was 18 months and overall survival was 24 to 36 months. One of the frequent complications of melphalan and prednisone therapy was
chemotherapy for myeloma and in subsequent years various other single agents and combinations have been investigated and reported to have significant
Standard-Dose Therapy

TREATMENT

The diagnosis of a monoclonal protein does not always require immediate treatment of the patient. Although multiple myeloma is generally a disseminated disease, patients can present with solitary plasmacytomas that can be treated with local therapy or they may present with indolent asymptomatic myeloma, which can smolder for a long period of time before becoming symptomatic and requiring treatment.

SOLITARY PLASMACYTOMA

Solitary plasmacytoma requires specialized techniques for more accurate staging including a CT scan and MRI to exclude more disseminated disease. Solitary plasmacytomas of the bone involve vertebral bodies in one-third of the patients and frequently affect men (70%) at a younger age (median, 56 years). A measurable monoclonal protein in the serum is observed in 24% to 54% of the patients and in a large proportion, no detectable monoclonal protein is observed, even on immunofixation. Extramedullary plasmacytomas are diagnosed less frequently and require a complete workup including MRI and positron emission tomography scanning to rule out any additional site or disseminated disease. The optimal therapy for true solitary plasmacytoma is curative-dose radiotherapy with 4000 to 5000 cGy. With such a dose, the local tumor recurrence rate has been less than 10%, and 30% of patients with solitary bone lesions compared with more than 70% of patients with solitary extramedullary plasmacytomas have a long disease-free survival. The monoclonal protein disappears after radiotherapy in 25% to 50% of the patients, suggesting possible eradication of all detectable disease. Reappearance of monoclonal protein predicts recurrence of disease. It can be anticipated that with better staging with MRI true solitary plasmacytoma of the bone can be cured in a high proportion of patients.

INDOLENT MYELOMA

Myeloma patients with a low tumor mass and slowly progressive disease may present without specific symptoms. These patients generally have less than 20% bone marrow plasmacytosis and low monoclonal protein levels as shown in Table 46.4-5. They have no lytic bone lesions, no hypercalcemia or renal disease, and hemoglobin greater than 10 g/dL. In patients with indolent light chain disease, Bence Jones proteinuria does not exceed more than 10 g/dL. These patients do not present with cytogenetic abnormalities using conventional karyotyping and do have a low labeling index and low b2m. Features predictive of early progression to symptomatic myeloma include lytic bone lesions, high serum myeloma protein levels (greater than 3 g/dL IgG or greater than 2 g/dL IgA), and focal MRI abnormalities. Median time to progression is 26 months for all patients, 10 months in patients with bone lesions and high monoclonal protein, and 61 months for those without any of these features. Such indolent myeloma patients are typically not treated with chemotherapy until disease progression, onset of symptoms, or development of new lytic bone lesions. However, pamidronate has been used as lead-directed treatment to delay the onset of bone-related complications. Additionally, cytogenetic analysis of bone lesions through CT-guided biopsy provides important prognostic information that may dictate the need for early chemotherapeutic intervention.

SYMPTOMATIC MULTIPLE MYELOMA

Standard-Dose Therapy

Since the observation of induction of remission defined as greater than or equal to 50% decrease in paraprotein levels with melphalan in one-third of the myeloma patients studied, various standard-dose chemotherapeutic combinations have been evaluated. Oral melphalan and prednisone was the first successful combination chemotherapy for myeloma and in subsequent years various other single agents and combinations have been investigated and reported to have significant antitumor activity. MELPHALAN AND PREDNISONE. Treatment of oral melphalan and prednisone was introduced 30 years ago and has remained the standard of therapy, providing symptomatic relief as well as tumor mass reduction. A partial response as defined by greater than 50% reduction in monoclonal protein has been observed in 50% to 60% of the patients and between 3% and 5% of patients achieve a complete response. The absorption of oral melphalan is unpredictable, requiring its ingestion on empty stomach and increase in dose if the patient does not develop cytopenia. With availability of the intravenous formulation, dose and pharmacokinetics are now predictable. In patients receiving melphalan and prednisone, a prompt response was associated with a poor survival, reflecting possibly a highly proliferative tumor. The median response duration was 18 months and overall survival was 24 to 36 months. One of the frequent complications of melphalan and prednisone therapy was the development of cytopenia and eventually myelodysplastic changes in the marrow. With successful treatment with high-dose therapy, melphalan and prednisone are not being used as induction therapy because the ability to mobilize adequate numbers of stem cells decreases with prolonged use of this combination; the incidence of treatment-related myelodysplastic syndrome and acute myeloid leukemia increases and partial resistance even to high-dose chemotherapy develops.

OTHER ALKYLATING AGENT-BASED COMBINATIONS. Various chemotherapeutic combinations have been investigated in myeloma, including vincristine (V), cyclophosphamide (C), carmustine (BCNU; B), melphalan (M), doxorubicin (Adriamycin; A), and prednisone (P). Commonly used combinations include VBMP or VAMP/VP16/AD. These combinations in randomized studies achieved similar response rates and event-free and overall survival when compared with melphalan and prednisone. Results from large studies evaluating standard-dose chemotherapy regimens are listed in Table 46.4-8 and Table 46.4-9. In the majority of the studies, there was no benefit of any of these combinations over melphalan and prednisone, and the toxicity problems, including bone marrow stem cell damage, remained the same. A metaanalysis of 18 published studies with 3814 patients randomized to receive melphalan and prednisone or various other chemotherapeutic combinations showed that melphalan and prednisone and other chemotherapeutic combinations are equivalent.
The role of high-dose corticosteroids was initially investigated in the late 1960s with an observation of therapeutic benefit in small numbers of patients. Glucocorticoids down-regulate IL-6 production and induce apoptosis in vitro. The molecular mechanism of corticosteroid-induced apoptosis in myeloma involves a decrease in NF-κB activity through IκB activation. Interestingly, myeloma cells can be rescued from glucocorticoid-mediated killing by addition of IL-6 to in vitro cultures or by coculturing them with stromal cells, which are a source of IL-6 in vivo. High-dose dexamethasone was evaluated in combination with vincristine and Adriamycin. The dosages of these agents (VAD) were vincristine at 0.25 mg/m² and Adriamycin at 9 mg/m² given by continuous infusion over 24 hours for 4 days, along with dexamethasone, 40 mg orally on days 1 to 4, 9 to 12, and 17 to 20, with the cycle repeated every 5 weeks. More than 50% of refractory myeloma patients showed rapid and marked response, defined as greater than 75% cytodestruction, with better efficacy in patients responsive to prior therapy. Response with VAD was much faster, with the median tumor halving time of 21 days compared with greater than 6 weeks for other combination therapies. The advantages of this combination include a quick response, effectiveness in hypercalcemia, quick relief of bone pain, applicability in patients with renal failure, and no cumulative bone marrow stem cell damage, allowing subsequent successful mobilization of stem cells. Studies using high-dose dexamethasone alone given in doses similar to the VAD regimen have shown response rates almost similar to those observed with VAD in primary resistant myeloma but higher in relapsing disease, indicating that dexamethasone is clearly an important agent in VAD. In a study evaluating glucocorticosteroid dose intensity, chemotherapy regimens with higher glucocorticosteroid dose intensity yielded higher response rates and improved survival (P = 0.01). VAD is associated with minimal bone marrow toxicity, and continuous infusion of Adriamycin prevents cardiac toxicity. Randomized comparisons between VAD and other chemotherapeutic combinations have failed to show any survival benefit for VAD; however, lack of stem cell damage provides an advantage in using VAD for initial cytoreduction before stem cell mobilization and transplant. Addition of cyclophosphamide to VAD (CVAD) has been shown to achieve responses in up to 40% of VAD-refractory patients.

**INTERFERON.** The role and efficacy of interferon in the management of myeloma remains controversial. It has been shown to have up to a 20% response rate in relapsed myeloma patients. Its mode of action remains multifactorial; direct growth inhibitory action as well as its antiangiogenic and immunomodulatory activity may contribute to its overall action. However, in combination with other chemotherapeutic regimens, it has failed to demonstrate beneficial effect. In a metaanalysis of 16 trials involving 2286 patients, response rate was 45.9% in the chemotherapy alone group versus 54.4% for the chemotherapy with interferon group. The difference in overall survival was 5 months. Its role in maintenance therapy after standard-dose therapy has generally been more positive, with demonstration in some of the studies of significant prolongation of survival for groups receiving interferon-a. However, other studies have failed to show benefit. A metaanalysis of eight trials involving 929 patients randomized to interferon versus no treatment showed prolongation of relapse-free survival by 7 months and overall survival by 5 months. However, in younger patients and those with lower tumor burden interferon was more effective. Its role, if any, after high-dose therapy is entirely unclear. It is associated with flu-like symptoms, weight loss, impotence, depression, mental status changes, and cytopenia, and its prolonged use has been associated with inability to mobilize stem cells.

**Radiation Therapy**

Radiation therapy was considered the mainstay of the treatment for myeloma before availability of chemotherapeutic options. However, with more effective chemotherapy, especially high-dose chemotherapy, the role of radiation has now been limited. A definitive role remains in patients with solitary bone and extramedullary plasmacytoma. In this setting, it provides excellent local control, and in a subset of patients it provides long-term disease-free survival when a solitary lesion is confirmed through extensive radiographic workup. Patients with solitary bone plasmacytoma following definitive radiation therapy (4000 to 5000 cGy) have progression-free survival of 30% compared with extramedullary plasmacytoma in which progression-free survival is around 70%. The indication for radiation therapy in multiple myeloma remains palliative in cases of impending pathologic fracture and spinal cord compression. In patients with bone pains or asymptomatic soft tissue masses, radiation is only considered when patients have failed chemotherapeutic options. Radiation to the extensive marrow-containing area, such as the pelvic bone, should be considered carefully in light of the need for collection of stem cells. The dose for palliative radiation therapy has been substantially lower, in the range of 1500 to 2500 cGy. Studies to date have failed to show any benefit of hemibody radiation in multiple myeloma. However, total body radiation has been used in relation with autologous transplantation as well as autologous transplantation. More recent studies have demonstrated that total body irradiation does not provide additional cytoreductive potential and it actually increases treatment-related morbidity and mortality and delays immune recovery following high-dose therapy possibly affecting disease control. Total body irradiation as part of conditioning for autologous transplantation is especially important in the optimal regimen for achieving engraftment; however, its role in cytoreduction in this setting also remains questionable. Newer studies are evaluating low-dose radiation therapy with or without chemotherapy in nonmyeloablative conditioning regimens that may be associated with lower morbidity and still achieve tumor control through graft versus myeloma effect.

**High-Dose Therapy with Periipheral Blood Stem Cell Support**

The low incidence of complete response with standard induction chemotherapy, even in newly diagnosed patients, suggests a marked drug resistance that is possibly acquired during a prolonged subclinical course of the disease evidenced by the presence of complex karyotypic aberrations and multiple molecular changes. This observation led to a pilot study by the late Tim McElwain and his colleagues at the Royal Marsden Hospital where they evaluated role of melphalan dose escalation (140 mg/m²). They reported complete remissions in refractory patients. However, treatment-related mortality was high due to bone marrow toxicity. Bone marrow support in the subsequent studies improved the treatment-related mortality and further dose escalation of melphalan to 200 mg/m² and by added total body irradiation provided further improvement in response. It is important to note that high-dose therapy with autologous hematopoietic stem cell support in newly diagnosed patients has led to series of evaluations by various institutions of this treatment with stem cell support to avoid prolonged cytopenia.

**TABLE 46.4-8. Results of Large Trials for Remission Induction with Combination Chemotherapy Regimens Showing a Statistically Significant Improvement in Survival**

| Table 46.4-8. Results of Large Trials for Remission Induction with Combination Chemotherapy Regimens Showing a Statistically Significant Improvement in Survival |

**TABLE 46.4-9. Results of Large Trials for Remission Induction with Multiagent Chemotherapy Compared with Simple Alkylating Agent Therapy That Failed to Show a Survival Advantage**

**VINCRI STINE, ADRIAMYCIN, AND DEXAMETHASONE AND HIGH-DOSE DEXAMETHASONE.** The role of high-dose corticosteroids was initially investigated in the late 1960s with an observation of therapeutic benefit in small numbers of patients. Glucocorticoids down-regulate IL-6 production and induce apoptosis in vitro. The molecular mechanism of corticosteroid-induced apoptosis in myeloma involves a decrease in NF-κB activity through IκB activation. Interestingly, myeloma cells can be rescued from glucocorticoid-mediated killing by addition of IL-6 to in vitro cultures or by coculturing them with stromal cells, which are a source of IL-6 in vivo. High-dose dexamethasone was evaluated in combination with vincristine and Adriamycin. The dosages of these agents (VAD) were vincristine at 0.25 mg/m² and Adriamycin at 9 mg/m² given by continuous infusion over 24 hours for 4 days, along with dexamethasone, 40 mg orally on days 1 to 4, 9 to 12, and 17 to 20, with the cycle repeated every 5 weeks. More than 50% of refractory myeloma patients showed rapid and marked response, defined as greater than 75% cytodestruction, with better efficacy in patients responsive to prior therapy. Response with VAD was much faster, with the median tumor halving time of 21 days compared with greater than 6 weeks for other combination therapies. The advantages of this combination include a quick response, effectiveness in hypercalcemia, quick relief of bone pain, applicability in patients with renal failure, and no cumulative bone marrow stem cell damage, allowing subsequent successful mobilization of stem cells. Studies using high-dose dexamethasone alone given in doses similar to the VAD regimen have shown response rates almost similar to those observed with VAD in primary resistant myeloma but higher in relapsing disease, indicating that dexamethasone is clearly an important agent in VAD. In a study evaluating glucocorticosteroid dose intensity, chemotherapy regimens with higher glucocorticosteroid dose intensity yielded higher response rates and improved survival (P = 0.01). VAD is associated with minimal bone marrow toxicity, and continuous infusion of Adriamycin prevents cardiac toxicity. Randomized comparisons between VAD and other chemotherapeutic combinations have failed to show any survival benefit for VAD; however, lack of stem cell damage provides an advantage in using VAD for initial cytoreduction before stem cell mobilization and transplant. Addition of cyclophosphamide to VAD (CVAD) has been shown to achieve responses in up to 40% of VAD-refractory patients.
single-institution study from the University of Arkansas for Medical Sciences evaluated intensive remission induction with three non–cross-resistant regimens [VAD, high-dose cyclophosphamide, and etoposide, dexaxethasone, Ara-C, and cis-platinum (EDAP)] followed by two cycles of myeloablative therapy with melphalan, 200 mg/m², with hematopoietic stem cell support. A total of 231 newly diagnosed multiple myeloma patients aged 70 years or younger were treated on this protocol. The partial remission and complete remission rates after induction therapy were 69% and 14%; after the first high-dose melphalan dose they were 82% and 30%, and after the second dose 95% and 48%, respectively. On an intent-to-treat basis, the true complete remission rate was 37%. With a median follow-up of 37 months, event-free and overall survival were 43 and 62 months, respectively. Treatment-related mortality in the first 12 months on the study was 4%. The median duration of neutropenia less than 500/mL and platelets less than 50,000/mL was 6 and 7 days, respectively.

**TABLE 46.4-10.** Results of High-Dose and Autologous Transplant in Myeloma

The superiority of high-dose chemotherapy with autologous bone marrow support was confirmed in a randomized trial conducted by Intergroupe Français du Myelome study. The reported response rate (greater than or equal to 50% reduction in myeloma protein) in 100 patients receiving high-dose therapy (Mel-140 + total body irradiation) and in a similar number of patients receiving standard-dose VMCP regimen was 81% (22% complete remission) and 57% (5% complete remission), respectively ($P < .001$). Significantly longer event-free (median, 28 vs. 18 months) and overall survival (median, 57 vs. 42 months) were reported with high-dose therapy (Fig. 46.4-9). The projected 5-year event-free survival is 28% and overall survival is 52% with high-dose therapy compared with 10% and 12%, respectively, for the standard therapy arm.

**FIGURE 46.4-9.** Comparative trials of high-dose therapy (HDT) versus standard dose chemotherapy (SDT). A: IFM-90 (Intergroupe Français du Myelome) randomized trial with 100 patients accrued to each arm comparing SDT with vincristine, melphalan, cyclophosphamide, prednisone/vincristine, carmustine, Adriamycin, and prednisone and HDT with melphalan, 140 mg/m², plus total body irradiation (800 cGy). Higher complete response rates and significantly longer event-free and overall survival were noted with HDT. B: Pair-mate comparison of 116 patients receiving HDT with standard therapy as opposed to mainly vincristine, Adriamycin, dexaxethasone (VAD)-based chemotherapy according to Southwest Oncology Group trials, matched for b₂m, creatinine, and age. With total therapy, complete response was obtained in 40% and both event-free and overall survivals were markedly extended. C: Randomized study of early high-dose therapy with melphalan, 140 mg/m², plus total body irradiation (800 cGy) versus standard dose standard therapy followed by high-dose therapy at relapse. With early high-dose therapy a superior complete response rate and event-free survival was observed with superior quality of life; however, overall survival was similar between the two arms. CR, complete response; EFS, event-free survival; OS, overall survival.

The superiority of high-dose therapy was also confirmed in a pair-mate analysis comparing 116 patients treated on the tandem transplant arm with a similar number of patients selected from 1123 patients treated with standard therapy on various Southwest Oncology Group studies and selected for important prognostic factors. Using an intent-to-treat-approach, compared with standard therapy, patients undergoing tandem transplant as part of the total therapy regimen had a superior partial response rate (86% vs. 52%; $P = .001$) and longer median duration of event-free survival (49 vs. 22 months; $P = .0001$) and overall survival (62% vs. 48 months; $P = .01$), with a projected 5-year event-free survival of 36% versus 19% and overall survival of 61% versus 39%.

The role of single versus tandem transplants has been evaluated by the French Intergroup. With a short follow-up, no differences in response, complete remission (32% and 33%), or event-free (54% and 57%) and overall survival (71% and 67%) were observed in the whole group. However, a subgroup of patients with low b₂m showed a significant survival benefit with tandem transplant. Longier follow-up will determine if all or a subset of patients may benefit from such an approach.

Other institutions have studied high-dose chemotherapy with stem cell support in myeloma. As seen in Table 46.4-10, complete remissions are obtained in up to 50% of patients and event-free and overall survival are extended to more than 3 years and more than 5 to 6 years, respectively.

**PREVIOUSLY TREATED PATIENTS.** Various investigators have studied high-dose therapy in previously treated patients showing its effectiveness in achieving complete responses. Harousseau et al. report 21% complete response and 66% partial response in 44 refractory or relapsed multiple myeloma patients treated with melphalan, 140 mg/m², plus peripheral blood stem cell support. The median overall survival was 17 months in this group. Vescio et al. studied 135 patients with advanced refractory myeloma treated with high-dose chemotherapy reporting event-free and overall survival of 21 and 43+ months, respectively. Patients with primary unresponsive disease (not responding to standard induction therapy) had outcomes superior to patients with resistant relapse (relapsing after initial response) with event-free survival of 37 versus 17 months ($P = .0004$) and overall survival of 43+ versus 21 months ($P = .0003$), respectively.

Molecular complete responses have been observed in myeloma after high-dose therapy. Björkstrand et al. have reported sustained molecular complete responses in four of five patients by allele-specific oligonucleotide polymerase chain reaction for CDRII up to 33 months from high-dose therapy.

**TIMING OF HIGH-DOSE THERAPY.** To obtain high-quality hematopoietic stem cells, ideal timing for stem cell collection is early in the course of the induction treatment. Ability to collect adequate stem cells (greater than or equal to 2 x 10⁹ CD34+ cells/kg) in patients with less than 12 months of prior therapy is 86% compared with 48% in patients with more than 24 months of prior therapy. The role of early high-dose therapy (n = 91) compared with initial standard-dose therapy followed by high-dose therapy at the time of relapse (n = 94) has been investigated by Femand et al. in a randomized trial. Overall survival was similar in both arms after early and late transplant (median, 84.6 and 64 months, respectively). Median event-free survival was 39 months after high-dose therapy, whereas median time to transplant after randomization to conventional chemotherapy was only 13 months (see Fig. 46.4-9). However, patients randomized to early high-dose therapy had a longer time without symptoms, treatment, and treatment-related toxicity, thus providing a rationale for early high-dose therapy. A delay in high-dose chemotherapy and
transplantation may lead to increased drug resistance, as well as further genetic changes resulting in more aggressive disease. An ongoing Intergroup trial in the United States randomizing patients to up-front high-dose therapy or standard therapy with high-dose therapy as a salvage treatment should also further define the role of high-dose therapy.

HIGH-DOSE REGIMEN. High-dose melphalan (140 to 200 mg/m²) with or without total body irradiation is the most common conditioning regimen used in myeloma. Melphalan's predominant myelotoxicity and metabolism independent of renal function is ideal for multiple myeloma patients who commonly have renal function abnormalities. Melphalan seems to be superior to thiopeta when given with total body irradiation, with patients achieving longer relapse-free and overall survival duration. A combination regimen containing high-dose carboplatin with etoposide and Cytoxan (cyclophosphamide) or a combination with CBV has also been investigated in resistant patients with only occasional responses. However, no regimen has shown marked superiority over others. The addition of total body irradiation has not been shown to improve cytoreduction, and in fact it increases morbidity and treatment-related mortality. A poor outcome in one study using total body irradiation was considered to be related to delayed immune recovery.

STEM CELL PURGING. Myeloma cell contamination as evaluated by polymerase chain reaction or sensitive immunofluorescence is universally observed in stem cell products. Purging of tumor cells by positive selection of CD34+ cells leads to a 3- to 5-log reduction in contamination. Negative selection by the monoclonal antibody cocktail containing CD10 (common acute lymphoblastic leukemia antigen); CD20 (a pan B-cell antigen); and PCA-1, (plasma cell-associated antigen) or peanut agglutinin (PNA) and anti-CD19 antibodies results in undetectable myeloma cells by conventional flow cytometry. The early follow-up results from these studies have not revealed any significant advantage in responses or survival, but they consistently show a delay in engraftment posttransplantation. Even when cells were purged using fluorescence-activated cell sorting of early hematopoietic stem cells (CD34+, Thy1+, Lin-) devoid of any clonal B cells, relapses were frequent and patients had delayed hematopoietic engraftment and suppressed immune status for prolonged periods of time. These effects lead to infectious complications. As complete responses are observed in 30% to 50% of patients, greater emphasis needs to be placed on achieving better tumor cytoreduction in the stem cell product.

HEMATOPOIETIC STEM CELL SOURCE. Mobilized peripheral blood stem cells provide faster engraftment compared with bone marrow. Myeloma patients with less than 1 year of prior therapy had faster granulocyte and platelet recovery after peripheral blood stem cell transplants compared with bone marrow autografts. The duration of prior chemotherapy, especially with stem cell–damaging agents (melphalan, BCNU, and high-doses of cyclophosphamide) along with radiation to bone marrow–containing areas, significantly affects the ability to procure adequate quantities of peripheral blood stem cells and engraftment kinetics posttransplant. Differential mobilization with cyclophosphamide and GM-CSF of normal hematopoietic stem cells during the first 3 days of leukapheresis is observed, while peak levels of myeloma cell contamination are present on subsequent days. These myeloma cells show a higher labeling index and a more immature phenotype of increased cell surface CD38 and CD71 expression. The presence of residual myeloma cells may affect the clinical outcomes of patients undergoing stem cell transplantation. Myeloma patients with renal dysfunction in the initial stage of the disease, and one-half of them recover renal function after correction of hypercalcemia, improved hydration, or effective chemotherapy.

Transplantation in Older Patients

Because myeloma is a disease of older patients, the role of high-dose chemotherapy has been evaluated in patients older than 65 years of age. No significant differences in clinical characteristics have been observed between younger and older patients. Age does not impair stem cell mobilization or engraftment. In a study of patients over the age of 65 years (range, 65 to 83 years) undergoing high-dose melphalan with stem cell transplant, 22% complete responses were achieved. A pair-mate analysis was conducted for these patients and patients younger than 65 with similar high-dose therapy who were matched for relevant prognostic features. Results showed no significant difference in event-free survival (2.1 vs. 1.5 years; \( P = 2 \)) and overall survival (3.9 vs. 3.7 years; \( P = 4 \)) for younger versus older patients, respectively (Fig. 46.4-10). In a study involving 71 older patients (age greater than 60 years) receiving intermediate-dose-melphalan at 100 mg/m² with stem cell support applied twice to three times, the older patients were compared with 71 pair-mates matched for age and b-value and treated with oral melphalan and prednisone. Complete response rates were observed in 47% versus 5% \((P < .001)\), median event-free survival was 34 versus 17.7 months \((P < .001)\), and median overall survival 56+ versus 48 months \((P < .01)\) in patients receiving high-dose therapy and melphalan and prednisone, respectively.

Transplant in Patients with Renal Failure

One-third of multiple myeloma patients have renal dysfunction in the initial stage of the disease, and one-half of them recover renal function after correction of hypercalcemia, improved hydration, or effective chemotherapy. Melphalan and busulfan, both active agents in myeloma, are pharmakokinetically independent of renal function, allowing high-dose administration in myeloma patients with renal dysfunction. Thirty-six patients with severe renal insufficiency (creatinine clearance less than 40 mL/min), including eight patients on chronic hemodialysis, were treated with high-dose melphalan followed by peripheral blood stem cell rescue. No effects on median half-life, area under the curve, and clearance of melphalan were observed in patients with renal failure compared with patients who had normal renal function. Renal insufficiency did not affect posttransplant engraftment or overall survival. However, the patients with renal insufficiency required longer hospitalization due to prolonged mucositis and anorexia.

Myelodysplastic Syndrome after High-Dose Therapy in Myeloma

Treatment-related myelodysplastic syndrome and acute myeloid leukemia are well-recognized complications following alkylating agent therapy. Myeloma patients with their advanced age may have coexisting myelodysplastic syndrome at a preclinical stage detected by cytogenetic changes that may be exacerbated by alkylating agent therapy and may be further affected by high-dose melphalan and stem cell transplant. In myeloma following high-dose therapy and stem cell support increased incidence of cytogenetically detected myelodysplastic syndrome is observed. The increase observed after 2 years was lowest in patients less than 50 years age and with less than 12 months of prior standard-dose therapy (1% to 2%); and it increased to 7% to 10% in older patients (>50 years) with more than 12 months of prior therapy, especially when CD34 mobilization was impaired (Fig. 46.4-11). Thus, in the background of older age and cumulative DNA damage caused by standard-dose alkylating agent therapy, the hematopoietic reconstitution following high-dose therapy may lead to excess telomeric shortening with genomic instability and an increased chance of myelodysplastic syndrome and acute myeloid leukemia.
BISPHOSPHONATES. The second- and third-generation bisphosphonates, pamidronate and zoledronate, reduce skeletal complications and bone pain in myeloma (Table 46.4-12). The mechanism of action includes down-regulation of osteoclast activity, decreased IL-6 production, and induction of apoptosis of osteoclasts through inhibition of farnesyl and geranyl-geranyl transferase activity. Besides reducing bone-related problems, continued administration over 21 months showed mass reduction, including true complete remission in 13% patients.

Salvage Therapies

Patients unresponsive or relapsing after standard alkylating agent therapies such as melphalan and prednisone are responsive to high-dose dexamethasone pulsing alone or in combination with drugs such as VAD or CVAD. Such patients still remain candidates for high-dose melphalan with peripheral blood stem cell rescue if adequate quantities of stem cells can be procured after salvage therapies. Patients relapsing after prior VAD and autotransplant have been treated with such combination chemotherapy consisting of dexamethasone in a pulsing fashion and cyclophosphamide, 400 mg/m²/d, etoposide, 40 mg/m²/d, and cisplatin, 15 mg/m²/d by continuous infusion for 4 days (DCEP). In a study of 57 patients relapsing after tandem transplant, more than 40% achieved greater than or equal to 75% tumor mass reduction, including true complete remission in 13% patients. The responses were seen in high-risk disease settings, including chromosome 13 abnormalities and high labeling index. The efficacy of thalidomide in this setting (see Fig. 46.4-12) has led to the evaluation of a combination of DCEP with thalidomide and Adriamycin (DTPACE) followed by G-CSF administration as induction therapy before transplantation. The preliminary results of this combination appear to be extremely promising, with more than 75% of previously treated patients achieving partial response after two cycles. These combinations, with success in the salvage setting, are now being investigated with nonmyeloablative transplants, TK gene–transduced donor lymphocyte infusion, and CD6-depleted transplants and CD4+ donor lymphocyte infusion to reduce treatment-related mortality and improve overall survival.

Allogeneic Transplantation

Patients with identical siblings have an option of syngeneic transplantation with true tumor-free graft. In the setting of maximal cytoreductive therapy data from the European Bone Marrow Registry involving 16 patients undergoing syngeneic transplant, a complete response rate of 50% and median event-free and overall survival of 32 and 60 months were seen.

HLA-matched sibling donor transplantation enables myeloma patients to achieve 15% to 30% long-term disease-free survival, as shown by various large groups and summarized in Table 46.4-11. In this study, between 30% and 50% of patients achieved a complete remission; however, an extremely high 1-year mortality (up to 50%) has been reported (Fig. 46.4-12). This unusually high treatment-related mortality compared with other diseases, including chronic myelogenous leukemia and acute leukemia, might be related to the older patient population, an immunosuppressed state due to the disease, corticosteroid treatment leading to higher bacterial and fungal infections, and the prior long duration of chemotherapy. Definitive evidence of graft-versus-myeloma effect has been demonstrated and is considered responsible for the reduced probability of disease progression. However, outcome after autografts are poor compared with autografts both as primary and salvage therapy. European Bone Marrow Transplant Registry retrospective analysis in a matched pair setting showed superior overall survival after autotransplants (34 vs. 18 months). Surprisingly, even autograft performed as salvage in patients with resistant or relapsed disease resulted in superior overall survival (32 vs. 20 months), compared with allograft. This is mainly due to excessive treatment-related mortality associated with autografts. Newer approaches are now being investigated with nonmyeloablative transplants, TK gene–transduced donor lymphocyte infusion, and CD6-depleted transplants and CD4+ donor lymphocyte infusion to reduce treatment-related mortality and improve overall survival.

Salvage Therapies

Patients unresponsive or relapsing after standard alkylating agent therapies such as melphalan and prednisone are responsive to high-dose dexamethasone pulsing alone or in combination with drugs such as VAD or CVAD. Such patients still remain candidates for high-dose melphalan with peripheral blood stem cell rescue if adequate quantities of stem cells can be procured after salvage therapies. Patients relapsing after prior VAD and autotransplant have been treated with such combination chemotherapy consisting of dexamethasone in a pulsing fashion and cyclophosphamide, 400 mg/m²/d, etoposide, 40 mg/m²/d, and cisplatin, 15 mg/m²/d by continuous infusion for 4 days (DCEP). In a study of 57 patients relapsing after tandem transplant, more than 40% achieved greater than or equal to 75% tumor mass reduction, including true complete remission in 13% patients. The responses were seen in high-risk disease settings, including chromosome 13 abnormalities and high labeling index. The efficacy of thalidomide in this setting has led to the evaluation of a combination of DCEP with thalidomide and Adriamycin (DTPACE) followed by G-CSF administration as induction therapy before transplantation. The preliminary results of this combination appear to be extremely promising, with more than 75% of previously treated patients achieving partial response after two cycles. These combinations, with success in the salvage setting, are now being evaluated as induction therapy and posttransplant consolidation. In fact, superior overall and event-free survival have been reported in high-risk patients (chromosome 13 abnormalities) receiving posttransplant DCEP consolidation.

Newer Phase I Agents

The second- and third-generation bisphosphonates, pamidronate and zoledronate, reduce skeletal complications and bone pain in myeloma. The mechanism of action includes down-regulation of osteoclast activity, decreased IL-6 production, and induction of apoptosis of osteoclasts through inhibition of farnesyl and geranyl-geranyl transferase activity. Besides reducing bone-related problems, continued administration over 21 months showed mass reduction, including true complete remission in 13% patients.

FIGURE 46.4-11. Development of myelodysplasia using cytogenetic criteria (-5 or del 5q, -7 or del 7q, trisomy 8, del 20q11) following autologous hematopoietic stem cell–supported high-dose therapy with melphalan, 200 mg/m² (one or two cycles). Cumulative incidence of cytogenetic myelodysplastic syndrome in relationship to months of prior therapy (€12 vs. >12 months) and age (€50 vs. >50 years). Patients with no more than 12 months of prior therapy and aged 50 years or younger had the lowest risk of myelodysplastic syndrome compared with the three other groups.

TABLE 46.4-11. Allogeneic Transplant Results

<table>
<thead>
<tr>
<th>Group</th>
<th>% Complete Remission</th>
<th>% Disease-Free Survival</th>
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<tr>
<td>control</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>DCEP</td>
<td>24</td>
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<td>thalidomide</td>
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FIGURE 46.4-12. Results of allogeneic transplantation from three large groups show high early mortality with relapse-free survival around 25% to 30%. However, later relapses are observed. EBMTR, European Bone Marrow Transplant Registry; Rx, treatment; Tx, transplant.
With the success of thalidomide, newer potent antiangiogenic agents and thalidomide analogues are of interest in myeloma. Other cells and Dutcher bodies. shows various subtypes from small lymphocytes to lymphocytes with varying levels of plasmacytoid differentiation to presence of mature plasma cells along with mast differences between cells in multiple myeloma, Waldenström’s macroglobulinemia, CLL, and normal B cells are shown in cells expressing various pan B-cell markers such as CD19, CD20, and CD22. CD5 and CD23 are observed in a small number of patients. The immunophenotypic Kaposi’s sarcoma herpes virus, which has been reported to be present in dendritic cells derived from bone marrow from patients with Waldenström’s tumor specimens, and the SCID-hu system. Preliminary reports of pamidronate alone administered frequently, every 2 weeks, have shown response or delay in disease progression in occasional patients. THALIDOMIDE. In 180 patients, thalidomide was investigated using incremental doses of 200 to 800 mg. Thalidomide may act in many different ways including through antiangiogenic activity, down-regulation of anti–TNF-a activity, immunomodulation, and changes in adhesion molecules. In this group of patients with advanced posttransplant relapsed myeloma, a partial response was attained in 26% and an overall response was observed in 34% of patients with single-agent thalidomide. As the major toxicities are somnolence, constipation, neurologic symptoms, and fatigue, it may be an ideal drug to combine with other traditional chemotherapeutic regimens (Fig. 46.4.13).

**FIGURE 46.4.13.** A: A patient initially undergoing allogeneic transplantation followed by interleukin-2 treatment and salvage therapy with DCEP (dexamethasone, cyclophosphamide, etoposide, cis-platinum) at relapse without response was treated with escalating doses of thalidomide starting at 200 mg and increasing to 800 mg daily. Within 12 weeks the patient had achieved a complete response, with normalization of bone marrow plasmacytosis from 95% involvement before thalidomide and reduction of immunoglobulin A from over 8 g/dL to normal range. The patient was maintained at a 400 mg daily dose. Following sustained response for over 16 months, the patient showed signs of relapse and is being treated with a higher thalidomide dose now. B: Event-free and overall survival of 89 relapsed or refractory myeloma patients treated with single-agent thalidomide.

OTHER POTENTIAL AGENTS. With the success of thalidomide, newer potent antiangiogenic agents and thalidomide analogues are of interest in myeloma. Other potential agents under investigation include TNF-a inhibitors, oral tamoxifen, arsenic trioxide, and a newer generation of bisphosphonates. Additionally, with altered ras activity and high telomerase levels in myeloma, approaches directed at these molecular targets are being investigated. The SCID-hu model provides a perfect setting for such evaluation before human studies.

**WALDENSTRÖM’S MACROGLOBULINEMIA**

Dr Jan Waldenström first described a condition in two patients characterized by bleeding tendencies from mucosa, anemia, lymphadenopathy, and high serum viscosity with high molecular mass M component. This disease subsequently was recognized to have lymphoplasmacytic differentiation that differed from myeloma in various aspects including absence of lytic bone disease and presence of hepatosplenomegaly, lymphadenopathy, or both. Macroglobulinemia is less frequent than myeloma, affecting approximately 1500 people a year in the United States, with a higher incidence in men and in whites than in African Americans and a median age at diagnosis of 63 years. The pathogenetic mechanisms are not well understood. However, mechanisms similar to those in myeloma can be considered. Familial occurrence and a case report of occurrence in monozygotic twins have been reported. A patient working as a canary breeder developed macroglobulinemia and showed reactivity of monoclonal IgM to an antigen in the canary droppings, suggesting a role of constant antigenic stimulation in the pathogenesis of the disease. Infrequency of the disease, however, has limited detailed epidemiologic and pathogenetic studies. Like myeloma the tumor cells are postantigen selection memory B cells with somatic hypermutation and rearrangement in the variable region and unique CDR. The normal B cells produce IgM as primary immune response and with further antigenic stimulation and selection undergo class switching and produce IgG. Waldenström’s macroglobulinemia cells, with production of IgM, are arrested before class switching. However, no clonal diversity is observed and no isotype switching is reported. Viral infections with hepatitis C virus appear to be a significant risk for cryoglobulinemia, which is often associated with Waldenström’s macroglobulinemia. The role of Kaposi’s sarcoma herpes virus, which has been reported to be present in dendritic cells derived from bone marrow from patients with Waldenström’s macroglobulinemia, and hepatitis G virus are unclear in pathogenesis of this disease. Phenotypically the malignant cells are surface and cytoplasmic Ig+ cells expressing various pan B-cell markers such as CD19, CD20, and CD22. CD5 and CD23 are observed in a small number of patients. The immunophenotypic differences between cells in multiple myeloma, Waldenström’s macroglobulinemia, CLL, and normal B cells are shown in Table 46.4.13. Bone marrow examination shows various subtypes from small lymphocytes to lymphocytes with varying levels of plasmacytoid differentiation to presence of mature plasma cells along with mast cells and Dutcher bodies.

**TABLE 46.4-12.** Summary of Published Placebo-Controlled Trials of Bisphosphonates in Patients with Multiple Myeloma

<table>
<thead>
<tr>
<th>Bisphosphonate</th>
<th>Regimen</th>
<th>Number of Patients</th>
<th>Event-Free Survival (%)</th>
<th>Overall Survival (%)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pamidronate</td>
<td>Oral</td>
<td>110</td>
<td>30</td>
<td>50</td>
<td>Increase in paraprotein level, no change in bone morphology.</td>
</tr>
<tr>
<td>Ibandronate</td>
<td>Intravenous</td>
<td>100</td>
<td>40</td>
<td>60</td>
<td>Increase in paraprotein level, no change in bone morphology.</td>
</tr>
<tr>
<td>Risedronate</td>
<td>Oral</td>
<td>90</td>
<td>45</td>
<td>65</td>
<td>Increase in paraprotein level, no change in bone morphology.</td>
</tr>
</tbody>
</table>

As the major toxicities are somnolence, constipation, neurologic symptoms, and fatigue, it may be an ideal drug to combine with other traditional chemotherapeutic regimens (Fig. 46.4.13).
Chromosomal changes have been reported in a small number of patients with Waldenström's macroglobulinemia, mainly due to low proliferative potential of this disease. Complex karyotypic changes include trisomies, deletions, and structural abnormalities of various chromosomes. As with myeloma and other B-cell tumors, translocations involving 14q32 are reported with various partners. These includes chromosome 18 (BCL-2), 8 (c-myc), 11 (PRAD-1), and importantly, chromosome 9 involving PAX5 gene, which is expressed at a higher level in normal pre-B cells, and its expression decreases as the cells become plasma cells.

The clinical presentation is variable and is related to high IgM levels and lymphoplasmacytic cell infiltration of various organs. The usual manifestations related to tissue infiltration include pulmonic symptoms with cough and dyspnea, gastrointestinal inflammation with diarrhea and bleeding, skin plaques, and periordial exophthalmes and navel pailes. The large molecular size of IgM leads to higher serum viscosity than seen with comparable levels of IgG or IgA. Hyperviscosity is seldom seen with IgG or IgA levels less than 5 g/dL, whereas IgM levels of greater than 3 g/dL may lead to clinical manifestations. Relative plasma viscosity above 5 cp is usually associated with symptoms. Hyperviscosity may present with fatigue, blurred vision, headache, shortness of breath, mucosal bleeding, and mental status changes or coma. Type 1 cryoglobulinemia, which is caused by physicochemical interactions with the paraprotein and observed in small numbers of patients, may present with purpuric skin lesion, Raynaud's phenomenon, acrocyanosis, malleolar ulcers, or necrosis. Cryoglobulinemia type II, which is due to antibody reactivity, may present with arthralgia, proteinuria, renal failure, polyneuropathy, and mononeuropathy. Additional special presentation may be related to the presence of cold agglutinins leading to a mild hemolytic anemia or exacerbation of Raynaud's phenomenon. Severe demyelinating sensorimotor neuropathies is observed in 10% of the patients. One-half of these patients have detectable antibodies against myelin-associated glycoprotein (anti-MAG antibodies). Sensory or ataxic neuropathy is observed more commonly in patients with anti-MAG antibodies. The frequency of common presenting features is listed in Table 46.4-13.

Laboratory evaluation usually shows anemia; however, early leukopenia and thrombocytopenia in untreated patients is uncommon. Elevated erythrocyte sedimentation rate, monoclonal IgM protein in serum with occasional light chains in the urine, and elevated b2m in a subset of patients is observed. Bone marrow shows typical lymphoplasmacytic infiltration with the presence of mast cells. CT scan evaluation of chest, abdomen, and pelvis may show the presence of lymphadenopathy with enlargement of liver, spleen, or both. Skeletal survey is done to rule out IgM myeloma as bone lesions are not seen in Waldenström's macroglobulinemia. Depending on clinical findings of immunologic effects or involvement of other organs, specialized test are required. Tissue infiltration may require confirmation with biopsies. Asymptomatic presentation of Waldenström's macroglobulinemia does not require immediate cytotherapeutic therapy as it does not alter the outcome and delays chemotherapy-related bone marrow suppression. Patients with preserved hemoglobin and low b2m are ideal candidates for observation. Patients with high IgM-related symptoms, such as hyperviscosity, hemolytic anemia, neuropathy, and cryoglobulinemia, benefit from plasmapheresis without conventional chemotherapy.

Patients who are symptomatic from the disease or have marked hepatosplenomegaly, cytopenia, or progressive disease have been treated with alkylating agents. Chlorambucil alone or with corticosteroids produces response rates as defined by greater than 50% drop in paraproteins and tumor mass in 60% to 75% of previously untreated patients, and complete responses observed in less than 5% of the patients. Responses are slow and may take up to 12 to 18 months from the beginning of treatment. Treatment is continued until maximal reduction is observed. Median survival from diagnosis is more than 10 years. More aggressive combination therapy with multiple agents has achieved more than 80% response rate. However, there is no improvement in overall survival. Prolonged alkylating agent therapy has led to development of myelodysplastic syndrome or acute myeloid leukemia in up to 10% of the patients.

Purine analogues fludarabine at a dose of 25 mg/m2 intravenously for 5 days every 4 weeks and cladribine at a dose of 0.1 mg/kg by continuous infusion for 7 days have produced responses in up to 80% of previously untreated patient populations and complete responses in 10% of patients. Effectiveness of purine analogues in previously treated patients has been in the range of 30%, with higher responses in patients relapsing after cessation of prior therapy and less frequent responses in patients with resistant relapse. Patients relapsing after receiving one purine analogue do not usually respond to another purine analogue. In a large prospective multicenter study by the Southwest Oncology Group in newly diagnosed patients, however, fludarabine showed only 39% response rate. Younger patients are shown to respond better than older patient populations. Anemia, b2m greater than 2.5 mg/dL, and IgM greater than 4 g/dL were predicative of poor outcome in that study. The major side effects with purine analogues are prolonged cumulative cytopenia and immunosuppression leading to opportunistic infections. Nonchemotherapeutic treatment options include Rituxan (anti-CD20 mo-ab) with 20% to 30% responses in small studies, and interferon-α with a 30% response rate. High-dose dexamethasone pulsed has produced some responses in refractory patients. There have been reports of occasional responses following splenectomy. The role of high-dose chemotherapy has been evaluated in six patients with extensive prior therapy showing five patients achieving a partial response and one patient achieving a complete response. However, as prolonged prior therapy affects stem cell mobilization, especially after purine analogues and chlorambucil, mobilization, at an earlier stage of the treatment, is necessary. The role of thalidomide in this disease remains under investigation.

**PERSPECTIVE**

New discoveries in molecular biology, better understanding of B-cell development and immune regulation, and improved imaging techniques have advanced our understanding of the biology of multiple myeloma and related plasma cell neoplasms in the last decade. A new entity of multiple myeloma with chromosome 13 abnormalities has been recognized, carrying an extremely adverse prognosis even with high-dose chemotherapy. A putative tumor suppressor molecule is under investigation and a risk-based therapeutic approach is applied with more aggressive treatment in this subgroup of patients, including up-front allogeneic transplantation. High-dose chemotherapy has been clearly shown to be effective in improving complete response rates and event-free and overall survival in comparison with standard-dose therapy. It has been successfully applied in older patients or in the presence of renal dysfunction. Over 40% of patients now achieve complete remission compared with 5% with standard-dose therapy a decade ago, and for the first time durable complete responses have been reported in patients without standard risk factors and absence of chromosome 13 abnormalities. MRI with inversion recovery images provides better assessment of bone marrow involvement with myeloma cells and CT- and MRI-guided fine-needle aspiration biopsies provide cytoclogic and molecular diagnosis of the residual bone lesions. Progress is being made in better defining complete responses and now includes normalization of MRI (MRI complete response). Preliminary investigations appear to predict superior survival in such patients. Allogeneic transplants continue to remain difficult, with up to 50% 1-year morality. However, nonmyeloablative allogeneic transplantation regimens are being evaluated to decrease treatment-related mortality while at the same time using graft-versus-myeloma effect to achieve disease control, especially in patients with chromosome 13 changes. The demonstration of the role of neoangiogenesis in myeloma has led to identification of an effective new agent, thalidomide, in refractory myeloma patients. With its different spectrum of adverse effects, it may be an ideal drug to be combined with chemotherapeutic agents. Soil-directed therapy with the use of biphosphonates has shown antitumor effects along with improvement in bone density and a decrease in skeletal events.

**TABLE 46.4-13.** Immunophenotype of Waldenström's Cells

<table>
<thead>
<tr>
<th>Immunephentype</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-cell</td>
<td>95</td>
</tr>
<tr>
<td>T-cell</td>
<td>5</td>
</tr>
</tbody>
</table>

**TABLE 46.4-14.** Clinical Manifestations in 260 Patients with Waldenström's Macroglobulinemia

- **Sensory or ataxic neuropathy:**
- **Hyperviscosity:**
  - IgM greater than 2.5 mg/dL
  - IgM greater than 4 g/dL
- **Cryoglobulinemia type II:**
  - Due to antibody reactivity
- **Cold agglutinins:**
  - Leading to a mild hemolytic anemia or exacerbation of Raynaud's phenomenon
- **Plasmapheresis:**
  - Without conventional chemotherapy

**PERSPECTIVE**

New discoveries in molecular biology, better understanding of B-cell development and immune regulation, and improved imaging techniques have advanced our understanding of the biology of multiple myeloma and related plasma cell neoplasms in the last decade. A new entity of multiple myeloma with chromosome 13 abnormalities has been recognized, carrying an extremely adverse prognosis even with high-dose chemotherapy. A putative tumor suppressor molecule is under investigation and a risk-based therapeutic approach is applied with more aggressive treatment in this subgroup of patients, including up-front allogeneic transplantation. High-dose chemotherapy has been clearly shown to be effective in improving complete response rates and event-free and overall survival in comparison with standard-dose therapy. It has been successfully applied in older patients or in the presence of renal dysfunction. Over 40% of patients now achieve complete remission compared with 5% with standard-dose therapy a decade ago, and for the first time durable complete responses have been reported in patients without standard risk factors and absence of chromosome 13 abnormalities. MRI with inversion recovery images provides better assessment of bone marrow involvement with myeloma cells and CT- and MRI-guided fine-needle aspiration biopsies provide cytoclogic and molecular diagnosis of the residual bone lesions. Progress is being made in better defining complete responses and now includes normalization of MRI (MRI complete response). Preliminary investigations appear to predict superior survival in such patients. Allogeneic transplants continue to remain difficult, with up to 50% 1-year morality. However, nonmyeloablative allogeneic transplantation regimens are being evaluated to decrease treatment-related mortality while at the same time using graft-versus-myeloma effect to achieve disease control, especially in patients with chromosome 13 changes. The demonstration of the role of neoangiogenesis in myeloma has led to identification of an effective new agent, thalidomide, in refractory myeloma patients. With its different spectrum of adverse effects, it may be an ideal drug to be combined with chemotherapeutic agents. Soil-directed therapy with the use of biphosphonates has shown antitumor effects along with improvement in bone density and a decrease in skeletal events.
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Myelodysplastic Syndromes

INTRODUCTION

The myelodysplastic syndromes (MDS) are heterogeneous clonal hematopoietic stem cell disorders grouped together because of the presence of dysplastic changes in one or more of the hematopoietic lineages. Dysplasia signifies abnormal or discordant nuclear cytoplasmic maturation and is the morphologic hallmark of apoptosis. Indeed, MDS is associated with apoptosis and excessive proliferation, resulting in the paradoxic picture of peripheral cytopenias and cellular marrows. The common findings in MDS include anemia-associated problems, infections and bleeding, generally in elderly patients, frequent exposure to carcinogens or leukemogenic agents, a wide range of transformation rates (10% to 80%) to acute leukemia, and a high incidence of cytogenetic abnormalities associated with poor prognoses. The MDS were previously referred to as smoldering leukemia or preleukemia, oligoblastic leukemia, or hematopoietic dysplasia, implying an indolent course. More recent studies have emphasized the aggressive nature and poor prognosis of some subsets of high-risk MDS, defined by excess marrow or peripheral blasts, cytogenetic abnormalities, or both.

INCIDENCE

The estimated incidence of MDS is 7000 to 12,000 new cases in the United States annually. With a median survival of 1 to 3 years, the estimated prevalence is 10,000 to 25,000 cases. The true incidence of MDS is probably underestimated, because the diagnosis is often overlooked or not reported. Those cases often receive no specific therapy because of older age, complicating medical illnesses, and unavailability of effective low-risk treatment modalities. Some MDS may be misdiagnosed as other entities such as hypoplastic or aplastic anemia (hypoplastic MDS), acute myelogenous leukemia (AML) (high blast percent), or myeloproliferative disorders (high white blood cell counts).

ETIOLOGY

The etiology of most MDS cases is unknown. Smoking and exposures to ionizing irradiation, organic chemicals, heavy metals, herbicides, pesticides, fertilizers, stone and cereal dusts, exhaust gases, nitroorganic explosives, petroleum and diesel derivatives, alkylating agents, benzene, solvents other than benzene (e.g., toluene, xylene), chloromphenicol, and marrow-damaging agents including chemotherapeutic agents may increase the risk of developing MDS. Patients with clear exposure to such agents are referred to as having secondary MDS or treatment-related MDS and constitute approximately 20% to 30% of MDS cases. Their proportion is increasing as more patients with other cancers are exposed to and cured with such treatments. Secondary MDS accounts for 30% of MDS cases referred to M. D. Anderson Cancer Center since 1990, compared with 15% before 1990. Alkylating agents (melphalan, chlorambucil, cyclophosphamide, procarbazine) and radiation therapy are associated with the highest risk of developing MDS. Their effects are synergistic, particularly in older patients. Patients with Hodgkin’s disease and other lymphomas, myeloma, breast and ovarian cancers, and those undergoing stem cell transplantation (SCT) are often exposed to such treatments. Among patients with Hodgkin’s disease or lymphoma undergoing autologous SCT with high-dose cyclophosphamide and total body irradiation, the estimated cumulative risk of developing MDS at 5 to 6 years is 11% to 18%, the risk being higher with use of total body irradiation, with increasing age, with longer time from first treatment to transplant, and with low platelet counts at time of SCT. X-chromosome inactivation analysis has shown replacement of polyclonal hematopoiesis with clonal hematopoiesis preceding the development of MDS in some patients. Patients with MDS are older than those with AML and have a higher incidence of unfavorable chromosomal abnormalities, including losses of parts or all of chromosome 5 or 7. There is no known association between viral or other infections and development of MDS. There may be an increased risk of MDS in families of patients with MDS. Rare familial forms of MDS or AML and monosomy 7 have been described. Studies of the frequency of specific polymorphism in enzymes activating, detoxifying, or both activating and detoxifying carcinogens in MDS patients versus normal controls may help in understanding the disease pathophysiology and identifying individuals at risk for developing MDS.

CLASSIFICATION AND RISK GROUPS

The French-American-British (FAB) classification categorizes patients with MDS based on the percentage of marrow and peripheral blasts and the presence of monosomy and Auer rods. Categories include refractory anemia (RA), RA with ringed sideroblasts (RARS), RA with excess blasts (RAEB), and RAEB in transformation (RAEBT). Chronic myelomonocytic leukemia (CMML), a hybrid disorder of excessive myeloid proliferation, monocytosis, and dysplastic changes in the erythroid and megakaryocytic series, is sometimes considered as a fifth MDS category or as a separate disorder.
TABLE 46.5-1. French-American-British Classification of Myelodysplastic Syndromes

The FAB classification of MDS has shortcomings. For example, Auer rods, which characterize RAEB-T, have been associated with favorable rather than poor prognosis. Confusion arises when monocytosis is present with 5% to 29% blasts as to whether such cases should be referred to as RAEB-T (if blasts more than 20%) or as a separate category of accelerated-phase CML. Finally, there is great variability in prognosis within a single FAB subtype, indicating the need to incorporate further information into the FAB system. Investigators have attempted to improve on the classification by including prognostically relevant variables such as the percentage of marrow blasts, chromosomal abnormalities, and cytopenias (anemia or thrombocytopenia).

An International Prognostic Scoring System (IPSS) was developed that assigns points to each of several prognostic factors. It divides patients into low, intermediate-1, intermediate-2, and high-risk groups with median survivals of 5.7, 3.5, 1.2, and 0.4 years, respectively. Although it is an improvement over the FAB system, the IPSS also suffers from variability within single-risk groups. For example, the median survivals of patients with IPSS low and intermediate-1 groups referred to M. D. Anderson were only 2.1 and 1.2 years, respectively, significantly different from those reported in the IPSS study (5.7 and 3.5 years, respectively), despite similar therapeutic measures. The IPSS was derived from newly diagnosed untreated patients, and survival was calculated from diagnosis. However, patients referred to tertiary centers have often had prior therapy, the patients were referred because of some need for therapy, and their survival was measured from the referral date. Thus, latent variables, unrecognized by the prognostic models and related to the referral, might account for differences in prognosis of different study groups categorized in the same IPSS risk groups. Investigations of aberrant cellular or molecular events in MDS (e.g., RAS mutations, apoptosis, clonality, loss of suppressor genes, methylation, and others) may yield new clinically relevant biologic prognostic factors.

TABLE 46.5-2. International Prognostic Scoring System and Model

TABLE 46.5-3. Prognosis in Myelodysplastic Syndrome According to the International Prognostic Scoring System (IPSS)

BIOLOGY AND PATHOPHYSIOLOGY

Preclinical studies have provided insight into different pathophysiologic processes in MDS, and several models of MDS evolution have been proposed. The clonal nature of MDS appears restricted to hematopoietic population subsets. Primitive progenitors (CD34+, Thy 1+) and T cells, perhaps in the earlier MDS phases, appear nonclonal. Late-stage hematopoietic cells of myeloid and erythroid lineage, as well as B-cell lymphocytes, were often clonal. Hematopoietic recovery in remission marrows is frequently nonclonal.

In some patients, nonclonal CD8+ T cells directed against HLA class I–restricted antigens may suppress normal hematopoiesis, as evidenced by enhanced in vitro growth of granulocyte-macrophage colony-forming units following T-cell depletion (cyclosporin, anti-CD8). This provides the rationale for the use of immunosuppressive therapy in MDS. Dysplasia appears to signify high apoptotic rates, explaining the unilineage or multilineage peripheral cytopenias. According to one hypothesis, the primary lesion in MDS is the high cell death rate, which is counterbalanced by a compensatory early phase of excessive hematopoiesis. This is supported by studies demonstrating both increased apoptosis and proliferation and may explain the apparent paradox of peripheral cytopenia and hypercellular marrows. Increased apoptosis has also been observed in the marrow microenvironment cells, suggesting that the primitive stem cell involved is a progenitor to both hematopoietic and stromal cells.
What might contribute to increased apoptosis? High levels of tumor necrosis factor-a (TNF-a) or other proapoptotic cytokines, and the effect of TNF-a on induction of Fas expression on CD34+ cells, may be pathophysiologic. Elevated TNF-a levels in MDS may be restricted to the earlier phases (RA, RARS) and were not found in normal control subjects or in patients with AML. The source of TNF-a production may be the increased marrow macrophages in MDS, which may be stimulated by elevated macrophage colony-stimulating factor (M-CSF) levels, through point mutations in c-fms, which encodes the M-CSF receptor. That TNF-a production in MDS is relevant is suggested by (1) enhanced in vitro colony growth in MDS by incubation with TNF-a neutralizing antibodies 2, and (2) the correlation of TNF-a levels with severity of anemia, poor response to erythropoietin, and increased apoptosis. Strategies to suppress TNF-a levels may help therapeutically.

Other proapoptotic cytokines of interest include interferon-g and IL-1b. Interferon-g production appears to be important in aplastic anemia but less so in MDS. IL-1b levels are highest in RA, tend to correlate with apoptosis but not proliferation, and may be due to deficient production of the receptor antagonist in MDS stromal cells, which increase IL-1b levels and thus apoptosis.

Involvement of the Fas/Fas ligand system in MDS apoptosis has also been proposed, as well as a role for other molecular events including Ras mutations or alterations in the RAS pathways that may be dysfunctional without Ras mutations. Understanding the pathophysiology of RAS in MDS and CMML (10% to 25% of Ras mutations) may result in rational intervention approaches with RAS inhibitors (antisense, farnesyl-transferase inhibitors). Antiapoptotic signaling pathways, including bcl-2 overexpression, and shortening of telomeres may be important in advanced MDS states.

Chromosomal abnormalities may serve as fingerprints for the molecular abnormalities. Chromosome 5 abnormalities (losses in the long arm, 5q-) are common. Many hematopoietic growth regulatory genes have been mapped to this region. These include M-CSF, GM-CSF, IL-4 and IL-6, CD-14, interferon regulatory factor-1, the receptors for platelet-derived growth factor and M-CSF (Fms), and others. Fms is a tyrosine kinase protooncogene, and the viral form of Fms (v-Fms) has transforming properties. Fms point mutations have been described in patients with MDS and AML and those receiving chemotherapy, suggesting its possible role in MDS pathogenesis. Other abnormalities include mutations in p53, overexpression of bcl-2 and c-mpl, deletions of IRF-1, methylation of p15 and others. C-mpl expression was low in risk MDS and high in RAEB, RAEBT, and CMML (40% to 45%). In RAEB and RAEBT, c-mpl expression correlated with other adverse features and with poor survival (P = .02).

How do these observations fit into a general multistep pathophysiologic process in MDS? It is possible that an initial injury results in suppression of normal hematopoietic stem cell growth and differentiation, directly or through stimulation of an immunologic response of polyclonal T cells. The cytotoxic suppressor T cells induce hematopoietic suppression through production of proapoptotic cytokines including TNF-a and the Fas/Fas ligand system. The roles of increased M-CSF, c-fms mutation, increased macrophages and contribution to TNF-a production, and interferon-g and IL-1b need further elucidation. These processes are more prominent in the early phase of MDS (RA, RARS), producing excessive apoptosis and cytopenias, and are more amenable to therapeutic approaches including growth factors, antiapoptotic strategies (e.g., against TNF-a), and immunomodulation (e.g., cyclosporin A, antithymocyte globulins [ATG], corticosteroids). As compensatory proliferation continues, and perhaps mediated by the process of telomeric shortening and genomic instability, the hematopoietic progenitor cells allow the escape and growth advantage of clonal malignant hematopoiesis. This process may predominate in MDS advanced phases (RAEB, RAEBT, CMML), in which proliferation and maturation arrest (rather than apoptosis) are frequent, and in which a new set of molecular events dictate the pathophysiology, including enhanced Bcl-2 and p53 mutations, RAS mutations and dysfunction, and hypermethylation of p15 (leading to suppression of tumor suppressor genes). In these stages, more appropriate investigations include AML-like strategies to suppress the abnormal clone, or ones directed against specific molecular targets including hypomethylating agents or RAS inhibitors.

Thus, MDS might appropriately be divided into two distinct entities, early and late MDS, which are governed by different sets of pathophysiologic processes and in which different directed strategies should be investigated.

**CLINICAL MANIFESTATIONS**

The median age in MDS is 65 to 75 years, with a clear-cut age-related incidence. Younger patients who develop MDS have generally had exposure to leukemogenic agents. There is a male preponderance with a male to female ratio of 1.3:1.0. Presenting manifestations are due to cytopenia-associated problems including fatigue, pallor, infections, and bleeding. Lymphadenopathy and hepatosplenomegaly are uncommon, occurring in less than 10% to 20% of patients. Central nervous system involvement is rare.

Table 46.5-4. Presentation of Myelodysplastic Syndrome (M. D. Anderson, 1980–1999, 1358 Patients)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAEB</td>
<td>1358</td>
</tr>
<tr>
<td>RAEBT</td>
<td>1358</td>
</tr>
<tr>
<td>CMML</td>
<td>1358</td>
</tr>
</tbody>
</table>

**LABORATORY FEATURES**

Anemia is the most common finding: neutropenia and thrombocytopenia are frequent. Monocytosis greater than 10 % in the peripheral blood, in the setting of other MDS features, leads to a diagnosis of CMML. Smears of the bone marrow and blood show various degrees of dysplasia (mild, moderate, severe) in one or more lineages (myeloid, erythroid, megakaryocytic). While the degree and lineage involvement by dysplasia have been correlated with prognosis, assessment of dysplasia may be subjective. Blasts in MDS are myeloid in origin as determined by histochemistry (myeloperoxidase-positive, positive monocyte stain results) and by immunophenotyping (CD13, CD14, CD33 positivity); some cases exhibit B-lineage lymphoid (CD19 or CD10) or mixed-lineage morphologies.

Bone marrow biopsies or aspirates are usually hypercellular, but may be normocellular or hypocellular. Twenty percent of cases may have a cellularity below 20%, which may be important in the context of immune-mediated mechanisms and of immunomodulatory strategies. Other abnormalities include hypogranulation or hypossegmentation (Pelger-Huët–like) of granulocytes, anisocytosis, poikilocytosis, and macrocytosis of peripheral red cells; and marrow dyserythropoiesis including ringed sideroblasts, asynchronous maturation, abnormal nuclear shapes, and chromatin clumping. Peripheral platelet dysplasia may be noted with large abnormally granular platelets or hypogranular platelets. Marrow micromegakaryocytes are also frequent.

Cytochemical stains of importance in the workup of MDS include stains for (1) iron to identify ringed sideroblasts, (2) myeloperoxidase to identify abnormal granulation of myeloblasts, (3) periodic acid–Schiff to identify abnormal erythroblasts, (4) reticulin to define the degree of fibrosis, and (5) platelet antibodies to mark micromegakaryocytes.

Blood chemistries should include B12, and folic acid levels to exclude vitamin deficiency–induced MDS-like changes. Serum and urinary lypozymsomes may be increased in CML. Hypokalemia (lysozyme-induced renal tubular loss), renal dysfunction (leukemic involvement), and hyperuricemia may be present. Testing for the human immunodeficiency virus excludes MDS-like changes associated with human immunodeficiency virus–positive disease.

Additional abnormalities observed in MDS include polyclonal gammapathies in up to one-third of patients, monoclonal gammapathies or hypogammaglobulinemia, the...
presence of autoimmune antibodies, and B- or T-cell abnormalities.

Cytogenetic studies demonstrate karyotypic abnormalities in 40% to 75% of patients. These are more common in higher risk MDS and secondary MDS and often involve chromosome 5 or 7 abnormalities, trisomy 8, 20q-, and complex abnormalities (see Table 46.5-4). A characteristic chromosomal abnormality involving 5q23, or the 5q- syndrome, is often associated with an indolent form of RA. Patients with MDS may infrequently demonstrate favorable chromosomal abnormalities such as t(6;21) or inversion 16.

DIFFERENTIAL DIAGNOSIS

Dysplastic changes in the bone marrow are not pathognomonic for MDS, and the first concern is to exclude more treatable conditions associated with cytopenias. These include B12 or folic acid deficiencies; exposure to antibiotics, chemotherapy, ethanol, benzene or lead; or a regenerating bone marrow following hypoplasia induced by drugs or infections. Patients with human immunodeficiency virus–positive disease, chronic inflammation, tuberculosis, liver disorders, hypersplenism, Hodgkin’s disease, lymphomas, and metastatic disease to the marrow may present with cytopenias and marrow dysplastic changes. In these situations, appropriate tests and an observation period clarify the diagnosis.

Hypoplastic MDS with a marrow cellularity of less than 10% to 20% may be confused with aplastic or hypoplastic anemia. Cytogenetic studies may help in the differential diagnosis, but some aplastic conditions may also be clonal or associated with cytogenetic abnormalities. MDS with maturation arrest at the promyelocytic stage may be confused with acute promyelocytic leukemia; this is clarified by the characteristic promyelocytic blastic morphology and appropriate cytogenetic and molecular studies. Predominance of myelofibrosis in MDS may confuse it with myelofibrosis or occasionally with hairy cell leukemia, because of the constellation of cytopenia, dry marrow aspiration, fibrosis, and splenomegaly in an elderly man. A high blast percentage may result in difficulty classifying MDS-RAEBT versus AML, but this distinction may not be critical for therapeutic choices or prognosis.

SIGNIFICANCE OF THE 30% BLAST CUTOFF TO DISTINGUISH HIGH-RISK MYELODYSPLASTIC SYNDROMES FROM ACUTE MYELOID LEUKAEMIA

The 30% blast cutoff has been traditionally proposed by the FAB classification to distinguish MDS from AML. The original intent was to avoid misdiagnosis and treatment of benign conditions as AML. This was supported by the view that MDS are indolent disorders often observed or treated with supportive care. More recent studies have shown that high-risk MDS has as poor a prognosis as AML, and that other factors, some known, such as cytogenetic abnormalities, and others yet to be discovered (apoptotic, proliferative, angiogenesis, and methylation patterns, molecular abnormalities), may provide more rational methods to classify AML and MDS. In multivariate analysis, when account was taken of cytogenetics, patients with AML and high-risk MDS had similar outcomes following the use of anti-AML chemotherapy, independent of the blast percent. Thus, the use of 30% marrow blasts to distinguish and to assign different treatments to AML versus high-risk MDS may not be relevant. A committee of the World Health Organization has recommended that patients with 20% or more marrow blasts be treated as they would for AML.

SPECIFIC SUBTYPES OF MYELODYSPLASTIC SYNDROMES

5Q SYNDROME

This syndrome is often found in elderly women who present with isolated anemia. The median age is 65 years; the female to male ratio is 3:1. The disease presents as RA or RARS, has an indolent course, rarely transforms to AML, and is associated with a median survival longer than 5 years. The peripheral blood shows macrocytic anemia and normal or slightly elevated white blood cell and platelet counts. The bone marrow may show characteristic monolobulated megakaryocytes. Cytogenetic studies usually demonstrate 5q-23 as the single abnormality. Additional chromosome abnormalities, when present, are associated with a worse prognosis. Since repeated transfusions are a major component of supportive care, iron-chelating therapy (desferoxamine) is important in these patients, particularly if they have received more than 20 units of packed red cells, or when serum ferritin levels exceed 400 to 800 mg/L.

OTHER MYELODYSPLASTIC SYNDROME SUBTYPES

Hypoplastic MDS, like aplastic anemia, may respond to immunomodulatory therapy such as corticosteroids, cyclosporin A, or ATG. Some cases may have disease induced by T-cell suppression of normal hematopoiesis. Myelofibrosis may predominate in some MDS cases and raises the differential diagnosis of acute or chronic myelofibrosis, AML-M7 (megakaryocytic leukemia), and occasionally hairy cell leukemia. Rarely, MDS may present with prominent eosinophilia or monocytosis without fulfilling the criterion of 10^9/L peripheral monocytes. These are referred to as MDS with eosinophilia or with monocytosis. The latter is probably a variant of CMML without excessive myeloproliferation.

CHRONIC MYELOMONOCYTIC LEUKAEMIA

Originally categorized as MDS, CMML is now recognized as a hybrid disorder characterized by increased myeloid proliferation with monocytosis and erythroid and megakaryocytic dysplasia. Thus, it shares characteristics of both MDS and myeloproliferative disorders in different lineages. The median age of patients is 65 to 75 years; there is a male predominance with a ratio of 2:1. Anemia and thrombocytopenia are common; hepatosplenomegaly is present in 25% to 50%; extramedullary disease involves the skin and subcutaneous tissues. Gingival or central nervous system involvement is rare. Patients with CMML and significant leukocytosis may present with organ infiltration and dysfunction including pulmonary insufficiency, cardiac decompensation, and renal failure. This may be exacerbated once treatment has started, and patients may develop bilateral lung infiltrates (leukemic cell necrosis and inflammation) and a picture resembling adult respiratory distress syndrome. Subtle renal dysfunction at the start may worsen transiently on therapy as tumor lysis complications develop. Patients presenting with severe leukocytosis, monocytosis, and organ dysfunction may benefit from leukapheresis, measures to prevent tumor lysis (allopurinol, alkalization, hydration, oral aluminum hydroxide to bind calcium), corticosteroids, and, at times, early hemodialysis for renal failure. Cytogenetic abnormalities are less frequent than in MDS. When present, they involve monosomy 7, trisomy 8, or other structural changes including 12p. Ras mutations are more common in CMML than in MDS (30% to 40%). The median survival of patients with CMML is approximately 18 months. Characteristics associated with shorter survival include increased marrow blasts, anemia, thrombocytopenia, cytogenetic abnormalities, and perhaps older age and excessive monocytosis.

THERAPY

BACKGROUND

The standard of care in MDS is generally accepted to be supportive care. This practice reflects the older age and concomitant medical problems of MDS patients, making AML-like combination regimens risky; (2) the lack of effective nontoxic modalities; and (3) the prevailing notion that MDS is an indolent disorder. However, as discussed, the 30% blast cutoff is arbitrary, and survival of patients with high-risk MDS is similar to that of patients with AML. Hence, the same treatment considerations in elderly AML patients also apply to MDS. The belief that MDS is incurable except with allogeneic SCT is now contradicted by studies using AML-type therapy and intensive supportive care for patients with MDS. In such studies, the overall 3-year complete response duration rates of 25% were similar, among comparable age groups, to patients undergoing allogeneic SCT.

There is marked heterogeneity in MDS. An indolent course is generally seen only in patients with RA or RARS, or low- and intermediate-1 IPSS risk groups. Other patients, making up the majority of referrals to specialized centers, have a poor prognosis and estimated median survivals of 1 year or less, similar to patients with AML. Low-risk MDS generally refers to RA and RARS in the FAB classification and to the low-risk IPSS group. High-risk patients include RAEB and RAEBT in the FAB classification and the high- and intermediate-2 IPSS risk groups. The intermediate-1 IPSS categorization depends on the population under study, being lower risk in community-based studies, and higher risk in studies from specialized centers (see Table 46.5-3).
GENERAL TREATMENT PRINCIPLES

Treatment strategies should be individualized to the patient's condition and disease manifestations. MDS may be appropriately divided into two generally distinct entities pathophysiologically and for therapeutic purposes: low-risk and high-risk MDS. Patients with low-risk MDS and minimal findings should be observed. If they develop significant cytopenias and complications, growth factor support, as single agents or in combinations, may be indicated depending on patient's symptoms and frequency of transfusions and infections. For patients with low-risk MDS, trials of high doses of vitamins (e.g., B	superscript 12), or androgens could benefit occasional patients. Immunomodulatory therapy with corticosteroids, cyclosporin A, and ATG may benefit 30% to 50% of selected patients. Low-risk patients may also be offered investigational single-agent chemotherapy, cytokines, antifolate, or targeted modalities. Because of the poor prognosis of high-risk MDS, efforts should be made to involve patients in investigational studies including novel single chemotherapy agents, cytokines, gene or other targeted approaches (e.g., RAS-inhibitors, monoclonal antibodies), or AML-type combination regimens.

SUPPORTIVE CARE

Most patients succumb to complications of marrow failure and cytopenias before transformation has occurred. Patients with anemia may be transfused with packed red cells when symptoms develop. If the frequency of transfusions increases (e.g., more than 1 to 2 per month), trials of vitamins, androgens, erythropoietin alone or in combinations, and immunomodulatory strategies may be indicated. With granulocytopenia and repeated infectious episodes (e.g., two or more) antibiotic prophylaxis with or without G-CSF appears reasonable, although not established in randomized studies or in high-risk patient subsets.

Thrombocytopenia may be managed with platelet transfusions when platelets are reduced below 10 × 10	superscript 3/L or if bleeding occurs. Patients may become refractory to platelet transfusions; investigational strategies with cytokines, immunomodulation, new agents, or chemotherapy combinations should then be considered.

VITAMINS, ANDROGENS, DIFFERENTIATING AGENTS, AND INTERFERON

Although occasional patients may benefit from vitamin B	superscript 12, androgens, and corticosteroids, the approaches have had a low success rate. Differentiating agents have been investigated including vitamin D, vitamin A, retinoids, hexamethylene bisacetamide, and sodium phenylbutyrate. These were associated with low response rates. Growth factors with low-dose cytarabine were not better than chemotherapy alone.

HEMATOPOIETIC GROWTH FACTORS

Erythropoietin has improved anemia and reduced transfusion requirements in 16% to 25% of selected patients, despite elevated endogenous erythropoietin levels in 85% of patients. Better responses are noted in RA and RAEB compared with RARS (22% vs. 7%). In patients without transfusion requirements, in the absence of ringed sideroblasts, or with low to normal serum levels of endogenous erythropoietin (below 2000 U/L), Erythropoietin, 10,000 U, 3 times weekly, or 40,000 U weekly, may show benefit within 8 weeks of therapy.

G-CSF and GM-CSF improve neutropenia in 70% to 80% of patients and occasionally in other lineage cytopenias. Randomized studies comparing supportive care with G-CSF or GM-CSF have not shown them to reduce infectious episodes, prolong survival, or influence the rate of transformation to acute leukemia. Combinations of G-CSF and erythropoietin may synergize in improving cytopenias. Other cytokines investigated include IL-3 alone and in combinations, IL-6, and IL-11, and thrombopoietins for thrombocytopenia. Growth factors with low-dose cytarabine were not better than chemotherapy alone.

LOW-DOSE CYTARABINE

Large-scale analyses of cytarabine, 10 to 20 mg/m	superscript 2 daily for up to 3 weeks, in MDS showed response rates of 10% to 15%. Cytotoxicity, rather than differentiation, was the anti-MDS mechanism. Morbidity and mortality were substantial, and survival was not improved. Randomized studies of low-dose cytarabine, one with GM-CSF, versus supportive care did not show a survival benefit with cytarabine.

ACUTE MYELOID LEUKEMIA–TYPE COMBINATION REGIMENS

In the early 1980s, two retrospective studies showed that regimens used to treat AML could induce complete response in patients with MDS. Since then, several studies reported on the use of intensive chemotherapy in MDS (Table 46.5-5). Remission rates have ranged from 40% to 60% and mortality from 20% to 40%. Appropriate supportive care measures and prophylactic antibiotics have reduced this mortality to 6% to 20%. Complete response rates were 70% to 80% with favorable or normal karyotypes, and 40% to 50% with unfavorable karyotypes. Cytogenetic remissions generally accompanied complete responses. Factors influencing outcome were age, karyotype, and FAB diagnosis. Patients most likely to benefit were younger than 50 years, had normal karyotypes, and had RAEB (Table 46.5-6). Long-term event-free survival was possible with intensive chemotherapy. Among age-comparable groups, the 3-year complete response and survival rates were similar with intensive chemotherapy versus allogeneic SCT (see Table 46.5-6).

**TABLE 46.5-5.** Combination Chemotherapy in Myelodysplastic Syndromes

**TABLE 46.5-6.** Outcome of Myelodysplastic Syndrome with Acute Myeloid Leukemia–Type Chemotherapy by Different Characteristics and Therapy
ALLOGENIC STEM CELL TRANSPLANTATION

Allogeneic SCT is applicable to a small subset of MDS patients because of age restrictions, concomitant medical conditions, and donor availability. Disease-free survival rates of 30% to 50% have been reported. Results were better in younger patients, with low-risk MDS, and if transplant was applied within 1 year from diagnosis. Failure was primarily due to transplant-associated mortality in low-risk MDS and to disease recurrence in high-risk MDS. In the latter disorders, the long-term follow-up to studies showed 3-year survival rates of 23%, similar to those with intensive chemotherapy. Allogeneic SCT after tumor reduction to less than 5% blasts in high-risk MDS produced better results, but may have selected inherently better patients. In an update of the Seattle experience, patients were evaluated by the IPSS. The disease-free survival rates were 60% in low-risk, 36% in intermediate-1, and 28% in intermediate-2 risk groups. This is compared with 5-year survival rates of 55%, 35%, and 7%, respectively, for unselected patients not receiving SCT. Considering the risk to benefit ratios (early transplant mortality but potential event-free survival) and the comparison of disease-free survival versus survival rates, it appears that SCT may benefit high-risk MDS patients.

While autologous SCT has been advocated as a treatment for MDS, this applies to patients who have achieved complete response, could be harvested, and were candidates for the procedure. The 2-year survival rate was only 39%, despite the highly selected nature of the patients.

Improvement in results of SCT may occur through (1) targeted narrow ablative approaches (e.g., radiolabeled monoclonal antibodies against CD33 or CD45); (2) reductions in SCT-related mortality (e.g., mini-SCT); (3) preleukemic and postleukemic SCT-effective chemotherapy or immunomodulation; and (4) broader application of safer procedures in the setting of matched unrelated donor transplant.

NOVEL AGENTS AND STRATEGIES

Topotecan

Topotecan, a topoisomerase I inhibitor, given as a single agent at 2 mg/m² by continuous infusion daily for 5 days every 4 to 6 weeks, produced complete response in 31% of patients. Side effects were severe mucositis and diarrhea (23% and 17%, respectively). Combinations of topotecan, 1.25 mg/m² daily × 5 and Ara-C 1 g/m² over 2 hours daily × 5, every 4 to 6 weeks, were given with intensive supportive care, prophylactic antibiotics, and the use of the protected environment among patients 50 years or older. Eighty-six patients have been treated (59 MDS, 27 CML). Their median age was 64 years; 35% had prior therapy and 50% had unfavorable chromosomal abnormalities. Complete response was observed in 56% and induction mortality in 7%. Complete response rates were higher with RAEB than with RAEBT and CML (complete response rate of 83% vs. 47% vs. 44%; P < .01), but were similar by different IPSS risk groups and cytogenetic abnormalities. Complete response duration was 8 months, and median survival was 14 months. Severe mucositis or diarrhea occurred in only 3%. This suggested a possible role for topotecan in patients with poor prognoses (older, poor cytogenetics), who have a high incidence of expression of the multidrug resistance phenotype and may benefit from agents that are not multidrug resistance–dependent, such as topoisomerase I inhibitors. Investigations to improve prognosis include (1) addition of cyclophosphamide to topotecan and Ara-C; (2) consolidation strategies in complete response (targeted therapies, immunomodulation, anticytokines); (3) newer topoisomerase I inhibitors; and (4) different dose schedules (e.g., oral topotecan in lower dose, longer exposure schedules).

Hypomethylating Agents

DNA site-specific methylation may be associated with tumor resistance and progression in many solid and hematologic cancers including MDS. In MDS, frequent hypomethylation of p15INK4a has been reported. Agents shown to induce general and selective hypomethylation include 5-azacitidine, decitabine, and the newer methyl transferase antisense inhibitors.

Following pilot studies of continuous intravenous and subcutaneous 5-azacitidine in MDS, Silverman et al. conducted a large-scale randomized trial of subcutaneous 5-azacitidine, 75 mg/m² daily × 7 every 4 weeks (n = 99), versus observation (n = 92) in 191 patients with high-risk MDS. Cross-over to 5-azacitidine was allowed if there was progression on the observation arm. Responses occurred in 61% of 5-azacitidine–treated MDS patients (9% complete response, 15% partial response, 35% hematologic improvement) versus 5% in the observation arm (P < .01). The median time to leukemia transformation (21 vs. 13 months; P < .001) and the median survival (24 vs. 14 months; P = .10) were longer among 5-azacitidine–treated patients. Quality of life was also improved. Thus, 5-azacitidine therapy effectively modified the natural history of MDS.

Wijermans et al. treated elderly patients with high-risk MDS with decitabine, 40 to 50 mg/m² over 24 hours daily × 3 every 6 weeks (120 to 150 mg/m²/course), and later at 15 mg/m² over 4 hours every 8 hours for 3 days (135 mg/m²/course) every 6 weeks. In an update of 125 patients in three studies (median age, 70; IPSS risk intermediate-1 in 35, intermediate-2 in 38, and high-risk in 52) 49% responded: complete response in 24 (20%), partial response in 12 (10%), and hematologic improvement in 23 (19%). Response rates were 58% in IPSS high-risk and 39% and 43% in IPSS intermediate-1 and -2 risk groups, respectively. Ten patients (13%) died during therapy. In 15 patients with chromosomal abnormalities who obtained complete response, disappearance of the cytogenetic abnormalities was noted. The median response duration was 9 months. The median survival was 15 months: 19 months in intermediate-1, 13 months in intermediate-2, and 14 months in high-risk patients. Hypermethylation at three cytosine residues in the 5' region of the p15 gene was detected in 59% of patients. Efficient reduction of methylation with decitabine therapy either accompanied or preceded suppression of bone marrow blasts and improvement of cytopenias. However, responses to decitabine also occurred in the absence of p15 hypermethylation, suggesting that p15 is one but not the only molecular target of pharmacologic demethylation in MDS, or that decitabine may induce anti-MDS activity through mechanisms other than hypomethylation.

Other Chemotherapeutic Agents

Homoharringtonine, a semisynthetic plant alkaloid, showed activity in chronic myelogenous leukemia and AML. Feldman et al. treated 15 patients with MDS with homoharringtonine, 5 mg/m² by continuous infusion daily for 8 days every month, and observed four responses (27%). Significant myelosuppression and high induction mortality discouraged further studies. Lower dose schedules of homoharringtonine, 2.5 mg/m² daily × 7, alone or in combinations, may prove effective and less toxic.

Amifostine

Amifostine, an organic thiophosphonate, increases normal hematopoiesis in vitro, suppresses apoptosis, and inhibits production of TNF-a and other inflammatory cytokines. In a multinational study, hematologic responses, obtained complete response in 15 patients with chromosomal abnormalities who obtained complete response, disappearance of the cytogenetic abnormalities was noted. The median response duration was 9 months. The median survival was 15 months: 19 months in intermediate-1, 13 months in intermediate-2, and 14 months in high-risk patients. Hypermethylation at three cytosine residues in the 5' region of the p15 gene was detected in 59% of patients. Efficient reduction of methylation with decitabine therapy either accompanied or preceded suppression of bone marrow blasts and improvement of cytopenias. However, responses to decitabine also occurred in the absence of p15 hypermethylation, suggesting that p15 is one but not the only molecular target of pharmacologic demethylation in MDS, or that decitabine may induce anti-MDS activity through mechanisms other than hypomethylation.

Other Therapy

Immunosuppression

Immunosuppression may be pathophysiologic in some MDS cases, and immune therapy may be beneficial. Patients with hypoplastic MDS have had complete and durable remissions with therapies similar to those used in aplastic anemia. ATG resulted in responses in 44% of patients. Cyclosporin A resulted in clinical improvements in 14 of 17 patients treated for low-risk MDS. Studies of combinations of ATG, cyclosporine A, growth factors, and corticosteroids are in progress.

Other Strategies

Monoclonal antibodies targeted against surface antigens expressed in MDS (e.g., CD33 and CD45) may be useful. Anti-TNF strategies using pentoxifylline-based combinations were not beneficial. Other anti-TNF strategies may incorporate amifostine and pentoxifylline or use soluble TNF receptors alone or in combination with amifostine, pentoxifylline, and anti-Fas ligand. Antiangiogenesis therapy with thalidomide, 200 to 800 mg orally daily, produced complete response in only one of nine patients in one study; another study reported clinical benefits in 10 of 20 evaluable patients (50%). Based on the association of p53 mutations with...
Agents with interesting differential properties include hexamethylene bisacetaimide and sodium phenylbutyrate. In two studies in MDS, hexamethylene bisacetaimide given as a 48-hour infusion produced complete remissions in six patients among a total of 57 patients treated (objective response rate, 17%).

Sodium phenylbutyrate, a histone deacetylase inhibitor, was given to 27 patients at doses up to 440 mg/kg daily 7 every 4 weeks: 17 had improvements in granulocyte counts and 3 had improvements in platelet counts.

Correlative Studies and Mechanism of Actions

While each of these new approaches has provided encouraging results, little is known about how they influence specifically the pathophysiology of MDS. Understanding how these agents affect methylation, cytokines, and genes involved in apoptosis or proliferation cascades may refine treatments to be more effective and less toxic and help combine them in more appropriate simultaneous and sequential schedules.

CHAPTER REFERENCES

While overall strategies, especially those intended to be hopeful in the future (e.g., low-dose Ara-C, growth factors), progress has been modest. Better understanding of the pathophysiology of MDS (e.g., apoptosis, DNA damage, cytokines) may produce tailored strategies. The improved classification of MDS may allow more appropriate therapies for low- versus high-risk groups. Growth factors and immunosuppressive strategies may improve results in low-risk MDS, while the combination of more selective anti-MDS agents (topoisomerase I inhibitors, hypomethylating agents) may improve outcome in high-risk MDS. Progress in SCT (graft-versus-MDS, mini-SCT, preparative regimens) will find its broader applications. Finally, it is hoped that new targets and targeted therapies will emerge that will add to our knowledge and better treatment of MDS.

INTRODUCTION

Tumors may produce signs and symptoms at sites distant from the primary tumor or its metastases and these are referred to as paraneoplastic syndromes. The syndromes may be due to (1) tumor production of substances that directly or indirectly cause distant symptoms, (2) depletion of normal substances that leads to a paraneoplastic manifestation, or (3) host response to the tumor that results in the syndrome. The evidence for the existence of a paraneoplastic syndrome may range from the mere association of the syndrome with the presence of an actively growing tumor to the cloning of the gene responsible for the syndrome. Among the best characterized of the paraneoplastic syndromes are those producing polypeptide hormones, such as adrenocorticotropin (ACTH) or parathyroid hormone, that affect organ function at remote sites. In such situations, the paraneoplastic syndrome parallels the underlying malignancy, and treatment of the underlying tumor leads to disappearance of the hormone. Additional tumor-derived proteins responsible for paraneoplastic syndromes have been identified, including various growth factors and cytokines such as interleukin-1 (IL-1) and tumor necrosis factor (TNF). Antibodies produced by certain malignancies may lead to neurologic paraneoplastic syndromes such as the Eaton-Lambert syndrome. Many paraneoplastic syndromes, especially those of an immune etiology, do not respond to treatment of the underlying malignancy.

The paraneoplastic syndrome may be the first sign of a malignancy, and its recognition may be critical for early cancer detection. Certain paraneoplastic syndromes that secrete proteins can be used as tumor markers in monitoring patients before and after therapy. In some situations, the underlying disease cannot be treated, but the symptoms and complications of the paraneoplastic syndrome must be treated. This chapter reviews the wide range of paraneoplastic syndromes including the endocrinologic, hematologic, gastrointestinal (GI), renal, cutaneous, and neurologic paraneoplastic syndromes.
patients with Cushing's disease (hypercortisolism secondary to a pituitary adenoma). The molecular control of this process lies in the fact that three promoter regions control transcription of the POMC gene. In normal pituitary glands the P₁, promoter is active, while in cancer-associated ACTH production, the P₁, promoter predominates. It is postulated that loss of tumor suppressor genes leads to overproduction of the C-fos oncogene, which leads to increased POMC gene expression, along with many other proteins in the oncogenic cascade. Some neoplasms then convert pro-ACTH to active ACTH, resulting in the ectopic ACTH syndrome.

Ectopic ACTH is commonly associated with small cell carcinoma of the lung, but can also be found in a variety of neoplasms. While 3% to 7% of patients with small cell carcinoma of the lung develop Cushing's syndrome, many patients with small cell carcinoma of the lung secrete ACTH precursors without the development of the syndrome.

**Clinical Presentation**

Cushing's initial description of the peripheral effects of a hyperfunctioning pituitary adenoma included truncal obesity, purple striae, hypertension, fatigue, moon facies, buffalo hump, weakness, depression, amenorrhea, hirsutism, and edema. The differential diagnosis of a patient with hypercortisolism includes Cushing's disease, adrenal dysfunction, ectopic ACTH production, and corticotropin-releasing hormone (CRH) overproduction. Pituitary overproduction (Cushing's disease) is the most common etiology, occurring in 55% to 82% of patients, while adrenal dysfunction occurs in 5% to 32%, ectopic ACTH production in 11% to 25%, and CRH overproduction in less than 1% to 2%. Although signs and symptoms of hypercortisolism are not specific, several features of ectopic ACTH production are distinguishing: Myopathy with weakness, muscle wasting, hyperpigmentation, and hypokalemia are more common in ectopic ACTH production. Cushing's disease is more common in young women (3 to 1), whereas older men (at higher risk for lung cancer) typically have ectopic ACTH production. Commonly, hirsutism, severe hypertension, and hyperpigmentation are noted on physical examination, while glucose intolerance, hypokalemia, and metabolic alkalosis make up the usual biochemical profile. The hypokalemia can be severe and life threatening.

**Diagnosis**

Distinguishing between pituitary adenoma, ectopic ACTH production, and primary adrenal disorders is the primary focus of the diagnostic workup. The two most common screening tests for cortisol overproduction are the 24-hour urinary free cortisol and the low-dose dexamethasone suppression test. In normal subjects cortisol production should be suppressed by a relatively low dose of dexamethasone, whereas patients with Cushing's disease or ectopic ACTH production are not affected.

With reliable radioassays of ACTH, plasma levels can be determined early in the diagnostic workup. In primary adrenal disease, ACTH levels are low, while in ACTH-dependent Cushing's syndrome the ACTH level is elevated. Classically, plasma ACTH and ACTH precursor levels in ectopic ACTH production are much higher than in Cushing's disease (pituitary adenoma); however, there is a great deal of overlap, particularly in the case of slow-growing malignancies such as bronchial carcinoids. Once primary adrenal disease is eliminated, with normal or elevated ACTH levels, a high-dose dexamethasone suppression test is indicated. High-dose dexamethasone suppresses cortisol production (and thus the urinary study results) in patients with Cushing's disease but not ectopic ACTH production or primary adrenal disorders. False-positive dexamethasone suppression test results are seen when dexamethasone is metabolized more rapidly than normal. Drugs such as diphenylhydantoin, phenobarbital, and primidone, as well as disease states such as thyrotoxicosis cause rapid dexamethasone metabolism. Furthermore, bronchial carcinoids can have ACTH and cortisol suppression with high-dose dexamethasone testing in 40% to 50% of cases.

While the reliability of the dexamethasone suppression test is good, the test is cumbersome and its performance characteristics (sensitivity and specificity) are not perfect. For these reasons, the metyrapone and CRH stimulation tests have been developed. In both tests the sensitivity of pituitary adenoma to stimulation by either cortisol deprivation (metyrapone) or directly (CRH) is exploited. Metyrapone blocks the production of cortisol in the adrenal by inhibiting the conversion of 11-deoxycortisol to cortisol, leading to an increased ACTH secretion in normal patients, thus testing the integrity of the adrenal-cortisol-pituitary feedback loop. Patients with Cushing's disease show stimulated ACTH production, whereas ectopic ACTH production is unaffected. In the largest reported study, the metyrapone test correctly predicted Cushing's in 71% of patients with ACTH-dependent Cushing's syndrome. The combination of the dexamethasone suppression test and the metyrapone test predicted 82% of the cases (significantly better than either test alone). Similarly, pituitary adenomas are generally responsive to ovine CRH stimulation, while ectopic ACTH-producing tumors are not. In one report of 41 patients with ACTH-dependent hypercortisolism, 29 of 33 patients with pituitary adenoma were stimulated with ovine CRH, whereas none of the 8 patients with ectopic ACTH production were stimulated. This led to a sensitivity of 88%, a specificity of 100%, and a diagnostic accuracy of 90%, which compared favorably with the standard dexamethasone suppression test. Again, the combination of CRH stimulation and dexamethasone suppression led to a superior diagnostic accuracy of 98%.

Other evaluations that are more invasive or less well established in diagnosing Cushing's syndrome include inferior petrosal blood sampling with or without CRH stimulation, continuous dexamethasone infusion, and serum chromogranin A. Inferior petrosal venous samples show a marked gradient with peripheral samples in pituitary adenoma. The diagnostic accuracy is high, but the test is expensive and invasive. One hundred twenty-one patients were evaluated with 7-hour continuous infusion dexamethasone at 1 mg/h. The sensitivity for pituitary disease was 100%, the specificity was 90%, and the diagnostic accuracy was 98%. This evaluation was thought to be more convenient and accurate, but these results have not been confirmed. Serum chromogranin A has been shown to be a potential marker of ectopic ACTH-secreting tumors.
production. The results, at this point, are preliminary, however.

**Treatment**

Localization is the most important aspect of therapy. Since a major portion of patients with ectopic ACTH have lung cancer, chest evaluation is initially in order. Plain radiographs followed by computed tomography (CT) detect more than 90% of the lung tumors associated with ACTH production. The exception is bronchial carcinoid tumors, which are visualized on 36% of initial radiographs, but are localized by CT scan in approximately 85% of cases. Octreotide receptor scintigraphy has been promoted for localizing ACTH-producing tumors, because many such tumors have octreotide receptors. An additional advantage of localizing tumors with octreotide receptor scintigraphy is the suggestion of possible therapy with either somatostatin analogues or radiolabeled octreotide.

Surgery is the treatment of choice in patients with early-stage tumors producing Cushing's syndrome because it can completely alleviate symptoms. In one series of 41 patients with ectopic ACTH and absence of small cell cancer of the lung, 16 of 21 (76%) patients with localized tumors were cured of Cushing's syndrome with surgery. Specifically, 81% of bronchial carcinoid tumors were cured with resection, and 9 of 12 (75%) patients with occult ACTH production were palliated with bilateral adrenalectomy. While bilateral adrenal removal is effective in treating Cushing's syndrome, the patient must have lifelong glucocorticoid and mineralocorticoid replacement. Patients with severe muscle weakness and uncontrolled hypertension are candidates for this approach. The use of laparoscopic adrenalectomy has been reported to effectively palliate patients with Cushing's with minimal morbidity and no mortality reported.

The majorities of patients do not have surgically resectable disease and may have ongoing symptoms related to Cushing's syndrome. Medical therapy for ectopic ACTH production centers on inhibiting cortisol production with mitotane, aminoglutethimide, metyrapone, or ketoconazole (Table 47.2). Mitotane is effective in lowering cortisol levels; however, it is rarely used because of its severe toxicity and slow onset of action. Aminoglutethimide is used in only limited situations, because of incomplete responses. Metyrapone is an effective treatment, particularly in combination with aminoglutethimide. Because of its rapid onset of action and favorable toxicity profile, ketoconazole has evolved as the therapy of choice for ectopic ACTH. In one small study, 66% of patients with ectopic ACTH production had a hormonal response and symptomatic improvement with ketoconazole at a dose of 400 to 1200 mg/d. A minority developed symptomatic hyponadrenalism.

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<th>Drug</th>
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<td>Ketoconazole</td>
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**SYNDROME OF INAPPROPRIATE ANTIDIURETIC HORMONE**

The syndrome of inappropriate antidiuretic hormone production (SIADH) was first reported in two patients with lung cancer and hyponatremia. The proposed etiology was an abnormal production of ADH or an ADH-like substance by the cancer. In 1968, arginine vasopressin (ADH) was extracted from cancers associated with this syndrome, confirming the original hypothesis. While the majority of small cell lung tumors positively stain for arginine vasopressin by radioimmunoassay, only 3% to 15% of patients with small cell lung carcinoma have this syndrome. Clearly, as with ectopic ACTH production, the vast majority of tumors that contain these substances does not produce the clinical syndrome.

The pathophysiology of SIADH is well described. After vasopressin is released, it binds to specific receptors in the renal collecting ducts and ascending limb of the loop of Henle. Excess water is reabsorbed and increased sodium is delivered to the distal nephron. This increases intravascular volume, which in turn increases renal perfusion and decreases proximal tubular resorption of sodium. ADH secretion continues in SIADH despite the decrease in plasma osmolality, causing eventual hyponatremia.

**Clinical Features and Diagnosis**

The cardinal features of SIADH are water intoxication and hyponatremia, including the following principal findings: decreased serum osmolality, inappropriate elevation of urine osmolality with urine sodium levels greater than 20 mEq/L, euvolemia (absence of hypovolemia), normal renal function, normal adrenal function, and normal thyroid function. Most patients are asymptomatic, but when symptoms develop they generally reflect central nervous system toxicity. In its early stages, patients complain of fatigue, anorexia, headaches, and mild altered mental status. As the syndrome progresses, patients may experience continued delirium, confusion, fatigue, and seizures. Ultimately, patients develop refractory seizures, coma, and rarely death. Most patients, however, experience minimal symptoms and are discovered on routine laboratory evaluation when they have hyponatremia.

In evaluating a patient with hyponatremia and cancer, other causes of hyponatremia need to be considered. In general, the first step in evaluating patients with hyponatremia is to assess volume status. SIADH is one of the so-called euvolemic hyponatremic states. Therefore, it is necessary to eliminate states associated with volume overload such as congestive heart failure, nephrotic syndrome, malignant ascites, and significant liver disease. It is also essential to exclude extrarenal volume depletion and renal sodium wasting. Once the patient is determined to be euvoletic, other causes of euvoletic hyponatremia must be ruled out, including hypothryroidism, renal dysfunction, and Addison's disease. A careful review of medications is also essential.

Once the diagnosis of SIADH is made, a wide variety of etiologies must be considered, including central nervous system diseases, pulmonary diseases, and drugs. Tumor-associated SIADH is a diagnosis of exclusion. For the purposes of treatment, however, differentiating tumor-related SIADH from other causes of SIADH is not necessary. Of note, it is rarely necessary to perform a water-loading test in order to make the diagnosis of SIADH. Because these patients are often unable to excrete free water, they can develop significant water intoxication, leading to serious morbidity in this setting.

The principal malignancy associated with SIADH is small cell lung carcinoma, although others have been described (non–small cell lung cancer, head and neck cancers, and others). Seventy-five percent of all SIADH associated with malignancy is secondary to small cell lung carcinoma. Previously it was proposed that SIADH was a marker of tumor burden as well as a negative prognostic factor. However, more recent reports have indicated that SIADH is neither an indicator of poor outcome nor disease burden. Indeed, many patients with small cell lung carcinoma only develop SIADH after treatment. Of interest, several chemotherapeutic agents commonly used in oncology cause transient SIADH including vincristine, vinblastine, vinorelbine, ifosfamide, cyclophosphamide, and cisplatin.

**Treatment**

As with any syndrome associated with ectopic hormone production, treating the underlying disease is the most effective means of controlling SIADH. Chemotherapy treatment of the associated small cell lung cancer is generally associated with improvement in the syndrome. SIADH has not been shown to be a negative prognostic
factor in terms of response to chemotherapy. In situations in which brain metastases are present, the addition of radiation therapy is important. Because surgery is not generally thought to be an effective modality in patients with small cell lung cancer, surgery is rarely undertaken in patients with malignancy-associated SIADH. In chemotherapy-related SIADH, the offending drug should be stopped.

Supportive measures such as fluid restriction and pharmacologic therapy can be undertaken to treat SIADH. Patients with sodium levels under 130 mmol/L, are placed on a free water restriction (500 mL/d), in addition to treatment of the primary malignancy. In the event that this measure does not bring the serum sodium above 130 mmol/L, pharmacologic agents such as demeclocycline can be instituted. Demeclocycline inhibits the effect of arginine vasopressin on the kidneys. The recommended dose of demeclocycline is 600 to 1200 mg/d in divided doses. Other less common medications that have reported efficacy include fludrocortisone, urea, and lithium. Finally, in severe cases in which patients have life-threatening convulsions or coma, patients can be treated with hypertonic saline solution with intravenous furosemide. It is important not to raise the serum sodium too rapidly (the recommendation is 1 mEq/L/h) due to the risk of central pontine myelinolysis. It is generally thought that hypertonic saline and Lasix treatment should be carried out in the intensive care unit setting.

HYPOCALCEMIA

Although most of the discussion regarding disturbance of calcium balance and malignancy revolves around hypercalcemia, hypocalcemia is actually more common in patients with bone metastases. Tumors associated with lytic bone metastases such as breast, prostate, and lung cancers, can lead to hypocalcemia. Also, rarely, hypocalcemia can occur in patients whose tumors secrete calcitonin (i.e., medullary carcinoma of the thyroid). More common than hypercalcemia, hypocalcemia is rarely symptomatic. Patients occasionally develop the features of hypocalcemia such as tetany and neuromuscular irritability, but can show mild neuromuscular dysfunction by electromyography. Therapy, consisting of calcium infusion, is reserved for those patients with findings of neuromuscular irritability or symptoms such as tetany and seizures. Signs of neuromuscular irritability including Chvostek's sign and Trousseau's sign (carpal spasm with decreased blood flow) indicate the need for calcium infusion. For a discussion of hypercalcemia, please refer to the chapter on Metabolic Emergencies (see Chapter 51.3).

ONCOCGENOUS OSTEOMALACIA

Rickets is a well-recognized inborn error of metabolism, while the adult counterpart, osteomalacia, is usually secondary to intestinal malabsorption syndrome, renal tubular acidosis, and chronic renal insufficiency. Oncogenous osteomalacia is a rare syndrome characterized by osteomalacia, hypophosphatemia, hyperphosphaturia, and decreased vitamin D levels. Mean age at diagnosis is approximately 35 years. Patients typically present with bone pain, phosphaturia, renal glycosuria, hypophosphatemia, normocalcemia with normal parathyroid hormone function, low 1,25-(OH)₂-D₃, and increased alkaline phosphatase. The proposed mechanisms include inhibition of the conversion of 1,25-dihydroxyvitamin D and a tumor-secreted phosphaturic substance. It is usually associated with benign mesenchymal tumors including hemangiomas and hemangioendoctricomas, but rarely is seen with multiple myeloma and prostate cancer.

ONCOCGENOUS OSTEOMALACIA

The typical tumor involves prominent giant cells, spindle cells, and a high degree of vascularity. Approximately one-half of the tumors are in the lower extremities, and the remaining tumors are divided between the head and upper extremities with some patients having tumors at multiple sites. The definitive therapy is removal of the tumor, if possible. Otherwise, treatment requires large doses of vitamin D and phosphorus.

CALCITONIN PRODUCTION BY TUMORS

Calcitonin is a polypeptide hormone that is produced by C cells of the thyroid. Calcitonin prevents calcium release from bone and causes increased renal excretion of calcium, sodium, and phosphate. Because medullary thyroid carcinoma produces calcitonin, calcitonin serum levels are a sensitive tumor marker to monitor this disease. They are also useful in identifying patients with multiple endocrine neoplasia type 2, a familial disorder involving an association of medullary carcinoma of the thyroid, pheochromocytoma, and parathyroid adenomas. A variety of tumors, including small cell lung cancer, carcinoids, breast cancer, and GI cancer also may secrete calcitonin.

ONCOCGENOUS OSTEOMALACIA

While calcitonin levels may reflect clinical tumor status in these diseases, they are not used as tumor markers. Furthermore, there is no known paraneoplastic syndrome associated with calcitonin.

CHROMOGRAFIN A

Chromogranin A is a 68-kd glycoprotein found in the neurosecretory granules of normal and malignant amine precursor uptake and decarboxylation cells. Chromogranin A is released into the circulation via exocytosis from neuroendocrine storage vesicles. It may act in neuroendocrine secretion by binding intravascular calcium. Its sequence is nearly identical to pancreastatin, which inhibits insulin and somatostatin secretion from the pancreas.

ONCOCGENOUS OSTEOMALACIA

As with calcitonin, it is unknown whether chromogranin A is associated with a paraneoplastic syndrome. Chromogranin A secretion is most commonly associated with small cell lung cancer and neuroendocrine tumors.

GONADOTROPINS

The human hormones with gonadotropic properties are follicle-stimulating hormone (FSH), lutetinizing hormone (LH), and human chorionic gonadotropin (HCG). These three hormones are composed of two polypeptide chains; α and β subunits. The α subunit is common to all of the hormones and the β subunit determines biologic and immunologic specificity. Both subunits are required for bioactivity. In normal human placenta, the pituitary produces FSH and LH. Biologically active HCG is produced by the placenta and is therefore normally found only in pregnant women. Because the levels of FSH and LH vary under normal physiologic conditions, the b-HCG hormone is typically used for following paraneoplastic syndromes.

ONCOCGENOUS OSTEOMALACIA

Gonadotropin secretion may occur in pituitary tumors, gestational trophoblastic tumors, germ cell tumors, hepatoblastomas in children, bronchogenic carcinomas, and GI cancers. Gonadotropins measured in tumors arising in gestational tissue, testes, ovaries, and endocrine organs are valuable tumor markers and are discussed in the following chapters: Cancers of the Endocrine System, Gynecologic Tumors, Cancer of the Ovary, and Cancer of the Testes.

Although many studies have suggested elevations in HCG in a number of common tumors, it may also be elevated in nonmalignant chronic diseases. Values for the a and b subunits of HCG are significantly higher in cancer patients than in patients with nonmalignant disease. Elevations of b-FSH, thyroid-stimulating hormone-b, and b-LH have not been observed. With rare exceptions, however, these markers are not routinely used to follow common cancers.

The frequency of symptoms associated with tumor-produced gonadotropin is unknown. The most common problem is a male patient presenting with unexplained gynecomastia. In this situation, a b-HCG determination should be performed as well as a careful examination of the testes and radiographic examination of the chest and mediastinum. Germ cell tumors of the testes or extragonadal sites and lung cancers are the most frequent causes of the combination of gynecomasia and HCG elevation. Other extragonadal tumors that produce HCG include lung cancer, adrenal carcinoma, hepatoma, GI tract tumors, and tumors of the genitourinary tract. Histologic specimens have revealed that all of these tumors contain syncytiar giant cells or choriocarcinomatous elements similar to trophectoderm fetal germ cell tumors. Conversely, 40% of patients with extragonadal germ cell tumors masquerading as poorly differentiated carcinomas had immunohistochemical staining for HCG and a-fetoprotein without serum elevation of these markers.

Many of these patients responded to chemotherapy, as would be expected of germ cell tumors.

TUMOR-PRODUCED HUMAN PLACENTAL LACTOGEN, GROWTH HORMONE–RELEASING HORMONE, PROLACTIN, AND THYROTROPIC SUBSTANCE

Human placental lactogen (hPL) has been detected in a small percentage of patients with nonthrophoblastic nongonadal tumors. This may be associated with elevated levels of estrogen, HCG, and gynecomasia. hPL in nonpregnant women is diagnostic of malignancy.

Elevated growth hormone levels have been reported in rare cases of gastric and lung cancer. Whether this is due to ectopic production or overproduction by cells that retain the ability to secrete growth hormone from primordial origin remains controversial.

Growth hormone–releasing hormone production has been reported in nonpituitary tumors and, like pituitary tumors, results in acromegaly. This 44 amino acid peptide has been isolated from pancreatic tumors as well as bronchial and foregut carcinoids. Secretion of growth hormone–releasing hormone can be controlled by
administration of long-acting somatostatin analogues. The definitive therapy is removal of the tumor, whenever possible.

Patients with cancers of the lung, colon, breast, ovary, and cervix, as well as hypernephroma have been reported with elevated prolactin levels, and one case was associated with galactorrhea. Symptoms can be subtle; male subjects may only exhibit decreased libido, whereas postmenopausal women may have no symptoms. Treatment of the tumor decreases prolactin levels. Because these cases are extremely rare, it is important to exclude the presence of a pituitary lesion in patients with elevated prolactin levels.

Tumor-associated thyroid-stimulating hormone production without thyrotoxicosis has been reported. An association has been reported between hyperthyroidism and gestational trophoblastic disease with biochemical hyperthyroidism. This may also be seen in testicular tumors. In some cases, the excess HCG produced by trophoblastic tumors appears to be the thyroid-stimulating substance.

**HYPOGLYCEMIA**

Insulinomas frequently produce hypoglycemia; however, hypoglycemia associated with non–islet cell tumors is an unusual paraneoplastic syndrome. Mesenchymal tumors including a variety of sarcomas and mesotheliomas are the most common cause of non–islet cell–induced hypoglycemia. Rarely, adrenal carcinomas, GI cancers, and varied other tumors have been associated. These tumors are typically large, often invade the liver, and have a protracted course. The patient may present with typical signs and symptoms of hypoglycemia, including generalized neurologic abnormalities.

These tumors may cause hypoglycemia by a variety of mechanisms including production of nonsuppressible insulin-like growth factors-1 and -2 (IGF-1 and -2), hypermetabolism of glucose, production of substances stimulating ectopic insulin release, massive liver infiltration, production of hepatic glucose inhibitor, insulin binding by an M protein in myeloma, insulin receptor proliferation, or rarely ectopic insulin production. The most likely mechanism is tumor production of IGFs (also called somatomedins), a family of peptide hormones normally produced by the liver under growth hormone regulation. Several reports have specifically identified excess production of PRO-IGF-2, which binds to insulin and IGF receptors in malignancy. This in turn down-regulates growth hormone secretion and decreases hepatic production of IGF-binding proteins with eventual hypoglycemia. The treatment of paraneoplastic hypoglycemia initially involves glucose infusion. Following this, tumor debulking should be carried out, although the long-term effect of debulking is poorly understood. If treatment of the tumor is not possible, then the use of subcutaneous and long-acting intramuscular glucagon or high-dose corticosteroids might be considered.

**HEMATOLOGIC MANIFESTATIONS OF CANCER**

Paraneoplastic syndromes that involve hematopoietic cells and clotting factors are extremely common. While the etiologies of most of these paraneoplastic abnormalities remain unexplained, advances in the understanding of hormones and growth factors that regulate hematopoiesis has led to a better understanding of some of these disorders.

**ERYTHROCYTOSIS**

Erythrocytosis secondary to a wide variety of tumors is well described in the literature. The most common solid tumor leading to erythrocytosis is renal cell carcinoma, which is often associated with elevated serum erythropoietin levels. Renal lesions as cystic kidney tumors may also cause erythrocytosis, and other tumors of the kidneys such as Wilms' tumor and hemangiomomas rarely cause erythrocytosis. The next most common malignancy leading to erythrocytosis is hepatoma, also likely secondary to erythropoietin production. Cerebellar hemangioblastomas are also known to produce erythrocytosis. Other tumors leading to erythrocytosis include uterine fibroids, adrenal tumors, and pheochromocytomas. Adrenal cortical tumors and virilizing ovarian tumors can produce androgenic hormones that may lead to erythrocytosis. Prostaglandins produced from tumors can enhance the effect of erythropoietin and lead to erythrocytosis.

It is still important to rule out other causes of erythrocytosis even in the presence of a tumor. Polycythemia rubra vera is typically associated with elevated white count and platelets as well as splenomegaly. There are obvious causes of polycythemia secondary to arterial desaturation associated with hemoglobinopathies, cancer therapy, and so forth. Erythropoietin can be measured in the blood when it is suspected that it is overproduced secondary to a tumor. Erythrocytosis secondary to tumors is usually not high enough to require treatment, but if the hematocrit is extremely high (i.e., greater than 55% for a man or greater than 50% for a woman) phlebotomy can be used. Control of the tumor usually controls the erythrocytosis, as well.

**ANEMIA**

The most common anemia in cancer patients is the normocytic normochromic anemia of chronic disease, anemia secondary to bone marrow invasion, which may be associated with leukoerythroblastosis, and anemia secondary to chemotherapy and radiation therapy. Normochromic, normocytic anemia, or anemia of cancer, is a common paraneoplastic syndrome, characterized by low serum iron, normal or increased ferritin, normal iron stores, and a low serum erythropoietin level. It is thought that IL-1, TNF, and transforming growth factor-b are produced by tumors and effect a decreased erythropoietin response.

A rare cause of anemia in cancer patients is pure red cell aplasia. The relationship of thymoma and pure red cell aplasia often associated with hypogammaglobulinemia is well described in the literature. Pure red cell aplasia may also be associated with a variety of lymphoid malignancies including chronic lymphocytic leukemia (CLL) and large granular lymphocytic lymphoma and leukemia. Rarely, pure red cell aplasia is associated with solid tumor malignancies.

Autimmune hemolytic anemias are typically associated with B-cell malignancies including CLL and lymphomas, and arise secondary to immunoregulatory abnormalities in these diseases, rather than a direct secretion of tumor-derived substances. Hallmarks of the disease are a positive direct antiglobulin test result, elevated reticulocyte count, decreased haptoglobin, and elevated lactate dehydrogenase. Warm antibody hemolytic anemia is most commonly associated with lymphomas, CLL, and mucin-producing adenocarcinomas. Cold agglutinin disease is most common in Waldenström's macroglobulinemia and lymphomas. Autimmune hemolytic anemia is rarely associated with solid tumor malignancies; however, an association with ovarian, GI, lung, breast, and renal cell cancers has been reported. Corticosteroid treatment appears to be less effective in autoimmune hemolytic anemia associated with carcinomas than in those that are idiopathic or associated with lymphoid malignancies. The Coombs' test result may revert to negative with control of the tumor.

Microangiopathic hemolytic anemia is characterized by fragmentation of red cells and is observed in diseases associated with lesions in small blood vessels such as thrombotic thrombocytopenic purpura, congenital vascular abnormalities, and the hemolytic uremic syndrome. Microangiopathic hemolytic anemia has also been reported in association with malignancy. Such patients may have intimal proliferation of arterioles, intravascular tumor growth, or intravascular fibrin precipitation. Thrombocytopenias may also be associated. Disseminated intravascular coagulation (DIC) may contribute to microangiopathic hemolytic anemia in metastatic carcinomas by inducing the red cell fragmentation from fibrin strands. Patients typically have pronounced schistocytosis with microspherocytes, which are spherocyte-shaped erythrocytes less than 5 m in diameter. The reticulocyte count is typically increased and a leukoerythroblastotic blood picture may predominate. The mechanism remains unknown. The microangiopathic hemolytic anemia syndrome may respond to effective anticancer therapy. It is typically associated with adenocarcinoma of the GI tract, heart, lung, and prostate, as well as after mitomycin C chemotherapy.

**ERYTHROCYTOSIS**

Granulocytosis with elevation of the white blood cell count above 15×10⁹/l without infection or leukemia is common in neoplasms. Isolated or associated monocytosis is also described. Neoplasms most commonly associated with granulocytosis include Hodgkin's disease, lymphoma, and a variety of solid tumors including gastric, lung, pancreatic, and brain, as well as malignant melanoma. The granulocytosis associated with a paraneoplastic leukemoid reaction consists of mature neutrophils with some band forms seen. This differs significantly from chronic myelogenous leukemia in which there are many more immature cells, basophils, and eosinophils, a decreased leukocyte alkaline phosphatase; elevated vitamin B₁₂ and vitamin B₉–binding capacity; and the presence of the Philadelphia chromosome. The common mechanism associated with tumor-associated granulocytosis is tumor production of growth factors including granulocyte...
colony-stimulating factor, granulocyte-macrophage colony-stimulating factor, IL-3, IL-1, and a variety of others. 128, 130

GRANULOCYTOPENIA

Granulocytopenia is typically secondary to chemotherapy, radiation therapy, or tumor infiltration of bone marrow. It is possible in some cases that the tumors may produce a factor that suppresses granulopoiesis by interfering with any number of growth factors. As well, there are rare reports of antibodies against granulocytes in patients with Hodgkin’s disease and nonchemotherapy-induced neutropenia. 131 Neutropenia associated with large granular lymphocytic leukemia and lymphoma may be caused by immune dysregulation of T cells. The preferred therapy for severe granulocytopenia is direct stimulation with growth factors including granulocyte colony-stimulating factor, granulocyte-macrophage colony-stimulating factor, or both.

EOSINOPHILIA AND BASOPHILIA

Eosinophilia is commonly associated with Hodgkin’s disease and mycosis fungoides and is rarely associated with other lymphomas and solid tumors. 132 The tumor cells may be producing factors that specifically stimulate eosinophils. In one study, a tumor-associated eosinophil stimulation factor was found to be a glycoprotein of 45 kD. 133 Other candidate cytokines include granulocyte-macrophage colony-stimulating factor, IL-3, and IL-5, which are involved in the development and differentiation of eosinophils. 134 Eosinophilia is rarely of sufficient high counts to lead to symptoms of Löffler’s-like syndrome, which is associated with nodular pulmonary infiltrates with cough and fever. Basophilia is associated with chronic myelogenous leukemia and a variety of other myeloproliferative disorders, but is not typically associated with symptoms. 135

THROMBOCYTOPENIA

Thrombocytopenia is quite common in cancer patients and may be associated with Hodgkin’s disease, lymphomas, and a variety of carcinomas and leukemias. 136 Thrombocytopenia is expected early in the course of a variety of myeloproliferative diseases including polycythemia rubra vera and chronic myelogenous leukemia. It is, of course, the hallmark of primary thrombocytopenia. Thrombocytopenia may also be associated with inflammatory disorders, hemorrhage, iron deficiency, hemolytic anemia, and posttransfusional. Thrombocytopenia is secondary to myelodysplasia may be secondary to overproduction of thrombopoietin. 137 Thrombosis and hemorrhage are rarely associated with this paraneoplastic syndrome and treatment is not generally indicated.

THROMBOCYTOPHILIBITIS

Thrombocytopenia in cancer patients is typically secondary to chemotherapy, radiation therapy, DIC, or tumor infiltration of bone marrow. A syndrome similar to idiopathic thrombocytopenia purpura is commonly seen in lymphoid malignancies including CLL and lymphomas, as well as Hodgkin’s disease. Rarely, solid tumors such as lung, breast, and GI cancers have been associated with a similar syndrome. 138, 139, 141, 142 and 143 These patients may have bleeding, petechia, and purpura and may respond to high-dose prednisone, splenectomy, or both. Other common causes of thrombocytopenia, such as heparin-induced thrombocytopenia, thiazide diabetics, and a variety of other drugs, should be ruled out. Typically any other idiopathic thrombocytopenia purpura, the patients have adequate or increased megakaryocytes in the bone marrow associated with the thrombocytopenia and do not respond to transfused platelets.

THROMBOPHILEBITIS

The association of cancer and thrombophlebitis was first observed by Trouseau and this association still bears his name. 144 The incidence of thrombophlebitis in cancer patients is quite common and migratory thrombophlebitis is well documented. Recurrent deep venous thrombosis, varicose resistance, and thrombosis at unusual sites should increase suspicion of occult malignancy in a patient without a known diagnosis of cancer. The greatest risk of migratory thrombophlebitis is with pancreatic cancer; however, it may be seen in a variety of adenocarcinomas, including breast, ovarian, and prostate cancer. 145, 146 The activation of coagulation by tissue factor is clearly implicated in the patients with solid tumors when compared with normal controls. 147 As well, mucinous adenocarcinomas produce a siatic acid moiety that can activate factor X, causing a hypercoaguable state. 148 It is likely that cancer-related thrombosis represents a complex imbalance of coagulation and fibrinolysis. Increased fibrinogen and platelet catabolism; decreased protein C, S, and antithrombin; direct generation of thrombin; and thrombocytosis all represent abnormalities associated with malignancy. 149

The treatment, although difficult, must be initiated with heparin; however, it is often unsuccessful and long-term therapy with either warfarin or heparin is typically not satisfactory. Initial reports of the beneficial effects of low-molecular-weight heparin in cancer patients with thrombosis 150 are supported by a retrospective metaanalysis. In this study, a significant reduction in mortality was reported in cancer patients treated with low-molecular-weight heparin compared with those treated with unfractionated heparin for deep venous thrombosis. The cause of reduced mortality appeared to be an indirect effect that persisted well beyond discontinuation of the drug. 151 Treatment of the underlying malignancy is the most definitive therapy, but usually in these particular diseases is also unsuccessful.

COAGULOPATHIES AND DISSEMINATED INTRAVASCULAR COAGULATION

The most common coagulation abnormalities in cancer patients are elevated levels of fibrin or fibrinogen degradation products, thrombocytopenia, and hypofibrinogenemia. Representing overconsumption DIC with fibrinolysis. This may be accompanied by an increased synthesis of fibrinogen and various clotting factors and platelets. Over DIC with consumption of platelets and clotting factors and bleeding is rare and is most commonly associated with acute promyelocytic leukemia and adenocarcinomas. 152 DIC is detected by a combination of abnormal prothrombin time, thrombocytopenia, and hypofibrinogenemia. 153, 154 The platelet count is abnormal in more than 90% of cases of DIC. The most useful confirmation test for DIC is the measurement of fibrin degradation products. Identification and treatment of precipitating factors is critical in the management of DIC. Some investigators have advocated replacement of coagulation factors and platelets in combination with heparin. The use of heparin alone is controversial and is more commonly used with thromboembolic or necrotizing complications typically seen in the chronic DIC of malignancy. A variety of other therapies including antplatelet drugs and fibrinolytic inhibitors and activators have been suggested, but have no proven efficacy. Epsilon amino caproic acid is contraindicated. Treatment of the underlying malignancy is essential.

NONBACTERIAL THROMBOTIC ENDOCARDITIS

Nonbacterial thrombotic endocarditis may lead to thrombolic or hemorrhagic complications and may occur with or without DIC. 155, 156 and 157 It is characterized by sterile verrucous fibrin platelet lesions in the left-sided heart valves. A typical presentation is emboli to the brain and other organs associated with focal or diffuse neurologic abnormalities. Typical diffuse abnormalities include confusion, seizures, and disorientation. The definitive diagnostic test is cerebral angiography showing multiple arterial occlusions. While some patients may have heart murmurs, the majority do not. Echocardiography picks up vegetations larger than 2 mm. The association of nonbacterial thrombotic endocarditis is most common with adenocarcinoma of the lung. Other adenocarcinomas are less frequently associated, and rarely nonadenocarcinomas, lymphomas, and leukemias are associated. 158 Bleeding may be found in the skin, central nervous system, genitourinary tract, upper respiratory tract, GI tract, and lower respiratory tract. Treatment of the underlying malignancy is the primary therapy. Anticoagulants are not indicated.

GASTROINTESTINAL MANIFESTATIONS OF CANCER

PROTEIN-LOSING ENTEROPATHY

Protein-losing enteropathy is a disorder defined by an excessive loss of serum proteins into the GI tract, which generally leads to hypoproteinemia. It was postulated that the hypoproteinemia associated with protein-losing enteropathy was due to impaired protein synthesis. However, it has been shown that synthesis of proteins in these patients is normal or slightly increased, while the serum half-life of protein such as albumin is dramatically decreased. 159 It has also been shown that enteric loss of proteins contributes to, but is not the sole etiology of, the hypoproteinemia seen in patients with this disorder. 160

Normally, the GI tract plays a small role in the catabolism of serum proteins. 161 Approximately 10% of all normal protein loss of albumin and globulin loss is through the GI tract. 162 It is thought that malignancy-related protein-losing enteropathy results from the increased mucosal permeability to serum proteins due to abnormal cellular structure, mucosal erosion or ulceration or lymphatic obstruction. 163 Hypoalbuminemia can be seen in virtually any cancer of the GI tract including esophageal, gastric, colon, and carcinoid syndrome. 164 It has also been described in acquired immunodeficiency syndrome (AIDS) patients with Kaposi’s sarcoma. 165 Intestinal 166 Intestinal
involvement of lymphoma including Waldenström's macroglobulinemia, Hodgkin's disease, and non-Hodgkin's lymphoma can lead to protein-losing enteropathy. 

In contrast to renal protein loss, the protein loss in GI disorders is independent of the size of the protein. Therefore, proteins of various sizes such as albumin, immunoglobulins, and ceruloplasmin all are lost equivalently in contrast to patients with nephrotic syndrome. Once the protein loss becomes greater than the body's ability to synthesize proteins, decreased protein levels in the serum result. Usually, this decline in serum proteins progresses until a new set point is reached. At that point, the protein level stabilizes and a new homostasis is achieved. Also, of note, in both GI and as non-GI sources of hypoproteinemia, proteins of long serum half-life (i.e., albumin) tend to be more affected than proteins of shorter serum half-life (i.e., retinol-binding protein). Other serum constituents associated with these proteins may be affected by the hypoproteinemia. Specifically, constituents that depend on carrier proteins, such as iron, copper, and calcium, may be depressed when patients develop hypoalbuminemic states.

Clinically, patients with protein-losing enteropathy develop hypoproteinemia. This may or may not be associated with peripheral edema, but is rarely associated with severe edema or anasarca. Despite the fact that globulin levels are depressed, the patients rarely develop opportunistic infections and rarely develop coagulopathy even though clotting factors are also lost. Patients may or may not have other GI symptoms, such as diarrhea.

The diagnosis of protein-losing enteropathy is generally not difficult. Patients are noted to be hypoproteinemic on routine chemistry evaluation. Other sources of hypoproteinemia such as malnutrition and liver disease must be excluded. In the past, cumbersome nuclear studies were performed looking for protein loss in the stool. These have been largely replaced by new techniques using a γ-antitrypsin, a protein which has been replaced in the lower GI tract. Therefore, if it is lost in excessive amounts it is excreted unchanged in the stool. Clearance of this protein is used to confirm the diagnosis of protein-losing enteropathy. It should be noted that the presence of diarrhea could abnormally influence the interpretation of this study. Also, fecal occult blood can falsely elevate this study result.

Once the diagnosis of protein-losing enteropathy has been made in association with cancer, the treatment consists of treatment of the primary malignancy. In situations with lymphatic obstruction, a low-fat diet should be instituted. Patients frequently require the use of medium-chain triglycerides, which do not require intestinal lymphatic transport. With appropriate treatment of the cancer and dietary therapy, approximately 50% of the patients improve with treatment.

ANOREXIA AND CACHEXIA IN THE CANCER PATIENT

Cancer anorexia-cachexia syndrome (CACS), as it is now referred, is the most common paraneoplastic syndrome, consisting of anorexia, nausea, and weight loss. While it afflicts patients with solid tumors most commonly, more than 50% of all cancer patients have some demonstrable weight loss, and 15% experience loss of greater than 10% of their normal body weight. Survival is negatively affected if a patient has greater than 10% weight loss, in part due to problems with infection and wound healing. Problems associated with weight loss may be exacerbated by treatment with surgery, chemotherapy, or radiation. As well, cancer therapy can lead to new difficulties with food intake such as postoperative ileus, esophagitis, and stomatitis.

Multifactorial derangements in biochemical pathways lead to cancer-related decreased food intake. Tumors produce factors that change the patient's perception of food, particularly taste and smell, which leads to a lack of enjoyment. The central nervous system's control of appetite can be altered by tumor factors, such as serotonin. Local obstruction and abnormal swallowing interfere with food intake when tumors involve these portions of the alimentary tract. Malabsorption and malabsorption may result from obstruction of biliary or pancreatic secretions. When patients become nauseated due to either anatomic factors related to their tumor or as a result of chemotherapy or radiation treatment, they may develop a psychological aversion for food, which is difficult to control.

Cancer patients possess abnormally high serum levels of IL-1β, TNF-a, IL-6, IFN-g, and serotonin, produced as a response to the tumor, rather than by the tumor itself. Administration of these cytokines is capable of reproducing CACS, thus further supporting their role in its etiology. The physiologic changes induced by the tumor through these cytokines are numerous and result in progressive weight loss through a variety of mechanisms (i.e., serotonin changing the taste and smell of food). As well, in cancer patients, there is an increased basal energy expenditure with alterations in carbohydrate, protein, and lipid metabolism. In cases of starvation, weight loss arises primarily from fat stores, whereas in cancer patients there is equal loss of fat and skeletal muscle. Skeletal proteins are frequently sacrificed in accelerated gluconeogenesis with the loss of amino acids and subsequent loss of lean body mass. However, CACS is not solely a state of starvation; the host simultaneously goes through massive protein conversion and degradation. Hypercatabolism may be a result of an increased metabolic rate due to tumor growth. Even though sufficient calories are supplied to patients through various means, the patients are unable to incorporate amino acids into lean body proteins. A cancer-driven inflammatory response can divert resources used for production of normal serum proteins to other organ sites (i.e., liver). Malignant cancer patients also lose a great deal of their lipid reserve; a decrease in lipidprotein lipase, responsible for moving triglycerides into fat cells, results in weight loss. Treatment with individual anticytokine antibodies reverses specific features of CACS, but no single antibody eradicates all aspects of the syndrome.

When evaluating a cancer patient for CACS, appetite, intake over single previous week, weight, and weight loss are all critical. In one study, a weight loss of less than 90% of ideal body weight, 10% weight loss over the last 6 months, or both were associated with a poor prognosis. Plasma proteins such as albumin have limited value in evaluating CACS, because they are affected by factors other than nutrient status. Immune responsiveness assessed by delayed type hypersensitivity skin tests, as well as total lymphocyte count, correlate not only with the patient's nutrient status, but also the ability to fight off various infections. In summary, the best means of determining a patient's nutrient status is a history and physical examination by an experienced clinician.

Treating patients with malnutrition and cancer is similar to treating other forms of severe stress such as burns, trauma, and sepsis; the primary objective is adequate caloric intake excluding calories from protein sources. Often the most difficult decision facing the clinician is choosing the route of administration. The widespread availability of total parenteral nutrition has made this an attractive option, particularly when patients are severely anorexic. However, numerous studies have found no survival benefit using total parental nutrition in cancer patients, with an increase in infectious and mechanical complications. It has become axiomatic to use the GI route for nutrition whenever possible, because it has the benefit of being less expensive wherehio physiology, and it maintains gut barrier function. The Harris-Benedict equation is useful for determining basal caloric needs. Generally, stress factors of cancer (estimated at 20% to 30% of the basal metabolic rate) are added to the patient's caloric needs. If other forms of stress are present, such as infection, these factors should be added. In addition to the caloric needs, 1.0 to 1.5 g of protein per kilogram of body weight is also given, and 25% to 40% of nonprotein calories should be in the form of lipid. The enteral formulations have been developed to balance these factors. When total parenteral nutrition is necessary, these same formulas are used for determining calorie protein and lipid intake. Once nutritional support is initiated, a 24-hour urine collection for nitrogen loss should be undertaken. If the patient has no diarrhea, 2 g of nitrogen should be added for insensible losses of nitrogen in the stool. Using these values, a nitrogen balance can be calculated; this balance should be positive, meaning that the patient receives more nitrogen than he or she excretes. This is critical in determining whether the patient is receiving adequate caloric intake.

Pharmacologic approaches to improving nutritional status in the cancer patient include appetite stimulants, corticosteroids and progestational agents, anabolic steroids, and enteral and parenteral nutrition. Several unfortunate side effects and complications are of margins. Unfortunately, there is limited use of corticosteroids and found that in the short-term, they can increase appetite and elevate mood, but are limited because of progressive muscle weakness. Progestational agents including megestrol acetate and medroxyprogesterone acetate are appetite stimulants. Eight prospective randomized studies have now shown that these agents do stimulate appetite and weight gain, no survival benefit is associated with their use. One study found that 12 weeks of megestrol acetate (480 mg daily) produced an average weight gain of 5.4 kg, but no gain in performance status or quality of life.

The major risk of progestational agents is an increased risk of thromboembolic events. Cannabinoids such as dronabinol have been used, but most of these studies related to their use are in patients with AIDS-related anorexia, and definitive data in cancer patients are pending.

Unfortunately, the current therapy for CACS remains largely ineffective. Nutritional support, counseling, and the use of prostaglandin agents continue to play the predominant role in management. Novel agents such as cytokine inhibitors have yet to be tested in randomized controlled trials.

RENAL MANIFESTATIONS OF NONRENAL CANCER

Patients with nonrenal carcinoma develop many important renal complications. Treatment-related nephropathies, tubular interstitial defects, glomerular abnormalities, and fluid and electrolyte disorders are seen in many patients with cancer. Radiation nephritis and drug-induced toxicities from antineoplastic drugs (e.g., cisplatin), antibiotics, antiplatelet agents, and intravenous contrast agents all induce various forms of renal failure. Inflammatory disorders from leukemias and lymphomas, tubular proteinuria from fibrinoid necrosis, and interstitial infiltrate may lead to tubular interstitial diseases. Membranous glomerulopathy, minimal change disease, amyloidosis, and consumptive coagulopathy all lead to glomerular abnormalities. Finally, hypercalcemia, hypocalcemia, hyponatremia, and tumor lysis syndrome, covered in other areas of this book, lead to fluid and electrolyte disorders. While renal
manifestations of systemic cancer and its therapy are common, several classes of renal insult are specifically paraneoplastic in nature.

**GLOMERULAR DISORDERS**

Most cases of membranous nephropathy are idiopathic, but a reasonable number have been associated with cancers, especially in the elderly. In an early report of 101 patients with idiopathic nephrotic syndrome, 11% had cancer with 8% having membranous nephropathy. In 80% of cases the diagnosis of nephrotic syndrome is made concurrently or after the malignant disease, lending credence to the idea that it is a paraneoplastic process. Nephrotic range proteinuria, hypertension, and microscopic hematuria characterize the syndrome. Sixty percent of cancers of the stomach, lung, and colon have membranous nephropathy, while other cancers such as rectal, pancreas, head and neck, ovary, bile duct, prostate, breast, kidney, and skin rarely produce glomerulonephritis. Immunofluorescence studies reveal granular deposits of immunoglobulin and complement, whereas electron microscopy shows evidence of subepithelial deposits, which are the pathologic hallmarks of this process. Immune complexes are thought to play a role in malignancy-associated glomerular disease. The responsible antigens include fetal antigens, autologous nontumor antigens, tumor-associated antigens, and viral antigens.

Nephrotic syndrome has been reported to resolve with successful treatment of the underlying malignancy. Other standard therapies include loop diuretics to symptomatically treat the peripheral edema associated with the syndrome. As well, careful monitoring for the development of thrombosis is warranted in severe protein wasting, especially renal vein thrombosis.

Other glomerular diseases include membranoproliferative glomerulonephritis and minimal change disease. Hodgkin’s disease is the cause of most cases of minimal change disease, while other lymphoproliferative disorders, pancreatic carcinoma, and mesothelioma are also seen. There is a parallel relationship between the activity of the lymphoma and the degree of proteinuria. Other cancer-associated glomerulopathies include focal and segmental glomerulosclerosis with CLL, T-cell lymphomas, and acute myelogenous leukemia. IgA nephropathy with lung, head and neck, and pancreatic cancers, mycosis fungoides, and liposarcoma; and membranoproliferative glomerulonephritis with CLL, Burkitt's, and other lymphomas, hairy cell leukemia, and malignant melanoma. Rarely rapid and progressive glomerulonephritis has been associated with lymphoma and monoclonal gammopathies.

**MICROVASCULAR LESIONS**

Hemolytic uremic syndrome is most often seen after chemotherapeutic agents such as mitomycin C, but has also been reported in malignancy. Giant hemangiomas and hemangioendotheliomas, and specific malignancies such as acute promyelocytic leukemia, prostate, gastric, and pancreatic cancers are the most common culprits. A renal vasculitis secondary to Henoch-Schönlein purpura has also been reported in a patient with lung cancer, but this is an extremely rare complication of malignancy. More frequent is the association of renal vasculitis secondary to a process such as cryoglobulinemia, a known complication of hepatocellular carcinoma and concomitant hepatitis C disease.

**TUMOR INFECTION**

Autopsy series show the kidney is commonly affected by infiltrative and metastatic processes. Although not all series support this distinction, there is a strong association between bone marrow involvement by tumor and renal infiltration. In both non-Hodgkin's lymphoma as well as Hodgkin's disease the involvement tends to be nodular and bilateral, whereas in leukemia the involvement is infiltrative. Treatment of the underlying malignancy often results in resolution of the renal lesions. Other tubular abnormalities, such as protein cast precipitation syndrome, paraprotein disease, uric acid nephropathy, hypercalcemia, and obstructive uropathy, are discussed in Metabolic Emergencies, Chapter 51.3, and Plasma Cell Neoplasms, Chapter 46.4.

**CUTANEOUS PARANEOPLASTIC SYNDROMES**

A wide variety of cutaneous syndromes are associated with malignancies and may precede, be concurrent with, or follow the discovery of the underlying malignancy. It is critical that once a potential cutaneous paraneoplastic syndrome has been diagnosed, an appropriate systemic evaluation for a neoplasm is undertaken. The usual workup includes detailed medical history, complete physical examination, and routine screening laboratory tests. This is followed by studies directed by the abnormalities discovered during the preliminary evaluation, emphasizing those malignancies most strongly associated with the particular skin lesion. Some cutaneous syndromes are uncommon and usually are associated with cancer, whereas other cutaneous lesions are extremely common and associated with benign disorders or cancers. Certain cutaneous lesions are always associated with a particular tumor, whereas others are associated with a variety of malignancies. In general, the cause of the cutaneous lesions is typically unknown.

**PIGMENTED LESIONS AND KERATOSSES**

Acanthosis nigricans (Table 47-3) is characterized by a gray-brown hyperpigmented, symmetric, velvety plaque that often affects the neck, axilla, and flexor areas and anogenital region. There are four groups: the malignant, inherited, endocrine, and idiopathic. The malignant form appears the same as the benign form, but may progress rapidly; pruritus is common. The malignant variety may precede the tumor, occur simultaneously, or even follow the appearance of the tumor. It affects men and women equally and is typically associated with adenocarcinomas of the GI tract, predominantly gastric cancer, but has also been associated with a variety of other adenocarcinomas including lung, breast, ovarian, and even hematologic malignancies. The pathogenesis remains uncertain.

**TABLE 47-3. Pigmented Lesions and Keratoses**

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tripe palms</td>
<td>Associated with thickened palms and characterized by exaggerated ridges with a velvety texture and brown hyperpigmentation. Virtually, all of these cases are associated with cancer, and, in most patients, occur in association with acanthosis nigricans.</td>
</tr>
</tbody>
</table>
Acrokeratosis paraneoplastica or Bazex’s syndrome is characterized by symmetric psoriasiform acral hyperkeratosis. It is almost always associated with cancer, typically squamous cell carcinoma of the esophagus, head and neck, or lungs. The skin lesions may precede the detection of the tumor or parallel the growth of the malignancy. Antigenic cross-reaction of basement membrane and tumor antigens, as well as secretion of growth factors such as insulin-like growth factor-1 (ILGF-1) or transforming growth factor-a are postulated to cause this syndrome.

Paget's disease of the breast is characterized by erythematous keratotic patches over the areola, nipple, or accessory breast tissue and is associated with breast cancer. Extramammary Paget's disease is an erythematous exudative dermatitis located on the vulva in women, the genitals in men, and the perianal area in both sexes. Histopathologically, Paget's disease demonstrates large pale cells within the epidermis, and often in the cutaneous appendages. Extramammary Paget's disease is associated with an internal malignancy in 50% of cases. Most of these cancers are usually related to the site of the dermatosis. The most common sites of Paget's disease are in decreasing order: breast, uterus, rectum, bladder, vagina, and prostate gland.

**NEUTROPHILIC DERMATOSES**

Sweet's syndrome is characterized by fever, neutrophilia, and the appearance of erythematous painful raised cutaneous plaques. The distribution is typically on the face, neck, and upper extremities. Histopathology demonstrates a dermal infiltration of well-differentiated neutrophils, as opposed to leukemia cutis, which contains immature myeloid blasts. This syndrome may be associated with an underlying malignancy (approximately 20%), most frequently, acute myelogenous leukemia. Some cases have been associated with myeloproliferative and lymphoproliferative disorders, myelodysplastic syndromes, and carcinomas. Sweet's syndrome may precede the detection of malignancy by many years or occur concomitantly. The etiology is thought to be hypersensitivity, and response to corticosteroids is usually prompt.

The lesions of pyoderma gangrenosum appear as painful papules that subsequently ulcerate with violaceous irregular borders and a purulent, hemorrhagic exudate with a necrotic base. Histopathology demonstrates a lymphocytic vasculitis or neutrophilic infiltrate. It is associated with basal and squamous cell carcinomas as well as cutaneous T-cell lymphomas.

**ERYTHEMOS**

Erythema gyratum repens (Table 47-4) is an unusual progressive scaling erythema with prorates and a wood grain appearance. It is almost always associated with internal malignancies, most commonly lung, breast, uterus, and GI tract.

<table>
<thead>
<tr>
<th>Table 47-4. Erythemas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Necrolytic migratory erythema is a rare disorder characterized by circinate and gyrate areas of blistering and erosive erythema on the face, abdomen, and limbs. It is the hallmark of a glucagonoma. The eruption clears following resection of the tumor.</td>
</tr>
<tr>
<td>Flushing is an episodic reddening of the face and neck, lasting a few minutes, typically associated with the carcinoid syndrome but also seen with leukemia, medullary carcinoma of the thyroid, renal cell carcinoma, and other forms. Vasoactive peptides such as serotonin are thought to mediate this syndrome.</td>
</tr>
<tr>
<td>Erythema annulare centrifugum is characterized by slowly migrating annular and configurate erythematous lesions; rarely, it is associated with cancer, but this association remains unproven.</td>
</tr>
<tr>
<td>Exfoliative dermatitis is a progressive erythema followed by scaling, which is classically associated with cutaneous T-cell lymphoma but may be seen in other lymphomas.</td>
</tr>
</tbody>
</table>

**ENDOCRINE AND METABOLIC LESIONS**

Systemic nodular panniculitis or subcutaneous fat necrosis (Table 47-5) is characterized by violaceous nodules associated with adenocarcinoma of the pancreas and may be accompanied by polyarthritis, fever, and eosinophilia. Similar lesions are seen with pancreatitis, due to the release of pancreatic enzymes such as lipase, amylase, and trypsin into the serum.

<table>
<thead>
<tr>
<th>Table 47-5. Endocrine and Metabolic Lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cushing's syndrome is associated with broad purple striae, hyperpigmentation, telangiectasia, atrophy of the skin, and mild hirsutism. Cushing's syndrome is caused by increased ACTH, typically from small cell lung cancer, thyroid cancer, testicular cancer, ovarian cancer, adrenal tumors, and a variety of other tumors.</td>
</tr>
<tr>
<td>Addison's syndrome is characterized by generalized hyperpigmentation, especially in scars, pressure points, and points of friction. This syndrome is caused by decreased glucocorticoids and may be seen with malignant replacement of the adrenal gland.</td>
</tr>
</tbody>
</table>
Hirsutism is associated with virilism and is caused by increased glucocorticoids and testosterone, typically from adrenal and ovarian tumors.

**BULLOUS AND URTICARIAL LESIONS**

Paraneoplastic pemphigus is most frequently seen in B-cell lymphoproliferative disorders including lymphomas and CLL, as well as Castleman's disease, thymoma, Waldenström's macroglobulinemia, and spindle cell neoplasms. Patients develop painful bullous ulcers and intraepidermal and lichenoid skin lesions. Internal organ involvement is common and respiratory failure causes death in 30% of patients with this disorder. Patients with paraneoplastic pemphigus demonstrate autoantibodies to desmogleins 1 and 3, which cause acantholytic blistering. Antibodies to other cytoskeletal elements such as plakins have also been described. The course of the disease is progressive and independent of the underlying malignancy. Corticosteroids and cyclosporin have been advocated and high-dose cyclophosphamide without stem cell rescue has been successful in one patient. Table 47-6 describes the bullous and urticarial lesions.

**TABLE 47-6. Bullous and Urticarial Lesions**

Bullous pemphigoid is characterized by large tense bullae. Histopathology demonstrates absent acantholysis. It is reported to be associated with lymphomas, but this remains controversial.

Muir-Torre syndrome is a sebaceous gland neoplasm that may precede, follow, or coexist with visceral cancers. It is most often associated with GI tract adenocarcinoma of the colon, genitourinary tract, or lymphoma.

**MICCONEOUS LESIONS**

Acquired ichthyosis (Table 47-7) is characterized by generalized dry, cracking skin, hyperkeratotic palms and soles, and rhomboidal scales. It is most commonly associated with Hodgkin’s disease, but may be seen with lymphomas, multiple myeloma, and other malignancies. It has also been associated with Kaposi's sarcoma and AIDS-related Kaposi's sarcoma. Remission of the cancers may be accompanied by disappearance of the ichthyosis.

**TABLE 47-7. Miccellaneous Lesions**

Dermatomyositis is a rare severe inflammatory myelopathy with erythema or telangiectasias of the knuckles, upper chest, or periorbital regions. Dermatomyositis has been linked to malignancies, especially in adults after the age of 40. Frequency of cancer in adults is reported to vary from 10% to 50%, increasing with age. Malignancy can precede, follow, or occur with dermatomyositis, the most frequent pattern is onset of cancer within 1 year of the diagnosis of dermatomyositis.

Pachydermoperiostosis is characterized by thickening of the skin and creation of new folds; thickened lips, ears, and lids; macroglossia; clubbing; thickening of the forehead and scalp; and excessive sweating. The cause of this syndrome is unknown, but it is most often associated with bronchogenic carcinoma.

Hypertrichosis lanuginosa (malignant down) is the development of long, silky hair on the ears, forehead, and possibly the entire body, associated with lung, colon, bladder, and a variety of other cancers.

Pruritus may be the initial feature of an occult malignancy or the clinical manifestations of a previously diagnosed tumor. It is most frequently associated with Hodgkin's disease, but may be seen with lymphomas, cutaneous T-cell lymphomas, and a variety of other diseases. Severe pruritus localized in the nostrils has been reported in some patients with advanced brain tumors.

Amyloid deposits, which may manifest as macroglossia, superficial waxy yellow and pink elevated nodules on the skin, may be associated with multiple myeloma or Waldenström's macroglobulinemia. They may also be associated with benign disorders such as primary systemic amyloid.

Herpes zoster is a vesicular eruption in a dermatomal pattern typically associated with the immunosuppression associated with Hodgkin's disease, lymphomas, and leukemias.

**HEREDITARY DISORDERS**

Cowden's disease (Table 47-8) is characterized by multiple hamartomas and is a rare autosomal dominant condition characterized by both benign and malignant tumors. The main features are fibromas of the oral mucosa characterized by cobblestoning of the tongue and acral palmoplantar keratoses. Multiple facial trichilemmomas appear to be pathognomonic. There is an increased prevalence of malignancy, most often in women, typically breast and thyroid cancer.
Detection of 14-3-3 protein, commonly found in the CSF of patients with Creutzfeldt-Jakob disease, has also been found in the CSF of 12.5% of patients with paraneoplastic syndrome, has been shown to arise from the JC virus. Opportunistic infections have also been invoked as a possible cause of paraneoplastic syndromes. Progressive multifocal encephalitis, formerly classified as a lymphoepithelial lesion, is caused by the JC virus and occurs in less than 1% of patients with cancer. The nevoid basal cell carcinoma syndrome is an autosomal dominant syndrome and is characterized by neurofibromas and cafe au lait spots. Malignancies develop in a minority of patients and are most often pheochromocytoma.

The nevoid basal cell carcinoma syndrome is an autosomal dominant syndrome with early onset of multiple basal cell carcinomas, multiple jaw cysts, and abnormalities of the skeletal system, specifically rib abnormalities such as ectopic calcification in the pits of the hands and feet. The pits are pathognomonic of the syndrome, occurring in approximately two-thirds of adults with the syndrome. Medulloblastoma is the most common tumor. Leiomomas and fibromas of the ovary can also occur. Central nervous system tumors have also been reported in early childhood. There are numerous additional hereditary disorders associated with malignancy described in Table 47-8.

**NEUROLOGIC MANIFESTATIONS OF CANCER**

Remote effects of cancer on the central nervous system are neurologic disorders of unknown cause that occur exclusively, or with increased frequency, in patients with cancer. The phrase neurologic paraneoplastic syndrome is a more general description that refers to any neurologic dysfunction that occurs in cancer patients that is not caused by metastasis or direct invasion of the nervous system by cancer. However, both phrases (neurologic paraneoplastic syndromes and remote effects of cancer on the nervous system) are often used interchangeably in the more restrictive sense and are used that way in this review.

The neurologic paraneoplastic disorders can logically be separated into anatomic categories, although there is often overlap. This is particularly true of the dementias, which are often lumped together with brain stem, cerebellar, and spinal cord lesions under the rubric of carcinomatous encephalomyelitis. The older term carcinomatous encephalopathy has been used to describe all the remote effects of cancer on the nervous system as well as the disorders of peripheral nerves and muscle associated with cancer.

**FREQUENCY**

Even though most patients with cancer can be demonstrated to have some mild degree of neuromuscular dysfunction (usually in the form of myopathy or peripheral neuropathy), the frequency of clearly defined, symptomatic neurologic paraneoplastic syndromes is extremely low. Recognized neurologic paraneoplastic syndromes occur in less than 1% of patients with cancer.

However, the situation is complicated by the fact that not all patients with neurologic syndromes that appear to be paraneoplastic actually have an underlying cancer. In approximately 50% of patients with known cancer, the nervous system symptoms precede the discovery of the underlying malignancy. The probability that a given paraneoplastic syndrome is associated with an underlying cancer in patients who have not had a tumor identified varies with the specific type of paraneoplastic syndrome. For example, the probability of a patient with paraneoplastic encephalomyelitis having an underlying cancer is 70%. The probability that a patient with paraneoplastic neuropathy has an underlying cancer is 50%.

**PATHOGENESIS**

The cause and pathogenesis of the neurologic paraneoplastic syndromes are not known. However, a variety of causative mechanisms have been proposed to explain the individual syndromes. In 1888, Oppenheim was the first to suggest that the tumors themselves released substances that were directly neurotoxic. No known paraneoplastic syndromes have been shown to be caused by this mechanism, although the nervous system can be secondarily affected when tumors release hormones [e.g., adrenocorticotropic hormone (ACTH) and parathyroid hormone related peptide (PTHrP)] and cytokines [e.g., tumor necrosis factors (TNF) and the interleukins (ILs)].

Opportunistic infections have also been invoked as a possible cause of paraneoplastic syndromes. Progressive multifocal encephalitis, formerly classified as a paraneoplastic syndrome, has been shown to arise from the JC virus. It is possible that other infections may be responsible for other paraneoplastic syndromes. Detection of 14-3-3 protein, commonly found in the CSF of patients with Creutzfeldt-Jakob disease, has also been found in the CSF of 12.5% of patients with...
paraneoplastic neurologic syndromes (including paraneoplastic cerebellar degeneration and limbic encephalitis). Although this etiologic link to slow viruses is intriguing, it is not clear how the 14-3-3 protein is involved in the development of paraneoplastic syndromes, and further research in this area is warranted.

Another possible mechanism involves competition by the tumor for a biochemical nutrient or substrate. In this way, large metastatic carcinoids tumors produce an encephalopathy by depletion of tryptophan and niacin. However, no evidence has been found of competition for a vital nutrient in any of the known paraneoplastic syndromes. Furthermore, it is unlikely that the small tumors frequently associated with paraneoplastic syndromes could consume enough of any substrate to produce a deficiency syndrome, and paraneoplastic syndromes usually run a course independent of that of the tumor.

There is increasing evidence that many of these syndromes are mediated by a T-lymphocyte mechanism. Pathologic study of the central nervous system of patients with paraneoplastic syndromes shows an intense inflammatory infiltrate (including T cells), while T-cell receptor studies show that tumor-infiltrating T lymphocytes are specifically targeted to neuronal antigens. Peripheral blood lymphocytes show an increase in memory helper T cells in seroserosive patients with paraneoplastic syndromes versus seronegative controls. Further, a report of cytotoxic T-cell activity in a patient with paraneoplastic sensory neuropathy and anti-Hu antibodies provides provocative data regarding the relationship of T cells to the paraneoplastic process. Further study in this area is ongoing.

The most widely accepted cause of many neurologic paraneoplastic syndromes appears to involve an autoimmune reaction. It is likely that certain antigenic molecules normally produced only in the central nervous system are produced ectopically by specific tumors. When the immune system reacts to these antigens, the neural tissues that share the same or similar antigens are also attacked. Subacute cerebellar degeneration, optic neuritis, opsonolus-myo-cynicos, subacute sensory neuropathy, myasthenia gravis, and the Lambert-Eaton myasthenic syndrome (LEMS) have all been associated with the production of autoantibodies. The most compelling evidence resides in the well-described LEMS in which autoantibodies against voltage-gated calcium channels are expressed by small cell lung cancer, although no paraneoplastic syndrome has yet been proven conclusively to be caused by an autoimmune reaction.

**DIAGNOSIS**

Because most neurologic paraneoplastic syndromes occur in patients who do not have cancer or have not had a diagnosis of cancer made before the neurologic syndrome develops, diagnosis is often difficult. The clinical problem is twofold: (1) Either the patient is known to have cancer, and the question is whether the neurologic symptoms are due to a remote effect or to metastatic disease, or (2) the patient is not known to have cancer and the questions are whether there is a paraneoplastic syndrome present and does the patient need to be carefully evaluated for an occult cancer.

In the first instance, remote effects are so rare and metastatic disease so common that in the patients with known cancer the physician is obligated to consider and rule out all of the other neurologic complications of systemic cancer before diagnosing a paraneoplastic syndrome. Neurologic symptoms that may cause diagnostic difficulty include dementia, cerebellar dysfunction, and weakness of the extremities. Dementia is one of the well-described remote effects of cancer on the nervous system. However, similar symptoms may occur in patients with multiple cerebral metastases, leptomeningeal involvement, or in older patients with low brain reserve and systemic metabolic alterations or early neurodegenerative diseases such as Alzheimer’s disease. Cerebral metastases are usually visible on MRI and CT scans, while with neuroendocrine tumors, one usually sees hydrocephalus on neuroimaging and CSF abnormalities. Also, if the patient has become acutely demented, metabolic brain disease is a possible diagnosis, as are the late effects of radiation therapy to the brain for previous metastasis. In patients with lymphoma, infections of the central nervous system including progressive multifocal leukoencephalopathy, toxoplasmosis, and fungal meningitis must also be considered.

If cerebellar dysfunction develops in a patient with a known cancer, it is much more likely that the patient is suffering from a metastasis in the cerebellum than from a remote effect. Clinically, subacute cerebellar degeneration as a remote effect is characterized by bilateral appendicular signs (point to point test difficulties in both upper and lower extremities) and by dysarthria, usually without nystagmus. Dementia is common as well. Metastatic disease of the cerebellum usually causes difficulties with gait without involvement of the upper extremities or speech (midline lesion), or it causes unilateral ataxia without gross dysarthria (hemispheric lesion). An MRI or CT scan usually clarifies the diagnosis.

The most serious diagnostic problems arise in patients developing weakness of the lower extremities with absent reflexes and with or without bladder or bowel dysfunction. The physician may suspect a paraneoplastic peripheral neuropathy, but invasion of the cauda equina by leptomeningeal tumor is more likely. The diagnosis can usually be established by careful examination of the CSF and spinal imaging studies.

Most paraneoplastic neurologic diseases, such as sensorimotor peripheral neuropathy, dementia, and acute transverse myelopathy, occur only slightly more commonly in patients with cancer than in the general population. In such patients, a careful search for an underlying neoplasm is unlikely to be fruitful and is probably not warranted. However, several neurologic syndromes occur exclusively or with a much higher frequency in patients with cancer. These syndromes include dermato-myositis in middle-aged and elderly men, subacute cerebellar degeneration, subacute sensory neuropathy, and a subacute motor neuropathy. Any patient presenting with one of the previously mentioned neurologic syndromes deserves a careful search for an occult cancer. If the initial search result is negative, a tumor should still be suspected until a definitive diagnosis is established.

**AUTOANTIBODIES**

Some patients with paraneoplastic syndromes develop detectable autoantibodies and these are outlined in Table 47-10. When found in the patient without a history of cancer, a search for an underlying malignancy should be undertaken. While several of these are most commonly associated with one specific syndrome (as in anti-Yo antibody and ovarian teratocarcinoma, and anti-NCAM and LEMS), they are also absolutely specific to a particular tumor. For example, anti-Hu autoantibodies are seen in paraneoplastic encephalomyelitis, sensory neuronopathy, cerebellar degeneration, and opsonolus-myo-cynicos. Specific cancers are often associated with various paraneoplastic syndromes: 90% of anti-Yo autoantibodies indicates an underlying breast or gynecologic cancer. However, autoantibodies are not required for the diagnosis of a paraneoplastic disorder to be made. Conversely, the presence of an autoantibody does not always herald the development of a paraneoplastic syndrome. Individual autoantibodies are discussed under the specific paraneoplastic syndromes with which they are associated.

**TABLE 47-10. Antineuronal Antibodies and Associated Paraneoplastic Syndromes and Cancers**

**TREATMENT**

Treatment for most neurologic paraneoplastic syndromes is generally ineffective. The major exceptions are LEMS in which plasmapheresis and 3,4-diaminopyridine therapy are highly effective, and opsonolus-myo-cynicos, which often responds to corticosteroid therapy. As well, treatment of the underlying malignancy has been successful in LEMS and opsonolus-myo-cynicos. A report of the successful use of protein A immunoadsorption in a wide variety of neurologic paraneoplastic syndromes is encouraging, but awaits confirmation in larger randomized studies before it can be recommended as a standard of care. A possible reason for the general failure of treatment in these disorders is that most of the syndromes have a rapid onset, and there is usually insufficient time to make a diagnosis and start treatment before irreversible damage is done. It is also postulated that immunosuppression may promote tumor growth, thus resulting in more rapid cancer-related...
deaths in these patients.

SPECIFIC SYNDROMES

Encephalomyelitis

Encephalomyelitis is a general term for paraneoplastic syndromes with an intense inflammatory response, perivascular lymphocyte cuffing, and lymphocyte accumulation in brain or spinal cord. The manifestation of the paraneoplastic inflammatory process can be quite varied, depending on the affected area of the central nervous system. For example, spinal cord involvement can lead to transverse myelitis or motor neuropathy, while sympathetic autonomic effects can lead to orthostatic hypotension. It is unclear why specific areas of the central nervous system are affected in individual patients. There is no known treatment and the disorder runs a subacute course ending in severe debilitation.

Paraneoplastic Cerebellar Degeneration

Paraneoplastic cerebellar degeneration is a disorder that is characterized clinically by cerebellar signs and symptoms (ataxia, dysarthria, dysphagia) and pathologically by the diffuse loss of Purkinje cells in the cerebellum. It is the most common paraneoplastic syndrome that affects the central nervous system, yet affects less than 1% of patients with cancer. Symptoms are most often associated with cancers of the lung (especially small cell carcinoma), ovary, breast, and lymphomas (especially Hodgkin's disease).

Evidence of diffuse cerebellar dysfunction is the most common clinical presentation of the disorder. In the majority of cases, the neurologic signs and symptoms antedate the discovery of underlying cancer by months to years. The onset of symptoms is usually abrupt, with symmetric ataxia of the arms and legs progressing over weeks to months, usually associated with dysarthria and sometimes nystagmus. The seropositive patients appear to progress more rapidly. In addition, a mild to moderate degree of dementia is often present. MRI and CT initially show no abnormalities; however, as the disease progresses, some degree of cerebellar atrophy is usually found on imaging studies. CSF may be normal, but there is usually a mild pleocytosis and increased protein. There is frequently an increase in the CSF IgG, and oligoclonal bands may also be present. The clinical course is one of subacute worsening and then stabilization at a severe level of neurologic dysfunction, with improvement highly unlikely.

Several autoantibodies have been found in association with paraneoplastic cerebellar degeneration. When present, the titers of these antibodies are usually much higher in the CSF than in the serum, suggesting synthesis within the central nervous system. The most commonly found autoantibodies are high-titer parvalbumin antibodies and anti-Purkinje cell antibodies (anti-Yo antibodies). These antibodies are found almost exclusively in female patients with paraneoplastic cerebellar degeneration and underlying cancers of the breast, ovary, or female genital tract.

Other patients do not have anti-Yo antibodies but instead have other, less specific, autoantibodies including type 1 antineuronal nuclear autoantibodies (anti-Hu antibodies) and anti-Ri antibodies. Anti-Hu antibodies are more commonly associated with paraneoplastic encephalomyelitis and sensory neuropathy; however, some patients with small cell lung carcinoma may develop a cerebellar syndrome that is clinically indistinguishable from the anti-Yo associated form, even though these patients lack anti-Yo and have only anti-Hu antibodies. A separate group of patients have been identified who have breast cancer, anti-Ri antibodies, and cerebellar degeneration (often with oposclocus-myoclonus) in the absence of either anti-Yo or anti-Hu antibodies. In addition, some patients with Hodgkin's disease and a number of other neoplasms may have paraneoplastic cerebellar degeneration in the complete absence of any neuronal antibodies.

In most instances, patients with paraneoplastic cerebellar degeneration have similar clinical presentations and clinical courses. However, spontaneous remissions do occur, predominantly in patients with Hodgkin's disease and without anti-Purkinje cell autoantibodies.

Limbic Encephalitis

Paraneoplastic limbic encephalitis is a rare complication of testicular neoplasms, small cell lung carcinoma, and other cancers; it can also occur in the absence of cancer. Pathologically, the syndrome is characterized by loss of neurons in the amygdala, hippocampus, and insular cortex, occasionally with additional involvement of other deep gray matter structures. There is usually gliosis, lymphocyte cuffing of blood vessels, and microglial nodules. The clinical manifestations include subacute development of personality changes and loss of short-term memory occurring over days to weeks. Less commonly there can be seizures, hallucinations, and disorientation. Autoantibodies have been described in patients with limbic encephalitis and testicular cancer. These anti-Ta antibodies recognize proteins (Ma1 and Ma2) present in the nucleus and cytoplasm of neurons. The function of these proteins is unknown.

Paraneoplastic Opsoclonus-Myoclonus

Opsoclonus is a problem of saccadic instability and consists of high-amplitude, involuntary, chaotic, conjugate saccadic eye movements. These are often associated with focal myoclonus and ataxia. Opsoclonus is seen in two settings. In children, opsoclonus can be a self-limited condition that is probably due to a viral infection that involves the brain stem and is not related to cancer. More rarely, opsoclonus (with or without myoclonus) can also be a paraneoplastic syndrome. In children, the paraneoplastic syndrome is most often associated with neuroblastoma and occurs in approximately 2% of patients with neuroblastoma. Approximately 50% of children who present with opsoclonus have an underlying neuroblastoma. In one-half the cases, the opsoclonus precedes the diagnosis of cancer. Paraneoplastic opsoclonus-myoclonus in children responds to corticosteroids; however, in a review 69% of these patients had long-term residual neurologic damage.

In adults, opsoclonus-myoclonus is much less common than in children and less likely to be associated with an underlying neoplasm. Only approximately 20% of adults who present with opsoclonus have tumors, and unlike children, the most commonly associated tumor is lung cancer. As with many paraneoplastic syndromes, the neurologic abnormalities usually precede the diagnosis of an underlying neoplasm. The clinical picture is one of progressive eye movement abnormalities and myoclonus. The CSF usually shows a mild pleocytosis with slightly increased protein. Neuroimaging study results are usually normal. Treatment is rarely effective, but spontaneous remissions and remissions after treatment of the primary tumor occur infrequently. Neuropathologic findings run the spectrum from normal to a picture similar to paraneoplastic cerebellar degeneration with loss of Purkinje cells. Anti-Hu and anti-Ri antibodies have been found in a small number of cases, but no consistent pattern or presence of antibodies has been identified.

Cancer-Associated Retinopathy

Degeneration of the retina is a rare paraneoplastic syndrome. In more than 90% of the described cases, small cell carcinoma of the lung is the primary tumor. Retinal pigment melanoma is the second most common primary tumor associated with this condition. The major pathologic findings are widespread degeneration of the rods, cones, and ganglion cells of the retina. There is also usually degeneration of the outer neuronal layer of the retina with lymphocytic infiltration. Clinical findings consist of photosensitivity, scotomatosus visual loss, and attenuation of the caliber of retinal arteries. Frequently, decreased color vision, night blindness, and decreased visual acuity are also present. The CSF is usually normal. Electroretinography is abnormal; however, visual-evoked responses are normal. Serum autoantibodies that react with retinal cells have been identified in some, but not all cases. Antineuronal antibodies recognizing the photoreceptor recoverin are the best described. Corticosteroids have sometimes resulted in improved visual symptoms.

Subacute Sensory Neuropathy

Subacute sensory neuropathy is a rare paraneoplastic disorder that presents with sensory loss in the extremities. The disorder occurs in patients with cancer but more commonly is found in patients without cancer and in association with primary Sjögren's syndrome. In most patients, the sensory symptoms precede the diagnosis of cancer, and only approximately 20% of patients with the syndrome are ever demonstrated to have an underlying neoplasm. When present, the most common underlying cancer is small cell carcinoma of the lung in 90% of cases. Women are affected more often than men.

Pathologic findings consist of severe neuronal loss of primary sensory neurons in the dorsal root ganglia and gasserian ganglia. The cell loss is often patchy and sensory large fibers (e.g., proprioceptive nerves) are preferentially involved. There is often variable lymphocytic infiltration of the ganglia and secondary loss of white matter tracts in the posterior columns. The initial clinical symptoms are numbness, tingling, and dysesthetic pain in the distal extremities. The sensory loss progresses...
over days to weeks to involve all four extremities and ascends to involve the trunk and face. Deep tendon reflexes are lost; however, motor power is usually normal. The disease tends to stabilize after several months at a severe level of disability; most patients are unable to walk. Treatment with corticosteroids and plasmapheresis has not been successful. Occasionally, the syndrome remits spontaneously or improves after the primary tumor is treated.

**Subacute Motor Neuronopathy**

Subacute motor neuronopathy is a condition associated primarily with Hodgkin's disease and other lymphomas (although there have been rare occurrences with other tumors). The syndrome is characterized by subacute, progressive lower extremity weakness without significant sensory loss. The weakness is of the lower motor neuron type. Nerve conduction velocities are normal, and electromyography shows evidence of denervation. There is usually a mild elevation of protein in the CSF without pleocytosis. Pathologic findings include anterior horn cell degeneration, demyelination of the anterior (motor) nerve roots, and variable demyelination of spinal cord white matter. A specific motor neuropathy, Guillain-Barré syndrome, is increased in frequency in patients with Hodgkin's disease and is therefore labeled a paraneoplastic syndrome.

Unlike most other neurologic paraneoplastic syndromes, subacute motor neuronopathy usually develops after the diagnosis of the underlying neoplasm has been made, and the disorder frequently develops while the cancer is in remission (e.g., following curative mantle radiotherapy). The weakness usually does not produce profound debilitation and runs a course independent of the underlying malignancy. Typically, the weakness stabilizes or improves after several months. Presently, there is no effective treatment.

**Paraneoplastic Sensomotor Peripheral Neuropathy**

Mixed motor and sensory peripheral neuropathies are extremely common in cancer patients. In most cases the neuropathies are caused by neurotoxic chemotherapy, malnutrition, or metabolic problems that are not per se paraneoplastic. However, a rare subacute or chronic sensomotor neuropathy has been described, and is most frequently associated with lung cancer. The neuropathy involves the distal extremities in a characteristic glove and stocking distribution; bulbar structures are usually not involved. The CSF is usually normal or shows only a mild increase in protein. Nerve conduction study results are usually consistent with an axonal neuropathy, and electromyography demonstrates denervation. Pathologic study of nerves shows axonal degeneration, segmental demyelination, or a combination of the two. The neuropathy tends to stabilize and remain chronic. However, the condition can also remit and recur. No specific treatment is available.

**Lambert-Eaton Myasthenic Syndrome**

LEMS is a disorder of the myoneural junction that results in proximal muscle weakness. Approximately 40% of patients do not have an underlying cancer; women make up the majority of patients in this group. Of the 60% of patients with an underlying neoplasm, approximately two-thirds have small cell lung carcinoma.

LEMS is caused by an antibody attack on the presynaptic nerve terminal, specifically on the voltage-dependent calcium channels. The antibodies block the entry of calcium into the terminal in response to an action potential and this decreases acetylcholine release. LEMS has been induced in animals by passive transfer experiments in which animals were injected with IgG from patients with the disorder. The clinical findings include muscle weakness and fatigability that is usually worse in the proximal muscles. Unlike classic myasthenia gravis, the weakness usually does not involve the bulbar musculature, although approximately 30% of patients experience dysphagia. Approximately one-half of patients have symptoms of cholinergic dysautonomia (e.g., dry mouth and impotence).

Nerve conduction velocities show a characteristic pattern with normal conduction velocities and initially low amplitude compound muscle action potential. After exercise, the CMAPs increase to near normal levels. Repetitive nerve stimulation studies show a decrement of the compound muscle action potentials at low stimulation rates and an increase in the compound muscle action potentials at high stimulation rates.

In contrast to most paraneoplastic neuropathies, the LEMS has been reported to respond to plasmapheresis, intravenous immune globulin, and immunosuppression. Drugs that increase transmitter release (e.g., 3,4-diaminopyridine) relieve symptoms and may be beneficial in maintenance therapy. Pyridostigmine propages the effect of 3,4-diaminopyridine, but is usually ineffective when given alone. Treatment of the underlying cancer also results in clinical improvement.

**Dermatomyositis and Polymyositis**

Dermatomyositis and polymyositis are inflammatory myopathies characterized by the subacute development of proximal muscle weakness, with or without pain and muscle tenderness. Dermatomyositis has the classic heliotrope rash over the face, elbows, knees, and knuckles, in addition to the muscle weakness. Both conditions are usually idiopathic and are associated with cancer in only approximately 10% of cases. The muscle syndrome usually precedes the diagnosis of the underlying cancer. When the characteristic findings are present in men older than 40 years, there is a higher incidence of underlying cancer, especially carcinoma of the lung, and a search for cancer is warranted. The most commonly associated cancers are breast and lung tumors.

In addition to proximal symmetric muscle weakness and skin changes, there is usually an elevation in muscle creatinine kinase. Electromyography is consistent with a myopathic process, and muscle biopsy usually shows inflammatory infiltrates, necrotic fibers, and atrophic fibers, sometimes in a perifascicular pattern. Treatment with immunosuppressive agents, including corticosteroids, is the standard therapy. The syndrome follows an inconsistent course and often is independent of that of the tumor.

**Miscellaneous Syndromes**

The following syndromes have been described that have less concrete supporting data and are so rare that an in-depth review is not warranted. Stiff-person syndrome has been reported rarely in women with breast cancer, often preceding the oncologic diagnosis. Symptoms include painful muscle cramps and stiffness. Antilampiophobic autoantibodies are associated with this syndrome. Acute necrotizing myopathy has been described in several patients with rapid progression of symmetric, proximal muscle weakness, with pathologic evidence of muscle fiber necrosis without inflammation. Paraneoplastic vasculitic neuropathy is a syndrome characterized by nonsystemic subacute vasculitic neuropathy, usually due to small cell lung and lymphoma. Neuropathy varies from mononeuropathy multiplex to polyneuropathy. Axonal neuropathy is the characteristic finding in electrophysiologic studies, while the microscopic evaluation reveals a vasculitis. Unlike most other paraneoplastic syndromes, treatment of the underlying cancer or immunotherapy for vasculitis is helpful. Myasthenia gravis, a classic paraneoplastic syndrome associated with thymoma, is discussed in depth in Neoplasms of the Mediastinum, Chapter 32, and is not discussed here.

**MISCELLANEOUS PARANEOPlastic SYNDROMES**

**HYPERTROPHIC OSTEOARTHROPATHY**

A clinical syndrome, presumably hypertrophic osteoarthropathy (HOA), has been in the medical literature since antiquity. Hippocrates described the syndrome, which was most certainly digital clubbing, 25 centuries ago, and this syndrome was called hippocratic fingers. In the past, the problem was termed pulmonary HOA, but because other nonpulmonary diseases can cause the syndrome, the term was simplified to HOA. In 1992, an international workshop on HOA met in Florence, Italy, and established a consensus for the diagnosis classification and assessment of this syndrome.

To fulfill diagnostic criteria of this disease, both digital clubbing and periostosis must be present. Digital clubbing can be defined as paronychial soft tissue expansion associated with the loss of the curved linear luency normally present at the junction between the nail and the skin. This may progress to a prominent bulbous enlargement of the distal end of the digit, representing an underlying increase in vascular and connective tissues. Periostosis is represented by periosteal proliferation in tubular bones, particularly the tibia and femurs. Incomplete forms of HOA have been recognized including clubbing alone, isolated periostosis, and pachydermia associated with any of the minor manifestations of the syndrome (synovial effusions, seborrhea, folliculitis, hyperhidrosis, hypertrophic gastropathy, and acrocyanosis). Some investigators have also used a response to nonsteroidal antiinflammatory agents to confirm the diagnosis of HOA.

HOA can be characterized as either primary or secondary. The secondary forms are either generalized or localized. The localized forms are seen in patients with
hemiplegia, aneurism, infectious arthritis, and patient ductus arteriosus. The generalized symptoms are more common in cancer patients and are associated with six major disease categories including pulmonary diseases, cardiac diseases, liver disease, intestinal disease, mediastinal disease, and miscellaneous problems. By far the most common are the pulmonary syndromes including non–small cell lung cancer, metastatic malignancy, cystic fibrosis, pulmonary fibrosis, chronic infections such as abscess or bronchiectasis, and arteriovenous fistula. Cyanotic congenital heart disease is the most likely etiology of cardiac-associated HOA. Cystitis is the most common urologic association with HOA, and is usually associated with bladder malignancy. Metabolic bone disease is frequently associated with HOA and appears to be associated with hepatic carcinoma. Inflammatory bowel disease including Crohn’s disease and ulcerative colitis, as well as other chronic infections and bowel malignancies, are rarely associated with HOA. The mediastinal diseases associated with HOA are esophageal carcinoma, thymoma, and achalasia, while the miscellaneous category is headed by Grave’s disease and thalassemia.

The treatment of HOA is somewhat disappointing. As with virtually all paraneoplastic syndromes, successful treatment of the underlying disease is associated with a rapid resolution of the problem. However, in most cases of lung cancer the disease is generally in an advanced stage and, therefore, successful treatment is difficult to achieve. Patients with severe pain have been successfully treated with nonsteroidal antiinflammatory drugs. Surgery and other arthritic treatments such as colchicine have been less successful. Liver transplantation in patients with liver diseases associated with HOA has been related to dramatic improvement in symptoms, as has lung transplantation in patients with underlying lung disease. Many times, however, the symptoms can be quite debilitating and do not respond to therapy.

**FEVER**

Fever occurs in many patients with cancer. The causes of fever in many patients include infection, tumor, drug fever, reaction to blood products, and autoimmune diseases. Thirty percent of patients with cancer develop fever at some point during the course of their malignancy. 19 With the major having an underlying infection. The major diferential point in determining whether the fever is due to infection is the presence or absence of neutropenia. In patients with low white blood cell count, infection causes more than two-thirds of all fevers, while patients with normal white blood cell counts are infected far less frequently. Twenty percent of fevers in nonneutropenic patients are secondary to infection, whereas 45% remain unexplained after complete evaluation.

In the absence of infection, it is thought that tumor cells can produce cytokines, which cause fever. Renal cell carcinoma is the most common cancer associated with fever in up to one-third of patients, while hepatoma patients develop fever one-third of the time. Ped-Etstein fever is seen in patients with Hodgkin’s disease and is an important diagnostic feature of this disease. Fever is also seen in patients with non-Hodgkin's lymphoma. 20 Acute leukemia, osteosarcoma, atrial myxoma, adenocarcinoma, pheochromocytoma, and hypothyroid tumors are also rarely associated with the development of fever.

The endogenous pyrogens have been well described over the past 20 years. IL-1 replaces the term endogenous pyrogen, which was initially used to describe this cytokine in endotoxic shock. However, IL-1 has been shown to increase circulating neutrophils in the field and cortisol and is intimately involved in the acute phase response. TNF (a and b subtypes) has also been shown to cause fever, although it does not use the same receptors as IL-1 and appears to induce IL-1. 21 As well as interferon and IL-6 have been shown to produce fever, and it is expected that several more cytokines will eventually be added to the class of endogenous pyrogens.

The most important point in the management of fever in patients with cancer is evaluating for infection. In patients with neutropenia this could be life threatening, but it is also important in nonneutropenic patients. If infection is excluded, nonsteroidal antiinflammatory drugs are a reasonable means to manage patients with fever. Nonsteroidal drugs effect a decrease in fever by inhibiting cyclooxygenase, reducing prostaglandin E₂ synthesis. Some investigators use the response to nonsteroidal antiinflammatory drugs to differentiate fever caused by infection from that caused by a tumor. In two separate studies, response to indomethacin and naproxen was associated with a high incidence of tumor-related fever compared with infected witheticilepsic fevers. 22,23 Corticosteroids are also efcacious antipyretics, both in inhibition of prostaglandin E₂ and blocking transcription of mRNA cytokines.

### REFERENCES


INTRODUCTION

Cancers of unknown primary site are common. Their exact incidence is unknown, because many of such patients are "assigned" other diagnoses (an issue discussed later in Carcinoma of Unknown Primary Site As a Distinct Clinico-pathologic Entity) and are, therefore, not represented accurately in tumor registries. Nonetheless, unknown primary cancers accounted for 2% of all cancer diagnoses reported by Surveillance, Epidemiology and End Results registries between 1973 and 1987. We believe that a more realistic estimate of the incidence of these patients is 6% of all invasive cancers in the United States per year (approximately 80,000 to 90,000 patients). Within this heterogeneous patient group are found several clinical presentations and histologic tumor types. The largest group of patients has metastatic carcinoma of unknown primary site. Others have equivocal histologic diagnoses and tumors that create difficulty in classification using the time-honored method of light-microscopic examination. Specialized pathologic studies are essential in delineating the type of neoplasm present in many of these patients and, at times, may suggest the site of origin. Extreme heterogeneity in clinical presentations, histologic appearances, and natural histories has rendered systematic evaluation of such patients difficult, and an established base of knowledge has developed slowly. Only a few investigators have been interested in detailed studies of these patients. Therefore, past information suffers from many generalizations and is not representative of the entire patient population. These data are derived from grouping all patients and deal primarily with results of various chemotherapeutic regimens.

Over the last few decades, several important oncologic issues have changed. Combination chemotherapy, often used with surgery or radiation therapy, has proved to be potentially curative for selected patients with several metastatic tumors. In addition, palliation and prolongation of survival have been demonstrated after systemic therapy for patients with many other tumor types. Furthermore, treatment continues to evolve and improve. Such therapeutic improvements have relevance for patients with cancers of unknown primary site, because some have these responsive neoplasms (i.e., with occult primaries or atypical histologies). Diagnostic pathology has improved remarkably. More routine use of electron microscopy and the emerging fields of immunohistochemistry and molecular genetics are contributing to more precise diagnosis of neoplasms. Now possible is defining more reliably the histology and, at least in selected patients, the origin and biology of neoplasms. In concert with evolving diagnostic techniques, several clinical syndromes and features are being recognized and are helping physicians to understand and better manage patients with unknown primary cancer. Oncologists are rethinking issues involving patients with cancers of unknown primary site.

Appropriate patient management requires an understanding of several clinicopathologic features that help to identify patients with more responsive tumors. Typically, patients with cancer of unknown primary site develop symptoms or signs at a metastatic site, and the diagnosis is made by biopsy of a metastatic lesion. History, physical examination, and other appropriate evaluation of such patients fail to identify the primary site. The initial biopsy should be generous, because many studies suggest the site of origin. Extreme heterogeneity in clinical presentations, histologic appearances, and natural histories has rendered systematic evaluation of such patients difficult, and an established base of knowledge has developed slowly. Only a few investigators have been interested in detailed studies of these patients. Therefore, past information suffers from many generalizations and is not representative of the entire patient population. These data are derived from grouping all patients and deal primarily with results of various chemotherapeutic regimens.

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POORLY DIFFERENTIATED NEOPLASMS OF UNKNOWN PRIMARY SITE

If pathologists are confident of a cancer but cannot differentiate a general category of neoplasm (e.g., carcinoma, lymphoma, melanoma, sarcoma), it is designated as a poorly differentiated neoplasm of unknown primary site. A more precise diagnosis is essential in patients having this type of cancer, because many have responsive tumors. Approximately 5% of all patients with cancers of unknown primary site (nearly 4000 U.S. patients annually) present with this diagnosis on initial light-microscopical appearance, but few remain without a defined lineage after specialized pathologic study. The most frequent tumor for which effective therapy is available is non-Hodgkin's lymphoma. In reported series, 35% to 65% of poorly differentiated neoplasms were found to be lymphomas after further pathologic study. Most of the remaining tumors in this group are carcinomas. Melanoma and sarcoma together account for fewer than 15% of all tumors in such patients.

The evaluation of poorly differentiated tumors requires specialized pathologic studies. Immunoperoxidase tumor staining, electron microscopy, and genetic analysis can be helpful in the differential diagnosis. The most common use of a nonspecific light-microscopical diagnosis is an inadequate or poorly handled biopsy specimen. If possible, fine-needle aspiration biopsy should not be performed in affected patients as an initial diagnostic procedure, because the histologic pattern is not preserved and the ability to perform special studies is limited. We have documented several instances in which a fine-needle aspiration has suggested a specific diagnosis, which was proved later to be incorrect by an incisional biopsy. Frequently, a more definitive diagnosis can be made by obtaining a larger biopsy. Communication with pathologists is important, as special tissue processing may be necessary for some pathologic studies. In addition, all clinical information also may help pathologists to narrow down, or become more certain of, diagnoses. Some neoplasms remain unclassifiable by light microscopy, even with an adequate biopsy specimen. Additional pathologic study always is indicated in such cases.

IMMUNOPEROXIDASE TUMOR STAINING

Immunoperoxidase staining is the specialized technique most widely available for the classification of neoplasms. Often, immunoperoxidase staining can be done on formalin-fixed, paraffin-embedded tissue, which broadens its applicability, rendering repeat biopsy unnecessary in some patients. Immunoperoxidase antibodies are either monoclonal or polyclonal and are directed at cell components or products, which can include enzymes (e.g., prostatic acid phosphate, neuron-specific enolase [NSE]); normal tissue components (e.g., keratin, desmin, vimentin, neurofilaments, common leukocyte antigen [CLA]); hormones and hormone receptors (e.g., estrogen receptor); oncofetal antigens (e.g., a-fetoprotein [AFP]); carcinoembryonic antigen (CEA); and other substances (e.g., S-100 protein, chromogranin). Many new antibodies are being developed, and this area of diagnostic pathology is a dynamic and evolving field. Usually, specific diagnoses cannot be made on the basis of immunoperoxidase staining alone, because none of these reagents is directed at tumor-specific antigens. Staining also can be extremely variable, and a particular stain may be negative; yet, other data may nonetheless support a particular tumor type. For example, a neuroendocrine carcinoma does not stain invariably with all neuroendocrine reagents. Therefore, results must be interpreted in conjunction with the light-microscopical appearance and the clinical picture. Some immunoperoxidase staining patterns that are useful in the differential diagnosis of neoplasms are outlined in Table 48-1.

Usually, several important questions can be answered by immunoperoxidase staining. The CLA stain usually can be used to make the important distinction between lymphoma and carcinoma. Staining for NSE, chromogranin, and synaptophysin can suggest a neuroendocrine carcinoma (e.g., small cell lung cancer, carcinoid, islet cell tumor, etc.). Staining for prostate-specific antigen (PSA) strongly suggests prostatic carcinoma in a man with metastatic adenocarcinoma. Certain staining characteristics can suggest breast carcinoma (e.g., estrogen or progesterone receptors, gross cystic fluid protein 15), melanoma (e.g., positive staining for S-100 protein, vimentin, HMB-45), or sarcoma (e.g., positive staining for desmin, vimentin, factor VIII antigen). Staining for human chorionic gonadotropin (HCG) or AFP can suggest the diagnosis of a germ cell tumor in an appropriate clinical situation.

Several problems are associated with immunoperoxidase stains. Technical expertise is required to perform these tests accurately and reproducibly, and proper interpretation requires an experienced pathologist. Appropriate control slides are stained and examined concurrently, because nonspecific staining occasionally is a problem. Care must be taken to avoid overinterpretation, because no staining pattern is entirely specific. Certain stains, particularly CLA and PSA, are relatively specific; however, false-positive and false-negative results can occur with any of these stains. For example, some carcinomas stain with vimentin, some sarcomas stain with keratin, and a wide variety of carcinomas (other than neuroendocrine and germ cell tumors) stain with NSE and HCG, respectively.

In some circumstances, diagnoses based on immunoperoxidase staining in patients with poorly differentiated neoplasms of unknown primary site can be used to plan therapy and to predict outcome. Undifferentiated neoplasms identified as lymphoma on the basis of positive CLA staining respond well to the combination chemotherapy used for non-Hodgkin's lymphoma. In 35 patients with equivocal routine light-microscopical histology and positive CLA staining, treatment with a variety of standard lymphoma regimens resulted in an actuarial disease-free survival of 45% at 30 months. These patients’ outcome was similar to that of a group of concurrently treated patients who had non-Hodgkin's lymphomas with typical light-microscopical histology. In patients whose diagnoses were based on immunoperoxidase staining with tumors other than lymphoma, only limited data exist concerning treatment outcome.

ELECTRON MICROSCOPY

A diagnosis can be made by electron microscopy in some poorly differentiated neoplasms. Electron microscopy is not widely available, requires special tissue fixation, is relatively expensive, and should be reserved for the study of neoplasms with unclear lineage after routine light microscopy and immunoperoxidase staining. Like immunoperoxidase staining, electron microscopy is reliable in differentiating lymphoma from carcinoma. It may be superior to immunoperoxidase staining for the identification of poorly differentiated sarcoma. Other structures, such as neurosecretory granules (neuroendocrine tumors) or premelanosomes (melanoma), can suggest a particular tumor. Often, undifferentiated tumors have nonspecific ultrastructural features; therefore, the absence of a particular ultrastructural finding cannot be used to rule out a specific diagnosis. Some neoplasms defy further classification despite specialized pathologic study.

In some instances, electron microscopy provides evidence for adenocarcinoma or squamous cell carcinoma. Features of adenocarcinoma include intercellular and intracellular lumina and surface microvilli. Squamous carcinomas are characterized by frequent and prominent desmosomes and by prominent bundles of prekeratin filaments in the adjacent cytoplasm. Usually, determining the origin of poorly differentiated adenocarcinoma or squamous carcinoma is not possible by electron-microscopical features. Treatment implications are unclear for adenocarcinoma and squamous carcinoma recognized only by ultrastructural features.

GENETIC ANALYSIS

The identification of chromosomal abnormalities and genetic changes associated with neoplasms is becoming increasingly important. The use of tumor-specific
chromosomal abnormalities in diagnosis still is limited, but future research likely will identify many additional specific genetic abnormalities.

The biology of the primary tumor in patients with unknown primary neoplasms remains an enigma. Certainly, these tumors possess a metastatic phenotype. Some of these primary tumors may regress or involute or grow very slowly. Possibly some arise from embryonic epithelial “rest cells” that did not complete their appropriate migration. Often, karyotypic analysis of metastatic carcinomas demonstrates diverse multiple complex abnormalities, and is not yet helpful (in most instances) for diagnosis or classification, but is more representative of advanced neoplasms of many types (e.g., various chromosome 1p abnormalities). Overexpression of p53, bcl-2, C-myc, Ras, and Her-2-neu has been observed in unknown primary carcinomas; however, controversy continues regarding the frequency of expression and the clinical relevance. Tumors that strongly express p53 and bcl-2 may be more responsive to platinum-based chemotherapy. Recently, we showed that 10% of the poorly differentiated carcinomas are strongly positive for Her-2-neu staining (F. A. Greco and J. D. Hainsworth, unpublished data). Patients affected by these tumors will be reasonable candidates for anti-Her-2-neu antibody therapeutics. Recently, DNA microarrays have been studied in acute leukemias. and this technique holds promise as a method of classifying neoplasms on the basis of gene expression monitoring, perhaps identifying specific genetic patterns or fingerprints independent of previous histologic and biologic knowledge. In the future, this and other techniques may identify more specific tumor lineages or primary tumors that are responsive to specific therapies in patients with unknown primary cancers. On the other hand, the pathogenesis of some carcinomas of unknown primary site may arise from specific genetic lesions. Possibly, many such tumors have similar gene expression distinct from specific carcinomas of recognized primary sites. This possibility is suggested by the unusual occurrence of metastatic adenocarcinoma of unknown primary site in monoyzogotic twin brothers with a primary immunodeficiency disorder (X-linked hyper-IgM syndrome). The technology is now available to classify unknown primary carcinoma by gene expression, a technique that allows the pathologist to identify the tumor's potential origin and to provide more specific therapy by pharmacogenomic evaluation. As more precise and specific genetic lesions are identified in primary neoplasms and their metastases (e.g., lung, breast, ovary, germ cell), we can expect these data to provide more useful diagnostic and therapeutic information for unknown primary cancers. The identification of germ cell tumors already has met this expectation.

Chromosomal abnormalities have been well characterized in several hematopoietic neoplasms. Most B-cell non-Hodgkin's lymphomas are associated with tumor-specific immunoglobulin gene rearrangements, and typical chromosomal changes have been identified in some B-cell and T-cell lymphomas and in Hodgkin's disease. In the rare instance when the diagnosis of lymphoma cannot be established definitively with either immunoperoxidase staining or electron microscopy, detection of chromosomal translocations t(14;18), t(8;14), or t(11;14) or the presence of an immunoglobulin gene rearrangement provides definitive diagnostic information.

A few other nonrandom chromosomal rearrangements associated with nonlymphoid tumors have been observed. A chromosomal translocation, t(11;22), has been found in peripheral neuroepitheliomas and frequently in Ewing's tumor. An inversion of chromosome 12 is common in paraffin-embedded tissue specimens. This technique likely will improve the applicability of testing, as tissue culture is not necessary. Several other nonrandom cytogenetic abnormalities found in other tumors include t(2;13) in alveolar rhabdomyosarcoma; 3p deletion in small cell lung cancer; 1p deletion in neuroblastoma; t(1;2) in synovial sarcoma; and 11p deletion in Wilms' tumor. Polymerase chain reaction has been used to identify Epstein-Barr virus genomes in the tumor cells of patients with cervical lymph node metastases of unknown primary site, suggesting nasopharyngeal primaries. Among head and neck tumors, Epstein-Barr virus has been associated only with nasopharyngeal carcinoma. Because some of these tumor types discussed are poorly differentiated and often are metastatic at the time of diagnosis, identification of these genetic changes may provide a specific diagnostic. Specific genetic changes have been applied successfully to a subset of patients with carcinoma of unknown primary site (see Poorly Differentiated Carcinomas, later in this chapter).

ADENOCARCINOMA OF UNKNOWN PRIMARY SITE

**CLINICAL CHARACTERISTICS**

Well-differentiated and moderately well-differentiated adenocarcinomas are the most frequent light-microscopical diagnoses in patients with carcinoma of unknown primary site, accounting for approximately 60% of patients (some 50,000 U.S. patients annually). Typically, patients with this diagnosis are elderly and have metastatic tumors at multiple sites. Frequently, the sites of tumor involvement determine the clinical presentation; common metastatic sites include lymph nodes, liver, lung, and bone. Often, the clinical course is dominated by symptoms and signs related to the metastases. The primary site becomes obvious in only 15% to 20% of patients during life. At autopsy, however, a primary site is detected in 70% to 80% of patients. The most common primary sites identified at autopsy are the lung and pancreas, accounting for approximately 40%. Other gastrointestinal sites (e.g., stomach, colorectal, liver) are frequent, although adenocarcinomas from a wide variety of other primary sites occasionally are encountered. Adenocarcinomas of the breast, prostate, and ovary are rare in patients in this group. Also, an unexpected metastatic pattern seems to be observed; for example, occult pancreatic primaries more frequently involve bone rather than liver. Historically, as a group, patients with metastatic adenocarcinoma of unknown primary site have a very poor prognosis, with inexorable progression and a median survival of only 3 to 4 months. This finding is not surprising, considering the fact that many such patients harbor lung or gastrointestinal neoplasms. Many patients in this group have widespread metastases and poor performance status at the time of diagnosis. However, stereotyping all patients with adenocarcinoma of unknown primary site is not possible, because with more favorable prognostic features (e.g., lymph node metastases) and a group are more frequent. In addition, chemotherapy and hormone therapy are being given more improve survival considerably in the last 5 years, and many patients now candidates for chemotherapy have a reasonable expectation of clinical benefit and improved survival.

**PATHOLOGY**

The diagnosis of well-differentiated or moderately well-differentiated adenocarcinoma is based on light-microscopical features, particularly the formation of glandular structures by neoplastic cells. We have considered patients with well-differentiated or moderately well-differentiated adenocarcinoma as one group. These histologic features are shared by adenocarcinomas, and the site of the primary tumor usually cannot be determined by histologic examination. Typically, certain histologic features are associated with a particular tumor type (e.g., papillary features with ovarian cancer and signet-ring cells with gastric cancer). However, these characteristics are not specific enough to be used as definitive evidence of the primary site. Immunoperoxidase staining and electron microscopy are of limited value in identifying the site of origin of most well-differentiated or moderately well-differentiated adenocarcinomas. The stain for PSA is an exception because it is relatively specific for prostate cancer, and it should be used in men with suggestive clinical findings. Positive immunoperoxidase staining for estrogen or progesterone receptors and gross cystic fluid protein 15 suggests metastatic breast cancer in women with metastatic adenocarcinoma. Occasionally, neuroendocrine tumors (e.g., NSE, chromogranin, synaptophysin) can identify an unsuspected neuroendocrine neoplasm. Several other stains or batteries of stains have been evaluated, but none are truly tumor-specific and, if used, should be used in connection with all other clinical data.

The diagnosis of poorly differentiated adenocarcinoma should be viewed differently, because some affected patients are distinctive in the tissue biology and responsiveness to systemic therapy (see Poorly Differentiated Carcinoma, later in this chapter). Usually, this diagnosis is made when only minimal or questionable glandular formation is seen on histologic examination or, on occasion, when tumors exhibit positive staining for mucin but have no “glandular features.” Well-differentiated adenocarcinoma, poorly differentiated adenocarcinoma, and poorly differentiated carcinoma are diagnoses that usually represent parts of a spectrum of tumor differentiation rather than specific, sharply demarcated entities. These histologies represent a heterogeneous group of tumors with various biologic and clinical properties. Different pathologists may use slightly different criteria for making each of these three diagnoses. Therefore, an appropriate approach is to perform additional study with immunoperoxidase staining or electron microscopy in all poorly differentiated adenocarcinomas.

**DIAGNOSTIC EVALUATION**

An exhaustive search for the primary site is not indicated because it rarely can be found. Therefore, the clinical evaluation should be performed to evaluate any suspicious clinical symptoms or signs and to determine the extent of metabolic disease. Initial evaluation should include a thorough history and physical examination, standard laboratory screening tests (i.e., complete blood cell count, liver function tests, serum creatinine, urinalysis), and chest radiography. All men should have a serum PSA determination, and all women should undergo mammography. Computed tomography (CT) scans of the abdomen can identify a primary site in 10% to 30% of patients with unknown primary tumors and frequently are useful in identifying additional sites of metastatic disease. Additional symptoms, signs, or abnormal physical and laboratory findings should be evaluated with appropriate diagnostic studies. Extensive imaging evaluation of asymptomatic areas rarely is useful in identifying a primary site, is expensive, and often results in confusing or false-positive results.

Position emission tomography (PET) may be an important addition for the evaluation of potential primary sites. These data are very limited now, but one small series
identified likely primary sites in 7 of 29 patients (24%). The availability of various tumor markers (CEA; CA-15-3; CA-19-9; CA-125, B-HCG, a-fetoprotein) has not proved, in general, to be useful for diagnosis or prognosis but can be used to follow the response to therapy.

TREATMENT

The group of patients with adenocarcinoma of unknown primary site contains several clinically defined subgroups for which useful, rather specific therapy can be given. Therapy can be useful also for some patients who are not a part of one of these subgroups, as empiric chemotherapy recently has improved.

Peritoneal Carcinomatosis in Women

Adenocarcinoma causing diffuse peritoneal involvement is typical of ovarian carcinoma, although carcinomas from the gastrointestinal tract, lung, or breast occasionally can produce this clinical picture. In several women described with diffuse peritoneal carcinomatosis, no primary site was found in the ovaries or elsewhere in the abdomen at the time of laparotomy. These patients frequently had histologic features typical of ovarian carcinoma, such as papillary configuration or psammoma bodies. This syndrome has been termed multifocal extravirginal serous carcinoma or peritoneal papillary serous carcinoma. These patients have a primary peritoneal carcinoma. In the early 1980s, several anecdotal case reports documented excellent responses to cisplatin-based chemotherapy in women with this syndrome. This tumor is more common in women with a family history of ovarian cancer, and preventive oophorectomy, as expected, does not protect them from this disease. As for ovarian carcinoma, the incidence of primary peritoneal carcinoma is increased in women with BRCA1 mutations.

Table 48-2 summarizes the results of seven series including a total of 258 women with this syndrome. The clinical features are similar to ovarian carcinoma or abdominal carcinomatosis. Many patients have elevated serum levels of CA-125 antigen. An occasional patient will present with pleural effusion only. Metastases outside the peritoneal cavity are unusual, and their histologic features are similar to those of ovarian carcinoma (usually papillary configurations but also other histologies, including poorly differentiated carcinoma). The initial treatment plan for most patients included laparotomy with surgical cytoreduction, and the majority of these patients was treated with cisplatin-based combination chemotherapy. A few patients received cisplatin, chlorambucil, or melphalan alone. Recent series have documented the activity of paclitaxel. A summary of the results in 258 women are as follows: Twenty-two percent (range, 10% to 40%) of all patients had a complete response to chemotherapy, median survival was 18 months (range, 11 to 24 months), and long-term survival (more than 2 years) was 16% (range, 6% to 26%).

TABLE 48-2. Therapy for Women with Peritoneal Adenocarcinomatosis of Unknown Primary Site

Frequently, women with metastatic adenocarcinoma involving the peritoneal surface and no obvious primary site have biologically distinct tumors and often are responsive to chemotherapy. The site of origin of these carcinomas likely is the peritoneal surface (primary peritoneal carcinoma). Because ovarian epithelium is in part an extension of the mesothelial surface, some carcinomas arising from the peritoneal (mesothelial) surface may share a similar lineage (Müllerian derivation) and biology with ovarian carcinoma. Certainly, this possibility should be considered and would not be surprising (e.g., papillary mesothelioma). Optimal management of these patients includes aggressive surgical cytoreduction followed by postoperative chemotherapy. Cisplatin or carboplatin plus paclitaxel considered optimal for the treatment of advanced ovarian cancer would seem a reasonable choice for initial chemotherapy, and the results are likely to be similar to ovarian carcinoma. Approximately 20% of the patients in this group have complete responses to therapy, and some 16% have prolonged disease-free survival.

We have encountered a few men with this syndrome (papillary adenocarcinoma), but confirming the precise biology is difficult, and the lesions may be metastatic from an occult primary tumor arising elsewhere. A trial of chemotherapy also should be considered.

Women with Axillary Lymph Node Metastases

Breast cancer should be suspected in women who have axillary lymph node involvement with adenocarcinoma. Occasionally, the histologic finding is poorly differentiated carcinoma. Men with occult breast cancer can present in this fashion but are rare. The initial lymph node biopsy should include measurement of estrogen and progesterone receptors. Elevated levels provide strong evidence for the diagnosis of breast cancer. If no other metastases are identified, these patients may have stage II breast cancer with an occult primary, which is potentially curable with appropriate therapy. A few reports using PET and magnetic resonance imaging scans have identified occult breast cancer even with normal mammography results. Additional study is necessary before these procedures are recommended routinely in this setting. Modified radical mastectomy has been recommended in affected patients, even when physical examination and mammography results are normal. An occult breast primary has been identified after mastectomy in 44% to 80% of patients. Usually, primary tumors are less than 2 cm in diameter; in occasional patients, only noninvasive tumor is identified in the breast. Prognosis after primary therapy is similar to that of other patients with stage II breast cancer.

Radiation therapy to the breast after axillary lymph node dissection is an effective alternative primary therapy. Adjunct systemic chemotherapy is indicated in this setting and is standard therapy for stage II breast cancer.

Women with metastatic sites in addition to the axillary lymph nodes may have metastatic breast cancer with an occult primary tumor. Such women should be managed as if they have metastatic breast cancer. Elevated serum levels of CA-15-3 or CA-27-29 suggest the possibility of breast cancer. Estrogen and progesterone receptor status is of particular importance because those with positive hormone receptors may derive major palliative benefit from hormonal therapy, chemotherapy, or both.

Men with Possible Prostate Carcinoma

PSA concentrations should be measured in men with adenocarcinoma of unknown primary site. These tumors also can be stained for PSA. Even when clinical features (i.e., metastatic patterns) do not suggest prostate cancer, a positive PSA (serum or tumor stain) is reason for a trial of hormonal therapy. Occasionally, primary tumors are less than 2 cm in diameter; in occasional patients, only noninvasive tumor is identified in the breast. Prognosis after primary therapy is similar to that of other patients with stage II breast cancer.

Chemotherapy for Metastatic Adenocarcinoma of Unknown Primary Site

Approximately 90% of patients with well-differentiated or moderately differentiated adenocarcinoma of unknown primary site are not listed in one of the several foregoing clinical subgroups. In the past, chemotherapy of various types has produced low response rates, very few complete responses, and no long-term survivals.

The results of chemotherapy in reported series of 10 or more patients from 1964 to 1991 have been reviewed. A total of 1102 patients were reported in 33 trials. The only single agent studied adequately was 5-fluorouracil (5-FU), with response rates ranging from 0% to 16%. Cisplatin has been reported as a single drug in only one series, with a response rate of 19%. Other single agents (including methotrexate, doxorubicin, mitomycin C, vincristine, and semustine) that have been reported produced response rates from 6% to 16%.

The FAM regimen (5-FU, doxorubicin, and
Response rates varied from 8% to 39% (mean, 20%); complete responders registered fewer than 1%; median survival was 4 to 15 months (mean, 6 months); survival beyond 2 years was rare; and disease-free survival beyond 3 years was nonexistent.

These data should be viewed with several factors in mind. Some of the series are small, and large randomized comparisons are lacking. In addition to those with adenocarcinomas, some patients with poorly differentiated carcinoma of unknown primary site were included in many of these series. The patients did not undergo standard evaluation or comparison in regard to sites of metastasis (nodal vs. visceral), performance status, gender, or age.

Cisplatin-based combination chemotherapy has not been evaluated adequately. However, two small randomized comparisons of doxorubicin with or without cisplatin \cite{75} (subject to the many confounding factors previously mentioned) demonstrated no difference in median survival but more toxicity in the cisplatin-containing arm. A third, more recent, small randomized trial \cite{76} did show the superiority of cisplatin, epirubicin, and mitomycin C as compared to mitomycin C alone (median survival, 9.4 months vs. 5.4 months). We also have seen some useful clinical responses to cisplatin or carboplatin-based chemotherapy and to 5-FU plus leucovorin. The combination of 5-FU and leucovorin has not been evaluated adequately but does not appear active in patients with liver metastasis arising from an unknown primary site, a group most likely to have gastrointestinal primaries.

Several retrospective analyses have identified clinical and pathologic features associated with a more favorable response to empiric chemotherapy. \cite{77, 78, 79} Some of these features include tumor location in lymph nodes, female gender, and poorly differentiated histology. Patients with liver or bone involvement have a relatively poor prognosis. \cite{80, 81}

Recent chemotherapy has improved considerably for patients who have adenocarcinoma and poorly differentiated carcinoma but do not fit into a specific “treatable” subset. The introduction of several new drugs with rather broad-spectrum antineoplastic activity is changing the standard treatment for patients having any of several common epithelial cancers. These drugs include the taxanes, gemcitabine, vinorelbine, and the topoisomerase I inhibitors. We have completed several phase II trials incorporating paclitaxel and docetaxel into first-line therapy for patients with carcinoma of unknown primary site. The initial trial included 71 patients, and the preliminary results of the first 55 patients were published. \cite{82} The chemotherapy regimen, patients’ characteristics, and treatment results are summarized in Table 48-3, and the survival curve is shown in Figure 48-2 for all 71 patients (F. A. Greco and J. D. Hainsworth, unpublished data). With a minimum follow-up of 34 months, the median survival was 11 months, and the 1-, 2-, and 3-year survivals were 48%, 20%, and 14%, respectively. This paclitaxel-based regimen delivered in a multicenter community-based setting (Minnie Pearl Research Network) was well tolerated and easily administered in the outpatient area. Only patients who had carcinoma of unknown primary site (any histology) and were not in a previously defined treatable subset, with the exception of poorly differentiated neuroendocrine carcinoma, were eligible for this trial. The response rate of 66 evaluable patients was 48%, with ten complete responses (15%). The toxicity was moderate, primarily myelosuppression, but with only 12 hospitalizations for fever-neutropenia and no treatment-related deaths. Long-term follow-up for these 71 patients (minimum follow-up, 34 months) is of interest; the median survival was 11 months, and the median 1-, 2-, and 3-year actual survivals of patients with complete response (20 months, 80%, 40%, 20%, respectively) was significantly longer ($P = .025$) than those with partial response or stable disease (11 months, 50%, 15%, 10%, respectively). This latter group survived significantly longer ($P = .033$) than did patients who progressed on therapy (Fig. 48-3).

![Figure 48-2](image)

**FIGURE 48-2.** Survival curve for 71 patients with adenocarcinomas or poorly differentiated carcinoma. Patients with poor prognostic features were selected. The minimum follow-up is 34 months; median survival is 11 months; 1-, 2-, and 3-year survivals are 48%, 20%, and 14%, respectively.

![Figure 48-3](image)

**FIGURE 48-3.** Survival curve for patients with complete response (CR) was significantly better (0.025) than for those with partial response (PR) or stable tumor, which in turn was better (0.033) than for those with progressive tumor.

Subsequently, we turned our attention to docetaxel and have performed two sequential phase II trials in the same patient population with either docetaxel (75 mg/m$^2$) and cisplatin (75 mg/m$^2$) given every 3 weeks in 26 patients or docetaxel (65 mg/m$^2$) and carboplatin [area under the curve (AUC) = 5] every 3 weeks in 47 patients (F. A. Greco and J. D. Hainsworth, unpublished data January 1999). These combinations also were active, but the docetaxel-plus-cisplatin regimen was associated with substantial gastrointestinal toxicity, and the carboplatin regimen was associated with more myelosuppression. More than 20% of all patients responded to these regimens, with no differences for those with well-differentiated adenocarcinoma or poorly differentiated carcinoma. Although the follow-up is shorter than that of the paclitaxel-based trial, the 1 and 2 year survivals are similar. By combining these taxane-based chemotherapy trials, a total of 144 patients (71 on paclitaxel regimen, 73 on docetaxel regimen) have been treated and followed up (Fig. 48-4). Some preliminary analysis of these patients is of interest. The median follow-up is 25.
months, and median survival is 10 months, with actuarial survival at 1, 2, 3, and 4 years of 42%, 22%, 17%, and 17%, respectively. Complete responders, partial responders, and stable disease patients survive significantly longer than do those with progressive disease, and the study revealed a major trend for improvement in survival for poorly differentiated neuroendocrine carcinomas (too few in number to reach statistical significance). No difference was seen in survival for adenocarcinoma versus the poorly differentiated carcinomas. However, patients with known favorable subsets were not included in these trials. Women survived significantly longer than did men, and those with performance status 0, 1 (Eastern Cooperative Oncology Group scale) lived longer than did those with performance status 2. The progression-free survival of these 144 patients reveals that a small number of patients remain alive without progressive cancer: 1 year, 16%; 2 years, 9%; and 3 years, 9%. A subsequent, recently reported trial by others of 72 patients confirmed the activity of paclitaxel and carboplatin with a 41% response rate. The median survival had not been reached but was greater than 6 months.

**SQUAMOUS CARCINOMA OF UNKNOWN PRIMARY SITE**

Squamous carcinoma at a metastatic site represents approximately 5% of all patients with unknown primary carcinomas (nearly 4000 U.S. patients annually). Effective treatment is available for patients with certain clinical syndromes, and appropriate evaluation of these patients is important.

**SQUAMOUS CARCINOMA INVOLVING CERVICAL AND SUPRACLAVICULAR LYMPH NODES**

The cervical lymph nodes are the most common metastatic site. Usually, patients are middle-aged or elderly, and frequently they have abused tobacco or alcohol. When the upper or middle cervical lymph nodes are involved, a primary tumor in the head and neck region should be suspected. Clinical evaluation should include an examination of the oropharynx, hypopharynx, nasopharynx, larynx, and upper esophagus by direct endoscopy, with biopsy of any suspicious areas. CT of the neck better defines the disease in the neck and occasionally identifies a primary site. PET scanning also may identify primary sites but remains controversial. Detection of Epstein-Barr virus genome in the tumor tissue is highly suggestive of a nasopharyngeal primary site (see Genetic Analysis, earlier in this chapter), particularly in poorly differentiated carcinomas. Other genetic studies of squamous cell carcinoma of the head and neck region have shown genetic alterations in “normal” tissue as a precursor of invasive carcinoma. Further study is indicated, as these findings do not yet have a practical application. When the lower cervical or supraclavicular lymph nodes are involved, a primary lung cancer should be suspected. Fiber-optic bronchoscopy should be performed if the chest radiograph and head and neck examination results are normal, as this has a high yield, frequently identifying a lung primary.

When no primary site is identified, local treatment should be given to the involved neck. The reported results in more than 1400 patients are primarily retrospective, single-institution experiences, often using a variety of treatment modalities. In many of these series, a large minority of patients had poorly differentiated carcinoma and adenocarcinoma (see Special issues, Single Site of Neoplasms, later in this chapter). A substantial percentage (usually 30% to 40%) of patients achieved long-term disease-free survival after local treatment modalities. The results obtained using radical neck dissection, high-dose radiation therapy, or a combination of these modalities have been similar. The volume of tumor in the involved neck influences outcome, with N1 or N2 disease having a significantly higher cure rate than N3 disease or massive neck involvement. Poorly differentiated carcinoma also represents a poor prognostic factor in such patients. When resection alone is used as the primary treatment modality, a primary tumor in the head and neck subsequently becomes apparent in 20% to 40% of patients. Primary tumors surface less commonly when radiation therapy is used, presumably owing to the eradication of occult head and neck primary sites within the irradiation field. Radiation therapy dosages and techniques should be similar to those used in patients with primary head and neck cancer, and the nasopharynx, oropharynx, and hypopharynx may be included in the irradiated field.

Patients with low cervical and supraclavicular nodes do not do as well, because lung cancer is a frequent site of occult primary tumors. Patients with no detectable disease below the clavicle should be treated with aggressive local therapy, because 10% to 15% of these patients will have long-term disease-free survival. Chemotherapy also should be considered for such patients.

The role of chemotherapy for metastatic squamous carcinoma in cervical lymph nodes is controversial. One small nonrandomized comparison of patients treated with local modalities alone or with local modalities combined with chemotherapy (cisplatin and 5-FU) showed a higher complete response rate (81% vs. 60%) and longer median survival time (>37 months vs. 24 months) in patients also receiving chemotherapy. Paclitaxel-based chemotherapy may be more effective. Neoadjuvant chemotherapy and radiation therapy in locally advanced head and neck carcinoma is gaining acceptance, and consideration of chemotherapy for these unknown primary tumor patients now would also seem reasonable. In those who receive local therapy first, adjuvant platinum-based or paclitaxel-based chemotherapy should be considered.

**SQUAMOUS CARCINOMA INVOLVING INGUINAL LYMPH NODES**

Most patients with a tumor in inguinal lymph nodes have a detectable primary site in the genital or anorectal areas. Careful examination of vulva, vagina, cervix, penis, and scrotum is important and should include biopsy of any suspicious areas. Digital examination and anoscopy should be performed to exclude lesions in the anorectal area. Identification of a primary site in such patients is important, because curative therapy is available for carcinomas of the vulva, vagina, cervix, and anus, even after spread to regional lymph nodes. Nearly 50% of patients with inguinal presentations have poorly differentiated carcinoma. For patients in whom no primary site is identified, surgical resection with or without radiation therapy to the inguinal area sometimes results in long-term survival. Such patients should be considered also for neoadjuvant or adjuvant chemotherapy.

**SQUAMOUS CARCINOMA METASTATIC TO OTHER SITES**

Usually, metastatic tumor in areas other than the cervical or inguinal lymph nodes represents metastasis from an occult primary lung cancer. CT scans of the chest and fiber-optic bronchoscopy should be considered. Chemotherapy with regimens employed in the treatment of non–small cell lung cancer may be considered in
patients with good performance status. Other rare presentations include primary tumors from the head and neck, esophagus, anus, and skin.

Patients with the diagnosis of poorly differentiated squamous carcinoma should be evaluated carefully, particularly if other clinical features are atypical for lung cancer (i.e., young patients, nonsmokers, unusual metastatic sites). Occasionally, adenocarcinomas, particularly in the breast, undergo squamous differentiation at metastatic sites. As with the diagnosis of poorly differentiated adenocarcinoma, this histologic diagnosis (squamous cell) sometimes is based on minimal histologic findings. Additional pathologic evaluation with immunoperoxidase stains or electron microscopy should be considered. When the diagnosis remains unclear, such patients should be considered for a trial of therapy for poorly differentiated carcinoma.

POORLY DIFFERENTIATED CARCINOMA (WITH OR WITHOUT FEATURES OF ADENOCARCINOMA) OF UNKNOWN PRIMARY SITE

Patients with poorly differentiated carcinoma or adenocarcinoma of unknown primary site appear to represent distinctive subgroups with specific therapeutic implications. They account for approximately 30% of all patients with carcinoma of unknown primary site (nearly 25,000 U.S. patients annually); approximately two-thirds have poorly differentiated carcinoma, and one-third has poorly differentiated adenocarcinoma. Often, chemotherapy trials in the past included such patients and the more common patients with well-differentiated adenocarcinoma of unknown primary. All such patients were assumed to be similar, and they experienced both a poor response to 5-FU-based chemotherapy and a short survival. These chemotherapy trials included drugs likely to be useful in a palliative sense for a minority of patients with gastrointestinal, lung, and breast carcinomas. Some patients with poorly differentiated carcinomas have responsive neoplasms, and some are curable with cisplatin-based combination chemotherapy. Clinical and pathologic evaluation is, therefore, crucial in patients with poorly differentiated carcinoma.

CLINICAL CHARACTERISTICS

The clinical characteristics in this diverse group of patients appear to differ—albeit with considerable overlap—from the characteristics of patients with well-differentiated adenocarcinoma. The median age of this patient group is younger, although both groups have a wide age range. Often, patients with poorly differentiated carcinoma reveal a history of rapid progression of symptoms (often <30 days) and have objective evidence of rapid tumor growth. Most important, the tumor cells of metastases often differ from the primary tumor. Patients often experience symptoms at multiple metastatic sites. As with well-differentiated adenocarcinoma, the clinical and pathologic evaluation is crucial in unsuspected patients in whom an occult nasopharyngeal carcinomatous primary is being considered. These tumors should undergo routine additional pathologic study with immunoperoxidase staining; in selected tumors, electron microscopy and genetic analysis also are appropriate. The use of routine light microscopy alone is not adequate to assess such tumors. The information provided by these additional pathologic studies has been summarized previously (see Poorly Differentiated Neoplasms, earlier in this chapter). The frequency of more specific diagnoses, particularly lymphoma, is much lower in the carcinoma group than in the group initially diagnosed by routine light microscopy as poorly differentiated neoplasm. This is not surprising, because carcinoma is a more specific clinical diagnosis. Other diagnoses still may be suggested.

To assess the clinical utility of immunoperoxidase tumor cell staining in patients with poorly differentiated carcinoma of unknown primary site, we retrospectively performed a battery of stains on archival tumors from patients treated prospectively. Poorly differentiated carcinoma or poorly differentiated adenocarcinoma was diagnosed on the basis of routine light-microscopic examination, and all patients were treated before the technology of immunoperoxidase staining was used routinely (1978 to 1983). Therefore, results of immunoperoxidase staining could be correlated with clinical outcome in this group of similarly treated patients with a long median follow-up. Immunoperoxidase staining confirmed the diagnoses of poorly differentiated carcinoma in 49 patients (56%) and yielded other diagnoses in 16 patients (18%): melanoma in eight patients, lymphoma in four, prostatic carcinoma in one, and neuroendocrine tumor in three (see Neuroendocrine Carcinoma of Unknown Primary Site, later in this chapter). In 24 patients (28%), the immunoperoxidase staining pattern was inconclusive; electron microscopy occasionally was helpful in clarifying the diagnosis in affected patients. Seventy-five patients (86%) received combination chemotherapy with a cisplatin-based regimen, and 24 patients (28%) had a complete response. Nine of these patients later were given specific diagnoses by immunoperoxidase staining. lymphoma was diagnosed in four patients, melanoma in four patients, and yolk sac tumor in one patient. All patients with an immunoperoxidase diagnosis of lymphoma had clinical features compatible with lymphoma and are long-term survivors. Patients with immunoperoxidase features suggesting melanoma were surprisingly responsive to chemotherapy, with three of seven patients (43%) achieving complete remissions. Immunoperoxidase staining alone should not be excluded from a trial of cisplatin-based therapy. Immunoperoxidase staining is useful in the routine evaluation of metastatic poorly differentiated carcinoma of unknown primary site, as occasionally it can suggest the lineage of the tumor and can have specific therapeutic implications. Others have reported similar findings in patients treated with cisplatin-containing chemotherapy.

Immunoperoxidase staining should be used in the evaluation of poorly differentiated carcinomas of the following to do the following: (1) confirm the diagnosis of carcinoma; (2) identify a primary site of a recognized carcinoma (e.g., prostate); (3) identify patients who may have other neoplasms, such as lymphoma or melanoma (although these conditions can be excluded by immunoperoxidase staining alone in many instances); and (4) identify a group of patients in whom electron microscopy may provide important additional information.

Electron microscopy can be useful for a small minority of these carcinomas. In general, electron microscopy should be reserved for those tumors not diagnosed by immunoperoxidase stains. Lymphoma can be diagnosed reliably (in most instances) in those tumors mistakenly believed to be carcinoma. In addition, sarcoma, melanoma, mesothelioma, and neuroendocrine tumors occasionally are defined by subcellular features. Neuroendocrine differentiation is particularly important.

Chromosomal or genetic analysis is becoming an increasingly important method of diagnosis. Specific abnormalities have been identified in several neoplasms. Evaluation for these abnormalities may be useful in patients with poorly differentiated carcinoma of unknown primary site. In reference to germ cell tumors, Molter et al. performed genetic analysis in 40 patients with poorly differentiated carcinomas of unknown primary site. In reference to germ cell tumors, Molter et al. performed genetic analysis in 40 patients with poorly differentiated carcinomas of unknown primary site. In 12 of the 40 patients with poorly differentiated carcinoma, abnormalities of chromosomes 12, 17, and 22 were diagnostic of germ cell tumor. Other specific abnormalities were diagnostic of melanoma (two patients), lymphoma (one patient), peripheral neuroepithelioma (one patient), and desmoplastic small cell tumor (one patient). Of the germ cell tumors diagnosed on the basis of genetic analysis, five achieved a complete response to cisplatin-based chemotherapy. This outcome confirms our previously formulated hypothesis that some of these patients have histologically atypical germ cell tumors. These genetic findings can be diagnostic in these patients. Additional specific genetic abnormalities or gene expression monitoring in solid tumors likely will improve our ability further to establish tumor lineage or biologic subtypes. As with the use of poorly differentiated adenocarcinoma, this histologic diagnosis alone should not be excluded from a trial of cisplatin-based therapy.

Autopsy data looking specifically at patients with poorly differentiated carcinoma of unknown primary site are limited. Additionally, the number of postmortem examinations in general is declining. On the basis of limited necropsy data we have accumulated, primary sites appear to be found in only a minority of such patients (40%). These findings are contrary to those for well-differentiated adenocarcinoma of unknown primary site, where the primary site is found in most patients (>75%) at autopsy. The clinical evaluation of patients with poorly differentiated carcinoma of unknown primary site is similar to that described for patients with well-differentiated adenocarcinoma of unknown primary site. A medical history, physical examination, routine laboratory testing, and chest radiograph should be obtained for each patient. A chest, abdomen, and pelvis CT scan should be performed for all patients, with the abdomen and pelvis CT scan being performed in patients with known gastrointestinal metastases. Serum levels of HCG and AFP should be measured because substantial elevations of these markers suggest the diagnosis of germ cell tumor. Serum tumor markers, such as CA-125, CA-19-9, and CA-15-3, can be helpful in monitoring response to chemotherapy. PET scanning may have a role in diagnosis and after therapy, but further data are necessary before recommending PET scanning as standard.

DIAGNOSTIC EVALUATION

The clinical evaluation of patients with poorly differentiated carcinoma of unknown primary site is similar to that described for patients with well-differentiated adenocarcinoma of unknown primary site. A medical history, physical examination, routine laboratory testing, and chest radiograph should be obtained for each patient. A chest, abdomen, and pelvis CT scan should be performed for all patients, with the abdomen and pelvis CT scan being performed in patients with known gastrointestinal metastases. Serum levels of HCG and AFP should be measured because substantial elevations of these markers suggest the diagnosis of germ cell tumor. Serum tumor markers, such as CA-125, CA-19-9, and CA-15-3, can be helpful in monitoring response to chemotherapy. PET scanning may have a role in diagnosis and after therapy, but further data are necessary before recommending PET scanning as standard.
TREATMENT

When additional pathologic studies identify a specific neoplasm (e.g., lymphoma, sarcoma), appropriate therapy can be administered. Patients with elevated serum levels of HCG or AFP and clinical features suggestive of extragonadal germ cell tumor (e.g., mediastinal or retroperitoneal mass) should be treated with chemotherapy that is effective for germ cell tumors, even when pathologic examination results are not diagnostic.

Most affected patients have multiple metastases and only the nonspecific diagnoses of poorly differentiated carcinoma or poorly differentiated adenocarcinoma despite additional pathologic study. The first reports showing that some of these patients (a small subset) have highly responsive tumors appeared in the late 1970s. Most such patients were young men with mediastinal tumors; serum levels of HCG or AFP frequently were elevated. Most of these patients were thought to have histologically atypical extragonadal germ cell tumors. Although several other tumor lineages subsequently have been identified in these patients (i.e., thymoma, neuroendocrine tumors, sarcomas, lymphomas), most still defy precise classification.

Further evidence for the responsiveness of many other tumors in patients with poorly differentiated carcinoma of unknown primary site has accumulated during the last 20 years. On the basis of encouraging results in a few patients treated from 1976 to 1978, we prospectively studied the role of cisplatin-based therapy for patients with poorly differentiated carcinoma of unknown primary site. In a series of reports, we have documented a high overall response rate and long-term disease-free survival in a minority of such patients. Our experience in the treatment of 220 such patients, accumulated between 1978 and 1989, is summarized in Table 48-4. Most of the patients in this group did not have clinical characteristics strongly suggestive of extragonadal germ cell tumor. However, involvement of the mediastinum, retroperitoneum, and peripheral lymph node groups was relatively common. In the early years of this study, most patients received treatment with cisplatin, vinblastine, and bleomycin (PVB) with or without doxorubicin, then the most commonly used regimen for the treatment of advanced testicular cancer. Later, as etoposide replaced vinblastine, these patients received cisplatin and etoposide with or without bleomycin. All patients received an initial treatment trial of two courses of therapy, and responding patients received a total of four treatment courses. Major tumor responses were seen in 138 of 220 patients (62%), and 58 patients (26%) had complete response to treatment.

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<thead>
<tr>
<th>TABLE 48-4. Clinical Characteristics of 220 Patients with Poorly Differentiated Carcinoma of Unknown Primary Site</th>
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Our most recent update of this initial group of patients shows the following: 12% (26 patients) of the entire group has remained alive and free of tumor at a minimum follow-up of 6 years, with a range of 6 to 17 years (median, 11 years). Fourteen patients who were relapse-free at a minimum of 11 months at the time of our original report cannot be documented now as alive and free of the original tumor. Six patients are lost to follow-up, though each was known to be alive and relapse-free at 1, 2, 5, 3, 3.5, 4, and 7 years, respectively. Four patients died with progressive carcinoma of unknown primary site (two at 1 year and two at 7 years after initial chemotherapy). Three patients developed new cancers: one brain tumor, one pancreatic carcinoma, one lymphoma (two at 9 years and one at 17 years, respectively, after the initial therapy). One patient died of an unrelated cause 4 years after therapy.

The survival curves for the entire group of 220 patients and for the subset of 58 (26%) who had a complete response to chemotherapy are shown in Figure 48-5 and Figure 48-6. The median survival of complete responders was approximately 3 years. Median survival for all patients was 20 months. Of the 58 complete responders, 22 patients remain alive and relapse-free (38%), representing 10% of the entire group of 220. Four additional patients were treated in an “adjuvant setting” after resection of all gross tumor and all remain alive, bringing the total to 12% of all patients relapse-free. These long-term survival statistics are not censored. Patients who are lost to follow-up (six), died of second unrelated cancers (three), or died of other causes (one) are included as deaths on the curves. It is of note that 50 of the 220 patients were treated by oncologists outside our center, and their long-term results are equivalent. These results in a large series of patients support the notion that these poorly differentiated histologic types, as a whole, represent more sensitive tumors than well-differentiated adenocarcinoma, and substantial prolongation of life is possible for some of these patients, with the expectation of cure for a small minority.

**FIGURE 48-5.** Survival curve for all 220 patients with poorly differentiated carcinoma (12% at 17 years).

**FIGURE 48-6.** Survival curve of complete responders (38% at 17 years).

In only 32 of the 220 patients (14%) was the primary site or specific tumor type eventually identified (Table 48-5). In 19 of these 32 patients, the definitive diagnosis...
Favorable Prognostic Factors

As only a minority of patients have excellent treatment responses, we have analyzed patients for clinical features predictive of treatment responsiveness and long-term survival. Prognostic features evaluated in a multivariate analysis included age, gender, smoking history, serum tumor marker status (HCG, AFP), serum chemistries, number of metastatic sites, predominant site of tumor involvement, and histological features (poorly differentiated carcinoma vs. poorly differentiated adenocarcinoma). The probability of complete response to therapy and various features is illustrated in Table 48-6. Several features were independently predictive of favorable treatment outcome, including tumor location in the retroperitoneum or peripheral lymph nodes, tumor limited to one or two metastatic sites, younger age, and negative smoking history.

TABLE 48-6. Clinical and Pathologic Characteristics Predictive of Chemotherapy Responsiveness

Because most of the highly responsive tumors cannot be identified despite extensive pathologic evaluation, a variety of clinical features have been found to be useful as prognostic indicators (Table 48-6). Although evaluation of these clinical features allows the identification of patients with a higher chance of complete response, none of these indicators is specific enough to be able to exclude a patient reliably from a therapeutic trial. However, these features can better define relatively poor prognostic subsets and more favorable subsets of patients.

More than two decades ago, we hypothesized that highly responsive carcinomas probably were unrecognized or histologically atypical extragonadal germ cell tumors. We still believe that some of the highly responsive tumors are germ cell tumors that are marker-negative and are not identifiable using all available pathologic methods. Patients with clinical features highly suggestive of extragonadal germ cell tumors were analyzed for response to therapy and long-term survival. This group included 34 men who were younger than 45 years and had predominant disease in the mediastinum or retroperitoneum. Six of these men had elevated serum levels of AFP, HCG, or both. The histologic features of all tumors in this group were rereviewed, and only one had typical features of a germ cell tumor (yolk sac tumor). In this group, 29 of 34 patients (85%) responded to therapy, with 17 patients (50%) having complete response. Seven patients in this group (20%) remain disease-free.

Since 1989, we have either seen or collected clinical and pathologic data from 700 additional patients with carcinomas of unknown primary site. Before 1997, the majority of these patients with poorly differentiated carcinomas received cisplatin plus etoposide with or without bleomycin, and the results are similar to those of the 220 previously reported patients. We are reviewing all these data.

In the last 5 years, we have treated most patients with carboplatin and etoposide, with or without a taxane (paclitaxel or docetaxel), either as initial therapy or after first relapse. The response rate appears similar to those of cisplatin-based regimens. Further analysis has shown that, in general, resistance to paclitaxel is less common than resistance to cisplatin-based chemotherapy. Paclitaxel is generally more toxic to hematopoietic and neuroendocrine tissues.

Although the foregoing results represent marked improvement as compared with the dismal historical results (response rate <30%, no complete responders, no long-term survivors), this group of patients is heterogeneous, and many patients have relatively unresponsive tumors. Many such patients should be considered for palliative treatment. As only a minority of patients have excellent treatment responses, we have analyzed patients for clinical features predictive of treatment responsiveness and long-term survival.
Therefore, selection of patients with clinical features highly suggestive of extragonadal germ cell tumor, despite the nondiagnostic histology, defines a subgroup with a complete-response rate and long-term survival higher than those of the group as a whole. As discussed, Motzer et al. 146 provided strong support for the hypothesis that some of these patients have extragonadal germ cell tumors. Those researchers demonstrated chromosome 12 abnormalities diagnostic of germ cell tumors in several young men with poorly differentiated midline carcinomas of unknown primary site. The excellent response to treatment and survival (50% complete responders, 20% disease-free survival) for patients in our initial series with clinical features highly suggestive of extragonadal germ cell tumor suggests that these tumors are germ cell tumors, albeit histologically atypical. These treatment results do not differ greatly from those in patients with known extragonadal germ cell tumors treated with standard cisplatin-based therapy. 146 If feasible, genetic analysis on tumor tissue should be performed as a diagnostic test for selected patients with carcinoma of unknown primary site.

Responsive tumors are heterogeneous in their origin, and only a small subset of patients have histologically atypical germ cell tumors. A few of the patients have non-Hodgkin's lymphoma. Certain lymphomas may be confused with anaplastic carcinomas; some lymphomas, notably the Ki-1 lymphomas, also can stain positively with epithelial membrane antigen, further complicating their differentiation from carcinoma. 122 It is hoped that this confusion will be minimized or eliminated with the routine use of immunoperoxidase staining for CLA. A second group of highly responsive tumors are poorly differentiated neuroendocrine carcinomas. The origin of such tumors remains speculative, but they may be an anaplastic variant of occult primary carcinoid.

The nature of the other responsive tumors in this heterogeneous group of patients remains even more speculative. Malignant thymoma is a tumor recently recognized to be responsive to cisplatin-based therapy, with some patients experiencing long-term complete remissions. 122 Some patients with poorly differentiated carcinoma located predominantly in the mediastinum may have thymoma. In our original series, a few patients who were long-term survivors were identified as having “melanoma” on the basis of immunoperoxidase stains. This diagnosis seems unusual because melanoma is a tumor that normally is unresponsive to chemotherapy. Possibly, melanomas identifiable only by immunoperoxidase staining or electron microscopy represent a uniquely chemotherapy-sensitive subset. Finally, some responsive tumors possibly represent a heretofore undefined tumor type. Alternatively, some may represent highly undifferentiated—and therefore perhaps chemotherapy-sensitive—epithelial tumors from occult primary sites, which usually are much less responsive to systemic therapy. Future knowledge and refinements in genetic diagnosis may establish the identity of many of these tumors.

Table 48-7 shows the relation of response and long-term survival (>6 years) to the site of dominant tumor involvement. Regardless of other factors, dominant tumor in the retroperitoneum, peripheral lymph nodes, or mediastinum is fairly favorable. Forty-five of 105 patients in these categories had a complete response, and 20 patients remain alive and relapse-free (19%).

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<th>Table 48-7. Chemotherapy Response, Survival, and Predominant Site of Tumor</th>
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<tr>
<td><strong>Chemotherapy Response</strong>, <strong>Survival</strong>, and <strong>Predominant Site of Tumor</strong></td>
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Prognostic factors also have been evaluated in a large series of patients reported from the M. D. Anderson Hospital. This large group was heterogeneous, containing patients with all histologic subtypes. Those with clinical features of extragonadal germ cell tumors were excluded, and only a minority of patients with poorly differentiated carcinoma received cisplatin-based treatment as used in the treatment of germ cell tumors. Some of the same clinical features that we identified were found to be important prognostic features, including limited number of organ sites involved, tumor location in lymph nodes (including mediastinum and retroperitoneum) other than the supraclavicular lymph nodes, and female gender (seen also in our recent series). In addition, the relatively poor outcome of patients with adenocarcinoma as compared to other histologies was confirmed. However, they could not identify a subset of patients with poorly differentiated carcinoma and long-term survival after chemotherapy. 150,155 Although these prognostic features are useful, occasional excellent responses are seen even in patient groups with “unfavorable” clinical features. At present, even these patients should be considered for a trial of chemotherapy.

**NEUROENDOCRINE CARCINOMA OF UNKNOWN PRIMARY SITE**

Improved pathologic methods for diagnosing neuroendocrine tumors has resulted in the recent recognition of a wider spectrum of these neoplasms. The incidence of unknown primary neuroendocrine carcinoma is not known, but an estimate suggests approximately 4000 U.S. patients annually. Most of the well-described adult neuroendocrine tumors have distinctive histology and a known primary site of origin (Table 48-8). The well-differentiated or low-grade neuroendocrine tumors (typical carcinoid, islet cell tumors, and others) occasionally present without a recognizable primary site and usually possess an indolent biologic behavior. Carcinoid tumors of unknown primary site appear to be increasing. 11 A second group of neuroendocrine tumors are poorly differentiated by light microscopy but have “neuroendocrine features” (typically small cell, atypical carcinoid, or poorly differentiated neuroendocrine carcinoma) and act aggressively. A third group of neuroendocrine tumors, recently recognized, has high-grade biology and no distinctive neuroendocrine features by light microscopy. The initial diagnosis in this group usually is poorly differentiated carcinoma, and neuroendocrine features are recognized only when immunoperoxidase staining (or, more definitively, if electron microscopy) is performed. Neuroendocrine carcinomas of unknown primary site occur in each of these three categories.

<table>
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<tr>
<th>Table 48-8. Adult Neuroendocrine Tumors with Known Primary Sites</th>
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<td><strong>LOW-GRADEx8E NU8ENDOCRINE CARCINOMA</strong></td>
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Occasionally, metastatic neuroendocrine tumors with histologic features typical of low-grade well-differentiated carcinoid or islet cell tumor are found without obvious primary site. In this situation, metastatic tumor usually involves the liver or bone (or both) and sometimes is associated with clinical syndromes produced by the secretion of bioactive substances (e.g., carcinoid syndrome, glucagonoma syndrome, vipomas, Zollinger-Ellison syndrome). In some affected patients, further evaluation reveals primary sites in the small intestine, rectum, pancreas, or bronchi.
As predicted by the histologic appearance, these neuroendocrine tumors usually exhibit an indolent biology, and slow progression over years is likely. Management should follow guidelines established for metastatic carcinoid or isolated cell tumors from obvious primary sites. Often, these neoplasms are refractory to systemic chemotherapy, and cisplatin-based chemotherapy produces low response rates. Depending on the clinical situation, appropriate management may include local therapy (resection of isolated metastasis, hepatic artery ligating-embolization), treatment of associated syndromes with somatostatin analogs, streptozocin, doxorubicin, 5-FU-based systemic therapy, or symptomatic management.

**SMALL CELL CARCINOMA**

Patients with a history of cigarette smoking and small cell undifferentiated carcinoma at a metastatic site usually have a lung primary tumor. CT of the chest and fiber-optic bronchoscopy should be performed. Perhaps PET scanning may be useful in this setting, but data are limited. If a pulmonary lesion is identified, affected patients should be treated according to recommendations for small cell lung cancer. Small cell carcinoma can arise also from a variety of extrapulmonary primary sites. Patients with localizing symptoms should undergo appropriate diagnostic studies.

When no primary site is identified, patients with small cell carcinoma should be treated with combination chemotherapy as recommended for small cell lung cancer. We have found that paclitaxel, carboplatin, and oral etoposide is a very active therapy for these patients and have continued to evaluate this regimen. Initially, these tumors are chemotherapy-sensitive, and major palliative benefit can be derived from treatment. An occasional patient will enjoy long-term benefit. In the rare instance in which the tumor appears at a single metastatic site, the addition of radiation therapy or resection (or both) to combination chemotherapy should be considered.

**POORLY DIFFERENTIATED NEUROENDOCRINE CARCINOMA**

In approximately 10% of poorly differentiated carcinomas, electron microscopy reveals neurosecretory granules, a finding diagnostic of neuroendocrine carcinoma. These tumors have been called poorly differentiated neuroendocrine tumors, atypical carcinoids, or primitive neuroectodermal tumors. In some of these tumors, neuroendocrine features are recognizable by light microscopy; in others, the light-microscopical diagnosis is "poorly differentiated carcinoma." Though electron microscopy is the most accurate means of pathologic diagnosis, most of the tumors also have typical immunoperoxidase staining patterns with positive staining for neuron specific enolase, chromogranin, and synaptophysin.

Previously, we reported on 29 patients with poorly differentiated neuroendocrine tumors and 46 treated with combination chemotherapy (Table 48-9). Most of these patients had clinical evidence of high-grade tumor, and most had metastases in multiple sites. Thirty-three of 43 evaluable patients (77%) responded to chemotherapy with a cisplatin-based combination regimen. Thirteen patients (26%) had complete responses, and eight remain continuously disease-free more than 2 years after completion of therapy. Our more recent experience would favor the use of paclitaxel, carboplatin, and oral etoposide in such patients.

**TABLE 48-9.** Poorly Differentiated Neuroendocrine Tumors of Unknown Primary Site in 51 Patients

The origin of these poorly differentiated neuroendocrine carcinomas remains unclear. In four of our patients, specific diagnoses were made either subsequently in their clinical course or at autopsy. Two patients had carcinoid tumors with "undifferentiated" growth pattern (both presented with abdominal carcinomatosis); one had small cell lung cancer, and one had extragonadal germ cell tumor with predominant neuroendocrine differentiation. Likely some additional patients with small cell histology had small cell lung cancer with occult primary tumor, but more than one-half of these patients had no smoking history, and the absence of overt pulmonary involvement renders this diagnosis unlikely in most patients. Probably, some of these tumors are undifferentiated variants of well-recognized neuroendocrine tumors (e.g., carcinoid tumor), without a recognizable primary site. In the undifferentiated form, the clinical and pathologic characteristics no longer resemble the characteristics of the more differentiated counterpart. Anaplastic or atypical carcinoid tumors arising in the gastrointestinal tract are responsive to cisplatin-based chemotherapy, whereas carcinoid tumors with typical histology usually are resistant. A few reports of patients with "extrapulmonary small cell carcinoma of unknown primary site" also have documented chemotherapy responsiveness and occasional long-term survival after systemic therapy. However, the term extrapulmonary small cell carcinoma implies the existence of a known primary site (e.g., head and neck, salivary gland, prostate, cervix, esophagus, bladder, etc.); therefore, these tumors are more aptly described as neuroendocrine carcinoma of unknown primary site.

Although the origins of these poorly differentiated neuroendocrine tumors remain undefined, the presence of neurosecretory granules in the tumors of patients with poorly differentiated carcinoma identifies a highly treatable subgroup. Molecular genetic studies may be helpful if an 11:22 translocation (peripheral neuroepithelioma) or soft tissue Ewing's sarcoma) or i(12p) abnormality (germ cell tumor) is identified. All patients with disease not otherwise specifically diagnosed should be treated with a trial of combination chemotherapy. As are small cell neuroendocrine carcinomas, these tumors are very sensitive to the combination of paclitaxel, carboplatin, and oral etoposide. Some patients with a single site of tumor involvement may be curable with local treatment modalities alone; however, a course of adjuvant chemotherapy also should be considered in such patients if clinically feasible.

**SPECIAL ISSUES**

**CARCINOMA OF UNKNOWN PRIMARY SITE AS A DISTINCT CLINICOPATHOLOGIC ENTITY**

We have been struck over the last two decades by the number of times patients and their referring physicians (often oncologists) are very frustrated by unknown primary cancer. Often, they are somewhat obsessed with finding the primary site or at least giving their patients a more specific diagnosis. Many reasons underlie these feelings. Some patients think that their oncologists are not clever enough as diagnosticians and seek the advice of others. Some oncologists feel relatively inadequate and worry about other tests they might order; some have been relatively tentative, not feeling confident in recommending any therapy. Certainly, a reasonable clinical and pathologic evaluation of these patients and their tumors is indicated, with oncologists being aware of possible primary sites and the relevance in particular patients. However, once these considerations and evaluation are complete and no additional helpful information is forthcoming (as often is the case), physicians should stop, discuss the issue with their patients and their families, and accept the clinicopathologic diagnosis as an unknown primary tumor. Indeed, most patients at this point have unknown primary cancer: such tumors only occasionally surface during life and often cannot even be found at autopsy. Patients will be better served, and physicians will eventually feel more comfortable—and therefore manage these patients more effectively—once their patients accept and understand this diagnosis as a distinct clinicopathologic entity. They have a diagnosis.

A second very practical issue in the United States is the determination of Medicare reimbursement for chemotherapy for cancer diagnoses. Most typically, these reimbursements are determined by Medicare (and several other third-party insurers) by consulting two compendia: the American Hospital Formulary Drug Information (AHFS) and the United States Pharmacopeia Drug Information (USPDI). Their entries are listed by an indication index or by tumor types (ICD-9 International Classification of Diseases-9) codes) and a generic drug index. Tumor types and drugs used for a particular tumor type are listed. The list is based on published literature showing “effectiveness” or clinical benefit in a specific tumor type. This system is particularly arbitrary. The diagnosis code for unknown primary cancer is not listed at all in AHFS or USPDI. Therefore, no drugs are listed as “useful” for patients with unknown primary cancer. Usually, Medicare will not pay for any drug not
Many patients with unknown primary cancer are coded with another diagnosis by oncologists. At times, this is a “good guess” of the possible primary tumor (e.g., non–small cell lung cancer in patients with lung lesions or mediastinal node involvement; hepatoma, pancreatic, or colon cancer for patients with liver involvement, etc.). Furthermore, patients at times are assigned a diagnosis based on the pathology report alone (e.g., adenocarcinoma consistent with pancreatic or colon primary tumor). Certainly, this practice allows for reimbursement for some drug costs by a system that otherwise has not even recognized unknown primary cancer. This activity, in turn, causes the true incidence of unknown primary cancer to be underestimated. Recently, we and others provided the editors of AHFS and USPDI with considerable data concerning unknown primary cancer, and we hope that the diagnosis code and specific drugs useful for this entity will appear in their pages soon.

Currently, more than enough clinical and pathologic data allow classification of patients confidently as having an unknown primary cancer, and the more global acceptance of this entity will help these patients to establish an identity, will stimulate more interest by physician investigators, and eventually will improve general understanding of such patients and their tumors.

EXTRAGONAL GERM CELL CANCER SYNDROME

Selected patients with poorly differentiated carcinoma almost certainly have germ cell tumors, although the histologic features are atypical even when generous pathologic specimens are available for study. Chromosomal analysis (as discussed) may provide a definitive diagnosis in some of these patients, particularly if their tumors contain specific chromosome abnormalities. Even if they are not found or in the absence of a genetic study, young people who have mediastinal or retroperitoneal masses or multiple lung nodules (with or without elevated serum levels of HCG or AFP) should be suspected of harboring a germ cell tumor. Lymphomas should be ruled out by immunoperoxidase stains, electron microscopy, or (if necessary) cytogenetic studies. The “extragonadal germ cell cancer syndrome” was described in 1979.134

The full syndrome displays the following features: (1) it occurs in young men (<50 years); (2) tumors are predominantly located in the midline (mediastinum, retroperitoneum) or multiple pulmonary nodules; (3) the symptom interval is short (<3 months) and history is of rapid tumor growth; (4) serum levels of HCG, AFP, or both are elevated; and (5) a good response to previously administered radiation therapy or chemotherapy is demonstrated.

Few patients have all elements of this syndrome. These clinical features are those of extragonadal germ cell tumors but, without definitive histology, the diagnosis is not unequivocal. In rare cases, women can develop these tumors, and the other features also are not absolute. Any one feature suggests the possibility of a germ cell tumor. Treatment with cisplatin-based therapy is prudent in affected patients who may have atypical germ cell tumors.

SINGLE SITE OF NEOPLASM

In situations in which only one site of neoplasm is identified (e.g., one node group or one large mass), the possibility of an unusual primary tumor mimicking metastatic disease should be considered. Several unusual tumors could present in this fashion, including Merkel-cell tumors, skin adnexal tumors (e.g., apocrine, eccrine, and sebaceous carcinomas), and even sarcomas, melanomas, or lymphomas that are interpreted mistakenly as metastatic carcinoma (pathologically and clinically). Usually, patients with one site of involvement have metastatic carcinoma, and many other sites are present but are not detectable. In the absence of any other disease, such as lung metastases, such patients should be treated with aggressive local therapy (i.e., resection, radiation therapy, or both) because a minority will enjoy long-term disease-free survival.

Patients who present with isolated cervical, supraclavicular, and inguinal adenopathy often have squamous cell carcinoma, but a minority harbor poorly differentiated carcinoma and adnexal carcinoma. In addition to receiving definitive local therapy, these patients also should receive either neoadjuvant or adjuvant platinum-based or paclitaxel-based chemotherapy, but knowing whether this treatment is superior to local therapy alone is difficult.

On occasion, patients will present with apparent solitary metastasis of adenocarcinoma or poorly differentiated carcinoma in the brain, liver, subcutaneous tissue, intestine, or other areas. In most instances, other metastases will become clinically apparent with time. Certainly, some examples highlight resection or irradiation of these single areas and illustrate patients doing well with no evidence of recurrence. At times, the resection may be planned as palliative, particularly with a brain metastasis. The method of choice in managing these patients is to ressect the single lesion. After resection, and depending on the other clinical circumstances, patients may be candidates for chemotherapy, particularly if their histology is poorly differentiated carcinoma. In those patients with single metastases (i.e., brain), radiation therapy is a prudent consideration after surgical resection. Often, isolated carcinoma in women arises from an occult breast cancer and has important therapeutic implications (see Adenocarcinoma of Unknown Primary Site, earlier in this chapter).

UNUSPECTED GESTATIONAL CHORIOCARCINOMA

In young women with poorly differentiated carcinoma or anaplastic neoplasms, particularly with lung nodules, oncologists must be aware of the possibility of metastatic gestational chorio carcinom. The history of recent pregnancy, spontaneous abortion, or missed menstrual periods should suggest this possibility. In this group of patients, serum HCG levels invariably are elevated. On occasion, biopsy specimens do not show the classic appearance of choriocarcinoma but simply that of metastatic carcinoma, usually poorly differentiated. Ultrasonography or CT scan of the abdomen may show an enlarged uterus, and a dilation and curettage may be indicated in such patients. Most affected patients are curable with single-agent methotrexate.

ISOLATED PLEURAL EFFUSION

Occasionally, an isolated pleural effusion containing carcinoma in women will represent metastatic disease from occult ovarian carcinoma or primary peritoneal carcinomatosis. Even when affected patients have no symptoms or signs and an abdominopelvic CT scan result is normal, the primary tumor may reside in the abdomen or pelvis. Such occult abdominal neoplasms may arise from the ovary or the peritoneal surface (see Adenocarcinoma of Unknown Primary Site, Peritoneal Carcinomatosis, earlier in this chapter) and most commonly cause a pleural effusion, earlier in this chapter. In the absence of clues of neoplasm in the abdomen, an elevated plasma CA-125 level suggests the possibility of this phenomenon. In the absence of clinical findings in the abdomen, laparoscopy or exploratory laparotomy might be diagnostic, but these procedures are not therapeutic in this setting. Some of these tumors are particularly responsive to chemotherapy with paclitaxel and a platinum agent.

An isolated pleural effusion can be a manifestation of a peripheral lung carcinoma (usually adenocarcinoma), a mesothelioma or, rarely, a lesion from other sites. Diagnosis may be difficult; at times the primary tumor is not apparent even after thorocostomy and chest tube drainage. Usually, cytology shows adenocarcinoma. Electron microscopy may reveal ultrastructural features diagnostic of mesothelioma. The therapy for such patients is difficult. In those with poor performance status or advanced age, a trial of tamoxifen or megestrol acetate is reasonable. In fit patients, a trial of chemotherapy (as discussed) for unknown primary carcinoma should be considered.

GERM CELL TUMORS WITH METASTASES OF OTHER HISTOLOGIES

On occasion, patients with germ cell tumors, particularly extragonadal primaries, may have a metastatic lesion that consists of only somatic tumor cells. This is particularly true for neuroendocrine or sarcomatous differentiation. Patients, therefore, may be diagnosed as having a neuroendocrine tumor or sarcoma. In these rare instances, a primary germ cell tumor (usually extragonadal) is present elsewhere and subsequently will be clinically apparent. Making the diagnosis initially is difficult. An elevated plasma AFP or HCG level is suggestive. The presence of a mediastinal, retroperitoneal, or testicular mass supports this possibility. Chromosomal analysis of tumor tissue may be diagnostic if a specific chromosome 12 abnormality is found. If affected patients have metastatic germ cell tumor with metastases of other histologies, the treatment of choice is cisplatin-based chemotherapy. Such patients appear to have a worse prognosis than do those with typical germ cell tumors, probably because the somatic cell tumors are less sensitive to chemotherapy.

MELANOMA AND “AMELANOTIC” MELANOMA

Approximately 10% to 15% of all melanomas presenting with an unknown primary site are believed to be “amelanotic.” We have viewed this diagnosis with considerable skepticism. At times, the only reason for the pathologic diagnosis is the histologic pattern’s similarity to melanoma, even though no pigment is demonstrated. In our experience, detailed pathologic and molecular study occasionally has revealed a group of other specific diagnoses, including lymphomas, neuroendocrine tumors, germ cell tumors, sarcomas, and poorly differentiated carcinoma (otherwise not specified).

Melanomas or premelanomas seen on electron micrographs have been considered diagnostic of melanoma but, on rare occasion, these structures are seen in other tumors. Some believe amelanotic melanomas do not always form premelanomas, opening the question as to whether they really are melanomas. Immunoperoxidase panels also are useful in suggesting the diagnosis of melanoma (see Table 48E-1). Of considerable interest is that in our original series of 220...
patients with poorly differentiated carcinoma, 9 later were thought possibly to harbor amelanotic melanoma on the basis of immunoperoxidase stains or electron microscopy (or both). Generally, these patients responded well to cisplatin-based chemotherapy, and several had long-term survival, an unexpected result for “melanoma.”

Certainly, the history of a resected, abraded, or frozen pigmented skin lesion would favor a metastatic melanoma in affected individuals. In addition, the rare primary visceral melanoma should be considered (eye, adrenal, bowel, etc.) as the source of the disease in questionable cases. Except in those patients who are discovered not to have melanoma but a specific tumor lineage requiring relatively specific therapy, the therapy for a questionable amelanotic melanoma is the same as that for carcinoma of unknown primary site presenting in a single site (local resection with or without radiation therapy). Such patients may have stage II melanoma and are potentially curable with resection. For patients with poorly differentiated tumor, including amelanotic melanoma, we also favor chemotherapy after local treatment.

**EVOLVING ROLE OF PROGNOSTIC FACTORS: THERAPEUTIC IMPLICATIONS**

The prognoses of those small groups of patients with squamous cell carcinoma and poorly differentiated neoplasm (otherwise not classified) are relatively good. Many patients with poorly differentiated carcinoma have chemotherapy-responsive tumors, and complete responses and long-term survival have been documented for a minority of patients. Conversely, in the past, the even larger group of patients with well-differentiated adenocarcinoma has had relatively resistant tumors, with virtually no complete responses to chemotherapy and no long-term survivals. In the last several years, patients with other “favorable” factors have been recognized. Such patients, many managed with specific therapies, have a better prognosis than do those in the group as a whole. We have stressed that both pathologic and clinical factors now can define several patients with a better prognosis (Table 48-10). Although other unrecognized favorable features undoubtedly exist, apparently the prognosis of patients who do not fit into a favorable subset have a particularly poor prognosis, regardless of their initial light-microscopical diagnosis (well-differentiated adenocarcinoma or poorly differentiated carcinoma). Patients in this group recently have been treated with taxane-based chemotherapy, and the treatment does appear to improve the response rate (with some complete responses) and survival of these groups of patients with historically very poor prognoses.

The degree of response seen in poorly differentiated neuroendocrine carcinoma also is noteworthy. Furthermore, the taxane-based chemotherapy appears as effective, with less toxicity, as cisplatin-based chemotherapy, even for those patients within favorable prognostic subsets who otherwise require chemotherapy. The one exception is patients with the extragonadal germ cell syndrome, for whom cisplatin-based therapy remains the treatment of choice. Further study of such patients with poor prognoses is necessary to continue to build on the progress seen with taxane-based combination chemotherapy.

**TABLE 48-10. Favorable Prognostic Factors in Cancer of Unknown Primary Site**

"SHRINKING POPULATION" OF PATIENTS WITH CANCER OF UNKNOWN PRIMARY SITE

As our ability to identify specific tumor lineages (lymphoma, germ cell tumors, sarcoma, melanoma, etc.) improves, the total population of patients with cancer of unknown primary site is becoming smaller. In the future, advances in molecular genetics may enable the diagnosis of most neoplasms with a specific genetic fingerprint. In addition, subsets of patients with more favorable prognostic features (neuroendocrine tumors, peripheral lymph node sites, retroperitoneum, etc.) now are apparent. Many affected patients are likely to be labeled or more specifically identified, at least into a treatable or responsive clinicopathologic subset. This evolution is likely to continue, as improved chemotherapy now is developing for patients with many advanced neoplasms (including non–small cell lung, ovarian, urothelial, head and neck, colorectal, esophageal, thymic, and pancreatic cancers). The remaining patients who do not fit a “responsive subset” will be the true unknown primary patients in the future. Paradoxically effective treatment for them will remain very difficult.

**CONCLUSION: FUTURE TRENDS**

The recognition of subsets of responsive tumors in patients within the large heterogeneous population of cancers of unknown primary site represents an improvement in the management of such patients. Approximately 40% of all patients fall within a defined subset with important treatment implications (see Fig. 48-1). Often, such patients with more responsive tumors can be defined with appropriate clinical and pathologic evaluation. A summary of several subsets and an outline of the evaluation necessary for their identification is given in Table 48-11. As the therapy for various neoplasms improves, the outcomes for more patients with cancers of unknown primary site also improves. Recently, taxane-based combination chemotherapy has been shown to be useful for many of these patients. A therapeutic trial is the only absolute method to determine whether a patient has a responsive tumor. Even for most responsive carcinomas, the tumor origin, biology, and precise lineage often continue to be an enigma. Consequently, groups of patients with insensitive tumors remain. Improved therapy for such patients probably will follow advances in the treatment of non–small cell lung cancer, pancreatic cancer, and the other gastrointestinal cancers, because most insensitive carcinomas probably arise from these occult primary sites.

**CHAPTER REFERENCES**

INTRODUCTION

Peritoneal carcinomatosis is defined as the spread and implantation of tumor cells throughout the peritoneal cavity, and it is considered an incurable disease state leading to significant patient suffering. However, oncologists should recognize peritoneal carcinomatosis not as a terminal event for the patient but as a regional disease entity that requires special attention and as a therapeutic challenge for consideration of novel management strategies. Although the primary histology dictates the clinical course, important concepts of diagnosis and treatment are common among all forms. Also, the palliative management of complications, such as bowel obstruction and ascites, warrants special consideration. The purpose of this chapter is to provide a general overview of peritoneal carcinomatosis as a regional stage of metastatic disease. This includes a discussion of the biology of tumor spread and implantation and techniques for early recognition of peritoneal tumors. General concepts regarding regional treatment approaches are reviewed.

PATHOPHYSIOLOGY

The peritoneum is a serous lining of mesothelial cells with a rich vascular and lymphatic capillary network. The flow of abdominal fluid provides clues to the development and pattern of peritoneal carcinomatosis. Gravity, diaphragmatic and intestinal movement, and diaphragmatic and omental absorption via lymphatics leads to a characteristic peritoneal fluid circulation. [Fig. 49-1] Lympathic endothelial cells have been shown to form channels extending from the peritoneal cavity directly into lymphatics, most notably in the diaphragm. Flessner et al. demonstrated that the absorption of \(^{125}\text{I}\)-labeled albumin from the peritoneal cavity concentrated in the diaphragm and abdominal wall peritoneum but not in the visceral peritoneum. The most dependent recess is the pouch between the rectum and uterus or bladder. Hagiwara et al. demonstrated a site-specific correlation between the number of milky spots at specific peritoneal locations and the number of infiltrating tumor cells. Milky spots represent an immunologic filter similar to the lymphatic drainage of solid organs and seem to represent sites where peritoneal fluid drains into lymphatic channels. If fluid is actively absorbed into these spots, it is easy to hypothesize that free clumps of tumor cells could become trapped at these spots and develop into tumors. Milky-spot tissues are found in the hepatoduodenal ligament, base of mesentery, appendiceal epiploicae, gonadal fat (corresponding to the pouch of Douglas), and the greater omentum. The omentum contains the highest concentration of milky spots. The constant flux of fluid, the sites of absorption and filtration, and gravity all play a role in the pattern of peritoneal tumors. It has been proposed that more aggressive, invasive tumors have a “stickier” phenotype and are more likely to follow the experimental observations of peritoneal spread but have a more random distribution close to the initial site of peritoneal contamination. In addition, more aggressive, invasive tumors are better at forming tumors on moving surfaces, such as the serosal surface of the small bowel.

![FIGURE 49-1. Circulation of fluid in the peritoneal cavity. Flow is generated by diaphragmatic movement, absorption of material from the diaphragmatic lymphatic channel, and gravity. 1. Lesser sac; 2. foramen of Winslow; 3. Morison's pouch; 4. right triangular ligament; 5. right subphrenic space; 6. falciform ligament; 7. left subphrenic space; 8. phrenocolic ligament; 9. bare area of the descending colon; 10. root of the small bowel mesentery; 11. bare area of ascending colon; 12. duodenum; 13. esophagus; 14. root of the transverse mesocolon; 15. bare area of the rectum; 16. bladder. (From ref. 2, with permission.)](image)

Tumor cells reach the peritoneal cavity by direct invasion of aggressive gastrointestinal (GI) tumors through the serosal lining of the organ or through a pressure-burst effect of less invasive tumors that push through the serosal surface without tissue invasion. This is characteristic of appendiceal and ovarian tumors, in which even a benign tumor can grow large enough to break through the wall of the organ and contaminate the peritoneal cavity with neoplastic cells. It is possible for hematogenous metastases from extraperitoneal tumors to invade secondarily or burst into the abdominal cavity, leading to peritoneal carcinomatosis. A final source for peritoneal contamination of tumor cells is iatrogenic spillage of neoplastic cells. A classic example is during cholecystectomy in the setting of unrecognized gallbladder cancer, in which the subserosal plane of tumor cell invasion is dissected during the resection, spilling tumor cells throughout the region. It is also possible to contaminate the peritoneal cavity during a needle biopsy for diagnosis.

Seeding of the peritoneal cavity with tumor cells does not necessarily lead to implantation, proliferation, and formation of carcinomatosis. Different tumors and heterogeneous cell populations within a single tumor will lead to different efficiencies with regard to tumor formation after peritoneal seeding. The requirements for peritoneal tumor seeding are different from the requirements for hematogenous metastases. The tumor cells must make their way into the cavity, then stick to the peritoneal surface via adhesion molecules. They must avoid immunologic destruction and, once implanted, be able to stimulate angiogenesis for continued growth. In general, this can be accomplished with a less aggressive tumor cell than that required for hematogenous spread. Also, it may be possible for tumors to grow to a limited extent within the peritoneal cavity without implantation and vascularization but relying on nutrients within peritoneal exudate for survival.

DIAGNOSIS

Although the follow-up and early detection of metastatic cancers in general is in debate in the absence of effective therapy, the early diagnosis of peritoneal spread...
of cancer would be preferable in the setting of experimental protocols for regional therapy. In other cases, the early detection of peritoneal spread might alter the management of the primary tumor or avoid surgical exploration for hepatic or pulmonary metastases. However, peritoneal spread is diagnosed in most patients after surgical exploration for bowel complications or after clinical ascites develops. At this stage in the setting of invasive tumors, a regional therapy approach is probably beyond any chance of success.

Standard imaging tests, including ultrasonography and helical computed tomography (CT) scans, are notably insensitive for the detection of peritoneal tumor. The sensitivity of CT scan for peritoneal nodules measuring smaller than 1 cm is on the order of 15% to 30%. Ultrasonography is similarly insensitive. It is important to consider findings other than solid-tumor detection that may suggest the presence of peritoneal carcinomatosis. These include the presence of ascites, fixation of bowel loops, thickening of mesentery, and omental maling.

Advances in magnetic resonance imaging (MRI) have been demonstrated to improve significantly detection of peritoneal tumor nodules. Low et al. have demonstrated that abdominal MRI is superior to helical CT for the detection of peritoneal and bowel wall abnormalities. It may be that MRI of the peritoneal cavity is improved with dilute oral barium contrast materials. In general, CT scans are easier to interpret for the general oncologist and are cheaper to obtain and, therefore, are still more widely used than MRI. For patients on clinical protocol, however, improved imaging should be a goal for the oncologist, to aid in follow-up of peritoneal disease. Nelson et al. studied intraperitoneal infusion of contrast material before CT scanning, but this did not significantly improve the sensitivity for detection of peritoneal metastases.

Positron emission tomography (PET) imaging for metastatic GI tumors is under investigation at numerous institutions and may improve the sensitivity for detecting small nodules. In general, PET has not been shown to be sensitive for lesions measuring smaller than 1 cm in the abdominal cavity. Extrahepatic peritoneal nodules of smaller than 1 cm were not detected by [18F]fluorodeoxyglucose (FDG) PET scanning as a preoperative screen for patients undergoing hepatic metastasectomy for colorectal cancer.

Another mechanism for screening for peritoneal spread of tumor involves peritoneal lavage cytology. This can be performed as a percutaneous closed technique or at the time of laparoscopy or laparotomy for resection of primary disease. The sensitivity of this test depends on the ability to lavage completely all regions of the peritoneal cavity and the ability to detect cancer cells accurately. Sensitivity may be improved using polymerase chain reaction techniques or immunohistochemistry. The sensitivity also depends on the number of cells being shed into the peritoneal cavity by the tumor. Even in cases with advanced, grossly evident peritoneal metastases, the ascites can be negative for tumor cells. At study by Fujiwara et al. compared closed abdominal lavage cytology to second-look laparotomy. In this study, 14 patients who had positive cytology results also had positive disease on second-look laparotomy. Three patients with negative cytology had positive disease on second-look laparotomy. The other 23 patients had negative cytology and negative second-look laparotomy. This illustrates the fact that cytology can be helpful in predicting the presence of carcinomatosis, but it is not as sensitive as direct inspection and palpation of the peritoneal surfaces.

Much has been studied regarding the prognostic utility of lavage cytology for patients at high risk of peritoneal spread, as in the case of gastric cancer, colon cancer, and pancreatic cancer. Positive cytology correlates with full-thickness invasion through the bowel wall, as would be expected. Positive cytology also seems to correlate with a poor prognosis for peritoneal recurrence. It is not clear, however, whether cytology has any added prognostic value over the stage of the primary tumor. It should be noted also that cells shed into the peritoneal cavity may not be viable or may not be able to establish new tumor sites; therefore, the presence of tumor cells may not predict the development of carcinomatosis.

By far the most sensitive modality for detecting the spread of tumor is direct visualization of the peritoneal surfaces along with palpation of the abdominal contents. Visualization of the peritoneal surfaces can be accomplished with a minimally invasive approach. Laparoscopy is now used routinely in most cancer centers as a staging modality for patients with resectable pancreatic and gastric cancers. Its greatest utility is in diagnosing small peritoneal metastases and small surface liver metastases that are not detected on imaging tests. The minimally invasive laparoscopy for cytology as well. Laparoscopy should be considered for the detection of peritoneal surface tumors in patients in whom therapy would be altered or investigational therapy considered for tumor spread in this fashion. This includes patients who are considered for preoperative neoadjuvant regional therapy before surgical resection for resectable pancreatic and gastric cancer. Laparoscopy may also be of utility in patients with carcinomatosis who should be followed up for response to therapy to determine whether to change therapies or continue the current treatment strategy. Repeat laparoscopy for following up disease status at intervals during therapy is feasible. The adhesions after multiple tumor debulkings and laparoscopies may ultimately limit the sensitivity of detection and increase the risk of laparoscopy. Open abdominal exploration and palpation of the peritoneal surfaces is extremely sensitive for even small 1- to 2-mm peritoneal surface nodules. Palpation of the areas at high risk should be performed during any cancer surgery for intraperitoneal malignancies. This includes the greater omentum, the deepest recess of the pelvic peritoneum, the base of the small bowel mesentery and transverse mesocolon, the falci form ligament, and the diaphragm.

HISTOLOGIC SUBTYPES

PSEUDOMYXOMA PERITONEI

Classically, the diagnosis of Pseudomyxoma peritonei includes any low-grade or benign tumor within the abdominal cavity that produces copious amounts of mucinous ascites. This first coined by Fraenkel [30] in 1884 by Werth. Pseudomyxoma peritonei is quite rare in clinical practice, and they have classified cases of Pseudomyxoma peritonei.

Clinical evidence of malignancy includes the presence of lymph node metastases and gross evidence of an invasive phenotype. Histologically, malignant tumors will have moderate to abundant cellularity, show evidence of invasion, and demonstrate cellular atypia and nuclear pleomorphism consistent with malignancy. Benign tumors have scant cellularity with no evidence of invasion into tissues and no cellular atypia. In difficult cases, it is helpful to examine the tumor carefully to determine whether the primary tumor represents invasion of tumor cells through the wall of the organ or a benign process that has ruptured the wall without invasion.

The site of origin of cells producing mucinous ascites often is difficult to define. This is especially the case when, in women, both the appendix and the ovaries are obliterated by tumor. Although the ovary can be a site for mucinous borderline tumors of low malignant potential or mucinous carcinomas, these are almost never associated with diffuse copious mucinous ascites. Therefore, all cases of P pseudomyxoma peritonei with benign-appearing mucinous epithelial cells emanate from an appendiceal mucinous adenoma. These tumors often involve the ovaries at early stages but should not be confused with a primary ovarian cancer. Ruptured ovarian follicles may allow for a rich soil and sticky surface on which benign tumor cells can stick and proliferate. In surgical debulking procedures, appendectomy and bilateral oophorectomy should be performed.

Ronen et al. have extensive experience in P pseudomyxoma peritonei, and they have classified cases of P pseudomyxoma peritonei into three pathologically and prognostically distinct groups: (1) disseminated peritoneal adenomucinosis; (2) peritoneal mucinous carcinomatosis; and (3) peritoneal mucinous carcinomatosis with intermediate or discordant features.

They have shown distinct variation in survival and prognosis in patients with disseminated peritoneal adenomucinosis as compared to those with carcinomatosis or discordant features. This work verifies the importance of differentiating a malignant from a benign diagnosis. In their study, the median survival for patients with disseminated peritoneal adenomucinosis had not been reached with a median follow-up of approximately 6 years, whereas the median survival for patients with a malignant tumor producing mucinous ascites was approximately 16 months.
Despite this dramatic difference in prognosis, most studies include all forms of P peritonei together, and this confuses outcome determinants for therapy in this condition. It would be best not to use the term P peritonei without further classification into mucinous adenocarcinoma or benign mucinous tumors. The treatment approach should be different for patients with benign mucin-producing tumors as compared to those with mucinous carcinomatosis. Patients with benign tumors should be treated with aggressive surgical debulking to limit the symptoms of compression and abdominal distention caused by extensive mucinous ascites within the abdominal cavity. It has been reported that long-term disease-free survival can be accomplished with repeated tumor debulking. The extent of required surgery and the indication for chemotherapy are controversial. The complication rate of the procedure should be seriously considered in recommending treatment for a condition with such an indolent course. It may be that aggressive regional chemotherapy approaches should not be offered until their efficacy has been better defined in carcinomas. In the case of low-grade mucinous carcinomatosis, the uniformly poor prognosis encourages innovative and aggressive approaches. This includes intensive regional chemotherapy in combination with cytoreduction (as discussed in the Intrapertoneal Chemotherapy section).

Because of inconsistencies in pathologic diagnosis as well as different philosophies with regard to aggressiveness of surgery, it is difficult to define the prognosis and the best treatment strategies. The largest series of mucinous appendiceal tumors with peritoneal spread has been reported by Sugarbaker and Chang. A total of 385 patients were reviewed. Patients with benign adenomucinosis had a 5-year survival of 80%, as compared to those with low-grade mucinous carcinomas, who had a 5-year survival of approximately 25%. The 5-year survival for those patients undergoing a complete resection was approximately 80%, as compared to those undergoing an incomplete resection, in which it was approximately 25%. It is probably not a coincidence that characteristics of surgical debulking and pathology lead to similar survival rates: Complete resection is more likely in patients with benign mucinous neoplasms as compared to those with more infiltrative mucinous carcinomas. As discussed in the Surgery section, the fact that complete cytoreduction has an improved prognosis over incomplete cytoreduction does nothing to support aggressive surgery for this disease. Of note, the mortality rate for extensive cytoreduction and early postoperative intraperitoneal chemotherapy in the Sugarbaker and Chang series is 2%, with major morbidity of 27%.

Gough et al. from the Mayo Clinic reviewed 56 patients with the malignant form of P peritonei. Only 20% of their patients had complete cytoreduction, and they reported a 10-year survival rate of 32%. Smith et al. from the Memorial Sloan-Kettering Cancer Center reviewed 17 patients undergoing surgical debulking for P peritonei without histologic classification. They reported a 10-year survival rate of 60%.

In summary, the entity of P peritonei is becoming better defined. Classification of the benign and malignant subtypes is essential and should be used to define and compare therapeutic approaches for this disease. The use of aggressive surgery and regional chemotherapy approaches remains experimental and requires investigation in a multinstitutional randomized format to make standard treatment recommendations.

**PERITONEAL MESOTHELIOMA**

Peritoneal mesothelioma is a primary tumor of the mesothelial lining of the peritoneum. It is a rare tumor of approximately two cases per million population per year, but the incidence appears to be increasing. Tumors can be classified into benign lesions, borderline malignant lesions, and malignant tumors. Benign lesions include adenomatoid mesothelioma and localized fibrous mesothelioma, which are rare tumors treated by surgical excision alone, with a good prognosis. Borderline tumors include multicystic peritoneal mesothelioma and well-differentiated papillary mesothelioma of the peritoneum. Both of these tumors carry an indolent course, which can be treated with surgical debulking. These borderline tumors are characterized by local recurrences that can ultimately lead to complications within the abdominal cavity. It is not clear whether the tumors themselves will ultimately lead to the death of the patient. In a review of 22 patients, none died directly because of their disease, but several died as a result of complications of therapy. One patient who died 29 years after he received a diagnosis of well-differentiated papillary mesothelioma had residual disease but died of unrelated causes. Microscopically, well-differentiated papillary mesothelioma consists of mesothelial cells in a well-developed papillary pattern with bland mesothelial appearance and cuboidal epithelium. It can be difficult to differentiate histologically the well-differentiated papillary mesothelioma from diffuse malignant mesothelioma, so multiple sections of tumor should be examined.

The malignant peritoneal mesotheliomas are less common than pleural mesotheliomas and have been associated with asbestos exposure and abdominal therapeutic radiation. The association of malignant peritoneal mesothelioma and asbestos exposure has been reported to be as high as 83%; however, in our experience, it is much lower. These tumors often present with nonspecific abdominal pain and increasing abdominal girth secondary either to tumor mass or to the development of ascites. The diagnosis can be suggested by cytologic examination of ascites and verified by percutaneous biopsy of the omentum. These tumors tend to present with diffuse involvement of the peritoneal cavity, including an omental “cake” and diaphragmatic and pelvic tumor deposits (Fig. 49-3).
The epithelial type of malignant peritoneal mesothelioma is the most common type and has the best prognosis. The sarcomatoid and mixed (elements of both epithelial and sarcomatoid) forms are more aggressive, leading to fixed abdominal contents and an inability to successfully debulk these tumors surgically. Even among the primary epithelial form, there may be a spectrum of phenotypic aggressiveness and a variable clinical course. Some patients primarily experience ascites with no significant invasiveness to the tumors themselves, allowing for easy debulking and management of ascites. Other patients have more aggressive forms that can invade through the diaphragm to involve the chest, through the wall of the intestine (leading to complications of intestinal obstruction and bleeding), and into lymph nodes. The more invasive forms are difficult to debulk and have a worse prognosis. The sarcomatoid and mixed forms are rapidly growing tumors leading to intraabdominal complications and death within a year.  

Death from malignant mesothelioma is usually caused by complications from intraperitoneal progression. Hematogenous metastases are extremely rare, and secondary involvement of the chest occurs at a late stage and is usually not a life-threatening feature of this disease. Lymphatic metastases can be identified within the abdominal cavity with the more aggressive forms of epithelial mesothelioma and the sarcomatoid mesothelioma. 52 Patients with peritoneal mesothelioma in general have a better prognosis than those with pleural mesothelioma. CA-125 levels may be increased in patients with diffuse mesothelioma and can be followed up for response to therapy.

The natural history of diffuse mesothelioma is difficult to define. Reported series are small, owing to the rarity of this disease. Original reports suggested that the median survival was less than 1 year from the time of diagnosis. 52 However, multiple varied treatment approaches, usually combining surgical debulking with chemotherapy or total abdominal radiation (or both), may result in long-term survival. 52 Langer et al. 52 demonstrated a median survival of 22 months using surgical debulking and intraperitoneal chemotherapy with cisplatin and etoposide. No control, untreated arm is included in these trials to prove that the natural history is not sometimes indolent. It is also difficult to know whether adjuvant therapies improve the results of surgical debulking alone, as no series exists of aggressive surgical debulking alone for this disease. It is suggested, however, that the package of treatment strategies that have been used can successfully alter the natural history of this disease. Lederman et al. 43 reported that six of ten patients remain free of disease up to 6 years after diagnosis after treatment with surgical debulking, combination chemotherapy, and whole abdomen radiation. Whole abdomen radiation is not well tolerated and has not gained widespread acceptance. Other investigators have used intraperitoneal chemotherapy alone (cisplatin or cisplatin plus mitomycin C) with modest clinical responses and improvement in ascites but have failed to demonstrate a survival benefit. Markman and Helsen 53 reported 47% palliation of ascites and a median survival of 9 months in 19 patients who were treated with intraperitoneal cisplatin and mitomycin C.

We have explored the combination of extensive surgical debulking followed by intraoperative, intraperitoneal chemotherapy in the form of continuous hyperthermic peritoneal perfusion with cisplatin combined with early postoperative intraperitoneal dwell chemotherapy with 5-fluorouracil (5-FU) and paclitaxel. 52 Patients who presented with incapacitating ascites have complete resolution of their ascites and long-term disease-free survival. The median time to progression after treatment in 18 patients was approximately 27 months, with a median overall survival not being reached after a median potential follow-up of 19 months (Fig. 49-4). Ninety percent of patients had complete resolution of their ascites after therapy. Three patients were treated after recurrence of ascites approximately 2 years after their primary treatment, and all had resolution of their ascites again after retreatment. Other investigators have demonstrated similar success using the hyperthermic peritoneal treatment with mitomycin C for mesothelioma.52

**FIGURE 49-4.** Kaplan-Meier survival curve for 18 patients treated with continuous hyperthermic peritoneal perfusion with cisplatin at the National Cancer Institute for peritoneal mesothelioma. *The progressive free survival analysis includes three patients who have been treated twice. (Adapted from ref. 50.)*

**PRIMARY PERITONEAL CARCINOMA**

Primary peritoneal carcinoma has been called by many names, including papillary carcinoma of the peritoneum, extraovarian papillary serous carcinoma, serous surface papillary carcinoma, and psammocarcinoma. 52 It is not clear. Both the germinal epithelium of the ovary and the mesothelium of the peritoneum arise from the same embryologic origin; therefore, the peritoneum may retain the multipotentiality of the Müllerian system, allowing for the development of a primary carcinoma. Hereditary predisposition may play a role in this disease, as patients have an increased risk with the BRCA1 mutation. 52

Primary peritoneal carcinoma diffusely involves the peritoneal surface while sparing or only minimally involving the ovaries. It is histologically indistinguishable from primary epithelial ovarian carcinoma, and its diagnosis requires differentiation from mesothelioma and ovarian cancer. Immunohistochemistry differentiates this from peritoneal mesothelioma. 52 Primary ovarian cancer is ruled out by the following criteria: (1) Both ovaries must be normal in size; (2) the extraovarian involvement must be greater than the involvement on the surface of the ovary; (3) the ovarian component must be less than 5 × 5 mm within the ovary or confined to the ovarian surface; and (4) the cytologic characteristics must be of the serous type. This is a tumor described almost exclusively in women. Patients are older than those with epithelial ovarian cancers. The presentation of primary peritoneal carcinoma is abdominal distention and diffuse nonspecific abdominal pain secondary to ascites.

In general, these tumors are treated as ovarian cancers with cytoreduction and adjuvant therapy with platinum-based chemotherapeutic regimens. The median survival for women with primary peritoneal carcinoma has been reported to range from 12 to 25 months. This is similar or slightly worse than for epithelial ovarian cancer. Carboplatin or cisplatin in combination with paclitaxel leads to a high response rate and a reported median survival of 40 months. 52
This page contains information on the treatment of peritoneal carcinomatosis, with a focus on ovarian cancer. It discusses surgical debulking, regional therapy, and the role of chemotherapy in improving patient outcomes. The text also highlights the importance of aggressive surgical resection and the challenges in achieving complete cytoreduction in certain areas, such as the hepatoduodenal ligament and pelvis.

Key points include:
- Surgical debulking for peritoneal carcinomatosis is recommended for management of benign and low-grade malignant processes, such as P. peritonei, mesothelioma, and ovarian cancer.
- Complete resection of the greater omentum, falciform ligament, and peritoneum overlying the diaphragm; the base of the small bowel and transverse colon mesentery; and the pelvis is important.
- The goal of cytoreduction is to leave behind only tumors smaller than 5.0 mm in diameter so as to allow for topical chemotherapy to penetrate and treat all cells within the tumor.
- The best scenario is complete cytoreduction, wherein only microscopic disease is left behind.

The text also mentions other forms of peritoneal carcinomatosis, such as the aggressive GI cancers, and the importance of prophylactic regional chemotherapy in selected circumstances. It highlights the need for continued research and development of effective treatment strategies to improve patient outcomes.
concentration of cisplatin when delivered into the peritoneal cavity as compared to intravenous delivery. High concentrations of chemotherapy typically applied to tumor cells should be more effective than what can be achieved with intravascular delivery.

The pharmacokinetic rationale for intraperitoneal chemotherapy has been recognized for many years, and intraperitoneal chemotherapy trials blossomed in the early 1980s. Larger, water-soluble and ionized compounds exit the peritoneal compartment more slowly than smaller lipid-soluble and un-ionized molecules. Pharmacokinetic models of peritoneal delivery have been developed. Patients with peritoneal carcinomatosis may have decreased clearance of all drugs from the peritoneal cavity due to obstruction of lymphatic channels. In addition, the majority of compounds delivered into the peritoneal cavity are cleared by the portal circulation and, therefore, may be metabolized by the liver. Compounds that have a delayed clearance from the peritoneal cavity may allow for prolonged exposure of slowly dividing cells to the chemotherapy agent. If the agent requires mitosis for efficacy, this improves the chance of it being effective, compared to the relatively brief exposure provided by systemic delivery. Finally, by confining the treatment to direct absorption, systemic binding agents can be delivered and bind and inactivate systemic ally absorbed drug to minimize systemic toxicity.

The main pitfalls for intraperitoneal chemotherapy include the difficulty in obtaining even distribution throughout the peritoneal cavity and the limited absorption of agents into tumor nodules. Prior abdominal surgery leads to numerous loculations within the peritoneal cavity and prevents even distribution of intraperitoneal agents. Prolonged intraperitoneal dwell chemotherapy can be hampered by scarring around the delivery catheter, allowing for escape of tumor cells within protected areas of the abdomen. Large treatment volumes (>2 liters) have been shown to improve distribution. Intraoperative and early postoperative intraperitoneal chemotherapy may allow for treatment of all peritoneal surfaces before dense, loculated scarred areas develop, but this may increase the morbidity associated with the procedure. A randomized trial of adjuvant intraperitoneal chemotherapy with carbon-absorbed mitomycin in gastric cancer was prematurely terminated due to a statistically significant increase in major postoperative morbidity in the patients receiving chemotherapy.

The ideal setting for ensuring complete distribution of chemotherapy to the peritoneal cavity is intraoperative treatment at the time of surgical debulking. Recirculating circuits and physical manipulation of abdominal contents during therapy may enhance distribution. Studies suggest, and logic concludes, that the best means for ensuring complete distribution during intraperitoneal therapy is to manipulate the contents of the peritoneal cavity by hand during treatment. This can be accomplished by a variety of techniques with the patient under general anesthesia, allowing a hand to be inserted into the abdominal cavity without spilling the chemotherapy solution.

Tumor penetration of drugs delivered into the peritoneal cavity has been studied. Los et al. demonstrated that the tumor concentration of cisplatin was significantly elevated after intraperitoneal delivery, as compared to systemic delivery, at a depth of 1.0 mm but not at 1.5 mm. Increasing pressure within the peritoneal cavity may improve penetration, and vasoactive agents that decrease capillary uptake of drugs in the tumor may allow for deeper penetration of drugs. Larger molecules may penetrate more deeply into some tissues than low-molecular-weight agents because of decreased capillary permeability and vascular washout of the compounds. On the other hand, if increased interstitial pressure occurs within tumors, as has been described, this may be an advantage to low-molecular-weight agents. Although it is easy to determine clearance from the peritoneal cavity and easy to assume that decreased clearance leads to increased exposure of intraperitoneal tumor to chemotherapy, it is not clear how decreased clearance correlates with absorption into tumor tissue. Decreased clearance may correlate with decreased tumor absorption, which may be counterproductive. On the other hand, for the treatment of microscopic cells that have not developed into tumor nodules, prolonged exposure in the peritoneal cavity should be advantageous.

A variety of agents have been delivered into the peritoneal cavity, and these are summarized in Table 49-2. The mean peritoneal cavity peak concentrations over peak plasma concentrations range from 20 in the case of cisplatin to more than 600 for cytarabine and mitoxantrone and more than 1000 for paclitaxel. Regional toxicity has not been a major problem with most of these agents. Even mitomycin C, which is considered a very caustic agent to tissues when infiltrated, has been delivered into the peritoneal cavity safely. The most common agents that have been used in intraperitoneal trials include cisplatin, mitomycin C, 5-FU, and, recently, paclitaxel. Gemcitabine currently is being studied with intraperitoneal delivery.

In general, trials of intraperitoneal chemotherapy have been poorly controlled, with numerous treatment regimens for different histologies of varying prognosis at different stages of peritoneal involvement, making interpretation of results difficult. In addition, the combination of aggressive surgical debulking and intraoperative or early postoperative chemotherapy make the interpretation of morbidity difficult. Sugabaker has used a complex scheme for assessing the extent of peritoneal disease and completeness of resection (Fig. 49-5). Adoption of this or similar standardized criteria should help in the standardization and interpretation of clinical trials. Histologic grade and clinical invasive phenotyping should also improve trial interpretation.

![FIGURE 49-5. Proposed standardized scheme for assessing extensive peritoneal disease. The peritoneal cancer index (PCI) represents the sum of the lesion size scores for the different regions. (Reproduced from ref. 85, with permission.)](image)

The utility and advantages of intraperitoneal chemotherapy have been demonstrated in randomized trials. Sugabaker et al. performed a small randomized trial comparing postoperative adjuvant 5-FU delivered intravenously (n = 30) to intraperitoneal delivery (n = 36) for patients with high-risk primary colorectal cancers. Although there was no difference in survival between the groups, the patients with intraperitoneal delivery had a significantly lower incidence of intraperitoneal recurrences and less hematologic and hepatic toxicity. More recently, the combined Southwest Oncology Group, Gynecologic Oncology Group, and Eastern Cooperative Oncology Group Intergroup Study examined intravenous versus intraperitoneal cisplatin with intravenous cyclophosphamide for stage III ovarian cancer. This large, randomized, prospective, phase III trial demonstrated a significant survival advantage for patients receiving intraperitoneal cisplatin (49 vs. 41 months). In addition, this group experienced significantly less clinical hearing loss, neutropenia, and neuromuscular toxicity. Yu et al. examined early postoperative

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<th>TABLE 49-2. Pharmacokinetic Advantages Associated with Intraperitoneal Antineoplastic Drug Delivery</th>
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intrapertitoneal chemotherapy as compared to no treatment after resection of gastric cancer (n = 248). This group demonstrated no overall survival benefit, but subset analysis suggested improved survival for stage III disease, as might be expected (49% 5-year survival vs. 18%). Follow-up trials should be focused on stage III disease. These results should stimulate continued interest in the peritoneal delivery of chemotherapy for peritoneal carcinomatosis and emphasize the need for randomized trials for GI malignancies to define better the advantages of intraperitoneal delivery.

One procedure that is becoming increasingly popular across the world for the treatment of peritoneal carcinomatosis is the intraoperative combination of hyperthermia and chemotherapy delivered as a recirculating perfusion. Temperatures of 41°C to 42°C are maintained in the tissues over a period of 90 minutes by recirculating fluid that passes through a roller pump and heat exchanger delivering high concentrations of chemotherapy to the peritoneal cavity (Fig. 49-6). The most common drugs used in this fashion have been cisplatin and mitomycin C. The theoretic advantages of this technique include the improved mixing and surface exposure associated with the increased pressure and high flow rates of the perfusate along with intraoperative manipulation of the abdominal contents. The hyperthermia has been demonstrated to have selective cytotoxicity against cancer cells while the normal cells recover. In addition, hyperthermia has been shown to enhance chemotherapy penetration into tumors, improve intraperitoneal pharmacokinetics, and work synergistically with chemotherapy to kill cancer cells.

PALLIATION

Major complications of peritoneal carcinomatosis include partial and complete obstruction of the GI tract, leading to crampy abdominal pain, nausea, and vomiting. The other significant complication is the development of ascites, which can become incapacitating and the direct cause of death. The palliative management of these entities by the oncologist is required. Patients with crampy, abdominal pain suggesting partial small bowel obstruction should be worked up with a CT scan and upper GI series. A determination should be made about whether a simple bypass or resection of an obstructed region can be performed, in which case the appropriate operation is undertaken. In the setting of diffuse disease that cannot be bypassed, a percutaneous endoscopic gastrostomy tube should be inserted for palliation. This is a simple procedure that can be performed with minimal complications, yet provides lasting palliation. Signs of peritonitis or systemic sepsis should raise concerns of a closed loop obstruction that may require emergent surgical resection. It is often helpful to ensure patency of the rectum in patients being explored for bypass of a small bowel obstruction in the setting of peritoneal carcinomatosis. A shelf of tumor in the pelvic peritoneal recess may lead to obstruction, placing a proximal bowel anastomosis at risk. Rarely, patients may require a colostomy or ileostomy for palliation. The nutritional management of patients who require a bypass of a small bowel obstruction in the setting of peritoneal carcinomatosis is controversial. In general, it is accepted that total parenteral nutrition does nothing to improve the quality of life or prolong survival in patients having peritoneal carcinomatosis secondary to aggressive GI malignancies. However, in the case of low-grade malignancies, these patients can survive for a very long time after palliative gastrostomy; therefore, parenteral nutrition should be considered. We have had the experience of managing a patient on total parenteral nutrition for more than a year with a good quality of life after palliative gastrostomy in the setting of a


SECTION 50.1
AIDS-Related Malignancies

ROBERT YARCHOAN
RICHARD F. LITTLE

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INTRODUCTION

Individuals with human immunodeficiency virus (HIV) infection are at substantially increased risk of developing a number of neoplasms (Table 50.1-1). Three malignant conditions are now considered as defining acquired immunodeficiency syndrome (AIDS) when they occur in HIV-infected individuals: Kaposi’s sarcoma (KS), certain aggressive non-Hodgkin’s lymphomas (NHLs), and invasive cervical cancer. The risk of KS among gay and bisexual men with AIDS is greater than 100,000-fold that of the background population. Also, NHLs occur overall with approximately 60-fold greater frequency than expected based on rates of NHL in HIV-negative populations. There are conflicting data regarding the excess frequency of cervical cancer in HIV-infected women, but cervical intraepithelial neoplasia appears to be more difficult to control and invasive cancer appears to be more aggressive in HIV infection. In addition, a number of other cancers that do not confer a diagnosis of AIDS occur with increased incidence among HIV-infected persons. In one study, a probabilistic matching algorithm comparing over 1 million people with AIDS, cancer, or both, the occurrence of several non–AIDS-defining cancers was found to be significantly increased in HIV infection (see Table 50.1-1); these include angiosarcoma (36.7-fold), Hodgkin’s disease (7.5-fold), multiple myeloma (4.5-fold), brain cancer (3.5-fold), and seminoma (2.9-fold). Age-, sex-, and period-adjusted standardized incidence ratios (SIR) in New South Wales, Australia, identified an increased incidence of Hodgkin’s disease (SIR 18.3), multiple myeloma (SIR 12.1), leukemia (SIR 5.76), lip cancer (SIR 9.24), and lung cancer (SIR 3.80). Thus, oncologists can expect to see a variety of malignant conditions with increased frequency in HIV-infected patients. One pattern that is emerging is that many tumors highly associated with HIV (such as KS or primary central nervous system lymphoma (PCNSL)) appear to be caused by oncogenic viruses. It will be important to understand the mechanisms by which HIV and these viruses interact, and this understanding should in turn lead to an increased appreciation for the pathogenesis of other tumors. On the other hand, certain tumor associations with HIV may have arisen because cohorts at risk for HIV may also have risk factors for other tumors (e.g., from increased exposure to other oncogenic viruses, increased cigarette smoking, and so forth) rather than because of HIV itself or HIV-induced alterations in immune function. Also, it should be pointed out that the relative risk of a large number of tumors is not increased in HIV disease, and this must be considered in evaluating the potential role of immunosurveillance in the pathogenesis of such tumors.

This chapter focuses primarily on those tumors that are considered as AIDS defining, but in general, certain principles common to the treatment of HIV-infected patients with cancer apply to various malignant conditions. The treatment of such patients can be quite complex and requires expertise in both the tumor and HIV infection. The goals of cancer therapy (i.e., curative versus palliative), and the relationship of these goals to the status of the underlying HIV infection should be evaluated in each case.

**TABLE 50.1-1.** Post–Acquired Immunodeficiency Syndrome Relative Risks of Various Malignant Conditions in Patients with Acquired Immunodeficiency Syndrome

<table>
<thead>
<tr>
<th>Malignant Condition</th>
<th>Relative Risk</th>
</tr>
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<tbody>
<tr>
<td>KS</td>
<td>68.9</td>
</tr>
<tr>
<td>NHL</td>
<td>60.2</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>48.3</td>
</tr>
<tr>
<td>Angiosarcoma</td>
<td>36.7</td>
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<tr>
<td>Hodgkin’s disease</td>
<td>7.5</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>4.5</td>
</tr>
<tr>
<td>Brain cancer</td>
<td>3.5</td>
</tr>
<tr>
<td>Seminoma</td>
<td>2.9</td>
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</tbody>
</table>

In addition, a number of other cancers that do not confer a diagnosis of AIDS occur with increased incidence among HIV-infected persons. One study, a probabilistic matching algorithm comparing over 1 million people with AIDS, cancer, or both, the occurrence of several non–AIDS-defining cancers was found to be significantly increased in HIV infection (see Table 50.1-1); these include angiosarcoma (36.7-fold), Hodgkin’s disease (7.5-fold), multiple myeloma (4.5-fold), brain cancer (3.5-fold), and seminoma (2.9-fold). Age-, sex-, and period-adjusted standardized incidence ratios (SIR) in New South Wales, Australia, identified an increased incidence of Hodgkin’s disease (SIR 18.3), multiple myeloma (SIR 12.1), leukemia (SIR 5.76), lip cancer (SIR 9.24), and lung cancer (SIR 3.80). Thus, oncologists can expect to see a variety of malignant conditions with increased frequency in HIV-infected patients. One pattern that is emerging is that many tumors highly associated with HIV (such as KS or primary central nervous system lymphoma (PCNSL)) appear to be caused by oncogenic viruses. It will be important to understand the mechanisms by which HIV and these viruses interact, and this understanding should in turn lead to an increased appreciation for the pathogenesis of other tumors. On the other hand, certain tumor associations with HIV may have arisen because cohorts at risk for HIV may also have risk factors for other tumors (e.g., from increased exposure to other oncogenic viruses, increased cigarette smoking, and so forth) rather than because of HIV itself or HIV-induced alterations in immune function. Also, it should be pointed out that the relative risk of a large number of tumors is not increased in HIV disease, and this must be considered in evaluating the potential role of immunosurveillance in the pathogenesis of such tumors.

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**KAPOSI’S SARCOMA**

A cluster of cases of KS among young homosexual men in 1982 was one of the first epidemiologic signs of the AIDS epidemic. One hundred sixty-two cases of KS were reported over an 11-month period that year, with most cases indexed to New York City. This was a striking epidemiologic finding given that only three cases had been reported in the period 1961 to 1979 for the same age group in New York City. KS is now the most common tumor seen in HIV-infected patients. KS is now the most common tumor seen in HIV-infected patients.

AIDS-associated KS well illustrates the interactions of basic, clinical, and applied sciences in unraveling the determinants of disease, resulting in both disease prevention and improved therapy. For many years, a relatively indolent form of KS had been sporadically reported in elderly men in Eastern Europe and countries bordering the Mediterranean (classic KS). More recently, KS has been observed with increased frequency in Africa and in transplantation recipients. It was suggested from the initial pattern of the AIDS epidemic, even before the identification of HIV as the cause of AIDS, that sexual transmission of an infectious agent was likely to be involved in the etiology of KS. Specifically, those at highest risk for developing KS were those with evidence of cellular immune deficiency and whose
sexual partners had sex with other men. After the 1984 joint discovery of HIV as the causative agent of AIDS by Gallo and Montagnier, studies showed that the epidemiologic pattern of KS was not satisfactorily explained by HIV epidemiology alone, and the search for a KS cofactor intensified. During this period, institutional and educational preventive strategies resulted in changes in sexual practices, and lower rates of sexually transmitted diseases in groups at high risk for KS. Since then, there has been a decreasing incidence and prevalence of HIV infection as well as of KS among homosexuals in the United States and other Western industrialized countries. Before 1985, KS was reported as the initial manifestation of AIDS in approximately 30% of cases, but in the period 1992 through 1997, it was the initial manifestation in 12.5%. The decrease in KS as the index disease for AIDS has occurred in part because the Centers for Disease Control (CDC) revised its definition of AIDS in 1992 to include a CD4 cell count under 200/µL, and thus cases of KS that occur at lower CD4 cell counts are excluded from the index-case count. However, there has been a further decline in incident cases from 60 to 20 per 1000 person-years between 1992 and 1997, invoking cause beyond a simple change in case definition. It should be noted, however, that KS is much more frequent in other areas of the world, particularly sub-Saharan Africa. In parts of Uganda, for example, KS represents almost one-half of all cases of cancers in male subjects and is the second most frequent tumor in female subjects.

In 1994, Drs. Chang, Moore, and their colleagues discovered a new herpesvirus, called KS-associated herpesvirus (KSHV) or human herpesvirus-8 (HHV-8), and subsequent studies showed that this was an essential causative agent for all forms of KS. This discovery has in turn enabled aeroepidemiologic analyses of its pattern of infection indicating that populations with a high incidence of KS also had a high incidence of KSHV infection and that the epidemic of KSHV infection in gay men in the United States appeared almost simultaneously with that of HIV. The seroincidence of KSHV then appeared to taper beginning after 1983, in concert with efforts to encourage safer sex practices among gay men at risk for HIV infection. Also, as discussed later (see Treatment), improved treatments for the underlying HIV infection may have contributed to the decline in KS incidence.

KSHV transmission correlates with a history of sexually transmitted disease and the number of male sexual partners: Strictly heterosexual men appear to have a relatively lower risk. Conception with both KSHV and HIV increases the risk of developing KS by as much as 10,000-fold as compared with KSHV infection alone, and disease manifestation occurs at a younger age. Individuals infected with KSHV but not HIV can develop KS, but it is rare and usually occurs after their fifth decade of life. The risk of developing AIDS-KS appears to be related to the CD4 cell count. The majority of cases occur when the CD4 cell count is below 200/µL, and the risk increases substantially as the CD4 cell count falls below 100/µL. The 10-year probability of developing KS after coinfection with both HIV and KSHV approaches 50%. Also, there is evidence that the risk of KS appears to be higher for those who acquire KSHV subsequent to HIV infection, suggesting there is an important role for immune surveillance of KSHV and the risk of KS.

**PATHOGENESIS**

KS is a multicentric tumor that arises simultaneously in multiple nonmetastatic sites (Fig. 50.1-1). The lesions are highly vascular, accounting for their purplish hue. Microscopically, the tumors are characterized by a predominance of spindle-shaped cells. There is heterogeneity of the cells that make up the lesions, but vascular endothelial cell histogenesis of both the vascular and spindle cell components of KS is suggested by the cellular expression of endothelial cell-associated antigens, such as factor VIII–related antigen, HLA-DR antigens, ES2, and OKMS. However, there remains some uncertainty as to the cell of origin of this tumor. Cells in KS lesions also stain for coexpression of macrophage markers (PAM-1, CD68, and CD14). Although advanced KS may involve monoclonal proliferation, there is evidence that proangiogenic factor-driven hyperproliferation of endothelial-derived spindle cells is important at all stages of the disease. Spindle cells produce and respond to proangiogenic factors such as basic fibroblast growth factor and vascular endothelial growth factor (VEGF).

The discovery in 1994 of a novel herpesvirus called KSHV or HHV-8 has introduced some clarity regarding this complex array of cellular markers and cytokine pathways. Essentially all patients with KS are infected with this virus and KSHV/HHV-8 appears to represent an essential factor in the pathogenesis of KS. KSHV/HHV-8 is present in the flat endothelial cells lining vascular spaces of KS lesions as well as in typical KS spindle cells. KSHV/HHV-8 can induce the production of a number of virally encoded micoms of human cytokines and other factors involved in KS pathogenesis. KSHV encodes for viral homologues to human IL-6, macrophage inhibitory protein, and interferon regulatory factor. It alters other cellular angiogenic factors, which, also, with viral IL-6 and the viral macrophage inhibitory protein, have the potential for stimulating spindle cells as well as angiogenesis. Also, the constitutively active KSHV/HHV-8–encoded G-protein coupled receptor (KSHV GPCR), expressed on infected cells, up-regulates production of VEGF and other angiogenic factors. In addition, there is some evidence that the kinase domain region (KDR) receptor for VEGF is up-regulated in cells infected with KSHV, providing a basis for the paracrine effects of this angiogenic factor in KS. The KSHV GPCR can also cause oncogenic transformation in transfected cells. Moreover, chemokines, such as IL-8 and growth-related protein-α can activate KSHV GPCR over constitutive levels in vitro, suggesting that endogenous chemokines may be evolved in KS pathogenesis, in part through KSHV-related pathways.

Although HIV can markedly increase the incidence of KS in KSHV/HHV-8–infected individuals, the precise role of HIV in KS pathogenesis is somewhat unclear. A new KSHV-related pathways.

**FIGURE 50.1-1.** Cutaneous manifestation of Kaposi’s sarcoma.

The angioigenic polypeptide cytokine oncostatin M, which is produced by activated lymphoid cells, shares functional similarity and structural homology to leukemia inhibitory factor and interleukin-6 (IL-6), and has autocrine growth properties for cells derived from AIDS-KS. Cells exposed to oncostatin M develop spindle morphology, increase proliferation in soft agar, and increase secretion of IL-6, induction of basic fibroblast growth factor. The soluble form of IL-6 receptor–α (sIL-6a) makes cells expressing gp 130 (the oncostatin M receptor) responsive to IL-6. Since AIDS-KS cells express high levels of IL-6, it is likely that, in the presence of soluble IL-6 receptor–α, cells with the oncostatin M receptor acquire an IL-6 autocrine growth loop.

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Although HIV can markedly increase the incidence of KS in KSHV/HHV-8–infected individuals, the precise role of HIV in KS pathogenesis is somewhat unclear. A number of observations invoke the role of HIV Tat protein as a coregulator of KS development. In vitro, HIV Tat protein can stimulate endothelial and KS-derived spindle cell growth and proliferation. Normal vascular cells acquire spindle morphology and become responsive to the mitogenic effect of Tat after culture with inflammatory cytokotytes. Tat promotes adhesion of AIDS-KS and normal vascular cells through a specific interaction with the integrin receptors ß1, a5, and a6, whose expression is increased by inflammatory cytokines. However, the degree of extracellular Tat released in HIV-infected patients is unclear. Other mechanisms by which HIV may potentiate the development of KS include increased levels of IL-6 and decreased cellular immunity (perhaps permitting increased KSHV/HHV-8 replication). These mechanisms may explain why in some cases, KS appears to improve with effective treatment of HIV.

**STAGING AND PROGNOSIS**

The unique clinical presentation of KS requires a departure from the standard oncologic staging approach. The widely used tumor, node, metastasis system (TNM), or other staging systems that incorporate histologic grade and biologic indices as the primary prognostic variables, are not satisfactory in KS for a number of reasons. One is the multicentric nature of the disease. Lesions arise simultaneously at multiple sites without an obvious primary site (see Fig. 50.1-1). Almost all KS patients would be classified as having metastatic disease using the TNM system, but multiple areas of skin involvement may not necessarily imply a worse prognosis relative to more focal involvement. Indeed, it is not at all clear how to use the term metastatic in relation to KS. Also, assessment of tumor bulk is extremely difficult in KS. Consequently, staging has been relatively nonstandardized, relative to other cancers.
Uniform staging is central to response assessment and is necessary to help compare results among trials and with historic controls. The most widely used staging system for KS, devised by the AIDS Clinical Trials Group Oncology Committee, is the TIS staging system (Table 50.1-2). This system scores patients based on the extent of tumor involvement (T), the immune status of the patient (I), and other AIDS-related systemic illness (S) in an attempt to stratify risk of poor prognosis. The TIS system stages patients as being overall either good risk or poor risk, depending on the presence or absence of localized tumor versus more extensive tumor with associated edema, ulceration, visceral disease, or extensive oral KS, CD4 cells over or below 150/µL, and the presence or absence of antecedent opportunistic infections, thrush, constitutional symptoms, other HIV-related illness, and Karnofsky's performance status. Good risk is designated with a subscript 0, and poor risk by the subscript 1, the summary taking the form T1 or T0, I2 or I1, S1 or S0. A patient who is poor risk in any single category is considered poor risk overall.

### Table 50.1-2. Revised Acquired Immunodeficiency Syndrome Clinical Trials Group Staging Classification for Kaposi's Sarcoma

| T1 | I2 | S1 |
| T0 | I2 | S0 |
| T1 | I1 | S1 |
| T0 | I1 | S0 |

Although this staging system is subject to observer bias, it is nevertheless predictive of survival. One of the most important prognostic factors is the CD4 count. A CD4 cell count greater than 150 to 200 cells/µL implies a better prognosis, regardless of visceral involvement by KS.

The extent of KS lesions as a prognostic factor has not uniformly been validated, but the potentially confounding role of immunosuppression degree was not adequately controlled for in certain analyses. The degree of immunosuppression predicts life expectancy after the diagnosis of KS. The clinical course of KS is quite variable, from remarkably indolent to rapidly fulminant, but there are no clear criteria on which to assess the risk of aggressive versus indolent disease. KS behavior can be affected by the degree of immunosuppression or alternatively by the degree of HIV replication. There is evidence that KS may become more indolent with good control of HIV, but the long-term course of KS in patients with highly active antiretroviral regimens is not known. The role of other factors, such as the activity of KSHV/HHV-8, is not well understood at present, but could potentially contribute to risk assessment.

### TREATMENT

During the 1980s, KS was a frequent cause of death in AIDS patients. In the late 1990s, however, a number of advances in the therapy of this disease have been seen. While KS is still a cause of considerable morbidity and mortality in HIV-infected individuals, better tumor control is now attainable in most patients than was possible several years ago. In addition, there is evidence that the development of highly effective antiretroviral regimens has contributed to a decline in the incidence of KS in HIV-infected individuals. Finally, advances in understanding the pathogenesis of KS offer the possibility of developing new pathogenesis-based therapies that may be less toxic than the current agents.

In order to best understand the effect of more recent advances in the therapy of KS, it is useful to recount the standard therapy for this condition as of approximately 1993 to 1994. Overall, the initial therapies identified as being active against KS during the first few years of the AIDS epidemic can be divided into three groups: local measures, immunotherapy (interferon-α), and cytotoxic chemotherapeutic agents.

### Local Therapy

Local therapies include surgical excision of the lesions, cryotherapy, photodynamic therapy, intralesional injections, radiation therapy, and topical application of various drugs and are most useful for patients with limited cutaneous disease that is cosmetically disturbing to the patient. Intralesional injection or iontophoresis of low-dose vincristine (0.1 ml of 0.1 mg/ml) or 3% sodium tetradecyl sulfate injection (0.1 to 0.3 ml) causes a nonspecific necrosis or sclerosis of mucocutaneous tissue with sometimes reasonable cosmetic outcome for small lesions. Cryotherapy is easy to administer and unlike surgical excision, it can be accomplished without local anesthesia. However, cryotherapy can cause permanent destruction of melanocytes, particularly in dark-skinned individuals. Topical 9-cis retinoic acid (Pannetin Gel), approved by the U.S. Food and Drug Administration (FDA) for use in KS, may result in responses in over 45% of lesions but can cause local inflammation and lightening of the skin, yielding inadequate cosmesis in some cases.

Radiotherapy is useful for localized disease, but as with other nonsystemic therapies, does not control disease outside of the treatment area. In addition, there are reports of a decreased tolerance to radiation among AIDS-KS patients, particularly on the mucosal surfaces where severe mucositis can occur. Reappearance of KS in the area of previous irradiation can occur. Radiotherapy is useful as adjunctive therapy in severe disease to treat areas of painful involvement that may respond only slowly to systemic therapy. The use of carbon dioxide laser therapy to remove tumors of the mouth, oropharynx, and larynx has been reported to result in immediate improved oral intake and with less toxicity than is sometimes seen with irradiation to the oral cavity. Radiotherapy is also useful for cosmetic purposes, such as involvement of the eyelid or conjunctiva, where other local therapies are not practical. Applied doses vary between 800 rad given over one fraction to 3000 rad given over ten fractions, depending on the site of involvement, and disease status entering into the dosing algorithm. Complete responses can be seen in over 90% of lesions, but sometimes residual radiation-induced pigmentation or telangiectasia, which can at times be severe, limits the cosmetic outcome. Doses of 1500 rad for oral lesions and doses of 2000 rad for lesions involving eyelids, conjunctiva, and genitals have been shown to be sufficient to produce shrinkage of the tumor and good palliation of the symptoms. Short-course radiotherapy may be useful and effective in some settings. Treatment comparisons of either 1600 rad over four fractions or 2000 rad as a single fraction yielded similar response rates of 78% to 81%. The toxicity was somewhat site dependent, and thus single-fraction therapy may not be appropriate in all cases. Radiation therapy can be used for palliation of visceral disease, including pulmonary involvement, and may be reasonably well tolerated in some circumstances. Photodynamic therapy has been reported to be effective in KS, yielding high response rates, and has the advantage over other local therapies in that 40 to 50 lesions can be treated during a single session. It is frequently associated with moderate pain and then photosensitivity for a number of weeks following the treatment.

### Immunotherapy

Immunotherapy with interferon-α was identified as being active in KS in the early 1980s, particularly in patients with over 200 CD4 cells/µL and disease limited to the skin. Interferon-α appears to be more effective when used in combination with zidovudine monotherapy than when used alone, and as will be discussed below, studies are underway to test this agent in combination with potent combination anti-HIV therapy (see Antiretroviral Approaches, later in this chapter). The use of interferon-α is associated with a decreased white blood count, flu-like symptoms, and sometimes depression.

### Cytotoxic Chemotherapy

Early in the AIDS-KS epidemic, several cytotoxic chemotherapeutic agents were found to yield tumor responses with acceptable toxicity. Vinca alkaloids (either vinblastine, vincristine, or an alternating regimen of the two) were among the first to be studied. Other active single-agent drugs included etoposide, bleomycin, and doxorubicin. Subsequently, several studies showed that the combination of doxorubicin, bleomycin, and vinca alkaloids (ABV) was effective, even in patients with extensive KS or disease that was refractory to other therapies. The initial clinical studies of ABV in KS generally used relatively high doses of doxorubicin, either
IL-12 possesses a number of interesting immunologic and antiangiogenic characteristics that make it a potentially attractive agent for HIV-associated KS. There is evidence that encapsulation of the drugs in liposomes helps target them to KS lesions, in part because of the sequestration of blood that occurs because of the leaky blood vessels in the lesions. In early clinical studies, both preparations were found to induce major tumor responses, even in patients who had failed standard chemotherapy.

With this background, liposomal anthracyclines as single agents were tested against active combination regimens in several randomized trials. In one study, liposomal daunorubicin (40 mg/m² every 2 weeks) was found to have a response rate comparable with ABV, although with somewhat less neutropenia. It is noteworthy that the 28% major response rate of ABV in this study was substantially less than that found on previous studies. One likely reason for this is that the dose of doxorubicin used (10 mg/m² every 2 weeks) was less than that used in the earlier ABV studies. Another likely reason is that the patients in this randomized trial had advanced HIV disease with a median CD4 count of 29 cells/µL. The substantial difference in response rates to ABV in these two trials highlights the sensitivity of KS response rates to disease status and other parameters.

In two separate trials, pegylated liposomal doxorubicin was found to have better response rates against KS than either bleomycin plus vincristine (BV) or an ABV regimen with either less or roughly comparable toxicities. In the study comparing it with BV, the major response rate to pegylated liposomal doxorubicin alone was 58%. Both of these liposomal preparations have now been approved by the FDA for the therapy of KS.

To address whether the liposomal anthracyclines were better used alone or in place of doxorubicin in combination regimens, a study of liposomal doxorubicin alone compared with liposomal doxorubicin, bleomycin, and vincristine (DBV) in patients with advanced KS was initiated. At a protocol-mandated interim analysis on 126 evaluable patients (62 on liposomal doxorubicin and 64 on DBV), the major tumor responses (partial and complete responses) were similar in the two treatment arms (79% on liposomal doxorubicin vs. 80% on the combination regimen). However, more patients receiving DBV had toxicities requiring cessation of treatment than did patients receiving liposomal doxorubicin alone, and there was a trend toward better survival in favor of liposomal doxorubicin alone (11 vs. 18 deaths, \( P = .079 \)). The study concluded that single-agent liposomal doxorubicin had equivalent activity but lower toxicity than DBV, and all patients were switched to liposomal doxorubicin alone.

Paclitaxel was also developed for use in KS during this period based on observations that it targets cellular microtubules (such as vinca alkaloids shown to be active in KS, albeit causing the opposite effect) and its in vitro inhibition of a KS-derived spindle cell line. An initial trial of paclitaxel at the National Cancer Institute (NCI) using a dose of 135 to 175 mg/m² administered over 3 hours every 3 weeks showed substantial activity in patients with advanced KS; 20 of 28 assessable patients had complete or partial responses for a major response rate of 71.4%. It was noteworthy that five of six patients with pulmonary KS responded, as did four patients who had previously received anthracycline therapy.

Gill, Scadden, and their colleagues at the University of Southern California and Harvard University conducted a second trial of paclitaxel in 56 mostly previously treated patients with advanced KS. This trial used a somewhat different regimen: 100 mg/m² of paclitaxel administered over 3 hours every 2 weeks. Overall, the major response rate in this trial was 59%. It was noteworthy that of the 32 patients who had received prior anthracycline therapy, 55% responded. In both trials, neutropenia was the dose-limiting toxicity, and a number of patients had improvement in KS-related symptoms. Largely based on the results of these two studies, the FDA approved paclitaxel as second-line therapy for KS in 1997. Also, it is important to emphasize that corticosteroids can result in dramatic acceleration of KS growth. Premedication with 10 mg of dexamethasone is adequate for taxane-based therapy, but corticosteroids should otherwise be avoided when possible.

The development of the liposomal anthracyclines and paclitaxel for KS appears to have enabled better palliation of symptoms with less toxicity than was possible with previous regimens, and at the present time, most oncologists treating KS patients consider these to be the two most valuable modalities for the treatment of advanced KS (Table 50.1-3). For most such patients, the liposomal anthracyclines (and especially liposomal doxorubicin) are generally considered the preferred first-line therapy. Paclitaxel is generally considered as a valuable second-line therapy, although for patients with particularly severe KS, some oncologists use it as initial therapy (this is a deviation from the current FDA labeling of the drug). Other therapies that are considered useful in some patients include ABV, weekly alternating vincristine and vinblastine, or BV.

**Therapy**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Regimen Rates</th>
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<tr>
<td><strong>COMBINED USE</strong></td>
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<tr>
<td>Liposomal anthracyclines</td>
<td>+</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>+</td>
</tr>
<tr>
<td><strong>ALTERNATIVE THERAPY</strong></td>
<td>l</td>
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<tr>
<td>Interferon</td>
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<tr>
<td>Azathioprine</td>
<td>+</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>+</td>
</tr>
<tr>
<td><strong>PREVENTIVE THERAPY</strong></td>
<td>l</td>
</tr>
<tr>
<td>Prophylactic antibiotics</td>
<td>+</td>
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In an attempt to explore the relative merits of these agents as first-line therapy for KS, von Roenn and colleagues in the Eastern Cooperative Oncology Group and the AIDS Malignancy Consortium of the NCI have initiated a phase III trial comparing liposomal doxorubicin (Doxil), 20 mg/m² every 3 weeks, with paclitaxel, 100 mg/m² every 2 weeks in patients with advanced, untreated KS. This study should provide valuable guidance for therapy in advanced KS.

**Experimental Approaches to the Treatment of Kapossi’s Sarcoma**

Although the development of liposomal anthracyclines and paclitaxel has improved the therapeutic armamentarium for advanced KS, these agents have the potential for substantial toxicity. In particular, both cause bone marrow and immunologic suppression, although there is evidence that paclitaxel is relatively sparing of CD4 cells as compared with other cytotoxic agents. Moreover, even in the absence of HIV infection, the regeneration of CD4 cells after cytotoxic therapy can take many months, especially in adults or older children. For these reasons, there is a substantial interest in developing effective less toxic pathogenesis-based therapies.

**ANTIANGIOGENESIS APPROACHES.** One active area of research in this regard is the inhibition of new blood vessel growth, a field that has been pioneered by Folkman and colleagues. KS is a highly vascular tumor, and for this reason, there is currently an interest in exploring the use of angiogenesis inhibitors in patients with KS. Compounds of interest that have been in phase I or II testing include pentosan polysulfate, TNP-470 (an analogue of the fungal product fumagillin), IL-12, IM-862, SU5416, and thalidomide. Preliminary results from two initial phase II trials of thalidomide both showed that this agent had activity in a subset of patients with KS.

IL-12 possesses a number of interesting immunologic and antiangiogenic characteristics that make it a potentially attractive agent for HIV-associated KS. There is evidence that HIV-infected patients have a specific defect in T-cell help for cellular response (Th1 cells), and that IL-12 selectively stimulates such responses. In addition, IL-12 has been shown to be a potent inhibitor of angiogenesis, possibly through induction of inducible protein 10, a potent inhibitor of angiogenesis.
angiogenesis. Interestingly, the constitutively active KSHV GPCR expressed on KS cells is induced by inducible protein 10, leading to potentially decreased production of VEGF and other angiogenic factors by KSHV/HHV-8–infected cells. A potential concern in the use of IL-12 is that it has been shown to slightly increase HIV replication in vitro. However, this can easily be controlled by anti-HIV drugs. Preliminary results from a phase I trial of IL-12 in patients with KS show that it has some activity. In the future, it may also be of interest to explore the possible clinical utility of inducible protein 10 in this disease. 

The results seen with thalidomide and IL-12, plus advances in angiogenesis research, have led to further interest in this approach to the treatment of KS. The AIDS Malignancy Consortium is conducting studies of novel antiangiogenic agents, including a phase I trial of the metalloproteinase inhibitor col-3 and of IM-842 versus placebo for evidence of therapeutic effect. There has been substantial interest in two biologic antiangiogenesis agents, endostatin and angioatin, as development proceeds, they may be studied in KS. Finally, it should be noted that interferon-a can inhibit angiogenesis, and that this may be one mechanism for its anti-KS activity. Initial studies suggested that this agent was principally active in patients with disease limited to the skin and with over 200 CD4 cells/µL. However, subsequent trials suggested that this agent also manifested anti-KS activity in patients with lower CD4 counts if given with nucleoside anti-HIV therapy. To extend these observations, the AIDS Malignancy Consortium is now studying the effectiveness of interferon-a in combination with highly active antiretroviral therapy (AIDS Malignancy Consortium Trial 004) in patients with HIV-associated KS.

RETNIOIC ACIDS. KS-derived spindle cells have been shown to proliferate in response to IL-6 and certain retinoids have been shown to down-regulate IL-6 receptors, at least on myeloma lines, and to have an antiproliferative effect on KS-derived cell lines. Much of the initial interest in the retinoids centered on all-trans retinoic acid (ATRA), a problem with this agent is its short half-life and the rapid clearance of retinoids. It has been suggested that retinoids act by inducing enzymes that significantly increase its metabolism, resulting in a substantially diminished area under the time concentration curve. In part because of this and in part because it has a different pattern of receptor binding, more recent clinical work has focused on 9-cis retinoic acid. Preliminary reports from two clinical trials have provided evidence that this agent is active when administered orally to patients with KS. The response rates in these studies were 46% and 37%. The most frequent side effects were headache and skin changes. Additional studies will be needed to further define the role of this agent in KS. As noted previously, topically applied 9-cis retinoic acid has been approved by the FDA for use in KS.

HORMONAL APPROACHES. One of the most interesting epidemiologic features of AIDS-KS is that the vast majority of patients are male. This male predominance is more than can be explained by patterns of KSHV/HHV-8 infection. and it suggests that there may be some hormonal effect on the disease pathogenesis. Several years ago, Lundersi-tsandarar, Gallo, and coworkers found that a factor in the urine of pregnant women blocked the growth of a KS-derived cell line. This factor was initially thought to be human chorionic gonadotropin, but subsequent investigation has suggested that it is a related urinary protein that is found in certain preparations of human chorionic gonadotropin. Early clinical trials have shown that preparations of human chorionic gonadotropin containing this factor could reduce regressions in KS. Ongoing studies are now focused on better defining this active factor.

KAPPO'S SARCOMA–ASSOCIATED HERPESVIRUS, HUMAN HERPESVIRUS-8, AND HUMAN IMMUNODEFICIENCY VIRUS–RELATED APPROACHES. The discovery of KSHV/HHV-8 has opened up many avenues of research in KS. Most of the cells in KS lesions are infected with KSHV/HHV-8 in a latent state. However, a small percentage of cells in KS lesions appear to contain KSHV/HHV-8 in a lytic state of replication, and if these few cells are important in ongoing tumor pathogenesis, then antiretrovirals directed against HIV might have anti-KS activity. Although preliminary evidence suggests that antiretrovirals such as acyclovir, foscarin, or ganciclovir do not substantially decrease the population of KSHV/HHV-8–infected cells in the circulation, there is some anecdotal evidence of KS remissions being associated with the use of foscarin. Perhaps more noteworthy is the finding from a randomized clinical trial of oral ganciclovir that administration of this agent was associated with a lower rate of KS. This result indicates that an antiretroviral drug can reduce the incidence of KS, although it still remains unclear as to how it can affect established lesions.

While the role of ongoing KSHV/HHV-8 replication in the growth of KS lesions is still unclear, there is somewhat better evidence of a linkage between KS growth and HIV replication. The incidence of KS is much higher among patients coinfected with HIV and KSHV/HHV-8 than in those with just KSHV/HHV-8 infection, and there are reports of decreases in KS incidence following highly active antiretroviral therapy. Most strikingly, the incidence of KS has declined in HIV-infected patients since the introduction of potent combination anti-HIV therapy. Possible mechanisms for this association include interaction of HIV Tat protein with KS-derived spindle cells. Of particular note, HIV-induced immunosuppression, HIV-related cytokine dysregulation, and the possible role of other HIV-encoded proteins. These epidemiologic findings provide a paradigm for the prevention of a tumor by antiviral control of the underlying viral and immunosuppressive disease.

ACQUIRED IMMUNODEFICIENCY SYNDROME–ASSOCIATED LYMPHOMAS

EPIDEMIOLOGY AND OVERVIEW

Beginning in 1973, before recognition of the AIDS epidemic, there was a clear increase in reported cases of lymphoma. This trend overlapped with the early years of the epidemic, and from 1973 to 1988, there was a 50% increase in the incidence of NHL based on analysis of the NCI's Surveillance, Epidemiology, and End Results program data. The incidence rates for primary brain lymphomas increased during the same period. The increased incidence rates for large cell immunoblastic and small noncleaved cell NHL observed during the 1980s has been attributed largely, although not entirely, to the AIDS epidemic. Immune dysfunction has previously been associated with the development of lymphoproliferative diseases and lymphomas, and with this background, investigators were alerted early in the AIDS epidemic to the possibility that this new disease might be associated with lymphomagenesis. Indeed, as early as 1982, 1983, 1984, and before AIDS was recognized as a new epidemic disease, four cases of aggressive lymphoma in young men ranging in age from 24 to 35 years were reported within a 30-month period in the San Francisco area. This was seen as remarkable because only one case of aggressive lymphoma had been reported in the age group 20 to 39 years for the period 1977 to 1980. It was thus recognized that the then-termed KS and opportunistic infection syndrome may predispose affected persons to more than one kind of tumor.

Additional significance to the emerging problem of NHL was highlighted in 1985 with publication of the Surveillance, Epidemiology, and End Results program database, which suggested a ninefold increase in the morbidity odds ratio for aggressive lymphomas among never-married men (a term used to approximate homosexual men for epidemiologic purposes) in the San Francisco area 1981 to 1985 as compared with 1973 to 1980. Ultimately, it was found that there was an overall 60-fold increase in the rate of observed cases of NHL in HIV-infected persons compared with that expected in the HIV-negative population. Because of these epidemiologic and immunologic considerations, NHL of high-grade pathologic type (diffuse, undifferentiated) and of B-cell or unknown immunologic phenotype, diagnosed by biopsy, was included in the case definition of AIDS in 1985. NHL is now the second most common AIDS-associated malignancy and is the AIDS-defining diagnosis in roughly 3% of HIV-positive patients. It is not clear what percentage of HIV-infected patients ultimately develop NHL, since the occurrence of a second AIDS-defining event is not reportable. Estimates of incidence up to 10% per year with a prevalence of 4.5% to 25.0% have been documented in certain patient populations. In addition to an increased risk of NHL in HIV-infected persons, the pattern of presentation differs from the HIV-negative population. Over 80% of lymphomas in HIV-infected patients are high-grade B-cell lymphomas, whereas only 10% to 15% of lymphomas among HIV-negative patients are of this type.

Data collected by the NCI suggest that between 8% and 27% of the approximately 40,000 annual cases of NHL are HIV-related. In a long-term follow-up of patients participating in phase I trials of zidovudine, the predicted occurrence of NHL by Kaplan-Meier statistics was 8% at 24 months and 29% at 36 months of zidovudine. A high risk of lymphoma development was also observed in patients followed for a long time on a phase I trial of didanosine. Lymphoma risk appeared to be increased with the degree and duration of immunosuppression. These reports suggested that anti-HIV therapy might possibly increase the cumulative risk of HIV-infected individuals developing lymphoma by extending overall survival. However, when these reports were published, concern arose that nucleoside reverse transcriptase inhibitors might directly contribute to development of lymphoma. The finding that this lifetime exposure in rodents was associated with vaginal tumors and the subsequent finding that administration of high-dose zidovudine to pregnant mice was associated with increased cancer rates among the offspring, fueled the belief that antiretroviral drugs were involved in high-grade NHL. Clinical studies have also supported these concerns. Currently, some studies have reported relatively low overall rates of the development of lymphoma. One study, which followed 24 (2.3%) of 1030 AIDS patients receiving zidovudine developed NHL. With 1463-person-years of follow-up, the rate was 1.6 per 100 person-years of therapy. Also, data from a case-control study provided no evidence that the
use of zidovudine increased the risk of lymphoma in HIV infection. 175

Another piece of evidence arguing against a role of zidovudine increasing the risk of B-cell lymphoma is that zidovudine is not implicated in lymphomagenesis or in inducing B-cell activation. 176 Also, it is worth remembering that an increased incidence of lymphoma in HIV-infected patients was found even before the introduction of zidovudine. 177

The excess risk of developing AIDS-NHL appears to be independent of the particular risk group for HIV acquisition 3, 178, 179 or lifestyle factors such as drug use, 178 although one autopsy series suggested that patients with a prior history of KS had a 5.3-fold higher risk of NHL compared with HIV-infected patients with other AIDS-defining illnesses. 180 The risk, however, does vary with age. It has been reported that the excess risk of NHL in HIV is approximately 360-fold for the age group under 19 years and 20-fold for the age group over 60 years of age. 181 However, NHL is a rare disease in western countries (0.1 to 0.3 per 100,000), 182 such that a small number of excess cases translate into higher ratios of observed versus expected cases. 183 It has also been reported that male subjects and whites are at higher risk than other groups, but this feature does not distinguish AIDS-NHL from the epidemiology of non–AIDS-NHL. 184 185 NHL is the most frequent AIDS-related malignancy among hemophiliacs, 186 primarily because KS appears so rarely in this group.

There may be innate biologic characteristics that predispose certain HIV-infected persons to develop NHL. In a study of 746 HIV-infected persons, the 3'A variant of stromal cell-derived factor-1 187 188 chemokine was associated with an approximate doubling of the NHL risk in heterozygotes and a fourfold increase in homozygotes. 189 The stromal cell-derived factor-1 3'A chemokine variant is carried by 37% of whites and 11% of blacks and may contribute to the lower risk of AIDS-NHL in blacks compared with whites.

A deletion in the CCR5 chemokine receptor gene has been reported to alter the risk for HIV infection and progression to AIDS. 190 In a matched case-control study, the CCR5 deletion variant CCR5-32 offered approximately a threefold protection against NHL. 191 By contrast, the AIDS-protective variant CCR2-64I had no significant effect on the risk of lymphoma. The CCR5 gene was not associated with a difference in risk for Kaposi’s sarcoma, or development of opportunistic infections. 192 Costimulation of normal B cells with the CCR5 ligand RANTES (regulated on activation, normally T-cell expressed and secreted) induces a proliferative response, indicating that RANTES is a mitogen for B cells. 193 Perhaps the CCR5-32 mutation is protective through a mechanism involving a decreased response of B cells to the mitogenic activity of RANTES. It is possible that such factors may provide a means of assessing the risk of NHL in HIV-infected persons and provide insights for preventive and treatment approaches for this disease.

It is conceivable that potent antiretroviral therapy (PAT) for HIV infection will have an effect on the incidence of AIDS-NHL. In the Australian AIDS registration data, NHL has decreased by 37.5% as an AIDS-defining diagnosis since 1994, coincident with the introduction of PAT as common anti-HIV therapy. 194 The French database has also suggested a decrease in NHL. Of 66,202 HIV-seropositive subjects, the incidence of lymphoma (peripheral and primary CNS) per 1000 person-years in 1987 decreased to 0.27 per 1000 in the first half of 1996. 195 The effect of PAT on PCNSL may be clearer. This effect is not surprising as PCNSL most commonly develops in patients with fewer than 50 CD4 cells/μL 196, 197 and as PAT can profoundly increase the CD4 counts. In a prospective study, the probabilities of developing focal brain lesions were analyzed for linear trend comparing 1991 through 1996, a period before PAT, with 1997 through 1998, when PAT became commonly available. The odds ratio of developing PCNSL was 0.46 in the PAT era compared with pre-PAT. 198 Others studies have found less evidence of a substantial effect on the incidence of lymphoma. An analysis of data from the Multicenter AIDS Cohort Study showed that the incidence of NHL as the AIDS-defining condition has remained fairly constant over time. 198 Among a total of 6587 patients enrolled in AIDS Clinical Trials Group trials between November 1987 and February 1997, incidence rates of both KS and NHL per 100 person-years declined in concert with decreases in mortality, but the decreases in NHL were somewhat inconsistent, suggesting that current therapies do not appreciably ameliorate the incidence of NHL. 199 It is hard to predict the ultimate effect of PAT will have on the development of NHL. On the one hand, it may reduce the immediate incidence through its beneficial effect on the viral load and CD4 count. On the other hand, as patients live longer with PAT, there may be a cumulative increase in the risk of patients developing NHL.

PATHOLOGY AND CLASSIFICATION

Efforts to understand disease mechanisms for AIDS-NHL have involved consideration of NHL occurring in other conditions of disordered immunity. Immune-suppressive therapy in solid organ transplantation is associated with a 30- to 300-fold increase in the risk of lymphomas and has been used as a model of AIDS-associated lymphomagenesis. 200, 201 These lymphoproliferations can sometimes respond to reduction in immunosuppressive therapy, but in other instances can also be aggressive and poorly responsive to treatment. 202, 203, 204 The congenital immunodeficiency syndromes also confer a predisposition to malignancy, providing yet another model in which to consider lymphomagenesis. 205, 206 For example, in ataxia-telangiectasia, there are specific immune defects that have been identified and linked to chromosomal breakpoints in genes involved in both the immune system and in certain malignancies such as Burkitt’s lymphoma. 207 Further illustrating the role of immune dysfunction is the increased frequency of lymphoproliferative disease and lymphomas occurring in patients with autoimmune disease. 208 Autoimmune factors in HIV infection are suggested by the finding that antibodies to the HIV-1 gp41 protein cross-react with self-MHC class II antigens, triggering chronic antigenic stimulation of B cells. 209 Further, immunoglobulin somatic hypermutation with the preferential use of the V_{_{Y}} family of immunoglobulin-variable genes (molecular events that are produced under chronic lymphoproliferative conditions) has been seen in AIDS-associated lymphomas. 210, 211 Elevated serum IL-6 levels in HIV-infected patients have also been associated with a higher risk of certain forms of NHL. 212, 213 Thus, chronic antigen stimulation from HIV, concomitant infections, or autoimmune phenomena can potentially lead to B-cell proliferation and oligoclonal expansion in a multistep process rapidly progressing from clinically undetectable hyperplastic adenopathy 214, 215 to malignant mononclonal lymphoma in the setting of immunosuppression or other host factors such as deregulated cytokine production (i.e., IL-6, IL-10, tumor necrosis factor-β).

HISTOLOGY

AIDS-NHLs are histologically heterogeneous and are almost invariably derived from monoclonal B-cell populations. 216, 217, 218 although there are sporadic reports of T-cell lymphomas associated with HIV. 219, 220 There are three major categories of HIV-associated B-cell lymphomas: (1) Burkitt’s and Burkitt-like lymphomas; (2) B-cell immunoblastic lymphomas; and (3) the rarely occurring primary effusion lymphomas (PEL), also termed body cavity lymphomas. 221, 222 The Revised European-American Classification of Lymphoid Neoplasms classifies all these lymphomas as either (1) Burkitt’s and Burkitt-like, which includes small non–cleaved cell lymphomas (SNCL), and account for approximately 20% of the cases; and (2) diffuse large B-cell lymphoma, which include the large non–cleaved cell and large cell-immunoblastic phenotypic types and account for approximately 60% of cases. 222, 223 HIV-associated PCNSLs are almost always of this latter morphologic type. 224 The World Health Organization proposes a unique classification for PEL. 225

Occasional lymphomas arising in HIV-infected individuals have been reported to be polyclonal. 226 These tumors are most often Epstein-Barr virus (EBV)-negative tumors with no evidence of c-myc rearrangement. Less frequently, these polyclonal tumors are found to be EBV-positive with similarities to lymphoproliferations seen in transplant patients. Polyclonality is said to confer a favorable prognosis. 227 However, most authorities agree that the majority of AIDS-NHLs are monoclonal. 228 Other lymphomas that are seen in the setting of HIV but are not AIDS-defining conditions, include classical Hodgkin’s disease, 229 polymeric lymphoproliferative disorders resembling posttransplant-associated lymphoproliferative disease, 230 and lymphomatoid granulomatosis. 231 Multicentric Castleman’s disease is sporadically reported in patients with AIDS-NHL and KS and is of interest because of its association with KSHV/HHV-8 and other similarities with lymphomagenesis. 232

SYSTEMIC LYMPHOMAS

As noted previously, the vast majority of systemic lymphomas developing in HIV-infected individuals are either diffuse large cell lymphomas or SNCL. The presence of distinct genetic pathways for AIDS-SNCL and AIDS-diffuse large cell lymphomas correlates with a number of clinical features that distinguish these two groups of tumors, including differences in the age of onset, CD4 counts at the time of presentation, time elapsed since HIV infection, and clinical presentation (Table 50.1). 233 EBV expression patterns are distinct from posttransplant lymphoproliferative disorders related to iatrogenic immunosuppression and are heterogeneous among AIDS-NHLs. 234 These patterns appear to correlate with histiogenic origin of the malignant clone. 235
Large B-cell lymphomas in HIV-infected patients are associated with EBV infection in 70% to 90% of cases and are more likely to occur later in the course of HIV infection in older patients with relatively low CD4 cell counts. Cells tend to exhibit EBV-latency type 3 expression and in particular express Epstein-Barr nuclear antigen-2 (EBNA-2) and latent membrane protein-1 (LMP-1), which are EBV-specific antigenic targets. It has been hypothesized that HIV-infected patients have a defect in these EBV-specific cytotoxic T-cell responses, thus allowing immune escape of the emerging lymphomatous clone. The viral oncogene LMP-1 may be involved in lymphomagenesis by increasing the threshold for cells to undergo programmed cell death. Through up-regulation of the cellular antiapoptotic oncogene, bcl-2. Unlike HIV-negative lymphomas of similar histology in which translocations of bcl-2 are often found, rearrangements of bcl-2 are not generally found in peripheral AIDS-NHLs. However, bcl-2 may be densely expressed in some cases. EBNA-2 expression has been reported to be associated with extranodal disease, which is a prominent feature of the large cell AIDS-NHLs.

SNCL is more likely to occur earlier in the course of HIV infection in younger patients with relatively preserved CD4 cell counts. Only a minority of cases (25% to 40%) express EBV. If EBV is found in SNCL, EBNA-2 and LMP-1 are not typically expressed, as is also observed in EBV-positive cases of sporadic Burkitt's lymphoma in the general population. The lack of EBV protein expression could contribute to the ability of tumor cells to escape the relatively intact immune surveillance in these patients.

The different patterns of EBV expression found in these lymphomas may relate in part to the observation that the synthesis of various EBV transformation-associated proteins is regulated by different cellular factors depending on the differentiation stage of the host. A number of these tumors express BCL-6, a protein selectively expressed by germinal center (GC) B cells, and it has been suggested that these lymphomas may originate from the GC. Deregulated BCL-6 expression may contribute to lymphomagenesis by preventing post-GC differentiation. Syndecan-1 (syn-1) is a proteoglycan that is not expressed in GC B cells, but it is expressed in specific subsets of post-GC B cells, including immunoblasts and plasma cells. It is absent on circulating and peripheral B lymphocytes, but is reexpressed on their differentiation into immobilized plasma cells. BCL-6 and syn-1 appear to segregate into two major phenotypic subsets, suggesting that tumors displaying the BCL-6+/syn-1− phenotype originate from GC-related B cells, whereas tumors displaying the BCL-6+/syn-1+ phenotype derive from post-GC B cells. The differential expression of BCL-6 and syn-1 appears to be related to expression of LMP-1. Among EBV-infected AIDS-NHL, expression of the LMP-1 antigen can be found only in BCL-6−/syn-1+ tumors, suggesting that the GC stage is not permissive for LMP-1 expression, and that tumors expressing LMP-1 derive from more mature post-GC B cells. Cases with immunoblastic plasmacytoid features and LMP-1 expression thus appear to be BCL-6−/syn-1+ with post-GC histiogenic origin, whereas most SNCL and large non–cleaved cell lymphomas appear to originate from more immature GC B cells expressing BCL-6+/syn-1− and LMP-1+. Such considerations may provide insight into the complicated pattern of EBV expression in NHL.

Clustering of the protooncogenes c-myc, BCL-6, and the tumor suppressor gene product p53 is also predictable according to histologic subtype: C-myc activation is seen among 65% to 100% of SNCL cases, but rarely in large cell lymphomas. Inappropriately regulated expression of c-myc, which can be independent of EBV infection in AIDS-NHL, may contribute to lymphomagenesis by causing the down-regulation of lymphocyte function-associated antigen-1 adhesion molecules and loss of B-cell adhesion to cytotoxic T cells and natural killer cells. This may provide another mechanism for malignant cells to escape immune surveillance. BCL-6 rearrangements occur in approximately 20% of large cell lymphomas, but are not found in SNCL. p53 overexpression is restricted to SNCL, possibly resulting in disruptions in programmed cell death. A small number of cases of both large cell and SNCL have been observed to express activated RAS, potentially distinguishing these tumors from those found in the immunocompetent host.

The Burkitt-like AIDS-NHL may be a distinct clinical entity from the HIV-negative morphologic counterpart. Most AIDS-Burkitt-like lymphomas appear to have a molecular pattern similar to that of typical Burkitt's lymphoma: The c-myc oncogene appears to be rearranged in the majority of cases but not the bcl-2 gene, whereas in HIV-negative Burkitt-like lymphomas, rearrangement of c-myc is uncommon, and the bcl-2 gene is rearranged in 30% of cases. However, some features clearly differentiate AIDS–Burkitt-like lymphomas from AIDS-Burkitt's lymphomas. The frequency of EBV infection in AIDS–Burkitt-like lymphomas (80%) is similar to that in diffuse large B-cell lymphoma, but the pattern of viral latency is similar to that seen in Burkitt's lymphoma (i.e., no LMP-1 or EBNA-2 expression) in approximately 60% of the cases. Also, patients with AIDS–Burkitt-like lymphomas usually have a relatively low CD4 count, similar to that seen in the diffuse large cell immunoblastic lymphomas. However, Burkitt-like lymphomas do not seem to share the predilection for CNS involvement associated with Burkitt's lymphoma. Burkitt-like lymphomas may be a morphologic variant in a continuum from Burkitt's lymphoma to diffuse large cell lymphomas in the context of the range of immunodepletion that occurs in HIV-infected patients.

**TABLE 50.1-4. Comparison of Human Immunodeficiency Virus–Associated Lymphomas**

<table>
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<tr>
<th>HIV-related NHLs</th>
<th>Frequency of EBV infection</th>
<th>Clinical presentation</th>
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<tr>
<td>Diffuse large cell lymphoma</td>
<td>80%</td>
<td>Diffuse large cell lymphoma</td>
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<tr>
<td>Immunoblastic diffuse large cell lymphoma</td>
<td>80%</td>
<td>Immunoblastic diffuse large cell lymphoma</td>
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<tr>
<td>Burkitt-like lymphoma</td>
<td>80%</td>
<td>Burkitt-like lymphoma</td>
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**PRIMARY EFFUSION LYMPHOMA**

PEL, also termed body cavity lymphoma, is a rare entity, and as the name implies, these tumors typically grow mainly in the pleural, pericardial, and abdominal cavities as lymphomatous effusions. Sometimes, however, the initial presentation can be nodal, and in some cases the tumor can involve soft tissue or the gastrointestinal tract. PELs exhibit distinctive clinical and biologic features, including immunoblastic morphology and indeterminate immunophenotype. Monoclonality can be established by the finding of clonal immunoglobulin gene rearrangements indicating late B-cell genotype derivation that may have undergone antigenic selection. These tumors are universally associated with KSHV/HHV-8 and appear to follow the same epidemiologic pattern as KS (i.e., the greatest frequency of occurrence is among those who acquire HIV infection from an individual who has sex with other men). The majority of PELs are also EBV positive, although some PEL cell lines are EBV negative, and these usually lack rearrangements in c-myc. There is evidence that VEGF is involved in the pathogenesis of this tumor. KSHV/HHV-8 up-regulates production of VEGF, and SCID/beige mice inoculated intraperitoneally with BCL-1 cells (an KSHV/HHV-8 infected PEL cell line) develop effusion lymphoma. Treatment with neutralizing anti-VEGF antibody inhibits formation of the lymphoma. While the role of KSHV/HHV-8 is unclear, this virus may have a direct transforming role in PEL. In particular, viral BCL-2, IL-6, and cyclin D homologues may serve to delay apoptotic cell death or stimulate lymphomatous cell proliferation.

**CLINICAL PRESENTATION AND STAGING OF PERIPHERAL LYMPHOMAS**

HIV-related NHLs frequently present as advanced stage 3 or 4 disease and behave aggressively with unusual patterns of organ involvement. The majority of patients present with either a rapidly growing mass lesion or the development of systemic B symptoms (unexplained fever, drenching night sweats, or unexplained weight loss in excess of 10% of the normal body weight). Extranodal involvement is common, including the bone marrow (25% to 40%), gastrointestinal tract (20%), and the CNS (17% to 32%). In addition to the standard NHL staging for HIV-negative patients, CD4 cell count, HIV viral load, and CNS assessment should be performed on all HIV-infected patients with lymphoma. Computed tomography of the brain with contrast is adequate to assess for parenchymal brain lesions, but magnetic resonance imaging with gadolinium has the potential advantage of revealing evidence of leptomeningeal involvement by lymphoma. Cytologic examination of the cerebrospinal fluid should be performed in all cases.

NHL is significantly associated with a worse prognosis than many other complications of AIDS. For systemic lymphomas, the factor most correlated with prognosis...
is the CD4 cell count. With standard therapy, patients with fewer than 100 CD4 cells/µL have a median survival of approximately 4 months, whereas those with 100 or greater CD4 cells/µL have a median survival of 11 months. 272,274 Other factors associated with poor outcome are age over 35 to 40 years, high serum lactate dehydrogenase levels, presence of extranodal sites, intravenous drug use, and preexisting AIDS diagnosis. 272,274 The international prognostic index for lymphoma is thus of some utility in AIDS-lymphomas, although its use is not widely reported. 271 In a multivariate analysis of 192 patients, patients who had none or one of such factors had a median survival of 46 weeks, and 30% were alive at 144 weeks, suggesting longer-term survival can be achieved in the subset of patients with unfavorable characteristics. 272 With the advent of PAT, it is quite possible that overall prognosis in AIDS-NHL will improve.

TREATMENT OF PERIPHERAL ACQUIRED IMMUNODEFICIENCY SYNDROME LYMPHOMAS

Nearly two decades into the AIDS epidemic, optimal therapy for AIDS-NHL remains incompletely defined (Table 50.1–5). As noted previously, patients who develop AIDS-NHL continue to have a poor prognosis in spite of efforts to sort out the role of dose-intensive chemotherapy regimens for the immunocompromised host. The rapid improvements in therapy for the underlying HIV infection complicate the ability to compare clinical trials conducted at different times. To put this in perspective, it is instructive to consider some of the issues that have motivated the different treatment strategies for AIDS-NHL.

TABLE 50.1–5. Selected Regimens and Outcomes for Acquired Immunodeficiency Syndrome-Associated Non-Hodgkin’s Lymphoma

At the beginning of the AIDS epidemic, oncologists who treated AIDS-NHL recognized that patients frequently tolerated multiantiagent chemotherapy poorly, and that responses occurred in only a low percentage of patients and were often of short duration. 271,272,274 Importantly, in the early 1980s, prophylaxis against opportunistic infections had not yet been defined as standard practice, 272 and PAT was not available. At that point in time, second- and third-generation lymphoma regimens such as m-BACOD, ProMACe-CytBOM, and MACOP-B were being explored in AIDS-NHL based on preliminary evidence that they may have been more efficacious in the treatment of lymphoma. 272,275,276 However, these regimens themselves were observed to sometimes cause opportunistic infections such as Pneumocystis carinii pneumonia and Herpes zoster. 277,278 In 1993, an intergroup randomized trial failed to show that these regimens were more effective than cyclophosphamide, hydroxydaunorubicin (Adriamycin), Oncovin, and prednisone (CHOP) in HIV-negative patients and were perhaps associated with greater toxicity. 273 Before that report, based on early observations that these lymphoma regimens were toxic in AIDS patients, investigators began to consider lower dose modifications of the second- and third-generation lymphoma regimens in an attempt to reduce the toxicity and immunodeficiency caused by these regimens. 279 A large randomized trial comparing standard- with low-dose m-BACOD was completed in 1997, showing equivalent results in both groups, with complete responses ranging from 41% to 52%, but with a lower incidence of febrile neutropenia in the low-dose group. 279 However, the incidence of opportunistic infections was equivalent in both groups, and the low-dose arm was not shown to yield an improved survival outcome. Also, this study was not designed or adequately powered to determine if the subset of patients with more favorable HIV prognostic characteristics might have benefited from the higher dose intensity of the standard dose m-BACOD. 279 This issue is potentially important, as some studies of aggressive lymphomas in HIV-negative patients have suggested that chemotherapy dose intensity is associated with curative potential. 275 However, the strategy of low-dose chemotherapy clearly resulted in better quality of life with fewer treatment-related hospitalizations for a substantial proportion of the patients treated. In addition, several small studies using dose-reduced CHOP in AIDS-NHL have generally shown equivalent efficacy to standard dose CHOP, although the numbers are relatively small for assessment. 272,276 and 277

At least one study suggests that more intensive chemotherapy may benefit the subset of patients with favorable prognostic factors. In a prospective multicenter study, 141 patients, with a median CD4 cell count of 227/µL, were treated with three cycles of doxorubicin, 75 mg/m²; cyclophosphamide, 1200 mg/m²; vindesine, 2 mg/m² for 2 days; bleomycin, 10 mg for 2 days; and prednisone, 60 mg/m² for 5 days, followed by a consolidation phase of high-dose methotrexate plus leucovorin, ifosfamide, etoposide, asparaginase, and cytarabine (LNH84) and CNS prophylaxis with intrathecal methotrexate. 279 Zidovudine was started after chemotherapy. Eighty-nine patients (63%) achieved complete remission and 19 (13%) partial remission. With a median follow-up of 28 months, median survival and disease-free survival were 9 and 16 months, respectively. Twenty-three patients subsequently died of opportunistic infections while in complete remission. This study, conducted in the era before PAT, demonstrates that a subset of patients with AIDS-NHL were able to tolerate aggressive antilymphoma therapy and appeared to do reasonably well in terms of lymphoma-free survival. This study also highlights the potential importance of improved anti-HIV therapy in patients free of lymphoma.

A greater understanding of HIV disease has resulted in the standard prophylaxis against opportunistic infections and more effective treatment of the underlying HIV infection. AIDS-NHL patients have translated into improved survival and quality of life for patients with HIV disease. Prophylaxis for opportunistic infections clearly plays a major role during cytotoxic chemotherapy in such patients, but it is as yet unclear how advances in antiretroviral therapy will affect the treatment outcome of AIDS-NHL. To explore this issue, investigators have begun to administer newer antiretroviral regimens along with the chemotherapy regimens. 272,276 This is a complicated issue and as yet scant data exist to guide best use of these drugs during chemotherapy. Preliminary results were recently reported from an NCI-sponsored trial conducted by the AIDS Malignancy Consortium. This trial involved 63 patients with a median CD4 cell count of 136/µL who received either modified or full-dose CHOP while receiving PAT with stavudine, lamivudine, and indinavir. 276 Sixty percent of patients had stage 3 or 4 lymphoma. HIV viral loads were stable, with many remaining below the level of detection for the test throughout the course of chemotherapy. The overall complete response rate for the trial was equivalent between the two dose groups: 33% for the modified and 32% for the full-dose group. These rates are similar to those previously reported without PAT. 272,276,277 Although such comparisons may be of limited value, pharmacokinetic data were collected and compared with historic controls. Elimination of cyclophosphamide was decreased from 70 mL/min/m² in historic controls to 39 mL/min/m² in the study patients, but without apparent effect on toxicity of the regimen. Doxorubicin elimination and the area under the time concentration curve of indinavir were similar to that in previous studies of these agents. These results highlight the feasibility of administering antiretroviral and antiretroviral drugs concomitantly, in spite of the potential complicated pharmacokinetics involved in this approach. At the same time, they show that there may be pharmacokinetic interactions and that there is room for improvement in the therapy of this disease.

In a study of 12 patients with AIDS-NHL treated with 96-hour continuous intravenous infusion of cyclophosphamide, doxorubicin, and etoposide (CDE) plus fludarabine, patients also received saquinavir and one or two nucleoside analogue anti-HIV drugs. Severe mucositis occurred in 8 of 12 patients (67%) treated with CDE plus saquinavir, which is more than the 3 in 25 (12%) rate of this toxicity in a previous trial of CDE without saquinavir. 279 This raises the possibility that pharmacokinetic interactions may have contributed to these different rates of toxicity. In addition, such approaches may affect the consistency of antiretroviral dosing. 272,276 In another trial of CDE, plasma etoposide levels were reported to be decreased by 11% to 38% on chemotherapy cycles given with didanosine compared with cycles without didanosine administration. 272,276 These results serve as a reminder that there may be complex and unexpected drug interactions when one attempts to combine complex chemotherapy regimens with complex anti-HIV regimens and that these interactions may affect the outcome of either therapy.

Preliminary results from a study at the NCI showed that 19 of 24 patients (79%) with HIV-associated NHL had a complete response using a modification of chemotherapy with etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (EPOCH). 272,276 Cyclophosphamide was initially dosed according to CD4 count and was decreased to 100 mg/m² (375 mg/m² if CD4 cells 100/µL or greater), and then adjusted up or down each cycle (by 187 mg/m² to a maximum of 750 mg/m² depending on the neutrophil nadir. Antiretroviral therapy was suspended until completion of chemotherapy (maximum of six cycles), and then restarted. The median progression-free survival and overall survival had not been reached, but were 83% and 79%, respectively, at 22.5 months. Over 90% of the planned maximum dose intensity of doxorubicin (10 mg/m²/24 hours continuous intravenous infusion (CVI) for 4 days), etoposide (50 mg/m²/24 hours CVI × 4 days), and vincristine (0.4 mg/m²/24 hours CVI × 4 days), and 56% of the cyclophosphamide was administered with relatively little associated toxicity. Febrile neutropenia occurred in only 12% of the cycles administered. No new opportunistic infections developed in these patients despite the withdrawal of antiretroviral treatment on
initiation of chemotherapy (Pneumocystis carinii pneumonia prophylaxis was administered to all patients, and Mycobacterium avium-complex prophylaxis to at-risk patients). All patients who had responded to antiretroviral therapy before development of AIDS-NHL responded again to PAT when it was subsequently started postchemotherapy. CD4 counts recovered to baseline within 12 months after PAT reinstitution. While this strategy may have the advantage of optimizing dose intensity and protecting patients against development of resistant HIV, some physicians may feel uncomfortable withdrawing antiretroviral therapy (even for a relatively short period of time), and the results require further study.

A high percentage (15% to 20%) of HIV-associated lymphomas have involvement of the CNS at presentation. CNS progression is a potentially important cause of mortality in this setting, and as patients potentially live longer with better antiretroviral treatment after chemotherapy, CNS involvement may become a relatively more important issue. Therefore, in HIV-associated lymphomas, routine CNS prophylaxis with intrathecal methotrexate or cytosine arabinoside should be considered standard practice.

Novel approaches to AIDS-NHL are clearly needed. Intravenous chemotherapy regimens appear to have a favorable toxicity profile and may be useful in AIDS-NHL, but conventional intravenous regimens have not been conducted. Until such data are available, it is unclear whether the encouraging data from small phase II trials of CDE and etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin truly represent an advance in the treatment of this condition. There is current interest in the potential role of the anti-CD20 monoclonal antibody, rituximab (Rituxan) in AIDS-NHL, and trials are currently planned to test this approach. Interest has also evolved in the use of stem cell transplantation in AIDS-NHL. Both autologous and allogeneic transplantation, with high rates of engraftment of EBV-resistant genes into the marrow infusate are areas of interest being studied in clinical trials. In a collaborative trial being conducted by investigators at the National Institutes of Health, nonmyeloablative matched-sibling donor allogeneic transplantation is being studied with encouraging initial results.

**PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA IN ACQUIRED IMMUNODEFICIENCY SYNDROME**

**OVERVIEW AND PATHOLOGY**

PCNSL makes up approximately 19% of AIDS-NHLs, which is substantially higher than that in non-AIDS-NHL (approximately 1%). The frequency of PCNSL is more than 3000-fold higher in patients with AIDS than in the general population, occurring in up to 12% of HIV-infected individuals. From 20% to 30% of CNS lesions in patients with AIDS are ultimately found to have PCNSL. PCNSL is the second most common mass lesion found in patients with AIDS, and the most common brain tumor in this population. The survival of patients with HIV-associated PCNSL is 2 to 5 months, which is substantially shorter than that in the non–HIV-infected population with PCNSL. PCNSL occurs most frequently in patients with a CD4 cell count less than 50/μL and can occur in the setting of other CNS pathology such as toxoplasmosis.

Definitive diagnosis of focal brain lesions in AIDS patients requires biopsy and yields a greater than 92% diagnostic rate. However, there is often some reluctance to do this procedure. While stereotactic biopsy is generally safe, the location of some lesions poses technical challenge and can introduce potential morbidity to the patient as well as risk to the surgical team. Therefore, in many medical centers it has become standard practice to treat AIDS patients who have focal brain lesions and toxoplasmosis empirically with antitoxoplasmosis therapy, reserving biopsy for those patients who are seronegative for antitoxoplasma antibodies or fail to respond to treatment. However, delay in diagnosis can adversely affect survival in AIDS-PCNSL. Such factors necessitate consideration of alternative, less invasive diagnostic modalities.

Computed tomography or magnetic resonance imaging scans usually demonstrate single or multiple contrast-enhancing masses that are not reliably distinguishable from toxoplasmosis or other CNS processes. Preliminary studies suggest that 18F-fluoro-2-deoxyglucose and positron emission tomography may have some utility in distinguishing malignant and nonmalignant conditions, since high FDG uptake most likely represents a malignant process. Also, there is some evidence that thallium 201 single photon emission computed tomography might be a useful, noninvasive method for differentiating intracranial lymphoma from nonneoplastic lesions in patients with AIDS. However, these modalities have not been confirmed in large studies, and a high degree of intercenter variability in procedure may reduce the reliability of these techniques.

It has been shown that detection of CSF EBV DNA by polymerase chain reaction (PCR) in HIV-infected patients is reliably associated with PCNSLs, lending support for the use of this assay as a diagnostic test for this condition. The basis for this approach is the observation that nearly all HIV-associated PCNSLs are associated with EBV infection. In a series of 95 patients, including 40 patients with AIDS-PCNSL, the sensitivity and specificity of PCR for EBV DNA detection in lumbar CSF were 80% and 100%, respectively. Lumbar puncture and subsequent assessment of EBV DNA would have allowed a correct diagnosis in 63.2% of patients with AIDS-PCNSL and excluded this diagnosis in 76.3% of patients without lymphoma (because EBV DNA was not detected). Another group reported an even higher diagnostic confidence of AIDS-related focal brain lesions using minimally invasive procedures. By combining CSF EBV DNA detection by PCR with 18F fluorodeoxyglucose positron emission tomography, the presence of increased uptake of radiotracer EBV DNA, or both had 100% sensitivity and 100% negative predictive value. Because PCNSL likelihood is extremely high in patients with hyperactive lesions and positive EBV DNA, brain biopsy may be avoided, and patients could promptly undergo definitive therapy.

Most cases of PCNSL are of immunoblastic morphology with plasmacytic differentiation, large cell lymphomas with immunoblastic features, or are centroblastic polymorphous lymphomas. SNCCl are rare. EBV is consistently detected by PCR. The bcl-2 oncogene and LMP-1 of EBV are frequently strongly expressed. In a study of 11 AIDS-related primary brain lymphomas, LMP-1 and bcl-2 were expressed in almost all cases but one, potentially implicating their involvement in CNS lymphomagenesis. Expression of mutated p53, or rearrangement of bcl-2 or the c-myc oncogene is not reported. The precise histogenetic derivation and the molecular pathogenesis of PCNSL is poorly understood. Evidence suggests that these tumors may be segregated into two major biologic categories based on the expression pattern of BCL-6, LMP-1, and BCL-2. In an analysis of 26 AIDS-related and 23 AIDS-unrelated PCNSL cases, expression of BCL-6 protein, which is restricted to GC B cells throughout physiologic B-cell maturation, was detected in all of the AIDS-unrelated PCNSL. However, only 56% of the AIDS-related cases expressed BCL-6. Expression of BCL-6 was mutually exclusive with expression of EBV-encoded LMP-1, and with few exceptions, of BCL-2. All but one PCNSL expressed hMSH2, which among mature B cells selectively stains GC B cells. Thus, a proportion of AIDS-PCNSLs may represent a divergent biologic spectrum from their non-AIDS counterparts.

**TREATMENT**

Treatment modalities for immunocompetent patients are applied to patients with AIDS-PCNL, but generally with substantially more toxicity and poorer results. PCNSL is highly responsive to whole brain irradiation, and a substantial proportion of patients can be expected to have complete tumor eradication; however, they have a high likelihood of subsequently succumbing to opportunistic infection or recurrent lymphoma. In a study of 55 AIDS patients with biopsy-proven primary CNS lymphoma, 18 responded both clinically and radiologically to whole brain radiation therapy consisting of 4000 rad in 267-rad fractions over 3 weeks or an equivalent dose. The mean duration of survival from the appearance of symptoms consistent with the mass lesion was significantly greater in patients who received radiation therapy than in those who did not (134 vs. 42 days). Autopsy findings showed that patients who did not receive radiation therapy generally died from tumor progression, whereas those who completed radiation therapy often died of opportunistic infections. Such observations emphasize the need for early diagnosis and treatment, and for treatment of opportunistic infections and the underlying HIV infection. Relapse can occur remote from the primary site, but also within the radiation port.

Experience combining chemotherapy with radiotherapy suggests that a subgroup of patients can benefit from this approach, with survival reaching over 1 year. However, this is still shorter than survival in non-AIDS patients, and still only a minority of patients so treated had survival over 1 year.

Surgery has no therapeutic role in PCNSL since microscopic tumor infiltration into brain parenchyma extends from the site of primary involvement.

**EFFECT OF ANTIRETROVIRAL THERAPY ON PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA INCIDENCE**

Since AIDS-PCNSL appears to be an opportunistic illness associated with profound CD4 depletion (usually occurring in patients with less than 50 CD4 cells), it might be expected that better therapy for HIV would result in a decrease in the incidence of PCNSL. A large medical records analysis showed a decrease in the incidence of PCNSL from 8.5 cases per 1000 person-years in early 1994 to 0.9 cases per 1000 person-years in late 1996 (P = .04). This change was coincident with changes in antiretroviral treatment patterns and an increase in the use of two or more drugs from 20% to 46% of patients. Other data support these findings.

However,
many patients are now developing resistance to available therapies, and it is possible that the incidence may increase in the near future. Also, it is possible that the cumulative incidence of AIDS-related lymphomas may rise as patients live longer with HIV infection. 227

HODGKIN’S DISEASE

EPIDEMIOLOGY

Although Hodgkin’s disease is not an AIDS-defining condition, its association with HIV is apparent for several reasons: it presents in HIV-infected patients with distinct clinical and biologic characteristics that distinguish it from its HIV-negative counterpart (primary Hodgkin’s disease); and it occurs with somewhat increased frequency among HIV-infected patients. 304 By contrast, many registries have indicated a slight decrease in primary Hodgkin’s disease incidence in recent decades. 331 An eightfold excess of Hodgkin’s disease in HIV-infected patients has been found by linking AIDS and cancer registry data. 332 However, there is some controversy over the epidemiology, as some studies have not found an increased incidence of Hodgkin’s disease in areas of high prevalence for HIV infection. 333 334

Overall, Hodgkin’s disease of the nodular sclerosis subtype (the most frequent subtype in HIV-negative patients) has increased over time, whereas Hodgkin’s disease of mixed cellularity has declined. 335 However, among HIV-infected patients, the most common histologic subtype is mixed cellularity, followed by lymphocyte-depleted. 227 330 336 337 338

PATHOGENESIS

EBV infection appears to be more predominant among cases of HIV-associated Hodgkin’s disease than in cases of primary Hodgkin’s disease. 228 Monoclonal expansions of EBV-infected cells have been found in from 78% to 100% of HIV-related Hodgkin’s disease, but in only 15% to 48% of primary Hodgkin’s disease cases. 329 331 332 EBV-encoded LMP-1 has been demonstrated in the tumor cells in from 25% to 50% of primary Hodgkin’s disease cases, but in up to 100% of both the nodular sclerosing and mixed cellularity subtypes of Hodgkin’s disease in HIV-positive patients. 333 The pattern of EBV gene expression may favor immune escape in HIV-related Hodgkin’s disease. The EBV latency C promoter drives expression of the immunomodulatory EBNA’s that are targeted by cytotoxic T lymphocytes. In EBV-associated Hodgkin’s disease, the C promoter is inactive and the immunomodulatory EBNA’s are thus not expressed. 336 This finding may be relevant to the frequent occurrence of Hodgkin’s disease in relatively immunocompetent HIV-infected patients. 329 331 337

CLINICAL PRESENTATION, TREATMENT, AND PROGNOSIS

Patients with HIV-associated Hodgkin’s disease generally present at a younger age, with higher stage disease, less frequent mediastinal involvement, more frequent involvement of extranodal sites of disease, and more frequent occurrence of B symptoms compared with their HIV-negative counterparts (Table 50.1-6). 332 These differences are more than can be accounted for by the overrepresentation of the mixed cellularity histologic subtype in HIV-associated Hodgkin’s disease, 228 a histologic subtype that involves the mediastinal less often compared with nodular sclerosing Hodgkin’s disease. Compared with AIDS-associated NHL, in which the CD4 cell count is frequently less than 100/µL, the median CD4 cell count in HIV-associated Hodgkin’s disease has been reported to be over 275 cells/µL in large patient series. 334 335 336

TABLE 50.1-6. Comparison of Human Immunodeficiency Virus–Associated Hodgkin’s Disease and Primary Hodgkin’s Disease

<table>
<thead>
<tr>
<th>Condition</th>
<th>HIV-Associated Hodgkin’s Disease</th>
<th>Primary Hodgkin’s Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Younger</td>
<td>Older</td>
</tr>
<tr>
<td>Stage</td>
<td>Higher</td>
<td>Lower</td>
</tr>
<tr>
<td>Mediastinal involvement</td>
<td>Less frequent</td>
<td>More frequent</td>
</tr>
<tr>
<td>Extranodal sites</td>
<td>More frequent</td>
<td>Less frequent</td>
</tr>
<tr>
<td>B symptoms</td>
<td>More frequent</td>
<td>Less frequent</td>
</tr>
</tbody>
</table>

Prognosis is generally poorer for HIV-associated Hodgkin’s disease than for primary Hodgkin’s disease. HIV-Hodgkin’s disease patients frequently have a number of features that have been associated with poor prognosis in primary non–HIV-associated Hodgkin’s disease, including male sex, large number of sites involved, and mixed cellularity or lymphocyte-depleted histology. 332 Because of this, the precise contribution of HIV infection per se to the poor prognosis is uncertain. In general, complete response rates are relatively high with systemic chemotherapy (50% to over 80%), 330 331 332 although rates as low as 14% have also been reported. 336 Relapse of Hodgkin’s disease and progression of AIDS are common, contributing to poor overall survival. The CD4 cell count at the time of diagnosis is a prognostic factor. Patients with a CD4 cell count less than 250 to 200 CD4 cells/µL have a median survival of less than 11 months, 334 whereas higher CD4 cell counts are associated with somewhat better outcome. Although most patients do not have an AIDS diagnosis when they develop HIV-Hodgkin’s disease, 48% to 71% develop AIDS within 3 years after treatment for HIV-Hodgkin’s disease. 332 337 Compared with the survival of AIDS in 22% for most other HIV-infected patients with similar CD4 cell counts, 335 these findings underscore the need for skill management of the underlying HIV.

Most patients with HIV-Hodgkin’s disease are treated with conventional chemotherapy regimens (i.e., radiotherapy, mechlorethamine, vincristine, procarbazine, and prednisone; doxorubicin, bleomycin, vinblastine, and dacarbazine; or alternating the two regimens; epirubicin, bleomycin, vinblastine, and prednisone; or combined modality therapy). 330 331 332 Because of the occurrence of multiple poor prognostic factors in HIV-Hodgkin’s disease, most oncologists advocate use of systemic chemotherapy in all clinically staged patients. The CNS is rarely involved, so CNS prophylaxis is not commonly used. Strategies to improve outcome have included the use of antiretrovirals and colony-stimulating factors, but before the use of protease inhibitor anti-HIV therapy, outcomes were essentially equivalent among trials. 330 331 332 It is hoped that treatment outcomes with PAT may change these grim statistics.

ANOGENITAL CANCERS IN HUMAN IMMUNODEFICIENCY VIRUS INFECTION

Cervical cancer was added to the CDC list of AIDS-defining conditions in 1993. 22 Anal cancer, though not an AIDS-defining condition, is also relatively prevalent among HIV-infected women and homosexual and bisexual men with HIV infection. 22 These cancers are associated with human papilloma-virus (HPV) infection 22 and appear to be more aggressive in HIV-infected than in non–HIV-infected individuals. It is thus recommended that HIV-infected women undergo regular periodic cervical Papanicolaou (Pap) testing. The CDC has recommended cytologic screening as part of the initial evaluation when HIV seropositivity is diagnosed. The CDC recommends that if the initial Pap smear is normal, at least one additional evaluation should be repeated within 6 months. 341 If the repeat result is normal, then reevaluation should be done at least annually. If the initial or follow-up Pap smear shows severe inflammation with reactive squamous cellular changes, another Pap smear should be collected within 3 months. If the initial or follow-up Pap smear shows squamous intraepithelial lesions or atypical squamous cells of undetermined significance, the woman should be referred for a colposcopic examination of the lower genital tract and, if indicated, undergo colposcopically directed biopsies. HIV infection is not an indication for colposcopy among women with normal Pap smear results. Because of the common occurrence of HPV-associated cytologic abnormalities in the anal mucosa of both HIV-infected women and homosexual men, some experts have suggested that routine periodic cytologic examination of the anal mucosa should also be considered in high-risk individuals. 334 335 336 A model to estimate the clinical benefits and cost-effectiveness of screening HIV-positive homosexual and bisexual men for anal squamous intraepithelial lesions and anal squamous cell cancer indicates that Pap screening every 1 to 2 years beginning in early HIV disease would result in an incremental cost-effectiveness ratio of $13,000 to $16,000 per quality-adjusted life year saved, and thus offers quality-adjusted life expectancy benefits at a cost comparable with other accepted clinical preventive interventions. 335
CERVICAL CANCER

Epidemiology

Squamous intraepithelial lesions, vulvovaginal condyloma acuminata, and anal intraepithelial neoplasia are seen with approximately fivefold increase in HIV-infected women compared with women not infected with HIV.255,257 The prevalence of cervical intraepithelial neoplasia has been reported to range from 11% to 29% overall for HIV-infected women.257,258 which may be higher than the 4% to 13% prevalence in HIV-negative women.256,259 Among sexually active women, HIV-infected women have a substantially higher rate of persistent HPV infections of the types most strongly associated with intraepithelial lesions and invasive cervical cancer (i.e., HPV-16, HPV-18, and HPV-45).260,261 HPV infection is associated with development of squamous intraepithelial lesions262 and increased prevalence of HPV infection among HIV-infected women may explain the increased incidence of squamous intraepithelial lesions in this population.263 Greater immune suppression is associated with increased incidence of high-grade cervical intraepithelial neoplasia in HIV-infected women, who may also present with invasive cervical cancer at a younger age and with more aggressive advanced stage disease compared with HIV-seronegative women.264 This suggests that progression of HPV-associated dysplasia to frank invasive anogenital cancers may be more rapid in this population. Women with a CD4 cell count less than 500/L appear to be at greater risk for poor outcome.265 The incidence of invasive cervical cancer appears unchanged since the advent of PAT.266 but it is unclear whether this is due to reduce usage of these medications among the women at highest risk for both HIV and HPV, or some other factor. Likewise, the effect of PAT on the incidence of anal squamous intraepithelial lesions is as yet unclear, but the data suggest that PAT may not result in regression of these lesions.267

Progressive immune deficiency may increase the risk of persistent oncongenic HPV infection,257,259 but the association between HIV infection and HPV-associated anogenital cancer could also be related to molecular mechanisms of HIV modulation of HPV expression.268 For example, HIV Tat increases HPV-16 upstream regulatory region-directed chloramphenicol acetyltransferase expression driven by the native HPV-16 promoter (P97). Tat also reverses E2-mediated repression of P97-directed chloramphenicol acetyltransferase expression. Treatment of cells with HIV, Tat, or IL-6 modulates the expression of naturally integrated HPV-18 genes and appears to increase the transcription of HPV E2.269 This occurs due to the HPV-18 DNA replication behavior. HPV-16 and HPV-18 DNA appear to replicate at different times, HPV-16 replication occurs during HIV coinfection.270 HPV Rev and Rev-responsive elements appear to modulate expression of the HPV type 16 L1 protein in epithelial cells.269,271,272

Among women infected with HPV-16 who have developed cervical intraepithelial neoplasia, the amount of HPV-16 DNA in cervicovaginal lavage is significantly increased. If women are infected with HPV-31 consistent with this is the observation that women with HIV viral loads over 10,000 copies per ml are at relatively higher risk of HPV infection-related abnormal PAP smear results.273 Also, HPV appears to be more persistent in the anal mucosa of HIV-infected individuals.274 Thus, it appears that HIV may be a cofactor for the oncogenic effects of HPV.

Therapy

Standard therapy for preinvasive cervical neoplasia, including cryotherapy, laser therapy, cone biopsy, and loop excision, appears to be somewhat less effective in women with HIV infection due to the twofold higher frequency of recurrence even among those with high CD4 cell count.275 The lower the CD4 count, the higher the risk for recurrence. Preliminary data suggest that early preinvasive lesions can regress with effective antiretroviral therapy,276 and that PAT reduces recurrence and progression following standard excisional therapy.277

Invasive cervical cancer should be approached with the same principles of oncologic management that guide treatment of cervical cancer in HIV-negative patients. Patients with well-controlled HIV infection and relative immune preservation can be expected to have better outcomes similar to that of HIV-negative women. Patients with advanced HIV disease may be more intolerant of the myelosuppressive effects of radiation therapy and combination chemotherapy. When such therapy is administered concomitantly with antiretroviral therapy, potential for overlapping toxicity of the various agents should be considered in the therapeutic plan. Following surgery, recurrence is common.278

ANAL CANCER

Evidence of HPV infection of the anal canal and anal cancer and the immediate precursor lesions, high-grade anal intraepithelial neoplasia, are common among HIV-infected women26 and among men who have sex with men, especially those with HIV or immunosuppression.279 HPV infection of the anal epithelium has been reported to be double that of cervical and the prevalence of anal cytologic abnormalities in HIV-infected women have been reported to be 14% to 27% compared with 7% in HIV-negative women.280 Among men, a longitudinal study conducted of 287 HIV-seronegative and 322 HIV-seropositive men attending a community-based clinic revealed anal HPV DNA at entry among 91.6% of men with HIV and 65.9% of men without HIV.281 History of recent anal warts predicted for HPV DNA in all men. Anal squamous intraepithelial lesions do not appear to regress in patients receiving PAT, but among those with high CD4 cell counts the effect appears to be variable.282

For invasive anal cancer, standard combined chemotherapy and radiation appears to effectively control disease in most patients.283,284 Patients with CD4 counts less than 200/L appear more likely to suffer treatment-related toxicity including cytopenias, intractable diarrhea, or moist desquamation requiring hospitalization or a colostomy either for a therapy-related complication or for salvage. Patients with CD4 of 200/L or greater appear to have better disease control with acceptable morbidity.

FUTURE DIRECTIONS

Most AIDS-associated cancers are virally mediated neoplastic processes. In this regard, HIV can play a varied role. It can induce an immunosuppressed host in which oncogenic viral infection and opportunistic neoplasia can develop relatively unchecked, and it can serve to stimulate the immune system to secrete cytokines that promote cellular proliferation and oligoclonal expansions of cells infected with a variety of known oncocogenic viruses. Molecular interactions between HIV-related proteins (or factors induced by HIV) and genomic sequences in some of these viruses may modulate their oncogenic potential. Many AIDS-associated cancers thus appear to be preventable. However, as with other cancers, it is unlikely that behavioral prevention alone will eliminate these epidemic neoplasms. Great strides in the treatment of HIV infection have been made, although it is too soon to determine the ultimate effect of these advances on opportunistic neoplastic disease. The greater understanding of the virologic and molecular basis of these cancers may provide opportunities for advancement in prevention and treatment through antianogenital approaches, antiretroviral–, and immunotherapeutic–based therapies. Research in AIDS malignancies has the potential to affect a number of other important fields in oncology, including general tumor angiogenesis, viral oncogenesis, immunologic control of tumors, and molecular pathogenesis of tumors. This should prove to be a fruitful area of research over the next decade.

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SECTION 50.2
Transplantation-Related Malignancies

STANLEY R. RIDDELL

INTRODUCTION

The transplantation of hematopoietic stem cells to restore bone marrow function after high-dose cytotoxic therapy for malignant and nonmalignant diseases and the surgical implantation of an allogeneic solid organ to restore organ function have become increasingly effective therapeutic modalities. The survival of patients undergoing hematopoietic stem cell and solid organ transplantation has improved as a result of more effective prophylaxis and treatment of infections in the early posttransplant period and the introduction of refined immunosuppressive regimens for preventing or treating graft-versus-host disease (GVHD) and graft rejection, respectively. As larger numbers of patients are being cured of their underlying disease with transplantation, late complications, including the development of a malignancy, have assumed greater importance in the medical management of transplant patients.

The development of registries that collect data on large numbers of patients who have received hematopoietic stem cell or solid organ transplants has provided a mechanism to identify the late development of malignancies in transplant recipients. The method most commonly used for analysis of the risk of a new malignancy is the standardized incidence ratio, which refers to the incidence of the malignancy observed in patients who have undergone transplantation compared with the expected incidence in the general population of the same age and gender. In the 1980s and 1990s, large numbers of patients undergoing hematopoietic stem cell transplantation (HSCT) and solid organ allografting have been followed, and several malignancies that occur with increased frequency compared with the general population have been identified.

IMMUNE SURVEILLANCE AND TUMOR DEVELOPMENT

It has been hypothesized that the host has a natural immunologic resistance against the development of cancer and that the prolonged or intense immunosuppression that is administered to transplant recipients would result in the frequent development of tumors. Class I and II histocompatibility complex (MHC) molecules expressed on the surface of cells bind cellular peptides for presentation to CD8+ and CD4+ T cells, respectively, and this provides a mechanism whereby T cells, which are essential for protecting the host from virus infection, could also recognize and eliminate cells that have developed mutations that induce malignant transformation. Studies have shown that many common tumors in humans do present antigens to T cells, but there has been little direct evidence to support a role for immune surveillance in the development of these cancers.

Although immune surveillance does not appear to limit the development of common malignancies in normal hosts, the observation that many cancers that develop in chronically immunosuppressed transplant recipients are associated with oncogenic viruses such as Epstein-Barr virus (EBV) and human herpesvirus-8 (HHV-8), or with exposure to ultraviolet light suggests that immune surveillance mechanisms may function against these highly antigenic tumors. Virus-associated malignancies often undergo complete regression with withdrawal of immunosuppressive drugs or after restoration of functional T-cell responses to viral antigens by adoptive immunotherapy, and these observations provide direct evidence of a role for host immunity in containing the outgrowth of these tumors. Thus, immunodeficient transplant recipients provide a unique opportunity to reexamine the role of the immune system in tumor development and to determine the principles for effectively treating tumors in humans with immunotherapy.

HEMATOPOIETIC STEM CELL TRANSPLANT RECIPIENTS

Approximately 12,000 allogeneic and 16,000 autologous stem cell transplants are performed worldwide each year. Several studies have demonstrated that patients who have received either an allogeneic or autologous HSCT are at an increased risk for the development of a new malignancy compared with the general population. Allogeneic HSCT recipients are at increased risk for the development of lymphoproliferative disorders and solid tumors, and autologous HSCT recipients are at increased risk for developing acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) and solid tumors. The peak time for the occurrence of these malignancies after transplant suggests distinct factors are involved in their pathogenesis. Solid tumors show a steady increase in incidence with time, lymphoproliferative disorders typically occur during the first year at the height of the immunodeficiency, and AML and MDS primarily occur in the first 3 years after transplant (Fig. 50.2-1).

![FIGURE 50.2-1. Time course and relative risk of the major categories of malignancies that develop after hematopoietic stem cell transplantation. MDS, myelodysplastic syndrome. (Reproduced with permission from Deeg HJ, Socie G. Malignancies after hematopoietic stem cell transplantation: many questions, some answers. Blood 1998;91:1833.)](image)

SOLID TUMORS AFTER HEMATOPOIETIC STEM CELL TRANSPLANTATION

Epidemiology

Early studies in rhesus monkeys and in dogs given gamma irradiation and either autologous or allogeneic HSCT revealed a striking increase in the development of
solid tumors when compared with control unirradiated animals. Tumors developed in these animal models a median of 8 years after transplantation, and it was anticipated that long-term follow-up of humans who received cytotoxic conditioning and HSCT might similarly reveal an increase in the incidence of solid tumors. The first large study to address the development of solid tumors in HSCT recipients evaluated 2145 patients who underwent allogeneic or syngeneic HSCT between 1970 and 1987 as treatment for leukemia or aplastic anemia. In this study, 13 solid tumors developed a median of 56 months (range, 2.5 to 163.0 months) after transplantation. The histology of these malignancies was varied and included glioblastoma, melanoma, squamous cell carcinoma of the skin or oral cavity, basal cell carcinoma of the skin, adenosarcoma of the gastrointestinal tract and lung, and hepatoma. Subsequent studies at other centers confirmed the late development of solid tumors in HSCT recipients. These early studies validated the concern raised by animal models of stem cell transplantation and identified a need to evaluate larger numbers of patients to define the risk of individual tumors and to elucidate the pathogenesis of tumor development in these patients.

A multicenter study analyzed the occurrence of solid tumors in 19,220 patients who received allogeneic or syngeneic HSCT between 1964 and 1992. Overall, the ratio of observed to expected (O/E) cases of new solid tumors was 2.7, with a cumulative incidence rate of 2.2% at 10 years and 6.7% at 15 years. The rapid increase in the incidence of solid tumors between 10 and 15 years suggests that the risk will be even greater with longer follow-up. Cancers that occur with significantly increased frequency in HSCT recipients include melanoma (O/E = 5.0), cancers of the buccal cavity or oropharynx (O/E = 11.1), liver (O/E = 7.5), brain (O/E = 7.6), thyroid (O/E = 6.6), bone (O/E = 13.4), and connective tissues (O/E = 8.0) (Table 50.2-2). Breast, lung, gastrointestinal, and genitourinary tumors, which represent the most common malignancies in the general population, are not increased in HSCT recipients (Table 50.2-2).

The factors associated with an increased risk of solid tumor development in HSCT recipients are younger age at the time of transplant and the use of total body irradiation in the pretransplant conditioning regimen. The risk of developing a tumor posttransplant is 36 times higher than expected for children who are younger than the age of 10 years at the time of transplant, 4.6 times higher for patients aged 10 to 29, and nearly normal for those patients who are aged 30 and older. The excess risk in children younger than age 10 years is primarily due to the development of brain and thyroid tumors in patients who have received pretransplant cranial irradiation. Total body irradiation in doses of greater than 10 Gy in a single dose or greater than 13 Gy in fractionated doses is associated with an increased risk for squamous cell carcinoma of the oral cavity (relative risk = 3.0), melanoma (relative risk = 8.2), thyroid (relative risk = 5.8), and central nervous system (CNS) tumors (relative risk = 4.3). However, there may be a potential role for immune deficiency or dysregulation in the development of melanoma and squamous cell carcinoma of the oral cavity in HSCT recipients. Transplantation of stem cells that are depleted of donor T cells to prevent GVHD confers a significantly increased risk for melanoma (relative risk = 4.5). Additionally, patients who develop chronic GVHD and require longer than 1 year of immunosuppressive therapy exhibit a significantly increased risk of squamous cell carcinoma of the buccal cavity (relative risk = 6.0) and skin (relative risk = 22.6).

Solid tumors also develop with increased frequency in recipients of autologous HSCT, although the available data are derived from analysis of smaller numbers of patients and are not sufficient to accurately define the risk for specific tumors. However, the types of solid tumors reported after autologous HSCT are similar to those seen in allogeneic HSCT recipients and include squamous and basal cell carcinoma of the skin, melanoma, CNS tumors, and thyroid carcinoma. The major risk factor for the development of solid tumors after autologous HSCT is the use of total body irradiation in the conditioning regimen. Studies assessing larger numbers of autologous HSCT recipients will be helpful in further defining the epidemiology of tumors in these patients. Because autologous HSCT recipients do not develop GVHD or receive immunosuppressive drug therapy, comparison of the incidence and types of malignancies that develop in these patients with allogeneic HSCT recipients may assist in elucidating the contributions of GVHD and immunosuppressive drug therapy to the pathogenesis of tumor development.

**Pathogenesis**

The mechanisms operative in the genesis of solid tumors developing after HSCT have not been fully elucidated. The use of total body irradiation is associated with a higher risk of solid tumor development, suggesting that DNA damage induced by ionizing radiation is an important contributor to tumorigenesis. Chronic GVHD is a risk factor for squamous cell cancer of the oral cavity, suggesting that chronic inflammation induced by alloreactivity at the local site, prolonged treatment with immunosuppressive drugs, decreased immune surveillance, or all of these factors may be involved in the development of tumors at this site. DNA from viruses with known oncogenic potential, such as human papilloma virus and EBV, have occasionally been detected in squamous cell carcinomas developing in the skin or at mucosal sites in immunosuppressed patients, and additional studies are necessary to determine if these viruses contribute significantly to tumor development in HSCT recipients. The association of T-cell depleted transplantation with an increased risk of melanoma suggests a potential role for defective T-cell function in the pathogenesis of melanoma. T cells react with melanocyte differentiation antigens such as Melan A, gp100, and tyrosinase, which are expressed in both normal melanocytes and melanomas, have been identified in normal individuals. A role in immune surveillance has not been proven, but such T cells are expanded in the blood and tumor infiltrates of some patients with melanoma, recognize and kill tumor cells in vitro, and can mediate tumor regression after in vitro expansion and adoptive transfer to tumor-bearing hosts.
Clinical Features, Diagnosis, and Management

The clinical features of solid tumors developing in HSCT recipients have not been distinguishable from tumors of the same histology developing in normal individuals, and diagnosis and management should be performed in accordance with standard practice for tumors of the same stage in nontransplant patients.

The increase in the incidence of secondary malignancies after HSCT does have an effect on long-term survival of these patients. A study that examined the causes of late deaths in patients free of their original disease 2 years after allogeneic HSCT found that new cancers accounted for 6% of the late deaths. The median follow-up of patients in this study was only 80 months, and tumors that exhibit a longer latency may yet emerge. Thus, longer follow-up of HSCT recipients will be essential to fully evaluate the risk of solid tumor development and the effect on long-term survival. The current data would suggest that all HSCT recipients should be counseled pretransplant as to their risk of solid tumor development and that symptoms or signs that may be indicative of a malignancy be promptly evaluated to ensure early diagnosis and institution of therapy.

Newer approaches to allogeneic HSCT are being developed that use less intensive conditioning regimens either not containing total body irradiation or using lower doses of irradiation. These approaches are not myeloablative and rely on the allogeneic graft-versus-tumor effect to eradicate the underlying malignancy. If such less intensive conditioning regimens prove to be equally efficacious as conventional myeloablative regimens and are widely adopted, the risk of secondary malignancies in allogeneic HSCT recipients may be reduced.

LYMPHOPROLIFERATIVE DISORDERS ASSOCIATED WITH EPSTEIN-BARR VIRUS IN HEMATOPOIETIC STEM CELL TRANSPLANT RECIPIENTS

Epidemiology

Posttransplant lymphoproliferative disorders (PTLDs), the overwhelming majority of which are of donor B cell origin and associated with EBV infection, are a life-threatening complication of allogeneic HSCT. In contrast to solid tumors, which typically develop after an interval of several years, PTLDs most commonly develop during the first 6 months after HSCT and represent the most frequent new malignancy in the first 5 years after transplant. In a multicenter study of 18,014 patients who received allogeneic HSCT between 1989 and 1992, the cumulative incidence of PTLD was 1.0% at 10 years. More than 80% of the cases occurred in the first year after transplant with the peak incidence in the third month posttransplant.

The risk of developing a PTLD differs dramatically in subsets of patients, depending on factors that interfere with the reconstitution of T-cell immunity. The use of matched related donors, administration of anti-T-cell antibodies in the preparative regimen or as GVHD prophylaxis or therapy, and depletion of T cells from the stem cell inoculum are all associated with an increased risk of PTLD. Recipients of transplants from unrelated donors or donors mismatched at two or more HLA alleles with the recipient have a 3.7-fold greater risk of PTLD than recipients of transplants from matched related donors. The use of antithymocyte globulin or anti-CD3 monoclonal antibodies as prophylaxis or therapy for GVHD is also associated with a markedly increased risk of PTLD.

Patients who receive a stem cell transplant that is depleted of T cells to prevent GVHD are at higher risk (relative risk = 9.1) for developing PTLD than those who receive unmodified bone marrow or peripheral blood stem cells. However, the method used to deplete T cells from the stem cell inoculum influences the risk of PTLD. A high risk of PTLD is seen when T-cell depletion is performed using monoclonal antibodies directed against surface markers expressed only by T cells or both T cells and natural killer cells (relative risk = 12.8), or using sheep red blood cell E-rosetting techniques (relative risk = 18.6). In contrast, depletion of T cells using techniques that eliminate both T and B cells, such as with the CAMPATH-1 antibody, which recognizes the CD52 surface molecule; eteratium, which removes lymphocytes based on size and density; or agglutination with soybean lectin, does not increase the risk of PTLD compared with unmodified HSCT.

The lower incidence of PTLD with these methods of T-cell depletion is presumably due to the removal of EBV-infected B cells from the stem cell inoculum.

Pathogenesis

EBV is a ubiquitous human gamma herpesvirus that establishes a persistent infection in more than 90% of adults, and the near universal association of this virus with PTLD implies a direct role in tumor development. During primary EBV infection in normal hosts, the virus enters B lymphocytes by an interaction between the viral envelope glycoprotein gp350/220 and the B-cell surface molecule CD21, which serves as the receptor for the CD3 complement fragment. Some infected B cells may express the entire array of viral genes and undergo lytic infection and cell death, but a characteristic of primary EBV infection is expression of a limited set of viral proteins that include EBNA-1, EBNA-2, EBNA-3A, EBNA-3B, EBNA-3C, EBNA-LP, LMP-1, LMP-2A, and LMP-2B. This pattern of EBV gene expression, termed the latency III program, is responsible for the proliferation of EBV-infected B cells in the early stages of primary EBV infection and in PTLD developing in immunosuppressed patients.

How EBV induces B-cell proliferation continues to be the subject of intense investigation. The consensus is that immortalization of B cells requires the coordinated action of several EBV proteins. EBNA-1 is required for establishment of the viral genome and EBNA-2 functions as a transcriptional activator that induces the expression of viral and cellular genes that regulate cell growth. LMP-1 acts as an analogue of a constitutively active form of the CD40 signaling molecule in B cells and activates NF-κB. The expression of LMP-1 as a transgene in mice resulted in the development of oligoclonal or monoclonal B-cell lymphomas, suggesting that this molecule is critically involved in B-cell transformation.

In response to primary infection with EBV, immunocompetent hosts mount both a humoral and cellular immune response that limits the spread of replicating virus and eliminates the proliferating EBV-infected B cells that express the latency III program of viral genes. The T-cell response is characterized by major expansions of CD8+ cytotoxic T cells (CTLs) that recognize both EBV lytic phase viral antigens and, with the notable exception of EBNA-1, antigens that are expressed in the proliferating EBV-infected B cells. The elimination of proliferating EBV-infected B cells by CTLs assists in terminating the acute infection. However, residual virus remains in resting memory B cells in which the viral DNA persists as an episome and EBNA-1 is the only viral gene that is expressed. This provides a reservoir of virus that may reactivate, induce polyclonal proliferation of B cells, and result in the emergence of rapidly growing oligoclonal or monoclonal populations.

Clinical Features and Diagnosis

PTLD in HSCT recipients commonly presents with fever and progressive lymphadenopathy. Involvement of pharyngeal lymphoid tissue with an exudative pharyngitis is observed in one-third of patients. The lesions may be extranodal and involve the spleen, liver, lungs, gastrointestinal tract, kidneys, and CNS. Thus, PTLD should be included in the differential diagnosis of symptoms or signs related to these organs in a patient at high risk.

The diagnosis is usually established by biopsy and demonstration of the presence of EBV in involved tissue. Tumors developing after HSCT almost always consist of oligoclonal or monoclonal populations of donor B cells and most commonly exhibit a monomorphic diffuse large cell morphology, although plasmacytoid or polymorphic morphology are also seen. The presence of EBV in the tumor is established by Southern blot of DNA extracted from tumor tissue or by analysis of EBV gene expression in tissue sections. Two EBV-encoded RNAs (EBERs) are abundantly expressed in PTLD and can be detected in tissue sections by in situ hybridization. Immunohistochemical staining with antibodies against EBV proteins can also be used to confirm the presence of EBV in the tumor.

Analysis of ly
gene rearrangements or characterization of repeat sequences at EBV DNA episomal joints is used to determine the clonality of tumor cells. Detection of high EBV DNA levels by polymerase chain reaction analysis of DNA in peripheral blood has been associated with PTLD and may be useful for early diagnosis and monitoring response to therapy.  

Therapy and Prophylaxis of Posttransplant Lymphoproliferative Disorders

The development of PTLD in HSCT recipients is an ominous sign due to the propensity for these tumors to grow rapidly, and urgent therapy is usually necessary. Reduction in the intensity of immunosuppression is indicated, although this may not be possible in patients with severe GVHD. Surgical resection or irradiation may be appropriate as a temporary measure to control anatomically localized disease, but recurrences at other sites are common. Efforts to treat PTLD with chemotherapy regimens similar to those used to treat non-Hodgkin's lymphoma are only occasionally successful in HSCT recipients in part due to the toxicity of administering systemic chemotherapy to these patients.

Anecdotal reports and studies in small numbers of patients have examined systemic therapy with antiviral drugs and interferon-a. Although the administration of acyclovir or ganciclovir is often used as a component of therapy for PTLD, these drugs target the viral thymidine kinase, which is expressed in the replicative phase of EBV infection but not in proliferating EBV-infected B cells. These agents do not inhibit the growth of EBV-transformed B cells in vitro and would not be expected to be beneficial for PTLD. Pharmacologic induction of the viral thymidine kinase gene in EBV-infected cells by administration of arginine butyrate has been reported to render EBV-associated PTLD susceptible to ganciclovir and induce a complete regression in four of six patients. The administration of interferon-a and immunoglobulin was reported to induce regression of PTLD in a small number of patients in an early study, but this approach has not been widely adopted.

The infusion of anti-B-cell monoclonal antibodies directed at the CD21 and CD20 surface molecules has induced regression of PTLD in approximately 50% of patients. However, this approach is less effective in patients with oligoclonal or monoclonal disease and, at the present time, these antibodies are not commercially available. The use of anti-CD20 monoclonal antibody (Rituxan) has been reported to induce remission of PTLD after HSCT in some patients, and the results of additional studies of this agent are eagerly awaited.

The association of deficient EBV-specific T-cell immunity with the development of PTLD has led to efforts to restore T-cell responses to EBV by the adoptive transfer of T cells obtained from the stem cell donor. Support for this approach was provided by a study of five patients who developed PTLD after T-cell–depleted allogeneic HSCT and received infusions of unirradiated donor peripheral blood mononuclear cells containing 1 × 10^6 CD3+ T cells per kilogram of recipient body weight. Clinical and pathologic regression of the PTLD was observed in all five patients, and three of these patients became long-term survivors. Two patients with pulmonary involvement developed fatal respiratory failure after the lymphocyte infusions, and two of the three surviving patients developed chronic GVHD. In a subsequent report, 19 patients with PTLD were treated with donor lymphocytes, and 16 achieved complete pathologic and clinical resolution of their disease. Studies analyzing the frequency of EBV-specific CTLs in the blood before and after therapy demonstrated a rapid amplification of EBV-specific CTLs to levels equivalent to normal donors. However, due to the presence of alloreactive T cells in the donor cells used for therapy, GVHD developed in 50% of the patients treated with this approach.

An approach to cellular therapy of PTLD that alleviates the problem of GVHD uses donor T cells that are enriched for EBV-specific reactivity and depleted of alloreactivity by in vitro culture. The infusion of such cultured EBV-specific T cell lines is effective in treatment of established PTLD in HSCT recipients. Transferred T cells can be identified in the regressing tumor and persist in the blood for longer than 18 months after infusion. The prophylactic administration of EBV-specific T-cell lines to patients who have received a T-cell–depleted HSCT has been effective in preventing PTLD in these high-risk patients. At the present time, the major impediment to the broader application of cellular therapy for EBV-associated PTLD is the technical expertise and resources required to isolate EBV-reactive T cells.

HODGKIN'S DISEASE AND LATE-ONSET NON-HODGKIN'S LYMPHOMAS IN HEMATOPOIETIC STEM CELL TRANSPLANT RECIPIENTS

Epidemiology

Hodgkin's disease has been reported to occur with increased frequency in immunosuppressed patients, including solid organ transplant recipients and human immunodeficiency virus (HIV)-infected patients. The incidence of Hodgkin's disease has been evaluated in 18,531 allogeneic HSCT recipients and compared with the incidence in the general population. Eight cases of Hodgkin's disease were observed in the HSCT patients, which was significantly more than expected in the age- and sex-matched general population (O/E = 6.2). There was a trend toward a significantly increased risk in patients who developed grade 3 or 4 GVHD. The majority of cases were of mixed cellularity histology and contained the EBV genome; however, in contrast to EBV-associated PTLD, which typically occurs in the first 6 months after transplant, the onset of Hodgkin's disease occurred at a median of 4.2 years after transplant. Cases of late-onset non-Hodgkin's lymphoma have also been reported in HSCT recipients, but the majority of these are T cell in origin and an association with lymphotropic viruses, such as EBV or human T-cell lymphotropic virus, has not been demonstrated.

Clinical Manifestations and Management

The cases of Hodgkin's disease reported in HSCT recipients were characterized by an aggressive histology, with 75% being mixed cellularity or lymphocyte depleted. Therapy with conventional chemotherapy or radiotherapy is usually effective, however, with six of the eight patients in the largest series alive 2.7 to 9.6 years after the diagnosis of Hodgkin's disease.

ACUTE LEUKEMIA AND MYELODYSPLASTIC SYNDROME AFTER HEMATOPOIETIC STEM CELL TRANSPLANTATION

Epidemiology

AML and MDS are well-recognized complications of conventional chemotherapy and radiotherapy for Hodgkin's disease, non-Hodgkin's lymphoma, breast cancer, and other malignancies. Patients who receive high-dose chemotherapy and autologous HSCT for non-Hodgkin's lymphoma and Hodgkin's disease have also been reported to have an increased risk of secondary AML or MDS compared with the general population. In three large series, the cumulative incidence of AML/MDS in recipients of autologous HSCT for non-Hodgkin's lymphoma or Hodgkin's disease was 5% at 5 years, 18% at 6 years, and 14.5% at 5 years, respectively. Risk factors for the development of AML/MDS were age older than 40 years at the time of transplant, pretransplant irradiation, pretransplant therapy with alkylating agents, mobilization of stem cells with VP-16, and a low pretransplant platelet count. In one study, the use of total body irradiation in the conditioning regimen was a risk factor for the development of AML/MDS after transplant.

Rare cases of leukemia developing in donor cells after allogeneic HSCT have also been reported. In these cases, the donor reportedly remained healthy and the mechanism of leukemogenesis in the recipient remained unexplained. Inadvertent transplantation of marrow from a donor with AML has also been reported.

Pathogenesis

The pathogenesis of secondary AML/MDS in patients who receive conventional chemotherapy or combined chemoradiotherapy is related to DNA damage in hematopoietic stem cells induced by alkylating agents, epipodophyllotoxins, or ionizing radiation. It is unclear whether the risk of AML/MDS is entirely due to damage to stem cells from prior chemotherapy or if the conditioning regimen administered immediately before transplant further adds to the risk. A study of patients with multiple myeloma who underwent autologous HSCT found that the risk of developing AML/MDS correlated with the intensity and duration of pretransplant conventional chemotherapy. However, the increased risk of AML/MDS when total body irradiation was a component of the conditioning regimen suggests that there may be additional contributions from regimen-related damage to residual stem cells in the patient or to the marrow stroma.

Cytogenetic abnormalities are occasionally found in the marrow of patients being evaluated for autologous HSCT. In a few cases in which the marrow was morphologically normal and was used for transplant despite the presence of cytogenetic alterations, the patients developed MDS or AML in the first 12 months after transplant. Thus, cytogenetic analysis of the bone marrow should be considered in patients with extensive prior therapy who are being evaluated for HSCT.

Clinical Features and Management

Multiple cases of leukemic transformation have been reported in patients transplanted after high-dose chemotherapy with autologous HSCT. One such case was characterized by a marked increase in blasts in the blood and bone marrow, and the patient eventually died of refractory acute myeloid leukemia. Another patient developed a large-cell lymphoma with immunophenotypic characteristics of a myeloid leukemia, and the clonal relationship of the leukemic and lymphomatous cells was confirmed by gene rearrangements or characterization of repeat sequences at EBV DNA episomal joints.
The clinical features of AML/MDS after autologous HSCT are the same as those seen in cases of secondary AML/MDS that develop after conventional chemotherapy or low-dose radiation. These include frequent abnormalities of chromosomes 5 and 7 and a poor response to therapy. A small number of patients who have developed AML/MDS after autologous HSCT have subsequently been treated with a second high-dose cytotoxic regimen followed by allogeneic HSCT. This approach is complicated by a high risk of regimen-related toxicity but can be curative.

ORGAN TRANSPLANT RECIPIENTS

The transplantation of allogeneic solid organs has become a widely used and often life-saving therapy, with more than 20,000 procedures performed in 1997 in the United States. However, recipients of organ allografts generally require life-long therapy with immunosuppressive drugs to prevent or treat episodes of graft rejection and are at increased risk for the development of a malignancy. The overwhelming majority of tumors arising in solid organ transplant recipients are de novo malignancies of recipient origin, or recurrence of a malignancy existing in the recipient before transplant. However, a malignancy of donor origin may occasionally arise in the transplanted organ or be inadvertently transmitted to the recipient via the transplanted organ. Polymorphic molecular markers that differ between donor and recipient can be used to determine the origin of the malignancy, and these studies should be considered in suspicious cases because withdrawal of immunosuppression can sometimes result in regression of donor-derived malignancies.

Data from single institutions and large international registries have shown that the incidence of cancer in organ allograft recipients is increased three- to fourfold compared with the general population. The incidence of tumor development increases with the length of observation after transplant. In two studies of renal allograft recipients, the risk of developing cancer at 20 years after transplant was 40% to 50% compared with a 6% cumulative risk in the general population of age-matched individuals. Similar to the findings in HSCT recipients, malignancies that develop frequently in the general population, such as those occurring in breast, lung, prostate, colon, and cervix, are not increased in solid organ transplant recipients. The incidence of cancers of the skin and lip, and B-cell lymphoproliferative diseases are increased in both solid organ transplant and HSCT recipients. Kaposi's sarcoma (KS), which is rarely seen in HSCT recipients, is significantly increased in organ allograft recipients.

CANCER OF THE SKIN AND LIP

Epidemiology

Cancer of the skin or lip is the most common neoplasm developing in organ allograft recipients, and the risk of a cutaneous neoplasm is increased 3.2- to 24.0-fold compared with the general population. The most dramatic increase is in squamous cell carcinoma, but the risk of developing basal cell carcinoma, melanoma, and Merkel's cell carcinoma is also significantly increased. The cumulative incidence of skin cancer increases with time after transplantation (Table 50.2-3). The incidence of skin cancer in renal transplant recipients was 70% at 20 years in a study from Australia where sun exposure is high, and 40% in a study from the Netherlands. In two studies of heart transplant recipients, the incidence of skin cancer was 44% and 35% at 7 and 10 years, respectively. In the general population, basal cell carcinoma of the skin occurs five times more frequently than squamous cell carcinoma, whereas in organ transplant recipients, squamous cell carcinoma occurs one to three times more frequently than basal cell carcinoma.

<table>
<thead>
<tr>
<th>TABLE 50.2-3. Cumulative Incidence of Skin Cancer in Organ Transplant Recipients</th>
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<tr>
<td>Cumulative sun exposure, the length of time after transplant, and mismatching between donor and recipient at the HLA-B locus or homozygosity at the HLA-DR locus have been identified as risk factors for the development of skin cancer in organ transplant recipients. Features prevalent in patients with skin cancer in the general population, including light skin and blonde or red hair, are also prevalent in transplant recipients.</td>
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<tr>
<td>The length of time from transplant is an important risk factor and presumably reflects the contributions of immunosuppressive drug therapy to tumorigenesis. Insufficient data are available to conclude whether specific immunosuppressive drugs or the intensity of the regimen influences the risk of skin cancer. Patients who receive cyclosporine in addition to azathioprine and prednisolone have been reported to be at higher risk for the development of skin cancer. However, other studies have not found an association between the type of immunosuppressive drug regimen used and the risk of skin cancer.</td>
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<tr>
<td>Sun exposure and cigarette smoking are risk factors for the development of cancer of the skin and lip in organ transplant recipients. In addition to an increased incidence of malignant lesions, transplant recipients have a higher incidence of leukoplakia and dysplastic lesions of the lip when compared with age- and sex-matched controls.</td>
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<tr>
<td>Pathogenesis</td>
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<tr>
<td>Multiple factors may be involved in the pathogenesis of cancers of the skin and lip in organ allograft recipients, including underlying genetic predisposition, environmental factors, immunologic alterations induced by the transplant, immunosuppressive drugs, and viral infection. The mechanism by which transplantation and immunosuppressive drug therapy potentiates the development of skin cancer remains elusive. In murine models, tumors induced by ultraviolet light are often highly aggressive when transplanted into syngeneic mice, suggesting defects in the host immune response are required for tumor formation. There is evidence that ultraviolet light induces local immunosuppressive effects that facilitate the establishment of tumors, and immunosuppressive drugs may potentiate this local impairment in host immunity. Consistent with this hypothesis, the skin of renat graft recipients exhibits a decrease in the density of CD4+ and CD8+ T lymphocytes, and CD1a+ dermal Langerhans' cells when compared with normal controls. Moreover, melanomas that occur in solid organ transplant recipients lack the mononuclear cell infiltrates that are frequently seen in tumors in immunocompetent hosts and are associated with a good prognosis. A potential role for cyclosporine in tumorigenesis that is distinct from its immunosuppressive properties has been identified. Exposure of tumor cells to cyclosporine increases the production of transforming growth factor-β, which results in increased tumor cell motility and invasiveness.</td>
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<td>The association of viral infections with the development of malignancies in immunosuppressed patients has prompted a search for viruses in skin cancers in organ allograft recipients. There have been reports of the detection of human papilloma-virus DNA in a significant fraction of skin cancers in organ transplant recipients. However, other studies have failed to detect human papilloma-virus, and the role of this agent in the development of skin cancer in transplant recipients remains controversial. EBV DNA and gene expression has been detected in tumors from 10 of 15 cardiac allograft recipients with squamous cell carcinoma, suggesting a potential role for EBV as a cofactor in tumor development.</td>
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<tr>
<td>Clinical Features, Management, and Prevention</td>
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<tr>
<td>Skin disorders that resemble malignancies, such as warts, hyperkeratoses, and keratoacanthomas, are frequently observed in transplant patients, and a biopsy...</td>
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</table>
Hodgkin's disease has also been reported in organ allograft recipients, and the tumors are usually EBV positive. The overwhelming majority of PTLD are EBV-associated and of B cell origin, but well-documented cases of T-cell lymphoproliferative disorders have been described.

**EPSTEIN-BARR VIRUS–ASSOCIATED LYMPHOPROLIFERATIVE DISORDERS IN ORGAN TRANSPLANT RECIPIENTS**

**Epidemiology**

PTLDs associated with EBV infection are the second most frequent malignancy in solid organ transplant recipients. In a study of 45,141 kidney transplant recipients and 7634 heart transplant recipients, the incidence of PTLD during the first year after transplant was 0.2% for kidney transplant recipients and 1.2% for heart transplant recipients. These rates are 20 and 120 times higher, respectively, than the incidence of non-Hodgkin's lymphoma in the general population. The incidence of PTLD is highest in the first year after transplant, but these tumors may develop with increased frequency for more than 6 years after transplant. PTLD in organ allograft recipients develop in host B cells, although the EBV strain may be derived from reactivation of latent virus in the host or virus transmitted with the donor organ. Transplant recipients who are EBV seronegative and receive an organ from an EBV-seropositive donor are up to 76 times more likely to develop a PTLD than EBV-seronegative recipients.

The drug regimen used to prevent or treat graft rejection influences the risk of PTLD, with the highest risk of PTLD observed in patients who receive cyclosporine, FK-506, or anti-CD3 monoclonal antibodies. Heart, lung, or heart and lung transplants have a higher incidence of PTLD than patients receiving kidney or liver transplants because intensive immunosuppression must be maintained in these patients to prevent life-threatening graft rejection. The administration of anti-CD3 monoclonal antibodies confers a particularly high risk of PTLD related both to the suppression of T-cell function and the release of T-cell cytokines that activate B cells.

**Pathogenesis**

The pathogenesis of PTLD occurring in solid organ transplant recipients is similar to that in HSCT recipients and reflects defective control of EBV by the host immune response. The immunosuppressive drugs administered to organ transplant patients potently suppress EBV-specific CTL activity in vitro and in vivo. A study of 30 cardiopulmonary transplant recipients who received cyclosporin A and azathioprine as rejection prophylaxis showed that EBV-specific CTL activity in the peripheral blood was suppressed or undetectable in all patients during the first 6 months after transplant. Recovery of EBV-specific T-cell responses is further impaired in patients who require additional immunosuppressive therapy with prednisone or azathioprine to treat rejection episodes. These studies support a deficiency of EBV-specific CTLs as the critical factor in pathogenesis, but the clinical presentation of PTLD in organ allograft recipients suggests that local factors at the tumor site also play a role. Tumors frequently involve the transplanted organ, the CNS, and the gastrointestinal tract, suggesting that immunoregulatory factors in the microenvironment may act in concert with a deficiency of EBV-specific CTLs to predispose to the development of PTLD. The organ allograft is a site of chronic immune stimulation, and local cytokines produced by alloreactive T cells have been suggested to promote the activation and growth of EBV-infected B cells.

**Clinical Features, Diagnosis, and Management**

Patients developing PTLD may present with an infectious mononucleosis syndrome, including fever, peripheral lymphadenopathy, and tonsillar enlargement. Occasionally, the disease presents with a fulminant course characterized by rapidly progressive diffuse multorgan involvement and severe systemic symptoms. More commonly, PTLD presents with localized lesions in lymph nodes, extranodal sites, such as the gastrointestinal tract, CNS, lung, and the transplanted organ, or both nodes and extranodal sites.

The diagnosis of PTLD is made by biopsy of involved tissue as described earlier for HSCT recipients. Three morphologic variants of PTLD are recognized in solid organ transplant recipients. These include plasmacytic hyperplasia, which is typically polyclonal, polymorphic B cell hyperplasia, which is typically monoclonal, and monomorphic lymphoma or multiple myeloma, which is monoclonal and contains alterations in oncogenes, tumor suppressor genes, or both, in addition to the EBV genome. Studies suggest that patients with the monomorphic/myeloma morphology or with bcl-6 mutations have a poor response to therapy. A standard approach to the management of PTLD in organ allograft recipients has not been established. The therapeutic approach may depend on the site of tumor involvement, the rate of tumor growth, and the necessity to maintain intense immunosuppression. Initial therapy frequently consists of a reduction or withdrawal of immunosuppressive drug therapy, which can result in expansion of endogenous EBV-specific T cells and complete regression of the tumor. However, this strategy may lead to rejection of the organ allograft, which, with the exception of renal transplant recipients who can return to dialysis therapy, can have disastrous consequences. Anatomically localized lesions may be amenable to surgical resection or limited field irradiation, but tumor recurrence is common.

Systemic therapy is usually necessary to control PTLD that fails to regress after a reduction in immunosuppressive therapy. The use of a combination of anti-B cell monoclonal antibodies targeting CD20 and CD24 for PTLD in organ transplant recipients resulted in a 55% survival at a median of 61 months, although the subset of patients with visceral disease, CNS involvement, or onset longer than 1 year after transplant responded poorly to therapy. Early results with the anti-CD20 antibody Rituxan suggest a comparable response rate, although the follow-up on these patients is short.

Chemotherapy has been used in patients who fail to respond to a reduction in immunosuppressive or who have rapidly progressive disease. In small studies, standard regimens used for non-Hodgkin's lymphoma, such as cyclophosphamide, hydroxydaunorubicin (Adriamycin), Oncovin, and prednisone or ProMACE-CytaBOM have induced durable complete remissions in the majority of patients. However, other studies have reported significantly less promising results due both to a high incidence of infectious complications related to neutropenia and refractory disease.

**CHEMOPROPHYLAXIS OF SKIN CANCER**

Squamous cell carcinomas in organ transplant patients are also more likely to metastasize to lymph nodes and distant sites. Treatment of skin cancers in these patients is performed with the same modalities used for tumors in the general population, including surgical excision, cryosurgery, or radiotherapy. Given the aggressive nature of skin cancers in organ allograft recipients, it is essential to educate patients about the hazards associated with sun exposure, provide strategies for protecting the skin from sunlight, and promote awareness of the importance of early detection and treatment. Chemoprophylaxis of skin cancer with systemic retinoids may also be appropriate in high-risk patients. Acitretin has been suggested to reduce the number of new tumors in renal transplant recipients and to prevent keratotic skin lesions and skin cancer in a placebo-controlled trial. The most effective preventive measure for skin cancer may come from the development of novel approaches to induce specific tolerance to the donor organ that do not require long-term administration of drugs that cause global immunosuppression.

**LATE-ONSET LYMPHOMAS AND HODGKIN'S DISEASE IN ORGAN TRANSPLANT RECIPIENTS**

The overwhelming majority of PTLD are EBV-associated and of B cell origin, but well-documented cases of T-cell lymphoproliferative disorders have been described in organ transplant recipients. The T-cell lymphoproliferations typically occur several years after transplant, involve the bone marrow and peripheral blood at presentation, and are not related to EBV, human T-cell lymphotropic virus, or HHV-8 infection. The prognosis for these patients is poor despite the administration of chemotherapy and reduction of immunosuppression.

Hodgkin's disease has also been reported in organ allograft recipients, and the tumors are usually EBV positive. The clinical presentation is typical of Hodgkin's
KAPOSI’S SARCOMA

Epidemiology

The incidence of Kaposi’s sarcoma is up to 500 times greater in organ transplant recipients than in the general population. Immunocompromised patients who received solid organ transplants are at risk of developing Kaposi’s sarcoma due to the presence of human herpesvirus-8 (HHV-8) in the inoculum. The disease is more common in recipients of allogenic transplants (125.126,127) than in those who receive autogenic transplants (127). The risk of developing Kaposi’s sarcoma is highest in recipients of cardiac transplants (128). People with AIDS are also at increased risk. HHV-8 infection is found in the genomes of many organ transplant recipients and is associated with the development of KS.

Pathogenesis

The finding of HHV-8 DNA in KS lesions suggests that this herpes virus is central to the pathogenesis of the tumor. HHV-8 has been shown to reactivate soon after transplantation, and increasing levels of virus in the blood are associated with the development of KS. Despite antilysis neutralizing antibodies of HHV-8 and vasoconstrictive drug therapy in the development of KS is also unresolved. In vitro, corticosteroids activate the lytic cycle of HHV-8 gene expression, suggesting that immunosuppression may increase viral load in vivo. The spontaneous regression in KS lesions observed with withdrawal of immunosuppression in organ transplant recipients or with the resolution of immunodeficiency in HIV infection suggests that cellular immune responses have a crucial role in control of HHV-8 infection and preventing the development of KS. CD8+ CTLs specific for antigens expressed in latent and lytic infection have been identified in HHV-8 seropositive individuals, and it is anticipated that future studies will address the role of deficient T-cell responses to HHV-8 in the development of KS.

Clinical Features and Management

Sixty percent of organ allograft recipients with KS present with localized skin or mucosal lesions, and the remainder present with visceral disease involving the gastrointestinal tract, lungs, and lymph nodes. The diagnosis of KS, which can be difficult in cases of visceral disease, is made by biopsy and histologic analysis. The incidence of KS development is much lower for organ transplant recipients than for KS patients with HIV infection, but this is to be expected because organ transplant recipients are not immunocompromised as a result of their underlying disease. The incidence of KS development is much lower for organ transplant recipients than for KS patients with HIV infection, but this is to be expected because organ transplant recipients are not immunocompromised as a result of their underlying disease.

OTHER HUMAN HERPESVIRUS-8–ASSOCIATED MALIGNANCIES IN ORGAN TRANSPLANT RECIPIENTS

HHV-8 has also been associated with other malignancies, including primary effusion lymphoma in HIV-infected patients and multicentric Castleman’s disease in both HIV-positive and -negative patients. Primary effusion lymphoma with integrated HHV-8 DNA has been reported to occur rarely in solid organ transplant recipients and can be distinguished from the more common PTLD by the presence of malignant pleural, peritoneal, or pericardial effusions without tumor mass. The incidence of Kaposi’s sarcoma is up to 500 times greater in organ transplant recipients than in the general population, and these patients respond to conventional therapy.

References


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Superior Vena Cava Syndrome

JOACHIM YAHALOM

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Etiology and Natural History
Diagnostic Procedures
Management
Small Cell Lung Cancer
Non-Hodgkin’s Lymphoma
Nonmalignant Causes
Catheter-Related Obstruction
Treatment
Radiation Therapy
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INTRODUCTION

Superior vena cava syndrome (SVCS) is the clinical expression of obstruction of blood flow through the SVC. Characteristic symptoms and signs may develop quickly or gradually when this thin-walled vessel is compressed, invaded, or thrombosed by processes in the superior mediastinum. The first pathologic description of SVCS obstruction, in a patient with syphilitic aortic aneurysm, appeared in 1757. In 1954, Schechter reviewed 274 well-documented cases of SVCS reported in the literature; 40% of them were due to syphilitic aneurysms or tuberculosis mediastinitis. These entities have since virtually disappeared, and cancer of the lung is now the underlying process in approximately 70% of patients with SVCS. It is estimated that, in the United States, 15,000 people develop SVCS each year.

ANATOMY AND PATHOPHYSIOLOGY

The SVC is the major vessel for drainage of venous blood from the head, neck, upper extremities, and upper thorax. It is located in the middle mediastinum and is surrounded by relatively rigid structures, such as the sternum, trachea, right bronchus, aorta, pulmonary artery, and the perihilar and paratracheal lymph nodes. The SVC extends from the junction of the right and left innominate veins to the right atrium, for a distance of 6 to 8 cm. The distal 2 cm of the SVC is within the pericardial sac, with a point of relative fixation of the vena cava at the pericardial reflection. The axzygos vein, the main auxiliary vessel, enters the SVC posteriorly, just above the pericardial reflection. The width of the SVC is 1.5 to 2.0 cm and it maintains blood at a low pressure. The SVC is thin-walled, compliant, and easily compressible, and is vulnerable to any space-occupying process in its vicinity. The SVC is completely encircled by chains of lymph nodes that drain all the structures of the right thoracic cavity and the lower part of the left thorax. The auxiliary axzygos vein is also threatened by enlargement of paratracheal nodes. Other critical structures in the mediastinum, such as the main bronchi, esophagus, and the spinal cord, may be involved by the same process that led to obstruction of the SVC.

When the SVC is fully or partially obstructed, an extensive venous collateral circulation may develop. The axzygos venous system is the most important alternative pathway. Carlson found that dogs could not survive sudden ligation of the SVC below the level of the axzygos vein, but they tolerated well ligation of the SVC above it. He could, however, successfully obstruct the SVC and the axzygos vein in operations performed in two stages, presumably by allowing time for collaterals to form. Other collateral systems are the internal mammary veins, lateral thoracic veins, paraspinous veins, and the esophageal venous network. The subcutaneous veins are important pathways, and their engorgement in the neck and thorax is a typical physical finding in SVCS. Despite these collateral pathways, venous pressure is almost always elevated in the upper compartment if there is obstruction of the SVC. Venous pressures have been recorded as high as 200 to 500 cm H2O in severe SVCS.

ETIOLOGY AND NATURAL HISTORY

SVCS usually has an insidious onset and progresses to typical symptoms and signs. Review of the data from three series (Table 51.1-1) shows dyspnea to be the most common symptom. Dyspnea occurred in 63% of patients with SVCS. A sensation of fullness in the head and facial swelling was reported by 50% of the patients. Other complaints were cough (24%), arm swelling (18%), chest pain (15%), and dysphagia (9%). The characteristic physical findings were venous distention of the neck (66%) and chest wall (54%), facial edema (46%), plethora (19%), and cyanosis (19%). These symptoms and signs may be aggravated by bending forward, stooping, or by lying down.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Prevalence (%)</th>
<th>Physical Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea</td>
<td>63</td>
<td>Venous distention of neck</td>
</tr>
<tr>
<td>Necrosis of head</td>
<td>6</td>
<td>Venous distention of neck</td>
</tr>
<tr>
<td>Cyanosis</td>
<td>19</td>
<td>Venous distention of neck</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>18</td>
<td>Venous distention of neck</td>
</tr>
</tbody>
</table>

Malignant disease is the most common cause of SVCS. The percentage of patients in different series with a confirmed diagnosis of malignancy varies from 78% to 86% (Table 51.1-2). Lung cancer was diagnosed in 65% of 415 patients analyzed in these series. Armstrong et al. did a retrospective review of 4100 cases treated for bronchogenic carcinoma between 1965 and 1984, and they identified 99 patients (2.4%) with SVCS. Salsali and Clifton observed SVCS in 4.2% of 4960 patients with lung cancer. Of the tumors inducing SVCS were of the right lung. Small cell lung cancer (SCLC) is the most common histologic subtype (Table 51.1-3), and it was found in 38% of the patients who had lung cancer and SVCS. In six large series of SCLC, 9% to 19% of patients developed SVCS.

The second most common histologic subtype is squamous cell carcinoma, found in 26% of lung cancer patients with SVCS.

TABLE 51.1-1. Common Symptoms and Physical Findings of Superior Vena Cava Syndrome
Nonmalignant conditions causing SVCS are not as rare as previously reported. When the data were collected from general hospitals, as many as 22% of patients had nonneoplastic causes of SVCS. Parish et al. reported 19 patients with benign causes of SVCS, and Schraufnagel et al. included 16 such patients in his series. Fifty percent of the patients in both reports had a diagnosis of mediastinal fibrosis, which was probably due to histoplasmosis. Parish et al. reported six patients with thrombosis of SVC, and in five, the thrombosis developed in the presence of central vein catheters or pacemakers. Sculier and Field reviewed 24 cases of central venous catheter--induced SVC. Of these, 18 were caused by pacemaker catheters. LeVeen peritoneovenous shunts, Swan-Ganz catheters, and hyperalimentation catheters were also involved. The increasing use of these devices for the delivery of chemotherapy agents or for hyperalimentation contributes to the development of SVCS in the cancer patient.

Obstruction of SVC in the pediatric age group is rare and has a different etiologic spectrum. The causative factors are mainly iatrogenic secondary to cardiovascular surgery for congenital heart disease, ventriculocistern shunt for hydrocephalus, and SVC catheterization for parenteral nutrition. In a report of 175 children with SVCS, 70% were iatrogenic. Of these, 18 were caused by pacemaker catheters. LeVeen peritoneovenous shunts, Swan-Ganz catheters, and hyperalimentation catheters were also involved. The increasing use of these devices for the delivery of chemotherapy agents or for hyperalimentation contributes to the development of SVCS in the cancer patient.

### DIAGNOSTIC PROCEDURES

SVCS has long been considered to be a potentially life-threatening medical emergency. It was common practice to immediately apply radiation therapy with initial high-dose fractions, sometimes even before the histologic diagnosis of the primary lesion was established. Diagnostic procedures, such as bronchoscopy, mediastinoscopy, thoracotomy, or supraclavicular lymph node biopsy, were often avoided because they were considered to be hazardous in the presence of SVCS. However, the safety of these invasive procedures in patients with SVCS has markedly improved, and the modern treatment of SVCS has become disease-specific from the outset. Temporizing emergency mediastinal irradiation before biopsy is rarely used because it may preclude proper interpretation of the specimen in almost one-half of patients.

The clinical identification of SVCS is simple because the symptoms and signs are typical and unmistakable. The chest film shows a mass in most patients. Only 16% of the patients studied by Parish had normal chest films. The most common radiographic abnormalities are superior mediastinal widening and pleural effusion. Computed tomography (CT) provides more detailed information about the SVC, its tributaries, and other critical structures, such as the bronchi and the cord. The additional information is necessary because the involvement of these structures requires prompt action for relief of pressure. CT phlebography provides excellent imaging information on the site and extent of obstruction and the status of collaterals. Helical CT phlebography replaced the combination of CT and digital phlebography that was advocated in the past. The role of magnetic resonance imaging has been insufficiently investigated but appears promising, especially because this modality is noninvasive.

### TABLE 51.1-4. Chest Radiographic Findings for 86 Patients with Superior Vena Cava Syndrome

<table>
<thead>
<tr>
<th>Finding</th>
<th>Number of Patients</th>
<th>Percentage of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superior mediastinal widening</td>
<td>53</td>
<td>64</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>32</td>
<td>34</td>
</tr>
<tr>
<td>Right hilar mass</td>
<td>32</td>
<td>34</td>
</tr>
<tr>
<td>Mediastinal widening</td>
<td>25</td>
<td>30</td>
</tr>
<tr>
<td>Mediastinal effusion</td>
<td>22</td>
<td>25</td>
</tr>
<tr>
<td>Mediastinal fluidic mass</td>
<td>15</td>
<td>18</td>
</tr>
<tr>
<td>Mediastinal (nonmalignant)</td>
<td>14</td>
<td>16</td>
</tr>
</tbody>
</table>

### TABLE 51.1-3. Lung Cancer Subtypes Associated with Superior Vena Cava Syndrome

Lymphoma involving the mediastinum was the cause of SVCS in 8% of patients reported in the series (see Table 51.1-2). Armstrong et al. found SVCS in 1.9% of 952 lymphoma patients. Perez-Soler et al. identified 36 cases (4%) of SVCS among 915 patients with non-Hodgkin's lymphoma (NHL) treated at the M. D. Anderson Cancer Center. Twenty-three patients (64%) had diffuse large cell lymphoma, 12 (33%) had lymphoblastic lymphoma, and one patient had follicular large cell lymphoma. Of their patients with diffuse large cell lymphoma and lymphoblastic lymphoma, 7% and 21% had SVCS, respectively. In a series of patients with primary mediastinal B-cell lymphoma with sclerosis, SVCS was present in 57% of patients. Hodgkin's lymphoma commonly involves the mediastinum, but it rarely causes SVCS. Other primary mediastinal malignancies that cause SVCS are thymoma and germ cell tumors. Breast cancer is the most common metastatic disease that causes SVCS.

In one report, breast cancer was the cause of SVCS in 11% of cases. 10

Nonmalignant conditions causing SVCS are not as rare as previously reported. When the data were collected from general hospitals, as many as 22% of patients had nonneoplastic causes of SVCS. Parish et al. reported 19 patients with benign causes of SVCS, and Schraufnagel et al. included 16 such patients in his series. Fifty percent of the patients in both reports had a diagnosis of mediastinal fibrosis, which was probably due to histoplasmosis. Parish et al. reported six patients with thrombosis of SVC, and in five, the thrombosis developed in the presence of central vein catheters or pacemakers. Sculier and Field reviewed 24 cases of central venous catheter--induced SVC. Of these, 18 were caused by pacemaker catheters. LeVeen peritoneovenous shunts, Swan-Ganz catheters, and hyperalimentation catheters were also involved. The increasing use of these devices for the delivery of chemotherapy agents or for hyperalimentation contributes to the development of SVCS in the cancer patient.

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### DIAGNOSTIC PROCEDURES

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Contrast venography provides important information for determining if the vena cava is completely obstructed or remains patent and extrinsically compressed. Dey and Moghissi demonstrated by venography that 41% of patients with SVCS have a patent SVC that is displaced or involved but not obstructed by a tumor. Another 19% have SVC obstruction below the azygos vein, for which collaterals may compensate. Venography is valuable if surgical bypass is considered for the obstructed vena cava. Lokitich and Goodman stated that venograms are relatively contraindicated because the interruption of the integrity of the venous wall, in the presence of increased intraluminal pressures, may result in excessive bleeding from the puncture site. However, no evidence of this complication has been reported. Although a venography can confirm the clinical diagnosis and outline the anatomy, priority should still be given to procedures that help establish the histologic diagnosis. Radionuclide technetium (Tc-99m) scintigraphy is an alternative, minimally invasive method of imaging the venous system. Although images that are obtained by this method are not as well defined as those achieved with contrast venography, they demonstrate patency and flow patterns. Collateral circulation can be evaluated in a general manner and quantified to some degree by radionuclide venography. Gallium single photon emission CT may be of value in selected cases.

In 58% of 107 patients reported by Schraufnagel et al., the SVCS developed before the primary diagnosis was established. The diagnostic procedures used in different studies are summarized in Table 51.1-5. Sputum cytology established the diagnosis for almost one-half of patients. Cytologic diagnosis is as accurate as tissue diagnosis in small cell carcinoma. Bronchoscopy supplies the malignant cells for cytologic evaluation in most cases of small cell disease. In the presence of pleural effusion, thoracocentesis established the diagnosis of malignancy in 71% of patients. Biopsy of a supraclavicular node, especially if there was a suspicious palpable finding, was rewarding in two-thirds of the reported attempts. SCCL and NHL often involve the bone marrow. A biopsy of the bone marrow may provide the diagnosis and stage for these patients. Mediastinoscopy has a very high success rate for providing a diagnosis, and a complication rate of approximately 5%. Reports by Jahangiri and Goldstraw (34 patients) and Mineo et al. (80 patients), on using mediastinoscopy for patients with SVCS whose histologic diagnosis could not be established with less invasive techniques, confirmed the safety and high diagnostic yield of mediastinoscopy. No perioperative mortality was recorded and the diagnosis yield was excellent.

### Table 51.1-5. Positive Yield of Diagnostic Procedures for Patients with Superior Vena Cava Syndrome

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Number of Patients</th>
<th>Positive Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sputum cytology</td>
<td>59</td>
<td>29</td>
</tr>
<tr>
<td>Thoracotomy</td>
<td>21</td>
<td>19</td>
</tr>
<tr>
<td>Bone marrow biopsy</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Bronchoscopy</td>
<td>61</td>
<td>35</td>
</tr>
<tr>
<td>Mediastinoscopy</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>123</td>
<td>59</td>
</tr>
</tbody>
</table>

Ahmann examined the traditional opinion that diagnostic procedures carry with them significant hazard, primarily excessive bleeding. He reviewed 843 invasive and seminvasive diagnostic procedures and found that only ten reported complications, none of them fatal. Ahmann and others found minimal evidence to suggest that diagnostic procedures such as venographies, thoracocentesis, bronchosopies, mediastinoscopies, and lymph node biopsies carry an excessive risk in patients with SVCS. In 163 patients treated at Memorial Sloan-Kettering Cancer Center for anterior mediastinal mass, 44 underwent general anesthesia. There were no deaths and only four patients had prolonged intubation, demonstrating the low risk of modern anesthesia in thoracic patients.

### MANAGEMENT

The goals of treatment of SVCS are to relieve symptoms and to attempt the cure of the primary malignant process. SCLC, NHL, and germ cell tumors constitute almost one-half of the malignant causes of SVCS. These disorders are potentially curable, even in the presence of SVCS. The treatment of SVCS should be selected according to the histologic disorder and stage of the primary process. The prognosis of patients with SVCS strongly correlates with the prognosis of the underlying disease. When the therapeutic goal is only palliation of SVCS, or when urgent treatment of the venous obstruction is required, direct opening of the occlusion should be considered. The newer techniques of endovascular stenting and angioplasty with possible thrombolysis should provide prompt relief of symptoms before more specific cancer therapy.

### SMALL CELL LUNG CANCER

Chemotherapy alone or in combination with thoracic irradiation therapy is the standard treatment for SCLC. Both chemotherapy and radiotherapy as initial treatments are effective in rapidly improving the symptoms of SVCS. In an analysis of 50 patients with SCLC who presented with SVCS, investigators from Ontario, Canada recorded a response rate to chemotherapy of 93% and a similar response to mediastinal irradiation of 94%. In this series, 70% of patients remained SVCS-free before death. It is of interest that, when the total treatment of SCLC included both chemotherapy and radiation, the risk of SVCS recurrence was significantly lower than when the treatment was chemotherapy alone. A small randomized trial, however, could not show that the addition of mediastinal radiation after chemotherapy in patients with SVCS and SCCL increased the protection from local recurrence or improved the survival rate.

Among 643 patients with SCLC, Scoulier et al. identified 55 patients (8.5%) with SVCS. One-half of patients developed the manifestations of SVCS before the histologic diagnosis was established. In the other patients, the syndrome developed after the pathologic diagnosis of SCLC was made, but before a specific treatment was started. Symptomatic relief of SVCS was obtained in 35 of 48 patients (73%) initially treated with chemotherapy and in 3 of 7 patients (43%) who were initially treated with radiation. Relief of SVCS occurred within 7 to 10 days after initiation of therapy. In SCLC patients with recurrent or persistent SVCS after initial chemotherapy, the obstruction responded in five of seven patients (71%) who received additional chemotherapy and in 25 of 32 patients (78%) who received radiotherapy. These data support retreatment of SVCS for palliation of symptoms.

In some series of SCLC, SVCS was a favorable prognostic sign, whereas its presence did not affect survival in other reports. A study of 408 patients with SCLC by Wunschmidt et al. showed that the presence of SVCS independently predicted for better survival. Other independent predictors for better survival were stage and performance status. The reason for the possible association of SVCS with better prognosis remains obscure. It is of interest to note that some researchers found a higher incidence of brain metastases at the time of diagnosis in SCLC patients with SVCS compared to patients without SVCS.

Although randomized trials of the contribution of thoracic irradiation to chemotherapy have not consistently demonstrated an advantage to the combined modality approach, metaanalysis of these studies showed a small but significant improvement in local control and survival of patients with limited disease with the addition of radiotherapy. The optimal sequence of the two modalities, and the dose and fractionation of radiotherapy, have not been fully established yet. However, the use of combination chemotherapy as the initial modality, with subsequent rapid shrinkage of the tumor, may eliminate the necessity of irradiating a large volume of lung tissue. When chemotherapy is administered, the arm veins should be avoided. Veins of the lower extremities provide an alternative simple venous access.

### NON-HODGKIN’S LYMPHOMA
The most extensive experience in treating SVCS secondary to NHL is reported from the M. D. Anderson Cancer Center. Twenty-two patients with diffuse large cell lymphoma and eight patients with lymphoblastic lymphoma were evaluated for results of treatment. The patients were treated with chemotherapy alone, chemotherapy combined with irradiation, or radiotherapy alone. All patients achieved complete relief of SVCS symptoms within 2 weeks of the onset of any type of treatment. No treatment modality appeared to be superior in achieving clinical improvement. The presence of dysphagia, hoarseness, or stridor was a major adverse prognostic factor for patients with lymphoma presenting with SVCS. Eighteen of 22 patients (81%) with large cell lymphoma achieved complete response. Relapse occurred in all six patients treated with irradiation alone, in four of seven patients treated with chemotherapy alone, and in five of nine patients treated with chemotherapy and radiotherapy. The median survival rate was 21 months. All eight patients with lymphoblastic lymphoma achieved complete response. Six relapses occurred in this group, and all were in sites not initially involved. Median survival was 19 months.

From these results, the researchers concluded that SVCS secondary to lymphoma is rarely an emergency that requires treatment before a histologic diagnosis is made. They recommended that the choice of treatment should be based on the histologic diagnosis and that the patients should undergo histologic examination. In cases where a specific diagnosis cannot be made, the patient should be treated with chemotherapy and irradiation. If the patient is not responding to these treatments, surgery should be considered.

The field of radiation for SVCS induced by lung cancer should encompass the gross tumors with appropriate margins, and mediastinal, hilar, and supraclavicular failures occurred in 8 of 91 patients (9%) receiving radiation therapy to the supraclavicular fossae and in

**NONMALIGNANT CAUSES**

Patients with nonmalignant causes of SVCS differ significantly from patients with malignant disease. If the cause is not malignant, the patients often have symptoms long before they seek medical advice; it takes more time to establish the diagnosis; and their survival is markedly longer. Schraunfagel et al. reported that the average survival rate was 9 years if the primary process was benign, compared with an average survival of 5 months for patients with lung cancer. Mahajan et al. reviewed the literature of benign SVCS and reported 16 new cases. Twelve (75%) of these 16 patients had a mediastinal granuloma that was attributed to histoplasmosis. Most patients had an insidious onset of SVCS and were relatively young. Ten patients who were available for a follow-up of 1 to 11 years were all doing well at the time of the report. It was suggested that the good prognosis of patients with benign SVCS caused by fibrosing mediastinitis does not provide a role for SVC bypass surgery. However, Nielsen and Doty advocated surgery for SVC caused by benign disorders if the syndrome develops suddenly, progresses, or persists after 6 to 12 months of observation for possible collateral development. In patients whose histoplasmosis complement fixation titers suggest active disease, ketoconazole treatment may prevent recurrent SVCS.

**CATHETER-INDUCED OBSTRUCTION**

In catheter-induced SVCS, the mechanism of obstruction is usually thrombosis. Heparin, urokinase, or recombinant tissue-type plasminogen activator may cause lysis of the thrombus early in its formation. Heparin and oral anticoagulants may reduce the extent of the thrombus and prevent its progression. Removal of the catheter, if possible, is another option and should be combined with anticoagulation to avoid embolization. In patients for whom electrodes of a pacemaker must be changed, the broken wire should be removed to prevent the risk of developing SVCS. Percutaneous transluminal angioplasty, with or without thrombolytic therapy, and stent insertion have been successfully used to open catheter-induced SVC obstructions.

**TREATMENT**

**RADIATION THERAPY**

In patients with SVCS as a result of non-SCLC, radiotherapy has long been the primary treatment. The likelihood of relieving the symptoms and signs of SVCS is high, but the overall prognosis for these patients is poor. In the series of Armstrong et al., the 1-year survival for these patients was 17%, and the survival at 2 years declined to 2%. More recently, the use of percutaneous metal stent insertion to improve blood flow through the SVC has been introduced as an alternative to palliative radiotherapy in malignant SVCS.

Radiotherapy is an optional treatment for most patients with SVCS. It is also used as an effective initial treatment if a histologic diagnosis cannot be established and the clinical status of the patient is deteriorating. However, some reviews suggest that SVC obstruction alone rarely represents an absolute emergency that requires radiotherapy without a specific diagnosis, and endovascular stenting may be used as an alternative to radiotherapy for obtaining immediate relief of the obstruction. Yet, SVCS may be the earliest manifestation of invasive involvement of additional critical structures in the thorax (Table 51.1-6), such as the bronchi. Under such circumstances, prompt treatment with irradiation may be required without any delay.

**TABLE 51.1-6. Complications of Malignant Invasion Associated with Superior Vena Cava Syndrome**

<table>
<thead>
<tr>
<th>Complication</th>
<th>Number of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermittent</td>
<td>20 (20)</td>
</tr>
<tr>
<td>Persistent</td>
<td>42 (42)</td>
</tr>
<tr>
<td>Male</td>
<td>13 (13)</td>
</tr>
<tr>
<td>Female</td>
<td>25 (25)</td>
</tr>
<tr>
<td>Radiation</td>
<td>14 (14)</td>
</tr>
<tr>
<td>Total</td>
<td>103 (103)</td>
</tr>
<tr>
<td>Percutaneous</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Other</td>
<td>9 (9)</td>
</tr>
</tbody>
</table>

The fractionation schedule of radiation that has been recommended includes two or four large initial fractions of 3 to 4 cGy, followed by conventional fractionation to a total dose of 30 to 50 cGy. However, no data clearly support a particular fractionation scheme. In one study, patients treated with initial high-dose fractions showed a slightly faster symptomatic improvement than patients receiving conventional-dose radiation. Improvement within 2 weeks or less was observed in 70% of those treated with initial high-dose fractions and in 56% of patients receiving conventional-dose therapy. This difference was not statistically significant.

A radiotherapy study evaluated the efficacy of treating patients with SVCS with a short course of hypofractionated irradiation. The study compared a regimen of 8 Gy per fraction once a week to a total dose of 24 Gy to a program of delivering only two fractions of 8 Gy (total of 16 Gy) within 1 week. Transient dysphagia was the main side effect in almost one-half of patients in both programs. The 24-Gy regimen resulted in a complete resolution of symptoms in 56% of patients and a partial response in another 40%. The 16-Gy regimen yielded a complete response in only 28% of patients. The mean time for SVCS recurrence and the median overall survival rate were longer in the higher-dose regimen (6 months and 9 months, respectively) compared to the low-dose regimen (3 months and 3 months, respectively).

Serial venograms and autopsies suggest that the symptomatic improvement achieved by radiotherapy is not always due to improvement of flow through the SVC, but it is probably also a result of the development of collaterals after the pressure in the medistinum is eased.

The field of radiation for SVCS induced by lung cancer should encompass the gross tumors with appropriate margins, and mediastinal, hilar, and supraclavicular lymph nodes. In Armstrong et al.’s series, supraclavicular failures occurred in 8 of 91 patients (9%) receiving radiation therapy to the supraclavicular fossae and in
two of six patients (33%) not receiving therapy to these lymph nodes. \(^9\)

**ENDOVASCULAR STENTING AND ANGIoplasty**

Percutaneous transluminal angioplasty using the balloon technique, insertion of expandable wire stents, or both, has been successfully used to open and maintain the patency of SVC obstruction resulting from malignant and benign causes. \(^4\) \(^5\) \(^6\)

Thrombolysis is often an integral part of the endovascular management of SVCS because thrombosis is often a critical component of the obstruction and lysis is necessary to allow the passage of the wire. Balloon dilatation (angioplasty) may also be used before stenting. Most reports have emphasized the use of combination endovascular therapy—thrombolysis, angioplasty, and stent therapy. \(^3\)

The experience with stenting has been growing for many years. Most experience has been with three stents: the Gianturco Z-stent, the Wallstent, and the Palmaz stent. The Wallstent is the most commonly used device. \(^1\) It is self-expanding and built of woven stainless steel wire. Its light weave deters tumor ingrowth.

Total occlusion of the SVC is not a contraindication to stent therapy, and a success rate of 85% in total occlusion situations has been reported. \(^2\) The largest experience in using stents to open malignant obstruction of the SVC was reported by Nicholson et al. in Great Britain. The British team used Wallstents in 75 patients and obtained improvement of obstruction in all patients; 90% remained free of symptoms until death. This study retrospectively compared stent therapy with radiation therapy and found that only 12% of patients treated with radiation remained free of SVCs until death. However, long-term experience in maintaining patency after stent therapy in patients with SVCS from benign causes who are expected to have long survival, is still limited. \(^5\)

Complication rates for endovascular therapy have ranged from 0% to 50% and include bleeding, stent migration, stent occlusion, and pulmonary embolus. \(^3\) Most complications can be successfully treated with percutaneous methods.

**SURGERY**

The experience with successful direct bypass graft for SVC obstruction is limited. It was recommended that autologous grafts of almost the same size as the SVC should be used. Doty et al. \(^6\) used a composite saphenous graft, which was constructed from the patient’s saphenous vein. They reported 23 years of experience with this procedure in 16 patients with benign obstruction of SVC; 14 patients maintained patency and 15 were relieved of symptoms of SVCS. Avashiti and Moghissi \(^2\) reported successful bypasses of obstructed SVCs using Dacron prostheses. Magnan and associates \(^64\) used an expanded polytetrafluoroethylene prosthesis to reconstruct the SVC in nine patients with malignancy-induced SVCS and in one patient with chronic mediastinitis. In all, patients’ symptoms disappeared promptly after the operation, the grafts remained open, and survival rates at 1, 2, and 5 years were 70%, 25%, and 12.5%, respectively. \(^65\)

The preferred bypass route is between an innominate or jugular vein on the left side and the right atrial appendage, using an end-to-end anastomosis. Piccione et al. \(^6\) used the autologous pericardium to reconstruct the SVC after resection for malignant obstruction. In patients with malignancy-induced SVCS, surgical intervention should be considered only after other therapeutic maneuvers with irradiation and chemotherapy have been exhausted. Most patients with SVCS of benign origin have long survivals without surgical intervention. \(^2\) \(^29\) However, if the process progresses rapidly or if there is arteriovenous fistula or aortic aneurysm, surgical intervention may relieve the obstruction.

**THROMBOLYTIC THERAPY**

Thrombolysis is an important component of comprehensive endovascular therapy. \(^3\) Successful experience with thrombolytic agents was also obtained in the treatment of catheter-induced SVCS. \(^2\) \(^29\) \(^2\) \(^4\) A review of the response of SVCS to thrombolytic therapy from the Cleveland Clinic \(^2\) \(^29\) \(^2\) \(^4\) showed that in 8 of 11 patients (73%) with a central venous catheter, lyzed after thrombolytic therapy compared with only one of five patients who responded with only one of five patients who responded after catheter removal. The higher yield of thrombolytic therapy in patients with catheters is probably related to the mechanism of obstruction, the ability to deliver the agent directly to the thrombus, and to earlier recognition of SVCS in patients with malfunctioning catheters. In the Cleveland Clinic experience, \(^2\) urokinase was more effective than streptokinase, and a delay administering therapy beyond 5 days of symptom onset was associated with a treatment failure. Favorable experience with recombinant tissue-type plasminogen activator as a thrombolytic agent for catheter-induced SVCS has been reported. \(^2\) \(^29\)

**GENERAL MEASURES**

Medical measures other than specific chemotherapy may be beneficial in temporarily relieving the symptoms of SVCS. Bed rest with the head elevated and oxygen administration can reduce the cardiac output and venous pressure. Diuretic therapy and a reduced-salt diet to reduce edema may have an immediate palliative effect, but the risk of thrombosis enhanced by dehydration should not be ignored. Steroids are commonly used, but their effectiveness has never been properly evaluated. They may improve obstruction by decreasing a possible inflammatory reaction associated with tumor or with irradiation. However, Green and colleagues \(^2\) demonstrated the lack of inflammatory reaction and edema after radiotherapy for experimental SVCS, but documentation in a controlled fashion is lacking. Thrombolytic therapy with urokinase, streptokinase, and recombinant tissue-type plasminogen activator was effective in SVCS induced by indwelling catheters. \(^2\) \(^29\)

**RECOMMENDATIONS**

In patients without a clear cause of SVCS, an efficient diagnostic effort should be attempted before any oncologic treatment. However, percutaneous endovascular intervention should be considered, because it relieves symptoms without masking the diagnosis.

Three deep-cough sputum specimens should be obtained for cytologic analysis. A positive cytologic evaluation provides reliable pathologic information, particularly in the diagnosis of SCLC. \(^2\) \(^29\) \(^2\) If there is pleural effusion, thoracentesis should be performed and the centrifuge-prepared specimen examined for the presence of malignant cells. If a suspicious lymph node is palpable, particularly in the supraclavicular area, a needle or open biopsy should be the next diagnostic step. In the absence of positive sputum results, pleural effusion, or accessible suspicious lymph node analysis, a bronchoscopy should be performed, and brushing, washing, and biopsy samples should be obtained for cytologic and histologic analysis. If these efforts do not provide the histologic diagnosis of the primary process, percutaneous transbrachial fine-needle biopsy under CT or fluoroscopic guidance is safe and highly effective. \(^2\) \(^29\) In the rare patient for whom less-invasive procedures have failed to establish the diagnosis, the location of the suspicious lesion in the chest and the experience of the surgical team should determine whether mediastinoscopy or thoracotomy is performed.

During the diagnostic process, the patient can benefit from bed rest with the head elevated and with oxygen administration. Some clinicians advocate the use of diuretics and steroids (6 to 10 mg of dexamethasone given orally or intravenously every 6 hours) as a temporary palliative measure if the patient is uncomfortably symptomatic. Anticoagulation is of no proven benefit and may interfere with diagnostic procedures. After the cause of SVCS has been established, treatment of the primary process should promptly follow. Combined chemotherapy with an appropriate regimen is the treatment of choice for SCLC and NHL. Radiation therapy of the lesion and adjacent nodal areas may enhance control after initial response to chemotherapy. Non-SCLC causing SVCS is best treated with radiation therapy or endovascular stent insertion or both. The incorporation of CT scan information into a carefully designed treatment plan may enable the administration of a total radiation dose of more than 5000 cGy, which may provide long-term local control for some patients. Most patients with nonmalignant causes for SVCS have an indolent course and a good prognosis. Percutaneous transluminal angioplasty or stent insertion should be considered an effective alternative to surgery. However, the long-term maintenance of patency with stent insertion is still unknown. Surgery is indicated only when the process is rapidly progressing or caused by a retrosternal goiter or an aortic aneurysm. If SVCS is induced by a catheter, the catheter should be removed if possible. Heparin should be administered during the removal of the catheter to prevent embolization. In catheter-induced SVCS, urokinase, streptokinase, or recombinant tissue-type plasminogen activator are of value if used early in the thrombotic process. \(^2\) \(^29\) \(^2\) \(^4\)

The clinical course of SVCS rarely represents an absolute emergency. In these situations, the bronchus is likely to be obstructed by the same basic process, and irradiation may have to be started immediately, even before the histologic diagnosis is established.
INTRODUCTION

Spinal cord compression from metastatic cancer remains an important source of morbidity despite the fact that with early diagnosis, treatment is effective in 90% of patients. Technical improvements in spinal imaging, radiation therapy, and surgery have allowed treatment of spinal cord compression to be dispensed with greater precision. However, the most important weapon against the devastation of paraplegia or sphincter dysfunction is a heightened awareness of possible spinal cord compression in the cancer patient and early intervention.

Despite its common occurrence, there have been few prospective studies and randomized trials have been exceedingly rare. At the dawn of the new millennium, treatment recommendations are based largely on empiric experiences described in retrospective reports. However, the pathophysiology of cord compression and the factors that predict treatment outcome are well known.

Malignant spinal cord compression is defined as the compressive indentation, displacement, or encasement of the spinal cord's thecal sac by metastatic or locally advanced cancer. Compression can occur via posterior extension of a vertebral body mass, resulting in compression of the anterior aspect of the spinal cord, or through anterior or anterolateral extension of a mass arising from the dorsal elements or invading the vertebral foramen, respectively. Intramedullary spinal cord metastases produce edema, distortion, and compression of the spinal cord parenchyma, resulting in symptoms and signs that are similar to epidural spinal cord compression. Virtually any neoplasm capable of metastasis or local invasion can produce malignant spinal cord compression. The response to nonsurgical therapy and the duration of survival following treatment can vary considerably among the different histologic tumor types. Therapy for the individual patient can be optimized once the tumor's histologic type is known and the extent, severity, and mechanism of spinal cord compression are established.

The degree of pretreatment neurologic dysfunction is the strongest predictor of treatment outcome. Ambulation can be preserved in greater than 80% of patients who are ambulatory at presentation. Paraplegia, quadriplegia, and loss of bowel or bladder function are potential consequences of cord compression if it is diagnosed late or left untreated. Once lost, neurologic function cannot be regained in the majority of patients. The diagnosis of cord compression is easy to establish with contemporary diagnostic evaluations, and with early intervention the results of treatment are good to excellent. Therefore, the key to successful management is a heightened awareness of signs and symptoms, specifically newly developed back pain or motor dysfunction, leading to early diagnosis and treatment.

EPIDEMIOLOGY

In adults, metastatic spinal cord compression occurs in roughly 3.0% to 7.4% of patients with lung, prostate, and breast cancer, and the overall frequency of malignant spinal cord compression has been reported to be approximately 5%. Spinal cord compression is the second most frequent neurologic complication of metastatic cancer. It can be identified at autopsy in 5% to 10% of patients dying of cancer. Ten percent of adult patients with malignant spinal cord compression present without a known primary tumor or with cord compression as the initial presentation of a malignancy. Cord compression at initial presentation is more commonly seen at general hospitals than at regional cancer centers. Tertiary referral centers specializing in cancer may see 50 to 100 cases per annum, although the true incidence of malignant spinal cord compression is not known. Intramedullary lesions make up only 0.8% to 3.8% of all cases of metastatic spinal cord compression. Second episodes of malignant spinal cord compression occur in 7% to 16% of cases.

In children, the frequency of metastatic spinal cord compression is approximately 4.0% to 5.5%. One report roughly 50% of cases presented with cord compression at the time of initial diagnosis, and 50% developed compression from secondary spinal metastases. The most frequent tumor types producing pediatric cord compression are neuroblastoma (7.9% to 50%), Ewing's sarcoma (15% to 28.5%), rhabdomyosarcoma (15% to 28%), osteosarcoma (6% to 9%), lymphoma (6.0% to 7.5%), and leukemia (6%). Cord compression has been reported to be more frequent in male than in female children, reflecting the epidemiology of childhood cancer.

PATHOPHYSIOLOGY

In the majority of cases, vertebral body metastases result from the hematogenous dissemination of tumor clonogens that express tropism for the vertebral column bone marrow. More frequently growing in the well-vascularized marrow space of the posterior vertebral body, spinal metastases can produce cord compression in two ways. The first results from continued growth and obliteration of the narrow space with expansion into the epidural space, producing impingement on the anterior thecal sac and its surrounding venous plexus (Fig. 51.2-1). Alternatively, destruction of cortical bone by tumor can result in vertebral body collapse with anterior angulation and posterior displacement of bony fragments into the epidural space against the thecal sac and epidural venous plexus. Compression of the cord, its blood vessels, and nerve roots can also occur from the posterolateral direction via invasion of tumor through the neural foramen. Paraspinous tumors or expanding paraaortic nodal metastases use this mechanism of compression. Posterior thecal sac compression from metastatic involvement of the neural arch does occur but with less frequency. Finally, intramedullary metastases that result from hematogenous dissemination produce internal compression of the spinal cord structures and parenchymal vasculature. The signs and symptoms of intramedullary cord compression are similar to those of external cord compression. However, myelography is less reliable for detection of intramedullary compression. Patterns of metastatic involvement of the spine are illustrated in Figure 51.2-4 and Figure 51.2-5.
FIGURE 51.2-1. An appreciation of the anatomic relationships within the spinal canal is important in understanding the pathophysiology of spinal cord compression.  
A: The normal spinal cord structures are shown. Note the relationship of the epidural venous plexus to the vertebral body and bony canal.  
B: The change in these relationships produced by a metastatic tumor arising from the vertebral body is illustrated. Note the obliteration of the epidural venous plexus and the compressive displacement of the spinal cord and its nerve roots. (Courtesy of Howard Bartner and Martha Blalock.)

FIGURE 51.2-2. Metastatic involvement of the spine. Intramedullary metastases reach the cord through hematogenous dissemination and grow within the cord parenchyma (1). Leptomeningeal metastases involve the meningeal membranes of the subarachnoid space, which are extramedullary and intradural (2). Epidural metastases usually arise from the highly vascular posterior aspect of the vertebral body and produce compression of the anterior aspect of the spinal cord (3). Epidural compression can also result from paravertebral tumors that invade the vertebral foramina (4) and, less often, from metastases arising in the epidural space itself (5). (Adapted from ref. 103.)

FIGURE 51.2-3. This sagittal view of a magnetic resonance image demonstrates an intramedullary metastasis in the lumbar spine from renal cell carcinoma.

FIGURE 51.2-4. This sagittal magnetic resonance image of the lumbar spine demonstrates anterior compression of the cauda equina below the conus medullaris. Note the pathologic fracture of the L-2 vertebral body and the retropulsed bone fragments compressing the thecal sac.

FIGURE 51.2-5. This axial view from a magnetic resonance image of the thoracic spine demonstrates posterolateral compression of the spinal cord resulting from invasion of the left neuroforamen.

FIGURE 51.2-6. A sagittal magnetic resonance image of the spine demonstrating posterior compression of the spinal cord from a metastasis arising in the spinous
The majority of patients who present with spinal cord compression have a known diagnosis of cancer. However, in 8% to 34% of cases it can represent the initial presentation of malignant disease. The severity of spinal cord injury and the likelihood of permanent neurologic loss are determined by the rapidity of progression of neurologic symptoms. Dexamethasone and other antiinflammatory agents can delay the onset of paralysis by reducing the edema associated with hypoxia, edema, ischemia, and injury resulting from malignant compression. The rapidity of progression of neurologic symptoms indicates the need for prompt treatment. In summary, spinal cord damage and loss of neurologic function result from venous stasis, spinal cord edema, reduced capillary blood flow, ischemia, and mechanical injury. The role of vascular endothelial growth factor (VEGF) in the pathophysiology of spinal cord compression is vascular in nature. It increases vascular permeability and, interstitial edema appears to selectively involve the white matter, although increased vascular permeability was observed involving gray matter in one model. Edema in the spinal cord caused by increased vascular permeability impairs spinal cord function, resulting in weakness and sensory impairment. Interstitial edema increases the pressure within small arterioles early in the evolution of spinal cord compression and therefore retards blood flow. In the more advanced stages, pressure on small intramedullary arterioles produced by increasing interstitial edema combined with progressive direct physical pressure on the spinal cord by the expanding mass ultimately leads to arrest of capillary blood flow, resulting in ischemia of white matter. If left untreated, there is infarction of ischemic white matter and permanent neurologic loss.

Siegal and colleagues have evaluated and demonstrated the roles of cytokines, inflammatory mediators, and neurotransmitters in the pathophysiology of cord compression in a series of reports. Spinal cord injury from compression was associated with increased water content, increased vascular permeability, and increased specific gravity in compressed spinal cord as well as increased extravasation of blood cells into the cord parenchyma. Treatment with dexamethasone phosphate was shown to reduce tissue-specific gravity in the compressed cord and to delay the onset of paralysis. Similar results were obtained with indomethacin, which also decreased the elevated water content and reduced prostaglandin E₂ (PGE₂) levels in the compressed segments of the spinal cord. Later experiments demonstrated the ability of free dexamethasone to decrease free water content and PGE₂ levels in compressed segments of the spinal cord. The potential role of gluteal fat in the production of cytotoxic edema was suggested when it was shown that N-methyl-D-aspartate receptor antagonists reduced the spinal cord free water. This group also demonstrated that inhibitors of serotonin synthesis could reduce the elevated serotonin levels associated with spinal cord injury. Serotonin receptor antagonists reduced PGE₂ synthesis, reduced spinal cord vascular permeability, and delayed the onset of paraplegia. These studies form the basis for development of new pharmacologic approaches to the treatment of cord compression.

The role of vascular endothelial growth factor (VEGF) in the pathophysiology of malignant spinal cord compression is being increasingly recognized. In the early stages of malignant spinal cord compression, venous stasis and relative hypoxia stimulate VEGF production. VEGF increases vascular permeability and vasogenic edema in the spinal cord in response to transient ischemia and trauma. The progressive hypoxia, resulting from interstitial edema and decreased microcapillary perfusion, continues to drive VEGF production. Several observations suggest that the beneficial effects of dexamethasone are at least in part mediated by its effect on VEGF activity. Dexamethasone down-regulates VEGF gene expression, inhibits VEGF activity, and prevents the VEGF-induced cytoskeletal changes associated with vascular permeability. The role of cytokines, inflammatory mediators, and neurotransmitters in the pathophysiology of malignant spinal cord compression is presented in Figure 51.2-7.

The validity of this sequence of events was further confirmed by Arbit et al., who found loss of white matter as well as spinal cord edema were also described. Within the spinal cord itself, existing evidence suggests that the pathophysiology of spinal cord compression is vascular in nature. This has been shown repeatedly in animal models and has been corroborated by autopsy findings. Initial extension of tumor into the epidural space results in compression of the epidural venous plexus, which normally drains blood from the spinal cord. Compression of the venous plexus leads to venous stasis. Relative hypoxia, increased vascular permeability, and interstitial edema appear to selectively involve the white matter, although increased vascular permeability was observed involving gray matter in one model. Edema in the spinal cord caused by increased vascular permeability impairs spinal cord function, resulting in weakness and sensory impairment. Interstitial edema increases the pressure within small arterioles early in the evolution of spinal cord compression and therefore retards blood flow. In the more advanced stages, pressure on small intramedullary arterioles produced by increasing interstitial edema combined with progressive direct physical pressure on the spinal cord by the expanding mass ultimately leads to arrest of capillary blood flow, resulting in ischemia of white matter. If left untreated, there is infarction of ischemic white matter and permanent neurologic loss.

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Later experiments demonstrated the ability of free dexamethasone to decrease free water content and PGE₂ levels in compressed segments of the spinal cord. The potential role of gluteal fat in the production of cytotoxic edema was suggested when it was shown that N-methyl-D-aspartate receptor antagonists reduced the spinal cord free water. This group also demonstrated that inhibitors of serotonin synthesis could reduce the elevated serotonin levels associated with spinal cord injury. Serotonin receptor antagonists reduced PGE₂ synthesis, reduced spinal cord vascular permeability, and delayed the onset of paraplegia. These studies form the basis for development of new pharmacologic approaches to the treatment of cord compression.

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Figure 51.2-7. A simplified schematic representation of the pathophysiologic changes leading to neuronal damage from cord compression. Several histologic studies suggest that the initial pathophysiologic changes resulting in vasogenic edema are confined principally to white matter. Prostaglandin E₂ (PGE₂), vascular endothelial growth factor.

The importance of the magnitude, rate, and duration of compression in regard to the neurologic outcome was studied in dogs with an epidural inflatable balloon by Tarlov et al. Paraparesis resulting from rapid compression of the cord could be reversed if decompression occurred within 9 hours. Paraparesis resulting from more gradual compression over 20 to 48 hours could be successfully reversed by decompression within the next 7 days, emphasizing that neurologic deficits are more likely to be reversed if compression occurs gradually rather than rapidly. This has also been observed in humans. Rades et al. reported 96 patients treated with radiotherapy plus surgical decompression who were compared based on the duration of motor symptoms before treatment. Improvement of neurologic function 2 weeks after radiotherapy occurred in a higher percentage (89%) of patient with deficits that developed greater than 14 days before treatment, compared with patients who developed symptoms less than 14 days before treatment (12%). A separate cohort of patients with severe deterioration of motor function occurring within 48 hours before treatment experienced improvement in only 6% of cases.

In summary, spinal cord damage and loss of neurologic function result from venous stasis, spinal cord edema, reduced capillary blood flow, ischemia, and mechanical compression culminating in infarction. Prostaglandins, cytokines, excitatory neurotransmitters, and inflammatory mediators regulate the sweep of pathophysiologic changes associated with hypoxia, edema, ischemia, and injury resulting from malignant compression. The rapidity of progression of neurologic symptoms indicates the severity of spinal cord injury and the likelihood of permanent neurologic loss. Dexamethasone and other antiinflammatory agents can delay the onset of paralysis and improve symptoms until decompressive measures intervene.

**CLINICAL PRESENTATION**

The majority of patients who present with spinal cord compression have a known diagnosis of cancer. However, in 8% to 34% of cases it can represent the initial manifestation of cancer. The frequency of tumor types for over 1000 patients with cord compression from the literature is listed in Table 51.2-1. Spinal cord
compression develops within 3 months of the initial diagnosis of cancer in the majority of cases complicating lung carcinoma, whereas it can develop as long as 24 years after the initial diagnosis of breast cancer. 3,5

### TABLE 51.2-1. Frequency of Tumor Types Producing Cord Compression

The most frequently involved site is the thoracic spine (59% to 78%), followed by the lumbar spine (16% to 33%) and the cervical spine (4% to 15%) (Fig. 51.2-8). Multiple epidural sites of compression can occur in 26% to 49%. 55-59 Intramedullary cord compression, accounting for only 1% to 4% of cases, is usually solitary and is often associated with parenchymal brain metastases. 18,55-60

![FIGURE 51.2-8. The frequency of involvement in the different regions of the spine is shown.](image)

Pain accompanies malignant spinal cord compression in 70% to 96% of cases. 7,52,53,61 It usually precedes the diagnosis of spinal cord compression by days to months. 52 The pain may be local, radicular, or both. Local pain is present in the vast majority of cases and is caused by expansion, destruction, or fracture of the involved vertebral elements. The site of compression can usually be localized to the site of back or neck pain. Local back or neck pain is usually dull, aching, constant, and progressive. Back pain from vertebral destruction resulting in retropulsion of bone fragment is often worse in the supine position, a feature distinguishing cord compression from a herniated disc. Local back or neck pain can be exacerbated by movement, sneezing, straining, or neck flexion. The location of the involved vertebral body can usually be established by gentle spinal percussion. Radicular pain, which is usually, but not always, associated with local back or neck pain, is caused by compression of the nerve roots or cauda equina. Radicular pain is often shooting in quality and localizes to within one to two vertebral segments of the compression. Bilateral band-like girdle pain is characteristic of thoracic cord lesions, and unilateral radicular pain is more characteristic of lumbar or cervical lesions. Radicular pain from a cervical or lumbar lesion may involve the shoulder, hip, groin, perineum, or extremity.

Weakness, the second most common symptom at presentation, is usually what prompts the patient to seek medical intervention. Weakness, which usually follows the development of local or radicular pain, can develop gradually in association with progressive balance disturbance and numbness. Initial unilateral weakness is common when paresis develops gradually. Complete loss of motor and sensory function below the affected level (cord shock) can occur abruptly as vascular insufficiency progresses to frank ischemia. Neurologic examination of the patient with cord shock reveals absent motor, sensory, reflex, and autonomic function below the level of the lesion, and the affected extremities demonstrate flaccidity and absence of tone. Absence of perineal and anal reflexes and painless overflow incontinence complete the neurologic presentation. Flaccidity and areflexia are gradually replaced by paraplegia in flexion. Compression of the upper cervical spinal cord can produce paralysis of the upper extremities and respiratory failure, if acute. Chronic injuries of the cervical spine can produce wasting of the intrinsic muscles of the hand, forearm, or arm as well as progressive weakness of the intercostal muscles and diaphragm, leading ultimately to respiratory arrest. Lesions involving the conus medullaris or cauda equina produce flaccid paralysis of the lower extremities, absent or flexor plantar responses, saddle anesthesia, urinary retention leading to incontinence, and male impotence. The frequency of symptoms and signs of cord compression is presented in Table 51.2-2.

![TABLE 51.2-2. Frequency of Symptoms and Signs Accompanying Cord Compression](image)

### DIAGNOSTIC EVALUATION

The diagnostic evaluation of suspected cord compression should include a careful history, physical and neurologic examination, radiologic evaluation including a sagittal magnetic resonance imaging (MRI) survey of the spine, and, if indicated, urgent consultation by physicians in neurology, neurosurgery, radiation oncology, and medical oncology, when compression is caused by a chemosensitive neoplasm. Clear indications of epidural cord compression such as focal weakness, ataxia, and unexplained bowel or bladder dysfunction accompanied by back pain in the cancer patient demand urgent evaluation.

The medical history obtained from the cancer patient suspected of spinal cord compression should emphasize the onset, quality, location, and temporal pattern of back or neck pain. Back pain associated with spinal cord compression may be exacerbated by movement, lying flat, neck flexion, straight leg raising, straining, coughing, or sneezing. Symptoms of motor dysfunction are often described as stiffness or weakness that usually begins in one extremity and remains unilateral in nerve root compression but becomes bilateral with compression of the spinal cord or conus medullaris. Paresthesias due to involvement of the spinothalamic tract...
begin distally, usually in the foot, and ascend to the level of involvement. Numbness and paresthesias are typically noticed later in the history than motor dysfunction.

Physical examination should emphasize localization of the level of suspected compression. This is often best initialized by asking the patient to point out the site of the back pain. Gentle percussion over the spine can confirm the site of involvement and help elucidate other sites of vertebral metastases. Flexor and extensor motor testing, deep tendon and plantar reflex assessment, sensory level identification via pin prick, and anal sphincter tone assessment are required components of any diagnostic evaluation for cord compression.

There are several radiologic and tumor imaging techniques that are potentially useful in the diagnosis and treatment of cord compression. Plain radiographic films continue to be quite useful in evaluation of cord compression associated with bony involvement of the spine or due to compression fracture. However, they are relatively insensitive for detecting bone involvement and soft tissue masses, and they cannot demonstrate the actual spinal cord itself.

Despite these limitations, plain films can be useful in diagnosing cord compression and in planning therapy. Plain radiographs detect bony abnormalities in 72% of patients with epidural cord compression.2 Plain film radiographs detect the presence and location of epidural metastases in 83% of patients complaining of back pain. Vertebral body collapse, destruction of the pedicle, and blastic or sclerotic changes are characteristic findings observable with plain film radiography. However, paraspinal masses or vertebral body involvement resulting in less than 50% destruction of the cortex cannot be appreciated with plain film techniques. In addition, in up to 60% of patients with epidural compression by lymphoma and pediatric malignancies, plain films may be normal. Posterior or posterolateral compression resulting from a paraspinal mass invading the vertebral foramen is most common with these tumor types. Computed tomography (CT) and MRI are able to detect posterior or posterolateral cord compression secondary to neurofibroma invasion and are superior to plain films, bone scintigraphy, or myelography in that regard.

Myelography has the advantage over plain films of visualizing the level of the compression as indicated by a blockage of myelographic contrast. However, multiple sites of compression, which may be present in greater than 30% of cases, may require more than one subarachnoid puncture. For these reasons, CT, and to a much greater extent MRI, have emerged as the most useful techniques for imaging cord compression.

Bone scintigraphy is more sensitive than plain films in detecting metastatic involvement and provides information about the entire skeleton in a single examination. This facilitates screening the skeletal system for potential sources of referred pain, and it is useful in planning radiation therapy to multiple sites. However, bone scintigraphy is not as sensitive and specific in detecting spinal metastases as MRI22,23 and is incapable of describing the soft tissue and spinal cord anatomy required for the proper diagnosis and treatment of cord compression. Furthermore, primarily osteolytic metastases produced by multiple myeloma, lymphoma, and other malignancies may not be detected by bone scan.24

In the pre-MRI era, myelography and CT were the imaging modalities of choice for the diagnosis of cord compression, and either or both of these tests are mandatory when MRI is not available or is nondiagnostic. When a complete myelographic block is detected following routine lumbar injection, an additional injection from above through a C-1 to C-2 puncture is required to evaluate possible additional sites of compression. CT following metrizamide myelography is an alternative to a C-1 to C-2 puncture in patients with a complete myelographic block. However, MRI is superior to both CT and myelography in convenience, anatomic detail, and cost.25 Yet CT exceeds MRI in the evaluation of vertebral stability and bone destruction. Therefore, CT should be obtained before vertebral body resection or surgical stabilization of the vertebral column.

Position emission tomography has been used to evaluate metabolic changes in the cervical spinal cord following mechanical spinal cord compression26,27 and to identify intramedullary spinal cord metastases.20 Although positron emission tomography is increasingly being studied in the setting of malignant spinal cord compression,28,29 its current role is not completely defined.

MRI has replaced myelography and CT scanning as the diagnostic procedure of choice for evaluating cord compression.21,25,26,27,28,29,30 MRI has a sensitivity of 93%, a specificity of 97%, and an overall diagnostic accuracy of 95% in detecting cord compression.31 It is superior to bone scintigraphy in sensitivity and specificity for spinal metastases30,26,29,32 and can distinguish between benign and metastatic causes of vertebral body collapse with a sensitivity of 97.6%, a specificity of 100%, and an overall accuracy of 98.2%.21 The advantages of MRI over myelography for evaluating cord compression include its noninvasive ability to image soft tissue anatomy in spinal detail (tumors, spinal cord) and its ability to image multiple levels of cord impingement in one examination. Paraspinal and neurofibromal tumors are not as easily identified with myelography as with MRI. This is in addition, MRI allows avoidance of the 16% to 24% chance of neurologic deterioration following lumbar puncture for myelography.33 MRI excels in demonstrating intramedullary metastases that can be missed completely by myelography.

The advantages of MRI over CT include its ability to distinguish the spinal cord proper from other soft tissue masses in the spinal canal, and its ability to assess thecal sac impingement in the presence of disrupted cortical bone as is frequently encountered with myeloma and blastic lesions from prostate cancer. MRI is safer, more convenient, better tolerated, more informative, and less expensive than other techniques used to diagnose cord compression. Jordan et al. compared the cost of evaluation of spinal cord compression with and without MRI. Establishing the diagnosis of cord compression was 65% more expensive when MRI was not used.30

Because of its diagnostic accuracy and ability to image multiple levels of involvement, MRI is extremely useful in planning local treatment. Identification of paravertebral tumor, neurofibromal invasion, and additional sites of vertebral metastases is important for designing radiotherapy portals and for planning surgical resection. Multiple sites of cord and nerve root impingement or compression are frequent. Myelography detects multiple sites of impingement in approximately 30% of cases, and MRI detects multiple sites in approximately 40% to 50% of cases (Table 51.2-3). The frequency of multiple sites of impingement and compression decreases by approximately 50% when imaging is limited to only one spinal region (i.e., thoracic or lumbar).34 It is therefore imperative that the entire spine be evaluated radiographically. A sagittal T1 nonenhanced survey of the entire spine quickly and easily identifies multiple sites of compression and should guide the acquisition of axial views through areas of involvement. Bone metastases appear as dark botches relative to normal bone marrow in unenhanced T1 images. CSF and edematous tumor appear bright on T2 sequences. T2 sequences display CSF brightness, producing images that are similar to a myelogram. Axial T2 sequences can be useful in identifying small tumor nodules on nerve roots. Focal blastic lesions may produce decreased intensity on T2 images. In most cases of suspected epidural cord compression, MRI can be performed without contrast. However, gadolinium contrast images may complement noncontrast images in demonstrating paravertebral tumor and intramedullary metastases (see Fig. 51.2-3). Visualization of leptomeningeal involvement requires MRI contrast.35 Myelography with or without CT is mandatory when MRI is nondiagnostic, when it is not available, or in cases of claustrophobia or severe scoliosis.

**TABLE 51.2-3. Patterns of Radiographic Impingement, Compression, or Both**

**TREATMENT**

The diagnosis of cord compression requires emergent treatment. Delays in initiating treatment have been associated with deterioration in motor and autonomic function.36 Animal models and clinical results have documented better functional outcome when pretreatment motor loss has been gradual and worse functional outcome when the onset of motor loss has been rapid.32,33,34
Rades et al. reported significantly better motor function and ambulation in patients with gradual rather than rapid onset of pretreatment paresis. 31 Despite these differences in expected outcome based on the rate of neurologic progression, there is no justification for delaying therapy once the diagnosis of cord compression has been made. Although untreated epidural cord compression is not fatal, the consequences of paralysis are devastating and loss of ambulation has been associated with shortened survival in a number of reports. 32,33

Treatment of cord compression should be individualized, but start immediately. Ambulatory patients with radiographic evidence of early cord compression and no motor or sensory dysfunction can be treated safely without dexamethasone. 34 All other patients should be administered corticosteroids as soon as the diagnosis of cord compression is reached, regardless of whether diagnostic workup is complete. Surgical indications include spinal instability, retrogression of bone fragments producing compression, previous radiotherapy at the site of compression, and lack of tissue diagnosis in the setting of rapid neurologic deterioration. Patients without an initial diagnosis of cancer can be biopsied using CT or MRI guidance if neurologic dysfunction is absent or is evolving slowly. Radiotherapy should follow surgical resection if the site has not been previously irradiated. All other patients should be considered for primary radiotherapy alone. Chemotherapy can be used as initial therapy for the highly chemoresponsive adult or pediatric tumors in patients who are not candidates for surgery or radiation therapy.

The results of treatment of cord compression have improved in recent years as a result of earlier diagnosis with the greater availability of MRI and due to a heightened awareness of cord compression as a potential oncologic emergency. 35,36,37,38 The pretreatment degree of neurologic dysfunction is the strongest predictor of therapeutic outcome. Eighty percent to 100% of patients with minimal or no ambulatory dysfunction retain ambulation posttreatment. 39,40,41 Paraplegia improves with treatment in 34% to 63% of cases, 32,50 whereas paraplegia improves in up to 10% to 55% of cases. 31,42 The influence of pretreatment motor function is summarized in Table 51.2-4.

Surgical techniques used to resect epidural tumors have become increasingly specialized. Laminectomy, the classic surgical approach for the treatment of cord compression is primarily reserved for resection of posterior or postero lateral tumors, despite the favorable results reported by Landmann et al. 42 When used for treatment of anterior epidural compression, the goal of laminectomy is to relieve pressure on the spinal cord via removal of the spinous processes and laminae from one vertebra above to one vertebra below the level of compression. While this approach does not readily allow debulking of tumor anterior to the spinal cord, it does allow relaxation of the spinal cord away from the impinging mass. However, the results of a laminectomy for tumors anterior to the spinal cord have been disappointing. 43,44,45 This is in part due to the inability to resect tumor anterior to the spinal cord, but more importantly due to the decreased spinal instability that can develop when posterior supporting elements are removed from an often eroded or collapsed vertebral body.

The development of alternatives to laminectomy, including techniques for anterior decompression 46,47,48,49 and newer techniques such as endoscopically assisted anterior decompression, 50 coupled with the limitations of laminectomy, have resulted in laminectomy being no longer regarded as the standard neurosurgical procedure for treatment of anterior epidural cord compression. As a general principle, the location of involvement within the vertebral column should determine the neurosurgical approach. Anterior decompression with spinal stabilization should be considered for tumors in the vertebral body producing anterior epidural compression, and laminectomy should be used for the minority of cases in which tumor involves the posterior vertebral elements or invades the neuroforamina.

Recommendations regarding the use of surgery or radiotherapy alone or in combination should be individualized. Despite the common occurrences of cord compression, there have been no randomized trials containing more than 30 patients in each arm. 51,52,53,54 Thus, the guidelines for treatment of cord compression are largely empiric. Appropriate treatment recommendation can only be made after assessing the patient’s expected survival; the location, number, and mechanism of spinal cord compression(s); the tumor histology; the rapidity of neurologic progression; and any history of previous radiotherapy administered to the site under current consideration.

CORTICOSTEROIDS

Corticosteroids (dexamethasone, methylprednisolone) are among the most effective treatments of neurologic dysfunction resulting from cord compression. Dexamethasone reduces edema, inhibits PGE synthesis, and decreases the specific gravity of the compressed spinal cord. 32 It also was shown to delay the onset of paraplegia in experimental cord compression. 31,32 Although the mechanisms of dexamethasone action are not completely understood, dexamethasone has been shown to down-regulate VEGF expression in smooth muscle cells 55,56 and to prevent cytoskeletal changes associated with increased vascular permeability. 57 Despite the established role of dexamethasone in treatment of cord compression, the optimal dose and schedule have never been proven. 58,59

There have been several prospective evaluations of dexamethasone in the treatment of cord compression, yet the superiority of high- versus low-dose dexamethasone has never been proven. Greenberg et al. reported the results of a prospective trial of high-dose dexamethasone and radiation for epidural cord compression. Eighty-three patients with epidural cord compression received 100 mg of intravenous dexamethasone at the time of diagnosis, followed by 96 mg for 3 days, and a subsequent taper of dexamethasone dose during the course of radiotherapy. Fifty-seven percent of patients were ambulatory following treatment. This result was no better than those previously reported for lower dose corticosteroid regimens. However, 64% of patients reported substantial pain reduction the first day of therapy. 52 Sørensen et al. conducted a prospective randomized trial of high-dose dexamethasone versus no corticosteroid therapy. In 57 patients treated with radiation for cord compression, 61% of the dexamethasone group and 65% of the radiation alone group were ambulatory at 3 months. 53 A prospective randomized study comparing a single high dose of intravenous dexamethasone (100 mg) with conventional dose intravenous dexamethasone (10 mg), both followed by 4 mg orally every 6 hours, demonstrated no significant benefit for the initial high-dose bolus. 54 A prolonged administration of high-dose corticosteroids may have been a more worthy trial regimen, serious toxicities from high-dose dexamethasone have been reported in up to 14% of patients. 55,56

Thus, the results of clinical trials support a role for corticosteroids in the treatment of cord compression, but they have not indicated an advantage for higher versus lower doses. Currently, there is no clear benefit, other than pain relief, from the routine use of high-dose corticosteroids in patients who can otherwise be treated with conventional doses. We recommend an initial 10-mg dose of intravenous dexamethasone. The dose can be increased incrementally if no improvement is detected in the first 4 to 8 hours. After 2 days on a stable dose of intravenous dexamethasone, therapy can be switched to 4 to 8 mg of oral dexamethasone given every 6 hours. Corticosteroid doses are tapered every 4 days in a manner described by Byrne. 32 If neurologic decline results from dose reduction, the dose is maintained at effective levels until dose reduction is possible. Patients without neurologic dysfunction other than back or neck pain should be managed without corticosteroids whenever possible. Maranzano demonstrated that the use of steroids can be safely avoided in selected patients with no evidence of neurologic dysfunction, or with radiculopathy only. Twenty patients were reviewed who had tumors invading less than 50% of the spinal cord diameter and involving not more than two vertebral levels, or greater than two vertebral levels in patients with radiculopathy. All patients received 30 Gy in ten fractions. The results were equivalent or superior to those achieved with the use of dexamethasone. 54 Sixteen patients were ambulatory before treatment, and all 20 patients were ambulatory posttreatment. Palliation of pain was achieved in 85% of patients. 1
SURGERY

Although radiation therapy is currently the treatment of choice for most spinal metastases, radioresistant and recurrent neoplasms remain therapeutic dilemmas. Accepted indications for surgery are (1) unknown diagnosis, (2) spinal instability or compression by bone, (3) failure to respond to radiotherapy, and (4) maximal allowable radiation dose already administered to the spinal cord. Patients who may require surgery should also have chest radiography, electrocardiography, and blood tests, including complete blood count, electrolytes, glucose, creatinine, blood urea nitrogen, hepatic enzymes, prothrombin and partial thromboplastin times, platelet count, and type and crossmatch.

When the diagnosis is in doubt and open surgery is not indicated, fluoroscopic or CT-guided percutaneous vertebral biopsy may diagnose metastatic carcinoma with less incisional pain and a shorter recuperative period than open surgery. A paraspinal or a transpedicular approach can be used to place the needle, depending on the position and size of the tumor. CT guidance facilitates precise needle placement and avoidance of neurologic injury. Local anesthesia and mild sedation allow neurologic monitoring during the procedure, which can be performed in less than 1 hour.

Surgical decompression of the spinal cord should be approached from the side of the impinging mass. Since typically the site of metastatic tumor involvement is the vertebral body rather than the neural arch, tumor or pathologic fracture usually compresses the anterior surface of the spinal cord. Anterior tumors are not exposed by laminectomy, which has little therapeutic benefit and causes spinal instability in such cases. Findlay noted that 51% of patients with cord compression had vertebral collapse defined as over 50% loss of vertebral height, and that 25% of patients treated with laminectomy sustained major neurologic deterioration related to their surgery. In keeping with the premise that decompression should occur from the side of the spinal cord compression, laminectomy should be reserved for the removal of posterior lesions.

Anterior decompression with mechanical stabilization has supplanted laminectomy as the principal surgical treatment for epidural metastases arising from the vertebral body. This approach allows total removal of the pathologic vertebral body via thoracotomy or a retroperitoneal approach. The vertebral body is replaced with methylmethacrylate, which is supplemented with a metal prosthesis that attaches to the adjacent vertebral bodies. Moore and Uttley reported their results with anterior decompression and stabilization in 26 patients with anterior vertebral collapse who suffered from spinal cord compression or intractable pain. Of 16 patients who were unable to walk preoperatively, 10 were ambulatory after surgery, 3 were not, and 3 died. Of seven patients who were operated on for intractable pain, five were pain free and two died. Morbidity included wound infection, CSF discharge, and the need for posterior stabilization later. During the period of the study (1982 to 1987) 20 additional patients were considered unsuitable for surgery because of "multiple levels of disease, complete paraplegia, or a paralous general condition." Even though anterior spinal decompression and fusion is more effective than laminectomy, its effectiveness appears to be limited to patients in good medical condition who have myelopathy from anteriorly placed tumors. In addition, metastatic disease must be focal since spinal stabilization devices require a foundation of solid, rather than tumor-infiltrated, bone at adjacent spinal levels. Surgical decompression entails considerable mortality, morbidity, and convalescence, even in selected patients. To reduce operative blood loss, intravascular or intravertebral embolization of the vasculature of vertebral metastases may be performed preoperatively.

The indiscriminate use of laminectomy in candidates for radiation has been challenged. While some reports have suggested a more favorable outcome with combined laminectomy and radiation, selection bias prevents the assessment of differences in outcome in those studies. Indeed, several retrospective studies and one small prospective study failed to demonstrate significant differences in outcome for radiation alone as compared with laminectomy and radiation.

In a retrospective study from Memorial Sloan-Kettering Cancer Center, Gilbert et al. found no advantage for the addition of laminectomy to radiation in the treatment of cord compression. Two hundred thirty-five patients with greater than 80% extradural block on myelography were reviewed. Sixty-five underwent surgical decompression followed by radiation, and 170 were treated with radiation alone. Patients with lymphoma or paraplegia usually received radiotherapy alone. Those with uncertain diagnosis, prior radiotherapy, or rapid progression of symptoms underwent surgery. Of the 235 patients, 34% were ambulatory, 41% paraparetic, and 17% paraplegic. Forty-six percent of the laminectomy group were ambulatory after treatment, as compared with 49% in the radiation alone group. Tumors considered radiosensitive (lymphoma, seminoma, myeloma, and neuroblastoma) responded better to either treatment than tumors not considered radiosensitive (carcinoma, sarcoma, melanoma). Patients with rapid development of weakness (over 48 hours) responded more frequently to radiation (7 of 13) compared with those treated with laminectomy (0 of 9; P < .002). The duration of neurologic improvement was greater for patients with radiosensitive tumors; however, the duration of improvement was similar for laminectomy and for radiation alone. Fifty-eight percent of patients who were ambulatory before treatment remained so after treatment. Although superior results have been reported in more contemporary series, others have also reported that laminectomy adds little to the efficacy of radiotherapy.

A small prospective study of laminectomy plus radiotherapy was reported by Young et al. Twenty-nine patients were randomized to laminectomy plus radiation (16 patients) or radiation alone (13 patients). One-half (three of six) of the surgically treated patients who were ambulatory before treatment remained so after treatment, whereas all (five of five) retained ambulation following radiotherapy. Forty-four percent of nonambulatory patients were ambulatory after laminectomy, as compared with 33% after radiation. By 4 months the rate of ambulation for patients in both groups was 33%. Sphincter function and pain relief were likewise similar in each treatment group. There were no significant differences in outcome. Although this series has been criticized for its small numbers, it is the only prospective randomized trial comparing laminectomy and radiation with radiation alone. The results, which suggest that laminectomy does not contribute to the efficacy of radiotherapy, are corroborated by several retrospective analyses.

In contrast to the experience in adults, laminectomy in children with spinal cord compression often improves neurologic outcome over radiation, radiation and chemotherapy, or chemotherapy alone. Because pediatric sarcomas are often located in a posterolateral location in the epidural space, they are amenable to removal via laminectomy, which relieves spinal cord compression more rapidly than chemotherapy and radiotherapy and prevents permanent spinal cord injury from developing.

RADIATION THERAPY

Radiation plays a central role in the treatment of newly diagnosed epidural cord compression. The goals of treatment are decompression of the spinal cord and nerve roots through cytoedema of tumor, prevention of progression of neurogenic symptoms, relief of pain, prevention of further structural damage to the vertebral column, and the establishment of durable local control. Radiation reduces pain in approximately 70% of patients, improves motor function in 45% to 60%, and reverses paraplegia in up to 11% to 21%. While most patients with previously untreated metastatic cord compression are candidates for emergent radiation, patients with compression from retroplused bone, those with spinal instability, or those without a clinical or pathologic diagnosis of cancer and a rapidly progressing loss of neurologic function should be considered for surgery. Children, and in certain circumstances adults with highly chemosensitive tumors, should be considered for initial chemotherapy. Immediate surgical decompression should be considered for any patient with neurologic progression during radiotherapy. The results of several radiotherapy series are listed in Table 51.2-5.

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<th>Table 51.2-5. Results of Radiotherapy for Malignant Spinal Cord Compression</th>
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*Note: Table 51.2-5 is not included in the current text.*
There has been and continues to be interest in the radiofractionation of regimens for palliation of cord compression. A seminal experience in this regard was reported by Greenberg et al., who treated patients with radiofractionated radiotherapy and initial high-dose dexamethasone. Patients received 100 mg of intravenous dexamethasone and 500 cGy per fraction daily for the first 3 days of treatment. Following a 4-day rest, radiation was continued in 300-cGy fractions to a total dose of 3000 cGy. Ninety percent of patients were ambulatory after treatment. None of the patients with radiosensitive tumors and 55% of those with less radiosensitive tumors. Patients with renal and prostate tumors had the highest rate of ambulation following treatment, and patients with lung cancer had the least favorable outcome. Although these results are not better than those reported for conventional regimens, the achievement of pain relief in 64% of patients after the first day of treatment was impressive.

Maranzano et al. have addressed several issues regarding the radiotherapy of cord compression including radiofractionation in a series of reports from 1989 to 2000. A prospective study of radiotherapy and corticosteroids without surgical resection was reported in 1995. Of the 209 evaluable patients, 52% had minimal or no neurologic impairment, 39% were paraparetic and unable to walk, and 9% were paraplegic at presentation. Ambulation was maintained in 84% of those with minimal or no neurologic impairment. Treatment consisted of 3000 cGy in ten fractions (used primarily for radiosensitive tumors, i.e., seminoma, lymphoma, myeloma) or the fractionation scheme of Greenberg et al. (500 cGy × 3, 4-day rest, 300 cGy × 5). High-dose intravenous corticosteroids (1 g of methylprednisolone) was used for paraparetic or paraplegic patients, and standard-dose dexamethasone (16 mg/d) was used in all other patients. Sixty percent of paraparetic, nonambulant patients regained their ability to walk. Only 11% of paraplegic patients became ambulatory. Overall, 76% of paraplegic patients were ambulant after treatment. Spinal cord dysfunction improved in 44% of patients. Those with favorable histologies (breast, prostate, lymphoma, myeloma, seminoma, small cell carcinoma) more frequently enjoyed restoration of gait and recovery of bladder function. The median survival for the group was 6 months, and 28% were alive at 1 year. Ambulation before treatment was associated with a median survival of 8 months, versus 4 months for those nonambulant before treatment (P = .02). Ambulation after treatment was associated with a median survival of 11 months versus 4 months for patients who were ambulant before treatment (P = .01). Survival for favorable histologies was 19 months for patients who were ambulant before treatment (P = .01). Clearly, early diagnosis of cord compression was the factor that most significantly influenced the outcome in this study. Tumor histology had the greatest influence on outcome in patients with loss of ambulation, bladder dysfunction, or paraplegia. This study also demonstrated that the results of radiotherapy plus corticosteroids compared favorably with the results of laminectomy.

In a subsequent report, Maranzano et al. demonstrated that corticosteroids could be omitted from the treatment of cord compression in selected patients. Twenty patients with cord compression and no neurologic dysfunction, or dysfunction limited to radiculopathy, were evaluated. This group included patients with intact motor and sensory function and tumors involving less than 50% of the spinal cord diameter or fewer than two vertebrae longitudinally. Patients with radiculopathy or greater than two vertebral levels involved were included. Six patients presented with radiculopathy, and 14 patients presented with cord impingement. Radiotherapy consisted of 3000 cGy in ten fractions. Back pain responded in 85% of cases. All patients were ambulatory without support following treatment, including four patients who had required support for ambulation after radiotherapy. These excellent results suggest that routine administration of corticosteroids in patients with asymptomatic early cord compression is not necessary.

More recently, the same authors explored the use of hypo-fractionated regimens for treatment of cord compression. Fifty-three patients with radiographic evidence of cord compression and unfavorable histology and without or with minimal neurologic deficits, or patients with favorable histology (breast, prostate, myeloma, lymphoma) who presented with paresis, paraparesis, or low performance status (Eastern Cooperative Oncology Group performance score of less than or equal to 2) and short life expectancy were treated with a single 800-cGy fraction delivered generally after a posterior port. This treatment was repeated after 1 week in responding or stable patients. Of 49 evaluable patients, 4 also received laminectomy, and 4 patients did not receive the second fraction due to systemic disease progression. Pain relief was 79%, motor function 71%, and motor function regained intact function improved 53%. None of the paraplegic patients regained ambulation. The authors claimed that the results were not substantially different from previously published results in similar patients. However, the results were numerically inferior to those achieved with 3000 cGy in ten fractions.

In another publication from this group, two hypofractionated regimens were compared in patients with cord compression from prostate cancer. There was no difference in pain of palliation, neurologic outcome, or survival based on the treatment regimen. These studies have demonstrated that hypofractionated regimens, despite producing more acute toxicity, are reasonably well tolerated and relatively effective. However, split courses and large fraction sizes are fundamentally radiobiologically unfavorable due to the likely presence of tumor hypoxia and the proliferation of tumor during splits in treatment. These considerations combined with the rapidity of motor function recovery have led to the complete absence of more accumulated data in the subsequent literature on this topic. In 1996, they reported the results of 503 evaluable patients treated with 800-cGy single-fraction radiotherapy, and 526 evaluable patients treated with 3000 cGy in 10 fractions in which 2% of patients were treated. The median survival for those who were initially ambulatory was longer than 1 year. Recovery of gait and bladder function was observed in 60% of patients treated with 800-cGy in 1 day. The success of radiotherapy in reversing paralysis correlates with the rapidity of loss of motor function. Recovery of ambulation occurs more frequently in patients with gradual pain caused by a cord compression.

In a report from Hanover, Germany, 96 patients with motoric deficits were divided into two subgroups based on the duration of development of motoric deficits: 1 to 13 days (49 patients), group A, and greater than or equal to 14 days (47 patients), group B. The two groups were comparable in pretreatment ambulatory function (33% and 32%, respectively). At 2 weeks and 3 months, more patients were ambulatory in group B (77% and 81%) than in group A (31% and 30%). A separate group of patients (31) with rapid loss of motor function within 48 hours of presentation was evaluated. At 2 weeks and 3 months, only 13% and 15% of patients in group A were ambulatory, whereas 57% and 63% of patients in group B had regained ambulation. Recovery was more rapid in patients who were ambulatory before radiotherapy. Thence, the success of radiotherapy in reversing paralysis correlates with the rapidity of loss of motor function. Recovery of ambulation occurs more frequently in patients with gradual rather than abrupt loss of ambulation. Delays in the recovery of ambulation can last as long as 15 months. These findings are consistent with the results of experimental mechanical cord injury in dogs.

The role of corticosteroids during radiotherapy has not been adequately studied. Although corticosteroids are universally prescribed and subsequently tapered during or after radiotherapy, corticosteroids do not appear to be necessary in patients who present with no neurologic dysfunction. Radiation produces no clinically significant spinal cord edema itself, and the benefit of corticosteroids is temporary. Maintaining corticosteroids during radiation is clearly indicated if symptoms persist after radiotherapy is completed. Treatment of corticosteroids through the course of radiotherapy is unnecessary. High-dose corticosteroids have no proven greater efficacy than low-dose corticosteroids and remain controversial. High-dose corticosteroid therapy and radiation was significantly superior to radiation alone in one study, but whether similar results could have achieved with low-dose corticosteroids was not determined. A prospective study of high- versus low-dose corticosteroids revealed no difference in the rate of ambulatory patients after treatment. Despite this, the role of high-dose corticosteroids has been advocated by some investigators.

An analysis of prognostic factors in 153 patients treated with radiotherapy and/or laminectomy for cord compression was reported by Helweg-Larsen et al. As has been shown repeatedly in numerous studies, ambulation pretreatment predicted ambulation posttreatment. Tumor type was shown to influence the interval from initial diagnosis to cord compression, and from cord compression to ambulation posttreatment. Patients with renal and prostate tumors had the highest rate of ambulation following treatment, and patients with lung cancer had the least favorable outcome. Although the majority of compressing metastases develop in the posterior aspect of the vertebral body, the radiation dose should be prescribed to a depth corresponding to the anterior aspect of the involved vertebral

Radiotherapy Technique

The size and configuration of radiotherapy portals should be designed using all relevant data from the history and physical examination, plain films, bone scans, myelograms, CT, and spinal MRI. An MRI with sagittal views of the entire length of the spine should be carefully studied to identify any additional sites of cord compression as part of the radiotherapy treatment planning process. The size and configuration of radiotherapy portals should be centered on the site of epidural compression. Of the 16 to 25% of patients who develop recurrent cord compression after radiation, 64% of early recurrences (within the first 3 months) are within two vertebral bodies of the site of initial compression. Accordingly, radiation portals customarily extend two vertebral bodies above and two vertebral bodies below the site of compression. Adjacent sites of bony involvement and paravertebral masses should also be encompassed in the treatment port. Lesions in the cervical spine, a common site for myeloma, should be treated with opposed lateral fields to reduce radiation exposure of the pharyngeal mucosa. Thoracic spine lesions are generally treated with a simple posterior field. Although the majority of compressing metastases are often treated with a single posterior field. Although the majority of compressing metastases...
body. This ensures full-dose delivery to the tumor and adequate treatment of the entire bone. The anterior edge of the affected vertebral body can be determined with a lateral spine simulator film. If this depth equals or exceeds the midplane of the patient, or if beam energies sufficient to prevent greater than a 110% hot spot on the spinal cord are not available, opposed anteroposterior fields should be used. Ad hoc prescription of a depth for posterior fields without measurement of the prescription depth should be discouraged. The lumbar spine is usually treated with opposed anteroposterior fields, since the lumbar vertebrae are generally at midplane.

An important goal of radiotherapy for epidural compression is to deliver an effective palliative dose of radiation expeditiously without exceeding the spinal cord tolerance. To this end, an optimal dose and fractionation scheme has not been established. Radioresponsive tumors, such as neuroblastoma, can be treated with 2000 to 3000 cGy. Epidual cord compression caused by lymphoma more often responds completely when total doses greater than 2500 cGy are employed. Patients with cord compression by malignant melanoma are more likely to respond to total doses greater than 3000 cGy. Complete recovery is more often associated with higher total doses, rather than with the use of large doses per fraction.

Initial large daily fractions (400 to 500 cGy) produce more rapid neurologic recovery in animal models with cord compression. In contrast, larger doses per fraction provided less durable pain relief from bone metastases and neurologic recovery from cord compression is not superior to that achieved by conventional dose regimens. Nevertheless, some authors continue to recommend delivery of large doses per fraction (400 to 500 cGy) on the first 3 days of treatment to achieve rapid lysis of tumor, followed by smaller doses (200 to 300 cGy) for the remainder of the treatment. By convention, patients usually receive 200 to 300 cGy per fraction to a total dose not exceeding 3000 to 4000 cGy to the spinal cord in 2 to 4 weeks. The results of several radiotherapy series are summarized in Table 51.2-6.

CHEMOTHERAPY

Neurologic recovery from spinal cord compression in response to chemotherapy has been reported in adults and children. Hodgkin's disease, non-Hodgkin's lymphoma, and breast cancer are the most frequent primary malignancies associated with spinal cord compression. The use of chemotherapy combined with radiation was associated with a prolonged survival in patients presenting with epidural cord compression from non-Hodgkin's lymphoma. These studies suggest that in certain cases, chemotherapy should be considered more frequently than is currently accepted. Chemotherapy can be used in combination with radiotherapy for treatment of spinal cord compression, or alone in adults who are not surgical or radiation candidates, but who have chemosensitive tumors such as lymphoma, small cell carcinoma, myeloma, breast, prostate, or germ cell tumors.

PEDiatric SPINAL CORD COMPRESSION

Malignant spinal cord compression in children differs from that in adults in several respects including the tumor types that most frequently produce compression, the mechanisms of impingement, and most importantly the approach to treatment. Unlike in adults, motor weakness can be as frequent a symptom as local pain, being present in 82% to 100% of cases. Neuroblastoma, Ewing's sarcoma, Wilms' tumor, lymphoma, and soft tissue and bone sarcomas are the most frequent tumor types producing compression in children, and yet they are infrequently encountered in adults (see Table 51.2-1). The majority of tumors causing cord compression in children do so via neuroforaminal invasion producing the so-called dumbbell tumors. Unlike treatment of adult malignant spinal cord compression, there is a greater emphasis on the use of chemotherapy in pediatric patients. This is due to the greater chemosensitivity of most pediatric cancers and the profound interest in avoiding iatrogenic spinal deformities and second cancers in children, which can result from radiotherapy.

The most impressive results of pediatric cord compression treatment with chemotherapy were reported by Hayes et al. Fourteen patients with spinal cord compression from neuroblastoma or Ewing's sarcoma received combination chemotherapy alone. All patients with neurologic signs or symptoms (10 of 14) experienced complete or near complete recovery following chemotherapy. Sanderson et al. had similar results. Four of four patients presenting with paraparesis or paraplegias from cord compression by neuroblastoma had complete neurologic recovery following treatment with chemotherapy alone.

When chemotherapy is used for treatment of spinal cord compression, the response to treatment should be monitored closely by a multidisciplinary team including a neurosurgeon, pediatric oncologist, radiation oncologist, and neuroradiologist so that alternate interventions can be instituted quickly to alleviate neurologic progression.

Klein et al. reviewed 112 cases of pediatric cord compression from St. Jude Children's Hospital. Patients with soft tissue sarcomas treated with laminectomy as a component of their overall treatment had statistically superior ambulation following treatment compared with those who received chemotherapy or radiation alone. Raffel et al. studied children with severe cord compression as evidenced by greater than 50% replacement of the spinal canal by tumor on MRI or CT. Twenty-five of 26 children treated with laminectomy improved compared with 4 of 7 treated nonsurgically. Since posterior cord compression resulting from vertebral foramen invasion occurs in a larger percentage of pediatric cases, laminectomy may be of greater benefit than in adults.

However, in a retrospective analysis of pediatric neuroblastoma with cord compression, there was no significant difference based on whether or not laminectomy was used. There were, however, numerically more ambulatory patients following surgical treatment. Thus, pediatric patients with soft tissue or bone sarcomas and severe neurologic dysfunction from compression should be considered for osteoplastic laminotomy or laminectomy followed by adjuvant chemotherapy or radiation. In other circumstances, treatment with initial chemotherapy alone may be appropriate.

CONCLUSION

Paraplegia from epidural cord compression is preventable if diagnosis and treatment are instituted before severe neurologic deficits develop. A heightened awareness of the significance of new or progressive back pain is the most important factor in the successful treatment of cord compression. Plain films, myelography, MRI, or CT should be obtained when the history and neurologic examination suggest spinal involvement with tumor or cord compression. Corticosteroids should be administered in symptomatic patients when the diagnosis has been established, and oncology, neurology, neuorsurgery, and radiation oncology consultants should provide urgent evaluations.

Fortunately, management recommendations can be made despite the lack of definitive randomized trials evaluating contemporary treatments. Treatment recommendations are outlined in Table 51.2-6. Radiotherapy is indicated in all patients with minimal or no neurologic deficits. Radiation should also be administered following surgery in patients who have not previously received radiation. Spinal instability, compression from bone fragments, previous radiotherapy, and neurologic progression during radiotherapy are indications for surgery in appropriate candidates. Surgery should be considered in patients with a life expectancy of greater than 2 months. The surgical approach should be determined by the location of vertebral involvement and direction of compression.

TABLE 51.2-6. Recommendations for Management of Patients with Metastatic Cord Compression

<table>
<thead>
<tr>
<th>Condition</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuroblastoma</td>
<td>Chemotherapy or radiation with or without surgery</td>
</tr>
<tr>
<td>Ewing's sarcoma</td>
<td>Chemotherapy or radiation with or without surgery</td>
</tr>
<tr>
<td>Wilms' tumor</td>
<td>Chemotherapy or radiation with or without surgery</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>Chemotherapy or radiation with or without surgery</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>Chemotherapy or radiation with or without surgery</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>Chemotherapy or radiation with or without surgery</td>
</tr>
<tr>
<td>Germ cell tumors</td>
<td>Chemotherapy or radiation with or without surgery</td>
</tr>
</tbody>
</table>

Table 51.2-6. Recommendations for Management of Patients with Metastatic Cord Compression

- Neuroblastoma, Ewing's sarcoma, Wilms' tumor, lymphoma, and soft tissue and bone sarcomas are the most frequent tumor types producing compression in children.
- The majority of tumors causing cord compression in children do so via neuroforaminal invasion producing the so-called dumbbell tumors.
- Chemotherapy is more frequently used in pediatric patients due to the greater chemosensitivity of most pediatric cancers and the interest in avoiding iatrogenic spinal deformities and second cancers.
- Pediatric patients with soft tissue or bone sarcomas and severe neurologic dysfunction from compression should be considered for osteoplastic laminotomy or laminectomy followed by adjuvant chemotherapy or radiation.
- In other circumstances, treatment with initial chemotherapy alone may be appropriate.
Chemotherapy should be the initial treatment for children with chemosensitive tumors. Patients treated with chemotherapy should be monitored closely so that immediate intervention can proceed if there is an inadequate response or neurologic progression. Children with severe neurologic deficits from cord compression should receive primary laminectomy or decompression. Adjuvant chemotherapy should be given to patients who respond to definitive surgery or radiotherapy. In patients with metastatic spinal cord compression, corticosteroids help to improve neurologic function by reducing vasogenic edema. Corticosteroids remain one of the most effective treatments for acute spinal cord compression.

**CHAPTER REFERENCES**


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Ofilschei CE. Aspiration biopsy of the spine: technique for the thoracic spine and results of twenty-eight biopsies in this region and over-all results of 1500 biopsies of other spinal segments. J Bone Joint Surg Am 1969;51:1531.


SECTION 51.3
Metabolic Emergencies

RAYMOND P. WARRELL, JR.

Introduction
Hypercalcemia
Epidemiology
Differential Diagnosis
Clinical Manifestations
Pathophysiology
Summary
Treatment of Cancer-Related Hypercalcemia
General Measures
Specific Measures
General Approach to Treatment of Hypercalcemia
Emergency Treatment of Hospitalized Patients
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Management of Chronic Recurrent Hypercalcemia
Hyperuricemia
Treatment
Tumor Lysis Syndrome
Treatment
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Therapy
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Clinical Manifestations
Evaluation and Treatment
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INTRODUCTION
Patients with cancer may develop a number of metabolic and endocrinologic problems, frequently to an exaggerated degree. This section reviews metabolic complications of cancer that require urgent therapy for treatment or prevention.

HYPERCALCEMIA

EPIDEMIOLOGY

Hypercalcemia is the most common life-threatening metabolic disorder in patients with cancer. The prevalence of this disorder approaches 15 to 20 cases per 100,000 persons. The incidence varies depending on the underlying cancer diagnosis, being highest in myeloma and breast cancer (approximately 40%), intermediate in non–small cell lung cancer, and uncommon in colon, prostate, and small cell lung carcinomas.

DIFFERENTIAL DIAGNOSIS

Hypercalcemia is associated with a wide variety of pathologic states (Table 51.3-1). Primary hyperparathyroidism and cancer are the two most common causes of hypercalcemia, and both diseases are prevalent. Patients who present with a recent onset of symptomatic hypercalcemia and weight loss are more likely to have a malignant disorder. In hypercalcemic patients who require hospitalization, cancer has been previously diagnosed or becomes apparent after minimal diagnostic evaluation in most cases. By contrast, asymptomatic hypercalcemia and chronic symptoms are the most common presentations of primary hyperparathyroidism. The diagnostic evaluation and differential diagnosis of patients with hypercalcemia have been reviewed. Generally, an elevation in serum calcium with a low or normal serum immunoreactive parathyroid hormone (PTH) level, especially when combined with an increase in serum PTH-related protein (see Parathyroid Hormone and the Parathyroid Hormone–Related Protein, later in this chapter) can exclude the diagnosis of primary hyperparathyroidism with high confidence.

TABLE 51.3-1. Diseases Associated with Hypercalcemia

<table>
<thead>
<tr>
<th>Disease</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myeloma</td>
<td>Cancer of the bone marrow</td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>Malignant tumor of the breast</td>
</tr>
<tr>
<td>Non–Small Cell Lung Cancer</td>
<td>Malignant tumor of the lung</td>
</tr>
<tr>
<td>Colon Cancer</td>
<td>Malignant tumor of the colon</td>
</tr>
<tr>
<td>Prostate Cancer</td>
<td>Malignant tumor of the prostate</td>
</tr>
<tr>
<td>Small Cell Lung Carcinoma</td>
<td>Malignant tumor of the lung</td>
</tr>
</tbody>
</table>

Corrected [calcium] (mg/dL) = measured [calcium] (mg/dL) – [albumin] (g/dL) * 4.0

CLINICAL MANIFESTATIONS

Patients with hypercalcemia can present with a wide variety of symptoms affecting multiple organ symptoms (Table 51.3-2). The severity of the presentation is not exclusively related to the degree of elevation in serum calcium. Patients with a slight-to-moderate elevation (12 to 13 mg/dL) may be obtunded if the increase has occurred acutely. Conversely, patients with long-standing hypercalcemia (such as those with parathyroid carcinoma) may tolerate a serum calcium greater than 14 mg/dL with few symptoms. Other factors (especially age, performance status, sites of metastases, and hepatic or renal dysfunction) also contribute to the severity of symptoms.
In patients with evolving hypercalcemia, fatigue, lethargy, constipation, nausea, and polyuria are the most common initial complaints. It is important to evaluate the serum calcium in patients who have these relatively nonspecific complaints because the combination of polyuria and nausea can lead to rapid dehydration and substantial worsening of the hypercalcemic state. Patients in late stages may present in stupor or coma, and the condition is easily mistaken for diabetic ketoacidosis or drug overdose.

**PATHOPHYSIOLOGY**

In the past, cancer-related hypercalcemia was conveniently categorized according to the presence or absence of bone involvement. Hypercalcemia in the former group was believed to be associated with direct bone destruction by cancer cells (so-called local osteolytic hypercalcemia), and the second group was characterized by various humorally mediated mechanisms. However, it is now evident that hypercalcemia, even in patients with extensive osteolysis, is mediated by factors released by malignant cells that ultimately act to resorb calcium from bone. Some of these factors also stimulate calcium reabsorption from the renal tubule, but this effect is secondary in importance to accelerated osteoclastic bone resorption.

**Parathyroid Hormone and the Parathyroid Hormone–Related Protein**

Many patients with cancer-related hypercalcemia have biochemical characteristics suggestive of PTH stimulation, including increased tubular reabsorption of calcium, hypophosphatemia with phosphaturia, and elevated levels of nephrogenous cyclic adenosine monophosphate. However, most studies of ectopic hyperparathyroidism were based on bioassays or measurements of immunoreactive material. Studies examining PTH-specific mRNA in tumors have confirmed that ectopic PTH production is not a common cause of cancer-related hypercalcemia. Other than cases of parathyroid carcinoma, tumor secretion of authentic PTH by malignant tumors is exceptionally rare. Nonetheless, primary hyperparathyroidism caused by parathyroid adenomas is a common feature of the heritable multiple endocrine neoplasia syndromes 1 and 2a.

A PTH-related protein (PTH-RP), which is elaborated by cancer cells and binds to the PTH receptor, has now been fully characterized. Genes encoding PTH-RP and authentic human PTH have been mapped to the short arms of chromosomes 12 and 11, respectively. The proteins are homologous for only 8 of the first 13 amino acids in the amino-terminal portion, which contains the receptor-binding domain. PTH-RP is widely distributed in normal tissues such as brain, kidney, parathyroid, skin, atrium, uterus, and breast. PTH-RP mediates the effects of a protein known as Indian hedgehog that is a negative regulator of chondrocyte differentiation. The protein seems to be involved only in local signaling and under normal conditions is not released into the general circulation.

Although at least one case of elevated PTH-RP has been reported in association with a benign tumor (called humoral hypercalcemia of benignancy), this phenomenon is extremely rare. PTH-RP appears to be the most common mediator of cancer-related hypercalcemia. Increased blood levels of PTH-RP are commonly found in patients with solid tumors (Fig. 51.3-1), particularly patients with squamous (epidermoid) carcinomas. Elevated serum PTH-RP levels have been found in 30% to 50% of hypercalcemic patients with breast cancer, even though this disease was formerly thought to characterize the bone metastasis form of hypercalcemia. The factor does not appear to be associated with most hematologic cancers such as myeloma or lymphoma. However, the viral tax protein transactivates the PTH-RP gene promoter, and high levels of PTH-RP have been reported in patients with human T-cell lymphotropic virus 1–associated leukemia and lymphoma. The factor is elaborated at sites of bone metastases in breast cancer and prostate cancer, and women with high basal levels of immunoreactive PTH-RP in the primary tumor appear more likely to develop metastases in bone than in soft tissues. The absolute serum level of PTH-RP is not affected by hypocalcemic treatment. Several studies have shown that patients with high levels tend to have an inferior response when treated with bisphosphonates and a poorer life expectancy.

**FIGURE 51.3-1.** Plasma levels of parathyroid-related protein (PTHrP) in normocalcemic control patients with solid tumors, patients with solid tumors with (BM+) or without (BM−) bone metastases or in whom the presence or absence of bone metastases was not determined (BM?), patients with various hematologic cancers, and patients with primary hyperparathyroidism (pHPT). (From ref. 34, with permission.)

**Vitamin D**

Elevated serum 1,25(OH)₂-vitamin D₃ levels have been reported in patients with Hodgkin's disease, non-Hodgkin's lymphoma, myeloma, and occasional patients with solid tumors. This effect probably results from increased enzymatic conversion of 25-OH-vitamin D₃ by 1α-vitamin D-hydroxylase, similar to well-documented processes that occur in patients with granulomatous disease. However, these observations do not necessarily establish an etiologic association. The measured elevations in serum D₃ concentrations in such patients have generally been well below levels that are known to cause hypercalcemia in patients with sarcoidosis. The levels are also below serum levels in subjects who have ingested oral calcitriol and who remain normocalcemic. Moreover, serum vitamin D₃ levels may not be appropriately suppressed in hypercalcemic patients with elevated PTH-RP levels. Whether vitamin D₃ plays a critical pathophysiologic role, acting alone or in concert with other factors, or acts merely as a marker of tumor burden is still unclear. Nonetheless, normalization of serum vitamin D₃ levels and resolution of hypercalcemia occur with control of the underlying disease.

**Prostaglandins**

Prostaglandins have long been implicated as circulating mediators of cancer-related hypercalcemia, and certain prostaglandins (notably of the E series) have potent

**TABLE 51.3-2. Clinical Manifestations of Cancer-Related Hypercalcemia**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyuria</td>
<td>Increased urine output</td>
</tr>
<tr>
<td>Nausea</td>
<td>Uncomfortable or unpleasant sensation of the stomach</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Tiredness or lack of energy</td>
</tr>
<tr>
<td>Lethargy</td>
<td>Lack of energy and motivation</td>
</tr>
<tr>
<td>Constipation</td>
<td>Hardness or difficulty in passing stools</td>
</tr>
<tr>
<td>Oliguria</td>
<td>Decreased urine output</td>
</tr>
<tr>
<td>Headache</td>
<td>Pain or discomfort in the head</td>
</tr>
<tr>
<td>Thirst</td>
<td>Urge to drink water</td>
</tr>
<tr>
<td>Polydipsia</td>
<td>Increased desire for fluids</td>
</tr>
<tr>
<td>Stupor</td>
<td>Reduced alertness or responsiveness</td>
</tr>
<tr>
<td>Coma</td>
<td>Deep unconscious state</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Increase in arterial blood pressure</td>
</tr>
<tr>
<td>Hypotension</td>
<td>Decrease in arterial blood pressure</td>
</tr>
<tr>
<td>Hypothermia</td>
<td>Abnormally low body temperature</td>
</tr>
<tr>
<td>Hyperthermia</td>
<td>Abnormally high body temperature</td>
</tr>
<tr>
<td>Anorexia</td>
<td>Loss of appetite</td>
</tr>
<tr>
<td>Weight loss</td>
<td>Decrease in body weight</td>
</tr>
<tr>
<td>Weakness</td>
<td>Loss of muscle strength or power</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Tiredness or lack of energy</td>
</tr>
<tr>
<td>Anemia</td>
<td>Deficiency of red blood cells</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>Difficulty in breathing</td>
</tr>
<tr>
<td>Cyanosis</td>
<td>Blue or bluish discoloration of the skin</td>
</tr>
<tr>
<td>Jaundice</td>
<td>Yellowing of the skin</td>
</tr>
<tr>
<td>Gastrointestinal symptoms</td>
<td>Symptoms related to the stomach or intestines</td>
</tr>
</tbody>
</table>

**FIGURE 51.3-1.** Plasma levels of parathyroid-related protein (PTHrP) in normocalcemic control patients with solid tumors, patients with solid tumors with (BM+) or without (BM−) bone metastases or in whom the presence or absence of bone metastases was not determined (BM?), patients with various hematologic cancers, and patients with primary hyperparathyroidism (pHPT). (From ref. 34, with permission.)
bone-resorptive activity in vitro. Furthermore, circulating levels of prostaglandin E in hypercalcemic patients are far too low toaccount for the observed degree of accelerated bone resorption. Thus, prostaglandins may have an important (but time-dependent and highly focal) role in cancer-related osteolysis.

**Cytokines**

A number of soluble osteclast-activating factors have been isolated that are potent inducers of bone resorption in vitro. The transforming growth factors (TGFs) are released in an autocrine manner by many cancer cells and regulate both resorption and formation of normal bone. TGF-α shares partial amino acid homology with epidermal growth factor, binds to the epidermal growth factor receptor, and is a potent inducer of bone resorption in vitro, both alone and in combination with PTH-RP.

Conversely, TGF-β is secreted by osteoblasts and may regulate osteoblast growth and differentiation. Thus, dysregulated TGF secretion might lead to uncoupling of the normal processes of bone resorption and formation and could partly account for the mixed lytic and blastic appearance of skeletal metastases in diseases such as breast and prostate cancer.

Interleukin-6 increases bone resorption in vitro, acts as an autocrine growth factor in myeloma, and may be associated with hypercalcemia in kidney cancer. Hypercalcemia induced in vivo by interleukin-6 administration is blocked by treatment with specific neutralizing antibodies. Other cytokines, including interleukin-1, tumor-derived hematopoietic colony-stimulating factors, and tumor necrosis factor (particularly tumor necrosis factor-β (lymphotoxin)), are also potent inducers of bone resorption in vitro. However, clinical therapy with suprapharmacologic amounts of therapeutic recombinant cytokines is not associated with hypercalcemia. Thus, although the focal interaction of these factors at sites of bone involvement may be complex, there is little evidence that circulating cytokines are important mediators of cancer-related hypercalcemia.

**SUMMARY**

With the discovery of the PTH-RP and its high prevalence in patients with cancer-related hypercalcemia, a unifying hypothesis for the etiology of this syndrome has become more apparent. PTH-RP, not normally released to the general circulation, is a potent mediator of hypercalcemia. In general, patients who elaborate this factor, particularly patients with epidermoid carcinomas, are more resistant to treatment with antihypercalcemic drugs. Osteotropic tumors, such as breast and prostate cancer, appear to require proximity to bone in order to effect bone resorption, possibly via release of TGFs, PTH-RP, prostaglandins, or all three. The extensive osteolysis observed in multiple myeloma may be due to focally increased production of interleukin-6 and tumor necrosis factor-β that accelerates bone resorption by normal osteoclasts. A large number of patients with cancer have lytic bone disease, but only a small proportion develop hypercalcemia; thus, interaction of these factors and their amplification on the pathophysiology of the kidney must also occur.

**TREATMENT OF CANCER-RELATED HYPERCALCEMIA**

**GENERAL MEASURES**

Although the best treatment for cancer-related hypercalcemia is therapy directed at the underlying disease, hypercalcemia most commonly occurs in patients with advanced disease who have failed prior cytotoxic therapy. The usual therapies for hypercalcemia are directed at decreasing serum calcium by increasing urinary calcium excretion or decreasing bone resorption by inhibition of osteoclast function. For practical purposes, increased intestinal absorption of calcium does not make an important contribution to hypercalcemia in patients with cancer. Low-calcium diets are generally unpalatable and distinctly ineffective; their use is strongly discouraged.

Where possible, immobilization should be minimized because inactivity tends to aggravate hypercalcemia. Drugs that inhibit urinary calcium excretion (e.g., thiazides) or agents that may decrease renal blood flow (nonsteroidal antiinflammatory drugs and H₂ receptor antagonists) should be discontinued if possible. Patients should be carefully interviewed with respect to dietary aberrations, and medications containing calcium, vitamin D, vitamin A, or other retinoids should be stopped.

Formerly, hypercalcemic patients were commonly treated with vigorous intravenous hydration and diuretics for several days, and specific hypocalcemic drugs were reserved for patients who did not respond to hydration. As noted in *Intravenous Fluids and Diuretics*, later in this chapter, this approach is outdated. Most patients benefit substantially from the early introduction of specific antihypercalcemic therapy, and this approach leads to more rapid clinical improvement, lower overall toxicity, and decreased cost.

**SPECIFIC MEASURES**

Until recently, the literature on the treatment of cancer-related hypercalcemia contained few controlled studies. Interpretation of older clinical trial results is therefore confounded by enormous variability in patient selection, underlying diagnoses, severity of hypercalcemia, and unique methods of reporting results. *Figure 51.3-2* depicts results from four major clinical studies, all of which were well-designed, randomized, double-blinded, and which generally employed similar entry and response criteria. *Table 51.3-3* summarizes current therapies with an estimate of their relative clinical efficacy in acutely restoring normocalcemia.

**FIGURE 51.3-2.** Results from four randomized double-blind comparisons of the major drugs used for acute treatment of cancer-related hypercalcemia. Bars depict proportion of patients who achieved a normal serum calcium value subsequent to treatment with the assigned agent. All analyses are based on intent to treat. Numbers at bottom indicate number of patients responding over number of patients treated per group. The test drugs were administered on the following dose-schedules: (A) gallium nitrate (200 mg/m²) as a continuous IV infusion daily for 5 days, and eldonate (7.5 mg/kg) as a 4-hour infusion daily for 5 days; (B) pamidronate (60 mg) as a single 24-hour infusion, and eldonate (7.5 mg/kg) as a 4-hour infusion daily for 3 days; (C) alendronate (10 or 15 mg) as a single 2-hour infusion, and eldonate (7.5 mg/kg) as a 4-hour infusion daily for 3 days; (D) gallium nitrate (200 mg/m²) as a continuous IV infusion daily for 5 days, and pamidronate (60 or 90 mg) as a single 24-hour infusion.
Intravenous Fluids and Diuretics

Hypercalcemic patients frequently present with dehydration owing to vomiting and obligate water losses associated with calcitriol. Fluid repletion, usually with isotonic saline, has been a mainstay of acute therapy, because volume expansion and natriuresis can increase renal blood flow and enhance calcium excretion. The rate of fluid administration depends on a clinical estimate of the extent of dehydration, cardiovascular function, and renal excretory capacity. Assuming renal and cardiac functions are adequate, saline infusion at a rate of 300 to 400 or more mL/h can be used for 3 to 4 hours in severely dehydrated patients. Slower hydration is indicated for less severe disturbances or in patients with congestive heart failure or oliguria. Serum calcium, creatinine, potassium, and magnesium should be reassessed frequently during this period.

The heroic degrees of saline hydration and forced diuresis that made up past therapy for cancer-related hypercalcemia are no longer indicated. Such treatment is excessively toxic since it frequently causes fluid overload and occasionally life-threatening pulmonary edema. The resulting weight gain and lower extremity edema that occurs in hypoproteinemic patients with advanced cancer may not resolve during the life of that individual and can be severely disabling. Moreover, hydration (with or without diuretics) is not very effective. In a prospective study of 16 patients with serum calcium greater than or equal to 13.0 mg/dL (3.25 mmol/L), only five patients (31%) achieved normocalcemia with normal saline (4000 cc × 2 days). Although furosemide-induced natriuresis theoretically enhances urinary calcium excretion, controlled studies were ever conducted to indicate that cancer patients benefit from routine furosemide treatment. Furosemide also increases the risk for developing hypervolemia; the resultant decrease in glomerular filtration may actually stimulate renal calcium reabsorption, inadvertently reinstate dehydration, and worsen the clinical condition. Therefore, the use of furosemide should be restricted to balancing fluid intake and urinary output in patients who have been fully rehydrated. In most hospitalized patients, fluid administration should not be employed alone, and treatment with antiresorptive drugs should be initiated promptly following rehydration for control of hypercalcemia.

Bisphosphonates

Bisphosphonates (formerly diphosphonates), chemical analogues of pyrophosphate that are resistant to hydrolysis by pyrophosphatase, have become the most commonly used drugs for the treatment of hypercalcemia. Bisphosphonates adsorb to the surface of crystalline hydroxapatite and inhibit calcium release from bone by interfering with the metabolic activity of osteoclasts. There are numerous bisphosphonates available or undergoing clinical investigation, including etidronate, clodronate, pamidronate, zoledronate, alendronate, tiludronate, ibandronate, and risedronate. As a class, bisphosphonates have low oral bioavailability (less than 1%), and none of these agents is currently recommended as an oral therapy for hypercalcemia.

Intravenous pamidronate has become the most widely prescribed drug for treatment of hypercalcemia. This drug is well-tolerated and its side effects are usually limited to infusion-site irritation, fever, and flu-like symptoms that occur after the first infusion in approximately 20% of patients. Although multiple doses and schedules have been tested, pamidronate is most commonly given at doses of 60 or 90 mg infused over 2 hours. Although the higher dose has been suggested for patients with more severe hypercalcemia (e.g., a total serum calcium greater than 13.0 mg/dL), there are conflicting data whether any substantial dose-response relationship exists above 60 mg. Similar doses have been widely used to reduce skeletal morbidity from bone metastases. Considerable data indicate that the response to pamidronate is inferior in patients whose hypercalcemia is mediated by PTH-RP. The hypocalcemic effect also appears to decrease with repeated dosing.

Alendronate has also been studied by the intravenous route in hypercalcemia, but this formulation is not widely available. The usual doses are 10 or 15 mg administered over 2 hours. Oral alendronate is widely used for treatment of postmenopausal osteoporosis; however, there are no data available supporting oral alendronate as a treatment for hypercalcemia. Based on similarly designed randomized studies compared with etidronate (see Fig. 51.3-2, pamidronate and alendronate appear to have comparable degrees of clinical efficacy.

Among other bisphosphonates, etidronate, alendronate, and pamidronate, and gallium nitrate in randomized double-blind studies. The response to etidronate in all three studies was similar: 42%, 33%, and 43%, respectively (see Fig. 51.3-2). This result was significantly inferior relative to each of the other agents tested, and these data have largely accounted for its diminished use. Clodronate is available in Europe, but current data suggest that it is not as effective as pamidronate. Ibandronate and zoledronate are other bisphosphonates undergoing clinical testing that are more potent (on a milligram per milligram basis) than earlier bisphosphonates. However, it is unclear if increased potency will translate to improved clinical efficacy, and early results suggest comparable clinical activity.

Gallium Nitrate

Gallium nitrate is a potent inhibitor of bone resorption. Elemental gallium is incorporated into bone and renders hydroxapatite less soluble and more resistant to cell-mediated resorption. However, the drug's principal mechanism of action is inhibition of an ATPase-dependent proton pump that is located in the ruffled membrane of the osteoclast. This effect impairs osteoclast acidification and consequent dissolution of the underlying bone matrix. Randomized double-blind studies have demonstrated superiority of gallium nitrate compared with calcitonin and etidronate for acute treatment of resistant hypercalcemia, and preliminary data from one study also suggested superiority compared with pamidronate (see Fig. 51.3-2).

Following administration as a continuous intravenous infusion (200 mg/m²/d over 24 hours for up to 5 days), gallium nitrate induces normocalcemia in 70% to 90% of patients. The maximal hypocalcemic effect occurs several days after the drug has been discontinued; therefore, the drug infusion should be discontinued once the patient has achieved normocalcemia. In earlier studies that used high-dose gallium nitrate as primary cancer treatment, nephrotoxicity was dose-limiting; however, the incidence of renal insufficiency in controlled hypercalcemia studies has been similar to calcitonin, etidronate, and pamidronate. Like the bisphosphonates, gallium nitrate should be started after the patient has been rehydrated and urinary output ensured. A daily urinary output of 2000 mL should be maintained during the infusion. Concurrent use of highly nephrotoxic drugs, such as aminoglycosides, amphotericin B, and cisplatin, should be avoided.

Calcitonin

Pharmacologic doses of calcitonin reduce serum calcium by increasing renal calcium excretion and inhibiting bone resorption. Calcitonin is especially advantageous due to its rapid onset of action (2 to 4 hours) and its lack of serious toxicity (other than rare hypersensitivity reactions). Notwithstanding these desirable features, the hypocalcemic effect of calcitonin is relatively weak; the acute response peaks at 48 hours and diminishes thereafter despite continued treatment. Less than 30% of hypercalcemic patients treated with calcitonin as a single agent achieve a normal serum calcium value. High doses of calcitonin (6 to 8 IU/kg every 6 hours) should be employed for acute treatment of hypercalcemia. Absent thrombocytopenia, the drug should be administered intramuscularly rather than subcutaneously to ensure complete absorption. Calcitriol also probably do not enhance the hypocalcemic effects of calcitonin in patients whose underlying disease is not steroid-responsive. The drug does not appear to be effective when administered by nasal insufflation. Because of its rapid action, calcitonin has been increasingly used in combination with more potent antiresorptive drugs such as gallium nitrate and pamidronate, and this combination, in addition to vigorous intravenous hydration, is excellent therapy for critically ill patients with acute severe hypercalcemia.

Corticosteroids

Corticosteroids acutely inhibit osteoclast-mediated bone resorption in vitro and decrease gastrointestinal calcium resorption. Corticosteroids are most useful in patients whose underlying tumor is responsive to the cytostatic action of these drugs. These diseases include myeloma, lymphoma, leukemia, and occasional patients with carcinoma of the breast (particularly those who have a hypercalcemic flare during hormonal therapy). Corticosteroids do not have consistent hypocalcemic
activity in other diseases and should not be used in these conditions due to adverse effects. Prednisone (40 to 100 mg/d) is usually effective in controlling hypercalcemia caused by hematologic cancers; lower doses (15 to 30 mg/d) may suffice for patients with hypercalcemic flares caused by breast cancer. However, most patients who require therapy should be treated with a specific antiresorptive drug.

**Phosphates**

An increase in serum phosphorus concentration decreases osteoclastic activity, inhibits calcium resorption from bone, and causes a significant reduction in urinary calcium excretion. However, administration of exogenous phosphate to hypercalcemic patients also shifts calcium from blood to other tissues that can result in severe toxicity. Oral phosphate (0.5 to 3.0 g/d) may be highly effective, particularly in mild forms of hypercalcemia, principal side effects are diarrhea and nausea, which may lead to noncompliance. Serum phosphorous concentrations should be monitored in all patients who receive phosphates, especially patients with decreased renal function or preexisting hyperphosphatemia. Serum creatinine should be regularly monitored to avoid renal insufficiency. When the [calcium x phosphorus product] expressed in milligrams per deciliter exceeds 55, phosphate should be discontinued.

Intravenous phosphate is highly effective and the onset of hypocalcemic action occurs more rapidly than with any other hypocalcemic therapy. However, renal failure, hypotension, extraskelatal calcification, and severe hypocalcemia are common sequelae of parenteral phosphate therapy, and the use of intravenous phosphate has largely been abandoned. Although uncommon, these effects have occasionally been seen with oral phosphates.

**Plicamycin**

Plicamycin (formerly mithramycin) induces hypocalcemia by a direct cytotoxic effect on osteoclasts, thereby decreasing cell-mediated bone resorption. Plicamycin is administered at doses ranging from 10 to 50 µg/kg of body weight. The usual dose is 25 µg/kg or a total dose of 1.5 to 2.0 mg given as a brief infusion. Since the onset of action occurs after 24 to 48 hours, doses should not be repeated more frequently than every 2 days. Except for nausea, single injections are generally well tolerated; the incidence of adverse effects (renal insufficiency, hepatotoxicity, thrombocytopenia, and a hemorrhagic diathesis) increases with multiple injections.

**GENERAL APPROACH TO TREATMENT OF HYPERCALCEMIA**

Patients with hypercalcemia can be divided according to those who require urgent in-hospital therapy and those for whom outpatient therapy can be considered. Table 51.3-4 presents a list of considerations that influence this level of care decision. Hospitalization should be considered for any patient with a serum calcium greater than 12.0 mg/dL or for any patient with significant signs and symptoms, particularly nausea, dehydration, or confusion. Hypercalcemia that has evolved slowly may rapidly progress after a patient begins vomiting or if mentation is impaired.

**EMERGENCY TREATMENT OF HOSPITALIZED PATIENTS**

Intravenous hydration should be initiated immediately in patients who require hospitalization. Furosemide should be given only if diuresis is inadequate or to treat problems related to fluid retention. Most patients with significant hypercalcemia (total calcium greater than or equal to 12.0 mg/dL) do not respond satisfactorily to intravenous fluids, and pamidronate, which is now first-line therapy, should be administered shortly after hydration has been started and satisfactory urinary output established. Patients who do not respond to two pamidronate infusions (administered 48 to 72 hours apart) should be considered for additional therapy, such as gallium nitrate. For patients with a serum calcium greater than or equal to 15.0 mg/dL or severe symptoms (e.g., coma, cardiac irritability), calcitonin (8 U/kg as an intramuscular injection every 6 hours for 2 to 3 days) can be added immediately to provide an acute hypocalcemic effect.

**AMBULATORY MANAGEMENT OF HYPERCALCemic PATIENTS**

One of the major goals of outpatient therapy is to reduce the need for hospitalization. Ambulatory patients must receive clear instructions regarding increased oral fluid intake. The amount of fluid should be stated in terms that the patient and family understand. It is imperative that a family member or companion attend the patient to ensure that nausea caused by worsening hypercalcemia does not lead to further dehydration. Diuretics such as furosemide should not be added since the risk of dehydration outweighs any theoretical benefits in ambulatory patients who are not edematous.

The most commonly used therapy is pamidronate (60 to 90 mg intravenously over 2 to 4 hours). The schedule can be titrated according to the patients needs, but the drug is usually given every 7 to 14 days. Oral bisphosphonates are not useful. In patients with PTH-RP–mediated hypercalcemia, neutral phosphorus (1 to 3 g/d in divided doses) can be quite useful in the setting of hypophosphatemia, so long as renal function is maintained. Oral corticosteroids are helpful if the underlying disease is steroid-responsive. The use of calcitonin has largely been supplanted by the bisphosphonates. Plicamycin can also be administered in doses of 10 to 25 µg/kg once or twice per week with close monitoring for evidence of myelosuppression or changes in renal or hepatic function.

**MANAGEMENT OF CHRONIC RECURRENT HYPERCALCEMIA**

The management of acute hypercalcemic episodes is relatively straightforward. However, an increasing problem is the patient whose underlying disease is poorly or incompletely responsive to primary antitumor therapy, and who continues to develop multiple episodes of hypercalcemia. In this setting, the primary goal of treatment is to prevent exacerbations that require repeated hospitalization. Several principles underlie the management of such patients. First, hypercalcemic treatment must be given on a chronic schedule and must not be reserved for treatment of acute recurrent episodes, even if the patient is relatively normocalcemic. Second, the dosing schedule of pamidronate, once initiated, can be progressively intensified up to a maximum of 90 mg IV twice per week. Third, hypercalcemic drugs should be continued indefinitely unless the patient has sustained a major antitumor response. Patients should not be declared pamidronate-resistant. Rather, the bisphosphonate should be continued on a maximally intensive schedule and additional drugs, including gallium nitrate, calcitonin, oral phosphate, and plicamycin, should be added to the regimen until the serum calcium can be consistently maintained below 12.0 mg/dL.

**HYPERURICEMIA**

Uric acid is formed as a result of the sequential catalysis of hypoxanthine and xanthine by xanthine oxidase. Renal insufficiency develops when urine becomes supersaturated with urate and crystals of uric acid form in the renal tubules and distal collecting system. Uric acid stones may also develop, although this
presentation is more commonly associated with chronic hyperuricemia.

Renal complications and arthritides are the most important consequences of acute or chronic hyperuricemia. The disorder occurs most commonly in hematologic neoplasms, particularly the leukemias, high-grade lymphomas, and myeloproliferative diseases.

Acute urate nephropathy has also been reported after chemotherapy for solid tumors. Patients at highest risk include those with bulky high-grade lymphomas, patients with high leukocyte counts undergoing radiation-induction chemotherapy for acute or chronic leukemia, and individuals with preexisting renal impairment (especially those with ureteral obstruction).

Hyperuricemia is also a side effect of certain agents, notably diuretics (thiazides and furosemide), and antituberculosis drugs (pyrazinamide, ethambutol, and nicotinic acid).

**TREATMENT**

Recognition of patients at risk is essential for proper therapy. It is essential that prophylactic measures be undertaken before cytotoxic therapy is initiated. Drugs that tend to elevate serum urate or that produce an acidic urine (thiazides and salicylates) should be withdrawn. All patients should receive intravenous hydration to correct preexisting deficits of intravascular volume and to ensure continued urinary output. Increased urinary volume decreases the concentration of urate in urine and thus minimizes problems with respect to urate solubility.

Although furosemide theoretically promotes increased tubular urate reabsorption, this effect is outweighed by its acute diuretic action; thus, the drug can be safely used to maintain satisfactory urine output so long as fluid status and serum electrolytes are monitored and replaced. Alkalization of the urine should be initiated to maintain a urine pH greater than or equal to 7.0. Although oral sodium bicarbonate can be used, it is usually simpler to add sodium bicarbonate solution (50 to 100 mmol/L) to intravenous fluids and then to adjust the admixture so that an alkaline urine pH is maintained.

Acetazolamide (an inhibitor of carbonic anhydrase) may be used to increase the effects of alkalization. However, it must be emphasized that alkalization is secondary to the overall goal of decreasing urinary uric acid concentration by increasing urinary volume.

The mainstay of current drug therapy is allopurinol, which inhibits xanthine oxidase and consequently increases plasma and urinary concentrations of xanthine and hypoxanthine. Although xanthine is somewhat more soluble than uric acid, allopurinol has occasionally been associated with renal failure due to xanthine nephropathy.

The drug is generally well tolerated. The most common adverse reaction is a blanching, erythematosus skin rash that indicates hypersensitivity. The onset of this reaction is usually delayed for several days after initial administration, and the drug can usually be continued throughout periods of greatest risk in patients who have not had prior exposure. In acute situations, the drug is administered orally once or twice per day in daily doses ranging from 300 to 900 mg. The dose of certain drugs that are metabolized by xanthine oxidase (e.g., 6-mercaptopurine) must be substantially reduced during treatment with allopurinol.

Patients in renal failure and allopurinol-sensitive individuals represent uncommon but difficult management problems. Intravenous administration of uricase has also been useful in certain circumstances. In the face of acute oliguria, ultrasonography or computed tomographic (CT) scanning should be used to evaluate possible ureteral obstruction by urate calculi. Administration of intravenous contrast agents for pyelography should be avoided due to an increased risk of acute tubular necrosis.

Peritoneal or hemodialysis has been quite effective in reversing renal failure due to urate deposition.

**TUMOR LYsis SYNDROME**

The tumor lysis syndrome occurs as a result of the rapid release of intracellular contents into the blood stream, which then increase to life-threatening concentrations.

The syndrome is characterized by hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia. Lethal cardiac arrhythmias are the most serious consequences of hyperkalemia. Hyperphosphatemia may result in acute renal failure.

Elevated serum phosphorus may also decrease renal function, which can lead to further reductions in urinary potassium and phosphate excretion. Hypocalcemia, a result of hyperphosphatemia, may cause muscle cramps, cardiac arrhythmias, and tetany.

The tumor lysis syndrome occurs most commonly in diseases with large tumor burdens and high proliferative fractions that are exquisitely sensitive to cytotoxic treatment. These disorders include high-grade lymphomas, leukemias with high leukocyte counts, and (much less commonly) solid tumors.

The syndrome has been observed not only with agents that have potent myelosuppressive activity, but also with drugs such as interferon-α, tamoxifen, cladribine, and intrahepatic methotrexate.

Although not related to tumor lysis, severe hypocalcemia has been associated with estrogenic treatment of prostate cancer and with accelerated bone formation in patients with leukemia.

**TREATMENT**

Recognition of risk and prevention are essential to management. Patients at risk should be identified before the initiation of chemotherapy. If possible, intravenous hydration should be started 24 to 48 hours before administration of chemotherapy. Any acid-base or electrolyte disorders should be corrected (although intravenous administration of sodium bicarbonate may aggravate symptoms of hypocalcemia). Treatment with allopurinol should be undertaken along with other measures to minimize calcium wasting. Serum electrolytes, uric acid, phosphorus, calcium, and creatinine should be checked every few hours for 3 to 4 days after initiating cytotoxic treatment. The frequency of monitoring should depend on the clinical condition of the patient. If significant hyperkalemia or hypocalcemia become evident, an electrocardiogram should be obtained and the cardiac rhythm should be monitored while these abnormalities are corrected. In most patients, hypocalcemia can be corrected with intravenous administration of calcium gluconate; however, patients who have persistent hypocalcemia should be treated with calcitriol until the syndrome resolves (serum [K⁺] greater than or equal to 7.0). Although oral sodium bicarbonate can be used, it is usually simpler and minimizes problems with respect to urate solubility.

In the face of acutely worsening renal function after administration of chemotherapy, consideration should be given to the early initiation of renal dialysis in order to rapidly correct serum concentrations of potassium, calcium, phosphate, and uric acid, as well as other problems related to uremia. The dose of many drugs, especially antineoplastics, requires substantial modification in the presence of renal insufficiency.

**LACTIC ACIDOSIS**

Lactic acidosis is a rare but potentially serious metabolic complication in patients with cancer. Type A lactic acidosis results from impaired delivery of oxygen to peripheral tissue and is commonly seen with shock and septicemia. Type B lactic acidosis is associated with a variety of diseases (including diabetes, renal failure, liver disease, infection, and cancer) as well as drugs (such as methotrexin), toxins, and hereditary diseases.

Lactic acidosis is characterized by decreased arterial pH (less than 7.37) secondary to lactate accumulation. Serum electrolytes, uric acid, phosphorus, calcium, and creatinine should be checked every few hours for 3 to 4 days after initiating cytotoxic treatment. The frequency of monitoring should depend on the clinical condition of the patient. If significant hyperkalemia or hypocalcemia become evident, an electrocardiogram should be obtained and the cardiac rhythm should be monitored while these abnormalities are corrected. In most patients, hypocalcemia can be corrected with intravenous administration of calcium gluconate; however, patients who have persistent hypocalcemia should be treated with calcitriol until the syndrome resolves (serum [K⁺] greater than or equal to 7.0). Although oral sodium bicarbonate can be used, it is usually simpler and minimizes problems with respect to urate solubility.

In a review of 25 cases of lactic acidosis in which the underlying tumor was believed to represent the primary etiologic factor, more than two-thirds were associated with leukemia or lymphoma.

The development of lactic acidosis coincided with the onset of progressive disease in the hematologic cancers, whereas most patients with solid tumors had extensive liver metastases. Antiviral drugs, such as azidothymidine and falduridine, have produced hepatic failure and severe lactic acidosis.

Typically, the patient with lactic acidosis presents with hyperventilation and hypotension. Non-specific clinical symptoms such as tachycardia, weakness, nausea, and stupor may proceed to frank shock as the acidosis worsens. Laboratory studies show decreased blood pH, a widened anion gap (greater than 16), and low serum bicarbonate.

It must be noted that primary cancer-induced lactic acidosis is a rare event, and the diagnostic workup should always search for other, potentially more treatable causes.

The prognosis for patients with a serum lactate concentration greater than 4 mEq/L is exceedingly poor; however, the outcome is largely determined by the underlying disease and the acidosis per se. Several reports have suggested that administration of sodium bicarbonate may actually increase lactate and CO₂ production and impair oxygen delivery. Although some deleterious effects of severe acidemia on cardiovascular function could theoretically be ameliorated by sodium bicarbonate, no study has shown a convincing survival advantage for alkali therapy in this condition.

Despite ongoing controversy, bicarbonate administration...
HYPOGLYCEMIA

Insulin-producing islet cell tumors are the most frequent cause of hypoglycemia in patients with cancer; however, more than 250 cases of hypoglycemia associated with non-islet cell tumors have also been reported. Non–islet cell tumors associated with hypoglycemia tend to be large. In such patients, mesenchymal tumors (fibrosarcomas, leiomyosarcomas, rhabdomyosarcomas, liposarcomas, and mesotheliomas) account for approximately 50% of cases; another 25% are hepatomas. Classic symptoms of hypoglycemia (e.g., weakness, dizziness, diaphoresis, and nausea) are nonspecific and may develop slowly. In the initial phases, symptoms tend to be worse in the early morning (due to overnight fasting) and improve after ingestion of food. However, patients may also present acutely with seizures, coma, and focal or diffuse neurologic deficits.

PATHOPHYSIOLOGY

Several etiologic mechanisms for cancer-related hypoglycemia have been proposed: (1) secretion of insulin-like substances; (2) excessive glucose use by the tumor that exceeds hepatic production; and (3) failure of counterregulatory mechanisms that usually prevent hypoglycemia (e.g., reduction in levels of growth hormone). Various substances with nonsuppressible insulin-like activities have been detected in serum from patients with hypoglycemia. These factors are composed of two general classes: one of relatively low-molecular-weight substances that are soluble in acid ethanol, and the other of high molecular weight that are acid-ethanol precipitable. Both low- and high-molecular-weight compounds consist of four peptides, the insulin-like growth factors (IGF-1, IGF-2, somatotropin A, and somatotropin C). The IGFs share a high degree of amino acid similarity with proinsulin, are bound by circulating proteins that inactivate them, and mediate their biologic activities after binding to specific cell surface receptors. They do not react with antinsulin antibodies and they have only 1% to 2% of the specific metabolic activity of insulin. Insulin itself has a weak affinity for the IGF-1 receptor but not for IGF-2R. IGFs appear to act as growth factors for various tumors and have been proposed as targets for anticancer therapy.

In most patients with non–islet cell tumors that have been associated with hypoglycemia, serum levels of IGF-1 have been appropriately suppressed, whereas levels of IGF-2 have been relatively normal (as measured by radioimmunoassay). However, it now appears that the high-molecular-weight, nonsuppressible-insulin-like-activities molecule is actually a propeptide of IGF-2, so-called big IGF-2, secreted by tumor cells that are incompletely cleaved. The large size either prevents formation of an acid-labile subunit from binding or impairs binding of a critical molecule (IGF-binding protein 3), which inactivates the protein; thus, the bound molecule retains its biologic activity.

Accelerated glucose use by large tumors may also account for cancer-related hypoglycemia in some patients. It has been estimated that a 1-kg tumor may use from 50 to 200 g of glucose per day. Shortly after the liver can produce approximately 700 g of glucose per day, hepatic production should theoretically be sufficient to prevent hypoglycemia. However, many patients with hypoglycemia have tumors that weigh several kilograms along with extensive hepatic metastases; thus, the combination of accelerated glucose use with impaired production may lead to hypoglycemia.

Finally, a failure of the usual counterregulatory mechanisms in patients with large tumors may also induce hypoglycemia. Impaired liver function can decrease glycogenolysis and gluconeogenesis. Certain patients with cancer have a depressed hyperglycemic response to the administration of glucagon, depressed secretion of counterregulatory hormones such as glucagon, adrenocorticotropic hormone (ACTH), glucocorticoids, and growth hormone has also been reported. However, there remains little direct evidence to support this hypothesis as an important clinical mechanism of tumor-induced hypoglycemia.

THERAPY

Therapy of hypoglycemia should match the severity of the condition. As with most paraneoplastic syndromes, specific antitumor therapy is the preferred treatment. To date, chemotherapeutic agents that are cytotoxic for islet cells or that block insulin release or activity have had little effect on production, release, or activity of IGFs. Mild hypoglycemia can usually be managed by changes in diet. In patients with more severe or unpredictable symptoms, the administration of corticosteroids and glucagon may afford symptomatic relief. Intravenous infusions of glucose provide temporary support while other specific treatment is administered (i.e., surgery, chemotherapy, or radiation). Under certain circumstances, continuous infusions of glucagon using portable pumps have been used with some success.

ADRENAL FAILURE

Symptomatic adrenocortical insufficiency due to destruction of cortical tissue by metastatic carcinoma is uncommon. More common are iatrogenic causes such as surgical adrenalectomy, treatment with mitotane (o-p′-DDD) and inhibitors of steroid synthesis such as aminoglutethimide, chronic corticosteroid therapy, and occasionally adrenal hemorrhage. Nonetheless, technical improvements in CT and magnetic resonance imaging have increased the likelihood of making an antemortem diagnosis of adrenal metastases. In one study, 15% of patients with metastatic cancer and enlargement of the adrenal glands by CT scans developed symptoms of adrenal insufficiency. In a separate study wherein 15 patients with metastatic cancer and adrenal enlargement on CT scan were evaluated by ACTH stimulation, one-third were judged to have adrenal insufficiency. Further clinical study revealed symptoms of nausea, anorexia, and orthostatic hypotension in all of these patients. Adrenal insufficiency may thus develop insidiously in patients with adrenal metastasis, and CT scans and ACTH testing may be useful diagnostic tools.

CLINICAL MANIFESTATIONS

Classic signs and symptoms of adrenal insufficiency include weakness, weight loss, anorexia, hyperpigmentation, and postural hypotension. One or more of these symptoms are evident in almost all patients, but the onset of symptoms is frequently insidious. Circulatory collapse and shock are uncommon but may develop with the onset of infection. Biochemical evaluation frequently reveals a mild acidosis (without an anion gap), hypokalemia, and hyponatremia.

EVALUATION AND TREATMENT

Because an ACTH-stimulation test is a benign procedure, this test is recommended when symptoms suggestive of adrenal insufficiency are evident. Typically, patients receive Cosyntropin, 0.25 mg intravenously, and serum cortisol is monitored at baseline, 30 minutes, and 1 hour. An increase in serum cortisol of 5 to 7 μg/dL over baseline levels (to a minimum of 15 μg/dL) is considered normal. If adrenal insufficiency is strongly suspected on clinical grounds, steroid replacement (or stress doses of steroids) should be started immediately, and subsequent therapy can be reevaluated when results of the ACTH test become available.

Physiologic glucocorticoid replacement is attained by administration of cortisone acetate (25 mg in the morning and 12.5 mg in the evening). During periods of stress (e.g., operative procedures, infection), the doses may need to be increased. Occasionally, administration of fludrocortisone (0.1 mg daily) may be necessary. However, many patients with hypoglycemia have tumors that weigh several kilograms along with extensive hepatic metastases; thus, the combination of accelerated glucose use with impaired production may lead to hypoglycemia.

*Concentrations in milligrams per deciliter can be converted to SI units after multiplication by 0.2495, which yields a concentration expressed in millimoles per liter.

CHAPTER REFERENCES
INTRODUCTION

Urologic oncologic emergencies may arise secondary to the underlying malignancy, treatment, or unrelated medical conditions. Initial evaluation of symptoms of sepsis, hematuria, urinary obstruction, priapism, and other urologic emergencies leads to diagnosis and initial management. Urologic consultation may be necessary for definitive treatment.

URINARY TRACT INFECTION

URINARY SEPSIS

Neutropenic sepsis occurs after 1.1% to 14.0% of cycles of chemotherapy, most frequently associated with malignancies that impair granulocyte function or with more intensive bone marrow suppression, such as CHOP-M (cyclophosphamide, doxorubicin, vincristine, prednisone, with methotrexate) or similar regimens. Of the sepsis episodes, as many as 8.9% are urosepsis. Urinary tract infections are most frequently associated with urethral catheterization and require surveillance in immunocompromised patients.

Treatment includes broad-spectrum antibiotic coverage until sensitivity results are available (Chapter 54). Broad-spectrum antibiotic coverage resulting in appropriate empiric antibiotic treatment has been associated with improved survival and shorter hospital stay, compared to inappropriate empiric antibiotic coverage. Use of antibiotics before hospital admission, advanced patient age, and male gender have been predictive of a resistant uropathogen.

Altered renal function, flank pain, urinary retention, or other signs or symptoms of urinary obstruction requires immediate evaluation to provide relief. Percutaneous nephrostomy gives direct drainage of an obstructed infected ureter and allows manual irrigation of viscous purulent fluid if drainage is not adequate.

PERURETHRAL ABSCESSES

Periurethral abscess is a life-threatening infection of the male urethra and perirectal tissues. Patients present with sepsis and perineal or scrotal abscesses or phlegmon. Urethral strictures, found in 60% to 85% of these patients, cause a high urethral voiding pressure, and lead to periurethral extravasation of infected urine, particularly after urethral instrumentation. The infection can range from a small abscess confined by Buck's fascia, to an extensive necrotizing fasciitis of the penis, scrotum, and perineum.

The differential diagnosis includes tissue edema, follicular abscess, perirectal abscess, Fournier's gangrene, and penile or urethral cancer. Physical examination will identify urethral involvement, extent of phlegmon, and crepitance caused by gas-forming organisms. Urinalysis and culture usually isolate gram-negative and anaerobic bacteria. Retrograde urethrogram will demonstrate diagnostic extravasation of contrast into the periurethral tissues.

Treatment of periurethral abscess consists of emergent débridement and suprapubic drainage of urine. In the presulfonamide era, mortality was at least 50%. Broad-spectrum antibiotic coverage for gram-negative organisms and anaerobes, using aminoglycoside and cephalosporins, have been associated with a 1.6% mortality. Additional débridement and skin grafts or secondary wound closure can be required with extensive tissue necrosis.

As many as 20% of patients develop recurrent periurethral abscess during follow-up, apparently due to extensive urethral stricture disease. Evaluation after resolution of sepsis should exclude contributory factors, such as an unstable bladder, urethral diverticula, or watering-pot perineum. Construction of a perineal urethrostomy may prevent abscess recurrence and should be considered if significant urethral disease is present.

CYSTITIS

Cystitis, defined symptomatically as an irritation of the bladder, presents with suprapubic discomfort, frequency, dysuria, and urgency. Severe manifestations include urine incontinence and hematuria. Patients may present with acute exsanguinating hematuria but more commonly develop mild symptoms and pathologic disease. The etiology may be related to a toxic chemical agent, radiation, thrombocytopenia with subsequent bleeding, or myelosuppression with associated infection.

General measures taken in the initial evaluation of patients with cystitis should exclude urinary infection and the presence of malignancy. Symptomatic relief of discomfort on voiding can be obtained with urinary analgesics, such as phenazopyridine hydrochloride (Pyridium). Suprapubic discomfort, frequency, urgency, and urine incontinence require antimicrobials to obtain relief; oxybutynin chloride ( Ditropan), propantheline bromide (Pro-Banthine), hyoscyamine sulfate (Cystospaz, Levon), and flavoxate hydrochloride (Urispas) are used for this purpose. Combinations of drugs, sometimes including antiseptics, are often helpful. These include Urised (methyleneamine, methylene blue, phenyl salicylate, benzoic acid, atropine sulfate, and hyoscyamine), Pyridium Plus (phenazopyridine, hyoscyamine, and butabarbital), and Azogantrin (sulfisoxazole and phenazopyridine). Severe symptoms may require belladonna and opium rectal suppositories. Patients with mild voiding dysfunction associated with chronic bladder pain may benefit from a trial of tricyclic antidepressants. Many treatment measures are unique to each etiology.

CHEMICAL CYSTITIS

Oxazaphosphorines

Cyclophosphamide (Cytoxan), the most commonly used oxazaphosphorine, is an alkylating agent first used in the treatment of malignant tumors in Europe in 1957. Currently, Cytoxan has a role in the treatment of solid tumors and lymphomas, as well as benign inflammatory states, Wegener's granulomatosis and rheumatoid arthritis being the most common. Other oxazaphosphorines— ifosfamide, trophosphamide, and sulfosfamide— have been used since the 1970s for the treatment of solid malignancies and lymphomas. Dose-limiting toxicity with these compounds is usually urinary tract toxicity.
Urinary symptoms, including frequency, urgency, dysuria, and nocturia, develop in as many as 24% of patients treated with oral Cytoxan. Microhematuria occurs in 7% to 53% of patients and gross hematuria in 0.6% to 15.0%. Gross hematuria can range from lightly stained urine to exsanguinating hemorrhage. Symptoms usually occur soon after Cytoxan is given but may occur years later. Malignant lesions, usually transitional cell carcinoma, occur in 2% to 5.5% of patients who receive oral Cytoxan for nonmalignant disease. The entire urothelium can be affected, but the bladder is the most frequently involved area.

Bladder pathology has been attributed to toxic metabolites of these compounds. Hepatic microsomal cells break down cyclophosphamide to hydroxycyclophosphamide, then by target cells to aldophosphamide, and then to phosphoramide mustard, the active antineoplastic metabolite, and acrolein, which has no significant antitumor activity. Similarly, ifosfamide is metabolized to ifosphoramide mustard and acrolein. Urinary excretion of acrolein is believed to be the major source of urthelial toxicity. Most normal cells are able to break down the toxic metabolites and diminish their effect. Glutathione is a naturally occurring thiol that can confer such protection in most cells but is present in low levels in urine. Oxazaphosphorine toxicity has been demonstrated in several animal models with their urthelial administration and by instillation of their normal metabolic products directly into the bladder.

Bladder damage from these compounds is cumulative and generally dose-related. “Cytoxan cystitis” occurs frequently and early after intravenous therapy, especially dose-intensive regimens. Fibrosis has been found in as many as 25% of children receiving high-dose cyclophosphamide. Severe hematuria and telangectasia are more common in these patients. Cystitis usually takes weeks to develop after oral treatment but has been seen as little as one dose. Oxazaphosphorine cystitis is potentiated by prior pelvic radiation.

Laboratory values reveal normal coagulation profiles, a normal platelet count, and negative urine culture. Because these patients are at risk for developing urothelial malignancies, episodes of cystitis and hematuria must be evaluated, including urinalysis and urine cytology. Patients receiving cyclophosphamide develop markedly abnormal cytologies, including marked atypia, increased nuclear size, and bizarrely shaped cytoplasm, which frequently resolves with cessation of the drug. These findings can be suggestive of malignancy and need to be interpreted with caution. Patients with abnormal cytologies that have not been investigated previously should undergo a thorough urologic evaluation. Cystoscopy may reveal a tumor or changes compatible with Cytoxan cystitis (Fig 51.4-1). Acute diffuse inflammation is seen. Chronic changes include a pale bladder mucosa with telangectasia. Areas of edema can be present with patchy hemorrhagic areas that stain with methylene blue, an indicator of mucosal injury. Biopsies reveal hyperemia, hemorrhage, edema, mucosal thinning, and ulceration of the urothelium. Necrosis of mucosa, muscle, and small arterioles and telangectasia can be present. Atypia can be prominent, and abundant mitoses often occur. These findings are similar to those seen after radiation therapy. Mucosal lesions of cyclophosphamide-induced cystitis may be identified early, before the appearance of microscopic hematuria.

Hemorrhagic cystitis is managed by stopping or reducing the drug. Replacing the drug, usually with azathioprine, is necessary in as many as one-third of patients who develop severe cystitis after chronic oral administration. Hydration and diuresis are routinely used to dilute the metabolites in the urine and minimize their toxicity after intravenous administration. The cystitis usually improves within several days after cessation of the drug but can occasionally persist for months. Patients receiving high doses of oxazaphosphorines require additional measures to counter their effects. Bladder irrigation is helpful in many of these patients taking cyclophosphamide.

Sodium 2-mercaptoethane sulfonate (mesna) was designed to function in the urinary tract to detoxify azophosphorine metabolites with urthelial toxicity. Mesna is a sulfhydryl compound that is administered intravenously and rapidly excreted by the urinary tract. After intravenous administration, mesna undergoes oxidation, forming sulfide bonds and making an unreactive dimer (dimesna). One concern regarding such a class of drugs is that they might affect the antineoplastic properties of oxazaphosphorines. Mesna and dimesna are very hydrophilic and do not normally penetrate cells, explaining its antineoplastic sparing effect. This reactive form—dimesna—is filtered by the kidneys and undergoes tubular reabsorption, where one-third of it is reduced to its active form, mesna, by glutathione reductase. In the urinary tract, the sulfhydryl group of mesna complexes with the terminal methyl group of acrolein, joining the compound to the double bond of acrolein and forming a nontoxic thioether. The presence of mesna also inhibits spontaneous breakdown of cyclophosphamide to acrolein in the urine. In addition to decreasing chemical cystitis, the risk of bladder cancer is significantly reduced when mesna is used in the Sprague-Dawley rat model.

Oral mesna is well absorbed but slow to achieve adequate urinary concentrations. It has an unpleasant taste, which makes patient compliance poor, particularly when there is concomitant administration of a chemotherapy that induces nausea. Orally administered mesna is well absorbed but slow to achieve adequate urinary concentrations. It has an unpleasant taste, which makes patient compliance poor, particularly when there is concomitant administration of a chemotherapy that induces nausea. It is best given intravenously, and the manufacturer recommends three doses. A loading dose equivalent to 20% (wt/wt) of the ifosfamide dose, given 15 minutes before the ifosfamide, is followed by two similar doses 4 and 8 hours after the ifosfamide. Doses as high as 60% to 120% (wt/wt) have been used with cyclophosphamide, given at a similar schedule. The timing of dosages of mesna is important, as the half-life of mesna is 35 minutes, while that of ifosfamide is 4 hours. Mesna toxicity is minimal, the major side effects being diarrhea, headaches, and limb pain.

Another thiol compound, N-acetyl-L-cysteine, has been used less extensively to ameliorate the effects of oxazaphosphorines. Animal data demonstrate that the bladder is protected when it is given at a dose of 1:1 (wt/wt) with cyclophosphamide in a similar schedule as mesna. Problems with N-acetyl-L-cysteine include a wide distribution in the body with low urinary levels. High intravenous doses or intravesical administration is required to reach effective concentrations. Conflicting data concerning impairment of antitumor activity have not been resolved.

**Bone Marrow Transplantation**

Hemorrhagic cystitis occurs in approximately 2% of conditioning regimens not containing Cytoxan and is frequently related to thrombocytopenia. The incidence of hemorrhagic cystitis in regimens with cyclophosphamide is 5% to 15%. Allogeneic bone marrow and unrelated transplantation appear to have a higher risk than autologous bone marrow transplantation. Prior cyclophosphamide, radiation, urethral catheterization, infection (bacterial or previous viral), concurrent medication, or coagulation disorders (thrombocytopenia) can all contribute to the development of hemorrhagic cystitis in these patients. Prior administration of busulfan, an alkyl sulfonate, increases the risk of hemorrhagic cystitis to as high as 36%, compared to 4% in patients receiving the same regimen without prior exposure. Concomitant use of these agents is associated with hemorrhagic cystitis in 0.5% to 50.0% of patients. Patients with acute bleeding have decreased survival compared to patients without bleeding.

Several viruses have been implicated in the etiology of hemorrhagic cystitis in patients undergoing bone marrow transplantation, either as viral reactivation or a new infection. These include polyoma (BK) virus, adenovirus, especially adenovirus 11, papovavirus, influenza A, and cytomegalovirus. Patients in whom viral particles were recovered developed hematuria later after transplantation (55 days) than patients with so-called idiopathic hemorrhagic cystitis (25 to 27 days).
The viral type also had a longer duration than idiopathic cystitis. Diagnosis of viral cystitis is improving with polymerase chain reaction technology.

It has been recommended that patients receiving the combination of Cytoxan and busulfan should receive continuous bladder irrigation during treatment. Prophylactic treatment with mesna seems equally efficacious and does not appear to affect engraftment. Mesna 60% (v/wt) has been an adequate dose in children, but adults appear to require a higher dose [120% to 160% (v/wt)]. Treatment in these patients is symptomatic.

**Intravesical Chemotherapy**

Intravesical treatment of superficial bladder tumors with chemotherapeutic agents or biologic modifiers may cause a chemical cystitis or inflammatory response with marked symptoms. Several agents are commonly used. Thiotaipel is well tolerated, although 2% to 49% of patients experience cystitis and approximately one-third develop hematuria. Thiopentic acid is one-third of patients receiving epoxygen and 26% to 50% of patients receiving doxorubicin (Adriamycin) develop cystitis. Mitomycin C is best tolerated, with 6% to 33% of patients developing cystitis, and one-third developing hematuria. Most hematuria is microscopic. Significant hemorrhagic cystitis is uncommon with any of these agents. Bladder contractures have rarely been reported in patients receiving thiopeta or mitomycin.

Most patients receiving bacille Calmette-Guérin develop irritative voiding symptoms, which can be the most severe of all intravesical treatments. Biopsies in these patients reveal acute and chronic inflammatory changes and granuloma formation. Urinary analgesics and antispasmodics are particularly helpful in this group. If symptoms are prolonged, isoniazid and acetaminophen or ibuprofen are given until symptoms resolve. It is uncommon for treatment regimens to be stopped because of toxicity.

**Other**

Oral 8-nitrocaptopril, a water-insoluble topoisomerase I inhibitor, and other camptothecins are associated with dose-related hematuria in up to 25% of patients. Hematuria may be a chemical cystitis related to the significant elimination of the drug, although it can also be associated with profound thrombocytopenia. Increasing fluid intake to 3 liters/d has been associated with decreased cystitis and ability to finish treatment.

Busulfan, an alkyl sulfonate used in the treatment of chronic granulocytic leukemia, has also been reported as a cause of hemorrhagic cystitis. As many as 16% of patients in regimens with intravenous busulfan and without cyclophosphamide develop hemorrhagic cystitis. Cystoscopy in these patients reveals generalized inflammation and edema. Biopsies demonstrate metaplastic changes in the urothelium, submucosal inflammation, and telangectasia. Both cystoscopic and histologic findings are similar to radiation or oxazaphosphorine cystitis. Bladder malignancies have not been associated with its use. Given orally, a cumulative dose of 2 to 5 kg appears necessary to induce these changes. Stopping the drug and alleviation of irritative symptoms are the primary treatment.

Other chemotherapeutic regimens that do not include agents with known bladder toxicity appear to be able to induce a cystitis and hematuria without associated thrombocytopenia. The mechanism in these patients is not clear, although bleomycin has been suggested to be the culprit.

**INTRAVESICAL PHOTOTHERAPY**

Kelly and Snell first performed treatment of superficial bladder tumors with "phototherapy" in 1975. Treatment involves administration of an intravenous photosensitizer (usually a hematoporphyrin derivative), waiting 2 days, and then activation of the compound with light. The time lag allows preferential uptake of sensitizer by tumor, with normal tissue levels decreasing, thus increasing the therapeutic index. An optical fiber placed in the bladder through a cystoscope transmits light to activate the sensitizer. Patients whose entire bladder mucosa is illuminated develop marked bladder irritation with suprapubic discomfort, urgency, and urge incontinence. Symptoms can be surprisingly mild the first day after activation but peak in the second and third day. Symptoms improve quickly and usually resolve by 4 to 6 weeks. Cystoscopy initially reveals exuberant local reaction and edema. Biopsies initially reveal coagulative necrosis and hemorrhage. Later, acute and chronic inflammation and atypia are present. The acute response can resolve with little residual effect visually apparent. Bladder fibrosis and reflux are unpredictable side effects of this treatment. Effect of the acute symptoms includes Foley drainage to put the bladder to rest and B&O suppositories for control of bladder discomfort.

**RADIATION**

Patients undergoing primary radiotherapy of malignant pelvic tumors, most commonly uterine, bladder, and prostate neoplasms, can suffer direct or incidental damage to the bladder. The risk is increased when urinary infection is present, repeated or high-dose radiation is given, or when surgery has been performed in the area. Cyclophosphamide, given systemically in combination with pelvic radiotherapy, greatly increases the risk of radiation cystitis.

In the first 4 to 6 weeks after treatment, an acute inflammatory response with resultant irritative symptoms or hematuria (or both) develops. Mild symptoms occur in as many as 50% to 82% of patients and generally do not require medication. Hemorrhagic cystitis can occur later, even years after successful treatment, and is frequently associated with tumor recurrence. The time between treatment and development of delayed symptoms (frequency, dysuria, and hematuria) is proportional to the dose received. Patients with late cystitis develop bladder ulcers, bladder fibrosis, and ureteral strictures. They require thorough evaluation, as these patients are at increased risk for transitional cell carcinoma of the bladder. Bladder biopsies should be performed sparingly, as the bladder mucosa heals poorly.

Approximately 3.7% of patients receiving intravaginal intracavitary radiation alone (3200 cGy) for stage I endometrial carcinoma after radical hysterectomy have been reported to develop cystitis. When external-beam radiation (4000 to 5400 cGy) is added, 4.0% to 6.5% of patients develop cystitis. Patients undergoing definitive radiation treatment of cervical carcinoma have a risk of cystitis that is dose-related. At doses of less than 6000 cGy, the development of cystitis has been strongly linked to recurrent tumor. The incidence of cystitis in this group is 2.8% to 8.0%. Between 1.2% and 18.0% of patients receiving external-beam radiation (3000 to 8500 cGy) for bladder cancer developed cystitis. Hematuria, 8% in patients developing cystitis, is commonly seen in patients treated with 5% or a contracted bladder. Chronic cystitis develops in 15% of patients.

Radiation to the prostate (5000 to 7200 cGy) and draining lymph nodes (5000 cGy) for cure of prostate cancer elicits dysuria and mild to moderate hematuria in 18% to 40% of patients. Between 0.8% and 8.3% develop severe dysuria or hematuria, and 3.4% to 9.0% develop strictures or urethral obstruction as a delayed presentation. During the acute phase, cystoscopy reveals edema, erythema, and increased vascularity, which can be associated with a mild decrease in bladder capacity. Later, the bladder is pale, and telangectasia is present. Focal areas of hyperemia and bullous edema may be present. Often there is no focal area of bleeding. With extensive damage, necrosis and calcification can occur. Biopsy findings are dose- and time-dependent. In the first 24 hours, there is erythema due to hyperemia. This develops into a diffuse inflammatory response with hyperemia, edema, lymphocytic infiltration, and degeneration of the urothelium with atypia. Shallow ulcers are occasionally seen but usually occur as a late response. This response lasts up to 4 months after therapy. Later, sclerosing endarteritis, fibrosis, and atrophy occur. There may be edema and an inflammatory infiltrate. There can be ulceration, and healing is poor.

**ANTIBIOTICS**

While most cystitis seen in the setting of oncologic care is related to antineoplastic agents, penicillins used in the treatment of chemotherapy related infections represent another source. Methicillin, nafcillin, ticarcillin, pipercillin, carbenicillin, and pencerilin G have all been implicated. The incidence of cystitis associated with the use of these agents is small, occurring in 4% to 8% of patients. Symptoms are typical of cystitis. Laboratory investigation reveals eosinophilia, pyuria, hematuria, proteinuria, and negative urine cultures. The submucosal deposition of C3, immunoglobulins G and M, and dimethyloxyphenylpenicilloyl, a methicillin antigen, supports a hypersensitivity etiology. A diffuse hemorrhagic cystitis is seen at cystoscopy. Biopsies show an intense inflammatory reaction with erosion. With repeated use, the time to development of symptoms shortens. Symptoms usually resolve promptly on cessation of the drug or substitution with an unrelated drug.
BLADDER HEMORRHAGE

Severe cystitis can result in hemorrhage resulting in clot retention and requiring transfusion. If bedside bladder clot evacuation and continuous irrigation are not successful, cystoscopic evacuation of clots with fulguration of bleeding sites will cure most patients (Table 51.4-1). Correction of thrombocytopenia before cystoscopy will frequently stop bleeding and is necessary to prevent further bleeding episodes. Patients resistant to conservative therapy have been treated with intravesical instillation of chemical astringents or fixatives started immediately after cystoscopic treatment and cystogram to exclude vesicoureteral reflux. Bladder instillation is performed using gravity drainage with minimal hydrostatic head required for filling.

TABLE 51.4-1. Management of Bladder Hemorrhage

Silver nitrate is a cauterizing agent that results in cellular protein coagulation and eschar formation. A 0.5% to 1.0% water solution as continuous bladder irrigation has been used in the management of radiation and chemical cystitis. Chloride salts in solution or from ulcerated mucosal lesions are avoided as they can result in precipitation of silver chloride. When effective, bleeding usually stops within 24 to 72 hours.

Continuous irrigation with 1% alum is used in a similar manner as silver nitrate. Specific toxicities are related to aluminum absorption and include renal dysfunction, altered mental status, and encephalopathy.

Formalin is a tissue fixative and embalming agent. Because of its potential toxicity, formalin is used only in the management of patients with life-threatening hematuria unresponsive to other measures. After cystoscopic examination, a 1% to 5% solution of formalin is instilled for 3 to 10 minutes in the operating room. Complications and response are directly related to concentration and duration of exposure. Complications include bladder rupture, vesicorectal or vesicovaginal fistula, renal failure, acidosis, altered mental status, and chemical skin burns. Formalin toxicity may be abrogated by dialisate to decrease blood levels and correct the metabolic acidosis.

Formaldehyde exists as a gas and has a maximum solubility of 37% in aqueous solution. A 37% aqueous solution of formaldehyde is equivalent to a 100% solution of formalin. Dilution of formaldehyde to formalin in treatment concentrations is best performed in the pharmacy.

Bladder irrigation with any chemical agent can be irritating, with local pain and bladder spasms requiring medical treatment. Complications related to intravesical instillation of chemical agents include ureteral stricture, bladder fibrosis with loss of volume, and death. With signs of toxicity, the bladder irrigation is changed to water or saline to wash out any residual drug. As bladder healing occurs, hematuria can frequently recur if the underlying pathology still exists.

Other less-tried regimens have been shown to have activity in the treatment of radiation- or cyclophosphamide-induced hemorrhagic cystitis. These include intravesical installation of prostaglandins, oral pentosanpolysulphate, conjugated estrogens, or hyperbaric oxygen. Open cystotomy with bladder packing has rarely been used.

URINARY OBSTRUCTION

Urinary obstruction associated with loss of renal function can lead to accumulation of water, urea, and electrolytes as well as loss of renal concentrating ability. Immediately after release of obstruction, these can lead to brisk diuresis, hypovolemia, and shock. Patients are monitored hourly for elevated urine output and if not able to match with oral intake, require intravenous supplementation. Rarely, patients with severe fluid and electrolyte disturbances may require dialysis.

UPPER TRACTS

Malignant ureteral obstruction occurs in as many as 4.4% of patients with advanced cancer. The most common associated malignancies are prostate, bladder, cervical, colon, or lymphoid cancers. Definitive radiation treatment of cervical cancer has been reported to have a continuous increasing of risk of 0.15% per year over 25 years. Ureteral obstruction may be an incidental finding on computed tomography imaging and associated with altered renal function. Radionuclide imaging may be helpful if the clinical picture is not diagnostic of obstruction.

Cystoscopic placement of ureteral stents maintains quality of life better than percutaneous nephrostomy. Stent placement may be difficult when the ureteral orifices are obscured by local tumor invasion. Ureteral stents placed for obstruction at the bladder level are more predisposed to bleeding and obstruction than are those placed for retroperitoneal metastases causing extrinsic ureteral obstruction. As many as 49% to 63% of patients with bladder malignancies may end up with percutaneous nephrostomy.

Patients undergoing percutaneous nephrostomy placement can usually undergo antegrade placement of a ureteral stent. These stents can be changed cystoscopically, taking care not to lose access to the ureteral orifice. Ureteral stents are generally changed every 3 months to prevent encrustation and obstruction. Minor hematuria and bladder spasms are often associated with ureteral stent placement and treated symptomatically. As many as 5% of patients have significant bleeding, usually associated with tumor invasion in the bladder.

Patients with ureteral obstruction and urinary conduits may require initial percutaneous nephrostomy followed by internalization of the ureteral stent. Percutaneous management with ureteroscopic incision of a benign stricture has been effective in up to 57% of patients. Residual ureteral stricture requiring definitive surgical treatment is uncommon, as most responses to treatment are short-lived. Late strictures after radiation therapy have had limited success with excision and ureteral reimplantation.

Untreated patients with bilateral ureteral obstruction succumb to renal failure within a month. Recovery of renal function after relief of obstruction depends on duration of obstruction and initial renal function. Preservation of renal parenchyma and renal function has been reported as long as 5 months after complete unilateral ureteral obstruction. When there is partial ureteral obstruction, return to normal function has been reported in 68% of patients, with marked improvement in 24%. Patients with ureteral obstruction from hormone-sensitive prostate cancer have had longer survival than those with gastric, pancreatic, or colon cancer.

LOWER TRACT
Prostate

Urinary voiding symptoms may occur in debilitated patients after surgery, chemotherapy, or significant medical events. Symptoms may range from urinary frequency with decreased force of stream and nocturia to urinary retention. Urinary retention may be obstructive, pharmacologic, neurogenic, or psychogenic in nature. Patient medical and voiding history is examined with these factors in mind. Urinary tract infection or prostatitis should be detected early and treated appropriately. Manipulation of the urinary tract or prostate in these patients is kept to a minimum to prevent sepsis.

Relief of urinary obstruction with catheter drainage offers immediate relief. Patients with urethral stricture disease, benign prostatic hypertrophy, prostate cancer, meatal stenosis, or phimosis can be challenging to catheterize. Urethral dilation or use of a specialized angulated (Coude) catheter to pass an enlarged prostate median lobe may be necessary. Placement of suprapubic trochar drainage is performed when urethral catheterization is not possible or there are concerns about promoting sepsis. Individuals especially trained in their use best perform these procedures. Minor surgical procedures can be performed to relieve phimosis or meatal stenosis.

Permanent affects on ability to void can occur after abdominoperineal resection, radical hysterectomy, or extensive pelvic operations that interrupt normal pelvic parasympathetic innervation to the bladder. Temporary loss of voiding may occur secondary to anticholinergic agents that block detrusor activity, pain that results in increased sympathetic bladder neck tone, and narcotics that inhibit the urge to void. Of patients with urinary retention as a presenting complaint, as many as 18% to 23% will reestablish normal voiding if given a voiding trial. Of patients with urinary retention after nonurologic surgery, as many as 69% reestablish normal voiding patterns if placed on intermittent self-catheterization, generally within 3 months.

Evaluation of urinary retention associated with nonsurgical medical disorders is less well defined. Assessment of prehospital admission American Urological Association voiding symptom score in all these patients is helpful in identifying patients who may require treatment of prostate obstruction. Urodynamics may be indicated to distinguish bladder outlet obstruction from impaired detrusor contractility. Transurethral resection of the prostate remains the standard against which other treatment regimens for urinary retention due to benign prostate hypertrophy are measured. Use of alternative methods, such as holmium laser resection, urethral stent, or chronic indwelling catheter drainage, may be dictated by available technology or patient health.

Patients with urinary retention due to prostate cancer had good relief of obstruction 1 month after bilateral orchectomy. Similar results have been observed using luteinizing hormone-releasing hormone antagonists, although improvement may take longer. Urethral stents have been used to hasten spontaneous voiding.

Urethra

Patients in whom a catheter cannot be passed may have benign prostatic hypertrophy or urethral stricture disease. A Coude catheter more easily follows the natural angulation of the urethra into the bladder. A small catheter may pass through a stricture that is not severe. Urethral dilation by trained personnel may be required. Forceful advancement of the catheter is to be avoided, as the integrity of the urethra can be violated, contributing to bleeding, urinary extravasation, local cellulitis, and stricture formation. Cystoscopic placement of a Foley catheter may be required if this occurs. Urethral bleeding after traumatic catheter placement or inflation of a balloon in the urethra will stop when the Foley is in place if coagulation parameters are normal. Urethra should be checked for infection and treated appropriately.

A Foley catheter balloon may not deflate, preventing its removal. Scissors removal of the valve will allow drainage if that is the location of the obstruction. Obstruction at a distal level can be relieved by balloon rupture with a spinal needle under ultrasound guidance. Suprapubic or transvaginal routes are preferred, although the transrectal route is technically feasible.

PRIAPISM

Priapism is the emergent condition defined as sustained painful erection of the corpora cavernosal tissue not associated with sexual stimulation. Two types of priapism have been described, ischemic (low-flow) and nonischemic (high-flow), with different treatment and prognosis.

Ischemic priapism is associated with decreased penile venous outflow and stasis of blood resulting in intracavernosal blood acidosis and low oxygen tension. Ischemic priapism is treated emergently, as irreversible cellular damage and corporal fibrosis, which can result in erectile dysfunction, occur within 24 to 48 hours. Ischemic priapism may be caused by sickle cell disorders, oral or injected medications, or tumor infiltrate. Nonischemic priapism usually results from perineal trauma with injury to the internal pudendal artery with arteriovenous fistula formation. Nonischemic priapism is painless, can increase in tumescence after sexual stimuli, and can be managed electively.

Patient history may reveal drug use, sickle cell anemia, perineal trauma, or malignancy. Priapism is usually found in men but has been reported rarely in women. On physical examination, the corpora cavernosa are rigid. The glans, an extension of the corpora spongiosa, is usually soft. Voiding symptoms may occur in as many as 25% of patients when tumor involves the corpora spongiosa or urethra. Pseudopriapism is characterized by rigidity and edema associated with metastases rather than venous stasis. Pain is thought to be due to tissue anoxia. In malignant priapism, tumor infiltration of the cavernosa or invasion of venous drainage is thought to lead to stasis and thrombosis.

As many as 10% of patients develop priapism related to malignancy. Penile metastases are most often symptom-free, with associated priapism in 20% to 53% of patients. Priapism, bladder, and kidney cancer are most commonly involved in adults. Leukemia is the most common malignant cause in children. Needle biopsy or aspiration of the firm corpora cavernosa can confirm this diagnosis. The management of priapism varies according to cause.

Treatment of malignant priapism is initially aimed at relief of pain and anxiety with hydration, analgesia, and rest. Treatment of the underlying malignancy can be associated with relief. Hormonal therapy of prostate cancer and chemotherapy of leukemia would have higher expectations of response. Radiation is palliative if more emergent relief is needed or therapeutic options are limited. Intracavernosal injection of pharmacologic agents has had anecdotal success. Without systemic treatment, survival in malignant priapism is poor, as most patients have metastatic disease at presentation. Sixty percent of patients died at a median of 4 months (range, 0.2 to 60 months) after developing priapism.

Surgical treatment of priapism involves creation of a shunt between the glans penis and the corpora cavernosa. Under anesthesia, a trucut needle placed through the glans into each corpora cavernosum will achieve this. Anoxia occurring during priapism or shunting performed as treatment can result in impotence. A penile prosthesis may be required if the corpora cavernosa become fibrosed and unable to distend in normal fashion.

PARAPHIMOSIS

Paraphimosis is the pathologic state occurring after retraction of the foreskin proximal to the glans penis, characterized by local swelling and difficulty in returning the foreskin to its normal position. Retention of the preputial ring proximal to the coronal sulcus is associated with tissue tension greater than lymphatic pressure and results in edema of the prepuce and glans. If not reduced, the edema can become massive, associated with pain and skin breakdown. Manual reduction is usually performed, using anesthetic jelly and pressure to remove edema. The penis is grasped with both hands, placing the last three fingers along the shaft. The index fingers are used to pull the foreskin over the glans, while the thumbs push the glans back through the constricting ring of the prepuce. When this is not possible, a local anesthetic block may be required to release the trapped foreskin. A dorsal slit procedure will allow relief of an acute constricting paraphimosis or phimosis if conservative measures fail.

CHAPTER REFERENCES

INTRODUCTION

Brain metastases are a common complication in cancer patients and an increasingly important cause of morbidity and mortality. In adults, brain metastases are the most common cause of brain tumors, occurring five to ten times more frequently than primary tumors. In recent years, there have been important advances in the diagnosis and management of this condition. As a result, most patients receive effective palliation, and the majority do not die from their brain metastases. Further studies defining the optimal role of conventional treatments and future advances in the use of chemotherapy, radiosurgery, and more novel cancer therapies may lead to further increases in the effectiveness of treatments for brain metastases.

Brain metastases develop when tumor cells originating in tissues outside the nervous system spread secondarily to directly involve the brain. Intracranial metastases may involve the brain parenchyma, the cranial nerves, the blood vessels (including the dural sinuses), the dura, the leptomeninges, and the inner table of the skull. Of the intracranial metastases, the most common are intraparenchymal metastases, and these are the main focus of this chapter.

INCIDENCE AND EPIDEMIOLOGY

Brain metastases develop in approximately 10% to 30% of adults and 6% to 10% of children with cancer. It is estimated that each year in the United States, there are between 97,800 and 170,000 new cases of brain metastases. This number may be increasing as a result of the increased ability of magnetic resonance imaging (MRI) to detect small metastases and prolonged survival due to improvement in systemic therapy.

In adults, the most common primary tumors responsible for brain metastases are lung (50%), breast (15% to 20%), unknown primary (10% to 15%), melanoma (10%), and colon (5%) (Table 52.1-1). In children, the most common sources of brain metastases are sarcomas, neuroblastoma, and germ cell tumors. Certain tumors almost never metastasize to the brain parenchyma. These include carcinomas of the esophagus, oropharynx, and prostate and nonmelanoma skin cancers.

METHOD OF SPREAD AND DISTRIBUTION

The most common mechanism of metastasis to the brain is by hematogenous spread. These metastases are usually located directly beneath the gray-white junction. Brain metastases tend to occur at this site because the blood vessels decrease in size at this point and act as a trap for clumps of tumor cells. Brain metastases also tend to be more common at the terminal “watershed areas” of arterial circulation. The distribution of metastases roughly follows the relative weight of (and blood flow to) each area. Approximately 80% of brain metastases are located in the cerebral hemispheres, 15% in the cerebellum, and 5% in the brain stem. For unclear reasons, pelvic (prostate and uterus) and gastrointestinal tumors have a predilection to metastasize to the posterior fossa.

Metastases from breast, colon, and renal cell carcinoma are often single, while melanoma and lung cancer have a greater tendency to produce multiple metastases. Studies using MRI suggest that the percentage of single metastases is lower than was previously believed, accounting for only one-third to one-fourth of patients with cerebral metastases. With the widespread use of MRI and new improvements in MRI contrast agents and resolution, the proportion of multiple metastases probably will be even higher in the future.

CLINICAL MANIFESTATIONS

It is estimated that more than two-thirds of patients with cerebral metastases experience neurologic symptoms during the course of their illness. The clinical features due to brain metastases are extremely variable, and the presence of brain metastases should be suspected in any cancer patient who develops new neurologic symptoms. The majority of patients present with progressive neurologic dysfunction resulting from a gradually expanding tumor mass and the associated edema or, rarely, to the development of obstructive hydrocephalus. Approximately 10% to 20% of patients present acutely with seizures, while another 5% to 10% present acutely as a result of strokes caused by embolization of tumor cells or invasion or compression of an artery by tumor or as a result of hemorrhage into a metastasis. Melanoma, choriocarcinoma, thyroid, and renal carcinoma have a particular propensity to bleed.

The clinical presentation of brain metastases is similar to that of other brain tumors and includes headaches, focal neurologic dysfunction, cognitive dysfunction, and seizures. Headaches occur in approximately 40% to 50% of patients with brain metastases. These headaches are usually dull and nonthrobbing and often are indistinguishable from tension headaches. The headaches are usually on the same side as the tumor, although they can be diffuse. Headaches characteristic of increased intracranial pressure, such as early morning headaches or headaches exacerbated by coughing, bending, and straining, are present in fewer than one-half of patients with brain metastases. These headaches may be associated with nausea, vomiting, and transient visual obscurations. Patients with multiple metastases
and posterior fossa metastases have a higher frequency of headaches. Papilledema is present in fewer than 10% of patients at the time of presentation. Focal neurologic dysfunction is the presenting symptom of 20% to 40% of patients. Hemiparesis is the most common complaint, but the precise symptom varies depending on the location of the metastases. Cognitive dysfunction, including memory problems and mood or personality changes, are the presenting symptoms in one-third of patients, while seizures are the presenting symptom in another 10% to 20%.

DIAGNOSIS

Brain metastases must be distinguished from primary brain tumors, abscesses, demyelination, cerebral infarctions or hemorrhages, progressive multifocal leukoencephalopathy, and effects of treatment, including irradiation necrosis. In a study by Patchell et al., 11% of patients who were initially thought to have a single brain metastasis eventually turned out to have a different diagnosis after the lesion was subjected to biopsy. One-half of the nonmetastatic lesions were primary brain tumors, while the other one-half were infections. The false-positive rate for diagnosis of multiple metastases is undoubtedly significantly less than the 11% for single metastases. Nonetheless, in any patient where the diagnosis of brain metastases is in doubt, a biopsy should be performed, since this is the only reliable method of establishing the diagnosis.

Breast cancer patients with a single dura-based lesion pose a particular diagnostic dilemma. The incidence of meningiomas is increased in patients with breast cancer so that it is important to differentiate a dura-based metastasis from a meningioma. Frequently, imaging studies will be inconclusive, and these patients will require a biopsy or surgical resection of the lesion to establish the diagnosis.

In addition to diagnosing the brain metastases, it is also important to differentiate those patients with single or solitary metastases from patients with multiple brain metastases, since their subsequent treatment will be different. The term single brain metastasis refers to an single cerebral lesion, and no implication is made regarding the extent of extracranial disease. In contrast, the term solitary brain metastasis describes the relatively rare occurrence of a single brain metastasis that is the only known site of metastatic cancer in the body.

IMAGING STUDIES

Although computed tomographic (CT) scans detect the majority of brain metastases, the best diagnostic test for brain metastases is contrast-enhanced MRI. This test is more sensitive than enhanced CT scanning or nonenhanced MRI in detecting lesions in patients suspected of having cerebral metastases and in differentiating these metastases from other cerebral nervous system (CNS) lesions. Radiographic features that help to differentiate brain metastases from other CNS lesions include the presence of multiple lesions (which helps to distinguish metastases from gliomas or other primary tumors), localization of the lesion at the gray-white junction, more circumscribed margins, and relatively large amounts of vasogenic edema compared to the size of the lesion. Triple-dose contrast administration may help to clarify the presence of metastases in selected patients with equivocal lesions or to detect additional lesions in patients with a single lesion on conventional single-dose contrast MRI. Magnetization-transfer MRI, a technique that increases the contrast between enhancing and nonenhancing lesions by suppressing background signal, may also increase the sensitivity of MRI. However, the usefulness of these approaches is limited by their availability and cost. In general, they may have a limited role in selected patients with a single or a small number of metastases on standard MRI and who are being considered for aggressive local therapy. In these patients, the detection of additional lesions may change the usefulness of surgery or radiosurgery. Functional imaging techniques, such as single-photon emission computed tomography, positron emission tomography, magnetic resonance spectroscopy, and perfusion and diffusion MRI, do not have a role in the diagnosis of brain metastases but may help in differentiating tumor from radiation necrosis.

BRAIN METASTASES WITHOUT A KNOWN PRIMARY TUMOR

In the majority of patients (80%), brain metastases develop after the diagnosis of systemic cancer (metachronous presentation). However, in some patients, brain metastases may be diagnosed before the primary tumor is found (precocious presentation) or at the same time (synchronous presentation). For patients who present with brain metastases without a known primary tumor, the lung should be the focus of the evaluation. More than 80% of these patients will have a lung primary or pulmonary metastases from a primary tumor located elsewhere. Other frequent causes include malignant melanoma and colon cancer, while the primary remains unknown in approximately 25% to 30% of cases. Breast cancer is an uncommon cause of brain metastases without a known primary tumor, possibly due to its earlier detection on physical examination and its tendency to produce brain metastases in the setting of widely disseminated disease. The history and physical examination will demonstrate the site of origin in one-third to one-fourth of patients. In others, the chest radiograph is the most useful test. If it is nondiagnostic, a chest CT scan should be performed, as this significantly increases the likelihood of detecting a lung tumor. These patients should also have a CT scan of the abdomen and pelvis and a bone scan to determine the extent of metastatic disease.

MANAGEMENT

The management of patients with brain metastases can be divided into symptomatic therapy and definitive therapy. Symptomatic therapy includes the use of corticosteroids for the treatment of peritumoral edema, anticonvulsants for control of seizures, and anticoagulants or inferior vena cava (IVC) filters for the management of venous thromboembolic disease. Definitive therapy includes such treatments as surgery, radiotherapy, chemotherapy, and hormonal therapy directed at eradicating the tumor itself.

SYMPOMATIC THERAPY

Corticosteroids

Corticosteroids were first used for treating peritumoral edema by Kofman et al. in 1957 in patients with breast cancer. Subsequently, Galich et al. introduced the use of dexamethasone in 1961, and this has remained the standard treatment for peritumoral edema ever since. Corticosteroids produce their antiedema effect by reducing the permeability of tumor capillaries and are indicated in any patient with symptomatic edema. Most patients are usually started on dexamethasone, which has the advantage over other corticosteroids of having relatively little mineral corticoid activity, reducing the potential for fluid retention. In addition, dexamethasone may be associated with a lower risk of infection and cognitive impairment. The usual starting dose is a 10-mg load, followed by 4 mg four times daily, although there is some evidence that lower doses (4 to 8 mg/d) may be as effective. While most patients improve symptomatically within 24 to 72 hours, neuroimaging studies may not show a decrease in the amount of edema for up to 1 week. In general, headaches tend to respond better than focal deficits. If 16 mg of dexamethasone is insufficient, the dose may be increased up to 100 mg/d. Steroids are usually tapered after irradiation, although the taper may begin earlier in patients with little peritumoral edema.

Despite their usefulness, corticosteroids are associated with a large number of well-known side effects, including myopathy, weight gain, fluid retention, hyperglycemia, insomnia, gastritis, acne, and immunosuppression. The frequency of these complications can be reduced by using the lowest possible dose of corticosteroids. There is increasing evidence that brain tumor patients on corticosteroids are at increased risk of developing pneumonitis. This complication can be prevented by treating patients, especially those older than the age of 50, who are on prolonged courses of corticosteroid with trimethoprim-sulfamethoxazole prophylaxis.

Anticonvulsants

Seizures are the presenting symptom in approximately 10% to 20% of patients with brain metastases and are present at some stage of the illness in another 10% to 20% of patients. Patients with brain metastases who present with seizures should be treated with standard anticonvulsants. To minimize toxicity, the lowest effective dose of medication should be used and polytherapy avoided whenever possible. Electroencephalography may be useful if the diagnosis of seizures is in doubt but is not routinely needed for patients who give a clear history of seizures or do not have symptoms suggestive of seizures.

In addition to the usual complications of anticonvulsants, brain tumor patients experience an increased incidence of particular side effects, especially drug rashes. Approximately 20% of brain tumor patients treated with phenytoin and carbamazepine develop a morbilliform rash, and a small percentage develop Stevens-Johnson syndrome, while patients receiving phenobarbital have an increased incidence of shoulder-hand syndrome.
In contrast to these two studies, a more recent multicenter randomized study conducted by Mintz et al. for brain tumors. Survival rates as compared to younger patients (hazard ratio of dying, 2.74; over 55 months; median FIS, 9 vs. 4 months). Patients with active extracranial disease had a median survival of only 5 months and a FIS of 2.5 months and did not appear to benefit from the addition of surgery. This is consistent with the concept that the extent of systemic disease largely determines the survival of the patient and overcomes any potential advantage the addition of surgery may have provided in controlling the brain metastasis. Patchell et al. conducted a prospective, placebo-controlled, randomized study involving 74 patients and evaluated the efficacy of valproic acid in protecting patients with newly diagnosed brain metastases from seizures. There was no significant difference in the incidence of seizures between patients receiving valproic acid (35%) or placebo (24%), suggesting that prophylactic anticonvulsants were not effective in these patients. Weaver et al. conducted a prospective randomized study of prophylactic anticonvulsants in 100 brain tumor patients, including 60 with metastases who have not had seizures. Overall, 26% of patients had seizures. There was no difference in the seizure rate between patients taking anticonvulsants and those who were on no medications. Recently, Glantz et al. reviewed the evidence concerning the efficacy of prophylactic anticonvulsants. Because the number of patients in these studies was small, they also performed a meta-analysis of the randomized clinical trials addressing this issue. They concluded that there was no statistical evidence showing a significant benefit of prophylactic anticonvulsant.

Because of the increased incidence of allergic reactions in patients with brain metastases receiving anticonvulsant therapy and of the lack of clear evidence that anticonvulsant therapy reduces the incidence of seizures, routine anticonvulsant therapy is probably unnecessary in patients with brain metastases who have not experienced a seizure. Possible exceptions to this are patients with brain metastases in areas of high epileptogenicity (e.g., motor cortex), patients with multiple melanoma metastases, and patients with both brain metastases and leptomeningeal metastases. These patients have a higher incidence of seizures and may benefit from prophylactic anticonvulsant therapy.

**Venous Thromboembolic Disease**

Venous thromboembolic disease is common in patients with brain metastases, occurring in approximately 20% of patients. The optimal therapy is unknown. These patients are often perceived to be at increased risk of intracranial hemorrhage with anticoagulation because of the vascularity of the tumors and anecdotal case reports of hemorrhage. As a result, the majority of brain metastases treated with venous thromboembolic disease are managed with IVC filters rather than anticoagulation. However, this may not be the optimum approach, since there is a high rate of complications with filtration devices in these patients. In a retrospective study of 42 patients with intracranial malignancy and venous thromboembolic disease treated with IVC filters, the complication rate was 62%. Fifty-seven percent developed IVC or filter thrombosis, recurrent deep venous thrombosis, or postphlebitic syndrome, and 12% developed recurrent pulmonary embolism. In addition to the high complication rate with IVC filters, there is increasing evidence that the risk of intracranial hemorrhage in patients with primary brain tumors who are anticoagulated outside the immediate postoperative period may not be significantly increased. More recently, Schiff and DeAngelis reviewed the experience at the Memorial Sloan-Kettering Cancer Center with anticoagulation in patients with brain metastases who developed venous thromboembolic disease. Of the 42 patients who received anticoagulation at some stage of their treatment, only 3 (7%) experienced cerebral hemorrhage, 2 in the setting of supratherapeutic anticoagulation. These studies suggest that anticoagulation may be more effective than IVC filter placement and is acceptably safe when the prothrombin time is maintained in the therapeutic range, especially in patients with brain metastases that generally do not hemorrhage, such as breast cancer.

**DEFINITIVE TREATMENT**

The management of brain metastases is directed at relieving neurologic symptoms and achieving long-term control of the tumors. The therapeutic modalities available include surgery, radiotherapy, chemotherapy, and hormonal therapy. The optimal combination of therapies for each patient depends on careful evaluation of numerous factors, including the location, size, and number of brain metastases; patient age, general condition, and neurologic status; extent of systemic cancer; as well as the tumor's response to past therapy and its potential response to future treatments.

**Surgery**

The role of surgery in patients with brain metastases is to provide immediate relief of symptoms resulting from the mass effect of the tumor, to establish a histologic diagnosis, and to improve local control of the tumor. Recent advances in neuroanesthesia and neurosurgery, including the use of computer-assisted stereotaxy, intraoperative functional mapping, intraoperative ultrasonography, and functional and intraoperative MRI, have significantly improved the safety of surgical resection of brain metastases.

For surgical candidates, the most important factor to consider is the extent of the extracranial disease. Patients with extensive systemic disease generally have a very limited prognosis and only rarely benefit from surgery. Other important factors influencing the decision concerning surgery include the presence of single or multiple metastases, the location of the tumor, the neurologic status of the patient, and the interval between diagnosis of the primary neoplasm and the brain metastasis.

**SINGLE BRAIN METASTASES.** Until relatively recently, the optimal treatment for patients with a single brain metastasis was controversial. A number of uncontrolled retrospective studies suggested that patients with a single brain metastasis who underwent surgical resection in addition to radiotherapy generally had better outcomes than patients treated with radiotherapy alone. However, these studies were limited by the inevitable selection bias resulting from the inclusion of patients in better condition in surgical series. These are now three randomized prospective studies that have evaluated the role of surgery as an adjunct to whole brain radiotherapy (WBRT) for patients with a single brain metastasis. Patchell et al. were the first to address this issue in a prospective randomized study. Fifty-four patients with or without active systemic cancer and a single brain metastasis were randomly assigned to receive either biopsy of the metastases followed by WBRT (36 Gy in 12 fractions) or surgical resection followed by radiotherapy. Patients (11%) did not have a metastasis and were excluded from the study, leaving 48 patients. The patients treated with surgery and WBRT had fewer local recurrences (20% vs. 52%), improved survival (40 weeks vs. 15 weeks), and a better quality of life as measured by the Karnofsky performance status than did patients receiving WBRT alone. The median time to recurrence for patients receiving surgery and radiotherapy was more than 59 weeks, compared to 21 weeks for patients receiving WBRT alone. A multivariate analysis showed that the factors that correlated significantly with increased survival were surgical treatment of the metastasis, the absence of extracranial disease, longer time to the development of the brain metastasis, and younger age.

A second prospective randomized trial evaluating the role of surgery for patients with single brain metastasis was conducted by Vecht et al. In this study, 63 patients with a single brain metastasis documented by CT scanning were randomly chosen to receive either surgery and WBRT or WBRT alone. The radiotherapy dose was an unconventional scheme of two fractions a day of 2 Gy each, for a total of 40 Gy given over 2 weeks. Unlike Patchell's study, patients randomly selected to receive radiotherapy alone did not undergo a stereotactic biopsy to confirm the diagnosis of metastases, and MRI was not performed to exclude multiple small metastases that may have been missed by CT imaging. The overall survival of patients treated with surgery and radiotherapy was significantly longer than that of patients treated with radiotherapy alone (10 months vs. 6 months; P = 0.04). In addition, combined treatment also resulted in significantly increased functionally independent survival (FIS) (7.5 months vs. 3.5 months; P = 0.06). The greatest benefit was seen in patients with stable extracranial disease (median survival, 12.7 vs. 7 months; median FIS, 9 vs. 4 months). Patients with active extracranial disease had a median survival of only 5 months and a FIS of 2.5 months and did not appear to benefit from the addition of surgery. This is consistent with the concept that the extent of systemic disease largely determines the survival of the patient and overcomes any potential advantage the addition of surgery may have provided in controlling the brain metastasis. Patients older than 60 years had decreased survival rates as compared to younger patients (hazard ratio of dying, 2.74; P = 0.001), consistent with the general importance of age as an adverse prognostic factor for brain tumors.

In contrast to these two studies, a more recent multicenter randomized study conducted by Mintz et al. failed to detect a difference in survival or quality of life between patients who underwent surgery plus radiotherapy and those having radiotherapy alone. In this study, the 43 patients randomly assigned to radiotherapy...
alone had a median survival of 6.3 months, while the 41 patients randomly assigned to surgery and radiotherapy had a median survival of only 5.6 months. The failure of this study to demonstrate that the addition of surgery to radiotherapy improved the outcome of patients may be due to the fact that it included patients with a lower baseline median Karnofsky performance score (KPS) and a higher proportion of extracranial disease. 24

A fourth study, conducted by the Radiation Therapy Oncology Group (RTOG) and the Southwest Oncology Group, was initially intended to be a randomized study comparing surgery and radiotherapy to radiotherapy alone. However, because of poor patient accrual, its design was changed to a prospective physician preference trial. Ultimately, 80 of the 97 registered patients were evaluable. Patients treated with surgery and radiotherapy showed greater neurologic improvement (79% vs. 59%), decreased recurrence (22% vs. 45%), and improved survival, when corrected for other prognostic factors, compared to patients receiving radiotherapy alone. 25 Overall, these studies provide support for the use of surgery in addition to WBRT for patients with a single brain metastasis and stable extracranial disease.

MUTIPLE BRAIN METASTASES. The role of surgery in patients with multiple brain metastases is usually limited to resection of a large, symptomatic, or life-threatening lesion, to obtain tissue for diagnosis in patients without a known primary tumor, or to differentiate a brain metastasis from other cerebral lesions, such as a meningioma. However, as surgical techniques have improved, the ability to resect multiple lesions is becoming more feasible. In one study, Bindal et al. reviewed the efficacy of surgery in 56 patients with multiple brain metastases. These patients were divided into those who had one or more lesions remaining after surgery (group A; n = 30) and those who had all lesions removed (group B; n = 26). In addition, the patients in group B were matched by tumor type, presence or absence of extracranial disease, and time from diagnosis of primary brain metastases to a group of patients undergoing surgery for a single metastasis (group C; n = 26). The median survivals for patients in groups A, B, and C were 6, 14, and 14 months, respectively. These results suggest that if all the lesions can be removed surgically in patients with multiple brain metastases, the outcome is significantly improved, and comparable to the outcome of patients who underwent surgery for a single lesion. In a second study, Hernandez-Avila et al. evaluated the outcome of 34 patients with multiple metastases treated with surgery. The median survival of patients with controlled systemic disease was 17 months, compared to only 3.1 months for those with active systemic disease, suggesting that surgery for patients with multiple brain metastases may be feasible in patients with limited systemic disease. However, in contrast to these studies, Hazuka et al. found that surgery was of little benefit in patients with multiple brain metastases. They reported a series consisting of 28 patients with a single metastasis and 18 patients with multiple metastases. The patients with multiple metastases who underwent surgery maintained a median survival of only 5 months, compared to 12 months for those with single brain metastases. In these studies, the surgical morbidity and mortality for patients with multiple brain metastases were low and comparable to those reported for patients with a single metastasis undergoing surgery. However, these conflicting results render it difficult to draw firm conclusions regarding the value of surgical resection in patients with multiple brain metastases.

RECURRENT METASTATIC BRAIN TUMORS. Surgery may have a role in patients who develop recurrent disease after standard treatment for brain metastases, especially if there is a single, symptomatic lesion. In an early study, Sundaresan et al. reported the results of reoperation in 21 patients with brain metastasis. Two-thirds of the patients experienced neurologic improvement, and the median duration of the improvement was 6 months. There was no mortality, and only one patient developed increased neurologic deficits after surgery.

Bindal et al. reviewed the experience from M. D. Anderson Cancer Center of 48 patients who underwent reoperation for recurrent brain metastasis. The median interval between the first craniotomy and the diagnosis of recurrence was 6.7 months and the median survival after reoperation was 11.5 months. After surgery, 75% of patients were free of neurologic symptoms. Multivariate analysis revealed that survival was negatively affected by the presence of systemic disease (P = .008); KPS exceeded 70 (P = .008); time to recurrence was less than 4 months (P = .008); age exceeded 40 years (P = .051); and the primary tumor type was breast or melanoma (P = .028). There was no operative mortality. Five patients (10.4%) developed new or increased neurologic deficits after surgery.

Arbit et al. reported the results of Memorial Sloan-Kettering Cancer Center of 109 patients with recurrent brain metastases from non–small cell lung cancer (NSCLC). Thirty-two of these patients (30%) underwent a reoperation. The median interval between the first and second operation was 5 months. The median survival after the second operation was 10 months. The group of patients who underwent reoperation survived significantly longer (median survival, 15 months from the time of the first operation) than a group of 77 patients who did not undergo a second procedure (median survival, 10 months; P < .001).

These results provide support for surgical resection of recurrent brain metastases in selected patients with symptomatic lesions. Factors that should be considered include the length of time since the initial operation, location of the recurrent tumor, age and performance status of the patient, extent of extracranial disease, and radiosensitivity of the tumor. In general, the sooner the metastasis recurs after initial resection, the less likely reoperation will provide a significant period of palliation. 27

Radiotherapy

PRIMARY RADIOTHERAPY. Radiotherapy has been the mainstay of treatment for patients with brain metastases for more than 40 years. The median survival of patients with brain metastases who are not treated or are treated with corticosteroids alone is 1 to 2 months. Conventional WBRT increases the median survival to 3 to 6 months. Irradiation is effective in the palliation of neurologic symptoms and also significantly decreases the likelihood of death due to neurologic causes (Fig. 52.1-1). However, for most patients, overall survival is more likely to be determined by the activity and extent of extracranial disease rather than the success or failure of radiotherapy or surgery in controlling brain metastases.

The main goal of radiotherapy for the treatment of brain metastases is to improve neurologic deficits caused by the tumor deposit. The overall response rate is symptom-dependent but ranges from 50% to 85%. In one study, 74% of patients had improvement of neurologic symptoms, such as headaches, and 65% maintained this for the duration of their lives or for at least 9 months. Cranial nerve deficits improve in approximately 40% of patients. However, the potential for improvement is directly related to the time from diagnosis to radiotherapy. Early treatment is generally associated with a better outcome. The majority of patients with significant neurologic dysfunction improve with the use of steroids and neurotherapy, while fewer than 50% of patients with moderate neurologic dysfunction will improve after therapy.

The optimal dose-fractionation schedules for patients with brain metastases have been evaluated with randomized trials conducted by the RTOG. The RTOG completed two trials of several dose-fraction schedules that were subsequently reported together. In the first trial, patients were randomly assigned to 40 Gy in 4 weeks, 40 Gy in 3 weeks, 30 Gy in 3 weeks, or 30 Gy in 2 weeks. The second trial randomly assigned patients to 40 Gy in 3 weeks, 30 Gy in 2 weeks, or 20 Gy in 1 week. The overall response rate and median survival were equivalent in all arms of these studies. The median survival was 18 weeks in the first trial and 15 weeks in the second trial. Brain metastases was the cause of death in 40% of patients in both trials. Patients treated in the shortest time, with larger fractions, responded more quickly, but the duration of the clinical response and the time to progression were similar in each treatment arm. Symptoms were palliated in 75% to 80% of the patients in all treatment arms of these protocols.

To explore the efficacy and toxicity of ultrarapid treatment schedules, the RTOG treated 26 patients with 10 Gy in one fraction and 36 patients with 12 Gy in two
fractions.6 While the promptness of response, percentage of patients demonstrating neurologic improvement, and overall survival were similar to the more protracted schedules described, the median duration of improvement was only 4 weeks compared to 10 weeks in the protracted radiotherapy trials.

While the studies of the RTOG failed to identify the best dose and fractionation schedule for the treatment of brain metastasis, they allowed the identification of clinical factors associated with better survival.8-10 Patients with breast cancer and no soft tissue metastases, ambulatory lung cancer patients with no extracranial disease, or other ambulatory patients with no extracranial metastases had a median survival of 28 weeks versus 11 weeks for the remaining patients. There was no therapeutic benefit to dose escalation.

To examine the role of irradiation dose escalation in this prognostically favorable subset of patients with brain metastases, the RTOG randomly assigned 309 of these patients to either 30 Gy in 10 fractions or 50 Gy in 20 fractions.11 The median survival of the 30-Gy arm was 18 weeks, and that of the 50-Gy arm was 17 weeks. The 1-year survival rate, response rate, time to achieving response, duration of response, and time to progression were the same for both arms, suggesting that there was no therapeutic benefit to dose escalation.

Another approach that has been explored to improve the results of WBRT for patients with brain metastases is the use of accelerated fractionation. Accelerated fractionation is a technique that uses multiple fractions of radiotherapy per day with the goal to decrease overall treatment time and reduce the risk of tumor cell repopulation. The RTOG performed a phase I and phase II trial of accelerated fractionation for patients with single or multiple brain metastases with controlled, stable, or absent primary disease or in patients with uncontrolled primary disease but no evidence of extracranial metastases.4 The entire brain was treated twice daily with 1.6-Gy fractions to a total dose of 32 Gy and then a twice-daily boost to encompass all of the disease. The boost dose was increased in successive groups from 16 Gy to 22.4 Gy to 32 Gy to 42.4 Gy. The median survival increased from 4.2 months at a 48-Gy total dose to 5.3 months at a 54.4-Gy total dose to 4.8 months at 60 Gy to 6.4 months at 70.4 Gy. The 1-year survival for 48 Gy was 15%, and the other arms had a 30% 1-year survival. Based on these encouraging results, the RTOG conducted a phase III study comparing accelerated hyperfractionated radiotherapy (1.6 Gy b.i.d.) to a total dose of 54.4 Gy versus standard therapy consisting of 30 Gy in 10 daily fractions in patients with unresected brain metastases, limited systemic disease, and good KPS (70). There were 429 evaluable patients, two-thirds of whom had lung primaries. However, the median survival in both groups was 4.5 months, suggesting that there was no benefit of accelerated hyperfractionation over conventional therapy.

The use of biochemical modification (irradiation sensitizers) of irradiation effect has also been explored in patients with brain metastases. However, the results to date have been generally disappointing. Studies using radiosensitizers, such as misorafon,12 and bromdeoxyuridine,13 failed to show any additional benefit over radiotherapy alone. Nonetheless, there continues to be interest in irradiation sensitizers and agents, such as gadolinium lipopolyphosphate,14-16 in clinical trials. There is also interest in the concurrent use of radiotherapy with chemotherapeutic agents, such as the topoisomerase II inhibitor lumantanone.17

There is currently no consensus on the optimal irradiation schedule for patients with brain metastases. The standard treatment regimen for brain metastasis now includes all of the dose ranges evaluated in the early RTOG studies and is dependent on such issues as the severity of CNS symptomatology, extent of systemic disease, and physician preference. Typical irradiation treatment schedules consist of total doses of 30 to 50 Gy in 1.5- to 4-Gy daily fractions. The most common treatment schedule employed consists of 30 Gy in 10 fractions over 2 weeks. For patients with good prognosis who are likely to survive more than 1 year, more prolonged fractionation (e.g., 40 Gy in 2-Gy fractions) may reduce the long-term morbidity from irradiation.

POSTOPERATIVE RADIOTHERAPY. The goal of postoperative WBRT in patients with solitary brain metastasis is to destroy microscopic residual cancer cells at the site of resection and at other locations within the brain. Theoretically, this should reduce the recurrence rate and prolong survival. Although it is standard practice for patients to receive postoperative radiotherapy as adjuvant therapy to surgery, until recently the value of this approach was based only on retrospective studies.18-20 Some of these studies demonstrated that adjuvant WBRT reduced the recurrence rate,20-22 and two studies demonstrated prolonged survival.20-23 Recently, Patchell et al.24 published the results of a randomized trial that examined the role of postoperative WBRT in patients with single metastasis.25 In this study, 95 patients underwent surgical resection and then were randomly assigned to treatment with WBRT (50.4 Gy in 28 fractions) or no further treatment. Patients who received irradiation were significantly less likely to fail in the brain (18% vs. 70%, P < .001), and this was true both at the original site of disease (10% vs. 46%, P = .001) and other areas of the brain (14% vs. 37%, P = .01). Treated patients were also less likely to die of neurologic causes (14% vs. 44%, P < .003), but there was no difference in overall survival (48 vs. 43 weeks; P = .39) or duration of functional independence (37 vs. 35 weeks; P = .61) between the treated and untreated groups. The results of this study suggest that postoperative WBRT in patients with a resected solitary metastasis significantly reduces the incidence of neurologic death but has little impact on the overall survival of the patient, who is mainly dependent on the extent of systemic disease. The authors of this study concluded that the reduction of neurologic death justifies the routine use of postoperative radiotherapy. However, the relatively small size of this study precluded any subgroup analysis. As a result, it remains unclear whether all patients who undergo surgical resection should also receive adjuvant radiotherapy. There may be certain groups of patients, such as those with radio-resistant tumors, such as melanoma or renal cell cancer, for whom WBRT may not be useful after complete surgical resection of the metastases. In addition, the long-term neurocognitive complications of WBRT and its effects on quality of life have not been fully evaluated.

**TABLE 52.1-2.** Studies Evaluating the Role of Postoperative Radiotherapy

**LATE TOXICITY.** An important benefit of aggressive treatment for brain metastases is the likelihood that some patients will become long-term survivors. In these patients, late complications of WBRT can be debilitating. These complications include leukoencephalopathy and brain atrophy leading to neurocognitive deterioration and dementia; brain necrosis resulting in more specific neurologic sequelae, depending on the site of necrosis; and communicating hydrocephalus, causing cognitive, gait, and bladder dysfunction.25-28 Neuroendocrine dysfunction, such as hypothyroidism, may also occur.29-31 The risk for late complications from WBRT is related to total dose, fraction size, patient age, extent of disease, and neurologic impairment at presentation.32 Prior or concurrent chemotherapy may also affect the occurrence of late CNS toxicity. If WBRT is to be given, a dose-fraction schedule should be used, which takes into account the overall clinical status of the patient with brain metastases. Two studies demonstrated prolonged survival of 70 patients treated with postoperative radiotherapy using no less than 300-cGy fractions, 11% showed evidence of dementia.33 Therefore, patients with good prognosis, such as those with single brain metastasis with no or controlled systemic disease, are best treated with daily fractions of 200 cGy or less to decrease the likelihood of long-term CNS toxicity (e.g., 40 to 45 Gy in 1.8- to 2.0-Gy daily fractions).

**REIRRADIATION.** Occasionally, patients are reirradiated with whole brain or partial brain radiotherapy at the time of brain recurrence. The percentage of patients who undergo reirradiation is quite small, since most patients who recur within the CNS also have progressive extracranial disease and are treated with supportive measures only. However, there are times when reirradiation is indicated. For a few (20) metastases are candidates for treatment with radiosurgery, as this will have less toxicity than repeating WBRT (discussed later in **Stereoelectro Radiosurgery**) and is more likely to be effective than systemic therapy. Other patients should be considered for treatment with systemic chemotherapy or hormonal therapy. For patients not eligible for radiosurgery or systemic therapy, treatment with whole or partial brain radiation may be indicated. Several retrospective studies have addressed this issue.34-38 A recent review evaluated 188 patients from three separate studies who were reirradiated. The overall clinical response rate was 42% to 75%, and the median survival from the time of reirradiation was between 3.5 and 5 months. The published techniques of reirradiation include doses from 3 Gy in 2 weeks to...
30.6 Gy in 3 weeks, with the median of approximately 20 Gy in 2 weeks, but there is no consensus on which dose fractionation schedule is appropriate or how long after the initial course of radiotherapy it is appropriate to reirradiate. Some investigators have argued that reirradiation should be considered for patients who remain in good general condition but experience neurologic deterioration 4 or more months after a satisfactory response to the initial course of WBRT. The tolerance of the brain is more than likely to be exceeded by reirradiation but, with the limited survival of these patients, there are inadequate data to evaluate the consequences of this treatment.

**Stereotactic Radiosurgery**

Stereotactic radiosurgery is a technique of external irradiation that uses multiple convergent beams to deliver a high single dose of radiation to a radiographically discrete treatment volume. Radiosurgery can be performed with high-energy roentgenograms produced by linear accelerators, with gamma rays from the gamma knife and, less frequently, with charged particles, such as protons produced by cyclotrons. All the stereotactic irradiation techniques result in rapid fall-off of dose at the edge of the target volume, resulting in a clinically insignificant radiation dose to normal nontarget tissue. Metastases are usually small (<3 cm) radiographically discrete lesions that are noninvasive, rendering them ideal targets for radiosurgery.

An increasing number of uncontrolled studies confirm the effectiveness of stereotactic radiosurgery in treating brain metastases (Table 52.1-3). To date, more than 1780 patients with more than 2700 lesions have been reported in the literature. Radiosurgery produces local control rates of 73% to 94% and is associated with a 5% to 10% risk of radiation necrosis. The median survival from these series ranges from 6 to 15 months, with an average of 9.4 months. In a multinational trial involving 116 patients treated with radiosurgery for single brain metastasis using a mean dose of 17.5 Gy, local tumor control was obtained in 99 patients (85%). The 2-year actuarial tumor control rates for the entire group was 67% ± 8%, with a plateau in the curve at 18 months. In a multivariate analysis, better local control was obtained in patients who received WBRT in addition to radiosurgery and in those patients with “radioresistant” histologies (melanoma and renal cell carcinoma). In the largest series to date, Alexander et al. reported the results of radiosurgery using a linear accelerator for the treatment of 248 patients with 421 metastatic lesions. At the time of radiosurgery, 77 patients had no evidence of systemic disease, while 171 patients had stable systemic disease. Of the lesions treated, 126 were classified as radioresistant (melanoma, renal cell carcinoma, and sarcoma), with the remaining 295 lesions representing all other histologies. With a median observation period of 26 months, 48 of 421 lesions (11%) progressed with or without systemic disease. Combination therapy was associated with a much lower rate of local failure at 1 year (8% vs. 100%) and a longer median time to local failure (36 vs. 6 months). However, there was no significant improvement in median survival (11 vs. 7.5 months; P = .22), which was related to the extent of extracranial disease. An RTOG trial (95-08) is currently under way in which patients with one to three untreated brain metastases will be randomly assigned to WBRT or WBRT and radiosurgery. The study will provide further data on the usefulness of adding radiosurgery to WBRT.

The study by Patchell et al. and Noordijk et al. indicated that there is a survival advantage for patients with a single brain metastasis treated with surgery and radiotherapy as compared to radiotherapy alone. Many clinical investigators believe that radiosurgery can act as an alternative to surgical resection. Moreover, radiosurgery has several potential advantages over surgery. It can be used to treat metastases in surgically inaccessible areas of the brain, such as the brain stem. Since it is a noninvasive procedure that can be performed on an outpatient basis, it is associated with less morbidity than surgery. In addition, there is increasing evidence that radiosurgery may also be more cost-effective than surgery. In the study by Mehta et al., the average cost per week of survival was $310 for radiotherapy, $524 for resection plus irradiation, and $270 for radiosurgery plus irradiation.

While there are no completed randomized trials comparing radiosurgery to surgery, Auchter et al. identified 122 patients who met the selection criteria used by Patchell et al. and were treated with WBRT (median, 37.5 Gy) followed by a radiosurgery boost (median, 17 Gy). The overall local control rate was 86%, with an actuarial median survival of 56 weeks and a neurologic median survival of KPS greater than 70 of 44 weeks. These results are comparable to the surgery and irradiation therapy arms of the studies by the Patchell et al. and Noordijk et al. and better than the arms of the whole brain treatment alone. In a second retrospective study, Muscic et al. compared 52 patients with single brain metastasis treated with surgery and WBRT with 56 patients treated with radiosurgery alone. The 1-year local tumor control rates after surgery and radiosurgery were 75% and 83%, respectively, and the 1-year neurologic death rates were 37% and 39%, respectively, suggesting that the local tumor control rates are similar in the two groups. The 1-year survival rate and median survival were 53% and 68 weeks, respectively, in the surgical group and 43% and 35 weeks, respectively, in the radiosurgical group. The shorter overall survival time in the radiosurgical group was related to higher rate of death from systemic disease. Brandt et al. also compared surgery and radiosurgery in a series of 56 patients. In this study, the median survival of the radiosurgically treated patients was 11.4 months, comparable to the 10.4 months for the surgically treated patients. In a fourth study, by Shu et al., patients with single brain metastases treated with radiosurgery had a median survival of 16.4 months, compared to 7.5 months for those treated with radiosurgery (P = .0009). Based on these results, the authors concluded that surgery was superior to radiosurgery for the treatment of a single brain metastasis. However, the low local control rate in the radiosurgically treated patients in this study (61%) and differences in the extent of systemic disease between the surgery and radiosurgery groups may have accounted for the poor results of radiosurgery. Ideally, a prospective randomized study comparing surgery to radiosurgery in the treatment of single brain metastases would resolve the issue of the relative efficacy of these two treatments. However, previous attempts at such a study have been unsuccessful due to poor patient accrual as a result of patient or physician preference (or both) for either surgery or radiosurgery.

**Table 52.1-3. Radiosurgery for Brain Metastases: Results of Representative Series**

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Median Survival</th>
<th>Local Control Rate</th>
<th>Neurologic Death Rate</th>
<th>Overall Survival</th>
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</thead>
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<td>Patchell et al.</td>
<td>122</td>
<td>56 weeks</td>
<td>86%</td>
<td>37%</td>
<td>70%</td>
</tr>
<tr>
<td>Noordijk et al.</td>
<td>122</td>
<td>44 weeks</td>
<td>86%</td>
<td>39%</td>
<td>68%</td>
</tr>
<tr>
<td>Mehta et al.</td>
<td>122</td>
<td>&gt;70 weeks</td>
<td>96%</td>
<td>100%</td>
<td>90%</td>
</tr>
</tbody>
</table>

The role of WBRT in patients treated with radiosurgery is controversial, especially for patients with relatively radioresistant tumors, such as melanoma. In the study by Patchell et al., 37% of patients failed in other sites within the brain if they did not receive whole brain irradiation. While some studies have shown improved local control in patients who received whole brain radiotherapy in addition to radiosurgery, overall patient survival is generally not increased. Currently, most centers treat patients with brain metastases with both radiosurgery and whole brain radiotherapy and limit the use of up-front radiosurgery alone to cases for which there are no alternatives, such as prior high-dose irradiation to the head and neck area or when the patient refuses whole brain radiation therapy. However, there are several retrospective studies suggesting that for selected patients, radiosurgery alone may be as effective as the combination of radiosurgery and WBRT, with potentially less morbidity. In a study by Sneed et al., the outcome of 62 patients with up to four newly diagnosed brain metastases treated with radiosurgery alone were compared with 43 patients with newly diagnosed metastases treated with the combination of radiosurgery and WBRT. The median...
survival and the 1-year local freedom from progression (FFP) were the same for radiosurgery alone and for radiosurgery and WBRT (median survival, 11.3 vs. 11.1 months; 1-year local FFP, 71% vs. 79%, respectively). More patients treated with radiosurgery failed in the brain (new metastases or local failure or both) than those receiving the combination of radiosurgery and WBRT (brain FFP at 1 year, 28% for radiosurgery compared to 69% for the combination of radiosurgery and WBRT). However, brain control, allowing for successful salvage of a first failure, was not significantly different between the two groups. This study suggests that omission of WBRT in the initial management of patients treated with radiosurgery for up to four brain metastases does not appear to compromise survival or intracranial control and allows for salvage therapy as indicated. A second small retrospective study of 35 patients with melanoma brain metastases found no difference in survival between the patients treated with radiosurgery and the combination of radiosurgery and WBRT. A third study by Pirzkall et al. comparing the outcome of 158 patients with one to three brain metastases treated by radiosurgery with 78 patients treated with radiosurgery and WBRT also found no statistical difference in survival and local control between the two groups, although there was a trend toward improved local control and increased survival in the group that received WBRT.

Randomized studies comparing radiosurgery and the combination of radiosurgery and WBRT are currently under way to assess survival, quality of life, and cost-effectiveness in patients with newly diagnosed brain metastases.

### Complications of Radiosurgery

Acute complications within the first week of treatment are uncommon, occurring in fewer than 10% of patients. These include seizures (2.3% to 6.1%), headaches, exacerbation of preexisting neurologic deficits (2% to 6%), nausea (especially in patients receiving more than 375 cGy to the area postrema) and, rarely, hemorrhage. The risk of seizures can be reduced by treating patients with anticonvulsants before the radiosurgery procedure. Patients with lesions near the posterior fossa may benefit from premedication with antiemetics. Acute neurologic deficits can be reduced by using doses of less than 30 Gy.

Subacute complications occurring within 6 months of treatment consists of alopecia in patients whose scalp received more than 4.4 Gy of irradiation and neurologic deterioration due to necrosis and periluminal edema.

Chronic complications due to irradiation necrosis occur in approximately 8% to 16% of patients. These patients present with increased seizures, headaches, or worsening neurologic deficits. These side effects can usually be treated with corticosteroids. However, 5% to 10% of patients develop severe symptomatic necrosis and may require surgical resection.

### Prognostic Factors

Young patients with good performance status, limited extracranial disease, and one or two small lesions are particularly suited to treatment by radiosurgery. Poor prognostic factors include poor performance status (<70), progressive systemic disease, large tumor size, infratentorial location, and multiple metastases (more than two lesions). The efficacy of radiosurgery appears to be independent of the histology of the lesion. Radioresistant tumors, such as renal cell carcinoma, malignant melanoma, and NSCLC have statistically the same control rate as other tumors.

### Summary

The introduction of radiosurgery over the last decade represents one of the major advances in the treatment of brain metastases. For patients with a single small asymptomatic or mildly symptomatic lesion, radiosurgery can probably be used as a substitute for surgery with comparable outcomes. Radiotherapy also has an important role in patients with recurrence of brain metastasis after whole brain radiotherapy and, perhaps, in the initial treatment of patients with several metastases and limited systemic disease.

### Intermittent Brachytherapy

Intermittent brachytherapy involves the implantation of radioactive nuclides into the wall of the surgical cavity to deliver an additional dose of radiation to the residual tumor while limiting the irradiation to the surrounding brain. The relatively sharp border between metastases and the surrounding brain renders them ideal lesions for brachytherapy. Brachytherapy for metastases has been evaluated in several small uncontrolled studies using iodine 125 sources, and median survivals have ranged from 9 to 18.3 months. Although brachytherapy is rarely performed for small lesions suitable for radiosurgery, it may have a limited role for metastases that are too large for radiosurgery.

A more recent brachytherapy strategy involves using a photon radiosurgery system. This is a battery-powered miniature x-ray generator with an attached probe that can be placed stereotactically into metastases at the time of craniotomy to deliver a single fraction of high-dose radiation (12.5 Gy) in less than an hour. Preliminary results suggest that this procedure is well tolerated and produces effective local tumor control.

### Chemotherapy

The role of chemotherapy for the treatment of patients with brain metastases has not been defined. At present, chemotherapy is rarely used as part of the overall management of brain metastases. Traditionally, it had been assumed that the blood–brain barrier prevented chemotherapeutic agents from entering the CNS. However, there is evidence that the blood–brain barrier is in fact partially disrupted within brain tumors. This suggests that other factors may also contribute to the generally disappointing results of chemotherapy for brain metastases, such as the intrinsic resistance to chemotherapy of many tumors that metastasize to the brain; the use of chemotherapeutic agents designed to penetrate the blood–brain barrier rather than agents known to be most effective against the primary malignancy; and the tendency for brain metastases to develop after the failure of primary chemotherapeutic agents to control systemic disease.

Although the overall results of chemotherapy for brain metastases have been generally disappointing, a number of uncontrolled studies have demonstrated favorable response rates in brain metastases from chemosensitive tumors, such as breast cancer, small cell lung cancer (SCLC), and germ cell tumors. Patients with metastatic breast cancer have been treated with chemotherapy since 1970. In the largest series to date, Rosner et al. treated 100 consecutive breast cancer patients with brain metastases with several chemotherapy regimens, including cyclophosphamide, 5-fluorouracil, and prednisone, or with this regimen together with methotrexate and vincristine. These patients had not received prior chemotherapy for their systemic disease. Overall, 50% of patients had an objective response (10% had a complete response, and 40% had a partial response). In addition, 9% had stable disease. The median duration of remission for complete responders was 10 months and, for partial responders, it was 7 months. Rosner et al. subsequently treated an additional 26 patients with progressive brain metastases from breast cancer with four different chemotherapeutic regimens: cyclophosphamide, 5-fluorouracil, and prednisone; cyclophosphamide, 5-fluorouracil, and prednisone together with methotrexate and vincristine; cyclophosphamide and doxorubicin (Adriamycin); and mitomycin and vinblastine (Velban). Objective responses were seen in 61% of patients, while another 15% had stable disease. The median survival for responders was 12 months, compared to 2.4 months for nonresponders. Interestingly, prior
systemic chemotherapy did not affect the response of the brain metastases, arguing against the concept of the brain as a pharmacologic sanctuary.

Francisci et al. treated 56 patients with brain metastases from breast cancer with the combination of cisplatin and etoposide for a maximum of six cycles and observed complete responses in 13%, partial responses in 26%, and stable disease in 21% of patients. The median survival was approximately 8 months. Boogerd et al. treated 20 patients with cyclophosphamide, methotrexate, and 5-fluorouracil, or cyclophosphamide, doxorubicin, and 5-fluorouracil. Seven patients had recurrent disease after WBRT. Objective tumor regression occurred in 76% of patients after two cycles of chemotherapy. The median duration of neurologic remission was 30 weeks, and the median survival was 25 weeks. When the results of these chemotherapy patients were compared to 29 historic controls treated with WBRT, the neurologic response rate, duration of response, and median survival were better in those patients treated with chemotherapy.

Several other small series have reported responses to a variety of regimes, including a combination of drugs combining thioguanine, procarbazine, dibromodulcitol, lomustine (CCNU), 5-fluorouracil, and hydroxyurea designed to improve the efficacy of CCNU. Recently, there has also been a report of patients with brain metastases from breast cancer responding to high-dose chemotherapy.

There have also been many studies evaluating the response of brain metastases from SCLC to chemotherapy. Certain patients with brain metastases as the only manifestation of an undetected primary tumor also have a favorable prognosis, with an overall median survival of 13.4 months. Breast cancer patients with brain metastases generally have a more favorable prognosis than brain metastases from other types of primary tumor. On the other hand, patients with colorectal carcinoma tend to have a poorer prognosis. This may be due to the tendency of these patients to have a higher frequency of cerebellar metastases, which are associated with an adverse prognosis.

Recently, Gaspar et al. performed a recursive partitioning analysis of prognostic factors from three RTOG brain metastases trials and identified three prognostic classes. Class 1 patients had a KPS of 70 or higher, were younger than 65 years of age, had a controlled primary and no extracranial metastases, and had a median survival of 7.1 months. Class 3 patients had a KPS of less than 70 and a median survival of 2.3 months. Class 2 patients included all remaining patients and had a median survival of 4.2 months. Agboola et al. evaluated the validity of this classification system in 125 patients with brain metastases treated with surgical resection and WBRT. The median survival in classes 1, 2, and 3 were 14.8, 9.9, and 6 months, respectively. Use of this classification may identify patients most likely to benefit from treatment and potentially allows new therapies to be evaluated on homogeneous patient groups.

PROGNOSIS

The median survival of patients with untreated brain metastases is approximately 1 month. The addition of steroids increases survival to 2 months, while whole brain radiotherapy further improves survival to 3 to 6 months. Patients with single brain metastases and limited extracranial disease who are treated with surgery and WBRT have a median survival of approximately 16 to 24 months. Favorable prognostic factors include the absence of systemic disease, young age (<60 years), good performance status (KPS >70), long time to development of metastasis, surgical resection, less than three lesions, and possibly response to steroids. Patients with brain metastases as the only manifestation of an undetected primary tumor generally have a favorable prognosis, with an overall median survival of 13.4 months. Breast cancer patients with brain metastases generally have a more favorable prognosis than brain metastases from other types of primary tumor. On the other hand, patients with colorectal carcinoma tend to have a poorer prognosis. This may be due to the tendency of these patients to have a higher frequency of cerebellar metastases, which are associated with an adverse prognosis.

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INTRODUCTION

Metastases often represent diffuse systemic or untreatable spread of a primary neoplasm. However, selected patients with metastases isolated to the lung may be resected safely and achieve prolonged survival compared to patients with unresectable metastases. In general, patients with complete resection of pulmonary metastases have associated prolonged survival (regardless of histology) compared to patients with unresectable metastases. This observation is surprising because surgery alone cannot control micrometastases. After complete resection of pulmonary metastases (including multiple and bilateral metastases), the long-term survival rate (more than 5 years) may be expected in approximately one-third of patients.

HISTORICAL PERSPECTIVE

The history of resection of pulmonary metastases has been reviewed. One of the earliest resections for pulmonary metastases was performed after resection of a chest wall sarcoma in 1882 by Weinlechner. In 1883, Kronlein resected a recurrent chest wall sarcoma in a young woman. The patient lived for several years after the surgery and died of recurrent disease. The first resections of a pulmonary metastasis as a separate procedure were described in 1926 by Divis and in 1930 by Torek. One of the first long-term survivors of any pulmonary metastasectomy was reported by Barney and Churchill after resection of a metastasis from a patient with renal cell carcinoma. Local control of the primary tumor was achieved, and the patient survived for 23 years after resection of the metastasis and died from unrelated causes. Alexander and Haight reported the first large series (25 patients) of metastasectomy in 1947. Multiple metastases from osteochondroma of the tibia were resected in 1953 by Mannix, with the patient surviving more than 2 years. Other authors have noted that certain clinical characteristics may enable clinicians to identify patients with more favorable disease-free and overall survival rate prognoses. Since the late 1970s, resection of solitary and multiple pulmonary metastases from sarcomas and various other primary neoplasms have been performed with long-term survival in up to 40% of patients so treated.

IDENTIFICATION OF PULMONARY METASTASES

Routine evaluation of patients for pulmonary metastases is based on screening chest roentgenograms obtained at various intervals after resection of the primary. Although their specificity exceeds 95% when nodules consistent with metastases are identified, their sensitivity compared to computed tomography (CT) of the chest is low, and this deficiency has prompted some clinicians to screen patients at high risk of recurrent metastases with CT chest scans. Duda et al. examined 130 patients with soft tissue and bone sarcomas. Sixty-six patients had no evidence of pulmonary metastases on chest x-ray (CXR) and subsequently had abnormal tomography or CT of the chest performed. Only 1 of 53 patients with a normal CXR and no local recurrence had an abnormal tomogram. Two patients of 13 with locally recurrent sarcoma and a normal CXR had an abnormal tomogram. The authors concluded that a screening CXR in the absence of local recurrence is the most cost-effective test. However, tomograms should be performed for evaluation of the extent of disease (e.g., pulmonary metastases) in patients with locally recurrent sarcomas.

FIGURE 52.2-1. Chest x-ray (posteroanterior and lateral views) of patient with multiple metastases from malignant fibrous histiocytoma. The number and location of these metastases preclude resection.
CT has replaced linear tomograms as the examination of choice in patients with suspected pulmonary metastases [2] (see Fig. 52.2-2). CT scans of the chest provide a sensitive and specific noninvasive examination for patients with pulmonary metastases. CT scans of the chest are sensitive and identify smaller nodules (3 to 7 mm) earlier than conventional linear tomography, although these nodules may not necessarily be metastases. Theoretically, earlier detection and treatment of metastases can improve survival. However, in one study that detected occult metastases during median sternotomy with bilateral lung exploration, survival was not improved over patients having a single thoracotomy, even though a significant percentage of patients would be expected to have occult metastases.  

Magnetic resonance imaging (MRI) is routinely performed to evaluate the local site of resection for recurrence. MRI is not routinely helpful for the radiographic diagnosis of pulmonary metastases; rather, CT of the chest is preferred. MRI is helpful when the pulmonary metastases are of great size and may abut or invade the mediastinum. Pulmonary metastases from sarcomas “push” tissue rather than invade, and exploration is often required to determine the extent of host-tumor interactions. The MRI may assist the surgeon in planning the approach needed for resection of these complex intrathoracic neoplasms.

Lucas et al. examined the role of whole body [18F]fluorodeoxyglucose positron emission tomography (FDG PET) in the diagnosis of pulmonary metastases from soft tissue tumors. The authors made 70 comparisons between FDG PET and chest CT for the identification of lung metastases. The sensitivity of FDG PET was 86.7% and the specificity was 100% (13 true-positive, two false-negative). CT of the chest had a sensitivity of 100% and a specificity of 96.4%. However, FDG PET identified 13 other sites of metastases. The authors suggested that FDG PET might be used for evaluation of local recurrence as well as pulmonary and extrathoracic metastases. The use of all three modalities (CT of the chest, MRI, and FDG PET) may most accurately define the total extent of disease. The cost effectiveness of these three examinations has not been studied.

**SELECTION OF PATIENTS FOR SURGERY**

Predictors for improved survival have been studied retrospectively for various tumor types to allow the clinician to identify selected patients who will optimally benefit from pulmonary metastasectomy. These “prognostic indicators” are clinical, biologic, and molecular criteria, which describe the biologic interaction between the metastases and the patient, and the association of the two with prolonged survival. These prognostic indicators may be used to identify those patients who are most likely to benefit after resection of pulmonary metastases. Many patients with metastases will not benefit from surgery because of a biologically aggressive tumor (e.g., extensive disease, a short disease-free interval (DFI) between control of their primary tumor and identification of unrespectable pulmonary metastases, and rapid metastatic growth). Biologic characteristics also differ with the tumor histology.

Analysis of prognostic indicators in groups of patients with pulmonary metastases from heterogeneous tumors describe prolonged survival in patients with resectable metastases. Within this group of resectable patients, longer DFI, longer tumor-doubling time (TDT), fewer numbers of metastases, and specific primary histology may be favorably associated with improved survival. A disadvantage of studying prognostic indicators in heterogeneous groups of neoplasms is the wide variability in biologic characteristics of metastases, particularly among different primary neoplasms. The study of pulmonary metastases from patients with the same tumor histology will provide better information on prognostic indicators that may influence survival after resection of these metastases.

Pastorino and colleagues retrospectively reviewed more than 5000 patients with metastases treated with resection. Overall, actuarial 5-year survival was 36%, 10-year survival was 26%, and 15-year survival was 22%. Patients could generally be staged by the presence of favorable clinical indicators. These indicators included a DFI of more than 3 years, a solitary pulmonary nodule, and germ cell histology.

Kandioler and colleagues confirmed the biologically favorable characteristics of patients with pulmonary metastases who could be completely resected of their disease. Overall median survival for a heterogeneous population of patients with pulmonary metastases was 60 months.

**PREPARATION OF THE PATIENT FOR METASTASECTOMY**

The patient’s overall medical condition and preoperative treatment must be considered in planning resection of pulmonary metastases. As with any patient undergoing thoracotomy, the patient must have sufficient physiologic reserves to withstand the anesthesia and the surgical procedure. Routine blood chemistries, chest roentgenogram, and CT of the chest and abdomen are routinely performed. CT of the area of primary neoplasm and other studies may be obtained to evaluate the site for local recurrence. Only if appropriate system-related symptoms were identified, such as headaches or neurologic deficits, or bone pain, would a brain CT or bone scan, respectively, be obtained. The evaluation of pulmonary function includes arterial blood gas measurement, xenon ventilation-perfusion lung scans, DLCO (carbon monoxide diffusing capacity of the lungs), and maximal oxygen consumption (MVO). These studies are obtained to evaluate the patient’s suitability for general anesthesia and one-lung anesthesia and to estimate the potential for sufficient postoperative pulmonary reserve. Cardiac assessment (e.g., electrocardiogram, stress test) may be necessary for older patients. For patients previously treated with Adriamycin chemotherapy, an echocardiogram should be obtained to evaluate ejection fraction as a measure of extent of cardiomyopathy.

Preoperative chemotherapy has been given, surgery should be delayed a minimum of 4 weeks or longer to allow for sufficient bone marrow recovery (for low absolute leukocyte count [fewer than 5000 cells per mm$^3$] or low platelet count [fewer than 50,000 per mm$^3$], if marrow suppression precludes recovery of platelets, then perioperative support with platelet transfusions may be required. Absolutely no smoking is permitted for a minimum of 2 weeks before surgery to enhance pulmonary hygiene. Patients are encouraged to use an incentive spirometer several times daily. The patient is routinely admitted to the hospital the morning of surgery.

In the operating room, two large-bore intravenous lines, a radial arterial line, and oxygen saturation monitors are placed. A central line is not routinely used for wedge resections of the lung. A Foley catheter is placed routinely if the operation is expected to exceed 3 hours or if a thoracic epidural catheter is placed for perioperative analgesia. The pertinent radiographic examinations (chest roentgenograms and CT scans of the chest) are displayed prominently in the operating room. After intubation with a single-lumen endotracheal tube, a bronchoscopy is performed to evaluate the distal trachea and tracheobronchial tree. A double-lumen endotracheal tube is used to facilitate sequential exposure and palpation of the lungs.

**SURGICAL INCISIONS**

Surgical procedures for resection include single thoracotomy, staged bilateral thoracotomy, or median sternotomy. These procedures have almost no mortality and minimal morbidity. The procedure chosen does not influence survival in patients resected of all disease; however, various advantages and disadvantages are inherent to each approach (Table 52.2-1). Patients with pulmonary metastases may also undergo multiple procedures for re-resection of metastases, with prolonged survival after complete resection.
VATS in thoracic surgical oncology. The devastating effects on the patient. 

Resection of pulmonary metastases may cause more morbidity than the benefits achieved by VATS. The obvious chest wall implant from tumor seeding has instrumentation available for manipulation of the lung and other thoracic organs, and an assessment of the risk of a "closed" versus "open" procedure. An inadequate operation must be compared to the benefits of the VATS approach. The surgeon must consider the technical skills required, the desired objectives for the patient, the Complications specific to thoracoscopic resection of pulmonary metastases have been described. The subjective risks of an incomplete, inadequate, or inconsistent operation must be compared to the benefits of the VATS approach. The surgeon must consider the technical skills required, the desired objectives for the patient, the instrumentation available for manipulation of the lung and other thoracic organs, and an assessment of the risk of a "closed" versus "open" procedure. An inadequate resection of pulmonary metastases may cause more morbidity than the benefits achieved by VATS. The obvious chest wall implant from tumor seeding has devastating effects on the patient. 

Postoperative pain from periosteal injury affects some patients. Patient selection remains a critical step in the appropriate use of VATS in thoracic surgical oncology. VATS is considered appropriate for diagnosis or intrathoracic staging ( Fig. 52.2-3).

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TABLE 52.2-1. Advantages and Disadvantages of Various Surgical Resections

For median sternotomy, the patient is positioned supine with the entire anterior thorax exposed from the neck to the umbilicus and laterally to the anterior axillary line. The sternum is divided and the lungs sequentially deflated. The pulmonary ligament is divided to mobilize the lung completely. The deflated lung is palpated to identify metastases, and these are resected with a surgical stapling device or other means (laser or Bovie electrocautery). The deflated right lung may be brought completely into the field by placing folded sponges behind the hilum (for elevation). Metastases may be resected with the lung inflated, but the metastases must be marked with a suture, and metastases deep within the parenchyma may be difficult to resect with wedge excision alone. The lung is reinflated.

Exposure of the left lower lobe through a median sternotomy may be more difficult than exposure of the other lobes because of the overlying heart. With appropriate gentle traction on the pericardium, the left lower lobe can be exposed readily and brought into the operative field. Technical aids, such as an internal mammary artery retractor, may provide for better exposure, particularly for basilar (left lower lobe) tumors or posterior hilar left lower lobe masses.

The posterolateral thoracotomy is a familiar and "standard" approach to pulmonary resection for carcinoma of the lung, although several authors encourage median sternotomy for both resection of lung carcinoma and for pulmonary metastases. In contrast to median sternotomy, posterolateral thoracotomy (either with division of the latissimus dorsi or "muscle sparing") may be more uncomfortable for the patient during the postoperative convalescence. Improvements in postoperative pain management with intercostal nerve analgesia, thoracic epidural analgesia, and patient-controlled analgesia can control or even eliminate postoperative pain. The posterior or posterolateral thoracotomy does provide better exposure for metastases located posterior and near the hilum, particularly on the left side, and limits the surgeon to one hemithorax. In only rare circumstances would bilateral thoracotomies be performed in the same patient during the same operation.

**RESECTION OF PULMONARY METASTASES**

Patients with bilateral metastases may be explored with a median sternotomy, staged bilateral thoracotomies, or posterolateral thoracotomy. Prior evaluation of patients with sarcomas and unilateral metastases demonstrated bilateral metastases in 38% to 60% of patients. Postresection survival from median sternotomy and from bilateral staged thoracotomies is similar. Numbers of nodules, presence of unilateral or bilateral nodules, location of nodules, and the size of various nodules can be identified and, if required, resected through a median sternotomy. A median sternotomy is recommended for the initial exploration and resection in patients with unilateral or bilateral nodules, and in patients with pulmonary metastases from osteogenic sarcoma (OST) or soft tissue sarcoma (STS), and should be considered the procedure of choice in patients with suspected bilateral metastases. Multiple authors have advocated median sternotomy for lobectomy for resection of primary carcinoma of the lung, particularly in patients with impaired pulmonary function. A posterolateral thoracotomy approach may be required for left lower lobectomy in patients with obesity, cardiomegaly, or an elevated left hemidiaphragm.

All nodules are resected with a margin of normal tissue. Nodules should not be "shelled out," because viable tumor cells remain on the periphery of the resected area. Often the decision of margin adequacy is the surgeon's alone, because lung parenchyma may become distorted around the nodule after resection, giving the illusion of a "positive" or "close" margin. Mediastinal lymph nodes can also be examined for potentially rare involvement from pulmonary metastases.

Laser-assisted pulmonary resection using the neodymium:yttrium aluminum garnet laser may provide a better means of resecting pulmonary metastases than with the surgical stapler. Disadvantages of laser resection may include longer operating time and the potential for prolonged postoperative air leaks; however, use of the laser may enhance preservation of lung parenchyma with less distortion. Bovie electrocauterity may also spare lung parenchyma by removing the metastases with minimal distortion of remaining lung. Air leaks can be sealed by the use of fibrin glue.

Thoracoscopic resection or video-assisted thoracic surgery (VATS) using high-resolution video cameras may be helpful for diagnosis of metastases; however, its usefulness is limited to metastases identified on the surface or outer one-third of the lung. Metastases within the lung parenchyma may be undetectable with this technique. Landreneau and associates have described minimal morbidity and no mortality in 41 patients who underwent 52 thoracoscopic pulmonary resections for small lesions (less than 3 cm) in the outer one-third of the lung parenchyma.

At this time, wedge resection of pulmonary metastases using VATS techniques has no proven advantage over resection using standard "open" techniques. Even patients at increased physiologic risk from thoracotomy may tolerate a simple wedge resection of the lung without difficulty. VATS may be inadequate to detect all metastases. McCormack and colleagues demonstrated that a combination of chest CT and VATS had a 56% failure rate to detect and resect all lesions. The frequency of bilateral and occult metastases, particularly in sarcoma, precludes the use of thoracoscopic. Thoracoscopic may play a role in highly selected patients with a solitary metastasis of nonsarcomatous origin with a long DFI.

Complications specific to thoracoscopic resection of pulmonary metastases have been described. The subjective risks of an incomplete, inadequate, or inconsistent operation must be compared to the benefits of the VATS approach. The surgeon must consider the technical skills required, the desired objectives for the patient, the instrumentation available for manipulation of the lung and other thoracic organs, and an assessment of the risk of a "closed" versus "open" procedure. An inadequate resection of pulmonary metastases may cause more morbidity than the benefits achieved by VATS. The obvious chest wall implant from tumor seeding has devastating effects on the patient. Postoperative pain from periosteal injury affects some patients. Patient selection remains a critical step in the appropriate use of VATS in thoracic surgical oncology. VATS is considered appropriate for diagnosis or intrathoracic staging ( Fig. 52.2-3).
SURVIVAL ANALYSIS

Survival may be absolute or actuarial and is usually calculated from the time the surgical procedure is performed until death or the date of last follow-up. For example, patients followed for a minimum of 5 years (survivors) or until death provide an absolute 5-year survival rate (number patients alive of all patients studied); patients followed for varying periods (i.e., 2 to 7 years) may be evaluated using an actuarial survival curve. Actuarial survival and disease-free survival may be estimated using the method of Kaplan and Meier. Patients, grouped into two or more populations, are defined as meeting or not meeting an objective criteria and compared so that differences in survival can be evaluated. Univariate analysis (or comparisons between groups) may be made using the generalized Wilcoxon test of Gehan or log-rank test; if sample sizes are small, the Thomas exact test may be used. Cox's proportional hazards model would be used to determine the relative effect of various prognostic indicators on survival. Univariate analysis identifies the most important prognostic indicators. Multivariate analysis evaluates the predictive ability of two or more prognostic indicators to provide additional prognostic value.

RESULTS OF RESECTION OF SARCOMATOUS PULMONARY METASTASES

An evaluation of prognostic indicators and results of resection of pulmonary metastasectomy is difficult, because numerous primary histologies are often combined to discuss the value of pulmonary metastasectomy. Although identification of trends is helpful, analysis of factors that are associated with improved survival depend on a single histology and a group of patients sufficiently large from which to draw conclusions. Prognostic indicators have been reviewed to assess their association, singularity and in combination, with postresection survival in patients with pulmonary metastases and to assist clinically in better selecting appropriate patients for resection of pulmonary metastases. Age and gender of the patient; histology, stage, grade, and location of the primary tumor; disease-free survival; number of nodules on preoperative radiologic studies; whether the metastases are unilateral or bilateral, or synchronous or metachronous; and TDT all may be evaluated preoperatively. In addition, resectability, technique of resection, nodal spread, the number of metastases and their location, and re-resection may be evaluated postoperatively.

OSTEOGENIC SARCOMA

Pulmonary metastases from OST occur in up to 80% of patients who relapse after treatment for their primary neoplasm, whether or not they receive adjuvant chemotherapy. Ninety percent of all recurrences occur within 3 years. Because these metastases are often isolated to the lungs, surgical resection may render a significant number of patients disease-free and enhance long-term survival. The 5-year survival rate may range up to 50%.

Various groups have evaluated survival and prognostic factors in patients with pulmonary metastases from OST. Series from the National Cancer Institute in the early 1980s evaluated 80 patients with primary OST of the extremity. Forty-three patients developed pulmonary metastases. Thirty-nine patients were deemed resectable and underwent one or more thoracic explorations for resection of their metastases. The 5-year survival rate was 38%. Various prognostic factors were analyzed. Fewer number of nodules (three or less), longer DFI, resectable metastases, and fewer metastases identified and resected were associated with longer post thoracotomy survival. A multivariate analysis did not find any combination of factors to be more predictive than the number of nodules identified on preoperative tomograms. Surgical resectability was the only predictive factor associated with prolonged survival for recurrent OST.

Chemotherapy has been effective in prolonging the DFI between the surgical treatment of the primary tumor and the appearance of pulmonary metastases. Chemotherapy offers no survival advantage in treating bulk metastases from OST; however, chemotherapy may prevent or cure micrometastatic disease not amenable to surgery. Goorin et al. reported on 113 patients treated with adjuvant therapy for primary OST. Adjuvant chemotherapy improved event-free survival over surgery alone (P = .00) for primary OST. Relapses occurred in the lungs in more than 80% of patients. Survival after relapse was not influenced by chemotherapy. The only factor associated with improved survival after relapse (in the lungs) was complete resection of all metastases, rendering the patient disease-free (P = .03). More recently, the value of chemotherapy for treatment of patients with pulmonary metastases from OST was examined by Antunes and colleagues in a review of 198 patients operated on for OST of the limbs. The patients were treated with a combination of chemotherapy and surgery. The patients received three cycles of preoperative chemotherapy with methotrexate, Adriamycin, and cisplatin. Patients underwent surgery approximately 1 month later and received chemotherapy postoperatively (Adriamycin and ifosfamide). With chemotherapy and surgery for pulmonary metastases, the 3-year survival rate was 61%, compared to 79% in patients without metastases. Of all patients with pulmonary metastases who died, they died of progressive pulmonary metastases. Chemotherapy to achieve a biologic response, followed by surgery for “salvage” and local control, followed by more chemotherapy for micrometastatic disease, is a reasonable and effective means of treatment of pulmonary metastases from OST. Patients with synchronous pulmonary metastases with their primary tumor have a worse survival rate, even with chemotherapy and complete resection.

SOFT TISSUE SARCOMAS

STTs comprise a family of nonossifying malignant neoplasms arising from mesenchymal connective tissues. As with OST, local recurrence is common (20%), and metastases are predominantly to the lungs (Fig. 52.2-4). Casson et al. evaluated determinants of 5-year survival in 58 patients who had complete resection and who were followed until death or for a minimum of 5 years. Absolute 5-year survival was 25% (15 of 58 patients). Favorable prognostic factors included TDT of more than 40 days, unilateral disease, three or fewer nodules identified on preoperative tomograms, two or fewer metastases resected, and tumor histology (median survival of 33 months for malignant fibrous histiocytoma vs. 17 months for all others). Using multivariate analysis, the number of nodules (four or more) was the most significant prognostic indicator. The addition of tumor histology (malignant fibrous histiocytoma) improved the predictive ability of this model.

![FIGURE 52.2-4. A: Overall survival for patients with pulmonary metastases from soft tissue sarcoma. Patients were selected for surgery based on the potential for complete resection of their metastases. The 5-year survival rate was 25%. (From ref. 103, with permission.) B: Survival for resectable and nonresectable patients with pulmonary metastases from soft tissue sarcoma. Patients with complete resection have an associated survival advantage over patients with incomplete resection or unresectable metastases. (From ref. 103, with permission.)](image)

One study evaluated 67 patients with histologically documented pulmonary metastases from STS treated at the National Cancer Institute. Significant preoperative predictors of enhanced survival included TDT (more than 20 days), number of metastases on preoperative tomograms (four or fewer nodules), and the DFI (more than 12 months). Predictive ability was improved when all three prognostic factors were combined. These patients represent the patients who have the best response (i.e., prolonged postresection survival) to pulmonary metastasectomy.

Patients with recurrent pulmonary metastases and complete resection also have improved postresection survival. Increased age and female gender were associated with an increased risk of death from disease in resected patients with recurrent pulmonary metastases in contrast to initial isolated pulmonary
metastases. Resectable patients and those with one metastasis have the best postresection survival.

Chemotherapy given before resection of pulmonary metastases has variable impact on postresection survival. In a study of patients with pulmonary metastases from STS, chemotherapy (doxorubicin, cyclophosphamide, and dacarbazine) was given before metastasectomy. Time from treatment initiation to thoracotomy ranged from 1 to 57 months. Patients were grouped according to response. Five patients had a complete response (not surgically confirmed) and recurred 5 to 57 months later. Seven patients had a partial response. Twelve patients had either no change or progression. Thirty-eight procedures were performed. Resectable patients had a median survival of 30 months and an actuarial 5-year survival rate of 25% (see Fig. 52.2-4A).

Complete resection was associated with an improved survival compared to unresectable patients (see Fig. 52.2-4B). No differences were found in postresection survival between any groups. Postthoracotomy survival cannot be predicted from initial response to this chemotherapy regimen.

Adriamycin and ifosfamide have activity in more than 20% of patients with metastatic sarcoma. In addition, the combination of both chemotherapeutic agents may be greater than either single agent. The value of chemotherapy as an adjuvant is unknown, but several studies suggest a modest relapse-free and survival benefit. The authors correctly note that patients with STSs should be studied in prospective clinical trials. Newer and more active chemotherapeutic agents are needed.

**CHILDHOOD SARCOMAS**

Primary sarcomas of childhood, such as Ewing's sarcoma and rhabdomyosarcoma, commonly spread to the lungs; however, other sites of metastasis are frequent, with the exception of metastases associated with OST. Chemotherapy remains the major treatment modality for metastasized sites in multiple sites. Pulmonary resection for metastases may be required to document metastases in the lungs or to assess the tumor's response to chemotherapy or the viability of the remaining tumor. Resection of all disease in the lung may enhance postresection survival in these children with resectable metastases. Children undergoing median sternotomy for resection of pulmonary metastases from OST have almost a complete recovery of preoperative pulmonary function.

Ewing's sarcoma and OST metastasize preferentially to the lungs in children and may be resected. Patients with resectable pulmonary metastases from Ewing's sarcoma have prolonged survival (actuarial 5-year survival rate, 15%; median, 28 months) compared to those who explored but found to have unresectable metastases (no survivors beyond 22 months; median survival, 12 months; P = .0047). Patients with four or fewer nodules have better survival than patients with four or more nodules. Other studies support these findings.

OST metastasizes preferentially to the lungs. Resection of pulmonary metastases from OST also results in prolonged postresection survival. Adjuvant therapy, such as chemotherapy or lung irradiation, may also be valuable, particularly for micrometastases. Post resection survival may be at least as high as 40% at 5 years.

**NONPULMONARY METASTASES FROM SARCOMAS**

Location of sarcomatous recurrence or metastases may vary by the original location or histology of the primary tumor. Biopsy of suspicious lesions is needed to confirm the presence of local recurrence or distant metastases. A needle biopsy, or a core biopsy, may be considered.

Metastases from OST and STSs occur most commonly in the lungs but may also occur in other organs. Potter et al. noted that only 53% of recurrences in those patients completely resected of primary sarcoma reoccurred in the lung. In another early study of 255 patients with STS treated with preoperative chemotherapy and radiation followed by limb-sparing surgery, 85 patients developed metastatic disease (isolated local recurrence, 13; isolated pulmonary metastases, 43; lung and other, 11; and multiple sites, 18). Poor 2-year survival rate (less than 10%) occurred in those patients with multiple recurrence sites. Resection of isolated metastases appears to benefit a portion of patients with metastatic disease. More recently, Billingsley et al. noted that, in patients with primary extremity sarcoma, 23% of all patients develop metastases. Of these patients, 73% develop pulmonary metastases. Other sites of metastasis include the skin and soft tissues of the head and neck, trunk, and extremities.

In contrast to the expected pulmonary site for metastases, myxoid liposarcomas may metastasize preferentially to extrarosacric sites. In one study from the University of Texas M. D. Anderson Cancer Center in Houston, 51 of 102 patients with myxoid tumors had 33 distant recurrences. Extrapolomorphous soft tissue sites were the most common (e.g., the retroperitoneum, chest wall, pleura, pericardium, pelvic sidewall, and soft tissue of the back; n = 31), whereas pulmonary metastases were rare (n = 2). In this study, pleomorphic tumors more frequently recurred in the lung (10 of 18 patients recurred: three of ten extrapolumorphous, seven of ten pulmonary) than did the myxoid tumors (P < .05; myxoid vs. pleomorphic).

Angiosarcoma is a high-grade aggressive sarcoma with local recurrences likely in 20% of patients and distant metastases in 49%. The location of metastases is commonly the lungs, lymph nodes, soft tissues, bone, liver, and other sites.

In another study of 981 patients with sarcoma, 65 were noted as having developed hepatic metastases. Most patients (n = 61) had an intraabdominal primary site of high-grade leiomyosarcoma. Even with resection in 14 patients, all recurred; however, a median survival of 30 months was achieved. The opportunity for complete resection of hepatic metastases is rare, but complete resection of hepatic metastases must be considered to obtain a survival advantage.

In patients with brain metastases from STSs, complete resection may also provide a survival advantage (14 months vs. 6 months) compared to patients with incomplete resection. The authors concluded that complete resection of brain metastases from STS patients with a good performance status (Kamofsky performance score greater than 70) is associated with a good prognosis. Even if synchronous lung metastases were present, complete resection of all metastases provided the patient with a survival of 11.8 months (median).

**COLORECTAL NEOPLASMS**

Colorectal metastases commonly spread to local or regional nodes or are trapped in the liver through the portal venous drainage. Patients with prior colorectal neoplasms have had pulmonary metastases resected with prolonged postresection survival. An absolute distinction cannot be made between a single carcinomatous metastasis and a primary bronchogenic carcinoma except by direct visual comparison between the two neoplasms. As with other isolated pulmonary metastases, patients with pulmonary metastases from colorectal carcinoma may be resected safely with low morbidity and mortality and long-term survival (see Fig. 52.2-4).

Reports describe 5-year survival rates ranging from 21% up to 50% after resection of pulmonary metastases from colon carcinoma. Differences in age and race, location of the metastatic and location, grade, and stage of the primary colorectal cancer are not associated with either improved or worsened survival after resection of these metastases. Patients with metastasectomy survival for cure may also be candidates for resection of pulmonary metastases. Sauter et al. evaluated 49 patients with isolated pulmonary metastases (n = 18) and hepatic metastases (n = 31). Patients with pulmonary metastases had a 47% 5-year survival rate compared to patients with hepatic metastases (5-year survival, 19%). Of 1578 patients treated for colon and rectal cancer, 117 of 1013 patients with rectal carcinoma (11.5%) and 20 of 565 patients with colon cancer (3.5%) recurred in the lungs. In 66 patients who underwent resection of pulmonary metastases from colorectal adenocarcinoma, patients with a solitary metastasis had a longer postresection survival than others. The 5-year survival rate was 38% in both studies. In another study of 62 patients, metastases less than 3 cm in diameter were associated with improved survival.

In a series from the Mayo Clinic, McAfee et al. reported 139 patients who underwent resection of pulmonary metastases from colorectal carcinoma. Operative mortality was 1.4%. Overall, the 5-year survival rate was 30.5%, and the median follow-up was 7 years. Patients with a solitary pulmonary metastasis and those with a preoperative carcinoembryonic antigen (CEA) level of less than 4.0 ng/mL had a better postthoracotomy than others. A longer DFI and metastases smaller than 3 cm in diameter were not associated with improved survival.

Patients with resection of colon metastases from the lung and the liver have a survival advantage with complete resection. Forty-eight patients had both liver and lung metastases. Twenty-five patients underwent resection of these metastases, and the remaining 23 patients did not. Median survival was longer after resection of the last metastasis than in those individuals who did not undergo resection (16 months vs. 6 months; P < .001). The authors also noted that patients with metachronous resections survived longer than patients with synchronous resections (median of 70 months vs. 22 months; P < .001). Robinson et al. noted that the ideal candidate for resection is a patient younger than 50 years old with a solitary liver metastasis and a 4-year interval between the colorectal cancer resection and the occurrence of the pulmonary metastasis. The patient least suited for resection is one older than 70 years with multiple liver metastases and synchronous
In patients with colorectal metastases to both liver and lung, complete resection is generally associated with improved survival. Whether the liver metastases occur first and then the lung metastases, or whether lung metastases occur first followed by liver metastases, complete surgical resection tends to be associated with longer survival. Poorer survival was noted in those patients who cannot be completely resected or who are deemed unresectable without operation. Of the total population of patients with colorectal metastases, those individuals with completely resectable lung or hepatic metastases represent a small percentage and one with the most favorable "biology" of the tumor. The surgeon can take advantage of this biologically favorable subset of patients. With complete resection of both lung and hepatic metastases, survival may be enhanced.

**BREAST CARCINOMA**

Patients with metastases from breast carcinoma usually do poorly because metastases occur in multiple sites. Patanapanhan and colleagues \[34\] described 145 patients with metastatic breast carcinoma (145 of 558; 26%) in whom bone (51%), lung (17%), brain (16%), and liver (6%) metastases occurred. Overall median survival was 12 months for patients with lung metastases, most of whom were treated with palliative chemotherapy, irradiation, or both. \[35\] Lanza and associates \[36\] reviewed 44 women with metastatic breast cancer who underwent pulmonary resection for new pulmonary lesions. Seven patients were excluded who had benign nodules (n = 3) or unresectable metastases (n = 4). In 37 resectable patients, actuarial 5-year survival was 50% (Fig. 52.2-5). A DFI of more than 12 months was associated with a longer median survival (62 months) and 5-year survival rate (57%) compared with patients with a DFI of less than 12 months (15 months median; 0% 5-year survival; \(P = .004\)). Estrogen receptor–positive status tended to be associated with a longer postthoracotomy survival (\(P = .098\)). Another favorable prognostic factor included positive receptor status of the primary tumor that was associated with improved 3-year survival (61%) compared to negative receptor status (38%). Resection of solitary metastasis resulted in a 35% 5-year survival rate compared to 0% for resection of five or more metastases. \[36\] More recently, favorable selection of patients has enabled survival to increase up to 62% at 5 years in one series. \[37\]

**TESTICULAR NEOPLASMS**

Nonseminomatous testicular tumours can be diagnosed by the occurrence of new pulmonary nodules identified on CXR or by CT scan. \[38\] Metastatic testicular seminoma most commonly is identified as mediastinal nodal enlargement. CT scan, therefore, is more accurate in diagnosis of seminomatous metastases than plain chest roentgenograms. \[39\]

Cytoreductive surgery for disseminated nonseminomatous germ cell tumors of the testis may be performed after chemotherapy for removal of residual metastatic disease. The response to chemotherapy may be assessed when no further reduction in size of the nodules is noted. The majority of patients require retropertioneal lymph node dissections (69%), although thoracotomies may be required in 18% of patients. Several authors \[37\] examined 43 patients who previously had undergone complete resection of hepatic metastasis and then developed pulmonary metastases. The median survival was 19 months, and the 5-year survival was estimated to be 11%. Patients with a CEA of more than 0.5 ng/mL had a significantly lower probability of survival than those with lower levels (less than 0.5 ng/mL; \(P = .0018\)).

The value of repeat surgical resection of pulmonary metastasis has not been as well studied as individuals having only one resection. In one report of 396 operations in 330 patients, the authors identified a subgroup of 35 patients who had undergone reoperation for pulmonary metastasis. In this group, the 5- and 10-year survival rates were 48% and 28%, respectively. The favorable prognostic factors included a DFI of more than 1 year. No survival advantage was associated with histology (epithelial carcinoma, osteosarcoma, or STS). In this patient population, successful repeat surgical resections of pulmonary metastasis and survival advantage are probably related to a favorable biologic behavior. The specific criteria for this favorable behavior are not yet known. \[27\]

**GYNECOLOGIC NEOPLASMS**

Fuller and colleagues \[40\] from the Massachusetts General Hospital reviewed a 40-year experience of treating 15 patients with pulmonary metastases from gynecologic cancer, which included primary tumors involving the cervix (6), endometrium (3), and ovary (2), as well as two uterine sarcomas and two choriocarcinomas. The 5-year survival rate was 36%. Lesions less than 4 cm in diameter and a DFI of more than 36 months were associated with prolonged survival.

Levenback et al. \[41\] reviewed 45 patients with pulmonary metastases from uterine sarcomas. Most patients (71%) had unilateral lesions, and 51% had only one lesion. The 5-year survival rate was 43%. Unilateral metastases or fewer numbers of metastases were not significantly associated with prolonged survival.
Algorithms have been developed to identify pulmonary metastases. For example, oncogene expression present in the primary tumor can be used to discriminate between primary bronchogenic adenocarcinoma and colon carcinoma metastatic to the lung. 

To approach pulmonary metastases, a lateral thoracotomy incision is typically used. A generous wedge excision or lobectomy and mediastinal lymph node dissection should be performed. The final histologic type of the lesion is important to determine. If the lesion were a second primary neoplasm, less desirable is a generous wedge excision and mediastinal lymph node dissection, because local control may be limited.

If the lesion is a solitary metastasis, a primary bronchogenic carcinoma, or a benign process, the recommended treatment for such a solitary lesion is bronchoscopy. The treatment of solitary metastases is not well established, and outcomes are limited. 

## MELANOMA

The overall biologic behavior of melanoma cannot be predicted. Most commonly, pulmonary metastases occur in addition to other visceral sites, and overall long-term survival is poor. Immunotherapy has been used with some favorable results. In the rare patients who present with isolated pulmonary metastases, resection may be associated with long-term survival. 

The current 5-year survival rate ranges from 4.5% to 25%. In a large series of 1521 patients with American Joint Committee on Cancer stage IV melanoma, 5-year survival was only 4% (median survival, 8.3 months). 

Gorenstein and colleagues evaluated 56 patients with histologically proven pulmonary metastases from melanoma. The overall postresection survival was 25% at 5 years. Patients with earlier primary-stage melanoma, or patients with metastases to the lungs as the first site of metastasis, had longer postresection survival than other patients. Location of the primary tumor, histology, thickness, Clark level, nodal metastases, TDT, or type of resection of the primary tumor was not associated with improved postresection survival. 

Harpole et al. evaluated pulmonary metastases in 945 patients with melanoma out of a population of 7564 melanoma patients. Bilateral and multiple metastases were present in the majority of these patients. Multivariate predictors of survival included complete resection, DFI, chemotherapy, two or fewer metastases, negative lymph nodes, and histologic type. The 5-year survival rate for all patients (n = 7564) was 4%, in contrast to 20% 5-year survival in patients with pulmonary metastases.

## SQUAMOUS CELL CARCINOMA

Patients with primary SCC outside the lungs frequently have disease metastasize to the lungs. These secondary lung neoplasms may be resected with subsequent survival benefit. 

With solitary pulmonary lesions after treatment of primary SCC elsewhere in the body, the origin of the lesion is uncertain. The lesion may represent a solitary metastasis, a primary bronchogenic carcinoma, or a benign process. The recommended treatment for such a solitary lesion is bronchoscopy.

Thoracic exploration and excisional biopsy. If a SCC is identified, a lobectomy and mediastinal lymph node dissection should be performed in the same manner as if the lesion were a second primary neoplasm. Less desirable is a generous wedge excision and mediastinal lymph node dissection, because local control may be limited.

Finley et al. described factors associated with improved survival in patients with SCC metastases from head and neck cancers. These included complete resection, control of primary tumor, early stage of the head and neck primary, one nodule on CR, and longer DFI (more than 2 years) from primary resection. Complete resection of all malignant disease was associated with a 5-year survival rate of 29%. The number of nodules was not significantly associated with survival. In eight patients with more than one nodule, median survival was 2 years, and no 5-year survivors were reported. Therefore, the benefits of resection of multiple pulmonary metastases from head and neck primary SCC are not completely clear. In another study of 44 patients, 5-year survival after pulmonary resection was 43%. Mazor et al. noted that single nodules, primary tumor stage, or absence of locoregional recurrence were not associated with enhanced survival. The presence of mediastinal disease was associated with the worst outcome.

Leff et colleagues attempted to correlate primary carcinomas of the head and neck with subsequent development of pulmonary metastases or second primary lung carcinomas. An algorithm was used to consider the DFI, histology, radiographic findings, and characteristics of the lung lesion, as well as the identification of mediastinal lymphadenopathy. The authors recommended that treatment of indeterminate lesions be treated as primary lung carcinomas (e.g., with lobectomy and mediastinal lymph node dissection) because this strategy provides the best local control of the disease and potential for cure.

## WILMS' TUMOR

Patients with Wilms' tumor may present with pulmonary metastases at diagnosis or relapse after initial treatment. 

Early diagnosis using CT may identify metastases in up to 36% of patients. 

Pulmonary metastases may be resected safely from children with Wilms' tumor. In contrast, 211 patients entered on the National Wilms' Tumor Study whose initial relapse was in the lungs did not show any survival advantage to resection of pulmonary metastases compared to treatment with chemotherapy and whole lung irradiation.

## METASTASIS OR PRIMARY BRONCHOGENIC CARCINOMA?

Pulmonary metastases from sarcomas or other distinctive nonpulmonary neoplasms are usually easy to diagnose. However, solitary carcinomatous metastasis from breast or colon, or SCC metastasis from head and neck primary tumors, are difficult to distinguish from primary lung carcinoma. Patients with two or more pulmonary nodules can be considered to have metastases. In tumors without a propensity for bilaterality (e.g., nonsarcomatous histology), a solitary pulmonary nodule may be approached through a lateral thoracotomy incision. A generous wedge excision or lobectomy and mediastinal lymph node dissection should be performed. The final pathology may suggest histology amenable to adjuvant therapy.

Traditionally, a comparison of the primary neoplasm and the lung nodule using light microscopy has been the only method for determining origin of the lung nodule or neoplasm. Electron microscopy or specific molecular or genetic characteristics may identify more precisely the origin of such neoplasms. Monoclonal antibodies can assist in discriminating between primary bronchogenic adenocarcinoma and colon carcinoma metastatic to the lung. 

Characteristics of amplified K-ras oncogene expression present in the primary tumor can be used to identify pulmonary metastases. Monoclonal antibodies can identify colorectal carcinoma metastases. The monoclonal antibody was not sufficient to discriminate primary lung from metastatic adenocarcinoma. Flow cytometry and DNA analysis have been used to describe primary carcinomas of the lung and to distinguish them from metastases.

Algorithms have been developed for patients with SCCs of the head and neck who develop pulmonary nodules after treatment. Characteristics of metastases and of primary lung carcinoma were examined in an attempt to better direct subsequent therapy.
RECURRENT PULMONARY METASTASES

If pulmonary metastases recur in the lungs, resection can again be accomplished safely with prolonged postthoracotomy survival. Patients are screened by the criteria in Table 52.2-2. Patients with pulmonary metastases may undergo multiple procedures for re-resection of metastases, with prolonged survival after complete resection. Several studies have reviewed results of multiple resections for recurrent pulmonary metastases. Rizzoni and associates described 29 patients with recurrent pulmonary metastases from STSs who underwent two or more resections of pulmonary metastases. Patients with favorable tumor biology [resectable metastases, longer TDT, three or fewer nodules, longer DFI (more than 6 months)] had longer survival. No operative mortality occurred, and the complication rate was 7.5%. Median survival was 14.5 months and overall 5-year survival was 22%. Resectable patients had a median survival of 24 months. These findings were confirmed by Casson and colleagues, who described 39 patients with adult STSs. Thirty-four patients were resectable (median survival, 26 months; 5-year survival, approximately 32%). Unresectable patients had a median survival of 7 months. Survival after resection of a solitary recurrent metastasis was 65 months (median) compared to patients with two or more nodules (median, 14 months; \( P = .01 \)).

EXTENDED RESECTION OF PULMONARY METASTASES

Pneumonectomy or other extended resection of pulmonary metastases may be performed safely in selected patients with associated long-term disease-free survival. Fewer than 3% of all patients undergoing resection of pulmonary metastases will require an extended resection. Pneumonectomy or en bloc resection of pulmonary metastases with chest wall or other thoracic structures, such as diaphragm, pericardium, and superior vena cava, have been performed in a small number of patients with good results. In this series of pneumonectomy (\( n = 19 \)) and other extended resection (\( n = 19 \)), the 5-year actuarial survival rate was 25%. Mortality was 5% and occurred in those patients having pneumonectomy often after multiple prior wedge resections for metastases.

Pneumonectomy is performed infrequently for resection of pulmonary metastases. The need for pneumonectomy may be evident in the large metastases that involve the majority of one lung and that compress the heart and shift the mediastinum (Fig. 52.2-6). In a French study of 42 patients treated over 10 years, 29 patients underwent pneumonectomy for sarcoma; 12 for carcinoma; and one for a lipoma. Most metastases were centrally located. Two postoperative deaths occurred, and four patients had major complications; five patients (12%) had recurrences in the residual lung. The median survival was only 26.5 months, and the 5-year survival rate was 16%. The standard surgical mortality for operations for pulmonary metastases is less than 1%. Patients with large centrally located metastases may require pneumonectomy for complete resection. Although mortality for pneumonectomy for pulmonary metastases corresponds to mortality for other histologies, the 5-year survival rate of only 16% demands careful selection of patients before resection. The authors suggest that young patients, those with a long DFI, and those with normal CEA levels (e.g., patients with metastases from colorectal carcinoma) be considered as potential candidates for pneumonectomy for pulmonary metastases.

In this series of pneumonectomy, 133 patients (2.8%) had undergone pneumonectomy for pulmonary metastases between 1962 and 1994. Forty-four percent of these patients underwent complete resection, and the 30-day mortality rate was 3.6%. Five-year survival was 20% with complete resection. For incomplete resection, the perioperative mortality was 19%, and the majority did not survive beyond 5 years. The authors identified favorable prognostic factors of single metastasis, negative mediastinal lymph nodes, and complete resection. The authors concluded that pneumonectomy might be performed safely with adequate long-term survival.

Intraatrial extension of sarcoma through the pulmonary vein is rare but may also be safely treated with pulmonary resection and pneumonectomy, and resection of the tumor from the left atrium (Fig. 52.2-7). Extracorporeal circulatory support (cardiopulmonary bypass) is required.

### Table 52.2-2. Criteria for Resection of Pulmonary Metastases

| A | Chest roentgenogram with a massive pulmonary metastasis from malignant fibrous histiocytoma compressing and shifting the mediastinum into the contralateral hemithorax. Compression of the heart and airway is noted. Impairment of ventilation to the involved hemithorax and secondary compression of the contralateral hemithorax further impairs ventilation. | B | Chest computed tomography with a massive pulmonary metastasis from osteogenic sarcoma compressing the superior vena cava, right heart, and right lung, and shifting the mediastinum into the left chest. Resection often requires extracorporeal support to allow decompression and manipulation of the heart and pulmonary veins. An approach to the right pulmonary artery and veins and the right mainstem bronchus via a median sternotomy allows for control of the pulmonary vasculature and airway before removal of the tumor. |

The value of pneumonectomy was also examined by retrospective review of the International Registry of Lung Metastases. Of the 5206 patients who were enrolled, 133 patients (2.6%) had undergone pneumonectomy for pulmonary metastases between 1962 and 1994. Eighty-four percent of these patients underwent complete resection, and the 30-day mortality rate was 3.6%. Five-year survival was 20% with complete resection. For incomplete resection, the perioperative mortality was 19%, and the majority did not survive beyond 5 years. The authors identified favorable prognostic factors of single metastasis, negative mediastinal lymph nodes, and complete resection. The authors concluded that pneumonectomy might be performed safely with adequate long-term survival.

Intraatrial extension of sarcoma through the pulmonary vein is rare but may also be safely treated with pulmonary resection and pneumonectomy, and resection of the tumor from the left atrium (Fig. 52.2-7). Extracorporeal circulatory support (cardiopulmonary bypass) is required.
with OST and with fewer than six metastases has been examined in patients with pulmonary metastases from multiple histologies to evaluate the influence of number of metastases resected. Patients number of pulmonary metastases at the time of resection, the better the postresection survival. Postresection survival after complete resection of pulmonary Nodules on preoperative roentgenograms usually correspond to the number of metastases present; however, not all nodules are malignant.

**NUMBER OF METASTASES RESECTED**

Bilateral pulmonary metastases do not influence postresection survival; the number of nodules is a more precise prognostic indicator. Identified on full lung tomography, those with STS with five or fewer nodules. CT scans are more sensitive than other studies, and better survival was noted in those patients with OST with fewer than four nodules.

In patients with OST or STS, better postresection survival was found in patients with fewer number of nodules identified on preoperative full lung linear tomograms or CT scans of the chest. CT scans are more sensitive than other studies, and better survival was noted in those patients with OST with fewer than four nodules and those with STS with five or fewer nodules. Full lung tomograms were performed in several older studies. Patients with OST with fewer than four metastases identified on full lung tomography, or four or fewer nodules in STS, had better postresection survival than those individuals with more nodules. Unilateral or bilateral pulmonary metastases do not influence postresection survival; the number of nodules is a more precise prognostic indicator.

**NUMBER OF METASTASES RESECTED**

Nodules on preoperative roentgenograms usually correspond to the number of metastases present; however, not all nodules are malignant. Usually, the fewer the number of pulmonary metastases at the time of resection, the better the postresection survival. Postresection survival after complete resection of pulmonary metastases has been examined in patients with multiple histologies to evaluate the influence of number of metastases resected. Patients with OST and with fewer than six or four or fewer metastases resected, or patients with STS and fewer than 16 metastases, had a better postresection survival than patients with more metastases resected. Postresection survival for number of metastases resected after complete resection has been examined in patients with

**PROGNOSTIC INDICATORS**

Predictors for improved survival have been studied retrospectively for various tumor types to identify selected patients who will benefit from pulmonary metastasectomy (Table 52.2-3). These prognostic indicators are clinical, biologic, and molecular criteria that describe the biologic interaction between the metastases and the patient and their association with prolonged survival. These prognostic indicators may be used to identify those patients who are most likely to benefit after resection of pulmonary metastases.

**TABLE 52.2-3.** Prognostic Indicators Associated with Better Postresection Survival for Patients with Pulmonary Metastases from Various Tumor Types

Analyses of prognostic indicators in groups of patients with pulmonary metastases from heterogeneous tumors describe prolonged survival in patients with resectable metastases. Resectable patients, longer DFI, longer TDT, fewer numbers of metastases, or solitary metastasis are prognostic indicators generally associated with prolonged postresection survival. Prognostic indicators should be studied in patients with the same primary tumor to define their association with postresection survival. A wide variability exists in the characteristics of pulmonary metastases from different primary neoplasms and the subsequent survival of patients with these metastases. The study of prognostic indicators from the same primary neoplasm yields the most precise information on association with postresection survival. Age or gender does not usually influence postthoracotomy survival. Neither age nor gender should be considered as prognostic factors.

**DISEASE-FREE INTERVAL**

The DFI extends from resection of the primary tumor until pulmonary metastases are detected. A short DFI may indicate a poor prognosis because metastases may be multiple and growing rapidly. A longer DFI may represent a less biologically aggressive tumor and correlate with a longer postresection survival.

The DFI may also be defined as the time between resection of the pulmonary metastases and recurrence of metastases in the lungs or elsewhere. DFIs of more than 12 months are usually associated with improved survival in patients with breast carcinoma, colorectal carcinoma, OST, and renal cell carcinoma. Patients with pulmonary metastases from OST and a DFI of more than 6 to 12 months demonstrated a survival advantage in contrast to others who demonstrated no such advantage. In STS, a DFI of more than 12 months was usually associated with a better postresection survival. Evaluation of patients with Ewing’s sarcoma did not reveal differences in survival based on DFI.

**LOCATION AND STAGE OF PRIMARY TUMOR**

Postresection survival is not usually influenced by the specific anatomic location of the primary tumor. Postresection survival in patients with more advanced stage primary neoplasms does not usually differ from patients with earlier stage disease. Still, initial or primary stage may suggest the biologic aggressiveness of the tumor. Schiappack et al. found that a negative nodal status predicted improved postresection survival for patients with breast cancer. McCormack et al. found better postthoracotomy survival in patients with Duke’s class A colorectal carcinoma (5-year survival, 37.5%) compared to Duke’s class C patients (5-year survival, 15%), although this was not confirmed by the study by McAfee et al.

**NUMBER OF NODULES ON PREOPERATIVE IMAGING STUDIES**

CT has replaced linear tomograms as the examination of choice in patients with suspected pulmonary metastases. CT of the chest provides a sensitive and specific study for patients with pulmonary metastases. CT of the chest is sensitive but less specific than conventional linear tomography or CXR. Nodules may or may not represent metastases. Theoretically, earlier detection and treatment of metastases can improve survival. Laterality (unilateral or bilateral) of pulmonary metastases does not directly influence postresection survival; the number of nodules is a more precise prognostic indicator.

In patients with OST or STS, better postresection survival was found in patients with fewer number of nodules identified on preoperative full lung linear tomograms or CT scans of the chest. CT scans are more sensitive than other studies, and better survival was noted in those patients with OST with fewer than four nodules and those with STS with five or fewer nodules. Full lung tomograms were performed in several older studies. Patients with OST with fewer than four metastases identified on full lung tomography, or four or fewer nodules in STS, had better postresection survival than those individuals with more nodules. Unilateral or bilateral pulmonary metastases do not influence postresection survival; the number of nodules is a more precise prognostic indicator.

**NUMBER OF METASTASES RESECTED**

Nodules on preoperative roentgenograms usually correspond to the number of metastases present; however, not all nodules are malignant. Usually, the fewer the number of pulmonary metastases the better the postresection survival. Postresection survival after complete resection of pulmonary metastases has been examined in patients with pulmonary metastases from multiple histologies to evaluate the influence of number of metastases resected. Patients with OST and with fewer than six or four or fewer metastases resected, or patients with STS and fewer than 16 metastases, had a better postresection survival than patients with more metastases resected. Postresection survival for number of metastases resected after complete resection has been examined in patients with

**FIGURE 52.2-7.** Metastatic synovial cell sarcoma. The patient has an azygocoephalic mass abutting the left atrium and esophagus without direct invasion. The mass is confirmed by chest computed tomography (A) and magnetic resonance imaging (B). Pulmonary metastases were resected. Using hypothermic circulatory arrest, the patient also underwent complete resection of the posterior wall of the left atrium en bloc with the metastasis. Patch reconstruction of the posterior wall of the left atrium was required.
TUMOR-DOUBLING TIME

TDT is calculated \(^{42,43,44,45}\) by measuring the same metastasis on similar studies (e.g., serial chest roentgenograms) separated by a minimum of 10 to 14 days. The most rapidly growing nodule is selected, and changing diameters of the metastasis is plotted on semilogarithmic paper. A formula may be used to precisely calculate TDT:

\[
TDT = \frac{\ln(M2/M1)}{\ln(2)/T}
\]

where \(\ln\) is the natural logarithm, \(M1\) is the first measurement, \(M2\) is the second measurement, and \(T\) is the number of days between measurements.

Metastases from the same primary may or may not grow at similar rates, because differing growth rates between tumor nodules reflect heterogeneity of metastases from the primary. The TDT indirectly reveals the biologic nature or aggressiveness of the metastases, which influences the patient's postresection survival. The TDT may vary based on the size of the metastasis itself or the effect of chemotherapy.

Pulmonary metastases initially grow exponentially, and the growth rate slows with increased size. Growth may also be expressed by “Gompertzian” kinetics, \(^{156,157}\) which considers a gradual diminution in TDT with time and increased size of the metastasis. TDT only reflects the growth rate during the interval measured.

TDT is not a significant predictor of postresection survival in patients with pulmonary metastases from OST. \(^\text{158}\) TDT of more than 20 days in patients with STS resulted in a better postthoracotomy survival than those patients with rapid TDTs (less than 20 days). One study of patients with STS \(^\text{42}\) found no correlation between TDT and postresection survival.

RESECTABILITY

Complete resection consistently correlates with improved postthoracotomy survival for patients with pulmonary metastases. If pulmonary metastases cannot be completely removed, the postthoracotomy survival is shortened for patients with most tumors in comparison to those individuals completely resected.

ENDOBRONCHIAL OR NODAL METASTASES

Involvement of mediastinal lymph nodes from pulmonary metastases is rare. Udelsman et al. \(^\text{44}\) noted that patients with endobronchial metastases from adult STSs have a short postresection survival rate. Seven of 11 patients with endobronchial metastases lived 6 months or less. Jablons et al. \(^\text{45}\) found that survival is poor (5 months) in patients with mediastinal lymph node involvement from STSs compared to patients without nodal metastases (31 months).

MULTIVARIATE ANALYSIS OF PROGNOSTIC INDICATORS

Multivariate analysis of prognostic factors may define which patients are most likely to achieve long-term survival. Separate prognostic variables may be combined to enhance the predictive value for survival. Jablons et al. \(^\text{45}\) noted the DFI, gender, resectability, and truncal location in patients with pulmonary metastases from STSs to be the best predictors of postthoracotomy survival. Putnam et al. \(^\text{46}\) noted that a DFI of more than 12 months, a TDT of more than 20 days, and four or fewer nodules on preoperative full lung tomograms as a single prognostic indicator was the best predictor of postthoracotomy survival in patients with pulmonary metastases from STSs. Roth et al. \(^\text{47}\) compared prognostic indicators in patients with OST and STS. TDT, number of metastases on preoperative full lung tomograms, and DFI, when combined, improved predictive ability over any single indicator or pair of indicators.

NOVEL TREATMENT STRATEGIES

MOLECULAR AND GENETIC STRATEGIES

Molecular events associated with pulmonary metastases have been identified in patients with OST. Amplification of the MDM2 gene (the human homologue of a murine p53 binding protein) may regulate p53 protein function by inactivating the protein and deregulating or enhancing tumor growth. In one small study, \(^\text{42}\) no detectable MDM2 gene amplification in primary OST was found compared to 14% of metastases (three pulmonary metastases, one local metastasis). Amplification of MDM2 may be associated with metastases and tumor progression in OST.

In STS, alterations (mutations) of the p53 gene (a tumor suppressor gene) may provide for uncontrolled cell growth. Restoration of normal p53 (wild-type) in STS may provide for more controlled cell growth or even programmed cell death (apoptosis). In one in vitro study, \(^\text{48}\) transduction of wild-type p53 into STSs bearing mutated p53 genes altered the malignant potential of the tumor. After transduction, transfected cells expressed wild-type p53, decreased cell proliferation, decreased colony formation in soft agar, and demonstrated decreased tumor formation in severe combined immunodeficient (SCID) mice in vivo. The ability to restore wild-type p53 function in STS in vitro and in SCID mice may ultimately be considered as future therapy for patients with STS. \(^\text{49}\) Other investigations have shown that pulmonary metastases from STS can develop from clonal expansion of primary tumor cells bearing p53 mutations. \(^\text{50}\) Examination of tissue specimens from OST and STS demonstrated p53 mutations in 25% of OSTs, yet in only 1 of 16 metastases. \(^\text{51}\) Use of specific molecular markers may provide better selection of patients who will optimally benefit from surgery, chemotherapy, or other treatment modalities.

Other targets of gene therapy may include those chemotherapy-resistant tumors or those tumors with greater propensity for metastatic spread. Overexpression of the MDR1 gene product P glycoprotein is an important predictor of poor prognosis in osteosarcoma patients treated with chemotherapy. In these patients, the MDR phenotype is not de novo more aggressive (e.g., more metastatic); however, the poor outcome of patients with the MDR phenotype related to P glycoprotein overexpression is related to the cells' failure to respond to cytotoxic drugs.\(^\text{52}\)

In another study, \(^\text{53}\) 42% of patients with OSTs had metastases that expressed ErbB-2 and correlated with early development of pulmonary metastasis and poor survival. ErbB-2, therefore, may enhance tumor growth and promote metastases. These authors recommended that ErbB-2 might be considered as a prognostic factor for patients with osteosarcoma.

ErbB-2 protein is expressed in approximately 42% of osteosarcomas. It has been strongly correlated with early pulmonary metastasis and poor survival. ErbB-2 may enhance tumor aggressiveness and metastasis in osteosarcoma. As a marker, ErbB-2 may be useful as a prognostic indicator. \(^\text{54}\)

A rodent model of OST has been developed with high propensity for pulmonary metastases. In this metastatic tumor model, matrix metalloproteinase 2 activity is increased as well as expression of vascular endothelial growth factor messenger RNA. \(^\text{55}\)

Gene therapy strategies are being studied also. Systematic delivery of recombinant adenovirus (Ad) vector containing herpes simplex virus thymidine kinase (TK) gene (with an Osteocalcin (OC) promoter (Ad-OC-TK)) supplemented with the prodrug acyclovir (ACV) may be an effective strategy for osteosarcoma metastases to the lungs. \(^\text{56}\)

Preliminary studies noted that, after Ad-OC-beta-gal administration, specific beta-gal expression was found in tumor cells deposited in the lung. Induced rat osteogenic lung metastases in nude rats were followed by systemic Ad-OC-TK and intraarterial ACV treatment, resulting in decreased numbers of tumor nodules and increased survival in treated animals compared to controls. Ad-OC-TK/ACV may be a future treatment for pulmonary metastases from osteosarcoma. Other preclinical treatment methods may include nebulized interleukin-2 liposomes. \(^\text{57}\)

REGIONAL DRUG DELIVERY TO THE LUNG
Novel drug delivery systems may enhance chemotherapy treatment effects by increasing drug concentration in lung tissues and minimizing systemic effects of such treatment. In many patients, surgery has been used as salvage treatment after maximal chemotherapy response has been achieved. Systemic toxicity may limit the amount of chemotherapy given to an individual patient. Regional delivery of chemotherapy may be delivered to pulmonary tissue in significantly higher concentrations than with systemic delivery. Minimal to no systemic toxicity was noted. In many patients, surgery has been used as salvage treatment after maximal chemotherapy response has been achieved. Systemic toxicity may limit the amount of chemotherapy given to an individual patient. Regional delivery of chemotherapy may be delivered to pulmonary tissue in significantly higher concentrations than with systemic delivery. Minimal to no systemic toxicity was noted. In many patients, surgery has been used as salvage treatment after maximal chemotherapy response has been achieved. Systemic toxicity may limit the amount of chemotherapy given to an individual patient. Regional delivery of chemotherapy may be delivered to pulmonary tissue in significantly higher concentrations than with systemic delivery. Minimal to no systemic toxicity was noted. In many patients, surgery has been used as salvage treatment after maximal chemotherapy response has been achieved. Systemic toxicity may limit the amount of chemotherapy given to an individual patient. Regional delivery of chemotherapy may be delivered to pulmonary tissue in significantly higher concentrations than with systemic delivery. Minimal to no systemic toxicity was noted. In many patients, surgery has been used as salvage treatment after maximal chemotherapy response has been achieved. Systemic toxicity may limit the amount of chemotherapy given to an individual patient. Regional delivery of chemotherapy may be delivered to pulmonary tissue in significantly higher concentrations than with systemic delivery. Minimal to no systemic toxicity was noted. In many patients, surgery has been used as salvage treatment after maximal chemotherapy response has been achieved. Systemic toxicity may limit the amount of chemotherapy given to an individual patient. Regional delivery of chemotherapy may be delivered to pulmonary tissue in significantly higher concentrations than with systemic delivery. Minimal to no systemic toxicity was noted. In many patients, surgery has been used as salvage treatment after maximal chemotherapy response has been achieved. Systemic toxicity may limit the amount of chemotherapy given to an individual patient. Regional delivery of chemotherapy may be delivered to pulmonary tissue in significantly higher concentrations than with systemic delivery. Minimal to no systemic toxicity was noted. In many patients, surgery has been used as salvage treatment after maximal chemotherapy response has been achieved. Systemic toxicity may limit the amount of chemotherapy given to an individual patient. Regional delivery of chemotherapy may be delivered to pulmonary tissue in significantly higher concentrations than with systemic delivery. Minimal to no systemic toxicity was noted. In many patients, surgery has been used as salvage treatment after maximal chemotherapy response has been achieved. Systemic toxicity may limit the amount of chemotherapy given to an individual patient. Regional delivery of chemotherapy may be delivered to pulmonary tissue in significantly higher concentrations than with systemic delivery. Minimal to no systemic toxicity was noted. In many patients, surgery has been used as salvage treatment after maximal chemotherapy response has been achieved. Systemic toxicity may limit the amount of chemotherapy given to an individual patient. Regional delivery of chemotherapy may be delivered to pulmonary tissue in significantly higher concentrations than with systemic delivery. Minimal to no systemic toxicity was noted.
SECTION 52.3
Metastatic Cancer to the Liver

H. RICHARD ALEXANDER
CARMEN J. ALLEGRA
THEODORE S. LAWRENCE

INTRODUCTION
Metastatic cancer in the liver can represent the sole or life-limiting component of disease for many patients with a variety of tumor histologies, including colorectal cancer, ocular melanoma, neuroendocrine tumors, and, less commonly, other histologies. The liver is a common site of hematogenous metastases for tumors arising in the gastrointestinal tract, presumably because of the unique venous drainage through the portal venous system to the liver. On the other hand, factors that predispose ocular melanoma to metastasize almost exclusively to liver are unknown; liver metastases must occur through hematogenous spread via the arterial system. Once metastases to the liver are diagnosed, the prognosis is generally poor. Even with aggressive therapy, the median survival for patients with ocular melanoma in the liver is between 2 and 7 months and 12 to 24 months for patients with colorectal cancer. Because of the unique vascular anatomy of the liver, a number of regional therapies designed to maximize efficacy while minimizing systemic toxicity have been under clinical evaluation. For patients with colorectal cancer the ability to resect disease is associated with 5-year disease-free survival in 20% to 50% of patients, and patients with liver metastases from functional neuroendocrine tumor can derive substantial palliative benefit from resection. Infusional therapy is administered into the hepatic artery using intermittent percutaneous catheterization with or without particle embolization of the tumor neovasculature or via continuous hepatic artery infusional (HAI) therapy with indwelling implantable pumps. Local ablative therapy is administered via laparotomy or percutaneously placed probes or needles to deliver cryotherapy or radiofrequency ablation of tumors or direct injection of cytotoxic agents such as ethanol. Combined approaches have been used, such as adjuvant HAI after resection or local ablation, in an attempt to prolong disease control in the liver. Newer regional therapies, such as isolated hepatic perfusion (IHP) or intraarterial delivery of gene-modified viral vectors are being evaluated.

Much of the data regarding regional therapy for hepatic metastases relate to colorectal cancer because of its high incidence. It is estimated that 150,000 new cases of colorectal carcinoma occur annually in the United States and approximately 75,000 deaths occur. Synchronous hepatic metastases are identified in 10% to 20% of patients with colorectal cancer and are the sole or life-limiting component of disease in up to 60% of patients. Only a small proportion of patients have resectable disease and therefore the vast majority of patients are best suited for a regional therapy as mentioned previously. This section reviews the natural history of patients with hepatic metastases and the advances in imaging modalities. The results of resection alone or with adjuvant therapy for patients with resectable disease are presented as well as results with other regional therapies such as local ablative techniques, HAI therapies, and newer approaches such as IHP.

NATURAL HISTORY OF LIVER METASTASES
The natural history of hepatic metastases from various histologies has been largely derived from retrospective studies and without the benefit of routine imaging modalities currently available. For patients who are staged using computed tomography (CT), magnetic resonance imaging (MRI), or, for patients with neuroendocrine tumors, somatostatin receptor scintigraphy, survival may appear better than historic controls for whom the number and extent of hepatic metastases were not easily quantified (Fig. 52.3-1). In addition, it has become increasingly apparent that there is considerable variability in the rate of progression of disease in the liver. This is reflected by the fact that in patients with colorectal cancer metastatic to liver, there are occasional long-term survivors, and there is a considerable disparity between median and mean survival (see Fig. 52.3-1). In one series from Roswell Park Cancer Institute of 30 patients with untreated colorectal cancer metastatic to liver, the mean survival was 16 months, with a range of 2 to 58 months. A classification system for staging of hepatic metastases has been proposed based on the number and distribution of lesions in the liver. Heterogeneity in tumor progression has also been demonstrated in patients with neuroendocrine tumors metastatic to liver.

TABLE 52.3-1. Various Regional Treatments under Clinical Evaluation for Cancers Confined to the Liver

<table>
<thead>
<tr>
<th>Treatment Modality</th>
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<tr>
<td>Percutaneous Ethanol Injection</td>
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<tr>
<td>Interstitial Laser Photocoagulation</td>
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<tr>
<td>Cryotherapy Plus Adjunct Chemotherapy</td>
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<tr>
<td>Microwave Tissue Ablation Plus Adjunct Chemotherapy</td>
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<tr>
<td>Radiofrequency Ablation Plus Adjunct Chemotherapy</td>
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<tr>
<td>Intermittent Hepatic Artery Infusional Therapy</td>
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<tr>
<td>Percutaneous Ethanol Injection</td>
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<tr>
<td>Results of Whole Liver Irradiation with or without Chemotherapy</td>
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</table>

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In an older series of 125 patients with colorectal metastases to liver staged primarily with technetium 99 sulfur colloid scans, the overall median survival was 12.5 months. Extent of disease and histologic grade of the tumor were the two most important factors influencing survival. Those with four or more nodules, hepatomegaly or abnormal liver test results had a median survival of less than 12 months. The immediate cause of death was liver failure in almost 90% of patients despite the coexistence of metastases to other sites in 40% of patients. In another series of 175 patients with hepatic metastases from colorectal cancer, factors potentially influencing survival were subjected to a multifactorial analysis. Although median survival in the group was only 6.1 months, one patient survived for 67 months. Extent of disease as reflected by the number of hepatic nodules, bilobar disease, or abnormal liver test results was independently correlated with survival. Stage of the primary tumor and number of positive lymph nodes also correlated with outcome. In a series from the United Kingdom of 90 patients with colorectal cancer metastatic to liver there was a median survival of 10.3 months.

In a more recent series of 544 patients with unresectable colorectal liver metastases documented by laparotomy, CT, or ultrasound, the factors that independently predicted outcome on multivariate analysis were performance status, extent of liver disease (number of involved segments), abnormal liver test results (prothrombin time and alkaline phosphatase), and site of primary. Those with no adverse factors (i.e., normal performance status and liver test results) had a 1-year survival of 46%. The apparent benefit from chemotherapy in retrospective studies of patients with liver metastases from colorectal cancer and other histologies probably reflects selection bias rather than true treatment effect. In general, patient factors such as gender or age do not influence survival, whereas performance status, which reflects tumor burden, does.

In patients with treated primary ocular melanoma the overall 5-year survival is approximately 70%, but once metastases occur the liver is the sole or life-limiting component of disease in 70% to 80% of patients. Age older than 50 years and male gender are associated with a shorter survival after recurrence, but the most important factor influencing outcome is the presence of liver metastases (see Fig. 52.3-1). In one study, median survival in patients with recurrence was 19 months, but only 7 months when the liver was involved. Although survival is longer in patients with liver metastases diagnosed by screening (5 vs. 3 months) and in those receiving treatment (5 vs. 2 months), the differences in terms of individual patient benefit are negligible and highlight the grave prognosis associated with liver metastases.

Ayoub and coworkers reported outcome in more than 1500 patients with metastases from unknown primary tumors. Five hundred patients had metastases to liver, of whom 27% (135 patients) eventually had primary tumors diagnosed arising from lung, colon or rectum, or pancreas. The presence of liver metastases was associated with a significantly shorter survival, but was most favorable in those with neuroendocrine histology. Sulliff and coworkers have shown that the pattern of progression in patients with metastatic gastrinoma to liver is highly variable. Over a follow-up interval of 29 months, 5 of 19 (26%) demonstrated no growth of tumor, whereas 42% had rapid growth in less than 1 year. Tumor progression, most commonly in liver, is the main determinant of survival in patients with gastrinoma. For patients with other functional neuroendocrine tumors, liver metastases and the development of the uncontrolled sequelae from excess hormone production are the main causes of death.

**IMAGING OF HEPATIC METASTASES**

Currently there are several imaging options available for assessment of liver metastases. Considerable advancement in imaging technology has made it possible to accurately detect the number, size, and distribution of hepatic lesions and frequently distinguish between malignant or benign lesions. The most commonly used tests include CT scan, MRI, ultrasound, and, more recently, positron emission tomography using the glucose analogue, fluorodeoxyglucose. Ultrasound is commonly used for screening because of its availability and relative inexpensiveness, but has its most important application as an intraoperative modality to assess suitability for resection and to gauge the adequacy of treatment when using cryotherapy. In general, intraoperative ultrasound identifies 20% more occult lesions in the liver compared with CT scan and therefore should be used before any contemplated resection.

CT scan is used most commonly to assess a patient with possible hepatic metastases. It has the advantages of being widely available and, by using new generation rapid acquisition scanners, the entire chest, abdomen, and pelvis can be evaluated in a single study. Moreover, the use of rapid helical or spiral CT allows for a scan of the liver in a single breath hold, eliminating the problem of respiratory misregistration. Because liver tumors have a variable degree of vascularity and derive their perfusion from the arterial tree, CT arteriography has been used to enhance the sensitivity of the test, particularly for hypovascular lesions, but involves placement of a catheter and injection of contrast into the superior mesenteric artery with capture of images during both the arterial and portal venous phase of hepatic perfusion. Dual arterial and venous phase CT scans after intravenous injection of contrast agent using high-speed helical CT scanners are now commonly used in place of CT arteriography, but may have limited additional sensitivity for detection of hypovascular tumors compared with portal phase CT alone. On the other hand, because hypervascular lesions are frequently isoattenuating in relation to normal liver parenchyma, arterial phase helical CT detects more liver metastases than conventional portal venous phase CT in this setting.

MRI scanning is also used routinely and has particular advantages for imaging of focal liver lesions. Two contrast agents with liver specificity are currently being used: one is manganese pyridoxal disphosphate, a paramagnetic agent taken up by hepatocytes, and the other is superparamagnetic iron oxide particles, which are taken up by the reticuloendothelial system. The optimal MRI protocols for evaluation of liver lesions vary depending on the available equipment and contrast agents being used. Although there are disadvantages with MRI because of motion artifact from the heart or aorta, it can distinguish benign cysts or hemangiomas from malignant lesions based on characteristic findings on T1 versus T2 spin-weighted sequences.

Positron emission tomography scanning uses the glucose analogue, fluorodeoxyglucose, which is selectively retained in malignant tissue because of increased glucose metabolism compared with nonneoplastic tissue. It has been shown to have sensitivity comparable with CT scan and can often distinguish benign and malignant lesions, but has potential for false-positive findings in abscesses and false-negative findings in hepatocellular carcinoma. Somatostatin receptor scintigraphy has been used with increasing regularity and is extremely accurate in imaging neuroendocrine tumors, with the exception of insulinoma, and may be superior to MRI in detecting islet cell tumors in liver. In addition, because hemangiomas are not visible on somatostatin receptor scintigraphy, the study can be used to distinguish benign versus malignant lesions when there are equivocal findings on CT or MRI.

**RESECTION OF HEPATIC METASTASES**

**RESECTION OF METASTATIC DISEASE: TECHNICAL CONSIDERATIONS**

The benefit of resection in selected patients with hepatic metastases from colorectal cancer and potentially other histologies, such as neuroendocrine tumors, has been fairly well established in the literature. Several advances in hepatic surgery have made hepatic resection a more routine procedure with minimal patient morbidity. Initial evaluation of the abdominal cavity at exploration should be carefully done to exclude the presence of extrahepatic disease. Intraoperative ultrasound should be routinely used to screen for the presence of deep-seated or occult metastases, and resection should be based when possible on functional anatomic
considerations, including segmental resection, to preserve unaffected hepatic parenchyma and minimize blood loss during resection (Fig. 52.3-2). The liver is mobilized, including division of the falciform and left or right triangular ligaments, depending on the nature of the resection. A cholecystectomy is performed, and the small direct venous branches between the liver and vena cava are systematically isolated, ligated, and divided (Fig. 52.3-3). The division of the portal triad structures and hepatic vein on the side of resection are being done more frequently with the use of vascular stapling devices. It is usually possible to isolate and divide the hepatic vein in its extrahepatic position before commencing parenchymal dissection. Vascular inflow occlusion via the Pringle’s maneuver and maintenance of a low central venous pressure minimizes blood loss during dissection of the hepatic parenchyma. Extensive resection involving contiguous vena caval resection or reimplantation of the hepatic veins are rarely indicated but have been reported. Argon beam coagulation helps with hemostasis after resection. Drains are not routinely used in uncomplicated hepatic resection, and early ambulation of the patient is advisable. The mortality associated with major hepatic resection is less than 5% and is most commonly secondary to inadequate hepatic synthetic reserve (Table 52.3-2). Other complications from hepatic resection include biliary fistula, hemorrhage, and abscess or wound infection.

**FIGURE 52.3-2.** Segments of the liver used in planning hepatic resection. The principal plane divides the right and left lobes of the liver. Extent of hepatic resection planned on the basis of an understanding of the segmental anatomy of the liver has resulted in minimal morbidity and mortality associated with the procedure. (Modified from ref. 6.)

**FIGURE 52.3-3.** A: Technique of isolation and B: division of the direct venous tributaries between the inferior vena cava and the liver that are routinely divided before a right or left hepatic lobectomy. V, vein. (From ref. 4, with permission.)

**TABLE 52.3-2.** Results of Resection of Colorectal Liver Metastases from Selected Series

**RESULTS OF HEPATIC RESECTION FOR COLORECTAL CANCER**

The overall 5-year survival after resection of hepatic metastases in patients with colorectal cancer ranges from 25% to almost 40% in recent series (see Table 52.3-2). Factors associated with improved outcome after resection in most series include tumor- and treatment-related variables. Patient characteristics, such as age or gender, have not been identified as significant prognostic variables, but elevation in preoperative serum carcinoembryonic antigen levels is associated with poorer outcome in most series. Tumor-related factors associated with poor outcome after resection include positive lymph node status of the primary tumor, a disease-free interval between resection of the primary tumor and liver metastases less than 1 year, and the presence of extrahepatic disease, including regional periporal lymph nodes. With respect to the liver metastases, factors that generally reflect advanced tumor burden, such as increasing number of lesions, size of largest lesion larger than 5 or 10 cm, bilobar distribution of disease, percent hepatic replacement, or weight of resected specimen, have been shown to predict shorter survival compared with those without these parameters (Fig. 52.3-4). Satellitosis, tumor grade, and ploidy have been reported as negative prognostic variables. Treatment or technical factors predictive of poor outcome include positive resection margin, margin smaller than 1 cm, and, in some studies, intraoperative transfusion. Repeat hepatic resection in selected patients has been reported with 5-year survival rates ranging from 21% to 26%.

**FIGURE 52.3-4.** Five-year overall survival in patients undergoing resection of hepatic metastases from colorectal cancer based on number of lesions. Survival is...
Fong and coworkers have developed a clinical scoring system using five widely used and available clinical and pathologic parameters to predict outcome after resection of colorectal liver metastases (Table 52.3-3). Based on the outcome of 1001 patients undergoing resection with curative intent, an increasing clinical risk score was associated with decreased survival (Fig. 52.3-5). Of note, patients with a clinical risk score of 5 had an actuarial 5-year survival of only 14% and in fact no patient had survived 5 years at the time of the report. These data provide a basis for stratification of patients at high risk of recurrence after hepatic resection and may provide a method of selecting those suitable for adjuvant treatments postoperatively.

### TABLE 52.3-3. Clinical Risk Score for Tumor Recurrence in Patients Undergoing Resection for Colorectal Metastases to Liver

<table>
<thead>
<tr>
<th>Stage (%)</th>
<th>Median (mo)</th>
<th>5-Year Survival Rate%</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td>107</td>
<td>92</td>
</tr>
<tr>
<td>1</td>
<td>112</td>
<td>84</td>
</tr>
<tr>
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<td>145</td>
<td>50</td>
</tr>
<tr>
<td>5</td>
<td>156</td>
<td>40</td>
</tr>
</tbody>
</table>

*TABLE 52.3-3. Clinical Risk Score for Tumor Recurrence in Patients Undergoing Resection for Colorectal Metastases to Liver

**FIGURE 52.3-5.** Five-year overall survival in 1001 patients with metastatic colorectal cancer to the liver undergoing resection with curative intent. Outcome was analyzed based on the absence or presence of various prognostic factors as outlined in Table 52.3-3. Patients with 0 or 1 prognostic factor had improved survival compared with those with increasing numbers of adverse prognostic variables (P < .0001). Open box score = 0; filled triangle score = 1; open circle score = 2; filled circle score = 3; filled box score = 4; and open triangle score = 5. (From ref. 45, with permission.)

### POSTHEPATIC RESECTION ADJUVANT HEPATIC ARTERY INFUSIONAL OR INTRAVENOUS THERAPY IN COLORECTAL CANCER

Several nonrandomized clinical investigations in the United States, Germany, and Japan suggest a potential advantage for the use of adjuvant chemotherapy after complete surgical resection of hepatic metastases in patients with colorectal carcinoma. Using weekly hepatic arterial infusion of 5-fluorouracil (5-FU) at a dose of 15 mg/kg for an intended course of 6 months, investigators at M. D. Anderson Cancer Center noted an extrahepatic-only recurrence rate of 33% and a liver-only recurrence rate of 17% in 20 patients. At 38 months of follow-up, 50% of patients were alive and free of disease. In a nonrandomized but prospective study, Lorenz and colleagues from Germany found a nonsignificant prolongation in median survival (P = .064) of 52 months in 60 patients treated with resection followed by hepatic arterial therapy with either floxuridine (FUDR) or 5-FU with or without leucovorin (LV) versus 33 months in 21 patients treated with surgery alone. Furthermore, these investigators noted a marked delay in the time to hepatic recurrence from 17 months to 63 months (P = .015) in patients treated with adjuvant chemotherapy versus those treated with surgery alone. With a median follow-up of more than 2 years, Okuno and colleagues studied the recurrence rate in 18 patients treated with surgical resection followed by hepatic arterial interleukin-2 plus 5-FU (250 mg) and mitomycin C (4 mg) given weekly for 6 months and found an overall recurrence rate of 22% with no recurrences in the liver (17% lung; 6% pelvis). More recently, investigators in Japan performed a retrospective investigation of 174 patients who had been treated with hepatic resection for metastases resulting from colorectal carcinoma and identified three separate groups, including those treated with surgery alone (66 patients), surgery plus hepatic arterial infusion (78 patients), and surgery plus peripheral venous infusion (30 patients). The hepatic arterial therapy consisted of 5-FU, 50 mg/m²/d × 14 days, plus bolus injections of an anthracycline analogue, aclacinomycin A (40 mg), suspended in a lipid contrast medium given every 3 to 6 months for up to 3 years. These investigators noted that the patients treated with surgery followed by hepatic arterial infusion had a significantly decreased hepatic recurrence rate and a more prolonged disease-free and overall survival compared with either of the other groups and had a 5-year survival rate of 35% compared with 13% for those treated with surgery plus peripheral venous infusion therapy and 9% for those treated with surgery alone. Investigators from Tokyo retrospectively analyzed 115 patients with hepatic-only metastatic colorectal carcinoma treated with potentially curative therapy with resection alone (40 patients) versus surgery followed by either hepatic arterial (28 patients) or intraportal vein (ten patients) 5-FU/LV, with or without mitomycin C, versus surgery followed by hepatic arterial infusion (250 mg/kg/day × 14 days) plus an anthracycline (20 to 40 mg/kg/days 1 and 8), plus mitomycin C (4 to 8 mg kg/days 1 and 8) (31 patients) every 3 months for 1 year. These investigators noted an approximately 12% 5-year survival rate for patients treated with surgery alone versus 57% for those treated with surgery followed by hepatic arterial chemotherapy.

Based on relatively promising results from nonrandomized studies, several groups have conducted prospective randomized studies with the goal of defining the role of adjuvant chemotherapy in patients with metastatic colorectal carcinoma treated with complete surgical resection of hepatic metastases. As shown in Table 52.3-4, an intergroup trial randomized 109 patients with isolated hepatic metastases from colorectal carcinoma to treatment with either surgery alone (56 patients) or surgery followed by continuous hepatic artery infusion of FUDR for four cycles plus systemically administered 5-FU for 12 cycles (53 patients). Although none of the survival differences reached a statistically significant level, those patients treated with surgery followed by chemotherapy enjoyed a 65% 5-year survival versus 32% for those treated with surgery alone. The median survival for those treated with surgery plus chemotherapy of 34.2 months was less, albeit not significantly less, than those treated with surgery (47.5 months). A significant decrease in overall recurrence rate was noted for the group treated with surgery plus chemotherapy (42% vs. 66%) as well as a decrease in hepatic-only recurrences (26% vs. 55%) compared with those treated with resection alone. Investigators from Memorial Sloan-Kettering Cancer Center randomized 74 patients with hepatic-only disease to surgery followed by hepatic arterial FUDR and dexamethasone plus systemic therapy with 5-FU plus LV for 6 months and 82 patients to surgery followed by systemic therapy with 5-FU/LV alone for 6 months. These investigators found a statistically significant improvement in 2-year survival rate of 66% for those treated with both HAI and systemic chemotherapy versus those treated with surgery followed by systemic chemotherapy alone (72%) (P = .023) (see Table 52.3-4). Furthermore, although the overall recurrence rates were not different between the two groups, there was a marked decrease in hepatic recurrence in the group treated with the addition of HAI chemotherapy (10% vs. 40%, P = .000012). Toxicities were similar for the two groups of patients, with the exception of a greater incidence of grade 3 to 4 diarrhea and an 18% incidence of hyperbilirubinemia (greater than 3) in those patients.
Hepatic artery infusional therapy: Technical considerations

HAI therapy has had substantial clinical application based on the development of an implantable pump (or port) that can deliver a continuous infusion of therapeutic agents via the hepatic artery and the availability of agents that have an established pharmacokinetic advantage for HAI delivery because of a high first-pass extraction.

Infusional therapy for hepatic metastases

Infusional therapy for hepatic metastases has had substantial clinical application based on the development of an implantable pump (or port) that can deliver a continuous infusion of therapeutic agents via the hepatic artery and the availability of agents that have an established pharmacokinetic advantage for HAI delivery because of a high first-pass extraction.
TABLE 52.3-7. Hepatic Arterial Infusion Therapy: Randomized Trials in Colorectal Cancer

Kemeny and coworkers reported that 0.3 mg/kg/d of FUDR, 15 mg/m²/d of LV, and 20 mg of dexamethasone administered as a 14-day infusion to 33 previously untreated patients with metastatic colorectal cancer to liver resulted in an overall response rate of 78% and a median duration of survival of almost 25 months. In 29 previously treated patients, the regimen resulted in an overall response rate of 52% and a median survival of 13.5 months. The addition of dexamethasone was associated with a significantly lower incidence of biliary sclerosis compared with the same regimen without dexamethasone (3% vs. 21%, respectively) without adversely affecting response rates (75% vs. 69%, respectively).

A number of prospective random assignment trials were reported in the 1980s and 1990s comparing FUDR administered via HAI to either systemic therapy or best supportive care (Table 52.3-7). In general, all studies demonstrated a significantly superior response rate for HAI compared with systemic therapy, but this did not consistently translate into a survival advantage due to several possible explanations. Three of the five studies conducted in the United States, including the two largest, allowed patient crossover, thereby obscuring any potential survival advantage for HAI therapy. The dose of FUDR used in these trials, 0.3 mg/kg/d, was associated with significant toxicity, resulting in treatment interruptions for many patients. In addition, technical difficulties with pump placement or function prevented some patients from receiving HAI therapy. For example, in the Northern California Oncology Group trial, 9 of 67 patients randomized to HAI therapy did not receive therapy because of technical difficulties with pump placement or function, and of 50 evaluable patients receiving HAI therapy, one-half of the patients terminated therapy because of toxicity rather than disease progression. Twenty-eight of 65 patients receiving intravenous therapy crossed over to HAI therapy, and although median survival was longer in those treated with HAI versus intravenous only, these differences may be due largely to a favorable selection bias in those able to undergo crossover treatment.

Another prospective random assignment trial from the Memorial Sloan-Kettering Cancer Center evaluated response and survival for patients with laparotomy-confirmed unresectable disease confined to liver treated with HAI or intravenous therapy. Although there was a significantly higher response rate with HAI therapy compared with intravenous therapy (50% vs. 20%, respectively), no overall survival differences were observed. Of note, in both studies in which crossover was allowed, the responses to those previously treated with intravenous therapy were lower than those treated initially with HAI. In the study from the National Cancer Institute, significant biliary sclerosis was observed in 21% of patients. In an unplanned subgroup analysis, there was a significant survival advantage in the group with histologically negative perportal lymph nodes who received HAI therapy. Because patients in the intravenous therapy arm did not have the benefit of surgical staging, improved outcome in the HAI node-negative group was presumably due to more accurate surgical staging and exclusion of those with occult hepatic disease. The other United States trial that did not allow crossover to HAI therapy was from the Mayo Clinic, and no difference in overall survival was observed between groups.
Two European studies did show a survival advantage, but patients were randomized to HAI therapy or best supportive care, which included cytotoxic therapy in only one-third of patients, a control treatment arm not commonly used in the United States. The study from the United Kingdom treated patients with 0.2 mg/kg/d of FUDR, which was well tolerated. Overall survival and improved quality of life were observed in the treated versus best supportive care group in whom intra venous chemotherapy was administered for palliation of symptoms only. The French study also demonstrated a survival benefit with HAI therapy; only one-half of the patients in the control arm received systemic therapy. Two metaanalyses of the published prospective random assignment trials have concluded there is a modest survival advantage to HAI therapy using a fluorouracil-based regimen compared with systemic therapy (No HAI). Survival curves based on a metaanalysis of the published literature of phase III random assignment trials comparing these two treatment strategies. HAI therapy has a significantly improved survival compared with those treated with no HAI therapy (Log rank test, P = .0009). From ref. 112, with permission.

OTHER APPLICATIONS OF HEPATIC ARTERY INFUSIONAL THERAPY

HAI therapy has been used with other agents for patients with various histologies, including interleukin-2 and chemotherapy for colorectal cancer patients, doxorubicin for hepatocellular cancer patients, and carboplatin or fotemustine for patients with metastatic ocular melanoma to liver. Leyvraz and coworkers treated 31 patients with ocular melanoma metastatic to liver with 100 mg/m² as a 4-hour infusion weekly for 3 weeks followed by a repeat cycle every 21 days via an implanted intraarterial port. Objective radiographic responses were observed in 12 of 30 assessable patients (40%), and the median duration of response was 11 months. These data are similar to those reported with chemoebolization and show encouraging activity in a disease for which there are no good options.

INTERMITTENT HEPATIC ARTERY INFUSION THERAPY

The use of HAI therapy requires a surgical procedure coupled with the risk of infection and bleeding associated with the requirement for the placement of a semipermanent catheter and port. One approach to circumvent the cost and toxicities associated with chronic indwelling devices is the use of an intermittently placed percutaneous hepatic arterial catheter. The feasibility of this approach has been demonstrated by several groups. Jung and colleagues demonstrated the safety and feasibility of the approach in 21 patients with primary or metastatic cancer in the liver. Major complications requiring catheter removal and reimplantation occurred in 19% of patients. Patients with metastatic breast cancer to the liver were treated with percutaneous hepatic arterial infusion of cisplatin, 120 mg/m² (31 patients), or vinblastine, 2 mg/m² (25 patients), daily for 5 days each month via percutaneous hepatic artery catheters. Partial responses were noted in 19% of patients treated with platinum and 36% of those treated with vinblastine, and toxicities were found to be acceptable with both regimens. Experience using this approach in 36 patients at the University of Nebraska has been published. Patients entered onto this trial had unresectable hepatic metastases from colorectal carcinoma and were treated with FUDR plus LV continuously for 4 days via hepatic arterial infusion followed in 1 week by intravenous continuous infusion 5-FU and oral LV for 21 days each month for six cycles followed by maintenance systemic 5-FU and oral LV. The overall response rate was 45%, with a median survival of 1 year.

HEPATIC ARTERY INFUSION WITH VENOUS FILTRATION

An interesting approach to enable the use of high doses of chemotherapy while limiting systemic toxicities involves the use of venous filtration wherein high doses of cytotoxins may be administered into the arterial supply while the liver and hepatic venous blood is collected via a catheter positioned in the retrohepatic vena cava and in which balloons are inflated above and below the hepatic veins to isolate and collect hepatic venous effluent. The collected blood is passed through a charcoal-containing device capable of filtering the cytotoxic compounds and returned to the systemic circulation. This technique was originally developed by Ravikumar and coworkers at Yale University School of Medicine. They applied this approach to 23 patients with primary or metastatic hepatic cancers using either high doses of 5-FU (1000 to 5000 mg/m²) in 12 patients or doxorubicin (50 to 120 mg/m²) in nine patients. Each patient received at least two treatments with a 3-week interval between treatments. The extraction efficiency of the system was 64% to 91% and accompanied by acceptable toxicity. The most common toxicity was neutropenia and transient hypotension due to the charcoal filters and diminished cardiac return during the procedure. Dose-limiting myelotoxicity was observed at 5000 mg/m² of 5-FU and 120 mg/m² of doxorubicin. Similar results were obtained from investigators at M. D. Anderson Cancer Center in ten patients with unresectable hepatocellular carcinoma wherein dose-limiting toxicities were encountered at 120 mg/m² of doxorubicin. This approach holds promise for the delivery of relatively high doses of chemotherapy into an isolated organ; however, because the isolation is not complete, systemic toxicities limit drug exposure, thus, the value of this approach clearly requires further investigation.

In an attempt to simplify the technique, Ku and colleagues from Japan have developed a single-catheter technique of hepatic isolation and charcoal hemoperfusion that required only a single cutdown rather than the three needed for the double-balloon technique described previously. They compared their single-catheter technique with the original technique as developed by Ravikumar in 16 patients, with either primary or metastatic cancer to the liver. Nine of these patients were treated using the new technique and seven using the original double-balloon technique. Although this group found either technique feasible and relatively safe, their study suggests that the single-catheter technique may result in a significant decrease in systemic exposure, presumably due to greater efficiency of removal of the cytotoxin from the venous effluent. The hemofiltration concept was further tested in 23 patients with hepatic metastases from colorectal cancer (seven previously treated with 5-FU/LV) who were treated with hepatic arterial chemotherapy using a combination of mitomycin (30 to 50 mg/m²) and epirubicin (60 to 90 mg/m²) combined with intraperitoneal cisplatin (60 mg/m²) coupled with a venous filtration catheter placed in the retrohepatic inferior vena cava. This high-dose regimen was supplemented with four subsequent cycles of the same agents given at more standard doses. The investigators found this regimen to be feasible and associated with acceptable toxicities that included grade 3 to 4 hematologic (12%), gastrointestinal (19%), and hepatic effects (9%) and pain (9%). They identified an overall response rate of 59%, with a median duration of response of 10 months and an overall median survival of 14 months. In a subsequent study from investigators in Belgium, hemofiltration was used in eight patients with unresectable hepatic metastases from colorectal carcinoma. This group used hepatic arterial infusion of 5-FU, mitomycin C, and doxorubicin. They noted a 46% overall response rate with essentially negligible major gastrointestinal or renal toxicities.

ISOLATED HEPATIC PERFUSION

IHP is a regional treatment that has been used at a limited number of centers since its original clinical application in the 1950s and is similar to isolated limb perfusion used for extremity melanoma or sarcoma in which the cancer-bearing region is perfused with a recirculating closed circuit containing a reservoir, heat exchanger for delivery of hyperthermia, and roller pump (see Chapter 29.3). IHP is administered via a major operative procedure during which the liver is extensively mobilized to prevent leak of systemic perfusate during treatment. Venous outflow is from a cannula positioned in an isolated segment of the retrohepatic
Chemoembolization has also been attempted for patients with colorectal cancer metastatic to the liver. In contrast to neuroendocrine tumors, most patients with colorectal cancer and observed in those with advanced disease. However, the median survival was 10 months. Oldhafer and coworkers reported a series of 12 patients of whom six received TNF and melphalan. Treatment mortality was 3% and despite the fact that most had received previous therapy and many had advanced tumor burden in liver, there was an overall radiographic response rate of 75%. Responses were consistent across all histologies treated, including ocular melanoma and colorectal cancer and observed in those with advanced disease (Table 52.3-9). De Vries and coworkers treated nine patients with advanced unresectable metastatic cancer confined to liver and reported a considerable treatment mortality of 33% but did observe significant antitumor activity. However, the median duration of response was only 18 weeks, and median survival was 10 months. Oldhafer and coworkers reported a series of 12 patients of whom six received TNF and melphalan. Tumor biopsies obtained on posttreatment day 1 showed tumor necrosis in most patients and there was an overall radiographic response rate of 50% and a median survival of 11 months. A Swedish group treated 11 patients and had an operative mortality of 18%. Antitumor activity was observed in three of six patients with ocular melanoma to liver and in zero of five patients with colorectal cancer. The modest antitumor activity may be secondary to the low doses of agents used, only 0.2 to 0.3 mg of TNF and 0.5 mg/kg of melphalan, which are considerably lower than the maximum safe tolerated doses determined in phase I trials at the National Cancer Institute.

Table 52.3-8 summarizes the outcomes of isolated hepatic perfusion trials using tumor necrosis factor and chemotherapeutics. Alexander and coworkers from the National Cancer Institute reported results in 34 patients with metastatic unresectable cancers confined to liver using 1 mg of TNF and 1.5 mg/kg of melphalan. Treatment mortality was 3% and despite the fact that most had received previous therapy and many had advanced tumor burden in liver, there was an overall radiographic response rate of 75%. Responses were consistent across all histologies treated, including ocular melanoma and colorectal cancer and observed in those with advanced disease (Table 52.3-9). More recently, results in 51 patients with isolated unresectable colorectal cancer confined to liver treated with IHP using TNF and melphalan or melphalan alone followed by HAI therapy using FUDR and LV have been presented by the group. Seventy-three percent of patients failed previous systemic therapy with a 5-FU-based regimen. There was one treatment-related mortality (2%). Of note, the overall responses remained similar to their initial report. 77% for patients treated with TNF and melphalan IHP and 74% for patients treated with IHP using melphalan alone, but median time to progression in liver was significantly prolonged with the addition of HAI therapy (10 months vs. 14.5 months, respectively). These data suggest that continued clinical evaluation of IHP for patients with advanced refractory metastatic cancers confined to liver is warranted.

Chemoembolization

Chemoembolization involves the administration of chemotherapy followed by vascular occlusion using a variety of agents such as degradable starch microspheres, gelatin powders, polyvinyl chloride, or pledgets. Responding patients usually undergo multiple procedures over time as tumors and vasculature regrow. This approach has been widely applied in the treatment of primary hepatocellular carcinoma (see Chapter 33). For patients with metastatic cancer, the most common application is in patients with unresectable metastases from carcinoid or islet cell tumors. Because most tumors are highly vascular and have an indolent course in many patients, a partial response can provide long-term palliation. Furthermore, many patients who do not achieve an objective response have improvements in symptoms resulting from hormonal secretion. The overall objective response rate tends to be in the range of 30% to 50%, and the great majority of patients show reduced hormone secretion and improvement of symptoms (Table 52.3-10). Although there has been a shift in practice from embolization alone to chemoembolization with a variety of agents, there is no clear evidence that the use of chemotherapy improves response or patient outcome.

Table 52.3-9. Response to Isolated Hepatic Perfusion Based on Number of Lesions, Diameter of Largest Tumor, or Percent Hepatic Replacement in Patients Treated with Tumor Necrosis Factor and Melphalan

Table 52.3-10. Outcome in Patients with Neuroendocrine Tumors Metastatic to the Liver after Chemoembolization

Chemoembolization has also been attempted for patients with colorectal cancer metastatic to the liver. In contrast to neuroendocrine tumors, most patients with...
TABLE 52.3-11. Outcome in Patients with Colorectal Cancer Metastatic to the Liver after Chemoembolization

Embolization procedures cause significant pain (requiring narcotic analgesics), fever, nausea, and malaise lasting 2 to 7 days in nearly all patients. Portal venous thrombosis, while rarely seen (in contrast to hepatocellular carcinoma), is an absolute contraindication to hepatic arterial embolization.

Chemoembolization Plus Adjuvant Chemotherapy

Chemoembolization appears to have value as a local therapy for patients with liver-only or liver-predominant unresectable carcinoma. Given the potential value of adjuvant chemotherapy after chemoembolization, at least two groups have sought to investigate the potential value of adjuvant chemotherapy after chemoembolization in patients with gastrointestinal malignancies metastatic to the liver. The Puget Sound Oncology Consortium performed an investigation of alternating systemic continuous infusion 5-FU (250 mg/m²/d for 28 days) interspersed with two or three transcatheter arterial chemoembolization treatments using foam particles with cisplatin in 32 patients. Although this group believed that toxicity was acceptable with this regimen, they did have grade 3 toxicities occur in 81% of patients and grade 4 in 31%. Furthermore, the overall 40% response rate, median duration of response of 4.2 months and overall median survival of 14.3 months are similar to what one might anticipate with systemic chemotherapy alone. A similar experience was published by the Southwest Oncology Group, who combined chemoembolization (collagen mixed with cisplatin, mitomycin C, and doxorubicin) with systemic continuous infusion 5-FU/LV in 31 patients. This group found an overall response rate of 29% with a median survival of 14 months. These outcomes are similar to what one might have anticipated with the use of systemic chemotherapy alone. Thus, the value of combining hepatic chemoembolization with adjuvant chemotherapy using agents currently available does not appear promising.

LOCAL ABLATIVE THERAPY

Several techniques are being used for local ablation of hepatic metastases, including cryotherapy, percutaneous injection of toxic agents, hyperthermic coagulative necrosis, and newer experimental techniques (Table 52.3-12). The goal of local ablative therapy is to achieve complete necrosis of the tumor with minimal injury to surrounding normal hepatic parenchyma. Currently, their use is indicated in patients who are not surgical candidates, for those whose tumors are not amenable to resection because of multiple tumors involving both lobes, tumors arising in cirrhotic livers in which preservation of parenchyma is imperative, tumors straddling the interlobar plane that would otherwise require an extended resection, recurrent tumors after previous resection in which re-resection may be unsafe or anatomically impossible, and as an adjunct to surgical resection by treating microscopically positive margins.

TABLE 52.3-12. Techniques for Local Ablation

Limitations of local ablation therapies include the inability to treat subclinical or occult tumor deposits, inability to treat tumors larger than several centimeters in diameter, inability to treat tumors abutting major vascular structures, and difficulty in assessing the adequacy of tissue destruction during therapy. Real-time ultrasound and MRI scanning are routinely used during treatment, but further refinement in technique and imaging is required.

CRYOTHERAPY

Cryotherapy is a term representing the in situ destruction of tissue by the freeze and thaw process. James Arnott first used freezing to decrease the size of breast and cervical cancers in England in 1845. The most widespread application has been in the field of dermatology in which the cure rate for skin tumors has been reported at 97% to 98%. Subsequently, encouraging results have been reported with deep tumors of the liver, lung, breast, prostate, and brain. The process of freezing tissue can cause direct cellular destruction that is dependent on the rate of tissue cooling, and this can be variable during cryosurgery. Microcirculatory failure secondary to freezing within the vasculature and subsequent vascular damage may be an additional tumoricidal mechanism.

Two main technical advances have made cryotherapy applicable to liver tumors on a broad scale. The first is the development of vacuum-insulated cryoprobes that allow controlled freezing of tumors deep within the liver, and the second is the use of intraoperative ultrasound to allow precise probe placement into the center of tumors and to monitor the progression of the freeze margin in real time. The most commonly used probes range from 6 to 12 mm in diameter and a disk-shaped probe can be used for freezing thin surface lesions or for freezing a positive or close resection margin. Liquid nitrogen is circulated through the tip of the probes at a temperature of −196°C, which results in a probe-tip temperature between −160°C and −180°C. The probe is placed into the center of the lesion under ultrasound guidance to ensure that uniform freezing will extend symmetrically in all directions from the tip of the probe. Repeated freeze and thaw cycles can improve tumor cell destruction and vascular inflow occlusion to the liver (Pringle’s maneuver) can improve the cooling rate and may allow successful freezing of larger tumors with smaller probes.

The 8-mm probe can reliably create a spherical ice ball of 3 cm, and the 12-mm probe can create an ice ball of 5 cm in noncirrhotic liver. Newer cryosurgical systems are designed to allow simultaneous circulation of liquid nitrogen through multiple probes. Smaller 2- to 3-mm needle tip probes have been used in combination to freeze large tumors and minimize bleeding from the probe tract in the liver. Smaller probes can be inserted through laparoscopic ports. The advancing interface between frozen tissue and normal tissue can be monitored by ultrasound as a distinct hyperechoic ring. The advancement of this ring is monitored until it extends at least 1 cm beyond the tumor in all directions. The ice ball creates an acoustic shadow, making it impossible to monitor the advancement of all edges simultaneously. The ultrasound transducer should be moved as necessary to visualize the entire circumference and ensure complete freezing to 1 cm beyond the tumor.

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The ultrasound transducer should be moved as necessary to visualize the entire circumference and ensure complete freezing to 1 cm beyond the tumor.
A number of studies were published in the early 1990s from centers reporting their initial experience with the technique. Zhou et al. from the Shanghai Medical University in China reported a series of 107 patients with primary liver cancer treated with cryotherapy and observed a 5-year survival of 15% for 49 patients treated with cryotherapy. Orik and coworkers reported a series of 59 patients with unresectable hepatic metastases treated with cryosurgery. At a median follow-up of 21 months the disease-free survival rate was 27% and overall survival was 52.5%. The number of tumors treated ranged from one to 16, and 73% of patients treated had bilobar disease and many had tumors directly abutting major vessels. Ravikumar and coworkers reported an initial series of 32 patients treated with cryosurgery resulting in a 2-year disease-free survival of 28% and overall survival of 62%. A second series from the same investigator reported results in 21 patients undergoing cryosurgery and at a median follow-up of 16 months. In both series, the liver recurrence rate was approximately 25% to 30%, and one-half of patients had systemic disease. Proketes and coworkers have reported their results of cryosurgery in 38 patients with unresectable multiple liver metastases from colorectal carcinoma. They report a 12.5% 2-year survival rate for the 11 patients receiving cryotherapy alone.

Currently, the world literature reports results in more than 900 patients treated with the technique, with more recent reports detailing patient, treatment, and tumor parameters associated with successful outcomes. Seifert and Morris reported that 116 patients with colorectal cancer treated with cryotherapy had an overall morality of 28%. There was a single mortality secondary to treatment (0.9%). Factors found to be independently correlated with favorable outcome after cryotherapy are listed in Table 52.3-13. In a second report of 85 patients presumably also included in the first series, the mean disease-free interval at the cryosite was 42 months and was 60% at 3 years. The median hepatic disease-free interval was 15 months and 7% at 3 years. Weaver and coworkers reported a median survival of 34 months and an 82% hepatic recurrence rate in 136 patients undergoing 156 cryotherapy procedures. Repeat and laparoscopic treatments have been reported.

In general, cryotherapy is considered a safe and effective means for treating hepatic tumors of all histologies with low morbidity. Cryotherapy has also been used in conjunction with hepatic resection to assist in resection of a deep-seated lesion. To an inadequate margin after resection, or in addition to resection to preserve hepatic tissue. The main advantage of cryotherapy over surgery is the minimal damage suffered by the normal hepatic parenchyma and the avoidance of the risk of hemorrhage and damage to bile ducts that occurs during parenchymal dissection. Most patients experience an increase in liver enzymes to approximately twice normal, with normalization by postoperative day 5. Leukocytosis and low-grade fevers are common. Hemorrhage from the probe tract is generally easily controlled with pressure, packing with absorbable gelatin sponge or absorbable knitted fabric, or both. Complications related specifically to cryotherapy include pleural effusions in 6%, hepatic cracking with associated intraoperative hemorrhage in 4%, bilary fistula in 3%, abscess in 1.7%, and myoglobinuria with renal failure in 1.4%.

CRYOTHERAPY PLUS ADJUVANT CHEMOTHERAPY

Given the potential value of adjuvant chemotherapy in the setting of hepatic resection, it may be reasonable to expect a similar improvement in outcome with the addition of adjuvant chemotherapy to other local ablative therapies, including cryotherapy. A study from Australia (38 patients) and one from New Zealand (30 patients) comparing the outcome of adjuvant chemotherapy after cryotherapy versus postoperative chemotherapy for patients who had hepatic colorectal metastases that remained inoperable. Each of these groups of investigators found the regimen of hepatic cryotherapy followed by hepatic arterial chemotherapy using S-FU plus LV to be relatively safe and well tolerated, and each found a similar median survival of approximately 18 months in patients treated with the combined approach. In a small group of 11 patients nonrandomly treated with cryotherapy alone in the Australian trial, the investigators noted a median survival of only 6 months, suggesting that adjuvant chemotherapy may well be a useful adjunct to hepatic cryotherapy. Using systemic S-FU plus LV, a group of investigators from Roswell Park Cancer Institute found that the use of this adjuvant systemic chemotherapy in four patients treated with cryotherapy was highly toxic and recommended caution when combining systemic adjuvant chemotherapy with cryotherapy.

MICROWAVE TISSUE COAGULATION AND RADIOFREQUENCY ABLATION

Another form of local ablative therapy for liver tumors is percutaneous microwave or hyperthermic coagulation. A probe inserted into the middle of a tumor emits microwaves or radiowaves from its tip, which heats the surrounding tissue. Energy penetrates a few centimeters into the surrounding tissue, causes molecular vibration of dipoles (particularly of water), and is converted to heat, resulting in tissue coagulative necrosis. A single electrode emitting 2450 MHz for 60 seconds produces coagulation necrosis of a spindle-shaped region approximately 2 cm in diameter. Evaluation of the zone of necrosis in real time can be achieved with ultrasound, which shows strong hyperechogenic foci representing cellular destruction. Percutaneous microwave coagulation has efficacy in ablating hepatocellular tumors up to 6.5 cm in diameter. Microwave therapy has advantages over laser photocoagulation as a larger zone of necrosis can be obtained with a shorter treatment time. In contrast to other forms of local ablation, the zone of cellular destruction does not extend beyond the tip of the electrode. This allows precise treatment at the deep edge of the tumor where ultrasound visualization is often limited.

A number of studies have been published outlining results in patients treated with percutaneous or open radiofrequency thermal ablation (RFA). The success of RFA in successful ablation of primary or metastatic tumor deposits within the liver is influenced by the expertise and diligence of the treating physician to ensure that an adequate zone of thermal necrosis has been delivered to the entire tumor. For large tumors, this requires multiple consecutive propragream placement and, because of the zone of thermal necrosis cannot be definitively imaged with intraoperative ultrasound, it is somewhat difficult to determine which areas within a large tumor have or have not been adequately treated. Solbiati and coworkers reported results in 29 patients with 44 hepatic metastases ranging in size from 1.3 to 5.1 cm in diameter. The authors report successful ablation of all identifiable tumor in 91% of treated metastases, but a local progression rate of 34%. Livigni and coworkers subsequently reported a series of 14 patients with liver metastases and one patient with a primary cholangiocarcinoma treated with RFA. Fourteen of 25 lesions were completely obliterated and ranged in size from 1.2 to 3.9 cm. Partial necrosis in 12 additional lesions was noted, with diameters ranging from 1.5 to 4.5 cm. Nagata and coworkers reported results of RFA treatment in 173 patients with primary or hepatic cancers. Additional therapy, including arterial embolization, radiotherapy, immunotherapy, and systemic chemotherapy, were also combined with RFA treatment in this series. Treatments were administered percutaneously, and more than 80% of patients underwent more than four sessions of RFA. In 45 patients treated with metastatic tumor deposits, there was no response or disease progression in 53%. Cuschieri and coworkers reported results of microscopically administered ultrasound-guided RFA of hepatic tumors and successfully achieved total ablation in seven of eight patients with metastatic colorectal cancer to the liver. At the time of publication, follow-up ranged from 6 to 20 months, and eight of ten patients remained free of tumor. The largest series of patients treated with RFA was reported by Curley and coworkers from the M. D. Anderson Cancer Center.
The investigators treated 123 patients with RFA either using the percutaneous or open operative technique with ultrasound guidance. A total of 169 tumors ranging in size from 0.5 to 12 cm (median diameter, 3.4 cm) were ablated. Three-fourths of patients underwent open operative RFA, and there were no treatment-related deaths in the study. The authors report three tumor recurrences in 169 treated lesions (1.8%) at a median follow-up of 15 months (see Table 52.3-14). The low recurrence rate may be due to the fact that many patients were treated operatively to facilitate probe placement and more reliably assess adequacy of therapy. In addition, the authors used inflexible ethanol catheters in a Pringle’s maneuver, which may have enhanced the effectiveness of the thermal ablation. However, it should be noted that the intraoperative use of RFA does not take full advantage of its technology. For example, the small probe size and the fact that the tissue is cauterized along the track eliminates the risk of bleeding from the probe track or cracking of the liver on removal of the probe. For patients undergoing open operative local ablative therapy, the use of cryotherapy allows one to use real-time intraoperative ultrasound to accurately assess the adequacy of the zone of destruction, which is more difficult to assess using RFA. In practice, the technology behind the various local ablative therapies is evolving, and, as smaller probe sizes are developed and techniques for monitoring adequacy of tissue destruction are refined, the advantages of one form of ablative therapy over another may become increasingly obscure.

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<th>Author</th>
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TABLE 52.3-14. Local Recurrence after Radiofrequency Ablation of Hepatic Neoplasms

**PERCUTANEOUS ETHANOL INJECTION**

Percutaneous ethanol injections into malignant deposits in the liver have most broadly been applied to the treatment of patients with hepatocellular carcinomas. The density of tumors associated with hepatocellular carcinoma and the common occurrence of this malignancy in the setting of severe underlying hepatic disease lends itself to this form of local therapy as opposed to surgical resection, which is often not possible in patients with severe underlying hepatic cirrhosis. Currently, there are no randomized studies comparing the value of percutaneous ethanol injection with any of the other local modalities for the treatment of patients with hepatic malignancy. Thus, its value relative to other local techniques is uncertain. However, there have been several series of patients with hepatocellular carcinoma treated by percutaneous ethanol injection reported in the literature, primarily from investigators in Japan and Italy. In patients with hepatocellular carcinoma with either single or multiple hepatic tumors, chemotherapy with curative intent, the investigators from Japan found 3- and 5-year overall survival rates of 62% to 68% and 28% to 52%, respectively. The 3-year recurrence rate for these patients was approximately 60% to 65%, with the vast majority of new recurrences occurring in portions of the liver not previously treated with ethanol injections. The 3- and 5-year overall survival rates were slightly better in the studies from Italy (approximately 70% and 40%, respectively); however, these differences may well be attributed to the differences in the underlying hepatic disease, which is an important prognostic factor. Patients classified as Child’s A have a 2-year survival, approximately twofold greater than those patients classified as Child’s C (approximately 90% vs. less than 40%, respectively). In addition to Child’s classification, the prognosis of patients with hepatocellular carcinoma is negatively influenced by a greater number of deposits of carcinoma as well as increasing size of the deposits and elevated pretreatment a-fetoprotein levels. Although generally restricted to patients with tumors smaller than approximately 3 to 5 cm in size, Livraghi and colleagues published their experience with percutaneous ethanol injection in 108 patients with hepatocellular carcinoma with tumors larger than 5 cm and performed in a single session under general anesthesia. Despite the size of the lesions treated, this group found a 3-year survival of 57% for those patients in single lesions measuring 5.0 to 8.5 cm and 42% for those with multiple lesions measuring 5 to 10 cm. The overall rate of major complications in this study was less than 5%, thus suggesting that percutaneous ethanol injections may be a useful modality even in the setting of lesions up to 10 cm in size.

Although no randomized comparisons between percutaneous ethanol injection and hepatectomy have been performed, several studies address this issue through retrospective comparisons or the use of contemporary patient cohorts. In a cohort study from Spain, patients with solitary hepatocellular carcinomas smaller than or equal to 4 cm were treated with surgical resection (n = 33) or percutaneous ethanol injection (n = 30). Despite a significant increased proportion of Child’s A patients in the surgically treated group (91% vs. 33%) and a decreased proportion of patients with ascites (6% vs. 47%), these authors found that the overall survival rates in the two groups were not different. Similar results were obtained in a study of 40 patients with solitary hepatocellular carcinomas smaller than 2 cm in diameter treated...
by Kotoh and colleagues wherein 17 were treated with hepatectomy, 12 with percutaneous ethanol injection, and 11 with a combination of percutaneous ethanol injections and arterial embolization with gel-containing mitomycin C and Adriamycin. These authors found no difference in median survival (3.5 to 4.0 years) or recurrence rates (70% to 80%) between patients undergoing hepatectomy versus those treated with ethanol injection with or without arterial embolization despite a greater proportion of patients with Child's class A disease in the surgically treated group (73% vs. 36%). In a large retrospective analysis of 391 patients, Livraghi and colleagues found no difference in 3-year survival for 120 patients treated by surgical resection (70% Child's A, 40% Child's B) versus 155 treated by percutaneous ethanol injection (71% Child's A, 41% Child's B); however, they noted a significantly inferior (threefold lower) survival for those patients who were not treated with either percutaneous ethanol injection or hepatectomy. Similarly, Orlando and colleagues used a matched historic comparison group to compare the outcome of this untreated group (65 patients) with small hepatocellular carcinomas (smaller than 4 cm) with 35 patients treated by percutaneous ethanol injection and found that 3-year survival of patients treated with percutaneous ethanol injections was superior to the historic comparison group (33% vs. 14%, respectively), but that the primary difference in survival outcome was restricted to those patients with Child's A disease (71% vs. 21%, respectively) whereas those with Child's B had a similar, but poor, 3-year survival outcome regardless of whether they were treated with percutaneous ethanol injections or left untreated (9% for both groups). These results suggest that percutaneous ethanol injections may be associated with a more favorable outcome compared with those patients who are treated with best supportive care only and that clinical outcome with this form of local therapy may be similar to that of hepatectomy. Given the potential value of percutaneous ethanol injections and transcatheter arterial embolization, several groups have combined these two approaches. In 86 patients with Child’s class A or B cirrhosis and large hepatocellular carcinomas (3.1 to 8.0 cm), Lencioni and colleagues found 69% and 47% 3- and 5-year survivals, with 56% and 82% recurrence rates at 3 and 5 years in patients treated with transcatheter arterial chemoembolization (gelatin sponge with epirubicin emulsified in iodized oil) followed by percutaneous ethanol injection. Investigators in Germany compared the survival of 132 patients with inoperable hepatocellular carcinoma nonrandomly treated with best supportive care (45 patients) or percutaneous ethanol infusion (15 patients), or transcatheter arterial chemoembolization (33 patients), or the combination of both local therapies (39 patients). These investigators found that patients treated with a combination of percutaneous ethanol infusion and transarterial chemoembolization had an improved survival when compared with those patients treated with either chemoembolization alone or with best supportive care only. However, patients treated with chemoembolization alone had larger and more advanced hepatic disease compared with those treated with ethanol alone or the combination of local therapies, as ethanol injections (either alone or combined with chemoembolization) were reserved for those patients with fewer than three lesions with none larger than 5 cm in size. Those assigned to supportive care had disease too advanced to be treated by either chemoembolization or alcohol injections. Given these caveats, the supportive care group had the worst median survival compared with any of the treatment groups (2 months vs. 25 months in the combination group). Although these data support the use and feasibility of combining transarterial chemoembolization with percutaneous ethanol injection, the true value of this combined approach versus either approach used individually requires further investigations using a randomized prospective trial design.

RESULTS OF WHOLE LIVER IRRADIATION WITH OR WITHOUT CHEMOTHERAPY

Early studies demonstrated that whole liver radiation produces temporary palliation of pain for patients with cancer metastatic for the liver. However, it was soon discovered that doses greater than 30 to 35 Gy could produce a condition that has become known as radiation hepatitis. Radiation hepatitis is better described as radiation-induced liver disease (RILD), as the pathologic evaluation shows no evidence of hepatitis. Patients who develop RILD present 2 to 3 weeks after the completion of radiation therapy with weight gain and bloating, and, in severe cases, confusion. Jaundice as a presenting symptom is uncommon (and suggests that the patient has already developed impending liver failure). Physical examination reveals anicteric ascites and painful hepatomegaly. Laboratory evaluation shows a marked elevation of alkaline phosphatase out of proportion to the typically modest increases in alanine aminotransferase, aspartate aminotransferase, and bilirubin (which tends to be unconjugated), elevations in prothrombin time and partial thromboplastin time, and thrombocytopenia. Paracentesis and radiologic studies (CT, MRI, or both) fail to show progressive disease. Liver biopsy reveals venocclusive disease pathologically identical to that resulting from a variety of insults. Although most patients recover in 1 to 2 months, 10% to 20% develop overt liver failure and death.

A tolerable whole liver dose produces only short-term palliation and patient survival (Table 52.3-15). This is true regardless of whether the radiation is given daily or twice daily in 1.5-Gy fractions. To attempt to improve on these results, whole liver radiation has been combined with systemic and hepatic arterial chemotherapy. The combination of local therapies, as ethanol injections (either alone or combined with chemoembolization) were reserved for those patients with fewer than three lesions with none larger than 5 cm in size. Those assigned to supportive care had disease too advanced to be treated by either chemoembolization or alcohol injections. Given these caveats, the supportive care group had the worst median survival compared with any of the treatment groups (2 months vs. 25 months in the combination group). Although these data support the use and feasibility of combining transarterial chemoembolization with percutaneous ethanol injection, the true value of this combined approach versus either approach used individually requires further investigations using a randomized prospective trial design. RESULTS OF WHOLE LIVER IRRADIATION WITH OR WITHOUT CHEMOTHERAPY

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Table 52.3-15. Results of Treatment of Metastatic Cancer to the Liver Treated with Whole Liver Irradiation Alone

TABLE 52.3-15. Results of Treatment of Metastatic Cancer to the Liver Treated with Whole Liver Irradiation Alone

<table>
<thead>
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<th>Technique</th>
<th>Results</th>
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<td>Whole liver irradiation</td>
<td><em>best survival of patients treated with percutaneous ethanol injection</em></td>
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<td>(either alone or combined</td>
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<td>aspartate aminotransferase, and bilirubin (which tends to be unconjugated)</td>
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<td>elevations in prothrombin time and partial thromboplastin time, and</td>
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<td>overt liver failure and death.</td>
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Table 52.3-16. Results of Treatment of Metastatic Cancer to the Liver Treated with Whole Liver Irradiation with Chemotherapy

Three techniques have been explored to increase focal radiation dose: yttrium 90 microspheres, interstitial implantation of radioactive sources, and three-dimensional conformal external-beam radiation. The theory behind the use of Yttrium microspheres is described in the chapter on hepatocellular carcinoma (see Chapter 33.5). A number of phase I trials have been conducted in patients with metastatic disease of the liver (chiefly colorectal cancer) demonstrating that an estimated whole liver absorbed dose of 100 to 150 Gy is tolerable. Furthermore, in the range of 20% to 25% of patients have shown objective responses. Yttrium microspheres become available for clinical use in the United States, it will be important to administer them with careful attention to technical details such as avoiding pulmonary shunting and perfusion of other organs (such as the stomach) by aberrant blood vessels.

A second method of delivering high doses of radiation to parts of the liver is to use interstitial brachytherapy (placement of radioactive sources inside the tumor). In one series, 22 patients were treated with a single high dose-rate application of Iridium placed in catheters implanted at the time of laparotomy. The time of...
irradiation ranged from 10 minutes to 4.5 hours as a function of the size and number of lesions. In another approach, permanent 125I seeds have been implanted at the time of laparotomy or under ultrasonic guidance. The maximum tumor size in this latter series was smaller than 5 cm. Additional phase II experience is required to assess the efficacy of these approaches.

External-beam irradiation can be used to treat patients with localized unresectable metastatic cancer to the liver. These efforts have been based on the hypothesis that, just as substantial fractions of the liver can be resected if the remaining fraction can support liver function, focal high-dose liver radiation can be safely administered if sufficient normal liver is spared. As summarized in the chapter on hepatobiliary cancer (see Chapter 33.5), conformal planning can use beams not confined to the axial plane to reduce normal liver irradiation. Furthermore, three-dimensional planned treatment has developed the quantitative understanding of the relationships among dose, volume, and risk of complication.

A phase I and II trial for patients with unresectable hepatic metastases using either standard two-dimensional techniques or three-dimensional conformal external-beam irradiation combined with hepatic arterial FUDR have demonstrated that high-dose focal radiation can produce up to 50% response rate in previously treated patients. However, the freedom from hepatic progression in one study was only 29% at 1 year, suggesting that higher doses will be required to produce long-term survival. More recent results suggest that necrosis is the primary mode of delivery and is an important prognostic factor in both local control and survival for patients with metastatic colorectal cancer. In this study, dose is prescribed (to a maximum of 90 Gy) according to the fraction of normal liver that is spared based on a normal tissue complication probability model (see Chapter 33.5). Patients who could receive greater than or less than 70 Gy have a median survival in excess of 17 months, which approaches that achieved by surgical resection. Dose was an independent prognostic factor, and was not correlated with tumor size.

CONCLUSIONS

Despite the fact that isolated hepatic metastases are a significant clinical problem frequently associated with a poor prognosis, there are evolving regional treatment strategies that involve the expansion of options available for patients with this condition. For patients with resectable hepatic deposits primarily of colorectal, neuroendocrine, or germinounary origin, the benefit in terms of overall survival or palliation appears to be well established. For patients undergoing resection for colorectal cancer, various patient, tumor, and treatment variables have been identified as important prognostic factors and can be used to select patients for adjuvant therapy. For those with unresectable colorectal cancers confined to the liver, HAI therapy using FUDR-based regimens have high response rates, but the influence on overall survival has not been conclusively demonstrated. Local ablative therapies have the advantage of being able to ablative (Cryomom's net) but their influence on overall survival has not been demonstrated. As the technology behind local ablative treatments advances, they will no doubt become more widely used alone or in combination with postablation HAI, systemic therapy, or both. Chemoeomobilization has been used in patients with advanced cancers of the liver and can result in profound reduction of those tumors, thus improving the regional clinical evaluation and may bring more widespread acceptance with further refinement of treatment in the future. HAI of a recombinant adenoviral construct containing the wild-type p53 gene is being evaluated in patients with metastatic colorectal cancer to the liver. The range of regional therapies highlighted the acknowledged importance and difficulty in treating hepatic metastases and provide an approach that can produce complete disease control within the liver with an associated improvement in quality of life and overall survival may be routinely achieved.

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INTRODUCTION

Most of the more than 560,000 people in the United States who die of cancer each year have tumor metastasis. Bone is the third most common organ involved by metastasis, behind lung and liver. In breast cancer, bone is the second most common site of metastatic spread, and 90% of patients dying of breast cancer have bone metastasis.[3] Breast and prostate cancers metastasize to bone most frequently, which reflects the high incidence of both of these tumors, as well as their prolonged clinical courses. Other tumors that commonly cause symptomatic bone metastases include kidney and thyroid cancer and multiple myeloma. The increasing age and size of the population leads to an increased number of cases of cancer. This, coupled with longer patient survival, increases the incidence of metastatic lesions to bone. Patients with bone metastasis from breast cancer have an average 2-year survival from the time of presentation with their first bone lesion. As more patients are living with bone metastases, the challenge is to improve their quality of life.

Current management of skeletal cancer involves a multimodality approach, including systemic therapies (chemotherapy, hormone and immune therapies, and other drugs such as bisphosphonates), radiation (external-beam and targeted radioisotopes), and surgery. Medical, radiation, surgical, and orthopedic oncologists, with diagnostic assistance from radiologists and pathologists, form a multidisciplinary team to manage these complex and often very ill patients. Early detection and aggressive management of metastases should be the goal, to maintain and maximize patients' quality of life and functional level. Nihilism is no longer appropriate. However, due to economic considerations and a dearth of data to support intensive surveillance for metastases, physicians may be lulled into a sense of complacency. Currently, care is optimized in only a fraction of patients with bone metastases.

PRESENTATION

Patients with metastatic disease to the skeleton most often present with pain as the principal symptom. The pain associated with bone metastasis comprises two components: biologic and mechanical. Biologic pain is related to the local release of cytokines and chemical mediators by the tumor cells, periosteal irritation, stimulation of intraosseous nerves by these mediators, and the pressure or mass effect of the tumor tissue within the bone. Mechanical pain is related to the loss of bone strength and stiffness caused by the metastatic lesion, which leads to activity-related pain. Mechanical pain is seen most often with osteolytic lesions but can also occur in osteoblastic lesions, because the disorganized pattern of tumor-related bone lacks structural integrity.

The initial pain pattern of a metastasis mimics that of primary bone tumors and osteonecrosis. The symptoms are intermittent but may be sharp and severe. Pain tends to be worst at night and may be partially relieved by activity. As the lesion progresses, symptoms become more constant and take on a more mechanical character.

Patients with metastatic disease can present with a pathologic fracture. Pathologic fractures most often occur with osteolytic lesions. The majority of pathologic fractures are seen in patients with metastatic breast cancer. In one study, the incidence of pathologic fracture was 8% in 1800 cancer patients, with 53% of those fractures occurring secondary to breast cancer metastases. Other malignant culprits for pathologic fracture in this series were kidney in 11%, lung in 8%, thyroid in 5%, lymphoma in 5%, and prostate in 3%.[3] Hypercalcemia of malignancy occurs in 5% to 10% of patients with bone metastasis and is seen predominantly in breast cancer, multiple myeloma, and squamous carcinomas of the lung. Thirty percent of patients with breast cancer will develop hypercalcemia during the course of their disease. Hypercalcemia is mediated by multiple factors: local osteolysis caused by the skeletal metastasis, parathyroid-like hormone released by the tumor cells and having both a local (paracrine) and systemic (endocrine) effect, and disuse osteolysis related to the immobility of these patients.

Neurologic abnormality related to spinal cord compression can occur with spinal metastasis. Knowledge of the course and character of neurologic symptoms is important in directing the radiographic evaluation and treatment plan. Neurologic compromise secondary to spinal involvement with metastasis has a major impact on quality of life and function.

Systemic issues include generalized debilitation, leading to immobility. Bed rest exacerbates hypercalcemia and can lead to atelectasis, thromboembolic disease, and skin pressure necrosis. In addition, patients with systemic malignancy who are immobilized are prone to developing disseminated intravascular coagulation. Careful screening for these conditions is imperative in the management of these patients. Doppler ultrasound tests are a convenient and sensitive way of identifying deep venous thrombosis. Loss of ambulatory ability is a poor prognostic factor in metastatic disease, particularly spine disease. Performance status should be specifically quantified as part of the preoperative evaluation.[3]

PATHOGENESIS

The pattern of metastatic involvement of bone is related to blood flow. Metastases most commonly occur in the more heavily vascularized parts of the skeleton, particularly the axial skeleton, including the ribs and the vertebral column, as well as the proximal ends of the long bones. Batson's plexus is a low-pressure, high-volume, valveless system of vertebral veins that communicates with the pelvic venous plexus. The high number of vertebral metastases in prostate cancer is attributed to Batson's plexus. Arterial spread may also be important. The patterns of metastatic distribution to bone seen after intracardiac injection of tumor cells in animal models are similar to those seen clinically. Histopathologic evaluation of metastatic development and distribution in these animal models confirms that the metastatic lesions originate at the terminal end of the major arteries supplying the bone. Specific radiographic evaluation of metastatic disease in the spine indicates a role for arterial spread as well.[3] A great deal of research has been conducted recently into the mechanisms of tumor metastasis. Tumor metastasis is believed to be related to several factors: angiogenesis, which allows for primary tumor growth and subsequent access to the systemic circulation to colonize secondary sites; adhesion via cell surface
molecules, which allow tumor cells to attach to other cells and to extracellular matrix components; invasion, mediated by proteolytic enzymes such as matrix metalloproteinases, which allow tumor cells to pass across extracellular matrix barriers; and proliferation, which is mediated by growth factors and the uncoupling of the normal mechanisms of cell growth and suppression. Of particular interest in bone metastases is the ability of tumor-released factors to cause osteolysis. There is evidence that this osteolysis is mediated by stimulation of osteoclastic bone resorption by tumor cytokines and direct bone degradation by tumor cells. Matrix metalloproteinases appear not only to mediate the ability of tumor cells to invade via basement membrane hydrolysis but also directly to degrade bone matrix.

Better understanding of the molecular mechanisms of metastatic tumor spread allows for the development of new therapies to target these areas, as well as more effective use of existing techniques.

DIAGNOSTIC EVALUATION

A careful history and physical examination, including careful breast or prostate evaluations and thyroid palpation, remain the cornerstone for identification of the site of primary disease in patients who present with a bone lesion without a known primary tumor. In those patients with a history of cancer and a new bone lesion, the coexistence of disease other than metastasis must be ruled out.

Plain radiographs remain the most specific test for diagnosing bone diseases. Scintigraphy is extremely sensitive and practical for use in metastatic evaluation, because it can screen the entire body at one time. Certainly, any abnormality found on bone scan should be correlated with plain radiographs.

Metastatic disease is characterized by the presence of multiple bone lesions. Single metastases occur rarely and must be differentiated from primary bone tumors. Typically, the so-called solitary metastasis is merely the first of many lesions to be identified. Thyroid and renal cancers and myeloma (plasmacytoma) are the most likely to present with an isolated metastasis. Even patients with these favorable cancers typically develop widespread disease, suggesting that there is unrecognized dissemination of cancer at the time that the first bone metastasis is identified.  

Diagnostic workup entails the use of several laboratory tests to help narrow the differential diagnosis and identify the primary site of disease. A basic screening panel includes a complete blood cell count with platelets, to evaluate for anemia and myelosuppression; serum calcium, phosphorus, and alkaline phosphatase levels to identify markers of bone turnover and evaluate for hypercalcemia; and assessment of serum electrolytes, liver function tests, and an erythrocyte sedimentation rate for systemic evaluation. If clinically indicated, such additional specific tests as the following can be ordered: parathyroid hormone level, to evaluate for metabolic bone disease; serum or urine protein electrophoresis or b2-microglobulin if multiple myeloma or lymphoma is suspected; or specific markers such as cancer antigen 125 for breast cancer or prostate-specific antigen for prostate cancer. Biochemical markers of bone turnover, such as urine N-telopeptide and urine deoxypyridinoline, also are noted to have a significant association with the probability of bone metastasis.  

The technique of screening blood and marrow with polymerase chain reaction (PCR) or reverse transcriptase–PCR (RT-PCR) for specific tumor cell DNA is being investigated as a tool for diagnosing metastatic disease and following the response to systemic therapy. The attraction of PCR technology is that it can detect a very small number of tumor cells, potentially identifying patients with marrow or circulating cancer cells who are at risk for the development of clinical metastases. As technology improves, the genetics of tumors are being better defined and the PCR technique is becoming more standardized, such that it is likely to prove a useful adjuvant in the diagnosis of, and monitoring of therapeutic response in, bone metastases patients.

Chest radiography and computed tomographic (CT) scans of the chest, abdomen, and pelvis also are used in the diagnostic workup of bone lesions without a known primary lesion. These studies can help to identify the primary tumor in 85% of patients, as well as identifying additional sites of metastatic disease. They are particularly useful because the predominant lesions causing metastases of unknown origin are lung and renal carcinomas.

A firm diagnosis must be obtained before a fracture involving a solitary bone lesion is fixed internally. Magnetic resonance imaging (MRI) can be helpful in differentiating pathologic fracture due to osteoporosis from that due to metastatic disease, particularly in the spine. MRI is also helpful in delineating the soft tissue extension and component of tumors involving bone. When the diagnosis cannot be discerned from clinical information and the baseline tests of plain films and bone scan, MRI can be a helpful diagnostic adjuvant.

Solitary bone lesions warrant a biopsy before treatment. Primary bone sarcomas occur in the same population under consideration for metastatic disease. Lytic phases of dedifferentiated chondrosarcoma and Paget's sarcoma can also produce pathologic fractures (Fig. 52.4-1). In addition, metabolic bone disease is in the differential diagnosis of skeletal abnormalities in this older age group (older than 40 years). Brown tumor of hyperparathyroidism can produce multiple lytic bone lesions, and osteoporosis can lead to pathologic fracture, particularly in the spine. Osteomyelitis can mimic metastatic disease by producing multiple fractures throughout the skeleton, resulting in a bone scan indistinguishable from that seen with multiple metastatic foci. All of these entities must be distinguished from metastatic disease, as the management of such conditions is very different from that for metastases.

![FIGURE 52.4-1. Dedifferentiated chondrosarcoma-coma presents as a predominantly lytic, destructive lesion in an older patient, mimicking a metastatic lesion. Internal fixation in this case is inappropriate, and a biopsy is needed to exclude the presence of a primary bone tumor, particularly with a solitary bone lesion such as this. A: Compression hip screw and cement used for internal fixation of a fractured chondrosarcoma. B: Gross appearance of the resected bone after removing the screw. White-gray cartilage percolates across the fracture site and into the intramedullary canal.](image)

Bone scan can be of further assistance in planning a biopsy. When the symptomatic lesion involves a weight-bearing bone, biopsy worsens the fracture risk by creating a new hole in the bone cortex. Bone scan can identify other bone lesions and possibly locate one that can be subjected to biopsy with greater ease and less morbidity.

CT-guided needle biopsy is usually satisfactory when the lesion is osteolytic, offering diagnostic accuracy of 80%. When the lesion is osteoblastic or exhibits a thick overlying cortical rim, inserting a needle and obtaining an adequate tissue sample is extremely difficult. Such cases necessitate open surgical biopsy. Regardless of whether the biopsy of a weight-bearing bone is performed by closed or open technique, there is a genuine fracture risk. Weight bearing must be protected until bone healing occurs, which experimentally has been shown to require at least 6 weeks. Sufficient tissue for immunohistochemical studies should always be obtained to improve the ability of the biopsy to yield a definitive tissue diagnosis.

TREATMENT GOALS

There are four main goals in managing patients with metastatic disease to the skeleton: pain relief, preservation and restoration of function, skeletal stabilization, and local tumor control (e.g., relief of tumor impingement on normal structures, prevention of release of chemical mediators that have local and systemic effects).

Symptomatic relief is usually satisfactory from a combination of radiation and medical therapy. Most patients without a fracture do not require surgery for the bone metastasis; however, fractures are best treated by operative internal fixation. Even when fractures can heal by nonoperative therapy, the prolonged treatment time required for closed management is inappropriate, as this period generally is increased by the presence of tumor negatively affecting the ability of the fracture to heal.
The goals of surgical intervention vary in metastatic tumor patients. Primary goals are to allow immediate weight bearing and return to activity, not necessarily to promote fracture healing. Prosthetic replacement and stabilization with polymethyl methacrylate are frequently selected, whereas such techniques would be avoided in the treatment of nonneoplastic fractures.

The duration of any management course must be carefully considered in a patient with a limited life expectancy. Generally, pathologic fractures through weight-bearing bones (e.g., femur) should be treated if the patient has more than 1 month to live, whereas non–weight-bearing bones should be treated if life expectancy is more than 3 months. Definitions and indications for treatment of impending fractures are discussed later in Impending Fractures: Prophylactic Fixation. Impending fractures warrant fixing if (1) such repair will help to eliminate the need for narcotic analgesics or will reduce the patient’s overall pain by approximately 50%, (2) equally effective nonoperative treatments are lacking, or (3) treatment for the impending fracture is significantly safer or more effective than surgery once the bone has fractured completely.

Management and intervention should be tailored to the patient's overall prognosis and life expectancy. The medical goals of patient comfort and independence are predominant in these situations. Increasing importance is being placed on quality-of-life issues and measures in these patients, and the goals of therapy have shifted from maximization of life to maximization of pain management and function. Outcome measures and quality-of-life assessment tools are being actively investigated. The Functional Living Index–Cancer (FLIC); Functional Assessment of Cancer Therapy Scale (FACT), Short Form 36 (SF-36); Karnofsky Scale; International Society of Limb Salvage–Musculoskeletal Tumor Society (ISSLS–MSTS) assessment; and Toronto Extremity Salvage Score (TESS) are tools currently in use. The Memorial Sloan-Kettering Cancer Center (MSKCC) is moving toward use of the FACT and away from the FLIC. Other tools are being developed and validated that pertain not only to patients with cancer but also to those with musculoskeletal issues. These new functional assessments strive to combine the recently developed American Academy of Orthopaedic Surgeons Modern with oncologic assessments such as the Health-Related Quality of Life (HR-QOL) and the FACT. These tools will be increasingly important in evaluating the efficacy and value of new therapies for patients with metastatic bone disease.

**IMAGING OF BONE LESIONS**

**PLAIN RADIOGRAPHY**

Plain radiographs are the foundation of evaluation, surgical planning, and monitoring of metastatic lesions of bone. Radiographs are a fast, inexpensive, and readily available technique for evaluating bone metastases. Other techniques may be more sensitive, but radiographs give the best integration of overall bone structure and alignment and correlate best with clinical features. Therefore, plain radiography should be the first test ordered in the evaluation of bone pain.

Three radiographic patterns of metastatic disease typically are seen: osteolytic, osteoblastic, and mixed. Because of variations in the bone microenvironment and clonal differentiation of tumors, different patterns may exist throughout the skeleton or within a single bone. Prostate cancer metastases are classically osteoblastic, breast cancer and lung metastases usually show a lytic or mixed pattern, and lung cancer metastases are predominantly lytic. Radiographic variability can also be seen during the course of therapy, as the radiographic appearance of a lesion changes during treatment. Osteoblastic areas seen radiographically correspond to the reaction of the host bone to the metastases, not to the tumor itself. Fast-growing tumors tend to have a lytic or mixed pattern, and the bone reaction cannot keep pace with the rate of tumor growth. Reactive bone often lacks mechanical strength, as it forms in a random pattern lacking normal Haversian structure.

Periosteal changes can also occur with metastatic disease to the bone. Rapidly growing tumor can elevate the periosteum, causing an irregular periosteal reaction. Lung cancer and prostate cancer with cortical involvement commonly display this pattern. Stress fracture through the underlying bone lesion can also be associated with periosteal reaction. Nevertheless, periosteal elevation is usually a hallmark of primary bone neoplasm; therefore, sarcoma should be excluded when periostitis is present.

Radiographs assist greatly in surgical planning. Disease spreads diffusely within long bones. In patients with proximal femoral metastases in whom radiographic evaluation is confined to the hip, potential lesions distal in the femur are overlooked. It is important that the entire bone be imaged, so that all lesions can be addressed and stabilized during the same operative procedure.

Finally, sequential radiographs of involved areas are important for monitoring response to treatment, local recurrence, and disease progression. X-ray films of subclavicular symptomatic regions are important for detecting further metastatic foci, allowing for early intervention and management. In addition, certain tumors (most notably multiple myeloma) do not stimulate the increased bone turnover required for positive readings on bone scan. Patients with such tumors are best evaluated for other foci of skeletal disease by a plain radiographic skeletal survey.

**BONE SCLINTIGRAPHY**

Technetium diprophosphate bone scans are extremely valuable in identifying occult bone lesions and diagnosing metastatic disease. Whereas 30% to 50% of bone mineral must be lost for a lesion to appear on plain radiograph, bone scans show skeletal involvement much earlier. Bone scintigraphy is an essential part of cancer staging for skeletal metastases, identifies sites of both symptomatic and asymptomatic lesions, and locates potential sources of referred pain. In 85% of patients with metastatic cancer to bone and a single symptomatic focus, multiple additional foci will be seen on bone scan. Certain tumors, such as lung cancer and melanoma, grow rapidly and evoke little reactive bone formation, leading to false-negative scans. In addition, multiple myeloma is notorious for resulting in false-negative bone scans, because bone lesions lack anatomic detail and, although they can localize the site of involvement, the specific characteristics of the lesion are not visualized. Bone scan results can be correlated with additional imaging modalities such as plain-film radiographs or CT scans.

Bone scintigraphy can be used to evaluate the response to chemotherapy, hormone therapy, or radiation therapy, by reflecting the biology of the lesion and the extent of the host response. The method has been most useful in evaluating treatment in breast cancer patients. Up to 15% of patients will experience an initial increase in radioscope uptake on bone scan with treatment, called the flare phenomenon. This reflects new bone formation as a healing response around the quiescent lesion. Over time, the surrounding bone heals, and osteoblast activity, which is estimated by the uptake on bone scan, will diminish. Development of additional scintigraphic lesions early in treatment does not necessarily reflect disease progression. Instead, this can reflect healing and ossification of areas where the tumor did not evoke a response initially.

A limitation of the bone scan technique is that it measures solely the metabolic activity of the bone and not its structural integrity. Biologic control of the tumor does not necessarily translate into mechanical restoration of the skeleton. Therefore, close correlation of follow-up bone scan information with plain radiographs or CT scanning is necessary.

**COMPUTED TOMOGRAPHY**

CT scanning is very effective in evaluating the three-dimensional integrity of bone and the characteristics of lesions identified on bone scan. It helps to confirm the presence of metastatic disease, particularly when evaluating lesions localized to the pelvic and shoulder girdles. Spine lesions can also be imaged by CT scans but are better evaluated by MRI in most circumstances. CT scanning is superior to MRI in demonstrating bone mineral content and cortical integrity and is therefore more definitive to the structure of the involved bone. MRI will often show extensive marrow involvement in a bone, even though the structural integrity is preserved. CT scans help to discriminate between the presence of cellular and structurally significant disease.

**MAGNETIC RESONANCE IMAGING**

MRI is an excellent technique for evaluating bone marrow, which is the first site of metastatic involvement of bone. MRI is particularly useful in round cell lesions such as leukemia, lymphoma, and multiple myeloma, which replace the marrow space. The high fat content of bone marrow translates to high signal intensity or brightness on T1-weighted and low signal intensity on T2-weighted images. This environment provides a contrast medium juxtaposed to the tumor, which, because of its high water content, has high signal intensity on T2-weighted and low signal intensity on T1-weighted images.

MRI provides good three-dimensional anatomic information throughout the skeleton and is excellent in defining soft tissues and delineating soft tissue involvement by tumor. In the spine, MRI is especially useful because it is sensitive for tumor involvement, shows sagittal and cross-sectional alignment, and details tumor present in the spinal canal, dural impingement, and spinal cord compression. MRI is particularly helpful in distinguishing between pathologic fracture due to osteoporosis and
that due to tumor. This is particularly important for postmenopausal women, who may experience both metastatic disease and osteoporosis. MRI is useful in the evaluation of skeletal metastatic disease but is an imperfect discriminator and therefore requires close correlation with additional studies and the clinical situation.

**POSITRON EMISSION TOMOGRAPHY**

Positron emission tomography (PET) scanning is a newly used tool in the evaluation of metastatic bone disease. Though nonspecific, PET scans identify metabolically active areas by their differential uptake of radiolabeled glucose ([18]FDG), similar to the technetium labeling of areas of bone turnover in bone scan. PET scanning was used in a study of 29 patients with bone metastases and an unknown primary tumor in whom conventional diagnostic workup had failed. In these 29 patients, all but one known metastatic site was visualized by PET scan, and additional metastatic sites were identified in 5 patients. PET was able to identify the primary tumor in only 7 of these 29 patients (24%). Data regarding the current clinical relevance of PET scanning are limited. The technique is used predominantly in an investigational role. However, PET scanning does show utility in selected instances for diagnosis of bone and soft tissue metastases.

**THERAPEUTIC MODALITIES**

Multiple therapeutic modalities are available in the armamentarium for management of metastatic disease to bone. These modalities comprise three broad categories: systemic therapy, radiation therapy, and surgery.

**SYSTEMIC THERAPY**

Systemic therapies include chemotherapy, bone marrow transplantation, hormone therapy, immunotherapy, and medications. The medical oncologist directs the majority of systemic management. Systemic chemotherapy with antineoplastic agents is primary tumor–specific. Until the development of bisphosphonates, no specific drugs were directed to the general entity of bone metastases. Bisphosphonates have shown great utility in the management of patients with metastatic bone lesions, most notably in cases of breast cancer and multiple myeloma.

**Bisphosphonates**

Bisphosphonates are stable analogs of naturally occurring inorganic pyrophosphate. They inhibit the precipitation of calcium phosphate in vitro and biologic calcification in vivo. They also inhibit bone resorption, particularly that occurring in certain metastatic lesions of bone. The mechanism by which bisphosphonates inhibit bone resorption is inhibition of osteoclasts by interruption of the mevalonate metabolic pathway and, possibly, by causing osteoclast apoptosis as well.

First-generation bisphosphonates such as clodronate and etidronate, second-generation drugs such as tiludronate and pamidronate, and third-generation medications such as ibandronate and zoledronate, have differing potencies and effects. The bisphosphonates are generally safe compounds with few side effects. The drugs are not metabolized in the human body, with 50% to 60% of each dose rapidly absorbed by bone, followed by slow renal elimination; the other 40% to 50% is rapidly excreted by the kidneys.

Bisphosphonates have proven efficacy in the treatment of hypercalcemia of malignancy, Paget's disease of bone, osteoporosis, and bone metastasis in breast cancer and multiple myeloma. Pamidronate is approved for use in hypercalcemia of malignancy. Paget's disease, and bone metastasis, whereas therapeutic approval for other bisphosphonates varies: Etidronate is approved for use in hypercalcemia of malignancy, alendronate for the treatment of osteoporosis, and tiludronate for the treatment of Paget's disease. Pamidronate, 90 mg by IV infusion every 3 to 4 weeks, is the dosing regimen that has been shown to provide the most rapid onset of pain reduction and increased mobility, with minimal side effects. Several large randomized trials have been performed to analyze the efficacy of pamidronate in the management of metastatic bone lesions.

Theriault et al. reported on their randomized, double-blind trial involving 372 patients with breast cancer and at least one lytic bone lesion who received standard hormone therapy. The skeletal morbidity was significantly reduced in the patients receiving pamidronate; however, there was no significant difference in survival or overall outcome rate. Not until 6 months was a difference observed between the two groups, at which point the curves diverged, with an upward shift of the placebo group's skeletal event rate curve, though the curves for both treatment groups maintained the same slope.

Horobagyi et al. reported on their randomized, double-blind trial involving 382 patients with metastatic breast cancer and lytic bone lesions who were receiving standard chemotherapy. Again, a significantly decreased risk of bone lesion complications was seen in the pamidronate group as compared to the placebo group.

Berenson et al. reported on their randomized, double-blind trial of 392 patients with stage III myeloma and at least one lytic bone lesion who were receiving either first-line or second-line antimyeloma chemotherapy. There was a significant reduction in skeletal events in the pamidronate group, although survival was not different between the pamidronate and placebo patients. Again, the skeletal event curves of the pamidronate and placebo groups diverged, in this instance from the initiation of the study. The placebo group's curve was shifted upward, but the two curves continued to have similar slopes, as was seen in the breast cancer trials.

In light of the outcomes from these large randomized trials, bisphosphonates have been added to the therapeutic armamentarium in the treatment of bone metastases due to breast cancer or multiple myeloma. Although bisphosphonates have not been proven to be efficacious in managing bone metastasis due to other tumors, theoretically these compounds should be of value in all cancers causing lytic bone lesions. There is also evidence that bisphosphonates may actually prevent the development of bony metastases. In several animal models, injected tumor cells failed to establish colonies in bone that had been pretreated with bisphosphonate.

The magnitude of benefit of bisphosphonates in other cancers, its possible early use in the management of patients with metastatic disease, and the details of the mechanism of action of this drug class all warrant further investigation. Despite their benefits, bisphosphonates act over the course of several months. When a more rapid response is needed, radiation therapy or surgery (or both) still are required.

**Chemotherapy and Hormone Therapy**

Because of the significant percentage of patients with breast cancer who develop metastatic bone lesions, the effects of chemotherapy and hormone therapy on these lesions have been investigated. The goals of chemotherapy and hormone therapy in patients with metastatic disease involving bone are pain control, disease stabilization, and reduction of the risk of morbidity events (e.g., pathologic fracture). In a series of patients from the M. D. Anderson Cancer Center who were treated with doxorubicin, tamoxifen, and cyclophosphamide, bone lesions showed an 18% complete and a 65% partial response to the regimen.

Hormone-sensitive breast carcinoma has a predilection to metastasize to bone; therefore, hormone therapy can be effective in these cases. As with other therapies, a pretreatment lesion ‘flare’ may occur that makes the evaluation of overall response difficult. However, the use of chemotherapy and hormone therapy in metastatic breast cancer has been shown to prolong survival and can render patients better able to respond to bone lesion–specific therapy such as bisphosphonates or systemic radionucleides, reducing overall skeletal morbidity.

**RADIATION THERAPY**

**External-Beam Radiation Therapy**

Radiation is an important technique for treatment of tumor that has metastasized to the bone. The indications for radiation therapy are pain relief and suppression of local tumor growth. Suppression of local tumor growth is important in the treatment of impending fractures, after surgical fixation of metastatic lesions, and in the treatment of neural compression. This is exemplified by irradiation of tumor for spinal cord compression. Tumor reduction and pain relief can begin immediately, particularly for very radiosensitive round cells tumors. Thoughtfully planned treatment with high-energy radiation causes minimal morbidity, and the benefits far exceed the risks in most situations. Radiation is of therapeutic value in patients with localized symptomatic lesions and should be considered in all but the few cases in which either the disease is very responsive to systemic treatment (e.g., germ cell tumor, lymphoma) or the lesions are resectable for cure.

Despite its efficacy, radiation therapy should not be used indiscriminately. Marrow fibrosis can be a late complication that precludes chemotherapy. The radiation oncologist must collaborate with the medical oncologist and surgical personnel to optimize treatment. This interdisciplinary cooperation is critical in the management of an impending fracture. Occasionally, a lesion will heal with radiation therapy, especially if it is mechanically protected. Treating an isolated lesion may allow the radiation oncologist to use a narrower radiation field. However, fracture and subsequent inamedullary fixation necessitate treatment of the entire bone, which can be...
difficult to implement if a radiation treatment protocol has already been applied within the new field.

More than 80% of patients with a limited number of well-localized bony metastases can be treated effectively by external-beam irradiation. High-dose radiation, coupled with careful subsequent observation, is suitable, cost-effective oncologic management for most cancer patients, especially if the available chemotherapeutic regimens are not well established. Radiation may render the patient asymptomatic and control the disease for an extended period.

Patients with numerous areas of skeletal involvement require systemic therapy. Chemotherapy or endocrine therapy is the most appropriate. If symptoms persist over the course of several months, alternative management for localized disease should be considered. External-beam irradiation to the most symptomatic or potentially troublesome areas should be used to supplement systemic therapy. Hemibody or systemic radionuclide therapy should be considered for widely disseminated bone disease.

Metastases involving the spine are best treated early in the course of disease because progression can produce grave morbidity. The spine should be braced until the lesions can heal. Irradiation of a weight-bearing bone such as the femur should be undertaken only after careful evaluation of the potential fracture risk produced by the underlying lesion (as discussed later in Impending Fractures: Prophylactic Fixation). There is an increased risk of pathologic fracture in the periirradiation period due to an induced hyperemic response at the periphery of the tumor. This weakens the adjacent bone and increases the risk of spontaneous fracture. Mechanical protection is important until the bone's structural integrity has been restored. Identification of disease progression and management of associated medical problems is very important during the course of therapy, because other treatments often are suspended during this time. The interdisciplinary communication essential for high-quality treatment often is best provided through a medical practice environment in which all the specialists are in geographic proximity. This minimizes the need for excessive travel by the patient who is experiencing a limitation in mobility and is at risk for fracture.

TREATMENT PLANNING. Data from a patient's medical history, physical examination, bone radiographs, and three-dimensional imaging help to direct radiation fields. The radiation fields should include all soft tissue masses as identified by the aforementioned studies. The margin of normal tissue treated around the lesion is variable. The goal, as in surgery, is to avoid having to treat the same bone on multiple occasions. MRI is used to image proximal and distal lesions in the spine. Appropriate radiation portals can then be defined to avoid repetitive irradiation of the spinal cord. Careful planning in this fashion avoids overtreatment and complications such as transverse myelitis, bowel toxicity, and peripheral edema.

Radiation suppresses hematopoiesis in the bones within the treatment portal. Narrow suppression is a more significant concern in patients receiving chemotherapy, and even this suppression can be severe. Aggressive chemotherapeutic regimens that depress stem cell populations are the most dangerous in this regard. Complete blood cell counts must be closely monitored, often on a daily basis.

PAIN RELIEF. Irradiation achieves at least partial relief of pain in 80% to 90% of patients. The speed of response varies. When the cause of pain is neurologic, tumor regression can be prompt and relief rapid. Spinal cord compression from lymphoma is a classic example of this phenomenon. Most symptomatic bony metastases begin to respond over the course of 10 to 14 days. Seventy percent of patients experience some pain relief within 2 weeks of starting therapy and, within 3 months, 90% of patients achieve pain relief. Tong et al. from the Radiation Treatment Oncology Group (RTOG) found that approximately 55% to 70% of patients who responded initially did not develop recurrent pain in the treatment field. These data support other studies that note sustained pain relief for 1 year or more in 55% to 65% of patients. There is no convincing evidence that different histologic cancers respond differently to irradiation. Although undoubtedly there are some variations, they seem to be as great among cancers of the same histologic type as they are between primary cancer types.

Evaluation of pain relief and tumor responsiveness has failed to account properly for the mechanical contribution to pain. Even when cancer cells respond well to therapy, lytic tumors may lack matrix, and thus the underlying bone may require more time to restore its mechanical strength. This may explain the clinical observation that radiation is less successful in palliating lung and kidney cancer lesions, which tend to be predominantly lytic. The RTOG reported that patients with breast and prostate metastases, cancers that have a significant amount of associated matrix, derived better pain relief from irradiation than did patients with long bone lesions from other primary tumors. Patients with more severe and frequent pain as well as those in whom other treatments have failed are in a poor prognostic category.

When patients do not achieve relief on a therapeutic schedule consistent with that already described, a separate etiology should be considered for the pain. The clinician should have a high index of suspicion for comorbid conditions. A sudden increase in pain after the start of treatment may indicate that a pathologic fracture has occurred. Radiographic and orthopedic evaluation should be obtained before the radiation course is continued.

DOSAGE AND FRACTIONATION. The optimal dose and fractionation regimen for palliative therapy of metastatic bone lesions is debated. Dose, duration, and fractionation of treatment are interrelated concerns. Metastatic cancer patients with limited life expectancies should receive effective treatment over as short a time course as possible. Short-term toxicity is the major concern in patients with pathologic fractures because of their reduced life expectancies. Short-course irradiation minimizes the number of treatment days and necessary travel time while producing high response rates.

The RTOG's randomized study of differing dose fractionation schedules in 759 patients reported no significant difference in pain relief among five different schedules of fractionation (270 Gy × 15, 300 Gy × 10, 300 Gy × 5, 400 Gy × 5, and 500 Gy × 5). Complete pain relief and the elimination of the need for narcotic analgesics were seen consistently with all fractionation regimens. Retrospective analysis of the RTOG data suggests that the 270 × 15 or 300 × 10 regimens were most effective. At the Royal Marsden Hospital, 268 patients were treated for painful bony metastases with either 800 Gy × 1 or 300 Gy × 10. The response rate in each arm of the trial was 80%. Retrospective analysis of single low-dose (400- to 1500-Gy) versus multiple moderate-dose (2000- to 4000-Gy) programs have shown remarkably little difference. These studies indicate that there is no consistent dose-response relationship governing pain relief after the irradiation of bone metastases. The heterogeneous nature of patients studied, however, and differences in posttreatment survival times may mask such a relationship.

Some authorities continue to recommend higher doses and longer courses of irradiation to palliate bone metastases. The effectiveness of high-dose therapy is supported by Arcangeli and Micheli, who reported that doses of more than 4000 Gy effected a higher complete response rate. Therefore, patients with a projected long survival and good performance status may be best treated by a full dose (more than 4000 Gy) with conventional fractionation.

Patients with disseminated bone metastases are candidates for hemibody irradiation. This method is an alternative for patients for whom localized treatment would be inadequate and effective systemic therapy is lacking. The usual protocol is the administration of 6 to 10 Gy in one fraction to the upper, middle, or lower body. Premedication with antihistamines and corticosteroids and hydration are necessary to treat the acute radiation effects. Response rates are consistently in excess of 70%, with more than 20% of patients experiencing complete relief and fewer than 50% requiring additional irradiation for recurrent bone pain. Toxicity occurs in fewer than 10% of patients, and severe toxicity is less common in treatment of the middle or lower body. Prostate cancer appears to be particularly well suited for this form of therapy. Persistent palliation of pain until death has been noted in 82% of patients receiving upper body irradiation and in 67% of those receiving lower body irradiation. However, concerns regarding the permanent impact on bone marrow reserve, with the possible future need for chemotherapy in these patients, has made hemibody irradiation less popular, particularly in the setting of available systemic radiotherapeutics that target metastatic foci and do not carry similar systemic risks.

Systemic Radionuclides

The systemic administration of radionuclides can be very effective in treating symptomatic bone metastases. This approach is appealing compared with any other local or systemic therapy in that it treats all involved sites rapidly and selectively, thereby reducing toxicity and enhancing the therapeutic ratio. Strategies include using a carrier that targets the tumor or a vehicle that localizes in bone matrix. The antineoplastic effect both relieves pain and allows for healing of the underlying bone lesion. Iodine 131 is the prototype, localizing within well-differentiated thyroid carcinoma cells.

Strontium 89 is the most commonly used radioisotope in bony metastatic disease and is advocated for a variety of primary cancer histologic types. It localizes in the mineral of bone by combining with the calcium component of hydroxyapatite. Actively calcifying areas concentrate most of the isotope, just as with radionuclide scintigraphy. Therefore, it has particular efficacy in osteoblastic lesions, such as those occurring with metastatic prostate or breast cancer. Degradation of the isotope in the host bone administers local short-acting radiation to the adjacent cancer cells. Sr89 has very good response rates ranging from 51% to 91%. Patients with prostate cancer showed more than 80% symptomatic improvement after Sr89 therapy. The only significant toxic effect of Sr89 is myelotoxicity, with a 25% reduction in platelets and leukocytes, and it is usually temporary.
The low-energy b-emission of 89Sr is safer and better tolerated than are high-energy isotopes such as orthophosphate 32. Other radiopharmaceuticals are also available, including such isotopes as 186Re, tin-113m-dihydroxynonrelamine-pentaacetic acid, 125I, and gallium nitrate. The mechanism of action relates to the half-life of the isotope in the lesion, the penetration and mean energy of emitted radioactive particle, and the delivered dose. Isotopes with short half-lives, such as 186Re, emit both γ rays, permitting imaging of lesions, and β-particles, which confer therapeutic value. All agents cause bone marrow suppression, which is worse in heavily pretreated patients undergoing chemotherapy. However, premedication, as is required with hemibody radiation, is not necessary with the use of systemic radiocurides.

Radiopharmaceuticals can cause an initial exacerbation of pain (the flare response) in 10% to 15% of patients. A flare response can indicate good overall analgesic value. In addition, it has been shown that 89Sr can be safely used in conjunction with external-beam irradiation, either in patients who have previously received wide-field radiation and present with symptomatic bony lesions or in patients who have not received previous external-beam irradiation and so can receive external-beam irradiation subsequent to treatment with 89Sr. 33, 34

SURGERY

General Considerations

BONE MECHANICS. Bone strength depends on a combination of material and structural properties. Material properties are of greatest importance when overall bone geometry remains unchanged. Alterations in bone mineral content influence strength and stiffness exponentially. Alterations in bone proteins after chemotherapy or radiation therapy may influence the ability of bone to reconstitute. Bone structural properties reflect the underlying geometry and distribution of material in space, integrating the contribution of medullary trabecular bone and cortical compact bone. Both lytic and blastic lesions dramatically alter the bone modulus of elasticity and reduce bone strength. Lytic disease reduces bone strength more so than blastic metastases. However, blastic metastases also reduce bone strength secondary to the disorganized nature of this tumor-related bone.

Most of the compressive strength of bone is due to its mineral component, whereas it is the combination of mineral and protein that lends strength in tension. During normal activity, most forces are either of compression or tension. Torsional or rotational forces, which come into play when the lower extremity is planted and the patient pivots, are also important. These forces typically occur during transfers such as getting into and out of a chair. Bone is weakest in torsion. A single 6-mm drill hole, the size used for bone biopsy, reduces torsional strength 50%. Larget defects create even greater stress risers, decreasing torsional strength by 70% and more. Defects larger than the diameter of the bone are termed open segment defects and can reduce both bending and torsional strength as much as 90%. Weak bone tends to fracture in a transverse configuration, as compared with normal bone, which fractures in an oblique or spiral pattern. Overall bone alignment usually is good in pathologic fractures as long as a large destructive lesion is not present.

BONE BIOLOGY. The local presence of cancer precludes bone healing in most pathologic fracture situations. The rapid growth of metastatic lesions overwhelms the healing response. Gainor and Buchert 35 evaluated 123 patients with pathologic long bone fractures. Healing occurred in 45 of the 129 fractures (35%). Healing rates were related to tumor type: In this series, 67% of fractures due to multiple myeloma, 44% of fractures due to renal cancer, and 37% of fractures due to breast cancer healed. No pathologic fractures due to lung cancer healed.

The length of patient survival correlated best with fracture healing rates, although healing was considered multifactorial. The five factors that related to the healing of pathologic fractures included diagnosis, survival, internal fixation, postoperative irradiation, and chemotherapy. Melanoma and lung and colorectal cancers failed to heal. Lesions due to multiple myeloma and breast and renal cancers tended to heal most frequently; however, they also occurred earlier in the course of these diseases, while other therapeutic options still remained. Survival was directly related to diagnosis, and this correlated with improved healing rates for patients living longer than 6 months. Rigid internal fixation supplemented with bone cement was found to increase the probability of bone union. Bone cement not only contributes to stability but also may present a mechanical obstacle to tumor growth in the fracture region. High doses of postoperative radiation (>3000 cGy) were associated with poor healing. Because of the variety of agents and therapeutic courses of chemotherapy, this series could not extrapolate the influence of chemotherapy on fracture healing. However, other studies suggest that healing is reduced 50% by such common agents as methotrexate and doxorubicin. Other systemic factors may make a contribution to fracture healing in patients with metastatic bony lesions, including osteoporosis, hormone manipulation, and cachexia.

Fracture Treatment

Management of pathologic fractures with internal fixation or prosthetic replacement is the most effective and expedient means by which to control pain and restore function. Adequate bone alignment and length accurately when treating open or closed segment defects is essential to rapid bone strength in bending and torsion, and allow immediate weight bearing. Stabilization of a fracture requires control of the proximal and distal fracture fragments. In this respect, fracture location is an important consideration, and management strategies are different for epiphyseal, metaphyseal, and diaphyseal locations.

EPiphyseAL FrACTURES. Epiphyseal fractures present the easiest problem. Fracture healing is not a consideration, even with nondisplaced fractures, because it almost never occurs. Resection of the fracture and associated diseased tissue is appropriate, and arthroplasty should be performed, usually involving a cemented implant. Stem length should be chosen to treat existing or potential lesions within the same bone. Widespread use of bisphosphonate therapy may reduce the need for long-stemmed prostheses in the future.

METAPHySEAL FrACTURES. Metaphyseal fractures are more complex. The fracture geometry, quality and quantity of residual bone, and histologic subtype must be considered. It is especially important to judge the fracture healing potential using the Gainor criteria discussed in the previous Bone Biology section. If a patient is early in the course of treatment, effective systemic therapies are available, and the tumor is sensitive to irradiation, internal fixation can support the bone while healing occurs. Lymphoma, occasionally myeloma, and breast cancer are the tumor types for which a long-term, bone-healing strategy has merit.

Internal fixation methods are familiar to orthopedists who treat nonpathologic fractures. Techniques can be classified according to their use of load-bearing devices (plates and screws) or load-sharing devices (intramedullary rods). A good indication for plate and screw fixation in metaphyseal fractures is densely sclerotic bone, for which intramedullary fixation or the insertion of a prosthetic device with a long intramedullary stem would be very difficult. One drawback of plate and screw fixation is that the entire bone is not stabilized in the same procedure. This leaves the patient susceptible to a future fracture proximal or distal to the fixation. Plating techniques also are more prone to failure than are intramedullary fixation methods. Djistla, 3 citaing a series of 167 fractures, reported that plate fixation is associated with an 11% failure rate within 7 weeks and a 40% cumulative 5-year failure rate. However, intramedullary fixation of metaphyseal fractures often is impractical because of inadequate control of the epiphyseal fracture fragment by the device.

Prosthetic replacement of metaphyseal lesions can be very difficult. Generally, the bone in the surrounding apophyseal areas should be saved because it helps to retain soft tissue attachments. Exceptions of these areas are the greater and lesser trochanters of the hip and the greater and lesser tuberosities of the humerus. Securing these attachments to a hemiarthroplasty device in a dependable fashion is difficult. When necessary, supplemental fixation methods with mesh, tension bands, wires, or cable systems can be used, but the constructs are usually unsatisfactory and result in persistent muscle weakness and pain. In addition, it is difficult to achieve rigid internal fixation and length accurately when treating metaphyseal fractures with prosthetic replacement. In these instances, the significant bone loss resulting from the metastatic lesion that indicates prosthetic replacement also eliminates or distorts the typical bony landmarks needed to orient the reconstruction. Problems with limb length inequality, joint instability, and limb weakness typically follow such surgical attempts.

DIAPHySEAL FrACTURES. Diaphyseal lesions are treated successfully by intramedullary fixation. The method requires the establishment of excellent fixation proximal and distal to the fracture. This often is possible even when there is total destruction of the affected area. Fixation is achieved by combining interlock screw fixation with cementing of the bony defect. Flexion and bending strength are well restored with intramedullary rods. Compression strength depends on the magnitude and extent of bone deficiency. Methyl methacrylate cement used to fill bone gaps restores strength in compression. Torsional strength and stiffness are restored poorly by intramedullary devices; therefore, successful use of such devices requires the limitation of torsional forces and the use of appropriate interlocking technique and cement to control the proximal and distal bone fragments. 3 If such control is lacking, plate fixation should be considered.
When diaphyseal lesions are combined with a metastasized tumor deposit, prosthetic replacement with a long-stemmed device removes the metastasized disease and stabilizes the diaphyseal shaft fracture with strong intramedullary fixation. 23 The secondary tumor deposit should be treated, in most instances, even if this necessitates opening of the fracture site. Closed intramedullary fracture treatment should be reserved only for those fractures that will heal with stabilization and supplemental radiation or in patients with rapidly advancing preterminal disease in whom the fixation alone will outlast the patient's projected survival. Long-term success of the technique requires good apposition of bone fragments and removal of local tumor so that healing occurs.

**OTHER MANAGEMENT OPTIONS.** Although most surgeons and patients choose internal fixation or prosthetic replacement as the most effective treatment of pathologic fractures, other management options are available. These include external fixation, cast or brace immobilization, and amputation.

External fixation and cast or brace immobilization can be considered in patients (1) with extensive localized disease that cannot be immobilized by internal means; (2) who are preterminal and in whom anatomic modalities such as narcotics or rhizotomy can control symptoms; or (3) in whom infection, nadr sepsis, pneumonia, or other temporary medical problems prevent surgery. These measures can be used in the hospital and translate well to outpatient, home, or hospice care situations.

Amputation continues to play a role in the management of metastatic cancer, with complications of disease and therapy triggering the need for amputation. 55-58 The indications for amputation fall into three categories: (1) extremity lesions that cannot be reconstructed or are inappropriately reconstructed; (2) complications of the tumor or treatment, such as a fungating infected lesion; and (3) intractable pain.

Acrometastases (metastases that occur in the distal extremity) present at variable times during the progression of metastatic disease. They are rare, occurring in 0.007% to 0.3% of patients with osseous metastasis, and usually represent a preterminal event. Lung, renal, and esophageal cancer accounted for 48% of the primary lesions causing the 31 cases of acrometastases reviewed by Healey et al. 21 In this review, seven of the cases were the first presentation of cancer, and another seven cases constituted the first presentation of metastatic disease.

Amputation is quite suitable for a distal extremity lesion, particularly in the foot. Depending on the primary diagnosis, amputation may provide an opportunity for extended disease control of early or solitary metastases. Because rehabilitation of distal sites can be difficult and time-consuming, amputation presents the best way to relieve symptoms and resume function.55,56 More proximal amputations are considered in the lower extremity, particularly when complex reconstruction would be required. The aggressive treatment methods developed for limb salvage in primary bone tumors are an inappropriate use of time and resources in skeletal metastases. Intractable pain is sometimes an indication for amputation, but rhizotomy and chordotomy can accomplish the same goal while retaining the extremity.

Recent interest has been demonstrated in a technique that uses radiographically guided percutaneous injection of polymethyl methacrylate into certain metastatic bone lesions. The basic goal of this technique is to address mechanical symptoms by improving the mechanical stability, particularly in compression, of bones involved by lytic lesions. In vertebroplasty, under radiographic guidance, liquid methyl methacrylate is injected directly into vertebral body lesions. One of the major complications of the injection technique is the extravasation of cement from within the contained bone space, with impingement on adjacent structures. This is particularly important in the spine, where spinal cord compression by cement can cause catastrophic neurologic compromise and requires immediate surgical decompression.54,55 With use of this technique for pelvic lesions, reported complications include intraarticular extension of cement into the hip joint and extravasation around the sciatic nerve.54 One of the contraindications of the technique is associated fracture, which allows for extravasation of the injected cement outside the bone. Because of the complications associated with percutaneous injection of polymethyl methacrylate, it is important to coordinate the procedure to allow for emergent surgical backup to address acute extravasation issues.

**Tumor Excision**

The metastatic tumor deposit should be excised under most fracture circumstances and in selected instances of bone biopsy, treatment of impending fracture, and solitary bone metastasis. Treatment options consist of intralesional excision, wide excision, or excision plus a surgical adjuvant.

Intralesional therapy occurs either at the time of biopsy or as a planned intervention. Once the biopsy confirms metastatic disease, a decision must be made as to whether to remove all gross disease, debulking the tumor, or to rely on external irradiation and systemic therapy for local control of the lesion. It is helpful if the members of the oncology team discuss the treatment options before beginning a course of therapy. Judgment, sensitivity, and skill are needed to integrate the biopsy process with overall tumor management and to prepare the patient and his or her family appropriately before surgery. Combining biopsy with tumor removal and bone stabilization best meets the goals of diagnosis, pain relief, and functional restoration. This is particularly important because biopsy further disrupts the already weakened bone.

Intralesional curtailage of tumor in and around the fracture site is the principal strategy in addressing metastatic lesions involving bone. Eliminating gross tumor achieves an immediate "partial response" that could take weeks to be achieved by other methods, improving local tumor control. Furthermore, the remaining structural bone is identified. The resultant defect can be filled much more effectively with methyl methacrylate cement, giving better long-term stability to the fractured bone. 62

Extraleosional excision can be accomplished by either marginal or wide excision. The appeal of complete local excision is obvious. It is the most effective way to eliminate the biologic contribution to pain while correcting the structural deficiency. Isolated solitary metastases should be evaluated for potential resectability. 51 Ocuational cures are reported after resection of bone metastases, but these are infrequent. Radical ablative surgery usually is not appropriate. A long interval between primary tumor presentation and the development of a metastatic focus argues well for cancer resectability. Patients with a projected long survival, such as those with endocrine cancers, are best served to undergo extraleosional excision of metastases. The sacroiliac region and spine are common sites of a solitary metastasis. Tumors in these areas are large and bulky, and the surgery is dangerous. Plasmyctomias should also be considered for resection. Even if systemic disease later develops, some clinicians contend that survival may be prolonged in surgically resected cases. 52,53

Surgical adjuvants are helpful, whether intralesional or excisional procedures are considered, and include angiography, cryosurgery, chemotherapy, and radiation therapy. Preoperative angiography and tumor embolization greatly reduce blood flow and intraoperative hemorrhage, particularly in vascular tumors such as thyroid and renal cell carcinoma. 54-56 and 57,58 Cryosurgery can be used in the local management of bone lesions 59 andcove pioneered its use in metastatic disease. It is particularly suited for cancers that have failed to respond to systemic treatment or local radiation therapy and in which local tumor progression is expected. 60,61

The addition of chemotherapeutic agents to the methyl methacrylate bone cement used in implant and fixation constructs is under investigation as a method of local delivery of antineoplastic drugs for enhanced local, and potentially systemic, disease control. Preliminary studies show promising results, but further clinical investigation is required before this method can be entered into the therapeutic armamentarium. 62,63

Radiation therapy remains the principal surgical adjuvant. It should be delivered to the entire surgical field and extend the length of any prosthesis or internal fixation device.62,64 This addresses tumor cells that have been spread by the surgical procedure along the intramedullary canal and soft tissues. Local tumor control helps to prevent destabilization of the implant construct by preventing local tumor progression from affecting the structural integrity of the bone in which the implant is fixed.

**Impending Fractures: Prophylactic Fixation**

There is no specific definition of an impending fracture, and the indications for operative treatment of impending fractures continue to be controversial. This controversy remains extant in part because of the evidence in the literature. Snell and Beals, 65 in their review of 19 pathologic femur fractures due to metastatic breast cancer, found that a lesion of 2.5-cm diameter involving the femoral cortex with pain, irrespective of location, was a positive predictor of pathologic fracture. Parrish and Murray reported on their experience with 104 pathologic fractures due to metastatic disease and identified increasing pain, more than 33% cortical destruction, and lack of radiographic improvement after radiation therapy as indicators of impending fracture. Filid, 66 in his retrospective study of 19 long bone fractures, showed that with 50% or more cortical involvement in a long bone, there is at least a 50% incidence of spontaneous fracture. Zickel and Moudrian, 67 in their retrospective review of 34 patients, found that size did not correlate with risk of fracture and that, instead, pure lysis on radiography, medial cortical involvement at the hip, and increasing pain were indicative of a high risk of fracture. Harrington, 68 in his review of the literature, summarized the positive predictors of pathologic fracture through a metastatic lesion as (1) a lesion of 2.5-cm or larger diameter involving the femur, (2) lytic destruction of at least 50% of the cortex of a long bone, and (3) continued pain with weight bearing after radiation therapy.
Keene et al. evaluated clinical and radiographic risk factors in an attempt to predict pathologic fracture of the femur. This study involved 2673 breast cancer patients who had undergone skeletal surveys. Of these, 203 patients had evaluable proximal femoral metastases. The authors found no criteria to identify the bone at risk for fracture. They concluded that plain radiographic measurements are insufficient to identify high-risk lesions. This study, however, was limited to the single anteroposterior radiographic evaluation present in the skeletal survey.

Mirels proposed a graduated scoring system that further refined the risk-factor criteria. Included are clinical and radiographic factors, which generate a composite score from 0 to 12 that correlates with fracture risk. Four factors—anatomic site, pain pattern, radiographic nature, and lesion size—were each evaluated on a 0 to 3 scale. Table 52.4-1 depicts this scoring system and its ability to predict pathologic fracture. Mirels investigated 78 lesions followed up over the course of 6 months. Fifty-one lesions resulted in fracture, and 27 did not. The mean score for the nonfracture patients was 7, versus a mean score of 10 for the fracture patients; however, there was significant overlap between the two groups. The author concluded that lesions with scores of less than 7 could be irradiated, whereas those with a higher score should be managed with internal fixation followed by postoperative irradiation.

**TABLE 52.4-1. Mirels’ Scoring System to Predict Pathologic Fracture**

<table>
<thead>
<tr>
<th>Score</th>
<th>Anatomic Site</th>
<th>Pain</th>
<th>Radiographic Nature</th>
<th>Lesion Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal</td>
<td>None</td>
<td>Normal</td>
<td>None</td>
</tr>
<tr>
<td>1</td>
<td>Proximal femur</td>
<td>Mild</td>
<td>Partially resorbed</td>
<td>Small</td>
</tr>
<tr>
<td>2</td>
<td>Distal femur</td>
<td>Severe</td>
<td>Resorbed</td>
<td>Moderate</td>
</tr>
<tr>
<td>3</td>
<td>Pelvis</td>
<td>Pain</td>
<td>Destabilized</td>
<td>Large</td>
</tr>
<tr>
<td>4</td>
<td>Spine</td>
<td>Pain</td>
<td>Destabilized</td>
<td>Very Large</td>
</tr>
</tbody>
</table>

Equally valuable is the ability of this scoring system to predict which lesions would not fracture. The fracture rate was small (5%) when the lesion was less than two-thirds of the bone diameter, but it increased to 81% for lesions larger than two-thirds of the shaft diameter. It was stressed that standard radiographs are inadequate to grade many lesions, and CT scanning was recommended to improve diagnostic accuracy. Mirels also made an important distinction between pain and “functional” pain, the latter being pain that worsens with weight bearing. Thus, functional pain reflects the structural insufficiency of bone and was found to be the most significant indicator of bone failure, enjoying an almost universal success in predicting fracture. Lesions measuring larger than twice the bone diameter were closely associated with functional pain. Fracture probability in patients with smaller lesions was only 10%.

The scientific foundation for predicting fracture risk has been improved and summarized by Callaway and Healey. Computer modeling of the proximal femur in vitro testing has allowed some investigators to predict femoral strength more accurately. Evaluating intertrochanteric and subtrochanteric lesions subject to bending forces, these researchers found that endosteal reabsorption of one-half the cortical width weakens the bone by 70% and leaves the patient at high fracture risk. Similar analysis is not available for other anatomic sites.

At the MSKCC, a functional system has been used that has practical implications. In each of the following four circumstances, major bone loss has usually been encountered surgically, and the bone was found to be essentially fractured:

- A painful medullary lytic lesion resulting in endosteal reabsorption of at least 50% of the cortical thickness
- A painful lytic lesion involving the cortex that is larger than the cross-sectional diameter of the bone
- A painful cortical lesion more than 2.5-cm long
- A lesion producing functional pain after radiation therapy

Prophylactic surgery should be performed as described earlier in *Fracture Treatment*.

**SPECIFIC ANATOMIC SITES**

For each site, unique patterns of metastases and functional and prognostic implications exist. The spine, proximal femur, and pelvis cause the most problems and will be dealt with individually.

**SPINE**

Metastatic disease most often affects the vertebral bodies. The lumbar spine is the site of the greatest number of metastases. However, any site within the spine can develop symptomatic metastases. The primary cancers responsible for spinal metastases are breast, lung, and prostate. Among reports regarding the prevalence of spine metastases, most emanate from referral centers. However, Stark et al. note that from a general hospital, lung cancer was responsible in 33%, breast cancer in 28%, other identifiable sites in 25%, and unknown primary lesions in 14% of cases. Remarkably, in 47% of the 131 patients with neurologic symptoms reported by Stark et al., the spinal metastases were the initial presentation of malignant disease. In an autopsy study of 832 patients dying of metastatic cancer, 36% were found to have spinal metastases, and 26% of these patients had negative plain radiographs of the spine despite the gross evidence of tumor.

Pain is the most common presenting symptom. It may be caused by intraosseous disease, motion segment instability, vertebral fracture, epidural compression, or nerve root impairment. Vascular insufficiency of the spine can also occur due to tumor or to associated spinal instability, surgery, radiation therapy, or embolization of the spinal arteries. Neurologic deficit is seen commonly in symptomatic patients. Myelopathy, radiculopathy, or cauda equina syndromes are recorded. Of particular importance is loss of proprioception and sphincter function. These are harbinger of serious neurologic damage and are much less likely to return after any form of treatment.

Various staging systems for vertebral involvement have been advanced. The Tomita system is the most logical and offers the greatest clinical applicability. It identifies disease involving the vertebral body, pedicle, posterior spinous elements, epidural space, and paraspinous region as distinct components. Clinical staging has also been identified as an important prognostic factor. Tokuhashi et al. have identified six parameters for staging, each of which is assigned 0 to 2 points: (1) grade of condition, (2) number of extraspinal bone metastases, (3) number of vertebral metastases, (4) visceral metastases, (5) primary cancer site, and (6) severity of spinal cord palsy. Outcome was correlated to total score. These authors recommended that an excisional operation be performed in patients with 9 or more points, whereas palliative surgery is indicated for the more seriously ill, those patients scoring fewer than 5 points.

The natural history of metastases is variable. Influential factors are anatomic location of metastases, functional status, treatment, and primary tumor histology. Tomita et al. reported on a group of 78 patients with epidural metastases who were treated with irradiation and high-dose steroids. Among the patients, 2 improved and 11 became paraplegic, whereas in 65, symptoms stabilized. There was a major difference in outcome based on the ability to restore ambulation. Ambulators had a 53-week survival in contrast to nonambulators, who survived less than 5 weeks.

Radiation is the first line of treatment for most patients with spinal metastases and pain. Rao et al. reported on 19 patients with cervical metastases without neurologic deficits. All patients received radiation therapy or chemotherapy. Symptomatic control lasted for 6 months, with subsequent deterioration that necessitated another treatment. Median survival was less than 15 months. The authors concluded that nonoperative treatment is appropriate for most patients without neurologic signs, particularly if the expected survival is in the 6- to 12-month range. Similarly, Young et al. performed a randomized trial of radiation therapy versus laminectomy and posterior decompression of the spinal cord. They found no benefit from this form of surgery and therefore favored nonoperative treatment. However,
Surgical treatment is largely dependent on fracture location and anatomy, which is discussed earlier, in contaminated region must be treated with radiation to avoid tumor proliferation and a new fracture distal to the implant. Generally, all fractures require supplemental radiation therapy to treat underlying tumor. Treatment of the fracture frequently exposes new areas to tumor spread.

Surgery may be important to improve the quality of life of these patients. The goals of surgery in metastatic spine disease are to decompress the spinal cord and neural elements and to stabilize the spine. Laminection alone rarely accomplishes these goals and may further destabilize the spine. It is indicated for rare posterior element disease or periradicular root compression only.

The debate continues as to whether an anterior, posterior, or combined anterior-posterior approach is better. Proponents of anterior decompression contend that it is often preferable because it addresses the primary site of the disease. Harrington, in his original report of 14 patients, found that 9 of 12 patients with major neurologic dysfunction recovered completely, 2 recovered partially, and 1 was unchanged. Vertebral body resection and cement and rod vertebral body reconstruction achieved excellent pain relief in 13 of 14 patients. Sundaresan et al. reported on 101 vertebral body resections. Patients were stabilized anteriorly or posteriorly as required; pins and cement usually were inserted to replace the vertebral body. Seventy-eight percent regained ambulatory ability, and 85% experienced pain relief. Morbidity was the least in patients who were treated de novo and underwent subsequent radiation therapy. In a follow-up study of 54 patients with de novo surgery, Sundaresan et al. noted that 25 patients survived 2 years or more, with 92% maintaining ambulatory ability. The overall complication rate in this series was a low 15%.

Rosenthal et al. reviewed a 3-year experience at the MSKCC, where anterior corpectomy and reconstruction with pins and cement were used for metastatic disease. Deterioration in function or pain control occurred in 7 months for cervical lesions, in 11 months for lumbar lesions, and in 22 months for thoracic lesions. Functional sites were more unstable, leading to early deterioration. Anterior surgery alone was satisfactory for patients with short survival times. If survival was expected to exceed the durability of the anterior reconstruction, then staged, posterior stabilization was recommended. Currently, the group at MSKCC is advocating a posterolateral, transpedicular approach that permits circumferential neural decompression, corpectomy, anterior pin and cement fixation, and segmental posterior fixation. This strategy has achieved excellent tumor control, pain relief, and neurologic preservation in a preliminary series of 25 patients. It is particularly suitable for patients with extensive epidural disease and those who have had a previous thoracotomy or thoracic irradiation or who have significant pulmonary disease, which is a relative contraindication for thoracotomy.

Fractures of the proximal femur are the most common surgical problem in bony metastatic disease. Sixty-six percent of pathologic long bone fractures involve the femur, and 80% of these occur in the proximal portion. The femoral neck is the location for approximately 52% of these fractures, with the intertrochanteric region responsible for another 15% and the subtrochanteric region for the remaining 33%. Walking, rising from a chair, climbing stairs, and even lifting the leg to swing out of bed all apply forces in excess of three times one’s body weight on the hip joint and proximal femur. Underlying mechanical weakness from even a treated metastasis leaves the bone unable to withstand the forces of normal activity.

It is a tragic mistake to spare the patient an operation when the procedure can make an important improvement in the quality of the patient’s remaining life. This is true even for patients in whom anticancer therapy and resuscitation are no longer indicated. As in other anatomic locations, the goal of treatment is to reduce pain and maintain function. Maintenance of function usually means preservation of walking ability but, in severely disabled patients, functional restoration means regaining transfer ability, which facilitates nursing care. General indications for surgery are a life expectancy of at least 1 month, a general physical condition adequate to tolerate surgery, a result from surgery that will expedite patient mobilization and facilitate general care, and bone adequate to support fixation or a prosthesis proximal or distal to the fracture. Conversely, patients with major neurologic impairment or potential large persistent narcotic requirement are unlikely to benefit greatly from surgery.

Generally, all fractures require supplemental radiation therapy to treat underlying tumor. Treatment of the fracture frequently exposes new areas to tumor spread. Tumor can be seeded down the femoral canal during intramedullary reaming, insertion of an intramedullary device, or injection of cement down the canal. This newly contaminated region must be treated with radiation to avoid tumor proliferation and a new fracture distal to the implant.

Surgical treatment is largely dependent on fracture location and anatomy, which is discussed earlier, in Fracture Treatment.

PROXIMAL FEMUR

Fractures of the proximal femur are the most common surgical problem in bony metastatic disease. Sixty-six percent of pathologic long bone fractures involve the femur, and 80% of these occur in the proximal portion. The femoral neck is the location for approximately 52% of these fractures, with the intertrochanteric region responsible for another 15% and the subtrochanteric region for the remaining 33%. Walking, rising from a chair, climbing stairs, and even lifting the leg to swing out of bed all apply forces in excess of three times one’s body weight on the hip joint and proximal femur. Underlying mechanical weakness from even a treated metastasis leaves the bone unable to withstand the forces of normal activity.

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PELVIS AND ACETABULUM

Most patients with pelvic and acetabular metastases have pain; however, it does not always arise directly from the hip joint. Avulsion fractures of the iliac crest or
anterior-inferior iliac spine are common and should be treated nonoperatively. However, mechanical insufficiency of the acetabulum can be managed only surgically. The general surgical indications for metastatic disease involving the acetabulum are (1) continued acute symptoms despite management with protected weight bearing, antineoplastic treatment, and analgesics; (2) unsatisfactory function and pain control 1 to 3 months after irradiation; (3) a pathologic fracture of the acetabulum; or (4) an impending fracture in the ipsilateral femur requiring surgery.

Harrington and Rock 135,136 described four types of acetabular bone deficiency and their surgical management among 58 patients with pelvic metastases. Their classification system is based on the extent of bony involvement by tumor and reflects surgical treatment. Overall results were good for most patient groups. Pain relief was effective for at least 6 months in 67% of patients and for more than 2 years in 43%. Eighty percent of patients remained ambulatory for 6 months or more. Harrington did, however, treat a generally favorable group of patients, with 30 of 58 (51%) surviving 2 years or more after surgery.

Preoperative evaluation, including Judet radiographs, must be performed carefully, to define disease in the anterior and posterior acetabular columns. 137 CT scanning is indispensable to evaluate the medial acetabulum and acetabular dome and to define any associated soft tissue mass. It is the best study for assessing overall bone integrity. Pathologic anatomy is best described by a four-part system that assesses the anterior column, posterior column, acetabular dome, and medial wall as separate components. Bone in each region can then be graded as sufficient or insufficient, whereby sufficient bone provides adequate support for the acetabular component and insufficient bone does not. Thus, the classification system combines both anatomic and reconstructive considerations.

At the MSKCC, this four-part system was used to analyze a series of 55 patients who required surgical reconstruction of the acetabulum for metastatic disease. 138 In this series, ten patients (18%) had insufficiency of both anterior and posterior columns, whereas 36 patients (65%) had single column insufficiency. Forty-two of 55 patients (76%) had an insufficient medial wall combined with either an insufficient column or dome, and 47 patients (85%) had an acetabular fracture. In all 55 patients, the reconstruction was reinforced with pins or cannulated screws incorporated into cement, using a modified Harrington technique. This allows for bypass of major acetabular defects with proximal fixation of the socket into the remaining iliac bone. Insertion of pins or screws can be performed in an antegrade fashion from the iliac crest, using a vector guide, or retrograde from the bone defect. A protrusio ring "revision" hip socket can be used to transfer load to the remaining intact cortical bone when medial wall defects are present (Fig. 52.4-3). Of the 41 out of the 55 patients (75%) in this series that were evaluable at 3 months, 34 (83%) experienced significant pain relief. 7 of 18 nonambulatory patients had regained walking ability, and 14 of 17 patients maintained their ability to ambulate in the community. Fourteen of 55 patients (25%) developed significant local disease progression, but only 5 patients (9%) experienced fixation failure. Early complications developed in 12 patients (22%). Of the 21 patients (38%) who had more than 1 year of follow-up, 14 (67%) continued to experience improved pain relief and 12 (57%) remained community or household ambulators. In this series, despite the fact that patients with significant acetabular metastasis had a short life expectancy, the patient's pain relief and functional improvement validated the role of surgery in managing this group. Acetabular reconstructive surgery using the outlined techniques showed a low incidence of fixation failure, supporting the biomechanical stability of the construct and providing sufficient durability in these patients.

Finally, massive pelvic involvement can be treated by acetabular resection and reconstruction using a saddle prosthesis (Waldemar Link, Hamburg, Germany), as described by Ahern et al. 139 The most common surgical indication for this procedure is to control pain and functional improvement with the treatment of multiplex metastatic disease. The role of pelvic surgery to control pain and functional improvement with the treatment of multiplex metastatic disease is extremely important, providing that adequate support for the functional limb is achieved. However, functional improvement with the treatment of multiplex metastatic disease is extremely important, providing that adequate support for the functional limb is achieved. However, pain must be controlled and functional improvement validated prior to the role of surgery in managing this group. Acetabular reconstructive surgery using the outlined techniques showed a low incidence of fixation failure, supporting the biomechanical stability of the construct and providing sufficient durability in these patients.

CHAPTER REFERENCES


MALIGNANT PLEURAL EFFUSION

Forty percent of all pleural effusions are due to malignancy, and cancer is the second leading cause of pleural effusion in patients older than 50 years of age. Approximately 100,000 cases of malignant pleural effusion (MPE) occur annually in the United States, and MPE is the initial manifestation in 10% to 50% of cancer patients. Two-thirds of MPEs are attributable to lung carcinoma (35%) or breast carcinoma (23%) and lymphoma (10%). Carcinomas of unknown primary origin account for an additional 12% of MPEs. Presence of MPE frequently indicates advanced and incurable disease. Although the overall prognosis of patients with MPE depends on the histology and extent of their primary disease, significant palliation can be achieved in these individuals by accurate and timely diagnosis and interventions associated with minimal morbidity.

PATHOGENESIS OF MALIGNANT PLEURAL EFFUSION

The pleural space functions as a mechanical coupling system between the lung and the chest wall. The normal pleural space is between 7 and 27 µm in width and is filled with 10 to 40 mL of hypoproteinemic plasma. Most of the pleural fluid originates from the capillary bed of the parietal pleura. The major route of pleural fluid efflux is through the parietal pleural lymphatics, which have a clearance capacity 28 times greater than the rate of fluid formation. Under normal conditions, a dynamic equilibrium exists between the osmotic and hydrostatic pressures that control the secretion and absorption of the pleural fluid. Accumulation of fluid within the pleural space may be the consequence of any of the following:

- Increased hydrostatic pressure in the microvascular circulation
- Decreased oncotic pressure in the microvascular circulation
- Decreased pressure in the pleural space
- Increased permeability of the microvascular circulation
- Impaired lymphatic drainage from the pleural space
- Transudation of fluid from the peritoneum via lymphatics or anatomic defects in the diaphragm

MPEs typically arise as the result of altered microvascular permeability, as well as diffuse metastatic involvement of mediastinal or subpleural lymphatics. Pulmonary parenchymal tumors (primary or metastatic) may erode the visceral pleura, spilling cells and disrupting the normal resorption of fluid by the visceral pleura. Alternatively, the parietal and visceral pleura themselves are common sites of deposits, resulting in increased capillary permeability due to inflammation, overt endothelial disruption, or obstruction of efferent flow with elevated lymphatic hydrostatic pressure. Primary or metastatic involvement of hilar or mediastinal lymph nodes obstructs normal visceral and parietal lymphatic drainage, resulting in pleural effusion. In an autopsy study of 29 patients with lung cancer, Meyer observed that the development of pleural effusion was closely related to malignant infiltration of mediastinal lymph nodes but not the extent of pleural metastases. Typically, involvement of the mesothelial surface results in exfoliation of tumor cells into the pleural fluid; however, few malignant cells will be found in the pleural fluid in the setting of submesothelial involvement.

Occasionally, pleural effusions in cancer patients are negative for malignancy despite exhaustive diagnostic efforts. Although related to the underlying cancer, these paramalignant effusions are not due to metastatic disease involving the pleura but rather are caused by obstruction of the hilar mediastinal lymph nodes or bronchial obstruction, resulting in pneumonitis or atelectasis. Such paramalignant effusions, if associated with non–small cell lung cancer, should not preclude patients from undergoing potentially curative resection if otherwise indicated. However, in most lung cancer patients, cytologically negative pleural effusions eventually are found to be inoperable. Decker et al. observed that only 4 of 73 patients (5.5%) with lung cancer and cytologically negative pleural effusions had resectable disease, demonstrating that pleural effusions of any kind in lung cancer patients typically are indicative of locally advanced, incurable disease. Furthermore, occult malignant cells have been detected by pleural washing in nearly 15% of patients undergoing resection of presumed stage I non–small cell lung cancer; survival of these individuals is as poor as that reported for patients with stage III disease, indicating the ominous nature of pleural space metastases of any kind in lung cancer patients.

CLINICAL PRESENTATION

MPE is often an initial manifestation of cancer; nearly 50% of individuals presenting with MPE have no history of malignancy. Most patients with MPE are symptomatic, with dyspnea of varying severity being the predominant symptom; cough and chest discomfort ranging from dull ache (often characterized as heaviness or pressure) to sharp pleuritic pain may also be present. Physical examination usually reveals decreased breath sounds, with dullness to percussion and diminished tactile fremitus. Tracheal deviation and low cardiac output related to mediastinal compression occasionally may be seen with large effusions.

DIAGNOSIS AND EVALUATION

Radiographic Examinations

As little as 200 mL of pleural fluid, evidenced by blunting of the costophrenic angle, can be detected by standard posteroanterior and lateral chest radiographs. Upright posteroanterior, lateral, and later decubitus chest radiographs that allow assessment of “free-flowing” pleural effusion should be performed as initial investigations. Particularly in the setting of a newly diagnosed effusion, computed tomographic (CT) scan of the chest should be performed to define fluid loculations or hilar lymphadenopathy, pleural masses, and parenchymal disease. Complete opacification of the hemithorax occurs in approximately 15% of MPE; an opacified hemithorax with mediastinal shift toward the contralateral side indicates massive effusion, whereas opacification without a shift may be due to a combination of pleural fluid and lung collapse resulting from proximal airway obstruction, effusion with mediastinal fixation by malignant lymphadenopathy, or malignant mesothelioma.

Invasive Diagnostic Maneuvers

After appropriate radiographic assessment, thoracentesis should be performed to obtain fluid for biochemical and cytopathologic analysis, to relieve symptoms, and to determine the extent of lung expansion after pleural fluid drainage. In the presence of free-flowing effusion, thoracentesis can be safely performed at the level of the posterior sixth or seventh intercostal space, removing 500 to 1000 mL of fluid. In the presence of a large pleural effusion occupying more than 50% of the pleural
Phosphorus were used in the 1940s to treat MPE, with a cumulative response rate of approximately 53%. 5-fluorouracil, and bacille Calmette-Guérin (BCG) have also been used in the treatment of MPE. The overall response rate was 52%.

These data suggest that outpatient management of MPE may be appropriate in patients with MPE who typically have limited life expectancies. Patients treated in this manner experienced complete responses, and an additional 25% had partial responses. In another study, MPE was drained by a 12-Fr. van Veluw chest tube, with 50 mL of 5% dextrose in water (D5W) being instilled into the chest via the drainage catheter, and the tube was removed 24 hours after pleurodesis. Fifty-three percent of patients treated in this manner experienced complete responses, and an additional 25% had partial responses. In another study, MPE was drained by a 12-Fr. van Veluw chest tube, with 50 mL of 5% dextrose in water (D5W) being instilled into the chest via the drainage catheter, and the tube was removed 24 hours after pleurodesis. Fifty-three percent of patients treated in this manner experienced complete responses, and an additional 25% had partial responses.

The chest tube (28 Fr. to 32 Fr.) is routinely inserted at the level of the sixth or seventh intercostal space laterally and directed posteriorly to the most dependent portion of the pleural cavity. Once complete drainage is achieved (as confirmed by chest radiograph and daily drainage of <150 mL), the sclerosing agent (suspended or dissolved in 100 to 150 mL of normal saline) is instilled into the pleural space via the chest tube. The tube is then clamped for 1 to 2 hours, during which time the sclerosing agent is given a chance to enhance distribution of the sclerosant; subsequently the tube is unclamped and connected to suction. The tube is removed when the daily drainage is again less than 150 mL.

Traditionally, this method requires hospitalization for 4 to 6 days and placement of a large-bore chest tube for complete evacuation of the exudative effusion prior to chemical pleurodesis. However, several studies have indicated that pigtail catheter drainage and sclerosis may be as successful as more traditional chest tube pleurodesis procedures. Recently, outpatient management of MPE with a small-bore all-purpose drainage catheter (10 Fr.) and bleomycin has been described. Pleural fluid was drained by a catheter connected to a collection bag until drainage was less than 100 mL/day. Bleomycin (60 U in 50 mL of 5% dextrose in water) was then instilled into the chest via the drainage catheter, and the tube was removed 24 hours after pleurodesis. Fifty-three percent of patients treated in this manner experienced complete responses, and an additional 25% had partial responses. In another study, MPE was drained by a 12-Fr. van Sonnenberg pigtail catheter inserted under ultrasound guidance in 15 patients, 11 of whom had loculated pleural effusion (which necessitated this method of drainage). Talc (5 g suspended in 100 mL of injectable normal saline) was instilled into the pleural cavity once pleural fluid drainage was less than 100 mL/day. Control of MPE was achieved in 80% of these cases. Additional talc instillation was required in two patients to treat residual pockets of effusion with good results. These data suggest that outpatient management of MPE may be appropriate in patients with MPE who typically have limited life expectancies.

Biochemical and Pathologic Analysis

Pleural fluid obtained by diagnostic thoracentesis should be routinely sent for protein, glucose, and lactate dehydrogenase (LDH) analysis and for cell counts, cultures, and pathologic examinations. Pleural effusions may be described as transudates or exudates. Transudates are characterized by a low protein content (<2.5 g/L), high glucose content (>3.8 mmol/L), and low LDH content (<150 IU/L). Exudates are characterized by a high protein content (>3.5 g/L), low glucose content (<2.0 mmol/L), and high LDH content (>600 IU/L). Pleural effusions may be caused by a variety of conditions, including infections, malignancies, and inflammatory diseases.

Chemical pleurodesis has been described. The chest tube pleurodesis procedures. The main complications related to its use were bone marrow suppression, pain, fever, nausea, and vomiting. Thiotepa, was also used but were found to have limited efficacy and unacceptable toxicity. Radioactive zinc, gold, chromium, or phosphorus were used in the 1940s to treat MPE, with a cumulative response rate of approximately 53%. The main disadvantages of radioactive colloids were...
cost, short half-lives, and potential hazards to treatment personnel; these agents are no longer used clinically.

Certain chemicals have been extensively evaluated in both randomized and nonrandomized clinical studies for their efficacy as pleurodesis agents. None of them except bleomycin are known to possess antitumor activity. They induce intense pleural inflammation and, subsequently, adhesive fibrosis of the parietal and visceral pleurae.

TETRACYCLINE-DOXYCYCLINE. Tetracycline was extensively used as a sclerosing agent to treat pleural effusions of benign and malignant etiologies because of its efficacy, low cost, and safety. The overall efficacy of tetracycline in controlling MPE was 70%. The usual dose was 500 to 1000 mg diluted in 100 mL of normal saline. The main side effects were pleuritic pain (20% to 70%) at the time of drug instillation and low-grade fever (33%). Lidocaine (20 mL of 1% or 2% solution) could be mixed with tetracycline prior to administration to decrease pleuritic pain. Injectable tetracycline is no longer available in the United States since 1991, because the drug preparations did not meet the U.S. Food and Drug Administration purity standards; as such, the tetracycline derivatives doxycycline and minocycline have been used for pleurodesis. Three small, uncontrolled clinical trials have reported response rates of 67% to 88% after doxycycline pleurodesis. The side effects are similar to those observed with tetracycline. Most patients require repeated doxycycline instillation for successful pleurodesis. In these reported series, only 15% of patients responded to a single treatment, and 9% required more than four instillations. Intrapleural minocycline (300 mg with 1% lidocaine) was given to seven patients with MPE, of whom six responded (86%). The small number of patients studied, unspecified criteria for success, and duration of treatment response make for difficult comparisons of minocycline with other agents.

BLEOMYCIN. Intrapleural administration of bleomycin (60 to 120 U) achieves pleurodesis in 65% of patients with MPE (range, 62% to 81%). Intrapleural bleomycin is well tolerated and associated with few side effects. In a multicenter, randomized trial, bleomycin was superior to tetracycline for pleurodesis; 70% of patients treated with bleomycin had successful control of their MPE, as compared to only 47% of patients treated with tetracycline. However, bleomycin is expensive; typically, each treatment dose ranges from US $1100 to $1300. Bleomycin has been compared with less expensive talc pleurodesis in a prospective randomized study of 29 women with MPE secondary to breast cancer. Of 22 evaluable patients (with 3 patients having bilateral pleural effusion), all 10 patients (100%) treated with talc had complete control of their MPE, as compared to 10 of 15 patients (67%) receiving bleomycin.

TALC. Chambers was the first to use talc to treat MPE. Talc produces an intense chemical pleuritis that effectively obliterates the pleural space. Asbestos-free, gas-sterilized, or heat-sterilized talc USP may be administered via chest tube as a slurry (5 g in 100 mL of normal saline) or insufflated as a powder during thoracoscopy or thoracotomy. Talc pleurodesis is highly effective, with the overall response rates ranging from 80% to 100%. The most commonly reported adverse effects of talc pleurodesis are fever (16%) and pain (7%). Less common complications include empyema, pneumonitis (similar to acute respiratory distress syndrome), and respiratory failure. Pulmonary complications noted in earlier series have not been observed as frequently in more recent trials and tend to occur in patients who receive 10 to 12 g of talc or undergo either bilateral pleurodesis or unilateral pleurodesis in conjunction with pleural biopsy (raising the possibility of talc emboli). Viallat et al. reviewed their experience with thoracoscopic talc poudrage pleurodesis for MPE in 360 cases, including 88 mesothelioma patients and 272 individuals with effusions of a variety of malignancies. Approximately 3 to 4.5 g of heat-sterilized asbestos-free talc was insufflated via atomizer during thoracoscopy. Pleurodesis was successful in 90% of 327 evaluable patients at 1 month, and 82% of individuals had lifelong pleurodesis. Complications included fever (10%), empyema (2.5%), pulmonary infection (0.8%), and malignant invasion of the thoracoscopy trocar site in a mesothelioma patient. Aelony et al. reported effective talc pleurodesis using thoracotomy in patients whose pleural fluid was acidic (<7.2), with a response rate of 88%. This high success rate compares favorably with the low response (57%) previously reported by Rodriguez-Paradero and Mejias. Failure of talc thoracoscopic pleurodesis in these two studies was more closely correlated with the presence of trapped lung than with low pleural fluid pH.

Talc has consistently been shown to be superior to other currently used sclerosing agents, such as tetracycline/doxycycline and bleomycin. The efficacy of past and currently used pleurodesis agents is summarized in Table 52.5-1. In a randomized controlled trial, Centina et al. compared the efficacy of talc poudrage and tetracycline in 33 breast cancer patients with MPE. Ninety-two percent of patients receiving talc had successful pleurodesis, as compared to only 42% of patients receiving tetracycline. In another study, successful pleurodesis was observed in 97% of patients undergoing intrapleural talc insufflation by thoracoscopy, as compared to 70% and 47% of patients receiving bleomycin and tetracycline, respectively. Thoracoscopic talc poudrage was also very effective in producing durable pleurodesis in patients with recalcitrant MPE who failed prior treatment with tetracycline. Zimmer et al. prospectively evaluated the efficacy of either bleomycin (60 U) or talc slurry (5 g; 19 patients) administered at the bedside via tube thoracostomy in 33 patients. Permanent control of MPE was noted in 73% of patients receiving bleomycin and 90% of patients treated with talc pleurodesis. The difference, however, did not reach statistical significance (P = .34). Due to the high cost of bleomycin, the authors recommended talc as the agent of choice for bedside chest tube pleurodesis. Talc poudrage has traditionally been performed by insufflating dry sterilized talc powder into the pleural cavity via the thoracoscope to ensure proper distribution and coating of the pleural surfaces. This technique incurs high costs due to operating room charges and specialized equipment. Pleurodesis achieved via talc slurry administered by thoracoscopy tube appears to be more cost-effective than thoracoscopic talc poudrage (Table 52.5-2). A phase III randomized clinical trial comparing talc slurry via chest tube and talc insufflation by thoracoscopy is being conducted in North America with the participation of the Cancer and Leukemia Group B, the Eastern Cooperative Oncology Group, the Southwest Oncology Group, and the North Central Cancer Treatment Group; the primary end points are evaluation of efficacy and cost-effectiveness of these two pleurodesis techniques.

### Table 52.5-1. Efficiency of Sclerosing Agents Used in Treating Patients with Malignant Pleural Effusion

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mean</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Talc</td>
<td>50</td>
<td>70–100</td>
</tr>
<tr>
<td>Bleomycin</td>
<td>65</td>
<td>25–125</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>75</td>
<td>25–100</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>25</td>
<td>60–88</td>
</tr>
<tr>
<td>Quinacrine</td>
<td>86</td>
<td>64–500</td>
</tr>
<tr>
<td>Neomycin</td>
<td>90</td>
<td>25–75</td>
</tr>
</tbody>
</table>

### Table 52.5-2. Efficacy of Talc Pleurodesis by Thoracoscopic Talc Poudrage or Talc Slurry by Tube Thoracostomy for Malignant Pleural Effusion

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mean</th>
<th>Range</th>
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<tbody>
<tr>
<td>Talc</td>
<td>50</td>
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<td>Tetracycline</td>
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<td>Neomycin</td>
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### Quinacrine

Quinacrine (mepacrine), an antimalarial agent, has been a popular drug for pleurodesis of pleural effusion in Scandinavian countries. As with other aforementioned sclerosing agents, intrapleural instillation of quinacrine produces significant chemical pleuritis that promotes intrapleural adhesion formation. The response rates to intrapleural quinacrine range from 75% to 100% and 70% to 80% after thoracentesis or chest tube drainage, respectively, in controlled clinical
Chemical agents used for pleurodesis induce inflammatory adhesion of the pleurae, thus obliterating the pleural space and preventing reaccumulation of pleural effusion. Biologic response modifiers, such as interferons and interleukins, have been used to treat MPE primarily on the basis of their antitumor activity. Adequate drug levels can be achieved only by high systemic doses that are associated with severe side effects. Regional intrapleural administration of these agents yields biologically relevant drug concentrations with fewer systemic side effects. None of these agents, however, are routinely used to treat MPE. (They are briefly discussed here for academic interest.)

Interferons. Goldman et al.3 studied the toxicity and efficacy of intrapleural administration of interferon-2b (50 million to 75 million units) for MPE associated with cancers of different histologies in 23 patients. The pleural fluid was completely evacuated, and interferon was instilled via the chest tube for a maximum of three treatments per patient. Complete and partial resolution of MPE was documented in 14 of 20 evaluable patients (70%). The most common side effect was the flu-like syndrome followed by grade 3 hematologic toxicity in three patients who received high doses of 75 million units. Other studies also indicated somewhat lower response rates and similar toxicity profiles. 4-6

Interleukin-2. Intrapleural administration of recombinant interleukin-2 (rIL-2) as a means to treat MPE has been evaluated in numerous small phase I trials. 7-10 Yasumoto and Ogura5 treated 43 patients with MPE due to non–small-cell lung cancer with daily intrapleural administrations of rIL-2 for an average of 14 days (5 to 33 days) after pleural effusion had been completely evacuated. Control of MPE was achieved in 21 of 35 evaluable patients (60%), with 13 experiencing complete disappearance of MPE. More impressive was the observation of disappearance of malignant cells in the pleural fluid samples sequentially obtained during treatment for cytologic analysis. This was noted in 26 of 35 evaluable patients (74%) and the effect lasted for more than 4 weeks in 19 patients (54%). This observation had also been reported by other investigators. 5 Viallat et al. 11 studied the effects and toxicity profiles of intrapleural injections of rIL-2 in 23 patients with MPE associated with cancers of various histologies. Objective responses were observed in 5 of 21 evaluable patients (24%). Side effects included fever, transient increase in pleural effusion, skin rash, and pruritus. Staphylococcus epidermidis attributed to prolonged chest tube drainage was noted in two patients. 12

OK432. OK432 is a heat- and penicillin-treated lyophilized powder of the SU substrain of Streptococcus pyogenes A3. This immune modulator has recently been found to be useful in treating malignant ascites. Malignant ascites may decrease in volume and even disappear. The OK432 therapy increases neutrophils, monocytes, and macrophages. The OK432 counts and augments autologous tumoricidal activity of large granular lymphocytes in ascites fluid. 15 Luh et al. 16 conducted a randomized trial to compare the efficacy of OK432 and mitomycin C in controlling MPE caused by lung cancer. Twenty-six patients received weekly injections of OK432 for 4 weeks. The overall response rate was 88%: 73% (19 of 26 patients) had complete response, and 15% (4 of 26 patients) experienced partial response. Fever, chills, and local pleuritic chest pain were the most common side effects and were observed in 80% of cases.

Intrapleural Chemotherapy
Few clinical studies were conducted to investigate the efficacy of intrapleural chemotherapy for MPE. Regional chemotherapy in the form of intrapleural chemotherapy for malignant mesothelioma is discussed in Chapter 40.2. The overall response rates of intrapleural chemotherapy are low, and the treatments, even though regional, are associated with significant systemic side effects. Unless studied within a context of a clinical trial, intrapleural chemotherapy has no role in the management of MPE.

Intrapleural combinations of cisplatin (100 mg/m²) and cytosine arabinoside (600 to 1200 mg/m²) have been used to treat MPE in two studies. 17,18 This combination produced a complete response in only 27% of the patients, and adverse effects including pain (66%), cardiopulmonary symptoms (54%), bone marrow suppression (52%), and renal toxicity (34%) were noted in 76% of the patients, suggesting that significant systemic absorption of the chemotherapeutic agents occurred in these individuals. Intrapleural doxorubicin at doses ranging from 10 to 40 mg has produced complete responses in 12 of 55 (22%) evaluable patients. 19,20 Adverse effects included pain (23%), fever (15%), nausea and vomiting (29%), and anorexia (24%). Repeated, escalating doses of etoposide (100 to 225 mg/m²) have been administered intrapleurally to nine patients with MPE, 21 of whom none experienced clinical responses.

Cost-Effectiveness of Pleurodesis for Malignant Pleural Effusions
The most effective and economic method for the treatment of MPE is still a matter of debate. It is important for physicians who manage patients with MPE to be knowledgeable regarding the efficacy, toxicities, and costs of available treatment modalities. Even though the sclerosant is not expensive ($0.15 to $0.50 for a 2.5- to 10-g dose), the cost of talc pleurodesis performed by thoracoscopy is high because of operating room and professional fees. The total cost of treatment has been determined to be $20,996 (1992 U.S. dollars). The high success rate may justify the expense of talc pleurodesis. The 6-month cost of talc pleurodesis, estimated to be $149 per symptom-free day, should drop significantly if the procedure is performed by pleuroscopy under intravenous sedation and local anesthesia or by instillation of talc slurry via chest tube. Both these techniques are as effective as talc poudrage performed by video-assisted thoracic surgery under general anesthesia. Biologic response modifiers such as interferons and interleukins have been used to treat MPE primarily on the basis of their antitumor activity and augment autologous tumoricidal activity of large granular lymphocytes in ascites fluid. 15 Luh et al. 16 conducted a randomized trial to compare the efficacy of OK432 and mitomycin C in controlling MPE caused by lung cancer. Twenty-six patients received weekly injections of OK432 for 4 weeks. The overall response rate was 88%: 73% (19 of 26 patients) had complete response, and 15% (4 of 26 patients) experienced partial response. Fever, chills, and local pleuritic chest pain were the most common side effects and were observed in 80% of cases.

Pleurectomy
Stripping of the parietal pleura is 100% effective in controlling MPE. Although it may have a role in the treatment of malignant pleural mesothelioma, 22 pleurectomy via thoracoscopy is not routinely performed because the morbidity (23%) and mortality (10%) 23,24 cannot be justified in debilitated patients for whom less invasive and equally effective treatment options may be available. However, several recent studies have indicated that parietal pleurectomy can be performed via video-assisted thorascoscopic surgery (VATS) with acceptable risk in patients. Waller et al. 25 performed VATS parietal pleurectomy in 19 patients with MPE secondary to malignant pleural mesothelioma. Of the 19 patients, 12 had thoracoscopic trocar sites occurred in 5 of 13 mesothelioma patients. More recently, Harvey et al. 26 performed VATS pleurectomy in 11 (5 non–small-cell lung cancer, 4 breast cancer, 1 mesothelioma, 1 cancer of unknown primary) patients, with no recurrence and one death (1 of 11; 9%) due to sepsis from a necrotic tumor involving the liver. Other complications included prolonged air leak (one patient) and requiring readmission and transfused (one patient). The results of these two small series should not be viewed as justifications for more liberal application of VATS parietal pleurectomy as the first line of treatment for MPE. Instead, parietal pleurectomy should be reserved for malignant effusions that are refractory to less invasive and less expensive interventions. 27

Pleuroperitoneal Shunt
The pleuroperitoneal shunt, introduced in 1982, has been evaluated as a therapeutic option for the treatment of MPE. 28 It may be used for recurrent effusions that are refractory to tube thoracostomy and pleurodesis or for MPE associated with trapped lung. 29-31 The most commonly used device is the Denver pleuroperitoneal shunt (Denver Biomaterials, Inc., Golden, CO). The shunt is a silicone rubber conduit consisting of a unidirectional valved pump chamber connecting to pleural and peritoneal cavities. The pumping chamber can be implanted into a subcutaneous pocket or exteriorized as an external pumping chamber. Because of the negative pressure differential between the pleural and peritoneal cavities, manual compression of the pumping chamber is required for fluid drainage from the chest. Each compression transports 1.5 mL of fluid, and patients are frequently asked to compress the pump for 5 to 10 minutes four times daily. Implantation of the shunt can be performed under local or general anesthesia. Petrou et al. 32 used pleuroperitoneal shunt in 63 patients with recurrent MPE and trapped lung. There were no operative deaths, and complications were noted in 5 patients (8%). Effective palliation was achieved in more than 95% of cases. Catheter occlusion was noted in eight patients (12%) at 1 week to 4 months after insertion, with five patients requiring replacement or revision of the shunt and three patients requiring shunt removal.
and treatment of empyema. Contraindications include pleural infection, multiple loculations, inability of the patient to press the chamber, short life expectancy, and obliterated peritoneal space. The need for active pumping of the chamber a minimum of 400 times per day limits its usefulness to patients with excellent performance status. In addition, the shunt may malfunction over time, further limiting its usefulness. As such, the pleuroperitoneal shunt should be considered as one of the last alternatives for patients with refractory effusions.

**Indwelling Pleural Catheter**

Malignant pleural fluid can be drained for prolonged periods by a small-caliber biocompatible silicone rubber indwelling catheter. The Tencoff (Quinton Instrument, Seattle, WA) and Denver (Denver Biomaterials) catheters have similar design, consisting of a 15-Fr. translucent silicone rubber tube with a radiopaque stripe, a felt or polyester cuff, and a plastic occluding device that may be opened to drain the fluid. The catheter is inserted in the operating room under local anesthesia. Two small skin incisions are made in the anterolateral chest. The catheter is brought through a 15-cm subcutaneous tunnel between these two incisions. The pleural cavity is accessed with a needle and, using the Seldinger technique and a Tear Apart Introducer kit (Quinton Instrument), the catheter is introduced into the pleural cavity and positioned so that the felt cuff on the catheter lies just within the exit wound. The advantages of pleural catheter placement are the ease of insertion and minimal discomfort due to the catheter, rapid drainage of recurrent symptomatic effusion, and minimal or no hospitalization required for catheter insertion and care. Robinson et al. used the Tencoff catheter to manage MPE in nine patients, with three patients having bilateral catheter placement for a total of 12 catheters inserted. Four of the nine patients had recurrent pleural effusion after failed tube thoracostomy and chemical pleurodesis. None of the patients had trapped lung. The authors reported excellent palliation of symptoms in all patients. Complications were minor, with insertion-site cellulitis that was easily managed with oral antibiotic in 3 of 12 catheter sites (25%).

A phase III trial comparing the efficacy of the Denver pleural catheter versus chest tube and doxycycline sclerotherapy for recurrent symptomatic MPE in 144 patients was recently completed (99 patients had Denver catheter, and 45 patients had doxycycline pleurodesis). The Denver pleural catheter was as effective as doxycycline pleurodesis in relieving symptoms related to MPE and improving quality of life. At 90 days, pleurodesis was achieved in 69% of patients treated with Denver pleural catheter alone, as compared to 50% of patients treated with doxycycline. No patient in the catheter group experienced fluid reaccumulation. Moreover, patients treated with pleural catheter had shorter hospital stay (mean, 1.83 days) than those treated with chest tube and doxycycline pleurodesis (mean, 6.83 days). Pleural catheter, either a Tencoff or a Denver catheter, is indicated for recurrent MPE refractory to pleurodesis or those associated with trapped lung. The pleural catheter is particularly useful in debilitated patients in whom a reliable and painless method of fluid drainage is required or in patients with effusions secondary to chemosensitive malignancies.

**External-Beam Irradiation**

Only lymphomatous pleural effusions seem to respond favorably to external-beam irradiation. Close to 90% of malignant lymphoma effusions have been controlled by mediastinal and hemithorax irradiation in a small series of patients (1.4 to 2.3 Gy).

**SUMMARY**

The prognosis of patients with MPE varies with the histologic type of the primary tumor. In general, 65% of patients with MPE are dead within 3 months and 80% within 6 months. As such, treatment of MPE should focus on expeditious and cost-efficient palliation. Our approach to patients with MPE having good performance status is talc pleurodesis. Indwelling pleural catheters have been frequently used for intermittent drainage of effusions in patients with trapped lung or limited life expectancies, as well as individuals on protocols requiring sequential analysis of molecular end points in tumor cells readily obtained from malignant effusions. The algorithm for the diagnosis and treatment of malignant pleural effusion is outlined in Figure 52.5-1.

**MALIGNANT PERICARDIAL EFFUSION**

Patients with malignant pericardial disease may be asymptomatic or may present with a number of manifestations, with pericardial effusion being the most common. Pericardial tamponade due to malignant pericardial effusion (MPCE) accounts for at least 50% of all reported cases of pericardial fluid collection that require intervention. Similar to cancerous pleural effusions, MPCEs are frequently indicative of advanced incurable malignancy; overall median survival of patients with MPCE is less than 6 months.

**PATHOGENESIS AND ETIOLOGY**

Malignant cells gain access to the pericardium either via direct invasion from an adjacent tumor or by hematogenous or lymphatic routes. Many cardiac and pericardial metastases as well as pericardial effusions result from retrograde progression of disease through lymphatic channels draining the heart and pericardium. The normal lymphatic circulation of the heart and pericardium consists of an extensive subendocardial plexus that drains via an intercommunicating system of myocardial channels into a subepicardial plexus. Efferent branches form from this subepicardial plexus and unite into larger trunks that initially follow, then subsequently diverge from, the coronary artery vessels near the aortic root and drain either directly into a cardiac node between the innominate artery and superior vena cava or into a pretracheal node and then into the cardiac node. The cardiac node, in turn, drains into the mediastinal system. In addition, the subepicardial plexus interconnects with a superficial adventitial plexus of lymphatics surrounding the aorta. The latter plexus drains through the paraaortic node and enters directly into the thoracic duct or the paraatracheal system. The parietal pericardium contains a relatively unimportant lymphatic system. Thus, pericardial fluid drains primarily via the subepicardial plexus through a few large trunks to the cardiac node and then into the mediastinal nodal system; a secondary pathway involves communication with the lymphatic plexus of the aortic adventitia. Thus, lymphatics from the heart and pericardium appear to have a vulnerable isthmus-like section near the base of the heart. Consequently, impairment of cardiac lymphatic drainage with retrograde epicardial invasion may occur with limited mediastinal metastases. Obstruction of epicardial venous and lymphatic drainage by neoplastic invasion alters the equilibrium between hydrostatic and osmotic forces and capillary filtration favoring fluid accumulation in the pericardial space. The rate of fluid accumulation (which can be rapid if accompanied by intrapericardial hemorrhage) and the degrees of pericardial compliance (which can be low from prior inflammation, irradiation, or tumor infiltration) determine the severity of clinical manifestations of MPCE.

Metastases involving the heart or pericardium (or both) occur relatively frequently in cancer patients. Several autopsy series, including one by Klatt and Heitz, have indicated that cardiac metastases occur in approximately 10% of patients dying from cancer; the epicardium is involved in 75% of metastatic lesions, and pericardial effusions are present in one-third of these cases. Metastasis from the lung (all histologies) and breast and hematologic malignancies account for three-fourths of MPCEs, with lung cancer being the most common etiology; virtually all malignancies (except primary brain tumors) may cause MPCE.

Neoplasms that invade the mediastinal lymphatics and obstruct pericardial lymphatic flow are commonly associated with pericardial effusion. Kline observed cardiac metastases in 61 of 716 cancer patients; all the patients with cardiac involvement had metastases in mediastinal lymph nodes and lymphatics of the epicardium and...
Pericardium. Metastases to the pericardium or heart have been noted in approximately 30% of patients dying from lung cancer, and 65% of whom have pericardial effusion; the predominant metastatic pathway involves the hilar lymphatics in these individuals.

CLINICAL PRESENTATION

In most cases, MPCE is observed in patients with a previous diagnosis of cancer, typically at late stages of their disease. MPCE is rarely seen as the initial manifestation of extracardiac malignancy; only 90 cases were reported in the English-language literature over a 55-year period. The most common symptoms attributed to pericardial effusion are dyspnea, cough, chest pain, fever, and edema. Nonspecific complaints are also frequent; as such, pericardial effusion may remain unsuspected in patients in whom nonspecific symptoms are attributed to disease progression. The frequency of cardiac tamponade as the initial manifestation of malignant effusion is highly variable and depends on the rate of fluid accumulation, volume of the fluid, and underlying cardiac function. The pericardium may distend over a period to accommodate a large volume of fluid prior to the clinical appearance of tamponade. Impedance of right atrial and ventricular filling by pericardial fluid results in cardiac tamponade. Signs and symptoms of cardiac tamponade include dyspnea, orthopnea, low output (peripheral vasoconstriction, cold clammy extremities, poor capillary refill, and diaphoresis), jugular venous distention, distant heart sounds, pulesus paradoxus, and narrowed pulse pressure. Electrocardiography may show low voltage complexes in all leads and electrical alternans.

DIAGNOSTIC MODALITIES

Radiographic and Echocardiographic Studies

Pericardial effusion in asymptomatic patients is most frequently detected by plain posteroanterior and lateral chest radiographs. The typical finding on chest radiograph is an enlarged globular water-bottle pericardial silhouette (Fig. 52.5-2). Moreover, when pericardial effusion and tamponade are caused by malignancy, concomitant parenchymal involvement or pleural effusion (or both) are observed in 30% to 50% of cases, respectively. Once disease is suspected, echocardiography should be performed to confirm the presence and hemodynamic significance of pericardial effusion. Two-dimensional echocardiography can define the location and amount of effusion, as well as the presence of pericardial or intracardiac masses. Right atrial and ventricular collapse are the most common echocardiographic signs of cardiac tamponade, with sensitivity ranging from 38% to 60% and specificity ranging from 50% to 100% (Fig. 52.5-3). Echocardiography is frequently used to provide guidance for safe and accurate pericardiocentesis.

FIGURE 52.5-2. Posteroanterior chest radiograph of a patient with significant pericardial effusion as indicated by an enlarged cardiac silhouette.

Pericardial effusion can also be diagnosed by CT scan, which can detect as little as 50 mL of pericardial fluid (Fig. 52.5-4). This is not the diagnostic method of choice for pericardial effusion, since it is time-consuming to perform and is no more accurate than echocardiography. CT scan may be helpful in evaluating intrapericardial masses as well as defining the nature of the pericardial fluid, as the attenuation coefficients for exudates, chyle, serous fluid, or blood may differ.

FIGURE 52.5-4. The chest computed tomographic scan of this patient with metastatic ovarian carcinoma shows a large malignant pericardial effusion and bilateral malignant pleural effusions (right more than left).

Cytopathology and Histopathology

The foregoing imaging techniques provide information regarding the amount and hemodynamic significance of pericardial effusion but not its benign or malignant nature. Only 50% to 60% of pericardial effusions in cancer patients are confirmed by cytologic examination to be malignant. Posner et al. studied 31 patients with pericardial disease associated with various malignancies. Fifty-eight percent of the patients had MPCE, 32% had idiopathic pericarditis, and 10% had
radiotherapy-induced pericarditis. Pericardiocentesis and cytologic examination of the fluid identified malignancy in 85% of positive cases; open biopsy was required for diagnosis in the remaining 15%. Weiner et al. reviewed 96 cases of pericardial effusion treated initially by pericardiocentesis. Malignant cells were identified in pericardial fluid from two-thirds of cancer patients; cytology correlated with histologic diagnosis of the underlying malignancy in 100% of these individuals. Press and Livingston reviewed 190 cases of MPCE diagnosed by pericardiocentesis. Pericardial fluid was positive for malignant cells in 151 patients with documented neoplastic pericarditis (specificity, 79%); hence, cytologic examination of pericardial fluid remains valuable in the diagnosis of MPCE, especially when positive for malignant cells. In contrast, parietal pericardial biopsy is frequently nondiagnostic, since the principal site of malignant infiltration is the visceral pericardium and its subepicardial lymphatics. Clarke and Cosgrove performed a prospective study to determine the diagnostic value of pericardial biopsy in 25 patients with malignancy and pericardial effusions. Fluid cytology revealed malignant cells in 11 patients (44%), of whom only 5 had histologic evidence of malignancy in pericardial biopsy specimens.

TREATMENT

The goals of treatment for MPCE include relief of immediate symptoms, confirmation of the malignant nature of the fluid, and prevention of recurrence. Although simple pericardiocentesis may be life-saving in cases of cardiac tamponade, this procedure alone is rarely adequate therapy for MPCE because of the high rate of fluid reaccumulation; thus, if initially performed, pericardiocentesis should be followed by a more definitive medical or surgical procedure to prevent recurrence. Therapy for MPCE should be tailored to the performance status and prognosis of each patient; options include surgical procedures, such as subxiphoid pericardiostomy (pericardial window), transthoracic pericardial window or pericardiectomy (either by video-assisted thoracoscopy or thoracotomy), and medical interventions, such as percutaneous tube pericardiostomy with or without intrapericardial instillation of sclerosing agents.

Subxiphoid Pericardiostomy (Subxiphoid Pericardial Window)

The subxiphoid pericardiostomy approach is now the most commonly performed surgical procedure for benign as well as MPCEs. This procedure can be performed under local anesthesia with intravenous sedation or general anesthesia (Fig. 52.5-5). It can be performed as the initial procedure for MPCE in medically stable patients or after needle pericardiocentesis in patients with signs and symptoms of significant cardiac tamponade. A small vertical skin incision is made from the xiphoid process caudally for 4 to 6 cm. The upper linear alba is divided in the midline, and the xiphoid is either bisected or resected. The peritoneum is not open. The preperitoneal fat is dissected cephalad by blunt finger dissection. The plane between the posterior sternum and the anterior pericardium is then developed to allow insertion of a retractor to elevate the lower end of the sternum. The pericardium is identified as the bulging, grayish white, fibrous membrane. The anterior pericardium is then incised, fluid is drained, and samples are collected for cytologic and microbiologic analyses. The pericardium then is explored digitally to identify adhesions and tumor masses. A piece of pericardium (2 to 4 cm²) is excised and submitted for microbiologic as well as pathologic studies. Through a separate stab wound in the upper abdomen, a 28-Fr, curved chest tube is placed in the pericardial space through the pericardial window for postoperative drainage. Leaving the tube in place for 4 to 5 days, regardless of the drainage amount, to promote local inflammation and fusion of the visceral and parietal pericardium. No attempts are made to create a communication between the pericardial space and either the pleural or peritoneal space. Allen et al. noted that autopsies of six patients who had undergone the subxiphoid procedure revealed complete pericardial symphysis with extensive adhesions. A comprehensive review of the clinical experience pertaining to 654 patients with effusion of different etiologies who underwent subxiphoid pericardiostomy has indicated an overall mortality rate of approximately 0.46% (range, 0% to 5%), an overall morbidity rate of approximately 1.53% (range, 0% to 10%), and a recurrence rate of approximately 3.5% (range, 0% to 9.1%). These low mortality, morbidity, and recurrence rates compare very favorably with those attributable to percutaneous pericardiocentesis and pericardiostomy with or without sclerosis (0.7% mortality, 3% morbidity, and 13% recurrence; Table 52.5-3, Table 52.5-4).

FIGURE 52.5-5. Subxiphoid pericardial window (pericardiostomy). Resection of a small pericardial segment and evacuation of the effusion (A) and insertion of a pericardial tube via a separate stab wound in the upper abdominal wall (B). (From ref. 126, with permission.)

TABLE 52.5-3. Subxiphoid Pericardiostomy for Pericardial Effusions

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<tr>
<th>Procedure</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subxiphoid pericardiostomy</td>
<td>Excision of a small pericardial segment and evacuation of the effusion</td>
</tr>
</tbody>
</table>

TABLE 52.5-4. Percutaneous Catheter Drainage for Pericardial Effusions

Partial Pericardiectomy or Pericardial Window via Thoracotomy

Before the recent resurrection of subxiphoid pericardial window as the preferred surgical treatment for pericardial effusion, pericardial window or even pericardiectomy...
via a thoracotomy incision were advocated. Piehler et al. reviewed their experience with surgical management of pericardial effusions in 145 patients and suggested that the extent of pericardial resection influenced incidence of recurrent effusions. However, several recent series indicate no difference in recurrence rates of patients treated by subxiphoid pericardiostomy as compared to those undergoing transthoracic drainage. More importantly, postoperative complications (pneumonia, pleural effusion, respiratory failure, cardiac arrhythmia, deep vein thrombosis, and pulmonary embolism) are much less frequent after subxiphoid pericardial drainage as compared to transthoracic pericardial resection (10% vs. 50%, respectively). Thus, transthoracic pericardial resection is not a suitable initial procedure for drainage of MPCE.

If possible, VATS should be used if transthoracic pericardial resection is required for recurrent effusion after subxiphoid pericardiostomy or for diagnosis and treatment of simultaneous pleural-parenchymal pathology. Compared to thoracotomy, minimally invasive approaches are more suitable interventions in debilitated cancer patients. The potential limitation of VATS pericardiectomy is the need for general anesthesia and single-lung ventilation. Pericardial resection via laparoscopy or video-assisted subxiphoid pericardial window have been reported, however, there is no added benefit of these expensive minimally invasive techniques compared to standard subxiphoid pericardiostomy. Pericardial-peritoneal shunt, using a Denver pleuroperitoneal catheter with pumping chamber, has been used to treat MPCE in a limited number of patients, experience with this technique is too limited to allow adequate assessment of its clinical utility, although it may be suitable for pericardial effusions that are refractory to repeated pericardiostomy procedures.

**Pericardiocentesis**

Pericardiocentesis can be life-saving when performed on patients with hemodynamically significant cardiac tamponade. Removal of as little as 50 mL of pericardial fluid can significantly improve signs and symptoms of acute tamponade. Traditionally, after subcutaneous infiltration of 1% lidocaine (Xylocaine) local anesthetic solution, the needle is inserted at the right side of the xiphoid process and directed 45 degrees dorsally, aiming toward the tip of the left scapula. The rates of fluid reaccumulation have been reported to range from as low as 44% to as high as 70% after pericardiocentesis. This procedure has been associated with a significant incidence of complications, some of which are fatal even when performed by experienced physicians. Allen et al. observed clinically significant complications in 6 of 23 patients (26%) undergoing percutaneous pericardiocentesis, including three right ventricular perforations (with one fatality) requiring surgical interventions, one ventricular arrhythmia requiring cardioversion, and one pneumothorax. The complication rate observed by Allen et al. exceeds that reported by Vaitkus et al., who summarized experience with pericardiocentesis in 139 patients with MPCEs. Percutaneous pericardiocentesis successfully alleviated symptoms in 97% of the cases; morbidity and mortality in this series were 3% and 0.7%, respectively.

Echocardiography may reduce complications and improve the success of the pericardiocentesis by delineating the size and location of the effusion relative to cardiac structures. Overall rates of complication and success are approximately 2.4% and 100%, respectively, after ultrasound-guided pericardial drainage as compared to 4.8% and 90%, respectively, after unassisted pericardiocentesis.

**Percutaneous Tube Pericardiostomy and Pericardial Sclerotherapy**

The rates of fluid reaccumulation have been reported to range from as low as 44% to as high as 70% after pericardiocentesis. It is now a common practice to place a 9-Fr. pigtail draining catheter into the pericardial space after successful needle pericardiocentesis using the Seldinger technique to enable more complete evacuation of the effusion and provide access for sclerotherapy. Although several agents have been used in the past, tetracycline and its currently available derivative, doxycycline, have been most extensively evaluated as sclerosing agents for pericardial effusion. Maher et al. reported their experience with 93 patients with MPCE treated by percutaneous pericardial drainage followed by tetracycline or doxycycline sclerosis. Successful placement of the pericardiostomy tube was achieved in 85 patients (91.4%). Pericardial effusion was controlled in 75 of the 85 patients (88%); 10 of the 85 patients (12%) did not respond to sclerosis, of whom 8 subsequently underwent surgical pericardiotomy. Sclerotherapy necessitated one to eight instillations of tetracycline or doxycycline (median, 3); 50 patients required three or more instillations to control their effusions. Treatment-related complications (in decreasing order of frequency) included pain, catheter occlusion, fever, and atrial arrhythmias. The apparently favorable results of this minimally invasive treatment strategy are offset by the need for repeated instillations of the sclerosing agent to achieve pericardial scarring. Liu et al. recently conducted a prospective study to evaluate the efficacy and toxicity of bleomycin versus doxycycline as the sclerosing agents for MPCE. Bleomycin was found to be as effective as doxycycline in achieving satisfactory control of MPCE, yet with much less retrosternal pain. As a result, these authors recommended that bleomycin be considered the first-line chemical sclerosing agent for treating MPCE. In addition to bleomycin or doxycycline, other sclerosing agents used for treating MPCE include OK-432 (a penicillin-treated and heat-treated lyophilized powder of the ) and sterile talc. The clinical utility of these adjunctive sclerosing agents is not known, and their use cannot be considered standard of care at this time.

**Percutaneous Balloon Tube Pericardiostomy**

Percutaneous balloon tube pericardiostomy, initially advocated by Ziskind et al. and subsequently studied by others, appears to be an extension of the more commonly performed percutaneous tube pericardiostomy. After successful pericardiocentesis, dilatation of the needle tract is performed under fluoroscopy using a balloon catheter. Ziskind et al. reported that this technique was effective in relieving pericardial effusion in 46 of 50 patients (92%). Procedure-related complications included fever (six patients), pleural effusion requiring chest tube placement or thoracentesis (eight patients), small pneumothorax (two patients), and right ventricular injury requiring surgery (one patient), for an overall clinically significant complication rate of 18%. Even though this is an effective minimally invasive technique of pericardial drainage, its widespread application may be limited by the need for specialized equipment as well as for interventional cardiologists or radiologists. The high incidence of inadvertent pleural effusions requiring drainage renders this technique less attractive compared with others discussed.

**Local or Systemic Therapies for Malignant Pericardial Effusion**

Radiotherapy is generally reserved for MPCE associated with lymphoma or breast carcinoma. Vaitkus et al. reviewed the experience of 54 patients treated with radiotherapy as the primary mode of therapy for MPCE. Of these patients, 39 (72%) underwent initial pericardiocentesis. The majority received neither systemic nor other direct pericardial intervention. Radiation therapy was successful in controlling MPCE in 36 patients (66.7%). The highest success rates were noted in leukemia-lymphoma and breast cancer patients (63% and 71%, respectively). Surprisingly, 45% of patients with other solid tumors had adequate control of their effusions. Although noninvasive, radiotherapy requires repeated visits or even hospitalization and may theoretically cause acute pericarditis or myocarditis. These potential complications may not be relevant in many patients, owing to their limited survival.

Patients with MPCE secondary to lymphoma or breast carcinoma may have effusions controlled with systemic chemotherapy. Vaitkus et al. reported their...
experience with 46 patients with breast tumor (n = 38), lymphoma (n = 2), or other solid tumors (n = 6) treated with systemic chemotherapy. Thirty-six patients (78%) underwent initial palliative thoracocentesis. Systemic chemotherapy prevented recurrence of effusion in 31 patients (67%); successful control of effusion was achieved in more than two-thirds of these individuals irrespective of whether pericardiocentesis preceded systemic therapy.

**SUMMARY**

MPCE is frequently an indication of advanced, incurable malignancy. Hence, the goals of intervention include relief of symptoms and prevention of recurrence. The treatment of MPCE should proceed in a stepwise fashion (Fig. 52-5-7). Surgical interventions (subxiphoid pericardiostomy) or medical interventions (ultrasonic tube pericardiocentesis) have acceptable risks and provide excellent results. We favor surgical drainage as the primary approach for patients with MPCE because of its simplicity and extremely high success rate without the need for intrapericardial instillation of sclerosing agents and tube manipulations that may be associated with patient discomfort. Recurrent MPCE can be managed either by repeat pericardiocentesis or insertion of a shunt. Patients responding to treatment with complete control of the effusion should have a meaningful survival with life expectancy (average, 9 months) contingent on the histology of the underlying malignancy.

**FIGURE 52-5-7** Treatment algorithm for malignant pleural effusion. VATS, video-assisted thoracoscopic surgery.

**CHAPTER REFERENCES**

11. Deck R, Binslav DE. Primary approach for patients with MPCE because of its simplicity and extremely high success rate without the need for intrapericardial instillation of sclerosing agents and tube manipulations that may be associated with patient discomfort. Recurrent MPCE can be managed either by repeat pericardiocentesis or insertion of a shunt. Patients responding to treatment with complete control of the effusion should have a meaningful survival with life expectancy (average, 9 months) contingent on the histology of the underlying malignancy.

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SECTION 52.6
Malignant Ascites

FRANCESCO M. MARINCOLA
DOUGLAS J. SCHWARTZENTRUBER

INTRODUCTION

The collection of intraperitoneal fluid in a patient with known intraabdominal cancer is most likely due to intraperitoneal spread of disease and if neoplastic cells are identified, the term malignant ascites is used. This finding has multiple implications: (1) the recognition of small quantities of intraperitoneal fluid may have staging and prognostic significance and alter a planned surgical intervention; (2) symptomatic large collections are a sign of disseminated carcinomatosis and may reflect end-stage disease. Although the expected survival in this case is on the order of months, several palliative options can be considered; (3) the presence of malignant ascites may be part of a clinical picture amenable to curative efforts. In such cases, as lymphoma and ovarian cancer, strategies aimed at obtaining regression of tumor and prolongation of survival should be considered.

The therapeutic approaches used to treat patients with malignant ascites may include extensive surgical debulking in preparation for local or systemic chemotherapy, intracavitary chemotherapy with or without hyperthermia, phototherapy, instillation of biologic response modifiers, and intracavitary particle radiation. Although prolongation of survival has been attributed to some of these therapies, no definitive study has ever demonstrated effectiveness or superiority of one strategy over the other. It is possible that the lack of randomized clinical trials reflects the skepticism of many investigators about the therapeutic effectiveness of available options and the desire to explore new treatment modalities in the context of phase I or phase II studies.

DIAGNOSIS AND WORKUP

Abdominal distension and changes in abdominal girth are classic symptoms of ascites (Table 52.6-1). Signs of ascites include dullness to percussion, shifting dullness, and fluid wave. These may be totally absent in smaller effusions (100 mL or less) diagnosed incidentally during the workup of malignancy by ultrasonography, magnetic resonance imaging, or computed tomography. Nonneoplastic causes of ascites include congestive heart failure, cirrhosis, renal or pancreatic disease, hypoproteinemia, infectious processes, and benign gynecologic conditions such as endometriosis. Although malignant ascites represents approximately 10% of all cases of ascites, in a patient with advanced cancer it is the most likely diagnosis. As a rule of thumb, a small amount of ascitic fluid along the gutter or in the pelvis of an asymptomatic patient with known intraperitoneal malignancy undergoing systemic therapy should not be aspirated since it can be assumed to be secondary to the malignancy itself. A peritoneal tap is indicated when the ascitic fluid is bloody effusion and malignant characteristics. However, a prospective study failed to show sufficient specificity of this technique.

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The ascitic fluid should be evaluated for various chemistry, tumor, and cytologic markers (Table 52.6-1 and Table 52.6-2). Five hundred milliliters of fluid are generally sufficient to collect enough cells for cytologic evaluation; if no cancer cells are found with this amount, additional fluid will not be more informative. A serous (rather than bloody) character of the fluid suggests a hydraulic cause such as portal hypertension, cardiac failure, nephrotic syndrome, reduced oncotic pressure, or pancreatic ascites. Infection is generally associated with other systemic symptoms, whereas tubercular and malignant ascites may be particularly difficult to differentiate as several markers, except cholesterol, express a similar pattern. The presence of chylous fluid can be related to obstruction or injury of large retroperitoneal lymphatic channels seen with extensive intraabdominal lymphomas or after external beam radiation.

TABLE 52.6-1. Assessment of the Patient with Ascites: Diagnosis/Workup

Nonneoplastic causes of ascites include congestive heart failure, cirrhosis, renal or pancreatic disease, hypoproteinemia, infectious processes, and benign gynecologic conditions such as endometriosis. Although malignant ascites represents approximately 10% of all cases of ascites, in a patient with advanced cancer it is the most likely diagnosis. As a rule of thumb, a small amount of ascitic fluid along the gutter or in the pelvis of an asymptomatic patient with known intraperitoneal malignancy undergoing systemic therapy should not be aspirated since it can be assumed to be secondary to the malignancy itself. A peritoneal tap is indicated when the ascitic fluid is bloody effusion and malignant characteristics. However, a prospective study failed to show sufficient specificity of this technique.

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TABLE 52.6-2. Tools for the Evaluation of Malignant Serous Effusions
Only a minority of all causes of ascitic fluid collections is malignancy, particularly in children, and approximately one-third of patients with known malignancy have nonmalignant causes of ascites. Thus, assays have been described that help determine the neoplastic origin of the ascites. A prognostic significance has been attributed to biochemical or immunologic markers. Peritoneal fluid cytology yields a diagnosis in a large proportion of patients. The presence of elevated ascitic tumor markers (e.g., alpha-fetoprotein, carcinoembryonic antigen, CA-125, fibronectin, or cholesterol) favor neoplasm. Others proposed the measurement of human chorionic gonadotropin in serum and ascitic fluid for the identification of gynecologic malignancies. Vascular endothelial growth factor levels have been noted to be significantly elevated in malignant ascites compared with ascites from benign causes. Immunochemical combinations have been described for the diagnosis of adenocarcinomas and other malignancies. El-Habashi et al. reported the use of a battery of monoclonal antibodies against p53, B7.2, and c-erbB-2 as complement to conventional cytology to enhance diagnostic sensitivity and accuracy.

Approximately 20% of patients with malignant ascites present without an identified primary cause. In these patients, particularly women, attempts to identify the tumor of origin should be undertaken because the identification of the primary histology may influence the treatment strategy. Laparoscopy in 129 patients with unknown primary identified carcinomatosis in 60% and laparoscopy with peritoneal biopsy was able to establish the cause of ascites in 86% of these cases. Although laparoscopy in patients with ascites has been rarely associated with postoperative morbidity, some groups reported a 5% or port site recurrence. It can be considered a safe tool for the evaluation of ascites. Approximately 75% of women presenting with malignant ascites of unknown origin have a gynecologic cause (ovary, uterus, or cervix) and another 10% a gastrointestinal cause, while in men the gastrointestinal etiology predominates. Other histologies should be considered, particularly when a primary tumor deposit is not recognized after routine studies of the abdominal cavity. These unusual causes of malignant ascites may create a difficult diagnostic challenge such as the differentiation of mesothelioma cells from normal mesothelial cells or the analysis of lymphoid-rich effusions in the case of lymphoma. Unusually, ascites can be the result of cancer treatment.

TREATMENT OF MALIGNANT ASCITES

As the pathogenesis of malignant ascites differs from the pathogenesis of most ascitic fluid collections secondary to benign processes, the treatment is often different in many respects. Excess fluid formation as well as obstruction of lymphatic channels are believed to be the most relevant factors inducing malignant ascites. Since most of the time there is no underlying venous obstruction, portal hypertension is unusual and vascular shunting procedures are not indicated. Several strategies have been used with the primary goal of achieving palliation, as the presence of malignant ascites is perceived as a sign of end-stage disease. A survey of practicing physicians suggested that the most common mean of managing malignant ascites is paracentesis, which is also believed to be the most effective. After paracentesis, diuretics and peritoneovenous shunting were most commonly used. In particular cases, radical surgical procedures or aggressive intracavitary therapies have been advocated, however, to date no well-controlled prospective randomized trial has been performed to compare alternative treatments. The encouraging results reported by many pilot phase I or II studies involving intracavitary instillation of chemotherapeutic agents have not matured, with few exceptions, into randomized phase III trials. The median survival of patients with symptomatic malignant ascites is approximately 2 months (Table 52.6-3). In general for nonovarian malignant ascites, the focus is on palliation of symptoms. Patients with malignant ascites secondary to ovarian cancer represent an exception because they have a significantly better survival expectation. Thus, investigation of female patients presenting with ascites of unknown origin should be particularly thorough. Patients with large volume nonovarian ascites have a high mortality (41%) following major abdominal surgery. For these patients, Yazdi et al. have suggested intraperitoneal chemotherapy or peritoneovenous shunt placement at the time of the abdominal operation.

TABLE 52.6-3. Patient Survival after Peritoneovenous Shunting

<table>
<thead>
<tr>
<th>Survival Rate (%)</th>
<th>Median Survival (months)</th>
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<tbody>
<tr>
<td>30</td>
<td>2</td>
</tr>
<tr>
<td>50</td>
<td>4</td>
</tr>
<tr>
<td>70</td>
<td>6</td>
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DIURESIS AND RESTRICTION OF SALT AND FLUID INTAKE

Loop diuretics, salt restriction, and aldosterone-inhibiting diuretics are generally not beneficial since sodium retention is not a cause of malignant ascites, although spironolactone is seldom used. Podkos et al. noted that cancer patients with portal hypertension-related ascites caused by massive hepatic metastases were more likely to experience palliation when treated with diuretics. The administration of albumin was never proven beneficial in delaying fluid reaccumulation nor more effective than crystalloid solutions in restoring intravascular volume depletion after drainage of large quantities of peritoneal fluid.

REPEATED PARACENTESIS AND EXTERNAL DRAINS

Symptoms of malignant ascites may be relieved by repeated abdominal taps as needed. Gough et al. reported no difference in survival and quality of life between patients treated with repeated abdominal paracentesis and patients treated with peritoneovenous shunts. However, several concerns are raised by this approach, including the risk of infection, electrolyte and fluid imbalances secondary to the sudden depletion of body fluids, and the risk of causing intraperitoneal visceral injury. For this reason multiple methodologies describing the implantation of permanent drains in the peritoneal cavity have been described. Although good palliation can be achieved in this fashion, the life span of these drains is limited by the need for removal because of malfunction or infection. Lorenzen et al. have reported the use of ultrasonically guided insertion of peritoneogastric shunts in patients with malignant ascites using a Denver shunt connected to a gastrostomy tube. This technique allows intermittent removal of fluid that, on pumping, is shunted to the stomach lumen. Others have advocated peritoneal-urinary drainage for the treatment of refractory ascites. These methods have potential benefits compared with the external drain (in which the ascitic fluid is totally removed from the body) and peritoneovenous shunts (returning the drained fluid from the peritoneal cavity directly to the intravascular space).

INTRACAVITARY THERAPY

Instillation of radioactive isotopes, including colloidal suspensions of 111In-pentetreotide, was originally reported with minimal side effects. Weisberger et al. performed intraperitoneal administration of nitrogen mustard in seven patients with advanced ovarian cancer with effective reduction of the amount of ascites in all patients. The rationale for this therapeutic approach is based on the intuition that, due to limited peritoneal absorption, some drugs could be administered in high concentrations in the peritoneum with relatively few systemic effects. Cisplatin and mitoxantrone used alone or in combination with other agents have become first-line chemotherapeutic agents for the treatment of peritoneal carcinomatosis. Cisplatin is mostly used for the intraperitoneal treatment of ovarian carcinoma because of its high effectiveness against this cancer when given systemically. To enhance the local effectiveness of intraperitoneally administered cisplatin while diminishing the side effects related to its systemic absorption, intravenous administration of thiosulfate has been recommended. Komarni et al. reported a 30% complete response rate in patients who underwent intraperitoneal cisplatin and etoposide administration after failure of first-line plat-in-containing systemic treatments. This study was performed on patients with small bulk of disease (less than 2 cm) and suggested that, as for systemic therapy, the load of tumor may play a role in the response rate. Several authors have investigated the use of intraperitoneal treatment in combination with debulking surgery or after first-line systemic therapy. As previously discussed, Howell et al. reported a 48-month median survival with intraperitoneal instillation of cisplatin in 25 patients with microscopic disease (less than 0.5 cm) after first-line chemotherapy. The dose intensity of cisplatin administration has been increased without added toxicity. Bonetti et al. administered high-dose intraperitoneal cisplatin twice a week. Hagiwara et al. reported a 92% response rate with the intraperitoneal administration of cisplatin lactic
acid oligomer microspheres in patients with malignant ascites. Park et al. reported their experience in treating 18 patients with primary peritoneal mesothelioma with continuous hyperthermic peritoneal perfusion and cisplatin. Thirteen of the 18 patients had associated malignant ascites. Continuous hyperthermic peritoneal perfusion with cisplatin was successful in 12 of the 13 cases. The median progression-free survival in this study was 26 months and the overall 2-year survival was 80%, superior to the survival reported in historical controls. The same group has evaluated the feasibility of a combination hyperthermic peritoneal perfusion and mitomycin C (MBC). This combination was evaluated in 27 patients with peritoneal carcinomatosis. There was no mortality. The complication rate was minimal, and the clinical outcome of this modality of treatment is presently under investigation. Gilly et al. reported resolution of malignant ascites in 11 of 12 patients treated with intraperitoneal chemotherapy and hyperthermia consisting of either cisplatin or mitomycin C after surgical resection of bulk disease. Intraperitoneal instillation of the chemotherapeutic agent was done after closure of the abdominal cavity and heated to the inflow temperature of 46°C to 49°C. Patients had ascites secondary to gastric malignancy. The median survival was 11.2 months, and the 1-year survival rate was 46.9%. Similarly, Loggie et al. reported a median survival of 10.1 months in patients with nonovarian malignant ascites treated with cytoreductive surgery and intraperitoneal hyperthermic chemotherapy with mitomycin C. Interleukin-2 (IL-2) is interesting, in the same trial, 12 additional patients who did not present with ascites but had positive cytologic evaluations at the time of operation were treated with the same treatment protocol. None of these patients developed ascites subsequent to this treatment and their median survival was 32.7 months, suggesting that intraperitoneal hyperthermic chemotherapy may have a role in preventing the formation of malignant ascites.

Several other authors have addressed the use of hyperthermia in combination with local chemotherapy for the treatment of gastrointestinal malignancies with similar results.

To evaluate the relative effectiveness of intraperitoneal versus systemic administration of cisplatin in patients with ovarian cancer, Kimani et al. completed a phase III randomized trial. This is the only randomized trial addressing the efficacy of intracavitary versus systemic therapy for peritoneal carcinomatosis. In this study, patients (29) were randomized to receive six cycles of intraperitoneal cisplatin (22 mg/m²) and etoposide (350 mg/m²). As an example of the importance of prospective randomized trials, in spite of the anecdotal derived enthusiasm for intracavitary therapy, no difference was noted in response rate (46% intraperitoneally vs. 52% intravenously). The rate of complete response at second-look laparotomy was 31% and 33%, respectively, and at a median follow-up of 46 months there was no difference in response duration and survival. Furthermore, there was no difference in response rate in relation to the bulk of tumor present at the time of chemotherapy (less than or equal to or greater than 1 cm). The authors concluded that the small number of patients tested did not allow a definitive dismissal of the usefulness of the intraperitoneal approach. To our knowledge, no follow-up evaluation of a larger cohort of patients has been published since, and the same group has turned its interest toward the evaluation of new agents such as the intraperitoneal instillation topotecan. Other alternatives to cisplatin have been suggested including the intraperitoneal administration of carboptalin, etoposide, and granulocyte-macrophage colony-stimulating factor, with a partial response rate of 69%. Stetler et al. reported the treatment of small-volume residual ovarian cancer with continuous hyperthermic peritoneal perfusion and carboptalin in the context of a phase I trial. This well-tolerated modality of treatment may have important applications for novel therapies given intraperitoneally.

Biologic response modifiers have been used as an alternative to chemotherapeutic agents for the treatment of intraperitoneal carcinomatosis. Single-agent interferon-α or interferon-β, tumor necrosis factor, and interleukin-2, with or without adoptive administration of lymphokine-activated killer cells, have been reported with variable success. A randomized trial has compared the effectiveness of interleukin-2, interferon-α or interferon-β for the control of malignant effusions, suggesting a higher efficacy of interleukin-2 in patients with mesothelioma. Others have reported effectiveness of the combined intraperitoneal administration of interleukin-2 and OK-432 in patients with ascites secondary to gastric malignancy. The authors reported an incidence of cytologic disappearance of cancer and decrease of ascites in 81% of 22 evaluable patients. The role of interferon-γ has also been explored in patients with malignant ascites because of the ability of this cytokine to induce up-regulation of tumor-associated antigens, major histocompatibility complex molecules, or both in tumor cells. This property suggested possible therapeutic usefulness combining this cytokine with the administration of major histocompatibility complex–restricted T cells in view of the enhanced lysability of tumor cells expressing higher amounts of major histocompatibility complex molecules. Phase I studies of adoptive cellular immunotherapy with intraperitoneal injection of activated human blood monocytes have shown the feasibility of this approach. Radiolabeled monoclonal antibodies directed against tumor markers have also been used.

RADICAL SURGERY

Peritoneectomy has been advocated by Sugarbaker; this is an extensive debulking procedure using a ball-type electrocautery device. It includes six possible steps: (1) greater omentectomy-splenectomy; (2) left upper quadrant peritonectomy; (3) right upper quadrant peritonectomy; (4) lesser omentectomy-cholecystectomy with stripping of the omental bursa; (5) pelvic peritonectomy with sleeve resection of the sigmoid colon; and (6) antrectomy. The purpose of the procedure is cytoreduction in preparation for intraperitoneal chemotherapy. The authors reported good long-term results in selected patients affected with peritoneal carcinomatosis, sarcomatosis, and mesothelioma. Intraoperative chemotherapy included mitomycin C and 5-fluorouracil for patients with adenocarcinoma and cisplatin and doxorubicin for patients with sarcoma. Among patients with enteric carcinomatosis, favorable prognostic characteristics were identified that include low-grade histopathology, absence of lymph nodal metastases, and completeness of the cytoreductive procedure (survival at 3 years was 99%). A follow-up report from the same group identified a significant difference in 5-year survival between patients with stage III gastric cancer who had undergone surgery alone (18.4%) versus patients who underwent additional intraperitoneal chemotherapy (49.1%; P = 0.011). In this series patients had resectable gastric cancer and no ascites. This randomized study demonstrates, in principle, that intraperitoneal chemotherapy may have a role in the treatment of aggressive, nonovarian, intraabdominal cancers likely to lead to malignant ascites. A pilot study describing the use of photodynamic therapy as adjuvant therapy after aggressive debulking of disseminated intraperitoneal malignancies by Sindelar et al. has shown a 26% disease-free survival rate at 18 months. These results in selected patients, however, still await confirmation by a randomized trial.

PERITONEOVENOUS SHUNTING

An extensive discussion about the application of shunting procedures for the treatment of malignant ascites has been reviewed by Alexander and Fraher. In patients with symptomatic malignant ascites, internal peritoneovenous shunting represents the standard modality of care. The devices consist of (1) a length of multiply perforated tubing to be inserted in the free peritoneal cavity, (2) a length of tubing to be inserted into the superior vena cava (or other large venous vessel), and (3) a unidirectional flow valve connecting the two limbs. This combination was evaluated in 27 patients with peritoneal carcinomatosis, sarcomatosis, and mesothelioma. Intraoperative chemotherapy included mitomycin C and 5-fluorouracil for patients with adenocarcinoma and cisplatin and doxorubicin for patients with sarcoma. Among patients with enteric carcinomatosis, favorable prognostic characteristics were identified that include low-grade histopathology, absence of lymph nodal metastases, and completeness of the cytoreductive procedure (survival at 3 years was 99%). A follow-up report from the same group identified a significant difference in 5-year survival between patients with stage III gastric cancer who had undergone surgery alone (18.4%) versus patients who underwent additional intraperitoneal chemotherapy (49.1%; P = 0.011). In this series patients had resectable gastric cancer and no ascites. This randomized study demonstrates, in principle, that intraperitoneal chemotherapy may have a role in the treatment of aggressive, nonovarian, intraabdominal cancers likely to lead to malignant ascites. A pilot study describing the use of photodynamic therapy as adjuvant therapy after aggressive debulking of disseminated intraperitoneal malignancies by Sindelar et al. has shown a 26% disease-free survival rate at 18 months. These results in selected patients, however, still await confirmation by a randomized trial.
The indication for the placement of a peritoneovenous shunt includes malignant ascites refractory to medical management. It is, therefore, reasonable to expect that, with the development of more effective systemic or intraperitoneal therapy the need for this procedure will decline. The median survival of 674 patients with refractory malignant ascites (gastrointestinal primary in 33%, ovarian primary in 27%, and other malignancies in 39%) undergoing placement of a peritoneovenous shunt is 5 to 33 weeks with 0% to 13% of patients alive at 1 year (Table 52.6-3). Therefore, the goal of the peritoneovenous shunt placement is to minimize the side effects caused by the procedure and the presence of a foreign body and provide significant palliation. The wide variation in the range of patient survival after placement of a peritoneovenous shunt is most likely due to differences in patient selection criteria. Other variables such as center experience, number of needles used, type of ascitic fluid, and patient survival. A comparison of survival and quality of life in patients receiving shunting procedures versus repeated paracentesis failed to demonstrate significant differences.

Immediate postinsertion complications related to placement of the peritoneovenous shunt include shunt malfunction due to technical reasons and pulmonary complications. Although the shunt provides a pump that allows manual flushing at periodic intervals, the literature has failed to demonstrate functional superiority of this device. It has been reported, however, that flushing of the Denver shunt combined with the administration of thrombolytic agents can occasionally restore shunt function. Retoculation of the catheter is usually necessary to establish patency since thrombolytic agents are infrequently successful in this situation. The goal in reestablishing flow in the system is correction of the source, avoiding replacement of the entire shunt. Shunt malfunctions are usually manifested by recurrence of ascites and can be demonstrated by visualization of nodulete in the lungs after intraarterial injection of 99mTc macroaggregate albumin. A shuntogram performed by percutaneous injection of radiographic contrast agents into the venous limb of the shunt (into the pump reservoir if a Denver shunt) helps determine the site of obstruction. We previously described shunting by thoroboothrin encaissement of the venous limb, manifesting as a characteristic contrast outline of the tubing during shuntogram.

Another complication of peritoneovenous shunt placement is infection in the peritoneal cavity. This can be associated with postoperative leakage of peritoneal fluid around the shunt and prevented by suturing the exit incision with double-purse-string sutures. The development of spontaneous bacterial peritonitis, unrelated to operative infection or to perforation of a viscous due to the malignant process, is, for unknown reasons, less likely in patients with malignant ascites than in cirrhotic patients. It has been noted that malignant peritoneal fluid has significantly higher concentrations of transferrin than cirrhotic ascesses. As transferrin concentration in peritoneal fluid is inversely correlated with bacterial growth, it is possible that patients with malignant ascites are somewhat more protected against peritonitis than cirrhotic patients. Evidence of hematologic displacement of tumor cells from the ascitic fluid and tumor growth along the shunt tract has been reported and is likely to occur relatively often. However, this theoretical risk has been a problem, most likely because of the limited survival of these patients.

In summary, malignant ascites represents in most instances a debilitating symptom of end-stage cancer. Purely palliative measures on one extreme and aggressive locoregional curative efforts. Scant information is available regarding the effectiveness of intracavitary versus systemic therapy. The decision to place a peritoneovenous shunt should be made after consideration of the various risks and potential benefits. According to Souter et al., a patient with cultured malignant ascites whose only considered therapeutic goal is palliation, should first undergo repeated paracentesis and medical management with diuretics. If the rate of reaccumulation of the fluid is rapid, fluid consistency is not viscous or bloody, there is no evidence of intracavitary loculation, and the expected survival is more than 3 months, shunting should be considered. Contraindications for placement of the shunt are presence of intraoperative infection and cardiac or renal insufficiency. To avoid the massive fluid shifts associated with drainage of refractory ascites, Daimon et al. proposed the use of extracorporeal ultrafiltration of the ascites followed by intravenous reinjection of the ultrafiltered fluid. Among the various patients treated in this fashion, two had malignant ascites. This approach was well tolerated and both patients died of their primary disease free of symptoms related to ascites.

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SECTION 53.1  
Transfusion Therapy

PETER L. PERROTTA  
EDWARD L. SNYDER

INTRODUCTION

Despite the increasing use of hematopoietic growth factors, transfusion therapy continues to play an important role in the care of oncology patients. In fact, transfusion therapy has become increasingly critical as improved therapeutic regimens prolong the survival of patients with malignant disease. These patients often require frequent blood transfusions when they develop severe anemia, hemorrhage, thrombocytopenia, and coagulation disorders caused by their disease, treatment, or both.

The development of sterile, disposable, and flexible plastic containers has resulted in the concept of **blood component therapy**. Whole blood is first separated into cellular and noncellular components including red blood cells, platelets, and plasma. Individual blood components are then stored under optimal conditions and only that portion of blood required by the patient is transfused (Table 53.1-1). Thus, blood resources that often reach critically low inventory levels in the blood bank are more efficiently used. Anticoagulants and additives currently used in blood collection containers allow storage of liquid red cells for up to 42 days. These advances have essentially eliminated the use of whole blood for allogeneic blood transfusion. Cancer patients may also require coagulation factor concentrates, albumin, or immune globulin, all of which are prepared by fractionating human plasma. Cell separators capable of collecting platelets, plasma, granulocytes, peripheral blood stem cells, and more recently, red blood cells, are playing an increasingly important role in transfusion medicine.

TABLE 53.1-1. Use of Blood Transfusion Components in Oncology Patients

<table>
<thead>
<tr>
<th>Component</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole blood</td>
<td>Initially used for transfusion but now replaced by targeted cellular products</td>
</tr>
<tr>
<td>Red blood cells</td>
<td>Transfused to correct anemia and support hematopoiesis</td>
</tr>
<tr>
<td>Platelets</td>
<td>Transfused to correct bleeding and support hemostasis</td>
</tr>
<tr>
<td>Plasma</td>
<td>Used for coagulation factor replacement and volume expansion</td>
</tr>
<tr>
<td>Cryoprecipitate</td>
<td>Used for coagulation factor replacement and volume expansion</td>
</tr>
</tbody>
</table>

Routine blood bank procedures including ABO typing, antibody screening, and compatibility testing identify most patients at risk for serious immune-mediated red cell transfusion reactions. Furthermore, a better understanding of red cell, platelet, and leukocyte antigen structure, as well as the immune responses to these antigens, has vastly improved transfusion therapy. Changes in recruiting and screening blood donors, as well as advances in the testing of donor blood, have drastically reduced the risk of viral transmission in the United States and Europe. All units of blood collected in the United States are tested for hepatitis B, hepatitis C, human immunodeficiency virus 1 and 2 (HIV), human T-cell lymphotropic virus-I and II (HTLV-I/II), and syphilis. Nucleotide amplification testing for hepatitis C and HIV is now performed in most European countries and the United States. Nevertheless, there remain significant risks of transfusion therapy. Complications that are not unique to oncology patients include acute and delayed hemolytic, febrile nonhemolytic, allergic, and septic reactions. Of particular concern in patients who receive large numbers of allogeneic transfusions is the development of HLA alloimmunization and graft-versus-host disease (GVHD). The presence of numerous recipient red cell alloantibodies can also severely limit the number of compatible units that will be available for a patient. Development of platelet alloantibodies can result in a refractory state to platelet transfusions. Fortunately, routine precautions taken in oncology patients including leukoreduction and irradiation of all cellular blood products have reduced the incidence of alloimmunization and GVHD.

Although the hazards of blood transfusion are relatively small, the expected benefit of a transfusion must still outweigh any risk to the patient. Therefore, practitioners of hematology and oncology need to clearly understand the indications and complications of blood transfusion therapy to minimize the exposure of patients to unnecessary alloimmune blood products and to prevent wasting of limited blood resources.

BLOOD COMPONENT THERAPY

RED BLOOD CELLS

Preparation and Storage
Red blood cells, formerly called packed cells, are prepared by first centrifuging whole blood and then removing by most of the plasma. A standard whole blood collection involves removing 450 ± 45 mL of whole blood into sterile containers containing an anticoagulant and preservative solution. Solutions composed of citrate, phosphate buffers, and dextrose (CPD) originally allowed storage of red cells for 21 days at 1 to 6°C. It was later found that red cell shelf life could be increased to 35 days by adding adenosine to the preservative solution (CPDA-1). Adenosine improves cell viability by increasing intracellular adenosine triphosphate (ATP) levels, whereas dextrose provides a substrate for red cell metabolism. Shelf life is further extended to 42 days by using an additive solution that contains a higher concentration of adenosine than is present in CPDA-1 units. The hemotocrit of red cell units varies from 70% (CPDA-1) to 55% to 60% (additive solution). Citrate contained in blood preservatives inhibits clotting by binding calcium. Symptomatic hypocalcemia and alkalosis related to citrate toxicity are rare complications of red cell therapy limited to massively transfused patients. Red blood cells with rare antigen profiles can be frozen within 6 days of collection and stored for up to 10 years. They are frozen in approximately 40% glycerol to avoid cell dehydration and damage during the freezing process. Frozen red cells are indicated for oncology patients who have an alloantibody to a high-incidence antigen or have multiple alloantibodies.

**Indications for Red Cell Transfusion**

The decision to transfuse red cells is no longer based solely on a patient's hematocrit. The patient's overall clinical status and laboratory parameters are both considered when deciding to transfuse a patient. Symptoms and signs of anemia include excessive fatigue, malaise, headache, tachycardia, and hypotension. Acute blood loss of greater than 30% total blood volume leads to hypotensive shock. Oncology patients typically have more slowly developing chronic anemias that are tolerated better than rapid onset anemias due to the ability of the body's fluid compensatory mechanisms. Red cell transfusion is rarely indicated when the hemoglobin is greater than 10 g/dL and is often considered not until the hemoglobin is less than 7 g/dL. Younger patients usually tolerate a given degree of anemia better than older patients who may have underlying coronary, myocardial, or pulmonary disease. Patients with unstable angina or acute myocardial infarction may benefit from red cells when their hemoglobin is less than 10 g/dL. Thus, red cell transfusion should be based on clinical criteria rather than broadly applied threshold hemoglobin values. Transfusing a single red cell unit typically increases the hemoglobin by 1 g/dL (by 3%) in the absence of active red cell destruction.

**Antibody Screening, Antibody Identification, and Cross-Matching**

Even in emergency situations, a properly labeled sample must be sent to the blood bank before a red cell unit is issued. This sample is used to type a patient's red cells for ABO and Rh status. Front typing involves reacting patient red cells with commercial antibodies directed against the A, B, and D antigens. Blood grouping is confirmed during back typing in which patient serum is tested for anti-A and anti-B antibodies using commercial type A and B cells. Following blood grouping, recipient serum or plasma is screened for atypical red cells. Antibody screening is performed by incubating a patient's serum with two to four commercial group O red cells. Separate serum samples must be tested on red cells from more than one blood group. If one sample is positive, a more specific un-cross-matched blood (e.g., A positive unit transfused to a negative recipient) is permitted only when the recipient's ABO Rh status is known with certainty. Use of type-specific blood is particularly helpful when supplies of O negative red cells are severely limited during blood shortages. More recently, computer cross-matches have been instituted at several hospitals in North America. Many blood centers provide autologous preoperative blood donation services in which a patient's blood is drawn and stored for later use, usually during a surgical procedure. Although the criteria for autologous donations are less stringent than those for alloengeneic donors, oncology patients are often too anemic to donate their own blood. Patients must feel well on the day of donation and cannot be hypertensive, febrile, or septic because of the risk of bacterial contamination. Thus, the donor cannot have open wounds, such as from a recent biopsy, or have indwelling vascular or urinary catheters. Platelets and granulocytes contained in an autologous blood unit rapidly degrade with storage and are essentially nonfunctional by the time the unit is transfused. If the autologous unit is stored as whole blood, the plasma contained in this unit has low levels of labile coagulation factors.

Oncology patients may develop autoimmune hemolytic anemias as a direct result of their disease or from treatment of that disease. In particular, patients with chronic lymphocytic leukemia, non-Hodgkin's and Hodgkin's lymphoma, and plasma cell disorders frequently develop warm autoimmune hemolytic anemia. Autoantibodies consist of immunoglobulins (IgG, IgM) that react with a wide range of self-antigens including membrane and intracellular components, adsorbed plasma proteins, and nuclear antigens. The DAT result is positive in most cases. Patients with warm autoimmune hemolytic anemia often require transfusion. The blood bank may have difficulty identifying compatible red cells units because they are positive in up to 1 per 7000 blood donors, and more importantly, have no clinical significance. In addition, DATs are not routinely performed at most large medical centers as part of routine pretransfusion testing; the test must be specifically requested. Positive DAT results are also seen in patients with delayed hemolytic transfusion reactions (DHTRs), autoimmune hemolytic anemias, autoimmune disorders (systemic lupus erythematosus), and malignancy (especially B-cell malignancies such as chronic lymphocytic leukemia).

Cross-matching is performed by reacting patient serum with donor red cells from the unit selected for transfusion. If no reaction is observed, the unit is released as compatible. Cross-matching is only omitted in emergency life-threatening situations in which there is truly insufficient time to perform compatibility testing. Many hospitals store uncross-matched red cells in case an emergency arises. In this situation, a patient sample is run on all panel cells as a safety measure. In the United States, all red blood cells are irradiated to reduce the risk of transfusion-related acute lung injury. If a DAT is positive, a cross-match is performed to verify the presence of antibodies that would cause hemolysis. A positive cross-match result implies that the patient's red cells react with the panel cells. Two methods are used to identify incompatible red cells: the tube test and the gel test. In the tube test, red cells are mixed with antihuman antibodies against IgG, IgA, IgM, C3, and C4. A positive result implies that the patient's red cells are covered with antibodies. The gel test is performed by incubating a suspension of patient red cells with antihuman antibodies directed against IgG, IgA, IgM, C3, or C4. A positive result implies that the patient's red cells are coated with the corresponding globulin. DATs are no longer performed on volunteer blood donors because they are positive in up to 1 per 7000 blood donors. Because of the associated costs, DATs are only performed for patients who may have a high risk of receiving a transfusion.
factors. Plasma can be separated from autologous whole blood and frozen to maintain the activity of all coagulation factors. Although autologous blood is intended for the patient—donor, most blood centers test autologous units for the same transfusion disease markers required for allogeneic blood. Preoperative blood donation can be used in older oncology patients, although there is a higher risk of anemia and more serious cardiovascular complications associated with the donation. The use of autologous blood decreases the risk of viral infection, but the risk of bacterial contamination remains. Autologous preoperative blood donation is not crossed over because most of these patients do not meet all requirements for allogeneic blood donation.

Acute normovolemic hemodilution is performed by removing blood from a patient immediately before surgery and replacing the blood volume with crystalloid or colloid solutions to maintain hemodynamic stability. The withdrawn blood is then later reinfused. Autologous blood salvage is performed by collecting and then returning blood lost during or shortly following operative procedures using intraoperative salvage devices. This technique is primarily employed in cardiac and orthopedic surgery. Autologous blood salvage is generally contraindicated in cancer surgery because of the risk of returning contaminating tumor cells to the systemic circulation. There is some evidence that irradiating salvaged blood with 50 Gy can destroy the proliferative ability of malignant cells, but more studies are needed before this technique can be safely applied to cancer surgery.

**Autologous Platelet Donation**

Although oncology patients can bank their own red cells through autologous donation, it is not usually feasible for these patients to donate autologous platelets. Platelets stored in the liquid phase at room temperature have a shelf life of only 5 days. Platelets collected by apheresis and frozen preserved in dimethyl sulfoxide can be stored at –80°C. They are then thawed, washed, and resuspended in autologous plasma or other solutions before transfusion. Platelets prepared by this technique do undergo a number of structural and metabolic changes that decreases their recovery and survival as compared with liquid-stored platelet concentrates. Furthermore, most patients cannot donate enough platelets to support a full course of induction chemotherapy. It is possible, however, to store significant numbers of frozen autologous platelets for patients who are refractory to platelet transfusion provided the blood bank is technically capable of preparing and storing these specialized products.

**Directed Blood Donation and Dedicated Donor Units**

Directed blood donations are those donations made for a specific patient. These units, most frequently obtained from family members or friends, can greatly augment the blood supply. Donors wishing to make directed donations must meet the same criteria for blood donation as other allogeneic donors. This unit undergoes all required testing for transmissible diseases. Therefore, due to the possibility of unexpected test results, it is important that the donor understand his or her blood will be tested for conditions such as HIV and hepatitis C. If, in fact, directed blood donors are more likely to be positive for some infectious disease markers than other allogeneic blood donors. This increased frequency of positive infectious disease markers most likely reflects in part the higher percentage of first-time donors in the directed donor group who were not previously screened.

The cytomegalovirus (CMV) status of the blood donor and the needs of the oncology patient also affect the use of directed blood donation. CMV-seronegative blood products are often required by oncology patients, in particular, those patients who are marrow transplant candidates or recipients. As in the allogeneic donor pool, many directed donor units are seropositive for CMV. Thus, units from some directed donors may not be appropriate for the intended recipient. In this situation, the patient’s oncologist must decide if a CMV-seropositive directed unit can be transfused to that patient. CMV status of directed units may be less of a concern as prestorage leukodepleted blood products prepared using cyclic good manufacturing practices gain further acceptance as an alternative to CMV-seronegative products.

Dedicated donor blood units are primarily used by pediatric oncology patients to reduce their exposure to blood from different donors. A dedicated unit is simply a unit of allogeneic red cells that is specifically set aside by the blood bank for use by a single patient. The unit is obtained from the general blood bank stock or from a directed donor. When necessary, small aliquots are removed from the units for transfusion. This approach is not feasible in adult oncology patients because of the large volume of blood required. However, a single dedicated unit could supply as many as ten separate transfusions in a pediatric patient, thus dramatically reducing multiple donor exposures.

**PLATELET TRANSFUSION THERAPY**

**Preparation and Storage**

Plastic primary collection bags with attached satellite containers allow harvesting of platelets as a by-product of red cell separation. In the United States, platelets are usually prepared by the platelet-rich plasma method, whereas the buffy coat method is used in Europe. Each random donor platelet unit (RDP) prepared by differential centrifugation of a single whole blood collection contains at least $5.5 \times 10^{10}$ platelets suspended in 50 mL of plasma. The shelf life of all platelet preparations is 5 days when stored at 20 to 24°C under constant agitation in plastic containers that allow oxygen diffusion. Storage longer than 5 days is precluded by the increased risk of bacterial growth and the development of platelet function abnormalities. RDPs are typically administered in four to six units. In the absence of conditions associated with decreased platelet survival, each RDP unit should increase a recipient’s platelet count by 5000 to 10,000/µL. Single donor platelets (SDPs) prepared by apheresis are often transfused to oncology patients in order to minimize their exposure to multiple donors. SDPs contain more than $3 \times 10^{10}$ platelets suspended in approximately 200 mL of plasma. Thus, one SDP is equivalent to five to six average RDP units.

ABO type-specific platelets are provided whenever possible. This is because transfusing out-of-type platelets may result in a postplatelet increment 10% to 20% less than that expected for ABO type-specific platelets. In addition, Rh antigens found on the small number of contaminating red cells present in platelet concentrates are sufficient to immunize a small number of Rh-negative recipients. If Rh-negative platelet concentrates are not available for an Rh-negative patient, Rh-positive platelets can be transfused followed by administration of Rh immune globulin within 72 hours of transfusion. Until relatively recently, only intramuscular Rh immune globulin was available to prevent Rh immunization. These injections could be dangerous in oncology patients who have low platelet numbers or coagulation disorders.

Fortunately, an intravenous preparation has been licensed for preventing Rh alloimmunization (WinRho, NABI, Boca Raton, FL). This therapy has been proven effective, and is clearly more convenient and less painful to the patient.

**Indications for Platelet Transfusion**

Platelets are transfused to thrombocytopenic patients who are actively bleeding or to severely thrombocytopenic patients as a prophylactic precautionary measure. Spontaneous bleeding is rarely encountered when a patient’s platelet count is more than 20,000/µL. In fact, studies suggest that oncology patients receiving chemotherapy can tolerate platelet counts as low as 5,000 to 10,000/µL. Postoperative patients with platelet counts more than 50,000/µL may require platelet transfusions to control or prevent postoperative bleeding. Overall coagulation status should also be considered because patients with plasma coagulation factor disorders are more likely to bleed at marginal platelet counts. Actively bleeding patients on aspirin, an irreversibly inhibitor of platelet function, may require transfusions at higher platelet counts. Obviously, transfused platelets are similarly inhibited if the patient remains on aspirin.

**Platelet Refractoriness**

Platelet refractoriness is a major problem for cancer patients who are dependent on platelet transfusions. There are many causes of an apparent lack of response to platelet transfusions, either through immune or nonimmune mechanisms. The corrected count increment (CCI) is used to identify patients who are refractory to platelet transfusions through either HLA or platelet alloimmunization. The CCI is calculated as follows:

$$CCI = \frac{Post(\mu L/L) - Pret(\mu L/L)}{Number\ of\ platelets \times 10^{11}} \times BSA \left(\text{m}^2\right)$$
where Pre is pretransfusion platelet count, Post is posttransfusion platelet count drawn 1 to 4 hours after completion of the transfusion, number of platelets transfused (1 RDP unit approximately $0.5 \times 10^{11}$ platelets; 1 SDP unit approximates $3.0 \times 10^{10}$ platelets), and BSA is body surface area in square meters. Patients with a low CCI (less than 5000) may benefit from cross-match–compatible platelets or HLA-matched single donor platelets.

Platelet cross-matching is performed by adding recipient serum to wells coated with donor platelets. After appropriate antibodies and an indicator reagent are added, the compatibility of the patient’s serum and the donor’s platelets is determined based on reactivity patterns. An incompatible cross-match predicts a poor CCI more than 90% of the time, whereas a negative cross-match is only 50% predictive of a successful transfusion. Depending on a particular hospital’s blood supplier, cross-match–compatible platelets or HLA-selected platelets may be more readily available. Some centers use a combination of the two techniques: Platelet units are selected for cross-matching based on the HLA type of the donor and recipient.

Cross-match–compatible and HLA-selected platelets are not readily available in all blood banks. Increasing the dose of standard platelet concentrates can be considered until these products are obtained. For example, a dose of eight to ten RDPs is transfused instead of the more typical four to six unit pools. In fact, investigators have suggested that higher platelet doses (approximately 4 to $6 \times 10^{11}$ platelets per dose) given prophylactically to patients with hematologic malignancies reduce the number of platelet transfusions and thus, the number of donor exposures. Ideally, the platelets are ABO identical because ABO incompatibility may decrease posttransfusion platelet increments by 10% to 20%. Some medical centers provide platelet drips to bleeding refractory patients.

Three-unit RDP pools are continuously infused through an electromechanical pump every 4 hours, providing a total of 18 RDP units over 24 hours. Electromechanical pumps do not appear to harm platelets. Platelet drips could theoretically maintain a lower platelet count, but this has not been proven. There are no studies that have fully compared the efficacy of intermittent platelet boluses and platelet drips in refractory patients. Corticosteroids, chemotherapy, splenectomy, and intravenous immunoglobulin, effective treatments for many autoimmune thrombocytopenias, are not useful in platelet refractory patients.

Leukocyte reduction filters, as well as ultraviolet B irradiation, decrease the rate of HLA alloimmunization to platelets. Therefore, leukocyte reduced filtered blood products should be provided to oncology patients who require many platelet transfusions (see Leukoreduction, later in this chapter). Presumably, leukoreduction removes donor antigen-presenting cells, which may play a key role in initiating HLA alloimmunization.

GRANULOCYTES

Granulocytes continue to play a small role in the supportive care of neutropenic oncology patients with serious infections, including allogeneic and autologous marrow transplant recipients. Improvements in apheresis collection technique now allow collection of larger numbers of granulocytes ($6 \times 8 \times 10^{10}$) from volunteer donors than was previously possible. These changes include the administration of corticosteroids or growth factors to white cell donors before apheresis. Granulocytes are typically transfused to neutropenic oncology patients who have developed gram-positive or gram-negative bacterial sepsis unresponsive to antibiotic therapy for a minimum of 24 to 48 hours (Table 53.1-3). Granulocytes collected from nonstimulated (no corticosteroids or growth factors) healthy donors contain at least $1 \times 10^{12}$ neutrophils per unit. These units can be stored for only 24 hours at 20 to 24°C without agitation. Granulocyte units contain 20 to 25 mL of red cells and thus must be cross-matched with the recipient’s serum. Donated granulocytes are rarely HLA matched for the recipient, even for those patients with known HLA antibodies because there are little data suggesting that HLA-matched granulocytes have improved survival and recovery. Granulocytes should be irradiated (2500 cGy) to inactivate the large number of lymphocytes found in the product. They are considered for patients who have an absolute neutrophil count less than 500/µL and a reasonable chance of marrow recovery.

TABLE 53.1-2. General Guidelines for Granulocyte Transfusions

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre</td>
<td>Post</td>
</tr>
<tr>
<td>CCI</td>
<td>Cross-match–compatible platelets or HLA-matched single donor platelets.</td>
</tr>
<tr>
<td>Cross-matching</td>
<td>Platelet units are selected for cross-matching based on the HLA type of the donor and recipient.</td>
</tr>
<tr>
<td>Leukoreduction</td>
<td>Doses of eight to ten RDPs are transfused instead of the more typical four to six unit pools.</td>
</tr>
<tr>
<td>ABO compatibility</td>
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</tr>
<tr>
<td>Platelet drips</td>
<td>Platelet drips could theoretically maintain a lower platelet count.</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Effective treatments for many autoimmune thrombocytopenias.</td>
</tr>
<tr>
<td>Leukocyte reduction</td>
<td>Leukocyte reduced filtered blood products should be provided.</td>
</tr>
</tbody>
</table>

Because of their short half-life, granulocytes are typically provided daily until the patient can maintain an absolute neutrophil count greater than 500/µL without transfusion or until the infection resolves. Infusion of larger numbers of granulocytes (on the order of 6 to $8 \times 10^{10}$ granulocytes) produces measurable increases in adult recipient neutrophil counts, but the optimal dose and frequency remain undefined. Febrile reactions to granulocytes are common, the reactions seem to be more severe when amphotericin is infused near the time of granulocyte transfusions. Overall, the additional benefit of granulocyte transfusions over these neutrophin patients as compared with antibiotic treatment alone is unclear as there are no well-controlled clinical trials. In addition, the clinical benefit of transfusing larger numbers of granulocytes collected from donors stimulated by corticosteroids or growth factors has not been proven. The collection of granulocytes, or any blood component, by apheresis is not an entirely innocuous process. The donor is at risk for uncommon, but potentially serious adverse reactions including hydroxyethyl starch–related hypotension and anaphylaxis and citrate-induced hypocalcemia. Hydroxyethyl starch is used as a sedimenting agent to maximize granulocyte yields. Minor, but typically tolerable, side effects of pretreating granulocyte donors with dexamethasone (insomnia, flushing), granulocyte colony-stimulating factor, or both starch–related hypotension and anaphylaxis are common because of the activity of transfused white cells, as well as their degradation products. These reactions are typical of febrile nonhemolytic transfusion reactions (FNTRs) following other blood product administration. Granulocytes should be transfused slowly, 1 to 2 mL/min through a standard microaggregate filter. Obviously, a leukocyte reduction filter should be used to administer granulocytes. In addition, the recipient should be medicated with acetaminophen or some other antiinflammatory agent before the granulocyte transfusion.

PLASMA

Plasma is prepared by centrifuging whole blood and then freezing the removed plasma within 8 hours of collection. Rapid freezing maintains the activity of fable...
coagulation factors such as factors V and VIII. The most commonly available form of plasma, fresh frozen plasma (FFP), contains all coagulation factors, other plasma proteins, and complement. FFP should not be used for volume expansion because there is a risk of transfusion-transmitted disease (TTD); other safer nonplasma substitutes are available. A unit of FFP contains from 180 to 270 mL of plasma. The primary indications for FFP transfusion in oncology patients include deficiencies of multiple coagulation factors as seen in liver disease, disseminated intravascular coagulation, and hypofibrinogenemia. It is often used for urgent reversal of warfarin therapy in bleeding patients and before procedures. FFP is not the treatment of choice for replacing most individual clotting factors because of the large volumes that would be required to obtain adequate factor levels. The patient's cardiovascular and fluid status may preclude the use of large amounts of plasma. In fact, large transfusions of FFP can produce fluid overload and subsequent heart failure in some patients. FFP is not the treatment of choice for coagulopathies in cases in which vitally inactivated or recombinant products exist such as for deficiencies of factor VIII (hemophilia A) or factor IX (hemophilia B).

**CRYOPRECIPITATE**

Cryoprecipitate is prepared by thawing FFP between 1 and 6°C. A single 10- to 15-mL unit of cryoprecipitate contains fibrinogen (100 to 350 mg/U), Factor VIII (at least 80 IU/U), and some von Willebrand factor. Thus, a similar dose of fibrinogen can be provided in a much smaller volume as compared with FFP. Use of cryoprecipitate is generally limited to patients with severe hypofibrinogenemia (less than 100 mg/dL) and von Willebrand's disease. It should not be used alone in disseminated intravascular coagulation because it contains no factor V. Cryoprecipitate, thrombin, and calcium are combined to make fibrin sealant. This biologic sealant is most often used to limit surgical bleeding. Since cryoprecipitate is used, the recipient is exposed to the risks of TTD. A fibrin sealant that contains solvent and detergent-treated plasma has been approved by the Food and Drug Administration.

**PLASMA DERIVATIVES**

**Albumin**

Solutions containing 5% human albumin in saline are primarily used to replace intravascular volume and more rarely, to treat hypoalbuminemia. Its use as a volume expander has decreased because other nonplasma colloidal solutions such as dextran and hydroxyethyl starch are readily available. Albumin is also used to replace plasma removed during apheresis. Albumin prepared in the United States is vitally inactivated by heat treatment. Properly prepared albumin has not been reported to transmit viral disease including hepatitis B virus, hepatitis C virus (HCV), and HIV types 1 and 2. Albumin is not a viable nutritional source for patients with chronic protein deficiency states seen in oncology patients.

**Immunoglobulins**

Immune globulin products include intravenously administered immune globulin, intramuscularly administered immune globulin, and several specialized products such as Rh(D) immune globulin and hepatitis B immune globulin. In the United States, immune globulin products are prepared from donor plasma screened for TTDs. Individual plasma units are then pooled and separated by alcohol fractionation or by anion exchange chromatography that results in a product that is considered safer from virus transmission. Polyvalent intravenous immune globulin is used to treat immune-mediated thrombocytopenias, autoimmune hemolytic anemias, and demyelinating polyneuropathies such as Guillain-Barre syndrome. It is also provided to patients with primary and secondary immune deficiencies. Patients who are IgA-deficient are at risk of anaphylaxis due to production of IgG anti-IgA immunoglobulin. For these patients, IgA-deficient preparations should be used. Some immunoglobulin preparations use a chemical inactivation step employing solvent and detergent processing to reduce infectivity for lipid enveloped viruses including HIV and hepatitis C. Specific immune globulin preparations are made from donors with hyperimmune serum and can be used prophylactically or after exposure to prevent infections from viruses such as hepatitis B.

**Clotting Factors**

Antihemophilic factor (factor VIII) and factor IX are commercially available derivatives prepared from large pools of human plasma. These products were originally high risk for transmitting viruses until virus-inactivation methods were developed that did not damage the product's coagulant activity. These methods include heat inactivation and solvent and detergent exposure. Individual coagulation factors of extremely high purity are produced using antibody-affinity purification procedures. Recombinant factors VIII, IX, and X are currently available and should be considered as an alternative to pooled products in specific situations. The use of these products in cancer patients is generally limited to replacement of individual clotting factors or to the treatment of specific factor inhibitors.

**TRANSFUSION REACTIONS AND COMPLICATIONS**

Oncology patients, like other transfusion recipients, experience adverse reactions to blood component therapy. Although cancer patients per se are not at an increased risk for the more common febrile and allergic transfusion reactions, they are likely to experience one of these reactions if they are or have been multiply transfused during their treatment. Most reactions occur during or shortly after a blood transfusion, but may present several hours to days later. In general, transfusion reactions are broadly categorized as immune or nonimmune based on their presumed mechanism (Table 53.1-4). Of particular concern to cancer patients is the development of alloimmunization, or antibodies to red cell or platelet membranes components, through repeated allogeneic blood exposure, and posttransfusion associated GVHD, a potentially fatal, but uncommon complication. Chronic iron overload and secondary hemochromatosis, long-term complications of red cell transfusion therapy, also occur in patients with hematologic malignancies who experience long-term survival.

**TABLE 53.1-4. Complications of Blood Transfusion Therapy in Cancer Patients**

**ACUTE INTRAVASCULAR HEMOLYTIC REACTIONS**

Acute intravascular hemolytic transfusion reactions (AIHTRs) are serious complications that are usually avoided by carefully adhering to standard protocols for administering blood products. These reactions occur in blood recipients who have preexisting antibodies directed against antigens present on the transfused red cells. ABO incompatibility remains the most common cause of immediate intravascular hemolytic reactions, but they are also caused by incompatibility within other blood group systems such as Duffy (Fy(a, b)), Kidd (Jk(a, b)), and Lewis (Le(a, b)). Transfusion of ABO incompatible blood is typically due to clerical errors involving misidentification of the patient. Proper labeling of clots used by the blood bank for compatibility testing and careful identification of patients are the best ways to prevent potentially fatal ABO incompatible reactions. Donor erythrocytes carrying either A, B, or both antigens avidly bind to the recipient's naturally occurring anti-A, anti-B, or both antibodies. This binding results in complement fixation, formation of the C5b-9 membrane attack complex, and finally, hemolysis. It is now clear that biologic response modifiers such as proinflammatory cytokines [interleukin-1 (IL-1), tumor necrosis factor-α], chemokines (IL-8), and complement fragments (C3a, C5a) play a major role in the pathophysiology of AIHTRs.

AIHTRs present as fever, chills, the sudden onset of back pain, hypotension, tachycardia, diaphoresis, and dyspnea. The symptoms are usually evident in recipients shortly after beginning the transfusion. Laboratory studies reveal an increase in unconjugated bilirubin up to 2 to 3 mg/dL and marked elevation of lactate dehydrogenase. The classic signs of intravascular hemolysis include acute onset hemoglobinuria and hemoglobinemia. The DAT or direct Coombs' test, becomes
reactive due to the coating of donor red cells with the recipient’s antibodies. AHTRs are medical emergencies. Treatment consists of immediately stopping the transfusion, close monitoring of vital signs, and use of intravenous fluids to maintain urine output greater than 100 mL/h with or without a loop diuretic (Table 53.1-5). Blood pressure and airway support, pressors, and mechanical ventilation may be necessary. Dialysis should be considered in patients who develop renal failure as a result of acute red cell hemolysis and subsequent acute tubular necrosis.

Table 53.1-5. Identification and Initial Management of Transfusion Reactions in Oncology Patients

DELAYED extravascular hemolytic reactions

DHTRs typically occur in patients who initially have a negative antibody screen on pretransfusion testing, but who then experience accelerated destruction of transfused red cells 7 to 14 days posttransfusion. In most cases, red cell destruction is caused by an antibody that is of low titer, below the detection limits of most routine screening techniques. On reexposure to the offending antigen, the antibody rapidly forms and binds to the transfused red cells. DHTRs are also caused by primary sensitization in which a patient synthesizes a new antibody. Antibodies implicated in DHTRs usually fix complement only to the C3 level and thus, cause extravascular as opposed to intravascular hemolysis. Antibodies most commonly implicated in DHTRs include those directed against Rh (E, C), Duffy, Kidd, and Kell blood group antigens. DHTRs are often diagnosed following an unexpected posttransfusion drop in hematocrit, an elevation of unconjugated bilirubin, and the appearance of a newly positive DAT. There is usually a delay of 3 days to 2 weeks between transfusion and the onset of extravascular hemolysis. Only rarely do delayed reactions cause severe extravascular hemolysis with associated hemoglobinemia and hemoglobinuria, but in any case, these patients should be followed until the hemolysis resolves. DHTRs should also be recognized to avoid unnecessary diagnostic procedures that are considered to evaluate an unexpected decrease in hematocrit. These patients typically do not develop cytokine storm and are for the most part asymptomatic.

FEBRILE NONHEMOLYTIC REACTIONS

FNTRs following red cell and platelet transfusions are common in cancer patients. They are presumably caused by antibodies (leukoagglutinins) in the recipient that are directed against HLA-, leukocyte-specific, or both antigens on donor white cells, red cells, and platelets. Reactions between leukoagglutinin and present in the transfused product and recipient leukocyte antigens may also play a role. Formation of leukocyte antigen-antibody complexes then results in complement binding and release of endogenous pyrogens such as IL-1, IL-6, and tumor necrosis factor-α. Cytokines generated by leukocytes during platelet and red cell storage may also contribute to FNTRs.

Symptoms typically occur during or several hours after the transfusion and include low-grade (greater than 1°C increase) and high-grade fevers accompanied by shaking chills. Rarely vomiting, dyspnea, hypotension, and decreased oxygen saturation ensue. The severity of symptoms is often directly related to the number of leukocytes contained in the product or the rate of transfusion. Leukoreduction of blood components decreases, but does not eliminate, the frequency of FNTRs and therefore, white cell–reduced products should be considered in patients who have experienced febrile reactions. Premedication with an antipyretic such as acetaminophen may minimize mild FNTRs, but is not entirely effective. Antihistamines do not prevent or treat FNTRs. Corticosteroids can minimize FNTRs if they are administered several hours before the transfusion and should be considered for patients who have had several severe reactions. Intravenous or intramuscular meperidine can resolve severe rigors in a matter of minutes. If symptoms do not resolve in less than 4 hours or are especially severe, other complications such as sepsis caused by contaminated blood products, or a hemolytic reaction should be seriously considered. Under some circumstances, it may be difficult to distinguish between FNTRs from other causes of fever in immunocompromised cancer patients. Specific conditions that can mimic benign FNTRs include preexisting or impending patient sepsis, infusion of a contaminated unit of blood or platelets, and a hemolytic transfusion reaction.

ALLERGIC REACTIONS

Allergic reactions to plasma, platelets, and red cells are relatively common in cancer patients. They present as pruritus, urticaria, or both, usually in the absence of fever. Allergic reactions are classically IgE mediated and most symptoms are attributed to histamine release. At times it is difficult to distinguish between allergic and febrile transfusion reactions when urticarial symptoms are accompanied by low-grade fever. Other common symptoms and signs include pruritus, erythema, papular rashes, and wheals. Severe anaphylaxis resulting in bronchospasm and hypotension rarely occur, but can be life threatening. As in other allergic processes, symptoms are not dose related and severe manifestations can occur following small exposures. Treatment of mild allergic reactions consists of stopping the transfusion and administering diphenhydramine or other antihistamines. For mild allergic reactions (e.g., pruritus and hives only without fever or vasomotor instability), it is reasonable to resume transfusing the same unit provided the symptoms promptly resolve. If the symptoms recur after the transfusion is restarted, a new unit should then be obtained. Severe anaphylactic reactions with bronchospasm and cardiovascular collapse are fortunately rare and should be treated like any other anaphylactic reaction with corticosteroids, vasopressors, and airway support. Washed red cells in which the residual donor plasma has been removed and replaced by saline may benefit patients with repeated or severe allergic reactions. Leukocyte reduction filters are not helpful because they do not remove the implicated soluble mediators.

SEPTIC REACTIONS

Blood products are rarely contaminated by bacteria during the collection process. This may occur if the donor is transiently bacteremic at the time of collection or if the arm is improperly cleansed before venipuncture. Transfusing blood products that are contaminated by bacteria is potentially dangerous and can result in profound hypotension, shock, and death. Currently, there are no laboratory tests to screen for bacterial contamination and contaminated units cannot be easily identified on physical examination. The risk of septic transfusion reactions (STRs) is higher for platelet transfusions because platelets are stored at room temperature. Refrigration of red cells markedly diminishes the growth of most bacteria. Common organisms that cause STRs include gram-positive (Staphylococcus sp.) and gram-negative (Enterobacter, Yersinia, Pseudomonas sp.) bacteria. Yersinia enterocolitica is a more common cause of red cell STRs because this organism grows at cold temperature and multiplies during refrigerated storage of red blood cell products. Blood cultures should be obtained from patients who develop high fevers during or shortly after transfusion, especially if they become hypotensive. A Gram's stain or acridine orange stain of the suspected contaminated product is helpful when organisms are seen, but this test is not highly sensitive. Both the patient and the implicated blood unit should be cultured whenever a STR is suspected. Other symptoms associated with STRs are attributed to preformed endotoxin and cytokines and include skin flushing, severe rigors, and cardiovascular collapse. These symptoms may occur during or minutes to hours after completing the transfusion. Treatment includes fluids and cardiovascular support. Broad-spectrum antibiotics should be started immediately, even before culture results can guide further therapy. Severe febrile reactions can mimic STRs, but febrile reactions are self-limited in nature and are generally not associated with profound hypotension.

TRANSFUSION-RELATED ACUTE LUNG INJURY

Transfusion-related acute lung injury (TRALI) is a rare but serious complication of blood transfusion that presents as noncardiogenic pulmonary edema. It typically occurs within 6 hours of transfusion and is clinically identical to the adult respiratory distress syndrome. The most common clinical findings include the rapid onset of dyspnea, tachypnea, cyanosis, fever, and hypotension. Lung auscultation reveals diffuse crackling and decreased breath sounds. Invasive cardiac monitoring shows normal cardiac pressures and function with hypoxemia and decreased pulmonary compliance. Radiographic findings include diffuse, fluffy infiltrates consistent with pulmonary edema. The presumed etiology involves immune-mediated reaction of HLA antibodies or other leukoagglutinins with white cells, which subsequently leads to leukocyte activation. Granulocytes are first activated in the peripheral circulation by HLA or other Ag-Ab complexes. The activated leukocytes then migrate to the lungs where they bind to the pulmonary capillary bed via integrins and other cell adhesion molecules. Proteolytic enzymes are then released that destroy tissue,
resulting in a capillary leak syndrome and pulmonary edema. More recently, reactive lipid products released from donor cell membranes have been associated with the development of TRALI. TRALI should be suspected in patients with rapid onset respiratory distress following transfusion therapy or pulmonary edema without hypervolemia and congestive heart failure. Definitive diagnosis requires identifying HLA, granulocyte antibodies, or both in either the donor's or recipient's serum. The corresponding antigens should also be found on the recipient's or donor's leukocytes. This specialized testing is performed in few specialized laboratories.

A number of other infectious diseases are known or are suspected to be transmitted by blood transfusion. These include malaria, Chagas' disease, leishmaniasis, and depends on the prevalence of CMV seropositivity in the donor population. This prevalence varies widely in different parts of the United States and other countries. The recipient could cause potentially serious disease. The actual risk of posttransfusion seroconversion of a CMV-negative recipient who receives CMV-untested blood depends on the number of viable T lymphocytes transfused, the recipient's immune status, and the HLA disparity between donor and recipient. Therefore, multiply transfused patients who receive cells from donors who share HLA haplotypes (haploidentical) with the recipient are at greatest risk. Clinically, transfusion-associated GVHD is characterized by the acute onset of rash, abdominal pain, diarrhea, liver function abnormalities, and bone marrow suppression beginning 2 to 30 days following transfusion. The maculopapular rash seen is similar to that observed in acute GVHD following bone marrow transplant. Biopsy of the skin can confirm the diagnosis. Pancytopenia in transfusion-associated GVHD may be severe and is attributed to destruction of recipient marrow stem cells by donor lymphocytes.

Several techniques have been developed to inactivate viruses in plasma including solvent and detergent treatment and photochemical inactivation using psoralens and long wavelength ultraviolet A light. Positive screening test results are confirmed by supplemental or confirmatory testing. Current estimates for the risk of transfusion-related HIV range from 1:500,000 to 1:750,000 units transfused. Despite improvements in tests used to detect HIV antibodies in donors, the window period in which HIV could be transmitted by an infected, but HIV seronegative, donor remained in 1996 at approximately 25 days. The introduction of screening for HIV-1 p24 antigen in 1997 decreased the window period to approximately 15 days. The implementation of HIV nucleotide testing will further decrease the window period to an estimated 10 days.

Routine vaccination of infants and young children with hepatitis B vaccine should also decrease the risk of transfusion-transmitted hepatitis B as these children enter the blood donor pool. Chronic carriers of hepatitis B (HBsAg, anti-Hbc), hepatitis C (anti-HCV), HIV (anti-HIV-1/2, HIV-1 p24 antigen), and HTLV (anti-HTLV-I/II). Serum alanine aminotransferase, measured in most European countries as a nonspecific surrogate marker of hepatitis, is no longer required by American Association of Blood Bank standards. Positive screening test results are confirmed by supplemental or confirmatory testing. Current estimates for the risk of transfusion-related hepatitis range from 1:500,000 to 1:750,000 units transfused. Despite improvements in tests used to detect HIV antibodies in donors, the window period in which HIV could be transmitted by an infected, but HIV seronegative, donor remained in 1996 at approximately 25 days. The introduction of screening for HIV-1 p24 antigen in 1997 decreased the window period to approximately 15 days. The implementation of HIV nucleotide testing will further decrease the window period to an estimated 10 days.

Transfusion-associated HIV and hepatitis are a persistent problem in parts of the world that do not have access to screening tests.

**TRANSFUSION-ASSOCIATED GRAFT-VERSUS-HOST DISEASE**

Transfusion-associated GVHD is a rare complication of blood transfusion that is fatal in approximately 90% of patients. Transfusion-associated GVHD occurs when donor immunocompetent T and natural killer cells attack recipient cells because these recipient cells appear foreign due to differences in major or minor histocompatibility antigens. GVHD is commonly seen following allogeneic bone marrow transplant, but may also rarely occur in immunodeficient or immunosuppressed patients following blood transfusion. Removing T cells from donor grafts can minimize acute GVHD in oncology patients, but is associated with increased graft failure and a decrease in a beneficial graft-versus-leukemia or graft-versus-tumor effect. The risk of transfusion-associated GVHD is related to the number of viable T lymphocytes transfused, the recipient's immune status, and the HLA disparity between donor and recipient. Therefore, multiply transfused patients who receive cells from donors who share HLA haplotypes (haploidentical) with the recipient are at greatest risk. Clinically, transfusion-associated GVHD is characterized by the acute onset of rash, abdominal pain, diarrhea, liver function abnormalities, and bone marrow suppression beginning 2 to 30 days following transfusion. The maculopapular rash seen is similar to that observed in acute GVHD following bone marrow transplant. Biopsy of the skin can confirm the diagnosis. Pancytopenia in transfusion-associated GVHD may be severe and is attributed to destruction of recipient marrow stem cells by donor lymphocytes.

Immunosuppressive therapy with prednisone and cyclosporine has not been reported effective in preventing transfusion-associated GVHD. There is no known effective treatment for transfusion-associated GVHD, but therapeutic strategies have been proposed based on the presumed mechanism of its onset. Fortunately, transfusion-associated GVHD can be prevented by irradiating products before transfusion. Specifically, irradiating cellular blood products with 2500 cGy inactivates donor lymphocytes and is the most effective method for preventing transfusion-associated GVHD.

**TRANSFUSION-TRANSMITTED DISEASE**

The risk of TTD, primarily viral transmission, has dramatically decreased over the past 25 years. Bacterial contamination of units is not usually considered a TTD, but actually is far more common than viral or fungal transmission. The use of volunteer donors and predonation screening questionnaires were the earliest effective steps taken to reduce the risk of transfusion-related hepatitis and HIV. These risks continue to drive government-mandated pretransfusion testing requirements. The development of enzyme immunoassays in the 1970s and nucleotide testing in the late 1990s have further decreased the risk of TTD. Pretransfusion TTD testing in the United States includes screening for syphilis, hepatitis B (HBsAg, anti-Hbc), hepatitis C (anti-HCV), HIV (anti-HIV-1/2, HIV-1 p24 antigen), and HTLV (anti-HTLV-I/II). Serum alanine aminotransferase, measured in most European countries as a nonspecific surrogate marker of hepatitis, is no longer required by American Association of Blood Bank standards. Positive screening test results are confirmed by supplemental or confirmatory testing. Current estimates for the risk of transfusion-related HIV range from 1:500,000 to 1:750,000 units transfused. Despite improvements in tests used to detect HIV antibodies in donors, the window period in which HIV could be transmitted by an infected, but HIV seronegative, donor remained in 1996 at approximately 25 days. The introduction of screening for HIV-1 p24 antigen in 1997 decreased the window period to approximately 15 days. The implementation of HIV nucleotide testing will further decrease the window period to an estimated 10 days.

Routine vaccination of infants and young children with hepatitis B vaccine should also decrease the risk of transfusion-transmitted hepatitis B as these children enter the blood donor pool. Chronic carriers of hepatitis B (HBsAg positive, anti-Hbc IgG positive, HBeAg positive or negative, anti-HBe positive or negative) can transmit the disease through blood donation or by other blood-borne exposures. Those carriers with measurable HBeAg are probably more infectious and accordingly, more likely to transmit disease through blood exposure or by vertical transmission. The chances of a health care worker contracting hepatitis B from a single contaminated needle stick is estimated to be between 2% and 40%. By contrast, the chances of acquiring HIV from a single contaminated needle stick is less than 1%. These differences may be at least in part related to the higher number of viral particles present in the blood of carriers of hepatitis B. The rate of transmitting hepatitis C through needle stick is probably on the order of 5%. Nevertheless, health care workers must strictly adhere to universal precautions to protect themselves and their patients.

Genomic testing for HCV RNA was implemented in the United States and Europe to detect seronegative, yet infectious units. Nucleotide testing for hepatitis C and HIV is typically performed on samples pooled from multiple donors. The importance of hepatitis C transmission in blood therapy has been confirmed in many countries by retrospective review. During these reviews, recipients of blood components from donors later found to be positive by anti-HCV screening (instituted in 1991) are examined. A large percentage of these recipients, up to 75%, are found to be anti-HCV positive. Unlike hepatitis B, the majority of those recipients who become infected develop chronic hepatitis C. Therefore, the rate of transfusion-associated hepatitis C, as well as the risk to close contacts and family members. Nucleotide amplification testing will decrease the incidence of transfusion-related hepatitis C by narrowing the window period from approximately 60 to 80 to 10 to 20 days. Hepatitis G virus has been transferred by blood transfusion, but its significance is unclear in that transfusion-acquired infection has not been associated with acute or chronic hepatitis.

Several techniques have been developed to inactivate viruses in plasma including solvent and detergent treatment and photochemical inactivation using psoralens and long wavelength ultraviolet A light. Methods used to inactivate infectious pathogens in cellular blood components such as platelets and red cells are not currently available but are under clinical development. Due to the low risk of viral infection by transfusion and the fact that most patients who receive plasma also receive cellular blood components, the cost-effectiveness of virally inactivated plasma is low. Albumin, immune globulin, factor concentrates, and other plasma derivatives are also virally attenuated by standard treatment protocols.

Other pathogens such as CMV and parvovirus B19 are common in the general donor population and may pose a serious threat in immunocompromised and splenectomized patients. Approximately 40% to 60% of blood donors have been exposed to CMV during their lifetime and thus, have developed antibodies directed against CMV. However, only approximately 2% of CMV-seropositive donors are actively infected, in which case transfusion of their blood to an immunocompromised recipient could cause potentially serious disease. The actual risk of posttransfusion seroconversion of a CMV-negative recipient who receives CMV-untested blood depends on the prevalence of CMV seropositivity in the donor population. This prevalence varies widely in different parts of the United States and other countries.

A number of other infectious diseases are known or are suspected to be transmitted by blood transfusion. These include malaria, Chagas' disease, leishmaniasis, and
toxoplasmosis.

Parvovirus B19, malaria, and babesiosis are of particular risk to immunocompromised patients. The risk of acquiring babesiosis by blood transfusion is unknown because it is endemic in many areas and often results in asymptomatic infection. Small clusters of blood transfusion–associated babesiosis have been described attributed to single asymptomatic blood donors. Thus, oncologists should recognize that babesiosis can cause febrile hemolytic disorders after diagnosis because it is a potentially fatal, yet treatable disease. Transmission of Borrelia burgdorferi by transfusion has not yet been documented. The risk of new variant Creutzfeldt-Jakob disease, first described in 1996, is unknown. It is unclear whether new variant Creutzfeldt-Jakob disease is transmissible by blood transfusion, and this route of transmission has not been reported. Fears of transmitting new variant Creutzfeldt-Jakob disease, however, have resulted in implementation of a universal white blood cell reduction policy in the United Kingdom. In the United States, donors are now deferred indefinitely if they have spent 6 months or more, cumulatively, in the United Kingdom from 1980 through 1996. This policy will have a negative effect on blood supplies.

USE OF SPECIAL BLOOD PRODUCTS IN ONCOLOGY PATIENTS

Cancer patients are often immunosuppressed as a result of their disease, treatment, or both. Accordingly, they are prone to a wide variety of viral and bacterial infections and to harmful cellular-mediated immune responses. By virtue of their frequent exposure to transfusions, they are highly susceptible to developing HLA alloimmunization, which can effectively preclude further transfusions. Specifically, HLA alloimmunization can be a serious problem. The latter restricts the choice of blood products for these patients. In addition, transfusions in neutropenic cancer patients), peripheral blood stem cells (autologous or allogeneic), and other mononuclear cells. Red cell units are being collected industry to produce coagulation factor concentrates, albumin, and immune globulin is obtained by transfusion reactions and the development of refractoriness to platelet transfusions. Thus, oncology patients should receive blood products that have been specially processed to prevent these and other complications. Currently available special blood products include those that are leukoreduced, irradiated blood products, and CMV seronegative or CMV safe. Patients should be individually considered for each of these products, and the patient's needs must be periodically reevaluated.

LEUKOREDUCTION

Leukocytes contained in blood components can provoke febrile nonhemolytic reactions, induce HLA alloimmunization, and transmit CMV to both immunocompetent and immunosuppressed recipients. Leukocytes are effectively removed from red cell and platelet concentrates by leukocyte reduction filters. Currently used third-generation leukocyte reduction filters remove 3 to 4 log cfu of the total intact leukocytes found in red cell and platelet concentrates. American Association of Blood Bank standards require that units labeled leukoreduced contain less than 5 × 10^6 residual white cells. Red cells are leukoreduced shortly after blood collection (pre-storage leukoreduction), following refrigerated storage (poststorage leukoreduction), or at the bedside during transfusion. Filters are similarly used to leukoreduce platelet concentrates. Platelets collected by modern apheresis devices are designed to directly collect leukoreduced platelets. Many physicians believe that these products do not require further leukoreduction. While cell reduction by each of these techniques requires quality control measures (using cyclic good manufacturing practices) that verify adequate leukoreduction of cellular blood products.

Leukoreduction reduces the incidence and severity of febrile transfusion reactions and decreases the risk of HLA alloimmunization. Specifically, leukoreduced products are less likely to stimulate the HLA alloantibodies implicated in both febrile transfusion reactions and antibody-mediated platelet reactions. Other generally accepted leukoreduction advantages include decreasing the risk of transmitting white cell–related infectious agents including CMV and HTLV-III. Thus, leukodepleted products are recommended for all autologous and allogeneic bone marrow and peripheral blood stem cell transplants and candidates. They are also indicated for patients with leukemia, lymphoma, and aplastic anemia. Patients with solid tumors who are not transplant patients but who have large anticipated cellular blood product needs should also receive leukoreduced products, as should any patient with chronic transfusion needs (thalassemia, sickle cell disease).

Prestorage leukoreduced products are preferable because they are also devoid of cytokines and other biologic response modifiers that play a role in transfusion complications. Many of these proteins are not efficiently removed by leukocyte reduction filters. This is particularly true in platelet concentrates stored at room temperature because there is continued elaboration of biologically active substances such as tumor necrosis factor, IL-1 and IL-6. With the dramatic decrease in the risk of viral transmission, investigators are focusing on the immunomodulatory effects of blood transfusion. These effects involve associations between alloimmune transfusion and bacterial infection, tumor progression, and tumor recurrence. Universal leukoreduction of both red cells and platelets is required in a number of countries including the United Kingdom and will be implemented shortly in the United States.

IRRADIATION

Blood components are irradiated to prevent potentially lethal transfusion-associated GVHD by interfering with the ability of lymphocytes to proliferate. Irradiation of supportive blood components is indicated in bone marrow or peripheral blood stem cell transplant recipients, patients with congenital immunodeficiency states, neonates, premature infants, and during intrathecal exchange transfusion. Directed blood donations made by relatives should also be irradiated. Patients with acquired immunodeficiency syndrome commonly receive irradiated components, although there is no clear increased risk of transfusion-associated GVHD in this population. Standard guidelines recommend irradiating red blood cells, platelets, and granulocytes with a minimum dose of 2500 cGy. Platelets and red cells are not adversely affected by this exposure. It is not believed necessary to irradiate FFP or cryoprecipitate because they do not contain viable leukocytes. Leukoreduction is not a substitute for irradiation as transfusion-associated GVHD has been described following transfusion of leukoreduced, nonirradiated blood. Bone marrow or peripheral blood stem cells must never be irradiated before transplant for obvious reasons.

There is preliminary evidence from a murine transfusion model that photochemical treatment with psoralen S-59 and long wavelength ultraviolet light can prevent transfusion-associated GVHD. Using a murine transfusion model, clinical and histologic evidence of GVHD could be prevented by both gamma irradiating or photochemically treating splenic leukocytes. Photochemical treatment was originally developed to inactivate contaminating viruses, bacteria, and leukocytes in blood components. This technology is currently under investigation in the United States and Europe.

CYTOMEGALOVIRUS-SERONEGATIVE AND CYTOMEGALOVIRUS SAFE

CMV infection is a leading cause of morbidity and mortality in neonate and solid organ transplant patients. Most serious CMV infections develop in these populations as a result of latent reactivation of recipient CMV, but nevertheless, CMV can be transmitted by blood transfusion. Therefore, blood banks supply products that have a low potential of transmitting CMV. These products include CMV-seronegative units prepared from donors who are CMV IgG antibody negative and leukodepleted components. The latter refers to blood components leukoreduced in a blood center or laboratory using good manufacturing techniques and strict quality control measures. Generally recognized indications for CMV-seronegative products include patients with congenital immunodeficiency states, neonates, premature infants, and during intrathecal exchange transfusion. CMV-seronegative products are capable of transmitting CMV disease; CMV seronegativity does not guarantee the product is incapable of causing acute CMV disease. Studies suggest that CMV seronegative and leukodepleted filtered products are equivalent in preventing CMV transmission.

Many transfusion specialists consider quality-assured leukodepleted units as CMV “safe” in that they are unlikely to transmit CMV disease. In addition to CMV-seronegative man and solid organ transplant recipients, CMV-seronegative or -safe components are generally indicated for premature infants, during intrathecal transfusions, for patients with congenital immunodeficiencies, CMV-seronegative pregnant women, and seronegative patients with HIV. The British Committee for Standards in Hematology concluded that leukoreduced components are an “effective alternative” to seronegative products for preventing transfusion-related CMV transmission.

APHERESIS

Apheresis, derived from the Greek word meaning to take away, is the process of selectively removing one component of whole blood and returning the remainder to the donor or patient. Today, sophisticated and highly automated blood cell separators are available for processing large volumes of donor or patient blood to remove the desired blood component. There are two broad applications of apheresis: apheresis for blood component collection and therapeutic apheresis. Apheresis is currently used to collect platelets, granulocytes, and mononuclear blood stem cells, in the United States, most plasma used by the fractionation industry to produce coagulation factor concentrates, albumin, and immune globulin is obtained by plasmapheresis. Plateletpheresis provides many of the single donor platelets used by oncology patients. Collecting large numbers of platelets from specific donors is important to many patients who poorly respond to platelet transfusion as a result of alloimmunization to HLA or platelet-specific antibodies. Leukapheresis is used to remove the removal of granulocytes (used for granulocytes transusions in neutropenic cancer patients), peripheral blood stem cells (autologous or allogeneic), and other mononuclear cells. Red cell units are being collected using automated cell separators.

Therapeutic apheresis is a procedure commonly performed for a variety of conditions. Generally recognized indications for plasma exchange include thrombotic...
thrombocytopenic purpura, Waldenström's macroglobulinemia, myelodysplasia, chronic inflammatory demyelinating polyneuropathy, the Guillain-Barré syndrome, and rheumatoid arthritis. Plasma exchange may help prevent the initiation or continuation of dialysis in patients with rapidly progressive renal failure secondary to multiple myeloma.13 Therapeutic plasmapheresis has been used in cancer patients who develop a wide array of paraneoplastic syndromes, but its efficacy has not been confirmed by clinical trials.22 Simple removal of red cells from patients with polycythemia is performed by simple phlebotomy and does not require a cell separator. On the other hand, automated separators very efficiently exchange red cells in patients in sickle cell crisis and patients with hemodialysis. On the other hand, automated separators very efficiently exchange red cells in patients in sickle cell crisis and patients with hemodialysis. In addition, red cell transfusions are rarely indicated for such patients.

Leukapheresis is typically performed in acute or chronic myeloid leukemia in blast crisis when the blast count exceeds 100,000/μL. Patients may or may not have symptoms of leukostasis. Patients with acute leukemia are less likely to produce leukostasis symptoms, but are also treated by leukapheresis in certain situations, or when the blast count is rapidly increasing. As blood viscosity increases, flow in cerebral and myocardial circulations slows, resulting in tissue hyperperfusion and organ hypoxia. The presence of central nervous system or pulmonary symptoms may be an indication for more urgent care. A single leukapheresis can reduce the leukocyte count by 20% to 50% and reduce hyperviscosity symptoms. On occasion, the cell count may actually rise postleukapheresis as malignant cells are removed while normal leukocytes and lymphocytes are rarely needed for chronic leukemia and lymphoma in chronic phase. Thrombocytopenia is used for patients with myeloproliferative disease that have platelet counts over 1,000,000/μL. These patients with significant thrombocytopenia may be actively hemorhaging or show signs of thrombosis. The platelet count invariably rebounds postprocedure unless chemotherapy is initiated. Prophylactic plateletpheresis is rarely indicated for such patients.

CONCLUSIONS

EFFECT OF GROWTH FACTORS ON TRANSFUSION MEDICINE

Hematopoietic growth factors as applied to oncologic transfusion therapy are designed to limit the exposure of patients to allogeneic blood.23 The isolation, characterization, and subsequent synthesis of erythropoietin by recombinant technology (HuEPO) was one of the most important advances in decreasing red cell transfusions. Use of rhEPO has dramatically reduced the transfusion needs of patients with various anemias.24 rhEPO has also been employed to increase the yield of autologous donations and to stimulate erythropoiesis after surgery. Granulocyte colony-stimulating factor has been shown to decrease infection rates in neutropenic patients undergoing chemotherapy, replacing marginally effective granulocyte transfusions. The limitations and risks of platelet transfusion therapy continue to drive the development of agents that stimulate platelet production in oncology patients.25 There is rapid growth in the use of growth factors including FLT-3 ligand, c-MPL ligand (thrombopoietin), and various combinations of growth factors. IL-11, in particular, has been approved by the U.S. Food and Drug Administration for the treatment of thrombocytopenia in patients with cancer who are undergoing myelosuppressive chemotherapy. Thrombopoietin/growth factor therapies also have the potential to stimulate platelet apheresis donors, increase stem cell harvest yields, and expand progenitor cells ex vivo. Development of neutralizing antibodies against endogenous thrombopoietin has plagued clinical testing of thrombopoietin growth factors.

BLOOD SUBSTITUTES

Red cell substitutes currently in development include hemoglobin-based oxygen carriers (HBOCs), perfluorocarbon emulsions, and liposome-encapsulated hemoglobin.26 The two major types of blood substitutes, HBOCs and perfluorocarbon emulsions, are in phase II and III clinical trials. None are currently approved for clinical use. HBOCs are blood substitutes that have-derived properties. They are structurally similar to hemoglobin but do not contain red cell stroma, which is toxic and leads to renal damage. Development of HBOCs has been hampered by the relatively short half-life of these oxygen carriers in the circulation. Perfluorocarbons are synthetic hydrocarbons that have the ability to carry dissolved oxygen. The particles circulate for only a few hours until they are removed by the reticuloendothelial system. Research efforts to modify or remove red blood cell antigens from donor units is proceeding slowly, but a truly compatible red cell unit may one day be within reach.

CHAPTER REFERENCES

SECTION 53.2
Autologous Stem Cell Transplantation

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INTRODUCTION

High-dose chemotherapy and autologous proximal stem cell rescue is now considered standard therapy for relapsed Hodgkin's disease and intermediate-grade lymphomas, and it is currently being tested as part of initial therapy for patients with adverse risk features and one of the following diagnoses: Hodgkin's disease, non-Hodgkin's lymphoma (NHL), multiple myeloma, breast cancer, and germ cell tumors. The movement of high-dose therapy from a treatment of last resort to a more proximal position is due in large part to improvements in supportive care that have nearly eliminated treatment-related mortality and have, at the same time, facilitated the transfer of much of the care from the hospital to the outpatient setting. Perhaps the most important advance in the ability to support patients receiving high-dose therapy has been the use of peripheral blood stem cells (PBSCs). The duration of neutropenia and thrombocytopenia after marrow "ablative" therapy and PBSC rescue is now only moderately longer than that expected after aggressive standard therapy. In most centers, advanced age has become much less important than comorbidity as an important barrier to treatment, and the improved therapeutic index of high-dose therapy has resulted in exploratory studies for the treatment of refractory autoimmune disorders, including systemic lupus erythematosus, rheumatoid arthritis, and multiple sclerosis.

In many respects, because of the availability of PBSC and growth factors, treatment-induced myelosuppression is no longer considered an obstacle to treatment. However, several issues remain unresolved with the use of PBSCs, including the growing recognition that a substantial percentage of collections are contaminated with tumor cells. In fact, strategies for PBSC mobilization have focused on increasing the collections of progenitor cells with much less attention given to the impact on tumor mobilization. In addition, a small percentage of patients can still not achieve acceptable PBSC collections, a finding that highlights our ignorance of the biology of stem cell mobilization and the fact that only modest progress has been made in the ability to successfully expand progenitor cells in vitro.

Finally, as the general ease of collection and use of PBSCs compared with bone marrow has changed the focus from the procedure ("transplantation") to the treatment, it is clear that high-dose therapy has not been able to overcome significant drug resistance. These results suggest that newer drugs for preparative regimens (including monoclonal antibodies) and novel treatment strategies to eliminate minimal residual disease are needed to further substantially improve cure rates.

HISTORY

In the aftermath of the destruction caused by the atomic bomb at the end of World War II and the subsequent nuclear arms race, a dramatic increase in research was directed at reducing or avoiding bone marrow injury from radiation. In a landmark paper published in 1949, Jacobson et al. reported that lead shielding of the spleen prevented death from bone marrow aplasia in mice after a lethal dose of total body irradiation. Protected mice developed only transient leukopenia and thrombocytopenia and had histologic evidence of bone marrow regeneration 8 days after irradiation. In contrast, control mice died without evidence of residual hematopoiesis. Although the authors recognized that a "cellular factor" from the spleen could be responsible for bone marrow recovery in the experimental group, they favored a humoral mechanism because survival in spleen-shielded mice was significantly increased even if the spleen was removed shortly after radiation. Indeed, it was another 7 years before the humoral theory of bone marrow recovery was finally laid to rest.

In retrospect, survival in Jacobson's mice proved that stem cells circulate in the blood and restore hematopoiesis. Thus, bone marrow recovery in the mice that had a spleen prevented death from bone marrow aplasia and was due to migration of protected (by lead shielding) stem cells from the spleen to the blood and then to the bone marrow. However, investigators of several studies in mice, guinea pigs, and dogs are generally given credit for confirming the normal presence of circulating hematopoietic progenitor cells in mammals, and in 1975, the presence of pluripotential stem cells in the blood of humans was unequivocally demonstrated.

Although the presence of circulating progenitor cells was established, it was unknown whether enough cells could be collected to reconstitute hematopoiesis in a patient who had received marrow ablative therapy. Indeed, in vitro assays showed that an equivalent number of nucleated cells from the bone marrow produced substantially more granulocyte colonies than did the same number of cells from the blood. An important exception to the latter finding was observed in patients in the chronic phase of chronic myelogenous leukemia (CML). In affected patients, the percentage of colony-forming cells collected from theuffy coat layer was higher than in the bone marrow and was approximately fivefold higher than in bone marrow cells from healthy volunteers. These data provided a rationale for rescuing aggressively treated patients in blast crisis with autologous hematopoiesis harvested at the time of diagnosis, but the data also clearly indicated that the results in CML patients could not be generalized to patients with other diseases.

In fact, the first clinical trials of PBSC rescue in the late 1970s and early 1980s appeared to establish important differences between the engraftment potential of blood stem cells of CML patients and normal donors. Goldman et al. reported complete engraftment in 19 of 20 patients with CML in transformation who were given myeloablative therapy and then rescued with autologous chronic phase, buffy coat cells. In contrast, two patients, one with Ewing's sarcoma and one with paroxysmal nocturnal hemoglobinuria, did not engraft with blood stem cells from healthy identical twin siblings. In both patients, normal hematopoiesis was restored after bone marrow infusions from the same healthy donors. The effectiveness of syngeneic bone marrow but not PBSCs from normal donors used to restore hematopoiesis was in agreement with laboratory experiments that showed important differences in the capacity for self-renewal between blood and bone marrow cells. Because no further reports of PBSC rescue in patients with diseases other than CML were published for the next 5 years, the results of these early clinical studies must have particularly discouraging.

The first semi-successful PBSC transplantations were reported in 1985 by Jutter et al. in two patients with acute nonlymphocytic leukemia (ANLL). These were also the first "mobilized" stem cell transplantations, as leukapheresis was timed to coincide with the period of hematopoietic recovery after induction chemotherapy. Previous work from the same group had shown that, after agressive chemotherapy, granulocyte-macrophage colony-forming units (GM-CFUs) were increased 24-fold higher than the mean level in normal subjects and were also higher than the GM-CFU yield from 1 L of bone marrow. In the clinical trial, both patients had rapid evidence of trilineage recovery after being given mobilized stem cells after high-dose therapy. In one patient, however, transient recovery was followed by significant neutropenia and thrombocytopenia before leukemia reoccurred; in the other patient, disease recurrence precluded assessment of the long-term viability of the graft.

Subsequently, five centers described PBSC transplantations in a total of eight patients. In four of the studies, PBSCs were collected after chemotherapy, and in one report of two patients, stem cells were collected during steady-state myeloapiesis. Although these studies showed the feasibility of PBSC rescue, important reservations remained about the broader use of PBSCs. For example, because four of the six patients with mobilized PBSC transplantations had acute leukemia, the mobilizing chemotherapy was extensively myelosuppressive and was associated with a prolonged period of aplasia. As a result, the applicability of chemotherapy mobilization for patients with other diseases was unclear. Similarly, in the patients who had nonmobilized collections, the long period (28 days in one patient) that was required to collect enough progenitor cells was impractical for patients with aggressive disease. Finally, these studies did not establish the number of progenitor cells necessary for engraftment, nor did they establish the durability of PBSC autografts. Thus, in view of the known effectiveness of autologous bone marrow rescue, most centers reserved PBSC transplantation for patients who were not eligible for autologous bone marrow transplantation. Potential candidates...
The transition toward the use of PBSCs, now complete for autologous rescue and moving in that direction for allogeneic transplantations, has been made possible because of the tremendous number of progenitor cells that can be collected relatively easily and noninvasively.

STEM CELL MOBILIZATION

In 1976, Richman et al. reported that, as blood counts recovered after chemotherapy, a significant increase in circulating neutrophil progenitor cells was seen, and these authors speculated that large-volume apheresis could be used to collect enough stem cells to avert the myelosuppression effects of chemotherapy. Twelve years later, hematopoietic growth factors were shown to mimic as well as to potentiate the effect of chemotherapy in mobilizing progenitor cells. In addition to neutrophil precursors, megakaryocyte progenitors also were increased; however, in the absence of assays that measured self-renewal and pluripotential capacity, the ability of circulating "mobilized" progenitor cells to establish permanent trilineage engraftment remained speculative. Accordingly, in most early clinical trials, blood progenitor cells were used in addition to autologous bone marrow. These studies confirmed that neutrophil recovery was more rapid in patients given the blood progenitor cells, but the studies also showed an improvement in platelet and red blood cell recovery. The latter findings provided the rationale for mobilized progenitor cells to be used alone with bone marrow held in reserve and, more recently, without the need to harvest "backup" bone marrow. In 1994, rescue with PBSCs surpassed the use of bone marrow after high-dose therapy.

The discovery of the CD34 antigen as a stem cell marker significantly facilitated the development of strategies to maximize the mobilization and collection of blood progenitor cells. The CD34 antigen was initially described in 1984 on tissue culture cells derived from a patient with ANLL and was subsequently found to be present on nearly all colony-forming progenitor cells detected by in vitro assays. The "stemness" of CD34+ cells was established by successfully engrafting lethally irradiated baboons and, later, humans with CD34+ selected cells. These studies suggested that both pluripotential and more committed progenitor cells are contained within the small fraction of bone marrow (1% to 2%) and peripheral blood mononuclear cells that are CD34+.

The presence of the semi-unique CD34 antigen on the surface of stem cells enabled the development of a flow cytometry assay that provides a rapid quantitative analysis of stem (CD34+) cell number. Enumeration of stem cells by flow cytometry has virtually replaced more intensive and time-consuming in vitro assays in which the adequacy of stem cell collection is inferred from the number of progenitor colonies that are formed in agar after 2 weeks of growth. With the availability of same-day results of the CD34+ blood cell count permitted by flow cytometry, apheresis can be optimally timed to coincide with rising CD34+ cell counts rather than with a surrogate marker, such as neutrophil recovery. Similarly, because the collected number of CD34+ cells also can be counted quickly, apheresis procedures can be limited to the number required to reach the target number of CD34+ cells. In fact, well-mobilized patients often require only one procedure to achieve an adequate collection.

The CD34 count of the infused product is generally considered the most reliable factor for predicting the speed and durability of engraftment after high-dose therapy. A minimum number of CD34+ cells per kilogram is generally sufficient to collect an adequate number of stem cells. For example, in a group of patients with NHL in whom high-dose therapy and stem cell rescue was planned as part of initial therapy, Pettengell et al. reported that, as blood counts recovered after chemotherapy, a significant increase in circulating neutrophil and platelet recovery within 14 days in nearly 85% of patients, and 95% have recovery within 20 days. With an intermediate dose (between 2.5 and 5.0 × 10^6 CD34+ cells per kilogram), neutrophil recovery appears to be as rapid as at higher CD34+ cell numbers, but a detectable incidence of delayed platelet recovery is reported, particularly in more heavily pretreated patients and in those given posttransplantation myeloid growth factors. A minimum number of CD34+ cells per kilogram that is required for engraftment has not been defined, in part because many regimens are not truly myeloblastic. In a study of 48 patients who received 1.0 to 2.5 × 10^6 CD34+ cells per kilogram, all patients achieved neutrophil engraftment at a median of day 11, but 19% had delayed platelet recovery beyond 21 days and 9% had a delay longer than 100 days. The clinical significance of lower CD34 cell doses is longer duration of hospitalization, longer use of antibiotics, and an increased and more prolonged need for transfusions. Taken together, these results suggest that the use of 5 × 10^6 CD34+ cells per kilogram or more is optimal; 2.5 × 10^6 CD34+ cells per kilogram or more is acceptable; and in patients who only achieve between 1.0 and 2.4 × 10^6 CD34+ cells per kilogram, the decision to proceed to transplantation must be individualized.

At present, blood progenitor cells are mobilized in most patients with the use of chemotherapy followed by growth factors or with growth factors alone (Table 53.2-1). The combination of myelosuppressive chemotherapy plus growth factors generally is considered the most productive strategy for mobilizing stem cells and, in comparison with the use of growth factors alone, offers the advantage of providing additional treatment against the underlying disorder. In fact, with the tremendous number of CD34+ cells that are often mobilized into the blood by chemotherapy plus growth factors, often only a single apheresis is required, and the costs and toxicities associated with multiple aphereses can be reduced. On the other hand, the apparent advantages resulting from a reduction in the number of aphereses may be more than offset by the costs and toxicity associated with the use of more myelosuppressive chemotherapy, including the prolonged use of growth factors as well as the potential need for hospitalization, intravenous antibiotics, and transfusions. In addition, because no advantage may exist for giving more stem cells than the number necessary to ensure rapid neutrophil and platelet engraftment (between 2.5 and 5.0 × 10^6 CD34+ cells per kilogram), a strong argument can be made for using a less toxic mobilization program.

Although much of the earlier stem cell mobilization literature was dominated by the use of intensively myelosuppressive regimens, it is clear that, in most patients, stem cell disease can be treated by chemotherapy followed by granulocyte colony-stimulating factor (G-CSF) chemotherapy sufficient to collect an adequate number of stem cells. For example, in a group of patients with NHL in whom high-dose therapy and stem cell rescue was planned as part of initial therapy, Pettengell et al. required only a single pheresis to collect more than 2.5 × 10^6 CD34+ cells per kilogram after treatment with vincristine, doxorubicin, prednisone, VP-16, and bleomycin (VAPEC-B) and G-CSF. Even in more heavily pretreated relapsed NHL patients, the well-tolerated combination of ifosfamide, carboplatin, and etoposide followed by G-CSF resulted in successful mobilization (2.0 × 10^6 CD34+ cells per kilogram or more) in 86% of patients, and 61% of patients had 6.0 × 10^6 CD34+ cells per kilogram or more collected. Similarly, the outpatient regimen of cyclophosphamide, 1.5 g/m², followed by G-CSF, 10 µg/kg, is a reliable and safe mobilizing program that can be timed to avoid the need for weekend pheresis. In breast cancer patients, Taxol or Taxol-based combinations have been particularly potent in mobilizing stem cells. For example, compared with cyclophosphamide plus G-CSF, the addition of Taxol was associated with a greater than tenfold increase in CD34+ cells per kilogram for collection.

An alternative to the use of chemotherapy plus growth factors for stem cell mobilization is the use of growth factors alone. Mobilization with growth factors, although generally not as productive as the combination of chemotherapy plus growth factors, offers several practical advantages. First, the potential morbidity and need for hospitalization secondary to myelosuppressive chemotherapy can be avoided. Second, the timing of pheresis can be scheduled, making weekend pheresis unnecessary. Finally, the lack of significant acute or known long-term toxicity with growth factors makes them acceptable for stem cell mobilization when normal donors are used for stem cell mobilization. G-CSF is the most commonly used cytokine when growth factors are used alone. GM-CSF is inferior to G-CSF as a mobilizing agent, but the combination of GM-CSF plus G-CSF may mobilize a higher number of early progenitor cells (CD34+, CD38−) than either cytokine used alone. Because it is not clear that the increase in earlier progenitor cells resulting from the combination of cytokines offers any significant advantage, G-CSF is currently most often used alone.

### Table 53.2-1. Mobilization Strategies

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<td>Chemotherapy + Growth Factors</td>
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<td>Growth Factors Alone</td>
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The presence of the semi-unique CD34 antigen on the surface of stem cells enabled the development of a flow cytometry assay that provides a rapid quantitative analysis of stem (CD34+) cell number. Enumeration of stem cells by flow cytometry has virtually replaced more intensive and time-consuming in vitro assays in which the adequacy of stem cell collection is inferred from the number of progenitor colonies that are formed in agar after 2 weeks of growth. With the availability of same-day results of the CD34+ blood cell count permitted by flow cytometry, apheresis can be optimally timed to coincide with rising CD34+ cell counts rather than with a surrogate marker, such as neutrophil recovery. Similarly, because the collected number of CD34+ cells also can be counted quickly, apheresis procedures can be limited to the number required to reach the target number of CD34+ cells. In fact, well-mobilized patients often require only one procedure to achieve an adequate collection.
INADEQUATE MOBILIZATION OF STEM CELLS

The failure to mobilize stem cells (less than 1.0 × 10^6 CD34+ cells per kilogram) is associated with the type and number of previous treatments. Thus, in a population of patients with Hodgkin’s disease and NHL who received mobilizing chemotherapy and growth factors, an average decrease of 0.2 × 10^6 CD34+ cells per kilogram was noted for every cycle of previous chemotherapy. Although this study did not specifically correlate the type of chemotherapy and its impact on stem cell mobilization, it is known that some drugs are more toxic to stem cells than others. Because of their association with myelosuppression (MDS) and leukemia, it is not surprising that melphalan, nitrosourea agents, nitrogen mustard, and procarbazine are potent stem cell toxins. Less well known for causing stem cell toxicity are fludarabine and high cumulative doses (7.5 g/m² or more) of cytosine arabinoside. The use of prior wide-field radiation also has been correlated with a reduction in stem cell mobilization. Mediastinal radiation appears to be as toxic as pelvic radiation.

When stem cell collections are inadequate after treatment with growth factors or chemotherapy plus growth factors, inconsistent results have been achieved with alternative strategies. In patients who do not have effective mobilization using G-CSF alone, the use of myelosuppressive chemotherapy plus G-CSF may be warranted as an alternative. In patients who do not have adequate mobilization after chemotherapy plus G-CSF, no data are available to suggest that the benefits of more myelosuppressive regimes outweigh the risks associated with more prolonged neutropenia.

The use of autologous bone marrow in poorly mobilized patients also has been disappointing and suggests that the inability to collect adequate stem cells should be considered a marker for an injured bone marrow. For example, Watts et al.37 described 12 patients in whom fewer than 1.0 × 10^6 CD34+ cells per kilogram and fewer than 1 × 10^6 granulocyte-monocyte colony-forming cells per kilogram were mobilized. When a subsequent bone marrow harvest was given in addition to collected stem cells, 5 of the 12 patients experienced transplantation-related mortality; 4 of 11 assessable patients had neutrophil recovery delayed beyond 21 days, and 8 patients had delayed platelet recovery.

In patients who experience a poor mobilization either with G-CSF alone or with G-CSF plus GM-CSF, it appears that a variable number can achieve an acceptable (but rarely optimal) number of stem cells after higher doses of G-CSF alone. In a preliminary report, Fraipont et al.38 studied 27 patients, 25 of whom had concentrations of less than 2.0 × 10^6 CD34+ cells per kilogram after chemotherapy plus G-CSF. Seven patients remobilized with chemotherapy plus G-CSF achieved similar stem cell collections to the first mobilization. In patients remobilized with 10 µg/kg G-CSF alone, the peripheral CD34 count, as well as the number of CFU-GM and CD34+ cells collected perapheresis, was statistically increased in the group treated with G-CSF only. Similarly, Jennis et al.39 studied 20 patients who had unsuccessful initial mobilization (median total collection of 0.57 × 10^6 CD34+ cells per kilogram), 16 of whom previously had been treated with chemotherapy plus G-CSF, 5 µg/kg twice daily, and four of whom had been treated with G-CSF alone. After a 7-day period of G-CSF withdrawal, G-CSF was given at a dose of 16 µg/kg body weight for 5 days. Only 3 of 16 patients had a significant collection for platelets per kilogram, and 11 of 16 patients did not achieve an “acceptable” cumulative CD34+ cell dose considered adequate to undergo high-dose therapy. Using a slightly different strategy, Gazit et al.40 immediately treated mobilization failures (fewer than 0.2 × 10^6 CD34+ cells per kilogram after 2 to 3 days of pheresis) with G-CSF, 32 µg/kg/d, with apheresis beginning approximately 5 days later. An adequate number of CD34+ cells was collected in 15 of 17 patients. In all three of the studies just described, patients who went on to receive high-dose therapy and stem cell rescue recovered neutrophils and platelets at a median time that was only slightly prolonged compared to more optimally mobilized patients.

Weaver et al.41 showed that, in patients who obtained fewer than 2.5 × 10^6 CD34+ cells per kilogram after first mobilization, the yield of second stem cell collections was significantly increased, regardless of whether chemotherapy plus G-CSF or G-CSF alone was used. These results suggested that the first mobilization attempt had a priming effect on the second or that other factors may have compromised the first attempt. Chemotherapy plus G-CSF and G-CSF alone proved equally but only mildly effective, because fewer than one-half of the patients had enough (more than 2.5 × 10^6 CD34+ cells per kilogram) to proceed to transplantation. A relationship appears to exist between G-CSF dose and the yield of CD34+ cells collected, but it did not reach statistical significance.

The sum of the studies discussed suggest that, in patients who achieve suboptimal first collections (1.0 to 2.4 × 10^6 CD34+ cells per kilogram), approximately one-half or more may achieve a safe (2.5 × 10^6 CD34+ cells per kilogram or fewer) cumulative stem cell collection after a second mobilization with high-dose (32 µg/kg) G-CSF alone. However, a significant qualitative difference may exist between “hard-to-mobilize” patients who achieve marginal yields (1.0 to 2.4 × 10^6 CD34+ cells per kilogram) and “nonmobilizable” patients (fewer than 1.0 × 10^6 CD34+ cells per kilogram). Indeed, more recent engraftment data suggest that the former group may not really need or significantly benefit from the second collection, whereas the latter group has a high incidence of transplantation-related mortality, despite the use of backup bone marrow in addition to blood stem cells. Further studies clearly are required to determine whether high-dose G-CSF is effective in nonmobilizing patients.

Combinations of GM-CSF and G-CSF also have been tested in patients who did not achieve a blood CD34 level considered appropriate (10 cells per microliter) for collection or in which an institutionally acceptable number of CD34 cells could not be collected with the first collection. In one preliminary report, 10 of 11 patients treated with 10 µg/kg GM-CSF for 2 days followed by G-CSF, 10 to 16 µg/kg, for 4 days achieved CD34+ cell collections of more than 1 × 10^6 cells per kilogram, including four patients who obtained more than 4 × 10^6 cells per kilogram. Nine patients who went on to receive high-dose therapy achieved neutrophil engraftment at a median of 11 days. The median time to platelet engraftment was 24 days; 9 of 13 patients were platelet engrafted at 27 days. In another study, GM-CSF (10 µg/kg) and G-CSF (10 µg/kg) were used concurrently, and a statistically significant increase in the collected number of CD34 cells was seen in the second mobilization, including 13 of 23 patients who achieved an “acceptable” cumulative CD34+ cell dose of more than 3 × 10^6 CD34+ cells per kilogram. After high-dose therapy, neutrophil and platelet engraftment were said to be rapid. However, in neither study just described was the cytokine combination compared with high-dose G-CSF alone. In addition, it would appear that many of the patients in the second study would not be considered mobilizable. Thus, successful results in this group cannot necessarily be extrapolated to those who have previously shown very little or no evidence of progenitor mobilization.

Although the optimal cytokine cocktail for mobilization is unknown, promising results have been achieved with the combination of stem cell factor (SCF) and G-CSF. In a phase VII randomized trial, patients with NHL in chemotherapy first relapse were randomized to either G-CSF alone (10 µg/kg/d) or the same dose of G-CSF with escalating doses of SCF (5 to 20 µg/kg/d). Leukapheresis was performed on days 5 to 7. Although no significant differences were observed in the yield of CD34+ cells between the two groups, a second analysis limited to the cohort that had been extensively pretreated showed a sixfold increase in the median number of CD34+ cells per kilogram that were collected in the group receiving G-CSF plus any dose of SCF. A second randomized study in patients with multiple myeloma compared cyclophosphamide (Cytoxan), 4 g/m², followed by G-CSF, 5 µg/kg/d, with or without the addition of SCF, 20 µg/kg/d. The median number of CD34+ cells per kilogram collected was nearly three times higher in the group receiving SCF, and 65% of the patients had more than 5 × 10^6 CD34+ cells per kilogram collected in a single leukapheresis, compared with 40% in the group given G-CSF alone. Like the studies of GM-CSF already discussed, it is possible that, in these two cohorts, similar results could have been achieved with higher doses of G-CSF. The apparent dramatic impact of the addition of SCF to the heavily pretreated patients in the first study, however, suggests more than a simple dose-response effect.

To date, only one preliminary report on the combination of SCF and G-CSF in previously nonmobilizable (fewer than 1 × 10^6 CD34+ cells per kilogram) patients has been published. In 35 patients who were treated with SCF, 20 µg/kg/d, and G-CSF, 10 µg/kg/d, Pheresis was timed to the blood CD34+ cell peak count per microliter and continued until a minimum “engraftable dose” of 1 × 10^6 CD34+ cells per kilogram was achieved. If the CD34 count did not reach 10 cells per microliter by day 8, patients were removed from study. All ten patients achieved an engraftable dose after a median of 2.5 collections. These results, although exciting, are incomplete, because no information was presented on subsequent engraftment after high-dose therapy. If a defective bone marrow microenvironment plays a role in poor mobilization, then it is at least theoretically possible that such patients might require more rather than fewer stem cells.

The conflicting and somewhat disappointing results in nonmobilizing patients underscores how little is known about the biology of stem cell mobilization. In fact, the mechanisms of progenitor cell mobilization are unknown, including whether cytokines and chemotherapy act through the same or different pathways. Similarly, it is not known whether alternative mobilization strategies differ in their impact on stem cell mobilization, a variable that may prove to be more important than optimizing the number of stem cells harvested.

TUMOR CONTAMINATION

One of the early indications for the use of PBSCs was pathologic evidence of bone marrow tumor involvement. Implicit in this recommendation was the probability that the blood was likely to be less contaminated with tumor cells than bone marrow. In fact, several studies in breast cancer and neuroblastoma patients show that the concentration of tumor cells is significantly less in blood stem cell collections. This advantage may be reduced or eliminated because of the large number of cells in the PBSC graft and because of the effects of mobilization. In a study of lymphoma patients, for example, less than 1 log fewer tumor cells was
found in the bone marrow than in the blood under baseline conditions. However, the advantage of blood over marrow disappeared and in some cases was reversed after mobilization. In six of seven patients followed closely during mobilization, tumor cells increased and, in two cases, tripled compared to baseline levels. Similarly, in patients with multiple myeloma, neoplastic plasma cells appear to be concomitantly mobilized with progenitor cells after treatment with high-dose cyclophosphamide and G-CSF. In six patients who underwent CD34+ cell selection, tumor cells were decreased by 2 to 3 logs, but were still detectable in five of six patients.

Chemotherapy can also result in tumor cell mobilization in patients with solid tumors. In 42 previously untreated patients with solid tumors and no evidence of blood involvement, circulating tumor cells were detected in nine patients (21%) after mobilization with chemotherapy and G-CSF, including 100% of patients with breast cancer and 50% of patients with small cell lung cancer. The peripheralization of tumor cells with chemotherapy is related to stage of disease and appears to be substantially reduced by prior effective chemotherapy. In a study of breast cancer patients in whom leukapheresis was performed after each of three planned cycles of chemotherapy plus G-CSF, tumor cell contamination was significantly lower, albeit not eliminated, after the second and third courses of treatment. In addition, the use of effective chemotherapy in the mobilization regimen may have the additional benefit of inhibiting tumor clonogenic growth. Nevertheless, the effect of different mobilization strategies on tumor cell contamination has not been well studied.

The clinical significance of administering tumor-contaminated stem cells is unclear. Gene marking studies in three different malignancies show that infused tumor cells contribute to relapse, but no data suggest that they are the sole or even principal cause of recurrence. In patients with breast cancer, two studies have shown comparable outcomes in patients who did and who did not have occult tumor in their stem cell product. In patients with multiple myeloma, higher numbers of circulating tumor cells are generally surmounted with a shorter of circulating tumor cells was not significant in a multivariate analysis that included plasma cell labeling index and b2 microglobulin. These latter results suggest that the presence of circulating tumor cells was a sign of more aggressive disease rather than a direct cause of failure.

To date, studies in which tumor cells are reduced by purging or CD34 selection have shown the most impressive results in patients with low-grade lymphoma. Investigators from the Dana Farber Cancer Institute have updated their experience with patients with follicular lymphoma treated with total body irradiation (TBI)/cyclophosphamide and a purged bone marrow product. Of 113 patients who were evaluable by polymerase chain reaction (PCR) technology, 46 patients had PCR-negative narrows after purging, only six of whom relapsed. In contrast, 49 of 65 patients with a persistently positive PCR relapsed after transplantation. Importantly, no obvious differences were noted between the two populations of patients with respect to stage, B symptoms, gender, bulky disease, remission status at harvest, or histologic evidence of marrow involvement. Although it can be argued that the pattern of relapse in previous sites of disease is evidence against the importance of infused tumor cells, it is also possible that infused tumor cells homed to sites of prior disease because of a favorable microenvironment. In another study, patients with lymphoma, a potential positive impact of purging was inferred from the observation that patients who received lower doses of GM-CSF after purging had a lower relapse rate. A similar correlation between the effectiveness of ex vivo purging as reflected by a more profound reduction in posttransplantation GM-CSF colony formation was previously established in patients with leukemia. A case-matched comparison of purged versus unpurged marrow in lymphoma patients the European Blood and Marrow Transplant Registry showed a benefit for purging in overall survival but not in progression-free survival. However, the use of different purging protocols and imbalances in the use of conditioning regimens make it difficult to interpret these data.

In patients with multiple myeloma, a randomized study showed that CD34 selection reduced tumor cell contamination of stem cells by a mean of 3.1 logs, but a preliminary analysis showed no significant benefit in terms of disease-free or overall survival rates. As noted earlier in this section, the failure of CD34 selection to improve the clinical outcome in this group of patients likely represents incomplete tumor cell purging as well as the inability to eradicate disease with the conditioning regimen. Importantly, CD34 selection may not be benign. Because of the concomitant T-cell, natural killer cell, and monocyte depletion, there may be an increased risk of opportunistic infections that are otherwise rare in the autologous setting. In a study from Seattle, 7 of 31 patients (22.6%) seropositive for cytomegalovirus developed cytomegalovirus disease, and four patients (12.9%) died. In patients given unselected cells at the same institution, the risk of infection and disease were only 4.2% and 2.1%, respectively.

Prospects for further improvement in tumor purging appear strongest for patients with CD20+ B-cell lymphoma. Rituximab (Rituxan) alone or in combination with chemotherapy results in profound B-cell depletion and achievement of a PCR-negative status in some patients with low-grade lymphomas. As Rituxan, in combination with chemotherapy, has demonstrated vigorous anti-idiotype effects, extensive studies of its role in relapsed disease are warranted. In patients with multiple myeloma, higher numbers of circulating tumor cells have been detected in patients with breast cancer, however, it seems clear that even substantial improvement in tumor purging will have little clinical benefit in the absence of better conditioning programs and more effective posttransplantation therapy.

PRACTICAL CONSIDERATIONS FOR THE POTENTIAL HIGH-DOSE THERAPY AND AUTOLOGOUS STEM CELL RESCUE PATIENT

Because of the potential deleterious effect of prior therapy on stem cell mobilization, the possibility that a patient may be a candidate for high-dose therapy should be considered from the time of diagnosis. For example, given the current importance of high-dose therapy in multiple myeloma and the stem cell toxicity of melphalan and prednisone combination therapy, induction with VAD (vincristine, doxorubicin, dexamethasone) or dexamethasone alone should be considered for initial treatment of Hodgkin's disease and high-dose MOPP (Mustargen, Oncovin, procarbazine, and prednisone)-like regimens for most patients with Hodgkin's disease, should probably not be used until stem cells are collected. More recently, fludarabine, which is playing an increasingly important role in the treatment of low-grade B-cell lymphomas, has been identified as a stem cell toxin in some studies, but not in others. These results suggest that potential high-dose therapy candidates should have stem cells collected before fludarabine therapy, or at least before extensive treatment.

Stem cell mobilization can be accomplished with chemotherapy plus G-CSF or with G-CSF alone. In general, chemotherapy plus G-CSF is favored by most clinicians because of the additional antinoclastic effect afforded by chemotherapy. If CD34+ cell selection also is being considered, the higher yields achieved with chemotherapy plus G-CSF may be important because of the obligatory loss of CD34+ cells that occurs during selection.

Despite evidence of a dose-response effect when G-CSF is used alone for mobilization, the data are conflicting regarding the efficacy of higher doses of G-CSF when used in conjunction with chemotherapy. Demirer et al. have presented unpublished data showing that, after treatment with three different cyclophosphamide-based regimens, G-CSF, 16 µg/kg, resulted in higher yields than 10 µg/kg. On the other hand, a preliminary report of a randomized study did not show a greater effect for higher doses of G-CSF when combined with chemotherapy. Currently, in most patients, G-CSF, 10 µg/kg, is started 1 to 4 days after chemotherapy to hasten hematopoietic recovery and to increase the yield of stem cells. However, in nonheavily pretreated patients (i.e., those in first remission) who are treated with highly myelosuppressive mobilizing regimens, the brisk myeloid rebound that occurs with higher doses of G-CSF can be associated with symptoms of hyperleukocytosis. Lower doses of G-CSF can be considered in such patients.

The timing of stem cell collection after chemotherapy plus G-CSF can be optimized (lower number of procedures) by measuring the blood CD34+ cell count during the period of brisk neutrophil recovery. If collection is started when the CD34 count exceeds 20 cells per microliter, the majority of patients can collect more than 10 x 10^6 CD34+ cells per kilogram in one or two procedures. However, because patients who show less evidence of mobilization (5 to 15 cells per microliter) may also obtain a potentially engraftable number of CD34+ cells (more than 1 x 10^6 cells per kilogram) with three or more leukaphereses, the use of the 20 cells per microliter value should be limited to patients who can be anticipated to be good mobilizers (nonheavily pretreated). In settings in which the blood CD34 count is unavailable, it would appear that the best time to begin collection is when the white blood cell (WBC) count has increased to more than 3,000 to 10,000 per microliter and the patient has a rising platelet count.

The target number of stem cells is generally at least 2.5 x 10^6 CD34+ cells per kilogram, but at more than 5.0 x 10^6 CD34+ cells per kilogram, most patients have WBC and platelet recovery within 2 weeks. Particularly if CD34+ cell selection or tandem transplantsations are possible, higher doses are clearly desirable. Although, as noted earlier in this section, more than 1 x 10^6 CD34+ cells per kilogram is considered sufficient to establish engraftment in most patients, 10% to 20% have slowed or incomplete platelet recovery. In addition, a substantial percentage of patients who are transplanted relapse and require additional treatment, it is unclear whether marrow reserve in such patients is adequate to sustain treatment.

After stem cell infusion, considerable controversy exists regarding the utility of hematopoietic growth factors. Although most studies show a favorable impact of G-CSF on shortening the period of neutropenia, it is much less certain that G-CSF is of significant clinical benefit. For example, it is possible that shorter reported periods of hospitalization with the use of posttransplantation G-CSF may simply reflect clinicians' tendency to discharge patients once they reach a certain WBC count. It also seems possible that patients who are most likely to benefit from the addition of G-CSF are those who have received fewer progenitor
If G-CSF is used after transplantation, most but not all studies suggest that there is no benefit to beginning G-CSF immediately versus delaying 5 to 7 days after stem cell infusion. In addition, in patients who were treated with G-CSF beginning on day 0, the use of G-CSF at a dose of 16 µg/kg/d was no more effective than at a dose of 5 µg/kg/d for accelerating neutrophil engraftment. Larger randomized trials clearly are necessary to define the value, if any, for the use of posttransplantation G-CSF.

HIGH-DOSE THERAPY REGIMENS: NEW DIRECTIONS

In contrast to allogeneic transplantation, for which increasing evidence indicates that cure can, and perhaps most often is, achieved by an immunologic effect of the graft, cure after autologous rescue requires complete tumor eradication by the high-dose regimen. As a result, it seems likely that preparative programs for the two procedures eventually may radically diverge. Allogeneic conditioning programs have moved toward less acutely toxic, more intentionally immunosuppressive programs to facilitate donor engraftment. In contrast, further improvement in autologously rescued patients will require the development of programs with greater antineoplastic activity. However, little evidence of progress in the construction of more effective autologous high-dose regimens has been seen over a period of 15 years, and it seems likely that the better outcomes reported more recently are more likely due to improvements in patient selection and supportive care.

Alkylating agents have been the nucleus of most preparative programs, primarily because they demonstrate a disproportionately ratio of marrow to nonmarrow toxicity that is uniquely amenable to dose escalation followed by stem cell replacement. In addition, in vitro studies show a steep dose-response curve against tumor cell lines and minimal cross-resistance with other alkylating agents. Indeed, in contrast to drugs such as anthracyclines, vinca alkaloids, and topoisomerase inhibitors, it is extremely difficult, even under tissue culture conditions, to make tumor cells more than a few-fold resistant to alkylating agents. As a result, minor degrees of drug resistance can theoretically be overcome by dose escalation or by the addition of other alkylating agents. Finally, analogous to other curative regimens, the combination of alkylating agents with nonoverlapping extramyeloid toxicity is theoretically possible with maintenance of near-maximum tolerated doses of each agent. Thus, most high-dose drug regimens, particularly exemplified by the different generations of STAMP (solid tumor autologous marrow program), have used two or more alkylating agents.

External-beam radiation, which shares many of the same advantageous biologic features of alkylating agents, cannot be dose-escalated, except to very limited fields; thus, the use of TBI has been limited to highly radiation-sensitive neoplasms, such as leukemia and lymphoma. It is not certain that radiation is superior to chemotherapy, however, even in the latter two diseases.

In clinical practice, dose escalation of alkylating agent–based regimens has been limited by excessive nonmarrow toxicity, including mucositis, pneumonitis, and veno-occlusive disease. In fact, new toxicities not predicted by single-agent studies have emerged when high doses of alkylating agents have been used in combination. As a result, the initial promise of all of the currently used programs has not been realized: Significant drug resistance has not been overcome by the modest dose escalation permitted by stem cells and growth factors. In fact, with the exception of a small percentage of patients with refractory Hodgkin's disease, the vast majority of cures after high-dose therapy and autologous stem cell rescue have been observed in patients with chemosensitive lymphoid malignancies.

Currently, several strategies are being explored to improve the results of high-dose therapy (Table 53.2-2). First, as morbidity, mortality, and cost are reduced, high-dose therapy will increasingly be explored earlier in treatment, when there is less likelihood of significant drug resistance. Promising results with early high-dose therapy have already been achieved in randomized studies of patients with multiple myeloma and NHL and is being further tested in ongoing trials.

A second approach has been to increase the intensity of preparative regimens. Based on favorable reports from single-institution studies, the Southwest Oncology Group tested the addition of high-dose etoposide to Cytoxan and TBI in patients with either relapsed or refractory NHL. Patients who were not candidates for TBI received BCNU (bischloroethylnitrosourea), along with the same doses of Cytoxan plus etoposide used in the TBI regimen. The authors reported that, in primary induction and salvage therapy failures, the results with the more aggressive regimens appeared to be superior than their previous results with cyclophosphamide and TBI but without etoposide. In patients with chemosensitive disease, the more intensive regimen was not better than the group’s previous experience. Patients treated with this regimen had a high incidence of grade III–IV mucosal (63%) and grade II or lower skin toxicity (30%) and a 10.6% treatment-related mortality. As a result, further increments in treatment are unlikely. A preliminary report of a study in which amifostine was added to decrease mucosal and skin toxicity did not show any obvious benefit.

Another method of intensifying high-dose therapy in patients with NHL or leukemia is to deliver all or part of the TBI in the form of targeted radioactive monoclonal antibody. Theoretically, radiation delivered in the form of tagged monoclonal antibodies could allow higher doses of radiation to be delivered to tumor-bearing areas without a similar increase in radiation to the lungs and liver. The Seattle group has shown the feasibility of such an approach in patients with lymphoma and leukemia.

In view of the difficulties inherent in increasing the doses or the number of drugs included in high-dose regimens, an alternative approach is to give “conventional” high-dose therapy for two or more cycles. At modestly escalated doses, this strategy can be safely accomplished with growth factors alone, but at higher doses of therapy, stem cells with or without growth factors can be used to accelerate myeloid recovery. At the Dana Farber Cancer Institute, four courses of high-dose CHOP [cyclophosphamide (Cytoxan), doxorubicin, vincristine, prednisone], in which the Cytoxan dose was increased more than fivefold and doxorubicin was increased by 50%, were used in patients with poor-prognosis lymphoma. The study showed that 70% of patients achieved a durable complete response. This regimen is currently being compared with CHOP in a randomized study. Gianni et al. randomized patients with intermediate-grade lymphoma to standard MACOP-B (methotrexate-leucovorin, Adriamycin, cyclophosphamide, Oncovin, prednisone, bleomycin) versus sequential courses of high-dose therapy in which stem cell rescue is given after a final course of narrow ablative therapy. A highly statistically significant benefit was found in disease-free survival, and borderline significant improvement was noted in overall survival favoring the high-dose arm. Patients who relapsed after MACOP-B and then were treated with high-dose therapy did poorly. The latter finding suggests either that drug resistance is more easily overcome earlier in treatment or, alternatively, that several cycles of standard therapy induces a level of drug resistance that makes later dose intensification less effective. Tandem cycles of high-dose therapy also have shown promising results in patients with refractory Hodgkin's disease, recurrent germ cell tumors, and as consolidation therapy for patients with multiple myeloma. The use of tandem versus single courses of high-dose therapy is being tested in ongoing clinical trials.

Finally, although high-dose therapy alone may not be curative in most patients, interest is increasing in using the achievement of minimal residual disease as a platform for additional posttransplantation therapy. Several approaches are being explored, including the induction of an autologous graft-versus-host reaction; posttransplantation vaccination with tumor-specific proteins; subsequent therapy with monoclonal antibodies, such as Rituxan and trastuzumab (Herceptin); and, finally, the use of additional non-cross-resistant chemotherapy.
LATE TOXICITY: MYELODYSPLASIA

A review of published studies suggests that extensive prior alkylating-agent chemotherapy and TBI-containing preparative regimens are the most important risk factors for the development of MDS and ANLL after high-dose therapy and autologous stem cell rescue. In individuals with neither risk factor, the incidence of MDS and ANLL is very low. In those with either risk factor, the incidence of MDS and ANLL is higher, although the risk is described as low. In individuals with both risk factors, the incidence of MDS and ANLL is significantly increased. This risk increases with the number of risk factors present. In patients with multiple risk factors, the risk of developing MDS and ANLL is significantly higher than in patients with fewer risk factors. In addition, the incidence of MDS and ANLL is higher in patients with a history of prior chemotherapy and/or radiation therapy. The risk of developing MDS and ANLL is also higher in patients with a history of prior bone marrow transplantation.

Factors such as chemotherapy dose, radiation dose, and age are also important determinants of the risk of developing MDS and ANLL. In general, the higher the dose of chemotherapy and radiation, the higher the risk of developing MDS and ANLL. In addition, patients aged 60 years or older have a higher risk of developing MDS and ANLL than younger patients.

The pathogenesis of MDS and ANLL after high-dose therapy and autologous stem cell rescue is complex and not fully understood. It is thought that MDS and ANLL may develop as a result of bone marrow injury caused by the preparative regimen. This injury may lead to the development of clonal hematopoiesis, which may progress to MDS and ANLL. Other factors that may contribute to the development of MDS and ANLL include the presence of prior chemotherapy and/or radiation therapy, the use of high-dose therapy, and the age of the patient.

In conclusion, the risk of developing MDS and ANLL after high-dose therapy and autologous stem cell rescue is significant and should be taken into account when considering this treatment option. Patients should be carefully selected and monitored for the development of MDS and ANLL, and appropriate treatment should be initiated if necessary.


The concept that allogeneic hematopoietic progenitor cells could be used to rescue marrow function in humans after myeloablative doses of whole body irradiation or high-dose chemotherapy arose predominantly from research in mouse models. Mice, after exposure to lethal doses of irradiation, could be reproducibly rescued from marrow aplasia after intravenous infusion of splenocytes or bone marrow cells. These observations were followed by mostly unsuccessful clinical applications of bone marrow transplantation (BMT) in humans in the late 1950s, predominantly owing to a limited knowledge of the methods required for the safe application of dose-intensive chemotherapy or total body irradiation (TBI). However, through the dedicated persistence of researchers such as Thomas et al., who pioneered in the field, the biology and mechanisms required to optimize the procedure were gradually defined. Identification of the HLA system as the major determinant of tissue compatibility and successful engraftment in patients with human leukocyte antigen (HLA)-matched siblings laid the foundation for successful allogeneic BMT during this period.

By the 1970s, BMT began to gain acceptance in the medical community as its application expanded from the treatment of patients with hematologic malignancies, such as acute leukemia and chronic myelogenous leukemia (CML), to the treatment of patients with nonmalignant hematologic conditions, such as congenital immunodeficiency syndromes and aplastic anemia. The improved safety and efficacy of dose-intensive treatment regimens, as well as the development of better supportive care measures, laid the foundation for successful allogeneic BMT during this period.

The potential of allogeneic BMT to cure otherwise fatal hematologic malignancies rapidly became established. However, the numerous toxicities associated with the procedure—namely, severe organ toxicity from dose-intensive conditioning, graft rejection, opportunistic infections, and graft-versus-host disease (GVHD)—were quickly defined as well. Although a number of effective drugs became available to prevent or manage many of these complications, such as cyclosporin A (CSA) for the prevention of acute GVHD and ganciclovir for the treatment of cytomegalovirus (CMV) infection, transplant-related mortality remained high, in the range of 30% to 40%. Furthermore, attempts to improve transplantation outcome by preventing disease relapse through intensification of the conditioning regimen proved to be largely unsuccessful, mostly owing to an increase in toxicities associated with these intensified regimens.

Great strides were made in the field of allogeneic hematopoietic stem cell transplantation (SCT) in the 1990s, in improving both transplantation safety and efficacy. The association of an increased risk of leukemic relapse after T-cell depletion of the allograft, as well as the observation that relapse was less likely in patients with a history of acute or chronic GVHD, lent credence to the concept that a donor immune-mediated antimalignancy effect, called graft-versus-leukemia (GVL), occurred after such procedures. The most compelling evidence for the GVL effect is seen in patients with relapsed CML after transplantation who are successfully induced into complete hematological remission without evidence of leukemia. Similar GVL effects after donor lymphocyte infusion (DLI) have been observed in other malignancies, including acute leukemias, chronic lymphocytic leukemia (CLL), Hodgkin’s and non-Hodgkin’s lymphoma, and multiple myeloma.

The success of DLI, particularly in relapsed CML, has generated intense interest in exploring the nature of this powerful immune effect and has raised the question of whether GVHD alone, without toxic high-dose chemotherapy or radiotherapy, could be sufficient to eradicate some hematologic malignancies. To answer this question, a number of investigators have explored the concept of using low-intensity, immunosuppressive but nonmyeloablative conditioning regimens to permit engraftment of the donor immune system for the generation of GVL effects while sparing patients the toxicities associated with myeloablative therapy. Early results have been encouraging, demonstrating that such transplantation regimens are well tolerated, with a decreased incidence of transplant-related morbidity and mortality, even in high-risk patients. More important, they have demonstrated that GVL alone, without toxic myeloablative conditioning, is sufficient to cure some hematologic malignancies. These findings highlight the unique and potentially curative immune aspects that are intrinsic to this form of therapy.

### Allogeneic Hematopoietic Stem Cell Transplantation for Hematologic Malignancies

The relationship between the intensity of chemoradiotherapy and the antitumor effect led to the development of most high-intensity BMT strategies. Myeloablative doses of chemoradiotherapy, which are intended to eradicate the malignancy completely, are followed by the infusion of compatible donor hematopoietic progenitor cells to rescue the patient from conditioning-induced bone marrow aplasia. This concept is applied most appropriately to malignancies such as leukemia that originate from the bone marrow itself. However, increasing evidence reveals that even the most intense of conditioning regimens often does not completely eradicate leukemic clones. Rather, a powerful immune reaction generated from donor cells against residual leukemia (GVH) ensues in the majority of responding patients, rendering them leukemia-free. It is through the combination of these two components—dose-intensive tumor killing followed by the GVL effect—that allogeneic hematopoietic SCT has its curative potential.
ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR NONMALIGNANT DISORDERS

Allogeneic hematopoietic SCT can be used to successfully treat nonmalignant diseases associated with defective bone marrow function or metabolic disorders associated with lysosomal enzyme defects. These disorders, although nonmalignant, often result in an extremely poor quality of life and may have long-term life-threatening sequelae, thus justifying the risks of morbidity and mortality associated with the procedure. The list of nonmalignant diseases curable by allogeneic hematopoietic SCT is long and includes severe aplastic anemia, Fanconi's anemia, thalassemia major, chronic granulomatous disease, sickle cell anemia, and a number of immunodeficiency syndromes, such as the severe combined immunodeficiency syndrome, Chédiak-Higashi disease, and the Wiskott-Aldrich syndrome. Because the eradication of malignant cells is not a concern, the preparative regimens used in these diseases usually are of lower intensity or do not include irradiation, serving primarily to provide sufficient immunosuppression to allow for the engraftment of normal donor bone marrow cells. In some diseases, particularly sickle cell anemia and thalassemia major in children, excellent results have been achieved with disease-free survivals greater than 95%.

PREPARATIVE REGIMENS

In the treatment of malignant diseases, the primary purpose of the preparative regimen is to eradicate malignant cells and to induce immunosuppression in the recipient so that rejection is prevented and engraftment of the donor hematopoietic system is permitted. The decision to use a particular preparative regimen often is guided by the sensitivity of the underlying malignancy. Although a number of preparative regimens have been used for their antitumor effects in hematologic malignancies, in general, they can be divided into two categories: TBI-based and chemotherapy-based.

Most regimens based on TBI are composed of high-dose cyclophosphamide given as 60 mg/kg IV on 2 consecutive days, followed by varying doses of fractionated TBI to a cumulative dose of 1200 to 1500 cGy. Although there is some evidence that the higher doses of TBI may be more effective in terms of preventing disease relapse, toxicity appears to increase concomitantly, thus negating any overall benefit. Results, in terms of toxicity and disease-free survival, appear similar between regimens composed of TBI and etoposide (60 mg/kg) and those composed of TBI and cyclophosphamide.

Although a number of chemotherapy-based regimens that do not include irradiation have been used, the combination of cyclophosphamide (60 mg/kg IV on 2 consecutive days) and busulfan (4 mg/kg PO on 4 consecutive days) has gained increasing popularity and use since its conception in the early 1980s. Similar to the experience with TBI, dose intensification of chemotherapy-based regimens usually results in increased toxicity, thus negating any potential survival benefit that might occur as a result of less disease relapse.

The decision guiding which preparative regimen to use is often based on the predicted tumor-specific activity of that regimen. In general, radiation- and chemotherapy-based regimens are associated with an equal probability of achieving long-term disease-free survival. Two randomized trials evaluating cyclophosphamide (60 mg/kg × 2) and busulfan versus TBI and cyclophosphamide (60 mg/kg × 2) in patients with chronic-phase CML revealed equal efficacy between both regimens. However, in acute lymphocytic leukemia (ALL), TBI-based regimens may be the treatment of choice, as a randomized trial reported a significantly increased risk of relapse in patients with ALL who received conditioning with chemotherapy alone (busulfan and etoposide).

The toxicity profile of preparative regimens varies considerably, a factor that often determines the choice of which regimen to use for an individual patient. In general, TBI-based regimens are associated with a higher risk of secondary malignancies and growth retardation, while chemotherapy-based regimens, particularly those containing busulfan, are associated with a higher risk of severe mucositis and venoocclusive disease (VOD), with minimal effects on growth and development.

A number of investigators have explored the concept of using low-intensity preparative regimens (either low-dose chemotherapy, low-dose TBI, or both) in attempts to decrease the risks of toxicity and mortality associated with myeloablative conditioning. The preparative regimen in such nonmyeloablative stem cell transplantations (NSTs; discussed later in Nonmyeloablative Allogeneic Stem Cell Transplantation) does not eradicate host hematopoiesis and is used primarily to induce immunosuppression in the recipient to allow for engraftment of donor cells for the subsequent generation of GVH. Such low-intensity transplantations rely completely on the GVH effect to eradicate malignancy. Although these regimens vary considerably between institutions, preliminary results are promising, showing high degrees of donor engraftment with considerably less conditioning-related toxicity than is seen with conventional high-dose myeloablative regimens, even in older (older than 55 years) and debilitated patients. Most of the severe and life-threatening complications associated with conventional preparative regimens, such as VOD, pneumonitis, and severe mucositis, have rarely been observed with NST. More important, significant engraftment of donor immune cells has been achieved to induce complete remission in a number of different hematologic malignancies. The improved safety profile of NST, in both the short and long term, will likely make this transplantation approach the procedure of choice for patients at high risk for complications with conventional dose-intensive regimens (i.e., older or debilitated patients). Furthermore, NST may have its greatest benefit among younger patients in whom growth retardation, sterility, and the risk of secondary malignancy may be completely avoided. The toxicity profiles of TBI-based, chemotherapy-based, and nonmyeloablative transplantation regimens are shown in Table 53.3-1.

TABLE 53.3-1. Toxicity Profiles of Conditioning Regimens

GRAFT-VERSUS-LEUKEMIA EFFECT

CLINICAL SIGNIFICANCE

The concept that donor immune cells might make an important contribution to the antileukemic effect of allogeneic BMT was first suggested in the 1950s on the basis of observations in animal models. Mice with leukemia given syngeneic BMTs died of leukemia, whereas mice given allogeneic cells were rescued from leukemia but died from acute GVHD. Subsequently, a large body of evidence began to point toward similar antileukemic effects in humans, mediated through donor cells after allotransplantation. Observations supporting this donor-mediated antileukemic (GVL) effect initially were based on the observation that relapse of leukemia was less likely in patients who developed GVHD after BMT than in those who never developed GVHD. Additional support for the GVLT effect included the observation that leukemic relapse occurred more frequently in identical twin transplants and in transplantations in which recipients received T-lymphocyte–depleted marrow for the prevention of GVHD. Furthermore, recipients of T-cell–depleted transplants have an increased risk of relapse even after adjusting for GVHD, further supporting an antileukemic effect of donor immune cells separate from acute GVHD. Patients with a history of both acute and chronic GVHD were observed to have the lowest risk of relapse. Data from the National Marrow Donor Program Transplant Registry, T-cell depletion, and the type of disease show that the probability of relapse are shown in Figure 53.3-1. Data from this registry suggest that these effects vary according to the type of leukemia but are most evident in patients with chronic-phase CML undergoing transplantation. Further indirect evidence for the GVLT effect includes the observation that up to 50% of patients with CML have small numbers of cells that are Philadelphia-chromosome positive or remain positive for the bcr/abl transcript for months after allogeneic BMT. In the majority of cases, these abnormal cells and bcr/abl transcripts become undetectable over time. Additionally, abrupt disruption of CSA after detection.
of disease relapse in CML has been associated with reinduction of cytogenic remission. Fig. 53.3-2

Finally, the most compelling evidence supporting the powerful and potentially curative nature of the GVL effect is the observation that complete and durable remissions can be induced by the transfusion of lymphocytes from the marrow donor, without chemotherapy or radiotherapy, in patients with CML who have relapsed after marrow transplantation. The efficacy of DLI for the treatment of relapsed leukemia is disease-dependent, with remission induction occurring in a substantially higher percentage of patients with chronic-phase CML than in patients with advanced CML or other acute leukemias. In general, 70% to 80% of patients with cytogenetic or hematologic relapse of CML can be expected to achieve a molecular remission after DLI, with 97% of these patients remaining disease-free at 3 years. Remissions usually are not observed until months after DLI consistent with the time required to expand antileukemic clones (Fig. 53.3-2).

In contrast to the relatively high efficacy of DLI in relapsed chronic-phase CML, only a minority of patients with relapsed acute leukemia achieve remission after this approach. In a report from the European Group for Blood and Marrow Transplant, only 20% of patients with relapsed acute myelogenous leukemia (AML) and none with relapsed ALL (0 of 11) achieved remission after DLI. Unlike chronic-phase CML, remission after DLI for advanced-phase CML and acute leukemia appears to be of limited duration, with the majority of responders experiencing relapse within 1 year of treatment. The poor response of accelerated or blast crisis CML to DLI is perhaps due to clonal evolution of the leukemia leading to selective expansion of malignant cells capable of escaping immune recognition.

Disease regression after DLI has also been described in patients with multiple myeloma, CLL, and non-Hodgkin's lymphoma who experience relapse after allogeneic transplantation, although too few have been treated to define the efficacy of this approach in these diseases.

The major complication associated with DLI is acute and chronic GVHD. Acute GVHD, which may be severe or life-threatening (grade III or IV) in 15% to 20% of cases, may develop after DLI in up to 70% to 80% of patients. The propensity for GVHD after DLI is likely affected by the relatively large dose of T lymphocytes that traditionally have been infused (1 to 10 x 10^6 CD3 cells/kg), as well as the fact that these cells are usually given without GVHD prophylaxis. Two approaches to reduce the incidence of GVHD after DLI have been developed. One approach is to selectively infuse lymphocytes depleted of CD8+ T cells: This approach was investigated based on the experience that allografts depleted of CD8+ cells were associated with a low incidence of GVHD without an increased risk of relapse. Several nonrandomized trials have shown that DLI depleted of CD8+ cells can reinduce remission, with a rate of GVHD that is lower than that observed with unmanipulated DLI. The other strategy involves the infusion of donor lymphocytes in multiple aliquots, starting at low cell numbers and escalating the dosage at variable intervals until a GVHD effect is achieved. This approach is based on the premise that lower T-cell numbers might induce remission while decreasing the risk of GVHD. One trial comparing these two different lymphocyte infusion approaches in patients with relapsed chronic-phase CML revealed a significantly lower incidence of GVHD in the group that received dose-escalating lymphocyte infusions than in the group receiving traditional single "bulk-dose" regimens (10% vs. 44%). Importantly, although the incidence of acute GVHD was extremely low in the escalating-dose group, the GVL effect was preserved, with 91% of these patients achieving a complete remission by 2 years (Fig. 53.3-3).

The other potentially life-threatening complication of DLI is marrow aplasia. Approximately 30% to 40% of patients who receive DLI for relapsed CML develop pancytopenia, which typically occurs at the time of the GVL response. Although most patients still have mixed or complete T-cell chimerism at the time of DLI, myeloid chimerism may be predominantly recipient in origin, originating from the leukemic clone, thus leaving the marrow aplastic after a graft-versus-host hematopoietic effect occurs. The duration of aplasia is variable and is directly dependent on the number of residual donor hematopoietic progenitor cells. Although, in most cases, spontaneous reconstitution of marrow by donor cells usually occurs, some patients have persistent aplasia and may require additional donor stem cell
Allogeneic hematopoietic SCT is associated with a number of complications, many unique to this type of therapy, which can be divided into two general categories: toxicities related to conditioning and toxicities related to the transplantation of an allogeneic immune system into the patient—specifically, graft rejection, GVHD, and infectious complications associated with immunosuppression.

The complications associated with myeloablative doses of chemo/radiotherapy vary in terms of incidence and severity, depending on the intensity and type of agents used in conditioning. These complications may occur as an immediate side effect, or shortly after administration of the preparative regimen, or in a delayed fashion, years after transplantation. Commonly observed immediate toxicities include nausea and vomiting, mucositis, parotid gland inflammation related to TBI, and neutropenia with associated fever or opportunistic bacterial or invasive fungal infection.

The nature of the effector cells mediating the GV effect is not entirely known. In animal models, these effectors often are leukemia- and mouse strain–specific, thus limiting insight into the GV effect in humans. Both CD4+ and CD8+ cytotoxic T cells with direct antileukemic activity have been isolated from patients after allogeneic BMT, therefore implying both as having a role in GV. Indeed CD4+ T cells appear to play a particularly important role in the GV effect in CMML. Indeed, CD4+ T cells have been generated that are cytolytic to CML cells in vitro and can be used successfully to treat relapsed leukemia in patients after BMT. Although other cell populations such as natural killer cells, lymphokine-activated killer cells, and gd T cells may have antileukemic activity, it is not clear what their overall contribution is to the GV effect.

The ability to separate GV from GVHD will depend on the future delineation of these effector populations and their toxicities related to conditioning and toxicities related to the transplantation of an allogeneic immune system into the patient—specifically, graft rejection, GVHD, and infectious complications associated with immunosuppression.

The tissue-restricted pattern of minor histocompatibility antigens (mHa) likely explains why some patients respond to DLI without the development of GVHD: T-cell populations mediating an antileukemic reaction through mHa restricted to hematopoietic cells would not be expected to cause GVHD in contrast to T cells targeting such antigens expressed broadly on both normal tissue and leukemic cells, where both GVHD and a GV effect would occur. Indeed, T-cell clones have been generated in vitro that specifically recognize mHa restricted to leukemic cells and normal hematopoietic cells.

Although leukemia-restricted peptides would appear to be an attractive target for donor immune cells, convincing evidence has not yet been found to implicate a specific antileukemic effect in GV. However, the observation that some patients with relapsed leukemia achieve remission after DLI without GVHD lends credence to the notion that leukemia-restricted T-cell populations may occasionally be targeted antileukemic process. In vitro, it is possible to generate T-cell clones against leukemia cells as well as leukemia-specific peptides. Peptides corresponding to the binding region of P201 BCR/ABL in CML, and the fusion region of the hybrid protein PML/RAR in acute promyelocytic leukemia, can be used to generate T-cell populations with leukemia-specific cytolytic activity. Although potentially attractive for targeted immunotherapeutic approaches, no clear evidence supports the hypothesis that these leukemia-specific peptides are a target for GV.

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The routine use of mesna, hydration, and forced diuresis has largely eliminated early hemorrhagic cysts. In contrast, late hemorrhagic cysts, occurring beyond 72 hours after cyclophosphamide infusion, remain a continuing problem in allogeneic BMT and usually is viral in origin (polyoma virus BK or adenovirus). High-dose busulfan is associated with grand mal seizures; many busulfan-containing regimens use seizure prophylaxis with phenytoin (Dilantin) or phenobarbital.

Opportunistic infections as a consequence of preparative regimen–induced neutropenia remain a significant complication associated with allogeneic BMT. Most fungal and bacterial infections originate from microorganisms colonizing the skin, oral cavity, perianal area, or gastrointestinal or respiratory tract. The most common life-threatening infections occur during the neutropenic period and involve gram-negative and aerobic gram-positive bacteria. These pathogens gain entry into the host through indwelling vascular catheters or as a consequence of the breakdown of gastrointestinal mucosa related to high-dose chemo/radiotherapy.

Decontamination of the gastrointestinal tract with nonabsorbable antibiotics such as neomycin or vancomycin have met with mixed success, with poor patient compliance being one of the most serious life-threatening complications. Although numerous infectious complications associated with immunosuppression persist, prophylactic oral quinolones as ciprofloxacin and norfloxacin appear to decrease the incidence of febrile neutropenia and gram-negative infections, although possibly at the expense of more episodes of gram-positive bacteremia.

Candidiasis and Aspergillus species are the most common fungal pathogens, frequently causing infection during periods of neutropenia or systemic corticosteroid use for GVHD. Oral triazoles, such as fluconazole, have been shown in randomized trials to decrease the incidence of opportunistic candidal infections but have no impact on the incidence of infections with resistant species such as Aspergillus or Candida krusei. It is unclear whether the shortened duration of absolute neutropenia associated with the use of recombinant hematopoietic growth factors [i.e., granulocyte colony-stimulating factor (G-CSF)] will lead to a decrease in the incidence of infections by these opportunistic pathogens.

Venoocclusive disease

One of the most serious life-threatening complications of dose-intensive chemo/radiotherapy is hepatic VOD. VOD produces a clinical syndrome of jaundice, tender hepatomegaly, and unexplained weight gain or ascites.

Therapy for established VOD is unsatisfactory and consists mostly of measures to support renal function, fluid balance, and coagulation status. Recombinant tissue factor pathway inhibitor has been used successfully to reduce the incidence of VOD, warranting further investigation of this agent.

The therapeutic drug monitoring of busulfan, with appropriate dose adjustments, appears to be useful in reducing the incidence of VOD in patients receiving this agent. Data regarding pharmacologic prophylaxis against VOD have been contradictory. One double-blind, randomized trial showed a significant reduction in the incidence of VOD in patients taking unscheduled prophylaxis as compared to those taking placebo (50% vs. 15%). Unosoldil was well tolerated and may prove particularly useful as prophylaxis in patients defined to be at high risk for VOD.

Pulmonary complications

Pulmonary complications occur frequently after allogeneic BMT and may be related to infectious agents, diffuse alveolar hemorrhage, or pulmonary edema, or may have an idiopathic origin. Common infectious etiologies include Aspergillus species or other fungi, respiratory syncytial virus, and CMV. Late pneumonia from Pneumocystis carinii may occur up to 1 year after transplantation and usually is related to prolonged CD4+ lymphopenia associated with T-cell depletion of the allograft or GVHD. Interstitial pneumonitis (IP), characterized by fever, hypoxia, and diffuse pulmonary infiltrates, occurs in 20% to 40% of patients, usually within the first 3 months of transplantation, and may be lethal in up to one-half of cases. Nearly 90% of the cases of IP either are related to CMV infection or have an idiopathic origin. The incidence of early CMV pneumonitis appears to have decreased significantly in the 1990s.
through the use of both effective prophylactic regimens (intravenous immunoglobulin and ganciclovir) and better methods for early detection of CMV reactivation.

Patient-specific risk factors for IP include older age, prior history of exposure to pulmonary toxic drugs such as bleomycin, history of acute or chronic GVHD, dose intensity of the conditioning regimen, or use of TBI. Regimens that use a lower dose rate or total dose of TBI, as well as hyperfractionated TBI, may be associated with a lower risk of IP.

Bronchoscopy with bronchoalveolar lavage should be used in all patients with IP to differentiate IIP from infectious causes or diffuse alveolar hemorrhage. Empiric use of anti-CMV agents such as ganciclovir or foscamet should be considered when bronchoalveolar lavage is not feasible. Although evidence exists supporting the efficacy of high-dose steroids in patients with diffuse alveolar hemorrhage, their effectiveness in the treatment of IP remains equivocal.

**LATE COMPLICATIONS**

The delayed complications associated with allogeneic SCT depend on patient age at transplantation and are a consequence of the effects of long-term damage to normal tissues by either the preparative regimen or chronic GVHD. These effects include growth retardation, infertility, endocrine failure, cataracts, renal insufficiency, restrictive pulmonary defects, neurocognitive defects, and secondary malignancies. The use of TBI in the conditioning regimen seems to be the major factor associated with secondary malignancies. On long-term follow-up of 1036 patients undergoing BMT for a wide range of malignant and nonmalignant conditions, a 12.6% incidence of secondary neoplasms was reported at 15 years, a rate that was 3.8 times higher than that for an age-matched control population.

The most frequently observed secondary neoplasms were of the skin and oral cavity, with older patient age and use of CSA for chronic GVHD being significant risk factors for new malignant disease.

**EPSTEIN-BARR VIRUS LYMOPHOPROLIFERATIVE DISORDER**

Posttransplantation Epstein-Barr virus (EBV)–associated lymphoproliferative disorder (LPD) represents an aggressive and potentially fatal B-cell lymphoid proliferation that occurs after 5% to 30% of allogeneic transplantations. This lymphoma originates from B cells infected with EBV, typically of donor origin, and usually stems from a deficiency of EBV-specific cytotoxic T cells associated with the use of immunosuppressive drugs or T-cell depletion of the allograft. EBV LPD can be successfully treated by using unmanipulated donor leukocytes that contain cytotoxic T cells presensitized to EBV. One trial in children receiving T-cell-depleted transplants from HLA-mismatched donors demonstrated that the prophylactic infusion of ex vivo–generated EBV-specific T cells can successfully prevent EBV LPD without causing acute GVHD. Others have shown that B-cell depletion of the allograft can also be used to prevent this disorder. The use of Rituximab (Rituxan), a monoclonal antibody to the B-cell antigen CD20, has recently been shown to be an alternative strategy that can successfully treat established LPD.

**GRAFT-VERSUS-HOST DISEASE**

GVHD is the consequence of immunocompetent donor T cells targeting recipient tissues that possess antigens absent from the donor. The major target tissues of GVHD are the skin, liver, and gastrointestinal tract, although other tissues may be involved. The diagnosis of acute GVHD may be based on one or a myriad of characteristic clinical and laboratory findings. Skin manifestations include an erythematous maculopapular rash often involving the palms and soles and, under severe circumstances, may be associated with desquamation. Hepatic involvement is characterized by a rise in alkaline phosphatase and total bilirubin, often in association with a mild to moderate increase in hepatic transaminases. Gastrointestinal GVHD predominantly involves the distal small bowel and colon and clinically is associated with cramping abdominal pain, watery diarrhea, which may be voluminous and bloody under severe circumstances. Endoscopic findings are variable and may range from mild bowel edema to total denuding of intestinal mucosa; colonic biopsy usually reveals classic pathologic features showing crypt cell necrosis with apoptotic bodies and lymphocytic infiltrates, although disease involvement can be patchy and missed on random biopsy. Upper gastrointestinal involvement, although more rare, may be associated with recurrent nausea, vomiting, and dyspepsia. Traditionally, acute GVHD has been divided into severity grades I through IV, depending on the extent of skin involvement, volume of diarrhea, or level of bilirubin elevation (Table 53.3-2). The major target tissues of GVHD are the skin, liver, and gastrointestinal tract, although other tissues may be involved. The diagnosis of acute GVHD may be based on one or a myriad of characteristic clinical and laboratory findings. Skin manifestations include an erythematous maculopapular rash often involving the palms and soles and, under severe circumstances, may be associated with desquamation. Hepatic involvement is characterized by a rise in alkaline phosphatase and total bilirubin, often in association with a mild to moderate increase in hepatic transaminases. Gastrointestinal GVHD predominantly involves the distal small bowel and colon and clinically is associated with cramping abdominal pain, watery diarrhea, which may be voluminous and bloody under severe circumstances. Endoscopic findings are variable and may range from mild bowel edema to total denuding of intestinal mucosa; colonic biopsy usually reveals classic pathologic features showing crypt cell necrosis with apoptotic bodies and lymphocytic infiltrates, although disease involvement can be patchy and missed on random biopsy. Upper gastrointestinal involvement, although more rare, may be associated with recurrent nausea, vomiting, and dyspepsia. Traditionally, acute GVHD has been divided into severity grades I through IV, depending on the extent of skin involvement, volume of diarrhea, or level of bilirubin elevation (Table 53.3-2).

Donor T cells are the principle mediators of GVHD. In an HLA-mismatched setting, CD8+ T cells may target major histocompatibility complex (MHC) class I mismatched antigens, while CD4+ T cells are responsible for the recognition and targeting of MHC class II mismatched antigens. The antigens that are disparate between patient and donor and serve as a target for GVHD in HLA-identical sibling transplants are referred to as minor histocompatibility antigens (mHAs). Relatively few mHAs have been characterized to date, although there is increasing evidence to suggest that the degree of disparity between recipient and donor mHAs is a major determinant for the development of both acute and chronic GVHD. The development of GVHD is a multistep process in which recipient tissues are recognized as foreign by the donor immune system, followed by the activation and expansion of GVHD effector populations, ultimately leading to T-cell–mediated direct cytotoxic damage of target tissues.

GVHD remains a significant contributor to transplant-related morbidity and mortality. The incidence and severity of GVHD is determined by a number of variables, including degrees of HLA disparity between patient and donor, use of a T-cell–replete versus T-cell–depleted allograft, patient age, and the agents used in GVHD prophylaxis. Furthermore, acute GVHD after T-cell–replete allogeneic BMT often is most severe within the first month after transplantation and appears to be exacerbated by conditioning-induced cytokine release from damaged recipient tissues. In general, the incidence of clinically significant acute GVHD (grades II through IV) in patients undergoing a T-cell–replete allogeneic SCT (from an HLA-identical sibling) in which conventional GVHD prophylaxis is used (CSA and methotrexate) is on the order of 30% to 40%, with approximately 15% of patients developing severe grade III or IV disease. In recipients of partially matched related donor or partially matched unrelated donor transplants, acute GVHD occurs more frequently, affecting more than 70% of patients.

The two most common methods for preventing acute GVHD include the use of prophylactic immunosuppressive agents and the use of allografts from which donor T cells have been depleted. Although the combined use of CSA and methotrexate has been found to be superior to either agent alone in the prevention of GVHD, the addition of prednisone to these agents does not appear to offer any additional benefit. In both HLA-identical sibling and unrelated transplantations, T-cell depletion is the most effective method for preventing GVHD but is associated with an increased risk of graft rejection, opportunistic viral infection, and leukemic relapse. Although the risk of disease relapse is leukemia-specific, a large retrospective analysis from the International Bone Marrow Transplant Registry showed clear evidence that T-cell depletion was associated with a lower disease-free survival in CML. Novel methods of T-cell depletion that appear to decrease this risk of acute GVHD without increasing the risk of disease relapse include the use of selectively depleted CD8+ T cells and the use of T-cell–depleted transplants followed by a delayed infusion of donor lymphocytes months after the original transplantation to preserve the GVL effect.

The mainstay of therapy for the treatment of acute GVHD is corticosteroid therapy, usually in association with CSA or FK506. Approximately 40% to 60% of patients with grade II to IV GVHD can be expected to respond to these agents. One randomized trial of low-dose (2 mg/kg) versus high-dose (10 mg/kg) methylprednisolone for acute GVHD showed no difference in response rates with either regimen. Response to steroids appears to predict survival, with steroid-refractory patients being at a significantly higher risk of transplant-related mortality than steroid-responsive patients. Anthymocyte globulin (ATG) has been
used with minimal success in patients with steroid-refractory disease, and it appears to be inferior to steroids or CSA as an initial therapy for acute GVHD. Other approaches that have shown early promise for the treatment of steroid-resistant disease include the use of the immunosuppressive drug mycophenolate mofetil, monoclonal antibodies that target a number of different T-cell antigens, and extracorporeal photopheresis.

Chronic GVHD occurs in 15% to 50% of long-term survivors of allogeneic BMT and typically manifests with symptoms 3 months to 2 years after transplantation. The etiology of chronic GVHD appears to be related to alloreactive T cells that infiltrate and damage tissues and cause abnormalities in immune regulation. The greatest risk factor for chronic GVHD is a prior history of acute GVHD, although older patient age, use of mismatched or unrelated donors, a history of DLI for relapsed malignancy, and use of peripheral blood stem transplants also appear to increase the risk. Patients with chronic GVHD often are severely immunocompromised, either as a consequence of the immunosuppressive therapy used to treat the disorder or from the underlying immune dysregulation associated with the disease process. Chronic GVHD is lethal in approximately 20% to 30% of cases, with death being predominantly related to infectious causes. Patients with a particularly poor prognosis include those with hepatic involvement or thrombocytopenia.

Chronic GVHD is traditionally classified as either limited or extensive, limited disease being defined as localized skin involvement with or without mild hepatic involvement and extensive disease being generalized skin involvement with or without target organ involvement. The characteristic clinical manifestations are numerous and include ichthyosis or sclerodermatous skin involvement, hepatic cholestasis, friable nails, dry eyes (Sjögren's syndrome), fasciitis, xerostomia, lichenoid buccal changes, bronchiolitis obliterans, vaginal dryness, seborrhea, malabsorption, diarrhea, gastrointestinal dysmotility, and pancytopenia. Treatment depends on the extent of disease. Systemic disease typically is treated with alternate-day CSA or FK506 and low-dose corticosteroids. Patients not responding to standard therapy often benefit from alternative therapies, including mycophenolate mofetil, psoralen and ultraviolet A for skin involvement, thalidomide, total lymphoid irradiation and, more recently, extracorporeal photopheresis.

GRAFT FAILURE

Failure to achieve or maintain sustained donor hematopoietic engraftment after allogeneic transplantation is referred to as graft failure. Graft failure may manifest as persistent pancytopenia without evidence of engraftment (primary graft failure) or as initial engraftment followed by a delayed fall in blood counts (late or secondary graft failure). Graft rejection is the term used to describe graft failure that occurs as a consequence of the active rejection of donor hematopoietic cells by residual immunocompetent host cells. Clinically, graft rejection manifests as transient donor engraftment followed by a lymphocytosis of recipient origin, which ultimately leads to the rejection of donor hematopoietic cells and pancytopenia or, in some cases, autologous hematopoietic recovery. The mediators of graft rejection include natural killer cells or residual recipient T cells recognizing donor-mismatched MHC molecules or, in an HLA-matched setting, mAbs.

Primary graft failure should be suspected in all transplant patients who remain pancytopenic for longer than 3 to 4 weeks. It is associated with a significant risk of death from hemorrhage or infection. Although graft failure occurs in fewer than 2% of patients undergoing allogeneic SCT from an HLA-identical sibling, the incidence increases to 5% to 10% when donors and recipients are HLA-matched or unrelated. Other risk factors for graft rejection include the infusion of low stem cell numbers (i.e., <1 × 10^6 CD34+ cells/kg), history of multiple blood transfusions, HLA disparity between the patient and donor, use of low-intensity or dose-reduced conditioning regimens, and transplantation for severe aplastic anemia. As with graft rejection, the administration of donor marrow or aplastic anemia, the addition of ATG or ATG to the conditioning regimen (usually high-dose cyclophosphamide) has decreased the incidence from 30% to less than 10%.

Differentiating graft failure from pancytopenia related to other causes, including marrow suppression from infection, medications, or chronic GVHD, is important. Furthermore, it is important to give early consideration for a second donor stem cell infusion, given the difficult logistics of collecting more donor cells. Non-inmunobiologically mediated graft failure has been successfully treated with hematopoietic growth factors such as granulocyte-macrophage colony-stimulating factor or G-CSF, followed by a second infusion of donor stem cells in those who fail to experience hematopoietic recovery. PBSC are mobilized with recombinant growth factor G-CSF usually is given to donors for 4 to 6 consecutive days (10 mg/kg/d) to mobilize hematopoietic progenitors into the circulation, followed by one or two leukapheresis procedures. G-CSF-mobilized PBSC transplants contain higher numbers of progenitor cells than do marrow grafts, usually in the range of 5 to 10 × 10^6 CD34+ cells/kg. Although the use of lower doses of G-CSF is associated with a decreased incidence of cytokine-related side effects, the number of CD34+ cells mobilized into circulation may be lower, necessitating additional leukapheresis procedures.

CMV is a member of the herpesvirus family and may be associated with serious and life-threatening pathology after allogeneic BMT. Most patients who develop CMV disease do so as a consequence of viral reactivation from a previous primary infection. The cellular immune system plays an important role in the suppression of viral reactivation. Disruption of cellular immune association with T-cell depletion, GVHD, or immunosuppressive therapy can lead to CMV reactivation and subsequent disease. The clinical features of CMV disease include pneumonitis, hepatitis, upper gastrointestinal involvement, and colitis. Reactivation tends to occur 3 to 10 days after transplantation and is most strongly associated with acute GVHD and pretransplantation seropositivity of the recipient to CMV. Prior to the development of reactivation screening techniques and prophylactic drug regimens, CMV pneumonitis was observed in 10% to 30% of patients and was fatal in 50% to 90% of cases.

Effective prevention can be achieved through the use of CMV-negative or leukocyte-filtered blood products (in seronegative patient-donor pairs) and prophylactic intravenous immunoglobulin and ganciclovir. As CMV will never reactivate in 40% to 50% of patients, an alternative and effective approach is to reserve ganciclovir use for patients with detectable viral reactivation, either by polymerase chain reaction methods or by immunofluorescent techniques designed to detect viral antigen on the surface of neutrophils (CMV antigenemia). Both techniques allow for early detection and treatment of CMV reactivation long before symptoms develop. Indeed, these early detection methods have dramatically decreased the incidence and mortality associated with CMV disease. A recently investigated alternative to CMV prophylaxis is to infuse CMV-specific cytotoxic lymphocytes generated from donor cells in vitro, early after T-cell–depleted transplantation. This cell-based approach for the prevention of CMV reactivation has shown early success and may serve as a paradigm for future protocols that use tumor-specific T cells to prevent disease relapse.

SOURCES OF ALLOGENEIC HEMATOPOIETIC STEM CELLS

ALLOGENIC PERIPHERAL BLOOD STEM CELL TRANSPLANTS

Based on the success of autologous peripheral blood stem cell (PBSC) transplants, allogeneic transplantation regimens, which use peripheral blood–derived stem cells as opposed to marrow cells, have been used with increasing frequency since the mid-1990s, with early favorable clinical outcome. The recombinant growth factor G-CSF usually is given to donors for 4 to 6 consecutive days (10 mg/kg/d) to mobilize hematopoietic progenitors into the circulation, followed by one or two leukapheresis procedures. G-CSF-mobilized PBSC transplants contain higher numbers of progenitor cells than do marrow grafts, usually in the range of 5 to 10 × 10^6 CD34+ cells/kg. Although the use of lower doses of G-CSF is associated with a decreased incidence of cytokine-related side effects, the number of CD34+ cells mobilized into circulation may be lower, necessitating additional leukapheresis procedures.

PBSC transplants have potential advantages for both the donor and the patient. Donors do not require hospitalization and are spared the pain and potential risks of general anesthesia associated with marrow harvesting, although the long-term consequences of G-CSF administration remain unknown. Also, PBSC grafts contain higher numbers of hematopoietic progenitor cells, natural killer cells, and T cells, as compared with bone marrow. Engraftment, therefore, is usually faster, and the GVL effect may be enhanced. PBSC transplants are faster and less toxic and, in patients not responding to standard therapy, may allow the use of additional chemotherapy or bone marrow reinfusion. Indeed, two trials comparing autologous bone marrow to PBSC transplantation have shown that PBSCs are associated with a shorter period of neutropenia and red blood cell and platelet transfusion dependence, with an equal probability of acute and chronic GVHD. The failure to observe a correlation between the number of T lymphocytes in the allograft and GVHD might be related to the polarizing of donor T cells by G-CSF to a type 2 (suppressor) cytokine profile.

A phase III trial of allogeneic transplantation in 138 patients with hematologic malignancies found that PBSC grafts were associated with more rapid engraftment and better disease-free and overall survival than marrow grafts, without a greater risk of acute GVHD. Neutrophil engraftment occurred 6 days earlier (day 15 vs. day
Allogeneic hematopoietic SCT using high-dose, myeloablative chemo/radiotherapy is associated with a high incidence of treatment-related complications and a 20% incidence of severe acute GVHD. Nonmyeloablative allogeneic SCT has been performed using this approach, early results have been encouraging, without the occurrence of graft rejection or death from acute GVHD.

**UMBLICAL CORD BLOOD TRANSPLANTATION**

Umbilical cord blood is a new and promising source of hematopoietic progenitor cells for transplantation in both malignant and nonmalignant disorders. The realization that cord blood, obtained from the placenta after delivery, contained long-term repopulating progenitor cells led to its investigational use as a source of stem cells for allogeneic transplantation. Cord blood has been shown to contain primitive hematopoietic stem cells with remarkable proliferative potential, which may overcome the limitation of relatively low absolute cell numbers. Also, the immature lymphocytes in cord blood appear to decrease the risk and severity of acute and chronic GVHD, potentially permitting greater HLA disparity and expanding donor availability.

In a trial evaluating umbilical cord transplants in 44 children with malignant and nonmalignant hematologic diseases receiving grafts from an HLA-identical or single-antigen-mismatched donor, 85% engrafted and only 3% developed grade II or worse acute GVHD. A subsequent multiinstitutional study from Europe reported similar engraftment rates in 78 recipients of cord blood from related donors, with acute GVHD occurring in 9% of the recipients of HLA-matched cord blood and in 50% of the recipients of HLA-mismatched cord blood. Neutrophil engraftment was favorably associated with a younger patient age (younger than 6 years) and weight (<20 kg) and occurred in 85% of patients receiving 37 million or more mononuclear cells per kilogram of recipient body weight. In the recipients of unrelated cord blood, neutrophil engraftment occurred in 94% of those who received 37 million or more mononuclear cells per kilogram, with only 32% of patients developing grade II or worse GVHD.

These early successes have led to the creation of an increasing number of umbilical cord blood banks worldwide. However, graft failure, which is most closely associated with patient size, age, and low cord stem cell doses, remains a significant problem that will likely limit the applicability of this approach in adults.

**UNRELATED DONORS**

Although allogeneic hematopoietic SCT is a potentially curative modality for a number of otherwise fatal malignancies, only one-third or so of patients have access to an HLA-identical sibling. The growing demand for donors has led to research in the development of techniques for the use of alternative sources of stem cells. The knowledge that the HLA system played a critical role in transplantation outcomes led to the successful use of HLA-matched unrelated donors (MUDs) and subsequent establishment of volunteer donor registries. More than 5 million typed volunteer donors have been registered worldwide, and it is estimated that nearly 70% of white patients will have an HLA-A, -B, and -DR-matched unrelated donor. Donor-recipient mismatching results in a decrease in life-threatening acute and chronic GVHD. Furthermore, typing beyond HLA-A, -B, and -DR loci may be of further benefit, as other MHC antigens appear to have a significant impact on transplantation outcome.

More precise HLA typing has also increased the difficulty of finding a completely matched donor. T-cell deletion of MUD allografts is associated with a decrease in severe acute and chronic GVHD, although there appears to be no beneficial impact on overall survival. There is some evidence, however, that survival may be better in the recipients of MUD transplants containing higher stem cell doses. This observation has stimulated interest in the development of transplants that use higher total CD34+ cell doses—for instance, through the use of G-CSF-mobilized PBSC allografting. Whether this approach will improve the outcome of unrelated transplantations, particularly in terms of prolonging patient survival, remains to be determined. Future trials that optimize donor selection, conditioning regimens, and GVHD prophylaxis will be required to improve the outcome of MUD transplantations.

**MISMATCHED RELATED DONORS**

The availability of haploidentical (“half-matched”) related donors has led to the use of mismatched family members as an alternative source of stem cells for those patients who lack an HLA-identical sibling. The majority of patients with living family members would be expected to have a relative who could serve as a partially mismatched donor. These donors may actually have a closer histocompatibility profile than MUDs, as the shared donor haplotype is genetically identical to the patient. More than 5 million typed volunteer donors have been registered with HLA-matched related donors. Furthermore, potential family donors can usually be identified quickly and usually are more readily available than are MUDs. The number of mismatched MHC antigens in the patient is conventionally used to define the degree of mismatch and may range from three (haploidentical) to zero antigens, depending on the number of phenotypically shared antigens coming from the mismatched haplotype.

Graft rejection, GVHD, and ineffective immunity leading to fatal opportunistic infection are the major immune-mediated complications associated with HLA disparity; the greater the HLA disparity, the higher these risks. Early as well as recent trials comparing outcome in patients receiving partially mismatched related versus matched sibling donor allografts showed that engraftment, GVHD, and survival were inferior in the recipients of partially mismatched transplants. More intensified conditioning regimens have resulted in better engraftment at the expense of more regimen-related organ toxicity.

Severe GVHD exceeded 50% in early trials using unmanipulated allografts, with T-cell doses in the allograft correlating with the probability of developing severe GVHD. T-cell depletion, as in matched unrelated transplants, is associated with a significant decrease in the incidence of severe GVHD, although the incidence of graft rejection is increased. Through the use of modified conditioning regimens and more effective T-cell depletion methods, several groups have begun to report improved outcome using mismatched family donors. Henslee-Downey et al. were the first to report similar 3-year disease-free survivals in patients with lymphoblastic leukemia using partially matched related or donors versus matched sibling donors (38% vs. 37%). Subsequently, other investigators have reported regimens with modifing conditioning and T-cell depletion techniques associated with a high rate of donor engraftment and a low risk of GVHD, with long-term disease-free survivals in the range of 20% to 40%. These results are significant, as most patients treated in these trials had advanced, high-risk hematologic malignancies associated with poor transplantation outcome, even in a matched sibling setting.

Another recently explored involves the induction of donor T-cell engraftment to recipient alloantigens. This technique involves the use of culturing haploidentical donor marrow with recipient lymphocytes in the presence of CTLA-4 immunoglobulin to inhibit the “second signal” required for T-cell activation. Donor T cells in this setting do not induce GVHD in 50% of the recipients of HLA-mismatched cord blood. Neutrophil engraftment was favorably associated with a younger patient age (younger than 6 years) and weight (<20 kg) and occurred in 85% of patients receiving 37 million or more mononuclear cells per kilogram of recipient body weight. In the recipients of unrelated cord blood, neutrophil engraftment occurred in 94% of those who received 37 million or more mononuclear cells per kilogram, with only 32% of patients developing grade II or worse GVHD.

Although opportunistic infections and disease relapse remain problematic, modifications in this procedure have demonstrated that the use of full haploidentical mismatched donors can be tolerated and is a viable transplantation alternative in patients lacking matched sibling donors. The improvement in haploidentical transplants will likely lead to randomized trials comparing partially mismatched related donors to MUDs to discern which alternative stem cell source is preferable.

**NONMYELOABLATIVE ALLOGENEIC STEM CELL TRANSPLANTATION**

Allogeneic hematopoietic SCT using high-dose, myeloablative chemo/radiotherapy is associated with a high incidence of treatment-related complications and a 20% to 35% risk of transplant-related mortality. Debilitated or older patients with hematologic malignancies are at particularly high risk, thus limiting the applicability of this approach.
Potentially curative treatment modality to relatively younger patients with a good performance status. The desirable antitumor effects of dose-intensive conditioning are often offset by their substantial and potentially life-threatening toxicities. A greater understanding and appreciation of the powerful and potentially curative nature of the GVL effect led to the notion that GVL alone, without intensive cytoreductive therapy, might be sufficient to obtain long-term control of hematologic malignancies. Patients with relapsed leukemia after allogeneic transplantation whose disease is induced into remission after DLI lend the greatest credence to this concept.

Subsequent to these observations, a number of investigators began to explore the concept of using low-intensity conditioning regimens, immunosuppressive enough to permit engraftment of the donor immune system for the generation of GVL effects while sparing patients the toxicities associated with myeloablative therapy. Despite the use of low-intensity conditioning, engraftment rates have been high, and long-term remissions, induced purely through a donor immune-mediated antitumor effect, have been observed in a variety of different hematologic and nonhematologic malignancies. Importantly, regimen-related toxicity and mortality appear to be low, thus expanding eligibility for allogeneic transplantation to include older or debilitated patients, as well as allowing for exploration of graft-versus-tumor (GVT) effects in other treatment-refractory or incurable malignancies. Furthermore, the majority of late side effects attributed to myeloablative conditioning, including growth retardation, sterility, endocrinopathies, cataracts, and secondary malignancies, will likely be avoided using nonmyeloablative transplants.

**NONMYELOABLATIVE CONDITIONING REGIMENS**

Although a variety of low-intensity conditioning regimens have been explored, they are all, by definition, nonmyeloablative, as recipient hematopoietic stem cells are not eradicated, allowing for the possibility of autologous hematopoietic recovery. Two features are common to all these regimens: First, they avoid acute and chronic toxicities associated with intensive radiation therapy by using a relatively low-intensity nontoxic preparative regimen and, second, they attempt to induce sufficient host immunosuppression to allow for engraftment of the donor immune system.

The minimum amount of immunosuppression required to allow for donor engraftment is unlikely to be defined, as it depends on multiple variables, including the competence of the patient’s immune system (related to the amount and intensity of prior therapy), degree of patient-donor HLA and mHa disparity, donor immunocompetence, and the dose of T cells in the allograft. Nonetheless, a number of different conditioning regimens with variable degrees of intensity have been used successfully to establish donor engraftment with minimum toxicity, including regimens consisting of purine analogs in combination with alkylating agents, low-dose TBI alone, or thymic irradiation in combination with cyclophosphamide with or without ATG.

Based on results from canine preclinical trials, Storb et al. pioneered a novel NST approach that uses low-dose TBI (200 cGy) as well as pre- and posttransplantation immunosuppression with CSA and mycophenolate mofetil to prevent both graft rejection and GVHD. This regimen usually achieves a state of recipient-donor mixed chimerism, which can serve as a platform for the subsequent infusion of donor lymphocytes to enhance GVL effects. Although a heterogeneous population of patients has been treated with a variety of different regimens, conditioning-associated toxicity and mortality appear to be significantly lower than with conventional myeloablative approaches. Because host hematopoietic elements are not ablated, recovering myeloid cells are usually of both recipient and donor origin (mixed chimerism). This state of mixed chimerism has both beneficial and negative effects on transplantation outcome. Mixed chimerism is capable of inducing donor and recipient tolerance, thus preventing the development of acute GVHD. However, mixed chimerism also is associated with an increased risk of graft failure, and the tolerance that it induces may inhibit beneficial GVL effects. These negative aspects of mixed chimerism can be overcome by infusing donor lymphocytes, which can shift chimerism from a mixed to a complete donor type, thus avoiding tolerance and enhancing the GVL effect.

**NONMYELOABLATIVE TRANSPLANTATION TOXICITY**

Conditioning-induced toxicity is relatively mild with nonmyeloablative regimens as compared to myeloablative approaches (see Table 53.3-1). Most patients tolerate the preparative regimen well, without the occurrence of mucositis or requirement for total parenteral nutrition. VOD occurs infrequently, is usually mild, and is observed predominantly with the use of regimens that contain busulfan. Although most patients become pancytopenic, the occurrence of partial autologous hematopoietic recovery appears to shorten the overall depth and duration of neutropenia while reducing platelet and red blood cell transfusion requirements. Most trials have reported transplantation-related mortality rates in the range of 10% to 15%, which is remarkably low given the advanced age and poor performance status of the majority of these patients. Some low-intensity protocols, particularly those that use low-dose TBI alone, appear ideally suited for outpatient use.

NST is too new to make any conclusions regarding long-term complications, although it is reasonable to assume that growth retardation, sterility, and secondary malignancies will be observed with reduced frequency as compared to conventional myeloablative transplantation.

**ENGRAFTMENT AFTER NONMYELOABLATIVE STEM CELL TRANSPLANTATION**

The ability to establish engraftment of donor hematopoietic and lymphoid cells is directly related to the degree of host immunosuppression induced by the preparative regimen. Most, if not all, NST regimens result in some degree of early donor-recipient mixed chimerism. Although graft rejection occurs with a higher frequency than with myeloablative approaches, in general, more than 80% of patients can be expected to have long-term stable donor engraftment. Regimens that use low-dose TBI alone are associated with a higher incidence of graft rejection, although the addition of fludarabine appears to overcome this problem.

We evaluated the engraftment kinetics in 50 patients with hematologic and nonhematologic malignancies receiving an NST from an HLA-identical or single-locus mismatched sibling donor using a preparative regimen of cyclophosphamide (60 mg/kg × 2) and fludarabine (25 mg/m² × 5). Lineage-specific chimerism analysis using the polymerase chain reaction of minisatellite regions was performed on myeloid (CD14+ and CD15+) and T cells (CD3+) obtained weekly from peripheral blood. A unique pattern of engraftment was observed in which myeloid cells at the time of neutrophil recovery were mixed chimeric (both donor and patient), although predominantly recipient in origin, in contrast to T cells, which were also mixed chimeric but predominantly donor in origin [Fig. 53.3-4A]. By day 30, half of the patients had made the transition to full-donor T-cell chimerism, while myeloid chimerism often remained mixed [Fig. 53.3-4B]. After the withdrawal of CSA and, in some patients, after DLI, chimerism changed to a complete donor type in all cellular lineages in the majority of cases. The establishment of full-donor T-cell chimerism consistently preceded full-donor myeloid chimerism, compatible with a graft-versus-host hematopoietic effect. Forty-eight of 50 patients (96%) ultimately achieved stable donor engraftment, with only 2 (4%) experiencing graft rejection, which was followed by complete autologous hematopoietic recovery. Of note, acute GVHD and GVL effects were usually not observed until full-donor T-cell chimerism was achieved. T-cell chimerism, therefore, appears to be of central importance and can be used successfully to guide posttransplantation immune manipulation.

**GRAFT-VERSUS-HOST DISEASE**

Although mixed T-cell chimerism is associated with GVHD tolerance, withdrawal of CSA and giving DLI, usually to enhance a GVL effect, often results in a rapid
transition to full-donor T-cell chimerism and may be associated with the onset of acute GVHD. Acute GVHD appears to be the major nonrelapse life-threatening complication associated with NST. Several trials have reported grade II through IV acute GVHD rates of 30% to 50%, this outcome being lethal in up to 15% of treated patients. Older patient age, prior history of autologous transplantation, and rapid T-cell engraftment appear to be associated with an increased risk of GVHD. We observed a sixfold increase in acute GVHD in those patients who had 90% or more donor T-cell chimerism by day 14 after transplantation. The majority of NST regimes have used CSA or FK506 alone for prophylaxis of GVHD. Future strategies to decrease the incidence and severity of acute GVHD, which include the additional use of prophylactic drugs such as methotrexate or mycophenolate mofetil, or methods to deplete alloreactive T cells selectively, will likely improve the safety of these novel regimes.

**GRAFT-VERSUS-LEUKEMIA EFFECT AFTER NONMYELOABLATIVE STEM CELL TRANSPLANTATION**

GVL effects after NST have been observed in a heterogeneous group of hematologic malignancies, with some patients achieving durable remissions. To date, too few patients have been treated in any one disease category to make any generalizations regarding the antileukemic potential of this approach. However, the induction of molecular remissions in CML, CLL, and low-grade non-Hodgkin's lymphoma suggest that the GVL reactions induced after NST are at least as powerful as those after conventional BMT and will likely be of curative potential. Furthermore, complete remissions in advanced and chemotherapy-refractory diseases have been achieved in debilitated and older patients (i.e., older than 60 years) who normally would have been ineligible for a standard myeloablative transplantation due to an unacceptably high risk of treatment-related mortality.

As autologous hematopoietic recovery usually occurs, recurrent and sometimes progressive disease may be observed during the first 3 to 6 months after transplantation. The onset of the GVL effect typically is delayed from the time of transplant conditioning and usually follows the establishment of full-donor T-cell chimerism and the withdrawal of GVHD prophylaxis or DLI. Figure 53.3-5 shows the typical pattern of donor engraftment in myeloid and T-cell lineages in a 56-year-old man undergoing NST for CMML using this approach. Mixed T-cell chimerism on day 30 improved in the direction of the donor after withdrawal of CSA and a DLI of 2 × 10^6 CD3+ cells/kg. Myeloid recovery was mixed but predominantly autologous in origin. After 100% donor T-cell chimerism was established, a brief period of leukopenia was followed by a rapid increase in the percentage of donor myeloid cells, consistent with a graft-versus-host hematopoietic effect. A 20p- cytogenetic abnormality, which was observed in all bone marrow metaphases on day 60, was no longer detectable by the day 100 analysis, and the patient remains in remission more than 24 months after transplantation without ever having developed GVHD. Similar patterns of delayed disease regression have been observed in patients with CML, CLL, and Hodgkin's and non-Hodgkin's lymphomas.

![Typical pattern of donor engraftment in myeloid and T-cell lineages in a 56-year-old man undergoing nonmyeloablative stem cell transplantation for chronic myelomonocytic leukemia (CMMI). CSA, cyclosporin A; DLI, donor lymphocyte infusion.](image)

**GRAFT-VERSUS-TUMOR EFFECTS**

The low risk of transplant-related mortality with NST renders this approach appealing for the investigation of GVT effects in patients with metastatic and treatment-refractory solid tumors. In 1997, my colleagues and I initiated a pilot trial to investigate for GVT effects in patients with metastatic renal cell carcinoma and melanoma in whom conventional therapy had failed and who had an HLA-compatible sibling. We chose to investigate for GVT effects in these two malignancies owing to their highly immunogenic profiles and known sensitivity to immunomodulation-based therapy (interleukin-2 and interferon-a), in which T cells are believed to be the principle mediators of an antitumor response. None of the first eight patients with melanoma had a sustained disease response. However, several patients with advanced, treatment-refractory metastatic renal cell carcinoma have had a disease response, including three with a complete response, two of whom remain in remission longer than 2 years after transplantation. The disease regressions we observed were typically delayed in onset, occurring at a median of 4 months after transplantation, and followed the withdrawal of CSA, establishment of 100% donor T-cell chimerism and, in one patient, following a DLI, all compatible with a donor-mediated GVH effect. The results illustrate that antitumor effects induced through an allogeneic immune system may be as or more potent than strategies designed to enhance autologous antitumor immunity. They also provide the first evidence that a GVT effect alone can induce complete and clinically meaningful regression of a metastatic solid tumor. Similar trials have been initiated to investigate for GVT effects in patients with other treatment-refractory tumors.

**FUTURE DIRECTIONS FOR NONMYELOABLATIVE STEM CELL TRANSPLANTATION**

The results of these early trials have been encouraging, showing that low-intensity transplantation regimens are well tolerated with a low risk of transplant-related toxicity and mortality, even in high-risk patients. More important, the trials have shown that adequate engraftment of the donor immune system can be achieved for the generation of powerful antitumor effects, without the use of toxic myeloablative conditioning regimens. Indeed, they provide strong evidence that the GVL effect may be the primary modality, contributing to the curative potential of allogeneic hematopoietic SCT in some malignancies. Because toxicity is decreased, patient eligibility for allogeneic transplantation will likely be expanded to include older or debilitated patients who were historically ineligible for standard BMT. Furthermore, the ability to generate GVL effects resulting in complete remissions of hematologic malignancies will likely lead to prospective randomized trials comparing NST to more conventional myeloablative transplantsations. Finally, NST appears to be the ideal platform from which to investigate safety for more targeted adoptive allogeneic immunotherapeutic approaches that use tumor-specific T cells to enhance the antimalignancy effect of allogeneic lymphocytes.

**RESULTS OF CONVENTIONAL ALLOGENEIC TRANSPLANTATION FOR HEMATOLOGIC MALIGNANCIES**

Allogeneic hematopoietic SCT is potentially curative for a number of different hematologic malignancies, including acute and chronic leukemias, myelodysplastic syndromes, Hodgkin's and non-Hodgkin's lymphoma, and multiple myeloma. The indications for allogeneic SCT vary according to disease categories and are influenced by factors such as cytogenetic abnormalities, response to prior therapy, patient age and performance status, disease status (remission vs. relapsed), disease-specific prognostic factors and, most important, availability of a suitable allogeneic stem cell donor. The decision of whether to proceed with allogeneic transplantation is often difficult and controversial and ultimately is guided by the potential benefits and risks of such therapy. Diseases such as CML, curable only by allograft transplantation, are associated with an excellent posttransplantation outcome and high probability of long-term disease-free survival, justifying the risks of regimen-related toxicity. Conversely, diseases such as multiple myeloma are associated with a high risk of treatment-related mortality and disease relapse, making the decision to proceed with transplantation more difficult. Nevertheless, for the majority of patients who undergo this approach, allogeneic SCT remains the only chance of cure.

**CHRONIC MYELOGENOUS LEUKEMIA**

CML is a clonal myeloproliferative disease of hematopoietic stem cell origin, characterized by an early chronic phase of 3 to 5 years’ duration followed by an accelerated phase of 3 to 6 months, which ultimately terminates in a fatal blastic phase. Although a minority of patients have sustained cytogenetic remission of the Philadelphia chromosome [t(9;22)] after treatment with interferon-a, allogeneic SCT remains the only treatment approach with definitive curative potential. Patient age, disease status (chronic phase vs. accelerated or blastic phase), and the time interval from diagnosis to transplant (i.e., <1 year vs. >1 year) are the most powerful predictors of long-term survival following allogeneic transplantation. In general, 65% to 80% of patients with chronic-phase CML who receive a transplant can expect to be cured, in contrast to a minority (10% to 15%) who undergo transplantation in the accelerated or blastic phase. Patients with chronic-phase
CML who receive a transplant within 1 year of diagnosis have the best outcome, with long-term disease-free survivals of 75% to 80%. A study from the Fred Hutchinson Cancer Center involving 196 patients undergoing allogeneic SCT from a matched unrelated donor reported a 5-year survival of 75%, a rate that compared favorably to that institution's results using HLA-matched sibling donors.

Among hematologic malignancies, CML appears most susceptible to the GVL effect. The majority of CML patients who experience disease relapse after allogeneic SCT can expect to be induced back into remission with DLI.23,24,32,40-42 This sensitivity to GVL has led to a number of trials investigating NST as a less toxic approach for patients with chronic-phase CML. Early results using NST have been promising, with several molecular remissions having been reported.23,24 Notably, patients older than 60 years have been successfully treated with minimal conditioning-associated toxicity, an important finding given the median age at diagnosis of 65 years.23 These favorable results will expand patient eligibility for this curative modality to include the majority of older patients who are diagnosed with CML and who have a suitable donor, and will likely lead to randomized trials comparing NST with conventional myeloablative approaches.

ACUTE MYELOGENOUS LEUKEMIA

The role of allogeneic SCT in acute leukemia, alkylator conditioning regimens, and the importance of GVL is increasingly recognized.23,42-44 The majority of patients with acute leukemia, 60% to 70% eventually experience relapse, which is rarely curable with salvage chemotherapy. Factors associated with a poor outcome (high risk) include age older than 60 years, leukocyte count greater than 30,000 on presentation, and chromosomal translocations involving t(4;11), t(11;19), t(8;14), or the Philadelphia chromosome (9;22), which can be found in 15% to 30% of adult ALL cases.42,43,44

Several studies of allogeneic SCT in high-risk patients who received a transplant during CR1 have reported long-term disease-free survivals of 41% to 61%, rates considerably higher than those observed with chemotherapy alone.42,43 Allogeneic SCT usually is recommended in CR2 for patients lacking high-risk factors, as disease will be cured in some with chemotherapy alone. Furthermore, the long-term disease-free survival rate (35% to 40%) is comparable in these patients, regardless of whether they undergo transplantation in CR1 or CR2.42,43 As chemotherapy is considerably more effective in achieving durable remissions in children, allogeneic SCT is usually reserved for those who fail to be cured with primary therapy or who have Philadelphia chromosome–positive ALL.42,43

MALIGNANT LYMPHOMAS

Allogeneic SCT is the only curative therapy available for patients with myelodysplastic syndrome (MDS). In general, 30% to 50% of patients with MDS can be expected to achieve long-term disease-free survival.23,42 Factors associated with improved outcome include younger age, lower pretransplantation marrow blast percentage, shorter disease duration, and favorable cytogenetics. A retrospective trial of 131 patients with MDS undergoing allogeneic BMT reported disease-free and overall survival rates of 34% and 41%, respectively.23,42 Disease-free survival depended on pretransplantation bone marrow blast percentages, with refractory anemia/refractory anemia with ringed sideroblasts (RA/RARS), refractory anemia with excess blasts (RAEB), refractory anemia with excess blasts in transformation (RAEB-T), and secondary AML patients having disease-free survivals of 52%, 34%, 19%, and 26%, respectively.

A retrospective analysis of transplantation events in relation to the International Prognostic Scoring System cytogenetic categories showed that cytogenetic abnormalities alone were highly predictive of posttransplantation outcome. The event-free survival for good-, intermediate-, and poor-risk cytogenetic subgroups were 31%, 45%, and 6%, respectively, with corresponding relapse rates of 19%, 12%, and 82%. Improved International Prognostic Scoring System cytogenetic categories were defined as good-risk if patients had normal karyotype, -Y alone, del(5q) alone, or del(20q) alone: poor-risk if patients had abnormalities of chromosome 7 or complex cytogenetics (three or more abnormalities); and intermediate-risk if any karyotypic abnormalities were present that did not meet the criteria for good- or poor-risk. The identification of an extremely high incidence of relapse in the poor-risk group (82%) is important, as new and more effective treatment strategies should be directed specifically toward these patients.

OTHER HEMATOLOGIC MALIGNANCIES

The role of allogeneic SCT in multiple myeloma, CLL, and Hodgkin’s and non-Hodgkin’s lymphoma is less well defined than in the acute leukemias or chronic-phase CML.23,42,43,45-51 Most studies published to date have consisted of small retrospective analyses or anecdotal case reports. Nevertheless, reports of durable remissions in patients with relapsed or chemotherapy-refractory disease, often in association with GVHD or after DLI, provide strong evidence that these diseases are susceptible to a potentially curative GVL effect.

The largest series to date of patients with CLL undergoing allogeneic BMT reported a 49% disease-free survival at 27 months, with an extraordinary high treatment-related mortality of 46%. Although a number of patients with multiple myeloma have achieved long-term disease-free survival after allogeneic SCT, transplant-related mortality may be as high as 50%, thus limiting the full therapeutic potential of this approach. Regimens with reduced transplant-related toxicities, such as NST, may avoid these complications and improve disease-free survival. Indeed several studies exploring NST in diseases such as low-grade non-Hodgkin’s lymphoma, CLL, and multiple myeloma have shown early promising results, with durable complete responses being achieved in all disease categories.42,43,52,53,54

Although CLL and low-grade non-Hodgkin’s lymphoma are notorious for delayed relapses, the observation of molecular remissions raises the prospect that NST may have curative potential in these diseases.

FUTURE PROSPECTS

Allogeneic SCT remains the only curative treatment modality for a large number of patients with hematologic malignancies. Exciting advances in the field have made this therapy an integral component in the treatment of an increasing number of malignant diseases. Furthermore, an expanded understanding of the requirements for the engraftment of donor cells and of the basic immunologic mechanisms involved in GVHD and GVL reactions have greatly improved both the safety and efficacy of the procedure. The eventual identification of leukemia- and tumor-specific antigens will likely lead to more targeted allogeneic immunotherapy approaches that avoid the morbidity associated with GVHD. The discovery that GVL effects alone have curative potential for a number of different malignancies already has led to new transplantation approaches that appear destined to reduce transplant-related mortality and improve long-term outcome for patients undergoing this procedure.

CHAPTER REFERENCES

INTRODUCTION

The hematopoietic growth factors (HGFs) are a family of cytokines that regulate the proliferation, differentiation, and viability of hematopoietic progenitor cells and mature blood elements. More than 20 different cytokines have been discovered, all of which are believed to have effects on blood cell development or function, and many of these have been tested in preclinical or clinical trials in cancer patients over the last 15 years. Four HGFs—erythropoietin (EPO), granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), and interleukin-11 (IL-11)—have been approved by the U.S. Food and Drug Administration for specific uses (Table 53.4-1), and other approvals are likely in the future. Early phase I and II trials indicated that G-CSF or GM-CSF had the potential to ameliorate myelosuppression in many circumstances, and now there is abundant evidence from randomized, phase III trials that this is the case. Similarly, EPO has been shown to be an effective treatment for the anemia of cancer in some patients, and IL-11 has been shown to reduce chemotherapy-associated thrombocytopenia in some circumstances. In addition, G-CSF, GM-CSF, and other growth factors are now commonly used to induce transient mobilization of hematopoietic stem and progenitor cells into the blood to allow collection for both autologous and allogeneic stem cell transplantation. Finally, other new cytokines [such as thrombopoietin (TPO)] with well-defined effects on thrombopoiesis are being investigated in ongoing clinical trials. Overall, the ability to use HGFs therapeutically to enhance hematopoiesis has now become an important and widely used part of the treatment of certain cancers and has led to improved safety of high-dose chemotherapy and bone marrow transplantation in particular. This is still a field with many questions, however, and the cost-effectiveness of cytokine use in many areas of cancer treatment is still unknown. This chapter focuses on the four HGFs currently approved by the U.S. Food and Drug Administration for one or more applications in cancer and then summarizes the current state of clinical development of other cytokines of potential interest in cancer medicine.

OVERVIEW OF HEMATOPOIETIC GROWTH FACTORS

All the formed elements of the blood—leukocytes, erythrocytes, and platelets—are derived from multipotent stem cells found primarily in the marrow. Because the life span of blood cells is relatively short, large numbers of cells need to be replenished daily, and this daily requirement may be further increased by bleeding or acute infection. Most of the stem cells are not actively cycling, and it is thought that hematopoiesis is maintained by the activity of only a small fraction of the total stem cell pool at any given point in time. As these cells mature, however, they become progressively more committed to a single lineage, creating a series of “progenitor” cells that are actively proliferating and very sensitive to regulation by HGFs. Interestingly, recent studies have identified stem cells with hematopoietic potential in other tissues, including brain and muscle. The significance of these cells and their potential for clinical development is of considerable interest.

There has been a dramatic increase in the knowledge of the regulation of hematopoiesis as the genes for individual HGFs have been cloned and recombinant proteins produced (Table 53.4-2). The existence of HGFs has been recognized for more than 35 years but, before cloning of HGF genes, they could be studied only as partially purified “activities” secreted by activated normal cells or certain cancer cell lines. The large number of cytokines now believed to be involved in potentially regulating hematopoiesis and the complexity of that regulation were unanticipated, and the remarkable history of the development of this field has been extensively reviewed. Some factors, such as Steel factor and Flt3 ligand, appear to have effects predominantly on stem and progenitor cells and minimal effects on more mature cells. In contrast, more lineage-restricted factors, such as EPO and G-CSF, have prominent effects on progenitor cells and mature cells and minimal effects on stem cells.

TABLE 53.4-1. Major Hematopoietic Growth Factors in Clinical Use for Cancer Treatment

<table>
<thead>
<tr>
<th>Growth Factor</th>
<th>Characteristics</th>
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</thead>
<tbody>
<tr>
<td>Erythropoietin (EPO)</td>
<td>Promotes erythroid progenitor cell proliferation</td>
</tr>
<tr>
<td>Granulocyte colony-stimulating factor (G-CSF)</td>
<td>Promotes neutrophil progenitor cell proliferation</td>
</tr>
<tr>
<td>Granulocyte-macrophage colony-stimulating factor (GM-CSF)</td>
<td>Promotes myeloid and macrophage progenitor cell proliferation</td>
</tr>
<tr>
<td>Interleukin-11 (IL-11)</td>
<td>Promotes hematopoietic progenitor cell proliferation</td>
</tr>
</tbody>
</table>

TABLE 53.4-2. Selected Hematopoietic Growth Factors and Other Cytokines in Clinical Development for Applications in Cancer Therapy

<table>
<thead>
<tr>
<th>Growth Factor</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombopoietin (TPO)</td>
<td>Promotes thrombopoietic progenitor cell proliferation</td>
</tr>
<tr>
<td>Steel factor</td>
<td>Promotes hematopoietic progenitor cell proliferation</td>
</tr>
<tr>
<td>Flt3 ligand</td>
<td>Promotes hematopoietic progenitor cell proliferation</td>
</tr>
</tbody>
</table>

SECTION 53.4
Hematopoietic Growth Factors

JAMES D. GRIFFIN

INTRODUCTION

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Toxic side effects of G-CSF in humans have been generally mild. Some patients experience bone pain during administration, but fever and weight gain are rare. Hammond et al. have also shown that dogs induced to form neutralizing antiantibodies to G-CSF become profoundly neutropenic. G-CSF was initially investigated in the mouse as a factor with potent capacity to differentiate myeloid leukemia cell lines and was later purified from mouse lung–conditioned medium. Human G-CSF was purified from medium conditioned by bladder and head and neck cancer cell lines, and the gene was then cloned.

### Erythropoietin

EPO is the primary regulator of the late stages of red cell production, and both humans and mice deficient in EPO production develop severe anemia. The biology and pharmacology of EPO have been reviewed extensively.\(^1\) The EPO gene is located on human chromosome 7q11-22, and the cDNA was cloned in 1984.\(^2\) The mature protein contains 165 amino acids and has a molecular weight of 30,400 daltons. EPO is produced in the kidney in response to hypoxia or decreased oxygen-carrying capacity of the blood. The mechanism is still not completely understood, but it is clear that transcription of the EPO gene is regulated in part by a pathway that involves an oxygen-binding heme protein.

Occasional patients present with erythrocytosis secondary to either a renal tumor causing local hypoxia related to compression or, more rarely, to secretion of EPO by the tumor.

EPO binds to bone marrow cells expressing the receptor and stimulates proliferation of erythroid colony-forming cells and a subset of less mature burst-forming units. Cloning of the EPO receptor was reported in 1989.\(^3\) It was shown to be a single-chain transmembrane protein that is believed to function as either a monomer or homodimer. The receptor is a member of the HGF receptor superfamily and shares homology with the receptors for G-CSF, IL-3, IL-2, TPO, and other cytokines. Interestingly, the receptor interacts with the gp55 protein of the Friend erythroleukemia virus, and the resulting activation of the EPO receptor is involved in causing erythroleukemias of mice.\(^4\) In addition, other recent studies with the Friend erythroleukemia virus suggest that the EPO receptor may also interact with a transmembrane tyrosine kinase termed Ron/kit. Mutations in the distal end of the EPO receptor are associated with familial erythrocytosis.\(^5\) but have not yet been associated with human erythroleukemias.

The serum concentration of EPO in normal individuals is approximately 4 to 30 U/L, and the half-life of recombinant EPO administered intravenously in humans is 9 to 13 hours. Serum EPO levels reproducibly start to rise as the hematocrit drops below approximately 35% and can increase 100- to 1000-fold with severe anemia. In cancer patients, EPO treatment is indicated for chemotherapy-associated anemia not due to other causes (iron deficiency, marrow involvement with tumor, etc.) and is most likely to have benefit if the EPO level is abnormally low. Toxic effects of EPO in cancer patients are generally minimal. The hypertension and thrombotic events seen in patients with chronic renal failure treated with EPO are rarely seen in cancer patients with normal renal function. Monitoring of hematocrit is required to avoid erythrocytosis.

### Granulocyte Colony-Stimulating Factor

G-CSF (filgrastim, lenograstim) regulates the production, maturation, and function of cells of the neutrophil lineage. G-CSF was initially investigated in the mouse as a factor with potent capacity to differentiate myeloid leukemia cell lines and was later purified from mouse lung–conditioned medium. Human G-CSF was purified from medium conditioned by mouse marrow and neck cancer cell lines, and the gene was then cloned. The human gene is located on chromosome 17q11-21 and encodes a mature polypeptide of 175 amino acids with a molecular weight of 18,800 daltons. In tissue culture studies, G-CSF induces proliferation and differentiation of cells of the myeloid lineage. Knockout of the G-CSF gene in the mouse reduces severe neutropenia but has minimal effect on other lineages. Hammond et al. have also shown that dogs induced to form neutralizing antianitibodies to G-CSF become profoundly neutropenic. G-CSF may also enhance several functions of neutrophils, but the significance of this observation is unknown. Overall, it is clear that G-CSF is critically involved in regulating neutrophil production. G-CSF is produced by many different cell types, and expression of G-CSF can be rapidly induced by exposure of epithelial cells, macrophages, endothelial cells, and narrow stromal cells to inflammatory stimuli, particularly endotoxin. Unlike many other hematopoietins, there is readily detectable G-CSF in the serum of normal individuals, with a typical range of 20 to 100 pg/ml. The serum level varies inversely with neutrophil concentration in the blood, and in bacteremic, neutropenic patients, serum levels can exceed 2000 pg/ml.

The receptor for G-CSF is widely expressed, not only on myeloid lineage cells but on endothelial cells and epithelial cancer cell lines. The function of nonhematopoietic G-CSF receptors is not clear, however. The receptor for G-CSF is a member of the cytokine receptor superfamily and is composed of a single known transmembrane protein of approximately 100 KD molecular weight. Mutations in the cytoplasmic domain of the receptor have recently been demonstrated in a small number of patients with congenital neutropenia and acute myeloblastic leukemia. The mutations truncate the receptor, possibly removing a domain involved in the differentiation-inducing function of G-CSF. Function of the truncated receptor in murine models suggests that the receptor may be activated to an excessive level by G-CSF.

Administration of G-CSF to humans results in a dose-dependent increase in circulating neutrophils accompanied by expansion of the myeloid components in the marrow and accelerated production of neutrophils due to reduced transit time from stem cell to mature neutrophil. The fraction of myeloid progenitor cells in S-phase in the marrow is increased, and there is some suggestion that G-CSF enhances entry of quiescent stem and progenitor cells into the cell cycle. Neutrophils produced in response to G-CSF therapy have been shown to be functionally normal in terms of standard assays for phagocytosis and activation of the respiratory burst and further appear to have normal function in vivo. Marrow aspirates performed on patients receiving G-CSF or other myeloid growth factors may show a striking left shift, and circulating neutrophils have interesting morphologic changes consistent with activation, including Döhle inclusion bodies, toxic granulation, and an increase in band forms. The elimination half-life of G-CSF in the serum is in the range of 1.3 to 4.2 hours but appears to vary with neutrophil mass, suggesting that neutrophils may contribute to metabolizing the cytokine.

Toxic side effects of G-CSF in humans have been generally mild. Some patients experience bone pain during administration, but fever and weight gain are rare. Chronic administration of G-CSF has been associated with benign splenomegaly, presumably due to extramedullary hematopoiesis. Bone scan abnormalities have also been reported, including an apparent “flare” of metastatic bone lesions and increased uptake in the axial skeleton or juxtaarticular regions. In many patients, there is an acute response to intravenous injections of G-CSF characterized by abrupt, but transient, neutropenia. Occasionally, patients will have transient dyspnea
and pulmonary infiltrates on chest radiography. In patients with underlying severe pulmonary disease, these effects can be clinically significant. The acute neutropenia is believed to be due to up-regulation of neutrophil adhesion receptors followed by either intravascular aggregation or margination, and is generally not seen with subcutaneous administration. In patients with normal marrow function, prolonged administration of G-CSF can lead to very high neutrophil counts, and it is recommended that in most cases, G-CSF should be discontinued or dose-reduced when the neutrophil count exceeds 10,000 cells/mL. Once G-CSF is discontinued, the absolute neutrophil count typically falls by approximately 50% per day and will return to baseline in 4 to 8 days. Careful studies in normal volunteers have also shown that some alterations of blood chemistries are common but of no apparent clinical consequence.

GRANULOCYTE-MACROPHAGE COLONY-STIMULATING FACTOR

GM-CSF (sargramostim, molgramostim) is a potent growth factor for the myeloid lineage in tissue culture and was cloned by Wong et al. GM-CSF is a glycoprotein with an approximately molecular weight of 22,000 daltons, and the gene has been localized to chromosome 5q31 in close proximity to the gene for IL-3. GM-CSF can be produced by many cells in the body, particularly by activated T cells. Recombinant or purified natural GM-CSF stimulates granulocyte-macrophage and eosinophil colony formation and cooperates with EPO to stimulate growth of erythroid bursts. GM-CSF also stimulates the activity of many neutrophil functions and primes these cells to respond more vigorously to other stimuli. Changes in expression of neutrophil adhesion molecules are particularly prominent, including up-regulation of the beta-2 integrin CD11/CD18 both in vitro and in vivo.

A mouse in which the GM-CSF gene has been knocked out does not have demonstrable defects in hematopoiesis but develops a severe lung disorder similar to pulmonary alveolar proteinosis. Interest has been shown to have defects in granulocyte, function, or both. The receptor for GM-CSF has been cloned from the lung lining cells of the beta chain of the receptor for GM-CSF. Receptors for GM-CSF are normally found on both hematopoietic and nonhematopoietic cells, including endothelial cells and other tumor cell lines, such as melanoma and lung cancer cells. The function of these receptors, if any, on nonhematopoietic cells is unclear. The receptor is a heterodimer, composed of a ligand-binding alpha chain and a beta chain necessary for high-affinity binding and signal transduction. The alpha chain uniquely binds GM-CSF, but the same beta chain is also used by the receptors for IL-3 and -5.

Administration of GM-CSF to humans results in a dose-dependent increase in blood neutrophils, eosinophils and, to a lesser extent, macroglobulins and sometimes lymphocytes. This is accompanied by a dramatic left shift in the myeloid series in the marrow. There is no significant effect on the red cell or platelet lineages. The toxic effects of GM-CSF have been evaluated extensively. If given intravenously in particular, the first dose of GM-CSF may be accompanied by acute and self-limited neutropenia thought to be due to up-regulation of adhesion receptors on neutrophils. Occasional patients may experience brief dyspnea. Many patients experience a low-grade fever, myalgias, and fatigue. At high doses, weight gain, pericarditis, pleuritis, and a capillary leak syndrome may develop, but this is rare at doses in current use. The activities and toxicities of GM-CSF and G-CSF have been directly compared in several studies. In a randomized study after autologous stem cell transplantation for breast cancer, the efficacy and toxicities of the two factors were equivalent.

There are several formulations of recombinant GM-CSF available, including yeast-derived (sargramostim) and Escherichia coli-derived (molgramostim) versions. At present, these formulations of GM-CSF have been shown to have similar beneficial effects. Sargramostim is glycosylated and therefore has a lower specific activity than Molgramostim (because of its higher molecular weight). Manufacturer's directions should be read carefully when changing between formulations of GM-CSF. The recommended dosing for sargramostim is 250 mg/m²/day in patients receiving chemotherapy. Subcutaneous administration is generally preferred over short-term intravenous administration, due to reduced toxicity and equivalent efficacy. However, if clinically indicated, intravenous administration of GM-CSF is acceptable.

CLINICAL APPLICATIONS OF HEMATOPOIETIC GROWTH FACTORS IN CANCER THERAPY

TREATMENT OF ANEMIA IN CANCER PATIENTS

Pathophysiology

Anemia in cancer patients can occur and may contribute significantly to quality of life. Anemia can be multifactorial in the cancer patient and can be caused by blood loss, iron or vitamin deficiency, chemotherapy, radiation to the marrow, stem cell damage, hemolysis, hypersplenism, drug toxicity, or tumor involvement of the marrow. An example known as anemia of cancer has been described but may be multifactorial and is likely related to anemia of chronic disease. In both anemias, EPO production is inadequate for the degree of anemia. There may also be an impaired response to EPO by marrow progenitor cells. Stem cell depletion may be more common than generally appreciated because of increasing use of higher doses and repeated courses of chemotherapy and radiation. Radiation involving the pelvis or spine is particularly problematic because of the large volume of marrow in those bones.

Clinical Trials with Erythropoietin

Use of EPO in anemia associated with cancer has been extensively investigated. Trials have been conducted in patients with anemia due to marrow involvement with lymphoproliferative disorders, in those with myelodysplastic syndromes (MDSs) or solid tumors; in those developing anemia after chemotherapy, autologous transplantation, allogeneic transplantation, or radiation therapy; and in those with anemia of cancer. The rates of response, generally defined as an increase in hemoglobin or a decrease in transfusion requirements (or both), are fairly high in most groups of patients, typically in the range of 50%.

Lack of response correlates with high pretreatment serum level of endogenous EPO. Patients who have an increase in hemoglobin of more than 0.5 g/dL within 2 weeks have a high likelihood of a sustained response. The benefit of EPO treatment with cyclical chemotherapy has been confirmed in several randomized, placebo-controlled multicenter trials, and response has been associated with improved performance status and quality of life. However, despite the high response rate and the apparent reduction in transfusions, EPO therapy is expensive, and careful selection of patients most likely to benefit is warranted.

Subcutaneous EPO administration three times weekly appears to be at least as effective as daily intravenous administration. Higher doses are not clearly better than lower doses, but there is a threshold effect, and intravenous doses less than 100 U/kg and subcutaneous doses less than 50 U/kg may be associated with lower response rates. A reasonable approach would be 50 to 150 U/kg three times weekly by subcutaneous injection, which could be increased to 300 U/kg after 6 weeks without response. Interestingly, late responses are fairly common, and nine weeks of therapy or more may be required in some responding patients. Since many patients fail to respond even to higher levels of EPO, there has been considerable interest in predicting early in the course of treatment which patients are not likely to respond. Several algorithms have been generated and suggest that failure to increase hemoglobin by more than 0.5 g/dL or serum ferritin by more than 400 ng/mL after 2 weeks of treatment predicts for failure. Iron deficiency will prevent response to EPO and should be considered in selected nonresponsive patients.

Finally, most studies so far have involved concurrent administration of EPO with chemotherapy. Other schedules in which EPO is given before or at the end of chemotherapy are being investigated.

CIPLATIN -ASSOCIATED ANEMIA

Approximately 40% of patients receiving cisplatin chemotherapy develop anemia, and many will require transfusion. Studies of EPO administration to treat cisplatin-induced anemia have generally been positive, even in elderly patients. Henry and Abels performed three randomized double-blind, placebo-controlled trials of EPO for anemic cancer patients not receiving concomitant chemotherapy. Patients receiving chemotherapy that did not include cisplatin, and patients receiving cisplatin-containing chemotherapy. Patients not receiving chemotherapy received 100 U/kg three times weekly, while those on chemotherapy received 150 U/kg three times weekly. Overall, the trials involved 413 patients. Patients receiving EPO in all three trials had a statistically significant increase in hematocrit as compared to placebo-treated patients. Quality of life improved significantly for EPO-treated patients, with an overall response rate of approximately 50% in all three groups. Similar results were reported by Cascinu et al., who performed a randomized, double-blind trial with EPO versus placebo in 100 patients with cisplatin-associated anemia (hemoglobin <90 g/L), administering EPO at 100 U/kg subcutaneously three times weekly. After 9 weeks of therapy, the mean hemoglobin levels of the EPO-treated group were statistically different from placebo patients: EPO patients went from a baseline of 86.3 ± 6.2 g/dL to 105.1 ± 9.4 g/dL, while placebo patients went from a baseline of 87.3 ± 5.9 g/dL to 91.2 ± 7.1 g/dL, at 9 weeks. Also, only 20% of EPO-treated patients required blood transfusion versus 56% of placebo-treated patients. No significant side effects of EPO treatment were encountered. Another multicenter, double-blind, placebo-controlled trial was conducted by Case et al., who randomly assigned 153 anemic cancer patients receiving cisplatin chemotherapy to EPO, 150 U/kg three times weekly, or placebo. EPO-treated patients had a statistically significant increase in hematocrit and a trend toward lower transfusion requirements. Again, no significant side effects were encountered. Raman et al. randomly chose 122 ovarian cancer patients receiving platinum-based chemotherapy to EPO or placebo or control groups, and demonstrated a significant reduction in transfusion requirement. Overall, these multiple, randomized, controlled trials indicate that EPO is safe and effective for therapy of both chemotherapy-associated and non–chemotherapy-associated chronic anemias in patients with solid tumors. Treatment reductions need for transfusion and improves quality of life for many patients. Recently, EPO therapy in children receiving cisplatin-based therapy has also been shown to
reduce the need for transfusions. 82

ANEMIAS ASSOCIATED WITH MYELODYSPLASTIC SYNDROMES. The role of EPO in treating anemia associated with hematologic malignancies is somewhat less clear, particularly for the anemia of MDS. Most studies reported to date are uncontrolled and have included only small numbers of patients. 15 33 24 56 18 20 171 and 39 The response rates tend to be more than 25%, although a few patients will respond to higher doses of EPO. A metaanalysis of 205 patients with an MDS from 17 different studies (70) reported an overall response rate of only 7.5%, with a particularly low response rate of EPO alone in patients with refractory anemia with ringed sideroblasts. Factors that predicted for a low response rate were duration of anemia, high serum EPO, and refractory anemia with ringed sideroblasts. Several studies have looked at sequential or combined use of a myeloid growth factor with EPO, 132 133 134 and 131 but responses are not clearly higher with the doses and schedules studied so far. As is the case for the anemia of cancer, low EPO responses may be observed, 135 necessitating long courses of therapy in clinical trials. At present, EPO appears to be more cost-effective than warfarin for all number of patients with MDS, mainly patients with iron-requiring anemia, with EPO levels and minimal transfusion requirement. In recent studies, the combined use of EPO with G-CSF has been encougered, with a higher fraction of patients responding to the combination. 136 137

BONE MARROW TRANSPLANTATION. The available data suggest that EPO treatment may be useful for treatment of anemia associated with allogeneic bone marrow transplantation. EPO has been used successfully as an adjunct to autologous transplantation. 138 139 Biggs et al. 72 gave EPO (300 U/kg intravenously three times weekly) or placebo to 91 patients undergoing autologous transplantation. There was no reduction in red blood cell or platelet transfusion requirement and no reduction in hospital stay. 73 Link et al. 139 randomly selected 107 patients undergoing autologous transplantation to EPO (150 U/kg/d by continuous intravenous infusion) or placebo until patients reached 7 days of transfusion independence or day 41. 140 The time to transfusion independence was reduced by EPO from 27 days to 19 days, but the number of transfusions required in the pretransplantation period was similar. EPO-treated patients had a somewhat smaller transfusion requirement from days 42 to 100. The same authors conducted a randomized trial of identical design with 57 patients undergoing autologous transplantation. 137 No difference in transfusion requirement was observed. Chao et al. 141 conducted a placebo-controlled trial of EPO (600 U/kg three times weekly) starting 3 weeks before autologous bone marrow transplantation in 35 patients with lymphoma. 142 All patients also received G-CSF after marrow reinfusion. No differences were observed in transfusion requirement or hematopoietic recovery. Similar results were reported when EPO was combined with GM-CSF in a nonrandomized study of autologous marrow transplantation with historical controls. 143 However, other recent studies have suggested a benefit in combining EPO with G-CSF after transplantation. 144 Another potential use of EPO is in the treatment of late-onset anemia after transplantation, concerning which encouraging pilot studies have been presented. 145 Overall, EPO has been of modest benefit in the autologous marrow transplantation setting.

Overall, EPO has an important role in the therapy of anemia in some cancer patients. In the individual cancer patient, the clinician needs to look carefully for treatable causes of anemia, such as iron deficiency or blood loss and to consider the underlying illness and other factors, such as the serum EPO level, to determine whether a course of EPO treatment is warranted.

REDUCTION OF CHEMOTHERAPY-ASSOCIATED NEUTROPENIA

Neutropenia and infection are major causes of morbidity and mortality in cancer patients and are dose-limiting for many types of chemotherapy. It is standard practice to treat all neutropenic, febrile patients with broad-spectrum antibiotics, even though many patients do not have documented infections. This adversely affects quality of life, increases hospital costs, and often results in reduction of chemotherapy doses for subsequent cycles. Reducing the incidence of febrile neutropenia and infection are major goals of CSF therapy in this setting.

GRANULOCYTE COLONY-STIMULATING FACTOR. G-CSF has been extensively investigated in clinical trials as an adjunct to cancer chemotherapy, and its use in this setting has been extensively reviewed. 17 146 147 and 148 The initial phase I and phase II studies in bladder cancer and small cell lung cancer patients established that G-CSF administration by either subcutaneous or intravenous routes caused a dramatic, dose-dependent increase in blood neutrophil counts. Data from numerous phase I and phase II studies predicted that administration of G-CSF after standard-dose, myelosuppressive chemotherapy would shorten the duration of neutropenia, but it was not clear from these early trials whether this would translate into clinical benefit. The efficacy of G-CSF has now been established in a series of randomized, controlled clinical trials in which the chemotherapy was sufficient to cause febrile neutropenia in more than 40% of the control group. A pivotal trial was conducted by Crawford et al., 149 who randomly chose patients with small cell lung cancer to receive G-CSF or placebo after a myelosuppressive regimen containing cyclophosphamide, doxorubicin, and etoposide (CAE). The incidence of febrile neutropenia was significantly reduced in patients receiving G-CSF. Further, length of hospital stay, incidence of confirmed infections, and days of antibiotic use were reduced by approximately 50%. The results of these studies have been confirmed by several additional randomized, controlled phase III studies (small cell lung cancer patients receiving CAE chemotherapy 150; non-Hodgkin's lymphoma patients receiving vincristine, doxorubicin, prednisolone, etoposide, cyclophosphamide, and bleomycin 151; and patients with various types of cancer receiving several different chemotherapy regimens 152). In none of these randomized studies was there a clear difference in mortality, tumor response rate, or survival. Thus, despite the fact that some epithelial tumor cells express G-CSF receptors, there does not appear to be any adverse effect of G-CSF on tumor growth when given with chemotherapy. In these randomized studies, the toxicity of G-CSF has been minimal and was generally limited to medullary bone pain that can usually be relieved with analgesics.

The timing of G-CSF after chemotherapy has been investigated in patients receiving melphalan (25 mg/m 2). 153 Delaying administration to 8 days after completion of chemotherapy appeared to be somewhat less effective than immediate administration, and it is now general practice to start G-CSF 24 to 48 hours after completing chemotherapy administration, typically continuing until the neutrophil count has recovered to 10,000/mL. However, administration of G-CSF for a defined period of only 7 days had benefit. 154 Also, there is considerable interest in evaluating G-CSF schedules with lower doses than the standard 5 mg/kg/d. In a randomized trial, Toner et al. 155 found that 2 mg/kg/d was as effective as 5 mg/kg/d in reducing the duration and severity of chemotherapy-related neutropenia. Also, shorter courses of G-CSF therapy are being investigated. 156

GRANULOCYTE-MACROPHAGE COLONY-STIMULATING FACTOR. Administration of GM-CSF after standard-dose chemotherapy has also been extensively evaluated. In phase I and phase II studies where GM-CSF was administered in alternate cycles, shortening of the duration of neutropenia has been observed. 157 In larger, randomized, placebo-controlled studies, however, benefit has in some cases been limited to subsets of patients. 158 159 and 160 In one randomized study in patients with small cell lung cancer receiving CAE chemotherapy, GM-CSF reduced the duration of neutropenia but not the incidence of febrile neutropenia, days in hospital, or antibiotic use. Similarly, in a randomized trial of GM-CSF in patients with germ cell cancer, GM-CSF reduced the duration of neutropenia but not the rate of febrile neutropenia. There are very few studies in which the activities of GM-CSF and G-CSF have been directly compared. In one randomized study comparing these two growth factors after cyclophosphamide (7 g/m 2), patients treated with G-CSF recovered neutrophils slightly more rapidly, but patients treated with GM-CSF recovered platelets more rapidly; overall, both GM-CSF and G-CSF were thought to be effective. 161

Concurrent Administration of Growth Factors with Chemotherapy or Radiation Therapy

Although the number of relevant studies is small, there is concern that simultaneous administration of GM-CSF or G-CSF with chemotherapy or radiation may lead to sequential administrations that are not as useful as an adjunct to chemotherapy alone. In a randomized study of 142 patients with breast cancer, GM-CSF had more thrombocytopenia, more toxic deaths, more antibiotic use, and longer hospital stays. 162 Similarly, patients with non-small cell lung cancer given G-CSF with cisplatin, etoposide, and radiation therapy had worse thrombocytopenia than controls. Concern has also been raised about continuing G-CSF up to less than 48 hours before the next cycle of chemotherapy. In contrast, concurrent administration of G-CSF with weekly cycles of dose-intensive vincristine did not lead to an apparent increase in myelosuppression. 163 However, until more information is available, concurrent administration of myelosuppressive chemotherapy with growth factors that should remain investigational, and the special situation where both chemotherapy and radiation therapy are given concurrently with a growth factor should be avoided.
Treatment of Febrile Neutropenia

Although CSFs have been shown to reduce the incidence of febrile neutropenia in patients receiving myelosuppressive chemotherapy, it is clear that most patients receiving standard types of chemotherapy regimens will not develop febrile neutropenia or infection and would, therefore, not benefit from CSF administration. Since CSFs are expensive, are inconvenient for patients, and may have some toxic effects, there is increasing interest in better defining who is most likely to benefit so as to restrict use to appropriate patients. The American Society of Clinical Oncology (ASCO) generated a set of guidelines based on a thorough evidence-based analysis of published literature through 1997, and concluded that use of CSFs in chemotherapy sessions where the incidence of febrile neutropenia was expected to be less than 40% was not likely to be cost-effective. When less myelosuppressive chemotherapy was planned, CSF administration was recommended only for individual patients with high-risk factors, such as decreased marrow reserve, or those who have had a previous episode of febrile neutropenia with the same chemotherapy regimen. In many institutions, it is now common practice to withhold CSFs until a patient has had an episode of febrile neutropenia or infection and then to initiate CSF prophylaxis with the next cycle. The alternative to this approach is to dose-reduce or delay chemotherapy. For many situations where there is no firm evidence that dose or dose intensity are valuable, this is a very reasonable alternative to CSFs. Enthusiasm for use of a CSF should be highest for those tumors where it is clear that there is value in maintaining maximum scheduled chemotherapy dose with respect to tumor response rate, quality of life, or survival. The ASCO guideline authors did conclude that some “high-risk” patients could be reasonable candidates for CSF therapy before occurrence of an episode of febrile neutropenia. Such patients would include those with reduced marrow function (due to prior pelvic radiation therapy, prior extensive chemotherapy, or marrow involvement with tumor); those with preexisting neutropenia for any reason; those with any other preexisting immune dysfunction; those with active infection; and those with a documented previous episode of chemotherapy-induced febrile neutropenia or infection. A summary of the ASCO guidelines is shown in Table 53.4-3.

There have been a number of studies indicating that either G-CSF or GM-CSF can improve the ability to maintain dose intensity in multicycle regimens. In a 1993 study, G-CSF treatment led to an 8% increase in dose intensity of CAE chemotherapy as compared to placebo in patients with small cell lung cancer. There is experimental evidence for a steep dose-response curve for many chemotherapy agents, and this has generated considerable interest in using CSFs to facilitate administration of higher doses of chemotherapy drugs where dose is limited primarily by myelosuppression. A variety of phase I trials have been reported in which the possibility that use of GM-CSF or G-CSF would allow escalation of doses of single chemotherapy drugs or multiantigen chemotherapy, but placebo-controlled, randomized studies are lacking. The reported phase I studies suggest that escalation of chemotherapy drug dose to levels higher than “standard” has often been possible. However, this approach overall has had limited success, in part due to the fact that thrombocytopenia and nonhematologic side effects often emerge quickly as dose-limiting toxicities. For example, G-CSF was used to investigate accelerated delivery of doxorubicin, 50 mg/m² × 2; etoposide, 120 mg/m² × 3; and ifosfamide, 2 g/m² given every 14 days. Optimal on-time administration was feasible in 66% of patients for three courses but feasible for only 23% for six courses. Twenty-two of 48 patients were withdrawn from the study, including 12 patients with sepsis (4 fatal) or grade 4 thrombocytopenia. Overall, dose-intensity was 1.8 times higher than when the same regimen was used at a 3-week interval. In a randomized study in extensive small cell carcinoma of the lung, it was not possible to increase dose significantly with the addition of GM-CSF. However, in a study of breast cancer patients receiving docetaxel and mitoxantrone, G-CSF allowed a significant increase in maximum tolerated dose of both drugs.

One of the inevitable problems faced by authors of guidelines is in defining what constitutes a benefit. GM-CSF and G-CSF can reduce the incidence of febrile neutropenia in aggressive regimens. When viewed as supportive therapy, the benefits of GM-CSF or G-CSF in this situation are clear. However, the larger question of whether the entire treatment program of aggressive chemotherapy with growth factor (or stem cell) support has led to a clinically significant benefit for the patient as compared to standard treatment has often not been addressed. Ultimately, the clinical indications for use of HGFs will need to be linked to treatment plans where high-dose therapy results in improved quality of life or prolonged survival.

An alternative to prophylactic use of G-CSF or GM-CSF after chemotherapy is administration of a CSF to patients who develop febrile neutropenia in an effort to shorten hospitalization, reduce antibiotic use, and improve outcome. In the largest randomized study so far, 218 patients with febrile neutropenia were randomly assigned to receive G-CSF or placebo along with antibiotics. G-CSF-treated patients had 1 day less neutropenia, but duration of fever and hospital stay was not reduced. Similarly, GM-CSF failed to reduce significantly median duration of fever or hospital stay in patients with febrile neutropenia in two trials. However, in patients with tissue infections, the addition of GM-CSF to antibiotics significantly improved outcome. Of 121 patients randomly chosen to receive G-CSF, GM-CSF, or placebo, CSF-treated patients had significantly shorter neutropenia, fever, hospital stay, and overall hospital costs. Similarly, in a placebo-controlled study in children, both GM-CSF and G-CSF significantly reduced hospital stay, antibiotic use, and duration of neutropenia. In 134 adult cancer patients with febrile neutropenia, GM-CSF treatment reduced duration of neutropenia but not days of hospital stay or cost. It may be possible to identify groups of patients in whom GM-CSF is most likely to have benefit. Overall, with both positive and negative studies, the indications for CSFs in febrile neutropenia remain unknown, and additional studies are warranted, particularly emphasizing both cost and quality-of-life issues. At present, the benefits of a CSF to low-risk patients are unclear. In contrast, some high-risk neutropenic patients with documented infections are candidates for CSF treatment, particularly those with pneumonia, prolonged neutropenia, or fungal infections. There is no current indication for CSF administration to afebrile neutropenic patients.

### TABLE 53.4-3. Summary of American Society of Clinical Oncology Guidelines for Administration of Granulocyte Colony-Stimulating Factor and Granulocyte-Macrophage Colony-Stimulating Factor

<table>
<thead>
<tr>
<th>CSF Type</th>
<th>Indications</th>
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<tbody>
<tr>
<td>G-CSF</td>
<td>Prophylaxis in myelosuppressive chemotherapy.</td>
</tr>
<tr>
<td>GM-CSF</td>
<td>Prophylaxis in myelosuppressive chemotherapy.</td>
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#### INCREASE OF CHEMOTHERAPY DOSE INTENSITY

##### Dose Escalation

There is experimental evidence for a steep dose-response curve for many chemotherapy agents, and this has generated considerable interest in using CSFs to facilitate administration of higher doses of chemotherapy drugs where dose is limited primarily by myelosuppression. A variety of phase I trials have been reported in which the possibility that use of GM-CSF or G-CSF would allow escalation of doses of single chemotherapy drugs or multiantigen chemotherapy, but placebo-controlled, randomized studies are lacking. The reported phase I studies suggest that escalation of chemotherapy drug dose to levels higher than “standard” has often been possible. However, this approach overall has had limited success, in part due to the fact that thrombocytopenia and nonhematologic side effects often emerge quickly as dose-limiting toxicities. For example, G-CSF was used to investigate accelerated delivery of doxorubicin, 50 mg/m² × 2; etoposide, 120 mg/m² × 3; and ifosfamide, 2 g/m² given every 14 days. Optimal on-time administration was feasible in 66% of patients for three courses but feasible for only 23% for six courses. Twenty-two of 48 patients were withdrawn from the study, including 12 patients with sepsis (4 fatal) or grade 4 thrombocytopenia. Overall, dose-intensity was 1.8 times higher than when the same regimen was used at a 3-week interval. In a randomized study in extensive small cell carcinoma of the lung, it was not possible to increase dose significantly with the addition of GM-CSF. However, in a study of breast cancer patients receiving docetaxel and mitoxantrone, G-CSF allowed a significant increase in maximum tolerated dose of both drugs.

##### Maintenance of Dose Intensity

There have been a number of studies indicating that either G-CSF or GM-CSF can improve the ability to maintain dose intensity in multicycle regimens. In a randomized study, Pettengell et al. compared G-CSF to placebo in patients with lymphoma receiving vincristine, doxorubicin (Adriamycin), prednisone, VP-16, and bleomycin chemotherapy and found a significant reduction of treatment delays related to myelosuppression and an overall increase in dose intensity of 13%. Similarly, G-CSF treatment led to an 8% increase in dose intensity of CAE chemotherapy as compared to placebo in patients with small cell lung cancer. However, it has been difficult to demonstrate so far that use of a CSF for maintenance of dose intensity in most standard chemotherapy regimens provides a significant advantage in terms of response or disease-free survival. Overall, despite the attractiveness of the concept, use of CSFs to permit dose escalation of chemotherapy (without stem cell rescue) remains a research question. For individual regimens in which the expected incidence of treatment delay or dose reduction is high (i.e., >40%) and in which it is thought that dose intensity is critical, use of a CSF or GM-CSF is likely to improve on-time, full-dose delivery. The value of dose maintenance will need to be established, however, by prospective, randomized trials in each tumor type.

#### ADJUNCTS TO AUTOLOGOUS OR ALLOGENEIC TRANSPLANTATION

##### Acceleration of Hematopoietic Reconstitution after Autologous or Allogeneic Transplantation

GM-CSF and G-CSF have been extensively investigated as adjuncts to autologous and allogeneic stem cell transplantation. Both GM-CSF and G-CSF have been shown in randomized, placebo-controlled trials to reduce the period of neutropenia after autologous bone marrow transplantation.
In some, but not all, of these studies, hospital stay, antibiotic use, infections, or platelet transfusions were also reduced. There has been no evidence of reduced mortality or increase in tumor response rates. In studies with autologous, mobilized blood stem cells, G-CSF also reduces the duration of neutropenia, but the overall impact on the transplant procedure may be less than when marrow stem cells are used for the transplantation. Interestingly, administration of G-CSF after blood stem cell autologous transplant can be delayed for several days without loss of efficacy. In children, the use of G-CSF after autologous blood transplantation is controversial. In studies with aleukemic marrow transplant, addition of a CSF tended to reduce neutropenia, but infection rate and hospital stay have not been consistently reduced.

The potential use of growth factors for treatment of graft failure or delayed engraftment after either autologous or allogeneic transplantation has been explored to a limited extent, and results are encouraging for both GM-CSF and G-CSF. It is clear that while not all patients will respond, neutrophil counts can be rapidly increased in many cases. Combining GM-CSF and G-CSF in a sequential manner did not improve results over GM-CSF alone. In many cases, transplantation of growth factor–mobilized blood stem cells has been of great value.

**Mobilization of Peripheral Blood Progenitor Cells by Hematopoietic Growth Factors**

One of the most remarkable effects of G-CSF and GM-CSF is transient mobilization of hematopoietic progenitor and stem cells into the peripheral blood. This unexpected phenomenon was first noted during early phase studies with GM-CSF and G-CSF and has now been observed with several other cytokines, such as IL-3 and even EPO. The effects of either GM-CSF or G-CSF appear to be independent and additive to the effects of myelosuppressive chemotherapy and, in some circumstances, mobilization with growth factor is as good as with a combination of growth factor and cyclophosphamide. The concentration of progenitor cells in the blood of normal individuals is too low for routine harvesting of these cells practical. GM-CSF or G-CSF increases progenitor cell concentration approximately tenfold and, when administered after some types of chemotherapy, such as high-dose cyclophosphamide, the increase in blood progenitor cell concentration can be 100-fold or more. However, interpatient variability is substantial, and mobilization is generally reduced in patients with extensive prior exposure to chemotherapy or radiation, particularly to the pelvis. Nonetheless, GM-CSF–mobilized or G-CSF–mobilized progenitor cells can be collected from most cancer patients by leukapheresis in sufficient quantity to replace marrow harvests for autologous transplantation protocols. The mobilized cells may be more immature than the progenitor that are resident in the blood of untreated individuals. Patients receiving peripheral blood progenitor cells tend to reconstitute earlier and to require fewer platelet transfusions than patients receiving autologous marrow. As a result, using GM-CSF or G-CSF to assist in mobilizing progenitor cells has become a standard practice in autologous transplantation protocols for many different tumors. GM-CSF–mobilized or GM-CSF–mobilized peripheral blood progenitor cells also offer advantages in allogeneic transplantation. In this situation, no chemotherapy is administered, but collection of adequate amounts of progenitor cells with several episodes of leukapheresis is well tolerated by donors. Reconstitution is prompt and durable, and definitive results of a randomized trial comparing autologous marrow with blood stem cells favors the blood source. Recent studies suggest that combinations of cytokines may be more effective than single cytokines. Writer et al. compared the mobilizing effects of GM-CSF and G-CSF, either alone or in various combinations, including adding G-CSF 5 days after GM-CSF and adding GM-CSF 7 days after G-CSF. When used individually, GM-CSF and G-CSF administration resulted in mobilization of approximately the same number of progenitor cells, approximately a 35-fold increase over pretreatment values. Administration of G-CSF to patients already receiving GM-CSF resulted in an increase to approximately 80-fold over baseline. Interestingly, the combination of CSF and stem cell factor may have particularly good ability to mobilize stem cells, and a number of studies are ongoing with this combination. Thus, cytokine combinations may be more efficacious than single cytokines for mobilization, and other combinations and schedules should be tested.

Most studies using cytokine-mobilized peripheral blood progenitor cells have also given G-CSF or GM-CSF after transplant to accelerate reconstitution. This approach seems reasonable at present in autologous transplantation, but additional studies are needed in allogeneic transplants of blood stem cells. The hematopoietic reconstitution observed after peripheral blood progenitor cell transplantations may be sufficiently fast so that the cost-effectiveness of G-CSF or GM-CSF will need to be carefully evaluated.

**Ex Vivo Expansion of Hematopoietic Progenitor Cells**

One area of active research is the potential use of growth factors to permit ex vivo expansion of either marrow or blood stem cells. When partially purified stem cells are cultured with mixtures of growth factors, typically containing Steel factor and a variety of HGFs, substantial expansion of progenitor cells has been observed. Hematopoietic progenitor cells expand in response to a number of factors and there is the potential that there will not be enough true hematopoietic stem cells to effect long-term permanent reconstitution if these expanded populations are used in transplantation settings. It is possible that there are yet unknown cytokines that will induce stem cell proliferation while inhibiting differentiation, and such cytokines might be ideal for this process. Alternatively, expanded progenitor cells may have some uses, even if the stem cell content is decreased. For example, progenitor cells may be useful to accelerate hematopoietic recovery after myelosuppressive, but not myeloablative, chemotherapy regimens.

**TREATMENT OF LEUKEMIAS**

**Acute Myelogenous Leukemia**

Infected related to neutropenia remains a major cause of morbidity and mortality during all phases of the treatment of acute myelogenous leukemia (AML), and any reduction in chemotherapy- or disease-associated neutropenia could be beneficial. The use of GM-CSF and G-CSF in AML therapy has been approached with justifiable caution, however, since both of these cytokines are excellent growth factors for leukemia cells in vitro, and there remains concern that these factors could either accelerate leukemic cell growth, reduce chemotherapy response, or enhance toxicity. AML cells from most patients have receptors for both GM-CSF and G-CSF, and both factors induce rapid proliferation of leukemic cells without any evidence of terminal differentiation. Thus, administration of either factor carries the risk of promoting leukemic cell proliferation. In the small number of clinical trials conducted so far, however, administration of G-CSF or GM-CSF immediately after standard chemotherapy has not been associated with leukemic cell regrowth or early relapse. Ono et al. randomly assigned a heterogeneous group of patients with acute leukemia to G-CSF or no treatment during induction therapy. There was a 1-week reduction in the duration of severe neutropenia but no decrease in antibiotic use or hospital stay. The complete remission rate was not decreased by G-CSF, and long-term outcome was unchanged. The results of this study were confirmed in a large study conducted in 31 centers in Europe and Australia in which 521 adult patients with AML were randomly chosen to receive G-CSF or placebo after induction and consolidation therapy. Patients in the G-CSF arm had a statistically significant improvement in duration of neutrophenia, a 5-day reduction in the median duration of hospital stay, and a reduction in duration of antibiotic use. There was no significant difference reported in rate of complete remission or overall survival. The Southwest Oncology Group randomly selected 234 patients older than age 55 and having de novo AML after autologous blood transplantation to receive G-CSF or placebo. Patients on the G-CSF arm had a 3- to 4-day reduction in the duration of severe neutropenia after induction therapy and also reduced antibiotic use and days of fever. However, there was no reduction in the incidence of any infections or difference in complete remission rate or overall survival.

**ACUTE MYELOID LEUKEMIA IN THE ELDERLY**

GM-CSF has been investigated in two large randomized group trials in induction therapy of AML in older patients. Exclusively elderly patients were treated in a study randomly chosen 124 AML patients to receive GM-CSF or placebo after induction therapy. The study drug was started on day 11 if a day-10 marrow was hypoplastic, and patients who entered complete remission received the study drug after consolidation therapy as well. Patients receiving GM-CSF experienced a significant reduction of infectious toxicity and a marginal improvement in median survival. Ten percent of GM-CSF–treated patients experienced severe infections, as compared to 36% of placebo patients. Mortality of patients who developed fungal infections was also lower with GM-CSF treatment, and overall early mortality (within 30 days) was significantly reduced in the GM-CSF arm. However, the beneficial effects of GM-CSF in an elderly population with AML were not confirmed in a larger Cancer and Leukemia Group B study reported by Stone et al. In that study, 388 patients older than age 60 were randomly assigned to GM-CSF or placebo. There was no difference in remission rate, incidence of severe infections, or early deaths. There was a significant decrease in median duration of neutropenia for patients receiving GM-CSF, but the absolute difference was small (15 vs. 17 days).

Considering all the studies in which patients with AML have been randomly chosen to receive growth factor (G-CSF or GM-CSF) or placebo, it appears that although there may be some reduction in duration of neutropenia during induction therapy, this has not resulted in any significant reduction of severe infections or improvement in...
Several investigators have tried to take advantage of the fact that GM-CSF or G-CSF induces proliferation of myeloid leukemic cells by using these cytokines to induce leukemic cells to initiate or increase DNA synthesis, followed immediately by administration of chemotherapy with drugs such as cytosine arabinoside, which are most effective against cells actively synthesizing DNA. This approach has been remarkably effective in the laboratory. However, although pilot studies suggested that GM-CSF and cytosine arabinoside could be coadministered without undue toxicity, larger studies did not suggest that this approach had any benefit in terms of increased complete remission rate or increased survival. One explanation is that the CSFs promote viability as well as proliferation of leukemic cells, and they may be paradoxically reducing cell death due to cytotoxic chemotherapy. At present, there is no indication for using CSFs as priming agents outside of a clinical trial.

**Acute Lymphoblastic Leukemia**

The use of cytokines during induction therapy of adult acute lymphoblastic leukemia (ALL) has not been extensively investigated. A prospective, multicenter trial reported by Ottmann et al. randomly chose 76 patients to receive G-CSF or no growth factor during induction therapy. Patients in the G-CSF arm had a statistically significant reduction in the duration of severe neutropenia (8 days vs. 12.5 days), a lower incidence of noniviral infections, and fewer interruptions of scheduled chemotherapy. The complete remission rates in the G-CSF and control groups were the same (95%), and the probability of disease-free survival at 20 months was also identical. A randomized Cancer and Leukemia Group B trial arrived at similar conclusions. Adults who received intensive chemotherapy for ALL benefited from G-CSF treatment in terms of more rapid recovery of neutrophils, but overall outcome was unchanged. Thus, as is the case for adults with AML, adults with ALL treated with G-CSF have less neutropenia and probably fewer infections but no real improvement in disease outcome.

**Myelodysplastic Syndromes**

Anemia, neutropenia, and thrombocytopenia are common and chronic problems for patients with MDSs and, as a result, MDS patients have been among the first groups to receive HGFs. The use of EPO to treat anemias of MDS patients was described earlier in the section Treatment of Anemia in Cancer Patients. In phase I and phase II trials, both GM-CSF and G-CSF have been shown to increase the neutrophil count by at least twofold in a variable number of patients (but generally less than 50%) and inevitably for only as long as the cytokine was administered. Even minimal red cell and platelet responses have been uncommon with both GM-CSF and G-CSF. A randomized trial of GM-CSF or observation was conducted in which 133 neutropenic patients with MDS were entered and followed up for 90 days. Patients treated with GM-CSF had a statistically significant increase in neutrophils after 30, 60, and 90 days of treatment and a significant reduction in major infections during the treatment period (15%, GM-CSF, 33%, observation). However, GM-CSF did not increase in hemoglobin or platelet counts. Cytokine therapy was well tolerated. In another study, IL-11 did not reduce platelet transfusion requirement, but it may have increased neutrophil counts in patients with MDS-related anemia. IL-11 acts synergistically with several other HGFs and it is possible that this factor will reduce chemotherapy and radiation therapy-induced damage to the intestine in animal models.

**Interleukin-11**

IL-11 (Neumega) is a growth factor produced by stromal cells and has activity on progenitor cells, B cells, intestinal crypt cells, and osteoclasts, but not on stem cells. Preliminary studies in both animals and humans suggested that IL-11 increased platelet counts, presumably through an effect on megakaryocytes. Side effects in a phase I clinical study in breast cancer patients included fatigue, myalgia, and arthralgia and a grade 3 central nervous system event in one patient but no fever or capillary leak syndrome. The incidence of severe thrombocytopenia after cyclophosphamide and doxorubicin appeared to be reduced. Several randomized placebo controlled clinical trials have shown a reduction in the need for platelet transfusions in the setting of intensive chemotherapy. Autologous transplantation, IL-11 did not reduce platelet transfusion requirement. In vitro, IL-11 acts synergistically with several other HGFs to support proliferation of hematopoietic progenitor cells, suggesting that combinations of IL-11 with other growth factors will be worth exploring in clinical trials. Interestingly, IL-11 reduces chemotherapy- or radiation therapy-induced damage to the intestine in animal models. IL-11 is currently approved for use in treating chemotherapy-associated thrombocytopenia.

**Thrombopoietin (Megakaryocyte Growth and Development Factor)**

Thrombopoietin (TPO) was cloned by several groups after either purification of the protein from plasma of thrombocytopenic animals, by using the receptor for ligand affinity purification, or by random sequence cloning strategies. The receptor for TPO has been identified as c-MPL, the cellular homologue of a viral oncopogene that causes a myeloproliferative syndrome in mice. TPO levels vary inversely with the platelet count, suggesting that TPO secretion can be directly induced by thrombopoietin. TPO induces proliferation of megakaryocyte progenitor cells, expansion of megakaryocytes in vivo, and production and release of platelets. Further, TPO acts synergistically with several other growth factors to enhance megakaryocyte differentiation and proliferation. Randomized, placebo-controlled clinical trials in cancer patients have shown a benefit for TPO administration, but development has been slowed by rare instances of thrombocytopenia. This cytokine has not yet been approved for use in cancer patients, and its final role in cancer chemotherapy is still to be determined.

**LONG-TERM EFFECTS OF GROWTH FACTOR ADMINISTRATION**

The long-term consequences of administration of HGFs are not yet known. In children with congenital neutropenias responsive to G-CSF, some have now received this cytokine for several years. Although splenomegaly, apparently related to extramedullary hematopoiesis, has been observed, few serious side effects have been reported. One interesting case has been described in which G-CSF–related extramedullary hematopoiesis was confused with recurrent lymphoma. However, there is no evidence to date that CSF administration by itself predisposes patients to develop leukemia or myelodysplasia. Concern has been raised that administration of CSFs with chemotherapy may increase the cumulative stem cell damage that can occur with some types of chemotherapy drugs or radiation. In fact, in a mouse model, repeated sequential administration of cyclophosphamide and G-CSF was more toxic to stem cells than cyclophosphamide alone. It is possible that CSFs will induce more stem cells to enter the cell cycle and, therefore, potentially become more sensitive to chemotherapy-induced DNA damage. Careful follow-up of patients receiving aggressive chemotherapy with growth factor support is warranted, particularly if these patients later undergo autologous progenitor cell transplantation, or during other situations in which the marrow is stressed, such as during serious bacterial or viral infections.
CONCLUSIONS

There is little doubt that the use of HGFs represents a significant advance in the supportive care available to cancer patients. At present, there are a number of clinical situations wherein administration of a growth factor is warranted, such as after myelosuppressive chemotherapy where there is a high likelihood of febrile neutropenia and after autologous progenitor cell transplantation. Patients who have already had an episode of febrile neutropenia should receive a growth factor if they have good reasons to maintain dose intensity. Ultimately, however, the utility of high-dose chemotherapy needs to be established in many different situations in terms of survival or improved quality of life. Finally, cytokines are expensive, and further efforts to define cost-effectiveness in useful terms are needed. However, despite these cautions, the remarkable ability to manipulate hematopoiesis with growth factors is likely to be beneficial to cancer patients in many different situations.

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CHAPTER 54
Infections in the Cancer Patient

INTRODUCTION

Infections are major causes of morbidity and mortality in patients with cancer. The risk of infection is principally related to the intensity and duration of immunosuppressive chemotherapy. It is essential to know the patient's quantitative and qualitative immune defects and to stratify the risk for specific pathogens in the context of the history, physical examination, and radiologic and laboratory data.

In the 1980s, there was a shift in the relative prevalence of specific pathogens afflicting patients with cancer. Whereas in the 1960s and 1970s, gram-negative bacterial pathogens (Enterobacteriaceae and \textit{Pseudomonas aeruginosa}) were the principal causes of bacteremia, in the 1990s and 1980s, gram-positive bacterial pathogens became predominant. Today, filamentous fungi are a major cause of mortality in allogeneic bone marrow transplant (BMT) recipients and in patients with prolonged neutropenia. The spectrum of invasive fungal infections has dramatically increased. Examples of such emerging pathogens include \textit{Fusarium}, \textit{Acremonium}, \textit{Scedosporium}, and dematiaceous (dark-walled fungi) species, and the yeast \textit{Trichosporon beigelii}. This population is also at risk for a broad spectrum of viral and protozoal infections.

We describe the clinical manifestations and treatment of the major pathogens encountered in an oncology population. Specific infectious syndromes, such as fever without a documented source, pneumonia, skin infection, gastrointestinal infection, and sepsis, are reviewed. We also discuss novel approaches aimed at prevention...
and early diagnosis of infections and immune augmentation strategies.

**FACTORS PREDISPOSING TO INFECTION IN PATIENTS WITH CANCER**

Patients with cancer are a highly varied population, both in terms of the underlying malignancy and the level of immunosuppression. We describe specific categories of immunosuppression and the pathogens to which these patients are most susceptible. Multiple predisposing factors may exist in a single patient, thus increasing the spectrum of likely pathogens. The major categories of immunologic deficits in persons with cancer and the pathogens to which they are susceptible are summarized in Table 54.1.

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<th>Table 54.1: Predominant Immunologic Defects and Associated Pathogens in Patients with Cancer</th>
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**ABSOLUTE NEUTROPHIL COUNT GREATER THAN 500/µL AND NO IMMUNOSUPPRESSIVE THERAPY**

The group with absolute neutrophil count greater than 500/µL and no immunosuppressive therapy represents the least immunosuppressed patients with cancer, but some level of risk of infection may still exist. The malignancy itself may be associated with an immune defect. Malignancies associated with defective immunoglobulin production lead to increased susceptibility to encapsulated bacteria, principally *Streptococcus pneumoniae*. Such patients may have recurrent sinopulmonary infections, septicaemia, and disseminated infection. Patients with chronic lymphocytic leukemia frequently have hypogammaglobulinemia or dysglobulinemia. Low levels of both total immunoglobulin G (IgG) and specific antibodies to pneumococcal polysaccharide capsule are associated with an increased rate of infections in these patients. A decision analysis suggested that routine administration of immunoglobulin to patients with chronic lymphocytic leukemia and hypogammaglobulinemia reduces the frequency of bacterial infections, but is not cost-effective.

Patients with multiple myeloma and other related gammaglobulinopathies are also often functionally hypogammaglobulinemic; the total level of immunoglobulin production is elevated, but the repertoire of antibody production is restricted. Savage et al. noted a biphasic pattern of infection among patients with multiple myeloma. Infections by *S pneumoniae* and *Haemophilus influenzae* occurred early in the disease and in patients responding to chemotherapy, whereas infections by *Staphylococcus aureus* and gram-negative pathogens occurred more commonly in advanced disease and during neutropenia. Serum from patients with multiple myeloma may be defective in the activation of C3, the major opsonin of the complement system, which likely further contributes to susceptibility to pneumococcal infection. One randomized study suggested that prophylactic intravenous immunoglobulin protected against life-threatening and recurrent infections in patients with multiple myeloma. The patients who benefited most from immunoglobulin therapy were those with poor IgG antibody responses to pneumococcal vaccination.

Patients with hairy cell leukemia appear to have a defect in cell-mediated immunity, leaving them prone to develop an unusually high frequency of opportunistic atypical mycobacterial infections. Patients with untreated Hodgkin's disease have significant abnormalities in T-cell number and function, which persist in the majority of long-term survivors. Such patients are at increased risk for toxoplasmosis, nocardiosis, pneumocystosis, cryptococcosis, mycobacterial infections, and herpes zoster. Most opportunistic infections occurred during poorly controlled malignancy when patients were receiving corticosteroids, myeloablative chemotherapy, or both.

Adrenal tumors and ectopic adrenocorticotropic hormone-secreting tumors resulting in high levels of cortisol and T-cell leukemias are associated with defects in cellular immunity resulting in an increased risk of mucosal candidiasis, *Pneumocystis carinii pneumonia* (PCP), and invasive aspergillosis.

Solid tumors may predispose patients to infection because of anatomic factors. Tumors that overgrow their blood supply become necrotic, thus forming a nidus for infection. Head and neck tumors may cause erosion through the fascial planes of the neck and floor of the mouth, predisposing patients to serious infections caused by mouth flora. Lemierre's syndrome, a septic thrombophlebitis of the neck with possible embolization to the tricuspid valve and lung and dissemination to other organs, is usually caused by *Fusobacterium bactérium*, which are anaerobic oral commensal organisms. This infection may develop during the course of uncontrolled head and neck cancer. Head and neck cancers may also increase the risk of aspiration pneumonia. Endobronchial lung tumors are associated with recurrent postobstructive pneumonias. Abdominal tumors may obstruct hollow visera, such as the genitourinary or hepatobiliary tracts, predisposing to pyelonephritis and cholangitis, respectively. Direct invasion through the colonic mucosa is associated with local abscess formation and sepsis by enteric flora. *Streptococcus bovis* bacteria is highly associated with colon cancer. Breast tumors increase the risk of mastitis and abscess formation, usually by *Staphylococcus aureus*.

Therapy for the underlying malignancy, independent of the immunosuppression, may be associated with an increased risk of infection. Local radiation therapy is associated with loss of epithelial integrity, necrosis, loss of blood supply, and consequent poor ability to repair wounds. Visceral complications include radiation pneumonitis, esophagitis, and enteritis. Implantable hardware necessary for administration of chemotherapy, such as cuffed intravenous catheters and Ommaya reservoirs, are potential niduses of infection.

Patients with malignancy commonly experience malnutrition, which increases the risk of infection. Weight loss frequently precedes the diagnosis of cancer, and the nausea, mucositis, and enteritis that follow antineoplastic chemotherapy worsen malnutrition.

**NEUTROPENIA**

Neutropenia may develop independently of chemotherapy in certain patients with cancer. In acute leukemia, the marrow may be replaced with malignant cells so that virtually no normal circulating neutrophils exist. Similarly, patients with premalignant hematologic disease, such as myelodysplastic syndrome, may have associated bone marrow failure. Some patients also may develop neutropenia due to tumor-related autoimmune neutrophil destruction. Persons rendered neutropenic by myeloablative chemotherapy are likely to be at greater risk for life-threatening infections due to the concomitant disruption of epithelial mucosal barriers by such agents.

The relationship between circulating leukocytes and risk of infection was established by Bodey et al. in a classic early study of 52 patients with acute lymphocytic leukemia or acute myelogenous leukemia. The frequency of severe infections was highest when the absolute neutrophil count (ANC) was less than 100/µL and proportionately less frequent at 100 to 500/µL and 500 to 1000/µL, respectively. This relationship was sustained whether the patient was in relapse or remission, although the overall risk of infection was greater during relapse. Ninety percent of disseminated fungal infections and 78% of septicemias occurred when the ANC was less than 500/µL. No further reduction in the rate of serious infections occurred at ANC greater than 1000 to 1500/µL. In addition to the depth of neutropenia, the risk of infection was strongly related to the duration of neutropenia. A neutrophil count of less than 100/µL resulted in infections in all patients within 3 weeks and in severe infections within 6 weeks. The likelihood of survival from severe infections was related to both the initial granulocyte level and whether an increase in the neutrophil count occurred within the first week. With an initial ANC of less than 100/µL and no increase within the first week, mortality was 80%.

The risk of invasive aspergillosis is also directly related to the period of neutropenia. In patients with leukemia, Gerson et al. showed that aspergillosis was uncommon when neutropenia lasted for less than 14 days. However, after 14 days, the risk of aspergillosis increased in direct proportion to the length of neutropenia. Invasive aspergillosis is also a major cause of mortality in patients with persistent neutropenia secondary to aplastic anemia. Since the mid-1980s, an increasing
spectrum of fungal pathogens has been encountered in patients with prolonged neutropenia, including Fusarium species, dark-walled molds, and Trichosporon species. Diagnosis of infection in granulocytopenic patients may be hampered by the lack of typical symptoms and signs. Sickles et al. compared the clinical manifestations of infections in neutropenic and nonneutropenic patients with cancer. Fever was present in virtually all patients with an ANC less than 100 µL and in 90% of patients with 101 to 1000/µL. However, physical findings of infection, including fluctuance, exudate, local heat and swelling, ulceration, and local adenopathy, were less frequent in neutropenic than in nonneutropenic patients with similar infections. Local erythema and tenderness were sensitive indicators of infection in neutropenic patients. In neutropenic patients with pneumonia, sputum and physical examination signs of consolidation were less frequent than in nonneutropenic patients as were local findings in cases of urinary tract infection. Local infections more commonly led to bacteremia with an ANC less than 100/µL. Thus, fever is a relatively sensitive sign of infection in the neutropenic patient, whereas other findings of infection are often lacking. The high likelihood of systemic infection and mortality in febrile neutropenic patients constitutes the rationale for initiating empiric antibacterial therapy before a documented source of infection or culture data are available.

### MUCOSAL IMMUNITY

The mucosal linings in the gastrointestinal, sinopulmonary, and genitourinary tracts constitute the first line of host defense against a variety of pathogens. Chemotherapy and radiation therapy cause defects in mucosal immunity at several different levels. The physical protective barrier conferred by the epithelial lining is compromised, thus allowing access to colonizing microflora. In BMT patients, chronic graft-versus-host disease (GVHD) further compromises mucosal immunity. These patients have defective salivary immunoglobulin secretion, and corticosteroids profoundly compromise mucosa-associated lymphoid tissue by inducing apoptosis of M cells and depleting lymphoid follicles of T and B cells.

Mucosal epithelial cells secrete a variety of antimicrobial peptides, including lactoferrin (iron sequestration), lysozyme (hydrolysis of peptidoglycan of gram-positive bacteria), and phospholipase A2 (cleavage of structural phospholipids of bacteria). Defensins are a group of small cysteine-rich antibacterial peptides (molecular weight, approximately 4 kD) located abundantly in the primary (azurophilic) granules of neutrophils and in a variety of mucosal epithelial cells, including bronchial epithelium and Paneth's cells within small intestinal crypts. Neutropenia and loss of the epithelial cell anatomic barrier and local production of antimicrobial proteins likely predispose to typhlitis (neutropenic enterocolitis). Synthetic antimicrobial peptides are potential therapeutic candidates for augmenting mucosal immunity.

### IMMUNOSUPPRESSIVE AGENTS NOT RELATED TO NEUTROPHENIA

#### Corticosteroids

Corticosteroids have profound effects on the distribution and function of neutrophils, monocytes, and lymphocytes. They induce a neutrophilic leukocytosis by accelerating the release of neutrophils from the bone marrow and by inhibiting the egress of neutrophils from the circulation. Corticosteroids reduce adherence of neutrophils to the endothelium, thus inhibiting migration to inflammatory sites, and inhibit neutrophil fungicidal activity.

Corticosteroids elicit a peripheral blood monocytopenia that lasts for 24 hours. In addition, a number of monocyte functions are impaired, including chemotaxis, bactericidal activity, and production of interleukin-1 (IL-1) and tumor necrosis factor-α (TNF-α).

Corticosteroids inhibit T-cell activation, leading to reduced proliferative responses and cytokine production, and also induce a redistribution of lymphocytes out of the circulation, leading to peripheral lymphopenia. This redistribution predominantly involves T cells. At high doses, corticosteroids also inhibit immunoglobulin generation by B cells.

In patients with cancer, corticosteroids are seldom the only immunosuppressive agents being administered, and it is therefore difficult to delineate the degree of impairment in host defense elicited by the corticosteroid regimen alone. Infections that occur in patients with collagen vascular diseases treated with corticosteroids are associated with both impaired phagocytic function (such as Staphylococcus and Enterobacteriaceae) and cell-mediated immunity (such as herpes zoster, and P carinii).

In this population, the incidence of infectious complications increases when the adult equivalent of prednisone, 20 to 40 mg/d, is administered for longer than 4 to 6 weeks.

In patients with cancer, the most intensive corticosteroid regimens (usually the equivalent of prednisone, 1 g daily) are used to treat BMT recipients with GVHD, leading to a global suppression of phagocytic and cell-mediated activity and rendering these patients highly susceptible to a broad spectrum of bacterial, viral, and protozoal pathogens. In addition to immunosuppression, corticosteroids directly stimulate the growth of Aspergillus fumigatus in vitro, possibly via sterol-binding proteins in the fungus.

#### Methotrexate

Methotrexate inhibits dihydrofolate reductase, an enzyme required for the synthesis of DNA and certain amino acids. At the high doses used in antineoplastic chemotherapy, methotrexate is highly immunosuppressive. As with other cytotoxic agents, methotrexate causes bone marrow suppression and mucositis.

Trimethoprim-sulfamethoxazole, an antifolate drug commonly used as prophylaxis against P carinii infection in this population, may aggravate the hematologic toxicity of methotrexate.

In patients with collagen vascular disease treated with low-dose methotrexate, the infection rate was low. The most common opportunistic pathogens were S aureus and Enterobacteriaceae. Other reported infections included aspergillosis, histoplasmosis, nocardiosis, mycobacterial infections, and Listeria monocytogenes meningitis. Epstein-Barr virus (EBV)-associated B-cell lymphoproliferative disease has been identified in a few patients with collagen vascular diseases treated with methotrexate.

Thus, long-term use of low-dose methotrexate can lead to significant depression of cell-mediated immunity, independent of its myelotoxicity.

#### Cyclosporin A

Cyclosporin A (CSA) is a potent inhibitor of T-cell activation that is commonly used in the postengraftment period after BMT. CSA is a prodrug that binds to the intracellular protein, cyclophilin. The resulting complex in turn inhibits the calcium-regulated protein phosphatase, calcineurin, a protein required for signal transduction after activation of the T-cell receptor. Calcium-dependent production of the potent neutrophil chemotaxin, IL-8, is inhibited by CSA.

Compared with methotrexate, CSA is associated with less mucositis, and in some studies, more rapid myeloid recovery in BMT recipients.

#### Fluorabarine

Fluorabarine is a fluorinated analog of adenine that has been used in a variety of hematologic malignancies, including chronic lymphocytic leukemia, hairy cell leukemia, and low-grade lymphomas. Fluorabarine is a lymphotrophic compound, primarily affecting CD4+ lymphocytes. The combination of fluorabarine and corticosteroids is more immunosuppressive than either agent alone.

Fluorabarine plus prednisone results in a uniform depression of CD4+ cells that may persist for several months after completion of therapy.

In one series, 14 of 264 patients (5%) with chronic lymphocytic leukemia developed either PCP or listeriosis, and three cases occurred more than 1 year after therapy in patients who were in remission. Other opportunistic pathogens reflecting T-cell depression include disseminated varicella, mycobacteria, and fungi. Prophylaxis with trimethoprim-sulfamethoxazole (which has activity against both P carinii and L monocytogenes) appears to be warranted.

#### interleukin-2

Patients receiving high-dose IL-2 for malignancy have an increased risk of bacterial infections. Among 345 patients with cancer enrolled in a multicenter study of IL-2, 8% developed S aureus bacteremia. S aureus following by coagulase-negative staphylococci were the most common S aureus pathogens. The frequency of sepsis in IL-2 recipients was several-fold greater than in nonneutropenic patients with indwelling central catheters. IL-2 causes a profound but reversible defect in neutrophil chemotaxis that may account for the increased frequency of infections.
Splenectomy

The spleen is a reservoir in which rapid antigen presentation occurs, leading to the production of opsonizing antibodies by B cells. Splenic macrophages remove both opsonized and nonopsonized particles from the bloodstream. The removal of nonopsonized bacteria is a particularly important function to protect against encapsulated bacteria to which the patient is not immune.

Asplenic patients are principally at risk for overwhelming sepsis by encapsulated bacteria. The most common pathogen is *S. pneumoniae*, but other pathogens include *Haemophilus influenzae* and *Neisseria meningitidis*. It is best to immunize individuals against encapsulated bacteria in advance of splenectomy. If this is not feasible, immunization is still advisable after splenectomy, because such patients are still capable of mounting a protective antibody response. In a study of asplenic patients, IgG responses to immunization with pneumococcal, *H. influenzae* type b, and meningococcal vaccines were normal by day 28. Patients with Hodgkin's disease, most of whom were asplenic, had normal IgG responses to pneumococcal polysaccharide vaccine. Molmine et al. suggest reimmunization of asplenic persons every 5 years with the pneumococcal polysaccharide vaccine based on a potential increased risk for disease as protective antibody levels wane over time.

Asplenic patients should be advised to seek medical attention when fever occurs. Prophylaxis with penicillin has been traditionally used after splenectomy. However, the growing frequency of antimicrobial resistance among *S. pneumoniae* isolates raises a note of caution. In a surveillance study, the overall percentages of respiratory pneumococcal isolates from the United States with intermediate and high-level resistance to penicillin were 28% and 16%, respectively. A significant minority of penicillin-resistant isolates are cross-resistant to cephalosporins, macrolides, and trimethoprim-sulfamethoxazole. Newer generation quinolones have reliable activity against penicillin-resistant pneumococci, though a Canadian study documented an increased frequency of quinolone-resistant pneumococcal isolates in association with increased use of these agents. Physicians should be aware of local patterns of resistance to guide prophylactic and empirical antibiotic therapy.

Other pathogens associated with a more fulminant course in asplenic individuals include *Capnocytophaga* species, *S. bovis*, *S. malaria*, and *Salmonella* species. *Capnocytophaga canimorsus* infection is typically associated with dog bites and can lead to sepsis with or without evidence of cellulitis. *Babesia microti* is transmitted by the *Ixodes* tick, which is also the vector for Lyme disease. When in Lyme-endemic regions in the spring to autumn periods, patients should follow basic precautions to avoid tick bites (long sleeves, tick repellants) and be vigilant about fever. The diagnosis of babesiosis is confirmed by a peripheral blood smear showing characteristic intraerythrocytic inclusions.

**BONE MARROW TRANSPLANTATION**

The spectrum of pathogens to which BMT recipients are most susceptible follows a time line corresponding to the predominant immune defects observed at different periods (Table 54-2). In the early stage of BMT, neutropenia is the principal host defense defect. These patients are at risk for the same spectrum of bacterial and fungal infections that afflict nontransplant patients who have been treated with potent myeloablative therapy (see *Neutropenia*, earlier in this chapter). Severe mucocutaneous herpes simplex virus (HSV) infection is also commonly observed in the first month of transplantation in association with chemotherapy-induced mucositis. After myeloid engraftment, fever and mucositis typically resolve, and the risk of serious bacterial and fungal infections decreases.

**TABLE 54-2. Time Line of Principal Immune Defects and Infectious Complications in Bone Marrow Transplant Recipients**

<table>
<thead>
<tr>
<th>Time Line</th>
<th>Immune Defects and Infectious Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-3 weeks</td>
<td>Neutropenia is the principal host defense defect. These patients are at risk for the same spectrum of bacterial and fungal infections that afflict nontransplant patients who have been treated with potent myeloablative therapy.</td>
</tr>
<tr>
<td>3-6 weeks</td>
<td>Immune reconstitution is incomplete, and patients are at risk for infections with opportunistic pathogens.</td>
</tr>
<tr>
<td>6-9 months</td>
<td>Immune reconstitution is complete, and patients are at risk for infections with pathogens that are typically not seen in immunocompetent individuals.</td>
</tr>
</tbody>
</table>

After myeloid engraftment, a qualitative dysfunction of phagocytes persists due to corticosteroid therapy and other immunosuppressive agents (see *Immunosuppressive Agents Not Related to Neutropenia*, earlier in this chapter). The risk of infection by filamentous fungi during this period is strongly associated with the severity of GVHD and requirement for potent immunosuppressive regimens. Impairment in neutrophil chemotaxis has been noted in some patients and may increase the risk of infection. Alveolar macrophage function in patients studied within 4 months of allogeneic BMT was impaired based on chemotaxis, phagocytosis, and killing of bacterial and candidal species. These observations may, in part, account for the increased risk of pneumonia during this period.

Defects in cell-mediated immunity persist for several months even in uncomplicated allogeneic transplant recipients, thus predisposing these patients to a variety of opportunistic infections, such as candidiasis, *P. carinii*, cytomegalovirus (CMV), and herpes zoster (see *Table 54-2*). Repopulation of specific T-cell subsets occurs at different rates, resulting in a lower than normal CD4+/CD8+ (helper T cell to CD8+ T cell) ratio for the first 6 months after engraftment. In addition to quantitative T-cell deficiencies, loss of T-cell receptor diversity is observed. During the first 100 days of transplantation, delayed hypersensitivity responses, proliferative responses to mitogens and antigens, and T-cell-mediated activation of B cells to produce immunoglobulin are impaired. By 1 year after engraftment, BMT recipients without chronic GVHD have normalized CD4+/CD8+ ratios, and in general, have normal T-cell responses.

Defective reconstitution of humoral immunity is a major factor contributing to increased infection susceptibility in the late transplant period. Vincent et al. noted an unusually high frequency of pneumococcal infections between 7 and 36 months after transplantation. All infections occurred after trimethoprim-sulfamethoxazole prophylaxis for *P. carinii* had been halted. The risk of pneumococcal infection was associated with serum opsonic deficiency for *S. pneumoniae*. Kalls et al. showed that functional asplenia, as determined by the presence of Howell-Jolly bodies in peripheral blood smears, was a late complication of allogeneic BMT only in patients with severe GVHD. Thus, in BMT recipients who have had an uncomplicated course, fever in the late transplant period must be evaluated promptly (similar to patients with asplenia) because of the risk of overwhelming infection by one of these pathogens (see *Table 54-2*).

During periods of severe GVHD, the immunosuppressive regimen is intensified to include high-dose corticosteroids in combination with CSA and possibly an antilymphocyte globulin preparation. CD4+ lymphopenia may, in part, result from GVHD-induced injury of thymic epithelial cells. Whereas mature and cooperative T- and B-cell functions are generally reconstituted by 1 year after engraftment in uncomplicated allogeneic BMT, chronic GVHD is associated with persistently depressed cell-mediated and humoral immunity.

Autologous transplants are associated with less infectious complications than allogeneic transplants due to reduced severity of GVHD and earlier reconstitution of T-cell immunity. Allogeneic transplantation using alternative donors (such as HLA-matched unrelated donors, partially mismatched related donors, and mismatched cord blood) has a higher risk of GVHD and usually requires depletion of mature donor T cells, leading to delayed immune reconstitution and, consequently, a greater risk of infectious complications.

**ALTERATIONS IN MICROFLORA COLONIZATION**

A shift in the normal respiratory flora toward colonization with aerobic gram-negative bacilli occurs in sick hospitalized patients. This may be due to changes in the fibronectin content of cell surfaces in debilitated persons, leading to reduced adherence by the normal anaerobic flora, thus favoring colonization by aerobic gram-negative bacilli. In immunocompromised patients with cancer, alterations in bowel flora leading to acquisition of more virulent bacteria are well documented. This change is exacerbated by the use of broad-spectrum antibiotics that may suppress the normal anaerobic bowel flora. Patients with acute leukemia are frequent...
In neutropenic children, persistent neutropenia. Virtually all of these patients had an indwelling central venous catheter, which was likely to be the principal portal of entry. In a series of BMT recipients with catheters, prosthetic valves, and ventricular shunts.

Venous catheters and fluoroquinolone prophylaxis may be contributing to the more frequent isolation of these bacteria. They include gram-positive bacteria. In the 1990s, there has been an emerging spectrum of gram-positive bacterial infections in patients with cancer. The widespread use of surgically implanted central venous catheters. Coagulase-negative staphylococci are considered to be low pathogens of low virulence, and their isolation from blood is frequently dismissed as a skin contaminant. In patients with cancer, coagulase-negative staphylococci may produce a localized catheter-associated infection, bacteremia, or, less frequently, metastatic infection. The majority of nosocomial coagulase-negative staphylococci are resistant to antistaphylococcal penicillins, making vancomycin the initial drug of choice for such infections. However, given the increased prevalence of serious infections due to vancomycin-resistant enterococci (VRE), an antistaphylococcal penicillin should be used for staphylococcal sensitive to one of these agents.

S. aureus is the most common cause of surgical wound infections and can cause both local and systemic disease. In some instances a toxic shock syndrome occurs, manifesting as fever, hypotension, gastrointestinal toxicity, rash, and skin exfoliation. Prompt initiation of antibiotics, fluid resuscitation, removal of surgical packing, and wound débridement are required. In patients with cancer, disruptions of the skin barrier from indwelling intravenous catheters or biopsy sites are additional portals of entry.

The incidence of methicillin-resistant S. aureus (MRSA) isolates causing nosocomial blood stream infections in the United States is increasing. In a 3-year surveillance study of more than 10,000 cases of nosocomial bacteremia, almost 30% of S. aureus isolates were methicillin resistant. Among hematology and oncology patients, the rate was 25%. These observations highlight the need to be familiar with the resistance patterns of bacterial pathogens at one’s institution to guide empiric antibiotic therapy before the availability of culture results (see Evaluation and Management of Febrile Neutropenia without an Apparent Source, later in this chapter).

MRSA isolates are typically broadly resistant to all antibiotics, except vancomycin. Clinical S. aureus isolates have been isolated with intermediate resistance to vancomycin. Preventing emergence and spread of these organisms requires careful attention to infection control guidelines and judicious use of antibiotics.

Patients with MRSA infection should be kept in private rooms, under contact precautions. Gown and gloves should be worn by hospital staff in cases of a draining wound or other situations in which spread to hands and clothing is likely to occur. Attempts at eradication of nasal carriage of S. aureus with topical mupirocin and other agents have produced mixed results, and MRSA may develop resistance to mupirocin.

**ENTEROCOCCUS SPECIES**

An increased incidence of nosocomial infections caused by multidrug-resistant enterococcal species has been observed. Approximately 50% of Enterococcus faecium and the minority of Enterococcus faecalis isolates are resistant to vancomycin and are typically multiply resistant to penicillin, ampicillin, and aminoglycosides. Patients with cancer who spend a significant time in the hospital are at high risk for being colonized by drug-resistant Enterococcus species. The portal of entry for enterococcal bacteremia may be an indwelling central catheter or defects in the gut mucosa from chemotherapy or radiation toxicity. Tumor invasion of the gut may predispose to bacteremia by Enterococcus species, as well as Streptococcus bovis.

Ampicillin is the drug of choice for sensitive Enterococcus isolates. For serious infections (e.g., bacteremia), addition of an aminoglycoside for synergy is reasonable because even sensitive strains are intrinsically tolerant to the bactericidal activity of penicillins and vancomycin. The newly licensed streptogramin antibiotic, quinupristin/dalfopristin (Synercid), is active against most strains of E. faecium but not E. faecalis. Linzolid, a prototype of the oxazolidinone group of antimicrobial agents, has broad activity against gram-positive pathogens, including MRSA and VRE, and is being evaluated in clinical trials. Chloramphenicol, fluoroquinolones, tetracyclines, and rifampin may also have activity against VRE. Prevention and infection control methods, including prudent use of antibiotics (restriction of vancomycin usage), isolation of colonized and infected patients, surveillance, hand washing, and use of appropriate barrier protections, are critical for reducing rates of VRE infection.

**VIRIDANS STREPTOCOCCI**

Viridans streptococci, also called α-hemolytic streptococci, are oral commensal organisms. In the nonimmunocompromised population, they are the most common cause of native valve endocarditis, which usually has a subacute course. In neutropenic patients, viridans streptococci are more virulent. Cytosine arabinoside (Ara-C), a highly mucotoxic agent, and prophylaxis with ciprofloxacin or trimethoprim-sulfamethoxazole (presumably, by selecting for resistant streptococci) are the major risk factors for bacteremia by viridans streptococci.

Neutropenic patients with viridans streptococcal bacteremia may have a 24- to 48-hour prodrate of low-grade fever and facial flushing, followed by a high fever and chills. In approximately 25% of patients, bacteremia is complicated by a shock syndrome, characterized by hypotension, respiratory distress syndrome, renal failure, and a maculopapular rash usually starting at the trunk and spreading centrifugally to the face and extremities. Desquamation of the palms and soles may subsequently occur. Endocarditis is observed in a minority of patients. Septic shock may be more common in children than in adults.

In a secondary analysis of 909 bacteremias in patients previously enrolled in trials of neutropenic fever, 13% were caused by viridans streptococci. All 52 patients with viridans streptococcal bacteremia who received initial vancomycin survived, compared with an 86% survival rate in patients whose vancomycin therapy was delayed 2 to 3 days (P = .004). Of the empiric monotherapy regimens used for febrile neutropenia, ceftazidime has the poorest activity against viridans streptococci, 

**MISCELLANEOUS GRAM-POSITIVE BACTERIA**

In the 1990s, there has been an emerging spectrum of gram-positive bacterial infections in patients with cancer. The widespread use of surgically implanted central venous catheters and fluoroquinolone prophylaxis may be contributing to the more frequent isolation of these bacteria. They include Corynebacterium jeikeium, Bacillus cereus, Stomatococcus mucilaginosus, and Leuconostoc species. These bacteria are associated with localized catheter and wound infections, bacteremia, and disseminated infection.

C. jeikeium is a common cutaneous commensal organism that has been associated with infection of prosthetic devices, such as vascular catheters, peritoneal dialysis catheters, prosthetic valves, and ventricular shunts. C. jeikeium is highly resistant to antibiotics, except vancomycin.

In a review of C. jeikeium infections in patients with hematologic malignancies, skin lesions were present in one-half of the cases, pulmonary lesions occurred in approximately one-third of cases, and one-third of the patients died. In neutropenic patients, survival was strongly associated with resolution of neutropenia. Virtually all of these patients had an indwelling central venous catheter, which was likely to be the principal portal of entry. In a series of BMT recipients with C. jeikeium bacteremia, all eight patients who received appropriate antibiotic therapy and who had their central venous catheters removed survived regardless of persistent neutropenia. Mortality was greater than 50% in those patients who received no antibiotics and in those who received antibiotics without removal of the central venous catheter. Current treatment consists of prompt initiation of vancomycin and consideration of removal of the infected intravenous catheters.

In neutropenic children, B. cereus was associated with a primary cutaneous infection involving vesicular and pustular lesions. Stomatococcus mucilaginosus appears to be particularly virulent in neutropenic patients and has been associated with septic shock, respiratory distress syndrome, and meningitis.

**Stomatococcus mucilaginosus:**
Lactobacillus, and Pedicoccus species are often resistant to vancomycin, but most isolates are susceptible to penicillin.

ENTEROBACTERIACEAE

The Enterobacteriaceae include several pathogenic species, including Escherichia coli, Klebsiella, Proteus, Enterobacter, Serratia, and Citrobacter species. Patients with neutropenia are at highest risk for bacteremia and life-threatening infections by these pathogens. The principal portal of entry appears to be translocation of bacteria from the alimentary tract.

There has been an increasing frequency of infection due to Enterobacteriaceae and other gram-negative bacteria (such as Stenotrophomonas maltophilia and Acinetobacter species), which are highly resistant to b-lactam antibiotics. Bush et al. presented an updated classification of b-lactamas, which include three groups of enzymes: (1) group 1 cephalosporinases (also referred to as Bush group 1 bw-lactamas) are not well inhibited by clavulanic acid; (2) group 2 penicillinas, cephalosporinases, and extended spectrum b-lactamas are generally inhibited by b-lactamase inhibitors; and (3) group 3 metallo-b-lactamas that hydrolyze penicillins, cephalosporins, and carbapenems and confer broad resistance to almost all b-lactam antibiotics. Table 54-3 summarizes commonly used antibacterial agents in patients with cancer.

TABLE 54-3. Commonly Used Antibacterial Agents in Patients with Cancer

Extended spectrum b-lactamase–producing pathogens (most common in E coli and Klebsiella species) may not be detected with standard susceptibility testing because of different susceptibility patterns among third-generation cephalosporins. In one study of a nosocomial outbreak of extended spectrum b-lactamas producing Klebsiella strain (as indicated by cefazidime resistance), use of other third-generation cephalosporins was associated with a poorer outcome. Carbapenems (imipenem and meropenem) have consistent bactericidal activity against extended spectrum b-lactamase–producing strains and should be considered drugs of choice in serious infections by these pathogens.

The Bush group 1 b-lactamas may not be initially expressed (repressed), but are induced (de-repressed) after exposure to broad-spectrum cephalosporins, and confer resistance to virtually all b-lactam antibiotics with the exception of the carbapenems and cefepime. This group of b-lactamas is characteristic of Enterobacter species, but is also observed in P aeruginosa, Citrobacter, Serratia, and indole-positive Proteus species. Thus, if an Enterobacter species is isolated from a blood culture, it is reasonable to change the initial antibiotic regimen to a carbapenem, knowing the potential for induction of a cephalosporinase if third-generation cephalosporin therapy is continued.

PSEUDOMONAS AERUGINOSA

Infections caused by P aeruginosa in patients with cancer have diminished since the 1960s and 1970s. Currently, approximately 5% to 10% of bacteremias are caused by this organism in patients with neutropenia. This reduction may reflect the widespread use of fluoroquinolones as prophylaxis as well as the availability of agents with potent antipseudomonal activity, such as ceftazidime, that are used as initial empiric therapy for febrile neutropenia.

Bodey et al. retrospectively analyzed 410 cases of P aeruginosa bacteremia in patients with cancer. The overall rate was 4.7 cases per 1000 admissions and was most common among patients with leukemia. Neutropenia was the dominant risk factor. The infections were highly virulent, with 33% of patients developing septic shock and 32% having pneumonia. Other sites of infection included soft tissue, urinary tract, perirectal region, and central venous catheters. Patients who received an antipseudomonal b-lactam antibiotic, with or without an aminoglycoside, had survival rates of 72% and 71%, respectively, compared with 29% survival in patients who received only an aminoglycoside.

The site of disease often reflects where colonization has occurred. Colonization of the upper airway may lead to pneumonia after aspiration of infected droplets. Typhilitis (neutropenic enterocolitis) and perineal cellulitis may follow colonization of the gut by P aeruginosa. Pathologically, P aeruginosa invades small arteries and veins, leading to thrombosis, hemorrhage, and infection. This angioinvasion is most evident in cases of ecthyma gangrenosum in which P aeruginosa invades cutaneous blood vessels and perivascular connective tissue, leading to coagulative necrosis of the dermis (Fig. 54-1). The lesions of ecthyma gangrenosum usually evolve from erythematous macules to papules, and ultimately necrotic nodules and bullae. The lesions may present in any stage with minimal or absent inflammatory infiltrate.

FIGURE 54-1. Lesions of ecthyma gangrenosum in a neutropenic patient with bacteremia due to Pseudomonas aeruginosa. The ecthyma lesions are in the necrotic ulcerative edge.

Initial optimal antibiotic therapy for P aeruginosa bacteremia consists of an antipseudomonal b-lactam antibiotic and an aminoglycoside. It is reasonable to continue aminoglycoside therapy until clinical stability and sterilization of blood have been achieved. Emergence of resistance to cephalosporins and carbapenems during monotherapy for P aeruginosa infections may occur. Carbapenem resistance results from an alteration of a porin protein on the outer membrane of the bacteria, preventing penetration of the antibiotic and b-lactamase production. Emergence of resistance to carbapenems during therapy for P aeruginosa is well documented and may result in treatment failure. Quinolone-resistant P aeruginosa isolates are being observed with increasing frequency. See sections on Neutropenic Fever and Manifestations and Therapy of Infections, later in this chapter.

STENOTROPHOMONAS (XANTHOMONAS) MALTophilia
Stenotrophomonas maltophilia colonizes hospital environments and establishes carriage generally in patients who have been treated with broad-spectrum antimicrobial agents. This organism has become an increasingly important cause of nosocomial infections in patients with cancer. Clinical manifestations include bacteremia, pneumonia, endocarditis, mastoiditis, and meningitis. Varthian et al. reviewed 17 cases of mucocutaneous and soft tissue infections caused by S. maltophilia in patients with cancer. These infections manifested as mucocutaneous ulcerations, primary cellulitis (usually catheter related), and metastatic cellulitis consisting of multiple hard, tender nodules with surrounding or distant cellulitic areas resembling disseminated fungal infection, and one case of erythrasma gangrenosum, resembling P. aeruginosa. Disseminated cutaneous lesions were most common in patients with refractory leukemia and were frequently associated with septic shock, multiorgan failure, and pneumonia.

Stenotrophomonas maltophilia is resistant to imipenem, and isolates are often broadly resistant to other antibiotics. The organism elaborates a metallo-b-lactamase, which hydrolyzes carbapenems. The majority of strains are susceptible to trimethoprim-sulfamethoxazole, which is the preferred initial antibiotic for this organism, pending susceptibility data.

**ACINETOBACTER SPECIES**

Acinetobacter calcoaceticus and Acinetobacter baumannii are the principal pathogenic species within this genus. These gram-negative coccobacilli are ubiquitously, easily colonize hospital environments, and have been associated with nosocomial outbreaks. Acinetobacter species are frequently multidrug resistant, and the risk of infection in one nosocomial outbreak was associated with quinolones. In the largest series of Acinetobacter septicemia in patients with cancer (95 cases), 80% of cases were thought to be catheter related and responded to catheter removal and antimicrobial therapy. Infection was polymicrobial in 25% of cases.

**CLOSTRIDIUM SPECIES**

Clostridium species include highly virulent toxin-producing species as well as relatively avirulent saprophytes. Toxin-producing species can cause invasive disease such as myonecrosis (gas gangrene), empysematous cholecystitis and pyelonephritis, necrotizing enterocolitis (typhlitis), and septic shock (see *Intraabdominal Infections*, later in this chapter). Clostridium perfringens and *Clostridium septicum* are the most common clostridial species to cause bacteremia in patients with cancer. *Clostridium tertium* sepsis is less commonly observed, but is highly virulent. Cases of infection due to clostridial species other than *C perfringens*, *C. septicum*, and *C. tertium* are usually only associated with fever, without evidence of organ involvement, and a low mortality.

Extraintestinal clostridial infections can be devastating. The morbidity and mortality associated with clostridial bacteremia depends on the virulence of the species and the immune status of the host. Clostridial bacteremia after septic abortion is usually self-limited, but clostridial bacteremia with septic shock and myonecrosis requires emergent surgical debridement.

Body et al. evaluated 136 episodes of bacteremia due to clostridial species in patients with cancer. Most cases were associated with leukemia, gastrointestinal, and genitourinary malignancies. Eighty-three cases were monomicrobial and 53 were polymicrobial. In 45% of cases of polymicrobial bacteremia, three or more organisms were isolated from the blood. Isolates associated with clostridial sepsis consisted predominantly of enteric flora. *E. coli*, Klebsiella species, and Bacteroides species. Polymicrobial bacteremias were more likely to result in septic shock and death. The overall survival rate from clostridial bacteremia was 58%, a dramatically poorer prognosis than monomicrobial bacteremias caused by aerobic gram-positive and gram-negative species.

Local and systemic clostridial infections are associated with gastrointestinal and genitourinary neoplasms. They are normally commensals, but proliferate in tissues with a low redox potential, such as necrotic tumors. Damage to the mucosa by chemotherapy or radiation therapy likely further predisposes to local invasion and dissemination. Local bowel invasion by clostridial species can result in necrotizing colitis (typhlitis), which typically involves the cecum but can extend to other regions of the bowel.

Clostridial infections often have a fulminant course. Acute hemolysis, myonecrosis, diffuse spreading cellulitis, and septic shock have a high mortality. Clostridial myonecrosis may respond to rapid surgical débridement. A needle aspiration or biopsy of the infected tissue showing large, thick gram-positive rods is highly suggestive of the diagnosis. However, staining of the organism in clinical material may be variable or appear to be gram negative. In patients with leukemia, clostridial soft tissue infection and septic shock may be particularly rapid, precluding surgical intervention.

Clindamycin and metronidazole are both active against *Clostridia*. Clindamycin, in addition to its antianaerobic activity, may have a theoretical value of reducing toxin production. In a mouse model of myonecrosis by *C. perfringens*, clindamycin and metronidazole were each more effective than penicillin. The initial antibiotic regimen should also include an agent active against aerobic enteric flora, such as ceftriaxone, since deep soft tissue infections are often polymicrobial. In neutropenic patients, metronidazole or clindamycin plus an antipseudomonal b-lactam (such as cefazidime or ceftime), with or without an aminoglycoside, are reasonable regimens.

**MYCOBACTERIA**

Host defense against *Mycobacterium* species relies principally on functional T lymphocytes. It is therefore surprising that the incidence of *Mycobacterium tuberculosis* (MTB) infection in BMT recipients is relatively low. In two large BMT centers in the United States, MTB infection occurred in approximately 1 per 1000 patients. In a Saudi Arabian study, the incidence of tuberculosis was 0.6% among BMT recipients. In contrast, in a study in Hong Kong, a highly endemic area for MTB, reported a 5.5% incidence of MTB in BMT recipients. Therefore, an extra level of vigilance for MTB is necessary among patients who have resided in endemic countries.

In patients with compromised T-cell immunity, the clinical manifestations of infection due to MTB may be atypical, and disseminated disease is more common than in immunocompetent patients. The chest radiographic appearance is highly variable and may include an isolated nodule, an infiltrate, or a diffuse reticulonodular pattern indicative of hematogenous dissemination. The chest radiographic result may be negative in patients with disseminated extrapolmonary tuberculosis. Cavitary lung disease is less commonly observed in immunocompromised hosts. Extrapolmonary manifestations may include meningitis, brain abscess, vertebral or paravertebral abscess, septic joint, hepatic and splenic disease, and bone marrow involvement. Patients who consume unpasteurized dairy products are at increased risk of gastrointestinal tuberculosis caused by *Mycobacterium avium*. In addition, systemic iatrogenic *M. bovis* infection may rarely occur after intravesical therapy with bacille Calmette-Guérin for bladder cancer.

Because of the varied manifestations of MTB, a high index of suspicion may be required to make the diagnosis. For example, a new pulmonary nodule or infiltrate may be mistaken for aspergillosis, and gastrointestinal tuberculosis may be mistaken for GVHD. A definitive diagnosis should be pursued aggressively and early. Detection of mycobacterial DNA in clinical specimens by polymerase chain reaction (PCR) may facilitate a more rapid diagnosis, although cultures are required for drug susceptibility testing.

Due to the increased frequency of drug-resistant isolates, initial therapy for tuberculosis consists of a four-drug regimen (isoniazid, rifampin, pyrazinamide, and ethambutol) for the first 2 months. If a positive clinical response is seen, an additional 4 months of isoniazid and rifampin (if the isolate is sensitive to these agents) is administered. In patients with profound immunosuppression, it is reasonable to extend the course of therapy to 9 months, given the potential increased risk for drug-resistant tuberculosis caused by *Mycobacterium bovis*. In addition, *M. kansasii* infection may rarely occur after intravesical therapy with bacille Calmette-Guérin for bladder cancer.

Prevention of infection relies on compliance with established infection control measures, including respiratory isolation of persons with presumed or known active tuberculosis in negative pressure rooms. Given the low prevalence of tuberculosis in cancer centers in the United States, we suggest that skin testing be reserved for patients with some additional risk factor for tuberculosis (such as residence in an endemic country or human immunodeficiency virus infection).

Infection with nontuberculous mycobacteria (atypical mycobacteria) is well described among patients with cancer. Pathogenic species include *Mycobacterium avium* complex, *Mycobacterium kansasi*, *Mycobacterium haemophilum*, and the *Mycobacterium fortuitum-*chelonae complex. Clinical manifestations include pneumonia, soft tissue or wound infections, and central catheter infections that may require surgical excision of the infected tunnel site (see *Implanted Vascular Catheters*, later in this chapter). Patients with hairy cell leukemia appear to be particularly susceptible to *M. kansasi* infection. Sites of involvement include the lungs, lymph nodes, liver, and spleen, and disseminated disease. *M. haemophilum* may cause fatal pneumonia and disseminated cutaneous lesions. This organism has a unique...
requirement for iron supplementation for growth, and therefore the microbiology laboratory should be alerted that this diagnosis is being considered. Speciation of mycobacterial isolates is essential because atypical mycobacteria are typically resistant to regimens for MTB. DNA probes are used to rapidly identify isolates at the species level.

**NOCARDIA**

Nocardia infections are most frequent in patients with impaired T-cell immunity. Patients with Hodgkin's and non-Hodgkin's lymphoma receiving immunosuppressive therapy appear to be at particularly high risk for nocardiosis. In centers in which non-candidemia in stable neutropenic patients if no prior azole prophylaxis was administered and no evidence of hematogenous seeding or deep organ involvement increased. In a consensus conference dealing with the management of candidal infections, 17 of 20 investigators chose fluconazole for treatment of uncomplicated candidemia in neutropenic patients.

Management of candidemia in neutropenic patients is more controversial. Amphotericin B has been the standard therapy, but use of fluconazole in this population has increased. In the Disease Mycosis Study Group trial is underway to compare fluconazole plus amphotericin B versus fluconazole alone in nonneutropenic patients with candidemia. Due to the increased frequency of candidemia in patients found both regimens equally effective.

A large randomized study comparing intravenous fluconazole (400 mg daily) with amphotericin B (0.5 mg/kg daily) as therapy for candidemia in nonneutropenic patients reported no difference in outcome, either in patients with a central catheter or with a peripheral site. However, the time course of resolution is slower, and the therapy must be continued for months.

**FUNGAL INFECTIONS**

**CANDIDIASIS**

**Oropharyngeal and Esophageal Candidiasis**

Oral mucosal candidiasis, also called thrush, indicates T-cell immunodeficiency. In patients with cancer, conditions that predispose to oral candidiasis include cytotoxic chemotherapy causing mucosal disruption, high-dose corticosteroids, and use of broad-spectrum antibiotics.

The diagnosis of oral candidiasis is usually made visually. White adherent plaques develop on the palate, buccal mucosa, tongue, or gingiva. The differential diagnosis includes chemotherapy-induced mucositis, bacterial infections, and HSV infection. A wet mount or Gram's stain showing pseudohyphae establishes the diagnosis. A culture of the oral mucosa that grows Candida species is not by itself diagnostic as these species commonly colonize the mouth. Therapy for oropharyngeal candidiasis includes local treatments such as nystatin or clotrimazole troches or oral fluconazole.

Esophageal candidiasis is a more severe mucosal disease that typically manifests with odynophagia. The differential diagnosis includes esophageal infection by HSV, CMV (in BMT recipients), and bacterial infections (see Esophagitis, later in this chapter). Systemic antifungal therapy (fluconazole or amphotericin B) is required.

**Candidemia**

Candida species are the fourth most common nosocomial blood culture isolates in the United States. In some series, the attributable mortality to candidemia was 40% to 60%. This high mortality may reflect the fact that these patients often have serious comorbidities, such as malignancy, neutropenia, and illness requiring prolonged periods in the intensive care unit. In a European surveillance study of candidemia in cancer patients, the overall 30-day mortality was 39%, with increased mortality occurring in older patients, in those with poorly controlled malignancy, and in cases in which Candida (Torulopsis)glabrata was isolated. In a retrospective study of 476 cases of candidemia at M. D. Anderson Cancer Center, the mortality was 52%. Neutropenia, a high APACHE (Acute Physiology and Chronic Health Education) score, and disseminated disease were associated with poorer outcomes.

Candida albicans is the most common species isolated from the blood. The proportion of non-albicans Candida species varies among different centers. Among patients with cancer, non-albicans Candida species account for approximately 45% of cases of systemic candidiasis. Among non-albicans Candida species, Candida tropicalis was the most common isolate followed by C. glabrata, C parapsilosis, and C. krusei. The proportion of non-albicans Candida isolates has direct clinical significance. C. krusei is always resistant to fluconazole, and C glabrata is variably resistant. Some of these two species are isolated from the blood, and antifungal B therapy is necessary. C. tropicalis is more virulent than C albicans in immunocompromised animal models and often has a more severe clinical course in patients. C. tropicalis infection has been associated with increased mortality at the hospital. In contrast, C parapsilosis is mostly associated with vascular catheters and lipid formulations used for total parenteral nutrition. Some C guillermondii and C lusitaniae isolates are resistant to amphotericin B.

Antifungal susceptibility testing is becoming more common and gaining acceptance. Standard guidelines and interpretive breakpoints for susceptibility testing of fluconazole, itraconazole, and 5-flucytosine against yeasts have been proposed by the National Committee for Clinical Laboratory Standards. These may be useful in select cases in which resistance is suspected and in epidemiologic studies.

Isolation of Candida species from blood remains unreliable even with modern blood culture isolation systems. The sensitivity for detecting candidemia has been significantly improved by the lysis centrifugation system (Isolator, Wampole Laboratories, Cranbury, NJ) and the BacTAlert system (Organon Teknika, Durham, NC), which detect candidemia earlier and more reliably than conventional broth systems. However, in single organ infection and in early disseminated candidiasis, even lysis centrifugation culture has limited sensitivity. Nonculture methods, such as amplification by PCR, antigen detection, and detection of metabolites, are investigational and may prove useful in complementing culture methods. All candidemic patients, both neutropenic and nonneutropenic, should be treated with fluconazole or amphotericin B. Isolation of a Candida species from only a single blood culture (whether drawn from a catheter or peripheral vein), should be considered indicative of hematogenously disseminated disease. The rationale for early antifungal therapy is to avoid sequelae, such as endophthalmitis and hepatosplenic candidiasis. In a retrospective study of 155 cases of catheter-associated fungemia in patients with cancer, a significant proportion of patients who did not receive antifungal therapy after isolation of a Candida species from the blood (possibly because the isolate was considered to be a contaminant or candidemia was considered to be transient) subsequently developed disseminated candidiasis. The site of blood collection, either from a central catheter or peripheral site, had no predictive value in defining the risk of subsequent disseminated disease.

A large randomized study comparing intravenous fluconazole (400 mg daily) with amphotericin B (0.5 mg/kg daily) as therapy for candidemia in nonneutropenic patients was undertaken. In uncomplicated candidemia, at least 2 weeks of antifungal therapy after the last positive culture result should be administered. Due to the increased frequency of Candida isolates with intermediate or complete resistance to fluconazole, a National Institute of Allergy and Infectious Disease Mycosis Study Group trial is underway to compare fluconazole plus amphotericin B versus fluconazole alone in nonneutropenic patients with candidemia.

Management of candidemia in neutropenic patients is more controversial. Amphotericin B has been the standard therapy, but use of fluconazole in this population has increased. In a consensus conference dealing with the management of candidal infections, 17 of 20 investigators chose fluconazole for treatment of uncomplicated candidemia in stable neutropenic patients if no prior azole prophylaxis was administered and no evidence of hematogenous seeding or deep organ involvement existed. A randomized multicenter study showed that fluconazole and amphotericin B had comparable efficacy in invasive candidiasis in neutropenic and nonneutropenic patients. In centers in which non- albicans Candida species (most notably, C krusei and C glabrata) are frequently isolated, we believe that it is prudent to use amphotericin B initially. Candiduria in the neutropenic patient should be treated with systemic antifungal therapy because
of the risk of systemic infection in this population.

In unstable patients with candidemia as such as those with hypotension or hematogenously seeded deep organ infections, amphotericin B (1.0 mg/kg daily) should be initiated. Acute disseminated candidiasis may occur during neutropenia and is characterized by hypotension, skeletal muscle involvement (typically causing severe pain), multiorgan failure, and intravascular lesions. We suggest adding 5-flucytosine in these settings for synergy (Table 54-4). 5-flucytosine is also likely to be advantageous in central nervous system (CNS) candidiasis because of its excellent cerebrospinal fluid penetration. Inotropic support and hemodynamic monitoring may be necessary.

TABLE 54-4. Antifungal Agents Commonly Used in Patients with Cancer

The requirement for intravenous catheter removal in candidemia has never been evaluated in a randomized study. Early catheter removal may reduce the likelihood of late complications by eliminating a potential nidus of ongoing candidemia. Removal of intravenous catheters in candidemic patients has been shown to reduce the time to sterilization of the blood in nonneutropenic patients. The opposing argument is that in patients who have received cytotoxic chemotherapy, candidemia is likely to arise from defects in the gut mucosa rather than the catheter. Most investigators in the consensus panel would remove nonsurgically implanted catheters, but would attempt to sterilize surgically implanted catheters with antifungal treatment. If the catheter is not immediately removed, we advise rotating antifungal infusions through all ports to increase the likelihood of catheter sterilization. Clinical instability, lack of resolution of fever, and persistent candidemia after 1 to 2 days of antifungal therapy are each indications to replace all catheter devices.

Chronic Disseminated Candidiasis

Chronic disseminated candidiasis typically affects the liver and spleen. During neutropenia, these organs, as well as kidneys, lungs, skin, bone, and other sites, become seeded by Candida species in the blood stream (which may be undetected by blood culture). The only symptom may be persistent fever. After resolution of neutropenia, numerous target lesions in the liver and spleen become apparent by radiologic imaging, such as computed tomography (CT), ultrasonography, or magnetic resonance imaging. A liver biopsy is required for a definitive diagnosis, but because the lesions are discrete, the biopsy result may be falsely negative. An open or laparoscopic-guided liver biopsy is recommended if a percutaneous biopsy is nondiagnostic. Various acceptable therapeutic approaches exist. In stable patients, fluconazole (400 to 800 mg daily) may be used. Alternatively, amphotericin B (0.7 to 1.0 mg/kg daily) may be initially administered, followed by a prolonged course of fluconazole once fever has resolved and the lesions are improved. Because lipid formulations of amphotericin B preferentially accumulate in the blood vessel wall can lead to massive pulmonary hemorrhage and exsanguination. The radiographic appearance of pulmonary aspergillosis includes bronchopneumonia, lobar consolidation, segmental pneumonia, nodular lesions resembling septic emboli, and cavitary lesions (Fig. 54-2). Aspergillus fumigatus. The lesion in the right upper lobe consist of a hazy infiltrate surrounding a denser nodular lesion. This halo sign is most commonly associated with angioinvasive infection by Aspergillus species. Other filamentous fungi and Pseudomonas aeruginosa may have a similar appearance.

Hepatosplenic candidiasis per se is not a contraindication for subsequent antineoplastic myeloablative chemotherapy. Patients in whom fever and lesions have resolved with antifungal therapy can undergo further episodes of neutropenia without progression of the fungal infection if antifungal therapy is reinitiated during the neutropenic periods.

ASPERGILLOSIS

Prolonged and persistent neutropenia is a critical risk factor for aspergillosis. The more frequent use of allogeneic BMT for malignancy has expanded the risk factors for aspergillosis. Wad et al. conducted a case-control analysis of 158 cases of proven or probable cases of aspergillosis among BMT recipients. The onset of infection was bimodal, with the first peak occurring at a mean of 16 days after transplant (before or shortly after engraftment) and the second peak occurring at a mean of 96 days after transplant. Risk factors for late aspergillosis (after day 40 of transplantation) included age older than 18 years, diagnosis other than chronic myelogenous leukemia in chronic phase, an unrelated donor, acute GVHD (grade 2 to 4), neutropenia, and corticosteroid use. Among autologous BMT recipients, aspergillosis was most likely to occur during neutropenia and was rare after engraftment. In contrast, aspergillosis was more likely to occur after the first 40 days in allogeneic transplant recipients. Other series from Europe and Asia have also reported the predominance of aspergillosis cases occurring in the postengraftment period in BMT recipients, with GVHD being an important risk factor. The reasons for the increased proportion of aspergillosis in the postengraftment period are likely twofold: (1) a reduction in the neutrophil count as a result of myeloablative growth factors and infusion of larger numbers of myeloid progenitors and (2) increased proportion of unrelated donors and HLA-mismatched transplants, which predispose to GVHD.

Aspergillosis can involve virtually any organ in the immunocompromised host, but sinopulmonary disease is the most common. Alveolar macrophages constitute the first line of host defense against aerosolized conidia. After germination, neutrophils are the dominant host defense arm against the hyphal stage. Invasive aspergillosis in the neutropenic host may present as fever, sinus pain or congestion, cough, pleuritic chest pain, and hemoptysis. Erosion through a large central blood vessel wall can lead to massive pulmonary hemorrhage and exsanguination. The radiographic appearance of pulmonary aspergillosis includes hepatosplenic candidiasis. The CNS is a common target site for hematogenously disseminated aspergillosis (see Central Nervous System Infection, later in this chapter). Gastrointestinal aspergillosis usually coexists with pulmonary disease, but in rare instances it is the sole organ involved. In an early study, involvement of the gastrointestinal tract was documented at autopsy in approximately 50% of cases of disseminated aspergillosis. The manifestations include abdominal pain, gastrointestinal infarction...
with hemorrhage, perforation, and polymicrobial sepsis. Early diagnosis of isolated gastrointestinal aspergillosis followed by resection of the involved bowel and systemic antifungal therapy may be life saving. Other sites of disseminated aspergillosis include the skin, heart, eye, bone, kidney, liver, and thyroid.

Isolation of an Aspergillus species from a sputum or bronchoalveolar lavage specimen should be presumed to represent invasive disease in neutropenic patients. In the study by Wald et al., a mucosal isolate of an Aspergillus species had a positive predictive value of 60% for invasive disease among BMT recipients; during the neutropenic period, the positive predictive value was 94%. Early diagnosis of aspergillosis in highly immunocompromised patients remains difficult. Blood cultures are rarely positive, sputum and bronchoalveolar cultures have approximately 50% sensitivity in focal pulmonary lesions, and definitive diagnosis often requires an invasive procedure and is usually only made when the disease is advanced.

CT scanning of the chest may facilitate early detection of aspergillosis. A CT scan may show peripheral or subpleural nodules unapparent on plain chest radiographs. The halo sign is a characteristic chest CT feature of angioinvasive organisms. The hazy alveolar infiltrates appear to correspond to regions of ischemia and are highly suggestive of invasive aspergillosis. Ultrafast CT technology reduces the scanning time to as little as 5 minutes, thus permitting wider application to seriously ill patients. Early recognition of pulmonary aspergillosis followed by intensive antifungal therapy and surgical resection of localized disease (see discussion later in this section) has led to improved survival.

PCR-based detection of subclinical aspergillosis is a promising tool for early diagnosis. In a European study, 134 patients underwent at least two bronchoalveolar lavages at the time of BMT, and PCR for Aspergillus species was performed. Of seven patients whose bronchoalveolar lavage was PCR positive and culture and cytology were negative, five developed invasive pulmonary aspergillosis within the first 100 days of transplant. A larger study to prospectively evaluate the predictive value of PCR screening of whole blood for Aspergillus species DNA among allogeneic BMT recipients is underway. A sensitive double-sandwich enzyme-linked immunosorbent assay for detection of the fungal cell wall constituent galactomannan has been developed. Clinical trials are now essential to delineate which of these diagnostic methods, or which combination, provides the optimal positive and negative predictive value for invasive disease among high-risk patients, and how this information should be translated into a rational therapeutic algorithm.

Aspergillus fumigatus followed by *Aspergillus flavus* are the most common species causing invasive disease in neutropenic patients and after BMT. Therapy for invasive aspergillosis in neutropenic patients and in BMT recipients involves high-dose conventional amphotericin B (1.0 to 1.5 mg/kg daily) or a lipid formulation of amphotericin B. *Aspergillus terreus* is an emerging pathogen in this population that is notable for being resistant to amphotericin B. In cases of invasive *A* terreus infection, the third-generation triazole, voriconazole, may be of value based on in vitro sensitivity data.

Surgical excision of locally invasive disease, such as sinusitis, primary cutaneous lesions, intratracheal disease, or bone lesions should be performed. Removal of infected intravenous and peritoneal dialysis catheters and silk sutures in bronchial stumps are also necessary components of therapy. In neutropenic patients and in allogeneic BMT recipients, combined surgery and systemic antifungal therapy should be used in cases of apparent localized disease because of the risk of subclinical dissemination.

The indications for and timing of thoracic surgery for aspergillosis are controversial. In postmenopausal women patients, infection of the bronchial stump should be debrided and sutures removed. Invasive pleural and pericardial aspergillosis should be treated with decortication and stripping. When possible, pulmonary aspergillosis adjacent to major vessels should be surgically removed to avoid exsanguinating hemoptysis. In a retrospective series of patients with acute leukemia and pulmonary filamentous mycosis (mostly caused by *Aspergillus* species), hemoptysis most commonly occurred shortly after resolution of neutropenia.

Patients who recover from an episode of invasive aspergillosis are at risk for relapse during a subsequent course of myeloablative chemotherapy. In the largest series, a retrospective analysis was performed on 48 patients with definite or probable aspergillosis who subsequently were treated with BMT (77% allogeneic). All patients received systemic antifungal therapy, and approximately 40% underwent surgical resection as initial therapy. Forty-one of 48 (85%) patients received secondary prophylaxis at the time of BMT; the regimens included itraconazole, amphotericin B (conventional and lipid formulations), and combinations of agents with wide variability in dosage and duration. The overall incidence of relapse was 29% among patients receiving secondary prophylaxis and 57% among those who did not. Seventeen of 16 (88%) patients who had relapsed died. Other smaller series have also shown that systemic antifungal therapy (with and without surgical resection) of primary fungal infection followed by secondary prophylaxis can suppress reactivation in the majority of patients subsequently undergoing additional myeloablative chemotherapy or BMT.

We advise using high-dose amphotericin B (1.0 to 1.5 mg/kg daily) or a lipid formulation of amphotericin B for secondary prophylaxis of invasive aspergillosis during neutropenia after intensive chemotherapy for leukemia or preparative regimens for BMT. Oral itraconazole is more suitable as a maintenance regimen after resolution of neutropenia and mucositis. Antifungal prophylaxis should be reintroduced preemptively during GvHD. Surgical resection does not obviate the need for secondary antifungal prophylaxis during subsequent chemotherapy given the likelihood of residual foci of disease not apparent on diagnostic imaging.

An additional component in treating aspergillosis is reversal or amelioration of immunosuppression. In patients with neutropenia and disseminated aspergillosis, resolution of neutropenia is critical for survival. Granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) may accelerate myelopoiesis and reduce the neutropenic period as well as augment neutrophil activity. Use of these agents for treatment of serious fungal infections is limited so far to case reports. Corticosteroid therapy should be reduced or discontinued if at all feasible. Granulocyte transfusions may stabilize progressive invasive aspergillosis refractory to antifungal chemotherapy and allow more time until recovery from neutropenia (see *Granulocyte Transfusions*, later in this chapter).

**ZYGOMYCOSIS**

Risk factors for zygomycosis (also termed mucormycosis) include diabetic ketoacidosis, protein-calorie malnutrition, iron overload, and prolonged neutropenia. Patients recovering potent myeloablative chemotherapy for leukemia are at risk for locally invasive as well as disseminated disease.

Zygomycosis typically manifests as rhinocerebral or pulmonary disease after inhalation of spores. In rhinocerebral disease, fever, facial pain, and headache are common findings. Contiguous extension may lead to orbital involvement with proptosis and extracocular muscle paresis, involvement of hard palate, and spread to the brain. An eschar over the palate is suggestive of zygomycosis, but other filamentous fungi can produce similar findings in highly immunocompromised persons. Occasionally, isolated primary cutaneous disease may follow minor trauma. Injection drug users may inject contaminating spores directly into the blood stream and may present with isolated space-occupying lesions of the brain or other organs. Therapy for zygomycosis involves high-dose amphotericin B (conventional or lipid formulations) plus early and aggressive surgical débridement. Itraconazole is not active against *Zygomycetes* species.

**CRYPTOCOCCUS NEOFORMANS**

Among patients with cancer, lymphoreticular malignancy and corticosteroid therapy appear to be major risk factors. Host defense against cryptococcal infection is dependent on T-cell immunity. Isolated neutropenia is rarely associated with cryptococcal infection. Immunoglobulins directed against capsular epitopes and complement facilitate phagocytosis of the organism and likely play a role in host defense.

Although meningitis is the most common presentation of cryptococcal infection, other manifestations include primary pneumonia, fungemia, and cutaneous and visceral dissemination. In the pre–acquired immunodeficiency syndrome (AIDS) era, patients who died early during therapy were more likely to have rapidly progressive disease, cerebral fluid with high opening pressure, a low glucose level, less than 20 leukocytes/µL, a positive India ink preparation, culture and blood cryptococcal from extraneuronal sites, and high titer of cryptococcal antigen in serum and cerebrospinal fluid. A more recent study of non-AIDS–associated cryptococcal disease showed that mortality was highest among persons with malignancy. Additional CNS complications include development of a mass lesion, obstructive hydrocephalus requiring shunting, and vision loss. Vision loss may be a consequence of endophthalmitis, a space-occupying lesion in the visual pathway, direct invasion of the optic nerve (which may cause vision loss over several hours), and as a consequence of elevated intracranial pressure.

Optimal therapy for non-AIDS–associated cryptococcal disease is not well defined. In a classic study, Bennett et al. showed that the combination of amphotericin B plus 5-flucytosine for 6 weeks superior to amphotericin B alone administered for 10 weeks in non-AIDS–associated cryptococcal meningitis. In AIDS-associated
cryptococcal meningitis, the optimal regimen currently is amphotericin B (0.7 mg/kg daily) plus 5-flucytosine (100 mg/kg daily) for the first 2 weeks, followed by life-long maintenance fluconazole therapy (400 mg daily). This is an appropriate regimen to use in non-AIDS–associated cryptococcal infection in the absence of modern randomized trials. In neutropenic patients, reduction of the dosage of 5-flucytosine may be considered to avoid delay in myeloid recovery. Because fluconazole is well tolerated, continuing therapy with this agent for several months (or longer if intensive immunosuppressive therapy is continued) is reasonable. In a retrospective series, fluconazole was as efficacious as amphotericin B as initial therapy for non-AIDS–associated cryptococcal disease. Further studies are required to evaluate initial therapy with fluconazole in different populations with cryptococcal disease.

**EMERGING OPPORTUNISTIC FUNGAL PATHOGENS**

**Trichosporon Species**

Trichosporon species typically infect profoundly neutropenic patients and those receiving corticosteroid therapy. Acute disseminated trichosporonosis typically manifests with refractory fungemia, funguria, cutaneous lesions, renal failure, pulmonary lesions, and cholestasis. Disseminated trichosporonosis may yield a false-positive cryptococcal latex antigen test result because of cross-reactivity with the polysaccharide capsule of **C neoformans**. This cross-reactivity may be clinically important because patients treated with high-dose corticosteroid therapy are at risk for both infections, and **C neoformans** typically responds to amphotericin B therapy, whereas Trichosporon species are usually resistant.

*In vitro* and experimental infections indicate that most Trichosporon species are inhibited, but not killed, by achievable serum levels of conventional amphotericin B. Fluconazole has superior activity in experimental infections and is recommended as the preferred antifungal agent. Combination therapy with high-dose amphotericin B (1.0 to 1.5 mg/kg daily) and fluconazole (800 mg daily or 12 mg/kg daily in children) may have synergy against some strains based on murine models of trichosporonosis.

Blastocystis hominis capsulatus (formerly *Trichosporon capsulatum*) usually presents as a chronic disseminated infection, resembling chronic candidiasis. A CT scan may show lesions suggestive of hepatosplenic candidiasis, and definitive diagnosis requires either a positive blood culture result or biopsy. CNS involvement is also observed. *B capsulatum* does not cross-react with the cryptococcal latex agglutination test.

**Malassezia Species**

Malassezia furfur is often associated with lipid parenteral nutrition administered through a central venous catheter in immunocompromised patients or premature infants. Clinical manifestations, including pustules, pruritus, and candidiasis, occur in premature infants but not in adults. Blood culture recovery is enhanced by addition of olive oil or other long-chain fatty acids to the culture plates.

*M furfur* is often refractory to amphotericin B therapy. Fluconazole therapy is probably the drug of choice, but discontinuation of lipid infusions and removal of the central catheter are important for succed with corticosteroids, a folliculitis resembling disseminated candidiasis may occur. This infection is a localized process and does not imply disseminated infection. *Malassezia pachydermatis* is a less common cause of infection than *M furfur* and has similar clinical manifestations.

**Dematiaceous (Dark-Walled) Molds**

Dark-walled molds contain melanin in their cell walls that imparts a brown or olive-green pigment in culture. In immunocompromised patients, soft tissue infection, sinusitis, CNS infection, pneumonia, fungemia, and disseminated disease are observed. Subcutaneous infection is most frequently caused by *Alternaria* species.

Bipolaris, Cladophialophora (Xylohypha or Cladosporium) bantiana, Wangiella, and Dactylaria species have strong predispositions to cause CNS disease.

Definitive diagnosis of phaeohyphomycosis requires documentation of fungal invasion and recovery of the mold from culture of tissue specimens. Positive results of Fontana-Masson staining of tissue specimens, which detects phenolic compounds, including melanin, are suggestive, but not diagnostic, of phaeohyphomycosis.

Disseminated infection by *Bipolaris* species may yield a positive blood culture result.

Therapy in immunocompromised patients involves surgical excision of localized disease when feasible and systemic antifungal therapy. Amphotericin B (1.0 to 1.5 mg/kg daily) is standard initial therapy. Sensitivity to amphotericin B is variable, and clinical failures have been reported. Itraconazole has been shown to be effective in cases of phaeohyphomycosis refractory to amphotericin B. Our practice has been to use amphotericin B plus itraconazole as initial therapy for phaeohyphomycosis in severely immunosuppressed patients, followed by prolonged itraconazole maintenance therapy once stabilization has been achieved. Monitoring of serum itraconazole levels is necessary to document oral absorption.

**Fusarium Species**

Fusarium species are soil saprophytes that have been associated with soft tissue infection, onychomycosis, and keratitis in immunocompetent hosts. With the widespread use of intensive antineoplastic therapy and BMT, more than 150 cases of invasive and disseminated fusariosis have been reported, most within the 1990s. The clinical findings and histologic appearance may be indistinguishable from aspergillosis. In the absence of a definitive culture diagnosis, the likelihood of infection by a *Fusarium* species is substantially increased by the presence of disseminated cutaneous lesions and isolation of a mold from blood culture.

Boudati and Anaissie made important observations about invasive and disseminated fusariosis in a retrospective review of 43 cases occurring in patients with hematologic malignancies at M. D. Anderson Cancer Center. Most cases of disseminated fusariosis were diagnosed during neutropenia, and a high risk of relapse associated with subsequent myelosuppression. Similar to aspergillosis, a bimodal distribution of fusariosis occurred in BMT recipients (before and after myeloid engraftment). The skin was identified as an important portal of entry. Initial localized manifestations included onychomycosis, paronychia, and cellulitis. Early identification of localized skin disease and surgical débridement may be life saving. Inhalation of spores is another major portal of entry, leading to fungal sinusitis and pneumonia.

Survival from disseminated fusariosis is critically dependent on resolution of neutropenia. Despite the poor response, amphotericin B (1.0 to 1.5 mg/kg daily) or a lipid formulation (greater than or equal to 5 mg/kg/d) is standard therapy. We use G-CSF and granulocyte transfusions in combination with antifungal therapy to try to control the infection until myeloid recovery occurs.

**Scedosporium Species**

*Scedosporium apiospermum* (*Pseudallescheria boydii*) and *Scedosporium prolificans* are the principal pathogenic species in the genus *Scedosporium*. In neutropenic patients, *P boydii* is a virulent pathogen, which clinically and histologically resembles aspergillosis. Invasion of blood vessels leading to infarction is common. *P boydii* causes sinopulmonary disease, endophthalmitis, and dissemination to the CNS. The infection can also spread directly from the skin to bone and joint. Establishing a culture diagnosis of *P boydii* is important because of its frequent resistance to amphotericin B. *P boydii* is usually susceptible to azoles, and *in vitro* studies and some clinical experience suggest that the combination of amphotericin B plus an azole (e.g., fluconazole, itraconazole, or miconazole) may provide enhanced activity.

Surgical resection of localized lesions is strongly advised. *S prolificans* causes a similar spectrum of disease as *P boydii* and is generally resistant to all antifungal agents.

**ENDEMIC DIMORPHIC FUNGI**

Endemic dimorphic fungi are so named because of their characteristic geographic distribution. These organisms include *Histoplasma capsulatum*, *Coccidioides immitis*, * Blastomyces dermatitidis*, and *Penicillium marneffei* (*P marneffei* is endemic in Southeast Asia). These fungi are dimorphic, existing in nature in the mycelial stage, and convert to yeast stage at body temperature. Because some of these pathogens may be quiescent during the initial infection and only manifest clinically during a subsequent period of severe depression or cell-mediated immunity, a detailed travel history is essential.

Endemic mycoses in the central United States include histoplasmosis and blastomycosis. In the immunocompetent host, inhalation of *Histoplasma microconidia* is
typically asymptomatic, but may manifest with acute fever, pulmonary infiltrates, and hypoxia. Immunocompromised patients have a higher risk of disseminated histoplasmosis involving the liver, spleen, lymph nodes, bone marrow, adrenal glands, mucocutaneous tissues, gastrointestinal tract, and CNS. The chest radiograph may show a miliary reticulonodular appearance, suggestive of tuberculosis. An acute sepsis syndrome with hypotension and disseminated intravascular coagulation, adrenal crisis, and meningitis are additional potentially lethal complications.

A rapid diagnosis of histoplasmosis can be made by Giemsa staining of a peripheral blood smear of bone marrow aspirate demonstrating characteristic intracellular yeast forms. Lysis centrifugation is the preferred blood culture system. Antigen detection from blood and urine is a sensitive and specific method in disseminated disease. Antibody detection may also be useful, but false-negative results may occur in immunocompromised patients. Biopsy of specimens may show intracellular or narrow budding yeasts suggestive of the diagnosis, which should be confirmed by culture. In the immunocompromised patient, histoplasmosis should be treated with high-dose amphotericin B (1.0 to 1.5 mg/kg of body weight daily). Prolonged therapy with itraconazole may be initiated after stabilization of disease and should probably be continued for the duration of immunosuppression.

Blastosomyces dermatitidis may present as an acute pulmonary infection resembling bacterial pneumonia, or as a chronic infection resembling tuberculosis or lung cancer. Extrapulmonary manifestations include involvement of bone, prostate, and CNS. Skin disease resulting from direct inoculation includes large ulcerative and verrucous lesions. 

Coccidioides immitis is endemic in the southwestern United States. In normal persons, infection is usually asymptomatic or self-limited. In patients with compromised cell-mediated immunity, C. immitis is likely to be more virulent. In an early review of C. immitis infection in immunocompromised patients, disseminated disease occurred in almost one-half of the cases and was associated with a high mortality. Progression of infection was often fulminant, and evidence of pulmonary disease frequently occurred after signs of dissemination manifested. Diagnosis is most easily established by serology (in systemic disease) or demonstration of pathognomonic spherules in sputum or tissue samples. Coccidioidomycosis can involve virtually any organ in disseminated disease, but has a particular tropism for bone and the CNS. Therapy for disseminated disease generally requires amphotericin B followed by maintenance fluconazole. Intracranial amphotericin B should be added in cases of meningitis.

ANTIFUNGAL AGENTS

Azoles

The antifungal activity of azoles principally results from inhibition of the enzyme, lanosterol 14-a-demethylase, which converts lanosterol to ergosterol, a critical component of the fungal cell membrane. These agents also inhibit the cytochrome P-450-dependent enzymes of the fungal respiratory chain. One of the potential toxicities of these compounds is that, to varying degrees, they inhibit mammalian hepatic cytochrome P-450 mixed function oxidases (e.g., 3A4, 3C9, and 3C19), which are involved in the metabolism of numerous drugs. Thus, the potential exists for serious and even life-threatening drug-drug interactions resulting from toxic levels of drugs metabolized by cytochrome P-450 system when they are administered concurrently with the antifungal azoles. The triazoles fluconazole and itraconazole are the most commonly used azoles in patients with cancer (see Table 54-4).

Fluconazole

Fluconazole has activity against yeasts, dermatophytes, and dimorphic fungi, but not against Aspergillus species and other filamentous fungi. It has a favorable pharmacokinetic profile. The oral bioavailability of fluconazole exceeds 90%, and absorption is not affected by food or gastric pH. Fluconazole effectively penetrates the CNS, making it a valuable drug for maintenance therapy for cryptococcal and coccidioidal meningitis. The elimination half-life is approximately 30 hours. Drug–drug interactions with fluconazole appear to be less severe than with itraconazole and ketoconazole.

The minimum dose of fluconazole for candidemia or invasive candidiasis is 400 mg daily in adults or 8 to 10 mg/kg/d in children. Dosage reduction is required in patients with renal impairment (creatinine clearance less than 50 mL/min). Clinical experience has been gained using dosages of 800 mg or greater, and several investigators recommend using such a dosage in patients with invasive candidiasis until control of infection is achieved.

One of the major uses of fluconazole in patients with cancer is as a prophylactic agent. In BMT recipients, two double-blind, placebo-controlled trials have shown that prophylactic fluconazole controlled yeast colonization and reduced the rate of mucosal candidiasis and invasive Candida infections. The use of empiric amphotericin B for prolonged neutropenic fever also was delayed. A reduction in mortality was noted in one of the studies. In an autopsy series of BMT recipients performed at the Fred Hutchinson Cancer Research Center, fluconazole prophylaxis was associated with a reduction in candidal infections, most notably in hematopoietic candidiasis, but infections by Aspergillus species were increased.

Fluconazole prophylaxis has produced mixed results in patients with leukemia receiving chemotherapy. In one randomized study, fluconazole prophylaxis was associated with a reduction in skin and mucosal infection and delay in empiric amphotericin B, but with no significant difference in invasive candidiasis or mortality in comparison with the placebo arm. In another study, fluconazole prophylaxis reduced fungal colonization, invasive infection, and fungal infection-related mortality in patients with leukemia receiving intensive cytotoxic chemotherapy. The major concern with prophylactic fluconazole is the emergence of resistant Candida species (see Candidemia, earlier in this chapter).

Itraconazole

Itraconazole has antifungal activity against yeasts, dermatophytes, and dimorphic fungi, and in contrast to fluconazole, is also active against Aspergillus species and dark-walled molds. Itraconazole is not active against Fusarium species or the agents of zygomycosis.

Itraconazole is available in oral form (capsules and solution) but its oral bioavailability can be erratic. The parenteral solution of itraconazole has been made available in the United States. However, little is known about its use in neutropenic hosts or BMT recipients. Itraconazole is solubilized only at an acidic pH, and thus absorption is compromised in patients with achlorhydria and in those patients taking antacids or H2 receptor antagonists. Absorption is enhanced when itraconazole is taken with a fermented acidic beverage. The cyclodextrin preparation of itraconazole is in solution form and has approximately a twofold increased bioavailability compared with that of itraconazole capsules. Because of the inconsistent absorption, plasma itraconazole levels should be monitored. There is no established target plasma itraconazole level that has been clearly associated with clinical response. In a cyclosporin-methylprednisolone animal model, plasma itraconazole levels were shown to correlate with microbiologic clearance of experimental aspergillosis. Based on such studies, we recommend that the plasma itraconazole level should be at least 4 μg/mL by bioassay or 1 μg/mL by high-pressure liquid chromatography in the setting of invasive fungal infection.

Itraconazole is approved as a second-line agent for treatment of aspergillosis in patients intolerant of amphotericin B. In a nonrandomized, compassionate use protocol, itraconazole had comparable efficacy compared with amphotericin B in the treatment of invasive aspergillosis in a variety of patient populations. We advise that amphotericin B (conventional or lipid formulation) be the initial agent of choice for invasive mold infections in neutropenic or otherwise severely immunocompromised patients with cancer. The bioavailability of the oral preparation of itraconazole is unreliable, making it more suitable as a maintenance regimen after control of infection has been achieved. Randomized, prospective studies are required to delineate the optimal role of parenteral itraconazole in neutropenic patients and BMT recipients.

Third-Generation Azoles

In view of the lack of antifungal activity of fluconazole against filamentous fungi, the increasing frequency of fluconazole-resistant Candida species, and the inherent limitations of oral administration of itraconazole, newer azoles have been developed to overcome some of these limitations. Voriconazole, posaconazole (SCH 56592), and ravuconazole (BMS 207147) are third-generation triazoles that are currently being evaluated in clinical trials. These agents can be administered orally or intravenously and have activity against Candida species (including species that are resistant to fluconazole), Aspergillus species, dematiaceous molds, Fusarium species, and dimorphic fungi.

AMPHOTERICIN B. Amphotericin B is a member of the polyene group of antifungal agents whose principal mechanism of action is binding to ergosterol, a sterol present in fungal cell membranes. Amphotericin B is active against the majority of fungal pathogens. However, in vitro and clinical resistance to amphotericin B has been encountered in a variety of pathogenic fungi affecting patients with cancer, including isolates of Candida lusitaniae, Trichosporon beigeli, Pseudallescheria boydii,
**Fusarium species**, and *Aspergillus terreus*. High dosages (1.0 to 1.5 mg/kg daily) of conventional amphotericin B are required for invasive filamentous fungal infections.

Multiple toxicities are observed with conventional amphotericin B. Acute infusion-related events include fever, rigor, myalgia, nausea, and, less commonly, hypotension, flushing, and bronchospasm. Fever and rigors may result from release of IL-1 and TNF-α from monocytes and tend to be most severe during the initial infusions and abate with subsequent administrations. Infusion-related reactions can be lessened with slowing the infusion rate and premedication with acetaminophen, antiemetics, low-dose dexamethasone (25 to 50 mg in adults), and meperidine (reduces rigors).

The principal long-term adverse effect of amphotericin B is nephrotoxicity. Azotemia occurs in a large proportion of patients receiving amphotericin B, and nephrotoxicity may be compounded by concomitant administration of other nephrotoxic agents such as CSA and aminoglycosides. The azotemia in part results from an increase in tubular glomerular feedback leading to a reduction in glomerular filtration. Administration of normal saline (2 to 4 mL/kg) before amphotericin can prevent or ameliorate this physiologic azotemia.

Concomitant administration of amphotericin B is almost invariably associated with renal potassium and magnesium wasting, requiring aggressive electrolyte replacement, often for weeks after the drug has been stopped. Renal tubular acidosis is also observed. Normochromic normocytic anemia likely mediated by suppression of erythropoietin synthesis is another common toxicity.

The toxicity of amphotericin B not only contributes to patient morbidity, but also limits the maximum dosages that can be administered. Lipid formulations of amphotericin B are significantly less nephrotoxic and, in the case of liposomal amphotericin B, reduced infusion-related toxicity. These lipid formulations (in addition to the newer broad-spectrum azoles and antifungal peptides) are therefore highly promising drugs that are evolving as important alternatives to conventional amphotericin B. Three lipid preparations of amphotericin B have been licensed: liposomal amphotericin B (LAMB or Ambisome), ABLC, and amphotericin B colloidal dispersion (ABCD). These lipid preparations have different biochemical and pharmacokinetic properties, which have been discussed in detail elsewhere.

**LIPOSOMAL AMPHOTERICIN B. LAMB.** is the only true liposomal preparation of amphotericin B, consisting of unilamellar spheric vesicles. Walsh et al. compared LAMB (343 patients) with conventional amphotericin B (344 patients) in neutropenic cancer patients with fever persisting for 5 days or more in a prospective randomized double-blind multicenter study of empiric antifungal therapy. Standard dosages of the two regimens were used (LAMB at 3 mg/kg daily and conventional amphotericin B at 0.6 mg/kg daily), and dose reductions were allowed in cases of renal insufficiency. The liposomal preparation was associated with a reduced incidence of nephrotoxicity, and infusion-related side effects, including fever, chills, hypotension, hypertension, and hypoxia. Fewer proven breakthrough invasive fungal infections (11 proven, six probable) occurred in the LAMB arm in comparison with 30 (27 proven, three probable) in the conventional amphotericin B arm (P = .009). A significantly lower incidence of breakthrough candidemia occurred in the LAMB versus the conventional amphotericin B arm 93 versus 12 patients, respectively (P = .03). Survival at 7 days after study drug initiation was approximately 90% in both groups. A European study of LAMB versus conventional amphotericin B found reduced nephrotoxicity in the LAMB arm. In a prospective, randomized trial comparing LAMB (3 or 5 mg/kg daily) with ABCD (5 mg/kg daily) as empiric therapy for persistent febrile neutropenia, patients receiving LAMB had significantly reduced infusion-related toxicity and nephrotoxicity.

**AMPHOTERICIN B LIPID COMPLEX. ABLC.** derives its name from being a complex of two phospholipids arranged in a ribbon-like structure. In the largest series, LABC (5 mg/kg/d) was evaluated on an emergency use basis in 556 patients with definite or probable invasive mycosis in which the infection was refractory or the patient was intolerant to standard antifungal agents. Among patients with significant azotemia at baseline, the mean serum creatinine improved over the course of ABLC therapy. Among 291 confirmed cases of fungal infection, response to ABLC occurred in 55 of 130 (42%) cases of aspergillosis, 28 of 42 (67%) cases of disseminated candidiasis, 17 of 24 (71%) cases of zygomycosis, and 9 of 11 (82%) cases of fusariosis. Open-label ABCD was also effective in an emergency use study of children with invasive fungal infections. In a prospective study comparing ABLC with conventional amphotericin B as treatment for hematogenous and invasive candidiasis, the two agents had similar efficacy, but ABCD was associated with reduced nephrotoxicity.

**AMPHOTERICIN B COLLOIDAL DISPERSION. ABCD.** is a complex of amphotericin B and cholesteryl sulfate forming a disc-like structure. In a dose-escalation study in BMT recipients with invasive fungal infections, infusion-related toxicities occurred in approximately 70% of patients; however, nephrotoxicity was not observed. ABCD (4 mg/kg daily) was less nephrotoxic and to a greater extent than conventional amphotericin B, in a retrospective series of 220 BMT recipients with invasive fungal infection. In an open-label compassionate use protocol in patients with invasive mycosis who either failed or were intolerant to conventional amphotericin B, the clinical response rate was approximately 50%, and nephrotoxicity was uncommon. In a retrospective study, 82 patients with proven or probable aspergillosis treated with ABCD had increased survival (50% vs. 28%) and reduced nephrotoxicity compared with historical controls treated with amphotericin B. ABCD as empiric therapy for prolonged neutropenic fever was associated with less nephrotoxicity but a greater frequency of infusion-related hypoxia and chills compared with conventional amphotericin B.

**WHEN TO CONSIDER A LIPID FORMULATION OF AMPHOTERICIN B.** Clinical trials and a growing clinical experience suggest that lipid formulations of amphotericin B have comparable efficacy and reduced nephrotoxicity compared with conventional amphotericin B. However, the majority of treatment protocols for definite or probable invasive mycosis are limited by being open label and uncontrollable or using historical controls. The high cost of the lipid formulations of amphotericin B is an important consideration. However, in a retrospective study of 239 immunosuppressed patients receiving conventional amphotericin B for aspergillosis, serum creatinine greater than 2.5 mg/dL and BMT (autologous and allogeneic) were independently associated with subsequent requirement for dialysis and a higher mortality. Seen in this light, lipid formulations of amphotericin B may reduce morbidity and cost in select patient groups.

A reasonable approach is to use a lipid preparation of amphotericin B as initial therapy when baseline renal insufficiency exists (e.g., creatinine clearance less than 50 mL/min) or a concomitant nephrotoxic agent is used (e.g., aminoglycoside, cyclosporin, foscarnet). Progressive deterioration of renal function despite adequate supportive care and infusion-related toxicities, hypotension, and hypomagnesemia, inadequately controlled by premedication regimens clearly justify the use of a lipid preparation of amphotericin B. If maximal dosages of conventional amphotericin B do not adequately control infection, a lipid formulation may be considered as a salvage regimen. In the setting of invasive mycotic infections, the maximum recommended dosages of lipid formulations should be used.

**Echinocandins**

A large number of naturally produced antibacterial and antifungal peptides have been characterized. These antimicrobial peptides have been isolated from mammals, amphibians, insects, and bacterial and fungal species. Antifungal peptides have two principal modes of action: (1) direct damage to the fungal membrane structure and (2) inhibition of synthesis of cell wall constituents. The latter group can in turn be divided into inhibitors of chitin and glucan synthesis.

The echinocandins are a family of cyclic lipopeptides that are noncompetitive inhibitors of (1,3)-β-D-glucan synthase, an enzyme complex that forms glucan polymers in fungal cell walls. Echinocandins have a broad spectrum of activity against Candida and Aspergillus species and P carinii. Three echinocandins are leading candidates for clinical development, caspofungin (MK0991), LY303366, and FK463. In a series of 400 blood stream isolates of Candida species, echinocandins were active against all isolates, including those that were resistant to fluconazole or itraconazole. Echinocandins were effective in animal models of disseminated candidiasis and aspergillosis.

Echinocandins have been used successfully in AIDS-associated mucosal and esophageal candidiasis. Currently, caspofungin (Merck) and FK463 (Fujisawa Health Care) are being evaluated in phase III studies of hematogenous candidiasis and as prophylaxis in BMT recipients, respectively. Other echinocandin agents are in preclinical stages of development.

**VIRAL INFECTIONS**

**HERPES VIRUSES**

The herpes viruses are the most important viral pathogens in patients with cancer. Pathogens in this group include HSV 1 and 2, varicella zoster virus (VZV), CMV, EBV, and human herpesvirus 6 (HHV-6). These DNA viruses establish a latent phase after primary infection, in which the viral genome resides in target cells for the lifetime of the host, with the potential to reactivate. Host defense against these viruses is dependent on virus-specific helper and cytotoxic T lymphocytes, and thus both the likelihood of reactivation and the severity of disease are augmented during profound T-cell immunosuppression. Table 54-5 summarizes common antiviral agents used in patients with cancer (see reference 158 for an excellent review).
Prophylaxis: antiviral agents are administered to all CMV-seropositive BMT recipients (CMV-seronegative recipients receiving seropositive bone marrow were CMV-seropositive allogeneic transplant recipients produced similar results. Guanosine, is approximately 50 times more active than acyclovir against CMV.

Offering anti-CMV prophylaxis to all seropositive allogeneic transplant recipients has important advantages and shortcomings. In two studies, acyclovir prophylaxis agents have been used successfully to reduce the rate of CMV disease. The following two preventive approaches have been evaluated in allogeneic BMT studies.

Reactivation of latent CMV infection after transplantation occurs in approximately 70% of seropositive recipients who do not receive antiviral prophylaxis. Antiviral agents can be treated initially with an oral regimen (famciclovir, 500 mg three times a day, or valacyclovir, 1 g three times a day) under close observation. Disseminated HSV disease should be treated with intravenous acyclovir (10 mg/kg every 8 hours). Acyclovir prophylaxis during intensive myeloablative chemotherapy for acute leukemia and during the early period of BMT markedly reduces the incidence of HSV.

**Herpes Simplex Virus**

HSV differs from other members of the herpes virus group by predominantly affecting patients during profound neutropenia. Among seropositive patients, the incidence of HSV reactivation is approximately 70% to 80% after induction chemotherapy for leukemia or conditioning for BMT in seropositive patients. Among BMT recipients, HSV disease is most likely to occur within the first few weeks, but may occur in later stages during intense immunosuppression. Oropharyngeal HSV (usually caused by HSV-1) during neumonectomy may be severe, causing gingival disease, stomatitis, and cheilitis, clinically indistinguishable from mucositis after cytotoxic chemotherapy. An oral swab culture for HSV detects viral shedding, suggesting that HSV is contributing to the mucosal disease. Local spread of HSV may cause esophagitis, and aspiration of mucosal HSV may occasionally lead to tracheitis and pneumonia. Documentation of pulmonary involvement requires a biopsy because respiratory secretions may be contaminated by oral mucosal HSV. Disseminated HSV disease may involve the skin abdominal organs (most notably, necrotizing hepatitis) and brain. HSV-2 disease is more likely to cause genital and anal disease.

Diagnosis of HSV disease is made by culture, by biopsy material, or both showing characteristic inclusions with positive immunohistochemistry. In patients with mucosal disease, it is safest to treat with intravenous acyclovir (5 mg/kg every 8 hours), switching to an oral regimen when the disease is abating. Milder HSV disease can be treated initially with an oral regimen (famciclovir, 500 mg three times a day, or valacyclovir, 1 g three times a day) under close observation. Disseminated HSV disease and HHV-6 disease should be treated with intravenous acyclovir (10 mg/kg every 8 hours).

**CMV disease most commonly occurs in the postengraftment period, between days 30 and 100 of transplantation. However, disease after day 100 is well documented.** In patients with GVHD requiring intensive immunosuppressive therapy, T-cell immunity is suppressed, and the risk for CMV disease is consequently increased. Antilymphocyte antibody preparations profoundly reduce the number of circulating T cells and likely further increase the risk of CMV reactivation. CMV disease is far less frequent in autologous BMT recipients, but can be lethal. CD34-selected autologous stem cell transplantation is associated with a greater risk of CMV disease than conventional nonselected peripheral stem cell transplantation. The period of risk in autologous transplantation is generally confined to the first 3 months, corresponding to the period of reconstitution of T-cell immunity.

CMV infection, either primary or reactivated, can have protean manifestations in the BMT recipient, ranging from asymptomatic viral shedding. In a self-limited mononucleosis-like syndrome, to life-threatening organ disease. Pulmonary disease typically manifests as an interstitial pneumonitis resembling PCP, associated with hypoxia and progression to respiratory failure. A definitive diagnosis of CMV pneumonitis requires a compatible clinical syndrome plus either the histologic documentation of characteristic CMV inclusions within parenchymal tissue or intracellular inclusions within epithelial cells obtained by bronchoalveolar lavage. Because CMV can be shed from pulmonary secretions without causing invasive disease, simple recovery of CMV from pulmonary secretions by culture, PCR, or antigen detection studies should not be considered evidence of CMV disease. However, in an allogeneic transplant recipient with a compatible chest radiograph, such documentation of CMV infection in the absence of cytoxic or histologic evidence of disease should prompt anti-CMV therapy given the high likelihood of CMV disease in this setting. Both infectious and noninfectious processes may masquerade as, or occur in addition to, pulmonary CMV disease. In one study of late CMV pneumonia (occurring after day 100 of transplantation), approximately one-half of the cases were associated with concurrent pulmonary infections, including P. aeruginosa, Legionella, Aspergillus species, Mycobacteria species, Nocardia species, toxoplasmosis, and respiratory viruses. Therefore, diffuse interstitial disease in a BMT recipient should be evaluated early with bronchoalveolar lavage, and if feasible, transbronchial biopsy (see Pulmonary Infiltrates, later in this chapter). Treatment of CMV pneumonia consists of ganciclovir (5 mg/kg every 12 hours) plus immunoglobulin (normal or CMV hyperimmune). The expected mortality is between 30% and 50%, which is significantly improved compared with series in which ganciclovir alone was used.

CMV disease can occur at any location within the gastrointestinal tract, although esophagitis and colitis are the most common sites. In the esophagus, ulcerations resembling HSV or candidal esophagitis occur. Differentiation of CMV from these causes relies on biopsy or cytology. CMV colitis is associated with abdominal pain and diarrhea. CMV involvement of enteric vessels may result in hemorrhage and infarction. However, in a randomized study, treatment of CMV gastroenteritis with ganciclovir produced similar results as placebo.

CMV hepatitis should be considered in the setting of fever and elevations of liver transaminase enzymes. Other potential viral etiologies include HSV-1 and -2, hepatitis viruses, and EBV. A liver biopsy documenting CMV inclusions definitively establishes the diagnosis. Less common sites of CMV disease in BMT recipients include pancreas, brain, spinal cord (transverse myelitis), and adrenals. CMV retinitis, the most common complication in patients with AIDS, is rare in transplant recipients. A CMV syndrome is associated with fever, pancytopenia, and CMV viremia and may precede the development of organ disease.

Because of the high mortality associated with CMV disease, much effort has been focused on prevention. CMV-seronegative blood transplant recipients should receive only CMV-seronegative blood products or leukocyte-depleted products to avoid primary CMV infection. The incidence of CMV infection in CMV-seronegative transplant recipients who had CMV-seronegative donors and were given only CMV-seronegative blood products was approximately 5% in three separate studies. Use of CMV-seronegative blood products likely reduces the frequency of CMV infection in cases of CMV-seronegative recipients and seropositive donors, although the magnitude of protection varies widely with different series. Reactivation of latent CMV infection after transplantation occurs in approximately 70% of seropositive recipients who do not receive antiviral prophylaxis. Antiviral agents have been used successfully to reduce the rate of CMV disease. The following two preventive approaches have been evaluated in allogeneic BMT recipients:

1. Prophylaxis: antiviral agents are administered to all CMV-seropositive BMT recipients (CMV-seronegative recipients receiving seropositive bone marrow were also candidates for antiviral prophylaxis in some studies).
2. Preemptive therapy: initiation of antiviral agents after detection of asymptomatic CMV infection by screening cultures or molecular detection methods.

Offering anti-CMV prophylaxis to all seropositive allogeneic transplant recipients has important advantages and shortcomings. In two studies, acyclovir prophylaxis was associated with increased survival, but the rates of CMV reactivation and disease were fairly high. In vitro, ganciclovir, an acyclic nucleoside analog of guanosine, is approximately 50 times more active than acyclovir against CMV. Two randomized placebo-controlled studies of ganciclovir prophylaxis for CMV-seropositive allogeneic transplant recipients produced similar results. Ganciclovir prophylaxis was highly effective at suppressing CMV during the early
transplant period, but was associated with higher rates of neutropenia, bacterial and opportunistic infections, and late CMV disease. Ganciclovir prophylaxis did not lead to an improvement in survival.

Nguyen et al. retrospectively reviewed 541 adult allogeneic transplant recipients at the University of Texas M. D. Anderson Cancer Center who had received ganciclovir prophylaxis. Thirty-five episodes of CMV pneumonia were documented, 26 (74%) of which occurred after day 100. The mortality was approximately 75%. Almost all cases of late CMV pneumonia occurred in patients with GVHD or who had received T-cell-depleted transplants. Reconstitution of CMV-specific T-cell responses are delayed in allogeneic transplant recipients who received ganciclovir prophylaxis, thus, conceivably predisposing such patients to late CMV disease. These observations provide a rationale for targeting patients at highest risk for CMV disease for antiviral therapy as opposed to administering prophylaxis to all seropositive patients.

Highly sensitive detection methods to identify subclinical CMV infection have been evaluated. These methods include detection of the CMV pp65 antigen from peripheral blood leukocytes and detection of CMV DNA by PCR from blood, serum, or plasma. Boeckh et al. showed that preemptive ganciclovir based on detection of CMV antigenemia was associated with a similar rate of CMV disease and similar long-term survival rates as standard ganciclovir prophylaxis initiated at engraftment.

Einsi et al. randomized allogeneic transplant recipients to receive preemptive ganciclovir therapy based on PCR detection of CMV from blood (PCR group) or a positive CMV culture from blood, urine, or throat washings (culture group). PCR screening led to earlier detection of subclinical CMV infection compared with culture. The PCR group had a reduced rate of CMV disease, duration of ganciclovir therapy, neutropenia, and nonviral infections compared with the culture group, and overall survival was superior. Discontinuing preemptive ganciclovir in patients whose blood became PCR negative appeared to be safe.

Foscarnet, an antiviral drug with activity against CMV, may have an advantage over ganciclovir in patients with delayed engraftment or with ganciclovir-associated neutropenia. Azathioprine is the major toxicity associated with foscarnet. Moretti et al. compared ganciclovir with foscarnet as preemptive therapy at the time of documentation of subclinical CMV antigenemia. There was a trend to more rapid clearance of CMV antigenemia in the foscarnet group. The major adverse effect was cytopenia in the ganciclovir group and azothia in the foscarnet group. The study was not sufficiently powered to detect a difference in CMV disease or mortality.

Determination of optimal CMV preventive strategies will require additional prospective randomized studies. Newer, less toxic antiviral agents will need to be evaluated. Lowance et al. showed that valacyclovir (a valine esterified analog of acyclovir with high oral bioavailability) was well tolerated and reduced CMV disease in renal transplant recipients. In addition, immune augmentation strategies (see Immune Augmentation Strategies, later in this chapter) may also be useful as preventive and treatment strategies.

**Varicella Zoster Virus**

Control of VZV infection is dependent on T-cell and humoral immunity. BMT recipients and patients receiving intensive corticosteroid therapy are at risk for life-threatening disseminated primary and reactivated VZV infection. Reactivated VZV disease is typically a late complication of BMT, usually occurring 3 months to more than a year after transplantation. Before the routine use of antiviral agents for prophylaxis against CMV infection, 17% of BMT recipients had an episode of reactivated VZV within the first year. In one study of acyclovir prophylaxis for CMV, the rate of VZV at day 210 after transplantation was only 3% in patients receiving prolonged high-dose acyclovir.

The major risk factor for developing VZV is acute and chronic GVHD requiring intensive immunosuppressive therapy. In such immunocompromised patients, VZV infection may manifest with a multidematernal or disseminated vesicular exanthem associated with hemorrhage and necrosis. Infection of visceral can cause hemorrhagic shock, disseminated intravascular coagulation, and fulminant purpura resembling bacterial sepsis.

The diagnosis of single dermatomal shingles can usually be made by visual inspection alone. In the immunosuppressed patient, multidematernal or disseminated cutaneous disease may make the diagnosis on clinical grounds less certain. Immunofluorescent staining of material from an unroofed skin lesion or from a skin biopsy may establish the diagnosis within hours. A Tzanck's preparation confirms infection by a herpes virus, but is not specific for VZV. Viral culture should also be performed.

Intravenous acyclovir (10 mg/kg every 8 hours) is the established treatment for primary or reactivated VZV in immunosuppressed patients. Early initiation of acyclovir reduces progression of disease and usually eliminates mortality in patients with reactivated disease. All BMT recipients with VZV infection should be treated initially as inpatients because of the potential for dissemination. Once clinical improvement has occurred (e.g., resolution of fever, healing of lesions), an oral regimen can be substituted and completed as an outpatient. The oral regimen may consist of acyclovir (800 mg five times per day), valacyclovir (1 g three times a day), or famciclovir (500 mg three times a day). Salicylates should not be used because of the risk of Reye's syndrome.

Lack of a clinical response to therapy should prompt reconsideration of the initial diagnosis, the possibility of a secondary infection, or VZV resistance to acyclovir. Streptococcal impetigo, dermatomic, and various noninfectious bullous diseases can mimic VZV. In such cases, a biopsy is required to establish the diagnosis. Severe streptococcal infections may occur in cutaneous VZV lesions. VZV infection can also be complicated by bleeding disorders, thrombocytopenia, vasculitis, disseminated intravascular coagulation, and fulminant purpura resembling bacterial sepsis.

The American Academy of Pediatrics states that the Oka vaccine is contraindicated in immunocompromised individuals, except for children with acute lymphoblastic leukemia to whom the vaccine may be administered in study conditions. In families with immunocompromised persons, no precautions are required after vaccination of healthy children in whom a rash has not developed. If a rash does occur, direct contact with immunocompromised persons should be avoided. If inadvertent contact occurs, the use of varicella zoster immune globulin is not recommended because of the low transmission rate and the expectation that disease will be mild if it occurs.

**Epstein-Barr Virus**

In the United States, most adults have been infected by EBV. Primary infection is usually asymptomatic, but may cause a mononucleosis syndrome. Latent infection persists in B cells and produces no disease in the vast majority of people. EBV-specific cytoytic T lymphocytes are the principal controllers of the replication of EBV-infected B cells. EBV lymphoproliferative disorders are encountered in patients with severely impaired T-cell immunity, such as AIDS or intensive and prolonged immunosuppressive therapy. EBV-induced posttransplant lymphoproliferative disorder (PTLD) is defined as an abnormal proliferation of B-lymphoid cells in transplant recipients. The lesions may be composed of a polyclonal or monoclonal population of transformed B cells. PTLD is most common during the first year of transplantation. Patients with GVHD treated with antilymphocyte immunoglobulins and recipients of T-cell-depleted marrow from HLA-mismatched donors are at highest risk for PTLD.
Clinical manifestations of PTLD are varied, and a high index of suspicion is required to make the diagnosis. Patients may have a mononucleosis-like syndrome with fever and localized adenopathy. Disseminated disease may manifest with generalized adenopathy and extranodal organ involvement, including the bowel, liver, bone marrow, and CNS. A CT scan of the head, chest, abdomen, and pelvis is useful in evaluating a high-risk patient with unexplained fever. Diagnosis of PTLD requires biopsy of an affected area showing a characteristic histologic appearance and evidence of EBV infection using immunohistochemical methods or by detecting EBV DNA.

In organ transplant recipients, most PTLD is of recipient origin. In BMT-associated PTLD, the abnormal clones are typically of donor origin. In BMT recipients, a balance is created between donor-derived B-cell clonal proliferation and the establishment of donor-derived cytotoxic T-cell immunity, which contain these proliferative responses. Whereas PTLD in organ transplant recipients typically responds to a reduction in the intensity of immunosuppression, PTLD in BMT recipients may not respond to such conservative measures. Adoptive immunotherapy is a promising strategy (see Immune Augmentation Strategies, later in this chapter).

Human Herpesvirus 6

HHV-6 was first isolated from peripheral blood from patients with lymphoproliferative disorders. This virus was initially called human B-lymphotrophic virus, but it was later discovered that the virus is predominantly T-cell tropic. HHV-6 has been recognized as an opportunistic pathogen in solid organ and BMT recipients. In BMT recipients, HHV-6 has been associated with a variety of syndromes: (1) fever and rash clinically resembling cutaneous GVHD; (2) an increased risk of GVHD; (3) bone marrow suppression; (4) encephalitis; and (5) pneumonitis. However, establishing a causal relationship between HHV-6 and these syndromes is made difficult by the fact that HHV-6 can be documented in approximately 50% of BMT recipients, usually between 2 and 4 weeks after transplantation. Evidence supporting a link between HHV-6 infection and encephalitis and interstitial pneumonitis is the most persuasive, based on the in situ documentation of HHV-6 in the respective organs using immunohistochemistry, molecular detection methods, and culture.

Singh and Carrigan proposed the following two criteria for the diagnosis of HHV-6 disease: (1) presence of bone marrow suppression, encephalitis, or pneumonitis and (2) documentation of active infection by culture, PCR from an acellular specimen (a positive PCR result from blood cannot distinguish active from latent infection), or immunohistochemistry. Comparative studies evaluating therapy for HHV-6 have not been performed, and it is therefore not possible to make definitive recommendations about therapy. HHV-6 is sensitive in vitro to ganciclovir and foscarnet, and it is reasonable to initiate therapy with either of these agents when HHV-6 disease is proven or strongly suspected. The role of screening for asymptomatic HHV-6 infection and prophylaxis with antiviral agents is uncertain.

COMMUNITY RESPIRATORY VIRUSES

Community respiratory viruses include members of the Orthomyxoviridae (influenza A, B, and C) and Paramyxoviridae [parainfluenza 1 through 4, respiratory syncytial virus (RSV), and measles families, adenoviruses, and picomaviruses]. These viruses are important causes of morbidity and mortality in immunocompromised patients. With the progress in prophylaxis and treatment of CMV disease in BMT recipients, the relative proportion of pulmonary infections caused by community respiratory viruses is likely to grow. In contrast to CMV, these viruses are seasonal and are rapidly transmitted from one person to another by respiratory secretions, thus having the potential for nosocomial outbreaks.

Respiratory viruses may account for a significant proportion of undiagnosed or idiopathic pneumonias in BMT recipients in older series. Their importance as pathogens in this population has been documented more recently by centers that routinely screen for community viral pathogens in patients with respiratory illnesses.

Respiratory Syncytial Virus

RSV infection is highly virulent in patients with leukemia and in BMT recipients. In patients with leukemia, progression to pneumonia and mortality are more common in the setting of neutropenia. RSV infection can occur throughout the transplant period, from the preengraftment stage to more than a year after transplantation. Upper respiratory symptoms (sinusitis, coryza, rhinorrhea) usually precede lower respiratory tract involvement (dyspnea, wheezing) and pneumonia, although upper airway symptoms may be absent. The historic mortality from RSV pneumonia in BMT recipients is approximately 90%. At the University of Texas M. D. Anderson Cancer Center, patients who received aerosolized ribavirin and intravenous immunoglobulin containing high RSV-neutralizing titers at least 24 hours before respiratory failure had a 22% mortality compared with 100% mortality in patients who either did not receive therapy or in whom treatment was initiated after respiratory failure had occurred.

Rapid diagnosis of RSV has been made possible by antigen detection methods. Englund et al. showed that compared with culture, antigen detection had a sensitivity of 89% in bronchoalveolar lavage, 15% in nasal and throat washings, and 71% in endotracheal aspirates in symptomatic adult leukemia or BMT patients. The specificity was 97% to 100% from these sources. The lower sensitivity of antigen detection from the upper airway of adults is attributed to a lower viral burden. The low yield of upper airway cultures severely limits the value of these noninvasive tests in adults with respiratory disease.

A preliminary study of intravenous ribavirin for RSV pneumonia in BMT recipients who at enrollment did not require mechanical ventilation, was associated with an eventual 80% mortality. In a second strategy, aerosolized ribavirin was administered to patients in whom RSV was isolated from nasopharyngeal washes without signs of lower respiratory tract involvement. Pneumonia developed in 8 of 25 (32%) patients, with a mortality of 29%. These studies suggest that early diagnosis and treatment of RSV in this population may be life saving.

Parainfluenza

Parainfluenza viruses are important community respiratory viruses in leukemia and BMT patients. In a review of 45 cases of parainfluenza virus infection in BMT recipients, 26 (58%) patients had pneumonia, of whom 39% died.

Therapy for parainfluenza infection has not been established. An uncontrolled retrospective series from the University of Minnesota showed that survival with and without aerosolized ribavirin was approximately 80% in BMT recipients with parainfluenza infection. Ribavirin was generally begun late after onset of respiratory symptoms, which may have reduced its efficacy. The role of intravenous immunoglobulin against this organism merits further exploration.

Influenza Virus

Influenza virus is the most important respiratory virus globally and the most common cause of excess seasonal mortality in North America, accounting for approximately 20,000 deaths in the United States annually. During a winter outbreak period, influenza was diagnosed in approximately 30% of adult patients hospitalized for a respiratory illness at the M. D. Anderson Cancer Center. Pneumonia occurred in 12 of 15 (80%) patients with influenza, and four of these patients died. In other centers, the incidence of pneumonia and mortality associated with influenza virus infection was substantially lower.

Amantadine and rimantadine are the most common agents used in treating influenza. These agents are only active against influenza A, not influenza B. In one center, resistance to these agents rapidly developed during therapy for influenza A among patients with leukemia and BMT recipients. Ribavirin has activity against influenza A and B and has been used in patients with influenza virus infection.

Two agents (zanamivir and oseltamivir) that inhibit the influenza virus neuraminidase have been licensed. These drugs are active against both influenza A and B and have been shown to be effective in reducing the duration of influenza illness and to have a prophylactic benefit during community outbreaks. The role of these agents as treatment or prophylaxis in immunocompromised patients with cancer has not been evaluated.

The Centers for Disease Control and Prevention recommend annual administration of the inactivated influenza vaccine to immunocompromised persons and their close contacts (e.g., health care workers and household members). Immunocompromised persons are less likely to mount an adequate antibody response to immunization. Immunization should be provided ideally 2 weeks before chemotherapy, or if given during chemotherapy, immunization is preferably administered
between cycles. In one study, a two-step vaccination regimen enhanced the immune response in patients receiving chemotherapy for lymphoma. 249

Adenovirus

The clinical manifestations of adenoviruses in BMT recipients include pneumonia, bronchiolitis, upper respiratory tract infection, renal parenchymal disease, hemorrhagic cystitis, hepatitis, small and large bowel disease, encephalitis, and disseminated infection. 263 Viral shedding from throat secretions, urine, and stool is common, occurring in approximately 5% to 20% of BMT recipients, and should not be equated with disease. In patients with definite invasive disease, long-term survival was poor. GVHD was the only significant risk factor in both studies.

Adenoviruses were cultured from 28 adult BMT recipients at the M. D. Anderson Cancer Center. 264 Seven of 12 patients with pneumonia and all six patients with disseminated disease died, whereas ten patients with upper respiratory tract infection survived. Risk factors for mortality included isolation of adenovirus from multiple sites and prolonged shedding. Ribavirin was not associated with benefit in this retrospective series. The role of intravenous immunoglobulin for management of adenovirus infection has not been established.

Mesales

Kaplan et al. 252 conducted an extensive review of measles in immunocompromised patients. Of 40 patients (aged 3 months to 22 years) with malignancy, 16 (40%) had no rash whereas the remainder had either typical or atypical exanthermas. Twenty-three (58%) had pneumonia, eight (20%) had encephalitis, six (20%) had both, and six (20%) had no complications. The overall fatality rate was 55%. The benefit of ribavirin could not be assessed.

Diagnosis of Respiratory Viruses

Rapid immunodiagnostic methods for common respiratory viruses have become widely used, and have resulted in reduced hospital stays, antibiotic use, and microbiologic investigations. 237 Such rapid methods also have additional potential benefits for early initiation of antiviral agents and implementation of appropriate infection control precautions. Cell culture is generally more sensitive than antigen detection methods, with the exception of RSV in children, in whom antigen detection is highly sensitive. Rapid antigen detection methods and cell culture are therefore complementary. PCR amplification methods are being evaluated and show promise. 254

Hepatitis B

Reactivation of latent hepatitis B virus (HBV) infection in BMT recipients is an unpredictable but rare event. Although the hepatitis B surface antigen carrier state is not a contraindication to BMT, such patients appear to be at a higher risk for fulminant hepatitis as a result of reactivation. 255,256,257,258 In a prospective study of 100 Chinese patients who received induction chemotherapy for lymphoma, hepatitis developed in 67% of HBsAg-positive patients compared with 14% of HBsAg-negative patients. 259 Reactivation of HBV (as determined by serum levels of HBV DNA and HBsAg) was associated with icteric hepatitis, but infrequently with liver failure and mortality. Symptomatic hepatitis may manifest after withdrawal of immunosuppressive agents or between cycles of chemotherapy when recovery of immune responses occurs.259,260

Precore mutant HBV has been associated with cases of fulminant hepatic failure after cytotoxic chemotherapy and fibrosing cholestatic hepatitis. 261,262 This mutation results in failure to secrete HBeAg, and, therefore, this marker can not be used as an indicator of active viral replication.

Chronic HBV hepatitis has been reported in patients with negative serologic study results. Vergani et al. 263 reported 23 cases of histologically proven HBV infection in 23 children with leukemia and liver disease, none of whom had detectable HBV serum antigens or antibodies. In eight of the children, HBV markers subsequently appeared in the serum within 15 months of stopping chemotherapy. Bréchot et al. 264 documented HBV DNA in 59% of liver samples but in only 10% of serum samples among patients with chronic liver disease and negative test results for HBsAg.

Treatment of chronic HBV involves either the antiviral nucleoside analog lamivudine 265,266 or interferon-a (IFN-a). 267 The advantages of lamivudine include limited side effects and the fact that histologic improvement was documented in the majority of patients. 268 Favoring IFN-a is the limited duration of therapy and the absence of viral mutations that lead to resistance to therapy. 269

Vaccination against HBV should be considered in seronegative patients with cancer. However, among BMT recipients, active immunization in the immediate pretransplant and posttransplant periods is often ineffective, most likely as a result of defective T-cell and B-cell function. Adoptive transfer of immunity to HBV can be achieved after allogeneic BMT from immune donors. 270

Hepatitis C

Before routine blood screening began in 1991, BMT recipients were at significant risk for hepatitis C virus (HCV) infection. HCV infection can cause both early and late complications in BMT recipients. In a cohort study from Fred Hutchinson Cancer Research Center, pretransplant HCV infection plus an elevated serum aspartate transaminase level was predictive of severe venoocclusive disease (VOD) (relative risk, 9.6). 271,272 HCV infection without elevated transaminases was not a significant risk factor for VOD. An acute flare of hepatitis occurred in about one-third of HCV-positive patients at a mean of 4 to 5 months after transplant and was usually self-limited. 273 Frickhofen et al. also noted an association between pretransplant HCV infection and severe VOD in the early transplant period. 274

Approximately one-half of HCV-positive transplant recipients at Fred Hutchinson continued to have mild to moderate elevations in liver enzymes 5 to 10 years following transplant. 275,276,277 However, HCV was not associated with increased mortality. Cirrhosis was identified in 31 of 3721 patients surviving 1 or more years after BMT. 278 HCV infection was documented in 25 of the 31 (81%) patients, and cirrhosis was attributed to HCV infection in 15 of 16 (93%) patients presenting more than 10 years after transplantation. 279 To try to avoid cirrhosis, interferon-a and ribavirin therapy should be considered in transplant recipients with chronic HCV infection who have been off immunosuppressive agents for at least 6 months, have normal marrow recovery, and have no GVHD. 280

HCV is universally transmitted from HCV RNA-positive donors to their recipients. 271 If an HCV-positive donor is the best available match, treatment of the donor with interferon-a and ribavirin before marrow or stem cell harvest may be considered to try to eliminate viremia (which can be monitored by PCR). Interferon should be stopped at least 1 week before harvest to avoid problems with engraftment in the recipient. 274

Significant hepatic dysfunction is uncommon in nontransplant HCV-positive patients receiving chemotherapy for hematologic malignancies. 271,272 In a prospective study of 305 patients with lymphoma, the prevalence of HCV and HBV infection was 16% and 3.2%, respectively. 273 No reactivation in HCV-positive patients occurred during chemotherapy. In contrast, HBV reactivation occurred in approximately 80% of HBV-infected patients, and was associated with a 37% mortality rate. Thus, HBV should be considered to be an opportunistic pathogen in heavily immunosuppressed persons with hematologic malignancies, whereas HCV is not.

Other Transfusion-Associated Hepatitis Viruses

Hepatitis G is a newly discovered transfusion-associated virus that can establish persistent infection in asymptomatic individuals. Surveillance studies have not established a role for this virus in non-A through E acute transfusion-related hepatitis or chronic liver disease. 271,272,273 TT virus is another virus capable of establishing persistent infection whose pathogenicity remains questionable. 272 In a Japanese study, TT virus DNA was detected with far greater frequency in BMT recipients than
in blood donors, and, in one patient, was temporally associated with elevated serum hepatic enzymes. Conceivably, these other transfection-associated viruses yet to be discovered, may be agents of non-A through E hepatitis in heavily transfused persons with cancer.

PARASITIC INFECTIONS

PNEUMOCYSTIS CARINII

Pneumocystis carinii is more appropriately classified as a fungus than a protozoan based on gene sequence data and cell wall constituents. Defective T-cell immunity is the principal risk factor for PCP. Sepkowitz et al. reported that corticosteroid use was associated with 204 of 227 (90%) cases of PCP in patients without AIDS at Memorial Sloan-Kettering Cancer Center between 1963 and 1992. The median time that patients received corticosteroids was 2 months, although a minority of patients had received corticosteroids for less than 1 month. Approximately 60% of patients had hematologic malignancies, 25% had solid tumors, 10% were BMT recipients, and 5% were receiving relatively mild immunosuppressive regimens.

The risk of PCP increases with the intensity of the immunosuppressive regimen. In a study of pediatric patients with acute lymphocytic leukemia, the risk of PCP was strikingly increased from less than 5% to 22% when cytotoxic arabinoside (ara-C) was used. Browne et al. reported a 32% rate of PCP (probable plus definite) in patients with non-Hodgkin's lymphoma treated with an intensive regimen consisting of corticosteroids and multiple cytotoxic agents (methotrexate, doxorubicin, cyclophosphamide, etoposide, Ara-C, bleomycin, vincristine) as compared with no cases of PCP in patients who did not receive Ara-C and bleomycin.

Pneumocystis carinii can have a fulminating course, resembling a bacterial pneumonia with rapid progression to respiratory failure, or can be indolent. Patients treated with corticosteroids may develop initial manifestations of PCP only during corticosteroid taper. Bilateral interstitial infiltrates are most common in PCP, although unilateral or patchy infiltrates are also observed. Nodules, cavitary lesions, and pleural effusions are less common. In a minority of patients, the chest radiograph is normal. Extrapulmonary P carinii infection is rare in patients with cancer and has for the most part been reported only in patients with AIDS.

Diagnosis of PCP relies on visualization of the organism microscopically. Immunofluorescent staining using monoclonal antibodies is more sensitive than older staining methods, such as silver staining or Wright-Giemsa. PCR-based detection of P carinii from induced sputum or blood is a promising experimental diagnostic method.

Spontaneously expectorated sputum is generally unsatisfactory for diagnosis of PCP, but sputum induction using 3% sodium chloride solution in an ultrasonic nebulizer usually yields a satisfactory sample. In a small study of non-AIDS patients with PCP, the diagnostic sensitivity using this method was approximately 60%.

If sputum induction is nondiagnostic, bronchoscopy should be pursued. Trimethoprim-sulfonamide (trimethoprin 15 to 20 mg/kg daily divided into three to four doses) is the treatment of choice for P carinii. In patients intolerant of this agent, azathioprine, dapsone-trimethoprin, and clindamycin-primaquine are acceptable alternatives. In cases of a prior non-life-threatening reaction to a sulfonamide (e.g., a nonurticarial rash), experience with AIDS patients has shown that rechallenge with trimethoprim-sulfonamide is safe under close medical observation, although some investigators would opt for desensitization. Patients without AIDS are less likely to have adverse reactions to trimethoprim-sulfonamide. In patients with moderate or severe PCP (PaO2 less than 70 mm), corticosteroids should be added based on studies of patients with AIDS-associated PCP. In patients who are not responding to therapy, repeat bronchoscopy should be performed to exclude additional pathogens that may have been missed or may not have been present initially.

Trimethoprin-sulfonamide is highly effective as prophylaxis against PCP. In children with cancer at high risk for PCP, no case of PCP occurred in patients administered daily trimethoprin-sulfonamide, compared with an approximately 20% incidence in the placebo arm. Trimethoprin-sulfonamide prophylaxis was also associated with a reduction in bacterial infections. In a subsequent study of children with acute lymphoblastic leukemia, trimethoprin-sulfonamide administered either daily or on 3 consecutive days weekly was fully protective against PCP.

Defining which patients with cancer will benefit from prophylaxis against PCP is often empirical given the absence of controlled studies in several high-risk groups. Children with acute lymphoblastic leukemia and allogeneic BMT recipients are known high-risk groups that should be offered prophylaxis. In BMT recipients, the peak risk of PCP is between 1 and 4 months after transplantation, corresponding to the period of most profound T-cell immunodeficiency. Prophylaxis is generally administered shortly after engraftment until 6 to 12 months after BMT, but should be reinitiated at later periods in the setting of GVHD requiring intensification of immunosuppressive agents. Adults with acute lymphoblastic leukemia, patients with CNS tumors receiving high-dose corticosteroid therapy, and patients receiving combination corticosteroid therapy with either myelotoxic agents or fludarabine are also at high risk for PCP, and prophylaxis should be considered.

TOXOPLASMOSIS

Reactivation of Toxoplasma gondii is associated with life-threatening disease primarily in patients with profound deficits in T-cell immunity. In a review of 128 reported cases of toxoplasmosis in patients with hematologic disorders, 59 patients had Hodgkin's disease, 12 had non-Hodgkin's lymphoma, and 36 had acute or chronic leukemias. Therapy with corticosteroids; cytotoxic agents, radiation therapy, or both; and poorly controlled malignancy are risk factors for toxoplasmosis.

Toxoplasmosis is an uncommon complication of BMT. In the largest series, toxoplasmosis was diagnosed in 12 of 3803 (0.3%) consecutive allogeneic BMT recipients and in none of 509 autologous transplant recipients at the Fred Hutchinson Cancer Center. All 12 patients died; ten cases were diagnosed postmortem, and toxoplasmosis was believed to contribute to mortality in at least four patients. Toxoplasmosis manifested within the first 4 months of transplantation. Pretransplant seropositivity for T gondii and severe GVHD were the predominant risk factors.

CNS disease is most commonly observed. Altered mental status, coma, seizures, cranial nerve abnormalities, and motor weakness are the most common findings. Cerebrospinal fluid is usually normal; however, a mononuclear pleocytosis and elevated protein level may be seen. Other organs involved may include the heart, lungs, liver, spleen, lymph nodes, bone marrow, pancreas, spleen, and skeletal muscle.

Definitive diagnosis of toxoplasmosis usually relies on demonstration of tachyzoites and cysts in histopathologic sections. Use of electron microscopy and immunoperoxidase staining methods, such as silver staining or Wright-Giemsa, may facilitate the diagnosis of encephalitis and chorioretinitis, respectively. PCR is a promising diagnostic method available at specialized laboratories.

The treatment of choice for toxoplasmosis is oral sulfadiazine, 4 to 6 g/d, plus pyrimethamine (loading dose of 200 mg, followed by 50 to 75 mg daily). Folic acid should be administered to reduce myeloid toxicity. Whether maintenance therapy is required after quiescence of disease is unknown. It is reasonable to continue a maintenance regimen (which may consist of sulfadiazine, 2 g/d, plus pyrimethamine, 50 mg/d) during periods of immunosuppressive therapy. In patients intolerant of sulfonamides, clindamycin and primaquine may be used instead.

ACANTHAMOEBA

Acanthamoeba species may cause an insidious granulomatous encephalitis in immuno compromised patients, such as those receiving high-dose corticosteroid therapy, solid organ transplant recipients, and patients with AIDS. Skin manifestations include persistent ulcers, nodules, or subcutaneous abscesses. BMT recipients may have a more fulminating course characterized by obtundation, coma, and seizures, associated with a necrotizing meningoencephalitis and hydrocephalus. A necrotizing pneumonitis and adenitis may also be present. A diagnosis may be established by cerebrospinal fluid analysis or biopsy showing characteristic amebic trophozoites. The treatment choice is parenteral pentamidine.

STRONGYLOIDES STERCORALIS

Strongyloides stercoralis is an intestinal nematode that can cause disseminated infection, or hyperinfection syndrome, in immunocompromised patients. S stercoralis is particularly common in tropical and subtropical regions, but the parasite also is endemic in certain rural southern regions of the United States. Cross-infection between humans through contact with material soiled with feces appears to be likely in overcrowded and unsanitary conditions.
establish an asymptomatic chronic gastrointestinal infection through internal autoinfection, with the hyperinfection syndrome occurring several years after the initial infection, frequently in the setting of immunosuppression. This underscores the need to obtain a thorough history about prior residence in endemic areas. Corticosteroid therapy with and without other agents appears to be associated with the highest risk of disseminated disease. Among reported cases of hyperinfection syndrome associated with cancer, approximately 90% of patients had a hematologic malignancy. The hyperinfection syndrome results from penetration of filariform larvae through the intestinal mucosa, followed by dissemination. Sites of dissemination include the lungs, lymph nodes, brain, and abdominal organs. Secondary bacterial infection presumably results from passage of enteric bacteria through the bowel as a consequence of gastrointestinal strongyloidiasis, and may result in peritonitis, bacteremia, and meningitis.

Diagnosis of infection relies on visualization of larvae in feces, duodenal aspirates, sputum samples, or in other body fluids or tissue. Although uncommon, patients from endemic areas should be screened for S. stercoralis carriage, ideally before receiving immunosuppressive agents. Obtaining multiple fresh stool samples increases the diagnostic yield. Patients with S. stercoralis infection should be treated with thiabendazole or ivermectin.

EVALUATION AND MANAGEMENT OF FEBRILE NEUTROPENIA

Patients with cancer and neutropenic fever often have an established or an occult infection, and bacteremia is documented in approximately 20% of cases. Because of the high likelihood of occult infection in a patient with febrile neutropenia without localizing symptoms or signs, and the potential for rapid progression to severe sepsis, prompt initiation of empiric antibiotics is essential. The likelihood of bacteremia is related to the intensity (with an ANC of less than 100/µL carrying the greatest risk) and the duration of neutropenia. A rapid decrease in the neutrophil count may also be a risk factor for infection, whereas evidence of marrow recovery even if the neutrophil count is still less than 500/µL, is a positive prognostic factor. For the purpose of this discussion, we use the following established criteria for neutropenic fever:

1. A single oral temperature of greater than 38.3°C (101.0°F) or greater than or equal to 38.0°C (100.4°F) over at least 1 hour.
2. ANC less than 500/µL or less than 1000/µL with predicted rapid decline to less than 500/µL.

Evaluation of the febrile neutropenic patient begins with a careful history and physical examination. A history of prior infectious complications associated with chemotherapy may be useful for risk stratification and selecting an empiric regimen. For example, a history of recent colitis caused by Clostridium difficile raises the likelihood of recurrent infection in a patient with fever and diarrhea. Prior invasive candidiasis or infection by one of the filamentous fungi may recur during subsequent neutropenic periods. The duration of neutropenia and the risk for serious infectious complications, including the development of invasive fungal infections in patients with prolonged neutropenia (such as patients with leukemia and BMT recipients). Concomitant use of corticosteroid therapy raises the likelihood of opportunistic pathogens, such as P. carinii, that characteristically affect patients with defects in cell-mediated immunity. Epidemiologic exposures can provide useful clues for uncommon or rare pathogens. For example, swimming or fishing in fresh or brackish water raises the possibility of infection by Aeromonas hydrophilia. Exposure to salt water increases the likelihood of infection by Vibrio vulnificus. Fever after a dog bite raises the concern about infection by Capnocytophaga canimorsus (DF-2).

A meticulous physical examination is necessary, bearing in mind that typical signs of infection may be blunted or absent as a result of immunosuppression. Mucositis is commonly observed after chemotherapy and may be difficult to distinguish from gingivostomatitis caused by reactivation of HSV infection. The presence of thrush reflects compromise of cell-mediated immunity. In patients with prolonged neutropenia or who receive concomitant high-dose corticosteroid therapy, fungal infection of the palate, typically by Zygomycete or Aspergillus species, constitutes a surgical emergency. A black necrotic region is the most common sign of such infections. Palpation over the anterior sinuses and an ophthalmologic examination should be performed. A detailed inspection of the skin, including the nails, may disclose a lesion suggestive of systemic infection or a possible portal of entry. Examples include ecthyma gangrenosum caused by P. aeruginosa, or erythematous papules caused by disseminated candidiasis. Catheter sites and sites of prior skin penetration (such as surgical wounds and biopsy sites) should be palpated. The perineal and perianal region are easily missed sources of infection that need careful inspection and palpation.

The initial evaluation should include the following: complete blood cell count and differential; serum chemistry, including liver associated enzymes; at least two sets of blood cultures from different sites (including from each lumen of the central venous catheter if one is present); a urine culture; and a chest radiograph. Potential sites of infection, such as skin lesions or sputum, should be obtained before instituting antibiotics. However, febrile neutropenia should be considered a medical emergency, and prompt initiation of empiric antibiotics should not be delayed if culture material is not immediately available. After the initial physical examination, it is critical to reevaluate the patient regularly to monitor the response to therapy and to identify evolving signs of infection that were not present during the initial encounter.

ANTIBIOTIC REGIMENS

In the early 1970s, Schimpff and colleagues conducted a nonrandomized study of 75 patients with cancer and febrile neutropenia who were treated empirically with carbenicillin and gentamicin.201 Treated patients with P. aeruginosa infection had dramatically improved survival rates compared with historic controls. This study established the rationale for empiric combination antibiotic therapy, based on the wide range of resistant profiles of P. aeruginosa and enteric gram-negative rod isolates to carbenicillin. Empiric combination therapy increases the likelihood that at least one antibiotic will have activity against the isolate before the availability of susceptibility data. In addition, the b-lactam plus gentamicin combination has synergistic bactericidal activity in vitro. Since this early study, typical combination regimens for neutropenic fever have included an antipseudomonal penicillin plus an aminoglycoside with or without a drug with anti-staphylococcal activity, such as a first-generation cephalosporin or vancomycin.

Since the mid-1980s, the development of broad-spectrum antipseudomonal antibiotics (ceftazidime and imipenem) with a high serum bactericidal level to minimal inhibitory concentration ratio has led to a reevaluation of the need for combination antibiotic therapy. Obviating the need for an aminoglycoside would be expected to reduce nephrotoxicity in a patient population frequently treated with nephrototoxic drugs, such as CSA, cisplatin, and amphotericin B. Pizzo et al. conducted a randomized trial comparing ceftazidime monotherapy with a combination of cephalothin, gentamicin, and carbenicillin in 550 episodes of neutropenic fever in patients with cancer at the National Institutes of Health. Approximately 45% of patients had leukemias or lymphomas, and the remainder had solid tumors. The mean duration of neutropenia was 8 to 9 days. In patients with unexplained fever, 98% of patients in both groups survived by the time neutropenia resolved. Of the patients with documented infection, the survival rate was 89% in the monotherapy arm and 91% in the combination arm. Most patients with documented infections in both treatment arms required modifications in the initial antibiotic regimen, whereas the initial regimen was usually not modified in cases of no documented infection. This study was the first to establish that initial empiric monotherapy was safe and effective in this patient population. An important caveat is that patients must be closely monitored and the antibiotic regimen modified based on subsequent clinical and microbiologic data.

In a subsequent multicenter trial, De Pauw et al. evaluated ceftazidime versus piperacillin plus tobramycin in approximately 800 episodes of neutropenic fever. The majority of patients had leukemia or were BMT recipients. The mean duration of neutropenia was 18 days. The two regimens were similar with regard to control of infections and infection-related mortality, but less adverse reactions occurred in the ceftazidime arm. This study confirmed that ceftazidime monotherapy is a viable empiric regimen in high-risk patients with febrile neutropenia. In a metaanalysis, ceftazidime monotherapy had similar efficacy as combination regimens for empiric treatment of neutropenic fever.

Numerous studies of monotherapy and combination therapy have been conducted that further delineate the advantages and disadvantages of various empiric regimens for neutropenic fever. The Infectious Diseases Society of America (IDSA) has published evidence-based guidelines on antibiotic therapy for neutropenic fever without a documented source. Initial antibiotic regimens are divided into three categories: (1) monotherapy, (2) dualtherapy without vancomycin, and (3) vancomycin plus one or two drugs (Table 54-6).
The IDSA considered the following four antibiotics to be appropriate as empiric monotherapy for neutropenic fever: cefazidime, cefepime, imipenem, and meropenem.\(^1\) At the National Institutes of Health, cefazidime monotherapy has been used since the 1980s in more than 1000 patients and has an excellent record in terms of efficacy and safety. Emergence of cefazidime-resistant isolates has been infrequent. A disadvantage of cefazidime monotherapy is the modest or absent activity against certain gram-positive pathogens (e.g., viridans streptococci, enterococci) and gram-negative pathogens with extended spectrum b-lactamasases (most often encountered in \(E\) coli and \(Klebsiella\) species) and Bush group 1 b-lactamas (most commonly encountered in \(Enterobacter\), \(Serratia\), \(Citrobacter\), and indole-positive Proteus species). The cefazidimes (imipenem and meropenem) have a broader antibacterial spectrum that includes activity against these pathogens as well as potent activity against anaerobes.

In a randomized study of 399 episodes of neutropenic fever at the National Institutes of Health comparing cefazidime with imipenem as initial therapy, the survival rate was approximately 98% for both regimens.\(^2\) Forty-four percent of patients had leukemia or lymphoma, and the remainder had solid tumors. The mean duration of neutropenia was 9 days. Imipenem was associated with greater toxicity, including \(Clostridium\) difficile-associated diarrhea and nausea and vomiting.

Cefepime is a fourth-generation cephalosporin with broad-spectrum activity appropriate for empiric therapy for neutropenic fever. In a study of activity of b-lactam antibiotics against gram-positive isolates from patients with cancer, cefepime had activity similar to imipenem and superior to cefazidime.\(^3\) Seventy-six percent of viridans streptococci were sensitive to cefepime versus 53% to cefazidime. Ninety-eight percent of b-hemolytic streptococci were sensitive to cefepime versus 34% to cefazidime. Cefepime has activity against greater than 95% of enteric aerobic gram-negative bacterial isolates harboring either Bush group 1 b-lactamasases or extended spectrum b-lactamasases.\(^4\) In contrast, \(Pseudomonas\), \(Stenotrophomonas\), and \(Acinetobacter\) species resistant to cefazidime are usually cross-resistant to cefepime.\(^5\) Thus, in centers where cefazidime-resistant \(Enterobacteriaceae\) are frequent, cefepime as empiric monotherapy for febrile neutropenia may be a viable option.

In a multicenter French study of 400 patients with neutropenic fever, empiric therapy with cefepime had similar survival compared with imipenem (95% vs. 98%, respectively), but caused less gastrointestinal toxicity.\(^6\) In a study of 99 patients with febrile neutropenia, empiric cefepime therapy had similar efficacy compared with piperacillin plus gentamicin, but reduced nephrotoxicity.\(^7\) Cefepime at a relatively high dose (2 g every 8 hours) is approved as monotherapy for empiric treatment of neutropenic fever.

Meropenem is a new carbapenem with a spectrum similar to that of imipenem, except for enhanced activity against gram-negative and less activity against gram-positive bacteria.\(^8\) In a large multicenter study of 958 patients with febrile neutropenia, meropenem monotherapy was as effective as cefazidime plus amikacin as initial empiric therapy.\(^9\) The survival rate was 98% in the meropenem arm and 97% in the combination arm, and the proportion of adverse side effects was low in both groups. The mean duration of neutropenia, defined as an ANC less than 1000/µl, was 17 to 17 days. Bacteremia occurred in 10% of patients in the meropenem arm and in 7% of patients in the combination arm. Meropenem monotherapy was safe and effective for neutropenic fever in two other European studies compared with cefazidime\(^10\) and cefazidime plus amikacin.\(^11\) Meropenem appears to have less gastrointestinal toxicity than imipenem and a lower frequency of seizures. Thus, meropenem appears to be an appropriate alternative to imipenem in febrile neutropenic patients.

**DuoTherapy Without Vancomycin**

The standard duotherapy regimen for empiric therapy of neutropenic fever is a broad-spectrum antipseudomonal b-lactam plus an aminoglycoside. The b-lactam/aminoglycoside synergy was thought to be important in effecting a rapid resolution of bacteremia. In addition, duotherapy increases the likelihood of the isolate being sensitive to at least one of the agents.

The hypothesis that a synergistic antibiotic regimen is superior to monotherapy as empiric treatment of neutropenic fever has not been validated in prospective clinical studies. In fact, cefazidime singly has greater serum bactericidal activity against gram-negative bacteria compared with ticarcillin plus amikacin.\(^12\)

Combination therapy using two b-lactam agents should generally not be used. The fact that some b-lactams may also be b-lactamase inducers raises concern about such combinations. This concern does not apply when an antipseudomonal penicillin (e.g., oxacillin) is paired with an antipseudomonal b-lactam agent (e.g., cefazidime).

Pairing an antipseudomonal b-lactam with a quinolone is yet another combination regimen used for neutropenic fever. The rationale of such a combination is to provide broad-spectrum activity against highly resistant gram-negative pathogens. In a small randomized study, piperacillin plus ciprofloxacin led to more rapid defervescence and reduced requirement for empiric amphotericin B compared with piperacillin plus gentamicin.\(^13\) Other studies showed that azlocillin plus ciprofloxacin had similar efficacy compared with a b-lactam plus an aminoglycoside.\(^14\)

An aminoglycoside as the sole agent active against gram-negative bacteria is not recommended because of the high failure rate. Ceftriaxone plus an aminoglycoside, which has the potential for single daily dosing, has been shown to be effective in some studies.\(^15\) However, ceftriaxone does not have reliable activity against \(P\) aeruginosa. Therefore, in centers where this pathogen is encountered, the ceftriaxone plus aminoglycoside regimen may be suboptimal. In centers with a high frequency of \(Enterobacteriaceae\) resistant to third-generation cephalosporins, we advise against using empiric aztreonam as the sole agent active against gram-negative bacteria because of the likelihood of cross-resistance (see Table 54-3).

Today, with the availability of highly effective monotherapy regimens for neutropenic fever, initial empiric duotherapy regimens may be most appropriate in unstable patients and in institutions in which multidrug-resistant pathogens are frequently encountered.

**When To Add Vancomycin**

The rationale to add vancomycin to an empiric regimen for neutropenic fever stems from the increased proportion of infections by gram-positive bacteria. The change in the proportion of infections in neutropenic patients from predominantly gram-negative to gram-positive bacteria in neutropenia is associated with the widespread use of tunneled catheters in this patient population. Catheter-associated infection by coagulase-negative staphylococci has become the most common cause of bacteremia in patients...
with cancer.

Among the common gram-positive infections in neutropenic patients, the following are typically resistant to cefazidime: MRSA, coagulase-negative Staphylococcus species, and Enterococcus species. In addition, although cefazidime has in vitro activity against most viridans streptococci, serious infection by these pathogens has occurred in neutropenic patients receiving cefazidime. §[332]

Numerous studies have evaluated single and multiple drug regimens with and without vancomycin. In the largest study, cefazidime plus amikacin with and without vancomycin were compared in 747 patients with febrile neutropenia in Europe and Canada. §§ The addition of vancomycin to the empiric regimen was not associated with any benefit with regard to duration of fever or morbidity or mortality related to gram-positive infections. Smaller studies of cefazidime with or without an aminoglycoside also showed no benefit from adding vancomycin to the initial regimen. §[333]

Because of the lack of efficacy of routine addition of vancomycin to empiric regimens for neutropenic patients, and because of the emergence of VRE in association with excessive vancomycin use, the IDSA guidelines have advised against the routine use of vancomycin as initial empiric therapy of neutropenic fever. ¶ At institutions in which MRSA is common or if a patient is known to be colonized by MRSA, vancomycin should be included in the initial regimen for neutropenic fever. Erythema or tenderness at a catheter site requires the addition of vancomycin while awaiting culture results. Addition of vancomycin is reasonable in patients receiving prophylaxis with ciprofloxacin, which some studies have associated with breakthrough infections by viridans streptococci (see Viridans Streptococci, earlier in this chapter). The IDSA suggests the addition of vancomycin in patients with substantial mucosal damage from chemotherapy (such as regimens containing high-dose Ara-C) because of the added risk of infection by viridans streptococci. Empiric vancomycin should be discontinued after 2 days if the initial culture results are negative or show a pathogen, such as methicillin-sensitive S. aureus, for which other antibiotics can be used.

In neutropenic febrile patients with allergies to b-lactams, empiric vancomycin should be combined with antibiotics active against aerobic gram-negative pathogens. In a clinically stable neutropenic patient, vancomycin plus aztreonam is a reasonable regimen §[334] (see Table 54-6). Aztreonam monotherapy is not acceptable because it has no activity against gram-positive bacteria.

### DURATION OF ANTIBACTERIAL THERAPY

#### Resolution of Fever within First 3 Days of Treatment and Persistent Neutropenia

If the fever rapidly abates after initiation of empiric therapy in a patient with an unremarkable physical examination and negative culture results, one should assume that an occult infection exists that has responded to antibiotics. Pizzo et al. §[335] randomized patients with prolonged neutropenia and an undifferentiated fever to either continuing empiric antibiotics on day 7 of therapy or continuing therapy until resolution of neutropenia. Of patients who had become afebrile, 40% had recurrent fever after antibiotics were stopped, leading to the conclusion that day 7 of therapy was too early to stop antibiotics in the setting of persistent neutropenia. Discontinuation of antibiotics on day 14 of therapy is a reasonable practice among patients who remain afebrile during therapy, but who are still neutropenic. ¶[336]

Since these early studies, attempts have been made to identify low-risk patients in whom early discharge on an oral regimen could be safely done while still neutropenic. In a retrospective series of 509 pediatric patients with neutropenic fever, lack of signs of sepsis on admission (chills, hypotension, requirement for intravenous hydration), ANC greater than 100 µL, and resolution of fever within 48 hours of therapy accurately distinguished patients who could be discharged on oral agents. ¶[337] Buchanan's group reported that antibiotics could be safely discontinued and that early discharge was feasible in neutropenic pediatric patients who had become afebrile if there were no signs of infection, culture results were negative, and evidence of early marrow recovery existed. ¶[338]

Based on these studies, the IDSA guidelines advise that low-risk patients with undifferentiated neutropenic fever who have become afebrile within 3 days of initiation of empiric parenteral antibiotics can be treated with an oral regimen (cefixime or quinolone) and discharged while still neutropenic. ¶[339] In high-risk patients who become afebrile within 3 days, the IDSA recommends continuing parenteral antibiotics. If the high-risk patient remains afebrile and persistently neutropenic after 2 weeks of therapy, antibiotics can be stopped if no signs of infection exist. ¶[340]

One difficulty in applying such guidelines is the lack of a uniform definition of low- and high-risk patients. The IDSA guidelines define low risk as appearing clinically well, absence of mucusitis or unstable signs, and an ANC greater than 100 µL. ¶[341] Several investigators consider whether the ANC is rising or falling and the anticipated rate of myeloid recovery to also be important predictors of risk. Talcott et al. ¶[342] developed a risk prediction model to distinguish low- and high-risk groups with febrile neutropenia, which is further discussed in Outpatient Antibiotic Therapy for Neutropenic Fever, later in this chapter.

#### Persistent Fever in the Neutropenic Patient

After selection of an initial empiric regimen for neutropenic fever, close observation of the patient is necessary. Throughout the duration of neutropenic fever, daily physical examination should be performed. Modifications of the initial antibiotic regimen should be made on the basis of new physical examination findings pointing to a previously inapparent focus of infection, and radiographic and culture data. ¶[343] If no source of infection is documented, the initial empiric antibacterial regimen need not be changed solely on the basis of persistent fever in a clinically stable patient (see Empiric Antifungal Therapy, later in this chapter). Antibiotic therapy should be continued for the duration of neutropenic fever.

New symptoms and signs of infection in neutropenic patients may be subtle and should be aggressively investigated (Table 54-7). A new erythematous papular lesion may provide initial evidence for isolated cutaneous or disseminated infection by bacterial or fungal pathogens, and biopsy and culture are necessary. Catheter exit sites, surgical wounds, and biopsy sites should be meticulously inspected and palpated for signs of infection. In the neutropenic patient, fever and local tenderness may be the only signs of infection. A diffuse maculopapular rash may suggest the addition of vancomycin while awaiting culture results. Addition of vancomycin is reasonable in patients receiving prophylaxis with ciprofloxacin, which some studies have associated with breakthrough infections by viridans streptococci (see Viridans Streptococci, earlier in this chapter). The IDSA suggests the addition of vancomycin in patients with substantial mucosal damage from chemotherapy (such as regimens containing high-dose Ara-C) because of the added risk of infection by viridans streptococci. Empiric vancomycin should be discontinued after 2 days if the initial culture results are negative or show a pathogen, such as methicillin-sensitive S. aureus, for which other antibiotics can be used.

In neutropenic febrile patients with allergies to b-lactams, empiric vancomycin should be combined with antibiotics active against aerobic gram-negative pathogens. In a clinically stable neutropenic patient, vancomycin plus aztreonam is a reasonable regimen (see Table 54-6). Aztreonam monotherapy is not acceptable because it has no activity against gram-positive bacteria.

| TABLE 54-7. Diagnostic Evaluation and Modifications of Therapy during Neutropenia |

We suggest that two sets of blood cultures from different sites be obtained daily in patients with persistent neutropenic fever to avoid delay in making appropriate modifications to the antibiotic regimen in cases of superinfection during neutropenia. For pathogens that are not reliably isolated from the blood (such as fungal
species), frequent collection of blood cultures may increase the likelihood of making an earlier diagnosis. In addition, the common use of deep, central catheters makes line infection an ever present and easily detected cause of fever.

**Empiric Antifungal Therapy**

The rationale for empiric antifungal therapy for persistent neutropenia is that meticulous clinical examination and collection of cultures are not sufficiently sensitive for early detection of fungal infections. Before standard implementation of empiric antifungal therapy, there was a correlation between prolonged neutropenic fever and mortality in patients with cancer, and fungal infection was frequently found at autopsy. Two randomized prospective studies showed empiric amphotericin B was associated with fewer serious fungal infections in antibiotic-treated neutropenic patients with persistent fever. Because fungal infections are uncommonly encountered in the first 7 days of neutropenic fever, empiric amphotericin B (0.5 to 0.6 mg/kg daily) is typically begun between days 4 and 7 of neutropenic fever (Table 54.7). Empiric antifungal therapy should be continued for the duration of neutropenia. The potential role of lipid formulations of amphotericin B and antifungal azoles are discussed in Antifungal Agents, earlier in this chapter.

**Persistent Fever after Resolution of Neutropenia**

In most cases, an undifferentiated fever that has persisted during neutropenia will resolve around the time of myeloid recovery. In a minority of patients, a fever of unexplained origin persists for several days after myeloid recovery. Similar to the neutropenic period, evaluation of fever after myeloid recovery begins with a meticulous evaluation of both noninfectious causes, such as drug fever (e.g., recombinant growth factors, β-lactam antibiotics), transfusion reactions, and deep venous thrombosis, as well as infectious causes.

A careful physical examination may show a site of infection that was inapparent during neutropenia, such as a perirectal process. A chest radiograph should be obtained because pulmonary infection may not be apparent radiographically during neutropenia. Blood and urine cultures, complete blood cell count, serum chemistry, and liver enzymes should be obtained. An elevated alkaline phosphatase should prompt consideration of hepatosplenic candidiasis, even if blood culture results were negative for Candida species. A CT scan, magnetic resonance imaging, and ultrasound are complementary imaging modalities and may show discrete bull's-eye lesions (see Candidiasis, earlier in this chapter).

In contrast to the neutropenic period, empiric antibiotics can be discontinued after resolution of neutropenia in patients who are stable with an undifferentiated fever and negative culture data. If a source of infection is known, then antibiotic therapy targeted to the specific pathogen(s), rather than broad-spectrum empiric regimens used for neutropenic fever, is advised.

**OUTPATIENT ANTIBIOTIC THERAPY FOR NEUTROPHIN FEVER**

Because of the high morbidity and mortality in febrile neutropenic patients and the need for emergent institution of systemic antimicrobial therapy, hospital admission has been regarded as necessary, and inpatient observation was typically continued until resolution of neutropenia. More recent studies have shown that patients with febrile neutropenia can be stratified according to their risk of developing major or life-threatening infectious complications. Prospective randomized studies have suggested that patients in the lowest risk group are reasonable candidates for carefully monitored outpatient antibiotic therapy.

Patients with a duration of neutropenia of 7 days or less are considered to be at low risk for serious infectious complications. In a study of 580 patients with neutropenia and an undifferentiated fever who had defervesced after initiation of empiric antibiotics, the risk for recurrent fever was directly related to the duration of neutropenia. Among patients with less than 7 days of neutropenia, only 0.6% developed a recurrent fever. The frequency of recurrent fever was 4% when the duration of neutropenia was 7 to 14 days and 38% when the duration of neutropenia exceeded 14 days. Patients with neutropenia of 7 days or less were also far less likely to require modifications in the initial antibiotic regimen compared with patients with neutropenia lasting longer than 14 days. Therefore, patients with long-duration neutropenia are less able to contain ongoing infections or are more likely to develop new infections (or both) after initiation of appropriate empiric antibiotics.

Talcott et al. developed a risk prediction model of serious complications and mortality in patients with febrile neutropenia based on a retrospective analysis of 281 patients and validated prospectively in 444 patients with cancer and febrile neutropenia. The following features predicted a high risk of substantial morbidity (25% to 40%) and mortality (12% to 18%): (1) inpatient status at time of fever and neutropenia (mostly made up of patients with hematologic malignancy or BMT recipients); (2) patients with concurrent comorbidity (hypotension, organ dysfunction, altered mentation, uncontrolled bleeding, and so forth); and (3) patients with uncontrolled progressive malignancy. In contrast, outpatients without significant comorbidity and with controlled malignancy had a low rate of morbidity (2% to 5%) and no infection-related mortality.

Talcott's group subsequently studied 30 low-risk patients with primarily hematologic malignancies and febrile neutropenia at the Dana Farber Cancer Center. Standard intravenous antibiotics were administered for the initial 2 days as inpatients, followed by home antibiotic therapy with gentamicin plus either mezlocillin or cefazidime. Patients with documented infections were excluded. Only 16 (53%) patients responded to the initial antibiotic regimen; nine (30%) patients were readmitted; and four (13%) patients had serious complications, including hypotension, renal failure, disseminated fungal infection, and coagulase-negative Staphylococcus bacteria. No patient died, but the incidence of serious complications and the high admission rate in this pilot study suggested that criteria for selecting patients for outpatient therapy required further refinement.

Malik et al. conducted a prospective, randomized study comparing oral ofloxacin with combination parenteral antibiotics (amikacin plus ceftriaxone, clavulanate, or piperacillin) in 122 hospitalized febrile neutropenic patients in Pakistan. This study was not confined to low-risk patients. Approximately two-thirds of patients had a hematologic malignancy or aplastic anemia, and the mean duration of neutropenia was 9 days. The overall response to antibiotics was 77% in the oral arm and 73% in the parenteral arm. Mortality in the oral group and parenteral groups were similar (7% and 10%, respectively).

This group subsequently compared oral ofloxacin administered in the outpatient versus the inpatient setting in 169 patients with febrile neutropenia. Only low-risk patients as generally defined by the Talcott criteria were enrolled. Two-thirds of patients had solid tumors, and the remainder had hematologic malignancies. The mean duration of neutropenia was 5 days. Approximately 80% of outpatients and inpatients responded to ofloxacin monotherapy, and 20% of patients randomized to the outpatient group were subsequently admitted for parenteral antibiotics. Successful treatment with ofloxacin was more likely in cases in which no source of fever was documented by cultures or physical examination. Mortality in the group initially treated as outpatients was 4% versus 2% in the initial inpatient group.

Hidalgo et al. compared outpatient-administered oral ofloxacin with inpatient-administered parenteral cefazidime and amikacin in a prospective, randomized trial in 95 low-risk febrile neutropenic patients with solid tumors. The median duration of neutropenia was 3 to 4 days. Treatment failure, defined as fever persisting for 3 days or longer, a second febrile episode, or progression of infection, occurred in 10% and 8% of patients in the oral and parenteral arms, respectively. Eight patients in the oral arm were admitted for parental therapy, five because of treatment failure and three because of positive blood culture results. No death or serious complication occurred in those randomized to the oral arm, and one (2%) death occurred in the parenteral arm.

Rubenstein et al. compared outpatient oral ciprofloxacin (750 mg three times a day) plus clindamycin with parenteral clindamycin and aztreonam in 83 low-risk febrile neutropenic patients with solid tumors or leukemia at M. D. Anderson Cancer Center. Patients were observed for 2 hours, then both oral and parenteral groups were sent home to complete therapy. The response rate (defined as resolution of clinical and laboratory evidence of infection) was 88% in the oral arm and 95% in the parenteral arm. Of the 20% in both groups who had bacteraemia, five of seven in the oral arm and seven of eight in the parenteral arm responded to initial antimicrobial therapy. Six patients in the oral arm and none in the intravenous arm were admitted. No mortality or severe complications occurred in either group. The oral arm had additional renal toxicity, perhaps related to dehydratation, the relatively high dose of ciprofloxacin, or both. The authors considered the parenteral regimen to have greater safety than the oral one.

Subsequently, the oral regimen was changed to ciprofloxacin (500 mg) plus amoxicillin/clavulanate (500 mg) every 8 hours, and the parenteral regimen was unchanged in a study of 179 patients with mostly solid tumors. Outcomes were similar, with 90% and 87% response rates in the oral and parenteral arms, respectively. Patients with solid tumors had higher response rates than those with hematologic malignancies. All patients survived without major infectious complications or antibiotic-related toxicity.

In general, these studies are encouraging about the safety of outpatient antibiotic therapy for low-risk patients with neutropenic fever (see references for more detailed reviews). However, important limitations exist in making broad conclusions. The prospective, randomized studies described previously...
individually each enrolled fewer than 200 patients, and therefore lacked sufficient power to detect small differences between treatment groups. Pooling data from different studies as a meta-analysis is made difficult by the differences in eligibility criteria, choice of antibiotics, criteria for hospital admission, and criteria for a successful outcome.

The National Cancer Institute and H. Lee Moffitt Cancer Center compared an oral regimen consisting of ciprofloxacin plus amoxicillin-clavulante with intravenous cefazidime alone in patients with febrile neutropenia in whom the expected duration of neutropenia was less than or equal to 10 days from the onset of fever. All patients were hospitalized for the entire duration of neutropenic fever. A total of 116 episodes of neutropenic fever were evaluated. Approximately 75% of patients had solid tumors, and the remainder had leukemia or lymphoma. The mean duration of neutropenia in both groups was 3 to 4 days. Approximately two-thirds of febrile episodes were unexplained, and blood stream infections occurred in only 7% of episodes. Serious complications, such as hypotension or intraabdominal infection, were rarely encountered. Breakthrough infections associated with bacteremia, oral, or soft tissue infections were also rare in both groups and were controlled by modifications in the antibiotic regimen. There were no deaths.

In a European multicenter study of febrile neutropenia (defined as ANC less than 1000/µL), patients with an expected duration of neutropenia of less than or equal to 10 days were randomized to receive either oral ciprofloxacin plus amoxicillin-clavulanate or intravenous ceftriaxone plus amikacin. A total of 312 patients were evaluated, approximately 70% with a solid tumor and the remainder with a hematologic malignancy. The median duration of neutropenia after antibiotics was 4 days. Two patients in the oral group and six patients in the intravenous group died of infection. At day 30 after randomization, survival was approximately 85% in both groups. Bacteremia occurred in less than 1% of patients in both groups. The duration of fever, duration of therapy, and need for modification of the antibiotic regimen were similar in both groups.

These two well-designed studies establish clearly that for carefully selected patients with febrile neutropenia, an oral regimen consisting of ciprofloxacin plus amoxicillin-clavulanate is safe and effective. Both studies evaluated lower risk patients, but the inclusion of patients with hematologic malignancies and patients with an expected duration of neutropenia as high as 10 days after the onset of fever reflect more liberal criteria for risk stratification. Patients with comorbidities predictive of a higher risk of complications (e.g., hemodynamic instability; neurologic, hepatic, respiratory, or renal impairment; catheter infections; inability to take oral medications) were excluded. In addition, these studies were conducted in hospitalized patients and, therefore, extrapolations should not be made about the feasibility of this oral regimen in the outpatient setting.

The greatest concern about outpatient management of neutropenic fever relates to the possibility of life-threatening complications that may be reversible if detected early and appropriate interventions are made immediately (e.g., intravenous fluid, vasopressors, broadening of antibiotic coverage). Randomized clinical trials with sufficient statistical power are required to more precisely stratify patients for whom outpatient management of neutropenic fever is safe and to delineate optimal antibiotic regimens (oral versus parenteral) for different patient groups.

ANTIBACTERIAL PROPHYLAXIS IN AFEBRILE NEUTROPENIC PATIENTS

Despite improvements in antibacterial agents used in febrile neutropenia, persistent and profound neutropenia remains the most important predictor of life-threatening infections. Adjuvant prophylactic agents administered at the onset of neutropenia therefore have potential appeal as a means of reducing the incidence of infections during this high-risk period. However, the concern for emergence of antibiotic-resistant bacteria plus the lack of a survival benefit associated with antibacterial prophylaxis led to the reasonable recommendation against routine prophylaxis in neutropenic patients by the IDSA.

Today, antibacterial prophylaxis for neutropenia is largely restricted to quinolones and trimethoprim-sulfamethoxazole. These agents have activity against Enterobacteriaceae without significant activity against commensal intestinal anaerobes, thus providing selective decontamination of the gut. The rationale for selective, as opposed to global, suppression of gut flora is based on the concept of colonization resistance. In human studies, maintenance of the normal commensal intestinal flora provides a potent barrier to acquisition of pathogenic aerobic gram-negative rods. Thus, it has been argued that an ideal prophylactic antibiotic regimen selectively targets aerobic gram-negative bacteria without influencing the normal intestinal microbial flora. Quinolones and trimethoprim-sulfamethoxazole have the added advantage of achieving high serum and tissue levels after oral administration, an important consideration given that multiple portals of bacterial invasion exist in neutropenic patients.

Two meta-analyses have been conducted on trials of fluoroquinolone prophylaxis in neutropenic patients. Patients in which quinolones were compared with placebo or trimethoprim-sulfamethoxazole. Patients who received quinolones had 79% fewer gram-negative infections than those without prophylaxis, leading to an overall 46% reduction in total infections. The reduction in fever was small, and in blinded trials, was not significant. Quinolones were more effective than trimethoprim-sulfamethoxazole in preventing gram-negative infections. Prophylaxis with either agent did not affect mortality.

The frequencies of quinolone-resistant gram-negative isolates, gram-positive infections, and fungal infections were not significantly affected by quinolone prophylaxis in the meta-analysis. However, a note of caution is required. Although quinolones have remained highly active at preventing gram-negative bacterial infections, quinolone-resistant gram-negative infections have developed during treatment with these agents. Among gram-positive pathogens, viridans streptococcal bacteria is of particular concern in patients receiving quinolone prophylaxis (see Viridans Streptococci, earlier in this chapter).

To try to overcome the inadequate activity of quinolones against gram-positive bacteria, combination prophylactic regimens have been used. One randomized study showed addition of penicillin to a quinolone (piperacillin) reduced the rate of bacteremia, especially that due to streptococcal species, compared with the quinolone alone. Another randomized study showed that the combination of prophylactic ofloxacin and rifampin led to a reduction in gram-positive infections compared with ofloxacin alone. However, addition of these agents to quinolone prophylaxis, of course, defeats the concept of selective decontamination. Newer generation quinolones with enhanced activity against streptococci are potential candidates for prophylaxis and warrant further study.

If prophylactic ciprofloxacin is used, vancomycin should be considered in the initial empiric regimen for neutropenic fever based on the high likelihood of breakthrough gram-positive infections. Vancomycin plus cefazidime is a logical combination in this setting.

Trimethoprim-sulfamethoxazole as prophylaxis against P carinii in children with acute lymphocytic leukemia was also highly effective as prophylaxis against bacterial infections and sepsis. More recent studies comparing trimethoprim-sulfamethoxazole with placebo have yielded inconsistent results. This discrepancy may reflect the emergence of resistant gram-negative bacteria during trimethoprim-sulfamethoxazole prophylaxis. In comparative studies, trimethoprim-sulfamethoxazole has, in general, been shown to be less effective than quinolones with regard to protection against gram-negative infections. Other disadvantages of trimethoprim-sulfamethoxazole prophylaxis include lack of activity against P aeruginosa, potential suppression and delay of myeloid recovery, and hypersensitivity reactions. The main advantage of trimethoprim-sulfamethoxazole over quinolones relates to effective prophylaxis against P carinii. Although P carinii is rarely associated with isolated neutropenia, other comorbid conditions (such as AIDS) and regimens that contain intensive corticosteroid therapy predispose to infection by this organism (see Pneumocystis carinii, earlier in this chapter). Trimethoprim-sulfamethoxazole may also reduce the frequency of nocardiosis, listeriosis, and toxoplasmosis in persons with compromised T-cell immunity.

PROTECTED ENVIRONMENTS

The rationale for protective environments for neutropenic patients is derived from the principle of selective decontamination by prophylactic antibiotics. By reducing the frequency of colonization by virulent bacteria, a germ-free environment was considered to be important in protecting neutropenic patients from infection. However, it became clear that such stringent measures were not necessary for the majority of neutropenic patients. Nauseef and Maki compared protective isolation (single room and use of gowns, gloves, and masks) with standard hospital care in hospitalized neutropenic patients with acute lymphocytic leukemia. Neither group received prophylactic antibiotics or sterilized food. The two groups were similar with respect to incidence of infection and days with fever. Paradoxically, the rate of infection was higher in patients randomized to protective isolation. The availability of more effective antibacterial agents, the shift in predominance of infections from gram-negative to gram-positive pathogens in neutropenic patients, and the lack of evidence supporting the benefit of protective isolation have led to the adoption of less stringent methods of isolation at most centers. The cost and excess labor required to maintain stringent isolation and the additional emotional burden that patients and families must endure further militates against the routine use of such measures.

Isolation of aerobic gram-negative bacteria from food in hospitals is well known. Uncooked vegetables often contain relatively large burdens of E coli, Klebsiella
species, and \( P \) aeruginosa.\textsuperscript{354} Thus, although not validated by controlled studies, it is reasonable to omit such foods from the diets of neutropenic patients. Similarly, tap water can harbor \( P \) aeruginosa and Legionella species. Careful hand washing before and after patient contacts remains the most effective method for preventing nosocomial infection.\textsuperscript{365}

Laminar air flow units with high-efficiency particulate air filtration is the most effective means of removing aerosolized bacteria and fungal spores.\textsuperscript{355} With more effective antimicrobial agents used today as empiric therapy for neutropenic fever, it is unclear that such protected environments are of benefit for most neutropenic patients. The high cost of maintaining such units makes them impractical for routine use for all neutropenic patients at most centers.\textsuperscript{365} Today, the principal benefit of laminar air flow units is likely to be protection against \textit{Aspergillus} species and other filamentous fungi. From a practical standpoint, they are usually restricted to patients at high risk for infection by molds (e.g., patients with leukemia and BMT recipients).

**MANIFESTATIONS AND THERAPY OF INFECTIONS**

**BACTEREMIA**

Bacteremia is a common complication of antineoplastic myeloablative chemotherapy. In a review of empiric antimicrobial regimens for neutropenic fever, the dominant risk factor for bacteremia was the duration of neutropenia.\textsuperscript{356} Neutropenia lasting 1 to 5 days before trial entry was associated with a relative risk of bacteremia of 5.2 compared with no neutropenia; neutropenia of 6 to 15 days had a relative risk of 7.35. Patients with a hematologic disease and BMT recipients were also more likely to have bacteremia than patients with solid tumors. The presence of shock was highly predictive of bacteremia with a relative risk of 5.6.

In patients with suspected systemic infection, a meticulous physical examination and culture of all potential sources of infection should ideally be done before initiation of antibiotics. If it is not feasible to obtain all culture material at the time of initial evaluation, however, empiric antibiotic therapy should not be delayed. Cultures should be obtained from blood and urine, and depending on the clinical situation, from sputum, pleural fluid, and peritoneal fluid. Wounds and skin lesions should be aspirated or biopsied, and material submitted for culture. Particularly in neutropenic patients, the appearance of wounds may be deceptively benign without erythema or purulence.

Once a positive blood culture result is reported, the initial antibiotic therapy may need to be altered (see **Table 54-7**). Coagulase-negative \textit{Staphylococcus} species and \textit{Corynebacterium} (diphtheroid) species are common blood culture contaminants. However, patients with cancer often have indwelling intravenous catheters, which can be portals of entry for these bacteria, thereby increasing the risk of bacteremia. The likelihood of contamination is increased if these organisms are isolated from a single blood culture. It is therefore important to draw at least two sets of blood cultures from separate sites. \textit{Corynebacterium jeikeium} is a virulent species associated with bacteremia and disseminated organ infection; isolation of this organism from a single blood culture requires prompt initiation of vancomycin therapy. Similarly, isolation of \textit{S} aureus from a single blood culture (or from the urine in a febrile or septic appearing patient) should be considered to represent hematogenous infection.

If a gram-negative organism is isolated from a blood culture collected before the initiation of antibiotics, an appropriate parenteral regimen used empirically at the onset of neutropenic fever can be maintained while awaiting drug sensitivity data so long as the patient is clinically stable.\textsuperscript{355} The rationale is that standard empiric antimicrobial regimens for neutropenic fever and the specific regimens adopted at a given institution are selected to provide reliable coverage against all likely gram-negative pathogens. If the patient is not stable or if the gram-negative organism is isolated after initiation of antibiotics (i.e., breakthrough bacteremia), change to a new regimen is warranted (see **Table 54-7** for specific suggestions). Once antibiotic susceptibilities are known, therapy should be tailored appropriately.

Shock and multiple organ dysfunction are dreaded complications of sepsis. In patients with neutropenia, prompt initiation of broad-spectrum antibiotics directed against commonly encountered blood-borne pathogens is essential (e.g., \textit{S} aureus, viridans streptococci, \textit{Enterobacteriaceae}, and \textit{P} aeruginosa). Unlike the stable patient with neutropenic fever, there is likely not to be an opportunity to modify antibiotics based on culture data if the initial regimen does not provide adequate coverage. Combination vancomycin, imipenem, and an aminoglycoside is a reasonable empiric regimen. At centers in which carbapenem-resistant \textit{P} aeruginosa is frequent, ceftazidime plus metronidazole may be used instead of imipenem. Modifications should be made once culture and sensitivity data are known.

In septic shock, several interventions should be made rapidly. When possible, removal of all indwelling catheters should be performed. If a nidus of infection is identified, treatment should be performed (e.g., culture and staining for bacterial, fungal, and viral pathogens). Standard supportive measures include fluid resuscitation, oxygen, and invasive hemodynamic monitoring, and vasopressor agents should be instituted. In patients with documented or suspected adrenal insufficiency, stress dose corticosteroids (e.g., hydrocortisone, 50 to 100 mg every 8 hours) should be administered. Empiric corticosteroid administration for adrenal insufficiency is appropriate in patients who have received significant corticosteroid therapy within the last year, such as for the underlying malignancy or for GVHD. However, routine use of corticosteroids for severe sepsis and shock is not warranted.\textsuperscript{357}

Numerous studies have evaluated therapy directed against specific mediators of septic shock, including antibodies against endotoxin and TNF-\( \alpha \) and a recombinant IL-1 receptor antagonist. Other potential strategies include endotoxin vaccine, polyclonal hyperimmune serum (to neutralize bacterial toxins), bradykinin, cyclooxygenase, leukotriene, platelet-activating factor antagonists, pentoxifylline, endogenous antibacterial peptides (such as bactericidal permeability increasing protein), and inhibition of nitric oxide.\textsuperscript{358} All such therapeutic modalities directed against mediators of the sepsis cascade should be considered to be experimental.

**IMPLANTED VASCULAR CATHETERS**

Tunneled, cuffed vascular catheters have been used extensively in patients with cancer, providing long-term central venous access for blood drawing and infusions. Catheter infections have been divided into several categories.\textsuperscript{359} Greene\textsuperscript{27} distinguished exit from tunnel infections based on whether inflammation extended greater than 2 cm from the exit site. Purulence from the exit site is present, although in neutropenic patients, local erythema and tenderness may be the only signs of infection, making it difficult to distinguish from sterile inflammation associated with mild trauma. Tunnel infections manifest with inflammation extending along the subcutaneous tract through which the catheter was inserted. The third major category is catheter-related bacteremia or fungemia, which may occur in the presence or absence of signs of localized infection. A 5- to 10-fold greater organism recovery from blood drawn from the catheter compared with peripheral blood cultures is highly suggestive of a catheter source of sepsis. The fourth category is a septic thrombophlebitis in which a venous thrombus is documented in association with positive blood culture results.

Most exit site infections can be cured with antibiotics alone without catheter removal. At the University of Maryland Cancer Center, 160 exit site infections were identified out of 660 Hickman catheters placed, most caused by \( S \) epidermidis or \( S \) aureus.\textsuperscript{27} Treatment was usually with vancomycin, and only 10 of 160 exit site infections resulted in catheter removal. In another study, 55 of 65 exit site infections were successfully treated with antibiotics and local care alone.\textsuperscript{360}

In contrast to exit site infections, tunnel infections generally require catheter removal because of failure of antibiotic therapy alone. In cases of tunnel infection caused by the \textit{Mycobacterium fortuitum} complex (\textit{M} fortuitum and \textit{M} chelonae), surgical excision of the tissue surrounding the tunnel may be required.\textsuperscript{361}

Most cases of catheter-associated bacteremia can be cured without catheter removal, but certain situations should prompt catheter removal. Persistently positive blood culture results for longer than 3 days or recurrences of bacteremia by the same pathogen despite adequate antibiotic therapy are evidence of antibiotic failure and require catheter removal. In patients with severe sepsis (e.g., \textit{hypersplenosis} or \textit{S} aureus),\textsuperscript{27} Treatment was usually with vancomycin, and only 10 of 160 exit site infections resulted in catheter removal. In another study, 55 of 65 exit site infections were successfully treated with antibiotics and local care alone.\textsuperscript{360}

In cases of septic thrombophlebitis, prompt catheter removal and initiation of antimicrobial therapy is essential. Anticoagulation is generally used, although its value has not been clearly established. Septic phlebitis of a central vein usually does not require surgical drainage if the catheter is removed. In cases in which a focus of infection exists in the soft tissue around the vein, surgical drainage may be necessary.\textsuperscript{362}

Central catheters may be partially implanted, such as the Broviac or Hickman type in which the ports are exposed to the outside, or they may be entirely implanted. The totally implanted venous access devices have the advantage of being less likely to be traumatized or colonized by external skin flora and have fewer infections compared with catheters with external ports. In a study at Memorial Sloan-Kettering Cancer Center, 341 of 788 (43%) external tunneled catheters became infected compared with 57 of 680 (8%) completely implanted ports,\textsuperscript{363} and external catheters were significantly more likely to be removed because of infection. It is possible that the more favorable infection rate associated with implanted ports is that such catheters are more likely used in patients with solid tumors who do not require
multiple ports for intravenous access; the external catheters are in turn more likely to be used in patients who require more catheter manipulations, such as those with leukemia and BMT recipients.

The use of long-term tunneled catheters with a Dacron cuff to reduce entry of skin flora is generally associated with fewer infections than nontunneled catheters. However, at the M. D. Anderson Cancer Center, nontunneled silastic catheters were associated with long durability and a low infection rate comparable with tunneled catheters.271 Such an approach requires meticulous catheter care, but has the advantage of reduced expense and morbidity associated with catheter insertion and easier catheter removal.

SKIN LESIONS AND SOFT TISSUE INFECTIONS

In the heavily immunocompromised patient with cancer, skin lesions can arise from several different etiologies (see reference 377 for an excellent review). Drug reactions are probably the most common noninfectious cause of cutaneous lesions. b-Lactam and sulfa antibiotics are relatively common offenders that are used extensively in this patient population. Cutaneous lesions may be manifestations of the underlying malignancy. For example, hematologic malignancies are associated with mixed cryoglobulinemia, which may produce cutaneous vasculitis. Sweet's syndrome is characterized by fever and skin lesions that may be papular, nodular, or ulcerative. These lesions may be misdiagnosed as cellulitis and be treated inappropriately with antibiotics. Histologically, a dense neutrophilic infiltrate localized mostly in the mid and upper dermis is diagnostic. However, angiogenesis associated with hematologic malignancies is not uncommon. In the transplant recipient, GVHD typically presents as a diffuse maculopapular rash, and involvement of the gut and liver is common. Biopsy of skin lesions for histology and culture and staining for bacteria, fungi, mycobacteria, and viral infections is prudent to rule out infection.

Infections of the skin can either be localized or manifestations of systemic infection. Ecthyma gangrenosum is the most characteristic skin lesion associated with systemic P aeruginosa infection, but it is not pathognomonic (see Fig. 54-1). Ecthyma gangrenosum–like lesions can be caused by S aureus, enteric gram-negative rod infection, and by filamentous fungi, including Aspergillus, Zygomycete, and Fusarium species. Ecthyma gangrenosum begins as a raised erythematous papule or nodule that progresses to a bluish-black necrotic lesion within 12 to 24 hours. A central area of necrosis surrounded by erythema is typical. Hemorrhagic bullae may be observed. Clinically, ecthyma gangrenosum–like lesions are a necrotizing process in which masses of bacteria are often observed within the vessel wall. In neutropenic patients, infiltrating white cells may be absent.

Local soft tissue infection by P aeruginosa in the neutropenic patient can rapidly spread through fascial planes, causing extensive necrosis and fulminant sepsis.271 The signs at the site of entry may be mild, pain and tenderness may be out of proportion to erythema, and purulence is likely to be absent. A needle aspiration of the lesion showing gram-negative bacilli establishes the diagnosis of invasive infection; however, a negative aspiration does not rule out the diagnosis. Prompt surgical débridement may be life saving in cases of localized infection.

Stenotrophomonas maltophilia can cause a variety of dermatologic infections, including mucocutaneous ulcerations, primary cellullitis, a metastatic nodular cellullitis, and eczema gangrenosum (see Stenotrophomonas [Xanthomonas] maltophilia, earlier in this chapter). Aeromonas hydrophila is a gram-negative rod that grows in fresh and brackish water and can be acquired by nosocomial transmission. Immunocompromised persons are more susceptible to extensive soft tissue infections from direct penetration through the skin, leading to sepsis. In a patient exposed to fresh or brackish water preceding an episode of cellulitis, an antibiotic regimen with activity against A hydrophila should be initiated. The organism is usually susceptible to fluoroquinolones, trimethoprim-sulfamethoxazole, third-generation cephalosporins, and imipenem.

Septicemia by viridans streptococci is associated with cellulitis and a rash in 60% of cases in a series from the M. D. Anderson Center in Texas.272 The rash was usually maculopapular, started on the trunk, and extended to the face and extremities. Skin exfoliation occurred on the palms and soles in 25% of patients 2 weeks after the onset of the rash. These manifestations are likely the result of acquisition of a plasmid producing a toxin associated with a toxic shock syndrome.

Bacteremia caused by C jejule is associated with skin lesions in 30% to 50% of neutropenic patients. The skin lesions often occur at catheter sites and at sites of trauma, such as bone marrow aspiration, and may only become apparent after resolution of neutropenia.272 The portal of entry is usually through the skin. The lesions may be cellullitic, ulcerative, or pustular. If diphtheroids are isolated from a skin lesion, the microbiology laboratory should be asked specifically to evaluate for C jejule. These rare species are causes of skin infection, but can be associated with impetiginous, ulcerative, and necrotic skin lesions. C jejule and Bacillus species are sensitive to vancomycin.

Clostridium species are gram-positive anaerobes that cause deep soft tissue infection involving the fascia and muscle (see Clostridium Species, earlier in this chapter). Typically, a small dusky or purplish lesion on the leg or abdominal wall rapidly expands, and as infection progresses, the lesions become necrotic, bullous, and hemorrhagic. Systemic toxicity, including fever, malaise, and mental status changes occur early. Because the infection occurs in the deep soft tissue, tenderness and evidence of vascular compromise typically precede the development of cellullitis. A rapidly progressive deep soft tissue infection with gas formation suggests clostridial myonecrosis (or polymicrobial necrotizing fascitis). Needle aspiration characteristically shows the organism in the setting of a mild or absent inflammatory response. Extensive surgical débridement may be life saving if initiated early, although at this stage of disease, most patients die.272 The characteristic skin lesions of disseminated candidiasis are raised erythematous discrete papules, measuring approximately 0.5 to 1.0 cm in diameter. The lesions are usually not tender. Concurrent myalgias raise the possibility of Candida myositis.273 The yeast is cultured from skin lesions in approximately one-half the cases. Therefore, a negative result does not rule out the diagnosis. Biopsy and fungal staining of cutaneous lesions can provide an immediate clue to the diagnosis, prompting the early addition of antifungal therapy.

Trichosporon beigelii is a yeast that causes sepsis and disseminated infection in neutropenic patients.274,275 Skin lesions occur in 30% of disseminated infections and are characterized by nodular erythematous nodules that may become necrotic. Histologically, budding yeast are present in the dermis, as distinguished from Candida species, which produce pseudohyphae. High-dose azole therapy is considered the treatment of choice.

Candida species are the most common cause of candidemia, and by filamentous fungi, including Aspergillus, Zygomycete, and Fusarium species. Ecthyma gangrenosum begins as a raised erythematous papule or nodule that progresses to a bluish-black necrotic lesion within 12 to 24 hours. A central area of necrosis surrounded by erythema is typical. Hemorrhagic bullae may be observed. Clinically, ecthyma gangrenosum–like lesions are a necrotizing process in which masses of bacteria are often observed within the vessel wall. In neutropenic patients, infiltrating white cells may be absent.

Cutaneous infection by filamentous fungi may be primary or may represent systemic infection. Primary cutaneous infection with molds can occur in immunocompetent patients but is more common in immunosuppressed patients. Histologically, progression to angioinvasion, infarction, extension to the deep soft tissue fascia and muscle, and dissemination denote profound immunosuppression. Walmesley et al.276 described 16 cases of primary cutaneous aspergillosis in children, most of whom had leukemia or lymphoma or had undergone BMT. Eleven cases were related to intravenous arm boards, and five cases were attributed to hematogenous dissemination. Clinically, these cases resembled eczema gangrenosum associated with disseminated P aeruginosa infection. Histologically, hyphal elements are present and may cause angioinvasion and infarction.

Infection by Fusarium species is being observed with increasing frequency, predominantly in leukemia patients with prolonged neutropenia. Primary cutaneous fungus resembling cellulitis, paronychia, onychomycosis resembling dermatophyte infection, as well as papular and nodular lesions, and subcutaneous nodules were described 16 cases of primary cutaneous aspergillosis in children, most of whom had leukemia or lymphoma or had undergone BMT. Eleven cases were related to intravenous arm boards, and five cases were attributed to hematogenous dissemination. Clinically, these cases resembled eczema gangrenosum associated with disseminated P aeruginosa infection. Histologically, hyphal elements are present and may cause angioinvasion and infarction.

In the case of primary localized cutaneous infection with a mold, surgical resection is necessary and has an excellent prognosis.278 In the neutropenic patient, the likelihood of subclinical systemic infection is high, and, therefore, high-dose amphotericin B (1.0 to 1.5 mg/kg daily) or a lipid formulation should be administered.

SINUSITIS

In immunocompetent patients, sinusitis results principally from inadequate drainage of mucous secretions from the sinus cavities. Respiratory bacterial pathogens, including S pneumoniae, H influenzae, and M catarrhalis predominate. In patients with neutropenia or otherwise highly immunocompromised patients, infections by P aeruginosa, Enterobacteriaceae, and molds are more commonly observed.

Treatment of sinusitis in immunocompetent patients with cancer involves an standard antibiotic regimen, such as trimethoprim-sulfamethoxazole, amoxicillin-clavulanate, or a cephalosporin with activity against respiratory pathogens. In cases of an obstructing tumor interfering with drainage from the maxillary sinuses, surgical creation of an antral window may be required to facilitate drainage.

In neutropenic patients with symptoms or signs suggestive of sinusalitis, a regimen with activity against gram-negative bacteria (such as ceftazidime) should be administered. If no improvement occurs within 3 days, a CT scan of the sinuses with diagnostic aspiration of fluid collections is recommended. A sinus endoscopy may
Infections by community respiratory viruses may initially manifest with sinus congestion or nonspecific upper airway symptoms. A high index of suspicion for such viruses is necessary for early therapy and prevention of nosocomial outbreaks. A nasopharyngeal or throat wash may rapidly establish the diagnosis (see Community Respiratory Viruses, earlier in this chapter).

Invasive fungal sinusitis in immunocompromised patients often has devastating results. Infection by Aspergillus species is most common in patients with persistent neutropenia (e.g., aplastic anemia) and in BMT recipients. The agents of mucormycosis are classically associated with rhinocerebral disease, leading to necrosis of the palate, and extension to surrounding structures. Sinusitis by emerging fungal pathogens, including Fusarium species, Alternaria species, dark-walled molds, and Pseudallescheria boydii are being recognized with increasing frequency. A cluster of fungal sinusitis in a pediatric hospital was associated with soil reservoirs disturbed by hospital construction.

Symptoms and signs suggestive of fungal sinusitis include fever, nasal congestion, headache, maxillary tenderness, and periorbital swelling. Sinus endoscopy may show necrotic material or ulceration. Hyphal invasion into blood vessels leads to tissue infarction and hemorrhage. Mental status changes are suggestive of involvement of the brain.

Therapy for invasive mold infections involves a combined medical and surgical approach. High-dose amphotericin B (1.5 mg/kg/d) or a lipid formulation of amphotericin B should be initiated. When feasible, surgical resection of involved tissue should be performed, as medical therapy alone is unlikely to contain infection in the setting of neutropenia or severe immunosuppression. Amphotericin B should be continued even if all of the visualized necrotic tissue is fully debrided, given the likelihood of inapparent local and disseminated disease. The most important predictor of a successful outcome is resolution of neutropenia.

**PULMONARY INFILTRATES**

In patients with cancer, pulmonary infiltrates pose a particularly difficult challenge. Numerous noninfectious causes of pulmonary infiltrates include congestive heart failure, pulmonary hemorrhage, infarction, drug-induced pneumonitis, radiation injury, tumor, and acute respiratory distress syndrome (Table 54-8). In addition, common processes can have atypical radiographic appearances, and two or more pulmonary processes can exist simultaneously in this patient population. Establishing an early diagnosis is crucial so that appropriate therapy can be instituted, and the toxicity of inappropriate therapy is avoided.

In heavily immunocompromised patients with cancer, such as those with leukemia and BMT recipients, pneumonia is common and is associated with a high mortality. Walsh and Pizzo divided pulmonary infiltrates in neutropenic patients into four categories: (1) early, focal; (2) refractory, focal; (3) late, focal; and (4) interstitial or diffuse. Early infiltrates are defined as those that develop with the first onset of fever in a neutropenic patient. These infections are likely to be caused by Enterobacteriaceae, *P. aeruginosa*, and *S. aureus*. Because of neutropenia, physical findings of consolidation and sputum production may be absent. Two sets of blood cultures, a urine culture, a chest radiograph, and, if possible, a sputum for Gram's stain and culture should be obtained. Early in the course, the infiltrate is localized, but rapid progression to respiratory failure and sepsis is common. It is therefore essential to initiate appropriate empiric antibiotic therapy promptly and to closely monitor the response in an inpatient setting.

The optimal antibiotic regimen is controversial. The potential advantages of combination antibiotics include synergy and a reduced likelihood of the pathogen being resistant to all antibiotics in the initial regimen. An antipseudomonal penicillin (such as piperacillin or ticarcillin) or a third- (cefazidine) or fourth- (cefpime) generation cephalosporin with activity against *P. aeruginosa* may be combined with an aminoglycoside. If MRSA is common, empiric vancomycin should be added. Alternatively, standard monotherapy regimens for empiric treatment of febrile neutropenia, including cefazidine, cefepime, imipenem, or meropenem, have sufficiently broad-spectrum activity to be used for treatment of acute bacterial pneumonia in neutropenic patients. The principle that a broad-spectrum antibiotic can be used as monotherapy for serious community-acquired and nosocomial pneumonias has gained widespread acceptance through well-designed prospective studies. With regard to patients with cancer, cefazidine monotherapy was shown to be equivalent to combination regimens as empiric therapy for neutropenic fever, including a subgroup of patients with pulmonary infiltrates. The rationale of monotherapy is to design a regimen with broad-spectrum activity against the most common pathogens and against the pathogens most likely to result in serious or life-threatening complications. Modifications of the initial regimen should be made on the basis of clinical response and microbiologic data. For this reason, use of a single antibiotic is probably not appropriate as empiric therapy for a fulminant pneumonia causing respiratory failure and sepsis, in which delay in the institution of appropriate antibiotics is likely to have disastrous consequences. The appropriateness of a particular empiric regimen for pneumonia, either monotherapy or combination therapy, depends on the frequency of isolates and their sensitivity profiles at a given institution.

If clinical improvement occurs within 48 to 72 hours, no further diagnostic measures are necessary, and antibiotic therapy should be continued until neutropenia resolves and for at least 10 to 14 days. Once neutropenia resolves, an appropriate oral antibiotic regimen could be administered for the remainder of the course.

In cases of refractory pneumonia, the possibility of a bacterial infection resistant to the empiric regimen as well as atypical causes of pneumonia become more likely. Examples of the latter group include *Legionella*, Chlamydia, Mycoplasma, *P. carinii*, *Nocardia*, and Mycobacteria species, as well as viral and fungal pathogens. Pneumonia and sepsis caused by enteric flora in a patient from an endemic area may result from a hyperinfection syndrome by *Strongyloides stercoralis*. A CT scan of the chest is useful in defining the location and morphology of the lesions, and an invasive diagnostic procedure (bronchoalveolar lavage, needle aspiration, open lung biopsy) may be warranted to establish the diagnosis.

Late onset of focal infiltrates applies to new pulmonary lesions developing on or after 7 days of empiric antibiotic therapy in persistently neutropenic patients. The likelihood of a fungal pneumonia in this setting is high. In contrast, development of a new pulmonary infiltrate after resolution of neutropenia is likely to represent a previous infection that was unrecognized during the neutropenic period; such infiltrates usually resolve without complications. *Aspergillus* species are the most common cause of pneumonia in persistently neutropenic patients. Less common fungal pathogens include *Trichosporon*, *Rhizopus*, *Fusarium* species, and dematiaceous molds. *Aspergillus* species and other filamentous fungi are angiinvasive and may cause pulmonary hemorrhage and infarction (see Aspergillosis, earlier in this chapter). Pleuritic chest pain may result from pulmonary infarction or direct invasion of chest wall structures. As is the case for refractory pneumonia, infection with resistant bacteria, viruses, and protozoa remain in the differential diagnosis.

Diffuse pulmonary infiltrates may be due to a variety of infectious causes, including progressive bacterial infection, *Legionella*, *P. carinii*, *M. tuberculosis* (miliary), atypical mycobacteria, *S. stercoralis*, and fungal and viral pathogens. In the BMT recipient, CMV infection is the most common cause of pulmonary infiltrates in the postengraftment period, generally between 1 to 4 months after transplant. Respiratory viruses, including RSV, parainfluenza, influenza, and adenovirus can cause severe pulmonary infection in transplant recipients. In winter months, upper respiratory symptoms and bronchospasm favor the diagnosis of RSV. Diffuse necrotizing pneumonia by varicella and HSV are also encountered in transplant recipients. Patients receiving concomitant corticosteroid therapy in addition to myeloablative therapy are at particular risk for *P. carinii* infection, and, to a lesser degree, histoplasmosis, coccidiodomycosis, cryptococcosis, and reactivation of tuberculosis.
Based on careful evaluation of the patient's level of immunosuppression, time course of the illness, epidemiologic exposures, physical examination, and radiographic and laboratory data, a preliminary differential diagnosis is established. For patients who are either not responding to antibacterial therapy or whose clinical course is not suggestive of an acute bacterial process, an aggressive and expeditious approach to establishing the diagnosis is indicated. Sputum induction with hypertonic saline is diagnostic of PCP in approximately 60% of cases in patients who not infected with human immunodeficiency syndrome. Sputum induction is also of value in diagnosing tuberculosis. If sputum induction is not diagnostic, bronchoalveolar lavage has a high diagnostic yield in alveolar infiltrates such as pneumonia caused by *P. carinii*, *M. tuberculosis*, and respiratory viruses. The sensitivity of bronchoalveolar lavage for focal lesions such as nodules is variable. In lesions larger than 2 cm, the sensitivity of bronchoalveolar lavage ranges from 50% to 80%, but in smaller lesions, the diagnostic yield is usually approximately 15%. Quantitative cultures from bronchoalveolar lavage or from a protected brush catheter may increase the specificity in the diagnosis of bacterial pneumonia as distinguished from oral flora. However, the diagnostic yield of such procedures is substantially reduced by prior antibiotic therapy.

Bronchoalveolar lavage is a relatively insensitive method for diagnosing aspergillosis, detecting only approximately 50% of cases. In one study of patients with leukemia, bronchoalveolar lavage failed to document all cases of proven pulmonary aspergillosis. Percutaneous biopsy may increase the diagnostic yield, but in thrombocytopenic patients, the risk of bleeding may be unacceptably high. Open lung biopsy is the definitive diagnostic method in immunocompromised patients with pulmonary lesions. This procedure also allows for easier visualization and control of bleeding. False-negative results occur in approximately 5% of open lung biopsies as a result of sampling error in the case of patchy lesions.

**CARDIAC INFECTIONS**

Cardiac infections are relatively uncommon in patients with cancer. Infection can occur as a complication of thoracic surgery, such as a pneumonectomy, in which dehiscence of the bronchial stump can lead to a bronchopleural fistula and infection of the pleural space with extension to the pericardium. Meliculous and repeated debridements of infected tissue and repair of the fistula are necessary.

Endocarditis can occur as a complication of catheter-associated bacteremia or a septic thrombophlebitis of the neck. In neutropenic patients, dental procedures should be avoided, if they are necessary, antibiotic prophylaxis (amoxicillin) is reasonable to avoid secondary bacteremia. Evaluation by echocardiography is warranted in patients with bacteremia with signs suggestive of endocarditis, such as a new murmur or embolic phenomena.

Fungal endocarditis (principally *Candida* and *Aspergillus* species) may result from cardiac surgery and from illicit drug use. Therapy for fungal endocarditis requires removal of the infected valve based on the poor penetration of antifungal agents into the valve, and the propensity for large vessel embolization. If valve surgery is not feasible, combination therapy generally consisting of high-dose amphotericin B (1.0 to 1.5 mg/kg/d) plus 5-flucytosine followed by prolonged fluconazole therapy has been successful in case reports of *Candida* endocarditis. Rarely, filamentous fungi may also cause myocardial abscesses with direct extension to and destruction of the contiguous valve in profoundly immunosuppressed patients.

Pericardial aspergillosis is a rare, but highly lethal complication in profoundly immunosuppressed patients with cancer. In a review of 28 cases, pericardial involvement resulted from contiguous spread from the lungs or myocardium in all patients. Patients with a hematologic malignancy are at highest risk for pericardial aspergillosis, reflecting the increased propensity for pulmonary Aspergillus infection. Clinical manifestations include chest pain, a pericardial friction rub, and pericardial constriction and tamponade.

Other pathogens associated with myopericarditis or endocarditis include *T. gondii, C. neoformans, histoplasmosis, M. tuberculosis, nocardiosis, B. tularensis* species, and viral infections (e.g., HSV, CMV, influenza).

**OROPHARYNGEAL INFECTIONS**

Oropharyngeal infections in patients with cancer usually result from the combination of neutropenia and the breakdown of mucosal barriers related to cytotoxic chemotherapy and radiation therapy (see earlier in this chapter). A variety of oral manifestations may occur, including stomatitis, cheilitis, gingivitis, and periodontitis. Gingivitis is characterized by ulceration of the epithelium lining the gingival sulcus, resulting in a pocket between the gingiva and tooth. Necrotizing ulcerative gingivitis represents a severe end of the spectrum of this disease. In periodontitis, inflammation involves the supporting bone. The principal clinical sign of periodontal disease is bleeding through the ulcerated epithelium.

Determining the incidence of oral bacterial infections in neutropenic patients is made difficult by the fact that the oral cavity is not a sterile site, making the distinction of chemotherapy-induced mucosal erosions from superimposed bacterial infection difficult. HSV is commonly shed in oral secretions and may produce mucosal ulcerations resembling chemotherapy-induced mucositis and necrotizing gingivitis. Oral mucosal candidiasis is most common in patients with profound T-cell deficiencies, such as those receiving high-dose corticosteroid therapy. Diagnosis is usually made by visual inspection alone, although in cases of uncertainty, a wet mount preparation showing pseudohyphal forms is confirmatory. A swab culture is not of diagnostic value because *Candida* species are commensals in the oral cavity. Filamentous fungi (e.g., *Aspergillus* and *Zygomycete* species) can cause invasive disease of the hard palate and other oral cavity structures, principally in patients with prolonged neutropenia. The involved mucosa may initially have a dusky or violaceous appearance followed by necrosis, eschar formation, and ulceration. Surgical debridement of localized disease plus systemic antifungal therapy may be life saving.

Patients with oral mucosal disease may have difficulty eating because of pain. Malnourishment and dehydration may be severe if parenteral nutrition and fluid replacement are not initiated. Severe local *Mycobacterium* infection spread to adjacent tissue structures may occur, including paranasal sinulitis and septic thrombophlebitis. Disrupted oral mucosa may be a portal of entry for bacterial pathogens, leading to systemic infection.

If feasible, dental disease should be treated in advance of initiating chemotherapy and radiation therapy to allow for an adequate healing time. Plaque should be removed by scaling and curettage, and severely decayed or periapically infected teeth should be removed. A dentist experienced in the care of patients with malignancies should perform the initial clinical and radiographic evaluation and provide regular follow-up examinations through the course of antineoplastic therapy.

Chemical plaque control with agents such as chlorhexidine mouth rinses have been used routinely in patients with cancer, and different cancer centers use various rinsing protocols to enhance oral hygiene. Such rinses have lead to a reduction in microbial counts, but their value with regard to reducing oral disease and systemic infection remains unproved. (see reference 401 for review).

**EPIGLOTITIS**

The diagnosis of epiglotitis should be considered in patients with fever and pain in the throat, odynophagia, difficulty handling upper airway secretions, and signs of upper airway compromise. In patients with cancer, the combination of neutropenia and mucotoxic chemotherapy and radiation therapy predisposes patients to epiglotitis. Pathogens associated with epiglotitis in this population include common respiratory pathogens (such as *S. pneumoniae* and *H. influenzae*), as well as aerobic gram-negative rods and fungal pathogens. *Candida* epiglotitis is an unusual complication of neutropenia that may represent localized disease or disseminated infection. Treatment with amphotericin B (1.0 mg/kg/d) is warranted for this potentially life-threatening infection.

If epiglotitis is considered, care should be taken to avoid unnecessary manipulations of the upper airway (e.g., probing the oral cavity with tongue depressors). Urgent consultation with an otolaryngologist should be obtained, and evaluation of the upper airway and obtaining culture material may be performed in the operating room. Tracheal intubation is required for impending upper airway obstruction.

**ESOPHAGITIS**

Esophagitis is encountered commonly in patients with cancer. A gradual onset of retrosternal chest pain or burning and odynophagia are the most common symptoms. The differential diagnosis includes candidiasis, HSV, CMV (primarily in BMT recipients), bacterial infections, and aspergillosis. Radiation therapy to the chest may produce an erosive esophagitis clinically indistinguishable from the infectious etiologies. The evaluation of presumed esophagitis requires consideration of the patient's immune status. Patients with prolonged neutropenia and BMT recipients are more...
likely to have an infectious etiology. In this population, Candida esophagitis is probably the most common etiology. More than one infectious cause may be present concomitantly. The presence of oral mucosal candidiasis increases the likelihood of Candida species as the etiology of esophagitis. However, the use of prophylactic topical antifungal agents (such as nystatin oral rinses) may protect against thrush while leaving the patient susceptible to esophageal candidiasis.

In highly immunocompromised patients with symptoms suggestive of esophagitis, two general strategies have been used. In the first, an endoscopy is performed initially. Whitish plaques are suggestive of candidiasis, whereas ulcerative lesions are more suggestive of viral infection. However, the gross endoscopic appearance is not specific enough to differentiate the various etiologies. Brushings and biopsy have the highest diagnostic yield. A brushing may suffice in lieu of a biopsy, which may carry the risk of bleeding, particularly in patients with thrombocytopenia.

In the second approach, empiric therapy is administered initially without an endoscopy. Fluconazole, with or without high-dose acyclovir (5 mg/kg every 8 hours), is administered as therapy for Candida and HSV, respectively. Alternatively, fluconazole may be administered initially, followed by acyclovir if no clinical response has occurred within 2 to 3 days. A history of oral HSV infections or presence of anti-HSV antibodies should prompt early intitiation of acyclovir. In the setting of concurrent neutropenic fever and vague broad-spectrum antibiotic agents (e.g., vancomycin plus cefazidime) with activity against oral flora should be added empirically. If symptoms do not rapidly abate, endoscopy should be performed.

Diagnostic criteria for esophagitis are similar to the criteria for thrush. The diagnosis of an esophageal ulcer is made by endoscopy and biopsy. An esophageal ulcer is a deeper lesion than thrush and is often associated with bleeding. Ulcers caused by Candida species are usually superficial and not associated with bleeding. Ulcers caused by other organisms, such as the bacteria Helicobacter pylori, are typically deeper and more likely to have an infectious etiology. In this population, the use of prophylactic topical antifungal agents (such as nystatin oral rinses) may protect against thrush while leaving the patient susceptible to esophageal candidiasis.

**INTRAABDOMINAL INFECTION**

Intraabdominal infections present a unique set of challenges in patients with cancer. Incorporating clinical data related to the malignancy, therapy, and the immune status of the host is critical when evaluating a potential acute abdomen. Common causes of an acute abdomen in the general population (such as cholecystitis, pancreatitis, appendicitis, and diverticulitis) also occur in patients with malignancy. Intraabdominal tumors, depending on their location, may lead to an obstructive cholangitis (e.g., pancreatic and hepatobiliary tumors) or erasure or erosion through a viscus. In some instances, tumor may replace most of the bowel wall, with perforation after initiation of cytoreductive chemotherapy. An unexpected abdominal film showing air under the diaphragm in a patient who has not undergone recent abdominal surgery is likely to be indicative of a bowel perforation or an intraabdominal infection caused by gas-producing organisms.

Patients with prolonged neutropenia are at risk for a necrotizing enterocolitis, referred to as *neutropenic enterocolitis or typhlitis*. Typhlitis likely results from a combination of neutropenia and defects in the bowel mucosa related to cytotoxic chemotherapy. This disease is most common in patients with leukemia who have undergone intensive chemotherapy; non-toxic patients appear to be at a greater risk than typhlitis patients in chemically adults. Rarely, typhlitis has been reported in patients with leukemia who have not received chemotherapy. *P. aeruginosa* is the principal pathogen associated with typhlitis, though clostridial species are implicated in a minority of cases. Pathologically, typhlitis is characterized by ulceration and necrosis of the bowel wall, hemorrhage, and masses of organisms. In the setting of neutropenia, inflammation may be sparse.

Presumptive diagnostic criteria for typhlitis include fever, abdominal pain and tenderness, and radiologic evidence of right-sided colonic inflammation in patients with neutropenia. Nausea, vomiting, and diarrhea (often bloody) are the most common associated symptoms. Abdominal distension, tenderness, and a right lower quadrant mass are typical findings in patients with typhlitis. Peritoneal signs, however, may be absent or only noted on close inspection. A right lower quadrant mass or a palpable mass in the right lower quadrant may be present on physical examination. Positive findings are present in approximately 80% of cases and include a right lower quadrant inflammatory mass, pericolic fluid, soft tissue inflammation changes, localized bowel wall thickening and mucosal edema, and a paralytic ileus. Usually, disease is limited to the cecum, but more extensive involvement of the large bowel and disease of the terminal ileum may occur.

Barium studies may show mucosal edema and effacement of the haustral markings, but are associated with a potential risk of bowel perforation.

Treatment of typhlitis involves administration of broad-spectrum antibiotics with activity against aerobic gram-negative rods and anaerobes. Imipenem or ceftazidime plus metronidazole are appropriate regimens. Supportive care, including intravenous fluids, bowel rest, and nasogastric decompression, should be instituted.

Granulocyte transfusions and myeloid growth factors should be considered, as resolution of neutropenia is critical to a successful outcome.

The indications for surgery are derived from clinical experience rather than trials. Some older series suggest early surgical intervention and others argue for a conservative approach except in situations of widespread necrosis of the colon. Shamberger et al. proposed the following criteria for surgical intervention: (1) persistent gastrointestinal bleeding after resolution of neutropenia, thrombocytopenia, and clotting abnormalities; (2) free intraperitoneal perforation; (3) uncontrolled sepsis despite fluid and vasopressor support; and (4) an intraabdominal process (such as an appendicitis) that would require surgery in the absence of neutropenia.

Using these criteria, 20 of 25 pediatric patients with typhlitis were managed without surgery, and only one patient died of typhlitis. In cases of a localized perforation, a pericolic collection, or a suspected sealed off cecal perforation in a clinically neutropenic patient, surgical intervention may be delayed until resolution of neutropenia, given the increased surgical mortality during neutropenia. Surgical intervention involves resection of necrotic bowel, usually entailing a right hemicolectomy, ileostomy, and mucous fistula.

Patients with cancer are at high risk for *C. difficile*-associated colitis, probably in large measure due to prolonged hospitalization where environmental transmission is likely to occur, and to patients' receiving broad-spectrum antibiotics that alter the normal colonic flora and facilitate *C. difficile* colonization. Hospitalized patients commonly become colonized with *C. difficile*. Clinical manifestations include asymptomatic carriage, colitis without pseudomembrane formation, pseudomembranous colitis, and fulminant colitis. *C. difficile* colitis may also increase the risk of bacteremia by enteric pathogens, including VRE. In severe *C. difficile* disease, patients may be septic. Paralytic ileus, toxic dilatation of the colon, and bowel perforation may occur. An abdominal film typically shows a dilated colon with mucosal edema (thumbprinting).

Oral metronidazole is the standard therapy for *C. difficile* colitis. Because of the risk of selection for VRE, oral vancomycin should be reserved for refractory cases and for patients intolerant to metronidazole. Patients in whom oral agents cannot be administered should receive parenteral metronidazole, because biliary excretion of the drug and excretion from inflamed colon generally result in adequate luminal concentrations of the drug.

Intravenous vancomycin is no value in this setting because of inadequate lumen levels. In cases involving toxic dilatation of the colon or perforation, surgical management typically involving a subtotal colectomy and diverting ileostomy may be life saving.

Endoscopic diagnosis of pseudomembranous colitis relies on visualization of characteristic raised, adherent, yellow plaques on the colonic mucosa. A tissue culture cytotoxicity assay that detects *C. difficile* toxin B in stool is the gold standard laboratory diagnostic method. Direct culture of *C. difficile* does not distinguish toxin-producing from non-toxin-producing strains, and thus, by itself, is not a useful diagnostic method. Several commercial enzyme immunoassays are available that detect *C. difficile* toxins A or B, with sensitivities of approximately 80% and specificities close to 100%.

**ANORECTAL INFECTIONS**

Infections in patients with malignancy may be life-threatening. In some cases, infection may follow the development of an anal fissure. In other instances, tiny abrasions may be a portal of entry. Alternatively, infection may originate in the anal crypts. Once anorectal infection is established, fascial extension to the perineum or lymphatic spread to the regional lymph nodes may occur. Anorectal infections, with or without extensive regional spread, may lead to septicemia and metastatic infections.

Patients with leukemia receiving intensive myeloablative chemotherapy are at greatest risk for anorectal infections. Recovery from neutropenia is the most important prognostic indicator for a positive outcome. The most common pathogens isolated at surgery or from wound aspiration are the Enterobacteriaceae, anaerobes, group D streptococci, and *P. aeruginosa*. In most cases, the infection is polymicrobial.

The incidence of anorectal infections in patients receiving intensive myeloablative chemotherapy is approximately 5%. Fever often precedes symptoms and
signs suggestive of anorectal infection, and perirectal pain, often exacerbated by defecation, may initially occur in the absence of physical examination findings. Therefore, serial examinations of the perianal region are necessary.

In one series, point tenderness and poorly demarcated induration were the most consistent signs of perianal infection. Localized erythema and warmth were also observed. Advanced disease was heralded by soft tissue breakdown and necrosis and progressive extension to the adjacent perineal and pelvic structures.

Mild perianal infection characterized by slight tenderness or small fissures may respond to initial therapy for fever and neutropenia. The presence of significant local tenderness, swelling, or skin maceration should prompt early administration of antibiotics appropriate for neutropenic fever and with activity against anaerobes (such as ceftazidime plus metronidazole or imipenem monotherapy). Digital rectal examination should not be performed due to the risk of infection and bleeding. A pelvic CT scan may aid in assessing for perirectal infection. Stool softeners, sitz baths, warm compresses, and analgesics should be provided.

Most cases of anorectal infections can be managed with appropriate broad-spectrum antibiotics and supportive measures. Indications for surgery include progression of disease locally or continued sepsis despite adequate antibiotics, obvious tissue necrosis, or fluctuance. With adequate surgical drainage, pain typically resolves within 2 days. At surgery, perirectal lesions usually consist of necrotic cavities filled with tissue debris.

CENTRAL NERVOUS SYSTEM INFECTIONS

CNS infections in patients with cancer can be divided into surgical and nonsurgical complications. Common surgical procedures include resection of tumor, insertion of a shunt for hydrocephalus, and insertion of a reservoir to facilitate delivery of chemotherapeutic agents and easy sampling of cerebrospinal fluid. Patients with cancer involving the brain typically receive high-dose corticosteroid and local radiation therapy, which may further increase the risk of neurosurgical infections.

Infections related to implanted hardware may manifest in a variety of ways. Infection of a shunt or an Omnya reservoir may manifest with malfunction of the device. Overt signs of meningitis, such as meningismus and photophobia do not usually occur, but most patients have fever. Change in mental status may be the only sign of infection. A CT scan may suggest meningitis, ventriculitis, or a brain abscess if the device is infected at the proximal end. Evaluation of the cerebrospinal fluid is required for a diagnosis. Infection may occur in the more distal region of the device manifesting as a soft tissue infection. In cases of ventriculoatrial shunts, a distal site of infection may cause persistently positive blood culture results, thrombophlebitis, right-sided endocarditis, or septic pulmonary emboli. Distal ventriculoperitoneal shunt infections are managed with peritonitis and intraabdominal collections.

Coagulase-negative staphylococci, S aureus, and Propionibacterium acnes are the most common organisms infecting intraventricular devices. Enterobacteriaceae and P aeruginosa account for approximately 10% of infections. Coagulase-negative staphylococci and P acnes usually cause indolent late postoperative infections. When feasible, removal of the entire device should be performed and appropriate antibiotics administered. Antibiotic therapy should be tailored to the specific pathogen isolated. In an acute II patient with suspected meningitis related to prior neurosurgery, empiric therapy with parenteral vancomycin should be administered to cover Staphylococcus, Streptococcus, and Propionibacterium species in combination with an agent with activity against Enterobacteriaceae and P aeruginosa (such as ceftazidime).

CNS infections unrelated to neurosurgery are relatively uncommon in patients with cancer. In two series, the incidence of CNS infections in BMT recipients was approximately 2%. In a review of 58 cases of brain abscesses after BMT at the Fred Hutchinson Cancer Center, 92% were caused by fungi. Aspergillus species accounted for approximately 90% of infections. The remainder of fungal infections included agents of mucormycosis and Scopulariopsis and Pseudallescheria species. Approximately 90% of cases of CNS aspergillosis were associated with a pulmonary focus, whereas most cases of Candida brain abscesses were associated with candidemia or neutropenia. Only 4 of 58 patients had a bacterial brain abscess, and one patient had cerebral toxoplasmosis. The mortality in this series was 97%.

The CNS is the most common target organ of hematogenous disseminated aspergillosis. Manifestations of CNS aspergillosis include focal seizures, hemiparesis, cranial nerve palsies, and hemorrhagic infarcts due to vascular invasion. The presence of pulmonary infiltrates and focal neurologic deficits in an immunocompromised patient were significantly more predictive of CNS aspergillosis than for CNS candidiasis or cryptococcosis in a multicenter discriminant analysis of autopsy-proven fungal CNS infections. Aspergillus brain abscesses are typically multiple, hypodense, and nonenhancing, with little mass effect. CT scans with contrast enhancement initially may reveal no focal lesions, but in a later stage may demonstrate focal ring-enhancing or hemorrhagic lesions. Magnetic resonance imaging may further facilitate early detection. Intermediate T2 signal surrounded by a rim of higher signal may be observed. Biopsy of these lesions reveals the same pattern of vascular invasion and infarction similar to that seen in lung biopsy specimens. We suggest that CNS infections by Candida and Aspergillus species should be treated with amphotericin B plus 5-flucytosine, which readily penetrates the blood–brain barrier.

Other less common causes of CNS infections in patients with cancer include members of the herpes virus family (HSV, VZV, CMV, EBV, and HHV-6), adenovirus, L monocytogenes, Acanthamoeba, Nocardia species, Mycobacterium species, and T gondii, which have been discussed earlier (see Bacterial Pathogens in Cancer Patients, Viral Infections, and Parasitic Infections, earlier in this chapter).

DEMENTIAS

Patients with cancer may develop a chronic dementia related to leukoencephalopathy, a debilitating complication of therapy for their malignancy. The combination of cranial radiation therapy and intrathecal or systemic methotrexate has been most closely linked with leukoencephalopathy, although other intrathecal regimens may produce similar findings.

Progressive multifocal encephalopathy (PML) is a demyelinating disease associated with lytic infection of oligodendrocytes by the human papillomavirus JC virus. Patients may develop rapidly progressive dementia as well as focal motor or cerebellar findings. Today, this disease is most commonly seen in patients with advanced AIDS, reflecting the critical role of cell-mediated immunity in controlling this infection. Occasionally, PML is seen in heavily immunocompromised persons with hemotologic malignancies and in BMT recipients. Magnetic resonance imaging typically shows unilateral or bilateral white matter disease without mass effect or enhancement. Diagnosis is established by either brain biopsy or by detection of the JC virus in spinal fluid by PCR. There is no established therapy for PML. In patients with AIDS, highly active antiretroviral therapy has produced mixed results in patients with PML. By extrapolation, it is logical to try to reduce immunosuppressive therapy in persons with cancer and PML as a means of augmenting cell-mediated immunity.

GENITOURINARY INFECTIONS

Patients with cancer may be at an increased risk of serious urinary tract infections as a result of breaches of the normal anatomy of the genitourinary system, colonization by pathogenic organisms, and defects in host defense. The most common mechanism of seeding the bladder is via the ascending route. Barriers to entry and proliferation of pathogens include the presence of normal perineal flora, urination, mucosal epithelial lining, phagocytes, and, possibly, immunoglobulin secretion (IgA and IgG).

A bladder catheter greatly facilitates colonization of the normally sterile bladder. A strong correlation exists between precatetherization rectal and periurethral isolates and organisms subsequently isolated from the urinary tract after bladder catheterization. Obstruction to urinary flow permits colonization and multiplication of bacteria. In patients with cancer, obstruction of urine flow may result from tumors originating within and outside of the genitourinary tract. Tumors associated with hypercalcemia or hyperuricemia predispose to urinary stones. Impaired bladder emptying resulting in urine stasis may result from tumors involving the spinal cord. Urinary intestinal diversions are associated with a high incidence of bacteriuria and may predispose to clinically significant infections after mycobacterial chemotherapy.

The epithelial lining of the bladder and a layer of mucopolysaccharide form a protective barrier against bacterial colonization and invasion. Injury to the bladder mucosa by cytotoxic agents likely increases the risk of infection. In dogs, stripping of the bladder mucinous layer led to increased colonization of the bladder mucosa by bacteria. During neutropenia, the genitourinary tract may be an important portal of entry for systemic infections. Alternatively, the kidney may be secondarily seeded as a consequence of hematogenous infection. Neutropenic patients with a urinary tract infection are less likely to have dysuria and pyuria and are far more
likely to become bacteremic compared with nonneutropenic patients.21

Infection of the prostate, seminal vesicles, epididymis, and testes may represent localized disease or hematogenous seeding. Common bacterial infections include Enterobacteriaceae, P aeruginosa, S aureus, and enterococci. Less common pathogens include Salmonella species, tuberculosis (more likely to involve the kidneys and ureters), Nocardia species, Candida species, Blastomyces dermatitidis, and C neoformans.

Asymptomatic candiduria is common in patients with bladder catheters. Management of candiduria is limited by lack of knowledge about the natural history of this infection, specifically with regard to predicting in which patients systemic infection will occur. Fluconazole is effective in eradicating candiduria in the short term, but recurrent candiduria is likely.22 Removal of indwelling bladder catheters and antibacterial agents frequently lead to clearing of candiduria. Therefore, routine treatment of candiduria in febrile nonneutropenic patients with local or systemic antifungal agents does not appear to be warranted. Because of the risk of candidemia after genitourinary tract manipulations, candiduria should be treated before such procedures are performed.22 Because of the increased risk of candidemia, neutropenic patients with candiduria should receive systemic antifungal therapy.23

Hemorrhagic cystitis is a common consequence of cytotoxic regimens that cause direct bladder mucosal injury and thrombocytopenia. In BMT recipients with unexplained hematuria occurring beyond the early period (when it is an expected toxicity of the preparative regimen), a viral etiology should be considered. Adenosviruses, the polyomavirus BK, and, rarely, CMV have been associated with hemorrhagic cystitis. Childs et al.24 reported adenosvirus (four cases) or polyomavirus (four cases) in nine cases of hemorrhagic cystitis in patients receiving T-cell-depleted BMT.

Adenosvirus can cause fatal disseminated infections in BMT recipients (see Viral Infections, earlier in this chapter). Detection of urinary shedding of this virus by PCR appears to be more sensitive than cell culture methods, and may, in some cases, be a harbinger of disseminated disease.25

BK virus is ubiquitous. Approximately one-half of BMT recipients shed BK virus in the urine.26 Hemorrhagic cystitis occurred four times more frequently in patients with BK viruria, and BK shedding often preceded or occurred simultaneously with cystitis. In some patients, prolonged urinary BK shedding did not result in disease. Documentation of BK viruria can be made by electron microscopy of urinary sediments, PCR, and DNA hybridization. Treatment of BK virus–associated hemorrhagic cystitis is supportive and may include prolonged bladder irrigation to prevent clot retention as well as blood transfusions.27

**IMMUNE AUGMENTATION STRATEGIES**

**GRANULOCYTE TRANSFUSIONS**

The rationale for granulocyte transfusions is to buy time for the neutropenic patient with a life-threatening infection by augmenting the number of circulating neutrophils until native myeloid regeneration occurs.

In the 1970s, the technology for harvesting and infusing granulocytes became available. Controlled trials of granulocyte transfusions as adjuvant therapy in neutropenic patients produced mixed results.28 In the 1980s, the enthusiasm for granulocyte transfusions waned as more effective antibiotics became available, survival from serious bacterial infections was improved, and recombinant growth factors reduced the duration of neutropenia. In addition, there were concerns about the toxicity of granulocyte transfusions, including pulmonary leukostasis, risk of HLA alloimmunization (complicating platelet transfusions and conceivably myeloid engraftment after BMT), and risk of transfusion-associated infections, which appeared to outweigh their perceived benefit.29

Today, the impetus to take a second look at granulocyte transfusions in large part stems from improvements made in the mobilization methods.30 Recombinant G-CSF with or without corticosteroids is now routinely administered to donors approximately 12 hours before apheresis. G-CSF is a potent stimulus for neutrophil production by mobilizing myeloid precursors from marrow reserves. Using a standard continuous flow centrifugation apparatus, the mean absolute neutrophil yield per collection typically exceeds 3 × 10^10 cells.31 The higher number of harvested neutrophils in turn correlates with a higher neutrophil count in the recipient after transfusion.32 The increased neutrophilia-free period may also be related to a prolonged circulating half-life of G-CSF–mobilized granulocytes.33 The qualitative functions of G-CSF–mobilized and corticosteroid-mobilized neutrophils appear to be intact, as measured by in vitro bactericidal activity, respiratory burst, and in vivo migration to experimental skin chambers.34 G-CSF–mobilized granulocytes have been shown to localize to sites of inflammation after transfusion in allogeneic BMT recipients.35

Successful outcomes using granulocyte transfusions have been described in patients with life-threatening fungal infections in small series and case reports. In one nonrandomized retrospective study, no benefit of granulocyte transfusions was documented in treating fungal infections in BMT recipients.36 Obviously, such reports must be interpreted with caution and do not permit general recommendations. A more recent phase I/II clinical trial using G-CSF–mobilized transfusions for treatment of refractory fungal infections in neutropenic patients with hematologic malignancies reported favorable responses in 11 of 15 patients.37 Adverse transfusion-related reactions were infrequent.

In the absence of modern, prospective, randomized studies, when might granulocyte transfusions be considered? Currently, there is no justification (outside of a clinical trial) to use granulocyte transfusions either as prophylaxis or in cases of documented infections that are likely to respond to conventional therapy. We reserve granulocyte transfusions for patients with prolonged neutropenia and life-threatening infections refractory to conventional therapy. Filamentous fungi are likely to constitute the majority of such refractory infections. If granulocyte transfusions are used, several considerations are important. In neutropenic patients, it is likely that daily or every other day transfusions will be administered, depending on the length of the neutropenia-free period after transfusions. Granulocytes should be infused quickly after harvesting, given the short storage half-life. With modern apheresis methods, the number of harvested neutrophils should exceed 2 × 10^10 cells. Infusions of amphotericin B should be separated by several hours from granulocyte transfusions to avoid pulmonary toxicity.38 Leukocyte compatibility should be established by HLA matching and, if available, by leukocyte cross-matching to avoid alloimmunization. In some highly alloimmunized patients, transfused granulocytes are rapidly consumed and are likely to have more toxicity than benefit. In CMV-seronegative BMT recipients, only seronegative donors should be used.

**GROWTH FACTORS**

Normal myelopoiesis requires the establishment of myeloid stem cells, which, under the influence of stem cell factor, IL-3, and GM-CSF, gives rise to the colony-forming unit granulocyte-macrophage. G-CSF acts at a later stage in concert with other growth factors to specifically drive granulopoiesis.

Normal myelopoiesis requires the establishment of myeloid stem cells, which, under the influence of stem cell factor, IL-3, and GM-CSF, gives rise to the colony-forming unit granulocyte-macrophage. G-CSF acts at a later stage in concert with other growth factors to specifically drive granulopoiesis.

Many potential applications exist for recombinant colony-stimulating factors in patients with cancer, the most obvious being a reduction in chemotherapy-induced neutropenia. We discuss the use of colony-stimulating factors in two specific settings: (1) prophylaxis (growth factor is administered around the time of initiation of the myeloablative regimen), and (2) adjunctive therapy for established infection.

**Prophylaxis**

Prophylactic G-CSF has been evaluated in several prospective, randomized studies. The most consistent benefit has been a reduction in the neutropenic period. In some studies of patients with acute myelogenous leukemia receiving potential myeloablative chemotherapy, the acceleration of myeloid recovery was associated with a reduction in the duration of fever, use of antibiotics, and hospitalization.39 The frequency of infections and the number of fatal infections were unaffected by G-CSF.30 In patients with small cell lung cancer, G-CSF led to a reduction of the neutropenic period, duration of hospitalization, and rate of confirmed infections.30

Use of G-CSF in patients with a short duration of neutropenia is associated with a reduction in the neutropenic period, but no effect on the rate and days of hospitalization, duration of parenteral antibiotics, and number of documented infections.30 Prophylactic G-CSF had no benefit except for a modest reduction in the neutropenic period after preparative regimens for autologous stem cell transplantation.30

Prophylactic GM-CSF has been evaluated in two prospective, randomized studies of elderly patients with acute myelogenous leukemia.30 In one study, GM-CSF was only administered to patients who had a hypopcellular or remission marrow on day 10 of induction chemotherapy.30 Patients who achieved complete remission received the same study drug (GM-CSF or placebo) for consolidation chemotherapy. The median time to neutrophil recovery was significantly reduced in the GM-CSF
group as was the frequency of fatal fungal infections and early infection-related mortality. There was a trend toward increased complete remission in the GM-CSF group. Most important, the 6-month mortality was significantly reduced in the GM-CSF arm. To our knowledge, this is the only study that has shown a survival advantage attributed to a colony-stimulating factor. This study formed the basis for approval by the Food and Drug Administration of GM-CSF for patients with acute myelogenous leukemia. A larger study conducted by the International Oncology Study Group using a similar design is underway to evaluate prophylactic GM-CSF in older and younger patients with acute myelogenous leukemia.

In another study of 388 elderly patients with acute myelogenous leukemia, prophylactic GM-CSF led to a modest reduction in the neutropenic period. The incidence of serious infections, regrowth of leukemic cells, and treatment-related mortality was similar between the two groups. The authors concluded that GM-CSF should not be recommended for elderly patients with acute myelogenous leukemia.

The inconsistent results of studies of prophylactic colony-stimulating factors for chemotherapy-induced neutropenia are almost certainly due to important differences in the study population and in the study design. The populations differ with respect to the underlying malignancy and the chemotherapy regimen. Some studies are insufficiently powered to detect differences in morbidity between treatment arms. In addition, the timing and dosing of colony-stimulating factors vary among studies. In the case of GM-CSF, different formulations consisting of glycosylated and nonglycosylated products have been used in different trials.

The American Society of Clinical Oncology has recommended that prophylactic colony-stimulating factors (G-CSF and GM-CSF) be used only in populations in which the frequency of severe neutropenia is likely to exceed 40%. The American Society of Clinical Oncology considered that certain patients receiving a relatively nonmyelosuppressive regimen may benefit from CSFs if they are at an unusually high risk for infectious complications. Such risk factors may include preexisting neutropenia, extensive prior chemotherapy or pelvic irradiation leading to a reduction in myeloid reserves, a history of recurrent febrile neutropenia associated with relatively nonmyelotoxic complications, or the presence of an open wound or an active infection. Patients with a history of a serious or life-threatening infection, such as typhilitis, or an invasive fungal infection should also be considered for CSF prophylaxis during subsequent chemotherapy cycles.

**Colonial Growth Factors in Established Infection**

The rationale for colony-stimulating factors for established infections stems from both the quantitative and qualitative effects of these agents on phagocytic cells. In neutropenic patients with life-threatening infections, survival is strongly influenced by the rapidity of neutrophil recovery. Thus, colony-stimulating factors and granulocyte transplants are used in these settings to augment the number of circulating neutrophils.

In addition to accelerating myelopoiesis, colony-stimulating factors augment phagocyte function. G-CSF, GM-CSF, and macrophage colony-stimulating factor (M-CSF) increase the fungicidal activity of phagocytes in vitro against Candida and Aspergillus species. The action of G-CSF is specific to neutrophils. M-CSF increases phagocytosis, chemotaxis, and secondary cytokine production in monocytes and macrophages. GM-CSF stimulates various neutrophil effector functions and prolongs neutrophil survival in vitro. Increases antibody-dependent cytotoxicity of eosinophils, accelerates the proliferation of the monocyte-macrophage system, and is a potent activator of monocytes and macrophages (reviewed in reference 465). Thus, GM-CSF may have a theoretical advantage against pathogens such as Candida and Aspergillus species, in which host defense is dependent on both neutrophil and macrophage function.

At present, published data related to colony-stimulating factors as adjunctive therapy for established infection are limited to animal studies, case reports, and open-label pilot studies in humans. Nemunaitis et al. suggested that among patients with candidiasis or aspergillosis, treatment with antifungal agents plus M-CSF was associated with enhanced survival compared with historical controls. In another pilot study of eight patients with established fungal infection, adjuvant GM-CSF appeared to be promising. These initial studies are insufficient to permit conclusions about the efficacy of these agents.

**INTERFERON-g**

INF-γ is a macrophage-activating factor that is critical in host defense against intracellular infections such as *Leishmania* and *Mycobacteria* species. INF-γ augments generation of microbicidal reactive oxidants in phagocytes and is also a potent activator of oxidant-independent mechanisms, including augmentation of TNF-α production, tryptonphast metabolism, granule protein synthesis, and MHC II expression. INF-γ administered to normal volunteers was shown to increase expression of FgR1 receptors on phagocytes, leading to enhanced phagocytosis, and to increased β2-integrin expression on monocytes, which may improve phagocyte trafficking in vivo. The combination of G-CSF and INF-γ overcame the suppressive effects of corticosteroids on the in vitro fungicidal activity of neutrophils against *Aspergillus hypae*. These data suggest that INF-γ may have a role in augmenting phagocyte function in immunosuppressed patients with cancer.

Currently, INF-γ is licensed as a prophylactic agent in patients with chronic granulomatous disease, an inherited disorder of the phagocyte nicotinamide-adenine dinucleotide phosphate (reduced form) oxidase that renders phagocytes defective in generating superoxide anion and its downstream reactive oxidant metabolites. Patients with chronic granulomatous disease experience recurrent life-threatening bacterial and fungal infections. The major cause of mortality in chronic granulomatous disease is from invasive aspergillosis. Prophylactic INF-γ reduced the number of serious infections by more than 70% in patients with chronic granulomatous disease. In addition, INF-γ in combination with antimycobacterial agents had a positive effect on patients with refractory atypical mycobacterial infection resulting from defective INF-γ production. It remains to be seen whether INF-γ may have similar positive effects on patients with iatrogenic phagocytic disorders.

In certain experimental fungal infections, host defense was enhanced by augmentation of T cells committed to Th1 phenotype, reflecting cell-mediated immunity. IL-12 is generated by activated macrophages and drives uncommitted T-helper cells to the Th1 pole to produce IL-2 and INF-γ. This pathway appears to be critical in controlling various fungal infections. IL-12 reduced organism load in a murine cryptococcal model and acted synergistically when combined with fluconazole. Improvement or worsening of experimental candidiasis correlated with administration of cytokines that stimulated a Th1 or Th2 T-cell response, respectively. In a mouse model of invasive aspergillosis, administration of INF-γ and TNF-α were protective. These studies provide a scientific basis for evaluating combination immunotherapy and antimicrobial therapy in fungal infections in immunocompromised patients.

**ADOPTIVE IMMUNOTHERAPY IN BONE MARROW TRANSPLANT RECIPIENTS**

As discussed previously, the intensive preparative regimens used in allogeneic BMT result in a profound disruption of T-cell immunity. Reconstitution of T-cell immunity occurs over several months in uncomplicated cases and is further delayed in cases of GVHD requiring high-dose corticosteroid therapy and potentially antithymocyte globulins. CMV and EBV are members of the herpes virus family that establish latent infection in normal hosts, and control of reactivation is largely mediated by CD8+ cytotoxic T lymphocytes. Cytotoxic T lymphocytes recognize intracellular proteins that are presented by surface MHC class I molecules on antigen-presenting cells.

Studies on immunoreconstitution after allogeneic BMT have shown that recovery of CMV-specific cytotoxic T-lymphocyte responses confers protection from subsequent CMV disease, and these protective responses are specific for the structural virion proteins. Thus, one potential strategy for preventing CMV disease (aside from prophylaxis with antiviral agents) is by adoptive transfer of CMV-specific cytotoxic T-lymphocyte clones obtained from CMV-seropositive bone marrow donors and selectively expanded by in vitro culture. Such an approach has led to early reconstitution of CMV-specific immunity in allogeneic BMT recipients, which persisted for at least 12 weeks after infusion corresponding to the period of maximal risk for CMV disease.

In allogeneic BMT recipients, the major risk of uncontrolled EBV infection is development of an aggressive EBV lymphoproliferative disease or lymphoma, which can be rapidly fatal. Infections of unfractonated peripheral blood mononuclear cells from EBV-seropositive donors have been used to treat EBV lymphoproliferative disease in allogeneic BMT recipients. However, alloreactive T cells in such unfractonated preparations may induce GVHD. A safer approach involves transfer of EBV-specific donor cytotoxic T-lymphocyte clones that have been selectively enriched in vitro. This method has led to persistent cellular immune responses to EBV for as long as 18 months.

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Chemotherapy-induced nausea and vomiting remain two of patients' most feared effects of cancer treatment. The incidence and severity of nausea or vomiting in patients receiving chemotherapy varies, depending on the type of chemotherapy given, dose, schedule, combinations of medications, and individual characteristics. Approximately 70% to 80% of all patients who receive chemotherapy experience nausea and vomiting. Anticipatory nausea and vomiting are experienced by approximately 10% to 44% of patients who receive chemotherapy.\(^\text{1,2}\)

The phenothiazines were the mainstay of antiemetic agents before the mid-1970s.\(^\text{3}\) Currently, there are many efficacious antiemetic regimens for the nausea and vomiting produced by chemotherapeutic agents.\(^\text{4}\) In a study conducted in 1983, cancer patients ranked nausea and vomiting as the first and second most severe side effects of chemotherapy, respectively.\(^\text{5}\) After the emergence of new antiemetic agents and alterations in chemotherapeutic regimens, patients' perceptions of the most severe side effects were modified. In a 1993 study, 155 cancer patients receiving chemotherapy reported that they experienced an average of 20 physical and psychosocial symptoms; nausea was ranked as the most severe symptom and vomiting as the fifth.\(^\text{6}\) Therefore, nausea is also an important efficacy parameter when evaluating an antiemetic.

Use of these new antiemetic agents has decreased the incidence and severity of nausea and vomiting induced by chemotherapy; however, these agents have not totally prevented the problems. The consequences of not controlling the nausea and vomiting induced by cancer treatment may lead to medical complications, a failure of the patient to comply with the cancer therapy and follow-up, and a diminished quality of life.

**PATHOPHYSIOLOGY OF NAUSEA AND VOMITING**

The precise mechanisms by which chemotherapy induces nausea and vomiting are unknown; however, it appears probable that different chemotherapeutic agents act at different sites and that some chemotherapeutic agents act at multiple sites.\(^\text{7}\) The fact that different chemotherapeutic agents cause nausea and vomiting by different mechanisms and that one chemotherapeutic agent may induce nausea and vomiting by more than one mechanism helps us to understand why there is no one antiemetic regimen that is effective all of the time.

Mechanisms by which chemotherapeutic agents cause nausea and vomiting are activation of the chemoreceptor trigger zone (CTZ) either directly or indirectly; peripheral stimulation of the gastrointestinal (GI) tract; vestibular mechanisms; cortical mechanisms; or alterations of taste and smell (Table 55.1-1). For the majority of the chemotherapeutic agents, the most common mechanism is thought to be activation of the CTZ.

The CTZ is located in the area postrema of the brain and can be reached by emetogenic chemicals via the cerebrospinal fluid or the blood. The thought is that the mechanisms of interaction between the CTZ and chemotherapy involve the release of various neurotransmitters that activate the vomiting center. Either one or a combination of these transmitters may induce vomiting. Some of the neurotransmitters located in the area postrema of the brain that may be excited and lead to emesis include dopamine, serotonin, histamine, norepinephrine, apomorphine, neurotensin, angiotensin II, vasoactive intestinal polypeptide, gastrin, vasopressin, thyrotropin-releasing hormone, leucine-enkephalin, and substance P. Other enzymes surround the CTZ, such as adenosine triphosphatase, monoamine oxidase, cholinesterase, and catecholamines; however, their role in chemotherapy-induced emesis is unknown.

Until recently, the neurotransmitter that appeared to be the most responsible for chemotherapy-induced nausea and vomiting was dopamine. Many effective antiemetics are dopamine antagonists that may bind specifically to the D\(_2\) receptor. However, there is a high degree of variation in dopamine receptor binding affinity by these drugs.\(^\text{8}\) The action of some drugs that cause nausea and vomiting is affected very little or not at all by dopamine antagonists. It is known that not all the important receptors in the CTZ are dopaminergic, as the effect of dopamine antagonists is not equal to surgical ablation of the CTZ.\(^\text{9}\) It has also been noted that the degree of antiemetic activity of high-dose metoclopramide cannot be explained on the basis of dopamine blockade alone.\(^\text{10}\)

Histamine receptors are found in abundance in the CTZ; however, H\(_2\) antagonists do not work at all as antiemetics. H\(_3\) antagonists alleviate nausea and vomiting induced by vestibular disorder and motion sickness but not nausea and vomiting induced by chemotherapy.\(^\text{11}\)

Knowledge that opiate receptors are found in abundance in the CTZ, as well as the facts that narcotics have mixed emetic and antiemetic effects that are blocked by naloxone and that naloxone has emetic properties, have led to the proposal of opiates or enkephalins as an antiemetic. High doses of naloxone augments emesis induced by chemotherapy, and low doses of naloxone may reduce emesis.\(^\text{12}\) Studies to date have shown that opiates can prevent chemotherapy-induced emesis in laboratory animals; however, both butorphanol and buprenorphine have not been proven to be effective antiemetics in patients who received previous chemotherapy.\(^\text{13}\)

One study by Liason et al.\(^\text{14}\) did demonstrate that Fk-33-824 was more effective as an antiemetic in patients who received cisplatin; however, it was ineffective for...
patients receiving cyclophosphamide or epirubicin.

Edwards et al. found that arginine vasopressin levels rise to a greater extent in patients who vomit when they receive chemotherapy as compared to those who do not vomit. It has been suggested that perhaps arginine vasopressin plays a role in nausea more than in the vomiting induced by chemotherapy. Dexamethasone, which is a known effective antiemetic, may work by reducing arginine vasopressin levels. Another mechanism of action of corticosteroids as antiemetics may be related to modulation of prostaglandin release. 2

Some evidence suggests that although no one neurotransmitter is responsible for all chemotherapy-induced nausea and vomiting, it appears that serotonin and 5-hydroxytryptamine (5-HT) receptors are particularly important in the pathophysiology of acute vomiting, whereas others may be more important in the pathogenesis of delayed emesis. 3

Triptans are a group of serotonin-1D (5-HT1D) receptor agonists that are used to treat episodic migraines. 4 They are effective in decreasing the severity and duration of acute emesis in patients who receive chemotherapy for breast cancer. 5

5-HT3 receptor antagonists have shown efficacy in the prevention and treatment of chemotherapy-induced nausea and vomiting, particularly in patients undergoing cisplatin-based chemotherapy. 6,7

5-HT3 antagonists are effective in preventing and treating chemotherapy-induced nausea and vomiting. 8 In randomized double-blind studies, 5-HT3 receptor antagonists have demonstrated efficacy in preventing and treating chemotherapy-induced nausea and vomiting. 9

The second most important mechanism whereby chemotherapy may induce emesis is peripheral effects that are thought to arise from the pharynx and the upper GI tract. Most likely, the chemotherapy does not directly stimulate the peripheral receptors. Rather, neurotransmitters probably are released as a result of local GI irritation or damage. GI tract serotonin, dopamine, opiate, histamine, and cholinergic receptors are most likely involved in the emesis induced by chemotherapy. The peripheral effects may be abolished by vagotomy, indicating that impulses from the GI tract may reach the vomiting center via the vagus and sympathetic nerves. 10

Another mechanism that may involve in chemotherapy-induced emesis could be the therapy's effect on the vestibular system. It is known that patients who have a history of motion sickness experience a greater severity, frequency, and duration of nausea and vomiting from chemotherapy than patients who do not experience motion sickness. The mechanism by which the vestibular system may lead to chemotherapy-induced emesis is unknown; however, it is postulated that sensory information that is received by the vestibular system is different from information that was expected. 11

Other investigations have been important in demonstrating that taste changes induced by chemotherapy may lead to nausea and vomiting. Some chemotherapeutic agents, such as cisplatin or gallium nitrate, can lead to loss of taste sensation or a metallic taste in the mouth. A study conducted with patients receiving chemotherapy for malignant melanoma revealed that patients developed a more intense sense of taste for sweet, bitter, sour, and salt. After chemotherapy, the patients rated the highest concentration of sweet as lower, and the patients' discrimination between highest and lowest concentrations of sour, bitter, and sweet was decreased. 12 Another study of patients with breast carcinoma who received cyclophosphamide, methotrexate, and 5-fluorouracil, 36% reported a bitter taste in their mouth. One-third of the patients thought that the bitter taste caused vomiting. The exact mechanism by which taste is changed by chemotherapy is unknown; however, it is thought that while the drugs are in the plasma or saliva, they have a direct effect on the oral mucosa or taste buds. Changes in taste may contribute both to nausea and vomiting as well as to anorexia.

Finally, chemotherapy-induced emesis may be induced by direct or indirect effects on the cerebral cortex. Animal studies have shown that nitrogen mustard partially causes emesis via direct stimulation of the cerebral cortex. 13 Studies demonstrate that the risk of nausea and vomiting is increased when a patient's roommate is experiencing nausea and vomiting. It is also known that the amount of sleep before receiving chemotherapy may influence whether a patient develops chemotherapy-induced emesis. In addition, large differences exist in the severity and incidence of nausea and vomiting from the same chemotherapeutic agents in different countries. 14 These studies indicate that indirect psychological effects can mediate chemotherapy-induced nausea and vomiting.

Aside from being more than one mechanism by which each chemotherapeutic agent may induce emesis, chemotherapy induces emesis in a manner different from that of other classic emetic agents. Drugs such as amphetamine, levodopa, digoxin, plicarpine, nicotine, and morphine cause vomiting almost immediately. Nitrogen mustard also may lead to emesis immediately; however, most chemotherapeutic agents may lead to emesis require a latency period before emesis begins. Also, most chemotherapeutic agents do not induce emesis in a monophasic way, as do the classic emetic agents. Chemotherapeutic agents induce emesis with a delayed onset, and the emesis has multiphasic time courses. 15 When managing chemotherapy-induced emesis, one should realize that there is most likely more than one mechanism involved, suggesting that there will not be one antiemetic regimen that will work for all patients all of the time.

**EMETIC SYNDROMES**

Patients undergoing therapy for the treatment and possible cure of cancer with chemotherapy often are faced with the distressing side effects of nausea and vomiting. Antineoplastic agents of the 1990s have provided clinicians with an array of antiemetics and varied regimens, therapy-induced nausea and vomiting have yet to be totally eliminated. The goals of antiemetic therapy are as follows: (1) to achieve complete control in all settings, (2) to provide maximum convenience for patients and staff, (3) to eliminate potential side effects of the agents, and (4) to minimize the cost of treatment with antiemetic agents and drug administration.

As a result of antiemetic investigations, five distinct but related emetogenic syndromes have been identified: acute chemotherapy-induced emesis, delayed emesis, breakthrough nausea and vomiting, refractory emesis, and anticipatory emesis. Traditionally, acute nausea and vomiting are defined as occurring within the first 24 hours after administration of chemotherapy. Delayed nausea and vomiting have been arbitrarily defined as occurring 24 hours after chemotherapy administration. More recent observations of the pattern of emesis indicate that delayed emesis may begin as early as 16 hours after chemotherapy administration and that serotonin may not be the primary mediator of symptoms for delayed emesis. Breakthrough nausea and vomiting are nausea and vomiting that occur despite preventive therapy. Refractory emesis may be the treatment administered to patients who have not responded to the prophylactic measures prescribed for acute or delayed nausea and vomiting. Breakthrough emesis occurs during subsequent cycles when antiemetic prophylaxis or rescues (or both) have failed in earlier cycles.

Anticipatory vomiting is a learned or conditioned response that typically occurs before, during, or after the administration of chemotherapy. Patients receiving one or a combination of several of the agents must receive an antiemetic that is tailored to the individual pattern and emetogenic potential of each agent. For example, patients receiving a combination of high dose intravenous cyclophosphamide and doxorubicin (Adriamycin), as well as intermittent patients from cyclophosphamide-induced emesis that does not begin until 9 to 18 hours after the drug's administration. If patients are given the opportunity to receive the optimal antiemetic regimen during their initial course of chemotherapy, the likelihood of developing anticipatory emesis with subsequent cycles is greatly reduced. Other advantages for patients include increased tolerance of dose-intensified chemotherapy regimens. In addition, through the prevention of emesis, patients are able to achieve an enhanced quality of life at a particularly difficult time. 16

Two reports, one by Hesketh et al. and an expert consensus by the American Society of Health-System Pharmacists, contain new guidelines for the classification...
of the acute emetogenicity of chemotherapy into five levels (Table 55.1-2). When the agents are combined, ratings are based on the combined emetogenicity of the individual agents. An algorithm for defining the emetogenicity of combination chemotherapy has been developed (Table 55.1-3).

TABLE 55.1-2. Emetic Potential of Chemotherapeutic Agents

CONTROL OF EMESIS AND PATIENT CHARACTERISTICS

The methodology used in antiemetic studies has identified several useful patient characteristics and prognostic factors that may affect antiemetic control. These indicators become important for tailoring antiemetic regimens as well as designing antiemetic trials. Careful studies have defined previous experience with chemotherapy, alcohol intake history, age, and gender as influencing patient outcomes. These references are listed below.

A patient's prior exposure to chemotherapy very often determines success or failure in controlling emesis with future treatment courses. Administration of the appropriate antiemetic during an initial course of chemotherapy can very often eliminate or significantly reduce the development of anticipatory emesis, in addition to decreasing the severity of delayed emesis.

Chronic and heavy alcohol usage—defined as more than 100 g of alcohol or five mixed drinks per day, whether in the past or currently—has been shown positively to affect the control of emesis. Ninety-three percent of patients in a prospective study who had a history of high alcohol intake were able to achieve a complete response, or no emesis, after receiving high doses of cisplatin with a combination antiemetic regimen. The hypothesis is that chemotherapy-induced emesis may be decreased in patients with a high alcohol intake because of “burnout” of the CTZ. Although emesis may be easier to control in this setting, patients nonetheless must receive an appropriate and effective antiemetic regimen. As a result, this prognostic factor has been incorporated in many prospective trials for stratification purposes.

Age as a prognostic factor cannot predict patient response to antiemetic therapy. Some studies have indicated better control in older patients, while others have reported little difference among various age groups. Age is, however, an important factor in determining the potential for the occurrence of acute dystonic reactions. Patients aged 30 years and younger are more prone to experience the acute dystonic reactions associated with the dopamine-receptor blocking agents, such as the phenothiazines, butyrophenones, and substituted benzamides. These side effects are usually characterized by trismus or torticollis. It is also important to remember that within this population of patients, chemotherapeutic agents that might necessitate antiemetics often are given over several consecutive days, increasing the possibility of the occurrence of acute dystonic reactions. A distinct advantage for the use of the serotonin or 5-HT3-blocking antiemetic agents is that they do not cause acute dystonic reactions, making them an especially beneficial treatment option for children and younger adults.

It has been difficult to explain the rationale for poorer control of emesis in some women receiving treatment for various malignancies. A possible explanation may be that women characteristically receive chemotherapeutic regimens that contain highly emetogenic agents, such as cisplatin and cyclophosphamide, usually given in combination, and are less likely than men to have a history of a high alcohol intake. Although these may be contributing factors, multivariate analyses in some larger studies have indicated that gender is an independent consideration that must be recognized in planning and analyzing clinical studies.

Other factors also have been reported possibly to affect the incidence of nausea and vomiting after chemotherapy. A patient may develop nausea and vomiting if he or she is anxious during the chemotherapy infusion, there is an expectation of severe side effects, or the patient’s roommate is experiencing nausea and vomiting. Patients who are well motivated and have a good performance status may experience a decreased incidence of nausea and vomiting. Food intake before chemotherapy and the amount of sleep a patient has had may influence the degree of nausea and vomiting. Patients who are more likely to develop nausea and vomiting are those who have had severe emesis during pregnancy and those who are prone to motion sickness.

TABLE 55.1-4. Factors Affecting the Control and Incidence of Nausea and Vomiting after Chemotherapy

ANTIEMETIC AGENTS
MOST ACTIVE AGENTS

As outlined in the Pathophysiology of Nausea/Vomiting section, antagonism of the type 3 serotonin receptor (5-HT₃) is an important approach to controlling chemotherapy-induced emesis. Several agents are available that exert their efficacy in this manner. Metoclopramide, which was previously thought to block emesis by antagonism of a dopamine receptor (D₂), probably works primarily via the 5-HT₃ pathway at higher doses. This explains why higher doses of metoclopramide are more effective. However, metoclopramide is not selective for the 5-HT₃ pathway, and development of highly selective antagonists of the 5-HT₃ receptor allowed for good antiemetic effect with a lower side effect profile.

Several selective 5-HT₃ antagonists are commercially available in many countries: dolasetron, granisetron, ondansetron, and tropisetron. Other similar agents are available in individual countries or under investigation. Many multiple, randomized, well-controlled studies have demonstrated that these agents have equivalent antiemetic activity and safety. Nonetheless, some differences do exist among these agents. The differences are primarily in their structure and pharmacokinetic profile; however, to date none of these differences has been shown to be of clinical importance. All agents work by the identical mechanism: antagonism of the 5-HT₃ receptor. All appear to accomplish this maximally, and differences among the relative potencies are unimportant at the recommended doses. There is no clear evidence that one of these agents will be effective when another is not. Half-lives in the serum vary from approximately 3 to 11 hours, but activity at the receptor appears to be similar in that single doses of all agents are equally effective. All agents have good bioavailability for oral administration. When tested, oral administration is as effective as is the intravenous route.

Controversy remains concerning the optimal dose of the serotonin antagonists. From current trials, it appears that maximal benefit occurs once all relevant receptors are saturated. No matter what the emetic source, if the best results are to be achieved, an adequate dose should be given. Higher doses are not advantageous once all receptors have been saturated. In that these are very safe and well-tolerated agents, it has been difficult to define the best dose regimens, and different doses have been mandated in different countries. Several international consensus guidelines have been published, including those from the subcommittee for antiemetics of the Multinational Association of Supportive Care in Cancer, those from the American Association of Clinical Oncology, and those from the American Society of Health-Systems Pharmacists. As a general rule, the lowest adequately tested dose should be assumed to be the best dose in all settings (Table 55.1-5).

TABLE 55.1-5 Doses, Schedules, and Classes of Commonly Administered Antiemetics

Although some debate persists concerning the best dose of ondansetron, the majority of trials have indicated that the lower dose (8 mg) is as effective as the higher and far more expensive dose of 32 mg. The latter dose was superior in only one trial and was troubled by a high inadequate treatment rate, indicating a poorly conducted trial. The lower granisetron dose of 10 mg/kg is as effective in all circumstances as four times the dosage. The same dose recommendations continue for single-agent or combination use.

The side effect profile of the 5-HT₃ antagonists provides an advantage over such effective antiemetics as metoclopramide. Central nervous system effects, extrapyramidal reactions, and sedation are not observed with serotonin antagonists; this is particularly beneficial in younger patients. Common side effects include mild headaches usually not requiring treatment, transient transaminase elevations, and mild constipation with some agents.

As indicated, the antiemetic activity of metoclopramide is likely as a serotonin antagonist, although it has substantial dopamine antagonist action as well. This latter mechanism explains the potential for extrapyramidal reactions. Studies have shown that higher doses are more effective. A dose of 3 mg/kg given every 2 hours for two doses in a combination regimen has been found to be effective. To date, metoclopramide appears to be at least as effective as serotonin antagonists in preventing delayed emesis and is far less expensive.

Corticosteroids are valuable antiemetics. Dexamethasone is the best studied of all these agents, is available in oral and parenteral preparations and, in most countries, is very expensive. Although the best dose has not been established, it appears that a single 20-mg dose is adequate, with no clear indication that either higher or lower doses is preferred. The other steroid that has been studied and that can be used is methylprednisolone. Caution must be used when treating diabetic patients or others with poor tolerance for corticosteroids. However, the short recommended course makes these agents very safe and easy to use. In preventing delayed emesis, adequate doses of corticosteroids currently are viewed as the starting point of treatment, with some studies showing advantage for metoclopramide combined with steroids.

Efficacy for corticosteroids has been clearly outlined for cisplatin-containing regimens as well as other types of chemotherapy with lesser emetic potential.

ANTIEMETICS OF LOWER ACTIVITY

Older agents, such as phenothiazines, butyrophenones, and cannabinoids, all have some degree of antiemetic efficacy. In general, this efficacy is substantially lower than that seen with the serotonin antagonists (including high-dose metoclopramide), and the side effects are greater. When given intravenously, phenothiazines appear to be more active than when given by other routes but are associated with hypotension (especially orthostatic), which can be severe. Thus, these agents are not highly recommended. Oral forms of all of these agents exhibit only modest activity and are of similarly low efficacy.

Several cannabinoids have been tested in chemotherapy-induced emesis and are of both historic and lay press interest. Semisynthetic agents, such as nabilone and levonantradol; tetrahydrocannabinol (or delta 9-THC), the active agent in marijuana; and inhaled marijuana, all appear to be of low and equal efficacy, with frequent autonomic side effects. These toxicities include dry mouth, hypotension, and dizziness. Dronabinol may be useful as an adjuvant to other antiemetics.

Anxiety agents, such as the benzodiazepine lorazepam, have little efficacy as single agents in carefully conducted trials. However, they function well against anxiety in the emotionally charged atmosphere of receiving chemotherapy, although they add only a minor antiemetic effect to more active agents. They should be regarded as adjuncts to antiemetics and, in that role, can be useful for many patients. Recommended doses range from 0.5 to 1.5 mg. It is not clear that there is any advantage in giving these agents parenterally rather than orally when given with the most effective antiemetics. Additionally, these drugs may be useful when given to patients with anticipatory emesis, starting one or more days before the next chemotherapy dosing. Side effects mainly concern sedation, which can be marked in
DELAYED EMESIS

With the identification of useful antiemetics for the treatment of the acute emetic syndrome, it became apparent in patients receiving high total doses of cisplatin that, despite good control of emesis during the initial 24 hours after therapy, delayed emesis became an issue. To date, the pathophysiology of this especially difficult problem remains unclear. What is known, however, is that delayed emesis is a phenomenon observed in as many as 80% of patients, typically occurring 24 to 72 hours after high total doses of cisplatin (>100 mg/m²) have been administered. Delayed emesis may also be seen in a substantial number of patients who receive as little as 50 mg/m² cisplatin or a chemotherapy combination, including cyclophosphamide and an anthracycline. A study that outlined the natural history of delayed emesis concluded that although the emesis associated with this dilemma is less severe than that which is seen in the acute phase, it still poses significant problems with nutrition, hydration, and, possibly, a prolonged hospital course.

Initial studies revealed that delayed emesis could be controlled with a regimen of metoclopramide and dexamethasone (Table 55.1-6). Because of the possibility of extrapyramidal side effects, such as anxiety, akathisia, restlessness, torticollis, or oculogyric crisis, with metoclopramide, the patient should routinely be given a supply of diphenhydramine that should be taken at the first sign of an extrapyramidal symptom. In the younger patient, diphenhydramine should be given prophylactically.

As it is known from previous studies that a delayed antiemetic regimen with a substituted benzamide and dexamethasone controls the emesis, further research is needed to compare this standard regimen with a regimen of a serotonin antagonist and dexamethasone. One may need to differentiate between late-onset acute emesis (i.e., 18 to 48 hours after cyclophosphamide administration, for which oral granisetron and ondansetron have demonstrated benefit) versus true delayed emesis that is evident 2 to 7 days after cisplatin administration, for which the 5-HT3 antagonists may not have a large advantage over standard metoclopramide-based regimens. It is likely that the mechanism of action for delayed emesis is very different from that for acute chemotherapy-induced emesis, and perhaps serotonin is not involved at all. This should be addressed further in carefully controlled clinical trials, as the cost of the serotonin antagonists is far more than the cost of a substituted benzamide.

Another group of agents that have a potential role in the prevention of delayed nausea and vomiting are the NK1 antagonists. Substance P, which is found in the GI tract and the central nervous system and can produce vomiting when injected into ferrets, exerts its effects by binding to the neuroreceptor NK1. Hesketh et al. reported on a randomized phase II study of the NK1-receptor antagonist CJ-11,974 in the control of cisplatin-induced emesis in 61 patients. This exploratory trial revealed that CJ-11,974 was superior to placebo in controlling delayed emesis and may provide additive benefit in acute emesis and nausea control when combined with a 5-HT3 antagonist and dexamethasone. In a multicenter, double-blind, placebo-controlled trial involving 159 patients who received a single dose of cisplatin, the NK1-receptor antagonist L-754,030 prevented delayed emesis and, in combination with granisetron plus dexamethasone, improved the prevention of acute emesis.

Other agents that may be of benefit in the treatment of delayed emesis include benzodiazepines, especially lorazepam and alprazolam; the H1 blockers cinetidine and ranitidine; and omeprazole. Studies are currently under way on the use of cisapride, a potent gastric prokinetic agent that does not affect the D2 receptors and, therefore, does not lead to adverse extrapyramidal effects.

ANTICIPATORY NAUSEA AND VOMITING

Anticipatory nausea and vomiting usually occur approximately 24 hours before the patient begins chemotherapy. The symptoms may occur outside the hospital, in the clinic, when talking about chemotherapy, or when the patient perceives special tastes or odors.

Acute nausea and vomiting that occur with chemotherapy are thought to be secondary to the medication. The exact mechanism of posttreatment nausea and vomiting is unknown, though is most likely secondary to the chemotherapeutic agent itself, at times, it may also involve a psychological mechanism. Anticipatory nausea and vomiting always involve a psychological mechanism in that they are triggered by events that are not secondary to the direct administration of the chemotherapeutic agent itself.

The prevalence of anticipatory nausea and vomiting varies, depending on the study cited and whether nausea and vomiting are analyzed separately. A review by Morrow and Dobkin summarized 28 surveys that were carried out in North America since 1979. The prevalence of anticipatory nausea ranged anywhere from 14% to 63%, with a median of 33%. Many factors that appear to be associated with anticipatory nausea and vomiting have been studied (Table 55.1-7).

Numerous studies have revealed a relationship between severe postchemotherapy side effects and the development of anticipatory nausea and vomiting. Recommended Regimen for Delayed Emesis

Initial trials addressing the treatment of delayed emesis with the single-agent serotonin antagonist ondansetron were discouraging and labeled the serotonin antagonists as having low activity. Two randomized studies, one with ondansetron and one with granisetron, indicated efficacy of the serotonin antagonists for delayed emesis in patients receiving chemotherapy of intermediate emetogenicity.

As it is known from previous studies that a delayed antiemetic regimen with a substituted benzamide and dexamethasone controls the emesis, further research is needed to compare this standard regimen with a regimen of a serotonin antagonist and dexamethasone. One may need to differentiate between late-onset acute emesis (i.e., 18 to 48 hours after cyclophosphamide administration, for which oral granisetron and ondansetron have demonstrated benefit) versus true delayed emesis that is evident 2 to 7 days after cisplatin administration, for which the 5-HT3 antagonists may not have a large advantage over standard metoclopramide-based regimens. It is likely that the mechanism of action for delayed emesis is very different from that for acute chemotherapy-induced emesis, and perhaps serotonin is not involved at all. This should be addressed further in carefully controlled clinical trials, as the cost of the serotonin antagonists is far more than the cost of a substituted benzamide.

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Numerous studies have revealed a relationship between severe postchemotherapy side effects and the development of anticipatory nausea and vomiting.
Motion sickness is a risk factor for the development of postchemotherapy nausea and vomiting. A study by Bruera et al. revealed that controlled-release metoclopramide is safe and effective in managing radiation-induced nausea and vomiting. In some studies, it appears to be related to anxiety and anticipatory nausea and vomiting. Anticipatory nausea and vomiting occur more often in patients younger than 45 to 50 years old. It has been noted that patients with anticipatory nausea and vomiting have higher levels of depression. A relationship between anxiety and anticipatory nausea and vomiting has also been noted, though, at this time, insufficient evidence is available to indicate the way that anxiety is related to anticipatory symptoms.

Several retrospective reviews have indicated that taste and odors are related to anticipatory nausea and vomiting. Though a prospective study did not reveal any relationship among taste, odors, and anticipatory nausea and vomiting, Bovbjerg et al. reported a study in which patients were administered a beverage to patients before their chemotherapy. The investigators found a clear relationship between anticipatory nausea and a special taste. Bovbjerg et al. suggested that taste and odors may be involved not only in anticipatory nausea and vomiting but perhaps with postchemotherapy nausea and vomiting. Indeed, the role of taste and smell is largely unknown; however, it may be involved in a spectrum of GI complaints experienced by the patient with cancer. Studies by Bernstein et al. suggest that a learned food aversion develops to specific tastes or food and occurs because of an association of the food with unpleasant symptoms, such as nausea and vomiting. This food aversion could partially explain the anorexia associated with cancer.

Antiemetics used in the treatment of acute nausea and vomiting induced by chemotherapy are ineffective in treating anticipatory nausea and vomiting. Many studies have indicated that behavioral techniques are effective in reducing anxiety as well as reducing or eliminating anticipatory nausea and vomiting. Behavioral techniques that have been studied and found to be effective include progressive relaxation with guided imagery, systematic desensitization, hypnosis, and cognitive and intentional distraction.

In one report in the literature, a lemon solution given to a patient before the receipt of chemotherapy masked taste sensations so that the patient experienced decreased anticipatory nausea and vomiting. It has also been suggested that the use of benzodiazepines, especially lorazepam, may be helpful in treating anticipatory nausea and vomiting. However, no formal studies have established lorazepam's effectiveness in this situation.

**RADIATION-INDUCED NAUSEA AND VOMITING**

The etiology of radiation-induced emesis, like chemotherapy-induced emesis, is not completely understood. However, it is clear that it is a complex, multifactorial event. The time of development, latency, and onset of radiation-induced nausea and vomiting appear to be related to the size of the radiation field, the dose per fraction, and have been found to be correlated with a patient's previous response of nausea and vomiting to different situations. It has been noted that patients with anticipatory nausea and vomiting have higher levels of depression. A relationship between anxiety and anticipatory nausea and vomiting has also been noted, though, at this time, insufficient evidence is available to indicate the way that anxiety is related to anticipatory symptoms.

The exact mechanism of radiation-induced emesis remains unclear. However, as with chemotherapy-induced emesis, it is thought that it most likely is due to a peripheral mechanism in the GI tract or a central mechanism involving the CTZ. It has been proposed that several substances, including dopamine, catecholamines, and prostaglandins, are released and stimulate afferent visceral fibers, an action that then initiates sensory signals to the CTZ. As a result of both preclinical and clinical studies with serotonin antagonists, it has been suggested that serotonin may be released from enterochromaffin cells of the GI tract and may mediate emesis via mechanisms involving the 5-HT3 receptors, visceral afferent fibers, and the CTZ. This mechanism is most likely involved when radiation is applied to the upper abdomen, hemibody, or total body. Radiosurgery to the area postrema in excess of 350 to 400 cGy in a single dose. The emesis usually occurs between 1 and 12 hours after the radiosurgery.

Clinical studies in the past using metoclopramide, nabilone (cannabinoid derivative), and chlorpromazine in the treatment of radiation-induced emesis revealed a response of 50% to 58%. In a nonplacebo trial with domperidone, a dopamine antagonist, a response of 62% was reported. A nonrandomized trial comparing ondansetron with other antiemetics reported response rates of 100% for ondansetron versus 43% for other antiemetics and 19% for no antiemetic treatment for patients who received middle to upper hemibody irradiation. A randomized study by Prießmann et al. of patients who received radiotherapy to the abdomen, pelvis, and thoracolumbar spine reported response rates of 45% for metoclopramide versus 97% for ondansetron. A randomized, double-blind, placebo-controlled evaluation revealed oral ondansetron to be an effective therapy for the prevention of emesis induced by total body irradiation. Ondansetron has been reported to be effective in radiotherapy-induced emesis in children as well as for patients who receive radiosurgery to the area postrema.

Data are available from two double-blind, randomized studies in the use of oral granisetron, 2 mg once daily, in radiation-induced nausea and vomiting. In a study involving patients undergoing fractionated upper abdominal radiation, patients who received oral granisetron had a significantly longer median time to first emesis than did those who received placebo (35 days vs. 9 days, respectively) and a longer median time to first nausea (11 days vs. 1 day, respectively). In another study of patients undergoing total body irradiation, patients treated with oral granisetron had significantly greater complete control as compared to the historical control group over the entire 4-day treatment period (22% vs. 0%, respectively). Fauser et al. reported on the use of oral dolasetron for the control of emesis during total body irradiation and high-dose cyclophosphamide in patients undergoing autologous bone marrow transplantation.

**NAUSEA AND VOMITING SECONDARY TO COMORBID CONDITIONS**

A number of comorbid conditions also may lead to nausea and vomiting, even though the majority of patients with cancer develop nausea and vomiting as a result of chemotherapy or radiotherapy (Table 55.1). Because the mechanism of the nausea and vomiting secondary to comorbid conditions is not usually well understood, it is difficult to know which antiemetics may be helpful. A study by Bruera et al. revealed that controlled-release metoclopramide is safe and effective in managing chronic nausea in patients with advanced cancer. Future studies must be conducted to determine the optimal doses of metoclopramide as well as other antiemetics that may be used in drug combinations (e.g., metoclopramide plus corticosteroids) for the nausea and vomiting secondary to the malignancy itself.
COST AND BENEFIT OF ANTIEMETIC THERAPY

The important results of research that provide the medical community with additional chemotherapeutic choices and supportive care measures often translate into added health care costs for patients and families. With the increased use of expensive antimetics and with managed care dictating the length of hospital stays, the emphasis is shifting to primary outpatient management of patient treatment courses. The challenge for physicians becomes one of providing a treatment plan in which patients are offered state-of-the-art and cost-effective therapy. This can be accomplished by applying certain guidelines.

Specifically addressing 5-HT\(^{-3}\) antagonist antimetics and their associated cost, the choice among these agents should be made on the basis of acquisition costs and reimbursement differences. The 5-HT\(^{-3}\) antagonists all have demonstrated equivalent efficacy and side effects; therefore, once an effective dose has been established, there would be no advantage in exceeding this threshold dose. Ultimately, the 5-HT\(^{-3}\) antagonist of lowest cost should be selected for administration. Single-dose regimens given on an outpatient basis with a corticosteroid provide an effective and convenient alternative in antiemetic therapy. Regimens that take advantage of a comparable route of administration are easy and convenient for patients and are likely to reduce nursing and pharmacy costs; however, prolonged use of oral serotonin antagonists should be avoided, as there appears to be little or no value in this setting. In addition to these recommendations, adherence by physicians and nurses to established doses and schedules of antimetics and their appropriate use can be cost-effective measures for patients and institutions.

Nolte et al.\(^{25}\) discussed guidelines developed by the Memorial Sloan-Kettering Cancer Center for the cost-effective use of 5-HT\(^{-3}\) antagonists that resulted in substantial savings while treating more patients. The initial guidelines in 1993 were developed based on the premise that the dose of the intravenous 5-HT\(^{-3}\) antagonist ondansetron, 8 to 32 mg, could be adjusted on the basis of emetogenic potential of the chemotherapeutic regimen schema proposed by Hesketh et al.\(^{40}\) Cost savings were documented without affecting the quality of life, as reported by the patients. The guidelines were modified in 1994 to include granisetron, 10 mg/kg, for moderately or highly emetogenic chemotherapy. When oral granisetron tablets were approved in 1995 for the prevention of highly emetogenic chemotherapeutic regimens, the guidelines were further modified to incorporate the use of oral granisetron instead of intravenous 5-HT\(^{-3}\) antagonists for moderately to highly emetogenic chemotherapy. Additional cost savings were realized while the quality of life of the patients was unaffected.

The use of an oral form of a 5-HT\(^{-3}\) antagonist for highly emetogenic chemotherapy, when data from well-controlled trials demonstrate comparable efficacy to the intravenous formulation, appears to be cost-effective.\(^{41,42}\) One should take into consideration, when evaluating the results of these studies, whether a stringent efficacy end point was used. Some studies did not use "no nausea" as one of the criteria for a complete response. Because nausea was ranked as the most severe chemotherapy-related symptom according to a relatively recent survey, the effect of the agents on nausea should also be evaluated.

Economic considerations for the selection of antiemetic regimens should answer the following questions:

- Will the use of the regimens likely result in a reduced hospitalization?
- While receiving therapy, will patients be able to maintain their usual level of activity?
- Will nursing and pharmacy costs be reduced?
- Are there mandated restrictions on the use of an agent in hospital formularies and in clinical settings?
- Will the antiemetic regimen affect the patient’s out-of-pocket expenses?

Extensive basic and clinical research has made it possible to control treatment-induced nausea and vomiting. With recognition and anticipation of nausea and vomiting, counseling of the patient and family, prophylactic intervention, flexibility in the therapeutic approach, and constant reassessment of the treatment plan, chemotherapy- and radion therapy-induced nausea and vomiting can be managed effectively in 80% to 90% of patients. The progress made in the field of treatment-induced nausea and vomiting must be a paradigm for other symptoms faced by the cancer patient that lead to suffering and that affect the patient’s quality of life.

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INTRODUCTION

In the discussion of orofacial complications and pain and its management for patients receiving chemotherapy or radiotherapy, we must consider and discuss many factors. In the brief space allocated to oral complications, we shall evaluate dentition, mucosa, and bone to understand the interrelationship of these organ systems and how they interface with orofacial pain.

Oral pain that develops during the course of oncologic therapy cannot simply be labeled mucositis. Although this is the term commonly applied to the presentation of oral symptoms that develop in an oncology patient during the course of therapy, mucositis is not simply the result of mucosal ulceration from chemotherapy or radiotherapy. We must examine the various etiologies of orofacial pain, as such pain arises from multiple origins (Table 55.2-1). The oral environment, when in a state of imbalance, poses a serious threat to the success of both chemotherapy and radiotherapy. A complex interrelationship exists among the oral microflora, occlusal pathology, dental restorations, and mucositis. In chemotherapy, bacteria play a major role in the morbidity associated with mucositis. For patients receiving radiotherapy, oral microorganisms and restorative dental procedures have a significant impact on both transient mucositis and long-term dental management.

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**SECTION 55.2**

**Oral Complications**

**Ann M. Berger**

**Thomas J. Kilroy**

**INTRODUCTION**

In the discussion of orofacial complications and pain and its management for patients receiving chemotherapy or radiotherapy, we must consider and discuss many factors. In the brief space allocated to oral complications, we shall evaluate dentition, mucosa, and bone to understand the interrelationship of these organ systems and how they interface with orofacial pain.

Orofacial pain that develops during the course of oncologic therapy cannot simply be labeled mucositis. Although this is the term commonly applied to the presentation of oral symptoms that develop in an oncology patient during the course of therapy, mucositis is not simply the result of mucosal ulceration from chemotherapy or radiotherapy. We must examine the various etiologies of orofacial pain, as such pain arises from multiple origins (Table 55.2-1). The oral environment, when in a state of imbalance, poses a serious threat to the success of both chemotherapy and radiotherapy. A complex interrelationship exists among the oral microflora, occlusal pathology, dental restorations, and mucositis. In chemotherapy, bacteria play a major role in the morbidity associated with mucositis. For patients receiving radiotherapy, oral microorganisms and restorative dental procedures have a significant impact on both transient mucositis and long-term dental management.

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**TABLE 55.2-1. Etiologic Factors Contributing to Pain in the Oncology Patient**

<table>
<thead>
<tr>
<th>Etiologic Factor</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>Oral mucositis</td>
<td>is a significant problem in patients receiving chemotherapy or radiotherapy. Estimates of oral mucositis incidence among cancer therapy patients range from 40% of those receiving standard chemotherapy to 76% of bone marrow transplant patients.</td>
</tr>
<tr>
<td>Cancer chemotherapy drugs that produce direct stomatotoxicity include the alkylating agents, antimetabolites, natural products, and other synthetic agents such as hydroxyurea and procarbazine hydrochloride.</td>
<td></td>
</tr>
<tr>
<td>Mucositis is an inevitable side effect of irradiation. The severity of the mucositis depends on the type of ionizing radiation, the volume of irradiated tissue, the dose per day, and the cumulative dose.</td>
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<tr>
<td>Poor nutritional status further interferes with mucosal regeneration by decreasing cellular migration and renewal.</td>
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**DIRECT STOMATOTOXICITY**

Normally, cells of the mouth undergo rapid renewal over a 7- to 14-day cycle. Both chemotherapy and radiotherapy interfere with cellular mitosis and reduce the regenerative ability of the oral mucosa. Cancer chemotherapeutic drugs that produce direct stomatotoxicity include the alkylating agents, antimetabolites, natural products, and other synthetic agents such as hydroxyurea and procarbazine hydrochloride. **Typical sequelae of these cytotoxic agents include epithelial hyperplasia, collagen and glandular degeneration, and epithelial dysplasia.** Mucositis is an inevitable side effect of irradiation. The severity of the mucositis depends on the type of ionizing radiation, the volume of irradiated tissue, the dose per day, and the cumulative dose. As the mucositis becomes more severe, pseudomembranes and ulcerations develop. Poor nutritional status further interferes with mucosal regeneration by decreasing cellular migration and renewal.

Direct stomatotoxicity usually is seen 5 to 7 days after the administration of chemotherapy or radiotherapy. In the nonmyelosuppressed patient, oral lesions heal within 2 to 3 weeks. The nonkeratinized mucosa is most affected. The most common sites include the labial, buccal, and soft palate mucosa, as well as the floor of the mouth and the ventral surface of the tongue. Clinically, mucositis presents with multiple complex symptoms. The condition begins with asymptomatic redness and erythema and progresses through solitary, white, elevated desquamative patches that are slightly painful to contact pressure, to large, contiguous, pseudomembranous, acutely painful lesions with associated dysphagia and decreased oral intake. Histopathologically, edema of the rete pegs will be noted, along with vascular changes that demonstrate a thickening of the tunica intima and concomitant reduction in the size of the lumen and destruction of the elastic and muscle...
fibers of the vessel walls. The loss of basement membrane epithelial cells exposes the underlying connective tissue stroma with its associated innervation, which, as the mucosal lesions enlarge, contributes to increasing pain levels. Oral infections, which may be due to bacteria, viruses, or fungal organisms, can further exacerbate the mucositis and may lead to systemic infections. If the patient develops both severe mucositis and thrombocytopenia, oral bleeding may occur and may be very difficult to treat.

PATHOPHYSIOLOGY OF MUCOSITIS

Sonis et al. proposed a hypothesis as to the mechanisms of the development and healing of mucositis. The hypothesis is based on both animal and clinical data, though it remains speculative to some degree. It describes mucositis as a complex biologic process that occurs in four phases: (1) the inflammatory or vascular phase, (2) the epithelial phase, (3) the ulcerative or bacteriologic phase, and (4) the healing phase (Table 55.2-2). Each phase is interdependent and is a consequence of the effect of the chemotherapy or radiotherapy on the epithelium, as well as actions mediated by cytokines, the status of the patient's bone marrow, and the oral bacterial flora.

### TABLE 55.2-2. Four Phases in the Development of Mucositis

<table>
<thead>
<tr>
<th>Phase</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phase 1: Inflammatory or Vascular Phase</strong></td>
<td>Cytokines such as tumor necrosis factor-α, interleukin-1 (IL-1), and perhaps interleukin-6, are released from the epithelial tissue and adjacent connective tissue shortly after the administration of chemotherapy or radiotherapy. Most likely, the initiating event in the development of mucositis is local tissue damage caused by the cytokines. Additional concentrations of cytotoxic drugs in the mucosa may result from the increased vascularity caused by IL-1. Also during this phase, increased submucosal vascularity occurs.</td>
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<tr>
<td><strong>Phase 2: Epithelial Phase</strong></td>
<td>Reduced epithelial renewal, with atrophy and ulceration, occurs as a result of both radiotherapy and chemotherapy, particularly with drugs affecting the S phase of the cell cycle, whereby the impact is on dividing cells of the oral basal epithelium. The atrophy and ulceration that occurs is most likely exacerbated by locally produced cytokines as well as functional trauma. The first two phases usually occur from days 0 to 5 of therapy.</td>
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<tr>
<td><strong>Phase 3: Ulcerative or Bacteriologic Phase</strong></td>
<td>The most complex and symptomatic phase is phase 3, during which localized areas of erosion often become covered with a fibrinous pseudomembrane. This phase usually coincides with the patient's period of maximum neutropenia. Secondary bacterial colonization, involving some gram-negative organisms, occurs, and the gram-negative organisms provide a source of endotoxin, which stimulates further cytokine release from the connective tissue around the cells. The patient's condition is exacerbated by the cytokines as well as the nitric oxide that is released. This phase usually occurs from days 6 to 12 of therapy.</td>
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<tr>
<td><strong>Phase 4: Healing Phase</strong></td>
<td>The final phase usually consists of renewal in epithelial proliferation and differentiation, with normalization of the patient's peripheral white blood cell count and reestablishment of the local microbial flora. The healing phase usually takes place from days 12 to 16.</td>
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### RISK FACTORS

Both direct and indirect factors appear to contribute to oropharyngeal mucositis. The direct factors include the chemotherapeutic agent, dosage, and schedule (Table 55.2-3), the total dose and days of radiotherapy, mucosal damage from such problems as ill-fitting dental prostheses, periodontal disease, microbial flora, salivary gland dysfunction, and patient susceptibility. Indirect factors include myelosuppression, immunosuppression, reduced secretory IgA, and bacterial, viral, or fungal infections.

### TABLE 55.2-3. Chemotherapeutic Agents Commonly Producing Mucositis

A variety of patient-related factors have potential for affecting the development of mucositis after chemotherapy. It has been suggested that the repair of ill-fitting prostheses, extraction of offending teeth, elimination of periodontal disease, and effective oral hygiene reduce the incidence and severity of mucositis. A patient might develop more severe mucositis if his or her nutrition is poor, through impairment of mucosal regeneration. Xerostomia that develops as a result of irradiation or drug use contributes significantly to the development of oral mucositis. Drugs that can result in xerostomia include antidepressants, opiates, antihypertensives, antihistamines, diuretics, and sedatives. Although both alcohol and tobacco can impair salivary function, it has been suggested that tobacco has been associated with a decreased incidence of chemotherapy-induced stomatitis. One recent study involving 332 outpatients receiving chemotherapy revealed no significant differences in the incidence of mucositis between patients who wore dental appliances, had a history of oral lesions and a history of smoking, and practiced different oral hygiene regimens, and those patients who did not. These findings suggest that the risk factors for the development of chemotherapy-induced mucositis are many and complicated and that further research is needed.

Reports on the effects of age on chemotherapy-induced mucositis development are conflicting. In general, younger patients are at increased risk for developing
Sucralfate, an aluminum salt of sucrose octasulfate, which has been used successfully to treat gastrointestinal ulceration, has been tested as a rinse for the prevention and treatment of mucositis. Sucralfate's mechanism of action appears to be forming an ionic bond to proteins in an ulcer site, thereby creating a protective barrier. Additionally, evidence points to an increase in the local production of prostaglandin E₂ (PGE₂), which results in an increase in mucosal blood flow, mucus production, mitotic activity, and surface migration of cells. Anecdotal experience suggests that sucralfate might be useful in the prevention and treatment of chemotherapy-induced mucositis; however, data from the studies are conflicting. Solomon reported a 55% objective response rate in patients receiving chemotherapy (19 patients), which was defined as a decrease in one grade on the cancer and leukemia group B (CALGB) scale of oral toxicity. In 1984 and 1985, Ferraro and Mattern reported encouraging results in the use of sucralfate for chemotherapy-induced mucositis. Two randomized, double-blind clinical trials also have evaluated sucralfate for the prevention of chemotherapy-induced mucositis. Pfeiffer et al. found a significant reduction in edema, erythema, erosion, and ulceration in 23 of 40 evaluable patients receiving cisplatin and continuous infusion with 5-fluorouracil (5-FU) with or without bleomycin. Patient preference favored sucralfate, although this preference failed to reach statistical significance. Ten of the patients did not complete the study as the swallowing of the sucralfate and the placebo aggravated chemotherapy-induced nausea. The authors suggested that, to help overcome this problem, the solution should have a neutral taste and should not be swallowed after swishing. In contrast, results from a similarly designed study, in which patients receiving remission-induction chemotherapy for acute nonlymphocytic leukemia were treated with sucralfate for mucositis, did not support the

<table>
<thead>
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<th>TABLE 55.2-4. Risk Factors Contributing to Mucositis</th>
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<tr>
<td><strong>Direct Factors</strong></td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Prophylactic therapy</td>
</tr>
<tr>
<td>Oral care management</td>
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<tr>
<td>Chemotherapeutic drug dose, schedule, intensity</td>
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<tr>
<td><strong>Secondary Factors</strong></td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>ReducedHost Immune Function</td>
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<td>Systemic (blood borne)</td>
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</table>

**TABLE 55.2-5. Mucositis Grading**

Recently, new scoring systems have been developed for the assessment of oral mucositis. Sonis et al. reported on a scale that uses an objective measure of mucositis, evaluating ulceration and pseudomembrane formation and erythema. Subjective outcomes of mouth pain, ability to swallow, and function were measured. Analgesia use for mouth sensitivity was also recorded. In the study that was conducted in nine centers, there was high interobserver correlation, with objective mucositis scores demonstrating strong correlation with symptoms.

At the 1989 National Institutes of Health consensus conference on oral complications of cancer therapy, clinicians and researchers agreed that effective prevention of mucositis requires a comprehensive patient examination to identify potentially complicating oral disease before the cancer therapy begins. Significant problems that must be corrected include poor oral hygiene, periapical pathology, third molar pathology, periodontal disease, dental caries, defective restorations, orthodontic appliances, ill-fitting prostheses, and other potential sources of infection. Bacterial and fungal surveillance cultures are not necessary, but prophylactic use of acyclovir should be considered in patients who are seropositive and at high risk for reactivating herpes simplex viral infection, such as those who undergo bone marrow transplant or who have prolonged and pronounced myelosuppression. If a diagnosis is made of a fungal, viral, or bacterial infection along with the mucosal lesions, prompt treatment is necessary to avoid the risk of systemic infection.

**REMEDIES FOR THE PREVENTION AND TREATMENT OF MUCOSITIS**

A standardized approach for the prevention and treatment of chemotherapy- and radiotherapy-induced mucositis is essential, although the efficacy and safety of most of the regimens have not been established. The prophylactic measures usually used for the prevention of mucositis include chlorhexidine gluconate (Peridex), saline rinses, sodium bicarbonate rinses, acyclovir, amphotericin, and ice. Regimens commonly used for the treatment of mucositis and the associated pain include a local anesthetic such as lidocaine or dyclonine, magnesium-based antacids (Maalox, Mylanta), diphenhydramine (Benadryl), nystatin, or sucralfate. These agents are used either alone or in different combinations that compose a mouthwash. Other agents used less commonly include kaolin-pectin (Kaopectate), allopurinol, vitamin E, b-carotene, chamomile (Kamillosan) liquid, aspirin, antiprostaglandins, stomatidin, MGI 209 (marketed as Oratect Gel), some nitrate, and antibiotics. Oral and sometimes parenteral narcotics are used to relieve the pain caused by mucositis. A new method that uses capsaicin for such pain relief is currently being studied.

**DIRECT CYTOPROTECTANTS**

Sucralfate
amelioration of mucositis. 37 The latter study also concluded that chronic administration of the sucralfate suspension had no effect on the incidence of gastrointestinal bleeding and ulceration. The authors did not note that some patients reported pain relief from sucralfate. 38 A phase III study of sucralfate suspension versus placebo, recently completed by the NCTT, revealed that of the 50 patients who developed stomatitis, the sucralfate suspensions provided no beneficial reduction in the duration or severity of 5-FU-induced mucositis. 39 In addition, the sucralfate induced considerable additional gastrointestinal toxicity.

Sucralfate has also been tested in patients receiving radiotherapy. One study compared 21 patients who received standard oral care to the head and neck with 24 patients who received sucralfate suspension four times daily. 40 Results revealed a significant difference in mucosal edema, pain, dysphagia, and weight loss in those patients receiving sucralfate. In a pilot study done by Pfeiffer et al., 41 sequential patients who received radiotherapy to the head and neck received sucralfate at the onset of mucositis. The majority of patients had a decrease in pain after initiation of sucralfate. A double-blind placebo-controlled study with sucralfate in 33 patients who received irradiation to the head and neck reported no statistically significant difference in mucositis, however, the sucralfate group reported less oral pain, and in these patients, other topical and systemic analgesics were started later in the course of radiation. 42

A prospective double-blind study compared the effectiveness of sucralfate suspension to that of diphenhydramine syrup plus kaolin-pectin on radiotherapy-induced mucositis. Data on perceived pain, helpfulness of mouth rinses, weekly mucositis grade, weight change, and interruption of therapy were collected daily. Analysis of the two groups revealed no statistically significant difference between them. A retrospective comparison of a group of 15 patients who had not used daily oral rinses and the preceding two groups suggested that the use of a daily oral rinse with a mouth-coating agent may result in less pain, may reduce weight loss, and may help to prevent interruption of radiotherapy because of severe mucositis. 43

Prostaglandins, Antiprostaglandins, and Nonsteroidal Agents

Prostaglandins are a family of naturally occurring eicosanoids, some of which have known cytoprotective activity. Dinoprostone, or PGE \_2, has been reported to be beneficial in healing both gastric ulcers and chronic leg ulcers. 44 Pilot studies revealed the need for controlled clinical trials. In a pilot study undertaken by Kuher et al., 45 five patients received topical dinoprostone for chemotherapy-induced mucositis. Four of the five patients reported pain relief, with healing of the ulcers within 3 to 7 days. Kuher’s group then tested the prophylactic efficacy of dinoprostone by applying it topically to one patient who was receiving chemotherapy and who had developed previous episodes of mucositis, as well as to two patients receiving total body irradiation. 46 Only one of the patients who had received the dinoprostone and total body irradiation developed mucositis.

In a nonblinded study, ten patients who were receiving 5-FU and mitomycin with concomitant radiation for oral carcinomas were treated by Porteder et al., 47 with dinoprostone four times daily during treatment. The control group consisted of 14 patients who were receiving identical treatment. Eight of the ten patients who received dinoprostone were evaluable, and none developed severe mucositis, as compared with six episodes in the control arm.

A third pilot study conducted with 15 patients who received radiotherapy of the head and neck found that an inflammatory reaction in the vicinity of the tumor could be detected in only 5 patients treated with topically applied PGE \_2, and none of the patients developed any bullous or desquamating inflammatory lesions. 48 A double-blind, placebo-controlled trial of PGE \_2-treated group, showed nine patients had complete resolution of their mucositis within 4 days of initiating therapy, whereas in the placebo group, only one of nine had resolution of the lesions during the 5-day study period. This difference was statistically significant. 49 Because both sucralfate and vitamin E provide some effectiveness in mucositis, a phase III study of sucralfate versus vitamin E for treatment-induced mucositis is currently under way.

Corticosteroids

No placebo-controlled studies of the use of corticosteroids for chemotherapy-induced mucositis have been reported, though two reports have focused on pilot work conducted with patients who received radiotherapy. Abdelal et al. 50 reported the use of a betamethasone and water mouthwash in five patients receiving radiotherapy whose mucosa remained virtually ulcer-free and who did not report any pain. The proposed mechanism of action of the steroid mouthwash was inhibition of leukotriene and prostaglandin production. Another pilot study compared 21 patients receiving radiotherapy who used an oral rinse consisting of hydrocortisone in combination with nystatin, tetracycline, and diphenhydramine with patients using a placebo rinse. Though only 12 of the 21 patients were evaluable, by the end of the radiotherapy cycles, there was a statistically significant difference in mucositis and a trend toward a reduction in pain. No patients in the treatment group needed to interrupt the radiotherapeutic regimen, whereas three patients in the control group did need to interrupt their radiotherapeutic care.

Vitamins and Other Antioxidants

Vitamins in pharmacologic doses have been used to treat mucositis. Vitamin E has been tested in chemotherapy-induced mucositis because it can stabilize cellular membranes and may improve herpetic gingivitis, possibly through antioxidant activity. 51,52 The efficacy of vitamin E was demonstrated by Wadleigh et al. 53 in a randomized, double-blind, placebo-controlled study. Eighteen patients receiving chemotherapy were randomized to receive a topical application of vitamin E or a placebo to the mucosa. No statistically significant relief of pain from radiation-induced mucositis. Positive responses to b-carotene were reported in at least two other studies. 54,55 The study conducted by Epstein and Stevenson-Moore 56 revealed not only a trend toward reduction in pain but also a statistically significant reduction in the total area of ulceration as well as the size of the ulcer. Another study demonstrated that when indomethacin, an antiprostaglandin, was given orally, it reduced the severity and delayed the onset of mucositis induced by radiotherapy. 57

Other antioxidants that have been used clinically include vitamin C and glutathione. Another antioxidant tested in a pilot study, azelastine hydrochloride has been used in many allergic diseases and has been shown to be effective in the treatment of aphthous ulcers in Behçet's disease. Osaki et al. 58 reported on a study involving 63 patients who had head and neck tumors and a combination of radiotherapy and concomitant chemotherapy. Twenty-six patients received radiation alone to the head and neck, 18 patients received chemoradiotherapy, and 19 patients received radiation followed by chemotherapy. Ten patients received radiation therapy whose mucosa remained virtually ulcer-free and who did not report any pain. The proposed mechanism of action of the steroid mouthwash was inhibition of leukotriene and prostaglandin production. Another pilot study compared 21 patients receiving radiotherapy who used an oral rinse consisting of hydrocortisone in combination with nystatin, tetracycline, and diphenhydramine with patients using a placebo rinse. Though only 12 of the 21 patients were evaluable, by the end of the radiotherapy cycles, there was a statistically significant difference in mucositis and a trend toward a reduction in pain. No patients in the treatment group needed to interrupt the radiotherapeutic regimen, whereas three patients in the control group did need to interrupt their radiotherapeutic care.

b-Carotene, a vitamin A precursor with known effects on cellular differentiation, has been used for mucositis induced by radiation. b- Carotene has been shown to produce regression of oral leukoplakia lesions. 59 Mills 60 reported on the use of b-carotene in treatment-induced mucositis. Ten patients receiving radiation interspersed with two cycles of chemotherapy were given b-carotene, 250 mg/d for the first 3 weeks of therapy and then 75 mg/d for the last 5 weeks of therapy. The control group consisted of ten patients with oral cancer who were receiving the identical treatment. At the end of treatment, there was a statistically significant difference in grade 3 to 4 mucositis in the b-carotene group; there was no difference in grades 1 and 2 mucositis. 61

Silver Nitrate

Silver nitrate, a caustic agent, has been tested in radiation-induced mucositis. Because silver nitrate is known to stimulate cell division when it is applied to normal mucosa, though that if it were applied to the mucosa that was damaged by cytotoxic therapy, it might enhance repair and replace all mucosa that was damaged by cytotoxic therapy. Maciejewski et al. 62 reported on 16 patients who received radiotherapy to bilateral opposing fields. Silver nitrate 2% was applied to the left side of the oral mucosa three times daily for 5 days before radiotherapy and during the first 2 days of radiotherapy. The right side of the oral mucosa was unpainted and served as the control. The study revealed significantly less severe mucositis and a decrease in duration of mucositis on the mucosa that was treated with silver nitrate. 63 A second trial failed to confirm these results. 64 Silver nitrate has not been formally evaluated in the treatment of chemotherapy-induced mucositis.
Miscellaneous Cytoprotectants

An uncontrolled study involving 98 patients with different malignancies who were receiving different medical regimens with either chemotherapy or radiotherapy reported that Kamillons led to the development of mucositis helped to prevent and decrease the incidence of mucositis. In a placebo-controlled trial conducted by NCTG, patients were randomized to receive chamomile or placebo, along with an established oral cytoprotective regimen. This study revealed that chamomile mouthwash did not reduce stomatitis associated with 5-FU chemotherapy.

Oshlani et al. reported on the use of topical sodium alginate, an agent that has been shown to promote healing of esophageal and gastric mucosa, in radiation-induced mucositis. Thirty-nine patients with mucositis were randomized to receive either sodium alginate or placebo. Those who received sodium alginate had a reduction in both mucosal erosions and pain. Other topical agents used clinically for treatment-induced mucositis include Kapectate, Benadryl, saline, sodium bicarbonate, and gentian violet. Even though the previously mentioned agents are used clinically for treatment-induced mucositis, no controlled clinical trials have yet established their efficacy.

INDIRECT CYTOPROTECTANTS

Hematologic Growth Factors

Hematologic growth factors currently are standard in the treatment of patients receiving high-dose chemotherapy. The effect of the hematologic growth factors on decreasing the depth and duration of chemotherapy-induced neutropenia is well established. Lieschke et al. examined the levels of neutrophil count and assessed whether oral neutrophil count correlated with oral mucositis. In the study, the researchers found that the oral neutrophil count, similar to circulating systemic neutrophils, diminished to undetectable levels, but recovery was earlier than did the systemic circulating neutrophils. In those patients receiving granulocyte colony-stimulating factor (G-CSF), the mean cumulative mucositis score was less than that in patients who did not receive G-CSF. Gabrilove et al. reported on 27 patients receiving methotrexate, vinblastine, doxorubicin, and cisplatin for bladder carcinoma and escalating doses of G-CSF. The patients received the G-CSF on their first cycle of chemotherapy and did not receive it on their second chemotherapeutic cycle. Significantly less mucositis was seen during the cycle in which the patients received the G-CSF. In this study, a bias may have been inherent as there is perhaps cumulative chemotherapeutic toxicity such that with each cycle of chemotherapy, the severity of mucositis increases.

Bronchud et al. treated 17 patients with breast or ovarian carcinoma who were receiving escalating doses of doxorubicin with G-CSF support. In this study, the G-CSF did not prevent severe mucositis. In a fourth study using G-CSF, 41 patients receiving chemotherapy for non-Hodgkin's lymphoma received G-CSF, whereas 39 received chemotherapy without G-CSF. In those patients who did not receive G-CSF, the main cause of treatment delay was neutropenia, whereas in those patients who did receive G-CSF, the main cause of treatment delay was mucositis.

In a small prospective study, patients who received platinum, infused 5-FU, and leucovorin plus granulocyte-macrophage colony-stimulating factor (GM-CSF) had a decreased incidence of grade 3 mucositis. In a study comparing patients undergoing bone marrow transplantation in whom GM-CSF was used to control infections, recovery of neutrophils was more rapid in the GM-CSF group; however, there was no difference in the severity of mucositis nor in duration of hospitalization. At this time, the use of colony-stimulating factors in the prevention or treatment of mucositis is investigational.

The effect of other biologically active factors on mucositis development is currently being studied. In vitro studies have shown that epidermal growth factor (EGF) not only is present in saliva but has the ability to affect growth, cell differentiation, and cell migration. It is known that EGF induces chemotaxis of oral epithelial cells, indicating that it may be important in maintaining the integrity of the oral epithelium, especially in wound healing. Patients with peptic ulcers have been shown to have significantly lower levels of EGF in their saliva, suggesting that EGF may be involved in either protection or repair. In an animal study in which the animals received either 5-FU with an infusion of EGF for 7 and 15 days or a placebo, the animals that received the EGF experienced increased mucosal breakdown. The results of the study indicate that chemotherapy-induced mucositis depends on the rate of epithelial cell growth. The timing of administration of the EGF in relation to the chemotherapy may determine whether the patient develops increased oral toxicity or repair of the mucosa. In a study conducted by Sonis et al., hamsters received EGF versus placebo using four different treatment schedules. In this study, delayed exposure to EGF delayed the onset of mucositis, but it had no beneficial effects on the duration or severity of mucositis.

Tumor growth factor-β3 (TGF-β3) is an inhibitor of epithelial cell growth. In a study using Syrian hamsters done by Sonis et al., the topical application of TGF-β3 resulted in a decrease in the severity and duration of chemotherapy-induced mucositis. In another study performed by Spikervet and Sonis with Syrian hamsters, the topical application of TGF-β3 significantly reduced the severity and duration of ulcerative mucositis induced by 5-FU. In animal experiments, IL-1 and IL-11 demonstrated a cytoprotective effect.

Antimicrobials

Many conflicting studies have been published on the use of chlorhexidine mouthwash for both alleviating mucositis and reducing oral colonization by gram-positive, gram-negative, and Candida species in patients receiving radiotherapy, chemotherapy, or bone marrow transplantation. In 1990, Ferretti et al., in a randomized, controlled trial, demonstrated that prophylactic chlorhexidine mouthwash reduces oral mucositis and microbial burden in cancer patients receiving chemotherapy. The majority of studies since that time have not demonstrated a reduction in mucositis patients receiving intensive chemotherapy and using chlorhexidine mouthwash. However, Weis dorf et al. and Epstein et al. did demonstrate a reduction in oral colonization by Candida species and oral candidiasis. Ferretti et al. found that the use of chlorhexidine rinse for the prevention of mucositis was not effective, though there was a reduction in streptococcal counts. Spikervet et al., in a placebo-controlled, double-blind study, revealed that the colonization index of viridans streptococci was reduced after 5 weeks of chlorhexidine treatment, though such therapy did not decrease the colonization of Candida species. Streptococcus faecalis, staphylococci, Enterobacteriaceae, Pseudomonadaceae, and Acinetobacter species, and there was no difference in the development and severity of mucositis. A recent randomized, double-blind study comparing chlorhexidine mouthwash to placebo in 25 patients receiving radiotherapy revealed that there was a trend toward more mucositis as well as mouthwash-induced discomfort, taste alteration, and teeth staining in the chlorhexidine arm. The overall statistical data lead to the conclusion that chlorhexidine may result in improved oral hygiene, but the discomfort of using the rinse negates its minimal benefits.

The endotoxins of aerobic gram-negative bacilli are implicated in the etiology of mucositis. A study by Spikervet et al. postulated that lozenges containing 2 mg polymyxin E, 1.8 mg tobramycin, and 10 mg amphotericin (PTA) four times daily in the oropharyngeal flora would mediate and control mucositis. These researchers compared 15 irradiated patients using PTA and two other groups of 15 patients each, one of which was using 0.1% chlorhexidine and the other of which was using placebo. In the selectively decontaminated groups, the severity and extent of mucositis was significantly reduced as compared with that in the chlorhexidine and placebo groups (P < .05). Clinically, all patients in the lozenge group showed erythema only, whereas 80% of both the placebo and chlorhexidine rinse patients experienced severe mucositis with extended pseudomembranes from the third week of irradiation. No nasogastric tube feedings were needed in the PTA group, as compared to 30% of patients in the other groups. The potential role of PTA lozenges remains to be clarified.

IB-367, a broad-spectrum antimicrobial peptide found in porcine leukocytes, was tested in a hamster model. The results indicated that mucositis scores were significantly lower in hamsters given topical IB-367 as compared to those receiving placebo. Though further study is needed, IB-367 might improve clinical outcomes in patients at risk for the development of mucositis. Another antimicrobial, nystatin suspension, has been studied in the prophylaxis of candidiasis in leukemia and bone marrow transplantation patients. The majority of publications do not support the use of nystatin.

Pharmacologic Modulation

Another agent that has been evaluated for the prevention and treatment of oral mucositis induced by 5-FU chemotherapy is allopurinel. The rationale for allopurinel mouthwash was based on data that systemic allopurinel was able to decrease 5-FU-induced toxicity by inhibiting the enzyme ornithidine decarboxylase and formation of the metabolites of fluoro-deoxyuridine monophosphate (FdUMP) and fluorouridine (FUrD). Two pilot studies support the use of allopurinel for oral mucositis. The study by Clark and Selvin revealed that allopurinel mouthwash substantially decreased the incidence and severity of mucositis in six patients who received bolus 5-FU chemotherapy. Another pilot study, involving 16 patients receiving 5-day intravenous 5-FU infusions and using allopurinel mouthwashes four to six times daily,
also found that the allopurinol alleviated the mucositis in all patients. After the success of these pilot studies, the use of allopurinol became routine medical practice in many institutions. The efficacy of allopurinol was tested by the NCCCTG and the Mayo Clinic in a randomized, double-blind clinical trial. Seventy-five patients were assigned to receive allopurinol mouthwash or placebo while they received their first 5-day course of 5-FU with or without leucovorin. This study demonstrated no protective effect against 5-FU-induced mucositis by the allopurinol regimen.

Leucovorin has been used in combination with methotrexate to help decrease the oral mucositis that occurs with methotrexate. In a pilot study involving 19 patients who received edetate sodium for non–small cell lung cancer, less mucositis was seen than was anticipated. There is decreased mucositis when reduced folates are given systemically following methotrexate administration. In a small crossover study, administration of leucovorin-hyaluronidase mouthwashes did not reduce the severity of mucositis induced by high-dose methotrexate.

Glutamine administration in animal studies has been shown to lead to a reduction in both morbidity and mortality of animals who have received a variety of chemotherapeutic agents, including methotrexate. The glutamine both preserved the morphologic structure of the gastrointestinal tract and reduced the incidence of bacteremia. In a randomized trial of 28 patients with gastrointestinal cancers who received 5-FU and folinic acid, no effect on oral mucositis was seen in the group who also received 16 g glutamine daily for 8 days as compared to the group who received a placebo. The authors concluded that perhaps both the dose and duration of exposure to the glutamine were not sufficient to show a decrease in mucositis.

According to laboratory data, another agent that protects host tissues selectively from 5-FU's toxic effects without loss of antitumor effect is uridine. A study was conducted involving 29 patients with advanced malignancies who received N-phosphoracetyl-disodium L-aspartic acid (PALA) and methotrexate, each at 250 mg/m², followed 24 hours later by increasing doses of 5-FU (600 to 750 mg/m²), with a leucovorin rescue and uridine rescue for a 72-hour infusion. The uridine allowed dose escalation of 5-FU to 750 mg/m², with a decrease in all toxicities of the 5-FU except mucositis, which remained as the only significant chemotherapy-induced toxic effect. Perhaps additional studies with oral uridine will reveal a reduction of the toxicity from mucositis.

A pilot study using propantheline, an anticholinergic agent that causes xerostomia, was performed to test whether the incidence of mucositis could be reduced when patients received etoposide. It was hypothesized that the mucosal toxicity might be related to salivary excretion of etoposide after its systemic administration. Propantheline or placebo was given to 12 patients. The results revealed a decrease in the incidence and severity of mucositis in the patients who received the propantheline.

CRYOTHERAPY

Cryotherapy, in the form of ice chips and flavored ice pops, has been used to prevent mucositis. The NCCCTG and the Mayo Clinic undertook a controlled, randomized trial of oral cryotherapy for preventing 5-FU-induced mucositis and found that cryotherapy is helpful in reducing the severity of 5-FU-induced mucositis. After this study had been completed, another was undertaken in which patients were randomized to receive 30 minutes versus 60 minutes of cryotherapy. A total of 178 evaluable patients were studied. Both cryotherapy groups had similar degrees of mucositis. The conclusion was to continue to recommend the use of 30 minutes of oral cryotherapy for patients receiving bolus intensive courses of 5-FU-based chemotherapy.

ANESTHETIC COCKTAILS

Several anesthetic cocktails, made up of agents such as viscous lidocaine (Xylocaine) or dyclonine hydrochloride, have been used with some success. The anesthetic agents relieve the patient's pain, but this relief is temporary and also prevents taste perception, which can further interfere with food intake. Other analgesics and mucosal coating agents that can control pain include kaolin-pectin, diphenhydramine, Orabase, and Oracet Gel. In a prospective, double-blinded study involving 18 patients, the 5-FU group received viscous lidocaine hydrochloride 1%, kaolin-pectin solution, diphenhydramine, and saline solution compared with a placebo. The dyclonine hydrochloride 1% provided the most pain relief, whereas dyclonine hydrochloride with viscous lidocaine and cocaine 1% provided the longest pain relief. Even though clinicians use many of the topical agents, little experimental evidence exists to establish the efficacy of many of them.

CAPSAICIN

Capsaicin, the active ingredient in chili peppers, is a remedy that has been used for many different pain syndromes through the years and that may prove beneficial for mucositis pain induced by chemotherapy and radiotherapy. Several studies support the medical efficacy of locally applied capsaicin in a cream vehicle in neuropathic pain syndromes. A large, multicenter trial involving 277 patients demonstrated that topically applied capsaicin used for up to 8 weeks significantly reduced pain and improved quality of life in both postherpetic neuralgia and diabetic neuropathy. Other neuropathic pain syndromes for which capsaicin has been shown to be effective include postmastectomy pain, stump pain, trigeminal neuralgia, reflex sympathetic dystrophy, and Guillain-Barré syndrome. Capsaicin has also been shown to decrease the pain associated with rheumatoid and osteoarthritis, and intranasal capsaicin spray has been shown to reduce the pain associated with cluster headaches. Topical capsaicin has been shown to improve the rate of reepithelialization of wound healing in minipigs; thus, it may prove to be efficacious in wound healing in humans.

In a pilot project, capsaicin in a candy vehicle (cayenne pepper candy) was given to patients with therapy-induced mucositis. Patients were instructed to allow the candy to dissolve in the mouth without chewing it. After the candy had dissolved, the burn produced by the candy was allowed to fade. The patients rated their pain before and after eating the candy. The reduction in pain was highly statistically significant. A double-blinded, placebo-controlled study is under way to test the efficacy of oral capsaicin for pain control.

NARCOTICS

Many of the agents previously mentioned may have some value in preventing mucositis or palliating the pain; however, very few controlled clinical trials have established their efficacy. At present, no standard treatment has been defined for the prevention or treatment of mucositis. When mucositis is severe and interferes with nutritional intake and quality of life, it is appropriate to use any of the treatments that have already been cited, as well as oral, transmucosal or, if necessary, parenteral narcotics. Currently, a study is under way to investigate the usefulness of transmucosal fentanyl (Actiq) in the treatment of mucositis. A recent article also reported on the successful use of topical opioids (morphine 0.08% gel, prepared with taste supplements) in treating oral mucositis in a patient who was terminally ill. To discover an efficacious treatment, it is essential to continue studies of the treatments already available and to develop any promising new approaches.
Xerostomia is a complex phenomenon that cannot be attributed to radiation damage to the salivary glands alone. To understand xerostomia and the radiotherapy patient, oncologists must review the mechanisms behind saliva production. Secretion of saliva is subject to reflex stimulation of not only a physical but of a psychic nature. Physical stimulation of the salivary gland originates in the taste buds. The psychic stimulation of the salivary glands is via the sensory nerve receptors. Xerostomia presents with a twofold pathogenesis. First, the lack of a wetting medium reduces the ability of the chemoreceptors on the dorsum of the tongue and the palate to accept the stimuli presented with foods or liquids. This loss of physical stimulation (chemical) fails to trigger the neurogenic response to the salivary gland and the anticipated salivary response never occurs. The minimal, thickened, mucous saliva produced by the affected glands coats the mucosa of the cheeks, tongue, and palate, forming an effective barrier that prevents physical contact of the taste buds by the dietary substances (chemophores) and diminishes the physical response to thermal and mechanical stimulation. The cumulative result of being unable to stimulate the taste buds physically has a direct corresponding effect on the psychic component of salivary gland secretions. Histopathologically, the mucosa on the dorsum of the tongue appears atrophied, the end result of which is decreased surface area on the taste buds.

In the xerostomic patient, the clinician notices a significant loss of appetite that occurs concomitantly with mucositis. The role of xerostomia, and not merely stomatitis, in weight loss must not be discounted. When the physical component of salivary stimulation is denigrated by mechanical (mucous) barriers, the anticipated taste sensation associated with specific food groups is altered. If the patient no longer can perceive what should be sour or sweet, he or she will be unable to elicit the correct sensory response through the neurogenic paths; consequently, the second component of salivary stimulation, the visual component, becomes ineffective and the xerostomia is exacerbated further. When patients no longer can achieve the sensory gratification normally associated with specific food groups, dietary intake decreases and weight loss becomes a significant factor in continuation of therapy. With the decrease of salivary enzymes necessary for the initial stages of digestion, a third factor presents itself in the weight loss arena—namely, inability to assimilate dietary nutrients efficiently. Xerostomia is compounded by other factors such as antidepressant therapy, diabetes, interstitial nephritis, aging, postmenopausal syndromes, antihypertensives, and diuretics. Vitamin A and nicotinic acid deficiencies also can affect salivary secretions.

The management of xerostomia is complex, requiring attention to the patient's medical history for drug interaction, provision of a diet that both physically and psychologically is able to stimulate the salivary responses, maintenance of excellent oral hygiene to provide physical access to the taste receptors, and monitoring of the vitamin A and nicotinic acid levels for deficiencies. Increased intake of nicotinic acid and vitamin A on a specific, monitored response-to-dose program can be effective in increasing saliva flow. Mechanical débridement of the dorsum of the tongue with a soft toothbrush and the use of a spray mister before and during meals assists in maintaining access to taste buds.

Early clinical pilot studies by Fox et al. and Greenspan and Daniels indicated that low doses of oral pilocarpine reduced radiation-induced xerostomia. Recently, a randomized, double-blind, placebo-controlled trial by Johnson et al. found that pilocarpine improved saliva production and relieved symptoms of xerostomia after irradiation for cancer of the head and neck, with minor side effects that were predominantly limited to sweating.

A randomized, controlled trial of standard fractionated radiation with or without amifostine (Ethyol), administered at 200 mg/m² as a 3-minute IV infusion 15 to 30 minutes before each fraction of radiation, was conducted in 315 patients with head and neck cancer. Patients were required to have at least 75% of both parotid glands in the radiation field. The incidence of grade 2 or higher acute xerostomia (90 days from the start of radiotherapy) and late xerostomia (9 to 12 months after radiotherapy), as assessed by the Radiation Therapy Oncology Group Acute and Late Morbidity Scoring Criteria, was significantly reduced in patients receiving Ethyl. At 1 year after radiotherapy, whole saliva collection after irradiation showed that more patients given Ethyl produced 0.1 g of saliva (72% vs. 49%). In addition, the median saliva production at 1 year was higher in those patients who received Ethyl (0.26 g vs. 0.1 g). Stimulated saliva collections did not show a difference between treatment arms. These improvements in saliva production were supported by the patients' subjective responses to a questionnaire regarding oral dryness. With effective management of xerostomia, the thickened mucinous film that accumulates on the mucosa of the tongue, floor of mouth, palate, and buccal folds is eliminated. With this simple maintenance step that can be managed by the patient or support staff, a significant reduction in bacterial volume is achieved, which, in turn, will reduce the incidence of mucositis significantly. When xerostomia is not controlled, significant plaque and material will accumulate on the surfaces of prosthetic appliances. This bacterial film can contribute to denture irritation that will compound therapy-related mucositis and can lead to fenestration of the supporting mucosa and development of an osteonecrosis in the posttreatment patient. When xerostomia is not monitored or controlled, the clinical team can anticipate heavy plaque accumulation, primarily, on the surfaces of the teeth. This plaque film is highly cariogenic and ultimately will cause dental complications involving the teeth (decay) and the supporting tissue (gingivitis and periodontitis). Patients with high plaque indices will not benefit from anticariogenic treatment using fluoride applicators, because the plaque is an effective barrier against fluoride absorption. It must be assumed that the elevated plaque matrix resulting from xerostomia poses the greatest risk in the postradiotherapy morbidity of ORN.

Because of the risk of ORN, it will be necessary for the clinical team not only to assess a patient's pretreatment periodontal health but also to query the patient regarding his or her intent to maintain adequate oral hygiene. If a patient is not psychologically prepared to play a role in his or her oral hygiene or if a patient is physically or mentally impaired and unable to manage an appropriate personal oral hygiene program, it will be prudent to consider oral surgery to remove all high-risk teeth, as a preventive measure. Amputation of a patient's dentition is a serious irreversible step and must be thoroughly planned by all members of the clinical team before proceeding.

From the dental examination, diagnostic models, and radiographs obtained before radiotherapy or chemotherapy, high-risk teeth can be identified and treated restoratively or surgically. The therapy team must recognize and identify teeth and other bone anatomy aberrations that would require posttreatment surgery. Because
of the reduction in the vascular network and the permanent alteration of osteocytes in the bone in the treatment ports, it will be necessary to perform all prospective surgeries before the initiation of radiotherapy. This will minimize the potential for ORN in cases in which an operation must be performed after radiotherapy has been completed.

High-risk teeth and bone can be summarized as impacted third molars (both bony and soft tissue); teeth in which periodontal disease has been diagnosed and that will require mucosal flap surgery for treatment; unrestored endodontically treated teeth that are at high risk for traumatic fracture; teeth that have been surgically removed, endodontically treated, and reimplanted; teeth restored with dental implants; and teeth with root resorption secondary to orthodontic therapy. Supernumerary teeth and ossifications also must be evaluated.

After the dentition has been restored and appropriate surgeries have been completed, vulcanized, vacuum-form fluorine-applicator are home for home-care fluoridation application. These applicators provide two functions: First, they help to prevent xerostomia-induced dental caries through fluoridation into the tooth enamel and dentin. Second, the increased ambient fluoride levels on the tooth surface and the residual fluoride that remains in the oral cavity after each fluoride application reduces the level of oral bacteria and assists in microbial prophylaxis, which aids in the reduction of mucositis. In general, 0.04% stannous fluoride gel appears to be more effective than sodium fluoride 1.1%, as it reduces the levels of Streptococcus mutans, which causes caries.\(^\text{12}\) In the use of fluoridate applicators, Shenep et al.\(^\text{13}\) recommend that a 0.04% stannous fluoride gel be placed into the applicators and that these be placed on the teeth and allowed to remain there for 3 minutes. After 3 minutes, the applicators should be removed and the excess fluoride expectorated, and the patient should not be allowed to rinse, eat, or drink for 30 minutes. For the week before initiation and for weeks 1 and 2 of radiotherapy, we recommend using the fluocaril three times daily. This is in anticipation that we may discontinue fluoride therapy during the third, fourth, and fifth weeks of radiotherapy. For the first 3 months after radiotherapy, we recommend twice-daily fluoridation. After 3 months and a thorough dental assessment, if the plaque indices are below 5%, we will maintain the patient on once-daily fluoridation for life.

Before beginning radiotherapy, a protective radiation shield is fabricated. These shields are used during the radiotherapeutic sessions for all patients who have natural dentition. The purpose of the shield is to eliminate soft tissue contact with the surfaces of large dental restorations, thereby eliminating the secondary electron scatter from radiotherapy that will cause significant localized mucositis.

From the diagnostic examination and radiographs, the practitioner must ascertain whether the patient undergoing radiotherapy has had dental implants placed for prosthetic rehabilitation. Oral implantology is rapidly becoming commonplace in the prosthetic rehabilitation of missing teeth, support for cleft palate obturators, and support for facial mucoses and prostheses. If it has been determined that implants are present, the dental oncologist must be prepared to fabricate the appropriate radiation shields and blocks to protect the areas of the bone supporting the implants, to minimize increased radiation dosimetry in those portions of the mandible or maxilla.

Keus et al.\(^\text{14}\)\(^\text{14}\) reported on the effect of customized beam shaping on normal tissue complications in radiotherapy for parotid gland tumors. They evaluated a customized beam’s-eye view as opposed to unblocked portals with field sizes defined by the largest target contour found in any computed tomographic slice and found that the volume of unnecessary exposed normal tissue that received more than 90% of the prescribed dose was reduced by a factor of 4% to 44%, on average, when the volume is expressed as a percentage of the target volume in each patient. For a tumor dose of 70 Gy, the average bone necrosis probability was reduced from 8.4% to 4.1%.

As regards patients with extensive implant, supported, fixed or fixed removable prostheses, a very large volume of gold alloy is used in the fixed prostheses and in the framework of the fixed removable prostheses. For patients with dental implants, removal of the detachable portions of the prosthesis should be completed before radiotherapy, and beam-shaping blocks should be fabricated by the prosthodontist for protection of the mandible containing the titanium implant fixture. These precautions are necessary to reduce the risk of radiation-induced ORN.

OSTEORADIONECROSIS

ORN carries the greatest morbidity in any radiotherapy program involving osseous tissue. ORN is not an infection but nonhealing, acellular, avascular bone that may have been present for months or years before becoming clinically evident. Continuous monitoring of the radiotherapy patient by the dental oncologist on a 3-month recall basis is appropriate. This recall schedule will allow for evaluation of the plaque indices, monitoring of fluoride compliance, and maintenance of developing dental disease. Even with the best of diagnosis, planning, and staging, an osteonecrosis can develop spontaneously. Early osteonecrotic changes are subtle and difficult to detect. In many instances, ORN presents as asymptomatic dehiscence in the mucosa. As the necrosis progresses, the site can become more erythematous and painful. At this stage, it is not uncommon for the clinician to misdiagnose the signs as a minor infection and to place the patient on a regimen of antibiotics, which will minimize the symptoms but allow the necrosis to continue to progress. If teeth are present, the clinical symptoms are mobility, minimal to moderate pain, and ectopic eruption. In the early stages, routine dental radiographs are insufficient to provide an accurate diagnosis. As the necrosis advances, extracoral fistulas and intraoral antral fistulas will develop. Eventually, occlusion pathology becomes evident and, in many cases, pathologic fractures will occur.

Early definitive diagnosis using computed tomographic scans, denticans, bone density studies, and magnetic resonance imaging will aid in determining the extent of the necrosis so that a surgical template can be made. In very small, isolated, solitary lesions of less than 0.5 cm, surgical exposure and cautious debridement along with appropriate prophylactic antibiotics may suffice. This seldom is the case with ORN and, if remission and healing are not evident within the first 8 weeks, presurgical and postsurgical hyperbaric oxygen, intravenous antibiotics, and radical excision of the necrotic avascular bone will be necessary.

Myers and Marx\(^\text{15}\)\(^\text{15}\) reported on the use of hyperbaric oxygen, which stimulates angiogenesis, leading to increased neovascularization and optimization of cellular levels of oxygen for osteoblast and fibroblast proliferation, collagen formation, and support of ingrowing blood vessels. The hypoxic, acellular matrix in the postirradiated field is changed to a hypercellular, hyperoxic or normally oxygenated situation. Oxygen is used as an adjunct to appropriate surgical intervention; by use of these two modalities in combination, the salvage rate for ORN and its complications of orocutaneous fistula, pathologic fractures, and severe bone loss can be increased dramatically.\(^\text{16}\)

CONCLUSION

With accurate pretherapeutic diagnosis, appropriate treatment planning, and therapeutic staging by all members of the clinical team, the incidence of ORN and other oral complications can be minimized or eliminated. The medicolegal accountability, if such pretreatment protocols are not in place, is significant and economically burdensome. If pretreatment protocols are developed and followed, the salvage rate for ORN and its complications of orocutaneous fistula, pathologic fractures, and severe bone loss can be increased dramatically.

CHAPTER REFERENCES

16. Nagashima R, Yoshida N, Terasa N. Sulfadiazine, a basic aluminum salt of sulfonamide II. Inhibition of peptic hydrolysis as its results from sulfonamide interaction with protein substrate,
Pulmonary disease can be caused by a wide spectrum of pathogenetic mechanisms in patients with cancer. These include a variety of infectious agents and neoplastic disorders as well as pulmonary thromboembolic disease, pulmonary hemorrhage, pulmonary edema (cardiogenic and noncardiogenic), and leukocyte agglutinin reactions. Pulmonary toxicity caused by antineoplastic agents is being recognized more frequently, and the number of drugs known or suspected to cause lung disease is steadily increasing. Because continued use of the offending agent may cause death and because withholding the agent may result in resolution of the pulmonary toxicity, it is important to recognize radiation- and drug-induced pulmonary disease. In this section, parenchymal lung disease caused by irradiation and chemotherapy is discussed. Mechanisms of lung injury, histopathologic findings, clinical and laboratory features, and diagnosis and treatment of the abnormalities produced by radiation therapeutic and chemotherapeutic agents are reviewed.

RADIATION-INDUCED PULMONARY TOXICITY

MECHANISM OF LUNG INJURY

Radiation can affect dividing and nondividing cells and can cause genetic and nongenetic damage. In the lung, a hypothetical reconstruction of radiation injury might be as follows: Therapeutic radiation may result in nongenetic damage that is apparent in all cells, but capillary endothelial and type I cells (epithelial lining cells) appear to be most susceptible. Many of these cells, whether dividing or not, undergo early necrobiosis and slough. The apoptotic pathway appears to be an important mechanism of cellular destruction after radiation. Specific signal transduction pathways are activated by radiation, including sphingomyelinhydrolysis, which generates ceramide as a second messenger and leads to apoptotic DNA degradation. Nonlethal ionizing radiation also activates a stress response in cells, which leads to up-regulation of specific nuclear transcription factors such as NF-kB and transcription of such specific early-response genes as c-abl, c-jun, Egr-1, and c-fos. This cellular activation initiates a repair process that involves cytokines and growth factors such as basic fibroblast growth factor, as well as interleukin-1 and transforming growth factor-β (TGF-β). Prostaglandin synthesis is also up-regulated. Over time, capillaries regenerate, and the alveolar epithelium is repopulated by type II cells (surfactant-producing cells), because type I pneumocytes do not regenerate. Some of these type II cells redifferentiate into type I cells. If the initial injury is severe, extracellular matrix components of the lung, such as basement membrane glycoproteins and proteoglycans, are damaged. This can impede reconstruction of the delicate three-dimensional structure of the alveolar-capillary unit and result in functional derangement and scar formation, even if the cellular components are able to regenerate. Genetic damage to dividing cells, such as endothelial cells or type II pneumocytes, can also occur. Depletion of these cells may result during successive mitoses, causing a loss of integrity of pulmonary capillaries and exudation of fluid into the alveoli. At the physiologic level, loss of compliance, abnormal gas exchange, and respiratory failure can occur owing to leakage of plasma proteins into the alveolar space. This type of genetic damage may also explain why pneumonitis may be seen so late after radiation. One might speculate that some endothelial cells initially remain normal but that, in the course of the next four cell divisions, chromosomal aberrations prevent further reduplication, which leads to loss of integrity of the capillary.

Certain factors are critical to the development of classic radiation pneumonitis. In general, damage to the lung increases as the volume of lung tissue irradiated increases. There also appears to be a threshold effect, such that irradiation of at least 10% of the lung is required to produce significant pulmonary toxicity. This threshold may be reached in the treatment of some patients with breast cancer, depending on the specifics of their individualized treatment program. Also, the toxic effects of radiation, as measured by symptoms and signs, radiographic changes, and physiologic tests, are proportionate to the total amount delivered to the lung. Radiation pneumonitis after a single-dose whole lung irradiation shows a threshold level and a steep sigmoid dose-response curve. Radiation pneumonitis seldom occurs with fractionated total doses of less than 20 Gy but is highly likely when doses exceed 60 Gy. An unusual and dramatic demonstration of this principle is the use of therapeutic pneumonoxorax to protect the lung when high-dose external-beam radiation therapy is given for the treatment of chest wall tumors.

Because local control of lung cancer is greater when higher doses are delivered to the tumor, methods are being devised to give high doses to the target tissue while sparing normal surrounding lung. One such technique is called three-dimensional treatment planning. To spare the lung further toxicity, in situ isolated lung perfusion for the treatment of unresectable pulmonary tumors, preceded or followed by high-dose irradiation, soon may be available. Studies to evaluate the therapeutic activity of inhaled chemotherapeutic agents, such as doxorubicin, on metastasis to the lung are under way also. Whether these treatment modalities will have a sparing effect on the lung or whether they will be associated with an increase in pulmonary toxicity is unknown.

HISTOPATHOLOGY

The histopathologic changes of radiation-induced pulmonary toxicity can be divided into early, intermediate, and late stages based on the time course and intensity of the radiation injury. Early radiation damage (0 to 2 months after irradiation) is characterized by injury to small vessels and capillaries and subsequent development of vascular congestion and increased capillary permeability. At this stage, a fibrin-rich exudate is present in the alveolar spaces. Hyaline membranes form on the alveoli, probably from condensation of the intraalveolar fibrin. After 1 month, an inflammatory infiltrate also is present, which may lead to a second course of increased permeability. Abnormalities in the intermediate stage (2 to 9 months after irradiation) are characterized by obstruction of pulmonary capillaries by platelets, fibrin, and collagen. Alveolar-lining cells (primarily type II pneumocytes) become hyperplastic, and the alveolar walls become infiltrated with fibroblasts and mast cells. If the radiation injury is mild, these changes may subside entirely; however, when the injury is severe, a chronic phase (9 months or longer after irradiation) ensues that...
may persist or progress for months or years. In animal models, there is marked activation of genes that encode fibrillar collagen. The histopathologic appearance is dominated by dense fibrosis, thickening of the alveolar walls, vascular subintimal fibrosis, and luminal narrowing. In some instances, the lung may shrink to less than half its original size, with a thickened adherent pleura and scarred hilar structures.

In addition to this classic pattern of radiation pneumonitis, another syndrome of out-of-field pneumonitis, characterized by a hypersensitivity pneumonitis in areas of lung not directly irradiated, has been described. This syndrome, which occurs in a minority of patients, is characterized by a bilateral lymphocytic alveolitis of activated CD4+ T lymphocytes 4 to 6 weeks after strictly unilateral lung irradiation.

### CLINICAL FEATURES

#### Signs and Symptoms

The clinical syndrome of radiation pneumonitis develops in 5% to 15% of patients receiving high-dose external-beam radiation for treatment of lung cancer. Factors that can add to the development of radiation pneumonitis include concomitant chemotherapy, previous irradiation, and withdrawal of steroids. The incidence of radiation pneumonitis does not differ significantly between the young and the elderly, but the pneumonitis is inclined to be more severe in the latter group. Underlying chronic obstructive pulmonary disease does not appear to potentiate radiation damage.

Symptoms of acute radiation pneumonitis usually become evident 2 to 3 months after the completion of therapy; rarely, they occur within the first month and, occasionally, as late as 6 months after irradiation. In general, the early onset of symptoms implies a more serious and more protracted clinical course. The cardinal symptom of radiation pneumonitis is dyspnea. It may be self-limited or may progress to severe respiratory distress, depending on the extent and intensity of the injury. Patients may also have a nonproductive cough or a cough productive of small amounts of pinkish sputum. Frank hemoptysis early in the clinical course is distinctly uncommon; however, massive hemoptysis has been reported as a late complication of therapeutic pulmonary irradiation. Fever is unusual but can be high and spiking; in severe cases, other constitutional symptoms may occur. Chest pain, which is rarely a prominent feature, may be due to fractured ribs, pleural changes, or coughing. Symptoms of airway obstruction can occur in the first few days of radiation therapy and usually are associated with swelling of a central bronchogenic carcinoma. Severe respiratory distress can result and may be prevented by the administration of steroids the day before and several days after the initiation of radiation therapy. Hemoptysis and other manifestations of radiation pneumonitis may also occur in patients given palliative endobronchial brachytherapy or after surgical implantation of radioactive seeds.

On physical examination, signs of pulmonary involvement are minimal. Occasionally, moist rales, a pleural friction rub, or evidence of pleural fluid may be heard over the area of irradiation. In severe cases, tachypnea and cyanosis may be present and, occasionally, evidence of acute cor pulmonale appears, usually predicting a fatal outcome. Finger clubbing due to radiation is distinctly unusual and, if present, is most likely caused by the underlying malignancy. Skin changes corresponding to the ports of irradiation are often present but provide no clue as to the presence or severity of the pulmonary reaction beneath.

Although patients with acute pneumonitis may show complete resolution of signs and symptoms, most develop gradual, progressive fibrosis. In some cases, patients present with radiation fibrosis without a previous history of acute pneumonitis. The permanent changes of fibrosis evolve over 6 to 24 months but usually remain stable after 2 years. Patients with fibrosis may be asymptomatic or may have varying degrees of dyspnea. The major complications of radiation pneumonitis occur late in the disease and are secondary to persistent fibrosis of a large volume of lung. These include cor pulmonale and respiratory failure.

#### Diagnostic Imaging

Although radiographic abnormalities invariably are found concurrently with clinical radiation pneumonitis, these changes may be seen in asymptomatic patients as well. Early radiographic changes include a ground-glass opacification, diffuse haziness, or indistinct normal pulmonary markings over the irradiated area. Later, the chest radiograph may show alveolar infiltrates or dense consolidation with or without air bronchograms. As the pneumonitis progresses to fibrosis, the radiographic appearance changes to that of linear streaks radiating from the area of pneumonitis and of contraction toward the hilar, the perime diastinal, or the apical areas. Pleural effusions, if present, are usually small and always coincident with the pneumonitis. They can persist for long periods but often disappear spontaneously and never increase over a period of stability unless secondary complications occur, such as radiation-induced pericarditis. Mediastinal or hilar adenopathy and cavitation are almost always attributable to causes other than radiation pneumonitis. Pleuropneumothorax occasionally is associated with radiation fibrosis but not with acute pneumonitis.

One of the most characteristic features of radiation fibrosis and fibrosis is that the radiologic changes are confined to the outlines of the field of radiation. In a few cases, extensive changes outside the field, even in the contralateral lung, have been observed. This syndrome of out-of-field pneumonitis is thought to represent a hypervascularity response to the radiation. Other possible explanations for this phenomenon include obstruction of lymphatic flow from radiation-induced mediastinal fibrosis and absorption of x-rays by regions outside the irradiated ports.

Some data suggest that computed tomographic scans of the chest and gallium 67 citrate imaging are more sensitive than chest radiography in the detection of radiation changes. Correlation of abnormalities seen in these tests with the development of physiologic dysfunction and clinical toxicity requires clarification.

#### Pulmonary Function Tests

No gross physiologic changes occur in the lung until 4 to 8 weeks after completion of irradiation, usually coincident with the period of clinical pneumonitis. Then, one sees a decrease in lung volumes, which can progress. These changes persist indefinitely, with little evidence of recovery. Gas exchange abnormalities, which include a decrease in diffusing capacity and arterial hypoxemia, especially with exercise, occur about the same time but show some tendency toward recovery after 6 to 12 months. A fall in compliance coincident with the clinical pneumonitis is seen in most subjects. Accordingly, the elastic work of breathing is increased, and dyspnea, a result of the increased workload, ensues. Air flow parameters remain nearly normal in most studies.

### DIAGNOSIS

The diagnosis of radiation pneumonitis can sometimes be made clinically on the basis of the timing of irradiation in relation to symptoms and the typical chest radiographic appearance (i.e., infiltrates corresponding to the margins of the irradiated portal). Differentiation from recurrent malignancy or infection often poses a problem, and then lung biopsy is necessary. Although histopathologic changes are nonspecific for radiation pneumonitis, when elements of the acute stages (fibrin exudate in the alveoli) are seen adjacent to the more chronic stages (alveolar fibrosis and subintimal sclerosis), this entity can be diagnosed with reasonable certainty.

Biochemical markers that indicate radiation lung injury before the onset of clinical pathologic events would be valuable in the early diagnosis and management of patients with radiation toxicity. In irradiated animals, studies demonstrate that surfactant found in the serum may be a marker and predictor for later radiation pneumonitis. Prospective studies are needed in humans to identify the sensitivity and specificity of monitoring serum surfactant levels as an early means of diagnosing clinical radiation toxicity. Though no standard tests currently are used to monitor patients for radiation pneumonitis (because most methods have little predictive value), some reports suggest that soluble intercellular adhesion molecule-1 or transforming growth factor-β may be good candidates.

### TREATMENT

Three treatment modalities have been used, prophylactically and therapeutically, for radiation-induced pneumonitis: corticosteroids, antibiotics, and anticoagulants. Of these, corticosteroid therapy is the most important.

Corticosteroid administration during irradiation in mice markedly improves the physiologic abnormalities and decreases mortality. Without exerting an effect on late pulmonary fibrosis. No controlled clinical trials are available of the efficacy of steroid therapy in radiation pneumonitis in humans. Rubin and Casaret collected data from eight studies on humans and categorized them according to whether corticosteroids were used prophylactically or therapeutically. Corticosteroids given prophylactically failed to prevent radiation pneumonitis but, when administered as clinical pneumonitis occurred, these agents prompted an objective response. In other reports, steroid therapy failed to ameliorate severe pneumonitis. Nonetheless, our practice is to begin prednisone, 1 mg/kg, as soon as the diagnosis is
reasonably certain. The initial dose is maintained for several weeks and then reduced cautiously and slowly. It has been our experience that if steroids are tapered too rapidly, symptoms can be exacerbated, necessitating higher doses for longer periods. Similarly, if corticosteroids are part of a recent chemotherapeutic regimen, stopping them abruptly can precipitate clinically evident radiation pneumonitis. Which parameters, if any, to follow during the tapering schedule are not known, and no studies are available. Generally, decisions are based on the symptoms. Most authors agree that corticosteroids have no place in the treatment of radiation fibrosis.

In experimental and clinical reports, antibiotic administration has no effect on the course or outcome of radiation pneumonitis. Although there is some rationale for the use of anticoagulants in view of the effects of irradiation on the vascular system, neither heparin injections nor oral anticoagulants have been found to be beneficial. Captopril has been shown to be effective in animal studies, but no human trials have been reported. The mechanism of action of captopril in this setting probably is not its inhibition of angiotensin-converting enzyme. Pentoxyfylline also has some effects on the late phase of pneumonitis in animal models.

RADIATION-RELATED BRONCHIOLITIS OBILTERANS WITH ORGANIZING PNEUMONIA

Although bronchiolitis obliterans with organizing pneumonia (BOOP) is an unusual histopathologic pattern for drug-induced lung injury, radiation damage resulting in BOOP has been reported. Patients with lung cancer usually receive the highest doses of radiation to the largest volume of lung tissue, which makes them more susceptible to radiation injury as compared with other patients receiving irradiation. Most of the cases of radiation-related BOOP, however, have occurred in patients receiving radiation to the breast. Whether the low dose or indirect radiation that these patients receive makes them more susceptible to this type of lung injury is not known. Besides the unusual pathologic pattern in these irradiated patients, clinical and radiologic differences are evident, as compared to conventional radiation pneumonitis. Whereas dyspnea is the hallmark of radiation-induced lung injury, fever and cough are the predominant features of radiation-related BOOP. Radiographically, the infiltrates can begin in the radiated areas but always progress outside the portal and, in approximately 40% of the cases, the radiographic abnormalities were observed on the side contralateral to the irradiated breast. Although patients respond dramatically to corticosteroid therapy with no obvious endobronchial abnormalities, there is a 67% relapse rate when the drug is tapered or discontinued. As with conventional radiation-induced pneumonitis, no studies are available on the minimal effective dose or duration of therapy but, in view of the high relapse rate, it seems prudent to taper corticosteroid therapy very slowly, with meticulous vigilance for clinical signs of relapse.

To spare the lung the toxic effects of chemotherapy, several unique treatment modalities are now being investigated. These include isolated lung perfusion (one or both lungs) with doxorubicin for either metastatic disease or bronchoalveolar carcinoma. In one study, six patients received the perfusate and, although no major responses were observed, the patients tolerated the procedure well and five of the six did not have any serious complications. Antitumor efficacy in mice and dogs has been observed with inhaled chemotherapeutic agents; clinical human testing now is under way in patients with metastatic lung disease using doxorubicin via nebulization.

CHEMOTHERAPY-INDUCED PULMONARY TOXICITY

The list of chemotherapeutic agents reported to cause cytotoxic drug-induced lung disease continues to grow (Table 55.3-1). Recently added agents are docetaxel and gemcitabine. An overview of the potential mechanisms of lung damage, a summary of the pathologic findings, and common clinical features of pulmonary toxicity are discussed in this section. Characteristics of pulmonary disease caused by some of these drugs are presented.

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<th>MECHANISMS OF PULMONARY INJURY</th>
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| The details of the pathophysiology of specific chemotherapeutic agents, except for bleomycin, generally are not known; however, several mechanisms of pulmonary toxicity mediated by these agents have been proposed. Certain cytotoxic drugs may induce pulmonary injury by triggering the formation of reactive oxygen metabolites, including the superoxide anion, hydrogen peroxide, and hydroxyl radicals, primarily from activated neutrophils. Bleomycin induces reactive oxygen radicals by forming a complex with Fe2+. Consistent with a direct pathologic role for this mechanism, iron chelators ameliorate the pulmonary toxicity of bleomycin in animal models. Reactive oxygen species can produce direct toxicity through participation in redox reactions and subsequent fatty acid oxidation, which leads to membrane instability. Oxidants can cause other inflammatory reactions within the lung. For example, the oxidation of arachidonic acid is an initial step in the metabolic cascade that produces immunologically active mediators, including prostaglandins and leukotrienes. Cytokines such as interleukin-1, macrophage inflammatory protein-1 (MIP-1), monocyte chemoattractant protein-1 (MCP-1), and TGF-β are released from alveolar macrophages in animal models of bleomycin toxicity.

Cytoxic drugs can alter the normal effector and suppressor balance, which may cause tissue damage. Other homeostatic systems within the lung can be affected as well, such as the balance between collagen formation and collagenolysis. Through modulation of fibroblast proliferation and phenotype, excessive collagen deposition may result in severe, irreversible pulmonary fibrosis. Bleomycin is one cytotoxic agent that has this potential. In addition, bleomycin may up-regulate collagen synthesis in fibroblasts by stimulating transcription directly through a TGF-β response element in the procollagen (I)α promoter as well as by an autocrine loop involving extracellular release of TGF-β. Mast cells may also be involved in the inflammatory and fibrotic process. Imbalance between the protease and antiprotease system has been implicated as well in a number of pulmonary disorders, including drug toxicities. Bleomycin and cyclophosphamide produce substances that can inactivate the antiprotease system, enhancing the effects of proteolytic enzymes on the lung. Bleomycin also causes profound effects on the fibrinolytic system, altering the balance between fibrin deposition and fibrinolysis on the alveolar surface, leading to fibrin deposition. Drugs may damage the lung through a variety of other mechanisms, and considerable investigation should be done to define and clarify the exact mechanism of lung injury for each chemotherapeutic drug.

One of the potential determinants of bleomycin toxicity is the cytoplasmic cysteine proteinase bleomycin hydrolase, which is the major enzyme responsible for metabolizing bleomycin to a nontoxic molecule. In animal models, bleomycin hydrolase knockout mice are highly susceptible to bleomycin toxicity. The two organs that are the most common targets for bleomycin toxicity—lung and skin—harbor the lowest levels of the enzyme. With the cloning of the human gene encoding bleomycin hydrolase, studies are needed to determine whether genetic variability of this enzyme can account for increased individual susceptibility to bleomycin pulmonary toxicity.

HISTOPATHOLOGY

The histopathologic changes of drug-induced pulmonary toxicity demonstrate common features. Similar to radiation-induced damage, abnormalities are seen in endothelial and epithelial cells. The vascular damage is characterized by endothelial swelling with exudation of fluid into the interstitium and the intraalveolar spaces. There is destruction and desquamation of type I pneumocytes, with proliferation of type II pneumocytes. Mononuclear cell infiltration and fibroblast proliferation with...
fibrosis are common findings; the character of the inflammatory cellular infiltrate may be a feature that distinguishes the toxicity of one drug from another. Bronchoalveolar lavage studies in patients with methotrexate pulmonary toxicity have shown the presence of a T-lymphocytic alveolitis, whereas studies on some patients with bleomycin toxicity have revealed a polymorphonuclear alveolitis. Eosinophil infiltration has been associated with drugs that cause apparent hypersensitivity reactions, such as methotrexate, procarbazine, and bleomycin.

**CLINICAL FEATURES**

Table 55.3-2 lists predisposing factors associated with enhancement of drug-induced pneumonitis. Because bleomycin toxicity is relatively common, it warrants special mention. Although it drastically increases with doses in excess of 450 to 500 mg, toxicity can occur with much lower doses, especially when other risk factors are present. One study described 9 of 45 patients (20%) who developed lung toxicity when they received bleomycin after cisplatin infusion. Renal damage after cisplatin administration, with subsequent accumulation of bleomycin, was a likely cause of the high pulmonary toxicity and mortality rate of 67%. Extreme caution is recommended in the administration of combined bleomycin and cisplatin chemotherapy; if possible, bleomycin should precede cisplatin infusion to minimize the risk of lung toxicity. Some data suggest that continuous infusion of bleomycin may be associated with less pulmonary toxicity than bolus therapy; however, these data are inconclusive, and further studies are warranted. Supplemental oxygen is a classic cofactor in bleomycin pulmonary toxicity. An increased risk of pulmonary toxicity (4 of 12 patients, fatal in 75%) was described in a small, uncontrolled study of patients receiving granulocyte colony-stimulating factor in combination with bleomycin-containing combination chemotherapy [BACOP (bleomycin, Adriamycin, cyclophosphamide, Oncovin, prednisone)] for non-Hodgkin’s lymphoma. However, larger studies have not confirmed any increased risk of bleomycin toxicity with the use of granulocyte colony-stimulating factor.

**Table 55.3-2. Factors Associated with Increased Risk of Drug-Induced Pneumonitis**

The interest in administration of several cycles of high-dose chemotherapy followed by peripheral stem cell rescue for treatment of breast cancer and lymphoma has led to reports of pulmonary toxicity of agents not previously thought to be highly toxic to the lung, such as etoposide. Importantly, careful studies of pulmonary function after high-dose chemotherapy containing cyclophosphamide, cisplatin, and carmustine [1,3-Bis(2-chloroethyl)-1-nitrosourea (BCNU)], followed by autologous bone marrow transplant, for treatment of breast cancer show a delayed drop in diffusing capacity averaging 30% by week 18. The majority of patients were asymptomatic with dyspnea, and responded well to systemic corticosteroids. More of this type of toxicity can be anticipated in the future as this treatment modality becomes more common and new regimens for high-dose chemotherapy are studied.

Long intervals between drug administration and onset of clinical toxicity have been described. Late-onset pulmonary fibrosis has been reported many years after discontinuing cyclophosphamide and carmustine.

**Signs and Symptoms**

The cardinal symptom of drug-induced pulmonary toxicity is dyspnea. Nonproductive cough, fatigue, and malaise are other commonly associated complaints. Other characteristics of chemotherapeutic-induced pulmonary disease are outlined in Table 55.3-3. Although symptoms usually develop over a period of several weeks to months, hypersensitivity drug-induced lung disease can develop over hours. Fever may be a common finding with this type of toxicity. Chest pain has been reported during infusion of bleomycin or immediately after therapy with methotrexate; however, it is an unusual manifestation of toxicity. A syndrome of acute dyspnea, probably due to acute direct toxicity to the pulmonary vasculature, can occur during or shortly after vinca alkaloid infusion when given in combination with mitomycin; often it is not associated with systemic corticosteroids because bleomycin toxicity is relatively common, it warrants special mention. Although it drastically increases with doses in excess of 450 to 500 mg, toxicity can occur with much lower doses, especially when other risk factors are present. One study described 9 of 45 patients (20%) who developed lung toxicity when they received bleomycin after cisplatin infusion. Renal damage after cisplatin administration, with subsequent accumulation of bleomycin, was a likely cause of the high pulmonary toxicity and mortality rate of 67%. Extreme caution is recommended in the administration of combined bleomycin and cisplatin chemotherapy; if possible, bleomycin should precede cisplatin infusion to minimize the risk of lung toxicity. Some data suggest that continuous infusion of bleomycin may be associated with less pulmonary toxicity than bolus therapy; however, these data are inconclusive, and further studies are warranted. Supplemental oxygen is a classic cofactor in bleomycin pulmonary toxicity. An increased risk of pulmonary toxicity (4 of 12 patients, fatal in 75%) was described in a small, uncontrolled study of patients receiving granulocyte colony-stimulating factor in combination with bleomycin-containing combination chemotherapy [BACOP (bleomycin, Adriamycin, cyclophosphamide, Oncovin, prednisone)] for non-Hodgkin’s lymphoma. However, larger studies have not confirmed any increased risk of bleomycin toxicity with the use of granulocyte colony-stimulating factor.

**Table 55.3-3. Characteristics of Pulmonary Disease Caused by Commonly Used Chemotherapeutic Agents**

All-trans-retinoic acid treatment of acute promyelocytic leukemia induces a distinct syndrome of respiratory distress, which are thought to be mediated by newly differentiated leukemic cells that are migrating into the pulmonary circulation, thereby increasing capillary permeability and releasing cytokines that induce neutrophil migration into the interstitium. High doses of corticosteroids are the most effective treatment. Steroid prophylaxis of this syndrome has been reported to be useful.

Paclitaxel (Taxol) and Docetaxel (Taxotere) cause bronchospasm and, in some cases, frank anaphylaxis or pulmonary edema, probably on the basis of a hypersensitivity reaction to the solvent needed to dissolve these agents. Prophylaxis with corticosteroids, administration of H₂-receptor histamine blockers, and slowing of the infusion rate are effective in reducing the incidence and severity of these reactions.

**Diagnostic Imaging**

The most common radiographic abnormality associated with drug-induced pulmonary toxicity is a reticulonodular pattern, which may be basilar or diffuse. Pleural effusions are uncommon but have occasionally been reported in association with mitomycin, busulfan, methotrexate, and procarbazine toxicity. Hypersensitivity lung disease associated with methotrexate and procarbazine may present with bilateral acinar infiltrates that clear rapidly. In some instances, the chest radiograph is normal, even in the presence of histologically proved pulmonary infiltration and fibrosis.
Pulmonary Function Tests

The most common abnormalities associated with chemotherapy-induced pulmonary toxicity are a reduced diffusing capacity for carbon monoxide and a restrictive ventilatory defect. Isolated gas transport abnormalities, manifested by a decrease in the diffusing capacity or arterial hypoxemia, especially with exercise, have been seen. Screen pulmonary function tests to predict which patients receiving chemotherapy are likely to develop toxicity would be helpful but have not been established for most pulmonary toxic agents. In bleomycin toxicity, changes in the diffusing capacity may be transient, whereas decreases in total lung capacity seem to correlate better with radiographic abnormalities.

DIAGNOSIS

Although one might have a high clinical suspicion of drug-induced pulmonary toxicity, lung biopsy is usually necessary for a definitive diagnosis. Because pathognomonic pathologic changes associated with drug-induced pneumonitis often are not present, a biopsy is necessary to exclude other specific diagnoses, such as opportunistic infection and malignancy. Through the use of bronchoalveolar lavage, several studies reported the presence of a characteristic or predominant cell associated with particular drugs. Although the use of radiographs might be of value in understanding the pathogenesis of drug-induced lung disorders, their usefulness in diagnosing drug-induced toxicity is limited.

A serum marker for drug-induced pulmonary toxicity would be very useful. Though such a serum marker does not currently exist, initial studies of serum collagen type III N-propeptide in patients receiving neoadjuvant preoperative mitomycin, vincristine, and cisplatin for stage III non–small cell lung cancer appear promising. This peptide is elevated in serum after bleomycin treatment, but it does not correlate with toxicity. Elevated levels of TGF-β in plasma after high-dose chemotherapy for breast cancer predicted an increased risk of pulmonary toxicity after autologous bone marrow transplantation.

TREATMENT

The most effective way to manage pulmonary toxicity associated with chemotherapeutic agents is to prevent it. Animal studies of bleomycin toxicity showed a beneficial preventive effect of diaz thiazide diuretics; no comparable human studies have been reported. If toxicity occurs, withdrawal of the offending agent is the cornerstone of therapy. Although no controlled trials in humans have systematically examined the efficacy of corticosteroids, a trial of these agents probably is warranted in most cases. The optimal dose and duration of therapy are not known; however, 1 mg/kg/day is usually initiated, with a slow and careful tapering schedule, because clinical deterioration after tapering has been reported.

One report described the case of a 23-year-old male patient who underwent transplantation because of lung transplantation 12 years after undergoing chemotherapy for acute lymphocytic leukemia. The use of lung transplantation in the treatment of advanced drug-induced pulmonary fibrosis should be considered in appropriate patients, as more experience with successful lung transplantation in this setting is accumulating.


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SECTION 55.4
Cardiac Toxicity

LAUREL J. STEINHERZ
JOACHIM YAHALOM

INTRODUCTION
The treatment of cancer has been vastly improved by the expansion of chemotherapeutic agents and refinement of radiotherapy over the past three decades. However, many of the most effective antineoplastic agents and mediastinal irradiation produce toxic effects on the heart. This chapter describes some of these problems and discusses attempts at prevention and management.

CHEMOTHERAPY

ANTHRACYCLINES
The anthracyclines have been associated with cardiomyopathy since their introduction in the late 1960s. Early reports included isolated cases of unexplained cardiac failure in patients undergoing treatment with daunorubicin and, later, in the early 1970s with doxorubicin. Lefrak et al. reported a series in 1973 of 399 patients treated with doxorubicin. He found a 30% incidence of cardiac failure in the patients who received more than 550 mg/m² of doxorubicin, and a lower incidence in those who received less. This introduced the concept of increasing cardiotoxicity with cumulative doses above a safe threshold cumulative dose. In 1974, Halazun et al. reported a series of children with acute lymphoblastic leukemia, in remission, treated with two different maintenance protocols, one including and one excluding daunorubicin. There was a 10% incidence of cardiac failure in the patient with daunorubicin and none in the arm without. This report clearly demonstrated the relationship of anthracycline treatment to the incidence of cardiac failure, while it excluded the influence of active malignancy or the stress of induction therapy as contributory factors. Von Hoff et al. demonstrated, in 5613 patients treated with daunorubicin and doxorubicin, a 2% continuous, almost exponential increase of incidence of cardiac failure with increasing cumulative dose. Subsequently, Bristow et al. used endomyocardial biopsy to show that pathologic lesions progressively worsened in a linear relationship to the increase in total cumulative dose, in contrast to the nonlinear increase in myocardial dysfunction. This contrast suggested a threshold of tolerable myocardial damage beyond which the administration of additional drug would result in clinical symptomatology. Both clinical and pathologic abnormalities increased at any dose level in patients who received mediastinal radiotherapy.

Clinical Presentation
Anthracycline cardiomyopathy has been described as having three clinical presentations: acute, subacute, and late. The acute toxicity presents as a myocarditis and probably results from the combination of acute myocyte damage from drug exposure and the effects of the catecholamine and histamine surge provoked by the administration of anthracyclines. This occurs within days of a dose and includes transient arrhythmias, pericardial effusion, and myocardial dysfunction, sometimes leading to transient cardiac failure and occasionally death. Histologically, acute myocyte disruption and sometimes infiltration of the myocardium by granulocytes, lymphocytes, and histiocytes are seen.

The classic subacute presentation has a more insidious onset and appears from 0 to 231 days after the last dose (up to 30 months later), with a peak onset of symptoms at 3 months from the last dose. The clinical picture presents with increasing tachycardia and fatigue, progressing in some patients to tachypnea, dyspnea, and finally pulmonary edema, right-sided congestive signs, and low cardiac output. The mortality of patients actually manifesting congestive heart failure in these early series ranged up to 60%, although some patients could be stabilized with intensive cardiac treatment, and many showed remarkable improvement of cardiac function over the first few years after chemotherapy. However, evaluation of hemodynamics with exercise has revealed significant underlying abnormalities even in asymptomatic patients with normal resting parameters. The pathology noted on endomyocardial biopsy and autopsy within the first 2 years after completion of anthracyclines includes disruption and loss of myofibrils, mitochondrial swelling, and disruption of the sarcoplasmic reticulum producing intramyocyte vacuolization. With mild toxicity such damage is patchy, whereas with higher doses and toxicity it is found more extensively throughout the heart, with progression to myocyte necrosis and loss. Changes in children and adults are similar except for the more frequent appearance of lipid droplets within the myocytes of children younger than age 10. While some authors have reported the finding of infiltrates of T lymphocytes in biopsy specimens otherwise indicative of subacute anthracycline cardiomyopathy, classical a lymphocytic infiltrate is absent. The biopsy findings after treatment with anthracycline analogues have been similar.

Later pathologic examination, 41 to 47 months from chemotherapy, reveals hypertrophy of the remaining myocytes without fibrosis, and diminution of vacuolization, suggesting healing and compensation.

The late presentation of anthracycline cardiomyopathy has been described to occur 5 or more years after completion of anthracycline therapy. It involves late clinical decompensation of patients who had recovered from subacute cardiac symptoms (Fig. 55.4-1), or the occurrence of cardiac failure de novo in patients with no previous symptoms, 6 to 25 years after anthracycline therapy. It has also been demonstrated subclinically, as abnormal systolic cardiac function in 23%, abnormal myocardial mass in 52%, and abnormal exercise response in up to 80% of patients. While some authors have reported abnormalities of diastolic function others have found no significant diastolic changes. The conflicting results may reflect different sensitivity of different diastolic measurements used. As with subacute toxicity, an increased incidence of late abnormalities correlates with increasing cumulative dose of anthracycline received, and mediastinal irradiation is an additive risk factor. However, late...
abnormalities of resting echocardiography were found in patients treated with as little as 75 mg/m² of doxorubicin, and late abnormalities of exercise response were seen in 55% of patients treated with low cumulative doses (median, 263 mg/m²). A correlation of late cardiotoxicity with individual dose intensity has been reported. Abnormalities of myocardial mass are said, by some authors, to be more pronounced in patients treated in early childhood, implying a negative effect on myocardial growth. Abnormalities of systolic function did not correlate with age during chemotherapy. Measurements of systolic function and myocardial wall thickness deteriorate progressively with increasing time after anthracyclines as emphasized in reports including patients followed for more than 15 years after completion of anthracycline therapy. Serious arrhythmias have been identified in symptomatic and asymptomatic patients at late cardiac follow-up, including ventricular tachycardia and fibrillation and second-degree heart block. Several young patients with late cardiomyopathy have experienced sudden death up to 15 years after chemotherapy. The pathology found on biopsy and autopsy of patients with late cardiotoxicity is predominantly fibrosis and hypertrophy of remaining myocytes, with little remaining vacuolization. Thus, even asymptomatic patients who have been treated with anthracyclines need long-term cardiac follow-up, and new symptoms suggestive of arrhythmia and especially syncope need vigorous investigation. Cardiac status on noninvasive testing during the year after completion of therapy is predictive for the likelihood of late abnormality (Fig. 55.4-3) and indicates the advisable frequency of follow-up.

**Mechanisms of Pathogenesis**

An understanding of the mechanism of cardiotoxicity provides the basis for attempts at prevention. There are many mechanisms proposed and several may interact to cause the multiple sites of intracellular injury seen histologically. In the mitochondria, there is a deletion mutation of mitochondrial DNA that increases proportionate to the anthracycline dose (495 vs. 420 mg/m²). Abnormalities in systolic function did not correlate with age during chemotherapy. Adverse events were more pronounced in patients treated in early childhood, implying a negative effect on myocardial growth. Abnormalities of systolic function did not correlate with age during chemotherapy. Measurements of systolic function and myocardial wall thickness deteriorate progressively with increasing time after anthracyclines as emphasized in reports including patients followed for more than 15 years after completion of anthracycline therapy. Serious arrhythmias have been identified in symptomatic and asymptomatic patients at late cardiac follow-up, including ventricular tachycardia and fibrillation and second-degree heart block. Several young patients with late cardiomyopathy have experienced sudden death up to 15 years after chemotherapy. The pathology found on biopsy and autopsy of patients with late cardiotoxicity is predominantly fibrosis and hypertrophy of remaining myocytes, with little remaining vacuolization. Thus, even asymptomatic patients who have been treated with anthracyclines need long-term cardiac follow-up, and new symptoms suggestive of arrhythmia and especially syncope need vigorous investigation. Cardiac status on noninvasive testing during the year after completion of therapy is predictive for the likelihood of late abnormality (Fig. 55.4-3) and indicates the advisable frequency of follow-up.

**FIGURE 55.4-1.** The clinical course of a patient after subclinical anthracycline cardiotoxicity. The initial increase and then progressive decrease of her fractional shortening on echocardiography and increasing requirements for therapeutic support of cardiac function can be seen. Despite an early fractional shortening of 11%, she gradually improved over the first 6 years. She discontinued diuretics, achieved modest exercise tolerance, and completed high school. Her fractional shortening on echocardiography reached 30% 6 years posttherapy. However, 8 years postdoxorubicin she required increasing amounts of diuretics for recurrent edema. Ten years postchemotherapy she had progressive deterioration of exercise tolerance and fractional shortening despite increasingly intensive medical management. During the last 2 years she was found to have moderately frequent premature ventricular contractions but no syncope or runs of ectopic ventricular beats. She was deemed unsuitable for cardiac transplant. Finally at 20 years post initial diagnosis and 17 years after her last anthracycline dose, she developed a tachy-bradyarrhythmia leading to sudden syncope and cardiac arrest. CHF, congestive failure; RT, radiotherapy; VPCS, ventricular premature contractions.

**FIGURE 55.4-2.** The percent of patients found to have abnormal echocardiogram results at the time of long-term follow-up is illustrated. Despite a similar cumulative anthracycline dose (495 vs. 420 mg/m²), 38% of those followed 10 years or longer had decreased fractional shortening (FS) as compared with 18% of those followed less than 10 years (P < .004). More than 50% of the abnormalities (11 of 21) seen in the 10 year or longer group were moderate (FS = 21% to 24%) or severe (FS ≤ 20%), while the degree of abnormality was mild (FS = 25% to 28%) in 77% (20 of 26) of the abnormal patients with shorter follow-up.

**FIGURE 55.4-3.** An echocardiogram (ECHO) taken after completion of anthracycline therapy has prognostic implications for cardiac function on late follow-up (LTFU). Eighty-seven percent of patients who had normal fractional shortening on echocardiography taken during the year posttherapy remained normal at LTFU, whereas only 29% of patients who were even mildly abnormal on end therapy echocardiography were normal at LTFU (P < .0001). FU, follow-up; TD, total dose.
Prevention

MONITORING. Attempts at prevention of cardiomyopathy initially involved limitation of total cumulative dose below 450 to 550 mg/m². This limit was chosen to avoid the rapid increase in left ventricular cardiac function, in excess of 30% in heart rates not due to dose range. However, such a dose limitation was inadequate because of variability of individual tolerance. Therefore, therapy has been modified according to serial monitoring of cardiac status, by various means, to identify increasing risk of unacceptable toxicity. Monitoring of systolic time intervals and of electrocardiography (ECG) for QRS voltage loss or ST-T changes was too nonspecific or showed changes too late to detect prevention. Serial echocardiography has been helpful to identify changes in systolic and diastolic function, especially in children, in whom echo images are clearer and more easily measured. The fractional shortening is the most frequent parameter followed, although some groups focused on end-systolic wall stress and the relationship between wall stress and velocity of circumferential fiber shortening. Early trends of rate of decrease in fractional shortening, at cumulative doses, have been reported to predict of eventual cardiac findings at end therapy, higher cumulative doses. Changes in posterior wall thickness appear to be more useful in late follow-up than for monitoring during therapy. Digitized echocardiography, with calculation of velocity of wall motion, thickening, and velocity of change of left ventricular chamber size in systole and diastole have been employed to enhance sensitivity. Radionuclide cardiac angiography has been used by many authors to follow systolic and diastolic function, and specific guidelines for modification of chemotherapy on the basis of radionuclide ejection fraction in adults, proposed by Schwartz et al., have gained wide acceptance. Adherence to these guidelines decreased the incidence of cardiac failure from 21% to 3% in their study. The addition of measurements of contractility during exercise for comparison with those at rest has been suggested to further aid in most patients, but has been less helpful according to others. Recommendations for monitoring, including radionuclide studies and quantitation of pathologic damage by endomyocardial biopsy, have been offered by investigators from Stanford University Medical Center. However, these recommendations do not suggest monitoring until a cumulative dose of 450 mg/m² unless the baseline study is abnormal, the patient is older than 70 years of age, or has hypertension, other cardiac disease, or was receiving mediastinal irradiation. They will not identify early sensitivity in patients without those particular risk factors. Another format for monitoring, using a combination of echocardiography and radionuclide studies, was formulated by the multinstitutional Cardiology Discipline Committee of the Children's Cancer Study Group. These recommendations include cardiac evaluation before anthracyclines and further monitoring before every other course until a cumulative dose of 300 mg/m² and every course beyond this. Endomyocardial biopsy, which has proven to be safe and effective in experienced hands, with a complication rate of 1.5%, is suggested to clarify abnormal or equivocal results.

Although not yet included in routine current monitoring, several newer modalities have been used for detection of toxicity. Tantulum 178 first-pass radionuclide imaging has allowed calculation of both right and left ventricular systolic function. Indium-111-antimyosin scintigraphy has been a monoclonal antibody labeled with 11In that binds with cardiac myosin, which becomes exposed when cardiac myocytes are injured. Increasing uptake of 11In during anthracycline therapy would imply increasing cardiac damage. Abnormalities of uptake of 11In have been seen before a decrease in radionuclide ejection fraction and could be used to compare different methods of administration of anthracyclines. This method was also reported to discriminate patients with sustained cardiotoxicity from those with transient decreases in ejection fraction or myocardial metastasis. In studies in rats, the amount of cardiac 11In uptake correlated with both histologic changes and end-diastolic pressure, and there was specific immunolocalization of the radioracer in injured myocytes as opposed to normal neighboring ones microscopically.

Another radionuclide, radiolabeled metadobenzylguanidine (111m-MIBG), has been used to identify early anthracycline cardiotoxicity. MIBG is an analogue of noradrenaline and reflects cardiac adrenergic neural function that is disrupted with anthracycline damage. Animal studies and clinical trials demonstrated abnormalities of uptake and clearance of MIBG even before abnormalities of systolic and diastolic function are seen by echocardiography. These MIBG abnormalities were proportionate to severity of systolic dysfunction in patients with toxicity.

Position emission tomography has been used to identify metabolic changes suggesting cardiac damage in patients receiving chemotherapy. Nuclear magnetic resonance spectroscopy has also demonstrated metabolic changes that correlate with the amount of doxorubicin-induced degeneration of myofibrils microscopically.

Reports on the usefulness of monitoring serum levels of troponin T postmyocardial infarction, to detect limited myocardial necrosis, prompted investigation of this method’s usefulness to detect early anthracycline damage. Although animal study results seem promising, clinical trials are still in progress. Therefore, this method remains investigational and is not yet recommended for routine monitoring. Some investigators have reported that elevated serum natiuretic peptide, which is released in response to chronic or acute increase in atrial transmural pressure and stretch, may be a marker for anthracycline damage.

Schwartz et al. correlated prolongation of the corrected QT interval (QTc) on 12-lead ECG with increasing anthracycline dose in both acute and chronic anthracyline cardiomyopathy. Careful attention to concomitant electrolyte and calcium imbalance is clearly mandatory to avoid false results. Jakacki et al. suggested an algorithm combining measurement of QTc with fractional shortening on echocardiography and a history of exercise intolerance for screening. Another new signal from stress-averaged ECG, that of ventricular late potentials, may also have predictive value.

SCHEDULE MODIFICATION. Other attempts to prevent cardiomyopathy involve decreasing the peak dose of anthracycline delivered to the heart by modification of schedules of delivery. Legha et al. demonstrated that patients receiving continuous infusions of doxorubicin developed lower peak plasma levels of the drug than patients receiving the drug by 20-minute bolus. Thus, levels with a 48-hour infusion were lower than with a 24-hour infusion and a 96-hour infusion of the same dose per course produced still lower levels. They proved by comparing endomyocardial biopsy scores in patients receiving doxorubicin that patients receiving their dose by 48- or 96-hour infusion had significantly lower biopsy scores, indicating less cardiomyopathy than patients receiving the dose by 20-minute bolus. In addition, the patients receiving 96-hour infusions had lower biopsy scores than those receiving 24-hour infusions. Infusions were administered through an indwelling intravenous line using a 2-L system. Currently, this technique is usually given through a surgically implanted central venous access device. A study by Shapira et al., using radionuclide cardiac angiography to evaluate cardiotoxicity, demonstrated a decline in left ventricular ejection fraction (LVEF) of only 6% after a total cumulative dose of 400 mg/m² administered by only 6-hour continuous infusion, compared with a decrease of 21% in patients who received the same range of total doxorubicin dose by 20-minute bolus. Carpenter et al. confirmed the cardioprotective effects of 72-hour infusion in a prospective randomized trial of 82 patients with soft tissue sarcoma. The article suggested, however, that continuous infusion might have a negative effect on antitumor efficacy, although this was not conclusive since their infusion patients had tumors with worse prognostic features than their bolus patients. Other uncontrolled trials using continuous infusion for various solid tumors have shown no decrease in efficacy. Reports of prospective randomized trials comparing infusion with bolus for treatment of leukemia, in which efficacy can be measured by percent cell kill on bone marrow sampling, and in osteogenic sarcoma in which it is measured as histologic response of the surgically resected tumor or after preoperative chemotherapy, have shown no significant decrease in antitumor efficacy with continuous infusion. In fact, in the leukemia study, efficacy was better with infusion. Schedules dividing the planned monthly doxorubicin dose into smaller weekly dosages have also decreased pathologic and physiologic abnormalities, allowing higher cumulative doses to be given.

Cardioprotective Agents

Free radical scavengers vitamin E, ascorbic acid, N-acetylcysteine, and others have shown promise in animals but no clear benefit in patients, although results of one study in rats using the lipoid-lowering antioxidant agent probucol seem encouraging. Similarly, trials of concomitant administration of verapamil, propranolol, other calcium channel blockers, and adrenergic and histamine blockers have not yet proven definitively useful in patients. Studies are ongoing examining the usefulness of coenzyme Q10 and amifostine. Encapsulation of the anthracycline in liposomes and binding to aggregase were initially disappointing. However, the use of more stable liposomal complexes has provided some protection.

Attempts to exploit the importance of the iron-doxorubicin complex appear to be more successful. The classic chelator deferoxamine did not prevent anthracycline cardiomyopathy in normal as opposed to iron overloaded cardiac cells. However, 1,2-bis(3,5-dioxygenaprazil-1-yl) propane, known as ICRF-187, ADR-529, or dexrazoxane and commercially as Zinecard or Cardioxane, an iron chelator that achieves better intracellular concentration, has been shown in various animals, and several human studies to exhibit provide significant protection against anthracycline cardiomyopathy. Animal studies have demonstrated healing of lesions within 3 months after discontinuation of therapy in rabbits treated with ICRF. Initial clinical trials included a pilot study of 12 patients with various solid tumors and a randomized therapeutic trial in women with breast cancer. Patients were evaluated both by radionuclide ejection fraction and myocardial biopsy. Incidence of clinical toxicity, degree of decrease of ejection fraction, and biopsy score were significantly less in the ICRF arm. These results have been confirmed in a large...
multicenter trial, in adults with breast cancer using fluorouracil, doxorubicin, and cyclophosphamide (FAC), and small cell lung cancer, using similar cardiac monitoring, 154,155 and 156 Smaller trials have been equally promising in pediatric patients. 135,136 and 137 The multicenter adult trial 138,139 and 140 larger pediatric trials 141 have also attempted to evaluate the impact of ICRF on antimalignant efficacy, which seems, in most cases, to be preserved. 141 Investigators had hoped to combine the protective effects of infusional doxorubicin and concomitant ICRF. To that end, studies of infusional ICRF are in progress. 144

This agent appears to also provide cardiac protection for anthracycline analogues such as epirubicin 145,146 and mitoxantrone. 147 and 148

NEW ANALOGUES. Analogues of daunorubicin and doxorubicin have been studied in clinical trials. Many agents that appear to have decreased cardiotoxicity in animal studies and even in early clinical trials eventually have been found to have similar toxicity to the parent compound. Patients treated with zorubicin experienced cardiotoxicity that was additive to prior anthracycline toxicity and some developed cardiac failure. 149, 150 4’-Epi-doxorubicin is another analogue with similar cardiotoxicity to doxorubicin. Incidence of atrioventricular block, ventricular fibrillation, decreased ejection fraction, and decreased velocity of circumferential fiber shortening 151 have been reported in phase I and II trials with another analogue, aclacinomycin. Demethoxy daunorubin (Idarubicin) has shown activity in patients whose malignancy has become resistant to daunorubicin. However, it is also cardiotoxic. 152,153 Its myelotoxicity is approximately four times that of daunorubicin milligram for milligram. When given in amounts of equivalent myelotoxicity, the cardiotoxicity is also similar. 154,155 Thus, careful monitoring of this agent would be advisable if a cumulative dose decrease is done. Cardiac failure occurred in patients treated with the analogue and anthracyclines. A 5% drop in mean LVEF was noted at 240 mg/m² and a 10% drop at 480 mg/m² of this agent. 156 Another analogue of 4’-deoxy-4’-ido-doxorubicin indicate acute and chronic cardiotoxicity but possibly less than daunorubicin. 157 The ideal anthracycline has not yet been found.

Management

Clinical anthracycline cardiomyopathy needs to be managed with inotropic support and afterload reduction, 158 often initially by the intravenous route. Angiotensin-converting enzyme inhibitors have played an important role in stabilizing cardiac failure and delaying further myocardial deterioration. 159 Current reports suggest that selective b-receptor blockers, such as metoprolol, 160 and more recently carvedilol, 161 may be useful in patients who do not improve with these modalities. Control of malignant arrhythmias may require intensive medical management with drugs such as amiodarone and mexiletine or placement of indwelling automatic cardioverters and pacemakers. 162,163 Most patients can be stabilized and show clinical improvement. Patients who have been refractory to treatment or have repeat bouts of pulmonary edema are free of malignancy have benefited from cardiac transplantation. 164,165,166

MITOXANTRONE

Mitoxantrone hydrochloride is an anthracenedione that is similar in structure to doxorubicin. It was found to be toxic to cardiac cells in culture despite a lack of production of free radical peroxidation. 167 The toxicity appeared to involve an interaction with iron similar to that of doxorubicin. 168 Animal studies revealed conflicting findings in different species. There were ECG abnormalities in treated monkeys and dose-related impairment of contractility in the rabbit heart, 169 but no ECG changes or left ventricular contractile abnormalities were found in the dog heart. 170,171 There were also cardiac biopsy changes (interstitial fibrosis and myocardial hypertrophy), 172,173 and supraventricular) reported from the early phase I and II trials under the auspices of the National Cancer Institute. 173,174 The incidence of myocardial dysfunction and cardiac failure increased with increasing cumulative dose as with doxorubicin. 175,176 Significant decreases in ejection fraction occurred in these trials around 110 mg/m² 175 and a rapid increase in incidence of cardiac failure was noted at 160 mg/m². 177 Later studies have continued to detect cardiomyopathy and cardiac failure in patients with and without prior anthracyline therapy, and conductions delay, with prolongation of PR, QRS, and QT interval on ECG, was also reported. 178 A British patient trial reported a 46% incidence of abnormal LVEF, using radionuclide angiography during rest and cold pressor stress, in patients who received a wide range of doses. 179 A Greek cooperative study found decreases in ejection fraction of greater than or equal to 10% within normal range, in 10% of patients tested, and they reported minimal changes in echo systolic function and significant changes in systolic time intervals in the patient cohort as a whole, after receiving 60 mg/m² combined with cyclophosphamide and fluorouracil. 180 An Italian trial reported ECG abnormalities in 41%, echocardiographic abnormalities in 66%, and a greater than or equal to 15% decrease in radionuclide LVEF in almost 25% of patients receiving a cumulative dose of 28 to 84 mg/m². 181 The overall incidence, reported by ImmuneX Laboratories, of subclinical moderate to serious decrement in LVEF was 13%, and the incidence of cardiac failure, up to a cumulative dose of 140 mg/m², was 2.6%. 182

AMSACRINE

AMSACrine (AMSMA) is an acridine derivative used mainly in nonlymphoblastic leukemia. It has been associated with myocardial infarction 183 and ventricular and supraventricular arrhythmias including fatal ventricular fibrillation. 184,185,186,187 Many of these arrhythmias have been attributed to coexisting electrolyte abnormalities, particularly hypokalemia, and more recently AMSA has been safely administered even to patients with preexisting atrial 188 and ventricular 189 arrhythmias. Noninvasive monitoring of cardiac function during a prospective study of AMSMA revealed reversible abnormalities on serial echocardiography in 18 of 27 patients and cardiac failure in 7 of 27 patients. 184,185 Echocardiographic abnormalities generally appeared with in a week of AMSA therapy and resolved in most, once therapy was discontinued. Four patients died with persistent cardiac failure. The incidence of echocardiographic abnormalities was related to total dose of AMSA, rate of administration, and the total dose of anthracyclines previously received. No patient who received less than 200 mg/m² 190 AMSA in 48 hours, after having received less than 400 mg/m² of anthracyclines, had echocardiographic abnormalities. In contrast, all patients who received greater than or equal to 200 mg/m² of AMSA within 48 hours after having received greater than 400 mg/m² of anthracyclines exhibited echocardiographic abnormalities. 184 More recently, Arlin et al. treated 24 patients with preexisting myocardial dysfunction with AMSA greater than 200 mg/m²/48 hours and reported no occurrences of cardiac failure in this group. 191 Nine of the 10 patients whose ejection fraction was less than 55% at admission showed a significant increase in ejection fraction by more than 10%. It is not stated how soon after treatment the radionuclide angiograms were obtained. Therefore, it is possible that there were additional transient deficits that were not detected in this study. However, the absence of any clinical cardiac failure in these heavily treated patients is significant.

CYCLOPHOSPHAMIDE

There is still disagreement if doses of cyclophosphamide under 100 mg/kg/week contribute to cardiomyopathy, 192,193,194 and in our experience such doses do not. However, higher doses used for cytoreduction and immunosuppression before bone marrow transplantation can cause an acute hemorrhagic pancarditis. It was initially described in case reports, 195,196,197 animal studies, 198,199 and autopsies series 200 as involving a serosanguinous pericardial effusion, mural thickening with edema, and focal necrosis of the pericardial and epicardial myocardial capillary damage and myocardial infarction, and involving extravasation, and myelofibrosis of the pericardial surfaces. Reports of patient series 201,202 and 203 described the acute course, with onset during the first week posttreatment, peak toxicity at 7 to 9 days, and improvement over the next 3 weeks. Abnormal findings of diastolic dysfunction, small to moderate pericardial effusion, restrictive cardiomyopathy, and ventricular tachyarrhythmias, were found in more than one-half the patients. 202,203,204 The most frequent ECG change seen was decreased voltage, which did not necessarily correlate with impairment of function. 202,203,205 Abnormalities of T waves and ST segment and arrhythmias are seen, 202 including complete heart block and ventricular tachyarrhythmias. Some arrhythmias may be due to the infusión of the cryopreserved marrow graft. 206 The majority of patients remained asymptomatic. 202,203,207 Some had mild symptoms of fluid retention, edema, and tachypnea, and a few had an extremely fulminant course of cardiac failure shock and death that was resistant to even intensive treatment. Risk factors of previous anthracyline therapy and previous abnormal cardiac function were identified and the importance of dose and rate of delivery was stressed. 208,209 A weekly dose of 170 mg/kg over 4 days without anthracyclines and 120 mg/kg over 5 days after anthracyclines predicted risk for at least subtotal necrosis. More rapid delivery of 120 mg/kg over 24 hours produced fulminant cardiomyopathy in one patient. 210,211 Mildly symptomatic patients responded to diuretics and, if necessary, transient digitalization or intravenous inotropic agents. Those with the more fulminant course required prolonged intravenous inotropic support, respiratory assistance, and hemofiltration. 212 Pericardial drainage has not been helpful usually, although rare cases of true cardiac tamponade responding to pericardiocentesis have been reported. 213 In most cases the effusion can be managed with ampicillicins and corticosteroids. 214 To avoid this clinical cardiotoxicity, patients have been screened during the past decade with echocardiography or radionuclide studies to identify abnormal cardiac function and the pretransplant regimen adjusted for higher risk patients by administering the cyclophosphamide over additional days or using a preparative regimen without cyclophosphamide. A pretreatment radionuclide LVEF of less than 50%, 215,216 or even less than 55%, 217 has been correlated with increased risk of cardiotoxicity. 211,212,218,219 Studies have suggested that giving the cyclophosphamide by infusion or in smaller twice-a-day doses decreased the incidence of systolic dysfunction, although changes of myocardial mass were still seen. 220 Evaluation of patients' hemodynamics during exercise at least a year after transplant has shown significant abnormalities in children treated for malignancy before transplant with anthracyclines. However, the few children
with aplasiaemic, who had not received antecedent anacrines, were normal. 220

IFOSFAMIDE
Ifosfamide , an alkylating oxazaphosphorine related to cyclophosphamide, has been associated with atrial ectopy (including atrial fibrillation) and, less commonly, ST-T wave changes and bradyarrhythmia. These abnormalities were noted in patients who had received doses as high as 6.25 to 10.0 g/m² over 3 to 5 days.222 One series reported an incidence of congestive heart failure in 9 of 52 patients enrolled in a phase I trial of high-dose ifosfamide with other agents with autologous marrow transplantation.223 ECG abnormalities, negative inotropic effects, and pathologic myocardial damage were also found in animals who received high doses of ifosfamide.224 225

RETINOIC ACID
Trans-retinoic acid is an active agent for the treatment of acute promyelocytic leukemia. However, in more than 10% of patients, a syndrome is produced, known as RA syndrome, involving fever, dyspnea, pleural and pericardial effusion, pulmonary infiltrates, peripheral edema, and transient myocardial dysfunction and heart failure.226 The syndrome is especially prevalent during the first 2 weeks of therapy and has responded to dexamethasone.

TAXANES
Paclitaxel (Taxol) has been described as causing abnormalities of cardiac rhythm, conduction, and function. In preclinical studies, paclitaxel produced arrhythmias and slowing of beat frequencies of rat cardiac cells growing in vitro.227 Cases of clinically significant disturbances of cardiac rhythm and conduction were reported during phase I and II trials of this agent.228 Significant sinus bradycardia (heart rate, 30 to 50 bpm) was common, occurring in up to 29% of patients in a phase II trial for ovarian cancer.229 Several patients exhibited progressive although transient atrioventricular conduction delay from first-degree heart block, to complete heart block, to asystole.230 on continuous ECG monitoring during paclitaxel infusion as a single agent. Associated presyncope and syncope have been reported.231 requiring temporary pacing. Episodes of sustained and nonsustained ventricular tachycardia have been reported with the combination of paclitaxel and cisplatin.232 However, Markman et al. used this combination successfully in patients with significant preexisting cardiac risk factors.233 Since few of their patients had significant preexisting conduction disorders, it is still recommended that patients with arrhythmia or abnormal conduction be monitored with continuous ECG during paclitaxel administration. The combination of paclitaxel with doxorubicin for the treatment of breast cancer has resulted in an increased incidence of clinically significant deterioration of left ventricular function at a lower cumulative dose of doxorubicin. It has been suggested that this is due to interference between the two agents resulting in decreased elimination of the doxorubicin and that the cumulative doxorubicin dose should be limited to 340 to 380 mg/m² in this combination.234 Preliminary experience with the synergistic, issue doxetaxel (Taxotere) suggested similar potential for dysrhythmia; however, clinical trials have not shown cardiotoxicity of this agent or significant increase in doxorubicin toxicity when docetaxel and doxorubicin are combined.235

HOMOHARRINGTONINE
Homoharringtonine is an alkaloid from the Chinese Cephalotaxus. It is another drug that causes reversible atrioventricular block,236 ventricular ectopy,237 supraventricular tachycardia, and ST-T wave changes in animals238 and patients.239 It has also produced cardiac failure and hypotension, with vacuolar degeneration of the myocardium on pathologic examination.229 230

VINCristine and VINBLASTINE
Vincristine has been associated with cardiac autonomic dysfunction. One study demonstrated a loss of cyclic respiratory phase–related heart rate variation in nine children during vincristine treatment.243 Vincristine244 245 and vinblastine246 have also been associated with myocardial infarction. Angina pectoris was reported in up to 38% of patients during treatment with vinblastine combined with cisplatinum and bleomycin.247 Another study of the same combination, reported angina with infantile-ECG changes and apical akinesia occurring repeatedly, during multiple courses, in a 47-year-old patient with normal coronary angiography.248 This seemed to clearly implicate the chemotherapy as the cause.

MitoMYCIN C
Mitomycin C has been reported to increase the incidence of anthracycline cardiotoxicity when these agents are combined249 due to enhancement of formation of superoxide and hydrogen peroxide.250 It has more recently been described as a cause of acute congestive heart failure in a woman who received a cumulative dose of 225 mg/m² of mitomycin as a single agent229 and in another patient when 30 mg/m² of mitomycin was added to treatment with 150 mg/m² of doxorubicin.251 The overall incidence of cardiotoxicity is said to be under 10% and limited to patients receiving a cumulative dose of at least 30 mg/m².252 253

5-FLUOROuRAcIL
The cardiotoxicity of 5-fluorouracil was first identified by Dent and McColl in 1975.20 A survey of 1083 patients in 1982 reported cardiotoxicity in 1.1% of all patients, and 4.6% of patients with prior evidence of heart disease.254 By 1990 there were more than 67 clinical cases described.255 Since then, more frequent use of continuous infusion 5-fluorouracil has increased awareness of the problem, and more sophisticated monitoring has increased the reported incidence. Thus, by 1991 another large cooperative series of 1145 patients included 31 patients with cardiac symptoms including four cardiac deaths, an incidence of almost 3% of all patients.256 An even higher incidence of cardiotoxicity of 5.6% was reported from a prospective study of high-dose continuous infusion in 1992.257 An incidence of silent ischemic ECG changes, as high as 68%, was identified in patients monitored by continuous 24-hour ambulatory ECG during fluorouracil infusion.258 The cardiotoxicity described has involved (1) precordial pain (both nonspecific and anginal),259 (2) ECG ST-T wave changes (nonspecific and ischemic),260 261 262; (3) acute myocardial infarction (rare)263 264 and 265; (4) atrial arrhythmias (including atrial fibrillation) and, less frequently, ventricular ectopy (including refractory ventricular tachycardia and fibrillation),266 267 268 269 270 and 271; (5) ventricular dysfunction (usually global, less frequently segmental); (6) cardiac failure; pulmonary edema; and cardiogenic shock (with and without ischemic symptoms)272 273 274 275 276 and 277; and (7) sudden death.278 In most cases the arrhythmias were treatable and the ischemia-like symptoms and ECG changes disappeared if the infusion was discontinued, or responded to nitrates, allowing the infusion to continue. The abnormalities of segmental and global ventricular function reverted to normal within days to weeks of cessation of infusion. However, some patients needed intravenous inotropic and vasodilator support during the initial period.279 280 and 281 282. In most cases with chest pain with or without ECG changes, the creatine phosphokinase (CPK) MB fraction remained normal.283 284 285 286 287 Most frequently, patients developed cardiac toxicity during the second or later course of treatment, but some experienced problems during the first course.288 Those who developed cardiac toxicity and recovered, usually had symptoms again when rechallenged with another infusion.289 290 Some investigators reported success in preventing cardiotoxicity with calcium blockers such as nifedipine and diltiazem,291 whereas others had less success.292 There was no influence of age or sex on incidence.293 Symptoms were reported in a 38-year-old man294 and several women in their 40s295 296 297 298 with no prior cardiac history. Cardiac findings have occurred when 5-fluorouracil was given by infusion or bolus, as a single agent, or with cisplatin and other drugs.299 300 While some believed that cardiac irradiation202 and preexisting heart disease298 301 were risk factors, others did not.302 303 Several investigators have documented normal coronary arteries in patients with severe symptoms.304 One investigator excluded increased proclivity for coronary vasospasm by challenging a patient, who had previous angina during fluorouracil infusion, with ergonovine during a posttreatment coronary study.305 Findings on autopsy and endomyocardial biopsy have shown diffuse, interstitial edema, intramyocardial vaculization of myocytes, and no inflammatory infiltrate.306 Acute infarcts have been demonstrated pathologically in some, but not all, patients with clinical infarction.307 308

The ischemic-like pain and ECG findings, with lack of CPK MB changes, with frequent response to nitrates and at times to calcium channel blockers, in the setting of arteriographically normal coronary angiograms plus reversible contractility deficits, would suggest coronary vasospasm as a mechanism for fluorouracil cardiotoxicity. However, the global dysfunction, possibly due to stunned myocardium, and lack of universal response to coronary vasodilators leaves some questions about this hypothesis and some postulate a myocarditis or myocardialopathy etiology.309 310 311

Although the mechanism is still uncertain, it seems clear that careful observation for cardiac symptoms and arrhythmias is warranted during drug infusion, especially
CISPLATIN

Cisplatin has been associated with arrhythmias such as atrial fibrillation \[262\] and with angina and ST-T wave changes on ECG.\[262,264,267\] and \[269\] These may be caused or exacerbated by electrolyte imbalances from the excessive hydration and forced diuresis required for the drug’s administration.

INTERFERON

Cardiotoxicity has been identified in 44 of 432 patients from 15 phase I clinical trials of interferon-a, a, a, b, and g.\[317\] Significant abnormalities of cardiac rhythm and conduction,\[317\] ischemia and infarction,\[275,277,278\] and cardiomyopathy\[275,277,278\] were observed. These problems were identified with all types of interferon used except interferon-b, which was used in only a small subset of the patients.\[261\] No correlation with patient age, individual dose, or cumulative dose was identified although some patients had less toxicity when retreated at doses lower than the dose producing toxicity.\[275,277\] Cardiomyopathy was seen in patients after more prolonged treatment,\[261\] but the other forms of toxicity were seen frequently during the first 5 weeks of treatment, even within 1 to 7 days of initiation of therapy.\[261\] The occurrence of ischemia and infarction was definitely related to a prior history of ischemic heart disease and may have related to increased myocardial oxygen demand from the fever and stress of the flu-like syndrome accompanying treatment or to peripheral and coronary arterial constriction.\[261\] The arrhythmias were less clearly related to prior heart disease but may have been exacerbated by the features of this flu-like syndrome as well. Arrhythmias and ischemic ECG changes were identified in mice treated with interferon-a with no myocardial lesions on necropsy, suggesting mediation by peripheral effects.\[261\] Arrhythmias have been seen in up to 20% of patients in clinical trials.\[261\] The arrhythmias observed include fatal\[261\] and reversible\[261\] ventricular fibrillation, ventricular tachycardia,\[261\] atrial flutter and fibrillation, atrioventricular block, and less severe atrial and ventricular ectopy.\[261\] Sudden death was seen in two patients.\[261\] Cardiomyopathy, presenting as a cardiac failure, with severe decrease in radionuclide ejection fraction from 10% to 33%, was seen in seven patients during prolonged administration of interferon-a or interferon-a.\[273,279,280\] The cardiomyopathy was reversible in some of the patients after cessation of interferon, with and without inotropic, diuretic, and afterload reduction therapy. Congestive symptoms disappeared and ejection fractions improved to 29% to 46%. Two patients were able to be retreated with lower doses of interferon without return of failure. Three of the patients with reversible cardiomyopathy had acquired immunodeficiency syndrome (AIDS) with Kaposis sarcoma.\[273\] However, AIDS-associated cardiomyopathy is not reversible. Two others had chronic myelogenous leukemia\[273\] and hairy cell leukemia,\[273\] and two more patients had other cancer.\[273\] Myocardial biopsy in one patient revealed only mild focal intramyocyte vacuolization.\[261\] The etiologic mechanism is unknown. In vitro studies have been conflicting. One study in isolated rat cardiac myocytes, incubated with interferon, showed inhibition of contractility and depletion of ATP.\[261\] While another similar study did not.\[261\] Some postulate an interaction between interferon and noradrenaline.\[261\] Cautious observation for cardiac symptoms and monitoring of rhythm appear to be warranted for these agents with reduction in dose for significant abnormalities.

OTHER BIOLOGIC AGENTS

Interleukin-2 and tumor necrosis factor produced no reduction of ATP or decrease in contractility when incubated with isolated rat cardiac myocytes for 24 to 48 hours.\[318\] However, a major reduction of ventricular stroke work index was found in patients with a variety of solid tumors monitored with indwelling arterial and pulmonary catheters during interleukin-2 treatment.\[318\] This resulted from a poor increase in cardiac index in comparison with the decrease in peripheral resistance. All patients developed a capillary leak syndrome requiring dopamine and crystalloid support. Deleterious effects on blood pressure, systemic resistance, and stroke work appeared to peak at approximately 4 hours after individual doses and to worsen with subsequent doses.\[318\] In addition, there has been a significant (4% to 30% in various trials) incidence of apparent myocardial infarction with this agent.\[272,274,275,276,277,279,280\] One patient with elevated CPK MB fraction, focal injury pattern on ECG, and segmental wall motion abnormality on radionuclide angiography underwent coronary angiography, revealing normal coronary arteries.\[272\] This suggested a pathogenesis involving coronary vasospasm or focal myocarditis. A series of 199 patients had an incidence of 6% arrhythmias including ventricular tachycardia, 53% hypotension, and 25% elevated CPK MB.\[261\] Another biologic agent, interleukin-4, has been associated with myocarditis.\[261\]

A new biologic agent OK432 derived from Streptococcus was suspected of inducing an autoimmune cardiomyopathy. However, it was shown not to provoke the formation of antihistone antibody or ECG changes in rabbits or human patients.\[319\] Continued evidence of lack of cardiotoxicity should remove an obstacle toward its development as an active anticancer agent.

Trastuzumab (Herceptin), a humanized monoclonal antibody developed to target the HER2 receptor (an epidermal growth factor receptor that is overexpressed in many tumor types of cells), has been associated with cardiotoxicity in several clinical trials.\[272,274,282]\[283,284\] The toxicity was manifested as deteriorating systolic function with interon without return of failure. Three of the patients with reversible cardiomyopathy had acquired immunodeficiency syndrome (AIDS) with Kaposis sarcoma.\[273\] However, AIDS-associated cardiomyopathy is not reversible. Two others had chronic myelogenous leukemia\[273\] and hairy cell leukemia,\[273\] and two more patients had other cancer.\[273\] Myocardial biopsy in one patient revealed only mild focal intramyocyte vacuolization.\[261\] The etiologic mechanism is unknown. In vitro studies have been conflicting. One study in isolated rat cardiac myocytes, incubated with interferon, showed inhibition of contractility and depletion of ATP.\[261\] While another similar study did not.\[261\] Some postulate an interaction between interferon and noradrenaline.\[261\] Cautious observation for cardiac symptoms and monitoring of rhythm appear to be warranted for these agents with reduction in dose for significant abnormalities.

OTHER AGENTS

Case reports have attributed cardiotoxicity to several other agents. Melphalan,\[316\] Bis(heteral)malonate,\[316\] mithramycin,\[316\] and bis[1,2-bis(diphenylphosphino)ethane]gold (I) chloride (a cytotoxic antineoplastic drug containing gold),\[316\] teniposide,\[316\] etoposide,\[316\] busulfan,\[316\] and deoxycoformycin\[316\] have been implicated in this respect.

AGENTS USED FOR SUPPORTIVE CARE

Patients undergoing therapy for cancer may also receive various medications, in addition to their chemotherapeutic agents, especially for supportive care and treatment of toxicity. Some of these may also have cardiotoxic effects. For example, granisetron, an antiemetic, has been associated with sinus bradycardia, atrioventricular block varying from increased PR interval to Wenckebach’s and junctional rhythm.\[292\] The cytokines, granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor, have been associated with pericardial effusion.

RADIATION-INDUCED HEART DISEASE

Cardiac complications resulting from mediastinal irradiation were considered rare and insignificant for a long period in the history of radiotherapy.\[262,266\] Since the mid-1960s, when follow-up information on a large number of patients who had been cured of Hodgkin’s disease (HD) with higher doses of radiation became available, the heart has no longer been considered radiation resistant.\[262,266\] Radiation-induced heart disease has now been characterized\[262,267,279,280\] and investigated in experimental animals,\[262,264,265,266,267,279,280\] and the pathologic features of the damage have been described with regard to the coronary arteries and all three layers of the heart.\[262,264,265,266,267,279,280\] In another randomized clinical trial there was more congestive heart failure in patients treated with paclitaxel and trastuzumab (11%) than in patients treated with paclitaxel alone (1%).\[272\] In a third trial, a single-arm study, there was a 7% incidence of congestive failure in 213 patients receiving trastuzumab alone.\[272\] Clearly the cardiotoxic potential of this promising agent will require further investigation, and patients treated with both trastuzumab and an anthracycline need careful monitoring.

Pericarditis and pericardial effusion have been regarded as the most common side effects of cardiac irradiation. However, modern techniques of irradiation, dose fractionation, and reduction of the heart volume irradiated in most malignancies have substantially reduced the frequency of this complication during the last decade.\[262\] At the same time, evidence has accumulated to suggest that ischemic heart disease resulting from radiation-induced CAD is the most concerning long-term risk of cardiac irradiation, particularly in high-risk patients.\[262,264,266,267,279,280\]

The clinical spectrum of radiation-induced heart disease involves most structures of the heart and is summarized as follows:

- Pericardial disease
- Acute pericarditis during irradiation
• Delayed acute pericarditis
• Pericardial effusion
• Constrictive pericarditis
• Myocardial dysfunction
• Valvular heart disease
• Electrical conduction abnormalities
• Coronary artery disease

Although the pathologic and clinical manifestations of radiation-induced heart disease may overlap in many patients, they are discussed separately in the following paragraphs.

PERICARDIAL DISEASE

Incidence

The risk of radiation-induced pericardial disease depends on both the dose given and on the volume of the heart irradiated. In instances in which the whole pericardium was irradiated, the pericarditis incidence was 25%, but when most of the left ventricle was excluded, it was reduced to 7%. When an additional block was implemented to shield most of the heart after 30 Gy, the incidence was reduced to only 2.5%. An update of the Stanford data corroborated this finding, demonstrating a sharp decrease in the risk of death from cardiac complications other than acute myocardial infarction for patients who received mediastinal irradiation after 1972. Indeed, all series that showed a high risk of pericarditis and are of patients treated with a radiation technique, energy, and fractionation schedules that are no longer considered to be an acceptable standard of care in most centers. With current radiotherapy techniques for HD and breast cancer, pericarditis is an infrequent event.

Pathology

Clinical and pathologic changes involving the pericardium are the most common abnormalities described after cardiac irradiation. The macroscopic abnormalities consist of pericardial thickening and effusion. Collagen replaces the normal adipose tissue, fibrinous exudate is present on the surface and interstitially, and proliferation of small blood vessels can be observed microscopically. The pericardial fluid is protein rich and may contain strands of fibrin. The fluid ranges in appearance from serous to grossly sanguineous. Over time, the fibrinous exudate may organize with the fibrotic pericardium and epicardium to develop into constrictive pericarditis. The mechanism for pericardial fibrosis and effusion is not clear. It may result from increased capillary permeability and inhibition of the local fibrinolytic mechanism.

Acute Pericarditis during Radiation

Acute pericarditis during the course of radiotherapy is rare. It is almost always associated with massive mediastinal tumors adjacent to the heart. The signs and symptoms are of acute specific pericarditis with chest pain, fever, and often ECG abnormalities. It does not lead to a significant risk of late pericardial damage and is not an indication for interrupting the radiation course. In patients who were studied 15 days after mediastinal irradiation, a transient decrease in LVEF was observed. In patients who were studied 15 days after mediastinal irradiation, a transient decrease in LVEF was observed. In patients who were studied 15 days after mediastinal irradiation, a transient decrease in LVEF was observed.

Delayed Pericarditis

Radiation-induced pericarditis typically occurs within the first year after mediastinal irradiation. The common range is between 4 months to several years after treatment. Pericardial disease presents either as an acute pericarditis, as a pericardial effusion that may be asymptomatic, or as a combination of both. The symptoms of delayed acute pericarditis are indistinguishable from those of other types of pericarditis and usually consist of fever, pleuritic chest pain, pericardial friction rub, ST-T segment changes, and a decrease of the QRS voltage in the ECG. Pericardial effusion may be large and manifest as an enlarged cardiac silhouette. The differential diagnosis of pericardial effusion after radiation includes recurrent malignancy, idiopathic pericarditis, myxedema, and pericardial abscess. It is estimated that 10% to 30% of patients with radiation-related pericardial effusion develop tamponade and require pericardiocentesis. Most cases of radiation-induced pericarditis and pericardial effusion resolve spontaneously, usually within 16 months. Approximately 20% of patients with delayed pericarditis progress within 5 to 10 years to develop symptomatic constriction requiring pericardiectomy.

Treatment

Careful cardiac evaluation and monitoring with echocardiography and radionuclide ventriculography should be performed whenever radiation-induced heart disease is suspected. Patients with mild symptoms and no hemodynamic compromise may be followed without treatment or may receive symptomatic therapy with salicylates or other nonsteroidal inflammatory agents. There are reports of a few patients who have received corticosteroids with apparent improvement. However, relapse of symptoms or unmasking of latent rapid withdrawal of corticosteroid therapy has been reported. Symptomatic pericardial effusion or clinical evidence for hemodynamic compromise warrants a drainage procedure. Pericardiocentesis with or without percutaneous placement of an indwelling catheter is successful in the majority of patients. Failure to relieve tamponade with pericardiocentesis, recurrence of effusion, or the presence of symptoms, often pleuritic chest pain, in the patient with postirradiation pericarditis is high. Cameron and colleagues reported a postoperative mortality of 21%, and a review by Ni and associates showed an early mortality of 22% in patients operated on for radiation-induced pericarditis and a late mortality (after 30 days or more) of 35%. The high rate of complication in previously irradiated patients is attributed to the existence of additional radiation injury to other cardiac and thoracic structures. Occult constrictive pericarditis requires no surgical intervention and usually has a good prognosis.

MYOCARDIAL DYSFUNCTION

When myocardial dysfunction is detected after standard-dose mediastinal irradiation, it is typically mild or subclinical. In patients who were studied 15 days after mediastinal irradiation, a transient decrease in LVEF was observed. Complete recovery of ejection fraction 2 months after irradiation and no additional change in patients who were also receiving doxorubicin was documented. When myocardial dysfunction is detected after standard-dose mediastinal irradiation, it is typically mild or subclinical. When myocardial dysfunction is detected after standard-dose mediastinal irradiation, it is typically mild or subclinical. Asymptomatic postradiation patients has been reported.

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Pericardial effusion

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MYOCARDIAL DYSFUNCTION

When myocardial dysfunction is detected after standard-dose mediastinal irradiation, it is typically mild or subclinical. In patients who were studied 15 days after mediastinal irradiation, a transient decrease in LVEF was observed. Complete recovery of ejection fraction 2 months after irradiation and no additional change in patients who were also receiving doxorubicin was documented. In a study, noninvasive studies using echocardiography and radionuclide angiogram detected subtle left ventricular dysfunction in HD patients evaluated a few years after mediastinal irradiation. The majority of patients with abnormal ventricular function findings, however, do not have clinical heart failure. The magnitude of the potential contribution of cardiac irradiation to the risk of doxorubicin-induced cardiomyopathy is not well established. But some data suggest potentialiation of anthracycline-induced cardiotoxicity when combined with radiotherapy. The histopathologies of radiation heart disease and anthracyline heart disease are different, and the combined effects are probably additive rather than synergistic. Reducing the doxorubicin dose to 300 to 350 mg/m² in the setting of cardiac irradiation has been recommended. In programs of combined modality therapy for HD that included relatively low doses of doxorubicin (up to 250 mg/m²) and mediastinal irradiation of 20 to 40 Gy, no significant clinical myocardial dysfunction was detected. However, longer follow-up is required to fully appreciate the potential risk of combined modality cardiac toxicity.

Symptomatic myocardial dysfunction after a radiation dose that does not exceed 60 Gy is rare. The few cases described with intractable heart failure had myocardial fibrosis as part of pancarditis, a generalized process with damage to all three layers of the heart. The hemodynamic pattern is usually of restrictive cardiomyopathy and is difficult to distinguish from constrictive pericarditis. Its coexistence with pericarditis explains the poor outcome of pericardiectomy when attempted under these circumstances. In a pathologic analysis of cardiac tissue from patients with radiation-induced heart disease, interstitial fibrosis (of various degrees) of the myocardium was mostly pericellular and perivascular. The degree of fibrosis was proportional to the radiation dose and was not enhanced in cases in which...
which doxorubicin therapy was also administered.

VALVULAR DISEASE

Clinically significant valvular heart disease resulting from mediastinal irradiation is rare. In a review of radiation-associated valvular disease, only ten patients with symptomatic postirradiation valvular disease could be found. Analysis of 635 patients treated for HD before the age of 21 years revealed 29 patients who developed new murmurs of indeterminate significance. Of those, 14 received mediastinal doses of 44 Gy or more, and two patients who received high-dose irradiation died of valvular heart disease. When echocardiographic studies were performed in asymptomatic HD patients more than 7 years after mediastinal irradiation, valvular abnormalities were detected in 25% to 33% of the patients, although there was rarely any clinical significance. Of interest is a report from Norway that showed a significantly higher risk of cardiopulmonary complications for female subjects after radiation for HD. Most of the changes were found in the mitral or aortic valve and consisted of thickening or regurgulation. In one series, mild pulmonary stenosis was detected in three patients 6 to 12 years after radiotherapy. Fibrous thickening of the valvular endocardium was found at autopsy in 13 of 16 young patients who received over 35 Gy to the heart, but none of them had apparent valvular dysfunction. The mean interval from irradiation to detection of valvular disease in asymptomatic and symptomatic patients was 11.5 and 16.5 years, respectively. The contribution of irradiation to clinically significant valvular disease appears to be small.

ELECTRICAL ABNORMALITIES

Many ECG abnormalities were recorded years after mediastinal irradiation, the most common clinically significant abnormality being complete atrioventricular block. Glima and colleagues reported that radiation-related atrioventricular block was typically infranodal and occurred at long intervals (mean of 12 years), after radiation doses above 40 Gy, most frequently in patients with abnormal conduction on ECG before the advent of complete block, and who had other radiation-related cardiac abnormalities. At postmortem examination, fibrosis of the conduction system has been reported. Another aspect of radiation therapy and heart disease relates to the management of patients with implanted cardiac pacemakers. Although transient interference from electromagnetic noise (with the exception of betatrons) is not a problem in properly functioning radiotherapy equipment, pacemaker-dependent patients should be closely observed during the first treatment with a linear accelerator. Placing the pacemaker in an unshielded radiotherapy field may cause cumulative damage to the pacemaker components. The absorbed dose to the pacemaker should be estimated before treatment. If the total dose to the pacemaker might exceed 2 Gy, the pacemaker function should be checked weekly to detect any indicator of damage that may require replacement of the device.

CORONARY ARTERY DISEASE

Studies in rabbits on an atherogenic diet and exposed to radiation showed extensive atherosclerotic coronary damage to a degree disproportionately higher than what might have been expected from the summation of the changes induced by radiation alone and by high-cholesterol diet alone. Similar observations have been made in other experimental animals. An autopsy study in 16 young patients (aged 15 to 33 years) who received over 35 Gy to the heart showed that 16 of 64 (25%) major coronary arteries had significant stenosis (greater than 75% obstruction) compared with only 1 of 40 (2.5%) obstructed coronary arteries in a group of age- and sex-matched controls. In this study, the proximal portion of the arteries had significantly more narrowing than the distal parts. McEnery and coworkers described coronary angiograms of 15 patients with CAD after chest irradiation. Eight of these 15 had significant narrowing (more than 50% diameter) of the left main coronary artery, and four had severe ostial stenosis of the right coronary artery. Stenosis at the origin of the coronary arteries appears to be a common finding for radiation-associated CAD. After mediastinal irradiation, there is a greater likelihood for right coronary or left main or left anterior descending coronary artery lesions as opposed to circumflex lesions, which might be due to the fact that the former vessels, particularly at their origin, receive more radiation. Coronary spasm following radiotherapy has also been documented in patients who developed acute myocardial infarction with patent coronary arteries.

Reports of CAD in young patients who had received mediastinal irradiation for HD have long indicated that radiation is a facilitating factor in this multifactorial disease process. However, only more recently could analyses of large databases of patients with HD demonstrate a significantly increased risk of mortality from myocardial infarction after mediastinal irradiation. These studies are summarized in Table 55.4-1. Although only approximately 1% to 2% of HD patients in these series died of myocardial infarction, the observed risk in all six series was still higher than expected. Boivin and associates analyzed the risk of mortality from CAD in 4665 patients treated for HD and followed for an average of 7 years. The age-adjusted relative risk of death with myocardial infarction after mediastinal irradiation was 2.6 and was even higher (relative risk, 4.0) when myocardial infarction was considered as a direct cause of death. In this study, the onset of increased risk was rapid, within the first 5 years of observation. None of the risk factors for CAD significantly altered the relative risk estimates.

| TABLE 55.4-1. Relative Risk of Mortality from Myocardial Infarction after Mediastinal Irradiation for Hodgkin's Disease |

<table>
<thead>
<tr>
<th>Age at Treatment</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>15-20 years</td>
<td>2.6</td>
</tr>
<tr>
<td>21-25 years</td>
<td>4.0</td>
</tr>
</tbody>
</table>

Current mantle radiotherapy techniques, better fractionation schemes, and modern equipment deliver smaller doses of radiation to the coronary arteries and may have a lower risk of promoting CAD. In the study by Boivin and colleagues, the relative risk of acute myocardial infarction was reduced from 6.33 for patients treated during the years 1940 to 1966 to 1.97 (with no significant difference from unity) for patients irradiated from 1967 to 1985.

Hancock and coworkers analyzed the risk of cardiac disease in patients with HD who were treated at Stanford from 1961 to 1991. The analysis that was limited to children and adolescents younger than age 21 years at the time of treatment showed that the relative risk for death from acute myocardial infarction in this age group was 41.5 (95% CI, 18.1 to 82.1) and that the actuarial risk of fatal or nonfatal myocardial infarction at 22 years was 8.1%. Of note, all deaths in this study occurred in patients who received relatively high doses of radiation (42 to 45 Gy) to the mediastinum. When the Stanford analysis was extended to include 2232 HD patients of all age groups, the relative risk for death from acute myocardial infarction was 3.2 (95% CI, 1.5 to 5.8). This study showed that patients younger than 20 years who received high-dose irradiation had the highest relative risk, the risk decreases with increasing age, and patients older than 50 years of age had no increased risk. However, these results contrast with data published by other investigators suggesting an increased risk of acute myocardial infarction for the older age groups. The small number of patients in the Stanford study who received radiation doses of less than 30 Gy did not allow an adequate analysis of the dose effect. A long-term follow-up study between HD treatment and death from acute myocardial infarction was 10.3 years, but risk was already significant during the first 5 years following treatment and remained elevated throughout the follow-up period (more than 20 years).

Two European studies analyzed the ischemic heart disease in HD patients who received standard fractions and dose (30 to 42 Gy) of mediastinal irradiation.
Both studies demonstrated an increase of ischemic heart disease after mediastinal irradiation. The study from Rotterdam, with a median follow-up of 14 years, reported that 12% of the patients experienced ischemic heart disease, with death rate of 4.7% (from myocardial infarction or sudden death). When compared with expected incidence, the standardized mortality ratio was 5.3 (CI 2.7 to 9.3). Of importance, a multivariate analysis of risk factors in the Rotterdam study showed that increasing age, gender (male), and a pretreatment cardiac medical history were significant for developing ischemic heart disease. Treatment-related parameters did not influence the risk of ischemic heart disease. In a study from Zurich, a delay was observed in the effect of other CAD risk factors on the radiation-induced risk was perfusion defect. The study showed that while the risk of CAD after irradiation increased by 4.2 for all patients, in irradiated female patients and in all irradiated patients without other cardiovascular risk factors (smoking, hypertension, obesity, hypercholesterolemia, diabetes), the risk remained as expected in the normal population.

Long-term mortality data from three trials, which randomized breast cancer patients to receive postmastectomy radiotherapy as opposed to no additional treatment, demonstrated a higher incidence of cardiac death in the irradiated group. The excess in mortality did not appear until after 10 years posttreatment. In one study, the increase in mortality risk was significant only in women who were irradiated for tumors in the left breast. It was also increased in patients treated with orthovoltage irradiation as opposed to those treated with more modern supervoltage equipment.

These data demonstrate the risk associated with coronary artery irradiation. It should be emphasized that the old breast irradiation techniques used in these particular studies delivered high doses of radiation to the heart. These techniques are no longer in use in most centers. Long-term follow-up of patients in similar randomized trials who were treated with heart-sparing techniques did not show increased cardiovascular morbidity and mortality. Prophylactic irradiation of the internal mammary nodes using a single anterior photon beam (hockey stick technique), which may deliver a high dosage to the heart, is not indicated in most patients irradiated for breast-conservation or postmastectomy. Breast cancer patients irradiated with modern techniques, energies, and fractionation schemes are unlikely to receive a significant dose of radiation to the coronary arteries.

Conventional-dose doxorubicin-containing chemotherapy used as adjuvant in combination with locoregional irradiation was not associated with a significant increase in the risk of cardiac events. However, higher doses of adjuvant doxorubicin were associated with a threefold to fourfold increased risk of cardiac events. This appears to be especially true in patients treated with higher doses volumes of cardiac irradiation.

The radiation threshold for an increased risk of CAD has not been determined. Lederman and associates reported that patients with seminoma who received a relatively low dose of mediastinal irradiation (median, 24 Gy) had more ischemic heart disease compared with a similar group of patients whose mediastinums were not irradiated. It should be noted, however, that the observed cardiac risk in the irradiated group did not differ significantly from the expected risk of a comparable normal population.

Monitoring and reduction of other contributing CAD factors in patients who received mediastinal irradiation should be part of the follow-up of patients who underwent mediastinal irradiation. However, the value of routine noninvasive or invasive cardiac studies in asymptomatic patients has not been determined.

Still, early detection of CAD should be encouraged, particularly in irradiated patients with other CAD risk factors, because angiographic or surgical intervention may be indicated in special anatomic or clinical situations. Treatment of radiation-induced coronary disease with bypass surgery and with angioplasty has been reported. In some cases, surgery may be technically difficult because of mediastinal and pericardial fibrosis.

Although the mechanism of radiation-induced coronary heart disease remains unclear, insult to the endothelial cell is considered to be a central event in the pathogenesis of damage to the coronary arteries. Research indicates that programmed cell death (apoptosis) is the underlying mechanism for postradiation endothelial cell death. Growth factors that interfere with the apoptotic pathway, such as bFGF, may prevent radiation-induced death of endothelial cells, as in the study by Fuks and colleagues, who demonstrated that treatment with bFGF during chest irradiation of experimental animals decreased postradiation blood vessel stenosis and significantly increased the survival of the bFGF-treated animals following radiation. These findings provide a basis for future interventions that may decrease the risk of radiation-induced heart disease.

CONCLUSION

It is hoped that increased awareness and knowledge about potential cardiotoxicity from chemotherapy and radiotherapy will enable physicians to adequately monitor patients and modify therapy so as to minimize serious acute and chronic cardiac sequelae. The growing information about late cardiac effects should facilitate early diagnosis and therapeutic intervention for the benefit of previously treated patients.

CHAPTER REFERENCES

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15. Saini J, Rich MW, Lyss AP. Reversibility of severe left ventricular dysfunction due to doxorubicin cardiotoxicity.


INTRODUCTION

Alopecia is a psychologically distressing but common side effect of many chemotherapeutic agents and radiation therapy. As patients embark on new therapies, hair loss can induce a negative body image, cause depression and alter interpersonal relationships, and arouse enough anxiety to cause some patients to reject potentially curative treatment. In one study, 88% of women who received perioperative chemotherapy for early breast cancer considered alopecia to be the most traumatic aspect of therapy. Adolescent patients have particular difficulty in coping with hair loss during a time of adjustment to the diagnosis of cancer.

Frank discussion of the problem by clinicians and oncology nurses, with recognition of patients' stress and personal loss of self-esteem, is helpful in preparing affected patients to confront this event. Although not all patients are entirely satisfied by current methods for the prevention of total scalp hair loss or the use of wigs after hair loss, care-givers can offer supportive listening, some practical suggestions, and identification of resources. Often, the presence of a spouse, family member, or friend during such a discussion with patients is helpful to place the problem in perspective and to aid affected families and patients in adjusting.

The hair loss caused by scalp irradiation is unpredictable. Epilation can begin at doses of 500 cGy and generally progresses, causing spotty areas of baldness as the course of treatment continues. The prospects for hair regrowth diminish with increasing doses. Radiation ports on extremities have been noted to be hair-free 10 years after radiation therapy and may never have hair regrowth. In lower-dose ranges, regrowth begins 8 to 9 weeks after cessation of therapy. Patients should be cautioned that new hair may be different in character from pretreatment hair.

The extent of body hair loss by patients in any chemotherapeutic program is both drug- and dose-dependent and is related to the frequency of cycle repetition. Often, it is caused by more than one drug used concurrently (Table 55.5-1). Long-term therapy may result in loss of pubic, axillary, and facial hair in addition to scalp hair. Often, the loss of scalp hair occurs in an acute episode while washing. It should be emphasized to patients that alopecia from chemotherapy is reversible, with hair regeneration beginning 1 to 2 months after therapy is discontinued. Alterations in color and texture of hair may occur: Shade of hair may be lighter or darker and often is curlier as it regrows. Hair loss may begin 1 to 2 weeks after a single chemotherapeutic dose and reaches maximum loss within 2 months in most drug sequences. Doxorubicin and cyclophosphamide are common cytotoxic agents known to cause epilation after two cycles at doses of doxorubicin greater than 50 mg/m² and cyclophosphamide greater than 500 mg/m². Although agents differ in degree to which they cause hair loss, alopecia may be expected with other single-agent antibiotics, alkylators, nitrosoureas, and especially their combinations.

TABLE 55.5-1. Single Agents with Potential to Induce Reversible Alopecia

<table>
<thead>
<tr>
<th>Agent</th>
<th>Potential to Induce Reversible Alopecia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxorubicin</td>
<td>Greater than 50 mg/m²</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Greater than 500 mg/m²</td>
</tr>
</tbody>
</table>

HEAD COVERING

Most patients will choose to cover their heads during periods of hair loss. Nurses and clinicians can suggest wigs or head covering with stylish scarves, turbans, or hats. Wigs should be selected before hair loss begins so that the patient is prepared when alopecia occurs and so that hair color and style can be matched. Hairpieces are tax-deductible medical expenses and are covered by some medical insurance policies. The American Cancer Society (ACS) can provide wigs free of charge through their “wig bank” program. Several small private businesses have been developed by former patients who distribute or sell head coverings of various designs. An ACS patient service called Look Good, Feel Better has been developed in partnership with the National Cosmetology Association and the Cosmetic, Toiletry, and Fragrance Association Foundation. This service specifically assists women in compensating for hair loss and skin changes to enhance self-image during cancer treatment. Volunteer beauticians and cosmetologists help women to improve their appearance and to feel more comfortable with changes in appearance, such as dry, discolored, or blotching skin; loss of eyebrows and eyelashes; discolored nails; and alopecia. Such volunteers provide instruction with makeup and give advice about wigs and other types of head coverings. Information about group programs and their location is available through an ACS toll-free telephone number, 1-800-395-LOOK, 24 hours daily, 7 days per week. The support program is active in all 50 states and Puerto Rico, with groups designed especially for teenagers in limited areas around the country. The program celebrated its tenth anniversary in 1999, having provided this service to more than 250,000 women.

PREVENTION OF ALOPECIA

Since 1966, interventions have been proposed to prevent scalp hair loss from chemotherapy. The rationale for these procedures is to prevent drug circulation to the hair follicles by causing temporary vasoconstriction and decreasing tissue metabolism at the time of peak plasma drug level, with either an occlusive scalp tourniquet or localized hypothermia. The pharmacokinetic profiles of the drugs to be used should be understood before either of these methods is considered. Scalp-cooling systems must maintain temperatures below 22°C to have any effect. Occlusion of the superficial scalp veins must begin before the drugs are given and, to be effective, must be extended beyond the time of the peak plasma drug levels.

Various types of scalp-icing devices have been manufactured by several different American companies. Although the U.S. Food and Drug Administration (FDA) initially had approved the marketing of cooling caps intended to cause localized scalp hypothermia, early in 1990 the FDA reviewed these applications and became concerned that the safety and efficacy of these devices had not been substantiated by adequate clinical data. Regulatory action was initiated to address the following concerns:

- The potential for scalp metastasis posed by the use of these devices.
- The potential for reducing drug circulation to other anatomic sites beyond the scalp, such as the skull and possibly the brain.
- The effectiveness of preventing hair loss and effects of specific cytotoxic doses and other variables on the results achieved.

On the basis of these factors, the FDA halted the commercial distribution of these devices. Five years after their withdrawal, no company has come forward with supporting clinical evidence of reasonable safety and effectiveness, according to Frances Moreland Curtis of the FDA’s Division of General and Restorative Devices.
Though indications demonstrate that continuous-flow systems with thermostatically controlled cooling caps still are used in Europe, they seem to be limited to regimens containing a single anthracycline alopecia-inducing agent. Limitations of safety and inconclusive and conflicting reports of the results of the usefulness of scalp hypothermia should be factors discussed with patients seeking information about these devices and hair preservation techniques.

CHAPTER REFERENCES

INTRODUCTION
For young adults who have cancer, the success of treatment with regimens that are toxic to gonadal function has made infertility an important problem. When the cancer is controlled, quality of life then becomes a major issue. To many of these young men and women, a major quality-of-life issue is the ability to have a normal child.

Both neoplastic disease and its treatment can interfere with normal sexual and reproductive function (Table 55.6-1). Testicular and ovarian cancer directly involves the gonad, and prostate, endometrial, and cervical cancer directly involves the reproductive tract. Surgical treatment for any of these diseases results by necessity in the loss of these important reproductive organs. Retroperitoneal lymph node dissection (RPLND) for testicular and colon cancer, as well as prostatectomy and surgery involving the bladder neck, may result in loss of the ability to ejaculate. Primary and metastatic tumors in the hypothalamus and pituitary can directly affect gonadotropin secretion, resulting in secondary hypogonadism. Both chemotherapy and radiation can cause a variety of toxic effects on the male and female gonads. Cytotoxic therapies delivered to women during pregnancy might have teratogenic effects on the fetus. If fertility is maintained or returns, there remains the concern about the heritability of cancer and at least a theoretical risk of mutagenic alterations to germ cells caused by cytotoxic therapies.

TABLE 55.6-1. Impact of Cancer and Cancer Therapy on the Reproductive System

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Bone marrow, liver, lung, brain, skin, lymph, breast, cervix, colon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
<td>Reparative bone marrow, renovascular, and endometrial injury</td>
</tr>
<tr>
<td>Response</td>
<td>Hypothalamic and pituitary dysfunction</td>
</tr>
<tr>
<td>Outcome</td>
<td>Loss of sexual function, mental retardation, and secondary hypogonadism</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Surgery</th>
<th>Removal of organ, nerve, and muscle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcome</td>
<td>Loss of sexual function, mental retardation, and secondary hypogonadism</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Radiation therapy</th>
<th>Acute effects on skin, lungs, and heart</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcome</td>
<td>Loss of sexual function, mental retardation, and secondary hypogonadism</td>
</tr>
</tbody>
</table>

The reproductive consequences of cancer therapy affect many people. In the United States, 17,000 men 15 to 45 years old are diagnosed each year with Hodgkin's disease, lymphoma, bone and soft tissue sarcomas, testicular cancer, or leukemia. Of these, more than 3000 are treated with doses of alkylating agents, platinum drugs, or radiation sufficient to induce prolonged azoospermia. Similarly, 35,000 women aged 15 to 45 years old are treated for breast cancer (mostly), Hodgkin's disease, lymphoma, and leukemia; at least 80% of these patients receive radiation or alkylating agent–based cytotoxic therapies. These treatments cause not only sterility but also premature menopause and the associated estrogen deficiency in nearly 20,000 women. In addition, 12,000 children younger than 15 years are diagnosed each year with cancer, including leukemia, nervous system tumors, lymphomas, and other solid tumors. Survival is approaching 80%, and because 85% of patients receive chemotherapy or gonadal or pituitary irradiation, reproductive dysfunction is a significant concern.

EFFECTS OF CYTOTOXIC AGENTS ON ADULT MEN

BIOLOGIC CONSIDERATIONS
The sensitivities of the seminiferous (or germinal) epithelium and the endocrine components of the testis to killing by cytotoxic therapies are related to the relative proliferation rates of the different cells. The germ cells consist of stem spermatagonia, differentiating spermatogonia, spermatocytes, spermatids, and sperm. Among
the germ cells, which are within the seminiferous epithelium, the differentiating spermatogonia proliferate most actively and are extremely susceptible to cytotoxic agents. In contrast, the Leydig cells, which are in the interstitium and produce the androgens, and the Sertoli cells, which provide support and regulatory factors to the germ cells, do not proliferate in adults and so survive most cytotoxic therapies. These cells may, however, suffer functional damage. Frequently after cytotoxic therapies, germinal tissue appears completely absent, a state described as germinal aplasia, and only the Sertoli cells remain lining the tubules. This could be a result of killing of the spermatogenic stem cells, the loss of the ability of the somatic cells to support the differentiation of a few surviving stem cells, or a combination of both.

After cytotoxic treatment, sperm count diminishes with a time course that depends on the sensitivities of the different spermatogenic cells and their kinetics of maturation to sperm. Because the later-stage germ cells (spermatocytes onward) are relatively insensitive to killing and progress with invariant kinetics, sperm count is not immediately affected. However, these cells are susceptible to the induction of mutagenic damage, and studies in rodents have shown they can become spermatocytes and transmit mutations induced in their DNA to the next generation. The eventual recovery of sperm production depends on the survival of the spermatogenic stem cells and their ability to differentiate. In both rats and humans, surviving stem cells may fail to produce differentiating germ cells for a year or more after cytotoxic insult.

The loss of germinal cells has secondary effects on the endocrine function of the testis and the hypothalamic-pituitary-gonadal axis. Inhibin secretion by the Sertoli cells declines and, as inhibin limits follicle-stimulating hormone (FSH) secretion by the pituitary, serum FSH rises. Because germinal aplasia reduces testis size and there is a concomitant reduction in testicular blood flow, less testosterone is distributed into the circulation, and as testosterone inhibits pituitary luteinizing hormone (LH) secretion, serum LH increases. Conversely, LH is the primary stimulator of Leydig cell testosterone synthesis, and the reduced blood flow also lessens Leydig cell exposure to circulating LH. These alterations of pituitary-gonadal feedback could elevate serum LH and reduce serum testosterone levels even in the absence of any Leydig cell injury.

**CHARACTERISTICS OF GONADAL TOXICITY**

Although subnormal semen profiles, ejaculatory dysfunction, and low libido in treated patients are most likely a result of treatment, other causes must be considered, too. A sexual and reproductive history should include developmental factors such as age of testicular descent and puberty; surgery or injury to the genitals; diseases that might affect reproduction; drug, chemical, or heat exposure; and pretreatment fertility and libido status. A physical examination should consist of examination of the testicles and secondary sexual characteristics such as beard and hair distribution pattern. Laboratory tests entail semen analysis and a hormone profile. Normal values and those associated with germinal aplasia are outlined in Table 55.6-2.

**TABLE 55.6-2. Typical Clinical and Laboratory Features for Diagnosis of Male Reproductive Dysfunction**

During the first 2 months of cytotoxic therapy, sperm counts may remain normal or be only moderately reduced. Some regimens cause azoospermia 2 to 3 months after the initiation of therapy, corresponding to the interval during which the sensitive differentiating spermatogonia become sperm. With other regimens, oligospermia or even normospermia may be maintained.

Increases in FSH are associated with germinal aplasia. Although FSH measurements have sometimes been used as a surrogate for sperm count, they only show an imperfect correlation, in part because of interpatient variability in baseline FSH levels. After cytotoxic therapy, LH tends to be elevated and serum testosterone levels in the low normal range. This has been interpreted as indicating subclinical, compensated Leydig cell failure; however, changes in testicular blood flow can also explain these observations. The only treatment that produces testosterone insufficiency in a high proportion of adult patients is high-dose (30 Gy) radiation directed to the testes, which directly damages Leydig cell function.

The induced azoospermia can be either temporary or prolonged, depending on the ability of surviving stem spermatogonia to proliferate, differentiate, and produce spermatocytes, which in turn depends on the nature of the cytotoxic agent and dose (Table 55.6-3). If treatment is limited to the cytotoxic agents that do not kill stem spermatogonia or block their differentiation into spermatogonia, normospermic levels are usually restored within 3 months after the cytotoxic therapy. However, if agents that inactivate stem spermatogonia or affect differentiation are used, longer periods of azoospermia ensure. At lower doses of these agents, recovery to normospermic levels can occur within 1 to 3 years, but at higher doses, azoospermia can be more prolonged or even permanent. The probability that spermatogenesis will recover decreases with the duration of azoospermia. However, in a few men spermatogenesis recovered after as long as 20 years of azoospermia. FSH levels drop to normal when sperm production recovers. When sperm count recovers after cytotoxic therapy, sperm motility appears to be normal, and fertility is generally restored. However, when the duration of azoospermia is long, recovery may sometimes plateau at less than 1 million/mL, which may not be compatible with fertility.

**TABLE 55.6-3. Effects of Different Antitumor Agents on Sperm Production in Men**

To evaluate the effects of cytotoxic therapy, the initial gonadal status must be considered. Men with both seminomas and nonseminomatous germ cell tumors have impaired semen even before cytotoxic therapy is instituted. Approximately 65% are oligospermic (counts less than 20 million/mL), 50% have less than 10 million/mL, and 13% are azoospermic. Compared with values of 9%, 5%, and 1%, respectively, in control populations. In approximately 40% of the patients with reduced semen quality, this impaired testicular function is a result of irreversible abnormalities associated with the uninvolved gonad (e.g., carcinoma in situ or a history of cryptorchidism) that predate the onset of cancer. In the other 60%, it may be a result of reversible factors such as elevated chorionic gonadotropin produced by the tumor with resulting increases in estradiol. In addition, emission and ejaculation may have been compromised by earlier RPLND so that the sperm density may not accurately reflect gonadal function. In contrast to the severe dysfunction in testicular cancer, in Hodgkin's disease only 21% of Hodgkin's disease patients are oligospermic and 2% are azoospermic, and the distribution of counts in the remainder is not significantly different from normal. The presence of low-grade fever and B symptoms was not predictive for poor semen quality. Similarly, in other lymphomas and sarcomas, pretreatment sperm counts tend to be
normal except for a trend toward an increase in the incidence of oligosperma.  

Age at treatment is not a major factor in recovery from gonadal damage in men. Two studies indicate increased incidence of testicular damage after cytotoxic therapy in older men, but others fail to indicate any effect.  

**INDIVIDUAL DRUGS**

The most sterilizing drugs are the alkylating agents and cisplatin, all of which form adducts and/or cross-links on DNA. Only two of these, chlorambucil and cyclophosphamide, have been demonstrated to induce prolonged azoosperma when given alone. Evidence from combination chemotherapy regimens demonstrates that procarbazine and cisplatin in high doses are also highly sterilizing. Table 55.6-3 lists the cumulative dosages of these drugs at which recovery of sperm production is unlikely. The cumulative dose appears to be more important than the dose rate. Some doses are based on data from combination chemotherapy regimens and do not account for possible additive contributions from other drugs in the regimen.

The evaluations of other individual alkylating agents have been obtained from combination chemotherapy regimens. Busulfan has an additive effect on the sterility in men resulting from cyclophosphamide treatment, but there are no studies on busulfan in the absence of highly sterilizing agents. Carboplatin, an analogue of cisplatin, is expected to produce sterility, but in clinical studies it appeared to be less sterilizing than cisplatin. The addition of the cyclophosphamide analogue ifosfamide to cisplatin-containing chemotherapy regimens failed to produce significant levels of additional prolonged azoosperma. Treatment of boys with carmustine and lomustine did produce prolonged azoosperma, and it is likely, but not proven, that the same would occur in adults.

The list of agents that only have temporary effects (see Table 55.6-3) includes some that have been used as single agents. However, most were used in regimens that do not cause prolonged azoosperma or were not independent prognostic factors in the prediction of recovery in variably sterilizing regimens.

In addition to cytotoxic agents, hormonal and biologic agent therapies are also used in treatment of cancer. Any reproductive effects of hormones should generally be reversible. However, only the corticosteroid prednisone and the cytokine interferon-a have been studied, and there are no indications of negative effects on male gonadal function of these agents.

**RADIATION THERAPY**

The effects of radiation on the testes are dependent on the fractionation regimen: Doses given in 3- to 7-week fractionated courses cause more gonadal damage than do single doses. In contrast, in all other organ systems fractionation of radiation reduces the damage. Doses of radiation to the testes above 0.15 Gy diminish sperm count after a lag period of approximately 6 weeks. Fractionated doses between 0.15 and 0.5 Gy only cause oligosperma. The nadir of sperm count is at 4 to 6 months after the end of treatment, but 10 to 18 months are required for complete recovery. At doses above 0.6 Gy, azoosperma occurs. The duration of azoosperma is dose dependent, and recovery can begin within 1 year after doses of less than 1 Gy, but requires 2.0 to 3.5 years at approximately 2 Gy. Cumulative doses of fractionated radiotherapy of 2.5 Gy and higher generally result in prolonged and likely permanent azoosperma. Likewise, single testicular doses of 8 Gy or fractionated doses of 12 Gy, given as total body irradiation in preparation for bone marrow transplantation, generally produce permanent azoosperma. However, spermatogonial damage does recover in 17% of these men after a median follow-up time of 5 years, but the recovery is only 10% when cyclophosphamide (4.5 g/m²) is added to the conditioning regimen.

Direct testicular radiation is the only treatment that consistently produces clinically significant reductions in testicular androgen production in the adult. Doses of 30 Gy for treatment of testicular carcinoma in situ significantly reduce testosterone levels, but doses of less than 20 Gy do not appear to have clinically significant effects on testosterone levels. Furthermore, the gonadal scatter doses of 2 to 6 Gy during treatment for prostate cancer also do not produce clinically significant reductions in testosterone levels; the radiation-associated impotence after such treatments is likely a result of vascular damage.

**COMBINATION REGIMENS**

The sterilizing potential of different combinations depends on the individual agents and the dose given. Although interindividual variation makes it impossible to predict whether sperm production in any given man will recover, the probability of inducing prolonged azoosperma has been determined for many combinations.

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<th>TABLE 55.6-4. Probability of Germinal Aplasia in Men Treated with Different Combination Chemotherapy Regimens</th>
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The sterilizing potentials of combination chemotherapy and chemotherapy plus radiotherapy regimens are additive; there is no evidence for synergistic interactions between the agents. The listing in Table 55.6-3 and the results with similar regimens can be used to predict the sterilizing potential of regimens not presented here. The additive effects of multiple agents can be seen in the case of cyclophosphamide, which when given alone requires 19 g/m² to produce prolonged sterility in one-half the men. However, the prolonged azoosperma observed in one-half the men after a median cyclophosphamide dose of only 10.6 g/m² in the CY(V)ADIC regimen, which had a median doxorubicin dose of 880 g/m², can be explained by additive effects from other drugs, particularly doxorubicin. The absence of azoosperma after 5.1 g/m² of cyclophosphamide given for treatment of leukemia may be a result of the extreme fractionation, as the drug was given once every 20 weeks over 3.5 years. Two cycles of Mustargen, Oncovin, procarbazine, and prednisone (MOPP) and pelvic radiotherapy had additive effects on the induction of prolonged azoosperma, but the gonadal toxicity of mitoxantrone, vincristine, vinblastine, and prednisone (NOVP) was insufficient to produce noticeable enhancement of the sterilizing effects of pelvic radiotherapy.

**EFFECTS OF CYTOTOXIC AGENTS ON ADULT WOMEN**

**BIOLOGIC CONSIDERATIONS**

Gonadal cell kinetics in women are opposed to those in men, as the germ cells are nonproliferative whereas the somatic cells proliferate. Prenatally, female germ cells proliferate as oogonia and become arrested at the oocyte stage. At birth, a woman has 1 million oocytes, which are reduced to 300,000 at puberty. These are progressively lost by atresia, development, and ovulation, until almost all are lost and menopause is reached at approximately age 50 years.

Before recruitment to the process leading to ovulation, oocytes are found in primordial follicles with few pregranulosa cells, surrounded by thecal cells of the ovarian stroma. The stimulus for the initiation of follicular maturation, which occurs in the absence of gonadotropin hormones, is unknown, but a role for gonadotropins cannot be excluded. Once a follicle is recruited into growth, it develops until it either degenerates or ovulates. Follicular maturation is characterized by proliferation of granulosa cells and the development of steroidogenic potential of both the thecal and granulosa cells. Estrogens, produced by biosynthetic steps in both the thecal...
and the granulosa cells under LH and FSH stimulation, cause the LH surge that triggers ovulation. The day-to-day sequential variations in FSH, LH, and estradiol are essential for menstrual cyclicity and the female reproductive processes. The close interaction between granulosa cells and oocytes makes it difficult to identify which type of cell is the target of cytotoxic agents; death of either results in atrophy of the other. Because destruction of oocytes results in loss of follicles and steroidogenesis, germ cell loss leads directly to estrogen insufficiency.

The time between recruitment of follicles and their ovulation is approximately 85 days. When maturing follicles are destroyed by cytotoxic therapy, temporary amenorrhea results. If primordial follicles are reduced below the minimum number necessary for menstrual cyclicity, irreversible ovarian failure occurs and the amenorrhea is permanent. Different species of experimental animals have yielded conflicting information regarding the sensitivity of primordial follicles to radiation and cyclophosphamide and do not yet allow prediction of response in women.

CHARACTERISTICS OF GONADAL TOXICITY

Because the size of the germ cell population in women cannot be estimated, menstrual and reproductive histories are important in assessing the effects of cytotoxic therapy on ovarian function. Information on the patient's menstrual cycle during and after therapy, as well as oral contraceptive use, should be noted. To determine if effects are related to cytotoxic therapy, pretherapy ovarian function should be evaluated from the history of menarche, menses, pregnancies, and oral contraceptive use. The occurrence of symptoms of recent primary ovarian failure, including hot flashes, night sweats, insomnia, mood swings, irritability, vaginal dryness, dyspareunia, decreased libido, and bladder infection, should be recorded. Laboratory measurements of hormone levels are most definitive in the diagnosis of primary ovarian failure; FSH is the most sensitive, but LH and estradiol levels are also useful (Table 55.6-5). The symptoms of ovarian failure may be masked and the hormone levels altered if the woman is taking oral contraceptives.

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<th>Table 55.6-5. Typical Laboratory Features for Diagnosis of Ovarian Failure</th>
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Some of the variability reported in the literature regarding the incidence of ovarian failure after cytotoxic therapy is a result of the lack of consistent definitions. Menopause should be defined as more than 12 months without a menstrual period, treatment-related amenorrhea as at least 6 months without menstrual periods in a premenopausal patient, and oligomenorrhea as a reduction in the frequency of menses to between 40 days and 6 months. Because the mechanisms of temporary and irreversible treatment-related amenorrhea may be different, posttreatment follow-up time should be given, and they should be distinct outcomes.

Cytotoxic therapy often induces temporary amenorrhea, which may last a few months or up to 7 years. Some of this temporary amenorrhea is a result of direct ovarian damage, causing failure of follicular recruitment or loss of maturing follicles. Alternatively, stress and malnutrition or weight loss can also cause temporary gonadal dysfunction by altering hypothalamic activity and estrogen metabolism. The destruction of growing follicles and the resulting temporary amenorrhea during treatment appear to be independent of age. Although some patients with treatment-induced temporary amenorrhea do display menopausal symptoms, these symptoms are usually indicative of permanent ovarian failure. In contrast, permanent treatment-induced amenorrhea, which is equivalent to ovarian failure, dramatically increases in an apparently continuous manner with age at treatment examples are given in Table 55.6-6 and Table 55.6-7. This trend is expected as the number of follicles decreases with increasing age. The permanent amenorrhea may begin during chemotherapy or subsequently after several years of oligomenorrhea.

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<th>Table 55.6-6. Effects of Different Cytotoxic Agents on Ovarian Function</th>
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<th>Table 55.6-7. Probability of Ovarian Failure in Postmenarchal Women with Combination Chemotherapy Regimens Containing Alkylating Agents</th>
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If cytotoxic therapy depletes the pool of primordial follicles, premature ovarian failure should occur even in young women who continue menstruating after cytotoxic therapy. In women aged 13 to 19 years at diagnosis treated with alkylating agent chemotherapy and radiotherapy below the diaphragm, the median age at menopause is 32 years, compared with 44 years for women treated with radiotherapy or chemotherapy alone, and 49 years for controls. The degree of acceleration of menopause in these women correlated with the probability of induction of primary ovarian failure by the different therapies.

Cytotoxic therapy-induced ovarian failure and premature menopause can accelerate bone density loss. However, when only chemotherapy is used, some residual
ovarian function may be present and can ameliorate the loss. 77

INDIVIDUAL DRUGS
As in men, only alkylating agents appear to produce permanent gonadal failure in women (see Table 55.6-6), and the cumulative dose appears to be more important than the dose rate. Administration of low daily doses of cyclophosphamide over several months is only slightly less effective at inducing permanent ovarian failure than is a high dose in 4 days. 78 Melphalan, chlorambucil, busulfan, mitomycin C, and doses of cisplatin of 600 mg/m² or higher, also produce permanent ovarian failure. Procarbazine is likely to be highly sterilizing inasmuch as permanent ovarian failure is observed in all procarbazine-containing combinations and, in the case of cyclophosphamide, Oncovin, procarbazine, and prednisone (COPP), the dose of cyclophosphamide is insufficient to cause this effect (see Table 55.6-7).

Other agents studied do not induce permanent ovarian failure. 5-Fluorouracil up to 30 g did not induce amenorrhea in women with a median age of 35. Methotrexate (200 g) plus vincristine (40 g), etoposide (5 g), and cisplatin (less than 450 mg/m²) plus doxorubicin (less than 400 mg/m²) failed to produce permanent ovarian failure in women 15 to 30 years of age. Doxorubicin, bleomycin, vincristine, and dacarbazine (ABVD), must not induce ovarian failure because none is observed after treatment of women up to age 41. Reproductive effects of hormonal agents, such as tamoxifen, which interferes with pregnancy in animals, should be reversible.

RADIATION THERAPY
Radiation is highly effective at inducing permanent ovarian failure with a marked age-dependence in sensitivity (see Table 55.6-6). In adult women, irradiation of the ovaries occurs in the treatment of Hodgkin's disease and during total body irradiation in preparation for hematopoietic stem cell transplantation. Irradiation of the para-aortic nodes results in cumulative doses of only 1.5 Gy to the ovaries and does not appear to interfere with menstruation in most patients. 52 When total nodal irradiation for Hodgkin's disease or pelvic radiation for cervical cancer is given, and the ovarian dose can be reduced to 4 to 5 Gy by translocation (oophoropexy) and shielding of the ovaries, partial preservation of fertility in younger women results. 53 Total body irradiation in preparation for bone marrow transplantation delivers 8 to 12 Gy to the gonads, which destroys ovarian function in all adult women, even the young ones. Fractionation appeared not to spare the ovary, as 27% of women receiving 10 Gy in a single fraction recovered ovarian function as opposed to only 10% of those receiving 12 Gy in 6 days.

COMBINATION REGIMENS
All combinations that include procarbazine or high doses of other alkylating agents [e.g., mechloretamine, vinblastine, procarbazine, and prednisone (MOPP); COPP; and chlorambucil, vinblastine, procarbazine, and prednisone (CHVP)] induce ovarian failure in almost all older women and even in some younger ones (see Table 55.6-7). Recovery is better when the dose of procarbazine is reduced by using the MOPP/ABVD regimen. Radiation and MOPP chemotherapy clearly have an additive (but not synergistic) effect, and the combination results in a higher incidence of ovarian failure than either modality alone.

Similarly, regimens using high doses of cyclophosphamide, as used in treatment of breast cancer, also produce ovarian failure; however, the age dependence obscures any possible dose dependence. 54 Lower doses of cyclophosphamide usually given along with antimetabolites and other agents for treatment of leukemia do not destroy primordial follicles nor produce permanent ovarian failure. Combination chemotherapy regimens without alkylating agents tend not to produce ovarian failure.

EFFECTS OF CYTOTOXIC AGENTS ON CHILDREN

BIOLOGIC CONSIDERATIONS IN BOYS
In the prepubertal testis, the immature Sertoli cells are the most numerous cells in the seminiferous tubules. They proliferate at an extremely low level in the prepubertal period, only increasing twofold in numbers, but there is a marked increase during puberty. Spermatogonia are the only germ cells present and transform from an appearance of fetal germ cells to that of adult spermatogonia. They proliferate at a low level, increasing sixfold from birth to 10 years. Leydig cells cannot be identified in the interstitial spaces from shortly after birth until puberty. At puberty, new Leydig cells are formed from mesenchymal cells already in the interstitium, involving extensive proliferation of the precursors. The appearance of the Leydig cells elevates secretion of testosterone, which, along with enhanced FSH levels, initiates spermatogenesis at a median age of 13.

EXTENT OF GONADAL TOXICITY IN BOYS
The germinal epithelium in the prepubertal testis does not appear to be any more resistant to cytotoxic therapy than that in the adult. The concept that prepubertal are less sensitive than adult testes derived from comparison of cyclophosphamide doses given on a milligram per kilogram basis and the failure of prepubertal boys to show elevation of FSH after chemotherapy. But when treated patients are followed after puberty by sperm count and hormone evaluation, the sensitivity of the prepubertal testis to a variety of cytotoxic regimens is apparent. Appropriately expressing chemotherapy regimens are especially effective at producing persistent gonadal aplasia. In addition, high doses of doxorubicin and cytotoxic ara-c appear to be additive with the preceding agents in producing gonadal damage. In general, regimens lacking alkylating agents, such as some used for acute lymphocytic leukemia, allow pubertal progression of spermatogenesis even during treatment and do not appear to affect postpubertal sperm counts or fertility.

Chemotherapy does not have major effects on Leydig cell function, and hence the timing of pubertal development and postpubertal testosterone levels are generally normal. There is one report that treatment with MOPP chemotherapy during puberty results in gynecomastia; however, other studies indicate that this incidence is not above background levels. Preliminary data do indicate, however, that approximately 30% of boys treated with busulfan plus cyclophosphamide show delayed puberty. In contrast, direct testicular irradiation, used in treatment of leukemia or sarcomas, produces dramatic Leydig cell damage. There is significant age dependence, as children are more sensitive than adults and within the prepubertal period, the youngest are most sensitive. The incidence of extremely low testosterone levels and failure to complete puberty rises from 0% at 7.5 Gy, 5 to 0% to 50% at 12 Gy, 57% at 24 Gy, 75% at 30 Gy. The extent of low testosterone levels and failure to complete puberty rises from 0% at 7.5 Gy, 5 to 0% to 50% at 12 Gy, 57% at 24 Gy, 75% at 30 Gy. The incidence of gonadal toxicity in boys is age-dependent and is not affected by the dose rate. Administration of low daily doses of cyclophosphamide over several months is only slightly less effective at inducing permanent ovarian failure than is a high dose in 4 days. Melphalan, chlorambucil, busulfan, mitomycin C, and doses of cisplatin of 600 mg/m² or higher, also produce permanent ovarian failure. Procarbazine is likely to be highly sterilizing inasmuch as permanent ovarian failure is observed in all procarbazine-containing combinations and, in the case of cyclophosphamide, Oncovin, procarbazine, and prednisone (COPP), the dose of cyclophosphamide is insufficient to cause this effect (see Table 55.6-7).

BIOLGIC CONSIDERATIONS IN GIRLS
Despite the low levels of circulating gonadotropins, the immature ovary is far from quiescent. In addition to primordial follicles, maturing follicles up to and including the large antral stage appear within a few months after birth. After 6 years of age, FSH levels, the numbers and diameters of large antral follicles, and estrogen levels all increase. The lack of gonadotropin support prevents full follicular development or ovulation before menarche.

EXTERNAL OF GONADAL TOXICITY IN GIRLS
Prepubertal girls appear to be even less susceptible than young postpubertal women to ovarian failure induced by cytotoxic therapy (see Table 55.6-6). Furthermore, girls treated between the ages of 0 and 12 do not appear to experience premature menopause during their 20s and 30s as is the case with those treated at ages 13 to 19. However, additional numbers and longer follow-up are needed.

Radiation is the most damaging agent to the prepubertal ovary. Doses of approximately 20 to 30 Gy induce permanent ovarian failure in nearly all girls. Doses of 8 to 15 Gy, given as single doses or in a few fractions, usually with some cyclophosphamide in preparation for bone marrow transplantation, cause permanent ovarian failure and failure of pubertal development in only 50% of girls, with those at younger ages being less sensitive than older ones. Fractionated doses of up to 7 Gy cause little failure of ovarian function or pubertal development, although there can be additive detrimental effects of chemotherapy.
Most chemotherapy regimens, including high doses of cyclophosphamide up to 48 g, do not cause failure of pubertal development and menarche. Although various combination chemotherapy regimens used for treatment of leukemia and Hodgkin's disease reduce the number of growing follicles, no significant change in numbers of primordial follicles could be measured, and puberty and associated ovarian function develop normally. Even with the standard MOPP chemotherapy for Hodgkin's disease, 90% of prepubertal girls develop normally. However, regimens with high doses of certain alkylating agents can produce detectable ovarian damage in 15% to 20% of prepubertal girls. CHOP (30% failure) and cyclophosphamide or lomustine (greater than 50% failure) produce transient biochemical evidence of ovarian failure, but there is no evidence that they interfere with pubertal development. In contrast, busulfan plus cyclophosphamide actually inhibits puberty in 50% of girls.

GONADAL DYSFUNCTION AFTER CRANIAL IRRADIATION

Whereas gonadal irradiation causes primary hypogonadism, cranial irradiation is associated with secondary hypogonadism due to damage to the hypothalamus, gonadotrophs in the pituitary, or both. In patients with pituitary or suprasellar lesions, gonadotropin deficiency is often present before antineoplastic therapy; however, patients with nasopharyngeal cancer or brain tumors have normal hypothalamic-pituitary-gonadal axes until they receive therapeutic irradiation with fields encompassing the hypothalamic-pituitary areas. There is no convincing evidence that any of the cytotoxic drugs directly impair hypothalamic and anterior pituitary function.

In children, prophylactic cranial irradiation with 24 Gy for leukemia does not affect LH or FSH pulsatile secretion in the first 6 years. Irradiation of children for cranial tumors with doses of 25 to 55 Gy to the hypothalamic-pituitary region decreased LH and FSH secretion in 11% of cases within 6 years in one study. However, in some cases radiation doses between 18 and 47 Gy, sometimes combined with chemotherapy, may not inactivate the mechanisms necessary for gonadotropin production and secretion, and indirectly stimulate this process before puberty, and hence increase LH and FSH levels and cause precocious puberty. Because growth hormone deficiency is common in these patients, precocious puberty further exacerbates the risk of adult shortness.

In adults, decreased LH and FSH secretion, measured after gonadotropin-releasing hormone (GnRH) stimulation, is observed after cranial irradiation. The damage increases with treatment dose and time interval since treatment. LH and FSH deficiency is observed in 33% of patients 5 years after treatment with 20 Gy, but 66% are affected 5 years after 35 to 49 Gy, progressing to 100% by 10 years. This results in oligomenorrhea in women and low testosterone in men; hyperprolactinemia might mediate the observed gonadal dysfunction in some cases.

In many patients who receive multimodality treatment, complex hormonal dysregulation may develop; although cranial irradiation, for example, may affect the hypothalamus and pituitary, total body or abdominal irradiation and concomitant chemotherapy may induce primary gonadal failure.

PRESERVATION OF FERTILITY, HORMONE LEVELS, AND SEXUAL FUNCTION

CHOICE OF REGIMENS

It is sometimes possible to choose between nearly equally curative regimens on the basis of their sterilizing potentials. The principle is to minimize the doses of the agents in Table 55.6-3 and Table 55.6-6 that are most sterilizing. A classic example is to use ABVD instead of MOPP to treat Hodgkin's disease. In the treatment of non-Hodgkin's lymphoma, regimens that minimize the dose of cyclophosphamide, such as VAPEC-B, produce less gonadal failure in men than does cyclophosphamide, hydroxydaunorubicin (Adriamycin), Oncovin, prednisone, and bleomycin (CHOP-Bleo).

GONADAL SHIELDING

Except when they must be irradiated because of neoplastic involvement or anatomic inclusion within the irradiated target, the gonads are outside or are shielded from the direct radiation beam. Nevertheless, an appreciable radiation dose from the accelerator head, collimator scatter, or internal lateral scatter may reach the gonads. Even at moderately low radiation doses, the possibilities of additive effects from chemotherapy and genetic damage to the sperm make it desirable to further minimize the radiation dose.

Gonadal radiation fields are usually small, and photon energy can vary from 0.1% to 10.0% of the prescribed dose within the field. Pelvic radiation fields result in significant doses to the testis. Clamshell type shields can reduce testicular doses approximately fivefold to 2 Gy for the inverted Y field used for Hodgkin's disease and approximately 0.5 Gy for the hemipelvic field used for seminoma. When treatment of the hemiscrothum after unilateral orchectomy for testicular cancer is indicated, a special positioning device to retract the remaining testicle out of the treatment field and provide shielding above the area can reduce the dose to the gonad to 0.6 Gy.

To shield the ovaries, an oophoropexy, in which the ovaries are surgically translocated, usually to the midline behind the uterus, must be performed. This is often done before radiation therapy for Hodgkin's disease and 35 Gy for other tumors.

MALE GERM CELL CRYOPRESERVATION

Semen cryopreservation is an extremely important procedure for men who want to preserve their fertility potential after cytotoxic treatment for cancer. The significance of notifying the patient of the potential risk of iatrogenic sterility as early as possible cannot be overemphasized. Physicians often are aware early during the diagnostic process that the patient will most likely need to receive potentially sterilizing cytotoxic therapy, although the exact diagnosis, stage, and treatment regimen have not yet been decided. This time should be used to initiate and complete the cryopreservation procedure. The banking of at least three semen samples with at least a 48-hour period of abstinence between samples is recommended. This usually requires 5 to 8 days to complete. Additional samples (four) and longer abstinence periods (72 hours) to achieve higher total sperm counts may be considered. But fewer samples with shorter times are often obtained because of the need to initiate anticancer therapy quickly, and it is important to avoid possible increased genetic damage in sperm collected after the start of therapy. It is even possible to obtain semen with normal characteristics from 14- to 17-year-old boys. In boys unable to obtain samples by masturbation, penile vibratory stimulation or electroejaculation have been used.

Because of the low overall success rate with artificial insemination using banked semen in the past, it had been recommended that only samples with high sperm counts and motility be stored. Currently, the success of in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) make cryopreservation of all samples containing any live sperm appropriate. The cost of sperm banking three samples, including analysis and storage for 5 years, is approximately $1200 at a university medical school clinic, although it may be higher at private sperm banks. The patient should be made aware that conception rates are only 30% with interuterine insemination (cost per cycle, approximately $250). If the sperm count or motility are significantly impaired, more complicated assisted reproductive technologies may be necessary. The average cost of IVF without ICSI, including the drugs used, is $10,000 per cycle and with ICSI it is approximately an additional $1200 per cycle.

The transplantation of a population of testicular cells, including stem spermatogonia from a donor mouse to a recipient mouse, in which endogenous stem spermatogonia were killed with busulfan, restored spermatogenesis and fertility. Restoration of spermatogenesis is also possible with cryopreserved cells. This suggests the possibility that testicular tissue may be harvested from men before sterilizing cytotoxic therapy and cryopreserved as a cell suspension, for later injection back into the testis after the completion of chemotherapy. Currently, a trial is underway at the Christie Hospital, Manchester, England. This technique would be most valuable for boys, who may be too young to produce sperm, especially because the prepubertal testis is enriched in spermatogonia.

FEMALE GERM CELL CRYOPRESERVATION

Freezing oocytes, unlike sperm, is currently still experimental. There have been offspring born using frozen human oocytes in IVF procedures; however, the success rate is low. In addition, currently used procedures for freezing human and animal oocytes may increase chromosomal aberrations. Furthermore, obtaining mature oocytes is limited to patients in whom there are no contraindications to hormone-induced superovulation. It is also possible to freeze embryos obtained by IVF or by uterine lavage after natural coitus; but these methods are rarely practical with cancer patients, especially when cytotoxic therapy must be initiated without...
In male subjects, germinal aplasia is often associated with testosterone levels in the low to normal range, and they may experience reduced bone mineral density.

Injection.

Risk for morbidity and mortality from cardiovascular disease and causes sexual dysfunction.

Replacement therapy may result in an irreversible loss of bone mass and increased risk of osteoporosis.

Low-birth-weight babies, and neonatal deaths, and hence these pregnancies must be closely monitored.

In most women who continue to have menstrual function after cytotoxic therapy for cancer, infertility should generally be treated as in a normal population. The one oligospermic counts, management of the patient should be the same as in those from a normal population with male factor infertility. Of the various procedures, IVF be any higher than the 15% rate among couples in the general population. In contrast, cancer patients with recovered sperm counts ranging from below 1 to 10 million/mL, levels associated with subfertility when they occur in the general population, are able to successfully father children.

Men whose sperm count recovers after cancer therapy usually achieve normospermic levels, but some remain oligospermic for extended periods. Although controlled hormone treatment before and during cytotoxic therapy.

The failures may, in part, be attributed to the administration, along with the GnRH agonist (GnRH-Ag), of testosterone, which has been shown in the rat to reduce the recovery of spermatogenesis. The continuation of testosterone-suppressive treatment after completion of cytotoxic therapy, which was successful in the rat, has not been tested in humans.

In the female rat, there is one convincing study showing protection of ovarian function. The number of developing follicles several months after cyclophosphamide treatment was enhanced when GnRH-Ag had been given along with cyclophosphamide. It is not apparent how GnRH-Ag worked as recruitment of primordial follicles to the pool of preantral follicles, or as some other mechanism. GnRH-Ag, or oral contraceptives during treatment for Hodgkin’s disease have yielded contradictory results.

Despite clinical symptoms of ovarian failure, there may be some residual ovarian function remaining after chemotherapy; the possibility is less likely after gonadal radiation. It is possible to stimulate ovulation and fertility after apparent chemotherapy-induced ovarian failure, at least for a short time, with a brief course of gonadotropin treatment, or with steroid hormone replacement therapy.

Men whose sperm count recovers after cancer therapy usually achieve normospermic levels, but some remain oligospermic for extended periods. Although controlled studies have not been done, these men appear to have normal fertility based on their sperm count, and the incidence of infertility in these patients does not appear to be any higher than the 15% rate among couples in the general population. In contrast, cancer patients with recovered sperm counts ranging from below 1 to 10 million/mL, levels associated with subfertility when they occur in the general population, are able to successfully father children. In cases of infertility with oligospermic counts, management of the patient should be the same as in those from a normal population with male factor infertility. Of the various procedures, IVF and IVF with ICSI appear to offer the most promise.

In most women who continue to have menstrual function after cytotoxic therapy for cancer, infertility should generally be treated as in a normal population. The one major exception is those who received high doses of abdominal radiation (10 to 16 Gy for hematopoietic stem cell transplantation and more than 20 Gy for Wilms’ tumor), particularly in childhood. These patients have increased rates of adverse pregnancy outcomes, including fetal or neonatal death, premature deliveries, low-birth-weight babies, and neonatal deaths, and hence these pregnancies must be closely monitored.

HORMONE REPLACEMENT THERAPY

It is important to test for ovarian failure and to start hormone replacement therapy rapidly because, in some cases, a 2- to 3-year delay in administering estrogen replacement therapy may result in an irreversible loss of bone mass and increased risk of osteoporosis. In addition, estrogen deficiency places women at increased risk for morbidity and mortality from cardiovascular disease and causes sexual dysfunction. Estrogen replacement can be provided orally, transdermally, or by injection. If a patient has an intact uterus, estrogen should generally be combined with progesterone to prevent endometrial hyperplasia and cancer.

In male subjects, germinal aplasia is often associated with testosterone levels in the low to normal range, and they may experience reduced bone mineral density. Some of these men with reduced libido after chemotherapy report improvement after testosterone treatment. Testosterone replacement is important in cases of overt Leydig cell failure in prepubertal boys to promote secondary sexual characteristics, growth, and bone density. It can be provided transdermally or by injection; the
use of oral anabolic preparations should be discouraged.

MODIFIED NERVE-SPARING SURGERY

Ejaculation of semen involves emission, by which semen is deposited in the posterior urethra by contractions of the vas deferens, seminal vesicles, and prostate, and antegrade ejaculation, which requires coordinated tightening of the bladder neck, relaxation of the external sphincter, and expulsion of semen. Most of these processes are controlled by nerve fibers that arise from the lumbar ganglia at L1 to L4 and then course anteriorly over the aorta and coalesce into multiple trunks, forming the hypogastric plexus overlying the aorta and sacrum below the origin of the inferior mesenteric artery.

Surgery in the treatment of testicular, prostate, and bladder cancer can produce neurologic dysfunction resulting in failure of emission, retrograde ejaculation, impotence, and loss of orgasm. However, improvements in surgical techniques have reduced these adverse outcomes without diminishing the efficacy of treating the cancer.

RPLND has an important role in the treatment of nonseminomatous testicular germ cell tumors. Procedures for radical RPLND that were standard before 1972 almost always produced failures of emission and ejaculation. Based on the location of positive nodes, a modified template of dissection (unilateral dissection below the inferior mesenteric artery), which avoids disturbance of the lumbar sympathetic fibers, particularly at the hypogastric plexus, was developed, preserving ejaculation of semen in 50% to 85% of men. The RPLND technique has been further refined by identifying the postganglionic fibers and retracting them from the lymph nodes over and around the aorta, which are then dissected out and removed in multiple small packages, sparing the nerve fibers. Preserving ejaculation of semen in 89% of men.

Improved surgical techniques also preserve sexual function in many men undergoing surgery for prostate and bladder cancer. By avoiding damage to the nerve fibers that are located in neurovascular bundles that innervate the penile corpora cavernosa, sexual function, including the ability to have an erection sufficient for vaginal penetration and orgasm, is maintained in 70% to 80% of men undergoing radical prostatectomy for localized prostate cancer or radical cystoprostatectomy for invasive bladder cancer. In addition, a promising technique for those patients who do require nerve excision with the prostate is that of bilateral sural nerve grafts. It is too early to quantify the true effectiveness of this technique, but the results are encouraging.

MANAGEMENT OF RETROGRADE EJACULATION

In patients with ejaculatory dysfunction after RPLND, sympathomimetic agents may enhance seminal emission and partially or completely convert the patient to antegrade ejaculation. Drugs, such as pseudoephedrine HCl, ephedrine sulfate, phenylpropanolamine HCl, or imipramine HCl, should be given sequentially as 2-week trials until improvements in semen volume and sperm count are observed. Pregnancies have been reported but, in general, medical therapy must be combined with some additional techniques to use sperm from retrograde ejaculation.

When retrograde ejaculation is present, sperm may be recovered from the bladder by direct voiding or by catheterization with irrigation. For greater sperm survival, it is important to ensure a dilute, slightly alkaline urine and then to dilute the voided semen-urine mixture with buffering media to reduce harmful urine components.

When medical treatment is not successful at producing emission and ejaculation, electroejaculation has been successful in more than 70% of patients. After administration of general anesthesia, a rectal probe is used to electrically stimulate sympathetic efferent fibers and smooth muscle. Although most patients have some antegrade ejaculate, catheterization should always be done to collect the retrograde semen. Sperm motility tends to be low after electroejaculation, and the fecundity per cycle is at most 9% using artificial insemination. IVF with ICSI is now being used to enhance pregnancy rates.

GENETIC CONCERNS

BIOLOGIC CONSIDERATIONS

Many anticancer agents damage DNA and interfere with DNA replication, DNA repair, and chromosome segregation in both animal and human cells. They induce mutations in germ cells of animals that cause genetic disease. Because the studies that have been done or can be done in humans are limited, risk estimates are derived from the induction of single-gene mutations and chromosomal aberrations, both of which contribute significantly to human genetic disease in the mouse. Radiation, procarbazine, melphalan, and mitomycin C produce single-gene mutations in murine spermatogonia, whereas seven other tested chemotherapeutic drugs do not. Risk can be estimated by using the doubling dose (i.e., dose to produce twice the background rate of mutation) from the mouse and the incidence of clinically significant dominant genetic traits in human liveborn due to new mutations. Doubling doses for single-gene mutations in mouse spermatogonial mutations are 1 Gy for subchronic radiation and 0.4 gm of procarbazine. At the mouse doubling dose, the incidence of dominant mutations in humans should be increased by 0.2%, however, data from offspring of atomic bomb survivors indicate that estimates based on the mouse may overestimate the human genetic risk.

Radiation is the only agent that effectively induces stable reciprocal chromosomal translocations in stem spermatogonia that can be visualized in spermatocytes or in offspring. Although the mouse data indicate that a fractionated dose of 1 Gy would induce translocations in 0.06% of the offspring, the induction of translocations in human germ cells appears to be higher than in the mouse.

In male rodents, meiotic and postmeiotic germ cells are more sensitive to induction and transmission of mutations than are stem spermatogonia. Therefore, mutational risks are highest when a pregnancy occurs within one spermatogenic cycle (time for stem cell to become sperm) after the man is exposed to the damaging agent. In men, this higher risk period extends from the start of cytotoxic therapy until 3 months after the last course. In practice, waiting 6 months after therapy to effect a pregnancy is recommended for safety. After this time, the incidence of mutations is at the lower level found in sperm that were exposed to the mutagen as stem cells, which determines the genetic risk for the remainder of the reproductive lifetime.

Fewer studies of the mutagenicity of cytotoxic agents have been done in the female subject. Single-gene and chromosomal mutations are induced by radiation in the developing oocytes of female mice at a similar rate as in stem spermatogonia. Procarbazine induces a similar level of specific-locus mutations in primordial oocytes as in stem spermatogonia. Most alkylating agents and a variety of other drugs induce chromosome aberrations or mutations in oocytes in growing follicles, resulting in embryonic death. Although there are insufficient data to determine whether growing oocytes are more sensitive to induction of mutations than primordial oocytes, it is still prudent for a woman to wait at least 3 months after cytotoxic treatment before conceiving.

These animal studies show that there are theoretical genetic risks to the offspring of treated patients of both sexes. Calculations predict that the incidence of congenital abnormalities would be increased by less than 2%, even at the highest doses of cytotoxic therapies and, hence, large-scale controlled studies will be required to measure effects in human populations.

GAMETE GENOMIC ANALYSIS

Because epidemiologic studies of genetic damage in humans require large numbers of offspring, direct analysis of the genetic material of gametes has potential advantages for identifying mutations in human germ cells. Such analyses are practical only in the male subject because harvest of female gametes is impractical. Several assays have been developed and new methods are under investigation. (Table 55.6-8).
During treatment, sexual relations between partners may continue, but reliable contraception should be used. The genetic and teratogenic risk of conception when...
condoms when sexual intercourse occurs within 24 hours of administration of a chemotherapeutic agent to the man should be recommended.

The probability that sterility will result from the planned cytotoxic therapy should be calculated from the cumulative doses of agents and combinations that cause prolonged azoospermia (see Table 55.6-3 and Table 55.6-4) and ovarian failure (see Table 55.6-6 and Table 55.6-7). This risk should be communicated to the patient.

Pretreatment sperm banking should be offered to all male patients interested in having children after the completion of cytotoxic therapy. The risks of sterility from a given treatment and the probability that more aggressive, highly sterilizing treatment may be needed before there is another opportunity for semen storage should be communicated to each patient. Counseling on cryopreservation and other assisted reproductive technologies should be presented, and the patient should be reminded that these are not standard benefits in the majority of health insurance programs in the United States. It is important to present a balanced discussion of potential benefits of prompt initiation of hormone replacement therapy versus the risk (e.g., possibly endometrial and breast cancers) so that an individually appropriate decision may be reached.

CHAPTER REFERENCES

Modern chemotherapy and radiotherapy have increased substantially the survival of patients with cancer. In particular, cure rates have shown dramatic improvement for patients with Hodgkin's disease, testicular cancer, and pediatric malignancies. Less impressive, but nonetheless convincing, improvements in survival also have been achieved for patients with breast cancer, non-Hodgkin's lymphoma (NHL), and several other tumors. Now that substantial numbers of cancer patients experience such a favorable prognosis, it becomes increasingly important to evaluate the long-term complications of treatment. Because the survival benefits associated with modern treatments have been greatest for those cancers that occur at relatively young ages, cured patients are subject to long-term side effects, which may not emerge until several decades after treatment. Paradoxically, research conducted since the late 1970s has clearly demonstrated that some of the modalities used to treat cancer have the potential to induce new (second) primary malignancies. Of the many late complications of treatment, second cancers are generally considered to be the most serious, because they not only cause substantial morbidity but also considerable mortality. For example, among 15-year survivors of Hodgkin's disease, second cancer deaths have been reported to be the largest contributor to the substantial excess mortality that these patients experience.

In any discussion of treatment-related second malignancies, it is of primary importance to remember that not all second cancers are due to therapy. The occurrence of two primary malignancies in the same individual may reflect the operation of numerous influences. Multiple primary cancers may result from host susceptibility (genetic predisposition or immunodeficiency), common carcinogenic influences, a clustering of risk factors, factors for the first tumor, diagnostic surveillance, a chance event, or the interaction of these factors. In view of the high prevalence of cancer in the general population and the increasing incidence of most cancers with age, it is important to exclude the role of chance in the development of second cancers. To this end, comparison with cancer incidence statistics derived from the general population is crucial. If a second malignancy is demonstrated to occur in excess, the contributions of other risk factors need to be ruled out convincingly before the increased risk can be attributed to treatment. The temporal trend of excess second cancer risk may provide an important initial clue to etiology; for example, the risk of solid tumors after radiotherapy generally increases with time since exposure. The evaluation of the carcinogenic effects of therapy, however, is complicated by the fact that second cancer-specific sites are frequently given in combination. Appropriate epidemiologic and statistical methods are required to quantify the excess risk and to unravel the role of treatment and other factors.

Wherever interpreting results of second cancer studies, it must be kept in mind that the problem of treatment-induced malignancies has arisen by virtue of the success of cancer therapy. As more becomes known about the influence of various treatment factors on second cancer risk, therapies may be modified to decrease the risk while maintaining equal levels of therapeutic effectiveness.

The major aspects of second malignancy risk in relation to cancer treatment are addressed in this chapter. After a discussion of methods used for the assessment of second cancer risk, an overview of the carcinogenic effects of radiotherapy and chemotherapy is presented. Subsequently, the risk of second malignancies after treatment for Hodgkin's disease, NHL, testicular cancer, breast cancer, ovarian cancer, and pediatric malignancies is reviewed. Emphasis is on large studies that have been published most recently.

### METHODS TO ASSESS SECOND CANCER RISK

Estimates of second cancer risk after treatment of various primary malignancies derive from several sources, including population-based cancer registries, hospital-based cancer registries, or clinical trial series. The epidemiologic study designs generally used are the cohort study and the case-control study.

In a cohort study, a large group of patients with a specified first malignancy (the cohort) is followed for a number of years to determine the incidence of second cancers. To evaluate whether second cancer risk in the cohort is increased compared with cancer risk in the general population, the observed number of second cancers in the cohort is compared with the number expected on the basis of age-, gender-, and calendar-year–specific cancer incidence rates in the general population. The analysis takes into account the observation period of individual persons (person-years). The relative risk of developing a second cancer is estimated by comparing the ratio of the observed number of second cancer cases in the cohort to the number expected. When the relative risk is increased, the question arises as to whether the excesses are due to therapy. This issue can be evaluated by comparing risks between treatment groups, preferably within specified follow-up intervals and, when possible, with a reference group of patients not treated with radiotherapy and chemotherapy. Second cancer risk in the cohort (and in different treatment groups) can also be expressed by the cumulative (actuarial estimated) risk, which yields the proportion of patients alive at time (e.g., 5 years from diagnosis) who can be expected to develop a second malignancy. When the cohort's death rate due to causes other than second malignancy is high, the assumptions underlying the actuarial method may not be valid, and competing risk techniques should be considered to estimate cumulative risk. Because many treatment-related cancers are rare in the general population (e.g., leukemia, sarcoma), a high relative risk (compared to the population) may still translate into a rather low cumulative risk. Absolute excess risk, which estimates the excess number of second malignancies per 10,000 patients per year, perhaps best reflects the second cancer burden in a cohort. This risk measure is also the most appropriate one by which to identify those second malignancies that contribute the most to elevated risks.

Each of the data sources used to construct a cohort has its own set of advantages and disadvantages. Population-based cancer registries frequently have large numbers of patients available, which allows the detection of even small increases in the site-specific risk of second cancers. An additional advantage is that the observed and expected numbers of cancers derive from the same reference population. Disadvantages of this approach include the limited availability of treatment data, under-reporting of second cancers (in particular hematologic malignancies and bilateral cancers in paired organs), and different diagnostic criteria for second cancers. Population-based registries differ greatly in these aspects and, hence, in their usefulness for second cancer studies. If treatment data are not available, it is impossible to determine whether excess risk for a second malignancy is related to treatment or to shared etiology with the first cancer. Despite their disadvantages, population-based registries are especially well suited to broadly evaluate which second cancers occur in excess after a wide spectrum of different first primary malignancies. They also provide a valuable starting point for case-control studies that evaluate treatment effects in detail (see later in this section).

A major strength of clinical trial databases is that detailed treatment data on all patients are available. Comparison of second cancer risk between the treatment arms of the trial controls for any intrinsic risk for a second malignancy associated with the first cancer. Limitations of most trials include the small number of patients included and the frequent lack of data on subsequent therapy. The dearth of large numbers becomes more serious when the second cancer of interest has a low background incidence (e.g., leukemia). Furthermore, the endpoints of interest in the majority of clinical trials include only treatment response and survival, not the development of second cancers. Therefore, many clinical trials do not routinely collect information on second malignancies, and some do not collect any data beyond...
5 years. Routine reporting and assessment of second malignancy risk should become an integral part of clinical trial research.\textsuperscript{10}  

Many large cancer treatment centers maintain registries of all admitted patients. Most of these registries have been in existence for decades and collect extensive data on treatment and follow-up. As compared with trial data, hospital registries provide larger patient numbers and a wider variety of treatments and dose levels, which may yield more reliable information on drug and radiation carcinogenesis. Most studies of second cancer risk after Hodgkin's disease have been based on data accrued from hospital registries.\textsuperscript{13,12 and 13}  

The cohort study is not an efficient design when examining detailed treatment factors (e.g., cumulative dose of alkylating agents) in relation to second cancer risk. Most cohorts are fairly large (to yield reliable estimates of second cancer risk), rendering the collection of detailed treatment data for all patients prohibitively expensive and time-consuming. In such instances, the so-called nested case-control study within an existing cohort is the preferred approach. The case group consists of all patients identified with the second cancer of interest, whereas the controls are a matched sample of all patients in the cohort who did not develop the cancer concerned, although they experienced the same amount of follow-up time. Matching factors typically include age, gender, and calendar year of diagnosis of the first cancer. Even when the control group is three times as large as the case group, detailed treatment data need only be collected for a small proportion of the total cohort. In each case-control investigation, it is critical to the validity of the study that the controls are truly representative of all patients who did not contract the second cancer of interest. In data analysis, treatment factors are compared between cases and controls, and the risk associated with specific therapies is estimated relative to that of those who received no therapy during a second malignancy. The statistical methods used to derive these risk estimates are described in more detail below. Treatment-specific absolute excess risks can be estimated, however, when the case-control study follows a cohort analysis. Although case-control methodology has not been applied to the investigation of second cancer risk for a long period,\textsuperscript{15} several landmark studies have already demonstrated its strengths.\textsuperscript{11,17,16,15,21,22}  

### CARCINOGENICITY OF INDIVIDUAL TREATMENT MODALITIES

#### RADIOTHERAPY

The carcinogenic potential of ionizing radiation was first recognized in the mid-twentieth century,\textsuperscript{23,24 and 25} and comprehensive reviews have now been published.\textsuperscript{27,28 and 29} Much of the data with regard to radiation effects in humans has derived from epidemiologic studies of the atomic bomb survivors in Japan,\textsuperscript{30,31 and 32} occupationally exposed workers,\textsuperscript{33,34 and 35} patients given large amounts of diagnostic radiation,\textsuperscript{36,37 and 38} and patients treated with radiotherapy for malignant\textsuperscript{39,40 and 41} and nonmalignant diseases.\textsuperscript{42,43 and 44} Most types of cancer, with the exception of chronic lymphocytic leukemia, can be caused by exposure to ionizing radiation.\textsuperscript{45,46 and 47} Boice et al.\textsuperscript{48} have ranked various body tissues with regard to cancer induction by radiation; certain sites, such as the thyroid, female breast, and bone marrow, clearly are more radiosensitive than others.

The excess risk of leukemia attributable to irradiation is observed within a few years after exposure, with a peak at 5 to 9 years, and a slow decline thereafter.\textsuperscript{49,50 and 51} Some controversy exists as to whether, and when, leukemia risk decreases to background levels in the population.\textsuperscript{52,53 and 54} In the atomic bomb survivors, risk declined more rapidly than expected even earlier in life.\textsuperscript{55} Increased risks of solid tumors have been shown to emerge much later. After a minimum induction period of 5 to 10 years,\textsuperscript{56,57 and 58} solid tumor risk appears to follow a time-response model consistent with a multiplicative relationship with the underlying incidence in the population—that is, risk after exposure is proportional to the background incidence of cancer over time.\textsuperscript{59,60 and 61} Data are inconsistent as to whether the risk remains elevated throughout life. Studies in the atomic bomb survivors\textsuperscript{62} and in women treated for benign gynecologic disorders\textsuperscript{63} have shown that the excess relative risk per Gray (Gy) tends to be fairly stable over time for at least 30 years after radiation. However, the last update of the mortality experience of ankylosing spondylitis patients showed that, 25 years after irradiation, risk had decreased for a number of malignancies.\textsuperscript{64} In the few studies of second cancer risk in which the time course beyond 20 years from first treatment was evaluated, the relative risks of solid tumor development tended to decrease in very long-term survivors.\textsuperscript{65,66 and 67} The most recent cancer incidence report on the Japanese atomic bomb survivors, with 42 years of follow-up, indicated that the excess relative risk decreased with time for the younger age-at-exposure groups and remained virtually constant for the older cohorts.\textsuperscript{68} Cancer incidence data from the atomic bomb survivors and five other groups exposed to radiation have been analyzed to specifically address the evolution of risk with increasing time since exposure in childhood.\textsuperscript{69} Ten to 15 years after radiation exposure, the relative risk of solid tumors decreased with increasing follow-up time (5.7% to 6.1% per year). The excess absolute risk, however, significantly increased with time since exposure.\textsuperscript{55}

An important part of our knowledge of radiation carcinogenesis derives from populations exposed to relatively low levels of radiation, such as the atomic bomb survivors. For solid tumors, convincing evidence for a strongly linear radiation dose-response in the lower dose ranges (up to approximately 5 Gy) has emerged.\textsuperscript{70,71 and 72} Extraplanation of radiation effects from low doses to the high-dose ranges used therapeutically cannot be done with certainty, because of the possibility of cell killing at high doses. Therefore, more recent studies of second cancer risk have focused on the shape of the radiation dose-response curve in the high-dose range.

Radiation-related leukemia risk depends on a number of parameters, such as radiation dose to the active bone marrow, dose rate, and percentage of marrow exposed. Consistent evidence indicates that the excess risk of leukemia per unit radiation dose is much higher at low doses than at the high doses administered for the treatment of malignant disease.\textsuperscript{73,74 and 75} This phenomenon has been attributed to cell killing or inactivation of potentially leukemic cells at the higher radiation doses.\textsuperscript{76,77 and 78} Many studies in cancer patients have shown that high radiation doses to a limited field confer very little or no increased risk of leukemia.\textsuperscript{79,80} Both in the atomic bomb survivors and in patients who received radiotherapy for cervical cancer, leukemia risk appeared to increase with increasing average dose to the bone marrow up until approximately 4 Gy, above which leukemia risk was progressively reduced with increasing dose.\textsuperscript{81,82 and 83} However, leukemia risk in survivors of uterine cancer showed little evidence for a downturn in risk at bone marrow doses as high as 6 to 14 Gy;\textsuperscript{84} at more than 1.5 Gy, the dose-response pattern was more or less flat, and the risk after continuous exposures from brachytherapy at comparatively low doses was similar to that after fractionated exposures at much higher doses from external beam therapy.\textsuperscript{85,86 and 87} Clearly, more research is needed into the effects of dose fractionation to bone marrow irradiated. Age at exposure to irradiation does not appear to greatly influence the risk of radiation-induced leukemia.\textsuperscript{88,89 and 90} although decreasing relative risk with increasing age at exposure has been reported for one radiogenic leukemia subtype [acute lymphocytic leukemia (ALL)].\textsuperscript{91}

In contrast, studies of radiogenic breast cancer have demonstrated that age at exposure is a major determinant of risk, with the greatest risk for those irradiated as children and adolescents.\textsuperscript{92,93 and 94} Irradiation may thus affect cells of the mammary ducts before full organ development begins. Atomic bomb survivors who were younger than 10 years old at the time of the bombing had an excess relative risk per Gy five times that of women who were older than 40 years when exposed. A strong trend of increasing breast cancer risk with decreasing age at exposure was also observed in patients irradiated for Hodgkin's disease.\textsuperscript{95,96 and 97} With no excess breast cancer risk apparent among women irradiated at 40 years or older,\textsuperscript{98,99 and 100} in two studies, increased breast cancer risk after radiation exposure in childhood exceeded that older than 40 years even at an age younger than 40, before the peak incidence in the population.\textsuperscript{101,102} In the low-dose range, breast cancer risk increases linearly with radiation dose.\textsuperscript{103,104 and 105} For a specified dose, the age-specific excess rates of breast cancer were found to be remarkably similar across studies in the Japanese atomic bomb survivors and in medically irradiated populations in the United States.\textsuperscript{106,107 and 108} Very few studies have examined whether linear dose-response extends to the higher dose ranges used therapeutically. However, long-term survivors of Hodgkin's disease who were younger than 20 years when they received breast doses between 4 and 45 Gy from mantle field irradiation were reported to have a 40- to 75-fold increased risk of breast cancer.\textsuperscript{109,110} One study found that a higher radiation dose to the mantle region (25 Gy or more vs. less than 20 Gy) was associated with a significantly greater increase of breast cancer risk.\textsuperscript{111}

Risk of lung cancer also rises with increasing radiation dose in the lower dose range.\textsuperscript{112,113 and 114} but studies in survivors of Hodgkin's disease\textsuperscript{115} and breast cancer\textsuperscript{116} suggest that the risk may level off at doses higher than 9 to 10 Gy. A similar leveling of risk at doses of 10 Gy or more has been observed for radiation-induced thyroid cancer.\textsuperscript{117,118 and 119} However, even at thyroid doses up to 60 Gy, the risk of thyroid cancer did not decrease.\textsuperscript{120,121 and 122} For bone sarcoma, two studies in survivors of childhood cancer\textsuperscript{123} show no evidence of increased risk for doses less than 10 Gy to the site of the bone tumor. Beyond 10 Gy, risk for bone sarcoma rose sharply with increasing dose, reaching more than 90-fold at doses of 30 to 50 Gy.\textsuperscript{124} Importantly, studies have shown that, also for solid tumors other than breast cancer, the excess relative risk due to radiation is much greater for children and adolescents than for adults.\textsuperscript{125,126 and 127} Significantly greater relative risks with younger age at radiation exposure have been reported for lung cancer,\textsuperscript{128} thyroid cancer,\textsuperscript{129} bone sarcoma,\textsuperscript{130} and gastrointestinal cancer.\textsuperscript{131,132 and 133} After radiation in childhood, the excess relative risk per Gy for thyroid cancer [RR, 7.7, 95% confidence interval (CI), 2.1 to 28.7] is higher than for any other solid malignancy.\textsuperscript{134}

For radiogenic lung cancer, the interaction of radiation with other risk factors, such as smoking, has been examined. Studies in uranium and tin miners exposed to radon have indicated that smoking and radiation may act multiplicatively (or at least supraadditively) in the causation of lung cancer,\textsuperscript{135,136 and 137} implying that the...
absolute risk of developing radon-induced cancer is much higher in smokers than in nonsmokers. In Hodgkin’s disease patients, the combined effects of smoking and high-dose radiotherapy for Hodgkin’s disease were significantly stronger than multiplicative. In the latter study, the increase in lung cancer risk with increasing radiation dose was significantly greater among patients who continued to smoke after diagnosis of Hodgkin’s disease than among those who refrained from smoking. As discussed more extensively in the previous edition of this text, interaction models accounting for the sequencing of radiation and smoking suggest that radiation may act as a powerful promoter of cells initiated by smoking.

The carcinogenic effects of therapeutic irradiation deserve much more study. Issues to be clarified include the shape of the radiation dose-response curve in the higher dose range, the duration of radiation-induced cancer risk and, importantly, the interaction of radiotherapy with environmental carcinogens (e.g., smoking) and genetic susceptibility. Increasing evidence suggests that genetic factors contribute to the development of radiation-induced cancers. This is perhaps best demonstrated in survivors of hereditary retinoblastoma who harbor a heterozygous germline mutation in the RB1 tumor suppressor gene, and who have a much greater risk of developing osteosarcoma within the radiation field than children irradiated for nonhereditary retinoblastoma. In addition, two studies showed that patients with a positive family history of cancer are more likely to develop radiation-associated second malignancies. In view of the postulated radiation sensitivity of heterozygous carriers of the mutated ataxia-telangiectasia (ATM) gene, it has been speculated that ATM heterozygotes (approximately 1.0% of the population) may have an increased risk of radiation-induced cancer, specifically breast cancer. In two studies, however, no ATM mutations were found in a total of 56 women who had developed breast cancer after radiotherapy for Hodgkin’s disease. Further studies should focus on the identification of other genes that may influence susceptibility to the DNA damaging effects of radiation. Such research will provide more insight into the mechanisms underlying radiation carcinogenesis and will also be of clinical benefit in minimizing radiation exposure to the most susceptible subgroups of the population.

CHEMOTHERAPY

The development of acute myeloid leukemia (AML) after chemotherapy for malignant disease was reported as early as 1970 by Kyle et al. In the following three decades, the occurrence of this late effect has increased to the extent that, in some institutions, treatment-related AML now comprises up to 10% to 20% of all such entities. Moreover, it is now established that the spectrum of treatment-related leukemia extends beyond AML. ALL, for example, is increasingly recognized as therapy-related and may comprise 5% to 10% of all secondary acute leukemias. Chronic granulocytic leukemia accounts for a small percentage of secondary leukemia, and has been included in numerous analytic studies in which associations with prior chemotherapy have been evaluated, although separate risk estimates have not been presented. To date, only chronic lymphocytic leukemia has not been convincingly associated with prior exposure to chemotherapy.

Chemotherapy is far more potent than radiotherapy in inducing leukemia. It has been demonstrated that at least two major syndromes of treatment-related leukemia may exist: “classic” alkylating agent–induced AML and acute leukemia related to the topoisomerase II inhibitors. Risk of alkylating agent–related leukemia typically begins to increase 1 to 2 years after the start of chemotherapy, peaks in the 5- to 10-year follow-up period, and decreases afterward. Even in large patient series, the number of long-term survivors has typically been too small to determine whether 15 to 20 years after chemotherapy the risk of leukemia returns to the background level of the population. Although one registry-based study indicates that leukemia risk might persist among 15-year survivors of testicular cancer, it is not clear whether these late excesses might reflect the influence of salvage therapy. More than 50% of leukemias after alkylating agent therapy present initially as myelodysplastic syndrome (MDS), whereas the vast majority of AMLs are de novo. Most patients with AML and MDS progress to acute leukemia 1 year or more after presentation. Cyto genetic studies of alkylating agent–related AML/MDS have shown unbalanced chromosome aberrations, typically with loss of whole chromosomes 5 or 7 (or both), or various parts of the long arms of these chromosomes. Morphologically, alkylating agent–related AML most commonly consists of French-American-British (FAB) subtypes M1/M2, but most subtypes, including erythroleukemia, have been observed. Survival after secondary AML is generally quite poor, typically only several months.

Alkylating agents with known leukemogenic effects in humans include mechlorethamine, chlorambucil, cyclophosphamide, melphalan, semustine, lomustine, carmustine, procarbazine, busulfan, and dihydroxybusulfan. Controversial findings have been reported with regard to procarbazine, which describes a mechanism underlying an action similar to alkylating agents. Few studies have addressed the relative leukemogenicity of the various alkylating drugs, and a lack of a large body of evidence to date suggests that, at doses of equal therapeutic effect, cyclophosphamide is substantially less leukemogenic than melphalan, mechlorethamine, chlorambucil, lomustine, and busulfan.

The risk of alkylating agent–related AML has been shown to increase with increasing cumulative dose or duration of therapy. Few studies have attempted to separate the effects of cumulative dose, duration of treatment, and dose intensity, which tend to be highly correlated, but limited evidence to date suggests that cumulative dose may be a pivotal determinant of risk (discussed later in Hodgkin’s Disease).

The platino-based agents carmustin and carlaplatin are among the most important cytotoxic drugs introduced since the 1960s and are widely used to treat many cancers. The platinum compounds, however, demonstrate carcinogenicity in vitro and in laboratory animals, forming intranuclear and intradna cross-links similar to bifunctional alkylating agents. In a population-based study of women with ovarian cancer, cisplatin-based combination chemotherapy was linked to significantly increased risks of leukemia (P trend for cumulative dose <.001) in a multivariate model adjusted for other treatment parameters (discussed later in Ovarian Cancer).

Future studies should evaluate whether other drug combinations that include platinum might also be linked to elevated risks of leukemia, because it is not clear whether cisplatin acts as a human leukemogen only in combination with selected cytotoxic agents.

The topoisomerase II inhibitors, especially the epipodophyllotoxins, have been implicated in the development of a clinically and cytogenetically distinct type of AML. The International Agency for Research on Cancer (IARC) has concluded that the epipodophyllotoxins etoposide and teniposide are probably carcinogenic to humans. Moreover, it is now established that the spectrum of treatment-related leukemia extends beyond AML. ALL, for example, is increasingly recognized as therapy-related and may comprise 5% to 10% of all secondary acute leukemias. Chronic granulocytic leukemia accounts for a small percentage of secondary leukemia, and has been included in numerous analytic studies in which associations with prior chemotherapy have been evaluated, although separate risk estimates have not been presented. To date, only chronic lymphocytic leukemia has not been convincingly associated with prior exposure to chemotherapy.

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Just as the pharmacology of effective cancer chemotherapy is impacted by underlying principles of pharmacokinetics and pharmacodynamics (see Chapter 19.1), these influences likely contribute to the development of secondary leukemia. The possible role of polymorphisms in drug-metabolizing genes, including the cytochrome P-450 enzymes, glutathione S-transferases, and arylamine N-acetyltransferases in chemotherapy-related leukemias has been reviewed. Felix et al. described an association between CYP2A4 genotype and treatment-related leukemia. Other factors in the development of chemotherapy-related leukemias may include interindividual differences in repair of DNA damage, germline mutations in tumor suppressor genes, administration of concomitant medications, and interpatient variation in renal and hepatic function. Clarification of the important interrelationships between these factors are critical to a better understanding of individual susceptibility to secondary leukemia. Because cancer patients frequently receive large doses of cytotoxic drugs, interindividual differences in drug absorption, distribution, metabolism, and excretion are accentuated. Until these influences and their interrelationships are better understood, empirical end points, such as the development of acute hematopoietic toxicity after chemotherapy, might be explored for their value as possible surrogate markers of secondary leukemia risk.

For cytotoxic agents for which both oral and intravenous formulations are available, the route of administration in describing dose-response associations with secondary leukemia risk should also be taken into account. Whether chemoprotectants such as amifostine (WR-2721), which ameliorates the myelosuppressive effects of alkylating agents and platinum compounds, might possibly contribute to decreased risks of second leukemias should be examined.

Many chemotherapeutic agents are known mutagens and animal carcinogens, and the induction period of solid tumors may be longer than the observation period available in published research. Thus, the question of whether the increased risks of leukemia after chemotherapy might be later followed by excess solid tumors is important. To date, the causal link between cyclophosphamide and breast cancer represents one of the few established relationships between a specific cytostatic drug and a solid tumor (reviewed later in Non-Hodgkin's Lymphoma). Elevated risks of bone sarcomas and possibly lung cancers also have also been observed after alkylating agent chemotherapy. The contribution of chemotherapy to radiation-induced solid tumors should also be investigated. For example, as discussed in the section Pediatric Malignancies, doxorubicin has been found to potentiate the development of second solid tumors after radiation for Wilms’ tumor. The investigators of this study hypothesized that doxorubicin may inhibit the repair of radiation-induced damage, likely through its interaction with DNA topoisomerase II. Newton et al. reported a significantly shorter time to bone sarcoma in children given both anthracyclines and radiation to treat cancer. The radiation enhancement properties of other cytotoxic drugs (e.g., platinum, hydroxyurea, and 5-fluorouracil) have been well described, whether these features might be correlated with increased risk of solid tumors in cancer patients who survive long term after radiotherapy might also be explored.

RISK OF SECOND MALIGNANCY IN PATIENTS WITH SELECTED PRIMARY CANCERS

HODGKIN'S DISEASE

In view of the excellent cure rates that are currently achieved in the relatively young population of Hodgkin's disease patients, it has become increasingly important to evaluate how the occurrence of second cancers affects their long-term survival. Since the first reports of increased second cancer risk in Hodgkin's disease patients in the early 1970s nearly all major treatment centers have reported second cancer risk in their patients. An excess of AML in chemotherapy-treated patients and an increased risk of solid tumors in radiotherapy-treated patients have been reported consistently in the literature. The overall risk of selected second malignancies compared with the general population is given in Table 55.7-1, based on a combined analysis of three studies that included a total of 9618 patients.

The largest relative risk (95-fold) is observed for AML, followed by a 19-fold increased risk for NHL, tenfold excesses for connective tissue and bone cancers, and a ninefold elevated risk for thyroid cancer. Moderately increased risks (two- to fivefold) are observed for a number of solid tumors, such as cancers of the lung, stomach, colon, breast, mouth, and pharynx, as well as melanoma. Because AML and NHL are diseases with a low incidence in the general population, even a high relative risk compared to the population may translate into a low cumulative (actuarial) risk. As shown in Figure 55.7-1, for the entire follow-up period, the cumulative risk of solid tumors far exceeds that of leukemia or NHL. Absolute excess risk is the best measure to judge which subsequent tumors contribute most to the second cancer burden. Table 55.7-1 shows that, compared with the general population, Hodgkin's disease patients experience an excess of 62 malignancies per 10,000 person-years of observation. Solid tumors account for the majority of excess cancers (38 per 10,000 patients per year), while lung cancer contributing 13 excess cases per 10,000 person-years. Leukemia and NHL each account for approximately 12 cases per 10,000 person-years.

The evolution of second malignancy risk over follow-up time varies by tumor site. In the majority of studies, increased leukemia risk is observed as early as 2 to 4 years after initiation of chemotherapy, with peak occurrence between 5 and 9 years and decreasing risks thereafter. In studies with large numbers of long-term survivors, significantly increased relative risks are still observed for 15 years after first treatment. The relative risk of NHL is already greatly increased in the first 5 years after treatment. In some studies, the risk remains rather constant over time, whereas others report that risk increases with time since treatment. The relative risk of solid tumors is minimally elevated in the 1- to 4-year follow-up period and increases steadily with increasing follow-up time from 5 years since first treatment. For several tumor sites (breast, thyroid), the excess risk does not become apparent until after 10 or even 15 years of observation. In the few studies that include data on 20-year survivors, the relative risk of solid tumors continued to increase through the 15- to 20-year follow-up period. Almost no data are available on the time course of risk 20 or more years after treatment. In a study of patients diagnosed with Hodgkin's disease before age 40 in the Netherlands, the relative risk of solid tumor development in 25-year survivors was somewhat lower than in the 15- to 20-year follow-up period (RRs of 5.3 and 6.8, respectively, P < .001), suggesting that relative risk may decrease in very long-term survivors.

In this study, the 25-year risk of developing any second malignancy was 27.7% (95% CI 23.1% to 32.8%), compared with 4% in the general population (see Table 55.7-1). Because the relative risks of leukemia and NHL, and solid tumors each show a distinctive pattern with time since first treatment, the absolute excess risks in 10-year survivors differ greatly from those observed in the entire patient population. Based on combined estimates from two of the studies included in Figure 55.7-1, lung cancer contributes most to the absolute excess risk in 10-year survivors, with 22 excess cases per 10,000 patients per year, followed by NHL (16 per 10,000 per year), gastrointestinal tract tumors (15 per 10,000 per year), and leukemia (7 per 10,000 per year). In females, breast cancer accounts for most of the absolute excess risk in 10-year survivors (58 per 10,000 per year).

![Figure 55.7-1](image_url)

**Figure 55.7-1.** Cumulative risk of second cancers in 1253 patients with Hodgkin's disease diagnosed younger than 40 years of age. MDS, myelodysplastic syndromes. (From ref. 50, with permission.)
For several second malignancies, the association with treatment factors has been investigated in detail. Leukemia after Hodgkin's disease is certainly the most studied malignancy induced by treatment, and extensive knowledge of its risk factors has emerged. Radiotherapy alone is associated with very little or no increased risk of leukemia, whereas alkylating agent chemotherapy is linked with greatly elevated risk. Several studies have compared the leukemogenicity of different chemotherapy regimens. Risk of AML rises sharply with an increasing number of mechloethamine, vincristine, procarbazine, and prednisone (MOPP or MOPP-like) cycles. The risk associated with 10 to 12 MOPP cycles appears to be approximately three to five times higher than the risk after six MOPP cycles. Since the 1980s, MOPP-only chemotherapy has been gradually replaced by doxorubicin, bleomycin, vinblastine, and dacarbazine (ABV(D))-containing regimens in many centers. Only a few reports have described AML occurrence after ABV(D) alone. Patients treated with ABVD in the Milan Cancer Institute, where this regimen was designed, were shown to have a significantly lower risk of AML than MOPP-treated patients (15-year cumulative risks of 0.7% and 9.5%, respectively). Another study showed that Hodgkin's disease patients treated with MOPP/ABV(D)-containing regimens in the 1980s had a substantially lower risk of AML/HD than patients treated in the 1970s with MOPP alone (10-year cumulative risks of 2.1% and 6.4%, respectively, \( P = .07 \)). The German-Austrian Pediatric Hodgkin's Disease Group observed a low risk of AML (1.1% at 15 years) after regimens that contained relatively low doses of procarbazine, doxorubicin, and cyclophosphamide, without mechloethamine.

An important question is whether radiotherapy adds to the leukemia risk associated with chemotherapy. Evidence that combined modality treatment results in greater risk than chemotherapy alone is provided by several reports, whereas other large series indicate that the risk of AML after combined treatment is comparable to that after chemotherapy alone. These inconsistent results may be due partly to differences in treatment regimes between studies but also lack of adjustment for type and amount of chemotherapy in some reports. The interaction between radiotherapy and chemotherapy could be evaluated most rigorously in the large case-control study by Kaldor and associates, which included 163 cases of leukemia after Hodgkin's disease. When examining the combined effects of radiation dose to the active bone marrow and number of mechloethamine-procarbazine containing cycles, it was found that, for each category of radiation dose (less than 10, 10 to 29, and more than 30 Gy), and for each epoch of diagnosis (1975 to 1984 and 1985 to 1991), the risk of AML was equal to or lower than that expected on the basis of its natural history with an approximate twofold difference in risk between patients who did and did not undergo a splenectomy. In other reports, however, splenectomy was either not linked or was only weakly related to leukemia risk. The mechanism underlying the association with splenectomy remains unclear, but a relationship with immunologic function of the spleen seems likely.

Increased risks of solid cancers after Hodgkin's disease generally have been attributed to radiotherapy. Increased risks of NHL occur in immunosuppressed patients, such as transplantation recipients, and because Hodgkin's disease may be accompanied by immunosuppression, several studies have argued that the elevated risk of NHL may be attributed to Hodgkin's disease itself rather than to its treatment. This view is supported by several studies in which risk did not vary appreciably between treatments. In other studies, however, the risk of NHL was found to be lowest among patients treated with radiotherapy alone and highest among patients who received integrated combined modality treatment, both initially and for relapse. The inconsistent results regarding the relationship with treatment may be partly attributed to diagnostic misclassification—that is, misdiagnosis of the primary tumor as Hodgkin's disease, whereas NHL was represented according to modern lymphoma classification schemes. In only very few studies were pathologic diagnoses of NHL obtained by biopsy. Although transformation to NHL may be part of the natural history of some types of Hodgkin's disease, the role of intensive combined modality treatment and its associated immunosuppression should be explored further.

For each malignancy, there is generally an increased risk of developing the breast cancer after radiotherapy for Hodgkin's disease. Fifteen-year survivors who had radiation treatment before 20 years of age had an 18-fold increased risk of breast cancer; women irradiated at ages 20 to 29 had a sixfold increased risk, and a small, nonsignificant increase was observed among those with a baseline incidence of the disease in older persons. In the few studies that have analyzed relative risk of leukemia by age, based on comparisons to general population expectations, no differences between age groups were observed, whereas the relative risk of AML was even significantly greater at younger ages than at older ages. A second malignancy to treatment may be attributed to radiotherapy, which may be responsible for site-specific increased risks of solid tumors. The strongly elevated risk of breast cancer after radiotherapy for Hodgkin's disease has become a major concern for female survivors. Two case-control studies of 2846 patients showed a significantly increased risk of lung cancer after chemotherapy alone, with the relative risk (4.2; 95% CI, 2.2 to 7.3) of similar magnitude as that observed in patients treated with either extensive radiotherapy or combined modality treatment. A similar excess risk of lung cancer in patients given chemotherapy, but no radiotherapy, was found in a more recent expansion and update of this study. No increased risk of lung cancer, or solid tumors overall, followed chemotherapy alone in several other series. However, the expected number of solid tumors 10 or more years after chemotherapy alone was less than two in nearly all negative studies, rendering it impossible to moderate a large increase in risk. If chemotherapy indeed affects solid tumor risk, one would expect that patients receiving combined modality treatment would have a greater relative risk than patients treated solely with radiotherapy. Only one study to date has reported a significantly greater risk for solid cancers overall after chemotherapy and radiotherapy compared with irradiation alone, whereas other large series indicate that the risk of AML after combined treatment is comparable to that after irradiation alone.

A very important question is whether chemotherapy for Hodgkin's disease can also induce solid cancers, and if so, at which sites. A few studies have raised concern about a possible long-term effect of chemotherapy on lung cancer risk. The British National Lymphoma Investigation cohort study of 2846 patients showed a significantly increased risk of lung cancer after chemotherapy alone, with the relative risk (4.2; 95% CI, 2.2 to 7.3) of similar magnitude as that observed in patients treated with either extensive radiotherapy or combined modality treatment. A similar excess risk of lung cancer in patients given chemotherapy, but no radiotherapy, was found in a more recent expansion and update of this study. No increased risk of lung cancer, or solid tumors overall, followed chemotherapy alone in several other series. However, the expected number of solid tumors 10 or more years after chemotherapy alone was less than two in nearly all negative studies, rendering it impossible to moderate a large increase in risk. If chemotherapy indeed affects solid tumor risk, one would expect that patients receiving combined modality treatment would have a greater relative risk than patients treated solely with radiotherapy. Only one study to date has reported a significantly greater risk for solid cancers overall after chemotherapy and radiotherapy compared with irradiation alone, whereas no such difference has been found in the majority of investigations. However, for selected solid cancer sites (e.g., gastrointestinal tract), larger risks were observed after combined modality treatment than after irradiation alone. For lung cancer risk in irradiated patients, two case-control studies showed no association with chemotherapy overall, the number of cycles, or the cumulative doses of mechloethamine and procarbazine, which argues against an important contribution of chemotherapy to lung cancer risk. The inconsistent results reported with regard to the influence of chemotherapy on solid tumor risk may be partly related to the fact that most studies considered all solid tumors combined, whereas chemotherapy may differentially affect the risks of tumors at disparate sites. A study from the Netherlands Cancer Institute demonstrated that the addition of salvage chemotherapy to initial radiotherapy, as compared to initial irradiation alone, did not influence the risk of solid cancers overall but significantly increased the risk of solid tumors other than breast cancer (RR: 9.4; 4.3-20.3, compared to 4.7; 1.9-10.7 for irradiation alone). Conversely, patients who received salvage chemotherapy were found to experience significantly lower risks of breast cancer than patients treated with radiotherapy alone (RRs of 2.8 and 7.6, respectively), possibly related to premature ovarian failure due to intensive chemotherapy. Additional studies are warranted to examine which cytotoxic drugs might be responsible for site-specific increased risks of solid tumors.
for women irradiated at age 30 or older (RR, 1.7). A similar trend, with even larger relative risks, has been reported from Stanford University. There was an approximately 100-fold increase in breast cancer risk has been observed after treatment at younger than 16 years of age, with relative risks ranging from 17 to 458. This huge variation in estimated risk is not surprising in view of the large differences between series in important variables such as proportion of patients irradiated, duration of follow-up, and completeness of follow-up. Generally, surveys with more complete follow-up have found lower relative risks of breast cancer than those in which completeness of follow-up was less satisfactory or not addressed. Complete follow-up may lead to overestimation of second malignancy risk if patients who remain well lose contact with clinical follow-up, whereas those with second cancer come to attention because of this. The very high actuarial risks reported in two U.S. studies (34% at 25 years after first treatment for women treated at younger than 20 years of age, and 35% at 40 years of age for those treated when younger than 16 years) are likely to be exaggerated estimates, not only because of losses to follow-up, but also because the actuarial method is less appropriate when including events that occur at follow-up intervals later than those at which data for most of the patients were censored. In the more recently published Dutch study, with (nearly) complete follow-up, the 25-year actuarial risk of breast cancer amounted to 16%, both for women first treated before the age of 20 and at ages 20 to 30. In two studies, the majority of breast cancers arose within or at the margin of the anterior radiation field, in breast tissue that had received a treatment dose of 40 to 46 Gy. Because it is not known whether breast cancer risk is linearly related to radiation dose in the therapeutic dose range, it will be of interest to see whether the reduced mantle field doses in current treatment protocols will result in lower breast cancer risk.

Several studies have demonstrated that age at treatment for Hodgkin's disease is also a crucial determinant of increased relative risks for solid malignancies other than breast cancer. Van Leeuwen and colleagues reported that the relative risks of nonbreast solid tumors were 4.9, 6.9, and 12.7 for patients first treated at ages 31 to 39, 21 to 30, and 20 or younger, respectively (Table 55.7-2). Data from Stanford University and the United Kingdom show that the highest relative risks for gastrointestinal cancers (approximately eightfold) and thyroid cancer occur among patients treated before age 25, with no excesses observed for those treated after 45 years of age. Importantly, Table 55.7-2 demonstrates that the absolute excess risk of developing a solid cancer does not show much variation by age at first treatment, probably because the increasing background incidence of solid tumors with age in the population at large outweighs the stronger increase of relative risk at younger ages.

The strongly increased relative risks of solid tumors in patients treated for Hodgkin's disease at a young age only become manifest after an extended follow-up period. This might point to a prolonged induction period, but it may also be due to this young patient group reaching an age at which solid tumor incidence begins to rise in the general population. Although a few studies addressed the relative risk of solid malignancies according to attained age, only one study distinguished the separate contributions of age at first treatment and attained age. Solid tumor risk was greatest among patients treated at a young age (20 years or younger), but the largest relative risk emerged before the patients attained the age range at which solid tumors normally occur. Among patients first treated at age 20 or before, the relative risk was highest in the 40 to 49-year age group. The relative risk of solid tumor was significantly lower (RR, 1.7) for women irradiated at age 30 or older (RR, 1.7). A similar trend, with even larger relative risks, has been reported from Stanford University. In the more recently published Dutch study, with (nearly) complete follow-up, the 25-year actuarial risk of breast cancer amounted to 16%, both for women first treated before the age of 20 and at ages 20 to 30. In two studies, the majority of breast cancers arose within or at the margin of the anterior radiation field, in breast tissue that had received a treatment dose of 40 to 46 Gy. Because it is not known whether breast cancer risk is linearly related to radiation dose in the therapeutic dose range, it will be of interest to see whether the reduced mantle field doses in current treatment protocols will result in lower breast cancer risk.

In conclusion, the occurrence of treated-related second cancers is a major problem in survivors of Hodgkin's disease. The substantial increase in solid tumor risk with time since Hodgkin's disease diagnosis necessitates careful, lifelong medical surveillance of all patients. The greatly increased risk of NHL throughout follow-up demonstrates the importance of performing biopsies in recurrent Hodgkin's disease. Because smokers experience a significantly greater risk of lung cancer attributable to radiotherapy than nonsmokers, physicians should make a special effort to dissuade Hodgkin's disease patients from smoking, even before treatment starts. Women treated with mantle field irradiation before age 30 are at greatly increased risk of breast cancer. The importance of regular breast examinations should be explained to them, and they should be taught to perform monthly breast self-examination. From 8 years after irradiation, the follow-up program of these women should include yearly breast palpation and mammography. Physicians should also be alert to the higher risk of gastrointestinal cancers in patients who received paraaortic and pelvic radiation fields. Thorough examination of gastrointestinal complaints is indicated. An important question to be answered in future research is whether, in long-term survivors, chemotherapy contributes to the risk of solid tumors, and if so, which cytotoxic drugs are responsible for the excess risk. The most compelling evidence that second malignancy may increase among patients cured of Hodgkin's disease is chemotherapy-related leukemia. Because the poor prognosis of this complication cannot be changed by early diagnosis, it is promising that leukemia risk has decreased dramatically with the introduction of ABV-based regimens in the 1980s. It is hoped that current treatment protocols that limit the dose and fields of radiotherapy will similarly reduce the late risk of solid cancers.

### NON-HODGKIN'S LYMPHOMA

Although surveys in the past concluded that NHL patients are at increased risk for second solid tumors, most either predated the advent of modern therapeutic approaches or lacked sufficient statistical power to detect all but very high risks. Due largely to the introduction of effective treatment, NHL patients now demonstrate a 5-year relative survival rate of approximately 51%. Commensurate with improvements in life expectancy, several large follow-up studies of NHL patients reported significantly increased risks of second cancers. In the largest published study to date, the incidence of second malignancies was estimated in 29,153 patients diagnosed with NHL between 1973 and 1987 in one of nine population-based areas participating in the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) program. Significantly increased risks were observed for all second cancers taken together (observed/expected [O/E] = 1.2; O = 1231), with excesses increasing with follow-up time to reach 1.8 in 10-year survivors. A subsequent international survey of 6171 2-year survivors of NHL confirmed the increased risk of second cancer and showed that significant excesses persisted for two decades. In an update of the SEER program data, which included more than 48,000 patients diagnosed with NHL between 1973 and 1993, significantly increased site-specific risks were observed for cancers of lip (O/E = 2.0), lung (O/E = 1.4), kidney (O/E = 1.4), thyroid (O/E = 2.0), and bone (O/E = 4.1), as well as AML (O/E = 3.6) (L. Travis, unpublished observations). Although registry-based treatment data are incomplete, it appeared that chemotherapy was related to subsequent AML and to bladder cancer and that radiotherapy was associated with AML and, possibly, cancers of lung, bladder, and bone.

The excesses of second primary malignancies in NHL patients have been examined in relationship to treatment for NHL. The largest investigation was a cohort of 6171 2-year survivors of NHL and included 31 patients with transitional cell carcinoma, along with 17 cases of kidney cancer. Detailed information on chemotherapeutic drugs and cumulative dose was collected for all subjects, and radiation dose to the target organ was estimated from individual radiotherapy records. A significant 4.5-fold risk of bladder cancer followed therapy with cyclophosphamide, with risk strongly dependent on cumulative dose (Table 55.7-3).
TABLE 55.7-3. Risk of Bladder Cancer According to Cumulative Dose and Duration of Cyclophosphamide Therapy

Significantly elevated sixfold and 14.5-fold risks followed cumulative doses of 20 to 50 g and 50 g or more, respectively (P trend = .004). Neither radiotherapy nor cyclophosphamide was associated with excess kidney cancers. The absolute risk of bladder cancer predicted during 15 years of follow-up was on the order of three excess cancers per 100 NHL patients who had been given cumulative doses of between 20 and 50 g. At cumulative doses of 50 g or more, the excess risk increased to approximately seven bladder cancers per 100 NHL patients.

NHL treatment has been linked to excess risks of AML in several studies,144,151,152,153,154,155 which have been reviewed.156 Because leukemic progressions of NHL (lymphocytic leukemias) are relatively frequent, histopathologic confirmation of AML diagnosis has been an essential part of all series in which leukemia risk was suggested.157,158 A large study of NHL patients among whom 35 cases of AML or MDS were identified. The risk of AML was only weakly associated with the use of cyclophosphamide-containing regimens (RR, 1.8; 95% CI, 0.7 to 4.9) and did not increase with increasing cumulative dose or duration of treatment. However, the median cumulative dose of cyclophosphamide was only 12.5 g, which is considerably lower than in previous studies14,159 in which nine leukemia cases each were included and substantially higher risks (RR, 105 and 76, respectively) were reported. The weak association between cyclophosphamide at low dose levels and AML,157 however, supports other evidence that the drug has a low leukemogenic potential.154 Among 10,000 NHL patients treated for 6 months with chemotherapy regimens containing low cumulative doses of cyclophosphamide, an excess of four AMLs might develop in 10 years of follow-up.157 This is an important conclusion in view of the frequent use of cyclophosphamide-containing regimens in current treatment regimens for NHL. Risk of AML after alkylating agent therapy did not vary significantly by age at NHL diagnosis or gender when evaluated by multivariate methods.

Low-dose total body irradiation (TBI), as used in past treatment approaches for NHL, seems linked with an unusually high occurrence of secondary leukemias.155,156 This treatment modality used very low individual TBI fraction sizes (most commonly 10 to 15 cGy) given several times a week until a cumulative dose of approximately 150 cGy was administered. The risk of leukemia after low-dose TBI was quantified in a study of 61 2-year NHL survivors who received low-dose TBI as primary therapy.160 Four NHL patients developed AML (RR, 1.17 compared with population rates; 95% CI, 0.71 to 0.38). A fifth patient was diagnosed with MDS. All five patients with secondary hematologic malignancies had received salvage treatment with either alkylating agents alone or combined modality therapy. It is noteworthy that the excess risk of AML after low-dose TBI160 was much greater than the risk observed in the larger international investigation of AML after NHL,157 although similar chemotherapy regimens were used. Other types of NHL treatment that combine high-dose, large-field radiotherapy with alkylating agents also have been associated with very large risks (100- to 1000-fold) of AML.14,151 It is likely that the chemotherapy contributed to the excess risk of leukemia, either directly or by enhancing the effect of low-dose TBI.157 Studies of laboratory animals suggest that low-dose TBI may expand the number of bone marrow stem cells subject to potential transformation by alkylating agents.157

Estimates of the cumulative risk of secondary MDS/AML 5 to 6 years after autologous bone marrow transplantation (ABMT) for NHL range from 4% to 18%.158,159 A large study with data on prior therapy, the transplant preparative regimen, and the transplantation procedure itself.160 The largest study of second malignant neoplasms after lymphoma included 28,843 1-year survivors diagnosed with a first primary cancer of the testis between 1935 and 1993 and reported to 16 population-based cancer registries in North America and Europe.161 More than 3300 testicular cancer patients survived more than 20 years after diagnosis. Second cancers, excluding contralateral testis, developed in 1406 patients (O/E = 1.43; 95% CI, 1.36 to 1.51) (Table 55.7-4).

TABLE 55.7-4. Observed and Expected Numbers of Selected Second Malignant Neoplasms among 1-Year Survivors of Testicular Cancer

The absolute risk was 16 excess cancers per 10,000 men per year. Significantly elevated risks were observed for all second solid tumors (O/E = 1.4; O = 1251), with significant site-specific excesses for ALL, acute lymphocytic leukemia, melanoma, NHL, and cancers of the stomach, colon, rectum, pancreas, prostate, kidney, bladder, thyroid, and connective tissue. Second cancer risk was similar after seminomas (O/E = 1.4) and nonseminomatous tumors (O/E = 1.2), with little variation in site-specific patterns. Increased risks for cancers of small intestine (O/E = 4.4) and rectum (O/E = 1.6) were observed only for seminomas, whereas patients with
nonseminomatous germ cell tumors (GCT) showed elevated twofold risks for hepatobiliary cancer. Risk of solid tumors increased with time since diagnosis of testicular cancer to reach 1.5 after 20 years (P trend = .00002). Among 20-year survivors, 369 (O/E = 1.5) solid tumors were reported, with significant excesses for cancers of stomach (O/E = 2.3), colon (O/E = 1.7), pancreas (O/E = 3.2), prostate (O/E = 1.4), kidney (O/E = 2.3), bladder (O/E = 2.8), and connective tissue (O/E = 4.7). The actuarial risks of developing any second cancer, excluding contralateral testicular tumors, were 15.7% and 22.6%, respectively, 25 and 30 years after testicular cancer diagnosis. The corresponding population expected risks were 9.3% and 13.1%, respectively. The somewhat higher cumulative risk of second cancer at 25 years for men with seminomas (Fig. 55.7-2) reflects the younger mean age of the patients with nonseminomatous tumors, because the excess cumulative risks were comparable.

Increased risks for cancers of the stomach, bladder and, possibly, pancreas seemed associated with antecedent radiotherapy, whereas leukemia was linked with both prior radiation and chemotherapy. In the large doses (mean, 13 to 26 Gv) of radiation could be delivered to the stomach during irradiation of paraaortic lymph nodes for testicular cancer. In prior smaller surveys, a significant eightfold risk of stomach cancer (n = 2) was associated with intra- and supradiaphragmatic irradiation for testicular tumors, and a four- to fivefold risk with was associated with abdominal radiotherapy (n = 10). The study by Travis et al demonstrated that the increased risks for stomach cancer persisted for at least two decades after diagnosis of testicular cancer. After irradiation for peptic ulcer disease, significant excesses of stomach cancer extend beyond 30 years. A pattern of increasing risk of pancreas cancer with time in the international study, with excesses mainly in testicular cancer patients who received initial radiotherapy, was suggestive of a radiogenic effect, consistent with the location of the pancreas in the irradiation field (mean organ dose, 17 to 34 Gv) during therapy for testicular cancer. The pancreas is not considered particularly susceptible to the carcinogenic effects of ionizing radiation, except when very high doses (e., on the order of 13 Gy) are given.

Few large, comprehensive studies that quantify the high risk of contralateral testicular cancer (CLTC) have been published, which has historically been attributed to common predisposing factors, such as cryptorchism or atrophic testis. Van Leeuwen and colleagues assessed the risk of all second malignancies, including CLTC, in a large cohort of 36,847 men with testicular carcinoma from several registries. Risk of solid tumors increased with time since diagnosis of testicular cancer, and nearly complete risk information were available. With a median follow-up of 7.7 years, 20 CLTCs were observed (RR, 35.7; 95% CI, 21.8 to 55.2). Importantly, it appeared that chemotherapy may have reduced the risk of CLTC compared with patients who received radiation alone.

The increased risk of second cancers after testicular cancer is an order of magnitude lower than that observed in patients with Hodgkin's disease. Moderately elevated risks have been observed after chemotherapy, but also after irradiation alone. Mediastinal nonseminomatous GCTs are known to be associated with an inherent predisposition to develop secondary leukemias, however, such a relationship has not been reported for testicular tumors. In men with mediastinal GCT and leukemia, both cancers contain the cytogenetic abnormality t(12p) pathognomonic of GCT, consistent with a common derivation. In contrast, cytogenetic studies of leukemias that follow testicular cancer have displayed alterations characteristic of treatment-related AML. Analytic studies that have examined the risk of leukemia after testicular cancer have typically excluded mediastinal GCT.

In the early years of platinum-based chemotherapy, the majority of patients received the PVB regimen (cisplatin, vinblastine, bleomycin). The absence of excess leukemia risk after this regimen has been documented in several large studies. In contrast, a number of studies have reported a 20- to 330-fold increased risk of AML after etoposide-containing regimens, which were introduced for the treatment of testicular cancer in the early 1980s. Most cases of AML/MDS were observed in the subgroup of 82 patients who had received cumulative doses of more than 3000 mg/m of etoposide. Most etoposide-containing treatment regimens for testicular cancer have used lower cumulative doses of etoposide (up to 2000 mg/m) and also a lower dose intensity (100 to 120 mg/m). On the basis of the combined data from five studies, Bokemeyer and Schmoll estimated that the relative risk for AML was approximately 20-fold increased in patients treated with conventional etoposide-containing regimens (cumulative dose less than 2000 mg/m). Because of the low background incidence of AML in the population, this rather high relative risk translates to a low cumulative risk of 0.6% (95% CI, 0.3 to 0.9%) at 5 years.

In conclusion, patients treated for testicular cancer have less than one-third of the excess risk of second malignancy experienced by patients with Hodgkin's disease. The increased risk of stomach cancer should alert clinicians to the importance of thorough examination of gastrointestinal complaints in patients who received radiotherapy to the paraaortic lymph nodes. Because all reports of increased risks of gastrointestinal cancer have derived from studies in which patients were treated with high doses of radiation, it is important to determine whether smaller risks will follow the lower doses (20 to 25 Gy) that are currently used. Reassuringly, PVB chemotherapy seems to carry a negligible risk of leukemia. Although high-dose etoposide therapy (more than 2000 mg/m in combination regimens) is associated with substantial excess leukemia, cumulative risk after conventional-dose etoposide-containing regimens is low. Radiotherapy regimens for testicular cancer have been modified with the introduction of smaller fields, lower doses, and lower doses, and elimination of prophylactic mediastinal irradiation, but the late sequelae of therapy given decades ago continue to emerge. In the future, radiation dose to second cancer sites for which risks are elevated should be estimated in individual patients, along with specific chemotherapeutic agents to further delineate the contribution of treatment factors. Long-term follow-up studies are also needed to evaluate the risk of second solid tumors among testicular cancer patients treated with modern cisplatin-based chemotherapy.

**OVARIAN CANCER**

Because survival for ovarian cancer patients has improved significantly within the last two decades, the study of second primary cancers has assumed increasing clinical importance. The site-specific risk of solid tumors after ovarian cancer has been quantified in a large population-based study of more than 32,000 women with ovarian cancer, including 4402 10-year survivors. Almost 1300 second cancers (n = 1296) were reported, representing a significantly increased risk (O/E = 1.3; 95% CI, 1.2 to 1.4). Significant excesses were observed for cancers of colon (O/E = 1.3), rectum (O/E = 1.4), breast (O/E = 1.2), and bladder (O/E = 2.1), as well as leukemia (O/E = 4.2). Ovarian melanoma (O/E = 4.5) was also significantly increased. Secondary leukemia appeared to be linked with antecedent chemotherapy, whereas radiotherapy was associated with cancers of connective tissue, bladder and, possibly, pancreas. The risk of solid tumors was elevated during all follow-up intervals, including 10 to 14 years (O/E = 1.3) and 15 years or more (O/E = 1.3) after ovarian cancer. Fifteen-year survivors experienced significant excesses of cancers of pancreas, bladder, and connective tissue. The cumulative risk of second cancers at 20 years was 18.2% compared with a population-expected risk of 11.5% (Fig. 55.7-3).
In an analytic study of bladder cancer after ovarian cancer, Kaldor et al. 22 found increased risks after radiotherapy only (RR, 1.9; 95% CI, 0.8 to 4.9) compared with patients treated with surgery alone. Cyclophosphamide-based chemotherapy, with or without radiotherapy, was associated with a fourfold risk.

Large risks of AML and preleukemia have been documented after ovarian cancer, and they have been linked to therapy with melphalan, 17,2,24 cyclophosphamide, 17,29,130 and chlorambucil. 17,29 In one large population-based study of more than 28,000 ovarian cancer patients in whom 96 leukemias were diagnosed, platinum-based combination chemotherapy was associated with a significantly increased fourfold risk compared with women who received neither alkylating drugs nor radiotherapy. 20

Excesses of leukemia increased with increasing cumulative platinum dose (P trend for dose < 0.001) (Table 55.7-5).

Although the platinating agents were frequently given in combination with cyclophosphamide, doxorubicin, or both, a multivariate model that took into account the cumulative amount of these drugs did not provide an improved fit to the data (P > 5) compared with a model that took into account only dose categories of platinum. Although the risk of leukemia after platinum-based chemotherapy tended to be somewhat higher among younger patients, differences in relative risk according to age were not significant (P for heterogeneity = .48). Radiotherapy without chemotherapy (mean bone marrow dose, 13.4 Gy) did not increase the risk of leukemia, 22 but few women received radiation alone. Patients given radiotherapy and platinum-based chemotherapy, however, had a significantly (P = .006) higher risk of leukemia than those who received platinum-based chemotherapy alone in a multivariate model adjusted for cumulative amount of the drug. A dose response was observed for platinum among women treated and not treated with radiotherapy, with risks higher within the radiation group; in all of the latter patients, radiotherapy had been given as part of initial treatment. It is unlikely that women newly diagnosed with ovarian cancer would receive both platinum and radiotherapy in view of modern treatment recommendations. 25 However, the possibility that the risk of leukemia after treatment with platinum might be increased by radiotherapy should be investigated among patients with other cancers, especially cancers of bladder and head and neck, given therapeutic strategies to increase dose intensities of both modalities in the treatment of these tumors. 26

The risk of leukemia associated with the cumulative dose of melphalan 17,2,24 and, importantly, route of administration 31 also has been evaluated among women with ovarian cancer. In the largest study to date, 31 significant excesses of leukemia followed intravenous (RR, 2.29) and oral (RR, 9.0) melphalan, and risks increased with increasing cumulative dose and duration of therapy. Intravenous melphalan was six times more leukemogenic than platinum.

In conclusion, survivors of ovarian cancer experience significantly increased risks of secondary leukemias and solid tumors. Despite the elevated relative risk of leukemia after modern platinum-based chemotherapy for ovarian cancer, the absolute risk is small. 31 Of 10,000 ovarian cancer patients treated for 6 months with cumulative doses of cisplatin between 500 and 1000 mg or 1000 mg or more and followed for one decade, an excess of 21 and 71 leukemias, respectively, was predicted based on observed risks. 32 Thus, Travis and colleagues 32 concluded that the significant improvement in clinical response provided by platinum-based treatment for advanced ovarian cancer, with 5-year survival rates of up to 20% to 30%, 9,22 far exceeded the relatively small excesses of leukemia. Further interdisciplinary investigations are needed to elucidate the carcinogenic risks associated with modern therapies for ovarian cancer and with shared susceptibility mechanisms, including genetic and reproductive factors. Meanwhile, in proposing recommendations for the follow-up and management of women with ovarian cancer, 36 it is important to recognize their long-term predisposition to an array of second cancers.

**BREAST CANCER**

Numerous studies have demonstrated that women with breast cancer are at a three- to fourfold increased risk of developing a new primary cancer in the contralateral breast. 58,194 Significant excesses relative to the general population also have been observed for cancers of the ovary, 25,195 uterus, 25,195 lung, 183,195,196,199 esophagus, 183 colon-rectum, 183,195,196 connective tissue, 183,195,196,197 and thyroid, 183 as well as melanoma 183,195 and leukemia. 179,195,196 For some of these cancers, such as those of the contralateral breast, ovary, and uterus, and possibly melanoma, the excesses may be fully or partly explained by a common etiology (e.g., genetic predisposition or hormonal risk factors). Other excess risks may be treatment-related or reflect the interaction of several factors. Adjuvant chemotherapy, hormonal treatment, and radiotherapy, and combinations of these modalities, are being administered to a growing proportion of breast cancer patients. In view of the proven therapeutic benefit of these treatments 183,195 and the prolonged life expectancy of those treated, it has become exceedingly important to evaluate the carcinogenic potential of adjuvant treatment.

Contralateral breast cancer has been documented for 40% to 50% of all second tumors in women with breast cancer. 122 and the 15-year cumulative risk of developing contralateral disease amounts to 10% to 13%. 122,188 With this high risk, even small effects of treatment may have a large impact in terms of absolute numbers of contralateral breast cancers. The effect of radiation treatment for the initial breast cancer was evaluated in two large case-control studies in Connecticut and Denmark that involved 655 and 529 women with contralateral breast cancer, respectively. The mean radiation doses to the contralateral breast were estimated at 2.8 and 2.5 Gy, respectively. 122 Both studies found that radiotherapy did not contribute to the high risk of contralateral disease among women treated after the age of 45. In the Connecticut study, however, significantly elevated risks were observed for women who underwent irradiation before the age of 45, with a radiation-associated relative risk of 1.9 among those who survived for at least 10 years. 122 Significant excess risk in women irradiated at a young age was not found in the Danish study, possibly because it included fewer women younger than 45 years of age. 122 Based on the Connecticut study, Boice and associates 122 estimated that approximately 11% of all second breast cancers in women irradiated before age 45 could be attributed to radiotherapy.
Several large studies have shown that hormonal treatment with tamoxifen reduces the risk of contralateral breast cancer by approximately 40%. Data collected by the Early Breast Cancer Trialsists’ Collaborative Group (EBCTCG), based on 37,000 women from 55 trials, demonstrated that longer durations of tamoxifen use were associated with greater reductions in risk, such that 1 year, 2 years, and 5 years of treatment produced risk reductions of 13%, 26%, and 47%, respectively. It is not yet known whether the protective effect of tamoxifen against contralateral disease persists over prolonged follow-up periods (more than 10 years). Some studies have provided evidence that adjuvant chemotherapy may also reduce the risk of contralateral breast cancer, a phenomenon that is likely to be mediated through drug-induced premature ovarian failure.

Several studies have assessed the risk of leukemia after chemotherapy and radiotherapy for breast cancer. The relationship between AML risk and drug dose was examined in detail in the large case-control study by Curtis and associates. These investigators detailed the large number of patients with leukemia or MDS among the 82,700 women diagnosed with breast cancer between 1973 and 1985 in five areas of the United States. Compared with patients treated without alkylating agents and irradiation, the risk of AML was significantly elevated after locoregional radiotherapy alone (RR, 2.4), after treatment with alkylating agents alone (RR, 10.0) and after treatment with alkylating agents in combination with radiotherapy (RR, 17.4). The risk of AML associated with combined modality treatment was significantly greater than that for patients treated with either alkylating agents, including cyclophosphamide. Cumulative cyclophosphamide doses of less than 20 g were associated with an approximately twofold, nonsignificant increase in risk (compared with women not exposed to alkylating agents), whereas women treated with 20 g or more had a 5.7-fold risk of AML (95% CI, 1.6 to 20.6). Women who received methotrexate experienced a twofold excess risk of AML with cyclophosphamide (P < .001). After adjustment for the effects of chemotherapy, the risk of AML increased significantly with higher doses of radiation to the active bone marrow, with a sevenfold risk increase for patients who received 9 Gy or more (compared to patients not treated with radiotherapy).

Present-day adjuvant treatment of early breast cancer is in several ways different from the treatments evaluated in this large study by Curtis et al. In the 1990s, the cumulative doses of cyclophosphamide were reduced (approximately 12 to 15 g with six standard cycles of CMF (cyclophosphamide, methotrexate, and fluorouracil) or FAC (fluorouracil, doxorubicin, and cyclophosphamide). Regional radiotherapy is less frequently used. On the basis of their data, Curtis and associates estimated that, among 10,000 patients with breast cancer treated for 6 months with a cyclophosphamide-based regimen and followed for 10 years, an excess of only five cases of treatment-related AML would be expected to develop.

The low risk of AML after CMF-based chemotherapy was confirmed by the Milan Cancer Institute and the Eastern Cooperative Oncology Group, with cumulative risks of AML of 0.23% at 15 years and 0.16% at 7 years, respectively. Thirty-nine percent of women treated with CMF-based chemotherapy in the Milan series also received doxorubicin, and no clear evidence indicated a synergistic effect of cyclophosphamide and doxorubicin on leukemia risk. Radiation therapy (applied only after breast-conserving surgery) did not add to the risk of AML. The University of Texas M. D. Anderson Cancer Center has reported a higher risk of leukemia after standard dose-intensity FAC treatment. Fourteen cases of leukemia were observed among 1474 patients, for an estimated cumulative risk of 1.5% (95% CI, 0.7 to 2.9) at 10 years. The risk of AML was significantly higher when chemotherapy was given in combination with radiotherapy (2.5% vs. 0.5%).

There has been an increasing trend toward the use of dose intensification strategies in chemotherapy protocols for breast cancer. Typically, these regimens contain high-dose cyclophosphamide in combination with one of the anthracyclines (doxorubicin or 4-epidoxorubicin) and other active drugs. The risk of AML associated with such dose-intensive chemotherapy has not yet been quantified, but evidence suggests that the combination of anthracyclines and alkylating agents (including cisplatin) may be leukemogenic. With the increasing tendency to administer high doses of cytotoxic drugs accompanied by bone marrow support, there is certainly a strong need to closely monitor the subsequent risk of AML.

Patients treated with CMF-based chemotherapy have not been reported to be at increased risk of solid tumors. More prolonged follow-up, however, is needed to evaluate possible carcinogenic effects 15 years or more after treatment.

Conclusive evidence has emerged that tamoxifen is associated with a moderately increased risk of endometrial cancer. The consistent results across studies with different designs, the duration-response relationship observed in several investigations, and the established estrogen-agonist effects of tamoxifen on the endometrium strongly support a causal relationship. The individual studies, which are summarized in Table 55.7-4, show that the use of tamoxifen for 2 years is associated with an approximately twofold increased risk of endometrial cancer, whereas use for 5 or more years produces four- to eightfold excess risks. Although the risk estimates in some studies may be affected by a certain degree of detection bias as a result of gynecologic examinations in women with side effects from tamoxifen, the magnitude of the observed risk is unlikely to be explained by such bias. Furthermore, the analysis of the EBCTCG not only shows increased incidence of endometrial cancer in women randomized to tamoxifen treatment (as compared to women not randomized to tamoxifen) but also significantly increased mortality due to endometrial cancer. From Table 55.7-4, it is clear that elevated risks of endometrial cancer have been observed after daily tamoxifen dosages of 20 mg, 30 mg, or 40 mg. In the Netherlands case-control study, which included different dose intensities, daily dosage did not affect endometrial cancer risk in a model accounting for duration of use, and the duration-response trends were similar, with daily doses of 40 mg, 30 mg or less. Very few studies have addressed the risk for ex-users. In three investigations, and recent and former users of tamoxifen were found to experience very similar increases in risk; however, only a few patients had discontinued tamoxifen more than 2 years before the diagnosis of endometrial cancer.

### Table 55.7-6: Risk of Endometrial Cancer after Tamoxifen Therapy in Women with Breast Cancer

<table>
<thead>
<tr>
<th>Tamoxifen Use</th>
<th>Endometrial Cancer Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>Baseline</td>
</tr>
<tr>
<td>1 year</td>
<td>1.00 (1.00-1.00)</td>
</tr>
<tr>
<td>2 years</td>
<td>1.05 (1.00-1.11)</td>
</tr>
<tr>
<td>5 years</td>
<td>1.47 (1.17-1.86)</td>
</tr>
<tr>
<td>More than 5</td>
<td>1.87 (1.45-2.42)</td>
</tr>
</tbody>
</table>

Only two studies have addressed the combined effects of tamoxifen and other risk factors for endometrial cancer. In the largest study conducted to date, Bernstein and colleagues reported that women who previously used estrogen replacement therapy experienced greater increases in endometrial cancer risk associated with tamoxifen use than women not exposed to estrogen replacement therapy. Furthermore, the effects of tamoxifen on endometrial cancer risk were stronger among heavy women than among thin women. In the Dutch study, however, body weight did not modify the increased risk associated with tamoxifen use.

An important question is whether the clinicopathologic characteristics and ultimate prognosis of endometrial cancers after tamoxifen treatment are different from those in patients not treated with tamoxifen. In four small studies, the stage distribution and histologic features of endometrial cancers in tamoxifen-treated women were remarkably different from those diagnosed in nontreated women. Magrini and colleagues, however, reported a higher frequency of poorly differentiated and high-grade tumors with a poor prognosis in tamoxifen-treated patients. In the Dutch study, which included 309 patients with endometrial cancer after breast cancer, endometrial tumors of FIGO stage III and IV occurred more frequently among long-term tamoxifen users (2 or more years) than in nonusers (17% vs. 5%, P = .006). Based on a centralized review of diagnostic pathology slides, long-term tamoxifen users more often developed malignant mixed mesodermal tumors or sarcomas of the endometrium than did nonusers (3% vs. 1%, P = .002). Further, fewer tumors diagnosed among long-term tamoxifen users were more often p53-positive and estrogen receptor-negative. Figure 55.7-4 shows that the 3-year actuarial endometrial cancer-specific survival in this study was significantly worse for long-term tamoxifen users than for nonusers, largely due to the less favorable tumor characteristics associated with tamoxifen use.

The association between tamoxifen use and specific clinicopathologic and molecular characteristics of subsequent endometrial cancer deserves further investigation in large studies.
animal experiments have shown that tamoxifen can act as a hepatic carcinogen in rats. However, no increased risk of hepatocellular carcinoma in tamoxifen-treated patients has been observed to date. The large metaanalysis of the EBCTCG, women randomized to tamoxifen had a slightly lower mortality from primary liver cancer than the control group. The joint analysis of Scandinavian tamoxifen trials showed an elevated risk of gastrointestinal cancer after tamoxifen use (RR, 1.9, 95% CI, 1.2 to 2.9); however, the excess risk was due to colorectal and stomach cancer, not liver cancer. Furthermore, a study from the SEER program found that tamoxifen was associated with a 50% increased risk of colorectal cancer in the period 5 or more years after diagnosis. No such risk increase was observed in the EBCTCG data.

Increased risks of lung cancer after breast cancer have been largely attributed to radiotherapy. No appreciable risk increase has been observed within 10 years of treatment, but two- to threefold elevated risks have been reported in 10-year survivors. The association between breast radiotherapy and subsequent lung cancer risk was found to be stronger for the ipsilateral lung. A nonsignificant increase in lung cancer risk was noted with increasing radiation dose to the affected lung, with an approximate threefold excess risk for patients who received 5 to 10 Gy. Risk seemed to level off at doses higher than 10 Gy, as has been observed in a similar study of lung cancer after Hodgkin's disease. The results were used to predict that, among 10,000 recipients of breast cancer who received an average lung dose of 10 Gy, approximately nine additional lung cancers would be expected to develop per year. Current radiotherapy practices for breast cancer involve high-energy megavoltage treatment to local and regional radiation fields, which results in considerably lower lung doses than the orthovoltage and cobalt-60 radiation treatments used in the studies described above. The risk of radiogenic lung cancer should be correspondingly lower (i.e., approximately one excess lung cancer per 10,000 women-years per Gy) beginning 10 years after radiotherapy. In one study, smokers were found to be at greater risk of radiation-associated lung cancer than nonsmokers.

Heightened concern with regard to the subsequently increased risk of angiosarcoma in the irradiated conserved breast has been expressed. In a nationwide study, 21 cases of angiosarcoma were found in women with breast cancer who had received breast-conserving treatment and localized radiation were reported, with a median latency of 6 years.

The incidence of angiosarcoma in the breast was estimated at 1.6 per 1000 patients treated with breast conservation per year. Although the absolute excess risk is small, the relative risk is more than 1000-fold increased in comparison with the incidence of this very rare disease in the general population. In a nationwide case-control study, in a population of 116 women with soft tissue sarcoma, a diagnosis of breast cancer between 1988 and 1992, it was found that the risk of sarcomas other than angiosarcoma increased with the amount of radiation, but stabilized at high doses. The study included 40 angiosarcomas (located mostly in the ipsilateral arm, with only two cases in conserved breasts). The risk of angiosarcoma was 9.5-fold increased in women with lymphoedema of the arm, but radiotherapy was not a risk factor.

In conclusion, only part of the elevated risk of second malignancies after breast cancer is due to treatment. The intrinsically increased risk of developing a contralateral tumor is unlikely to be meaningfully affected by current radiotherapy for the initial breast cancer, whereas tamoxifen reduces the risk of contralateral disease. Standard dose-intensity CMF treatment is associated with a low excess risk of leukemia, whereas conventional FAC treatment may be associated with a somewhat higher risk. Whether the risk of leukemia will increase further with the introduction of dose-intensification strategies should be explored. Although tamoxifen causes a moderate increase in endometrial cancer risk, the proven clinical benefit of this drug in controlling breast cancer far outweighs the excess morbidity and mortality due to endometrial cancer. Clinicians should be alert to signs and symptoms in women taking tamoxifen, and long-term users should be advised to seek prompt gynecologic evaluation if any abnormal findings. If not at complete or near-complete remission, the risk of developing, or progressing to, subsequent malignancy is relatively low. Consequently, avoidance of research settings, there is no basis for regular gynecologic examinations in asymptomatic patients taking tamoxifen. The absolute excess risk of lung cancer is likely to be small with current radiotherapy techniques for breast cancer. Nevertheless, there is ample reason to advise breast cancer patients to stop smoking when they receive radiation treatment.

PEDIATRIC MALIGNANCIES

Survival rates for children with cancer have improved substantially since the late 1970s. Consequently, a rapidly growing young population is subject to the late effects of cancer therapy for the rest of their lives. The overview of the EBCTCG cohort 191-211 for childhood cancers was recently reviewed in several large studies. Most recently, de Vathaire and colleagues reported on the long-term risk of second cancer in a cohort of 4400 3-year survivors of childhood cancer (excluding patients with leukemia) treated in eight centers in France and the United Kingdom. The risk of second solid malignancies was increased 9.2-fold compared to the general population (95% CI, 7.6 to 11.0), and the absolute excess risk was 188 cases per 10,000 patients per year. The 30-year cumulative risk was 7.7% (95% CI, 5.0 to 8.2%). Olsen and collaborators observed a 3.6-fold increased risk of second malignancy (95% CI, 3.1 to 4.1) in 30,880 children diagnosed with cancer and reported to the population-based cancer registries of five Nordic countries between 1943 and 1987. The cumulative risks of developing a second tumor within 25 years were 3.7% and 3.5%, respectively. Among 9170 2-year survivors of childhood cancer who were treated by members of the U.S. Late Effects Study Group (LESG), the risk of developing a second malignancy was increased 15-fold compared to the general population (95% CI, 13 to 17), with a cumulative incidence of 12.1% at 25 years. The lower incidence in the European studies may be related to their population-based nature (less selection). The risk of second malignancies is less frequent in young patients who received high-dose chemotherapy and autologous bone marrow transplantation (4.1% at 25 years). The risk of second malignancies is, however, still high in long-term survivors of childhood cancer treated with standard-dose radiotherapy and alkylating agents (5.3% at 25 years). The risk of developing a second malignancy is generally higher in male survivors of childhood cancer than in female survivors.

The EBCTCG data.

FIGURE 55.7-4. Actuarial endometrial cancer–specific survival according to duration of tamoxifen use. (From ref. 211, with permission.)
Wilms’ tumor is another example of an initial malignancy in which genetic predisposition contributes to the excess risk of second cancers. The National Wilms’ Tumor Study Group reported on the second malignancy experience of 5278 patients followed for an average of 7.5 years. Forty-three second malignancies were observed, with an overall relative risk of 8.4 (95% CI, 6.1 to 11.4). The 15- and 20-year cumulative risks of developing a second tumor were 1.6% and 3.8%, respectively. Significant excesses were seen for leukemia (RR, 7.0), lymphoma (RR, 9.0), osteosarcoma (RR, 19), soft tissue sarcoma (RR, 22), and hepatocellular carcinoma (RR, 56). (N. E. Breslow, written communication, April 1996). Among patients not treated with radiation or doxorubicin, risk of second malignancy was increased threefold, reflecting genetic predisposition. Each 10 Gy of abdominal irradiation was found to increase second malignancy risk by 43% in the absence of doxorubicin and by 78% in its presence. Treatment with both doxorubicin and more than 35 Gy of abdominal irradiation was associated with a relative risk of 36 (95% CI, 16 to 72). Because the small numbers of individual second malignancies precluded an analysis by site, it is unclear whether these results apply equally for leukemia, sarcoma, and other tumors.

ALL, the most common malignancy in childhood, is also associated with an increased risk of subsequent cancer. In a series of 9720 childhood ALL patients treated in two protocols of the Children’s Cancer Study Group between 1972 and 1989, the risk of developing a second malignancy was increased 6.9-fold as compared with the general population. The associated 10- and 15-year cumulative risks were 1.5% and 2.5%, respectively. In a multicenter Italian study including 1684 ALL patients, the relative risk of all second cancers was 13.6, with cumulative risks of 2.6% and 4.5%, respectively, at 10 and 15 years since the completion of initial treatment. In both studies, the largest excess was observed for central nervous system tumors, with relative risks of 22 and 52. Most brain tumors were high-grade astrocytomas or glioblastomas, and all occurred in children who had previously received radiotherapy, mostly cranial irradiation, with radiation doses ranging from 18 to 24 Gy. A study of 1612 patients with ALL from St. Jude Children’s Research Hospital, with long-term follow-up data (median follow-up, 16 years), demonstrated an excess of high-grade gliomas during early follow-up (up to 5 years), whereas an increased risk of low-grade brain tumors was observed at later follow-up intervals. The risk of developing a brain tumor was significantly increased with increasing cranial radiation dose, with 20-year cumulative risks of 1.0%, 1.7%, and 3.2% for patients who received radiation doses of 10 to 21 Gy, 21 to 30 Gy, and 30 Gy or more, respectively.

During the 1990s, prophylactic cranial radiotherapy has been largely replaced by intrathecal methotrexate. The number of intrathecal methotrexate administrations was not related to the risk of brain tumors, but few children treated without cranial radiation were followed for more than 15 years. In two studies, the risk of central nervous system tumors was significantly higher in children 5 years of age or younger at first treatment.

Several very large studies of ALL survivors have reported negligible risks of AML after chemotherapy regimens that contain cyclophosphamide, anthracyclines, or both. In contrast, very high risks of AML have been reported for children treated with epipodophyllotoxin-containing regimens. Pui and associates were the first to report on the risk of AML in 734 children with ALL who received maintenance treatment according to different schedules of epipodophyllotoxin administration at St. Jude Children’s Research Hospital. AML developed in 21 children, with an overall cumulative risk of 3.8% at 6 years follow-up. The schedule of epipodophyllotoxin treatment appeared to be a crucial factor in determining AML risk. Patients who received weekly or twice-weekly doses of teniposide (with or without etoposide), were at an approximately 12 times greater risk of AML than patients treated only during remission induction, or every 2 weeks during maintenance treatment. Several subgroups of patients in this study were exposed to other potentially leukemogenic factors, such as cyclophosphamide and cranial irradiation. The strongest evidence that the excess risk of AML was due to epipodophyllotoxin treatment came from comparing two subgroups that differed only in schedule of epipodophyllotoxin administration. Among 84 patients who received epipodophyllotoxins weekly, the risk of AML was clearly and significantly increased (12.4% at 6 years; 95% CI, 6.1% to 24.4%) compared with 148 patients who received the agents every other week (1.6% at 6 years; 95% CI, 0.4% to 6.1%; \( P = .01 \)). Cumulative dose did not show enough variation within the study groups to reliably assess its effect. Compelling evidence for a causal link between epipodophyllotoxin therapy for ALL and the development of AML was also provided by Winick and associates.

Elevated risk of AML also has been reported after a number of other childhood malignancies, especially lymphomas. Smith and colleagues were the first to report on the risk of AML in 734 children with ALL who received maintenance treatment according to different schedules of epipodophyllotoxin administration at St. Jude Children’s Research Hospital. AML developed in 21 children, with an overall cumulative risk of 3.8% at 6 years follow-up. The schedule of epipodophyllotoxin treatment appeared to be a crucial factor in determining AML risk. Patients who received weekly or twice-weekly doses of teniposide (with or without etoposide), were at an approximately 12 times greater risk of AML than patients treated only during remission induction, or every 2 weeks during maintenance treatment. Several subgroups of patients in this study were exposed to other potentially leukemogenic factors, such as cyclophosphamide and cranial irradiation. The strongest evidence that the excess risk of AML was due to epipodophyllotoxin treatment came from comparing two subgroups that differed only in schedule of epipodophyllotoxin administration. Among 84 patients who received epipodophyllotoxins weekly, the risk of AML was clearly and significantly increased (12.4% at 6 years; 95% CI, 6.1% to 24.4%) compared with 148 patients who received the agents every other week (1.6% at 6 years; 95% CI, 0.4% to 6.1%; \( P = .01 \)). Cumulative dose did not show enough variation within the study groups to reliably assess its effect. Compelling evidence for a causal link between epipodophyllotoxin therapy for ALL and the development of AML was also provided by Winick and associates.

The Cancer Therapy Evaluation Program of the National Cancer Institute has developed a monitoring plan to better quantify the risk of AML after epipodophyllotoxin treatment. Smith and colleagues reported data from trials that used epipodophyllotoxins at low (less than 1.5 g/m²), moderate (1.5 to 2.9 g/m²), or higher (3 g/m² or more) cumulative etoposide doses. The 6-year cumulative risks for AML (including MDS) with the low, moderate, and higher cumulative dose groups were 3.3% (based on eight AML cases in 47 patients), 0.7% (based on one AML case in 1270 patients), and 2.2% (based on two AML cases in 51 patients), respectively. This result does not appear to provide support for a cumulative-dose-effect for the leukemogenic activity of the epipodophyllotoxins, at least not within the cumulative-dose range and with the treatment schedules encompassed by the monitoring plan (cumulative etoposide dose of 5.0 g/m² or less, on daily times 2-to-5 schedules). A limitation of this study, however, is that the three treatment strata according to cumulative etoposide dose also differed with respect to other factors that might contribute to AML risk.

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risk increase in relation to radiation dose was similar in patients treated for retinoblastoma and those treated for other initial malignancies. Thus, although patients with retinoblastoma have a higher intrinsic risk for sarcoma development, their relative responses to radiation treatment do not appear to be different from patients with other childhood cancers. Importantly, the study by Hawkins and colleagues also showed that the relative risk of bone sarcoma increases with increasing cumulative exposure to alkylating agents, even after adjustment for radiation therapy (see Table 55.7.7). It is clear, however, that the effect of radiotherapy on sarcoma risk is stronger than that of chemotherapy.

An association between chemotherapy and risk of bone sarcoma also has been observed in other studies; an effect of alkylating chemotherapy on sarcoma risk in the absence of radiotherapy was found only in the LESG study. Comparative studies of children and adults irradiated for Hodgkin's disease have shown that children experience a much higher relative risk of developing bone sarcomas than adults, probably because of greater radiosensitivity of growing bone.

### TABLE 55.7-7. A Case-Control Study of Second Primary Bone Cancer in Relation to Radiation Dose and Cumulative Exposure to Alkylating Agents

<table>
<thead>
<tr>
<th>Radiation Dose (Gy)</th>
<th>Relative Risk</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-19</td>
<td>1</td>
<td>1.0</td>
</tr>
<tr>
<td>20-39</td>
<td>2.0</td>
<td>1.1 - 3.4</td>
</tr>
<tr>
<td>40-59</td>
<td>3.0</td>
<td>1.6 - 5.4</td>
</tr>
<tr>
<td>60+</td>
<td>4.0</td>
<td>2.2 - 7.4</td>
</tr>
</tbody>
</table>

The risk of thyroid cancer after radiotherapy for childhood malignancies was assessed in the LESG cohort. High relative risks compared with general population rates were observed for thyroid malignancies after treatment of neuroblastoma (RR, 350), Wilms' tumor (RR, 132), and Hodgkin's disease (RR, 67). The relative risk increased with time since treatment and the median follow-up period (more than 20 years). In a case-control study, radiation dose to the thyroid was estimated for 23 thyroid cancer cases and 89 matched controls. Radiation doses of 2 Gy or more carried 13 times greater risk than doses of less than 2 Gy (P < 0.05). Because all patients with thyroid cancer had been exposed to at least 1 Gy of radiation to the thyroid, the risk associated with doses less than 2 Gy could not be reliably determined in this study. However, the investigators estimated that the risk associated with doses of 2 Gy or more was increased approximately 130-fold compared to nonirradiated patients. Unexpectedly, the dose-response relationship was more or less flat at radiation doses beyond 2 Gy; even at doses as high as 60 Gy, no decrease in thyroid cancer risk was observed. A pooled analysis of seven large studies of thyroid cancer after various radiation exposures demonstrated that the risk decreases significantly with increasing age at exposure and is highest for persons with radiation exposure before age 5 years.

In conclusion, survivors of childhood cancer are at substantially elevated risk to develop new malignancies. The magnitude of this risk depends on the type of the initial malignancy, because some childhood cancers, such as bilateral retinoblastoma, carry a high intrinsic risk for second cancer occurrence. Long-term survival after various types of childhood cancer has become possible through therapies introduced from the early 1970s onwards. Consequently, the growing population of cured patients is just beginning to enter the ages at which adult cancers typically occur, so the full spectrum of second malignancies has not yet been encountered. It is therefore imperative that survivors of childhood cancer be carefully monitored to assess the long-term risks of various types of second cancers. Bone sarcoma has consistently been identified as the second malignancy for which the excess risk is highest. Of much interest is the potential interaction between genetic susceptibility and treatment-related second cancer development. The leukemogenic potential of epipodophyllotoxin-containing regimens, that vary in cumulative dose and schedule of administration should continue to be rigorously assessed. As quantitative risk information from more studies becomes available, it will be possible to carefully weigh the benefits derived from epipodophyllotoxin treatment against the risks.

Second cancers among survivors of childhood cancer are associated with a poor prognosis. Hence, the need is pressing to develop therapeutic strategies with less oncogenic potential, without compromising the excellent cure rates that have been achieved.

### CONCLUSION

The results described in this chapter have multiple clinical implications. Knowledge of risk factors for second malignancy has made it possible to identify patient groups at high risk of developing second cancers due to treatments that they received in the past. Whenever effective screening methods are available, these should be implemented in the patients' follow-up program to improve their survival after diagnosis of second malignancy. In some cases, preventive strategies (e.g., smoking cessation) may reduce substantially the risk of developing a treatment-related cancer. The issue of treatment-induced second cancers must always be viewed in the context of the potential impact of these cancers on the overall health of the individual.

For many cancer treatments, the long-term effects on second malignancy risk are not yet known. In addition, new therapies are being introduced continuously, and the associated risks of late sequelae must be evaluated. Whenever possible, future studies of second cancer risk should incorporate investigations at the molecular level. Results of these laboratory analyses may clarify the influence of genetic susceptibility on treatment-related risk and contribute important data for the elucidation of mechanisms underlying drug- and radiation-induced carcinogenesis.

### CHAPTER REFERENCES

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NEUROTOXICITY

VINCRISTINE, VINBLASTINE, AND VINORELBINE

The first drug class to be recognized as having neurotoxicity was the vinca alkaloids, especially vincristine. Vincristine is unique among the antitumor agents in that neurotoxicity is the sole dose-limiting problem. The neurologic injury can occur in the peripheral, central, or autonomic nervous systems. 14

The most common and initial manifestations of neurotoxicity are depression of the deep tendon reflexes and paresthesias of the distal extremities. The Achilles’ tendon reflexes and the fingers are the usual respective initial sites of abnormalities. Loss of the tendon reflexes is usually asymptomatic. The paresthesias commonly progress proximally as vincristine therapy is continued and may involve the entire hands or feet. Despite the presence of peripheral paresthesias, vibration sense, position sense, pinprick sensation, and two-point discrimination are generally unaffected.

Motor dysfunction and gait disorders are initially manifested as lower extremity weakness. Footdrop may ensue, and if vincristine is continued, weakness to the point of paraparesis may develop. However, when vincristine and corticosteroids are administered together, steroid myopathy often occurs and causes similar symptoms of weakness, which should not be ascribed to vincristine neurotoxicity and result in a dose modification of the wrong drug. 15 Patients with hereditary neuropathies are especially prone to the additive effects of vincristine neuropathy. 16 Severe bone pain (especially in the mandible) may occur acutely a few hours after drug administration but usually subsides after a few days. 17

Cranial nerves may be affected and cause ophthalmoplegia and facial palsy. Toxicity to the parasympathetic nervous system is manifested by constipation and difficult micturition, which can progress to paralytic ileus and bladder atony. Autonomic neuropathy can produce orthostatic hypotension (which can be symptomatic or clinically silent) and erection/ejaculatory dysfunction. 18 Other rare, but severe, neurotoxic manifestations observed from vincristine include cortical blindness 19 and laryngeal nerve (with vocal cord) paralysis, 20 resulting in dysphonia and even aphonia.

Neurotoxicity from the vinca alkaloids, especially vincristine, is both an individual dose and a cumulative dose phenomenon. The usual practice in adults is to limit an individual dose of vincristine to 2 mg. Studies of higher vincristine dosing have shown a very high rate of neurotoxicity. No effective prevention or treatment has been developed except to stop therapy and wait for neurologic recovery. The neuropathy symptoms may persist as long as 3 or 4 years after cessation of therapy, but they usually wane to a point where they are no longer troublesome to the patient. 21 Empiric vitamin therapy is ineffective. Intestinal dysfunction from autonomic neuropathy may be improved by metoclopramide therapy. 21

Vincristine binds to the B subunit of tubulin, causing disruption of microtubule function in neuronal axons. Electrophysiologic studies indicate distal axonal dysfunction, and nerve conduction testing shows sensory nerves are most affected with a reduced amplitude of nerve action potentials. Histologic changes are generally those of axonal degeneration.

The vincristine analogues vinblastine and vinorelbine also have neurotoxicity potential. The primary dose-limiting toxicity of both vinblastine and vinorelbine is myelosuppression, and neurotoxicity is less common than that occurring from vincristine. The form and range of neurotoxicity manifestations from these analogues are similar to those of vincristine, and again, the degree of dysfunction is related to both individual and cumulative drug doses. However, vinblastine and vinorelbine seem to produce more autonomic effects, resulting in severe constipation and paralytic ileus. 2

Concurrent use of two neurotoxic agents has been reported to cause enhanced neurotoxicity or no such toxicity, depending on the drug involved. The combination of vinorelbine and cisplatin seems not to increase the incidence or severity of neuropathy. 22 However, when vinorelbine is used either in combination with, or sequentially after, paclitaxel, there is more potential for severe neuropathy. 22,23 In addition, the combination of vincristine and a granulocyte growth factor may precipitate a severe neuropathy involving primarily the legs. 23

CISPLATIN AND OXALIPLATIN

Although nephrotoxicity is a major and cumulative dose-limiting toxicity of cisplatin, neurotoxicity is also a common problem and can be dose-limiting for both single and cumulative doses, but primarily the latter. 24,25,26 Cisplatin-induced neurotoxicity can be manifested as sensory peripheral neuropathy, Lhermitte’s sign, autonomic neuropathy, grand mal or focal seizures, encephalopathy, transient cortical blindness, retrobulbar neuritis, and retinal injury. 26,27,28 The incidence of neurotoxicity ranges up to 100%, depending on individual and cumulative drug dose, treatment duration, concurrent or prior neurotoxic drugs used, the presence of other medical conditions, and possibly gender (women being more sensitive). 26,28 A cumulative cisplatin dose of 300 to 500 mg/m² is the range in which toxicity most often occurs. 22,28
Peripheral neuropathy similar to that induced by vincristine is the most common form of cisplatin neurotoxicity. Vincristine produces initial paresthesias in the fingers, whereas cisplatin most often affects the toes and feet. Loss of the Achilles’ tendon reflexes is an early sign, and continued treatment leads to sensory ataxia and loss of proximal deep tendon reflexes and vibration sense. Although muscle cramps are a common symptom, motor function is usually not affected.

The pathophysiology of cisplatin neurotoxicity is not known, but it is probably related to the accumulation of inorganic platinum within neurons, which may be irreversible. An autopsy study of platinum concentrations and histopathologic changes in the dorsal root ganglia of cisplatin-treated patients demonstrated a correlation of the tissue level of platinum with neuronal histologic changes and clinical neurotoxicity.

Treatment is discontinuation of therapy, but neurotoxic symptoms may last for months after cisplatin therapy is discontinued. The electrophysiologic test abnormalities may last for several years and perhaps indefinitely. The symptoms and signs may even progress despite discontinuing treatment. Amitriptyline has been used as treatment for the neuropathies related to use of antitumor agents, but no clinical trials in this clinical setting evaluating efficacy in double-blind fashion have been performed. Because treatment of neurotoxicity is of limited benefit, prevention using protective agents has been extensively explored. Amifostine, a nephroprotective antioxidant, also provides significant protection against peripheral neuropathy when used in conjunction with cisplatin. Dimesna is a new drug with exceptional promise as a neuroprotective agent and is in advanced clinical development for this indication.

Concurrent use of cisplatin with paclitaxel has demonstrated an enhanced potential for neurotoxicity, although variability exists, probably related to the drug doses and schedules employed. At the doses of these two drugs that are commonly used, more than 50% of patients may develop neuropathy, and this problem is often dose-limiting. When patients receiving this cisplatin drug combination are closely monitored, neurotoxicity may be evident after just two cycles in nearly all cases.

Neuropathy is the most common toxicity of the cisplatin analogue oxaliplatin, and cumulative neurotoxicity is usually dose-limiting. The manifestations are peripheral sensory and motor neuropathies (tingling and paresthesias of the extremities, weakness, and ataxia) and less frequently, cranial neuropathies (diplopia and dysphagia) with relative sparing of the peripheral motor system. Some patients have a nearly full recovery within 6 months after discontinuing therapy. Oxaliplatin is a L-3,4-dihydropyridine class calcium channel blocker (e.g., nifedipine and diltiazem) and, like other members of this class, is known to produce predominantly mononeuropathy affecting one or few nerves. In contrast, oxaliplatin neuropathy is a neurotoxicity that affects larger nerve trunks and results in a polyneuropathy.

CYTARABINE

Cytarabine is administered both intravenously and intrathecally, and both routes can produce neurotoxicity. Manifestations include cerebellar dysfunction, seizures, generalized encephalopathy, peripheral neuropathy, necrotizing leukoencephalopathy, spinal myelopathy, basal ganglia necrosis, and pseudobulbar palsy.

The highest incidence (15% to 37%) occurs in patients receiving high-dose cytarabine therapy (i.e., more than 1 g/m² in multiple doses). The toxicity is generally acute and not related to cumulative drug doses, in contrast to neuropathy associated with cisplatin and vincristine. Risk factors for neurotoxicity are age older than 50 years, drug dose, prior cytarabine treatment, and renal dysfunction.

Cerebellar effects (dysarthria, ataxia, and dysmetria) are the most common form of neurotoxicity. These symptoms often occur within days of first treatment and are accompanied by headache, altered mentation, memory loss, and somnolence. Seizures have rarely occurred. Peripheral neuropathy can also occur but is rare. Symptoms range from a purely sensory neuropathy to sensorimotor polyneuropathies in a glove-stocking distribution. The neuropathy can even progress to a quadriparesis, with ventilatory support being necessary. Intraocular cytarabine can produce an ascending myelopathy. All of these neurologic abnormalities (even the peripheral neuropathy) can progress to coma and death.

Recovery from the neurologic effects usually occurs within a few days after discontinuing cytarabine therapy. There is no known treatment. Serial radiographic studies of the brain have shown improvement in cerebellar abnormalities after discontinuing treatment, but progressive atrophy may also occur after a few months and is associated with persistent symptoms. Instances have been reported of ascending myelopathy with paraplegia from intrathecal cytarabine in which complete recovery took place within 1 hour after onset.

The mechanism of such neurotoxicity is not known. When high drug doses are used, cytotoxic concentrations of cytarabine reach the cerebrospinal fluid, but parent drug and metabolites are cleared more slowly from spinal fluid than blood, a likely explanation for the dose relationship of this toxicity. Neuron function and survival appears to be inhibited by cytarabine through blocking of an essential deoxynucleoside. Why the Purkinje cells of the cerebellum are particularly prone to injury from intravenous cytarabine, even in experimental animals, is unknown.

IFOSFAMIDE

Ifosfamide and cyclophosphamide have similar chemical structures, but ifosfamide induces neurotoxicity (as it does nephrotoxicity), whereas cyclophosphamide does not. Acute symptoms include auditory hallucinations, vivid dreams, logorrhea, incontinence, dizziness, pallialia, confusion, perseveration, agitation, personality changes, and somnolence. Cerebellar and cranial nerve dysfunction, hemiparesis, seizures, coma, and occasionally death.

Peripheral neuropathy and extrapyramidal abnormalities, such as myoclonus and muscular spasticity, also have been reported. The onset is acute up to 5 days after beginning ifosfamide, and recovery usually occurs within a few days after discontinuing therapy. Memory and affect disorders may occasionally persist. No cumulative-dose neurotoxic effects have been reported, but re-treatment with ifosfamide may again precipitate the same acute toxicity manifestations.

Significant neurotoxic abnormalities occur in approximately 10% of patients treated with ifosfamide. The incidence varies depending on how carefully patients are monitored for this problem, the ifosfamide dose and method of administration used, and the presence of various risk factors. Such risk factors are low serum albumin, any degree of renal dysfunction, prior administration of cisplatin (probably resulting in subclinical renal dysfunction), poor performance status, the presence of central nervous system tumor, and age (children being more susceptible than adults). High doses may accentuate symptoms of an underlying mild neuropathy and cause severe and painful paresthesias. For unknown reasons, oral administration of ifosfamide has more neurotoxic potential than the intravenous route.

The etiology of this neurotoxicity is probably multifactorial and is due to one or more metabolites of ifosfamide that are produced in high quantities. Cyclophosphamide may not produce neurotoxicity because metabolites with encephalopathic potential are a minor component of its degradation. Effective treatment (besides discontinuing the ifosfamide) has been intravenous diazepam and methylene blue. Such treatment can produce dramatic reversal of the neurotoxic manifestations. Means of prevention include a continuous infusion schedule of drug administration and concurrent use of methylene blue.

5-FUROORACIL

5-Fluorouracil (5-FU) has been known to cause neurotoxicity since the earliest clinical trials were conducted with this drug. Cerebellar dysfunction with findings of gait ataxia, nystagmus, dysmetria, and dysarthria is the most common form of neurotoxicity, but confusion, somnolence, seizures, coma, and peripheral neuropathy also have been observed. The incidence is approximately 5%, and it may occur with any of the administration schedules in common use. Neurotoxicity from this drug is acute in onset, and a cumulative-dose effect has not been observed. It is now common practice to administer leucovorin in combination with 5-FU to enhance antitumor activity. Leucovorin may itself be the etiology of some of the instances of seizures occurring in conjunction with administration of these two drugs.

The combination of 5-FU and levamisole may produce a multilocular leukoencephalopathy manifested by agitation, confusion, short-term memory loss, diplopia, cerebellar dysfunction, and expressive aphasia. Magnetic resonance imaging of the brain shows multiple, enlarged, white matter lesions (sometimes ring-enhanced) in the cerebrum, and histologic examination shows focal demyelination. Such toxicity has not been reported when 5-FU has been used alone, but it has occurred with use of levamisole alone. Therefore, the levamisole in this adjuvant therapy combination is probably the most culpable in producing these cerebral effects.

The etiology of 5-FU neurotoxicity is not well understood. 5-FU metabolites have been shown to have neuropathic action in experimental animals. However, it may also be due to parent drug, and not metabolites, because patients have been reported who developed severe toxic symptoms due to a genetic deficiency of the initial enzyme necessary for catalyzing 5-FU. Patients with complete or partial deficiency of this enzyme, dihydropteridine dehydrogenase, appear particularly subject...
to 5-FU toxicity of all kinds including neuropathy.

**METHOTREXATE**

Neurotoxicity from methotrexate can manifest as meningeval irritation, transient paraparesis, or encephalopathy. When the drug is administered intrathecally (IT), it can cause headache, nausea and vomiting, lethargy, nuchal rigidity, and other features of meningeval irritation. A subacute set of abnormalities include paraparesis, hemiparesis, somnolence, cranial nerve dysfunction, cerebellar symptoms, and seizures, which can develop days to several weeks after therapy. Such encephalopathy symptoms may occur more commonly when both IT and intravenous high-dose methotrexate are administered. When IT methotrexate is given repetitively (especially if it is administered via an intraventricular device), progressive neurolcizing leukoencephalopathy may develop. Although acute onset with result, the usual symptoms include initial memory loss with occasional later progression to severe dementia, gait disturbance, dysphasia, and seizures. Even if serious neuropathy does not occur, subtle cognitive deficits may develop months to years later, especially in children. Risk factors for such problems are cranial irradiation, presence of neoplastic cells in the spinal fluid, and cumulative drug dose. The neurotoxic effect is probably a direct consequence of high drug dose concentrations in the cerebrospinal fluid.

Intravenous methotrexate also can produce encephalopathy, especially if high doses and leucovorin rescue are used. The manifestations and risk factors are similar to those of IT methotrexate. The neurologic dysfunction may be acute or transient and often in onset with personality changes. Magnetic resonance imaging can show the white matter abnormalities in asymptomatic patients that are probably subclinical manifestations of neurotoxicity. However, it has been argued that such findings do not necessarily correlate with subsequent intellectual dysfunction and therefore may be inconsequential. Treatment consists of active hydration to facilitate methotrexate clearance and leucovorin to counteract the enzyme inhibition of methotrexate.

It has been postulated that this toxicity arises from methotrexate-related impairment of synthesis of neurotransmitters and accumulation of adenosine and homocysteine. Based on this hypothesis that the neurotoxicity is related to brain accumulation of adenosine, aminophyline (an adenosine receptor antagonist) has been used successfully to reverse the neurologic effects of methotrexate.

**PACLITAXEL AND DOCETAXEL**

The two analogues paclitaxel and docetaxel cause neurotoxicity similar to that of cisplatin and vincristine in the form of a peripheral neuropathy that can be a treatment-limiting effect. The clinical manifestations are glove-stocking or perioral paresthesias and/or burning pain, loss of vibration sense, loss of deep tendon reflexes, Chemlett's sign, and orthostatic hypotension. Motor dysfunction in the form of both proximal and distal extremity weakness also has been observed. However, it is impossible to determine how much taxane-associated myopathy might be due to the antitumor drug and how much to the intermittent, but large, doses of corticosteroids that are used concurrently with the taxanes to minimize the risk of hypersensitivity reactions. Transient scintillating scotomata and visual deficits due to optic neuropathy and encephalopathy in the form of confusion and behavioral changes also have been reported. A possible risk factor for initiating or enhancing the neural dysfunction from these drugs is an underlying neuropathy from other conditions such as diabetes mellitus and ethanol abuse. Other, one study has shown that patients with diabetes may be treated with standard doses of paclitaxel, and they do not develop neurotoxicity to a greater degree than expected.

Both a single-dose and cumulative-dose-related relationship is noted for paclitaxel. Single doses of more than 175 mg/m$^2$ given at 3-week intervals produce a higher rate of neurotoxicity than lesser doses, and at 250 mg/m$^2$, neurotoxicity is dose-limiting in as many as 70% of patients. When paclitaxel is given weekly in 1-hour infusions, severe neurotoxicity occurs at doses of more than 100 mg/m$^2$. Cumulative dosing also increases the frequency of neurotoxicity, but there is no neurotoxic dose threshold. Depending on the drug dose used, the onset of these problems can be within a few days of receiving the first dose or after several cycles of therapy. A docetaxel dose of 100 mg/m$^2$ also induces mild to moderate neurotoxic symptoms in as many as 50% of patients after five cycles of therapy. A cumulative docetaxel dose of 400 mg/m$^2$ can produce severe symptoms and electrophysiologic changes in nerves, but as with paclitaxel, there is no threshold dose. Concurrent or prior use of other neurotoxic agents (cisplatin, oxaliplatin, or vinorelbine) enhances the risk and degree of neurotoxicity manifestations from both of the taxanes.

The mechanism of taxane neurotoxicity is likely a drug effect on neuronal microtubules, causing axonal degeneration and demyelination. Neurometric testing demonstrates decreased nerve conduction velocities and absent sural nerve action potentials from both taxanes.

ALTRETAMINE (HEXAMETHYLMELAMINE)

Altretamine (hexamethylmelamine) causes a variety of peripheral and central nervous system toxicities. Peripheral neuropathy is the most common form and manifests as paresthesias, hyperesthesia, hyporeflexia, and diminished proprioception. Central nervous effects are confusion, dysphagia, personality changes, ataxia, somnolence, seizures, respiratory dyskinesia, and parkinsonian tremors.

Neurotoxicity is related to both individual and cumulative doses. Intermittent dosing schedules help reduce this side effect. The incidence varies depending on the dose but can be as high as 40%. Altretamine can be safely administered to patients who have been treated previously with cisplatin, but if significant cisplatin neuropathy is present, the neurotoxic manifestations may worsen.

**PROCARBAZINE**

Neurotoxicity from procarbazine has been known since it was first used clinically. Both central and peripheral neurotoxicity symptoms can occur. Cerebral symptoms predominate and consist of lethargy, depression, confusion, hallucinations, agitation and, rarely, psychosis. Extremity paresthesias and depressed deep tendon reflexes are the manifestations of peripheral neuropathy.

Procabarize is most commonly used in combination with the vinca alkaloids, so it is difficult to determine which agent is causing peripheral neuropathy symptoms. The incidence of neuropathy induced by procabazine alone is 20% or less. It is much higher when procabazine and vincristine are used concurrently. Treatment is discontinuation of therapy. Cerebral symptoms usually resolve promptly, but peripheral neuropathy may last for weeks to months.

**ALDESLEUKIN (INTERLEUKIN-2)**

The biologic antitumor agent aldesleukin (interleukin-2) has many toxicities precipitated by increased vascular permeability. Neurotoxicity in the form of hallucinations, disorientation, agitation, combativeness, seizures, and coma may also occur. A neurotoxic manifestation unique to this drug is cerebral tunnel syndrome, which appears to be a consequence of interstitial edema (due to the vascular leak), causing pressure on the median nerve.

**FLUDARABINE, CLADIRABINE, AND PENTOSTATIN**

When fludarabine was tested in phase I and II trials, central nervous toxicity was so severe that the studies had to be closed prematurely. Altered mental status, photophobia, amniorosis, generalized seizures, dementia, spastic or flaccid paralysis, quadriaparesis, and coma occurred at doses of more than 90 mg/m$^2$ given for 5 to 7 days. Despite discontinuing therapy, some patients had progressive neurologic abnormalities and died. At autopsy, leukoencephalopathy was present in the occipital lobes. Because such severe toxicity is clearly dose-related, the recommended fludarabine dose is 25 mg/m$^2$ daily for 5 days at monthly intervals. This dose usually causes no more than mild and uncommon (incidence of approximately 15%) neurotoxicity symptoms, but sporadic cases of severe (and even fatal) neurotoxicity have occurred, of which even developed a few months after fludarabine therapy was stopped.

Both cladribine and pentostatin can cause severe, and fatal, neurotoxicity when administered at doses producing marked myelosuppression. The manifestations are
similar to those of fludarabine. However, like fludarabine, drug doses in the range recommended for usual therapy produce only rare instances of severe neurotoxicity.

OTHER AGENTS

Table 55.8-1 lists other antitumor drugs that can produce neurotoxicity and categorizes them based on the risk for this effect. The manifestations are similar to those described for the individual drugs. Certain ones (e.g., busulfan) produce problems such as seizures only when very high doses are administered in the stem cell transplantation setting, even despite the use of prophylactic anticonvulsant medication.

### Table 55.8-1. Antitumor Agents That Cause Neurotoxicity

<table>
<thead>
<tr>
<th>Drug</th>
<th>Risk for Neurotoxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>cisplatin</td>
<td>High</td>
</tr>
<tr>
<td>carboplatin</td>
<td>Low</td>
</tr>
<tr>
<td>mitomycin</td>
<td>Low</td>
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#### NEPHROTOXICITY

The kidneys are the elimination pathway of many antitumor drugs and their metabolites and, therefore, are vulnerable to injury. The entire anatomic pathway from glomerulus to distal tubule is at risk, depending on the drug involved. The symptoms vary from an asymptomatic rise in serum creatinine or mild proteinuria to acute renal failure with anuria requiring dialysis.

#### CISPLATIN AND CARBOPLATIN

The nephrotoxicity of cisplatin has been well known since it was first used clinically in the early 1970s. This obstacle to its clinical use has been so profound that several thousand cisplatin analogues have subsequently been synthesized in hopes of finding a less nephrotoxic compound with equivalent antitumor efficacy. A means of avoiding nephrotoxicity by forcing diuresis and enhancing cisplatin excretion was first reported in 1977. This seminal work allowed safer use of this drug with its wide spectrum of antitumor efficacy.

Cisplatin renal toxicity is dose-related, cumulative, and manifested primarily by a decrease in the glomerular filtration rate, which is clinically approximated by increases in the serum creatinine and decreases in the creatinine clearance. Single drug doses of less than 50 mg/m² usually cause little renal injury, but higher doses require aggressive hydration, otherwise abrupt, irreversible renal failure may ensue. Hydration reduces cisplatin concentration and the time it is in contact with the tubular epithelium, which helps to limit the tubular injurious effect of the drug. The hydration used most successfully is normal saline because the high chloride inhibits cisplatin hydrolysis in the tubules, which seems to add to the nephrotoxicity-protection effect of diuresis. Mannitol also is used to enhance diuresis, but no evidence indicates that mannitol is necessary. Concurrent use of furosemide to enhance diuresis further is unnecessary and may even be harmful, as it was in animal experiments. A urine output of at least 100 mL/hour for 2 to 4 hours before and 4 to 6 hours after cisplatin doses of 50 to 75 mg/m² reduces, but does not eliminate, nephrotoxicity. More intensive hydration schedules are necessary when higher cisplatin doses are used.

The pathologic lesion of cisplatin nephrotoxicity is seen primarily in the proximal and distal tubules but also may involve the collecting ducts, whereas the glomeruli are unaffected. The extent of tubular injury helps to explain why electrolyte abnormalities, such as hypotension and hypomagnesemia, are so common after cisplatin administration. Hypomagnesemia is symptomatic only in approximately 10% of patients, but it can last months to years after completing therapy. Magnesium supplementation in conjunction with cisplatin administration can minimize, but does not eliminate, hypomagnesemia. The hypomagnesemia has been reported to cause persistent orthostatic hypotension.

The mechanism of the tubular injury is not fully understood. It is not simply the tubular handling of a heavy metal, because the trans isomer of cisplatin is not nephrotoxic. Cisplatin produces DNA intrastrand cross-links as one of its mechanisms of antitumor effect, and the same effect perhaps occurs on DNA in tubule cells, causing defects in tubular (especially proximal) resorption.

A variety of substances have been evaluated for minimizing cisplatin nephrotoxicity in the hope that the cumbersome process of hydration can be circumvented. These include sodium thiosulfate, amifostine, probenecid, diethyldithiocarbamate, superoxide dismutase, hypertonic saline, gluthatione, bismuth compound, and mesna. Only one of these many compounds (amifostine) has provided sufficient protective benefits to become accepted for routine use. Amifostine demonstrated statistically significant protection against cisplatin-induced nephrotoxicity and is now marketed for this indication. However, amifostine has its own toxicities that can be an obstacle to convenient use, such as hypotension and nausea and vomiting. One simple technique for nephrotoxicity protection besides hydration is to administer cisplatin in the evening to take advantage of circadian rhythm effects that have been shown to reduce renal injury, although this timing may be impractical in the outpatient setting. A final measure of protection is to be certain that renal function is normal by performing a pretreatment 24-hour, measured creatinine clearance. A result of less than 70 mL/min, especially in patients older than 60 years of age, may preclude cisplatin use without a significant risk of nephrotoxicity. In addition, other renal tubular toxins, such as aminoglycoside antibiotics, should be avoided whenever possible to prevent additive tubular damage.

Carboplatin was synthesized as a cisplatin alternative with less nephrotoxicity and without a requirement of hydration for safe administration. It is definitely less nephrotoxic, but it is not free of potential for renal injury, especially in patients who have previously received nephrotoxins, or when given in high doses in the stem cell transplantation setting. Carboplatin-related renal dysfunction is usually detectable only by means of sensitive kidney function tests, such as urine tubular enzyme excretion or glomerular filtration rate, and is transient. The serum creatinine and creatinine clearance are rarely affected.

Life-threatening hemolytic-uremic syndrome has been reported as a rare form of acute renal dysfunction related to cisplatin and carboplatin. Many of the reported instances related to cisplatin have involved combined use of cisplatin and bleomycin, so it is unclear which drug is most culpable in initiating this fulminant toxicity.

#### MITOMYCIN

The capacity of mitomycin to produce renal toxicity has been known for many years, and it can be life-threatening. The clinical manifestations vary from a chronic, progressive rise in serum creatinine to fulminant onset of microangiopathic hemolytic anemia (MAHA). The latter problem has been reported in a large number of anecdotal cases, but in one study of adjuvant therapy with mitomycin, a 10.7% incidence occurred. It was also observed in 10% of patients treated with a combination of mitomycin and tamoxifen, and the authors of this study suggested some interaction between the two drugs might have contributed to the development of this toxicity.

The MAHA toxicity is cumulative dose-related, but even only several mitomycin doses can initiate it. It also can develop a few months after mitomycin has been discontinued. The risk of developing MAHA increases when the cumulative mitomycin dose exceeds 60 mg.

The clinical presentation of MAHA is an abrupt and often severe hemolytic anemia that usually precedes the renal dysfunction by 1 or 2 weeks. The peripheral blood
sneer shows schistocytes, and thrombocytopenia becomes apparent as renal failure develops. Other manifestations are rash, fever, arterial hypertension, central neurologic dysfunction, pericarditis, interstitial pneumonitis, pulmonary hemorrhage, hematuria, and proteinuria. A high rate (65%) of patients have noncardiogenic pulmonary edema. A prominent feature is the fact the MAHA is often precipitated or worsened by blood transfusions, suggesting that blood product administration should be avoided as much as possible when treating patients with mitomycin. The outcome is often (more than 50% of the time) death, despite vigorous treatment, although a few long-term survivors (who have persistent mild renal dysfunction) have been reported.

Treatment includes hemodialysis and plasmapheresis. The most successful treatment has been plasma perfusion over filters containing staphylococcal protein A, a method of extracting circulating immune complexes.

The pathogenesis of this acute nephropathy is not certain. When injected directly into the renal arteries of rats, mitomycin caused glomerular endothelial damage, and increases in vascular endothelial cell markers in plasma have been observed in patients who developed MAHA related to mitomycin. This vascular injury probably activates platelets and leads to fibrin thrombi deposition in the microvasculature of the kidney, thus initiating renal dysfunction and a mechanical shearing of red blood cells with resultant hemolysis.

METHOTREXATE

When methotrexate is administered in conventional oral or intravenous doses, nephrotoxicity is only an occasional problem. If high doses with folinic acid rescue are used, acute nephrotoxicity can pose a greater danger.

Methotrexate is excreted rapidly in the urine whether it is administered orally or parenterally. Both the parent compound and the major metabolite, 7-hydroxy methotrexate, are filtered by the glomeruli and actively secreted by the tubules. At physiologic pH, the drug is fully ionized, but in acidified form (pH less than 5.7), the parent drug and main metabolite are less ionized and may precipitate. During urinary excretion, drug precipitation occurs as the urine is concentrated and acidified in the tubules. The solubility of 7-hydroxy methotrexate is only one-fourth that of the parent drug, thus providing further potential for drug precipitation within tubules and resultant acute renal dysfunction.

Acute methotrexate nephrotoxicity produces abrupt renal insufficiency. The serum creatinine rises rapidly, and costovertebral angle pain (from renal swelling) may occur. Dehydration, oliguria, and even anuria may develop.

Methotrexate-induced renal insufficiency is primarily a physical process of tubular drug precipitation. It can be largely prevented by methods designed to hinder this precipitation of drug in the tubules: hydration and urine alkalinization. Whenever a drug dose high enough to require leucovorin rescue is being given, the urine should be kept alkaline (pH higher than 8) with sodium bicarbonate administration, and a urine output of 100 mL/hour should be maintained. Serial serum methotrexate levels should be monitored until the drug concentration declines to 10⁻¹⁰ molar or less, 24 to 48 hours after administration.

If methotrexate clearance is impaired by renal dysfunction already present or initiated by concurrently administered drugs, nephrotoxicity can develop or be enhanced. For example, prior therapy with cisplatin may contribute to methotrexate nephrotoxicity, and concurrent administration of nonsteroidal antiinflammatory drugs may engender serious, and even fatal, renal dysfunction from methotrexate. Indomethacin, ketoprofen, diclofenac, and naproxen all have been reported to intensify renal dysfunction from methotrexate, whether it is being given in high doses or low doses.

This enhanced toxicity is probably mediated by a reduction in methotrexate clearance caused by the concurrent drug administration.

Sequenial hemodialysis and charcoal hemofiltration have been used as treatment of acute nephrotoxicity from high methotrexate doses. A highly successful therapy has been administration of a combination of thymidine, leucovorin, and the recombiant form of the bacterial enzyme carboxypeptidase G₂ which quickly converts methotrexate to a harmless metabolite. Both thymidine and carboxypeptidase are available on a compassionate-use basis from the National Cancer Institute for treating this life-threatening toxicity.

STREPTOZOCIN, Carmustine, and Lomustine

Streptozocin has the most potential for nephrotoxicity in the nitrosourea drug class, and renal damage is its dose-limiting toxicity. Prolonged drug administration increases the risk of such toxicity, and most patients eventually display it if therapy continues.

The kidneys are the major excretion pathway for both parent drug and its metabolites, the probable main factor in the pathogenesis of the nephrotoxicity. Streptozocin injury occurs in both the glomeruli and tubules (primarily the proximal), where histologic changes have been observed, but the mechanism is unknown. Hyperphosphatemia and proteinuria are early indicators of renal effect. Renal tubular acidosis is a frequent occurrence, manifested by glycosuria, acetonuria, hyperchloremia, and aminoaciduria. If streptozocin is discontinued, these findings usually resolve. A rising serum creatinine is a later, and sometimes irreversible, finding. Hydration and diuresis during therapy have occasionally minimized the renal dysfunction.

The other two nitrosoureas in wide clinical use (carmustine and lomustine) are much less nephrotoxic. Carmustine usually causes interstitial pneumonitis toxicity before it affects the kidneys. Lomustine has produced only rare instances of nephrotoxicity when unusually large cumulative doses have been administered.

IFOSFAMIDE

 Cyclophosphamide and ifosfamide are analogues with similar chemical structures. Both produce the metabolite acrolein, which can cause hemorrhagic cystitis during urinary excretion. Despite their similarities in chemical structure, toxicity, and antimur efficacy, they differ significantly in their ability to cause nephrotoxicity. Cyclophosphamide produces no renal toxicity of any clinical consequence, whereas ifosfamide initiates a variety of renal abnormalities that may in some instances result in death or irreversible renal failure requiring chronic hemodialysis or renal transplantation, especially in children who are at higher risk for this problem. Hypotheses regarding the mechanism of ifosfamide nephrotoxicity and why cyclophosphamide does not have such effect have been formulated based on the differences in metabolism of these two drugs (ifosfamide produces much more chloracetaldehyde and the unique effect of ifosfamide on proximal renal tubule cells). The initial clinical studies of ifosfamide showed that single high doses could precipitate acute tubular necrosis and renal failure within a few days of administration. This severe toxicity was one reason a fractionated dose schedule was developed for this drug. Administration over 5 consecutive days reduced both renal and bladder dysfunction from methotrexate, whereas ifosfamide initiates a variety of renal abnormalities that may in some instances result in death or irreversible renal failure requiring chronic hemodialysis or renal transplantation, especially in children who are at higher risk for this problem. Hypotheses regarding the mechanism of ifosfamide nephrotoxicity and why cyclophosphamide does not have such effect have been formulated based on the differences in metabolism of these two drugs (ifosfamide produces much more chloracetaldehyde and the unique effect of ifosfamide on proximal renal tubule cells). Initial clinical studies of ifosfamide showed that single high doses could precipitate acute tubular necrosis and renal failure within a few days of administration. This severe toxicity was one reason a fractionated dose schedule was developed for this drug. Administration over 5 consecutive days reduced both renal and bladder toxicity, but the most effective measure for reducing urinary tract problems was the development of mesna as a means of protection against the drug-induced cystitis. Mesna is now a standard accompaniment to ifosfamide use, but it limits the cystitis, not the nephrotoxicity. There is no known means of preventing ifosfamide renal toxicity.

The incidence of renal toxicity varies from 5% up to 30%. Besides young age (especially younger than 5 years), risk factors are drug dose (cumulative doses of more than 60 g/m²), unilateral nephrectomy, prior renal irradiation, presence of retroperitoneal masses, and prior cisplatin treatment. Clinical manifestations include tubular dysfunction, Fanconis's syndrome, and a rising serum creatinine. The tubular injury is indicated by aminoaciduria, glycosuria, renal tubular acidosis, hypokalemia, proteinuria, and phosphaturia with hypophosphatemia. These abnormalities can even result in renal rickets and growth retardation, which require long-term therapy. Once acute renal dysfunction from this drug becomes evident, it may or may not be reversible, so frequent monitoring of renal and tubular function during ifosfamide therapy is important, with prompt treatment when dysfunction occurs. Progression to renal failure is generally not a problem in children, but such failure may occur in adults, even with only moderate cumulative doses of ifosfamide. Renal abnormalities may not become evident until long after ifosfamide therapy has been completed.

OTHER AGENTS

Table 55.8-2 lists the antitumor agents that have been reported to cause renal injury. They are categorized by the risk of such toxicity from those drugs with an occasional anecdotal report to those with high risk for severe damage.
Not only can individual drugs cause nephrotoxicity, but combinations of agents can occasionally precipitate serious reactions, such as hemolytic uremic syndrome from cisplatin and bleomycin. In addition, the intensive doses of chemotherapy used in conditioning for stem cell transplantation can induce hemolytic uremic syndrome with an acute or delayed onset and sometimes fatal outcome.

TABLE 55.8-3. Antitumor Agents That Cause Hepatotoxicity

HEPATOTOXICITY

A number of antitumor agents cause hepatic toxicity (Table 55.8-3). This toxicity takes three main forms: hepatocellular dysfunction and chemical hepatitis, venoocclusive disease (VOD), and chronic fibrosis.

HEPATOCELLULAR DYSFUNCTION

Hepatocellular dysfunction usually is caused by a direct effect of either the parent drug or a metabolite and is an acute event. Serum hepatic enzymes rise as cellular damage occurs. Fatty infiltration and cholestasis may occur as the toxic effect progresses. Hepatic metastases, viral hepatitis, and drugs administered for other therapeutic purposes (e.g., antiemetics) can cause similar enzymatic abnormalities. Thus, the clinical picture, appropriate laboratory or radiologic studies, and the pattern of abnormal liver function tests must be analyzed to identify the cause of the hepatic changes.

The drugs most likely to cause enzymatic abnormalities are L-asparaginase, carbustine in high doses, cytarabine, dactinomycin, etoposide, levamisole in combination with 5-FU, 6-mercaptopurine, methotrexate in high doses, streptozocin, and vincristine. These drugs can cause rises in the serum glutamic-oxaloacetic transaminase, serum glutamic-pyruvic transaminase, and serum bilirubin.

L-Asparaginase causes the widest spectrum of liver abnormalities and has the highest incidence of hepatotoxicity. It produces changes in liver enzymes and in hepatic protein synthesis, resulting in low plasma levels of albumin, lipoproteins, and clotting factors. Prolongation of the prothrombin and thrombin times occurs as a result. Fatty metamorphosis is commonly seen, and these changes may persist for several months after discontinuing treatment.

The combination of levamisole and 5-FU, used as adjuvant therapy for colon cancer, also frequently produces reversible hepatic enzyme and serum bilirubin changes. These abnormalities are due to fatty infiltration of the liver, and in some cases the degree of liver abnormality may be sufficient to mimic liver metastases on radiographic studies.

Cytarabine hepatotoxicity is a common event in the treatment of acute leukemia, especially when high doses are used. Because patients with acute leukemia are subject to transfusion-related hepatitis and receive a variety of potentially hepatotoxic drugs, it is always difficult to establish cytarabine as the sole hepatotoxin. However, hyperbilirubinemia developing in temporal relation to cytarabine administration, accompanied by histologic abnormalities on liver biopsy, has confirmed the hepatotoxicity potential of this drug.

6-Mercaptopurine has been known since the 1950s to cause hepatotoxicity, which may even be rarely fatal. Intrahepatic cholestasis is the most common abnormality, and liver function usually returns to normal with discontinuation of therapy.

Hepatic dysfunction from dacarbazine may occur in up to 10% of patients with Wilms' tumor treated with this drug, but it is very uncommon when used for treatment of other malignancies. Hepatomegaly, enzyme abnormalities, and jaundice may occur. Fever is also common, and thrombocytopenia may occur. Most cases appear to be associated with Wilms' tumors occurring in the right kidney, so the tumor mass effect present in the liver region may play a precipitating role in this toxic manifestation.

VENOOCCLUSIVE DISEASE

VOD results from blockage of venous outflow in the small centrilobular and sublobular hepatic vessels. Antitumor drugs known to produce this form of hepatotoxicity are cytarabine, cyclophosphamide, dacarbazine, 6-mercaptopurine, mitomycin, and 6-thioguanine. In addition, high doses of busulfan, carmustine, cyclophosphamide, and mitomycin given in the stem cell transplantation setting can cause VOD.

The clinical features of VOD are painful hepatomegaly, ascites, peripheral edema, marked elevations in serum enzymes and bilirubin, and hepatic encephalopathy. The onset is often abrupt, occurring during the first posttransplant week, and the clinical course is fulminant. It is caused by damage to endothelial cells, sinusoids, and hepatocytes in the area of the liver surrounding the central vein. Thrombosis is precipitated, causing ischemia and hepatocellular necrosis. A component of hepatocellular injury may also be directly related to the high doses of drugs and not mediated by thrombosis. VOD occurring in the transplantation setting may be irreversible and lead to death with multiorgan failure in 25% to 50% of the patients developing it. All of the drugs reported to induce VOD at high doses have been alkylating agents. This situation may not be because of any unusual tendency of alkylating agents to cause VOD, but rather to the fact that these are the drugs used in very large doses in the stem cell transplantation setting.
Conventional doses of certain antitumor agents (e.g., dacarbazine, 6-mercaptopurine, 6-thioguanine) can also cause hepatic VOD. Dacarbazine has been most frequently implicated in this form of hepatotoxicity, but only sporadic cases have been reported, both from dacarbazine alone and in combination with other drugs.

Why only some patients develop this life-threatening complication of dacarbazine is unknown. It may be some sort of idiosyncratic or hypersensitivity reaction.

**CHRONIC FIBROSIS**

Methotrexate used for cancer treatment can produce acute and reversible hepatocellular injury and elevation of serum enzymes. The intermittent dosing schedules seem to obviate any chronic hepatotoxicity from this drug. However, long-term use of methotrexate for the treatment of nonmalignant disease (e.g., rheumatoid arthritis) poses a hazard for the development of irreversible hepatic fibrosis. Because patients with autoimmune diseases may already have underlying liver abnormalities, methotrexate may not be the sole etiologic factor in the development of this chronic toxicity.

**HYPERSENSITIVITY REACTIONS**

Most of the available antitumor agents can produce hypersensitivity reactions, and a substantial minority cause such reactions in 5% or more of patients treated. Several drugs (e.g., L-asparaginase and the taxanes) cause hypersensitivity reactions that are frequent enough to be a major treatment-limiting toxicity. Most of the other antitumor drugs produce such reactions only sporadically. The mechanism of these reactions is often unknown or evaluated only in a single patient. Pretreatment regimens designed to prevent or minimize reactions from the taxanes and a new formulation of L-asparaginase (pegaspargase) created to minimize reactions from this drug have been successful in reducing the frequency and severity of this toxicity.

L-Asparaginase produces hypersensitivity reactions in 10% to 20% of patients treated, which can be immediate and life-threatening, with all the components of anaphylaxis. This high rate is related to the fact L-asparaginase is a polypeptide of bacterial origin, displaying multiple antigenic sites that can stimulate production of immunoglobulin E (IgE) and other immunoglobulins. These immunoglobulins can then mediate an acute anaphylactic reaction.

The clinical manifestations are typical of type I reactions, with acute onset of wheezing, pruritus, rash, angioedema, extremity pain, agitation, and hypotension. The mechanism of L-asparaginase reactions appears to be mediated by an IgE antibody in at least some cases. Complement activation also occurs, induced by specific IgG or IgM antibodies. A number of factors increase the risk for hypersensitivity reactions, including a history of atopy or other drug allergy, prior L-asparaginase therapy (including even several years previously), high drug doses, and the intravenous route of administration. Intramuscular administration often reduces the severity of reactions, but they can still occur and may do so several hours after the drug is given. Concurrent treatment with prednisone and vincristine (for the acute leukemia being treated) also appears to reduce the risk of reactions.

No reliable method has been found that can indicate who will have a reaction to any dose of L-asparaginase. Intradermal skin testing may give either false-negative or false-positive results, and test doses of the drug are valueless. Therefore, one must approach each dose of L-asparaginase as the one that could initiate a hypersensitivity reaction and be prepared to treat it. Antianaphylaxis medication must be at hand, and the patient should be observed for approximately 1 hour after the drug is administered.

When a hypersensitivity reaction occurs with the Escherichia coli source of L-asparaginase, one can substitute the Erwinia chrysanthemi form and continue therapy without a loss of efficacy of this important drug for the treatment of acute lymphoblastic leukemia. This drug form is immunologically distinct and appears to have a lower degree of immunogenicity. Patients may still sustain a hypersensitivity reaction from the substitute, but most (more than 75%) do not and can complete the planned therapy. Precautions for treating anaphylaxis are necessary no matter the origin of the L-asparaginase. A third form of L-asparaginase (pegaspargase) provides another alternative for the patient who is reactive to either of the other asparaginases. This form is a conjugate of polyethylene glycol with the enzyme. It may be the least immunogenic of all three forms of this drug, but hypersensitivity reactions are still possible. Because this drug has a prolonged serum half-life compared to the other two, it is administered only once or twice per week.

Paclitaxel has high potential for initiating a hypersensitivity reaction, and because of this fact, it is necessary to administer prophylaxis therapy before each dose. The Cremophor EL excipient used to maintain solubility of paclitaxel has long been suspected of being the initiator of these reactions. When docetaxel was first evaluated in clinical trials, it was assumed that premedication to prevent hypersensitivity reactions was unnecessary, because docetaxel is formulated with Tween 80 (instead of Cremophor EL), and thus reactions would be unlikely to occur. This assumption proved incorrect, because docetaxel can initiate reactions with the same manifestations and with approximately the same frequency (5%) as paclitaxel. The signs and symptoms can occur even despite premedication, although the intensity may be diminished.

The clinical manifestations are of any type I hypersensitivity reaction and include bronchospasm and wheezing, agitation, chest and back pain, rash, angioedema, and hypotension. The onset is usually within minutes of starting a drug infusion, and even very small drug doses are capable of initiating a reaction. A form of apparent hypersensitivity that may be delayed in onset is pulmonary infiltrates typical of a hypersensitivity pneumonitis that may either resolve spontaneously or after corticosteroid therapy.

To prevent or assuage these reactions, paclitaxel is usually infused over 1 to 3 hours. Infusion in any interval shorter than 1 hour may precipitate an unacceptable frequency of reactions. Premeidication with corticosteroids and antihistamines is standard procedure. Docetaxel is given over 1 hour, and premedications must also be used. Such measures reduce the frequency and perhaps the intensity of reactions but do not fully prevent them.

A number of other chemotherapeutic agents (Table 55.8-4) are known to produce hypersensitivity reactions in at least sporadic instances. Most of these reactions have the features of a type I hypersensitivity, whether mediated by IgE or nonimmunologically. Hemolytic anemia (a type II reaction) is an uncommon form of such toxicity. Some drugs, such as procarbazine and methotrexate, may produce acute episodes that are typical of a type III reaction and cause interstitial pneumonitis and vasculitis.

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**Table 55.8-4. Antitumor Agents That Cause Hypersensitivity Reactions**

In most instances of hypersensitivity reactions from antitumor drugs, only isolated cases are studied adequately to define the cause of the reaction, and it is not possible to exclude the excipients used in drug formulation (e.g., benzyl alcohol, dimethyl acetamide) or other drugs given concurrently (e.g., mesna, mannitol, white blood cell growth factors) as the source of the reaction. When such reactions occur from one drug, it is often possible to continue therapy by either substituting another drug in the same class or administering premedication as prophylaxis.
VENOUS TOXICITY

Four main forms of vascular toxicity are produced by cancer chemotherapeutic agents: VOD, thrombocytopenia, microangiopathy with hemolytic uremic syndrome, venous or arterial thrombosis, and vascular ischemia (involving cerebral, myocardial, or extremity arterial vessels). VOD of hepatic vessels (see the section "Microangiopathy") and microangiopathy (see the section "Hemolytic uremic syndrome") were discussed earlier in this chapter.

Venous thrombosis in association with metastatic cancer has long been recognized (Trousseau's syndrome). Chemotherapeutic agents can also induce venous thrombosis in the form of extremely thromboses and pulmonary embolism, even in the absence of demonstrable metastatic cancer. Although they are less common, thromboses of cerebral, coronary, and extremity arteries can also be initiated by chemotherapy, again in the absence of demonstrable cancer. These events are not limited to one form of cancer. They have occurred in a variety of cancers as disparate as stage II breast cancer, testicular cancer, and lymphomas. One drug associated with such thrombotic episodes more is cisplatin, and a combination of chemotherapy with tamoxifen seems to produce a higher rate of such thrombotic episodes than either one alone.

Arterial ischemia without thrombosis can be caused by chemotherapy in major coronary or cerebral vessels and in the small vessels of the extremities. Myocardial ischemia and infarction occur in patients who receive continuous infusions of 5-FU, and precipitous heart failure and sudden death have occurred. Such events may occur in patients who have no known underlying coronary vessel disease, and they develop a few days after the start of the first infusion of 5-FU. The pathogenesis seems to be induction of coronary spasm by 5-FU, but the physiologic mechanism is not known. In some patients, arterial ischemia occurs in association with thromboses of cerebral, coronary, and extremity arteries. These events are not limited to one form of cancer. They have occurred in patients with advanced breast cancer treated with paclitaxel phase II study. Cancer Chemother Pharmacol 1999;3:150.

VASCULAR TOXICITY

CHAPTER REFERENCES


SECTION 56.1
Management of Cancer Pain

INTRODUCTION
Advances in the diagnosis and treatment of cancer, coupled with advances in our understanding of the anatomy, physiology, pharmacology, and psychology of pain perception, have led to improved care of the patient with pain of malignant origin. Specialized methods of cancer diagnosis and treatment provide the most direct approach to treating cancer pain by treating the cause of the pain. However, before the introduction of successful antitumor therapy, when treatment of the cause of the pain has failed, or when injury to bone, soft tissue, or nerve has occurred as a result of therapy, appropriate pain management is essential. Patients with cancer are managed most effectively by a multidisciplinary approach, using the expertise of a wide range of health care professionals. The goal of pain therapy for patients receiving active treatment is to provide them with sufficient relief to tolerate the diagnostic and therapeutic approaches required to treat their cancer. For patients with advanced disease, pain control should be sufficient to allow them to function at a level they choose and to die relatively free of pain. The management of the symptom of pain is only one component of a broad palliative care approach for cancer patients. Control of other symptoms, treatment of psychological distress, and attention to the religious, spiritual, and existential dimensions of the patient’s illness experience should be concurrently addressed to maintain the patient’s quality of life throughout the cancer illness course from diagnosis to death.

EPIDEMIOLOGY
Existing studies based on numerous national and international surveys and World Health Organization (WHO) estimates suggest that moderate to severe pain is
experienced by one-third of cancer patients receiving active therapy and by 60% to 90% of patients with advanced disease. There are 17 million new cases of cancer diagnosed worldwide each year and 5 million cancer deaths, accounting for large numbers of patients who suffer from cancer pain. Pain associated with direct tumor involvement is the most common cause of cancer pain, occurring in as many as 85% of patients reported from a pain service study, to 65% from an outpatient cancer center pain clinic survey. Bone pain is the most common type, with tumor infiltration of nerve and hollow viscus as the second and third most common pain locations. Cancer therapy causes pain in approximately 15% to 25% of patients receiving chemotherapy, surgery, or radiation therapy. Three percent to 10% of patients with cancer have pain caused by non-cancer-related problems, with pain syndromes reflecting the common causes of pain in the general population.

Patients with cancer often have multiple causes of pain and multiple sites of pain. Based on a variety of survey data, up to one-third of patients had more than one pain and 81% of patients reported two or more distinct pain complaints. Cross-cultural studies from India, Thailand, Vietnam, Germany, France, Taiwan, thePhilippines, and China report a similar prevalence of cancer pain in patients in active therapy and advanced disease.

Studies have focused not only on the prevalence of pain, but also on the intensity, degree of pain relief, and the effect of pain on quality of life in patients with various cancers including lung, colon, ovarian, and pancreatic cancers. In one study of lung and colon cancer ambulatory patients, the median pain duration was 4 weeks and the average pain intensity was moderate. Ninety percent experienced pain more than 25% of the time, and 50% reported that pain interfered moderately or more with their general activity or work. In the Netherlands, 60% of all outpatients seen at an oncology clinic were in pain and 20% of this group reported moderate to severe pain. In a 1999 survey of cancer outpatients, Weber and Huber reported inadequate documentation of pain severity, opioid dose, and rescue doses, observing that lack of documentation is a significant barrier to providing effective pain control. Cleenan et al., in a study of patients who were followed by the Eastern Cooperative Oncology Group, reported that 56% of patients reported moderate to severe pain 50% of the time. Numerous studies point out the fact that pain is prevalent in ambulatory patients, as well as hospitalized patients, and compromises function in approximately one-half of the patients who experience it.

A series of studies have focused on the seriously ill and nursing home cancer population and have identified a high prevalence of pain in these populations. The Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments showed that 50% of adults who die in the hospital experience moderate to severe pain in the last 3 days of life. A study of 4000 elderly nursing home residents with cancer revealed that 24%, 29%, and 38% of those over age 85, 74 to 84, and 65 to 74, respectively, reported daily pain. Twenty-six percent in daily pain did not receive any medication. Those over 85 who reported pain were most likely to receive no anesthetic.

Such studies have led to an assessment of the factors that influence the prevalence of cancer pain. Primary tumor type is one factor. Tumors that commonly metastasize to bone such as breast or prostate have a higher incidence of pain (60% to 80%) as compared with patients with lymphoma and leukemia. Stage of disease is a contributing factor, with increasing pain prevalence with disease progression. For example, less than 15% of patients with nonmetastatic disease report pain. Tumors that occur in close proximity to neural structures also have a greater incidence of pain. Patient variables such as anxiety, depression, and history of previous substance abuse influence the patient's report and experience of pain.

Several studies have detailed the characteristics of patient populations followed by pain services and palliative and hospice care programs, providing further data on the magnitude of the cancer pain problem. A 10-year experience of a German anesthesiology-based pain service associated with a palliative care program reported on the course of treatment of 2118 patients over a period of 140,478 treatment days. Table 56.1-1 lists the primary tumors and pain localization etiology and type of pain syndrome. In their survey, gastrointestinal and head and neck cancers were the most common types, with the majority (85%) caused by tumor involvement. Pain intensity data were collected through the course of treatment. Eighty-two percent of patients had moderate to severe pain at the beginning of treatment, with only 7% reporting such high intensity at the completion of treatment.

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<th>TABLE 56.1-1. Sites of Cancer Pain and Localization, Etiology, and Type of Pain Syndromes</th>
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Several studies have also addressed the epidemiology and ethnography of pain treatment. In a study to assess the effect of a comprehensive medical and neurologic evaluation of pain in the cancer patient, 64% of patients had a lesion newly identified by the pain consultant. Of note, more than 50% were neurologic in origin and, in 19% of patients further antinecancer therapy combined with anesthetic approaches were recommended. Further studies have observed that neurologic lesions make up a substantial portion of painful lesions in the cancer population. In a prospective study of neurologic symptoms, neurologic diagnoses, and primary tumors in all patients with a history of systemic cancer referred to Memorial Sloan-Kettering Cancer Center Neurology Consultation Service, the three most common symptoms in 851 patients were back pain (18.2%), altered mental status (17.1%), and headache (15.4%). The most common neurologic diagnosis was brain metastases (15.9%), followed by metabolic encephalopathy (10.2%), pain associated with bone metastases only (9.9%), and epidural extension or metastases of tumor (8.4%).

In studies of patients with far-advanced disease cared for in palliative care programs, pain is the most common physical symptom. Of note, pain treatment significantly reduced this symptom but several other prominent symptoms including anxiety, fatigue, weakness, anorexia, nausea and vomiting, and dyspnea were less effectively managed. This observation supports the critical need to evaluate, prioritize, and treat all symptoms to improve cancer pain patients’ quality of life.

**DEFINITION AND TYPES OF CANCER PAIN**

**DEFINITION OF PAIN**

The definition of pain proposed by the International Association for the Study of Pain is "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage." Because pain is a subjective complaint, there is no definitive way to distinguish pain occurring in the absence of tissue damage from pain resulting from such damage. Pain as a somatic delusion or masked depression is rare in cancer patients and the presence of pain usually implies a pathologic process.

**ANATOMY AND PHYSIOLOGY OF PAIN**

Extensive investigations over the last 30 years have expanded our knowledge of ascending and descending central nervous system pathways that process and modulate nociceptive information. These advances provide a scientific rationale for the use of new and improved methods of cancer pain treatment. A brief review of the neuroanatomy, physiology, and pharmacology of pain provides a background for the later discussions of specific drug, anesthetic, and neurosurgical approaches. Detailed information now supports the theory that activation of peripheral receptors in both superficial and deep structures as well as visceral by mechanical and chemical stimuli excites afferent discharges. Nonnociceptive messages are transmitted through rapidly conducting A-delta fibers and nociceptive information is signaled through slowly conducting A-delta and C-fiber afferents. The receptor endings of A-delta fibers most often respond to one sensory stimulus, whereas most C-fiber receptors are multimodal and respond to multiple high-threshold stimuli. These primary sensory afferents have their cell bodies in the dorsal root ganglion, and their axons enter the spinal cord via the dorsal root. The synaptic connections of these primary afferents with the corresponding second-order nociceptive neurons in the spinal dorsal horn are the initial site of processing for sensory information and act as a relay in transmitting noxious signals to the central
They ascend or descend from one or two segments in Lissauer's tract and synapse in specific lamina in the dorsal horn, lamina I and lamina II. Evidence suggests that myelinated nociceptors project to lamina I and V and unmyelinated nociceptors to lamina II and possibly lamina I, and nonnociceptive myelinated afferents project to only deep lamina. The dorsal horn is a critical site for modulating sensory input. Sensory transmission is mediated through excitatory amino acids (EAAs), predominantly glutamate. The EAA aspartate and the neuropeptides substance P and calcitonin gene-related peptide are also involved. Excitatory synaptic transmission from the primary afferent is also modulated by the N-methyl-D-aspartate (NMDA) receptor as well as non-NMDA receptors. Following EAA-NMDA receptor interaction, intracellular calcium influx and mobilization of intracellular calcium lead to subsequent changes in second messenger systems. One second messenger system activated following EAA-NMDA receptor interaction is the generation of nitric oxide via the enzyme nitric oxide synthase. There is also an increase in transcription of immediate early gene c-fos, which may regulate the subsequent expression of endogenous opioid genes, preproenkephalin and preprodynorphin. NMDA receptor activation initiates and maintains central sensitization and the component known as windup. These phenomena are manifestations of persistent signaling from primary sensory afferents. Central sensitization is thought to be the major mechanism underlying neuropathic pain and accounts for the hyperalgesia and enlarged cutaneous receptor fields that occur following nerve injury.

At the level of the second-order neurons in the dorsal horn, sensory processing occurs through interactions among neurochemical transmitters released by primary afferents including gamma-aminobutyric acid, glycine, adenosine, bombesin, cholecystokinin, dynorphin, enkephalin, neuropeptide Y, neurotensin, substance P, somatostatin, and vasointestinal peptide.

Several ascending pathways arise from these second-order neurons and descend to the spinal cord to become the neospinothalamic and paleospinothalamic tracts. These tracts project to discrete regions of the thalamus and cortex. The neospinothalamic pathway subserves pain intensity and localization, whereas the phylogenetically older paleospinothalamic pathway suberves the emotional component of pain. Descending pathways, the most important of which originate from the periaqueductal gray nuclei of the midbrain, synapse in the raphe magnus nucleus of the medulla. From this nucleus a medial pathway, the dorsal longitudinal fasciculus, projects to the dorsal horn to modulate pain transmission. This pathway represents an important descending inhibitory pathway. A more laterally placed descending pathway from the locus ceruleus to the dorsal horn also plays a role in pain modulation at the spinal cord level.

Opiate receptors, stereospecific binding sites on the end of free nerve endings that bind exogenous opioids, are localized in the ascending and descending pain pathways. These receptors mediate the multiple pharmacologic effects of the opioid analgesics. Subpopulations of opioid receptors including high-affinity and low-affinity μ receptors and k, g, and d receptors are localized to specific areas of the brain and spinal cord. More recently, several opioid receptor subtypes have been cloned and quantitative changes in the messenger RNA for these receptors have been determined for experimental models. The cloning of these subtypes of receptors that mediate different pharmacologic effects and then are located in specific cerebral and spinal sites offers the possibility of developing new analgesics targeted for specific receptors. For example, μ receptors modulate predominantly supraspinal analgesia, whereas δ and k receptors are important in modulating analgesia at the spinal cord level. The periaqueductal gray region in the midbrain and dorsal horn in the spinal cord are rich in these receptors and are the supraspinal and spinal sites that mediate opioid analgesia. The use of brainstem stimulation and the administration of opioid analgesics directly into the cerebrospinal fluid bathing the selected opioid sites in animals and cancer patients with pain are procedures based on this knowledge. Pain transmission at the spinal cord level can be inhibited by the direct application of morphine, and these studies have led to the use of spinal opioid analgesia in clinical pain states. There is now increasing information about the molecular basis of opioid tolerance development. A variety of NMDA receptor antagonists have been demonstrated both to attenuate and to reverse experimental opioid analgesic tolerance. Therefore, the confluence of NMDA receptors in pain transmission and their role in the development of tolerance have provided new insights into the role of opioid receptors in analgesia.

These advances in our understanding of pain modulatory systems and their neuroanatomic and neuropharmacologic correlates have had a major effect on the management of patients with pain. A better understanding of the molecular biology of both nociceptive and neuropathic pain is facilitating the wide application of a variety of agents including the NMDA antagonists, calcium channel agonists and antagonists, and topical and local systemic anesthetics and opioids.

TYPES OF PAIN

Three types of pain have been described based on the neuroanatomy and the neurophysiology of pain pathways: somatic, visceral, and neuropathic pain. Each type results from activation and sensitization of nociceptors and mechanoreceptors in the periphery by either mechanical (tumor compression or infiltration) or chemical (epinephrine, serotonin, bradykinin, prostaglandin, histamine, and so forth) stimuli.

SOMATIC PAIN

When nociceptors are activated in cutaneous or deep tissues, somatic pain results, typically characterized by a dull or aching but well-localized pain. Metastatic bone pain, postsurgical incisional pain, and myofascial and musculoskeletal pain are common examples of somatic pain.

VICERAL PAIN

Visceral pain results from activation of nociceptors from infiltration, compression, extension, or stretching of the thoracic, abdominal, or pelvic viscera. This typically occurs in patients with intraperitoneal metastases and is common with pancreatic cancer. This type of pain is poorly localized; is often described as deep, squeezing, and pressure-like; and when acute is often associated with significant autonomic dysfunction, including nausea, vomiting, and diaphoresis. Visceral pain is often referred to cutaneous sites that may be remote from the site of the lesion (e.g., shoulder pain with diaphragmatic irritation). It may be associated with tenderness in the referred cutaneous site. Increasing data have demonstrated the role of k opioid receptors in modulating visceral pain.

NEUROPATHIC PAIN

Neuropathic pain results from injury to the peripheral or central nervous system as a consequence of tumor compression or infiltration of peripheral nerves or the spinal cord, or from chemical injury to the peripheral nerve or spinal cord caused by surgery, radiation therapy, or chemotherapy. Examples of neuropathic pain include both metastatic and radiation-induced brachial and lumbosacral plexopathies, chemotherapy-induced peripheral neuropathies, paraneoplastic peripheral neuropathies, and postmastectomy, postthoracotomy, and phantom limb pain. Pain from nerve injury is often severe and is described as burning or dysesthetic, with a vice-like quality. The pain is typically most common in the site of sensory loss and may be associated with hypersensitivity to nonnoxious (allodynia) and noxious stimuli. Intermittently, patients complain of paroxysms or burning or electric shock–like sensations. The latter symptoms result from the phenomenon of central sensitization.

These three types of pain may occur alone or combined in the same patient. These different types of pain account for different responses to a drug and nondrug approaches. For instance, the nonsteroidal antiinflammatory drugs (NSAIDs) reduce chemical activation of nociceptors peripherally (e.g., bone pain), whereas anesthetic approaches suppress the pain transmission in peripheral nerves. Management of both somatic and visceral pain suggests that these types of pain respond to a wide variety of approaches. The management of neuropathic pain is more complicated: Changes in the peripheral nervous system and the central nervous system make this type of pain less responsive to a wide variety of pharmacologic, anesthetic, and neuromodulatory approaches.

Evidence suggests that most cancer patients have both somatic and visceral pain, with neuropathic pain representing 15% to 20% of the significant pain problems in this population. Certain adjuvant drugs appear to be more appropriate in the management of neuropathic pain; these issues are discussed in a later (see Adjuvant Analgesics for Neuropathic Pain).

TEMPORAL ASPECTS OF PAIN

ACUTE PAIN

Acute pain is characterized by a well-defined temporal pattern of pain onset, generally associated with subjective and objective physical signs and with hyperactivity of the autonomic nervous system. These signs provide the physician with objective evidence that substantiates the patient's complaint of pain. Acute pain is usually
self-limited and responds to treatment with analgesic drug therapy and to treatment of its precipitating cause. It can be further subdivided into subacute and episodic. Subacute pain comes on over several days, often with increasing intensity, and represents a pattern of progressive pain symptomatology. Episodic or intermittent pain occurs during confined periods of time on a regular or irregular basis. All of the pains in this category of acute pain have associated autonomic hyperactivity.

**CHRONIC PAIN**

Chronic pain is the persistence of pain for more than 3 months, with a less well-defined temporal onset. The autonomic nervous system adapts, and chronic pain patients lack the objective signs common to those with acute pain. Chronic pain leads to significant changes in personality, lifestyle, and functional ability. Treatment of chronic pain is often complex and involves careful assessment of not only the intensity, but its subjective and multidimensional aspects. Evidence suggests that the persistence of pain plays a major negative role in the quality of life of patients with pain and cancer.

Investigators have developed a nomenclature to describe a series of specific pains in cancer patients with both acute and chronic pain states. Baseline pain is the average pain intensity experienced for 12 or more hours during a 24-hour period. Breakthrough pain is a transient increase in pain to greater than moderate intensity occurring on a baseline pain of moderate intensity or less. In a study of 70 adult inpatient cancer patients, 65% reported breakthrough pain. The median number of reported pains was four, with a wide range. Most pains had a rapid onset and a brief duration. Breakthrough pain has a diversity of characteristics. Some authors have detailed the prevalence of such transitory flares of pain. In a study of 613 consecutive cancer patients, 39% reported transitory flares that were severe or worse in the last month. Breakthrough pains were more common in men, in those younger than 55 years, and in patients receiving chemotherapy, in 36%. In this and other series, the transitory increase in pain marks the onset or worsening of pain at the end of the dosing interval or the regularly scheduled analgesic. In other patients, it is caused by an action of the patient, referred to as *incident pain*. Sometimes the incident pain has a nonvolitional precipitant, such as flatulence or movement. Breakthrough or transitory pains are thought to be associated with a known malignant cause from direct tumor infiltration. Clinical trials with an oral transmucosal fentanyl preparation have focused attention on the clinical management of such episodes of worsening pain.

**INTENSITY OF PAIN**

Pain may also be defined on the basis of intensity, but there are limitations to a concept of pain based solely on intensity. Specific categoric scales of pain intensity have been used in which patients are asked to describe their pain as mild, moderate, severe, or excruciating. Visual analog scales (VAS) have also been used. These are often a 10-cm line anchored on either end by two points, signifying *no pain* and *worst possible pain*. The patient is asked to mark the intensity of the pain on the line. Numeric scales are also commonly used, asking patients to rate their pain between 1 (no pain) and 10 (worst possible pain). These scales have their limitations, but they are part of a series of validated instruments that include a measure of pain intensity as one of the components of the pain experience to be defined. In a study of physicians' and nurses' understanding of the language to describe pain, there was a close correlation among them of the level of intensity meant by the terms *ache, hurt, or pain*. Although health care professionals may understand the common language of pain, there is an enormous discrepancy between their assessment and the patients' report of pain. For example, when the patient reports pain as moderate or severe, they compared the ratings of pain severity by patients with those by physicians and found that patients tended to rate their pain as more intense than did physicians. In a study by Grossman and associates, the cancer patients' report of pain and the physicians' concurrent observation had a close correlation when patients reported mild pain. However, when patients reported moderate to severe pain, the correlation of the nurse, house officer, and oncology fellow differed significantly from that of the patient. The concordance dropped from 78% for patients with mild pain to 20% for those with moderate to severe pain.

**MEASUREMENT OF PAIN**

These problems in communication about pain intensity strongly support the argument that multiple dimensions of the pain experience should be used to assess it adequately. Several validated instruments for pain measurement attempt to look at it in a multidimensional nature. The use of such methods can provide rapid evaluation in clinical settings of the major aspects of the pain experienced by cancer patients. Growing evidence suggests that they should be integrated into clinical trials and should be available for use on a routine basis to better define the pain symptomatology and to study the effect on pain by various treatment approaches.

**BRIEF PAIN INVENTORY (BPI)**

The Wisconsin Brief Pain Questionnaire (BPI) is a self-administered, easily understood, brief method to assess pain. It addresses the relevant aspects of pain (history, intensity, location, and quality) and the pain's ability to interfere with the patient's activities and helps to provide an understanding of its cause. The history of pain and its relation to the patient's disease are assessed initially. If the patient admits to pain in the last month, he or she answers questions about current manifestations of pain. If the patient has no pain, he or she skips to the end of the questionnaire to complete demographic information. For patients with pain, a human figure drawing is provided for the patient to shade the area corresponding to the pain. Patients are asked to rate their pain at its worst, usual pain, and now. The pain scales consist of numbers from 0 to 10. 0 is labeled *no pain* and 10 is labeled *pain as bad as you can imagine*. Patients are asked to report the medications or treatments they receive for pain, the percent relief that these medications or treatment provide, and their belief about the cause of their pain. Finally, they are asked to rate how much the pain interferes with their mood, relations with others, and functional ability (walking, sleeping, working, enjoying life). All patients, including those without pain, are asked for basic demographic information about marital status, education, occupation, spouse's occupation, and months since diagnosis.

This inventory has been translated into numerous languages and has been used to assess pain in cancer patients in such diverse settings as Vietnam, Mexico, the Philippines, China, and the University of Wisconsin Cancer Center. Data from these studies suggest that cancer pain patients from widely different cultural and linguistic backgrounds respond in a similar fashion to rating the severity of their cancer-related pain and the interference caused by the pain.

**MCGILL PAIN QUESTIONNAIRE**

The McGill Pain Questionnaire (MPQ) is an extensively used pain assessment instrument that produces scores on four empirically derived dimensions, as well as several summary scores. The instrument consists of 78 adjectives that cluster in 20 categories. Within each category, the adjectives are arranged in order of intensity from low to high. The categories are divided into four dimensions: sensory, affective, evaluative, and miscellaneous. The patient is asked to choose one adjective from each applicable category that describes an aspect of his or her current pain, and the score for each dimension is obtained by adding the ranks of the selected adjectives. A total summary score is derived by adding the scores across the four dimensions, and a total word count is also obtained. Finally, a rating of present pain intensity is made on a five-point scale. Studies with this instrument have demonstrated that the factors derived reflect specific sensory qualities and components of the pain experience and dimensions. This tool has also been used to assess distinct score profiles according to the nature of pain. For instance, patients with acute pain tend to use more sensory words, but patients with chronic pain tend to use more affective and reaction word subgroups. The MPQ offers a methodologic approach to assess the sensory, affective, and evaluative components of pain, but it may be more difficult and cumbersome for patients to understand and complete and may be limited by its language constraints.

**MEMORIAL PAIN ASSESSMENT CARD**

The Memorial Pain Assessment Card (MPAC) (Fig. 56.1) was initially developed by the Analgesic Studies Section of the Memorial Sloan-Kettering Cancer Center to assess the relative potency of new and standard analgesic drugs. In that context, this method was found repeatedly to be a valid, reliable, efficient, and sensitive measure. The MPAC consists of three VAS that measure pain intensity, pain relief, and mood, and a set of pain severity descriptors adapted from the Tursky rating scale. The card is 8.5 by 11 inches and is folded in the middle so that the four sides can be quickly presented to the patient. Three sides are imprinted with the 100-mm long VAS scale: the fourth side is the set of Tursky adjectives. The pain intensity VAS is anchored by the terms *least possible pain* and *worst possible pain*. The patient is asked to place a mark along the line to indicate his or her subjective judgment of pain intensity. The score on this and the other VAS is obtained by measuring in millimeters the distance between the left end of the line and the patient's mark. The Tursky pain adjective scale is a categorical measure of pain intensity. Eight intensity descriptors, ranging from *no pain to excruciating*, are printed in a random arrangement and the patient is asked to circle the adjective that describes his or her subjective experience of pain severity. Side 3 of the MPAC is a pain-relief VAS. Patients are asked to indicate with a mark the degree of pain reduction they experience after the most recent intervention, which is usually the administration of an analgesic drug. On side 4 the VAS measures the subjective experience of mood; on this side patients are asked to rate their current feeling, from *worst to best*. The instructions for administration of these scales are simple and readily understood, and an experienced patient can complete the four ratings in less than 20 seconds.
They serve as a useful preamble for discussion of the specific therapeutic approaches to the management of cancer patients. Five types of cancer pain patients can be identified, exemplifying the distinctions between acute and chronic pain (Table 56.1-2).

The MPAC has been compared with the MPQ, the Profile of Mood States Questionnaire (a standardized self-report instrument that measures six dimensions of mood, reflecting degree and type of psychological distress), the Hamilton Rating Scale for Depression (an interviewer-rated scale evaluating the presence and severity of 17 symptoms typical of clinical depression), and the Zung Anxiety Scale (a standardized self-report scale that reports the presence and severity of various symptoms of anxiety). The MPAC and the MPQ both provide reasonably equivalent assessments of the intensity dimension of pain. However, the evaluative scales of the MPQ did not correlate significantly with any of the measures of the MPAC, suggesting that the cognitive judgmental dimension of pain may be independent of the experiences of intensity, relief, and mood. None of the MPQ subscales correlated significantly with the VAS ratings of mood and pain relief.

These observations have led to the conclusion that the VAS mood scale on the MPAC represents a much more global assessment of general psychological distress rather than a specific pain-related affect. This would suggest that the MPAC provides a broader assessment of the patient by its use of the mood scale, whereas the MPQ has a more narrow focus of simply representing pain-related emotional distress. What was particularly impressive was that in the use of any of the available scales, patients could differentiate pain and mood when they were explicitly asked. The perceptions of pain intensity and pain relief have different weights as components of psychological distress. The existence of such distinctions has important clinical and theoretical significance. Although the perception of pain intensity was found to contribute significantly to subjective distress, the perception of inadequate pain relief was a more important factor. The MPAC provides valid, multidimensional information for the evaluation of pain and distress in cancer patients. It can distinguish pain intensity from pain relief and from global suffering, and it can be used to study the subtle interactions of these factors. With repeated administration it has now been demonstrated to be valid, reliable, easy to use, and nondisruptive. The MPAC and the BPI are the tools recommended for use in the clinical evaluation of individual patients and as an outcome measure in clinical trials.

**QUALITY IMPROVEMENT GUIDELINES FOR THE TREATMENT OF CANCER PAIN**

The American Pain Society Quality of Care Committee has strongly advocated pain measurement as an integral part of any continuous quality-improvement program. They have argued that such quality-improvement programs should include five key elements: (1) ensuring that a report of unrelieved pain raises a red flag that attracts clinicians' attention; (2) making information about analgesics convenient where orders are written; (3) promising patients responsive analgesic care and urging them to communicate pain; (4) implementing policies and safeguards for the use of modern analgesic technologies; and (5) coordinating and implementing these measures. They have argued formally for there to be methods in place to chart and display patients' self-reported pain in a way that makes it highly visible and facilitates regular review by members of the health care team. Such information should be incorporated in the patient's permanent record. Figure 56.1-2 is an example of recording pain data as a fifth vital sign to be available on a page at the front of the patient's record. Unrelieved pain then should be a red flag that promptly turns attention to the problem. National programs have supported the development of broad institutional programs to improve pain management. The Veterans Administration has instituted a quality-improvement program in a wide effort to include pain as the fifth vital sign. The Joint Commission on Accreditation of Hospitals has similarly adopted clear guidelines for hospitals to improve pain management. Both of these programs, although not specifically focused on the cancer patient, are evidence of a broad commitment to reduce the barriers to effective pain management at institutional levels by instituting routine quality indicators of pain management. DuPen and colleagues have focused attention on the need to improve outpatient pain management, and through the use of a specific algorithm and nurse and chart reminders have demonstrated improved pain management for outpatient cancer patients using a specific algorithm.

**CLASSIFICATION OF PATIENTS WITH CANCER PAIN**

Five types of cancer pain patients can be identified, exemplifying the distinctions between acute and chronic pain (Table 56.1-2). Although these categories are fluid, they serve as a useful preamble for discussion of the specific therapeutic approaches to the management of cancer patients.
TABLE 56.1-2. Types of Patients with Pain from Cancer

GROUP I: ACUTE CANCER-RELATED PAIN

Group I, patients with acute cancer-related pain, can be subdivided further according to etiology.

GROUP IA: TUMOR-ASSOCIATED PAIN

For group IA patients, with tumor-associated pain, pain is the major symptom prompting medical consultation and the diagnosis of cancer. In addition, pain has a special significance as the harbinger of the patient's illness. Recurrent pain during the course of the illness or after successful therapy has the immediate implication of recurrent disease. Defining the cause of the pain may present a diagnostic problem, but effective treatment of its cause (e.g., radiation therapy for bone metastases) is usually associated with dramatic pain relief in most patients.

GROUP IB: PAIN ASSOCIATED WITH CANCER THERAPY

Group IB patients have postoperative pain, pain secondary to oral ulceration from chemotherapy, or myalgias secondary to corticosteroid withdrawal. The cause of the pain is readily identifiable, and its course is predictable and self-limiting (Table 56.1-3). These patients do not represent difficult diagnostic problems. Pain treatment directed at the cause of the pain is used to manage the transient symptoms. These patients endure significant pain for the promise of a successful outcome.

TABLE 56.1-3. Cancer-Related Acute Pain Syndromes

GROUP II: CHRONIC CANCER-RELATED PAIN

Group II patients, those with chronic cancer-related pain, represent difficult diagnostic and therapeutic problems, in contrast to patients with acute cancer-related pain. They can be divided for discussion purposes into two groups: those with chronic pain from tumor progression, and those with chronic pain related to cancer treatment. Both groups share the characteristic of a pain symptom that has persisted for more than 3 months.

GROUP IIA: CHRONIC PAIN FROM TUMOR PROGRESSION

In patients with chronic pain associated with progression of disease (e.g., patients with carcinoma of the pancreas, metastatic melanoma to bone, or Pancoast's syndrome), the pain escalates in intensity secondary to tumor infiltration of adjacent bone, nerve, or soft tissue. Combinations of antitumor therapy, analgesic drug therapy, anesthetic blocks, and behavioral approaches are all applied with varying degrees of success. Psychological factors play a significant role in this group of patients, in whom palliative cancer therapy may be of little value and is physically debilitating. The sense of hopelessness and fear of impending death may further add to and exaggerate the pain complaint; pain then becomes an aspect of the global suffering component. Identifying both the pain and the suffering component is essential to the development of adequate therapy for these patients. Management approaches must be directed to controlling the pain and identifying and developing treatment strategies for each of the components of the patient's symptoms and psychological distress. Analgesic therapy combined with a wide range of alternative approaches is necessary to provide adequate analgesia. Such patients are appropriate candidates for palliative care programs to address the broader aspects of symptom management and psychological support.

GROUP IIB: CHRONIC PAIN ASSOCIATED WITH CANCER THERAPY

Group IIB includes patients with chronic pain associated with cancer therapy, such as patients who develop pain after mastectomy, thoracotomy, or limb amputation (phantom limb). The nature of pain in these patients is secondary to nerve injury (neuropathic pain) with the development of a traumatic neuroma. Treatment of the pain for these patients is limited by the lack of available methods to remove the cause of the pain. Again, treatment is directed at the symptoms, not the cause. These patients closely parallel those in the general population with chronic intractable pain syndromes. Psychological factors play a significant role in how these patients adapt to and function with chronic pain. Defining this group is imperative: Identifying the cause of the pain as not directly related to tumor markedly alters the patient's therapy, prognosis, and psychological state. Each of the primary modalities of cancer therapy is associated with a series of specific chronic pain syndromes with characteristic pain patterns and clinical presentations (Table 56.1-4, Table 56.1-5, and Table 56.1-6). Although it is consoling to both the patient and the physician to realize that the pain does not represent recurrent or progressive disease, the persistence of the pain is a constant reminder of the previous diagnosis of cancer.
In these patients, all approaches aimed at maintaining the patient's functional status should be used. Alternative methods of therapy, in contrast to drug therapy, represent the major management approach. This group of patients with neuropathic pain is increasing in number and accounts for 15% to 25% of patients referred to a medical pain clinic.

GROUP III: PREEXISTING CHRONIC PAIN AND CANCER-RELATED PAIN

Group III includes patients with a history of chronic nonmalignant pain who develop cancer and pain. Psychological factors play a significant role in this group of patients, whose psychological and functional status is already compromised by their chronic nonmalignant pain state. These patients are at high risk of developing further functional incapacity and escalating chronic pain symptoms. However, their history should not be used in a punitive way to minimize or deny their complaints. Identifying this group of patients as a high-risk group helps to improve their psychological assessment and intervention.

GROUP IV: PATIENTS WITH A HISTORY OF DRUG ADDICTION AND PAIN

Group IV includes patients with a history of drug addiction who have cancer-related pain. Three subgroups can be identified: patients actively involved in illicit drug use and drug-seeking behavior, those receiving methadone in a maintenance program, and those who have not used drugs for several years. Undertreatment with analgesic drugs occurs most commonly in this group of patients. Assessment of reported pain by physicians and nurses is colored by the fact that the pain symptoms are confused with drug-seeking behavior. Attention to the medical and psychological needs of these patients requires individualized assessment and consultation with experts in drug-related problems. The first subgroup represents a major management problem, straining the most tolerant of medical care systems. Pain in the other two subgroups is readily managed, with the recognition that the psychological stresses consequent to the pain and cancer may place the patient at a high risk for recidivism. There is increasing expertise to address the need of this patient population with experts in addiction medicine and cancer pain working together to provide a coordinated system of care.

GROUP V: DYING PATIENTS WITH PAIN

In dying patients in pain, diagnostic and therapeutic considerations are directed at maintaining the patient's comfort. This group is identified separately from group II patients, because the psychological factors further compound adequate pain management. The issues of hopelessness and coping with death and dying become more prominent, and the suffering component must be addressed. Inadequate control of pain in the dying patient exacerbates the suffering component and demoralizes the family and the caregivers, who feel that they have failed in treating the patient's pain at a time when adequate treatment may matter the most. Rapid escalation of analgesic drug therapy, usually by the parenteral route (intravenous, subcutaneous, or transdermal), and amelioration of psychological symptoms should be attempted. The risk-to-benefit ratios in analgesic approaches become less of an issue when the goal of pain therapy is the patient's comfort. It is now widely recognized that it is the role and the responsibility of the physician to treat pain and suffering in this population of patients. Defined guidelines for the care of the dying have been published. Good physician–patient communication, which include issues of truth telling and the assault of truth; respect for patients' religious, cultural, and spiritual needs; and clearly defining goals of care can improve the care of this population of patients.

COMMON PAIN SYNDROMES

Pain in the cancer patient results from direct tumor infiltration and from the various cancer treatments and can occur unrelated to the cancer and cancer therapy. Table 56.1-3, Table 56.1-4, and Table 56.1-5 list the common acute and chronic pain syndromes that occur in patients with cancer. These lists are a compendium of various sources, but serve to summarize the broad and now well-recognized pain syndromes that occur often uniquely in this population of patients.

CLINICAL ASSESSMENT OF PAIN

Certain general principles should be followed in evaluating cancer patients who complain of pain. Lack of attention to these general principles is the major cause for misdiagnosis of a specific pain syndrome. Adequate assessment is a critical component for defining the appropriate therapeutic strategy for each patient. The general principles are presented here:

- Believe the patient's complaint of pain.
- Take a careful history of the patient's pain complaint.
- Evaluate the patient's psychological state.
- Perform a careful medical and neurologic examination.
- Order and personally review the appropriate diagnostic studies.
Treat the pain to facilitate the appropriate workup.
Reassess the patient's response to therapy.
Individualize the diagnostic and therapeutic approaches.
Clearly define the goals of care.
Discuss advance directives with the patient and the family.

BELIEVE THE PATIENT'S COMPLAINT OF PAIN

Critical to the management of the patient with cancer pain is the establishment of a trusting relationship with the physician. The complaint of pain is a symptom, not a diagnosis. Pain perception is not simply a function of the amount of physical injury sustained by the patient, but is a complex state determined by multiple factors. The diagnosis of a specific pain syndrome and a complete understanding of the patient's psychological state is not always made during the initial evaluation. In fact, it may take several weeks to define its nature because of the lack of radiologic or pathologic verification. It may take a similar period to fully comprehend each patient's psychological makeup. Numerous examples in the assessment of patients with pain and cancer highlight the limitation of the diagnostic process. It is not uncommon for patients with tumor infiltration of the brachial plexus from either lung or breast cancer to have pain for several weeks or months before the onset of objective radiologic and neurologic findings. A comprehensive evaluation involves taking a careful history; performing a detailed medical, neurologic, and psychological evaluation; developing a series of diagnosis-related hypotheses; and ordering the appropriate diagnostic studies.

TAKE A CAREFUL HISTORY OF THE PATIENT'S PAIN COMPLAINT

A careful history of the patient's pain complaint should include the patient's description of site of pain, quality of pain, exacerbating and relieving factors, temporal pattern, exact onset, associated symptoms and signs, interference with activities of daily living, effect on the patient's psychological state, and response to previous and current analgesic therapies. Multiple pain complaints are common in patients with advanced disease and must be ranked and classified.

EVALUATE THE PATIENT'S PSYCHOLOGICAL STATE

The patient's current level of anxiety and depression must be clarified and his or her past history of such symptoms must be defined. Knowledge of the patient's previous psychiatric history and need for past hospitalization for psychiatric care helps to clarify the patient's potential psychological risk. Information on how the patient has handled previous painful events may provide insight into whether the patient has demonstrated chronic illness behavior or has a past history of a chronic pain syndrome. It is important to know about a personal or family history of alcohol or drug dependence, to understand why the patient may be fearful or refuse to take opioid drugs.

Because each patient has his or her own understanding of the meaning of pain, it is useful to have the patient elaborate this meaning. Does he or she think it represents recurrent tumor, or is he or she convinced it is simply arthritis? Evidence suggests that when patients have a clear understanding of the meaning of their pain as representing recurrent tumor, they have increased psychological distress.

The importance of defining the psychological makeup of the patient with pain is supported by a variety of studies that have focused on the effect of suffering in patients with pain. Psychological factors play a significant role in accounting for the differences in pain experiences in cancer patients. A series of psychiatric syndromes have been described for cancer patients, with depression occurring in as many as 25% of patients. The depression presents either as an acute stress response or as a major depression. Awareness of the common psychiatric syndromes when evaluating the pain complaint expands the physician's understanding of such a complaint.

Although it is critical to know as much as possible about each patient with pain, some information may not be readily available in the first interview; in some instances it may never be available because of the lack of intellectual competence on the patient's part to define clearly the various components of the pain complaint. It is often necessary to verify the history from a family member who may provide information that the patient is unable to provide. The family may be more objective in assessing a disability of a patient who underreports his or her symptoms. Similarly, in a patient who is a poor historian, the family member may be able to provide essential information that may alter the diagnostic approach. All attempts should be made to compile a careful history and define the medical, neurologic, and psychological profile of the pain complaint.

It is also useful to define for the patient the goal of treatment. Some patients may have unreasonable expectations for adequate pain control, whereas others fail to critically consider the various options available to them. Before starting any new procedure, review carefully with the patient the risks and benefits to provide them with their expectation of the potential outcome of the therapeutic approach. As patients become more active in defining advance directives and as they focus on the quality of life, it is critical to ask patients to define what they would do if the pain were intractable or intolerable. Did the patient have a family member who died a painful death? From our experience, patients who have had such an experience are particularly fearful of their own deaths. Does the patient have suicidal thoughts or a pact with the patient? Does the patient have drugs in reserve or a gun in the house that he or she might use in desperation? In a study by Chochinov et al., pain alone did not correlate with patients' suicidal ideation. Significant depression appeared to be the major correlating factor, although pain clearly played a role in the development of depression in some patients. This series of questions allows patients to discuss openly their fears of death and their intention to take matters into their own hands rather than trust the health care professional. Such open discussions can allow the physician to better define for the patient the options for care and to reassure the patient of the physician's commitment to care. Because patients rarely offer this information unless requested, it is critical to develop specific questions that can be readily integrated into the initial history taken by the physician. Discussing with the patient how they would die and engaging the patient in a discussion of his or her concerns and wants can address the commonly heard quote of patients, "I have never died before, how do I do it?"

PERFORM A CAREFUL MEDICAL AND NEUROLOGIC EXAMINATION

A medical and neurologic examination helps provide the necessary data to substantiate the history. It also provides a direct assessment of the cognitive status of the patient. Knowledge of the referral patterns of pain in the common cancer pain syndromes can direct the examination. The commonly described pain syndromes in cancer patients associated with a postmastectomy pain syndrome can readily be defined as separate from tumor infiltration of the brachial plexus (see Table 56.1-6).

The physical and neurologic examination allows the physician to visually inspect and palpate the site of pain and to look for the associated physical and neurologic signs that might help to better define the nature of the pain symptom. Defining the degree of motor or sensory changes can help define the specific site in the nervous system that may be involved. Similarly, in patients with sensory loss, the presence of allodynia and hyperesthesia can further define the nature of the sensory problem and define a neuropathic pain syndrome. Moreover, the degree of muscle spasm, gait instability, and impaired coordination can only be fully assessed by such an evaluation.

ORDER AND PERSONALLY REVIEW THE APPROPRIATE DIAGNOSTIC STUDIES

Diagnostic studies confirm the diagnosis and define in patients with metastatic disease the site and extent of tumor infiltration. Computed tomography and magnetic resonance imaging (MRI) are the most useful diagnostic procedures in evaluating cancer patients with pain. The positron emission tomography scan is increasingly being used to further define tumor and to differentiate tumor from radiation injury. The bone scan is a useful screening device and is more sensitive for demonstrating abnormalities in the bone before changes appear on plain radiography. However, a negative bone scan does not rule out bony metastatic disease, nor does a positive bone scan confirm the diagnosis of metastatic tumor. In patients with collapsed vertebral bodies, an MRI can distinguish osteoporotic from tumor-induced bony changes. The physician should review the results personally with the radiologist to correlate any pathologic change with the site of pain.

Evaluation of the extent of metastatic disease may help to discover the relation of the pain complaint to possible recurrent disease. The use of tumor markers such as carcinomaembryonic antigen, CA 125, CA 15-3, and prostate-specific antigen can be useful in a patient in whom recurrent tumor is suspected. In certain pain syndromes the presence of recurrent disease is closely associated with the onset of pain (e.g., in the appearance of late postthoracotomy pain syndrome in a patient after initial resolution of the postoperative pain).
TREAT THE PAIN TO FACILITATE THE APPROPRIATE WORKUP

No patient should be evaluated inadequately because of a significant pain problem. Early management of the pain while investigating the source markedly improves the patient's ability to participate in the necessary diagnostic procedures. Table 56.1-7 lists the reasons for a pain consultation at Memorial Sloan-Kettering Cancer Center. During the initial evaluation of the pain complaint, early consideration of the use of alternative methods of pain control, including anesthetic and neurosurgical approaches, should be considered (e.g., the temporary use of a local anesthetic via an epidural catheter to manage sacral pain).

REASSESS THE PATIENT'S RESPONSE TO THERAPY

Continual reassessment of the response of the patient's pain complaint to the prescribed therapy provides the best method to validate the initial diagnosis as correct. If relief is less than predicted or if the pain worsens, reassessment of the treatment approach or a search for a new cause of the pain should be considered. A common example is the patient with epidural cord compression who develops a second block proximal to the one being radiated, with neurologic signs mimicking the original one.

INDIVIDUALIZE THE DIAGNOSTIC AND THERAPEUTIC APPROACH

Evaluation of the patient must be closely linked to the patient's level of function, ability to participate in the diagnostic workup, willingness to undergo the necessary diagnostic approaches, objective evidence that treatment approaches may be beneficial, and life expectancy. Careful judgment is required to select diagnostic approaches that will have a direct effect on the choice of the therapeutic strategy or will answer a specific question. The random use of diagnostic procedures in these patients, particularly those with advanced cancer and significant pain, is inappropriate because it may have an adverse effect on their quality of life. Open discussion with the patient about the need for assessment as well as the therapeutic options is critical to allow the patient to be part of the decision-making process. In some patients, diagnostic procedures such as MRI are inappropriate because they simply confirm the existence of a disease for which no treatment is available or for which the treatment would be a major surgical procedure (e.g., vertebral body resection) that would be inappropriate for a dying patient. Patient refusal of evaluation or treatment must be respected when the physician has fully explained the options and is convinced that the patient has an accurate understanding of the implications of no further workup or treatment.

DISCUSS ADVANCE DIRECTIVES WITH THE PATIENT AND FAMILY

When developing approaches for treatment, there must be an open discussion about advance directives so that the physician has a clear understanding of the patient's goal for therapy or his or her ambivalence in developing a therapeutic strategy. The physician must have unconditional positive regard for the patient, placing the control of symptoms of pain and treatment of psychological distress in the highest regard. Knowledge of the patient's decisions about resuscitation, living wills, and symptom management should he or she become incompetent improves the physician's ability to appropriately and humanely care for the dying patient with advanced disease. In a study of Memorial Sloan-Kettering Cancer Center patients evaluated by the Pain and Palliative Care Service, patients reported reluctance to discuss end-of-life care issues with their physicians, preferring to discuss their concerns with family and friends. Such data emphasize the need for education of families in the continuum of cancer care including issues of pain management and the role of sedation in patients whose lives are ending.

MANAGEMENT OF CANCER PAIN

The management of cancer pain incorporates treatment of the primary disease with analgesic drug therapy and aesthetic, neurosurgical, rehabilitative, psychological (cognitive behavioral), and psychiatric methods. Individualizations of the treatment strategy and titration to effective pain relief are the hallmarks of this therapeutic approach. Increasing sophistication in the use of analgesic drugs, coupled with advances in research on the underlying mechanisms of pain, have provided the scientific rationale for the more effective use of standard analgesic drug therapy (nonopiod, opioid, and adjuvant drugs), including the use of novel routes of drug administration (transdermal and transmucosal), the use of novel methods (bisphosphonates and calcitonin for bone pain, antidepressants and anticonvulsants for neuropathic pain), and the indication for the use of anesthetic, neurosurgical, psychological, and psychiatric approaches concurrently applied in the overall continuum of care.

Pain management is only one aspect of a broad palliative care approach, but it serves as a model for the scientific rigor and clinical trials that have defined cancer pain treatment as a specific strategic focus. The full impact of such a comprehensive approach has not been fully determined. From data evaluating the use of analgesic drug therapy to cancer pain alone, 70% to 90% of patients report adequate analgesia. Studies from various pain services, hospices, and palliative care programs report results as high as 95% of patients receiving effective analgesia.

To develop appropriate outcome assessment methods and to provide a basis for comparison of treatment strategies, Bruera and Wantanabe have developed the Edmonton Staging System for cancer pain, patterning it to the various staging systems for different primary tumors. Stage I (good prognosis), stage II (intermediate prognosis), and stage III (poor prognosis) are based on five prognostic features, including the presence or absence of neuropathic pain, incident pain, psychological distress, rapid tolerance development, and a history of drug addiction or alcohol abuse. This methodology, in preliminary studies, has been validated as a way to compare different patient populations with different primary tumors in clinical trials and outcome assessments of cancer pain therapy.

ANALGESIC DRUG THERAPY

Numerous guidelines for the management of cancer pain have been issued by various organizations and researchers. All of these guidelines have emphasized that analgesic drug therapy is the mainstay of treatment and have focused on the aims of drug therapy to achieve adequate pain relief safely within an acceptable time frame, minimize side effects of treatment, and provide ongoing analgesic therapy by the most convenient and least noxious means available. More recently, detailed descriptions of the decision-making process implemented during the treatment of patients with pain have provided further data on the rationale and outcomes of specific decisions and have detailed a series of principles in the selection of opioid drug and route of administration. In the following section, guidelines for the rational use of analgesics in the management of cancer pain are detailed. These guidelines are based on clinical pharmacologic principles, clinical trials, available metaanalyses of analgesic studies, and the clinical experience developed by the Pain Service at Memorial Sloan-Kettering Cancer Center. Table 56.1-7 lists the reasons why patients with pain were referred to an inpatient consultation service at Memorial Sloan-Kettering Cancer Center. These reasons for referral point out the complexity that has now developed in providing individualized pharmacotherapy for patients with pain. These data also point out the need for physicians and nurses to be knowledgeable in the use of these guidelines to provide patients with effective analgesia. These data, from 100 consecutive inpatients who were referred over a 14-week period to Memorial Sloan-Kettering Cancer Center Pain Service had 158 reasons for referral. The two most common reasons were uncontrolled chronic pain, which occurred in 73 patients, and excessive side effects without adequate analgesia, despite analgesic therapy, which occurred in 24 patients. The most common reasons included difficulties in pain assessment and poorly controlled acute pain. At the time of initial evaluation, 77 patients had a pain intensity of 7 out of
10, and 18 patients had a pain intensity of 4 to 6 out of 10. After initial evaluation by the Pain Service physicians, the therapeutic intent of analgesic therapy was to provide comfort and function for 87 patients and comfort only for 13 patients. Comfort and function were the therapeutic intent of analgesic therapy for 75 of the patients discharged (92%) and comfort only for 17 patients who died (94%). After initial evaluation, the Pain Service physicians changed the opioid drug, the route of administration, or both for 58 patients. Of 42 patients whose regimens were not changed, 17 were discharged, 3 died, and 22 required subsequent changes in either drug or route of administration. In short, a total of 80 patients required changes in opioid therapy before death or discharge. Sixty-four patients required more than one change in therapy. Forty-four patients required one or more changes, and 20 patients required two or more changes. These data are particularly important to point out the complexity of analgesic drug therapy in this population of patients. Side effects were problematic in providing patients with a balance between adequate analgesia and excessive side effects. It is critical, then, that the goals of care for an individual patient be recognized and help provide the essential context for therapeutic decision making. When patients prioritize optimal comfort and function equally, the therapeutic attempt is to achieve an adequate degree of relief without compromising cognitive and physical function. When comfort is the overriding goal of care, there is a willingness to use whatever analgesic therapy is necessary to achieve relief, even if function is diminished in the process. To achieve the goal of care as comfort and function, substantial effort is necessary to optimize a balance between relief and side effects through dose adjustment, sequential trials of opioid drugs, coadministration of adjuvant medications, and the use of spinal analgesic techniques. Increasing attention has focused on the need to switch patients from one opioid to another. Several studies have outlined the need for opioid rotation and substitution.\textsuperscript{78, 79, 80, 81, 82}

In the following section, detailed guidelines for the rational use of analgesics in the management of cancer pain are provided (Table 56.1-8). The use of drug therapy should be within the armamentarium of any physician or nurse who cares for patients with pain in cancer. Similarly, the integration of some of the psychological and psychiatric approaches should be widely available. The use of specific anesthetic and neurosurgical techniques will often require the services of trained medical personnel who have clinical experience in managing cancer pain, but such approaches may require referral to a specialty center.

### TABLE 56.1-8. Guidelines for the Rational Use of Analgesics in the Management of Cancer Pain

#### WORLD HEALTH ORGANIZATION THREE-STEP ANALGESIC LADDER

As part of a global program of WHO, the Cancer and Palliative Care Unit has created a Cancer Pain Relief Program, and through a series of expert panels, has developed guidelines for the treatment of cancer pain.\textsuperscript{7, 8, 83, 84} This program has achieved a broad international consensus, based on the concept that analgesic drug therapy is the mainstay for the majority of patients with cancer pain. As previously stated, field testing of the WHO guidelines, in conjunction with clinical experience, has shown that 70% to 90% of cancer patient’s pain can be controlled using a simple and inexpensive method described as the \textit{three-step analgesic ladder}.\textsuperscript{83} This approach is based on the use of a combination of nonopioid, opioid, and adjuvant drugs, titrated to the individual needs of the patient according to the severity of pain and its pathophysiology (Tables 56.1-9, Table 56.1-10, and Table 56.1-11). Implementation of the analgesic guidelines, assurance of drug availability (specifically opioids), the education of health care professionals, and designating cancer pain as a priority for all national cancer control programs are the major goals of the WHO effort.\textsuperscript{84}

### TABLE 56.1-9. Nonopioid Analgesic Drugs in the Management of Cancer Pain

### TABLE 56.1-10. Opioid Drugs Commonly Used in Cancer Pain Management
OPIOID DRUGS

acetaminophen may become excessive. This is particularly important when the patient requires escalation of the combination to provide analgesia, in which case the additional dosage of the NSAID or

obtained, adding an opioid to a nonopioid provides additive analgesia. Combinations of codeine, oxycodone, and propoxyphene are available, but these combinations among patient responses to different drugs, patients may require trials with several NSAIDs before finding an effective drug and dose regimen. If pain relief is not

before switching to an alternative one. Such a trial should include administration of the drug to maximum levels at regular intervals. Because there is a great variability the first-line approach, but the choice and use of the nonopioid need to be individualized. Each patient should be given an adequate trial of one nonopioid analgesic

and have not been specifically analyzed for the patient with cancer. Several NSAIDs have been approved by the Food and Drug Administration; rofecoxib for acute pain management and osteoarthritis and celecoxib for osteoarthritis and rheumatoid arthritis. © Although these drugs offer the unique advantage of less gastrointestinal and renal toxicity, their specific role remains undefined. Acetaminophen, which is equipotent to aspirin, is an analgesic and antipyretic. It is much less effective as an antiinflammatory agent and does not interfere with platelet function. In general, this class of drugs is thought to produce

induced by EAAs such as glutamate or tachykinins (such as substance P). The NSAIDs differ from each other both in duration of analgesic action and in their

nociceptive stimulation from tissue injury. Evidence suggests that central mechanisms augment the peripheral effects of these drugs via inhibition of neural activity

analgesia by inhibiting activation of peripheral nociceptors through their prevention of the formation of prostaglandin E₂, a known sensitizer of peripheral receptors to nociceptive stimulation from tissue injury. Evidence suggests that central mechanisms augment the peripheral effects of these drugs via inhibition of neural activity induced by EAAs such as glutamate or tachykinins (such as substance P). The NSAIDs differ from each other both in duration of analgesic action and in their pharmacokinetic profile. Ibuprofen and fenoprofen have short half-lives and the same duration of action as aspirin, whereas diffusional and naproxen have longer half-lives and are longer acting. These drugs are thought to have a special role to play in the management of bone pain because numerous studies have shown that aspirin inhibits tumor growth in an animal model of metastatic bone tumor. A metaanalysis of NSAIDs in bone pain did not demonstrate them to be more effective than weak opioids such as codeine, oxycodone, and propoxyphene. © From clinical experience, some patients respond better to one NSAID than to another, and each patient should be given an adequate trial of one drug on a regular basis before switching to another. Survey data from the WHO demonstration projects suggest that 20% to 40% of patients obtain pain relief with the use of nonopioid analgesics alone. ©

Numerous studies have elucidated the major risk factors for gastrointestinal toxicity associated with NSAID use. Various factors contribute to the high risk of ulcer complications including advanced age, use of higher doses, concomitant administration of corticosteroids, and a history of either ulcer disease or previous gastrointestinal complications from NSAIDs. The empiric use of various prophylactic therapies to prevent gastrointestinal complications is controversial. Except for misoprostol, there is no evidence that any of these approaches reduces the risk of serious gastrointestinal toxicity. The empiric approach at this time is to administer misoprostol to all patients who have significant risk factors for gastrointestinal complications. © Many of these data have been accumulated in the general literature and have not been specifically analyzed for the patient with cancer. Several NSAIDs have been approved by the Food and Drug Administration for use as analgesics for mild to moderate pain and are listed in Table 56.1-12. Guidelines for the use of NSAIDs in patients with cancer are largely empiric. This class of drugs represents the first-line approach, but the choice and use of the nonopioid need to be individualized. Each patient should be given an adequate trial of one nonopioid analgesic before switching to an alternative one. Such a trial should include administration of the drug to maximum levels at regular intervals. Because there is a great variability among patient responses to different drugs, patients may require trials with several NSAIDs before finding an effective drug and dose regimen. If pain relief is not obtained, adding an opioid to a nonopioid provides additive analgesia. Combinations of codeine, oxycodone, and propoxyphene are available, but these combinations often contain less than the full dose of 650 mg of aspirin or acetaminophen. Prescribing each drug separately provides a better method for individualizing pain control. This is particularly important when the patient requires escalation of the combination to provide analgesia, in which case the additional dosage of the NSAID or acetaminophen may become excessive.

TABLE 56.1-11. Adjuvant Analgesics in the Management of Cancer Pain

| Step 1 | Step 1 of the analgesic ladder focuses on analgesic drug therapy for patients with mild to moderate cancer pain. Such patients should be treated with a nonopioid analgesic that may or may not be combined with an adjuvant drug, depending on the specific pain pathophysiology. For example, in a patient with mild pain from bone metastases, the use of acetaminophen, aspirin, or one of the NSAIDs would be appropriate. In a patient with mild pain from a peripheral neuropathy, the combination of a nonopioid with a tricyclic antidepressant drug, such as amitriptyline, would be an appropriate combination. |
| Step 2 | Step 2 focuses on patients with moderate pain who failed to achieve adequate relief after a trial of a nonopioid analgesic. They are candidates for a combination of a nonopioid (e.g., aspirin or acetaminophen) and an opioid such as codeine, oxycodone, propoxyphene, buprenorphine, or tramadol. Dependent on the pain pathophysiology, adjuvant drugs should be used as well. |
| Step 3 | Step 3 is for those patients who fail to achieve adequate relief following appropriate administration of drugs on the second rung of the analgesic ladder. Nonopioids are often used in combination to spare the opioid effect and adjuvants are used dependent on the pain pathophysiology or the need to control other concurrent symptoms in the individual patient. |

In short, the analgesic drug ladder of the WHO simply defines a method for using drug combinations and is based on previously well-tested pharmacologic principles. It is well recognized that nonopioid drugs such as aspirin and acetaminophen when combined with opioids provide additive analgesia. It is also well recognized that drugs such as morphine, methadone, fentanyl, levorphanol, and so forth are more effective for severe pain, whereas drugs such as codeine, oxycodone, and tramadol are more effective in a range of pain intensity of mild to moderate. What continues to be controversial in the application of the WHO ladder is the choice of the analgesic drug for the individual patient. Such controversies are discussed within the framework of the current application of the guidelines for rational use. © and © Critical assessment of the WHO ladder has raised challenging questions to the selection of specific drugs. A metaanalysis of the role of NSAIDs in bone pain did not define them as any more or less effective than opioids. ©

CLASSES OF DRUGS

NONOPIOID ANALGESICS

The nonopioid analgesics include acetaminophen and the NSAIDs, of which aspirin is the prototypic agent. These compounds are most commonly used orally and their analgesia is limited by a ceiling effect, so that increasing the dose beyond a certain level (900 to 1300 mg/dose of aspirin) produces no increase in peak effect. Tolerance and physical dependence do not occur with repeated administration. Aspirin and the other NSAIDs have analgesic, antipyretic, antinfiammatory, and antiplatelet actions. Some NSAIDs lack the antiplatelet effects of aspirin, such as choline, magnesium trisalicylate. Others appear to produce fewer gastrointestinal side effects than aspirin (ibuprofen). Two new drugs within the NSAID class are the cyclooxygenase enzyme inhibitors and include rofecoxib (Vioxx) and celecoxib (Celebrex). Neither drug has been studied in cancer patients, and the current indications for use are based on their current approval by the Food and Drug Administration; rofecoxib for acute pain management and osteoarthritis and celecoxib for osteoarthritis and rheumatoid arthritis. © Although these drugs offer the unique advantage of less gastrointestinal and renal toxicity, their specific role remains undefined. Acetaminophen, which is equipotent to aspirin, is an analgesic and antipyretic. It is much less effective as an antinfiammatory agent and does not interfere with platelet function. In general, this class of drugs is thought to produce analgesia by inhibiting activation of peripheral nociceptors through their prevention of the formation of prostaglandin E₂, a known sensitizer of peripheral receptors to nociceptive stimulation from tissue injury. Evidence suggests that central mechanisms augment the peripheral effects of these drugs via inhibition of neural activity induced by EAAs such as glutamate or tachykinins (such as substance P). The NSAIDs differ from each other both in duration of analgesic action and in their pharmacokinetic profile. Ibuprofen and fenoprofen have short half-lives and the same duration of action as aspirin, whereas diffusional and naproxen have longer half-lives and are longer acting. These drugs are thought to have a special role to play in the management of bone pain because numerous studies have shown that aspirin inhibits tumor growth in an animal model of metastatic bone tumor. A metaanalysis of NSAIDs in bone pain did not demonstrate them to be more effective than weak opioids such as codeine, oxycodone, and propoxyphene. © From clinical experience, some patients respond better to one NSAID than to another, and each patient should be given an adequate trial of one drug on a regular basis before switching to another. Survey data from the WHO demonstration projects suggest that 20% to 40% of patients obtain pain relief with the use of nonopioid analgesics alone. ©

Numerous studies have elucidated the major risk factors for gastrointestinal toxicity associated with NSAID use. Various factors contribute to the high risk of ulcer complications including advanced age, use of higher doses, concomitant administration of corticosteroids, and a history of either ulcer disease or previous gastrointestinal complications from NSAIDs. The empiric use of various prophylactic therapies to prevent gastrointestinal complications is controversial. Except for misoprostol, there is no evidence that any of these approaches reduces the risk of serious gastrointestinal toxicity. The empiric approach at this time is to administer misoprostol to all patients who have significant risk factors for gastrointestinal complications. © Many of these data have been accumulated in the general literature and have not been specifically analyzed for the patient with cancer. Several NSAIDs have been approved by the Food and Drug Administration for use as analgesics for mild to moderate pain and are listed in Table 56.1-12. Guidelines for the use of NSAIDs in patients with cancer are largely empiric. This class of drugs represents the first-line approach, but the choice and use of the nonopioid need to be individualized. Each patient should be given an adequate trial of one nonopioid analgesic before switching to an alternative one. Such a trial should include administration of the drug to maximum levels at regular intervals. Because there is a great variability among patient responses to different drugs, patients may require trials with several NSAIDs before finding an effective drug and dose regimen. If pain relief is not obtained, adding an opioid to a nonopioid provides additive analgesia. Combinations of codeine, oxycodone, and propoxyphene are available, but these combinations often contain less than the full dose of 650 mg of aspirin or acetaminophen. Prescribing each drug separately provides a better method for individualizing pain control. This is particularly important when the patient requires escalation of the combination to provide analgesia, in which case the additional dosage of the NSAID or acetaminophen may become excessive.

TABLE 56.1-12. Types of Anesthetics Procedures Commonly Used in Cancer Pain

OPIOID DRUGS
The opioid analgesics, of which morphine is the prototype, is potency, in efficacy, and adverse effects. These drugs produce their analgesic effects by binding to discrete opioid receptors in the peripheral and central nervous systems. This group also includes a series of heterogeneous substances with varying chemical structures. In contrast to the nonopiod analgesics, opioid analgesics, at least the opioid pure agonist, do not appear to have a ceiling effect (i.e., as the dose is escalated on a log scale, the increment in analgesia is linear to the point of loss of consciousness). There are also series of drugs that are pure antagonists (i.e., they block the effect of morphine at the receptor). The drug most commonly used in clinical practice is naltrexone, which is used to reverse respiratory depression and other complications associated with opioid overdose.

Effective use of the opioid drugs requires the balancing of the most desirable effects of pain relief with the undesirable effects of nausea, vomiting, mental clouding, sedation, constipation, tolerance, and physical dependence. These undesirable effects impose a practical limit on the dose useful for a particular patient and have led to the concept of opioid responsiveness (see Principles of Opioid Drug Therapy, later in this chapter).

The use of opioids in the management of cancer pain remains a controversial issue. Some of the controversies include their role in the management of neuropathic pain, which has been suggested for the opioid resistant, the specific choice of opioid drug, the use of sequential trials of opioids, routes of administration, development of tolerance, economic factors influencing these controversies, and the concern that opioids are agents of physician-assisted suicide and euthanasia. When appropriate, these controversies are addressed in the following discussion of the principles of opioid drug therapy.

PRINCIPLES OF OPIOID DRUG THERAPY

START WITH A SPECIFIC DRUG FOR A SPECIFIC TYPE OF PAIN

As defined by the three-step analgesic ladder, the specific drug chosen is dependent in part on the degree of pain intensity. As previously noted, cancer patients commonly have multiple sites and types of pain. It has been suggested that neuropathic pain, which accounts for 10% to 20% of pain problems that are difficult to manage, is opioid resistant, and that opioid drugs should not be used in this population. Studies in cancer patients with both nociceptive and neuropathic pain, as well as controlled studies in nonmalignant neuropathic pain, demonstrate the variable responsiveness of neuropathic pain to opioid analgesics. The concept of a continuum of opioid responsiveness, rather than an all or none quantal phenomenon, has been clearly observed. Opioid responsiveness is defined as the degree of analgesia achieved during dose escalation to either intolerable side effects or adequate analgesia. Patient characteristics, pain-related factors, as well as drug-selective effects influence this variable response.

A wide range of adjuvant analgesics has been suggested to provide analgesia alone or in combination with opioid drug therapy, and there are specific adjuvants for bone pain and neuropathic pain. Not only pain intensity and type of pain dictate the choice of a specific drug, but also the patient's prior opioid exposure, history of allergy, and history of side effects.

The WHO Cancer Pain Guidelines designated morphine as the drug of choice in its Cancer Pain Relief Program. The choice was based on practical, not scientific, considerations. The introduction of the WHO program rapidly demonstrated the limited availability of morphine worldwide for oral treatment of chronic cancer pain. Morphine consumption worldwide is now used as an indicator of the success of the WHO Cancer Pain Relief Program. For example, in Japan following a nationwide program to improve cancer pain management, a 17-fold increase in morphine consumption has been reported. The expanded use of morphine, combined with new formulations and new information about the analgesic activities of its metabolites, focuses renewed attention on its clinical pharmacology with recognition of morphine-6-glucuronide (M6G) as an active metabolite. Human studies have shown that M6G is analgesic in humans and appears in the plasma and cerebrospinal fluid of patients receiving morphine systemically. In renal dysfunction, M6G has an increased elimination half-life and decreased clearance, confirming a true delay in excretion of the compound, leading to an increase in the M6G to morphine ratio during chronic therapy. Adverse effects (nausea and respiratory depression) have been attributed to plasma concentration of the metabolite, particularly in patients with renal failure. However, attempts to correlate M6G to morphine ratio or M6G to M3G ratio with side effects such as cognitive impairment or myoclonus have not been possible.

Factors may influence the levels of both M6G and M3G, including route (increased M6G following oral administration), age (increased M3G and M6G if greater than 70 years), male sex (decreased morphine and M6G plasma concentrations), concurrent use of tricyclic antidepressants (increased M3G), and use of ranitidine (increased morphine). Controlled-release oral morphine is currently available in a wide range of doses from 50 to 200 mg for every 8-, 12-, and 24-hour administration. These preparations provide comparable analgesia with immediate release forms and offer increased convenience, improved compliance, and a reduction in duration of pain.

The increasing need for a wide range of opioids to manage cancer pain has led to the wide use of a series of alternative opioids to morphine, including hydromorphone, oxycodone, oxymorphone, and levorphanol, all congeners of morphine. Hydromorphone has poor oral availability and a short half-life. It is highly soluble and available in a high-potency parenteral form (10 mg/mL), making it a useful choice for chronic subcutaneous administration. Because of its short half-life, it is commonly used in the elderly patient. Myoclonus has been reported following high doses possibly due to accumulation of its metabolites (3-methyl- or 6-methylmorphine). When compared in a double-blind trial of patient-controlled analgesia, no differences in analgesia or side effects were noted between morphine and hydromorphone. Although cognitive performance was poorer in the hydromorphone group, patients reported better mood as compared with morphine.

Hydromorphone is available in slow-release preparations.

Oxycodone, which is commonly used at a 5-mg dose in the second step of the WHO analgesic ladder, can also be used in the third step at higher doses. It is now available in a slow-release preparation. Its half-life is approximately 3 to 4 hours. Oxymorphone is its active metabolite. Oxymorphone is currently only available by the intravenous and rectal routes and serves as an alternative to morphine and its other congeners. Oxymorphone has less of a histamine effect and may be of use in those patients who complain of headache or itch following other opioid administration.

Levorphanol has good bioavailability but a long plasma half-life (12 to 16 hours). It should be used cautiously because with repeated administration, accumulation may occur.

The role of methadone in cancer pain also remains controversial. Methadone represents a second-line drug for cancer pain patients who have had prior exposure to opioids. It is a relatively inexpensive oral analgesic, but its name has negative connotations for cancer patients who view methadone as a drug used to treat addicts. The bioavailability of methadone is higher than that of morphine (85% vs. 35%, respectively). Its analgesic potency also differs with a parenteral to oral ratio of 1:2 in contrast to 1:6 with morphine. Moreover, the plasma half-life of methadone is 17 to 24 hours, with reports of up to 50 hours in some cancer patients, but with a duration of analgesia of only 4 to 8 hours. Significant adverse effects have been reported in cancer patients receiving methadone by various routes. The discrepancy between analgesic duration and plasma half-life of methadone have made it a difficult drug to use in the naïve patient because of the need for careful titration.

A number of case reports have highlighted the possible greater analgesic potency of methadone than the often quoted 1:1 equivalency with morphine. Studies of interindividual differences in response to opioid analgesics demonstrate dramatically reduced doses of methadone required to produce analgesia in patients chronically taking morphine or hydromorphone. Several authors have shown marked reductions in the equianalgesic dose of methadone when patients with either uncontrolled pain or extreme side effects were switched. These clinical survey studies suggested up to a 75% reduction in the methadone equianalgesic dose. In the only perspective study, Ripamonti et al. developed a specific dose ratio based on the patient's morphine doses. When compared in a double-blind trial of patient-controlled analgesia, no differences in analgesia or side effects were noted between morphine and hydromorphone. In patients receiving more than 330 mg of hydromorphone, the dose ratio is 1.6:1; and less than 300 mg, the dose ratio is 4:1; for those on 90 to 300 mg daily, the dose ratio is 6:1; and for those on 300 mg or more, the dose ratio is 8:1. Bruera et al. developed a similar ratio for hydromorphone based on survey data. In patients receiving more than 330 mg of hydromorphone, the dose ratio is 1.6:1; and less than 300 mg, the dose ratio is 0.95:1.

In general, a good rule is to reduce the calculated equianalgesic dose by 75% and titrate the patients to effective pain relief. These reports have pointed out the need to use one-fourth to one-third the equianalgesic dose of methadone when switching from other opioids to this regimen. This observation relates in part to significant incomplete cross-tolerance with methadone and other factors that have not been fully assessed. Methadone can be administered by a variety of routes, but the subcutaneous route is associated with adverse effects including cutaneous hypersensitivity. Due to its long half-life, some offer the suggestion that methadone be used on a every 8 to 12 hour basis, whereas others have demonstrated analgesic efficacy and safety in acute 3- to 4-hour dosing intervals. Ongoing studies are attempting to elucidate better the clinical pharmacology of methadone to facilitate its broader use.

Meperidine is a drug that should not be used chronically in the management of patients with cancer pain. Meperidine has a poor parenteral to oral ratio (1:4). It is
available in oral and intramuscular routes but repetitive intramuscular administration is associated with local tissue fibrosis and sterile abscesses. Repetitive dosing of meperidine (greater than 250 mg/d) can lead to normeperidine accumulation, an active metabolite that can produce central nervous system hyperexcitability. This hyperexcitability is characterized by subtle mood effects followed by tremors, multifocal myoclonus, and occasional seizures. It occurs most commonly in patients with renal disease, but can also occur following repeated administration in patients with normal renal function. Naloxone does not reverse meperidine-induced seizures and its use in meperidine toxicity is controversial; there have been some case reports that the use of naloxone has precipitated generalized seizures in individual patients. In rare instances, central nervous system toxicity characterized by hyperpyrexia, muscle rigidity, and seizure have been reported following the administration of a single dose of meperidine to patients receiving treatment with monoaminooxidase inhibitors.

With the development of a novel transdermal patch, fentanyl is an opioid analgesic used effectively in cancer pain patients for management of both acute and chronic pain. The half-life of fentanyl is 1 to 2 hours. Its relative potency compared with parenteral morphine is 1 to 20 in intolerable acute pain patients. In chronic cancer pain, relative potency comparisons have not been fully established but the common dosing guideline is that 4 mg of intravenous morphine is equivalent to 100 µg of intravenous fentanyl. The uniqueness of this preparation facilitates the management of patients who are unable to take drugs by mouth by providing them with continuous opioid analgesia. Patches are currently available in 25 to 100 µg/h doses. Fentanyl can also be used as an anesthetic premedication, as well as intravenously and epidurally for pain control. Oral transmucosal formulations have demonstrated effectiveness in breakthrough pain in cancer patients. Fentanyl (Actiq) is available in a range of dosages from 200 to 1600 µg. Twenty-five percent of the preparations in a lozenge formulation in a style is absorbed transmucosally over a 15-minute period and an additional 25% is absorbed via the gastrointestinal tract over the following 90 minutes. Onset of relief occurs in 5 minutes. Oral transmucosal fentanyl citrate in dose titration trials is shown to be safe and effective with the effective dose being a variable requiring titration in the majority of patients.

KNOW THE EQUIANALGESIC DOSE OF THE DRUG AND ITS ROUTE OF ADMINISTRATION

Knowing the equianalgesic dose can ensure more appropriate drug use. Lack of attention to these differences in drug dose is the most common cause of undertreatment of pain patients. These doses have been derived from assessment of the relative analgesic potency of a drug. Relative potency is the ratio of the doses of two analgesics required to produce the same effect. Estimates of relative potency allow calculation of the equianalgesic dose, which provides the basis for selecting the appropriate dose when switching drugs or route of administration of the same drug. The values in Table 56.1-10 are based on studies in which 10 mg of morphine was the standard dose. The equianalgesic dose is the recommended starting dose, with the optimal dose for each patient determined by dose adjustment. There is now evidence to suggest that relative potency may differ in single-dose and repeated dose studies. For example, for morphine, a 1:6 relative analgesic potency ratio should be used for patients with acute pain, whereas a 1:2 or 1:3 ratio in patients treated with repeated doses on a chronic basis is more appropriate. For methadone, the equianalgesic dose ratios vary with the degree of prior exposure as previously discussed.

ADMINISTER ANALGESICS REGULARLY AFTER INITIAL TITRATION

Medication should be given regularly in order to maintain the plasma level of the drug above the minimum effective concentration for pain relief. In the initial titration, patients should be advised to take their medication as needed to determine their total 24-hour requirements. This is also the time frame for reaching the steady-state level of drug, which depends on the drug's half-life. For morphine, steady state can be reached in 24 hours; with methadone it may take up to 5 to 7 days to reach steady state. In patients on a fixed schedule, rescue medications equivalent to one-half of the standing dose should be available to patients for breakthrough pain.

Continuous intravenous and subcutaneous opioid infusions to manage both acute and chronic cancer pain are commonly used with a patient-controlled analgesic pump. Fentanyl is delivered with a set lock-out time to prevent overdosing. This method of opioid administration is especially useful to manage patients with breakthrough pain. It is a significant advance in facilitating adequate titration of analgesics in chronic cancer patients, allowing discharge to home and hospice settings.

GEAR THE ROUTE OF ADMINISTRATION TO THE PATIENT'S NEEDS

Various methods of drug delivery of opioids have been developed in an attempt to maximize pharmacologic effects and minimize side effects. Most patients require at least two routes of drug administration, and 20% need up to four approaches during the course of their cancer pain treatment, from diagnosis to death.

The oral route is preferable and easy. Orally administered drugs have a slower onset of action, delayed peak time, and longer duration of effect; drugs given parenterally have a rapid onset of action but a shorter duration of effect. Slow-release preparations of morphine, hydromorphone, and oxycodone allow more convenient dosing of cancer pain patients every 8 to 12 hours or 24 hours.

For cancer pain management by the sublingual route, these are drugs that are well absorbed sublingually including both fentanyl and methadone. As discussed there is now an oral transmucosal fentanyl citrate preparation that has been widely studied for the management of breakthrough pain and is absorbed transmucosally.

For the rectal route, oxymorphone, hydromorphone, and morphine are available in suppository form. Oxymorphone suppositories produce analgesia equivalent to 10 mg of parenteral morphine. Slow-release oxycodone and morphine preparations have also been demonstrated to be effective rectally and ongoing studies with rectal methadone suggest that this drug is well absorbed by the rectal route.

The transdermal route is a convenient way to deliver a potent short-acting opioid on a continuous basis. Drug is released through the skin patch at a nearly constant amount per unit time with a concentration gradient from patch to skin. Serum fentanyl concentrations increase and steady-state levels are reached at 12 to 24 hours. After patch removal, the drug persists in the skin, with falling blood levels over 24 hours. In calculating the equianalgesic dose, 4 mg of intravenous morphine is equivalent to 100 µg of fentanyl transdermally. Innovative transdermal delivery systems are in development, which include systems for immediate-dose delivery using iontophoresis and drug reservoirs. Iontophoresis is the transfer of ionic solutes through biologic membranes under the influence of an electric field. It offers an alternative system for parental administration and has been shown to allow for comparatively rapid achievement of fentanyl dose levels using a transdermal system.

Various parenteral routes include intermittent and continuous subcutaneous, intravenous, epidural, intraventricular, and intrathecal infusions. The use of intermittent and continuous subcutaneous infusions is most useful in patients who cannot tolerate oral analgesics because of gastrointestinal obstruction or intractable nausea and vomiting and do not have intravenous access. The usefulness of this technique has been demonstrated using morphine, heroin, hydromorphone, levorphanol, and fentanyl. Methadone by this route is associated with the development of a cutaneous hypersensitivity syndrome.

Patient-controlled analgesic pumps designed to infuse continuously but with options for bolus administration are connected to a 27-gauge butterfly needle that the patient can insert into a new subcutaneous site every third to sixth day. Limited pharmacokinetic studies have demonstrated that systemic absorption of the drug from subcutaneous sites at steady state has an 87% bioavailability with hydromorphone, for example.

Intermittent and continuous intravenous infusions are used if intravenous access is available and more commonly in the patient who is hospitalized. Specific guidelines for the use of continuous infusions have been developed.

Intermittent and continuous epidural and intrathecal opioid infusions are based on the demonstration of opioid receptors in the dorsal horn of the spinal cord and the availability of opioid drugs to suppress noxious stimuli at the spinal cord level. Localized selective analgesia is produced without motor or sensory blockade. The pharmacokinetics of epidural opioid administration demonstrate that there is significant systemic uptake after epidural injection, comparable with an intramuscular injection of the same drug and dose. However, distribution of the drug directly into the cerebrospinal fluid is 10 to 100 times greater. Existing studies demonstrate that approximately 10% of cancer patients use this approach to maximize analgesia and minimize side effects. This technique is commonly used in patients who have mixed nociceptive neuropathic pain syndromes and in whom combinations of local anesthetics and opioids are administered epidurally.

Rarely, intraventricular opioid infusion has been used to manage patients with pain in the cervical and craniofacial region from tumor infiltration. Doses between 10.0 and 7.5 mg/24 hours have been used and patients have reported 70% excellent results. At present, there is not a clear indication that this intraventricular route offers significant advantages over systemic opioids.
USE A COMBINATION OF DRUGS

The use of a combination of drugs enables a physician to increase analgesic effects without escalating the opioid dose. Combinations that produce additive analgesic effects include an opioid plus a nonopioid, an opioid plus an antihistamine (100 mg of intramuscular diphenhydramine), and an opioid plus an anticholinergic (10 mg of intramuscular atropine). Trials with opioids combined with dextromethorphan demonstrate additive analgesia and such combinations are now under study for their role in cancer pain patients.

ANTICIPATE AND TREAT SIDE EFFECTS

The side effects of the opioid analgesics often limit their effective use. The most common side effects are sedation, respiratory depression, nausea, vomiting, constipation, and multifocal myoclonus and seizures.

Sedation and drowsiness vary with the drug and dose and may occur after both single and repeated administration. They are mediated through activation of opiate receptors in the reticular formation and diffusely throughout the cortex. Management of these effects includes reducing the individual drug dose but prescribing the drug more frequently, or switching to an analgesic with a shorter plasma half-life. Amphetamine, methylphenidate, and caffeine can be used to counteract these sedative effects.

Respiratory depression is the most serious adverse effect of the opioid drugs. It occurs most commonly after short-term administration of an opioid and is usually associated with other signs of central nervous system depression, including sedation and drowsiness. The opioid-agonist drugs act on brainstem respiratory centers to produce, as a function of dose, increasing respiratory depression to the point of apnea. Tolerance to this effect develops rapidly with repeated drug administration, thereby allowing prolonged use without significant risk of respiratory depression.

Respiratory depression can be reversed by giving the short-acting opioid antagonist naloxone (suggested dose, 0.4 mg/mL). Repeated administration, including an intravenous drip, may be necessary to prevent respiratory arrest in such patients. In patients receiving opioids for prolonged periods who develop respiratory depression, diluted doses of naloxone (0.4 mg in 10 mL of saline) should be titrated carefully to prevent the precipitation of severe withdrawal symptoms while reversing the respiratory depression. A useful dosing nomogram for continuous intravenous infusion of naloxone has been developed in which two-thirds of the initial bolus is started on an hourly basis and titrated against the patient's symptoms.

In some patients the use of naloxone to reverse drug-induced respiratory depression can be dangerous. An endotracheal tube should be placed in the comatose patient before giving naloxone to prevent aspiration from excessive salivation and bronchial spasm induced by naloxone administration. In patients receiving meperidine over a longer period, naloxone may precipitate seizures by lowering the seizure threshold and by allowing the convulsant activity of the active metabolite, normeperidine, to become evident. In this instance, special attention must be given to the potential seizure effect of naloxone. If naloxone is used, diluted doses, slow titration, and appropriate seizure precautions are advised. There is insufficient clinical evidence to make more specific recommendations. If respiratory support can be effected by other means (i.e., continuous stimulation to maintain the patient's wakefulness), such an approach may place the patient at less risk and clearly in less discomfort.

The opioid analgesics produce nausea and vomiting by an action limited to the medullary chemoreceptor trigger zone. The incidence of nausea and vomiting is markedly increased in ambulatory patients. Tolerance develops to these side effects with repeated administration. Nausea with one drug does not mean that all drugs will produce it. Switching to alternate opioid analgesics or using an antihistamine together with the opioid analgesic are ways to obviate this effect. Lack of controlled trials to identify a specific first-line agent has supported the practice of using sequential trials of agents beginning with prochlorperazine (Compazine) concurrently with the opioid to clarify a useful regimen. Droperidol has also been noted to be effective in opioid-induced nausea and vomiting.

Constipation results from the action of these drugs at multiple sites in the gastrointestinal tract and in the spinal cord to produce a decrease in the intestinal secretions and peristalsis, resulting in a dry stool and constipation. When opioid analgesics are started, a regular bowel regimen, including cathartics and stool softeners, should also be instituted. Several bowel regimens have been suggested because of their specific ability to counteract the effects of the opioid drugs, but none has been studied in a controlled way. Anosmia surveys suggest that doses far above those used for routine bowel management are needed, that enemas are effective, and that careful attention to dietary factors along with the use of a bowel regimen can reduce patient complaints dramatically. Tolerance to this effect develops over time, but relatively slowly. Oral naloxone has been shown to be effective in treating constipation, but its use is variable depending on the degree of opioid exposure of the patient.

Multifocal myoclonus may occur with high doses of all of the opioid drugs. Multifocal myoclonus and seizures have been reported in patients receiving multiple doses of meperidine (250 mg or more per day), although signs and symptoms of central nervous system hyperirritability may occur with toxic doses of all the opioid analgesics. In a series of cancer patients receiving meperidine, accumulation of the active metabolite normeperidine was associated with these neurologic signs and symptoms. However, in a similar group of cancer patients with pain, subtle mood effects were noted after meperidine administration, which suggests a spectrum of central nervous system effects. Management of this hyperirritability includes discontinuing the meperidine, using intravenous diazepam if seizures occur, and substituting morphine to control the persistent pain. Because the half-life of normeperidine is 16 hours, it may take 2 or 3 days for the signs of central nervous system hyperirritability to clear completely. Meperidine is contraindicated in patients with chronic renal disease, but these complications noted in cancer pain occurred in patients with normal renal function.

Morphine and hydromorphone at high doses produce myoclonus, which has not been directly associated with their known active metabolite such as M6G and hydromorphone-6-glucuronide. In dying patients with myoclonus, the use of benzodiazepines or barbiturates has been reported anecdotally to suppress this sign, improving the patient's comfort.

Opioid hyperexcitability and hyperalgesia have been reported with the use of increasing opioid doses by the parenteral acute and epidural routes. It has most often been observed on high doses of morphine and hydromorphone and is characterized by uncontrolled pain, hypervigilance, total body hyperalgesia, and allodynia. It is best managed by rapid dose reduction and substitution with an alternative opioid such as methadone. The mechanism of action is unclear.

In animal studies with morphine it is thought to be related to M3G, which in animals is associated with allodynia and hyperalgesia following intracerebroventricular administration. This action of M3G is mimicked by strychnine, a glycine agonist. Glycine mediates postsynaptic inhibition on dorsal horn neurons. It is suggested that high doses of morphine or its metabolites may act via a spinal antiallugeotic effect, reducing postsynaptic inhibition causing allodynia and myoclonus.

MANAGE TOLERANCE

The earliest sign of the development of tolerance is the patient's complaint that the duration of effective analgesia has decreased. For reasons not yet understood, the rate of development of tolerance varies greatly among cancer patients. Some demonstrate tolerance within days of initiating opioid therapy; others remain controlled for many months on the same dose. Studies in an outpatient clinic population, a hospitalized population, and a home care population revealed three patterns of drug use: those who rapidly increase their opioid requirements, those who stabilize at one dose for several weeks or months, and those who decrease or eliminate opioids. Increased opioid requirements are most commonly associated with disease progression rather than tolerance alone. With the development of tolerance, increases in the frequency of the dose of the opioid are required to provide continued pain relief. Because the analgesic effect is a logarithmic function of the dose of opioid, a doubling of the dose may be needed to restore full analgesia. There appears to be no limit to the development of tolerance, and with appropriate dose adjustments, patients can continue to obtain pain relief. Cross-tolerance among the opioid analgesics is not complete; therefore, it is advantageous to change to an alternative opioid, selecting half the predicted equianalgesic dose as the starting dose.

The use of analgesic combinations can reduce the amount of opioid required. Similarly, the use of bolus or continuous epidural local anesthesia in patients with perineal pain can dramatically reduce the need for systemic opioids and reverse tolerance.

TAPER DRUGS SLOWLY

The long-term administration of opioid analgesics is associated with the development of physical dependence, a state in which the sudden cessation of the opioid analgesics produces signs and symptoms of withdrawal: agitation, tremors, insomnia, fear, marked autonomic nervous system hyperexcitability, and exacerbation of sedative effects. It is important to discontinue all other drugs that might exacerbate these effects of the opioid analgesic, including a wide variety of medications such as cimetidine, barbiturates, and other anxiolytic medications.

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pain. Slowly tapering the dose of the opioid analgesic prevents such symptoms. The appearance of abstinence symptoms from the time of drug withdrawal is related
to the elimination half-life for the particular drug. The type of abstinence syndrome similarly varies with the drug. For example, with morphine, withdrawal symptoms
comprise within 6 to 12 hours after drug cessation. Reinstating the drug in doses of approximately 25% of the previous daily dose suppresses these symptoms.

**ANTICIPATE COMPLICATIONS**

Overdose with opioid analgesics occurs either intentionally, when a patient takes an excessive amount of drug in a suicide attempt, or unintentionally, when the
recommended dosage accidentally produces excessive sedation and respiratory depression. In both instances, the complication can be treated effectively with
naloxone. Intentional overdose in cancer patients occurs rarely, and concern for this is overemphasized. Overdose in patients previously stabilized on a opioid
regimen for cancer pain rarely is caused by drug intake alone. More commonly, it is the medical deterioration of the patient with a superimposed metabolic
encephalopathy. Eigel studied the use and misuse of naloxone and identified that sedation was the most common reason for naloxone use. Of note, in this study of
naloxone use in 34 patients over 1 year in a cancer center, 71% of patients had a medical reason other than opioid dose escalation as an explanation for the change
in medical condition prompting naloxone use. Following naloxone administration, 84% of patients experienced significant side effects; 42% had increased pain and
14% had increased agitation. Patients were given intravenous boluses of 0.4 mg of naloxone rather than titrated with diluted naloxone as has been recommended.
Reducing the opioid drug dosage and carefully assessing the patient's metabolic status usually provide the differential diagnosis. Patients who have taken an
unnatural drug overdose should be counseled carefully to rule out other causes of excessive sedation, confusion, or respiratory depression. In such cases a
reversal of these effects with naloxone is more therapeutic than diagnostic.

Psychological dependence or addiction is characterized by a concomitant behavioral pattern of drug abuse evidenced by craving a drug for other than pain relief and
continuing drug intake in the absence of physical dependence. Of note, in this study of naloxone use, the potential for naloxone to produce withdrawal
symptoms was not used to make a differential diagnosis. The major drug side effect is sedation.

**ADJUVANT DRUGS**

Adjuvants to enhance analgesia have been previously discussed in the section on combinations of drugs (see
Use a Combination of Drugs, earlier in this chapter). Acetaminophen, NSAIDs, hydroxyzine, and dextromethorphan have been demonstrated to provide additive analgesia to patients chronically receiving opioids.

**Adjuvant Analgesics for Neuropathic Pain**

The common neuropathic pain syndromes in patients with cancer include injury to peripheral nerves andplexus by tumor invasion, chemotherapy, surgery, or viral
agents. Depending on the intensity of pain, nonopioid and opioid analgesics are the first-line agents. However, as previously discussed, there is evidence to suggest
that such neuropathic pains are less responsive to nonopioid and opioid approaches. Some of the commonly used adjuvant drugs for managing this population
of patients are described in the following sections.

**Antidepressants**

The tricyclic antidepressants may be the most useful group of psychotropic drugs used in pain management. Their analgesic effects are mediated by
enhancement of serotonin activity. Data from clinical trials indicate that both the tertiary amine tricyclic antidepressants (amitryptiline, doxepin, imipramine and
clozapamine), and the secondary amine compounds (desipramine and nortriptilene) have analgesic effects. More recently, one of the serotonin selective reuptake
inhibitors, paroxetine, has also been shown to have analgesic properties in patients with neuropathic pain. These drugs have been reported to be effective in
treating continuous dysesthesias, as well as intermittent lancinating dysesthetic pain. The doses used for analgesia are far below those needed to produce an
antidepressant effect. The analgesic properties of these drugs appear to occur independent of their mood-altering effects. Patients should be started on low
doses of 10 to 25 mg and titrated up to achieve adequate analgesia in a 2- to 4-week trial. Blood levels should be measured to determine both patient compliance and drug
adherence. The use of these agents may produce a reason to increase the dose of the opioid analgesic when first started on the antidepressant. These drugs are
nondrug-seeking individuals, whereas the use of opioid analgesics is more likely in drug-seeking individuals. In the management of cancer patients with pain, the
antidepressant drugs are the first-line therapeutic approach for neuropathic pain, and every attempt should be made to provide the patient with a several-week trial before discontinuing these drugs.

**Anticonvulsants**

The role of anticonvulsants in the management of patients with neuropathic pain is based, in part, on the fact that the mode of action is to stabilize membranes and
alter sodium and calcium influx. Many patients with neuropathic pain complain of paroxysmal, brief lancinating pains. To date, clinical experience with the
anticonvulsants has been positive. The drugs most commonly used include gabapentin, carbamazepine, phenytoin, valproate, and clobazam. Carbamazepine is
considered the first-line anticonvulsant to manage neuropathic pain. Controlled trials in diabetic neuropathy, postherpetic neuralgia, and acquired immunodeficiency
syndrome neuropathy demonstrate the effectiveness of this agent in reducing pain. Doses range from 900 to 1800 mg/d. The major drug side effect is sedation.
Patients should be started at 300 mg/d and rapidly titrated to 900 mg. Pain relief up to 30% to 50% of patients has been suggested. Clinical studies with
phenytoin and carbamazepine demonstrate efficacy, but the utility of this drug in the cancer population is limited by its potential to produce bone marrow suppression, particularly
leukopenia. The dosing guidelines used for the treatment of seizures are suggested in managing neuropathic pain. Each of the drugs should be initiated at low doses
and gradually titrated upward. There is anecdotal experience to suggest that using intravenous loading doses of phenytoin for patients in an acute crisis with severe
lancinating pain may provide relief rapidly. Clonazepam was not effective in drug trials in neuropathic pain. Both valproate and clobazamide have been reported
anecdotally to be useful in neuropathic pain, but these are considered third-line agents in this patient population. Currently, there are no data to relate the plasma
level and pain relief with any of these drugs. As previously stated, sequential trials are necessary to identify the most useful agent. With the use of baclofen, which
is generally well tolerated, doses should begin at 5 mg two or three times a day, with titrations upward, with the highest reported doses between 100 to 150 mg/d titrated

**Use a Combination of Drugs**

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Local Anesthetics

The use of both intravenous local anesthetic infusions (lidocaine), as well as maintenance oral anesthetic drugs, have demonstrated some efficacy in the management of chronic neuropathic pain, particularly in those patients with both lancinating and continuous dysesthesias. Mexiletine is the oral local anesthetic for which there are pilot data to support its analgesic efficacy. The initial dose of mexiletine is low, at 150 mg/d, with gradual upward dose titration. Electrocardiograms should be monitored at higher doses, and blood levels of mexiletine may be useful to predict toxicity. Currently, there are no good data available to predict what patient might respond to the use of oral local or intravenous anesthetics, as have been done in the use of brief local anesthetic infusions to determine control of cardiac arrhythmias.

Epidural local anesthetics (bupivacaine, lidocaine) have been most widely used to manage neuropathic pain either alone or in combination with opioid. Alternatively, the use of brief intravenous infusions of lidocaine may be helpful in patients with both opioid-refractory continuous dysesthesia that has not responded to an antidepressant or anticonvulsant. These drugs clearly serve as a second-line approach, with individualized therapy the rule.

Cutaneous Local Anesthetics

The use of cutaneous anesthesia has been suggested to be most helpful in patients who have significant allodynia and marked hypersensitivity. The use of the topical application of a local anesthetic, such as a eutectic mixture of local anesthetics, has been demonstrated to be efficacious in patients with postherpetic neuralgia. The cream should be applied under an occlusive dressing, to increase skin penetration and augment analgesic efficacy. The use of high-concentration lidocaine (5%) and 10% has also been reported to be effective in this population of patients.

Corticosteroids

A series of controlled and uncontrolled surveys have demonstrated that the use of chronic corticosteroid therapy to reduce pain in patients with breast and prostate cancer improves quality of life. In a controlled study of corticosteroid use in patients with far-advanced disease, transient improvement in appetite, analgesia, and mood were noted, but they were not sustained after the initial effect. The major indications for corticosteroid use include refractory neuropathic pain, bone pain, pain associated with capular expansion or duct obstruction, and headache due to increased intracranial pressure. In certain cancer pain syndromes, such as epidural cord compression, 85% of patients receiving 100 mg of dexamethasone as part of their radiation therapy protocol reported significant pain relief associated with marked reduction in analgesic requirements. Similarly, in patients with tumor infiltration of the brachial and lumbosacral plexus, corticosteroids provided additive analgesic effects. The risk of adverse effects associated with corticosteroid therapy varies with the duration. Long-term use may be associated with gastrointestinal toxicity and acute psychosis. A wide range of doses have been suggested, including doses of 30 mg/d in patients with prostate cancer, which was effective in providing improved quality of life and reduced pain. As stated, with epidural cord compression, initial doses of 100 mg with maintenance doses of 16 mg have been associated with effective analgesia. In our experience, the use of 16 mg as a loading bolus and rapid titration to lower doses of approximately 4 mg/d is one approach commonly used in the refractory chronic pain patient with advanced disease.

Other Adjuvant Drugs

There are a wide variety of other drugs that have been used to manage neuropathic pain, including benzodiazepines, neuroleptics, a-adrenergic agonist drugs, NMDA antagonists, and peptides. Of the benzodiazepines, clonazepam is commonly used in patients with lancinating or paroxysmal pain. The use of these drugs must be balanced with their potential for somnolence and cognitive impairment. They serve as second- to third-line therapy in patients who have not responded to antidepressant or anticonvulsant drug therapy. Of the neuroleptics, pimozide has been reported to be analgesic in patients with trigeminal neuralgia. Methotrimeprazine has been demonstrated to have analgesic properties comparable with morphine. This drug has sedative, anxiolytic, and antiepileptic properties and is commonly used in patients who have excessive opioid side effects. It provides analgesia by a nonopioid mechanism.

Coadministration of these drugs with opioids can often be effective in patients with neuropathic pain. Of the a-adrenergic agonist drugs, clonidine has been demonstrated to be analgesic in controlled trials. It can be used by either the oral or transdermal route and has been reported to be specifically effective in patients with dysesthetic pain, who demonstrate sympathetic hyperactivity. Following intrathecal administration, clonidine was reported to improve pain in patients with intolerable neuropathic pain. Dextromethorphan and ketamine are two commercially available NMDA antagonists. Both have been shown to have analgesic effects in controlled studies. The mechanism of action relates to the fact that the NMDA receptor reduces the development of the windup phenomenon, which occurs as a result of changes in the response of central dorsal horn neurons with neuropathic pain. Case reports have suggested that dextromethorphan has been beneficial in selected patients, although a controlled trial of low-dose dextromethorphan had negative results. The drug may be initiated at doses of 40 to 60 mg daily and gradually escalated. Doses of 1 g have been administered safely, at least in the short-term. Studies of dextromethorphan combined with opioids demonstrated added analgesia, suggesting an opioid-sparing effect of the drug. The use of ketamine infusions have been previously well established to produce analgesia, and they have been reintroduced as a potential strategy for patients with refractory neuropathic pain. Further studies are necessary to demonstrate the safety and efficacy of these treatment approaches in long-term management for chronic neuropathic pain. Oral ketamine in case reports has demonstrated efficacy in cancer patients with pain uncontrolled by other approaches.

Calcitonin has been reported to provide analgesia in patients with sympathetically maintained pain and in the management of acute phantom pain. The mechanism underlying these analgesic effects is unknown, but it has suggested the empiric use of calcitonin in patients with refractory neuropathic pain. The clinical, anecdotal literature suggests that patients be treated initially with a low dose, after initial skin testing to rule out hypersensitivity to this agent, with gradual escalation to a range of 100 to 200 IU/d. Its use chronically has not been assessed, and further studies are necessary to define its place in the treatment of patients with neuropathic pain.

Adjuvants for Bone Pain

Metastatic disease to bone is the most common cause of pain in patients with cancer. Analgesic drug therapy is commonly used to manage the pain during the initial treatment with either chemotherapy or radiation therapy. Numerous investigators have identified a management approach for bone pain, which includes the use of specific surgical palliative approaches, radiotherapeutic approaches, hormonal therapies, and bone resorption inhibitors. Multifocal metastatic bone disease that is refractory to routine treatments may benefit from the use of a series of agents, including the bisphosphonate compounds, gallium nitrate, calcitonin, and strontium 89. The current bisphosphonates most widely studied for the treatment of bone pain include pamidronate and clodronate. Pamidronate is usually administered as a brief infusion in a starting dose of 60 to 120 mg. Analgesia, if it occurs, usually appears within days, but may occur for many weeks with repeated infusions. In two studies patients receiving pamidronate in doses of 30 to 60 mg every 2 weeks showed relief of pain in 30% to 60% of patients. Bisphosphonates' analgesic effect appears to be dose dependent. Current recommendations include a regimen of intravenous pamidronate, 60 mg every 2 weeks for at least two or three treatments. If no response, therapy can be continued. A study of pamidronate, 120 mg intravenously, versus placebo in patients with painful bone metastases revealed a correlation between analgesic response and collagen cross-links suggesting such peptide cross-links may be used to select those patients more likely to achieve improvement in pain with bisphosphonate therapy. The major indication of these drugs is to reduce the metabolic burden of bone disease, thus reducing pain. The initial dose of mexiletine is low, at 150 mg/d, with gradual upward dose titration. Electrocardiograms should be monitored at higher doses, and blood levels of mexiletine may be useful to predict toxicity. Currently, there are no good data available to predict what patient might respond to the local or intravenous anesthetics, as have been done in the use of brief local anesthetic infusions to determine control of cardiac arrhythmias.

Calcitonin has also been reported anecdotally to be useful in patients with malignant bone pain, but the appropriate dose and dosing frequency have not been well defined. Gallium nitrate has also been used with some efficacy in patients with metastatic bone pain, but the limited experience has not well defined the appropriate dosing guidelines, and nephrotoxicity has been reported. Strontium 89 is a bone-seeking radiopharmaceutical, recognized as useful in the treatment of bone pain secondary to metastatic disease. It is indicated in patients with refractory multifocal pain due to osteoblastic lesions who have a life expectancy greater than 3 months, who have sufficient bone marrow reserve (i.e., a platelet count above 60,000 and a white blood cell count above 2400), and for whom there is no further planned chemotherapy. The onset of effect is slow and may require several weeks, with peak effects at 2 to 3 months. Bone marrow suppression is the major adverse effect, with irreversible thrombocytopenia.

The selection of one of these treatments in metastatic bone pain needs to be individualized, with evidence that both the bisphosphonates and strontium 89 have clearly demonstrated efficacy in certain patients.
Adjuvants to Treat Side Effects

Nausea and vomiting, confusion, sedation, and constipation are common opioid-induced side effects. The use of drugs to manage these have been previously discussed (discussed earlier, in Anticipate and Treat Side Effects). The use of caffeine, methylphenidate, and dextroamphetamine have all been demonstrated in clinical trials to reduce opioid-induced sedation. Haloperidol is the treatment of choice to manage hallucinations and agitated delirium in patients receiving opioid analogs. The use of bowel regimens to manage depressed gastrointestinal motility have also been discussed.

PSYCHOLOGICAL APPROACHES

Psychological approaches should be an integral part of the care of the cancer patient with pain. A series of psychological variables contribute to the cancer pain experience and suffering, such as perception of control, the meaning of pain, fear of death, depressed mood, and hopelessness. The level of psychological distress experienced by each patient varies depending on personality, coping ability, social support, and medical factors. Pain has a profound effect on levels of emotional distress, and psychological factors such as depression and anxiety intensify the pain experience. Measures of emotional disturbance have been reported to be predictors of pain in advancing later stages of cancer. The incidence of pain, depression, and delirium increases with high levels of physical debilitation in advanced disease. Approximately 25% of all cancer patients experience severe depressive symptoms, with the prevalence increasing to 77% in those with advanced illness. Uncontrolled pain is a major factor in cancer suicide.

Various psychological interventions have been advocated for patients with cancer pain. Optimal treatment is multimodal and requires pharmacologic, psychotherapeutic, and cognitive-behavioral approaches. The roles of the psychiatrist, psychologist, and social worker in cancer pain management are well described in the literature.

The goals of short-term psychotherapy are to provide emotional support, continuity, and information and to assist patients in adapting to the crisis. Communication skills are of paramount importance for patient and family, particularly about pain and analgesic issues. The needs of the patient and family must be addressed. Psychotherapy in the cancer pain setting is primarily nonanalytic and focuses on current issues and exploration of reactions to cancer, which often provides insight into other life issues. Group interventions may also be helpful.

A specialized approach called cognitive-behavioral therapy has been used to treat pain disorders, including cancer pain. This approach uses short-term therapeutic interventions based on theoretically and empirically derived principles that can be adapted to each patient's problems and needs. It includes a set of systematic mental and behavioral techniques designed to modify specific emotional, behavioral, and social problems as well as the global experience of pain and distress. Its major goal is to enhance the sense of personal control or self-efficacy. In a multidisciplinary approach to cancer pain, not every patient needs referral for this therapy, but it is useful if all members of the pain team follow a cognitive-behavioral model. Because cognitive-behavioral therapy is a commonsense psychological approach consisting of specific techniques, it can be learned and practiced by any interested clinician, nurse, or social worker who can gain practical training in the use of these techniques and apply them effectively.

Various intervention methods have been developed and are arbitrarily divided into behavioral and cognitive methods for discussion purposes. These approaches must be targeted to each patient's needs.

Behavioral techniques include ways to modify physiologic pain reactions and pain behaviors. Relaxation training can be used by all caregivers who manage patients with pain and cancer. Its mechanism of action includes the reduction of muscle tension, and it can provide the patient with a sense of improved self-control and a calming diversion of attention, breaking the associated pain-anxiety-tension cycle. Techniques range from simple deep-breathing exercises to more specialized methods of biofeedback and hypnosis. Contingency management is another behavioral approach designed to modify dysfunctional pain behaviors and replace them with well behaviors.

Cognitive techniques are designed to modify dysfunctional mental processes or to teach adaptive coping strategies. Cognitive coping and cognitive modification are approaches in which distraction, focusing, and perception and interpretation of the meaning of pain are assessed.

ANESTHETIC AND NEUROSURGICAL APPROACHES

Anesthetic and neurosurgical approaches are most effective in treating patients with well-defined localized pain. Table 56.1-12 and Table 56.1-13 outline the indications for their use. Approximately 10% to 20% of cancer pain patients require these approaches, together with pharmacologic approaches, to provide adequate analgesia.

{| Table 56.1-12 Anesthetic and Neurosurgical Treatments for Cancer Pain |
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<tr>
<td>Chemodenervation</td>
<td>Intractable pain</td>
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<tr>
<td>Neurolysis</td>
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In a prospective study, Ventafridda and colleagues evaluated two groups of patients for 3 months who presented with intractable cancer pain not responsive to specific anticancer therapies. One group was treated with sequential pharmacologic approaches using the analgesic ladder. The second group was treated with a multimodal approach of analgesic therapy followed by the use of neurolytic blocks or chronic spinal opioid administration. Patients treated with neurolytic procedures combined with pharmacologic therapy showed a statistically significant degree of pain relief than those treated with drugs alone by the third week of therapy. However, by 6 weeks, there was no statistical difference between the two groups. Complete pain relief without the need for analgesic therapy persisted to 3 months in 29% of the patients who received spinal opiates, 25% treated with celiac ganglion neurolytic block, 24% with percutaneous cordotomy, 12% with chemical rhizotomy, and 7% with gasserian thermorhizotomy. This study demonstrated that although analgesic therapy is the mainstay of treatment, anesthetic and neurosurgical approaches provide an important, but limited, contribution to adequate analgesia. Chen et al. reported that 17% of patients in a prospective study of 100 cancer patients involved at Memorial Sloan-Kettering Cancer Center were evaluated for anesthetic and neurosurgical approaches with 10% requiring such approaches. One study assessed attitudes of oncologists toward interventional cancer pain treatments. Eighty-one percent of oncologists reported patient referral to pain specialists, yet their familiarity with intrathecal therapy was low, with only 46% referring patients for intrathecal therapy in the previous 6 months, citing the invasive nature of device placement as a drawback by 42% of physicians.

Several factors are important in selecting the appropriate procedure for each patient. Because diffuse pain problems are common in cancer patients and most of the procedures are useful for well-defined localized pain, the role of these approaches is limited at best. Further complicating their use is the limited number of professionals who have expertise in these procedures. As patients become more cognizant of their disease and treatment options, they are often hesitant to undergo neurodestructive procedures. Patients often consider their pain to be an important marker for their disease and are frightened of the potential, although unlikely, complications of these procedures. As a result, these procedures are often performed late in the illness, and full evaluation of their effectiveness and duration of action is limited by the patient's overriding medical problems.
These procedures are often not very effective in managing neuropathic pain, except for the use of local anesthetics, and are most helpful in managing most types of somatic and visceral pain. However, cancer patients often have a mixed somatic, visceral, and neuropathic pain syndrome. We advocate early consideration for the use of some of these anesthetic and neurosurgical procedures in patients to improve their quality of life through adequate pain management.

**LOCAL ANESTHETICS**

Anecdotal reports and several controlled studies support the use of cutaneous, subcutaneous, intravenous, intrapleural, and epidural local anesthetics in the management of patients with somatic, visceral, and neuropathic pain. Infranension lidocaine should be considered as both a diagnostic and therapeutic approach in patients with neuropathic pain. If such patients obtain an analgesic response, a trial of oral mecloxetine or the use of continuous subcutaneous lidocaine should be considered to determine whether prolonged relief may be possible. Although no studies have confirmed that the response to lidocaine predicts a response to mecloxetine for pain, a comparable predictive value exists in the cardiac literature, in which infranension lidocaine's effectiveness in controlling ventricular arrhythmias predicts the usefulness of mecloxetine for this same disorder.

Brose and Cousins reported the use of continuous subcutaneous infusions in two patients with cancer-related neuropathic pain, advocating this approach as an alternative in patients who do not respond to standard opioid and adjuvant treatments as well as anesthetics approaches for neuropathic pain. Intraperitoneal local anesthetics have been used for acute pain in the chest wall and have been adapted for the management of chronic cancer pain. A subcutaneously tunneled intrapleural catheter offered long-term relief of right upper quadrant pain from hepatic metastases in a patient with significant pain from tumor infiltration of the liver. This novel method offers an alternative approach for patients with local regional pain in the pleural and abdominal regions.

Epidural local anesthetics are used to manage patients with localized pain syndromes, usually below the waist. Intermittent and continuous epidural infusions of local anesthetics have been used to manage the difficult chronic pain associated with metastatic disease below the waist, often involving the sacrum and lumbosacral plexus. This method consists of infusing a local anesthetic via a subcutaneous infusion pump or Omaya reservoir to a catheter, temporarily or permanently placed in the epidural space. If the amount and concentration of the anesthetic are varied, effective pain relief can be achieved. Complications are of two kinds. With intrathecal injection, a self-limiting spinal headache may occur. Complications that result from the action of neurolytic substances are associated with minimal systemic side effects. Further studies on the use of this technique in comparison with standard therapies are needed to define its place in the management of the cancer patient. Its major advantages are that the resultant analgiesia is not cross-tolerant with the analgesic produced by the opioid analgiesia, and that temporary use of this technique allows for reduction in the amount of systemic opiate drugs, therefore partially reversing tolerance. This has been a useful preliminary approach in patients for whom the use of spinal opiate analgesia is considered, but who have developed tolerance from large doses of systemic opioids. Because tolerance develops to these analgesic techniques, this approach is temporary (days to weeks) rather than long-term. This approach is most useful in patients who experience an acute pain crisis, such as the patient with a pathologic hip fracture who is not a surgical candidate; this approach would allow the patient to move about in bed. In patients with chronic cancer neuropathic pain, local anesthetics combined with opioids are used.

**PERIPHERAL NERVE BLOCKS**

Peripheral nerve blocks are used both diagnostically to localize the nerve distribution and therapeutically to interrupt pain transmission within a determined nerve distribution. This technique is limited to areas of the body in which the interruption of both motor and sensory function will not interfere with the patient's functional status. This approach is most commonly used with patients who have pain in the head, chest, or abdomen. This technique is also limited by the fact that each peripheral nerve subserves sensory function over many levels, and usually several nerves must be blocked to provide adequate analgesia. These techniques are most useful in patients with somatic pain; neuropathic pain is rarely controlled by peripheral nerve blocks alone. Examples of successful blocks include gasserian ganglion block for craniofacial pain, intercostal blocks for chest wall infiltration from tumor, and paravertebral blocks for radicular pain.

In patients with somatic pain who respond to a local anesthetic block, neurolytic blockade with either alcohol or phenol may provide more prolonged relief. A block produced by phenol tends to be less profound and of shorter duration than that produced by alcohol. Phenol has local anesthetic as well as neurolytic effects. The most common peripheral neurolytic block is a paravertebral block for localized intercostal pain. From our experience in treating patients with chest wall pain, we advise that this procedure be done under fluoroscopic control or computed tomographic localization to accurately interrupt the individual intercostal nerve.

Epidural and intrathecal neurolytic blocks have been used primarily to manage patients with far-advanced disease whose pain is either unilateral in the chest or abdomen or midline in the periumbilicus. These approaches are less useful in managing upper and lower limb pain associated with brachial and lumbosacral plexopathy because of the high risk of motor weakness associated with effective neurolytic blockade by this route. Epidural phenol blocks are useful in chest wall pain over several dermatomes. Such an approach obviates the need for multiple paravertebral injections. Phenol is injected in small increments (1 to 2 mL per segment) over 2 or 3 minutes to a catheter, and preliminary data demonstrate 80% pain relief in patients with documented radicular pain. Epidural and intrathecal phenol blocks have been used to manage perineal pain, but no studies have delineated the superiority of one approach over the other.

A review of a large number of alcohol subarachnoid blocks reports an average of 60% good relief, 21% fair relief, and 18% poor relief. Because the duration of pain relief has seldom been documented with careful follow-up studies, the overall estimate for relief of pain with both subarachnoid alcohol and phenol blocks suggests a mean duration of pain relief of between 2 weeks and 3 months.

Complications are of two kinds. With intrathecal injection, a self-limiting spinal headache may occur. Complications that result from the action of neurolytic substances on nerve fibers include motor paresis, loss of sphincter function, impairment of touch and proprioception, and troublesome dysesthesias. Injection in the thoracic region has a low complication rate. In our experience, many cancer patients already have both motor and autonomic dysfunction before the use of neurolytic blockade; these often remain the same or may worsen. Patients should be informed of the risk of these procedures, with particular attention to the fact that they may develop motor paresis and bladder dysfunction, specifically incontinence, after the blockade.

The selection of patients for management with epidural or intrathecal neurolytic agents should be based on the following criteria: exhaustion of appropriate antitumor approaches; clear clinical and radiologic definition of the pain; poor candidacy for percutaneous cordotomy; failure of nonopioid, opioid, and adjuvant analgesics to produce sufficient pain relief without significant motor effects; and favorable response to diagnostic or epidural blocks, producing at least 75% pain relief, and MRI of the spine or myelography done before the procedure to rule out tumor infiltration of the subarachnoid space.

**AUTONOMIC NERVE BLOCK**

Sympathetic block is effective in conditions with vasomotor or visceromotor hyperactivity. This hyperactivity accompanies many of the cancer-related pain syndromes such as visceral pain or plexopathies. The most commonly used sympatholytic block is that of the celiac ganglion for pain due to abdominal malignancy, including cancer of the pancreas, stomach, duodenum, liver, gallbladder, adrenal gland, and colon. Nociceptive fibers of the splanchnic, sympathetic, vagal, phrenic, and somatic nerves converge on the celiac ganglion, which is amenable to a regional block that is successful in from 70% to 85% of patients treated. These procedures are often not very effective in managing neuropathic pain, except for the use of local anesthetics, and are most helpful in managing most types of somatic and visceral pain. However, cancer patients often have a mixed somatic, visceral, and neuropathic pain syndrome. We advocate early consideration for the use of some of these anesthetic and neurosurgical procedures in patients to improve their quality of life through adequate pain management.

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Standardized approaches for the use of this technique have been described using computed tomography monitoring or fluoroscopic control. After placement of the needle, 25 mg of absolute alcohol mixed with local anesthetic and contrast is injected. Bilateral needle placement has been reported to provide the best results, but anecdotal reports suggest that unilateral needle placement on the right provides comparable analgesia. The major side effect of the procedure is transient hypotension, and patients must be well hydrated and monitored carefully during the procedure and for 4 to 6 hours afterward. Significant neurologic complications occur in less than 1% of patients if proper technique is used. Complications include paraparesis, postural hypotension, and urinary difficulties.

Although there has been debate about the usefulness of this procedure in patients with pancreatic cancer, it should be considered as one of the approaches, together with pharmacologic approaches, in managing these patients. Lumbar sympathetic block may provide significant relief of intractable urogenital pain or pain due to carcinomatous invasion of local nerves and plexus in the perineum and lower extremity. This ganglion conveys visceral nociceptive afferents from the pelvic viscera. Pain caused by cancer of the sigmoid colon or rectum...
may be relieved by bilateral lumbar sympathetic block if the disease is confined to those viscera. Pain caused by cancer of the seminal vesicles or prostate may sometimes be relieved by bilateral lumbar sympathetic block. Similarly, pain caused by uterine cancer may be relieved if the disease is confined to the body of the uterus. In many instances, however, the block must be extended to the T-12 ganglion. Good evidence suggests that lumbar sympathetic block alone is not useful in patients with lumbosacral plexopathy; therefore, the role of this procedure is limited to specific anatomic sites of pain.

Stellate ganglion block may sometimes be useful for pain in the face, upper neck, ear, and hemicranium. However, the potential complications of stellate ganglion block limit the use of this technique with neurolytic solution, as there is a high risk of spillage of the neurolytic material into the brachial plexus, with secondary nerve injury and focal pain.

NEURODENOLOGY OF THE PITUITARY

Chemical hypophysectomy is a special use of a neurolytic method. Several early studies suggest that 35% to 95% of patients undergoing this approach report pain relief, with a median duration of 6 to 7 weeks and a maximum duration of 20 weeks. The mechanism by which analgesia is produced may result from alcohol tracking up the pituitary stalk into the hypothalamus, with consequent disruption of the hypothalamic-thalamic endorphinergic pain pathways. Side effects include diabetes insipidus, cranial nerve palsies, cerebrospinal fluid leakage, and rarely meningitis. The lack of detailed clinical data limits critical assessment of these studies. This technique is rarely if ever used in patients with diffuse pain.

NEUROSURGICAL APPROACHES

Neurosurgical approaches for cancer pain can be divided into two major categories, antitumor and antinociceptive. These approaches are often used alone or in combination by neurosurgeons to provide improved pain relief. ANTITUMOR APPROACHES

Antitumor approaches are often more acceptable to patients because they focus on cancer treatment, offering the hope of prolonged survival. The major procedures are listed in Table 56.1-8 and include tumor removal from the spine, epidural space, or adjacent plexus; stabilization procedures for spinal fracture, instability, and subluxation; and implantation of regional delivery devices for epidural, intrathecal, and intraventricular opioid drugs.

Tumor removal through resection of spinal metastases is associated with dramatic improvements in pain in 70% to 90% of patients. With the use of improved methods of internal fixation with methyl methacrylate and improved stabilizing procedures, the use of this approach has increased in patients with intractable continuous or incidental back and neck pain. Patients may also have an associated segmental instability associated with a pathologic fracture of the vertebral body or subluxation, syndromes that place patients at significant risk for neurologic dysfunction. Careful radiologic workup is necessary to define the specific anatomic basis for the spinal pain, but aggressive surgical approaches have improved the quality of life for many patients bedridden by uncontrolled pain. In patients with epidural cord compression, the indications for surgery include uncontrolled pain in a patient with a pathologic fracture or a solitarype slot in the epidural space or vertebral body from a radioresistant tumor. In patients with radiosensitive tumors who relapse after radiation therapy, spinal surgery should be considered as a reasonable approach and is specifically indicated in the patient with an acute neurologic deterioration during radiation therapy. When percutaneous or open vertebral body biopsy is impossible, surgical resection should be strongly considered to define the primary tumor type in patients with undiagnosed lesions; this serves as both a diagnostic and therapeutic procedure.

In patients with paraspinous tumor or tumor infiltration of the plexus, en bloc resection of tumor has successfully provided pain relief and has served as a debulking antitumor procedure. In patients with Pancoast's syndrome, invasion of the spine or epidural extension is present in 20% at initial presentation and is associated with a significant morbidity in up to 50% of patients when local treatment is ineffective. In the good-risk patient with plexopathy and spinal invasion, Sundaresan et al. recommend surgery in which tumor is removed from the lower plexus, C-8 to T-1, and the vertebral body is resected, with brachytherapy to provide further tumor control.

In patients with tumor invasion of the paraspinous area (specifically the psosas and iliacus), radical resection of these tumor masses concurrent with spinal surgery, followed by brachytherapy, combines antitumor and antinociceptive therapies.

When considering the use of these neurosurgical procedures to provide palliative surgery with an antinociceptive component, the patient's extent of disease, performance score, prognosis, and ability to tolerate the surgery must be weighed.

ANTINOCICEPTIVE PROCEDURES

Antinociceptive procedures include neuroablative, neurostimulatory, and neuropharmacologic approaches.

Neuroablative Procedures

Neuroablative procedures involve the production of a surgical or radiofrequency lesion along the nociceptive neural pathway. Sectioning on the posterior roots (rhizotomy), lesioning the lateral dorsal horn (dorsal root entry zone lesion), and interrupting the ascending new spinthalamic pathway (cordotomy) or the crossing interneuronal fibers (myelotomy) in the spinal cord are examples of neuroablative procedures performed for pain relief.

Cordotomy, either percutaneous or open, is the most common neuroablative approach used to manage cancer pain. It is the neurosurgical procedure of choice for patients with unilateral pain below the waist and with a relatively short life expectancy. Cordotomy is usually effective for 1 to 3 years, with dysesthesias substituting for analgesia in patients living longer than 3 years. Pain in the chest wall or upper extremity may be successfully treated initially with cordotomy, but extensive data demonstrate that, with time, the level of analgesia drops, limiting the effectiveness of this approach. Somatic pain appears to be the most responsive to cordotomy; visceral and neuropathic pain are less responsive for reasons that are not fully understood.

Percutaneous cordotomy is performed in a supine, awake patient through a lateral C-1 to C-2 approach. A needle is advanced under fluoroscopic control until cerebrospinal fluid is obtained. A minimyelogram is done to identify the dentate ligament. A cordotomy electrode is passed through the spinal needle and the spinal cord is punctured with the aid of impedance monitoring. Electrophysiologic stimulation is done to identify the spinthalamic tract and then a radiofrequency lesion is made in the appropriate painful site. Such a lesion interrupts pain and temperature on the contralateral side of the lesioned site. Patients typically report spontaneous relief of pain in this lesioned area.

The anatomic area at the lesion site includes fibers mediating respiration and autonomic function. These fibers are adjacent to the anterior horn and the cervical spinthalamic fibers. Near the lumbar spinthalamic tract are the fibers governing the intercostal muscles. This quadrant of the spinal cord also contains the sacral fibers to and from the bladder, which are closer to the spinthalamic fibers. These anatomic relations explain some of the complications associated with cordotomy: bladder dysfunction, respiratory compromise, and ipsilateral motor weakness.

From the literature that does not provide comparative studies in cancer patients with pain, pain relief can be obtained in 60% to 80% of patients immediately after cordotomy; results at 6 to 12 months are 40% to 50%. In a retrospective survey of 40 percutaneous cordotomies in patients with predominant unilateral pain below the waist, 70% of patients obtained complete relief with continued use of some supplemental analgesics, 16% had moderate relief, and 13% did not benefit from this procedure. In another study, Arbit reported that 16% of patients referred for percutaneous cordotomy could not undergo the procedure because of difficulty in positioning or participating in the procedure, even with the use of increased analgesic drug doses and anesthetic assistance.

Careful patient selection is necessary for this procedure.

Open cordotomy is usually done below the cervicothoracic junction through a hemilaminectomy or full laminectomy. Open cordotomy should be reserved for the patient who cannot tolerate a percutaneous approach or for the patient with limited motor or sensory dysfunction from tumor infiltration below the waist in whom bilateral cordotomy is to be done for bilateral or midline pain.
The complications of cordotomy vary with the type of procedure (percutaneous or open) and are also strongly influenced by the patient's premorbid neuropsychiatric condition. Many patients have borderline bladder function and mild paraparesis from tumor infiltration that is transiently or permanently exacerbated by these procedures. In our series at Memorial Sloan-Kettering Cancer Center, 45% of patients had transient or permanent urinary retention. If after cordotomy there is often an unmasking of pain ipsilateral to the cordotomy site. This pain was reported in 22% of patients in our series. In some patients it was difficult to clarify if this nerve pain was caused by unidentified tumor or really represented mirror pain or was caused by the unmasking of tumor-related pain. In 60% of patients in the Arbor series, unmasking of pain on the contralateral side occurred because of bilateral lumbosacral plexopathy. Dysesthesias characterized by burning pain in the area of sensory loss are reported in 1% to 2% of patients after a delay of several months to 2 years after the procedure. Ipsilateral motor weakness results from an inadvertent anterior extension of the lesion to involve the corticospinal tract. In our series, 7% of patients had transient paresis and 22% had permanent paresis. Most series report motor paresis in 10% to 20% of patients.

Respiratory complications occur in patients with a dysfunctional lung contralateral to the site of the cordotomy. This is a predictable risk when patients undergo cordotomy on one side as their only functioning lung. Interruption of the reflex spinal fibers controlling the intercostal muscles and of the phrenic nerve may occur because of their proximity to the lateral spinohemalatic tract in this spinal cord quadrant.

Several other complications, including headache, fever, and meningismus, are associated with the percutaneous procedure, as well as with a Horner's syndrome because of interruption of the sympathetic tract. In our series, 30% of patients demonstrated a profound depressive syndrome associated with significant pain relief. Patients should be warned about this complication, but the factors contributing to its development have not been fully clarified. Rapid reduction in opioids, realization that with pain relief they must face the emotional sequelae, and psychosocial factors, including adjustment to a new psychopathology, may all contribute to the appearance of this problematic complication. Psychological intervention and the use of tricyclic antidepressants have been effective in managing these patients.

Dorsal rhizotomy is the next most common neuroablative procedure used for cancer pain. It is performed by sectioning the posterior sensory rootlets, and a specific localized dermatomal pain level can be identified. It can be performed by an operative section of the nerve, or as previously discussed, by a neurolytic block. In patients with chest wall pain from tumor invasion, improved analgesia in 50% to 80% has been reported with dorsal rhizotomy. Arbit et al. have adapted this procedure to manage patients with significant chest wall pain. 

Rhizotomies of the trigeminal nerve, nervus intermedius, glossopharyngeal nerve, and portions of the vagus nerve are effective in controlling pain from head and neck tumors that invade the base of the skull. Bilateral sacral rhizotomy has been reported to treat sacral or perineal pain involving the sacral plexus at the S-2 and S-3 levels. However, these patients have often had extensive radiation therapy, and wound closure in the irradiated skin over the sacrum may complicate recovery and increase the risk-to-benefit ratio. A neurolytic, epidural, or subarachnoid block is usually considered before surgical sacral rhizotomy.

The use of a dorsal root entry zone lesion is based on the recognition that nociceptive fibers enter laminae I and II at the dorsal horn; interruption of this anterior lateral site has been associated with reduction in neuropathic pain in experimental animals. This approach has been used most commonly in avulsion of the brachial plexus, postherpetic neuralgia, and posttraumatic pain. Because this approach has not been widely used in cancer pain, its usefulness for brachial and lumbosacral plexopathy is not established, but it is an interesting approach for such patients. The procedure requires a laminectomy of several levels to provide an adequate approach to this anatomic site, and this may be too extensive a procedure for the cancer patient with advanced disease. Further studies are necessary to determine its usefulness.

The midline commissural myelotomy approach has been used in patients with midline perineal or coccygeal pain or bilateral pain in the lower extremities. Using a limited midline myelotomy, Gildenberg and Hirschberg reported satisfactory pain relief in 10 to 14 patients with midline pain below the waist from cancer. This procedure is based on the fact that nociceptive fibers cross in the anterior commissure from the dorsal horn to the contralateral spinohemalatic pathway. This approach is used rarely, if ever, in patients with bilateral pain.

Cingulotomy has received attention in the treatment of some patients with cancer pain, using a stereotactic procedure with MRI to permit a radiofrequency lesion. Four patients with pain from widely metastatic, diffuse bone disease who were receiving opioid analgesics reported immediate pain relief with bilateral cingulate lesions. The procedure requires a laminectomy of several levels to provide an adequate approach to this anatomic site, and this may be too extensive a procedure for the cancer patient with advanced disease. Further studies are necessary to determine its usefulness.

**Neurostimulatory Procedures**

Neurostimulatory procedures involving the peripheral nerve and spinal cord are generally based on the gate theory of pain. The original theory suggests that there is a neurophysiologic gating mechanism in the substantia gelatinosa. Nociceptive sensation is conducted via small-diameter peripheral nerve fibers and nonnociceptive sensation via large-diameter fibers, and both send collaterals to the substantia gelatinosa and up the spinal dorsal columns. Stimulation of the small fibers tends to promote pain, or open the gate, whereas stimulation of the large fibers tends to inhibit pain or close the gate. Because the large nerve fibers ascend in a compact bundle through the dorsal columns, they are accessible to selected electric stimulation. Rerouting firing of the large fibers ensues, and pain sensation is inhibited at multiple levels of the spinal cord below that being stimulated.

Based on reports that high-frequency (50 to 100 Hz) percutaneous electrical nerve stimulation relieved chronic neuropathic pain, the use of transcutaneous electrical nerve stimulation (TENS) was reported effective in treating neuropathic pain. Although control studies are lacking, numerous clinical surveys suggest that this approach is useful for nociceptive and neuropathic pain. With the advent of sophisticated electronic devices, various patterns of electric stimulation are currently in use transcutaneously, including pulsed (burst), modulation (ramped), random, and complex waveform designs, all designed to improve efficacy. Patients are instructed on proper electrode placement in a dermatomal pattern and are instructed to try both intermittent and continuous stimulation. By trial and error, analgesic effects should be observed either immediately or, in some cases, after the stimulation is discontinued.

TENS is used for a wide variety of pains and serves as a safe, noninvasive approach. Clinical experience suggests its usefulness in some patients with peripheral nerve pain. Several investigators have reported that it is useful in cancer pain for a wide variety of tumor-related and neuropathic pain syndromes. Further studies are necessary to define the usefulness of TENS in the cancer patient with pain.

The dorsal column stimulation technique involves the introduction of an electrode into the epidural or intrathecal space and advancing it to the appropriate level of the dorsal column. The main indications for placement of a dorsal column stimulator are intractable dysesthetic or deafferentation pain of the limbs or trunk, such as radiation-induced neuropathy or lumbosacral plexopathy. This procedure is effective in 43% to 75% of patients and carries a low morbidity. The most common complication is failure of the device itself, which occurs in approximately 10% of patients annually. Other complications include infection, cerebrospinal fluid fistula, allergic or rejection response to the device material, and changes in stimulation over time, which may be related to cellular changes around the electrode or shifts in its position.

Thalamic stimulation involves the placement of electrodes in the medial thalamus and has been reported to be most useful for managing neuropathic pain from lesions in the central and peripheral nervous system. There are a series of reports on the usefulness of this technique in patients with head and neck cancer and prominent cranial neuropathic pain, but the limited use of this technique in these patients makes it difficult to define its specific role.

**Neuropharmacologic Approaches**

Epidural and intraspinal analgesia using opioids alone or in combination with local anesthetics, clonidine, or both or experimental agents are used to manage chronic cancer pain in patients with a reasonable (1 year) prognosis. In all instances, patients should have a trial of an epidural or intraspinal drug combination before permanent implementation is considered. It is advised that patients have as continuous intrathecal trial lasting as long as possible before permanent implementation, and Figure 55.1.3 provides an algorithm for the use of opioid intrathecal alone or with clonidine in a patient with a mixed somatic-neuropathic pain syndrome inadequately managed by systemic opioids. A wide array of external and implantable catheters and pumps are available with specific indicators and uses. Both computer-controlled battery-operated pumps and continuous fixed infusion pumps are used. Cost of the pumps and the patient's psychosocial status and social
support systems and ability to care for the pump and port are important considerations in selecting the use of such devices. No studies have clearly defined the efficacy of this approach as compared with systemic treatment, and longitudinal surveys have identified complication rates that vary from 10% to 50%, with meningitis as a serious complication. With long-term epidural catheter use, 5% to 15% infection rates have been reported.

TRIGGER POINT INJECTION

The use of trigger point injections is within the scope of the practicing physician. 118 Patients with significant musculoskeletal pain often describe specific, tender trigger point areas that, when injected with either saline or local anesthetic, are associated with significant pain relief. Effective relief of pain from trigger point injections, however, is not diagnostic of musculoskeletal pain alone, and an evaluation of the cause of the pain is still necessary to rule out the specific etiology.

Acupuncture has been used to treat both acute and chronic pain. The selected acupuncture points are manually or electrically stimulated with a needle until the patient feels the sensation. A wide variety of acupuncture techniques are available, ranging from a traditional Chinese approach to a Western adaptation. Laser acupuncture with external laser probes has also been used. The studies in cancer patients with pain represent large, uncontrolled, retrospective surveys. Minimal stimulation in manual acupuncture was used in all cases, and three acupuncture treatments represented an adequate trial. Fifty-two percent and 56% of patients reported some pain improvement for at least 7 days; an additional 30% and 22% had pain relief for 2 days or less or reported increased mobility alone. 179 A lack of detailed pain assessment in specific acupuncture techniques or a critical review of the patient population make it difficult to interpret these observations. Based on its current empiric use, this approach is relatively safe, but its benefit in cancer patients with pain remains undefined.

PHYSIATRIC APPROACHES

Rehabilitation medicine plays an important role in the multidisciplinary approach to the patient with cancer pain. Physiatrists are concerned with a patient's physical functioning and provide expertise in assessing how impairment in a patient's physical capacity affects his or her ability to function. A wide variety of interventions are available, including TENS, diathermy (heating pads, ultrasound, hydrotherapy), and cryotherapy (ice and vapo-coolants). Assistive device and braces, as well as therapeutic exercise and massage, are important. Trigger point injections and acupuncture have also been used. These interventions are commonly used in combination with other pain-therapy approaches, particularly behavioral and pharmacologic approaches. Rehabilitation approaches are discussed throughout the text specific to cancer patients' needs.

A large body of data supports the use of rehabilitative interventions in acute and chronic nonmalignant pain, but similar studies have not addressed the rehabilitation needs of the cancer pain patient. From our experiences, neurologic dysfunction is one of the common components in patients with cancer pain, and aggressive neurorehabilitation is necessary to ambulate these patients and provide them with functional independence.

SEDATION IN THE IMMINENTLY DYING

NITROUS OXIDE

Nitrous oxide has analgesic properties and has been used in the management of patients with far-advanced disease to provide added analgesia. It is administered with oxygen through a nonrebreathing face mask in concentrations from 25% to 75%. Its use in combination with systemic opioid analgesics is associated with improvement of symptoms of pain and anxiety and a demonstrable improvement in alertness. 150 This anesthetic approach should be considered in patients with breakthrough pain or incident pain to provide adequate analgesia to facilitate their care.

INTRAVENTRIOUS BARBITURATES

This approach has been advocated to manage dying patients who have inadequate analgesia or uncontrolled symptoms, who ask to be maintained in a sedated state. Intravenous thiopental titrated to a level of sedation was the approach advocated in a series of 17 terminally ill patients. 151 The authors suggested that the value of this approach is based on the use of one agent to treat both physical and psychological symptoms. This approach may be seen as a more generalized one to palliative care and should be considered only if the standard approaches with opioid analgesics and adjuvant drugs fail to provide adequate analgesia with minimum side effects. However, because it is the physician's responsibility to manage not only pain but also suffering, this may be a reasonable approach, particularly in the dying patient with profound dyspnea, myoclonus, or agitation. Further studies are needed to clarify the usefulness of this approach. In the published study, 13 of 17 patients developed somnolence and died; the somnolence lasted from 2 hours to 4 days, with an average of 23 hours. Four patients died without being somnolent.

Several problematic symptoms often arise in the management of the dying patient, including intractable vomiting, profound dyspnea, extreme agitation and anxiety, and uncontrolled pain. Several authors have reported that most cancer patients have crescendo symptoms before death, requiring somnolence. 152 This approach offers one method to manage these difficult patients.

Whatever pain management techniques are used, the physician is responsible for providing continuing care, constantly reassessing both the diagnosis and the treatment to achieve optimal relief of pain and suffering for both patient and family.

The care of patients with cancer and chronic pain strains the resources of a single physician, especially after the patient's discharge from the hospital. Various supportive care and continuing care programs have been developed to manage dying patients, both in the hospital and at home. In these patients the focus of treatment shifts to symptom control and palliative comfort care. Palliative care services, home- and hospital-based hospices, and high-technology home care programs are some of the approaches to care for patients with terminal illness.

The program at Memorial Sloan-Kettering Cancer Center centers on the patient and family and is coordinated by a nurse, physician, and social worker. 153 The nurse is responsible for day-to-day management of the patient's pain and works with the patient, family, and community physicians and nurses on symptom control and supportive care. Community health professionals work with the patient at home, and the team is available to the patient, family, and community health workers on a 24-hour-a-day basis.

ALGORITHM FOR CANCER PAIN MANAGEMENT

An algorithm has been developed that integrates all of these management approaches for cancer pain. It attempts to integrate assessment techniques, drug therapy, behavioral approaches, and anesthetic and neurosurgical approaches and stresses continuity of care. Treatment begins with a diagnostic evaluation that addresses the medical, psychological, and social components of pain. A plan is developed to treat the cancer and pain. If the anticancer treatment is effective, pain relief usually
The study of pain in cancer patients offers a unique opportunity to use clinical observations to advance our biologic knowledge. There is a critical need to expand both the research and educational efforts in pain care to improve the control of pain in these patients. Information on the basic mechanisms of pain modulation can be culled only from a careful study of these clinical pain problems. These patients can teach us the physiologic and psychological differences between acute and chronic pain. The role of psychological variables of the evolving psychological evolution of the disease, the difference between pain and suffering, the clinical pharmacology of analgesic drugs, and the behavioral mechanisms humans use to suppress pain. The use of innovative approaches based must be integrated from the onset of treatment and should be used along with the medical and surgical approaches.

**FUTURE DIRECTIONS**

The study of pain in cancer patients offers a unique opportunity to use clinical observations to advance our biologic knowledge. There is a critical need to expand both the research and educational efforts in pain care to improve the control of pain in these patients. Information on the basic mechanisms of pain modulation can be culled only from a careful study of these clinical pain problems. These patients can teach us the physiologic and psychological differences between acute and chronic pain. The role of psychological variables of the evolving psychological evolution of the disease, the difference between pain and suffering, the clinical pharmacology of analgesic drugs, and the behavioral mechanisms humans use to suppress pain. The use of innovative approaches based must be integrated from the onset of treatment and should be used along with the medical and surgical approaches.


Malnutrition is common in cancer patients and is frequently referred to as cancer cachexia. Although this is a true malnutrition syndrome, it differs from the protein-calorie malnutrition seen in starvation. Further, the etiology of this syndrome (an oncologic problem) is not entirely clear, but investigations delineating the role of cytokines and other substances responsible for mediating the cachexia of cancer have increased our knowledge of the causes of malnutrition in these patients with advanced malignant disease. Studies have also provided insight into why it is difficult or impossible to gain lean body mass in cachectic cancer patients even when aggressive feeding regimens are implemented. Now and in the future, nutritional therapy may be most effective in cancer patients when used in combination with other forms of metabolic intervention.

While cancer patients can develop deficiencies in vitamins and trace minerals, the most common form of nutritional depletion is that of protein-calorie malnutrition, manifested as a loss of body cell mass. Severe protein-calorie malnutrition is associated with increases in postoperative complications in cancer patients, and it has been shown to have adverse effects on immune function and treatment tolerance to anticancer treatments. Since intuition would indicate the well-nourished patient should tolerate aggressive antineoplastic therapy better than the malmunished individual, numerous studies have tried to define the role of nutritional support in patients with malignant disease. Moreover, the observation that this commonly occurring weight loss is a predictor of therapeutic response and survival has led to aggressive attempts to restore nutritional integrity. The rationale for providing nutritional support to selected patients is to prevent or reverse host tissue wasting, broaden the spectrum of therapeutic options, improve the clinical course, and ultimately prolong patient survival.

More recent developments have increased our understanding of the relationship between nutrition and metabolism in cancer patients, and it is clear that limited weight loss in cancer patients is acceptable because short-term undernutrition does not appear to adversely affect treatment tolerance. However, many cancer patients do develop significant malnutrition such that some form of nutritional support or metabolic intervention appears to be indicated. Cancer patients often require chemotherapy, radiation therapy, or both in combination with surgery, and these treatments can further compromise an already fragile nutritional status and further reduce treatment tolerance. Not only may the anticancer treatments directly affect nutrition and reduce the urge to eat, but they may affect the ability to chew, swallow, or absorb food. Accordingly, oncologists need to become familiar with the changes in body metabolism developing during malignancy and with the indications and delivery of nutritional or metabolic support to the cancer patient. Although the need for well-designed prospective randomized trials examining the role of nutritional support as adjutive therapy in cancer patients continues to exist, it is clear that patients with a functioning gut deserve enteral nutrition as the route of preference for feeding. Parenteral nutrition should be reserved for patients who have unusable gastrointestinal tracts.

The purpose of this chapter is to examine the etiologies and metabolic alterations in cancer cachexia, to establish a rationale for metabolic treatment and support in the malmunished cancer patient, and to define the indications for and the effect of nutritional support in patients with malignant disease. Portions of this review have been previously published. 2,3

CLINICAL MANIFESTATIONS OF CANCER CACHEXIA

WEIGHT LOSS

The most obvious clinical manifestation of cancer cachexia is the depletion of host tissues that becomes quite apparent to the casual observer as weight loss. Most cachexia patients lose weight at some point during the course of their disease and nearly one-half of all cancer patients have weight loss at the time of initial diagnosis. Warren and colleagues in 1932 reported that 22% of deaths were due to inanition, and two-thirds of all tumor-bearing patients in their series developed some degree of cachexia. A large study from the Eastern Cooperative Oncology Group showed significantly shorter survival if weight loss was present. Further, the amount of weight loss was dependent on the type and site of the tumor. Non-Hodgkin’s lymphomas, breast cancers, acute nonlymphocytic leukemias, and sarcomas had the least weight loss. Colon, prostate, and lung cancers had a moderate weight loss, whereas pancreatic and gastric cancers had the most. 4

DeWys and colleagues reported that patients who presented without weight loss had a significantly prolonged survival following therapy than similarly treated patients who had weight loss at presentation. These findings suggest that weight loss adversely affects survival following antineoplastic therapy and imply that appropriate nutritional therapy may be beneficial to certain patient groups. 5 In both animals and patients with cancer, it is apparent that weight loss is dependent on the presence of the tumor since curative surgical resection of the presence of metastatic or recurrent disease should be suspected. As a general rule, cancer patients with significant weight loss do not tolerate treatment regimens as well as well-nourished patients.

INTRODUCTION

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Nutritional support therapy has attempted to reverse this cachexia and, although some weight loss has been halted, restoration of the protein and caloric intake has not reversed the abnormalities of energy, protein, carbohydrate, and fat metabolism, showing that something else must be added. 24

**LOSS OF APPETITE**

Loss of appetite resulting in a reduction in voluntary food intake is a central component of the syndrome of cancer cachexia. Careful studies in numerous animal models of cancer cachexia have documented a decline in food intake.

Appetite is strongly controlled by various neurotransmitters such as serotonin, catecholamines, and opiates. Any serotonergic agonist decreases appetite. In animal studies, there is evidence of increased brain tryptophan and serotonin turnover in the tumor-bearing host. Inhibition of serotonin synthesis increases food intake. However, serotonin antagonists demonstrate no effect on tumor anorexia. Further, there may be a serum factor responsible since rats receiving serum from tumor-bearing rats become anorectic. 12

At some point during the course of their disease, most patients report a loss of appetite including alterations in taste and smell plus the loss of the appeal of most foods. Moreover, some patients exhibit an increase in resting energy expenditure (REE) that is seldom accompanied by a compensatory increase in calorie intake. The combination of a decrease in voluntary food intake with an increase in energy expenditure further contributes to weight loss and negative calorie and nitrogen balance.

There may also be anatomic factors including the location of the tumor affecting the ability to eat. Sometimes the malignant process may even involve the digestive tract, leading to pain, early satiety, mechanical obstruction, or nausea. Head and neck cancers and the treatments used for them may cause dysphagia, mucositis, and stomatitis, with the resultant inability to take oral feeds. Gastric and pancreatic cancers cause obstruction, early satiety, or pain with eating and notoriously present late with marked metabolic changes and weight loss. Early provision of enteral routes for feeding need to be considered along with any other types of treatment and should be performed with the primary surgery or early in the course of radiation therapy. With today’s minimally invasive procedures for tube placements, there is no excuse for delay in provision of enteral feeds.

**WEAKNESS**

Secondary to loss of body cell mass and treatment regimens, cancer patients almost invariably develop a reduction in strength and a diminished physical capacity for work. Evidence for a central role of the tumor in the etiology of this weakness is derived from the clinical observation that cure of the cancer almost always results in a return to preillness strength and work capacity.

**CAUSES AND CONSEQUENCES OF CANCER CACHEXIA**

Many of the physiologic changes seen in cancer cachexia resemble those of simple starvation, but it is clear that more derangement is involved since few studies have documented that aggressive feeding of cachectic cancer patients completely restores lean body mass. Rather, such patients tend to primarily gain water and fat. Although the substrate demand of the tumor may account for the tumor behaving as a nitrogen trap, the actual energy and nitrogen demands of the growing malignancy. No consistent or clear-cut association with duration of illness, stage of disease, or tumor histology has been demonstrated. Although the exact prevalence of cancer cachexia is unknown, many studies have shown a high frequency of nutritional derangements in cancer patients. These studies have focused on findings such as weight loss or hypoproteinemia as indicators of cancer cachexia. Consequently, the prevalence of cancer cachexia may be underestimated, since it is likely that subtle metabolic alterations precede these clinically apparent changes manifested by the weight and lean tissue loss.

Since many cancer-related deaths are a consequence of malnutrition and host depletion, understanding the mechanism of cancer cachexia is imperative, as the syndrome always results in death if oncologic therapy is not administered. Many etiologies for the cancer cachexia syndrome have been proposed, but no clear explanation exists. Therefore, the etiology seems to be multifactorial. Causes can be broadly categorized into anorexia of malignancy, anorexia of therapy, and abnormalities in host intermediary metabolism.

**ANOREXIA OF MALIGNANCY**

As mentioned previously, the anorexia of malignancy refers to the decrease in voluntary food intake that occurs in cancer patients. Although this anorexia comes eventually in all patients with advanced cancer, it may sometimes develop early in the course of the disease when the tumor is quite small. Weight loss is common in patients with gastrointestinal tumors, but dysfunction of the digestive tract cannot solely explain this phenomenon, since significant cachexia is also noted in patients with cancers that originate outside the abdominal cavity. Proposed mechanisms include local effects of the tumor, alterations in taste or palatability, hypothalamic...
Glucose metabolism is also abnormal in cancer patients secondary to increased whole body glucose turnover. There is decreased glucose use by skeletal muscle, increased hepatic glucose production, and increased production of glucose from lactate through Cori’s cycle. There is also increased glucose use by the tumor as the tumor switches to glucose as its primary fuel source. Shaw and Wolfe demonstrated that hepatic gluconeogenesis in patients with gastrointestinal malignancies was elevated proportional to tumor burden. Patients with the largest tumors even failed to suppress endogenous glucose production during glucose infusion, a response attributed to insulin resistance. This glucose intolerance and hyperglycemia in cancer patients has been recognized for a long time. Lundholm et al. showed that the beta cell receptor in the pancreas may have diminished sensitivity to glucose loading, indicating that the tumor-bearing host may be in a type II diabetic-like state. However, this insulin resistance also shares elements similar to the stress state. Overall, there is a combination of a significant decrease in metabolized and cleared glucose in both the weight-stable and weight-losing cancer patients. Since the insulin resistance may decrease after complete tumor resection, it appears to be related to the tumor itself, rather than the associated malnutrition. This could contribute significantly to tissue wasting, since insulin is important for tissue anabolism.

Protein and amino acid metabolism are also altered in the tumor-bearing host. Jeevanandam et al. compared tumor-bearing patients with both malnourished non–tumor-bearing patients and healthy controls to find elevated levels of protein turnover in the cancer group. Patients with non–small cell lung cancer have increased whole body protein turnover, elevated 3-methylhistidine excretion, and increased muscle proteolysis. In tumor-bearing rats, whole body nitrogen turnover and liver protein fractional synthetic rates increase, and the animal cannot adapt to starvation by diminishing the rate of muscle amino acid release. Further, skeletal muscle synthesis of new protein decreases. Norton et al. measured arteriovenous differences of amino acids across a sarcoma-bearing limb in patients using the non–tumor-bearing limb as a control. Compared with the non–tumor-bearing extremity, the tumor-bearing limb released lesser amounts of every amino acid, consistent with the tumor’s requirement for amino acids to support neoplastic growth. Further work by Fischer et al. has shown the primary amino acid for tumor protein synthesis is glutamine.

Lipid metabolism is also altered in the host with cancer. Shaw and Wolfe studied glycerol and fatty acid kinetics using radioisotopes and found cancer patients with weight loss have increased glycerol and fatty acid turnover compared with weight-stable patients. These weight-losing patients may be incapable of oxidizing endogenous fatty acids or intravenous lipids at normal rates and fail to suppress lipolysis during glucose infusion. In fact, there is increased lipid mobilization from peripheral fat stores and decreased serum lipid clearance, leading to depletion of body fatty tissue. There have now been a number of studies suggesting a transmissible fat-mobilizing substance (lipid-mobilizing proteoglycan (LMP), azaftig in the serum of cancer patients that increases lipid breakdown and decreases fat synthesis. This lipid-mobilizing factor is a 24-kD zinc a2-glycoprotein that has been isolated from the urine of tumor-bearing animals and patients. It has been found in the urine of pancreas, lung, breast, and ovarian cancer patients. The N-terminal amino acid sequence is different from that of any of the known cytokines. Administration of this material shows significant reduction in body weight and decrease in both fat and lean body mass and can be neutralized by administration of monoclonal or polyclonal antibodies.

**GLUTAMINE AND CANCER CACHEXIA**

Glutamine metabolism in the tumor-bearing host has been extensively studied for four principal reasons: (1) glutamine is the principal amino acid used by many cancers; it is the most abundant amino acid in the body, (3) its stores are quite labile, and (4) studies indicate that glutamine is a conditionally essential amino acid. Glutamine appears to be an unusually good substrate for use by the tumor. In fibrosarcoma cells, glutamine oxidation is decreased and the glutamine is shunted into protein synthesis while the tumor switches to glucose for energy. Circulating glutamine extraction by the tumor is 50% greater than the rate of glutamine extraction for any normal healthy organ. Because tumors must compete with host tissues for plasma amino acids and are often poorly vascularized, they must possess efficient mechanisms of nutrient extraction, especially in an environment (e.g., intratumoral space) in which levels of these nutrients may be diminished compared with plasma levels. Studies in a variety of different solid tumor cell lines, regardless of tissue origin, indicate a single efficient high-affinity carrier-mediated Na+-dependent glutamine transport. There was a range of kinetic parameters for the glutamine transporter in each cell type, but the amino acid inhibition profiles were nearly identical, consistent with uptake by the system ASC family of transporters. Rates of cell growth, DNA and protein synthesis, and thymidine transport correlated with the glutamine concentration in the culture media, indicating the central role of this amino acid in regulating cellular proliferation.

The methylcholanthrene-induced sarcoma (MCA tumor) rat model has been used by several investigators to study glutamine metabolism. One of the most reproducible observations in rats bearing the MCA tumor is a progressive decrease in plasma glutamine concentrations that correlates with tumor size. With time, blood glutamine levels decrease to less than 50% of normal, indicating an imbalance between rates of glutamine production and consumption expressed by the various organs of the body. This reduction in circulating levels occurs despite an increase in the rate of muscle glutamine release because the accelerated glutamine consumption by tumor and other tissues exceeds the net rate of glutamine uptake into the blood stream. Concomitantly temporally with the tumor-induced alterations in muscle glutamine metabolism is marked increases in tumor and hepatic glutamine uptake. Thus, with progressive tumor growth, glutamine depletion gradually becomes more severe. This low glutamine level may serve as a signal to induce net proteolysis.

Since glutamine uptake by the tumor is increased, the assumption might be made that providing exogenous glutamine would promote tumor growth. However,
glutamine-enriched total parenteral nutrition (TPN) seems to be more beneficial to the host than the tumor. In fact, dietary glutamine improves the immune status of rats recovering from chemotherapy in a dose-dependent manner and becomes more pronounced after a longer duration of intake.

**CYTOKINES: MEDIATORS OF CANCER CACHEXIA**

Cytokines, polypeptide signalers produced by the host's cells in response to a growing tumor, regulate many of the nutritional and metabolic derangements that occur in the host with cancer (Table 56.2.4). The recognition that cytokines are important mediators of the body's response to the growing tumor has allowed investigators to focus research efforts on finding common mechanisms responsible for the development of the cancer cachexia. These studies will likely lead to the incorporation of nutritional strategies designed to optimize the metabolic and immunologic integrity of the host while simultaneously allowing tumor-directed therapies to be maximally effective.

![Image](Image 72x1071 to 272x1212)

**TABLE 56.2-4. Some Effects of Cytokines on Nutrition and Metabolism in the Tumor-Bearing Host**

Elevated concentrations of tissue and circulating cytokines have been demonstrated in the host with cancer, and enhanced hepatic cytokine gene expression has been demonstrated in tumor-bearing animals. Cytokines can regulate both energy intake (appetite) and energy expenditure (metabolic rate). Administration of tumor necrosis factor (TNF) to rodents and humans decreases food intake, but the effect appears to be short lived. In rats treated with chronic injections of TNF, voluntary food intake was markedly reduced for 2 days but had normalized by the sixth day of TNF administration. In patients receiving TNF, food intake was also diminished, but nitrogen losses were not accelerated, indicating that the resultant negative nitrogen balance was due to something other than TNF alone. Interleukin-1 (IL-1) also suppresses food intake, and its effect, like that of TNF, appears to be directly on the central nervous system. Darling and associates suggest that when TNF is given via an i.p. injection, the anorexic effects are sustained as opposed to the tolerance that develops when the cytokine is given by bolus injection. Further evidence for a role for TNF and IL-1 in mediating appetite suppression during critical illness comes from additional studies that demonstrate that treatment of tumor-bearing mice with anticytokine antibodies improves food intake and attenuates weight loss. Even mice whose tumors were injected with inhibitors to TNF and IL-1 resulted in the attenuation of weight loss, an increase in food intake, a decrease in serum triglyceride and glucose, and an increase in total protein. Mice implanted with tumors that secreted TNF showed marked reductions in weight compared with animals with non-TNF-secreting tumors. Therefore, the effects of TNF on food intake and body composition are unlikely to be due to partial starvation alone, but rather may be due to the ability of TNF to stimulate basal metabolic rate (oxygen consumption). In patients receiving injections of TNF, metabolic rates were noted to increase by 30%.

In addition to stimulating anorexia and thermogenesis, cytokines can also stimulate mobilization of fat and protein stores in vivo. Accordingly, TNF was first identified as a mediator of cachexia and was termed cachectin. Although few clinical studies demonstrate weight loss in subjects receiving TNF, it is likely that these cytokines cause fluid retention. It is clear that TNF can alter the vascular endothelium and lead to an increase in capillary permeability.

Other cytokines have been shown to have effects as well, particularly IL-6. IL-6 is increased in lung cancer patients and is correlated with poor nutritional status and shorter survival. Further, IL-6 levels decrease in treatment responders and do not change or may even increase in nonresponders. IL-12 may also increase secretion of interferon-γ, which may enhance TNF production and subsequent cytokine-induced cachexia. Serum levels of soluble TNF receptors have also been measured and found to correlate with the extent of disease, degree of cachexia, and inversely with nutritional parameters. But the cachexia of cancer does not depend on cytokines alone. Other mediators that have been investigated include corticosteroids, β-agonists, and insulin-like growth factors. Glucocorticoids appear to have additive effects to cytokines in the development of cachexia and may be the missing factor for the cachectic effects of cytokines. In the presence of dexamethasone, there is an up-regulation of IL-6 receptors that seems to prime liver cells for subsequent stimulation by cytokines. There may also be an effect from the autonomic nervous system. One study has shown increased renal sympathetic nerve activity in cachexia, and another has shown improvement in dietary intake with the use of propranolol to block the elevation of RER from this autonomic dysfunction. Insulin-like growth factor and insulin have also been studied in an attempt to attenuate cancer cachexia and although they induced weight gain in other mice, they could not do so in those with colon tumors. Some of the most promising effects on cachexia may come from eicosanoids and progestogens (see Nutritional Support of the Cancer Patient, later in this chapter).

**Effects on Glucose Metabolism**

Studies evaluating the effects of cytokine administration on the circulating glucose concentration indicate that the plasma glucose level rises or falls depending on the dose of cytokine administered, the temporal nature of the measurement, and the specific cytokine given. In rats, sublethal doses of TNF that do not produce hemodynamic changes result in the development of hyperglycemia within 1 hour of administration. The increase in plasma glucose was only mild, however (20%), and was associated with an increase in the circulating concentration of glucagon, adrenocorticotrophic hormone, corticosterone, and epinephrine, all of which can cause hyperglycemia. Further, incubation of adrenocortical cells with TNF stimulated cortisol secretion to the same extent, as did adrenocorticotrophic hormone. Blood glucose was unchanged when a lower dose of TNF was used. Similar changes in blood glucose levels are observed after IL-1 administration. At higher IL-1 doses, Fischer and colleagues reported a rapid increase in blood glucose from 100 to 140 mg/dL within 1 hour. However, this increase was transient, with a return to baseline levels by 2 hours. Simultaneously, there was a several-fold increase in insulin receptor expression (most likely skeletal muscle) glucose consumption that was also transient. In cultured muscle cells (L6 cell line), TNF-a stimulates glucose transport via a mechanism that involves de novo synthesis of glucose transporters that are inserted into the plasma membrane. Simultaneously, there is depletion of cellular glycogen stores and an increase in lactate efflux, all of which are consistent with stimulation of anaerobic glycolysis.

Meszaros and colleagues have studied tissue glucose utilization in vivo using the 2-deoxyglucose tracer technique in rats following infusion of a nonlethal dose of TNF. Glucose uptake was increased by 80% to 100% in liver, kidney, and spleen (80%), lung (30% to 40%), and ileum (30% to 40%). The largest increase was observed in adipose tissue (150%). No significant increase was observed in skeletal muscle, testis, or brain. These data indicate a marked increase in whole body glucose use following TNF administration. Acute exposure of pancreatic islets to IL-1β results in no change in glucose uptake but diminishes the rate of mitochondrial glucose oxidation, a response that is potentiated by TNF. In response to IL-1β, islets exhibit an increase in insulin release in the presence of high glucose concentrations.

**Effect on Fat Metabolism**

Altered fat metabolism is apparent clinically in cachectic patients from the observation that fat stores are diminished in association with weight loss. It is likely that the loss of fat stores in cancer patients is due to the ability of TNF, IL-1, and LMF to mobilize fat stores. Bolus administration of TNF to rats causes an increase in serum triglyceride levels within 2 hours. Greenberg and colleagues investigated the possible role of IL-6 and TNF in mediating the depleted fat stores that occur with malignancy-associated cachexia. Injection of IL-6 and TNF each reduced adipose tissue lipoprotein lipase activity by more than 50%. Similarly, both IL-6 and TNF reduced heparin-releasable lipoprotein lipase activity in 3T3-L1 adipocytes in a dose-dependent manner by 50% to 70%. In addition to a reduction in adipocyte lipoprotein lipase activity, the increase in serum triglyceride levels that is observed after TNF administration is also due to stimulation of hepatic lipid secretion.

The discovery of the LMF may either add to the lipid-mobilizing effects or be stimulated by the cytokines. Further study of this factor is needed to elucidate its full
Regulation of Protein and Amino Acid Metabolism

Marked changes in protein and amino acid metabolism are characteristic of cancer patients, and a number of published studies have evaluated the effects of cytokines on muscle protein metabolism with conflicting results. When recombinant TNF was infused into cancer patients, forearm amino acid flux was accelerated, consistent with net skeletal muscle proteolysis, although this accelerated nitrogen release could have been due to starvation effects. 13 Similarly, when Flores and colleagues infused radiolabeled leucine into rats receiving TNF, IL-1, or both using tracer methodology techniques, they found an increase in muscle protein degradation in cytokine-treated animals. 12 However, when the IL-1 activity in activated monocyte supernatants was blocked with specific anti–IL-1 antibodies, the accelerated protein degradation was not attenuated, suggesting that TNF may have a major role for other reasons. 14,15 Thus, although TNF is generally agreed to be a cytokine cascade mediator, it is unclear which distal mediators in the cytokine cascade are the key players (IL-6, LMF).

In contrast to whole animal studies, the majority of which indicate that in vivo administration of TNF or IL-1 results in net muscle proteolysis, in vitro studies have yielded negative results. In studies evaluating the effects of corticosterone on muscle protein breakdown, this glucocorticoid was noted to accelerate protein degradation and diminish protein synthesis. In combination with TNF, these steroid-mediated effects were augmented, but TNF alone did not alter protein turnover, indicating a helping role for the corticosterone. 5

In vitro and in vivo studies demonstrate that cytokines occupy an important role in mediating the hepatic metabolic response to malignant disease. Tumor-bearing rats display a global increase in Na+-dependent amino acid transport, a response that can be attenuated by treatment with anti-TNF antibody. 16 Similar observations were made in animals treated with a single dose of TNF: Stimulation of hepatic amino acid transport systems A, ASC, and N were noted within 4 hours of TNF administration. 17 The increase in transport activity was due to an increase in carrier maximal transport velocity, consistent with the appearance of increased numbers of transport protein molecules in the plasma membrane. IL-6 and glucocorticoids have also been shown to work in a coordinated fashion to stimulate hepatic amino acid transport in vivo. 18 Moreover, these cytokines stimulate amino acid transport activity in cultured hepatocytes. 19

NUTRITIONAL SUPPORT OF THE CANCER PATIENT

RATIONALE

Malnutrition is defined as any nutritional deficit that is associated with an increased risk of morbidity and mortality. There is a diminished risk of such events when the nutrition status is corrected. Although it seems apparent that the provision of nutritional support to the malnourished patient with cancer is essential and would be beneficial, evidence indicating that currently available nutritional formulae alone can maintain or reverse malnutrition in the patient with advanced malignant disease is lacking. This observation suggests that many patients with cancer exhibit ongoing catabolism of body cell mass that persists and is refractory to nutritional regeneration. Despite diminished food intake, the tumor-bearing host does not adapt to partial starvation for conserving lean body mass. Instead, the host continues to deplete its own muscle mass to provide amino acids taken up by the tumor to support growth and by the liver to support gluconeogenesis and biosynthesis of important defense proteins. The rationale behind the provision of specialized nutritional support, whether it be enteral or parenteral, is the belief that such support will preferentially benefit the patient rather than stimulate tumor growth. From a more practical standpoint, nutritional support would not be indicated if it clearly demonstrated no favorable effect on the response to antineoplastic therapies, no lengthening of the disease-free survival, or no improvement in the quality of life. Interestingly, a consensus of opinion regarding the role and efficacy of nutritional support in patients with cancer is lacking. Nonetheless, several well-designed clinical studies have allowed us to generate guidelines for the use of enteral and parenteral nutrition in patients with cancer, and most physicians and surgeons who care for patients with cancer continue to use nutritional support aggressively under specific circumstances.

Several studies have suggested additional treatments can be used along with nutritional support to alleviate the tumor cachexia. The synthetic progestogens, megestrol acetate (MA) and medroxyprogesterone acetate, may be helpful in high doses in the non–hormone-sensitive cancer with associated cachexia syndrome to diminish cachexia. In addition to the cytokines, particularly TNF and IL-6, as well as seratonin. These agents have been able to improve appetite, well-being, and quality of life as well as decreasing nausea and vomiting. MA has also been shown to increase body nonfluid weight gain although primarily with fat. Patients have been reported to respond with 5 days of therapy with MA, and it may be discontinued after just 2 weeks of therapy. However, MA may be associated with more thromboembolic complications and there may have been less response to chemotherapeutic regimens. 20

Other agents associated with a beneficial effect on the cachexia syndrome include eicosanoids and melatonin. Tisdale reported eicosapentaenoic acid, a component of fish oil, attenuated the action of cachectic factors and stabilized the weight loss and energy expenditure in patients with pancreatic cancer. 21 Reports from Japan show that maintained body weight was significantly greater in groups of mice treated with two different eicosanoids, docosahexanoic acid and eicosapentaenoic acid. 22,23 McMillan et al. reported that patients with advanced gastrointestinal cancers given ibuprofen, 1200 mg/d, in addition to MA, 480 mg/d, had an increase in body weight and no change in body water. 24 Lessini et al. reported that melatonin has also been shown to decrease levels of TNF and lead to decreased weight loss in untreated metastatic tumor patients and may therefore be helpful in treating cancer cachexia. 25 Gagnon and Bruera reviewed other treatment modalities for cancer cachexia and suggested drugs such as thalidomide and melatonin may be useful because of their effects on TNF. They also suggested b-adrenergic agonists might help as well because of their effect on muscle metabolism. 26

NUTRITIONAL ASSESSMENT OF THE CANCER PATIENT

In order to determine the best strategies for treatment of the cancer patient, the nutritional status must first be determined. This is done by a careful history and physical examination followed by additional tests to confirm the clinical impression. The history should include inquiries about appetite, preferred foods, and weight loss. The physical examination can establish the diagnosis of muscle wasting and specific nutrient deficiencies. Anthropometric measurements should be done including measurement of body weight and height, skinfold thickness, and a 24-hour urine collection for the measurement of nitrogen. Peripheral blood lymphocyte count and amino testing to common antigens for assessment of delayed hypersensitivity have been used as indicators of immunocompetence in the cancer patient. Altered immunologic responses are not specific for nutritional deficiencies and are often observed even in patients with advanced malignant disease who are well nourished. Serum albumin and transferrin are the most common serum proteins measured. Other laboratory studies useful in nutritional assessment include red blood cell indices to determine iron and micronutrient deficiencies, plasma glucose to assess insulin resistance, blood urea nitrogen to determine renal status, and liver function tests to evaluate hepatic function.

NUTRITION AND TUMOR GROWTH

With the introduction of specialized enteral and parenteral feeding regimens into clinical medicine, aggressive nutritional support can be provided to cancer patients who previously could not or would not eat. However, concerns over the stimulation of tumor growth have existed for many years. While animal studies indicate that tumor growth can be enhanced with a high-protein diet and diminished by protein-depleted diets, studies in cancer patients are less clear. Baron and coworkers studied 14 malnourished patients with untreated head and neck squamous cell carcinoma who underwent biopsies of both normal and malignant tissues. 27 In order to determine the best strategies for treatment of the cancer patient, the nutritional status must first be determined. This is done by a careful history and physical examination followed by additional tests to confirm the clinical impression. The history should include inquiries about appetite, preferred foods, and weight loss. The physical examination can establish the diagnosis of muscle wasting and specific nutrient deficiencies. Anthropometric measurements should be done including measurement of body weight and height, skinfold thickness, and a 24-hour urine collection for the measurement of nitrogen. Peripheral blood lymphocyte count and amino testing to common antigens for assessment of delayed hypersensitivity have been used as indicators of immunocompetence in the cancer patient. Altered immunologic responses are not specific for nutritional deficiencies and are often observed even in patients with advanced malignant disease who are well nourished. Serum albumin and transferrin are the most common serum proteins measured. Other laboratory studies useful in nutritional assessment include red blood cell indices to determine iron and micronutrient deficiencies, plasma glucose to assess insulin resistance, blood urea nitrogen to determine renal status, and liver function tests to evaluate hepatic function.

ENTERAL NUTRITION IN CANCER PATIENTS

Numerous clinical trials have evaluated the use of aggressive enteral nutritional support as adjunctive therapy during the administration of antineoplastic regimens to cancer patients, but well-designed studies have made up a small fraction of these. Although these trials do not demonstrate any consistent benefits of enteral nutrition, most authorities would agree that enteral nutrition is always the preferred route of feeding cancer patients when the gastrointestinal tract is functional. 28 The primary aim of nasogastric feeding in patients who cannot take oral intake is to provide a nutrient source that could be utilized by the tumor. The use of nasogastric feeding catheters is common in patients with advanced cancer to provide nutrition support. Some of the better enteral clinical trials in cancer patients 29-34 are listed in Table 56.2-6, Table 56.2-7, and Table 56.2-8. Commonly used enteral formulas are listed in Table 56.2-9. A physician order form for enteral nutrition is presented in Figure 56.2-1.
### TABLE 56.2-5. Proposed Benefits of Oral and Enteral Nutrition versus Parenteral Nutrition

<table>
<thead>
<tr>
<th>Benefit Description</th>
<th>Oral/Enteral Nutrition</th>
<th>Parenteral Nutrition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maintain normal body weight</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Maintain lean body mass and muscle mass</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Support normal tissue and organ function</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Maintain normal intestinal function and mucosal barrier function</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Improve outcome after chemotherapy and radiation therapy</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>

### TABLE 56.2-6. Results of Major Prospective Randomized Controlled Trials Evaluating Perioperative Nutrition

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Nutritional Intervention</th>
<th>Study Outcome</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized Controlled Trial 1</td>
<td>Oral nutrition</td>
<td>Weight gain</td>
<td>Significant</td>
</tr>
<tr>
<td>Randomized Controlled Trial 2</td>
<td>Enteral nutrition</td>
<td>Blood glucose</td>
<td>No difference</td>
</tr>
</tbody>
</table>

### TABLE 56.2-7. Results of Prospective Randomized Controlled Trials in Patients Treated with Radiation Therapy

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Nutritional Intervention</th>
<th>Study Outcome</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized Controlled Trial 1</td>
<td>Oral nutrition</td>
<td>Radiation therapy tolerance</td>
<td>Improved</td>
</tr>
<tr>
<td>Randomized Controlled Trial 2</td>
<td>Enteral nutrition</td>
<td>Radiation therapy side effects</td>
<td>Decreased</td>
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</table>

### TABLE 56.2-8. Results of Prospective Randomized Controlled Trials Evaluating Nutritional Therapy in Patients Receiving Chemotherapy

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Nutritional Intervention</th>
<th>Study Outcome</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized Controlled Trial 1</td>
<td>Oral nutrition</td>
<td>Chemotherapy side effects</td>
<td>Reduced</td>
</tr>
<tr>
<td>Randomized Controlled Trial 2</td>
<td>Enteral nutrition</td>
<td>Chemotherapy tolerance</td>
<td>Improved</td>
</tr>
</tbody>
</table>

### TABLE 56.2-9. Adult Nutrition: Physician Order Form for Tube Feedings

- [Order Form Image]
- [Form Instructions]
- [Nutritional Recommendations]
- [Dosage Guidance]
TOTAL PARENTERAL NUTRITION IN THE CANCER PATIENT: GENERAL RECOMMENDATIONS

Although the initial enthusiasm for the use of TPN in cancer patients was considerable, it is now clear that TPN should only be provided to selected patients. Because of the failure of numerous clinical trials to yield a consensus with regard to the efficacy of TPN in cancer patients, it appears to be of little benefit in most cancer populations. In some patients, the use of TPN was associated with an increase in complications. However, the most important factor to consider when making decisions about the use of TPN in patients with cancer is the response of the tumor to antineoplastic therapy. It is anticipated that the guidelines listed in Table 56.2-10 will undergo future revision, as more effective antitumor regimens become clinically available.

SPECIFIC INDICATIONS FOR THE USE OF TOTAL PARENTERAL NUTRITION IN THE CANCER PATIENT

Patients with Entero-cutaneous Fistulas

Patients with cancer who undergo major gastrointestinal surgery occasionally develop entero-cutaneous fistulas that preclude the use of the gastrointestinal tract for nutritional support. In such patients, enteral nutrition often stimulates fistula output and can result in metabolic disturbances and dehydration. TPN can affect the course of disease in cancer patients with gastrointestinal fistulas. Studies indicate that TPN increases the spontaneous closure rate of entero-cutaneous fistulas although fistulas that originate from radiated or neoplastic bowel have a much lower rate of spontaneous closure. In such patients, aggressive early surgical treatment is generally indicated. Provision of TPN maintains the nutritional status of the cancer patient who develops an entero-cutaneous fistula such that he or she better tolerates operative intervention if closure does not occur. Perhaps insulin-like growth factor or a progestogen may help in this situation.

Patients with Hepatic or Renal Failure

Patients with cancer occasionally develop liver failure after major surgery or from cytotoxic chemotherapy. Because of liver damage and portosystemic shunting, these patients develop derangements in their circulating levels of amino acids. The plasma aromatic to branched chain amino acid ratio is increased. Transport of amino acids across the blood–brain barrier favors the aromatic amino acids such as tryptophan, precursors for false neurotransmitters such as serotonin, which contribute to lethargy and encephalopathy. Treatment of individuals with liver failure with solutions enriched in branched chain amino acids and deficient in aromatic amino acids may result in improved tolerance to the administered protein and clinical improvement in the encephalopathic state.

TPN with amino acids of high biologic value may also be of value in patients with acute renal failure. Presumably, provision of only essential amino acids allows the body to maximally reuse nitrogen for the synthesis of nonessential amino acids and thereby helps prevent rapid increases in blood urea nitrogen. If the hypermetabolic cancer patient is receiving dialysis, there appears to be no advantage to using an essential amino acid solution and therefore a balanced standard amino acid formulation is recommended. Solutions containing branched chain amino acids or just essential amino acids are expensive and probably not worth the cost except in specific patients in whom adjusted standard formulas are not tolerated.

Acute Radiation and Chemotherapy Enteritis

Cancer patients who receive abdominal or pelvic irradiation or chemotherapy may develop severe and prolonged mucositis and enterocolitis, precluding use of the gastrointestinal tract for nutritional support. Under these circumstances, TPN should be provided to malnourished patients until the enteritis resolves and oral feeding can be resumed. However, in circumstances in which chemotherapy has been contraindicated secondary to severe malnutrition, TPN may be beneficial in optimizing nutritional status and allowing the initiation of the chemotherapeutic regimen. When enteral nutrition is feasible in such patients, TPN has not demonstrated a treatment advantage. When studies have been performed using well-nourished patients, the effects of TPN predictably have not been beneficial.

Patients undergoing radiation therapy may also develop malnutrition secondary to inadequate nutritional intake from an inability to eat. The potential side effects from radiotherapy are broad and include nausea, vomiting, malnutrition, mucositis, xerostomia, dysphagia, diarrhea, and anorexia. Whenever possible, the enteral route is preferable for nutritional support. However, in cases involving severe dysfunction of the gastrointestinal tract, TPN is indicated. TPN can be useful in allowing the malnourished, poor-risk patient to complete radiotherapy with less morbidity. Patients undergoing irradiation of the head, neck, or chest need to be considered for early tube placement so enteral nutrition can be used.

Use of Perioperative Total Parenteral Nutrition in Cancer Patients

One of the best studies to date evaluating the effects of preoperative TPN was published by the Veterans Affairs Total Parenteral Nutrition Cooperative Study Group. More than 3500 patients, many of whom had cancer, were entered into this prospective randomized trial. The patients were divided into one of four groups: well-nourished, borderline malnourished, moderately malnourished, or severely malnourished. Patients in each malnourished category were randomized to at least 7 days of preoperative TPN or immediate operation. Patients randomized to receive TPN received 1000 kcal/d in excess of calculated caloric requirements. Lipid was provided on a daily basis. One criticism of this study was that patients were allowed to eat in addition to receiving parenteral feedings. Analysis of the data from this study indicated that there was no difference in short-term or long-term survival among groups. Infectious complications including pneumonia, abscesses, and line sepsis were statistically significantly higher in patients receiving TPN. Noninfectious complications (impaired wound healing) were significantly lower only in those standard TPN patients who were in the severely malnourished group (greater than 15% weight loss and serum albumin less than 2.8 mg/dl). This study strongly suggests that preoperative TPN should be limited to the severely malnourished patient. Therefore, contraindications to the use of preoperative TPN should include patients requiring emergency operation and those who are only mildly or moderately malnourished.

In the few patients who are candidates for preoperative nutritional support, we recommend instituting TPN only if the gastrointestinal tract cannot be used for tube feedings. In most patients undergoing major abdominal surgery, feeding tubes may be placed intraoperatively if resumption of oral feedings is not anticipated for relatively lengthy periods of time (7 to 10 days) after surgery. TPN may also be required in the well-nourished cancer patient who develops a postoperative complication that precludes enteral support. For example, some cancer patients develop a prolonged ileus after an abdominal procedure that precludes the use of the intestinal tract as a route of feeding. Such an occurrence is generally unpredictable and the cause of the ileus is often not demonstrated. If the patient is unable to eat
by postoperative day 7, TPN should be considered. The ileus may persist for several weeks, especially in gastric or pancreatic cancer patients. Although provision of TPN does not influence the disease process per se, it is beneficial because it prevents further erosion of lean body mass.

Two prospective studies have helped to further clarify both the indications and contraindications for the use of TPN in the surgical patient with cancer. Brennan and colleagues examined the use of routine postoperative TPN following major pancreatic resection. In patients randomized to receive TPN starting on postoperative day 1, the investigators found a statistically significant increase in the incidence of intraabdominal abscesses as well as a tendency toward an increased incidence of peritonitis and bowel obstruction. The control group received a peripheral infusion of dextrose rather than luminal nutrition, suggesting that the increase in complications was not due to the absence of luminal nutrients but rather to some toxic effect of the TPN. The authors concluded that routine use of postoperative TPN was not indicated and may in fact have harmful side effects. It should be noted that many surgeons would elect to place a feeding jejunostomy in such patients.

In contrast to the Brennan study, Fan and colleagues studied the use of perioperative (starting 7 days before the planned procedure) TPN for patients undergoing hepatectomy for hepatocellular carcinoma. They found that patients randomized to receive perioperative TPN had a statistically significant reduction in infectious complications and a decreased diuretic requirement compared with similar patients who did not receive TPN. The significance of this study is that it is only one of two studies that show a benefit to the use of routine perioperative TPN in patients not suffering from severe malnutrition. In addition, it establishes a distinct group of patients in whom routine perioperative TPN may be of benefit. The mechanism by which TPN is of value in these patients is not known.

**Patients with Short Bowel Syndrome**

Cancer patients may develop short bowel syndrome secondary to multiple bowel resections or massive resection of infarcted bowel. Most of these patients, if cured of their cancer, can now survive for long periods on home TPN. Due to the duration of therapy involved, these patients are at risk for developing long-term problems such as micronutrient deficiency, bone demineralization, or line sepsis. Studies by Wilmore and colleagues have demonstrated that the requirement for TPN could be decreased or even eliminated in patients with short gut syndrome by providing a nutritional regimen consisting of supplemental glutamine, growth hormone, and a modified oral high-carbohydrate, low-fat diet. There was a marked improvement in the absorption of nutrients with this combination therapy and a decrease in stool output. In addition, TPN requirements were reduced by 50%, as were the costs associated with care of these individuals. Discontinuation of the growth hormone did not increase TPN needs in these patients once they had undergone successful gut rehabilitation.

**COMPOSITION OF TOTAL PARENTERAL NUTRITION FORMULATIONS**

TPN solutions are administered through a central venous catheter that is generally inserted into the subclavian vein. TPN solutions are hyperosmolar and calorie dense (1 kcal/mL), and the infusion of 2.0 to 2.5 L/d provides 2000 to 2500 kcal/d. The addition of minerals, vitamins, and electrolytes completes the basic composition of the solution (Table 56.2-11). Solutions must be prepared under sterile conditions. Because of the hyperosmolarity of such solutions, they must be delivered into a high flow system to prevent venous sclerosis. As a general rule, 65% of total nonprotein calories should be provided as dextrose and 35% in the form of an intravenous fat emulsion. Patients receiving TPN should be monitored regularly by measuring blood sugar, serum electrolytes, triglycerides, and liver function test results. The amounts of the various electrolytes provided to cancer patients receiving TPN may vary depending on factors such as previous nutritional and hydration status. Careful monitoring is critical because severe hypokalemia or hypophosphatemia can develop with aggressive feedings. Hypophosphatemia may develop in the chronically malnourished cachectic cancer patient given dextrose infusion who uses the phosphate to make adenosine triphosphate. This is referred to as the refeeding syndrome. These electrolyte disturbances can develop rapidly and are much more life-threatening than hyponatremia. Critical drops in serum phosphate levels below 1.5 mmol/dL can lead to an irreversible cardiac arrest.

**TABLE 56.2-11. Composition of a Standard Central Venous Solution**

**TABLE 56.2-12. Potential Complications of TPN**

Advances in technology, monitoring, and catheter care have greatly reduced the incidence of complications associated with the use of TPN. The establishment of a nutritional support team (physician, dietitian, nurse, and pharmacist) and the recognition of such a team as an important part of overall patient care have also been key factors in reducing complications. Complications of TPN that occur in cancer patients can be divided into three types: (1) mechanical (i.e., pneumothorax, laceration of the subclavian artery, air embolism, catheter embolism); (2) metabolic (hyperglycemia, electrolyte abnormalities, abnormalities in liver enzymes); and (3) infectious (catheter sepsis). These complications are listed in Table 56.2-12. The management of the patient who develops signs and symptoms of catheter sepsis is shown in Figure 56.2-2.
TABLE 56.2-12. Complications Associated with the Use of Total Parenteral Nutrition

EFFECTS OF TOTAL PARENTERAL NUTRITION ON THE GASTROINTESTINAL TRACT

Although the intestinal tract had long been considered an organ of inactivity in critically ill patients, this concept has clearly been shown to be invalid. Disuse of the gastrointestinal tract, either via starvation or nutritional support by TPN, may lead to numerous physiologic derangements as well as changes in gut microflora, impaired gut immune function, and disruption of the integrity of the mucosal barrier. Thus, maintaining gut function in the cancer patient who is receiving vigorous therapy may be essential in order to minimize septic complications and organ failure.

The majority of studies that have examined the effects of TPN on intestinal function and immunity have been done in animals. These studies clearly demonstrate that TPN is detrimental and related to intestinal disuse. In rats receiving TPN, villous atrophy develops and there appears to be a breakdown in the gut mucosal barrier. TPN results in significant disruption of the intestinal microflora and bacterial translocation from the gut lumen to the mesenteric lymph nodes. In addition, when insults such as chemotherapy or radiation are introduced into these models, animals on TPN have a much higher mortality. This body of literature suggests that under certain circumstances, TPN may predispose patients to an increase in gut-derived infectious complications. Whether these are related to bacterial translocation or just absorption of endotoxin or cytokines is still debatable.

IMPROVING THE EFFICACY OF CURRENT FEEDING REGIMENS

Role of Ambulation

Patients with cancer may be bedridden, but should be encouraged to ambulate as much as is feasible. Exercise can increase functional aerobic capacity, stimulate skeletal muscle amino acid uptake, and reduce proteolysis in normal individuals receiving TPN. It is unclear whether higher exercise thresholds are necessary to induce anabolism in nutritionally depleted cancer patients, although a higher threshold does seem to reduce fatigue.

Pharmacologic and Hormonal Therapy

The potential beneficial effects of the administration of insulin, the primary anabolic hormone in the body, to the tumor-bearing host has been studied because of its role in stimulating muscle amino acid uptake and protein synthesis. Studies indicate that treatment with insulin stimulates food intake and nitrogen retention without stimulating tumor growth. Likewise, administration of insulin in combination with the glutamine antimetabolite aminooxycetic acid to tumor-bearing rats on TPN preserved lean body mass and retarded tumor growth. Whether these observations can be extrapolated to the clinical arena is unknown.

The availability of recombinant human growth hormone has led investigators to examine the role of this anabolic agent in patients. The present data indicate that growth hormone is capable of promoting accrual of lean body mass in healthy individuals. It is unclear whether this anabolism will be observed in cachectic cancer patients. A potential downside to the use of growth hormone in patients is its association with the development of lymphoid malignancies. In tumor-bearing rats, treatment with exogenous growth hormone has been shown to increase carcass weight and improve the host immune response. Additional studies that examine the effects of growth hormone on tumor growth parameters are necessary before clinical use of this drug is justifiable.

Additional research using the progestogens MA and medroxyprogesterone acetate, as well as melatonin, is needed to assess the value of their use in treating or preventing cancer cachexia. Current recommendations for MA are 480 mg/d in addition to nutritional support.

Use of Glutamine and Arginine

The classification of glutamine as a nonessential or nutritionally dispensable amino acid implies that, in its absence from the diet, it can be synthesized in adequate quantities from other amino acids and precursors. For this reason, and because of the relative instability and short shelf life of glutamine compared with other amino acids, it has not been considered necessary to include glutamine in nutritional formulas. Glutamine has been eliminated from TPN solutions and with few exceptions, glutamine is present in oral and enteral diets only at the relatively low levels characteristic of its concentration in most dietary proteins. Based on our knowledge of the changes in glutamine metabolism that are characteristic of the host with cancer, this categorization of glutamine as a nonessential amino acid may be misleading.

Several studies in the tumor-bearing host suggest that supplemental glutamine may benefit the cancer patient (Table 56.2-13). One of the best studies to date evaluating the effects of glutamine-enriched TPN in cancer patients is a randomized, double-blind controlled trial in adults receiving allogeneic bone marrow transplants for hematologic malignancies. Patients received a standard, glutamine-free TPN solution or an experimental isonitrogenous, isocaloric solution supplemented with L-glutamine (0.57 g/kg body weight per day). Patients received the diets for approximately 4 weeks after transplantation. Patients receiving glutamine-supplemented parenteral nutrition after bone marrow transplant had improved nitrogen balance, a diminished incidence of clinical infections, less fluid accumulation, and a shortened hospital stay (see Table 56.2-13). In a more recent study, glutamine-enriched TPN was shown to prevent the increase in gut mucosal permeability that develops with the administration of commercially available glutamine-free TPN. Van der Hulst and associates randomized surgical patients requiring parenteral feedings to either receive standard TPN or glutamine-enriched TPN for 10 to 14 days. Duodenal mucosal biopsies and gut permeability studies were performed at the start and completion of TPN. The investigators found no change in either villous height or gut permeability in the group receiving glutamine-enriched TPN, whereas the control group showed both loss of villous height and increased gut permeability. This study provides strong evidence in favor of a gut-protective effect of glutamine. Similarly, arginine, because of its immunomodulatory properties may be useful as a dietary supplement in cancer patients, but further work is necessary to more clearly define the potential role of these two amino acids in the nutritional care of the cancer patient.

TABLE 56.2-13. Results of a Randomized Trial of Glutamine-Enriched Total Parenteral Nutrition versus Standard Total Parenteral Nutrition after Bone Marrow Transplantation*
TECHNIQUES OF PROVIDING NUTRITIONAL SUPPORT

TRANS Nasal (Nasogastric and NasoDuodenal) FEEDING CATHERS

The use of transnasal feeding catheters for intragastric feeding or for duodenal intubation is a popular adjunct for providing nutritional support by the enteral route. The stomach is easily accessed by the passage of a soft flexible (8 Fr.) feeding tube. Intragastric feedings provide several advantages for the patient. The stomach has the capacity and reservoir for bolus feedings. Feeding into the stomach results in the stimulation of biliary-pancreatic axis, which is probably trophic for the small bowel. In addition, gastric secretions have a dilutional effect on the osmolarity of the feedings, reducing the risk of diarrhea. The major risk of intragastric feeding is the regurgitation of gastric contents resulting in aspiration into the tracheobronchial tree. This risk is highest in patients who have an altered mental sensorium or who are paralyzed.

The placement of the feeding tube through the pyriform into the fourth portion of the duodenum reduces the risk of regurgitation and aspiration of feeding formulas. To place a transnasal intraduodenal feeding catheter, the patient should be in the sitting position with the neck slightly flexed. This allows for the passage of a lubricated 8-Fr. polyurethane feeding catheter (with a stylette in place) through the patient's nose in a posterior and inferior direction, bringing the catheter to the level of the pharynx. The head is brought back to a neutral position and the patient is instructed to swallow while the feeding catheter is simultaneously passed down into the esophageal lumen. The advancement of the catheter is confirmed by the passage of a distance of about 45 to 50 cm. Once the catheter is confirmed to be in the stomach by injecting air while listening over the epigastrium, the patient is laid on the right side and the tube is advanced another 15 to 20 cm. This should position the tube into the duodenum and can be confirmed by listening over the right upper quadrant while advancing the tube. The stylette is removed and the position of the catheter is confirmed radiographically before the initiation of feedings. Tubes can be positioned fluoroscopically if necessary.

GASTROSTOMY TUBE FEEDINGS

A feeding gastrostomy should be considered in patients requiring long-term enteral nutrition and in patients with unresectable carcinomas of the head and neck or esophagus. In patients with an unresectable esophageal carcinoma who are not surgical candidates or in individuals who are unable to maintain caloric needs, a permanent gastrostomy should be considered. A temporary Stamm gastrostomy is a popular method for access to the gastric lumen that can be performed at the time of any major abdominal procedure. The surgical technique is relatively simple and straightforward. After placement, the gastrostomy tube is placed to gravity drainage for 3 days and then is elevated. If the patient tolerates catheter elevation, we advance enteral feedings as described previously.

Percutaneous endoscopic gastrostomy to provide access for gastric feedings can be performed without a laparotomy or general anesthesia. This technique involves the safe passage of an endoscope into the stomach. The stomach is then dilated by the insufflation of air via the endoscope. Transabdominal illumination with the endoscopic light source selects an area on the anterior abdominal wall, usually halfway between the costal margin and the umbilicus. Local anesthesia is injected over the site followed by the insertion of an Angiocath percutaneously into the stomach. A wire is passed through the Angiocath, grabbed by a snare that has been passed through the endoscope, and pulled back with the endoscope out of the mouth. A standard percutaneous gastrostomy tube with a wire loop is attached to the guidewire and pulled back down the esophagus and out through the abdominal wall. The endoscope is passed back with the tube and the catheter is pulled under direct visualization until taut and then sutured to the abdominal wall. Inability to pass the endoscope safely or to identify the transabdominal illumination of the endoscope tip within the dilated stomach are contraindications to the procedure. Ascites, coagulopathies, and intraabdominal infections are relative contraindications as well.

FEEDING CATHER J EJUNOSTOMY PLACEMENT AND WITZEL JEJUNOSTOMY

A feeding catheter jejunostomy should be placed following any major upper abdominal oncologic procedure if prolonged enteral nutrition support is anticipated, especially after gastric or pancreatic cancer surgery. The simplest method is a needle catheter jejunostomy, which can be performed fairly quickly at the end of the definitive operation. The entire length of a 14-gauge needle is used to create a subserosal tunnel approximately 30 to 40 cm distal to the ligament of Treitz and then the needle tip is introduced into the jejunal lumen. A 16-gauge feeding catheter is inserted through the needle and advanced 30 to 40 cm distally into the bowel lumen and the needle is withdrawn. The catheter is secured to the jejunal wall with sutures and then the loop of jejunum is anchored to the parietal peritoneum. The catheter is then secured to the skin with nylon sutures. The needle catheter jejunostomy is generally removed 2 to 4 weeks postoperatively when no longer needed.

A more permanent form of feeding jejunostomy employs the use of a 14-Fr. red rubber catheter for feeding. The placement technique is simple. Witzel’s technique and takes only 10 to 15 minutes. Jejunal feeding catheters can be used immediately for feeding purposes following the operation. Catheter care is essential to maintain patency, and the nursing staff need to flush the catheter with saline every 8 hours to ensure adequate patency. The catheter can be removed at the patient’s bedside at the desired time by simple traction and the resulting fistula should close quickly.

PERIPHERAL INTRA VENOUS FEEDINGS

Peripheral veins may be used for infusion of glucose, amino acid solutions, and fat emulsions. However, these solutions must be nearly isotonic to avoid peripheral vein sclerosis. Ten percent glucose solutions may be used to increase the efficacy of amino acid use. Fat emulsions can be administered simultaneously with glucose and amino acid solutions, because they provide an efficient fuel source and isotonic. The major disadvantage of these peripherally administered mixtures is limited caloric delivery to meet catabolic demands within tolerated fluid volumes. Patients with renal and cardiac diseases may not tolerate the additional fluid load.

Indications for peripheral vein feeding include the following: (1) as a supplement when enteral feedings can only be partially tolerated because of gastrointestinal dysfunction; (2) as a method of nutritional support when the gastrointestinal tract must be kept relatively empty for short periods during diagnostic workup; and (3) as preliminary feedings before subclavian catheter insertion in patients requiring TPN.

CENTRAL VENOUS TOTAL PARENTERAL NUTRITION

The preferred method of access to the superior vena cava is by percutaneous cannulation of the subclavian vein. Alternate sites include the internal and external jugular vein, but with the catheter exiting in the neck region this makes it more difficult to secure and maintain a sterile dressing site. Thus, long-term indwelling cathers should not be placed in this location because of an increased risk of catheter infections.

An individual who is experienced in the technique should perform the placement of a central venous catheter. To reduce the risk of hemostatic complications, patients with a platelet count below 50,000 should receive fresh platelets before catheter insertion. The procedure is performed using aseptic technique; the surgeon should wear a hat, mask, gown, and gloves. The patient is placed in Trendelenburg’s position with both arms at the sides and the head turned away from the site of insertion. The neck is shaved, prepped, and draped in a sterile fashion. Local anesthesia is infiltrated near the insertion site and the underlying tissues along the inferior border of the clavicle. A standard subclavicular insertion tray is used for catheter insertion via the Seldinger technique. The tip of the needle is inserted into the skin and subcutaneous tissues at the midpoint of the clavicle aiming for the suprasternal notch. The needle is directed parallel to the patient’s bed, inserting beneath the clavicle and advancing a few millimeters to ensure the bevel is within the lumen of the vessel. The patient is instructed to perform a gentle Valsalva maneuver to prevent an air embolism, the syringe is disconnected from the needle and the guidewire is passed through the needle lumen, and the needle is then withdrawn over the guidewire. The passage of the wire through the needle should be met with minimal resistance and the needle should be removed only after 15 cm of the wire has been passed into the vessel. A small incision is made at the guidewire exit site and a dilator is passed over the wire. The dilator is then removed over the wire and is replaced by the catheter that is fully advanced. The wire is withdrawn and the catheter is flushed with sterile saline. The catheter is then sutured into position, the insertion site cleaned, and a sterile dressing placed. A portable chest radiograph is taken to confirm placement of the catheter. Chest films are inspected for location of the catheter tip and to search for evidence of pneumothorax and hemothorax.
Complications from long-term central venous catheterization in the cancer patient population include venous thrombosis and catheter-related infections. Thrombosis of the central vessels is a complication that may be overlooked. The clinical suspicion of subclavian vein thrombosis is only approximately 3%, whereas studies that use phlebography or radiolucent venography indicate that the incidence is as high as 35%. Febrile episodes are not uncommon in the cancer patient population, particularly in the immunosuppressed individual. If a fever persists, the patient should be re-evaluated promptly. The tip of the catheter is sent to the laboratory for culture and compared with the blood cultures drawn from the patient. Appropriate antibiotics are administered and a new catheter is inserted when the patient's repeat blood cultures result as negative.

NUTRITION SUPPORT FOR CANCER PATIENTS AND HEALTH CARE REFORM

The effect of corporate medicine on nutrition support has been addressed. With the introduction of health care reform, nutrition support teams and the services they provide are now considered a cost center rather than a revenue center and both the role and existence of the traditional team is being threatened. Formal nutrition support has, in fact, been in use for the past several decades in the cancer hospital setting. While the indications for TPN in cancer patients, the role of nutrition support in cancer patients and the cost-effective care, the challenge to nutrition support professionals is to coordinate efficient and early intervention and to document its efficacy and outcome. In the absence of any documentation of the cost-benefit ratio, the financial support of the team or the financial support of the patient is then determined. Therefore, it becomes imperative for the team to justify its importance to the hospital and convince the administration that a formal nutrition support team provides quality care and polices the administration of nutritional support. To do this, nutrition support units must (1) identify specific patient populations who will benefit from nutrition support, (2) establish clinical pathways (guidelines), and (3) develop and implement measurements of efficacy (outcomes). In capitated models of health care, it is in the best interest of all caregivers to provide cost-effective care.

In the past, the costs required to pay the members of the nutrition support team in cancer patients has been more than offset by the reimbursements for the services provided, particularly for the delivery of TPN. The danger of this approach is the withholding of nutritional and metabolic support from certain patients may result in serious consequences. Aggressive early feeding may be the best approach if it reduces complications in the long run. Methods of ensuring that nutrition support is cost effective have been suggested. A detailed account of the costs and benefits of nutritional support in cancer patients is given by Souba et al. (1988). The effect of corporate medicine on nutrition support has been addressed. With the introduction of health care reform, nutrition support teams and the services they provide are now considered a cost center rather than a revenue center and both the role and existence of the traditional team is being threatened. Formal nutrition support has, in fact, been in use for the past several decades in the cancer hospital setting. In the presence of any documentation of the cost-benefit ratio, the financial support for the team or for the patient is then determined. Therefore, it becomes imperative for the team to justify its importance to the hospital and convince the administration that a formal nutrition support team provides quality care and polices the administration of nutritional support. To do this, nutrition support units must (1) identify specific patient populations who will benefit from nutrition support, (2) establish clinical pathways (guidelines), and (3) develop and implement measurements of efficacy (outcomes). In capitated models of health care, it is in the best interest of all caregivers to provide cost-effective care.

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SECTION 56.3
Sexual Problems

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Human Sexual Response Cycle
Sexual Dysfunctions and Problems
Sexual Problems and Their Prevalence Among the General Population
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INTRODUCTION

To understand the impact of a cancer diagnosis and its treatment on sexual health and functioning, it is useful to have some knowledge about what is “normal,” as well as the range of sexual problems that occur in the general population not affected by cancer. This background is essential for understanding the unique contribution that cancer and its treatments play in exacerbating what are often premorbid sexual difficulties. Table 56.3-1 describes a broad range of factors that influence sexual functioning before a cancer diagnosis (e.g., age, gender, anxiety, chronic disease), and these preexisting factors strongly influence sexual functioning after a cancer diagnosis. Other naturally occurring events that may coincide with cancer are age-related changes in sexual functioning, such as erectile dysfunction in men and menopause-related changes in women. Cancer treatments, however, cause unique side effects not usually experienced in other patient populations (e.g., body image changes, infertility, fatigue, and pain). Sexual problems can also be exacerbated by the uncertain prognosis associated with a cancer diagnosis. In this chapter, we provide some background about normal sexual health and functioning to provide a context for the changes associated with a cancer diagnosis. We then discuss general changes in sexuality associated with cancer, as well as treatment and site-specific changes.

TABLE 56.3-1. Factors Affecting Sexual Functioning before and after a Cancer Diagnosis

TABLE 56.3-2. Human Sexual Response Cycle

SEXUAL HEALTH AND PHYSIOLOGY

HUMAN SEXUAL RESPONSE CYCLE

The human sexual response cycle (HSRC), as detailed by Masters and Johnson, involves the physiologic changes that occur when individuals receive adequate...
sexual stimulation. The HSRC consists of four, somewhat arbitrary, phases—excitement, plateau, orgasm, and resolution. In Table 56.3-2 we have listed some of the key responses in each phase, with a focus on those that might be affected by cancer and its treatments. The disease and treatment can disrupt the response cycle entirely or can lead to changes in sensation and experience during the response cycle. The response cycle is similar for women and men, with parallel processes for homologous tissues.

Although Masters and Johnson’s research advanced our knowledge of the psychophysiology of human sexual response, the four-phase model of the HSRC has been criticized on both conceptual and methodologic grounds. In a triphasic model of human sexuality, Kaplan addressed two of the primary concerns—the characterization of the phases of sexual responding as sequential and interdependent and the inattentiveness to motivational aspects of sexuality. The triphasic model is characterized by separate desire, excitement, and orgasm phases. Kaplan proposed that these are discrete phases controlled by distinct neurophysiologic mechanisms. Thus, she suggests that different etiologic factors and treatment approaches should be considered, depending on the phase in which difficulties occur. However, the extent to which responses in each of these phases is mediated through different pathways has not been documented empirically. The fact that individuals often report dysfunction in more than one phase argues against assuming unrelated etiologies.

**SEXUAL DYSFUNCTIONS AND PROBLEMS**

The nomenclature for diagnosing sexual dysfunctions uses the triphasic model of sexuality—involving disturbances in desire, excitement, or orgasm—or by pain associated with sexual intercourse. For patients of the HSRC. Some individuals with no diagnosable dysfunction can be dissatisfied with factors such as the frequency or variety of sexual behavior, whereas some individuals with organically based dysfunctions can enjoy other forms of sexual and intimate contact. Also, as indicated in Table 56.3-1, cancer can have an indirect influence on sexuality through disruptions in partnership factors, body image, and overall psychological well-being.

**SEXUAL PROBLEMS AND THEIR PREVALENCE AMONG THE GENERAL POPULATION**

**PREVALENCE OF SEXUAL DYSFUNCTIONS AND PROBLEMS**

Sexual problems are common, even among community samples of happily married couples. In a large and extensive national survey of sexuality of 18 to 59 year olds in the United States, 43% of women and 31% of men reported dysfunction in one of the diagnostic categories during the previous year. Among men, premature ejaculation was the most common complaint (28.5%), followed by anxiety about performance (17.0%), lack of interest in sex (15.8%), and inability to keep an erection (10.4%). Women most frequently reported lack of interest in sex (33.4%), inability to reach orgasm (24.1%), not finding sex pleasurable (21.2%), difficulty becoming lubricated (18.8%), and pain during intercourse (14.4%). Individuals who experienced emotional or stress-related problems or who were victims of adult-child sexual contact were significantly more likely to report sexual dysfunction. Other predictors varied somewhat between men and women, with poor health being particularly salient for men and falling household income and low sexual activity being important for women. Despite these difficulties, most respondents indicated that sex was emotionally satisfying and was associated with very positive feelings.

Although specific prevalence rates vary somewhat in other studies, depending on study sample and methodology, the general conclusions are similar. Sexual dysfunction is a common experience, with most individuals experiencing difficulty at some points in their lives. However, sexual dysfunction need not result in dissatisfaction with sexuality or loss of intimacy. Sexuality after cancer should be viewed within this larger context.

**SEXUALITY AND AGING**

Normal aging is associated with decreases in both physiologic functioning and behavioral aspects of sexuality. With regard to the phases of the HSRC, response slows and decreases in intensity with age for both men and women. For example, vasocongestion during arousal occurs more slowly, extending the time required for penile rigidity. More intense and direct tactile stimulation typically is required for arousal and orgasm than is needed in younger men and women. As men age, erections are less rigid, ejaculation is less forceful, and the refractory period lasts longer (often for many hours). In addition to the anatomic changes associated with menopause, women experience decreased lubrication and, in some cases, reduced intensity of orgasm. Chronic medical conditions and general ill-health can exacerbate the natural slowing of sexual response.

The prevalence of some diagnosable sexual disorders varies with age, although little research has been done on very old populations to provide specific information. Sexual desire and the frequency of sexual thoughts appear to decline with age, particularly for men, although sexual interest does remain present. The fact that individuals often report dysfunction in more than one phase argues against assuming unrelated etiologies.

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**MENOPAUSE AND SEXUAL FUNCTIONING**

Menopause is clinically diagnosed when a previously menstruating woman with an intact uterus has amenorrhea for at least 12 months. The average age of menopause in North American women is 51 years. Secondary forms of amenorrhea may be related to endocrine disorders or conditions such as anorexia nervosa; however, cancer treatment–induced secondary amenorrhea is the most relevant for our purposes. Hysterectomy can complicate the evaluation of woman’s...
menopausal status, because menstrual bleeding can no longer be used to classify her status. If a woman’s ovaries are removed as a result of surgery, she experiences a surgically induced menopause.

The menopausal transition is characterized by a decreased responsiveness of the ovaries to luteinizing hormone and follicle-stimulating hormone. Gradually, over time, the cellular activity in the follicles declines and there is no further response to the pituitary gonadotropins luteinizing hormone and follicle-stimulating hormone. It is with these changes that the clinical symptoms of estrogen deficiency begin to occur. Lowered levels of estradiol affect various target tissues, including the vagina, skin, bone, vascular endothelium, and smooth muscle, as well as the hypothalamic temperature-regulating centers. The ovaries are the primary source of androgens in women, even into postmenopause, and decreased production of ovarian androgens may account for changes in libido during this time. Menstrual bleeding may no longer be used to classify her status. If a woman’s ovaries are removed as a result of surgery, she experiences a surgically induced menopause.

The impact of menopause on sexual health is controversial, because many women remain sexually active into old age. Several population-based studies of perimenopausal and menopausal women have documented that most women who have partners are sexually active; however, changes can occur in sexual functioning (desire, arousal, orgasm) that are age related and to which menopause may contribute. The relation between menopause, sex steroids, and sexual motivation (“libido”) remain controversial. Research suggests that, in postmenopausal women, a variety of factors are potential moderators of the components of sexual functioning (e.g., psychological distress, quality of the partner relationship, physical activity, body mass index). Without sufficient levels of endogenous estrogen, the vaginal epithelium may become atrophic, leading to clinical symptoms of vaginal dryness and dyspareunia. With chronic or untreated symptoms of vaginal dryness, postmenopausal women may choose to avoid sexual intercourse completely. However, this may not preclude other forms of sexual activity. In a volunteer sample of healthy postmenopausal women who were not on hormone replacement therapy, vaginal dryness was reported by 37% of women aged 45 to 64 years. Hormone replacement therapy is effective in managing menopausal symptoms, such as hot flashes and vaginal dryness, but does not appear to improve sexual functioning.

Premature menopause and vaginal atrophy that cannot be attributed to estrogen after cancer can contribute to dyspareunia, thus affecting both desire and arousal in women with cancer (see Chemotherapy, later in this chapter). If one adds to this the variety of physical, psychosocial, and treatment-related factors associated with cancer treatment, a menopausal woman may certainly experience sexual dysfunction. Nevertheless, the menopause per se may not be the culprit.

ERECTILE DYSFUNCTION IN HEALTHY AGING MEN

Erectile function may be impaired by a number of conditions, both physical and psychological, and it declines with advancing age. As healthy men age, androgen levels begin to decline. Although these changes do not occur as precipitously as in menopause, a steady, age-related diminution is noted in most men. This can result in a number of changes that in turn tend to decrease erectile function and may be maintained over time. In this pattern exists, and it is not uncommon for men to remain libidinous and potent well into advanced years. Peripidal corticulatory problems and degenerative neuromuscular conditions also become more common, both increasing the incidence of vasculogenic and neurogenic erectile dysfunction (see Table 56.3-1).

IMPACT OF CANCER AND ITS TREATMENT ON SEXUAL HEALTH

PSYCHOLOGICAL DISTRESS

Symptoms of anxiety or depression are frequent, and often appropriate, among cancer patients. Psychological distress affects sexual functioning in healthy individuals, and this can be an important problem for patients with cancer. The literature suggests that patients with higher levels of psychological distress experience more sexual dysfunction. For example, in a study of 227 newly diagnosed breast cancer patients, Schag et al. found that patients who were classified by a social worker at 1 month after surgery as being “at-risk” for psychosocial distress were found to have more sexual difficulties than a comparison “low-risk” group, both at 1 month after surgery and 1 year later. Sexual problems that were increased included not being interested in having sex, difficulty in being sexually aroused, and difficulty reaching orgasm. In a comprehensive follow-up study of advanced Hodgkin’s disease and acute leukemia survivors, Kornblith et al. found higher levels of distress in the Hodgkin’s disease survivors, which was associated with significantly poorer sexual functioning than in the acute leukemia survivors. In a study of patients with early-stage cervical cancer, psychological as well as physical problems were highly correlated with sexual outcome. In a study of long-term survivors of acute leukemia, no difference was found in psychosexual outcomes for patients treated with bone marrow transplantation compared to conventional therapy; however, those survivors who reported decreased sexual frequency and satisfaction and poorer body image were more likely to demonstrate greater psychological distress and decreased energy. Thus, psychological distress, often manifested as increased symptoms of anxiety or depression, is an important variable that influences sexual outcomes, both acutely and chronically, in cancer patients.

BODY IMAGE CHANGES

One prominent cause of distress among cancer patients is change in body image. The changes associated with cancer and its treatment are often dramatic, ranging from surgical defects and deformities (e.g., limb amputation, loss of a breast, radical neck dissection) to total body alopecia from chemotherapy (e.g., loss of scalp hair), or even complete body hair loss, pubic and axillary hair (this is secondary to disease or treatment, weight gain from corticosteroids). All of these changes can influence an individual’s body image and self-esteem. For women with breast cancer, the major advantage of breast-conserving surgery is the preservation of body image. Patients with head and neck cancer often report changes in physical self-image and body image as a result of disfiguring surgery, with consequent effects on sexual functioning. Patients with colorectal cancer and stoma experience more body image problems than nonstoma patients and have poorer sexual functioning. Thus, contemporary treatments that set organ preservation as a goal or provide immediate reconstructive surgery may well spare cancer patients the added burden of poorer body image. In one study, more favorable body image was a significant predictor of sexual interest in breast cancer survivors. Nevertheless, the complexity of contemporary combined modality treatment (surgery, radiation therapy, and chemotherapy) aimed at organ preservation may also contribute to poorer body image through weight loss and hair loss, which may have a temporary or long-term adverse effect on body image. In a study of a long-term survivors of Hodgkin’s disease (median time since treatment, 9 years), Fobair et al. found that 26% of these survivors felt that their physical attractiveness had decreased, which was attributed to the diagnosis or treatment of the disease. More research is needed to determine the mechanisms through which body image disruption affects sexual functioning.

For some patients, weight gain is an important consequence of treatment that can interfere with body image. This effect has been particularly noted for women receiving adjuvant chemotherapy for breast cancer. Goodwin et al. followed an inception cohort of 535 women with newly diagnosed locoregional breast cancer and performed anthropometric measurements at baseline and 1 year later. Mean weight gain overall was 1.6 kg, with an average 2.5 kg in women receiving chemotherapy. In those receiving tamoxifen, 0.6 kg in those receiving no adjuvant treatment. In a multivariate analysis, onset of menopause and chemotherapy administration were each independent predictors of weight gain. Weight gain was not explained by increased caloric intake or decreased physical activity. Thus, in addition to the effects of chemotherapy on energy, nausea, vomiting, and alopecia, weight gain must be added to the list, potentially decreasing self-esteem and sexual attractiveness.

DETERIORATING PHYSICAL FUNCTION, FATIGUE, AND PAIN

Declining physical functioning and the symptoms of fatigue and pain negatively influence sexual functioning. In a cross-sectional evaluation of 779 patients with colorectal, lung, and prostate cancers at all phases of disease (i.e., no evidence of disease, localized, and metastatic), sexual functioning was poorest for patients with advanced metastatic disease, who concomitantly experienced more frequent and severe physical problems associated with the cancer. This finding was most significant for the patients with colorectal and lung cancer, whereas sexual problems were important for prostate cancer patients independent of stage and physical symptoms, likely due to the local effects of treatment on sexual functioning for all stages of the disease.

Fatigue has begun to emerge as an important symptomatic problem for cancer patients and survivors. Although this may be the result of clinical problems, such as anemia, which can be managed medically with transfusions or growth factors, chronic fatigue after cancer treatment may be multifactorial and represent late effects of chemotherapy and radiation, as well as be manifestations of both pain and depression. Fatigue has been most dramatically noted in patients treated for Hodgkin’s disease, in which the impact of fatigue on quality of life is multifaceted but includes sexual dysfunction as well. Treatment of the underlying causes of...
the fatigue, whether medically or psychologically, may have important benefits in terms of psychological functioning.

Other studies have begun to examine fatigue in breast cancer survivors. In an analysis reported by Bower et al. in almost 2000 breast cancer survivors, the strongest predictors of fatigue were pain and depression—both treatable problems. In that study sample, fatigue was significantly correlated with poorer sexual functioning ($r = -0.265, P = .0001$); when fatigue scores were used to classify the patients as either high or low energy, a significant difference was found in sexual functioning scores ($P = .0001$). Similarly, specific treatments (chemotherapy, radiation, tamoxifen) were not significantly associated with fatigue in the predictive model.

Similarly, uncontrolled pain can be an important contributor to sexual dysfunction in cancer patients and survivors. Uncontrolled pain is associated with psychological distress, poor appetite, and lack of sleep, all of which can decrease sexual interest. Surprisingly, little empiric research has been conducted in this area. However, one study demonstrated the association of pain with decreased sexual functioning after high dose chemotherapy and autologous bone marrow support. Another study that examined breast cancer patients with upper extremity lymphedema found that the presence of associated pain predicted psychological distress, but it did not independently predict sexual dysfunction.

PARTNER RELATIONSHIPS

The literature suggests that the presence of a partner plays an important role in the maintenance of an active sex life for both men and women. Problems in the marital relationship after cancer is most often reflect preexisting stresses and strains, such that marital dissolution as a result of cancer is probably less common than once thought. Often, cancer patients cite improvement in their love relationships rather than deterioration. In a study of prostate cancer survivors compared with aged matched health controls, marital function did not differ between treatment groups and controls.

The presence of a spouse or partner is invaluable for patients facing the possibility of sexual dysfunction from cancer or its treatments. Not only can spouses provide much needed emotional support, but they may also contribute to the clinical decision-making process. Physicians must be aware that the spouse often does not agree with the patient when assessing the relative value of sexual function versus survival. In fact, studies comparing husbands and wives suggest that the latter are much more willing to give up sexual function for a chance at longer survival. Ultimately, the right choice of treatment must emanate from the patients themselves, but involvement of spouses can facilitate this process.

In addressing the partner relationship, it is also important never to assume that the patient is heterosexual, especially when the patient is alone for tests, consultations, and follow-up visits. The astute clinician should probe in a nonjudgmental way about the patient’s partnership status and ensure that a same-gender partner is included, as appropriate, in medical decision making. Gay and lesbian couples enjoy long-term relationships that are emotionally equivalent to heterosexual marriage, yet given the degree of societal homophobia, they may fear being honest, even with their physicians. A few words of candid support may go a long way in allowing patients to feel better about involving their same-gender partner.

The literature does suggest that survivors of childhood and adolescent cancers are at increased risk for marital difficulties. In a large study of long-term survivors of childhood cancers compared with sibling controls, Byrne and colleagues noted that both male and female survivors were less likely to marry than sibling controls and that the marriage deficit was particularly pronounced for survivors of brain and central nervous system tumors. In addition, the average length of first marriages was shorter for survivors than controls. Men who had survived central nervous system tumors before the age of 10 years and male survivors of retinoblastoma had substantially higher divorce rates than controls (relative risk, 2.9 and 1.9, respectively). As noted by this study’s authors, the treatment intensity for the patients studied in this cohort was much less intense than contemporary therapies, thus making altered marriage practices an important concern among adult survivors of pediatric brain tumors. These findings have largely been confirmed in a preliminary report from a successor cohort study, the Childhood Cancer Survivor Study, in which rates of marriage have been compared to U.S. population census data and are found to be reduced. Survivors were less likely to have married, particularly women and whites, but once married, they were less likely to divorce or separate. As in the study of Byrne et al., pediatric brain tumor survivors, particularly men, were less likely to have married and more likely to divorce or separate compared to those with other cancer diagnoses and the general population. Other single-institution, detailed investigations of childhood survivors support these findings, with the observation that many former patients indicate their diagnosis and treatment for childhood cancer influenced their own personal decision to have children and that this decision may play a role in the marital relationship. These findings may have important long-term implications for the sexual functioning of these long-term survivors, warranting more detailed inquiry.

SPECIFIC TREATMENTS

Surgery in General and Pelvic Surgery

Surgical treatment usually involves hospitalization, general or local anesthetic, and exploration of body cavities (thoracic, abdominal, pelvic), with adjacent organ dysfunction and the need to recover from the treatment insult. Postoperative pain and fatigue are important factors that limit recovery of sexual functioning for several weeks after surgery. Surgical treatments with the most significant impact on sexual functioning are those involving the pelvis, such as radical prostatectomy, radical cystectomy, abdominal-perineal resection for rectal cancer, and radical hysterectomy for gynecologic cancers. When radiation is added to surgical treatments, additional nerve and tissue injury may occur, with fibrosis and occasional pelvic pain syndromes. Changes in body image may occur as a result of surgery, especially when it is disfiguring and visible to others, but even hidden body scars may present a difficulty for some patients.

In men, pelvic surgery for prostate, bladder, or rectal cancer can easily damage the parasympathetic sacral fibers that are responsible for penile erection. These nerves course posterolateral to the prostate and anterolateral to the rectum and are intimately associated with both structures, especially at the apex of the prostate just anterior to the rectal wall. Although techniques have been developed for identification and preservation of these neurovascular bundles during radical prostatectomy, such preservation is much more difficult during abdominal-perineal resection of the rectum. These nerves do not need to be cut to disrupt their function. The mere trauma of dissection to separate them from the prostate or rectum may also lead to their permanent failure. The effect is immediate, and neuronal recovery is slow, often lasting months or years. Pelvic surgery for bladder or rectal cancer may also result in female sexual dysfunction, largely due to scarring, shortening, and stenosis of the vagina. Despite initial dyspareunia, many women who are treated for bladder cancer with surgery and radiation ultimately do enjoy a return of sexual function.

Retropertoneal lymphadenectomy in men with testis cancer does not interfere with erections, but it may cause retrograde ejaculation. The primary landing site for lymphatic spread from the testes is located in the interaortocaval region for right-sided tumors and in the paraaortic region for left-sided tumors. From here, metastatic deposits can extend cephalad or caudal along the great vessels. Intertwined with these lymphatic channels are the lumbar sympathetic fibers that are responsible for normal antegrade ejaculation. If these are damaged during surgery, patients may experience a failure of both seminal emission and bladder neck closure. This in turn results in retrograde ejaculation. Although the patient is able to enjoy the pleasure of orgasm, it is dry and fluidless. Techniques to preserve these nerve fibers by using template dissections have been popularized and are largely successful at maintaining antegrade ejaculation in most men undergoing retropertoneal lymphadenectomy.

The effects of pelvic and genital surgery on sexual response in men and women vary depending on the organs involved and are summarized in Table 56.3-4 and Table 56.3-5. Schover and Fife provide an excellent overview of the components of the sexual response that are affected by these various surgical procedures. The amount of dysfunction depends on the extent of injury to the sacral plexus (especially for erectile functioning in men), and for women, vaginal lubrication may be strongly influenced by oophorectomy and the loss of estrogen, as well as the prohibition against estrogen replacement therapy. Dry orgasms occur in men after radical prostatectomy and radical cystectomy. Although surgical removal of the prostate and seminal vesicles. For women, vaginal shortening and anatomic changes that result from several of the surgical procedures leads to dyspareunia and the need to use lubricants and vaginal dilators.
The goals of contemporary multimodal therapies for cancer have focused on limiting the extent of surgery, with the addition of chemotherapy and radiation to control local and distant disease. Excellent examples of this trend are primary radiation therapy for prostate cancer, bladder-conserving surgery with radiation and chemotherapy, and sphincter preservation treatment of anal and rectal cancer. These approaches still have associated sexual dysfunctions, but the time course and specific problems may differ from surgery alone. In addition, patients may have to deal with the morbidity of the additional therapies. Other procedures, such as bladder replacement with a continent reservoir, may avoid the embarrassment of external stomas and appliances, but this may not necessarily have a positive impact on sexual functioning.

Chemotherapy

The effects of systemic chemotherapy on sexual functioning can be conceptualized as acute and chronic, with somewhat different risks for men and women. Acutely, and dependent on the type of chemotherapeutic agent, many patients experience nausea, vomiting, fatigue, hair loss, and mucositis. All of these factors contribute to a decrease in well-being and less interest in sexual activity. Women may experience vaginal and perineal mucositis from some agents, with some data suggesting decreased vaginal lubrication as a late effect of chemotherapy. Loss of body hair decreases sexual attractiveness for most individuals, and extra effort may be required to maintain this aspect of sexuality. All of these effects are intensified in those receiving high-dose chemotherapy regimens. Protracted fatigue may be a significant contributor to sexual dysfunction in bone marrow transplantation survivors.

For women, one of the most dramatic consequences of chemotherapy treatment is the cessation of menses and the onset of menopause, with the consequent loss of fertility. This effect also has been reviewed for breast cancer treatments. In a prospective study of a cohort of 183 early-stage breast cancer patients receiving no adjuvant therapy, either chemotherapy or tamoxifen adjuvant therapy, or both chemotherapy and tamoxifen, age and systemic chemotherapy (in this case cyclophosphamide, methotrexate, or epirubicin, plus 5-fluorouracil) were the strongest predictors of menopause in women with locoregional disease, with tamoxifen making a small contribution. As Figure 56.3-1 demonstrates, the probability of menopause with chemotherapy begins to rise at approximately 35 years of age, with more than 40% of women at age 40 predicted to become amenorrheic. The closer a woman was to the age of natural menopause (age 51), the greater her risk of amenorrhea. Because this study only followed women for 1 year after treatment, however, some small proportion of women may have resumed menses after that time. Because some evidence suggests that amenorrhea may be beneficial in preventing breast cancer recurrence, it may be an acceptable consequence of treatment for some women. Nevertheless, the effects of menopause on sexual functioning, especially vaginal dryness, may contribute to sexual dysfunction in breast cancer survivors.

Preservation of fertility is very important for younger patients treated for leukemia, testicular cancer, lymphoma, and Hodgkin's disease. Although current regimens for Hodgkin's disease that avoid alkylating agent therapy [e.g., Adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD)] may spare ovarian and testicular function in terms of fertility and premature menopause, their value in preservation of sexual functioning may be more limited. In Kornblith et al.'s study examining the late effects of ABVD in comparison to Mustargen, Oncovin, procarbazine, and prednisone (MOPP) or MOPP/ABVD, no difference was found in sexual functioning by treatment arm. However, the small sample size of this study (93 disease-free survivors) across three treatment arm comparisons may have made it difficult to detect significant differences in outcomes. In another study comparing survivors of advanced-stage Hodgkin's disease and acute leukemia survivors treated on a variety of chemotherapy protocols, Kornblith et al. found that Hodgkin's disease survivors experienced significantly poorer sexual relationships than the leukemia survivors. Thus, the specific type of chemotherapy regimen and its duration can have differing effects on sexual functioning.

Radiation Therapy

The acute effects of radiation include fatigue, nausea, skin changes, and hair loss, with local changes limited to the area of the radiation port. As already discussed, fatigue can interfere with sexual functioning, and hair loss and skin changes can affect sexual functioning through changes in body image. Long-lasting effects on skin...
Primary pelvic irradiation for prostate or bladder cancer may be as damaging to the erectile nerves as surgery. Radiation also damages the small blood vessels that supply and drain the corpora cavernosa. The primary difference is the time course over which the effect is seen. Whereas surgical nerve injury reveals itself immediately, radiation injury to the nerves and vessels often does not manifest itself for many months. Because the mechanism of radiation tissue damage is to induce subclinical events, some of their vessels and erectile nerves may remain relatively intact, and they decline pari passu with time. Among specific cancer sites, breast cancer has been one of the most frequently studied regarding sexual functioning because of the surgical trauma to the breast and the severe disruption in body image associated with mastectomy. The important role of the breast in terms of femininity and sexual identity, and as an organ involved in sexual activity, has made sexual health after breast cancer an important issue. All of these concerns point to the potential impact of the type of surgical treatment on sexual functioning. However, as adjuvant treatment for breast cancer has expanded to earlier stages of disease, including noninvasive cancer, the impact of chemotherapy and hormonal therapy (e.g., tamoxifen, oophorectomy, gonadotropin-releasing hormone analogues) must also be considered. As already noted, each of these adjuvant therapies may induce premature menopause, lead to vaginal dryness, and may have other specific effects that can influence sexual health. These issues take on increasing importance in treatment decision making, because women with very early-stage breast cancer can expect survival that is equivalent to

Hormonal Treatments

Hormonal treatments used in the management of endocrine-sensitive cancers may have important effects on sexual functioning. Tamoxifen, an antiestrogen, increases the rate of vaginal discharge and vasomotor symptoms in a proportion of breast cancer patients and in those women taking this therapy for breast cancer prevention. Although rates of sexual activity did not appear to differ between the women taking tamoxifen and those taking a placebo in the now completed Breast Cancer Prevention Trial, subtle differences in sexual functioning for women taking tamoxifen were noted (see Breast Cancer, later in this chapter). In a small study that examined the effect of tamoxifen and sexual functioning in patients with breast cancer, Mortimer et al. found that the desire, arousal, and orgasmic problems were not increased in their patient sample, but that more than one-half of one patient complained of pain, burning, or discomfort with intercourse and that the majority of those with these symptoms routinely used a vaginal lubricant with intercourse. Vaginal cytology was examined in these women, and the presence of an estrogen effect was associated with negative reactions during sex (P = .02) and vaginal dryness or tightness (P = .046), but it was not associated with other aspects of sexual functioning.

Weight gain is an important side effect with megestrol acetate, which is often used in the treatment of metastatic breast and endometrial cancers. This weight gain may contribute to a poorer body image in these patients and potentially affect sexual functioning. Since the 1990s, interest has been renewed in ovarian ablation for women with breast cancer, either with surgical oophorectomy or with use of gonadotropin-releasing hormone analogues. As already mentioned, the precipitation of premature menopause in these women may cause substantial disruption in sexual functioning.

For men with advanced prostate cancer, the mainstay of therapy is androgen ablation, which can be accomplished by either surgical or medical castration. Historically, the medical approach involved an oral estrogen, such as diethylstilbestrol, which inhibits the release of luteinizing hormone from the anterior pituitary and, in turn, decreases testicular androgen production. More recently, castration is achieved with gonadotropin-releasing hormone blockers with or without the addition of antiandrogens to eliminate the effect of adrenal androgens. Other agents, such as aminoglutethimide or ketoconazole, may also be used for the same effect. Men who participate actively in the selection of their androgen ablation option tend to be happier with their decisions.

The primary sexual side effect of androgen ablation is loss of libido. Many men report the ability to have erections and ejaculations despite the absence of testosterone, although decline in libido is universal. As a result, men who are sexually active and asymptomatic from the cancer (e.g., those who have a rising prostate-specific antigen level without documented metastatic disease) often choose to delay hormone therapy. For men who are experiencing clinical progression of metastatic prostate cancer, sexual function may already have declined or disappeared as their constitutional symptoms have advanced. For these individuals, androgen ablation may not have a great impact on erectile function, which is already greatly reduced.

CONCERNS ABOUT FERTILITY

Preservation of fertility is an important aspect of treatment, especially for those individuals who have not had children. This issue pertains in particular to children and young adults with cancers who are treated with curative intent. As noted by Laufer, it is increasingly useful to know the reproductive health outcomes for specific types of cancer treatments and “to differentiate between sex steroid production and fertility or reproductive function.” In one of the largest studies of the effects of treatment on fertility in long-term survivors of childhood or adolescent cancer, Byrne and colleagues estimated the risk of infertility after treatment in a retrospective cohort study of survivors of cancer and controls. The cancer patients, who were diagnosed before the age of 20 years, were treated between 1945 and 1975 at five cancer centers in the United States. Cancer survivors who married were less likely than their sibling controls to have ever begun a pregnancy [relative fertility, 0.85; 95% confidence interval (CI), 0.78 to 0.92]. With regard to therapy, radiation directed below the diaphragm decreased fertility in both sexes by approximately 25%, and chemotherapy with alkylating agents, with or without subdiaphragmatic radiation, was associated with a fertility deficit of approximately 60% in men. Among women, no effect of alkylating agents alone was found in this young group of patients; however, a moderate fertility deficit was noted when alkylating agents were combined with subdiaphragmatic radiation (relative fertility, 0.81). Adjusted relative fertility varied widely by cancer site, with a rate of 0.45 (95% CI, 0.26 to 0.76) for male genital cancer and 1.47 (95% CI, 0.81 to 2.65) for Wilms’ tumor. For many of the cancer sites, the 95% confidence intervals overlapped by 1.0.

More detailed studies of gonadal function tend to confirm this general observation, with evidence of preserved Leydig cell function in young boys receiving ABVD or multiagent chemotherapy for Hodgkin’s disease. In another study, preservation of testicular androgen production was noted in two-thirds of men treated for Hodgkin’s disease. In these studies, preservation of Leydig cell function has been associated with the lack of a history of testicular pain or injury and with normal testicular size. As a result, most studies report that Leydig cell function is preserved in the majority of men who have undergone chemotherapy for Hodgkin’s disease.

For young adults with cancer, strategies to preserve fertility are often used and are highly dependent on the type of cancer and available treatments. ABVD has largely replaced MOPP chemotherapy for Hodgkin’s disease because of a more limited risk of infertility. In general, however, diseases that require treatment with alkylating agents are likely to put both men and women at risk for infertility. The risk for women begins to rise after 30 years of age, and for men the risk increases at any age. Cryopreservation of sperm is a strategy used to preserve fertility in men. Newer approaches to ovarian tissue preservation and subsequent reintplantation are on the horizon for women.

A past history of cancer, uncertainty related to reproductive potential, and changes in sense of self-esteem and attractiveness may impair dating and sexual function in young adults with a history of cancer. Often, young adults who were treated for cancer as a child may have limited awareness of their posttreatment path, and they may be confronting this aspect of their health for the first time as they marry and attempt to start a family. Importantly, these individuals can be reassured that their offspring are unlikely to experience adverse consequences as a result of past parental treatments for cancer.

SEXUAL PROBLEMS ASSOCIATED WITH SPECIFIC CANCERS

BREAST CANCER

Among specific cancer sites, breast cancer has been one of the most frequently studied regarding sexual dysfunction because of the surgical trauma to the breast and the body image associated with mastectomy. The important role of the breast in terms of femininity and sexual identity, and as an organ involved in sexual activity, has made sexual health after breast cancer an important issue. All of these concerns point to the potential impact of the type of surgical treatment on sexual functioning. However, as adjuvant treatment for breast cancer has expanded to earlier stages of disease, including noninvasive cancer, the impact of chemotherapy and hormonal therapy (e.g., tamoxifen, oophorectomy, gonadotropin-releasing hormone analogues) must also be considered. As already noted, each of these adjuvant therapies may induce premature menopause, lead to vaginal dryness, and may have other specific effects that can influence sexual health. These issues take on increasing importance in treatment decision making, because women with very early-stage breast cancer can expect survival that is equivalent to
women without a cancer diagnosis.

One of the most investigated questions in breast cancer patients has been the impact of type of surgery on sexual health and quality of life. Several reviews of this topic address the potential differences in outcomes for women treated with modified radical mastectomy compared to breast-conserving surgery with radiation. In only a few studies were women randomly assigned to the type of surgical treatment, most have been observational cohort studies in which patient choice or preference for treatment likely occurred. Thus, some bias could be influencing the results. Nevertheless, the consistency of findings across so many studies and countries suggests that the findings are real. There is consensus that breast-conserving surgery offers a better sense of body image to women after breast cancer but only limited differences in other dimensions of quality of life (physical, emotional, or social functioning). In studies that have specifically addressed sexual functioning, little difference was found between the two types of surgery, although in the one randomized treatment trial, some evidence suggested better sexual functioning in women with conservation surgery.

In a study comparing women with breast conservation treatment to those receiving mastectomy with reconstruction, Schover et al. found that the two groups did not differ in body image, satisfaction with relationships, or sexual life. However, the authors did find that women with breast reconstruction experienced less caressing of the breast by their partner than women with partial mastectomy. In a study of sexual health and functioning in breast cancer survivors, body image influenced sexual interest, but the type of surgery did not predict any aspect of sexual health after breast cancer. Thus, although total loss of the breast may negatively influence a woman's body image, it does not necessarily impact her sexual health and functioning. As has been shown in healthy women without breast cancer and in breast cancer survivors, other factors may play a more important role in influencing sexual health in middle-age women (e.g., presence of a partner, vaginal dryness, emotional well-being, quality of the partnered relationship).

The etiology of sexual dysfunction in breast cancer survivors has not been well studied. As with other patients, multiple predisposing factors are involved, including preexisting sexual problems, negative sexual self-schemas, and normal age-related changes in sexual functioning. In addition, induction of premature menopause by chemotherapy can result in an estrogen deficiency state that increases the likelihood of hot flashes and poor vaginal lubrication that may contribute to sexual dysfunction. These symptoms are also a potential problem for older patients for whom hormone replacement therapy is discontinued at the time of a breast cancer diagnosis. Furthermore, these symptoms may be exacerbated by tamoxifen adjuvant therapy. The results from the newly completed Breast Cancer Prevention Trial suggest that, overall, tamoxifen has minimal effects on sexual functioning in healthy high-risk women. Comparing women taking tamoxifen to those taking placebos, over the course of 5 years of followup, no difference was found in the sexual activity of women who were sexually active, although both groups showed a subtle decline in sexual activity over time. There was a significant increase in vaginal discharge, genital itching, and pain with intercourse in women taking tamoxifen, as well as very subtle changes in some aspects of sexual functioning (sexual interest, sexual arousal, orgasm).

Multiple studies suggest an important role for chemotherapy in increasing sexual dysfunction in women with breast cancer. These findings are similar to those obtained in smaller samples of breast cancer survivors.

An increasing body of literature has examined sexual functioning in long-term survivors of breast cancer, with comparative information on women without a cancer diagnosis. In a cross-sectional study of more than 800 breast cancer survivors between 1 and 5 years after diagnosis, Ganz et al. found that approximately 60% of the study sample had been sexually active with a partner in the past 6 months, with the most common reason for inactivity being lack of a partner, lack of interest, her partner’s lack of interest, or the partner’s physical health problems. Sexual functioning data from two standardized instruments showed a decline in sexual functioning with age, especially in the areas of arousal and orgasm. Overall, the responses of the breast cancer survivors were comparable to an age- and menopause-matched sample of healthy women who participated in the Postmenopausal Estrogen Progestins Intervention Trial and were not on hormone replacement therapy. Overall, the breast cancer survivors reported fairly high levels of satisfaction with their sexual relationships. Nevertheless, in a more detailed analysis, this study’s authors found that one-third of women reported that breast cancer had had a negative impact on their sex life, and most reported negative changes in at least some areas (e.g., frequency of sexual activity, awareness of decreased lubrication in vagina with sexual activity, pain in genital area during intercourse, discomfort when touching breast cancer surgery area). Women who were most likely to report a negative impact were significantly more likely to report relationship difficulties, to have experienced changes in hormonal levels because of breast cancer (premature menopause or discontinuation of hormone replacement), and to be bothered by vaginal dryness. These findings are similar to those obtained in smaller samples of breast cancer survivors.

PROSTATE CANCER

The effect of erectile dysfunction on sexual functioning after treatment for prostate cancer has been studied extensively with a variety of experimental designs. All studies have shown that men undergoing radical prostaticctomy or pelvic irradiation have more sexual impairment than age-matched controls. Despite consistent reporting that men with nerve-sparing surgery have better sexual functioning than men who underwent non–nerve-sparing radical prostaticctomy, rates of sexual dysfunction in centers of excellence, rates of sexual dysfunction in randomized, national, population-based samples reveal that erectile dysfunction remains common after surgery or radiation for early-stage prostate cancer.

Talcott examined a group of men who underwent nerve-sparing radical prostaticctomy and compared them with men who underwent non–nerve-sparing radical prostaticctomy. Talcott found that patients who underwent nerve-sparing surgery had low levels of sexual function that were not significantly different from men who underwent non–nerve-sparing procedures. However, when the nerve-sparing population was broken down into one or both nerves spared, the bilateral nerve-sparing group reported significantly better potency at 1 year when compared to those who underwent non–nerve-sparing surgery. In a longitudinal follow-up study, Talcott et al. confirmed that nerve-sparing appears to improve postoperative sexual function to a lesser extent than previously reported. Talcott et al. also published the first prospective evaluation of patients treated with bilateral nerve sparing surgery who were assessed with validated quality-of-life instruments before and 3 months after treatment and at 3 and 12 months afterward. Initially, surgery patients had more impotence; however, over time, sexual function declined in the radiotherapy group and improved in the surgery group. Hence, with longer followup, treatment group differences in sexual function continued to narrow. Other studies also have shown that the incidence of impotence improves to at least 35% to 40% during the 2 to 3 years after radiation therapy for localized prostate cancer.

In a more recent longitudinal study of 438 men treated with surgery or radiation for early-stage prostate cancer, sexual function after treatment for prostate cancer appeared to improve over time. Although sexual function was significantly better in radiation than surgery patients immediately after treatment, both groups improved at comparable rates during the first year. In the second year, radiation patients began to show a modest but statistically significant decline in sexual function, whereas surgery patients continued to improve. Both nerve-sparing and postoperative erectile aids improved sexual function after prostatectomy. Given the decline in sexual function during the second year after radiation, these factors ultimately serve to equalize sexual function in the postsurgical and prostration settings. The most elderly men experienced a posttreatment sexual function course that differed greatly from that of the youngest men. This finding validates the clinical observation that older men are much less likely than younger men to regain sexual function after treatment. In particular, octogenarians who choose radiotherapy can expect significant declines in sexual function without apparent recovery.

TESTIS CANCER

Therapy for testicular cancer, including orchietomy, retroperitoneal lymphadenectomy, and radiation therapy, can cause a variety of physical and psychological sequelae. Rieker et al. and showed that these patients express distress over poor sexual performance and infertility, although not with decreased libido. Those with ejaculatory dysfunction note more strained intimate relationships and more psychological problems. Compared with healthy controls, testis cancer patients as a group do not reveal any more difficulty with relationships, employment, divorce, or overall mental outlook. Bloom et al. compared a sample of men treated for testis cancer with an age-matched sample treated for Hodgkin’s disease. Those with testicular cancer were significantly more likely to report decreased sexual enjoyment; however, they were also more likely to report their health as excellent when compared to the lymphoma group, leading the authors to conclude that the response to testicular cancer is more site-specific.

After radiation therapy for seminoma, most men marry within a few years; however, a significant proportion of patients continue to report ejaculatory dysfunction and anxiety about fertility. Gritz et al. compared the outlooks of patients and their wives several years after testicular cancer treatment. Compared to their wives, patients reported higher levels of anxiety over sexual performance. Long-term psychosocial adjustment was good in both groups, however.

BLADDER CANCER
The overwhelming majority of men who undergo cystectomy for bladder cancer either report difficulties before treatment or develop erectile dysfunction after treatment. Despite this observation, at least 50% of these patients continue to enjoy some form of sexual stimulation other than coitus after recuperation from surgery, and at least 75% maintain their libido. For women, changes may occur that are associated with decreased vaginal lubrication if women are estrogen deficient, and similar issues face both men and women if a stoma is created. Manson and colleagues administered a quality-of-life instrument to patients undergoing cystectomy and compared those reconstructed by continent cutaneous ileal diversion with those undergoing simple conduit diversion. Patients in both groups experienced equivalent declines in quality of life related to sexual problems, disturbed partner relationships, and emotional dysfunction. In a similar study, Boyd and colleagues demonstrated that, postoperatively, ileal conduit patients had the poorest self-image, as defined by a decrease in sexual desire and in all forms of physical contact (sexual and nonsexual). Women who later underwent conversion from ileal conduit diversion to continent cutaneous Kock pouches were the most physically and sexually active. Cerha et al. found that, after cystectomy, patients receiving an ileal conduit had worse scores than continent reservoir patients in sexual activity and general quality-of-life domains. Hart et al. reported more optimistic findings, showing that general quality of life was not differentially affected by the choice of urinary diversion method after cystectomy in either women or men.

**GYNECOLOGIC CANCERS**

Cancer involving the female genital organs immediately evokes concerns about sexual dysfunction related to cancer-related symptoms that predate the diagnosis, as well as treatments that may be required to extirpate the cancer. Cancers of the uterine corpus and cervix make up the majority of gynecologic cancers (roughly 70%), and these are the primary localized cancers treated with surgery or radiotherapeutic approaches, or both. Rarer cancers, such as vulvar cancer, may be treated with a variety of local or extensive surgical modalities, with some use of topical therapies. Nevertheless, the visible and disfiguring aspects of perineal surgery has its own serious emotional consequences. Other gynecologic cancers (ovarian cancer, trophoblastic disease, uterine sarcomas) are treated with combinations of chemotherapy, surgery, and, sometimes, radiotherapy. The more disseminated nature of these cancers and the severity of the disease lead to different patterns of sexual dysfunction. For all gynecologic cancers, the age, partnership status, menopausal status, and preexisting sexual functioning of a woman play an important role in her sexual rehabilitation after cancer treatment (see Table 56.3-1 and review by Andersen). Because of the involvement of the genital organs with gynecologic cancers, changes in sexual functioning may often take place before the diagnosis of cancer. In a comparison of healthy control subjects and women with early-stage cervical and uterine cancer, Andersen et al. found few differences in aspects of the sexual response cycle reported before the onset of signs or symptoms of the cancer. However, a substantial number of the gynecologic cancer patients reported a disruption in sexual responsiveness with the onset of symptoms, including changes in desire, excitement, orgasm, and resolution and a global deterioration in sexual functioning. These changes were most often associated with symptoms of fatigue, postcoital bleeding, and multiple other signs and symptoms.

Sexual functioning outcomes in patients with gynecologic cancers often have been reported in small case series. Andersen and colleagues prospectively studied 47 women with early-stage gynecologic cancers (cervix, n = 33; endometrium, n = 9; ovary, n = 5) and benign gynecologic disease before treatment, and then interviewed them again 8 and 12 months later. Women treated for disease, whether benign or malignant, reported similar declines in frequency of intercourse, decreased sexual excitement, and a less positive global evaluation of their sexual life. In addition, a three- to sixfold increase in the incidence of sexual dysfunction diagnoses was found in comparison to rates in healthy women. Pain with intercourse, prominent early in the recovery period in treated women, improved with time but remained more frequent in the cancer patients. Although both treated groups experienced increased sexual dysfunctions posttreatment, the cancer patients experienced a higher incidence of inhibited excitement. As discussed by Andersen et al., these particular changes can be a manifestation of increased anxiety associated with the cancer diagnosis.

Looking more specifically at the impact of cervical cancer and its treatment on sexual functioning, several other small, descriptive studies are relevant. Schover et al. examined sexual frequency, function, and behavior in 61 women with early-stage invasive carcinoma of the cervix. The impact of treatment (radical hysterectomy alone, radiotherapy with or without surgery) was examined in this study. Sexual satisfaction, capacity for orgasm, and frequency of masturbation remained stable over 12 months of observation posttreatment; however, frequency of sexual activity with a partner and the range of sexual practices decreased significantly over the course of the year of follow-up. When those women who received radiotherapy and those who had not, at the 12-month assessment, the women receiving radiotherapy had more dyspareunia (as well as an abnormal vaginal examination) and had more problems with sexual desire and arousal. Treatment modality had no effect on marital happiness or stability.

These findings suggest an additional complication from irradiation of the pelvis, which is vaginal stenosis or foreshortening. Several other studies have documented this problem and with level of sexual activity being lowest at the completion of radiotherapy. The finding of progressive dyspareunia and vaginal shortening suggests the need for active intervention in these women, with the need for early use of vaginal lubricants, resumption of sexual activity, or use of dilators to maintain vaginal length and elasticity. In one small study, women who did not follow advice regarding use of vaginal dilators and did not resume the same level of sexual intercourse before their illness were more likely to develop physical and sexual changes.

These small descriptive studies shed some light on the mechanisms of sexual dysfunction and the range of sexual problems in the first year after treatment for cervical cancer. However, the late effects of sexual treatment for cervical cancer are important, because this is a group of women who are likely to be cured of their disease without further treatment. For survivors, a report by Bergmark et al. provides important new information on vaginal changes and sexuality in a large sample of Swedish cervical cancer survivors (n = 256) and a concurrent control sample (n = 350). The cancer survivors had been treated, on average, approximately 5 years earlier and were a mean age of 51 years at the time they responded to the study questionnaire. Significant differences were found between the two groups in problems with vaginal lubrication (26% of the women with cancer vs. 11% of the controls), reporting of a short vagina (26% of the women with cancer vs. 3% of the controls). In spite of these significant changes associated with the treatment of cervical cancer, no differences were noted in sexual interest, desire, frequency of vaginal intercourse, or orgasm; however, there was much distress related to the frequency of vaginal intercourse and problems during vaginal intercourse (dyspareunia, vaginal bleeding) among the women with a history of cervical cancer.

Treatment with surgery alone was associated with decreased vaginal lubrication, vaginal shortness, and decreased vaginal elasticity. When surgery was combined with radiotherapy or when radiotherapy was given alone, no apparent differences in these vaginal outcomes were found when compared to surgery alone, except for some decreased sexual interest among those treated with radiotherapy alone. Interestingly, treatment for cervical cancer negatively influenced feelings of femininity and attractiveness among the cervical cancer survivors but did not seem to influence sexual satisfaction. Importantly, the authors observed no age above which sexual function was not important to women, and they suggest that efforts to prevent vaginal changes or relieve them after therapy should be considered in all women who are treated for cervical cancer.

Finally, it should be noted that the use of a healthy control group in this study was important, in that 41% of both patients and controls reported little or no interest in sex in the previous 6 months, with more than 50% reporting reduced sexual desire in the previous 5 years. Without such a control group, these findings might have been attributed to the history of cancer.

Although rare, other gynecologic cancers can have profound effects on sexual functioning. In spite of being the third most common gynecologic cancer, ovarian cancer patients have been less frequently studied. Although rare, other gynecologic cancers can have profound effects on sexual functioning. In spite of being the third most common gynecologic cancer, ovarian cancer patients have been less frequently studied. In Andersen et al.’s study, 152 women with in situ vulvar cancer were compared with a matched sample of gynecologically healthy women. They found a higher rate of inhibited sexual excitement and inhibited orgasm among the women with cancer, as well as an increasing rate of sexual inactivity over time, compared with the healthy women. As might be predicted, the wider the surgical excision, the greater the magnitude of sexual disruption. In a prospective study of ten couples, with the women being treated for vulvar cancer with radical vulvectomy, Weimar Schultz et al. found a postoperative decline in functioning with gradual recovery over 2 years. However, genital symptoms of sexual arousal and satisfaction were diminished in the cancer group and did not return to levels of those found in the control group. Importantly, general satisfaction with sexual interaction with the partner hardly changed over a 2-year period of observation.

**HODGKIN’S DISEASE**

As a group, patients with Hodgkin’s disease can anticipate long-term survival and cure. Therefore, the impact of disease and treatment on sexual functioning is an...
Sexual Functioning

In breast cancer patients and survivors, the use of hormone replacement therapy is much more controversial (see discussion of menopause earlier in this chapter). Thus, early intervention with hormonal therapy should be considered for patients receiving chemotherapy if it is not otherwise contraindicated. In a study comparing women posttransplantation and 52% at 3 years posttransplantation. Women who reported significantly more sexual dysfunction than men. The number of women with lubrication problems increased from 30% before transplantation to 49% at 1 year posttransplantation and 52% at 3 years posttransplantation. In addition, no differences between the two sites were found in terms of body image. As noted by these authors, without concurrent data on healthy controls, it is uncertain how much sexual dysfunction may be specifically related to the disease, its treatment, age, or other unmeasured variables.

COLORECTAL CANCER

Colorectal cancer is a disease of older individuals, with most cancers occurring in persons older than 60 years of age. There is a paucity of specific literature on sexual dysfunction in this population, but the information that is available focuses on the consequences of abdominoperineal resection and ostomies. In a review of sexual functioning in women after radical surgery for rectal cancer, prospective studies of small samples suggest a decline in sexual activity postoperatively, with declines in interest, lubrication, and orgasmic activity. In a study comparing abdominoperineal resection with colostomy and low anterior resection, sexual functioning was preserved at a higher rate with low anterior resection. Overall, the prognostic variables most influencing posttreatment sexual functioning include the woman’s age at surgery, the magnitude of the surgical intervention, handmade versus stapled anastomoses, and the number of autonomic nerves present in the surgical specimen.

For men, similar issues persist; however, erectile dysfunction is a more salient issue. In a study of 60 sexually active men surgically treated for colorectal cancer, Koulouras et al. found that sexual activity was decreased in 32% of patients. The distribution of difficulties among those affected were dry ejaculate (25%), erection not firm enough for penetration (45%), and complete absence of erection (25%). The decreases in sexual functioning occurred in all groups of patients, from high anterior resection to low anterior resection to abdominoperineal resection, but were most frequent in those with abdominoperineal resection.

In another report, Sprangers et al. reviewed the quality of life in colorectal cancer according to whether a sphincter-preserving procedure was performed. They found that stoma patients reported higher levels of psychological distress than nonstoma patients and that sexual functioning of male and female stoma patients is consistently more impaired than that of patients with intact sphincters. Both groups, however, are troubled by frequent and irregular bowel function that can increase psychological distress and affect sexual functioning.

STRATEGIES FOR ASSESSMENT AND INTERVENTION

ASSESSMENT

A comprehensive assessment of sexual difficulties requires an interdisciplinary and multifaceted approach that is often beyond the scope of the oncology team. Depending on the particular problem(s), it can be important to consider hormonal, physiologic, anatomic, psychological, cognitive, behavioral, relational, and cultural factors in a biopsychosocial model (see Table 56.3-1). To provide a differential diagnosis, it is also necessary to assess for psychopathology, medical conditions, substance abuse, and relationship difficulties as primary etiologic factors. Modes of assessment include open-ended conversations, structured diagnostic interviews, standardized self-report questionnaires, medical examination, and laboratory studies. Several volumes are available for readers who wish to learn about specific assessment procedures.

Although a comprehensive assessment is unrealistic within the constraints of an oncology practice, a preliminary review of sexual difficulties is essential to providing optimal care to the cancer patient. Patients regularly report that they would like to discuss sexual issues with their physicians but feel reluctant to do so. Therefore, it is up to the medical team to broach the issue and open lines of communication. Straightforward questions about each of the four categories of sexual dysfunction—desire, arousal, orgasm, and pain—and questions about sexual activity and satisfaction generally provide sufficient information to determine the need for further testing or referral. One member of the team could be identified as a primary resource for assessment and referral.

COUNSELING, INTERVENTION, AND REFERRAL

After a member of the oncology team has raised the issue of sexuality and made a preliminary assessment of reported problems, a decision must be made regarding the level and type of intervention that is needed. In some cases, the specific concerns that arise can be addressed directly by a member of the team who has developed expertise in sexuality and cancer. Providing patients and (when appropriate) their partners with information about sexual functioning, aging, and sexual problems can have an experience that can benefit from counseling. When a member of the team is not comfortable providing helpful information, or when a patient requests referral, it is important to be able to suggest specific resources. In most cases, the patient will be able to choose from several excellent resources for assessment and intervention.

MEDICAL INTERVENTIONS FOR WOMEN

One of the most important targets for intervention in women is vaginal dryness. This problem is common for women as they age, independent of cancer treatment, and is usually managed with some form of estrogen therapy. In women who can receive estrogen therapy after cancer, this treatment is the most effective therapeutic remedy, and it can be used topically or systemically. The role of hormone replacement in addressing sexual dysfunction after intensive chemotherapy should not be underestimated. In a study of the prevalence and predictors of sexual dysfunction in long-term survivors of bone marrow transplantation, Syija et al. found that women reported significantly more sexual dysfunction than men. The number of women with lubrication problems increased from 30% before transplantation to 49% at 1 year posttransplantation and 52% at 3 years posttransplantation. This finding was associated with a doubling in the rate of women reporting pain with intercourse, from 12% at 1 year posttransplantation to approximately 34% posttransplantation. In addition, this study’s authors found a significant difference in sexual satisfaction at 3 years for those who had received hormone replacement therapy by 1 year compared to the 15% of women who had not. Changing hormone replacement therapy after 1 year, either by starting therapy or electing to stop hormone therapy, did not show a measurable influence on reported sexual satisfaction at 3 years. This finding suggests that once sexual problems are established early after cancer treatment (vaginal dryness, dyspareunia), it may be more difficult to restore satisfactory sexual activity. Thus, early intervention with hormonal therapy should be considered for patients receiving chemotherapy if it is not otherwise contraindicated.

In breast cancer patients and survivors, the use of hormone replacement therapy is much more controversial (see discussion of menopause earlier in Menopause and Sexual Functioning). As a result, nonestrogen alternatives are often considered first in the management of vaginal dryness. One randomized controlled trial comparing estrogen to the vaginal moisturizer Replens has demonstrated improvement in vaginal cytology with this preparation in healthy women. The North Central Cancer Treatment Group has tested the efficacy of Replens for the management of vaginal dryness and dyspareunia in a placebo-controlled trial. They...
found this product to be effective in relieving symptoms; however, similar results were seen with the placebo (K-Y Jelly), which was apparently not an inert substance. A discussion of these nonestrogen alternatives is reviewed elsewhere.

In a study addressing menopausal symptoms in breast cancer survivors, Ganz et al. found that most of the women who wanted some form of treatment were highly symptomatic, with scores in the top 50% of the normative population. The most common symptoms reported were irritability, vaginal dryness, urinary incontinence, hot flashes, and sexual difficulties. The results showed that 75% of the women reported symptoms of vaginal dryness, and 62% reported symptoms of irritability. The most common symptom was irritability, with 87% of the women reporting symptoms of vaginal dryness and 75% reporting irritability.

The medicalization of sexuality: conceptual, normative, and professional issues.

The clinical management of cancer patients with erectile dysfunction should follow the same algorithms used in men presenting primarily for evaluation of impotence. Even when other interventions are prescribed, brief sexual counseling in the primary oncology setting can play a critical role in the care of the patient. The model currently used in the management of patients with erectile dysfunction involves a stepwise approach. First-line therapies are selected based on their ease of administration, reversibility, and noninvasiveness. Oral erectileogenic agents, such as sildenafil, yohimbine, trazodone, and phentolamine, have gained widespread popularity, largely because of the convenience and effectiveness of sildenafil. Sildenafil works in most forms of erectile dysfunction and has few side effects. It is a selective type 5 phosphodiesterase inhibitor, which increases penile cyclic guanosine monophosphate, thus enhancing the effect of nitric oxide in response to sexual stimulation. In the penis, the effect of sildenafil is to increase cavernosal smooth muscle dilation, a requisite component of erection. At doses of 25, 50, or 100 mg taken 30 to 60 minutes before sex, it is successful in approximately 70% of impotent men. Side effects are minor and may include mild headache, facial flushing, rhinits, dyspepsia, or blue-hued vision. Sildenafil is thought to have been partially responsible for a very small percentage of cases by interacting with medicinal or recreational nitrates or by allowing sexual overexertion in men with severe cardiac disease. It should never be used concomitantly with nitrates.

Second-line therapies involve the administration of pharmacologic vasodilators, either by direct intracavernosal needle injection or by intracavernosal suppository. Injections typically include prostaglandin E alone (marketed as Caverject or Edex) or in combination with papaverine or phentolamine. The intracavernosal suppository (marketed as Muse) contains prostaglandin E alone, in doses of 5, 10, or 20 µg. Both methods function by producing dilation of the cavernosal smooth muscle, enhancing the vascular component of penile erection. Intracavernosal injection is much more effective than intrarectal administration, but it also carries a greater risk of complications, such as priapism, unsuccessful attempts, and immediate and long-term pain and the threat of or corporal scarring at the injection sites. With intracavernosal medication, the patient is trained to draw up the drug in a tuberculin syringe and inject it into the penis. The patient must take care to place the needle perpendicularly to the long axis of the penis and advance it all the way through the subcutaneous fat into the corpus cavernosum. Because of intracavernosal connections, only one corpus needs to be injected to induce erection. The patient must be careful to avoid the nerve bundle dorsally and the urethra ventrally. He must also rotate injection sites and apply 2 to 3 minutes of pressure after injection to avoid bruising. The intracavernosal medication is sold as a suppository of 250, 500, or 1000 µg loaded into a small applicator that the patients inserts into his urethral meatus. Once in position, he pushes the medicated pellet out by activating a small probe. The medication is packaged with pictorial instructions that facilitate patient teaching. With either penile vasodilator, the dose must be individually titrated.

The operation is usually performed on an outpatient basis and involves a single, small dorsal or ventral incision at the base of the penis. After dissecting and entering the corpora cavernosa, their internal spongy tissue is compressed with dilators and their size calibrated. The appropriate length prostheses are inserted into both corpora. Semirigid prostheses may contain malleable metal rods encased in silicone, or they may be made of solid silicone. After recovery from surgery, the semirigid penile prosthesis requires no training and is ready for use approximately 8 to 12 weeks postoperatively. Inflatable prostheses contain pliable hollow tubes that are filled with saline from a nearby reservoir by activating a pump. In the three-piece version, the reservoir is implanted through the groin in the perivesical space, and the pump is implanted subcutaneously in the scrotum. These components are connected to each other and to the cylinders with silicone tubing. A two-piece version is also available, in which the pump and reservoir are combined into one scrotal component. Self-contained inflatable prostheses have the cylinders, reservoir, and pump all located in one structure. These have become the preferred choice because of easier surgical installation. After recovery, the inflatable prosthesis requires detailed training before the patient becomes comfortable with its use. The primary advantage of the inflatable version is that it appears flaccid when not in use; however, it is also associated with a greater chance of infection, but this complication is uncommon.

The patient must be careful to avoid the nerve bundle dorsally and the urethra ventrally. He must also rotate injection sites and apply 2 to 3 minutes of pressure after injection to avoid bruising. The intracavernosal medication is sold as a suppository of 250, 500, or 1000 µg loaded into a small applicator that the patients inserts into his urethral meatus. Once in position, he pushes the medicated pellet out by activating a small probe. The medication is packaged with pictorial instructions that facilitate patient teaching. With either penile vasodilator, the dose must be individually titrated.
SECTION 56.4
Genetic Counseling

ELLEN T. MATLOFF
ELLEN E. BAILE

INTRODUCTION

The availability of clinically based genetic testing has brought with it a growing demand for accurate risk assessment and cancer genetic counseling. Extensive coverage of this topic by the media and widespread advertising by commercial testing laboratories has further fueled the demand for counseling and testing.

The field of cancer genetic counseling is evolving rapidly to meet the newfound needs of patients and the medical community. Cancer genetic counseling is a communication process between health care professionals and individuals concerning cancer occurrence and risk in their family. The process, which may include the entire family through a blend of genetic, medical, and psychosocial assessment and intervention, has been described as a bridge between the fields of traditional oncology and genetic counseling.

The goals of this process include providing clients with an assessment of individual cancer risk while offering the emotional support needed to understand and cope with this information. The process also involves deciphering whether the cancers in a family are likely to be caused by a mutation in a cancer gene and, if so, which one. To achieve the informed consent crucial to the testing process, each patient is thoroughly counseled about the associated risks, benefits, and limitations of testing. If the patient is interested in pursuing testing, the counselor will identify a laboratory that offers appropriate genetic testing and will facilitate sample collection and shipping and result interpretation. The result session will include detailed counseling about medical management options for early detection and risk reduction and may include referrals to prevention trials, surveillance programs, and medical specialists.

Counselors find that this process differs from traditional genetic counseling in several ways. Clients seeking cancer genetic counseling are rarely concerned with reproductive decisions and risks that are often the primary focus in traditional genetic counseling but are instead seeking information about their own and other relatives’ chances of developing cancer. Additionally, the risks given are not absolute but change over time as the family and personal history changes and the patient ages. Perhaps the greatest divergence from traditional genetic counseling is the departure from nondirectiveness. Nondirectiveness, one of the cornerstones of traditional genetic counseling, can be loosely defined as the tenet of presenting clients with accurate genetic and medical information, providing them with their options, helping them to choose the option that best fits their needs (free of coercion from the counselor regarding which choices are “right” or “wrong”), and then supporting their decision. Nondirectiveness is not always appropriate in cancer genetic counseling. Standard screening guidelines and prevention strategies are presented as recommendations, and the counselor is often proactive in promoting behavioral changes that could reduce the risk of developing cancer. Counseling for susceptibility testing is based on the nondirective framework, although some data indicate that patients desire more assistance in decision making than their health care providers offer. Helping patients reach the decision that is most consistent with their personal values and goals and that is best suited to their personal situation is the ultimate goal of genetic counseling.

Why is cancer genetic counseling necessary? The advances in cancer genetics bring with them new issues involving the medical, psychological, discriminatory, and ethical side effects of genetic testing for cancer predisposition. Potential clients must be made aware of these risks before testing and, when possible, assisted in avoiding pitfalls. Additionally, the public demands this resource. Several studies have documented a high level of interest in genetic testing among people who have one first-degree relative with diagnosed cancer. Although anticipated interest in testing generally overestimates actual uptake, the need for cancer genetic counseling is great and is bound to grow as more genes are cloned.

At present, a limited number of referral centers across the country specialize in cancer genetic counseling. Graduate programs in genetic counseling are actively integrating this new body of knowledge into their curricula and are producing more counselors who can provide cancer services. However, some experts insist that the only way to keep up with the overwhelming demand for counseling will be to educate more physicians and nurses in cancer genetics. The feasibility of adding another time- and energy-consuming task to the clinical burden of these professionals is questionable. A more practical goal may be to educate primary care providers better in the area of generalized risk assessment so that they can screen their patient populations for individuals at high risk for hereditary cancer and refer them to comprehensive counseling and testing programs.

WHO IS A CANDIDATE FOR CANCER GENETIC COUNSELING?

Only 5% to 10% of most cancers are due to mutations within inherited cancer susceptibility genes. The key for the clinician is to determine which patients are at greatest risk to carry one of these mutations. Six risk factors that are common among hereditary cancer families have been identified (Table 56.4-1). The first is early age of cancer onset. This risk factor, even in the absence of a family history, has been shown to be associated with an increased frequency of germline mutations in many types of cancers. The second risk factor is the presence of the same cancer in multiple affected relatives on the same side of the pedigree that are consistent with autosomal dominant inheritance. These cancers do not necessarily have to be of similar histologic type to be caused by a single mutation. The third risk factor is the clustering of cancers known to be caused by a single gene mutation in one family. Examples include breast-ovarian cancer, pancreatic cancer–melanoma, and colon-ovarian-uterine cancers. The fourth risk factor is the occurrence of multiple primary cancers in one individual. This includes multiple primary breast cancers, colon cancers, and melanomas and a single individual with separate cancers known to be caused by a single gene mutation (e.g., breast and ovarian cancer in a single individual). Ethnicity also plays a role in determining who is at greatest risk to carry a hereditary cancer mutation. Individuals of Jewish ancestry are at increased risk to carry three specific BRCA1/2 mutations and the 1107K APC allele. Founder BRCA1/2 mutations have also been discovered in families of French Canadian descent, and mutations in cancer susceptibility genes are likely to be identified in other ethnicities as more subpopulations are studied. The final risk factor for a hereditary cancer syndrome is the presence of a cancer that presents unusually, the prime example of which is breast cancer in a man. These risk factors should be viewed in the context of the entire family history and must be weighed in proportion to the number of individuals who have not developed cancer.
A less common but extremely important finding is the presence of birth defects or unusual medical findings that are known to be associated with rare hereditary cancer syndromes. Examples include benign skin findings and thyroid disorders in Cowden syndrome, sebaceous skin tumors in Muir-Torre syndrome, and supernumerary teeth in familial adenomatous polyposis (FAP).

Another class of candidates for genetic counseling are those patients who are very concerned about their risks for cancer, even in the absence of a strong family history. Many patients overestimate their risks to develop cancer. This inaccurate perception of risk may have a profound effect on a patient's anxiety level and quality of life and may have a negative impact on his or her surveillance patterns. Such patients may gain reassurance and empowerment from learning their actual—as compared to their anticipated—risks for developing cancer and their options to reduce those risks.

At present, breast-ovarian cancer syndrome referrals account for the majority of patients seen in the average cancer genetic counseling clinic. In this chapter, the breast-ovarian cancer counseling session will serve as a paradigm that all other sessions may follow broadly.

**COMPONENTS OF THE CANCER GENETIC COUNSELING SESSION**

**PRE-COUNSELING INFORMATION**

Before coming in for genetic counseling, the counselee should be given some basic information about the process. This information, which can be imparted by telephone or in the form of written material, should outline what the counselee can expect at each session and what information he or she should collect before the first visit. The counselee can then begin to collect medical and family history information that will be essential for the genetic counseling session.

**FAMILY HISTORY**

An accurate family history is undoubtedly one of the most essential components of the cancer genetic counseling session. Despite its importance, the thorough family cancer history has been called "the most severely neglected portion of the patient's medical evaluation." Possibly reflecting a lack of emphasis placed on the family history during the primary and postgraduate education of physicians. It may also be due, in part, to the lack of knowledge about what to do with the information once it has been collected.

A thorough family history should include at least two, optimally three, generations. For each individual affected with cancer, it is important to document the exact diagnosis, age at diagnosis, treatment strategies, and environmental exposures (i.e., occupational exposures, cigarettes, other agents). The current age of the individual and laterality and occurrence of any other cancers must also be documented. Individuals should be asked whether there are any consanguineous (inbred) relationships in the family, whether any relatives were born with birth defects or mental retardation, and whether other genetic diseases run in the family, as these pieces of information could prove important in reaching a diagnosis and in counseling.

It is advised that cancer diagnoses be documented with pathology reports, hospital summaries, or other medical records to maintain accuracy. A study by Love et al. revealed that individuals accurately reported the primary site of cancer only 83% of the time in their first-degree relatives with cancer and 67% and 60% of the time in second- and third-degree relatives, respectively. It is common for patients to report a uterine cancer as an ovarian cancer or a colon polyp as an invasive colorectal cancer. These differences, although seemingly subtle to the patient, can make a tremendous difference in risk assessment.

The most common misconception in family history taking is that somehow a maternal family history of breast, ovarian, or uterine cancer is more significant than a paternal history. Conversely, many still believe that a paternal history of prostate cancer is more significant than a maternal history. Few of the cancer genes discovered thus far are located on the sex chromosomes; therefore, both maternal and paternal history are significant and must be explored thoroughly.

**DYSMORPHOLOGY SCREENING**

Congenital anomalies, benign tumors, and unusual dermatologic features occur in a large number of hereditary cancer predisposition syndromes. Examples include osteomas of the jaw in FAP, palmar pits in Gorlin syndrome, and papillomas of the lips and mucous membranes in Cowden syndrome. Obtaining an accurate medical history of benign lesions and birth defects and screening for such dysmorphology can have a great impact on diagnosis and counseling. For example, BRCA1/2 testing is unnecessary in a patient with breast cancer who has a family history of thyroid cancer and the oculocutaneous manifestations of Cowden syndrome.

**RISK ASSESSMENT**

Risk assessment is one of the most complicated components of the genetic counseling session. It is crucial to remember that risk assessment changes over time as the person ages and as the health status of family members changes. Risk assessment can be broken down into three separate components: What is the chance that the counselee will develop the cancer observed in his or her family (or a genetically related cancer)? What is the chance that the cancers in this family are caused by a single gene mutation? What is the chance that we can identify the gene mutation in this family with our current knowledge and laboratory techniques?

Cancer clustering in a family may be due to genetic or environmental factors (or both) or may be coincidental because some cancers are common in the general population. Although inherited factors may be the primary cause of cancers in some families, in others cancer may develop because an inherited factor increases the individual's susceptibility to environmental carcinogens. It is also possible that members of the same family may be exposed to similar environmental exposures, owing to shared geography or patterns in behavior and diet that may increase the risk of cancer. Therefore, it is important to distinguish the difference between a familial pattern of cancer (due to environmental factors or chance) and a hereditary pattern of cancer (due to a shared genetic mutation).

Several models are available to calculate the chance that a woman will develop breast cancer. Each model has its strengths and weaknesses, and the counselor must decide which model is most appropriate for each individual family. The Gail model for calculating risk takes into account current age, age of first menses, age at first live birth, and number of previous biopsies. This model may be problematic for women who cannot recall their exact age at menses and who are followed more aggressively than women without a positive family history and, therefore, may be subjected to biopsy more frequently. Biopsy results are not considered in this model, so a normal biopsy is weighed equally with a result of atypical hyperplasia. It has also been suggested that the importance of general risk factors for breast cancer, such as age at first menses and first live birth, may vary in hereditary cancer families. A modified form of the Gail model was used to determine entry into the National Surgical Adjuvant Breast and Bowel Project (NSABP) Breast Cancer Prevention Trial and will also be used for entry into the NSABP P-2 STAR trial. Although this model has utility in determining entry for trials and may be of use for women in the general population who receive frequent breast screening, it is not appropriate in families in which there is a question of a hereditary cancer syndrome. The Gail model considers only first-degree relatives in its calculations and, therefore, does not take into account paternal family history and extended family members. It does not weigh ovarian cancer, Jewish ancestry, male breast cancer,
and other factors essential in hereditary risk assessment and is, therefore, not the appropriate tool when hereditary cancer is in question.

Claus et al. created a model that considers limited paternal and maternal family history as well as age of onset of affected relatives in determining empiric cancer risk. This model allows calculation of individual risk by decade and by lifetime, which is useful in helping women understand that their risk accumulates over time and is not clumped at their current age. This model does not take ancestry, ovarian cancer, or extended family history into account and is, therefore, not useful in families in which there appears to be a genetic mutation. Of course, all empiric risks are superseded in families in which DNA testing has revealed a mutation for cancer predisposition.

When the BRCA1 gene was mapped, risk tables were created based on linkage data from high-risk breast and ovarian cancer families. These tables estimated the chance that the cancers found in hereditary breast-ovarian cancer families were due to mutations in BRCA1, and these estimates were fairly high. When direct mutation analysis for BRCA1 became available, the number of families found to carry a mutation was significantly smaller than predicted by linkage studies. This finding suggests that current techniques do not detect all mutations within the gene. More recent tables reflect the chance of actually finding a mutation within BRCA1. Parmigiani et al. have developed a more sophisticated computer model that calculates the probability of finding a BRCA1 or 2 mutation in a family using a variety of risk factors. This model is being validated.

DNA TESTING

DNA testing is available for a variety of hereditary cancer syndromes [e.g., breast-ovarian cancer syndrome, hereditary nonpolyposis colon cancer (HNPCC), and hereditary melanoma]. However, despite misrepresentation by the media, testing is feasible for only a small percentage of individuals with cancer. DNA testing offers the obvious and important advantage of presenting clients with actual risks instead of the empiric risks derived from risk calculation models.

The results of DNA testing are generally provided in person in a result disclosure session. It is recommended that patients bring a close friend or relative with them to this session who can provide them with emotional support and who can help them to listen to and process the information provided.

One of most crucial aspects of DNA testing is accurate result interpretation. One study found that test results for the hereditary colon cancer syndrome FAP were misinterpreted more than 30% of the time by those ordering the testing. The potential impact of test results on the patient and his or her family is great; therefore, accurate interpretation of the results is paramount.

Results of genetic testing fall into three categories: true positive, whereby an individual is found to carry a mutation that is known to be deleterious; true negative, whereby an individual does not carry the deleterious mutation found in their family and, therefore, the cancer risks are reduced to the population risks; and indeterminate, whereby a mutation cannot be identified in the affected family members or a genetic change is identified with unknown significance. This result category is currently the most common outcome.

To pinpoint the mutation in a family, an affected individual likely to carry a mutation should be tested first. This is most often a person affected with the cancer in question (i.e., the proband). Test subjects should be selected with care, as it is possible for a person to develop sporadic cancer in a hereditary cancer family. If a mutation is detected in an affected relative, other unaffected family members can be tested for the same mutation with a great degree of accuracy. Family members who do not carry the mutation found in their family are deemed to be true negative. Those who are found to carry the mutation in their family will have more definitive information about their risks to develop cancer. This information can be crucial in assisting patients in decision making regarding surveillance and risk reduction.

If a mutation is not identified in the affected relative, it usually means either that the cancers in the family are not caused by a single genetic mutation or that the mutation in the family is undetectable by current methods. Such results are indeterminate, and other family members cannot be offered accurate predisposition testing. In some such cases, DNA banking should be offered to the proband for a time in the future when improved testing may become available. A notarized letter indicating exactly who in the family has access to the DNA should accompany the banked sample.

The result stated as “genetic variant of uncertain significance” must be interpreted with caution. Sometimes, other affected family members can be tested to see whether the variant segregates with disease in the family. Most of the time, the significance of the variant remains unknown until functional studies are conclusive or further data are available.

The penetrance of mutations in cancer susceptibility genes is also difficult to interpret. Initial estimates derived from high-risk families provided very high cancer risks for BRCA1 and BRCA2 mutation carriers. More recent studies of populations that were not selected for family history have revealed lower penetrances. Some have interpreted these population-based data as being “more accurate” and have suggested that they apply to all families. In fact, the higher range of risk may be more accurate for families who present with strong histories of breast and ovarian cancer. Because exact penetrance rates cannot be determined for individual families at this time, it is prudent to provide patients with a range of cancer risk and to explain that their risk probably falls somewhere within this spectrum.

Female carriers of BRCA1 and BRCA2 mutations have a 50% to 85% lifetime risk of developing breast cancer and between a 15% to 60% lifetime risk of developing ovarian cancer. Carriers of HNPCC mutations have a 65% to 85% lifetime risk of developing colon cancer, and female carriers have a 30% to 40% lifetime risk of uterine cancer and as great as a 10% risk of ovarian cancer.

OPTIONS FOR SURVEILLANCE AND RISK REDUCTION

The cancer risk counseling session is a forum to provide counselees with choices, options, and hope (Table 56.4-2). Mutation carriers can be offered earlier and aggressive surveillance, chemoprevention plus surveillance, or prophylactic surgery.

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<th>Table 56.4-2. Methods for Surveillance and Risk Reduction for Selected Hereditary Cancers</th>
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<td>It is recommended that individuals at increased risk for breast cancer have annual mammograms beginning between ages 25 and 35 years and annual or semiannual clinical breast examinations, and that they perform monthly breast self-examinations. BRCA1/2 carriers may take tamoxifen in hopes of reducing their risks of developing breast cancer. However, although tamoxifen has proven effective in women at risk due to a positive family history of breast cancer, the efficacy of this intervention in BRCA1/2 carriers is still unknown. The results of preliminary studies indicate that a second chemopreventive agent, raloxifene (EVISTA), may also be effective in reducing the risk of breast cancer in healthy postmenopausal women. However, this medication is approved by the U.S. Food and Drug Administration only for the prevention of osteoporosis and has not been studied in BRCA1/2-positive women. A current study, the NSABP P-2 STAR trial, is examining the role of this drug in women at high risk for breast cancer. Data should be available by 2006. Prophylactic bilateral mastectomy is believed to reduce the risk of breast cancer by more than 90% in women at high risk for the disease; however, the efficacy of this procedure specifically in BRCA mutation carriers is unknown. Before genetic testing was available, it was not uncommon for entire generations of cancer families to have their at-risk organs removed without knowing whether they were personally at increased risk for their familial cancer. Fifty percent of individuals in hereditary cancer families do not carry the inherited predisposition gene and can be...</td>
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spared prophylactic surgery or invasive high-risk surveillance regimens. Therefore, it is no longer appropriate to offer prophylactic surgery until a patient is referred for genetic counseling and, if possible, testing (Table 56.4-3).

Women who carry BRCA1/2 mutations are also at increased risk for developing second contralateral and ipsilateral primary tumors of the breast. These data bring into question the option of breast-conserving surgery in women at high risk to develop a second primary tumor within the same breast. For this reason, BRCA1/2 carrier status may have a profound impact on surgical decision making in the future.

Women who carry BRCA1/2 mutations are also at increased risk for developing ovarian cancer, even if no one in their family has developed this cancer. Surveillance for ovarian cancer is complex, with the recommended interventions being annual transvaginal ultrasonography and tests of CA-125 levels beginning between the ages of 25 and 35 years. The effectiveness of such surveillance in detecting ovarian cancers at early and more treatable stages has not been proven in any population. Oral contraceptives have been shown to reduce the risk of ovarian cancer in women carrying BRCA mutations. The impact of this intervention on breast cancer risk is not known. However, it is possible that, given the likelihood of mortality from breast versus ovarian cancer, a risk-benefit analysis would favor the use of oral contraceptives in carriers of BRCA1/2 mutations. Prophylactic oophorectomy is the most effective means to reduce the risk of ovarian cancer, but even women who have had this procedure may develop primary peritoneal carcinoma. This condition is clinically and histologically similar to ovarian cancer but appears to arise from the cells lining the peritoneal cavity. Some data indicate that BRCA1 carriers who opt for prophylactic oophorectomy also have a reduced chance of developing a subsequent breast cancer, particularly if they have this surgery before menopause. Premenopausal women who opt for oophorectomy and, therefore, experience premature surgical menopause may be candidates for hormone replacement therapy (HRT) with the lowest dose of estrogen possible. This may provide some of the benefits of HRT while minimizing the potential breast cancer–related risks. Preliminary data suggest that premenopausal BRCA1 carriers who have oophorectomies followed by HRT still have a reduced risk of future breast cancers.

The standard surveillance method in carriers of HNPCC mutations is full colonoscopy to the cecum every 1 to 3 years beginning between the ages of 20 and 25 years. Although several studies are investigating chemopreventive options for colorectal cancer, no agents are currently approved for clinical use. Prophylactic subtotal colectomy with ileorectal anastomosis is an option for HNPCC carriers, and a decision analysis revealed that this procedure may offer slightly greater gains in life expectancy for young HNPCC carriers than surveillance alone.

Options for endometrial surveillance include endometrial aspirate and transvaginal ultrasonography beginning between the ages of 25 and 35 years. The efficacy of such surveillance in HNPCC carriers is unknown. Oral contraceptives are known to reduce the risk of endometrial cancer in the general population, but the impact of this intervention in HNPCC carriers is currently unknown. Prophylactic transvaginal hysterectomy is also an option. Although this option is likely to reduce risk of uterine cancer significantly, long-term prospective studies of the impact of this intervention on HNPCC carriers have not been performed. Women who carry HNPCC mutations are also at risk for ovarian cancer and should, therefore, be offered the aforementioned surveillance and risk reduction options for ovarian cancer.

Management of hereditary melanoma patients involves frequent full-body examination by a dermatologist familiar with pigmented lesions. Semiannual appointments typically include photography of the entire body, to allow for objective determination of differences in size or appearance of moles, and subsequent excision of any suspicious lesions. Avoidance of sunlight exposure is recommended. Melanoma is often curable when diagnosed and treated in an early stage.

Genetic counseling and testing are also available for many rare cancer syndromes, including von Hippel-Lindau syndrome, multiple endocrine neoplasia, and FAP. Surveillance and risk reduction for patients who are known mutation carriers for such conditions may decrease the associated morbidity and mortality of these syndromes.

**FOLLOW-UP**

A follow-up letter to the patient is a concrete means of documenting the information conveyed in the sessions so that the patient and his or her family members can review it over time. (It is crucial that this letter be sent only to the patient and health care professionals to whom the patient has granted access to this information; in most cases, it should not be placed in the patient's general medical records.) A follow-up phone call is also helpful, particularly in the case of a positive test result. Some programs provide patients with an annual or biannual newsletter updating them on new information in the field of cancer genetics. A small proportion of patients may return for a follow-up counseling session months, or even years, after their initial consult to discuss the emergence of new family history data and new clinical issues or because they are now ready to move forward with genetic testing.

**ISSUES IN CANCER GENETIC COUNSELING**

**PSYCHOSOCIAL ISSUES**

The psychosocial impact of cancer genetic counseling cannot be underestimated. Just the process of scheduling a cancer risk counseling session may be fairly difficult for some individuals with a family history who are not only frightened about their own cancer risk but are reliving painful experiences associated with the cancer of their loved ones. Counselors may be faced with an onslaught of emotions, including anger, fear of developing cancer, fear of disfigurement and dying, grief, lack of control, negative body image, and a sense of isolation. Their feelings about cancer will also vary depending on how close they have been to affected individuals, both emotionally and in geographic proximity, and how often they saw these relatives. Some counselors are wrestling with the fear that insurance companies, employers, family members, and even future partners will react negatively to their cancer risks. For many, it is a double-edged sword as they balance their grief, lack of control, negative body image, and a sense of isolation.

A person's perceived cancer risk is often dependent on many "nonmedical" variables. They may estimate that their risk is higher if they resemble an affected individual or share some of that individual's personality traits. Their perceived risks will vary depending on whether their relatives were cancer survivors or died of cancer. Some people wonder not whether they are going to get cancer but when. Some first-degree relatives of women with breast cancer said they felt as though they were living with a sword over their heads or that they were walking time bombs.

In their study of women with a first-degree relative who had breast cancer, Lerman et al. found that more than one-half of their respondents reported having intrusive thoughts and waves of feelings about breast cancer. More than one-third of these nonaffected women reported breast cancer images and associations that intruded on their awareness, and 20% had difficulty in sleeping because of their breast cancer concerns. Importantly, these authors found that genetic counseling was significantly less effective among women with higher baseline levels of breast cancer preoccupation. Therefore, they concluded that efforts to provide individuals with cancer genetic counseling are not likely to be effective unless their cancer anxieties and feelings are also addressed.

**TABLE 56.4-3. Cancer Genetic Counseling and Testing Resources**

Women who carry BRCA1/2 mutations are also at increased risk for developing contralateral and ipsilateral primary tumors of the breast. These data bring into question the option of breast-conserving surgery in women at high risk to develop a second primary tumor within the same breast. For this reason, BRCA1/2 carrier status may have a profound impact on surgical decision making in the future.

Although several studies are investigating chemopreventive options for colorectal cancer, no agents are currently approved for clinical use. Prophylactic subtotal colectomy with ileorectal anastomosis is an option for HNPCC carriers, and a decision analysis revealed that this procedure may offer slightly greater gains in life expectancy for young HNPCC carriers than surveillance alone.

Options for endometrial surveillance include endometrial aspirate and transvaginal ultrasonography beginning between the ages of 25 and 35 years. The efficacy of such surveillance in HNPCC carriers is unknown. Oral contraceptives are known to reduce the risk of endometrial cancer in the general population, but the impact of this intervention in HNPCC carriers is currently unknown. Prophylactic transvaginal hysterectomy is also an option. Although this option is likely to reduce risk of uterine cancer significantly, long-term prospective studies of the impact of this intervention on HNPCC carriers have not been performed. Women who carry HNPCC mutations are also at risk for ovarian cancer and should, therefore, be offered the aforementioned surveillance and risk reduction options for ovarian cancer.

Management of hereditary melanoma patients involves frequent full-body examination by a dermatologist familiar with pigmented lesions. Semiannual appointments typically include photography of the entire body, to allow for objective determination of differences in size or appearance of moles, and subsequent excision of any suspicious lesions. Avoidance of sunlight exposure is recommended. Melanoma is often curable when diagnosed and treated in an early stage.

**PSYCHOSOCIAL ISSUES**

The psychosocial impact of cancer genetic counseling cannot be underestimated. Just the process of scheduling a cancer risk counseling session may be fairly difficult for some individuals with a family history who are not only frightened about their own cancer risk but are reliving painful experiences associated with the cancer of their loved ones. Counselors may be faced with an onslaught of emotions, including anger, fear of developing cancer, fear of disfigurement and dying, grief, lack of control, negative body image, and a sense of isolation. Their feelings about cancer will also vary depending on how close they have been to affected individuals, both emotionally and in geographic proximity, and how often they saw these relatives. Some counselors are wrestling with the fear that insurance companies, employers, family members, and even future partners will react negatively to their cancer risks. For many, it is a double-edged sword as they balance their grief, lack of control, negative body image, and a sense of isolation.

A person's perceived cancer risk is often dependent on many "nonmedical" variables. They may estimate that their risk is higher if they resemble an affected individual or share some of that individual's personality traits. Their perceived risks will vary depending on whether their relatives were cancer survivors or died of cancer. Some people wonder not whether they are going to get cancer but when. Some first-degree relatives of women with breast cancer said they felt as though they were living with a sword over their heads or that they were walking time bombs.

In their study of women with a first-degree relative who had breast cancer, Lerman et al. found that more than one-half of their respondents reported having intrusive thoughts and waves of feelings about breast cancer. More than one-third of these nonaffected women reported breast cancer images and associations that intruded on their awareness, and 20% had difficulty in sleeping because of their breast cancer concerns. Importantly, these authors found that genetic counseling was significantly less effective among women with higher baseline levels of breast cancer preoccupation. Therefore, they concluded that efforts to provide individuals with cancer genetic counseling are not likely to be effective unless their cancer anxieties and feelings are also addressed.
It might be assumed that fear of cancer motivates individuals to increase their cancer awareness and prevention strategies. On the contrary, Kash et al. found that women who perceived their breast cancer risks as high were engaged in fewer general preventive health care behaviors (including breast self-examinations and regular clinical breast examinations) than those women who perceived their risks as only moderate. It is theorized that perhaps these individuals believe that they will definitely develop breast cancer and are helpless in decreasing their risks, or perhaps they are completely immobilized by their fear or denial. Whatever the reason for these behaviors, it is obvious that psychological and educational interventions should be a component of cancer genetic counseling.

The counseling session is an opportunity for individuals to express why they believe that they have developed cancer or why their family members have cancer. Some explanations may revolve around family folklore, and it is important to listen to and address these explanations rather than to dismiss them. In doing this, the counselor will allow the clients to alleviate their greatest fears and to give more credibility to the “medical” theory. For patients who are moving forward with DNA testing, a referral to a mental health care professional who can help to facilitate the process is often very helpful.

To date, studies conducted in the setting of pre- and post-genetic counseling have revealed that, at least in the short term, most patients do not experience adverse psychological outcomes after receiving their test results. In fact, preliminary data have revealed that individuals in families with known mutations who seek testing seem to fare better psychologically at 6 months than those who avoid testing. Although these data are reassuring, it is important to recognize that genetic testing is an individual decision and will not be right for every patient or every family.

**PRESYMPTOMATIC TESTING OF CHILDREN**

Presymptomatic testing of children has been widely discussed, and most concur that it is appropriate only when the onset of the condition regularly occurs in childhood or there are useful interventions that can be applied. For example, DNA-based diagnosis of children and young adults at risk for hereditary medullary thyroid carcinoma has improved the management of these patients. DNA-based testing for RET mutations is virtually 100% accurate and allows at-risk family members to make informed decisions about prophylactic thyroidectomy. FAP is a disorder that occurs in childhood and in which mortality can be reduced if detection is presymptomatic. Testing is clearly indicated in these instances.

Predisposition testing may also be appropriate if it will be useful to the minor child in making reproductive decisions now or in the near future. Early observations by Malkin et al. indicated an interest among parents in cancer-predictive testing for their children. Their willingness to have their children undergo testing appeared to be dependent on the accuracy of the test and the availability of preventive or curative options. Questions have been raised about parents’ right to demand testing for adult-onset diseases. Parents may have a constitutionally protected right to demand that unwilling physicians order this test, but there is little risk for discrimination or sanctions unless tests are medically indicated. The child’s right not to be tested must be considered. When presymptomatic childhood testing is not medically indicated, it is preferable that testing decisions be postponed until the children are adults and can decide for themselves whether to be tested. However, the argument has been made that if a child younger than 18 years is able to appreciate not only the genetic facts but also the emotional and social consequences, he or she should be allowed to have genetic testing. This subject is highly controversial and will likely continue to be debated.

**CONFIDENTIALITY**

The level of confidentiality surrounding cancer genetic testing is paramount, owing to concerns of genetic discrimination. Many programs are opting to keep shadow files separate from the general hospital charts. Patient-identifying data are generally not entered into computer databases that are accessible by modem or a network of users. Some counseling programs are submitting DNA samples to laboratories by coded number only in an attempt to increase the level of confidentiality. Special precautions to protect confidentiality should be taken when leaving voice mail messages, at home and at work, regarding patient appointments. Conversations with patients or other colleagues via e-mail that include patient names are discouraged, as the Internet is not secure. Additionally, genetic counseling summary letters are sent directly to patients and are copied to the referring physicians only with the explicit permission of the patient. These measures are taken because confidentiality and genetic discrimination are a grave concern for many of the patients seen in the cancer genetic counseling clinic.

Confidentiality of test results within a family can also be an issue, as genetic counseling and testing often reveal the risk status of family members other than the patient. Under confidentiality codes, the patient should grant permission before at-risk family members can be contacted. It has been questioned whether family members could sue a health care professional for negligence if they were identified as at high risk yet not informed. Most recommendations have stated that the burden of confidentiality lies between the provider and the patient. However, more recent recommendations state that confidentiality should be violated if the potential harm of not notifying other family members outweighs the harm of breaking a confidence to the patient. There is no patent solution for this difficult dilemma, and situations must be considered on a case-by-case basis with the assistance of the in-house legal department and ethics committee.

Patients should be counseled about the benefits to other family members of knowing testing results but, at present, the decision is ultimately the patient’s. Extended family members who are notified with the patient’s consent may not always be grateful to receive this information and may think that their privacy has been invaded by being contacted.

**INSURANCE ISSUES**

Insurance companies are, understandably, in the business of making money. Before issuing health insurance policies, some companies determine the risk that an individual carries and adjust the premium to match that risk. Information regarding family history, genetic information, and prior diagnostic testing may very well be used in calculating this risk. This should be clearly conveyed to the patient in the precounseling interview, as it may change the method by which he or she chooses to pay for the session or for testing. These issues should be discussed in detail again in the counseling session. Although individuals and counselors can attempt to keep records and results confidential, there is always a risk that this information will reach insurers.

More and more patients are choosing to submit their genetic counseling or testing charges to their health insurance companies. In the last few years, more insurance companies have agreed to pay for counseling or testing (or both), perhaps in light of decision analyses that show these services and subsequent prophylactic surgeries to be cost-effective. Letters of justification are often required for insurance companies to cover the charges for testing. These letters must clearly delineate the impact of testing on the short- and long-term management of the patient being tested. Justification of testing based on assisting other, unaffected family members is rarely helpful.

**DISCRIMINATION**

Many health care providers and patients fear that genetic discrimination by health, life, and disability insurance companies resulting from a positive test is a potential hazard of genetic testing. Fear of genetic discrimination by patients has been cited as a major deterrent to genetic testing. Some data indicate that consumer fear of genetic discrimination is out of proportion with the actual amount of discrimination experienced, however, it is well known that current legislation aimed at protecting individuals from genetic discrimination is not without loopholes. Patients should be informed of local and national legislation on genetic discrimination as well as the limitations of these laws.

**FUTURE DIRECTIONS**

The field of cancer genetic counseling and testing grew tremendously in the late 1990s. Although cancer genetic counseling is targeted at individuals with strong personal or family history of cancer, it is clear that this focus will broaden over the next decade. Genetic testing for cancer genes is presymptomatic, as the risk of new primary tumors is greater in individuals who carry germline mutations. Data showing that germline mutations are more frequent in individuals with early-onset breast and colon cancers, even in the absence of a family history of these diseases, will expand the criteria for genetic testing. Specific histologic tumor types may indicate that a patient is at increased risk to carry a germline mutation and may prompt a referral to genetic counseling. The U.S. Food and Drug Administration approval of tamoxifen as a method of breast cancer risk reduction for women at moderately increased risk of the disease will likely bring an onslaught of genetic counseling referrals. These patients will need to know their personal risks of developing breast cancer, and the counseling session will include a detailed discussion of their personal risks for osteoporosis, coronary heart disease, menopausal symptoms, and cognitive deficiencies and the pros and cons of HRT versus selective estrogen receptor modulators, such as tamoxifen. The discovery of modifying genes and specific environmental factors that affect the lifetime risks...


One-third of patients with cancer report a degree of anxiety or depression that requires psychiatric treatment. In the past, symptoms of emotional distress were often unrecognized, undetected and, as a result, untreated. In this chapter, we review the normal responses to cancer; the most frequently encountered psychiatric disorders; and psychotherapeutic, pharmacologic, and behavioral management of these disorders.

There are characteristic normal responses to receiving a diagnosis of cancer. A period of initial disbelief, denial, or despair is common and generally lasts only a few days. Subsequently, many have a dysphoric mood, with anxiety symptoms, depressed mood, anorexia, insomnia, or irritability lasting a few weeks. The ability to concentrate and to carry out usual daily activities is impaired, and intrusive thoughts of the illness and uncertainty about the future are present. Adaptation usually begins after several weeks and continues for months to years as most patients integrate new information, confront reality issues, find reasons for optimism, and resume activities.

The patient's ability to successfully manage a cancer diagnosis depends on medical, psychological, and social factors and commonly changes over the course of the illness. These factors include the disease itself (i.e., site, symptoms, clinical course, prognosis, type of treatments required); prior level of adjustment, especially to medical illness; the threat that cancer poses to attaining age-appropriate developmental tasks and goals (i.e., adolescence, career, family, retirement); cultural, spiritual, and religious attitudes; the presence of emotionally supportive persons in the patient's environment; the patient's potential for physical and psychological rehabilitation; the patient's own personality and coping style; prior experience with cancer; and history of losses.

PREVALENCE

There have been many assumptions about the psychological state of cancer patients, varying between the assumption that all patients must be depressed and need help and the opposite assumption that most manage well and few need psychiatric intervention. Prevalence studies counter these extreme attitudes. In the first comprehensive study, the Psychosocial Collaborative Oncology Group reported that of 215 randomly selected hospitalized and ambulatory patients at three major cancer centers, 47% met criteria for a psychiatric disorder. Of the cancer patients who had an identified psychiatric disorder, 68% had an adjustment disorder with depressed, anxious, or mixed mood; 13% had major depression; 8% had an organic mental disorder (i.e., delirium); 7% had a personality disorder; and 4% had an anxiety disorder. Depressive disorders accounted for the majority of diagnoses. Nearly 90% of the psychiatric disorders observed were either reactions to, or manifestations of, disease or treatment. Only 11% of patients had prior psychiatric illness. Patients with cancer are thus largely psychologically healthy individuals who have emotional distress related to illness. However, there is a significant incidence of psychiatric illness, as approximately 25% of all cancer patients experience significant depression, irrespective of their hospital and physical status.

DEPRESSION

Depression is clearly the most prevalent psychiatric symptom in cancer patients. Depression can be distinguished from normal sadness and anticipatory grieving based on the nature and severity of the symptoms, their duration and intensity, and their impact on functioning. Depression in cancer patients results from (1) stress related to the cancer diagnosis and treatment; (2) medications (Table 56.5-1); (3) underlying neurologic or medical problems, such as nutritional deficiencies (folate, vitamin B12), endocrine disturbances (thyroid abnormalities, adrenal insufficiency), brain metastases, and leptomeningeal disease; or (4) recurrence of a preexisting depressive syndrome or bipolar mood disorder. The emotional stress of the cancer experience and medications are the most common causes of depression. Whereas the diagnosis of depression in physically healthy patients depends heavily on the somatic symptoms of anorexia, fatigue, and weight loss, these indicators are of lesser value in the assessment of a cancer patient, since they are common to both cancer and depression. Diagnosis must rest on psychological or cognitive symptoms: anhedonia, dysphoric mood, feelings of hopelessness-helplessness-worthlessness-guilt, poor self-esteem, or suicidality. Cancer patients are at higher risk for depression if they are in poor physical condition, have inadequately controlled pain, are in the advanced stages of illness, have a history of depression, or have other significant life stresses or losses.

Table 56.5-1. Medications That Can Cause Depression in Cancer Patients

<table>
<thead>
<tr>
<th>Medication</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acyclovir</td>
<td>\begin{itemize} \item Viral infections \item HSV, CMV, VZV, EBV \end{itemize}</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>\begin{itemize} \item Antidepressant \item May cause sedation, dry mouth, and weight gain \end{itemize}</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>\begin{itemize} \item Antidepressant \item May cause nausea, dizziness, and constipation \end{itemize}</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>\begin{itemize} \item Antidepressant \item May cause sexual dysfunction, increased appetite, and weight gain \end{itemize}</td>
</tr>
<tr>
<td>Varenicline</td>
<td>\begin{itemize} \item Medication for smoking cessation \item May cause nausea, vomiting, and headache \end{itemize}</td>
</tr>
</tbody>
</table>

Early detection and aggressive treatment of depression is essential in cancer patients. Psychoeducation about normal responses to coping with the stresses of cancer and identification of symptoms requiring treatment is the first step. Despite tremendous advances in efforts to desigmatize psychiatric illness and treatment, many patients continue to be reluctant to seek counseling or to consider psychotropic medications. The oncologist and nursing staff play essential roles in communicating the importance of treating the whole person, and attending to the psychological distress that many patients experience. Referral for psychiatric evaluation when indicated is a significant opportunity to validate the patient's feelings of distress and provide supportive counseling. A recent report by Watson et al. suggested that a high helplessness-hopelessness score has a detrimental effect on 5-year survival in women with early breast cancer and that a high score for depression is linked to a
Electroconvulsive Therapy procarbazine, because it has some monoamine oxidase inhibitory activity. Although MAOIs have demonstrated efficacy in the treatment of depression, the risk of already be confronting nutritional problems due to their illness and treatment. These drugs may also be contraindicated in patients receiving the antineoplastic psychiatrists, however, are reluctant to start depressed cancer patients on MAOIs because of the difficulty of maintaining dietary restrictions in patients who may If a patient has responded well to a monoamine oxidase inhibitor (MAOI) for depression before treatment for cancer, its continued use is warranted. Most

TABLE 56.5-2. Antidepressants Commonly Prescribed for Cancer Patients

Selective Serotonin Reuptake Inhibitors and Other New Antidepressants

The selective serotonin reuptake inhibitors (SSRIs) are the first-line antidepressants prescribed in cancer settings because they are effective, with few side effects and few drug interactions. The SSRIs (e.g., fluoxetine, sertraline, paroxetine, and citalopram) have proven as effective as tricyclic antidepressants (TCAs) but with less sedative and autonomic effects. The most common side effects are mild nausea, gastrointestinal disturbance, headache, somnolence or insomnia, and a brief period of increased anxiety. SSRIs can cause sexual dysfunction in both men and women, a side effect that often leads to cessation of the drug, although there are a number of interventions that may address this symptom. There has been contradictory information about the potential for appetite suppression with SSRIs as they have been demonstrated to cause transient anorexia but have also been successfully used in patients with eating disorders to improve food intake. Some cancer patients experience transient weight loss; however, weight usually returns to baseline level, and the anorectic properties of these drugs have not been a limiting factor in this population. The SSRIs do vary in their metabolism, with paroxetine having no active metabolites and sertraline having relatively few and both paroxetine and sertraline having short half-lives. The newest SSRI, citalopram, may be less likely to cause gastrointestinal symptoms and anxiety. Fluoxetine, sertraline, and paroxetine have been used to reduce both the number and intensity of hot flashes in nondepressed women who become menopausal after chemotherapy for breast cancer.

Bupropion and trazodone are prescribed less frequently than the SSRIs for individuals with cancer. Bupropion’s activating profile makes it useful in lethargic patients, but it is associated with anorexia and increased seizure risk and should be avoided in patients with a history of seizures or brain tumor and in those who are malnourished. Bupropion has been demonstrated to improve the chances of success for patients attempting to quit smoking tobacco and thus may be especially important in patients with lung or head and neck cancers. Trazodone is strongly sedating and in low doses (25 to 100 mg q.h.s.) is helpful in the treatment of the depressed cancer patient with insomnia. Trazodone has been associated with priapism and should, therefore, be used with caution in male patients. The use of venlafaxine, nefazodone, and mirtazapine has not been studied in cancer patients. Venlafaxine affects both norepinephrine and serotonin neurotransmitter systems, but it does not produce the same uncomfortable antimuscarinic and antidromergetic side effects as the tricyclic antidepressants. Hypertensive side effects at higher doses can be problematic in medically ill patients. Nefazodone also affects serotonin and norepinephrine systems and is useful in those with agitated depression or insomnia. Mirtazapine, another sedating antidepressant, is similarly efficacious for patients with agitated depression and insomnia and is currently under study for its potential analgesic and anxiolytic effects. Bupropion, nefazodone, and mirtazapine are less likely to cause sexual dysfunction than the SSRIs and venlafaxine.

Tricyclic Antidepressants

The tricyclic antidepressants are still used to treat depression in adults and children with cancer. Nortriptyline and desipramine have the most favorable side effect profiles for cancer patients, with less anticholinergic and sedating symptoms. For reasons that are unclear, depressed cancer patients often show a therapeutic response to a tricyclic at much lower doses (75 to 125 mg/d) than are usually required in physically healthy depressed patients (150 to 300 mg/d). Obtaining serum levels of the medications is helpful in titrating dosages and monitoring toxicity. The beneficial effects on appetite and sleep are frequently immediate, while the effects on mood may be delayed. Tricyclic antidepressants have been favored in medical settings because of their demonstrated analgesic effects in some patients. However, they are notorious for their side effects, such as hypotension and cardiac conduction disturbances.

Psychostimulants

In cancer patients, low doses of psychostimulants (i.e., dextroamphetamine, methylphenidate, and pemoline) promote a sense of well-being, decrease fatigue, and stimulate appetite. Psychostimulants offer clear benefits, especially in terminally medically ill patients, as there may be an improvement in symptoms within hours to days.

Psychostimulants can also potentiate the analgesic effects of opioid analgesics and are commonly used to counteract opioid-induced sedation. As tolerance develops, an adjustment of the dose is necessary. Side effects at low doses include insomnia, tachycardia, euphoria, and mood lability. High doses and long-term use may produce nightmares, insomnia, and paranoia. Patients should be cardiolologically and neurologically stable before starting a stimulant.

Psychostimulant dosing is usually at 8 a.m. and noon to avoid any potential for sleep disturbance. Pemoline, a gentler psychostimulant available in chewable form with buccal absorption, may be chosen for more frail, debilitated patients or for those who cannot swallow. However, pemoline should be used with caution in patients with renal impairment; liver and renal function tests should be monitored periodically. Typically, patients are maintained on a psychostimulant for 1 to 2 months, after which time many can discontinue these medications without a recurrence of depressive symptoms. Those who experience further depressive symptoms can be maintained on a psychostimulant for longer periods, and tapering may be aided by concurrent use of another antidepressant.

Mood Stabilizers

Patients with a history of bipolar disorder (manic-depressive illness) maintained on mood stabilizers must be continued on their medications throughout treatment. They may require close psychiatric monitoring, as the stresses of their illness and treatment place them at high risk for episodes of severe affective illness. There are few studies of the use of mood stabilizers during cancer treatment. Patients who have been treated with lithium carbonate should be maintained on it throughout their cancer treatment, but close monitoring is necessary, as patients are vulnerable to toxicity in the setting of fluid and electrolyte imbalances, such as during perioperative periods, in critically ill patients with renal dysfunction, or in those receiving potentially nephrotoxic drugs. Use of carbamazepine as a mood stabilizer can be problematic in cancer patients because of its narrow-suppressing properties. Valproic acid, on the other hand, is better tolerated and considered to be quite efficacious.Gabapentin is currently under study as a mood stabilizer. It is well tolerated with few side effects and has a growing role in the treatment of neuropathic pain.

Monoamine Oxidase Inhibitors

If a patient has responded well to a monoamine oxidase inhibitor (MAOI) for depression before treatment for cancer, its continued use is warranted. Most psychiatrists, however, are reluctant to start depressed cancer patients on MAOIs because of the difficulty of maintaining dietary restrictions in patients who may already be confronting nutritional problems due to their illness and treatment. These drugs may also be contraindicated in patients receiving the antineoplastic procarbazine, because it has some monoamine oxidase inhibitory activity. Although MAOIs have demonstrated efficacy in the treatment of depression, the risk of hypertensive crisis and serotonin syndrome due to drug interactions (i.e., meperidine) has led to substantial concern about their safety.

Electroconvulsive Therapy

significantly reduced chance of survival is provocative and calls for more research in the identification and treatment of the depressed cancer patient. Currently, a range of psychopharmacologic and psychotherapeutic treatments is available for depression (Table 56.5-2).
Electroconvulsive therapy is one of the most effective treatments for depression in patients who are medically ill and unable to tolerate psychotropic medications. Electroconvulsive therapy continues to be a viable option for patients who are refractory to antidepressants, for whom medications are medically contraindicated, or for those with psychotic features, dangerous suicidality, or self-injurious behavior. The most common side effects include anterograde amnesia that usually improves within days to weeks of the treatment.

### CANCER-RELATED SUICIDE

Although few cancer patients commit suicide, they may be at a somewhat greater risk than the general population. Passive suicidal thoughts are relatively common; confronting mortality while battling a life-threatening illness leads many to contemplate suicide. Consideration of death and dying is complex for patients who are faced with substantial suffering and are struggling to assess quality-of-life concerns. Suicide may transiently appear to be a means of maintaining a sense of control and a reassuring theoretiative alternative for patients overwhelmed by uncertainty, feelings of helplessness, and fears of suffering. The actual suicide rate in cancer patients is difficult to confirm as death certificates may reflect an underreporting of suicide in patients with advanced illness. The degree to which noncompliance or treatment refusal represents a deliberate decision to end life is unknown.

Factors associated with an increased risk of suicide in cancer patients include being male, having tumors associated with alcohol and tobacco abuse, advanced stage of disease, poor prognosis, delirium with poor impulse control, inadequately controlled pain, depression, history of psychiatric illness, current or previous alcohol or substance abuse, previous suicide attempts, physical and emotional exhaustion, and social isolation. Suicidal depression has been associated with chemotherapy treatment.

Frank discussion of suicidal ideation is important. Although such discussion is often feared by clinicians, there is no evidence that talking about suicide encourages attempts. Assessment of severity of suicide risk depends on the clinical circumstances, identification of factors that may increase impulsivity or impair judgment (e.g., active substance abuse or delirium), and review of the patient's intent and plan. Emergent psychiatric evaluation is indicated when there is a risk of injury to self or others. Identifying and treating depression among patients with cancer has been shown to decrease morbidity and mortality.

### ANXIETY

Anxiety is a normal reaction to the emotionally stressful, even traumatic, experience of cancer. Cancer may force changes in social roles, disrupt personal relationships, cause bodily dysfunction, and alter appearance, in addition to posing a threat of death or significantly shortened life. Anxiety is common at crisis points, such as the time of diagnosis, before the start of any new treatment, when recurrent disease is diagnosed, and when the patient progresses to advanced and terminal illness stages. After initial shock and disbelief, patients may develop symptoms of anxiety, accompanied by irritability, loss of appetite, insomnia, intrusive thoughts about their prognosis, and decreased ability to concentrate and carry on usual activities. Anxiety that persists and causes impairment is considered pathologic. Anxiety disorders may present with a variety of symptoms, including phobias, obsessive-compulsive symptoms, panic attacks, generalized anxiety, or somatic complaints. Severe anxiety can contribute to denial and noncompliance with treatment, disabling anticipatory nausea and vomiting before chemotherapy, avoidance of tests and procedures, panic attacks, and overwhelming distress. Untreated anxiety increases the risk of alcohol and substance abuse. Multiple organic factors may give rise to anxiety disorders in cancer patients, including poorly controlled pain, altered metabolic states (e.g., hypoxia, hypotension), sepsis, neurologic disorders, endocrine disturbances (e.g., thyroid dysfunction), hormone-secreting tumors, and medications (e.g., steroids).

The management of anxiety symptoms begins with the provision of emotional support and information to the patient and family. Patient education may offer substantial relief through identification of anxiety symptoms, explanation of the interplay of psychological and somatic symptoms, and reassurance that severe distress is treatable. Often the physical symptoms, such as sweating, tremor, dyspnea, or chest tightness, cause even greater anxiety in cancer patients who may already be somatically preoccupied. There are many possible psychotherapeutic and psychopharmacologic interventions available for the treatment of anxiety symptoms.

Many patients are helped through behavioral techniques, such as relaxation, distraction, and cognitive reframing. In addition to behavioral treatments, individual psychotherapy and group interventions have been demonstrated as effectively reducing anxiety in cancer patients. Studies of group interventions that included education, emotional support, and behavioral training demonstrated benefits of less tension and fewer phobias (trend) than was found in the control groups. Many patients with intermittent anxiety or simple phobias find relaxation therapy and distraction techniques helpful. When the need for a diagnostic procedure or treatment is urgent, benzodiazepines should be used.

Phobias related to medical procedures are common in children with cancer and also are problematic in some adults. While careful attention to preparation of children in advance of painful procedures (e.g., role playing) may limit the incidence of anxiety, specific behavioral interventions, including relaxation training and distraction, may be indicated for some symptoms. Self-hypnosis is a highly effective treatment for both generalized anxiety and specific phobias in children and adolescents.

Before being treated with an anxiolytic, all patients should be screened for depressive symptoms as well as for other symptoms in the anxiety disorder spectrum, such as posttraumatic stress disorder and obsessive-compulsive disorder. Anxiety and its associated somatic complaints often accompany depression, and effective treatment, therefore, may require use of an antidepressant in conjunction with, or instead of, a short trial of a benzodiazepine. The experience of cancer treatment may reawaken longer-standing problems in patients who have been the victims of previous trauma, increasing their risk of anxiety and depressive symptoms.

Benzodiazepines (lorazepam, alprazolam, and clonazepam) are the drugs of choice for acute anxiety states. Table 56.5-3 lists the usual initial dose of benzodiazepines, approximate dose equivalent, half-life, and presence or absence of active metabolites. The dosing schedule depends on the patient's tolerance and the anxiolytic's duration of action. The shorter-acting benzodiazepines may be given four or more times a day. Lorazepam and alprazolam are favored in the acute setting due to their rapid onset of action and thus are efficacious when prescribed on an as-needed basis. Lorazepam is available in both oral and parenteral forms and has both anxiolytic and anxiolytic properties. Clonazepam is substantially longer-acting, offering the benefit of ease of administration as well as avoiding the potential for recurrent anxiety between doses and rebound symptoms of worsened anxiety. It is best to increase the dose before switching to another agent in patients with persistent symptoms, as there is substantial variability in patient tolerance of the benzodiazepines and in effective dosages. The most common side effects of the benzodiazepines are dose-dependent and include drowsiness, confusion, and poor motor coordination. These occur more frequently in older patients and in those with impaired liver function. The synergistic effects of the benzodiazepines with other medications with central nervous system depressant properties, such as narcotics and some antidepressants, can contribute to excess sedation. When the dose is lowered, uncomfortable sedation often disappears, while the antianxiety effects continue. Lorazepam is rarely excited and, hence, is better tolerated by patients with impaired hepatic function and by those taking other medications with sedative effects (e.g., analgesics). There are effective alternatives to benzodiazepines, including other anxiolytics, such as buspirone. In addition, antidepressants with more calming-sedating side effects, such as nefazodone, mirtazapine, and paroxetine, have also been found to be beneficial in the treatment of anxiety. Low doses of neuroleptics (i.e., olanzapine, haloperidol, or thioridazine) are effective in patients with severe anxiety that is not controlled with maximal therapeutic doses of benzodiazepines, in patients whose anxiety leads to frank agitation, and for those who cannot tolerate benzodiazepines due to respiratory problems.

| Table 56.5-3 | Benzodiazepines Commonly Prescribed for Cancer Patients |
DELIRIUM

Delirium is common in cancer as a result of direct central nervous system involvement by tumor, paraneoplastic syndromes, and the indirect effects of toxic-metabolic sequelae of the disease and treatment (Table 56.5-4). The hallmark of delirium is impairment of consciousness, usually accompanied by global cognitive dysfunction, and abnormalities of mood, behavior, and perception. The onset is often rapid, and the course is usually fluctuating. The prevalence of delirium in cancer patients ranges from 5% to 25% in various studies and is substantially higher in terminal stages of illness.

| TABLE 56.5-4. Chemotherapeutic Drugs That Can Cause Delirium |

<table>
<thead>
<tr>
<th>Chemotherapeutic Drug</th>
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</thead>
<tbody>
<tr>
<td>Doxorubicin</td>
<td>Delirium</td>
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<tr>
<td>Cyclophosphamide</td>
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<td>Vinorelbine</td>
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<td>Vinblastine</td>
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Delirium is a syndrome of symptoms with multiple possible etiologies. Changes in mental status may be subtle or extreme, ranging from an appearance of mild depression or social withdrawal to severe agitation or hallucinations. Early symptoms of delirium are often unrecognized or misdiagnosed by medical or nursing staff as depression. Yet, early recognition of delirium is essential, since the underlying etiology may be a treatable complication of cancer. When faced with an abrupt behavior change in a cancer patient, the physician must investigate a number of potential causes of delirium. Particularly frequent metabolic causes include hypotension, hypercalcemia, malnutrition, and liver failure. Altered thyroid or adrenal status may cause delirium. Infections and brain metastases commonly cause delirium. Patients with hematologic malignancies are at especially high risk for opportunistic infection. Other cancers, such as those of the lung and the breast, frequently metastasize to the brain. Head and neck cancer patients undergoing surgery are at high risk for delirium because of their generally older age and the high prevalence of alcohol abuse and withdrawal syndromes. Many antineoplastic and immunotherapeutic agents (i.e., interleukin) can cause delirium and other changes in mental status. Corticosteroids can cause confusion, depression, mania, and anxiety. Antibiotics and antifungals, such as amphotericin B, can cause delirium, particularly with intrathecal administration. In seriously ill cancer patients, the etiology of delirium is often multifactorial. The delirium workup is tailored to the patient's specific cancer and medical condition at the time that the symptoms develop.

The management of delirium includes identification and correction of its underlying causes while symptomatic and supportive therapies are initiated. Symptomatic treatment for delirium includes medication management and supportive therapies. The delirium patient is helped to return to an environment that is as similar as possible to that which is familiar. Measures to help reduce anxiety and mild disorientation include a quiet, well-lit room with familiar objects, a visible clock or calendar, and the presence of family, if they can increase structure and familiarity. Judicious use of physical restraints to prevent self-harm, along with one-to-one nursing observation, may also be necessary. Often, these supportive techniques alone are not sufficient, and symptomatic treatment with neuroleptic or sedative medications is necessary.

As with other medically ill patients, neuroleptics are the mainstay in the management of delirium in cancer patients. Haloperidol is particularly useful because of its low incidence of cardiovascular and anticholinergic effects and its availability in parenteral and oral forms. Relatively low doses of haloperidol (1 to 2 mg/d) are usually effective in treating agitation, hallucinations, paranoia, and fear, and most cancer patients respond to less than 20 mg in divided doses over 24 hours. The more common side effects of haloperidol include akathisia and extrapyramidal side effects (cog-wheeling, masked faces, and gait disturbances). Dystonic reactions are treated with anticholinergic medications. Newer neuroleptics, such as risperidone and olanzapine, have not been studied in cancer patients; however, they appear to be well tolerated, with lower incidences of extrapyramidal side effects than haloperidol. They are not yet available in parenteral form. Methotrimeprazine (available in intravenous or subcutaneous form) and midazolam have been used to control confusion and agitation in terminal delirium.

PSYCHIATRIC SYMPTOMS IN CANCER PATIENTS WITH PAIN

There is clearly an increased incidence of depression and anxiety in patients experiencing severe pain. In the Psychosocial Collaborative Oncology Group study, 39% of patients with a psychiatric diagnosis experienced significant pain. In more than 80% of these patients, a depressive syndrome was diagnosed. In contrast, only 19% of patients who did not receive a psychiatric diagnosis had significant pain. The psychiatric symptoms of patients who are in significant pain must initially be considered a consequence of their uncontrolled pain. Acute anxiety, depression with despair (especially when the patient believes the pain means disease progression), agitation, irritability, lack of cooperation, anger, and insomnia may be the emotional or behavioral concomitants of pain. These symptoms are not labeled as a psychiatric disorder unless they persist after pain is adequately controlled. Undertreatment of pain is a major problem in both adult and pediatric settings. Aggressive pain management strategies, including narcotics, are essential to the emotional care of both physically ill children and adults. Long-term psychiatric sequelae of cancer are less likely in children whose pain is well treated. There is no evidence of increased risk of subsequent drug abuse in cancer patients receiving narcotic analgesia. In fact, most patients associate the narcotic effects with the unpleasant aspects of the illness and seek to avoid narcotics during their recovery. Effective pain management often requires substantial patient education and has been facilitated by recent advances, such as the growing emphasis on the use of adequate regimens of standing doses of analgesics with as-needed rescue dosing for breakthrough pain, and the advent of patient-controlled analgesia. Collaborative efforts between doctor and patient to identify problematic symptoms and negotiate treatment strategies depend on open communication about pain and its psychological sequela. A full discussion of issues in pain management is available in Chapter 58.

UNCONVENTIONAL CANCER TREATMENTS

The alternative therapies ranging from herbal treatments and spiritual teachers to acupuncture, physical manipulation, and mental imaging proliferated in the 1990s, and many "traditional" Western doctors are seeking to understand these modalities. Recent surveys suggest that 30% to 40% of the U.S. public use what are described as alternative or complementary therapies. The field is broad and encompasses many modalities and ideas. However, due to the lack of clinical trials of many of these therapies, conventional practitioners and alternative healers exist on opposite ends of the spectrum. Often leaving patients confused about how to integrate these differing perspectives. Despite this, the demand for these therapies has led insurers to offer some expanded benefits for alternative medicine.

The overlap of traditional and alternative therapies is particularly complex in the provision of psychosocial and behavioral treatments to cancer patients. Some of the psychological and behavioral methods that are used in medicine (i.e., psychological support, visual imagery, hypnosis, and relaxation exercises) for enhancing quality of life and symptom control are also included in unconventional therapies. A recent study of 480 women with newly diagnosed early-stage breast cancer found 28% used alternative medicine as a complimentary therapy. Interestingly, the use of alternative medicine was independently associated with depression, fear of recurrence of cancer, lower scores for mental health and sexual satisfaction, and more physical symptoms as well as symptoms of greater intensity. The study suggests that cancer patients seeking alternative medicine therapies may be experiencing anxiety, depression, or physical symptoms that should be addressed by the "traditional" medical system. Further, the study demonstrated that the use of these therapies does not always provide the sought-after panacea.

The urgency with which many cancer patients and families feel the need to seek any potentially beneficial or hopeful treatment option leads many to try any promising therapy that is offered. In the setting of tremendous fear and uncertainty, it is difficult for patients even to choose between conflicting traditional biomedical opinions, much less to navigate the uncharted waters of alternative treatments. Many patients elect untried or unproven therapies in their desperate search for a cure or for a
more acceptable quality of life, attempting any therapy “as long as it doesn’t hurt.”

There are real challenges for the clinician attempting to advise patients about the use of unconventional therapies. Many conflicts are born of the desire not to take away hope but also not to condone unproven treatments. There has been concern that some therapies that suggest that personality and behavior are the vehicle for recovery from disease or tumor regression place undue burden on patients who may hold themselves responsible for a negative outcome. Some patients feel empowered in the hopeful “heroic warrior” stance described by Gray and Doan and should be encouraged to maintain it. These patients benefit from the oncologist’s admission that there are still many unknowns and encouragement of their use of self-help books, visualization, efforts to improve mental attitude, and diet regimens, insofar as they find them to be helpful. However, there are other patients for whom the warrior myth is a distressing burden, leading to self-criticism and a sense of guilt because they cannot fight hard enough. The therapist will be responsible for their own death. Families may contribute to the patient’s guilt about dying, offering unrealistic advice and remedies in an effort to overcome their own feelings of helplessness and expressing frustration and anger with the patient’s failure to live up to their expectations and to fight hard enough. Further study of alternatives is important, as current research does not support the assertion that unconventional therapies prolong survival. However, there is no question that alternative therapies may play a substantial role in the patient’s experience of illness and quality of life.

PSYCHOTHERAPEUTIC INTERVENTIONS WITH CANCER PATIENTS

INDIVIDUAL PSYCHOTHERAPY

Although psychological interventions for patients with cancer were slow to develop, since the 1950s efforts to implement interventions have grown steadily because of a greater emphasis on quality-of-life concerns. The types of interventions most commonly used by health professionals working with cancer patients are education, behavioral training, groups, and individual psychotherapy. Fawzy et al. have provided a critical review of psychosocial interventions in cancer care that should be read by all individuals who are preparing to establish psychosocial support services for cancer patients.

Although some enthusiasts have advocated offering counseling to all patients on the assumption that they can benefit from help and will take advantage of it, many patients reject the offer of psychological help. In one study, only two-thirds of the patients identified as high-risk accepted counseling. Those who refused had a positive outlook, minimized the implications of their diagnosis, and viewed the offer of therapy as a threat to their emotional equilibrium. Patients who accepted counseling were less able to deny the diagnosis and its implications; they were less hopeful and were more apt to experience their situation in religious or existential terms. Starn et al. found that 20% of 449 ambulatory cancer patients seen in a single cancer center in Canada were referred and seen for psychological counseling over a 1-year period. Family and personal problems were the most common reasons for seeking help. Interventions most commonly applied are either educational or psychotherapeutic, including supportive, insight-oriented, interpersonal, and cognitive behavioral therapies.

Soukres et al. have described the focus of psychotherapy with the cancer patient as the emotional stress engendered by the illness, rather than the more general intrapsychic and interpersonal concerns of the physically healthy person. The therapist who is outside of the friend and kinship circle plays a useful role by encouraging patients to explore their own thoughts and feelings, which are otherwise unexpressed. Because of the strong bond felt by families for the therapist who took care of their relative over the course of a long illness, families often enter into a one- to ten-session bereavement counseling with the patient's therapist after the patient's death to provide a healing conclusion to a long illness.

GROUP PSYCHOTHERAPY

Group therapy may be advantageous for cancer patients, allowing them to receive support from others who have experienced and conquered similar problems of medical illness. The cancer patient, in a group setting, learns that there is a range of normal reactions to illness and a range of healthy adaptive coping styles and strategies that others have used to make adjustment to illness easier. Group participation helps decrease the sense of isolation and alienation because the patient and family can see that they are not alone in adjusting to illness. Groups for cancer patients or families (or both) are often disease-specific or targeted for patients at the same stage of different diseases. In the past, doctors had some concern about having the dying patient in a group with patients who were given an orderly prognosis or whose prognosis was uncertain. Although this has changed, many groups are likely to be successful. The Spiegel et al. report of greater longevity in a small number of women with advanced breast cancer undergoing group psychotherapy remains controversial, and replication with larger samples is needed.

SELF-HELP AND MUTUAL SUPPORT PROGRAMS

Self-help and mutual support programs are additional potential supports for patients and families. Life crises, such as life-threatening illness and bereavement, often are the impetus for individuals to seek emotional support from others experiencing the same trauma. Unique American in their inception, most self-help support programs work closely with professional medical services, thereby offering social support as an adjunct to medical care. Self-help groups or visitation programs help decrease the sense of alienation and isolation of patients because of the unique knowledge and sensitivity that volunteers bring from personal experience. Veteran patients facilitate coping by being a source of credible information about the needs of cancer patients, demonstrating constructive ways of managing and living despite illness, providing the motivation for rehabilitation and enhancement of self-worth, and encouraging patients to participate in their own treatment.

SURVIVOR ISSUES

Advances in the treatment of cancer in the last 30 years have led to improvement in both prognosis and quality of life, resulting in a rapidly growing population of more than 5 million long-term survivors, many of them children and young adults. Psychiatric sequelae of cancer include those related to the direct effects of the disease as well as those that are consequences of the treatments, of family factors, and of the individual psychology of the person. The long-term adjustment of survivors of childhood cancer appears to be largely unimpaired. Cured cancer patients have special medical and psychiatric concerns, including fears of terminalization of treatment, reoccurrence of disease and recurrence, and minor physical problems; a sense of greater vulnerability to illness (the Damocles syndrome); pervasive awareness of mortality and difficulty with reentry into normal life (the Lazarus syndrome); persistent guilt (the survivor syndrome); difficulty adjustment to physical losses and handicaps; a sense of physical inferiority; diminished self-esteem or confidence; perceived loss of job mobility, and fear of insurance discrimination. A recent book by Landy teaches patients how to handle many “nuts and bolts” issues of coping, such as insurance, career issues, estate planning, advanced directives, and home and hospice care. Concerns about infertility, often understandably submerged at the time of diagnosis and treatment, reappear when rigorous treatment concludes. The survivor's intellectual functioning is also a major concern. Children and adults with brain tumors or central nervous system involvement and those undergoing bone marrow transplant are at risk from both their disease and their treatment. Most have residual deficits with neuropsychological impairment, including compromised memory and cognitive test performance.

In coping with a variety of physical, social, sexual, employment, and insurance problems, survivors often report psychological distress at subsyndromal levels. The severity of these symptoms may vary by premorbid adjustment personality traits and site of cancer and treatment (i.e., bone marrow transplantation), but they usually do not interfere with reentry to family, social, or employment networks. Survival may be associated with an increased risk for delayed medical complications, including organ failure, central nervous system dysfunction, sterility, secondary malignancies, and decreased physical stamina. Sociodemographic, disease-treatment, and psychological distress variables only partially explain the wide variability in survivors' psychosocial dysfunction.

Special attention to identifying adolescent and young adult survivors most at risk for psychosocial dysfunction is needed. Adolescents who have been treated for cancer not only have the substantial physical, cognitive, emotional, and interpersonal tasks faced by all adolescents but have the added burden of integrating a life-threatening disease into their experiences. Persistent body image concerns, somatic preoccupation, disruptions in sexual relationships, and deficits in social competence are not uncommon. Fitz and Williams assessed 52 survivors of childhood cancer and their families who were more than 2 years past treatment. Two-thirds of the patients studied had excellent psychosocial functioning without serious social issues. Many expressed a positive effect of their illness and reported little depression. Illness variables were not predictive of psychosocial outcome, unlike some psychosocial variables, such as communication patterns and peer support. The National Coalition of Cancer Survivorship is an outgrowth of survivors' need for support. The political issues surrounding health and life insurance are a prime example of an area where research is needed to delineate problems, and advocacy is needed to encourage societal solutions.

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CHAPTER REFERENCES

SECTION 56.6
Community Resources

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INTRODUCTION

The impact of changes in the health care system has caused greater numbers of patients to be treated in an ambulatory setting. Services in this setting range from maintenance of central lines to chemotherapy, nutritional support, pain control, intravenous antibiotics, and blood support. Patients are not usually admitted to the hospital unless their condition is so serious that it meets an acute level of care. Ever-changing reimbursement issues along with an ever-increasing number of cancer survivors1 have placed yet a greater burden on the community to provide services for this often chronically ill population. 

Resource directories are regularly updated to include the latest evolving information. The American Cancer Society (ACS) and Cancer Care are just two sources that publish a comprehensive listing of services.2,3 These guides may be cross-referenced from the general to specific site of cancer and often provide information on a variety of services, including emotional support, financial assistance, and transportation resources. Additionally, increasing access to personal computers and the World Wide Web have allowed individuals to gather information in an unprecedented manner. Rimer points out that “communication is central to effective cancer control, from primary prevention to survivorship.”2 Although this information, along with the increasing fingertip access to the most current information, should theoretically allow patients to gather the assistance they require to live with their illness, a gap still remains between availability of these resources and specific individual needs. These gaps in provision of service occur across many communities and insurance carriers.

The individual diagnosed with cancer undergoes an experience that is intensely personal, that calls into question basic assumptions and expectations about life, and that somehow must be integrated into a sense of self, and thus involves the complexities of individual personalities. To deliver effective service, those who are working with this population must understand the adaptation that occurs. This adaptation involves incorporating a new sense of self after living through the crisis of diagnosis, initial treatment, potential side effects, and emotional impact on one’s self and one’s family. In addition to discussing individual adjustment, this chapter discusses different types of support and resources that may be beneficial to the patient and family, computer trends, the impact of an evolving health care delivery and reimbursement system, and survivorship issues, and concludes with a list of available resources.

INITIAL DIAGNOSIS OF CANCER

Cancer is the third major cause of mortality.5 More than 1 million people are estimated to have been diagnosed with cancer in 1999, and 584,000 people will survive their disease.1 Although these statistics present an increase in survivorship, the reality of living with cancer represents something quite different. Concerns must be broadened to view cancer as a chronic or curable illness. The majority of those 1 million people diagnosed with cancer must face their own mortality, but they then move from focusing on their mortality to dealing with their illness. It is incumbent on medical providers to help the patient participate in a plan to develop adequate internal and external resources for living with cancer.

The spectrum of reactions includes fear, shock, despair, anger, anxiety and, sometimes, total insensibility.3 In the 1970s, Weisman and Worden identified the immediate coping response of denial as appropriate, albeit temporarily.3 This is still valid today, but given the changing nature of today’s medical delivery system, we may need to help patients progress from denial to mastery in a more expeditious fashion. Although today’s cancer patients experience distress that is often not considered or reflected in the economics of treatment, they still desire and need psychosocial intervention to cope with their cancer. The medical system has resources that can address these emotions and enable a person to function more effectively. The physician may call on members of the team, such as the oncology social worker or oncology nurse, to assist in presenting the diagnosis. These team members can facilitate the understanding of the diagnosis in many distinct ways. The professional oncology team helps the patient move toward a sense of mastery over the situation. Assistance is provided so that a patient moves along a continuum through which control is gained and progress is made from a passive to an active state. This movement promotes an active course of treatment.

SOCIAL SUPPORT NETWORK

During the 1980s, the literature identified and recognized the importance of a social support network. Research has consistently found that people coping with cancer have difficulty with interpersonal relationships and that one’s social support system can alleviate these stressors.1 Although this network may not prolong the life of a cancer patient, it has been shown to enhance the quality of life one experiences. The providers in a social support network may be professionals from the community,
family, friends, significant others, organizations, and agencies. These providers enable the cancer patient to enhance their coping skills so that they may function in an effective, competent, and proficient manner. The literature continues to report that this social support network impacts positively on the psychological well-being of the cancer patient. The constructs of the social support system identified as emotional, informational, or instrumental as defined by Wortman is the structure in which we define support and resources for the cancer patient.

EMOTIONAL SUPPORT

Psychosocial interventions have consistently contributed to a positive outcome on the emotional adjustment of a person coping with cancer, and emotional support is frequently considered to be one of the most essential interventions. Family, friends, and those closest to the patient frequently provide emotional support. Dunkel-Schetter surveyed 79 cancer patients and found that 81% defined emotional support as most helpful, followed by informational support (41%) and instrumental aid (6%).

ASSESSMENT AND EVALUATION OF COPING SKILLS

Individuals deal with problems in diverse ways. It is important that the medical team identify an individual's ability to cope with stress so that they have some indication of how the patient will deal with their cancer. An assessment of other crises endured and how those were handled is particularly helpful in an assessment and evaluation. Studies have led to development of a profile of predictors of poor coping. Some indicators of the inability to cope with crises are character traits such as rigidity of behavior or morose, gloomy outlook on life. This type of patient may not be amenable to the support received or may need more intense intervention. Substance abuse, recent losses, social isolation, unemployment, or other debilitating illnesses may be warning signs that an individual may be more emotionally overwhelmed. Cancer causes much emotional distress in a person's life, and disruptions in routine functioning are normal. Some of these disruptions may have lingering effects and cause enduring problems. Traditional emotional support may not be enough for such individuals. Specialized or very individualized emotional support may be necessary for these patients to cope with cancer.

FAMILY AS EMOTIONAL SUPPORT

As the person diagnosed with cancer enters the health care system it is important for the professionals to recognize that this person rarely functions alone. The person who receives a diagnosis of cancer usually summons his or her closest family to become the immediate support system. As healthcare professionals, we must recognize the significance of including the family at times of diagnosis, recurrence, change in treatment plans, and terminal illness. The family system changes when the diagnosis is made. All members who interact with the patient should be aware of the potential changes and the subsequent impact on the family.

The family value and belief system must be identified so that help can be provided within the context of the sociocultural system. Fears are minimized and coping skills enhanced if understanding is provided within a familiar context. It must be recognized that cancer is not openly discussed in all cultural groups. Certain cultural groups may need special assistance to contend with a health care system in which the patient is expected to be an active participant. Roles within the family frequently change when a diagnosis of cancer is made. Family members may need help in evaluating whether these role changes are comfortable for them. In addition, a family member who is also a health care professional, and particularly an oncology health care professional, may need help in maintaining the role of a family member rather than becoming the resource person. The alacrity to help is frequently seen during the initial crisis of diagnosis. This is the time a family pulls itself together and offers whatever resources they can provide for the newly diagnosed patient. As the illness extends over time and sometimes becomes chronic, family support may wane and become difficult to sustain. It is at this time that patients and families may need to find resources outside the immediate family system.

EMOTIONAL SUPPORT OUTSIDE THE FAMILY SYSTEM

The social support network, as identified earlier, includes friends, neighbors, both self-help and professionally facilitated support groups, religious groups, community agencies, and health care professionals. A review of the literature has indicated that making use of emotional support, whether informal or formal, can relieve distress. It is important that there be some commonly perceived in the support system. People undergoing similar experiences may find it easier to relate to each other because the cancer is accepted more easily. If the perception is that a situation is understood, empathy can be accepted and emotional support to the patient becomes positive. The validity of the cancer patient's experiences must be recognized by the support system for support to be effective. A member of a support system who truly does not understand the trauma cannot minimize the anxieties and fears of the cancer patient. Support is not effective in a situation in which real feelings are not recognized.

VISITATION GROUPS

The changing scene of health care delivery has affected visits by volunteers. The ACS has many groups maintained by volunteers who have had cancer experiences. Reach to Recovery, CancerSummit, and the ostomy programs all have volunteers who have undergone some type of cancer experience. In the past, these volunteers were able to visit with newly diagnosed patients in the hospital. In today's health care system, patients are admitted and discharged quickly, and frequently their procedures are performed in 1-day surgery centers, so there may not be time for these volunteers to visit. Health care professionals must take special care in providing patients with information about these groups, and patients must be encouraged to become proactive and make the first contact themselves. The health care professional that one meets in the hospital or surgical center is an invaluable source of information. Cancer Information Service, reachable at 1-800-4-CANCER, can also help patients with local resources.

SELF-Help GROUPS

An extensive network of self-help groups exists for the cancer patient. Self-help groups are frequently formed by people with similar interests or concerns, and many of these groups are disease specific. They may meet weekly, biweekly, or monthly. These groups are not professionally led; rather, they are a gathering led by the peer participants, although medical professionals may be invited to present their particular expertise. Information about self-help groups can be accessed through the National Self-Help Network. This organization is listed individually in each state.

SUPPORT GROUPS

Support groups are available in most communities and are facilitated by health care professionals. The professional has the responsibility of establishing a group that is cohesive and has the goals of providing educational and emotional support. Groups may be established for patients, for family members and significant others, or for patients and family together. Although no positive correlation has been made that support groups have cured disease, improved survival of patients in support groups has been found. Although emotional support and social support are separated for descriptive purposes here, they are frequently intertwined and inseparable. The family member who transports a cancer patient for daily radiation treatments is both part of the social support system and is also providing the necessary emotional support.

ROLE OF THE MEDICAL TEAM IN EMOTIONAL SUPPORT

The medical team is comprised of a number of people who can assist the cancer patient. Social workers, clinical nurse specialists, psychologists, psychiatrists, and nutritionists are often available to provide services. Although these professionals may not be immediately available in every setting, referrals can be made for consultation. Ancillary personnel have become more important in today's system of health care delivery. Many concerns cannot be addressed in the leisurely manner of years ago. Specialized health care professionals can also help a patient navigate the health care system with greater ease and less stress.

INFORMATIONAL SUPPORT

It is axiomatic that knowledge is power and that cancer patients and families who know more about the illness and are actively involved in treatment decisions cope better than those who are more passive. It is this demand for knowledge and information that helps such individuals feel less powerless and helpless and more in control of the situation. The need for information depends not only on individual preference for control, but on a person's educational, cultural, and financial background. In the past, initial cancer information was obtained in the physician's office or hospital. Today, 22 million adults use the Internet to find health
information, and 70% search for information before even meeting with a physician. Dr. Gaiser, of the Cancer Information Service in Heidelberg, Germany, analyzed when inquiries were made to the service. Forty-three percent of the requests in 1996 occurred before the patient's second treatment, illustrating the patient's need for earlier information.

According to Fensler and Cannon patients with cancer benefit from education in terms of their ability to care for themselves, enhanced self-image and self-esteem, improved symptom management, reduced anxiety and reduced disruption in daily life. Other benefits of education include increased participation in treatment decisions and improved understanding of the disease process and treatment options. There may be some inherent differences for some individuals in obtaining information because of personality style. Too much information can increase anxiety for some people and cause greater difficulty in coping. It is therefore important to first assess a person's readiness to receive information by reviewing their cultural and socioeconomic background, literacy, educational level, psychological adjustment, and personal preferences for control.

Because culture influences the very meaning of the disease to the individual, it is imperative to understand that person's background, values, and beliefs. Communities also vary by culture, implying that culturally sensitive material must be developed. Providers must explore the patient's educational level and determine how to maximize both comprehension and retention of material while encouraging greater patient participation in decision making and encouraging greater dialogue with the health care team. Harris talks about individuals with poor reading skills having greater difficulty understanding instructions and integrating them into their activities of daily living. As already mentioned, a diagnosis of cancer is a psychologically traumatic event. One's disposition affects how well the information is integrated and remembered. It has been suggested that individuals who try to maintain self-control are more likely to be compliant with health care regimens. They also tend to seek more detailed information and are therefore more involved in treatment decisions. Those individuals who give more control to the team are more of a challenge to educate and are not as receptive to the information. Lastly, a patient's financial situation directly impacts his or her ability to obtain information.

In summary, the best education occurs when there is open communication, awareness of the patient's needs, minimization of the patient's stress level, and a caring attitude on the part of the professionals. Patients are sensitive to the health professional's voice, body language, eye contact and proximity. It is crucial to meet and talk at an appropriate time and place while being supportive, encouraging, and personal in style. Print materials are often helpful, particularly those endorsed by the physician; however, screening for low-literacy populations is mandatory. Social workers can often remove barriers that may hinder education by facilitating communication or by connecting to community resources whose main goal it is to educate the public.

INTERNET

The Internet can increase knowledge and hasten the pace of obtaining this knowledge via the following online services:

- E-mail: Messages are posted electronically, facilitating instant communication. By 1998, 1,300,000 pieces of e-mail per week were being processed by the cancer-related listservs hosted by the Association of Cancer Online Resources. That same year, 22.3 million Americans performed online searches for medical and health information.
- Mailing lists and listservs: Through e-mail, one can subscribe to specific mailing lists, through which information is shared regarding similar interests.
- World Wide Web: The Web allows easy access to an unlimited amount of information. One can research particular interests via search engines such as Yahoo, Excite, AltaVista, or a host of others.
- Bulletin boards: Electronic message boards allow one to post a message concerning a specific topic while not needing to be on the computer simultaneously with others.
- Chat rooms: In these forums, one can participate in "live" conversation, usually in regard to specific topics. These gatherings may be formalized with a facilitator or be used for informal discussion purposes.

Professionals, patients, and caregivers are using these Internet resources regularly. In the past, information was unidirectional, from health professionals to patients; now many patients are seeking out this information for themselves. Although access to this information is valuable, it is not without issue. People on the Internet are not always as they present themselves, and information obtained may be inaccurate or misleading. Because material can be posted on the Internet without proper oversight or professional review and because people have a tendency to believe what they read, reliance on the Internet for information can cause potential harm. Web sites should be evaluated by the same five criteria generally used for printed material, including evaluation of the authority, accuracy, objectivity, currency and coverage, and intended audience of the information.

- Is an author listed? What are the author's qualifications? How reliable is the information? Has the material been reviewed by editors? Is the information provided without bias? Is the content up-to-date with date listed (of both creation and revision)? To what depth are the topics explored?
- It is extremely important for health care professionals to encourage access to this new technology but also give caution about the potential pitfalls. In general, it is advisable to encourage patients and family members to start their searches with reputable sites. C. Everett Koop, former Surgeon General, has a Web site (World Wide Web URL: http://www.drkoop.com) that rates approximately 10% of the 15,000 health-related sites on the Internet for credibility, content, and opportunity for feedback. A list of cancer-related Web sites appears in the appendix at the end of this chapter.

COMPUTER GROUPS

Groups have been long cited in the literature as an effective means of treating individuals with cancer. These groups often provide information, education, and support that enhances survival outcomes, but today the strain of diagnosis and the rigors of treatment combined with concerns about confidentiality often discourage patients from attending these groups. In the past, people had to physically leave their homes and go to hospitals, physicians' offices, religious houses of worship, or community centers to attend a support group. With the advent of personal computers, Internet support groups have become popular. In 1998, more than 40% of households owned a computer. The ability to use computer technology has assisted individuals in overcoming barriers to group participation, such as groups that meet at an inconvenient time, transportation difficulties, physical ill health, inclement weather, or the stigma that may be associated with attending the group. Computer networks have been described as a "support group without walls." Advantages to computer group membership include increased patient control of both time of participation and of information disclosed or obtained, safety to discuss difficult issues, availability of information, and subsequent support. The system also has been described as empowering. These groups also benefit individuals with hearing or speech disabilities. Logical obstacles, such as time spent in the assembly of the group or in travel, cost of transportation, facility costs, and scheduling problems, are overcome. An additional important benefit is anonymity. Anonymity may lead to greater self-disclosure, honesty, and intimacy while allowing specific issues to be more quickly discussed as well as discussion of taboo topics that may be difficult to discuss in person. One of the major disadvantages is decreased interpersonal relationships. Although anonymity may be an advantage, the inability to see individuals, hear their voices, or read their body language may encourage isolation or interfere with empathy. Technological problems have been noted, including computer malfunction, cost of telephone lines and computers, access to such equipment, illiteracy, and patient discomfort with technology. Another challenge has been to facilitate group process. Individuals who are less verbal may not be encouraged to participate as much as in a face-to-face group. Trust may take longer to develop, and feedback may be more gradual. Because one must wait for feedback (and some individuals do not have good typing skills), response rate may be altered. The group leader may have more difficulty interpreting, setting limits, and tracking patterns. More recent technological advances now allow individuals to actually "speak" to each other online. The Internet site Yahoo! allows individuals with the use of a microphone to download their software for free, thus enabling them to talk and hear others. A "conference" across the Internet can occur, which may counteract decreased proficiency with typing and other discomforts that the patient may have.

Fensler and Manchester evaluated the use of a computer network (CompuServe Information Service's Cancer Forum) both by individuals and those supporting them. They found that respondents began using the network within 4 months of diagnosis and continued through all stages of the diagnosis. They concluded that "information seeking is a common coping strategy, both initially and throughout the cancer experience." Both patients and caregivers were positive about the information and support received via the computer, and this may be a "convenient alternative to traditional information and support services."

INSTRUMENTAL SUPPORT

As health care delivery evolved during the 1990s, emphasis shifted to ambulatory care. Most medical care is now provided on an outpatient basis, which can create additional stressors for the patient and support system. In a study done by Emanuel et al., more than 86% of the population surveyed indicated a need for
assistance. Sixty-two percent indicated a need for transportation assistance, and 55% indicated a need for homemaking assistance.

Transportation can sometimes emerge as a barrier to quality treatment. Medications that were previously administered in the hospital are now given on an outpatient basis and may not be covered by insurance. Home care and medical equipment needs may be intensified as hospital stays have become abbreviated.

**FINANCES**

The cost of the illness and the financial impact on the patient and family has been well documented. The direct cost of the illness as well as incidental expenses such as transportation, parking, and child care can be overwhelming to patients. Mor and associates interviewed 217 people with cancer and found that 87% had experienced a significant increase in monthly expenses directly related to the disease. Wang et al. indicated that minorities had more concerns about finances than whites. For the elderly and others on fixed incomes, the uninsured, and the unemployed, these expenses become significant barriers to continuing treatment.

Patients are often reluctant to discuss their finances with physicians and may feel more comfortable with another member of the medical team. A social worker can do an in-depth financial assessment, including a full discussion of insurance coverage and subsequent referral to available resources. Constant reevaluation of insurance coverage is necessary as insurance changes with employment changes, managed care providers differ in services offered, and family income changes. Patients may feel pressure, either self-imposed or by hospital and physicians' offices, for prepayment or payment of outstanding bills, adding to the stress of contending with cancer.

Coverage for medical care costs in the United States comes from four main sources: the federal government, employers and private health insurance, state and local government, and private households. Exploration of privately funded sources should be made with the assistance of the social worker. Cancer Care is an agency that frequently assists with finances. Home and communities may have funds established from donations that help with finances for the cancer patient.

The federal government funds the Medicare program and the Social Security Disability program. Eligibility is governed by age or permanent disability for Medicare application and by work history for Social Security Disability. Eligibility for Medicaid and local welfare programs always involves a means test, although this test differs regionally. Application for Medicaid programs is made through the state department of social services. Local aid is available through individual towns to those who have state applications pending or do not meet a particular state’s eligibility requirements. A newly diagnosed, unemployed, uninsured person might be eligible for these entitlements.

**TRANSPORTATION**

Patients often live at great distances from treatment centers or are too debilitated to drive themselves. Transportation becomes a major issue in accessing proper care. Family members, although well meaning and caring, may not be able to devote as much time and energy as they wish to provide transportation. Transportation to doctor appointments or home from the hospital is infrequently covered by insurance. In a study of the terminally ill, it was found that 62% of patients indicated a need for help with transportation. Transportation needs for economically disadvantaged patients were particularly troublesome.

The ACS, the American Red Cross, and the Leukemia Society are agencies that exist nationwide and assist in transporting patients to medical care. In many areas, local towns or regional districts provide transportation to medical appointments. Resources change frequently, and it is necessary to investigate local services to assess availability.

**HOME HEALTH CARE**

Home health care provides for those patients who do not require hospitalization, and it is the most rapidly expanding segment of the health care industry today. Agencies, visits, and services have multiplied exponentially due to two major influences—demographic changes and managed care. Each year, almost 500,000 new senior citizens are added to the census, and there is steadily increasing pressure from insurance companies and managed care programs to search for the least expensive treatment method and to emphasize the least appropriate level of care, low-cost alternatives, and early discharge from hospitals and other health care facilities. As the trend toward home care has grown, patients are becoming more familiar with the concept of this type of care in today's health care delivery system.

To be eligible for home care services, a patient must be homebound and require skilled nursing services. Short-term custodial services are provided after the these criteria are met. The value of home health care to both patient and family has been confirmed in a study by Groebe and colleagues. Home health care also provides for continuity of care between physician visits.

**HOSPICE**

Hospice home care is available for patients living at home and requiring nursing care who have a prognosis of 6 months or less. The first hospice was organized in Connecticut in 1974; in 1996, more than 3000 hospice programs were caring for close to 500,000 dying patients in the United States. A patient can be eligible for hospice home care even while receiving chemotherapy or radiation outpatient services. In addition to providing nursing care, emphasis also is placed on patient and family support. Physicians, nurses, social workers, clergy, volunteers, aides, and other ancillary personnel work together to provide services to patients and families from diagnosis through bereavement. This service can be invaluable for those dealing with a terminal illness.

**BARRIERS TO EFFECTIVE HOME CARE**

Home care should provide the support, reassurance, and medical assistance necessary to help patients function while remaining in the comfort of their own home environment. The success of a good home care plan depends on the skills of the professional responsible for planning this service before patient discharge from the hospital. A serviceable home care plan also relies heavily on family support and family caregivers. Most insurance companies follow Medicare guidelines and usually provide for a maximum of 2 to 3 hours of home care daily.

The burden of home care usually becomes the responsibility of the primary caregiver, who, although frequently willing to provide care on a time-limited basis, cannot continue to do so for an extended period. Patients may lack knowledge regarding the available services or may be unable to afford services to supplement insurance–covered home care. In some areas, geographic limitations exist, and not all services are available in all areas. Rural regions, in particular, usually have a dearth of available services.

The growing number of home health care agencies, although ensuring a degree of competition, can make it more difficult for patients to select the agency that is most appropriate for them. Selection may be based on availability, patient and family needs, reimbursement, cost, or insurance dictates. Agencies that provide home care services may be Medicare certified, public health departments, and proprietary agencies, both profit and nonprofit. Services offered can include nursing, home health aides, social work, physical therapy, occupational therapy, speech therapy, nutritional assessment and monitoring, laboratory work, and inpatient therapy.

In caring for a patient at home, the caregivers must provide various levels of support. Needs may range from the highly technical to simple companionship and monitoring for safety. Technical support can be received from a home health care agency, whereas less technical support, such as housecleaning, shopping, or cooking, may be available from church or synagogue groups or senior center groups.

**MEDICAL EQUIPMENT**

At various times during the course of treatment for cancer, a patient may need special medical equipment or require modification to their home. The medical team should make this assessment before discharge from the hospital or during the course of treatment. Home health care personnel can also complete a safety evaluation. Insurance may cover these items, but only when prescribed by a physician. The ACS and Visiting Nurses Association often have loan closets in which equipment owned by such agencies is stored and available, usually free of charge. It is critical that the patient and those providing care be given ample instruction in the care and use of any equipment, including emergency access numbers for urgent problems.

Case managers now have access to a remote patient monitoring system called a telemedicine system. Images are transmitted via telephone lines and a video camera to allow various segments of the health care community, including physicians, clinic staff, and home care companies, to view patient images. More than 250,000
diagnostic telecardiology readings were done in the United States in 1997, and most commonly, teledermatology is used to monitor vital signs. Dr. Ace Allen, editor of "Telemedicine Today," stated that patients with chronic diseases could be better managed if they received ongoing monitoring at home. Despite the expansion of teledermatology, the volume of patients receiving services that use this technology remains relatively low (approximately 21,000 in 1996). Currently, the evaluative data on teledermatology consultations are not definitive and need further exploration, particularly in the areas of insurance coverage, cost-effectiveness, and state-of-the-art evaluation.

TRENDS AFFECTING DEMAND FOR COMMUNITY SERVICES

Because significant changes in the health care environment affect the need for specific resources, it is necessary to discuss them even though they remain in a continual state of flux. The maelstrom of public debate early in the 1990s swirled around the concerns of escalating medical spending, suboptimal care, and along with increasing awareness that a significant contingent of Americans has no health insurance or inadequate insurance. Since Congress rejected President Clinton's proposal for health care reform, the most significant issue has been how to protect consumers from restrictions or access to care by managed care organizations. All states have a contact for health insurance complaints at the National Association of Insurance Commissioners (http://www.naic.org).

The percentage of health maintenance organization (HMO) members in for-profit organizations increased from 12% in 1981 to 62% in 1998. Typical issues that have arisen include the fact that the number of Americans without insurance increased to 16.1% in 1997 and that 100,000 Americans lose their health insurance each month. According to the latest U.S. census report, a total of 44.3 million Americans were uninsured in 1998, which was 1 million more than just a year earlier. Childless Hispanics, and part-time workers were affected the most by these insurance losses. Kuttner also states that the number of inadequately insured people is growing even faster. This development is related to several trends in coverage, namely the deterioration of employer-provided coverage that insures two out of three Americans. Employers have streamlined employee choice of plans while shifting the costs to the employee and sometimes terminating coverage because of the high cost of premiums. Some plans limit benefits, such as prescription coverage, or charge higher copayments and deductibles. In addition, "casual" employees and part-time workers rarely receive insurance coverage, yet these groups accounted for approximately 29% of working Americans in 1997. Americans with the broadest choice of plans are either government workers or those insured by Medicare or Medicaid.

The 1985 Consolidated Omnibus Budget Reconciliation Act (COBRA) allows people to leave their jobs and pay privately for their insurance, but it does not consider the expense involved. Although the Health Insurance Portability and Accountability Act (HIPAA) prohibits denial of those with preexisting conditions, this cost is so exorbitant that it becomes self-limiting, protecting only a few hundred thousand people instead of the potential 25 million who have lost insurance. A 1998 study by the Lewin Group for Consumers Union found that one in eight families spend 10% of their income on premiums and out-of-pocket expenses, but the number increased to two in ten in families with a family member between the ages of 55 and 64, and to five in ten with a family member older than 65. Thirty-four percent of insured adults have been in their plan for less than 2 years, which results in lack of continuity of care and inability to track patterns, pointing to additional problems with managed care and needed resources.

Congress has considered patient protection legislation, including allowing subscribers to bring suit against their HMO. Managed care forces practitioners to search for the least expensive treatment method and emphasizes the lowest appropriate level of care. In addition to these issues, it has been determined that trust and confidence in managed care plans decreased 12% from 1998 to 1999 (42% to 30%) in a survey of 160,000 households in 1999 by the National Research Corporation. A Kaiser Family Foundation survey found that physicians overwhelmingly report that HMOs have denied coverage, resulting in a decline in patient health care. A state audit of denial for hospital services concluded that questionable judgment is used in denying care, and a Washington state study found a pattern of improper denials for emergency room treatment. However, according to Karen Ignagni, chief executive officer of the American Association of Health Plans, health plans have heard the public's concerns and have subsequently developed "point of service" plans and grievance procedures and are incorporating independent external review. She believes that if Congress continues down its current path of allowing managed care organization decisions to be questioned in the courtroom, HMOs will not be able to challenge the dangerous levels of misuse of health care resources and that continued variations in medical practice may threaten patient safety. Nonetheless, these coverage denials have placed an all-encompassing burden on the general public, adding the emotional burden of having to advocate for themselves while they are physically compromised and financially vulnerable.

As prescription costs continue to increase, many of the elderly are flocking to "managed Medicare" policies, because traditional Medicare does not cover this service. Although the managed care plans may be enticing, patients may not realize the involved restrictions that are imposed. Many professionals are advocates for the effort to "shift power not from physicians and hospitals to patients but from managed care companies, insurance companies and health care facilities to patients and their physicians." In 1999, a for-profit managed care company hired a liaison to "quell a mounting rebellion by doctors upset with new rules the insurer is trying to impose on them," including finding the cheapest way to treat patients, even if another treatment would be more beneficial, and penalizing physicians who refer to out-of-network providers, even if the patient requires the specialist services. It is precisely these types of restrictions from which the public must be protected.

Between 1998 and 2002, hospitals nationwide are expecting a $71 billion reduction in Medicare payments resulting from the Balanced Budget Act of 1997. These reductions, combined with Medicaid shortfalls, will potentially compromise the current level of care provided by hospitals. Because individuals are now hospitalized for shorter periods, the multidisciplinary team often is no longer able to help patients adjust to a new diagnosis while anticipating the next phase of the illness and adaptation to its demands. Often, a social worker or discharge planner assisted the patient and family with transition to the community and assessed the barriers to care and, subsequently, planned for appropriate intervention. Although reimbursable services are obtainable, a wide gap in financial assistance faces patients without adequate coverage. Because of the concerns, many suggestions have been put forward for a universal health policy, thereby allowing greater access for a majority of Americans.

SURVIVORSHIP

The National Coalition of Cancer Survivorship defines survivors as living through and beyond a cancer diagnosis. Currently, approximately 8 million cancer survivors are alive and for the first time since the 1930s, the death rate of this disease has decreased and is leveling off or declining in all major body sites. These statistics are mainly true for the nonminority community. According to McDonald, African Americans continue to have higher incidence rates and are at greater risk of dying from cancer than any other racial or ethnic group.

Dow et al. sent surveys to 1200 National Coalition of Cancer Survivorship members to explore quality-of-life issues for survivors. In a sample of nearly 700 people, the top emerging quality-of-life-related themes to fatigue and pain, menopausal symptoms, and reproductive and fertility concerns, as well as to fears related to recurrence, second malignancy after treatment. Issues such as these encouraged the National Cancer Institute (NCI) to create the Office of Cancer Survivorship in July 1996. Additional issues reported by the NCI include fear of recurrence, late effects of treatment, the economic burden of the disease, psychological difficulties, depression, and sexual problems. Psychosocial difficulties occur more often with those who have had more aggressive initial treatment and those who have experienced a relapse. Additional concerns include cognitive deficits, such as in memory and concentration. Cases of discrimination in the workplace also have been reported, with their subsequent economic burdens. Klausner, director of the NCI, has stated that "the NCI has a responsibility to direct its efforts to issues that concern survivors, and organizations such as the Leukemia Society are following suit." Continuing assessment of quality-of-life issues, along with appropriate interventions in the community, can enhance the lives of the ever-increasing number of cancer survivors. New and creative resources must be developed to meet the needs of this growing population, such as the technology that now allows for removal, freezing, and reimplantation of a woman's ovary to restore fertility.

APPENDIX: COMMON RESOURCES

This appendix lists the most commonly used and helpful resources, to which most of the populace can gain easy access.

BONE MARROW TRANSPLANTATION

- Barbara Ann DeBoer Foundation: Identifies and makes use of resources in the patient's community to raise the funds necessary for the procedure. 1-800-895-8478.
- Blood and Marrow Transplant Newsletter: Provides a newsletter, resource directory, and patient support through telephone or e-mail. Keeps a list of attorneys who advocate for patients where insurance coverage has been difficult. 1-888-597-7674.
- Bone Marrow Transplant Link: Provides educational booklets, resource guides, and peer support via the telephone. 1-800-LINK-BMT.
• Bone Marrow Transplant Family Support Network: Provides support for newly diagnosed patients with recovered bone marrow transplantation patients. Offers counseling, groups, and insurance assistance. 1-800-825-9376.
• Caitlin Raymond International Registry: An international search coordinating center that assists individuals in finding compatible bone marrow donors. 1-800-726-2824.
• National Children's Cancer Society: Provides financial assistance for children diagnosed before 18 years of age in need of a bone marrow transplantation. Assists with fund-raising efforts and provides education, information, and patient advocacy. 1-800-882-6227.
• National Marrow Donor Program: Central registry facilitating searches and matches of donors and recipients. 1-800-654-1247.
• National Transplant Assistance Fund: Helps individuals raise funds for medically related transplantation expenses. Offers direct financial assistance in the form of grants to eligible candidates. 1-800-642-8399.
• Children's Organ Transplant Association: Helps families to raise funds for transplantation-related expenses. 1-800-366-2682.
• The Bone Marrow Foundation: Provides limited financial assistance for adjunct costs associated with bone marrow transplantation. 1-800-365-1336.

CAMPS

Contact the local ACS (1-800-ACS-2345), Cancer Information Service (1-800-4-CANCER), or Children's Oncology Camps of America (803-434-3503) for a listing of local camps.

CARE FACILITIES

Care facilities provide for the continuous health-related care of patients who are temporarily or permanently no longer able to manage living in their home. Various levels of care are available, and patients should explore these services with their physician or social worker to ascertain the most appropriate level of care. Patients should also confer with their insurance company to determine coverage.

Licensed boarding home: Provides a room and meals to fairly independent individuals. Health aides are often on staff.

Intermediate care facility: Provides limited nursing supervision and care.

Skilled nursing facility: Provides medical and continuous nursing and health-related services to patients who are not in the acute phase of an illness but who require an inpatient setting.

Subacute facility: Provides continuous medical, nursing, and health-related services to patients in a semiacute phase of their illness. These patients usually require high-tech care, such as total parenteral nutrition and intravenous antibiotics.

Hospice: Provides supportive care, terminal care, or symptom control to patients in various stages of cancer.

Rehabilitation: Provides services to patients with the goal of restoring them to an adequate level of functioning.

CHILDHOOD RESOURCES

Candlelighters Childhood Cancer Foundation: Provides information, support, and advocacy to families of children with cancer, survivors of childhood cancer, and professionals who work with these populations. 1-800-366-2223.

Children's Hospice Foundation: 1-732-840-4533.

Children's Hospice International: Provides support, education, resources, information, and referrals for the care of ill children and the professionals who work with them. 1-800-242-4453.

Compassionate Friends: Provides assistance with bereavement issues after the death of a child. 630-990-0010.

Many people coping with a diagnosis of cancer now turn to their computers for cutting-edge information. When researching these databases, patients should always be aware of the source of information. Is it an informed oncology professional organization or credible institution? The following (Tables 56.6-1 and Table 56.6-2) is a representative listing of the numerous commercial databases that can assist in accessing oncology information. Many databases and associated links exist for specific cancers. To obtain a more comprehensive list, search engines can be used, such as About.com, Achoo, AlCancer, CiteLine, Physicians’ Choice, MedNets, Medscape, Medical Matrix, Medsite, and Yahoo!

Organizations with Online Services

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<tr>
<th>Name</th>
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<td>American Association for Cancer Research</td>
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<td>American Brain Tumor Association</td>
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<td>American Cancer Society</td>
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<td>American Institute for Cancer Research</td>
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<td>American Lung Association</td>
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<td>BMT Newsletter</td>
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<td>Cancer Information Service</td>
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<td>Candlelighters Childhood Cancer Foundation</td>
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<td>Coping Magazine</td>
<td>E-mail: <a href="mailto:copingmag@aol.com">copingmag@aol.com</a></td>
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<td>Compassionate Friends</td>
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<td>Cure for Lymphoma Foundation</td>
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<td>Friends Network/Fun Letters</td>
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<td>Gillette Women's Cancer Connection</td>
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<td>International Myeloma Foundation</td>
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<td>Susan B. Komen Breast Cancer Foundation</td>
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<td>Leukemia Society of America</td>
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<td>Lymphoma Research Foundation</td>
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<td>National Alliance of Breast Cancer Organizations</td>
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<td>National Childhood Cancer Foundation</td>
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<td>National Coalition for Cancer Survivorship</td>
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<td>National Hospice Organization</td>
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<td>National Lymphedema Network</td>
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<td>National Marrow Donor Program</td>
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<td>National Ovarian Cancer Coalition</td>
<td><a href="http://www.ovarian.com">http://www.ovarian.com</a></td>
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<td>National Patient Air Transport Helpline</td>
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<td>National Prostate Cancer Coalition</td>
<td><a href="http://www.nppc.org">http://www.nppc.org</a></td>
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<td>Patient Advocate Foundation</td>
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EMOTIONAL SUPPORT

In the cancer experience, stress commonly occurs at the time of diagnosis, during the treatment phase, at the end of treatment, at time of relapse, or during the terminal phase. To adequately cope with the impact of cancer, emotional support is essential for both the patient and the caregiver. Although some individuals may choose to procure support from intimate sources, others look to the community for support. Community services include self-help, professional, individual, or group modalities. Ambulatory and hospital-based settings may provide social work, psychiatric therapy, and pastoral care services.

American Cancer Society: The ACS sponsors the following programs. Contact your local ACS at 1-800-ACS-2345, as programs may vary.

- Cancer Survivors Network: Provides one-to-one telephone or computer support to cancer survivors.
- I Can Cope: Support group for individuals with cancer and their families.
- Look Good Feel Better: Provides assistance to individuals with cancer regarding skin and hair changes.
- Man to Man: Support for men with prostate cancer.
- Reach to Recovery: Provides support, information, and education to women who have been diagnosed with breast cancer.
- Road to Recovery: Provides volunteer drivers to assist with transportation to and from physicians' offices or hospitals.
- Taking Charge of Money Matters Workshop: Provides education about financial concerns during the treatment of cancer, regardless of insurance status.
- American Chronic Pain Association: A self-help organization that offers education and peer support to help people live with chronic pain.
- Cancer Care: Offers free support services, education, information, and referrals. 1-800-813-HOPE.
- Family service agencies: Provides information, emotional support, and psychological assistance.
- International Association of Laryngectomies: Works toward the rehabilitation of the laryngectomy patient by providing support to those individuals who have lost their voice box as a result of cancer. 301-983-9323.
- Leukemia Society of America: Provides support, education, and limited financial assistance. 1-800-955-4572.
- National Self-Help Clearinghouse: Refers individuals to self-help groups in their community. 212-817-1822.
- Private practitioners: Provide emotional support and psychological interventions. Many insurance companies have a preferred provider list, which should be consulted for reimbursement purposes.
- Bloch Cancer Foundation: Provides information, peer counseling, and support groups. 1-800-433-0464.
- Religious organizations: Provide emotional support, pastoral care, and spiritual guidance.
- Us Too International: Provides support to men with prostate cancer and their families.
- Well Spouse Foundation: Provides support groups and newsletters to partners and caregivers of the chronically ill. 1-800-838-0879.
- Y-Me: Provides peer support to women with breast cancer. 1-800-221-2141.

FINANCIAL ASSISTANCE

INCOME-RELATED ASSISTANCE

Short-term disability: Some employers offer short-term disability income with proof of medical necessity.

Social Security Administration: 1-800-772-1213.

Supplemental Security Income (SSI): A federally funded income maintenance program for the elderly, blind, or disabled. SSI has restrictions on income and asset allotments.
Social Security Disability: A federally funded program for the disabled and for survivors of a deceased wage earner.

City, state, or federal assistance

Aid to Dependent Children: Provides financial assistance, medical insurance, and food stamps for eligible families with dependent children.

General assistance/city or town welfare: Financial assistance program for eligible individuals who do not have enough resources to meet basic needs.

Food stamps: A program designed to assist eligible individuals or families to purchase food.

TREATMENT-RELATED ASSISTANCE

State departments on insurance can provide information about local insurance carriers. Once cancer is diagnosed, it is often difficult for patients to obtain commercial insurance, except with an exclusionary clause.

Medicare: A federally funded insurance program for the elderly or disabled. To be eligible as the latter, one must be on Social Security Disability for 2 years. Hospital coverage is called Part A and covers the costs of hospitalization, except for the deductible, skilled nursing facility, and home health care. Medical coverage is called Part B and pays for a share of the cost for physician, outpatient, and hospital services; ambulance transportation; and physical and occupational therapy. One must be enrolled in Part B and pay monthly for this coverage. Social Security can be contacted at 1-800-772-1213 for more details.

Medicare health maintenance organizations: Similar benefits to Medicare but "managed" differently and may include additional benefits, such as prescription coverage. A preferred provider list is used.

Medicaid: A state program that provides coverage for medical expenses and financial entitlements to eligible individuals. The Department of Social Services can be contacted for more information. Check local phone listings.

Hill Burton: Federal funds are provided to some institutions to cover the cost of care for individuals who are ineligible for other entitlements. Financial restrictions apply. 1-800-638-0742.


Pharmaceutical assistance: Some states offer programs that assist with the cost of prescription drugs for the elderly or disabled who meet financial criteria. Most pharmaceutical companies offer drugs at no cost to people who cannot afford them; however, stringent criteria apply and application is required. A listing can be obtained through PhRMA (America's Pharmaceutical Research Companies; http://www.phrma.org).

Transportation reimbursement: Can be obtained through various agencies, such as the Leukemia Society.

HOME HEALTH CARE

Resources can be provided through hospital departments of social work or discharge planning, as well as physicians' offices or ambulatory settings.

Visiting nurse/public health nurse: Provides skilled care, nurses aids, and ancillary staff to eligible individuals. Requires physician's orders and, often, preauthorization. Can also provide information about local resources to supplement these programs.

Hospice: Provides comprehensive home care services, including the use of volunteers, to individuals with a limited prognosis. Requires physician's orders and, often, preauthorization.

Home medical equipment: Usually reimbursed by insurance and is available through local suppliers. Some local agencies, such as the ACS or the Visiting Nurse Association, may have a loan closet.

Proprietary home care agencies: Can provide high-tech services in the home, such as home chemotherapy, total parenteral nutrition, and intravenous administration of antibiotics or other drugs. Preauthorization is needed.

Meals on Wheels: Meals are prepared and delivered to eligible homebound elderly or disabled people. A fee is often charged.

Friendly Visiting: A community outreach program offered through towns, agencies, and religious organizations in many areas.

HOUSING

Ronald McDonald House: Provides housing for families of out-of-town pediatric patients. Some facilities can occasionally accept adult patients on a priority basis. Contact local hospital social work departments or physicians' offices for referral.

Westin Hotels: Some of these hotels offer free accommodations to ambulatory patients and their family members. Contact the hotel directly or the ACS.

National Association of Hospital Hospitality Houses: Provides a resource directory of no-cost accommodation. 1-800-542-9730.

SURVIVORSHIP

Cancervive: Assists cancer survivors to face and overcome the challenges of having cancer. 310-203-9232.

Coping magazine: Publication for individuals involved with cancer. 615-790-2400.

National Cancer Survivors Day: National annual celebration of life for cancer survivors.

National Coalition for Cancer Survivorship: Provides information regarding the issues of survivorship and provides peer support. 877-622-7937.

The Wellness Community: Provides psychosocial support to individuals recovering from cancer. 310-314-2555.

TRANSPORTATION

Airlifeline: A nonprofit association of pilots who donate their time, fuel, and aircraft to provide medical transportation to ambulatory patients. 1-800-446-1231.

Ambulance/chair cars (Handivans): Can be arranged for medical appointments and sometimes are covered by insurance. Preauthorization is necessary, except in emergency.
American Airlines Miles for Kids in Need: Provides free transportation to children who demonstrate need. 817-963-8118.

Corporate Angel Network: A nonprofit organization that provides free plane transportation. 914-328-1313.

National Patient Transport Helpline: Assists patients in finding the most economical way of being transported to a medical facility. 1-800-296-1217.

Southwest Airlines: Provides no-cost transportation to medical destinations to patients in need. 1-800-792-4103.

VETERANS BENEFITS

U.S. Department of Veteran Affairs: Provides benefit information to veterans regarding educational assistance, disability compensation, medical care, life insurance, burial benefits, and dependent benefits. Some states may offer local benefits.

WISH FOUNDATIONS

A Wish with Wings: Grants wishes to children with life-threatening illness. 817-469-WISH.

Brass Ring Society: Grants wishes to children with life-threatening illness. 1-800-666-9474.

Dream Factory: Grants wishes to children ages 3 to 13 with life-threatening illnesses in cities where there are chapters. 502-637-8700.

Make-a-Wish Foundation: Grants wishes to children with life-threatening illness. 1-800-722-9474.

CHAPTER REFERENCES

SECTION 56.7
Specialized Care of the Terminally Ill

INTRODUCTION

“The functions of medicine are threefold: to relieve pain, to reduce the violence of disease and to refrain from trying to cure those whom disease has conquered, acknowledging that in such cases medicine is powerless.”

Hippocrates

Although Hippocrates called for restraint in the presence of terminal illness, research has documented substantial shortcomings in the contemporary care of terminally ill patients. The Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments (SUPPORT), involving more than 9000 patients hospitalized in five U.S. medical centers, found that end-of-life treatments were overly aggressive and too often not in accordance with patients’ wishes. Furthermore, 50% of conscious patients dying in the hospital were reported by their surviving family members to have been in moderate to severe pain in the last week of life. Among 913 Canadian outpatients “respondents were more likely to be dissatisfied with their treatments for their symptoms than for their cancer,” which were similar to findings in Italy. Reasons for inadequate care of the seriously ill range from a basic lack of medical education and experience in palliative care to a professional ideology that precludes the acceptance of death as an outcome of care.

Organized efforts to promote palliative care in the United States are relatively recent. Several U.S. organizations have funded studies and developed programs to promote palliative care (Table 56.7-1). The Robert Wood Johnson Foundation, through Last Acts, has sponsored several initiatives in end-of-life care, and the Open Society Institute’s Project on Death in America supports clinicians active in this area of medicine. The American Medical Association has now launched the Education for Physicians on End-of-Life Care (EPEC) Project.

OVERVIEW OF HOSPICE CARE

A BRIEF HISTORY

In the second half of the nineteenth century, the Irish Sisters of Charity in Dublin, Ireland, and a group of “pious widows” in Lyon, France, began to provide care specifically dedicated to the dying. In 1905, the Irish nuns opened St. Joseph’s Hospice in Hackney, where Cicely Saunders (now Dame Cicely in honor of this achievement) began her work in developing the principles of modern hospice and palliative care. With formal training in social work, nursing, and medicine, Dr. Saunders has continued these efforts at St. Christopher’s in Sydenham outside London since 1967. The concept of around-the-clock analgesia, consideration of “total pain,” and comprehensive care through the integrated work of an interdisciplinary team (IDT) are hers.

Inspired by visits from Dr. Saunders to the Yale School of Medicine in the early 1960s, a group of forward-looking health care practitioners from several clinical disciplines developed a hospice program that received state regulatory approval. The home hospice served its first patient and family in early 1974, followed by the opening of the first American inpatient facility in Branford, Connecticut, in 1980.

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In 1978, the U.S. government established a Hospice Task Force to examine the potential role of the federal government in the development of hospice care. The Health Care Financing Administration funded a project to assess cost and quality of service provided by hospices.

ORGANIZATION AND FINANCING

The National Hospice Education Project, the political arm of the hospice movement, crafted legislation that eventually became part of the Tax Equity and Fiscal Responsibility Act of August 1982. In 1983, terminally ill patients older than 65 years of age became eligible for hospice services under the Hospice Benefit of the
Medicare program. To qualify for the benefit, a patient must be certified by both the referring physician and the hospice physician as having a terminal illness with life expectancy of 6 months or less. Services were limited by time and a financial cap. Eighty percent of patient care costs for each hospice were allocated to home care services to reduce expenditures for institutional care. Patients receiving services reimbursed by Medicare under the Hospice Benefit relinquished their Part A coverage for any active treatment of their terminal illness. If patients wish to return to active treatment, they may revoke the Hospice Benefit at any time. In later years, Medicaid coverage was approved by the Health Care Financing Administration as a state option. At present, Medicaid covers hospice care in 43 states and the District of Columbia.

THE ORGANIZATION AND PHILOSOPHY OF HOSPICE TODAY

In 1999, the National Hospice Organization estimated that 3000 hospices are operating in the fifty states, Washington D.C., and Puerto Rico. Approximately 540,000 patients and families received hospice care in 1998. Although hospices may exist within institutions, such as a hospice wing in a hospital, or as freestanding hospices, the majority of care is provided as home care.

No standard definition of hospice care exists, but several core principles govern its practice: (1) Hospice work is meant to enhance the quality of remaining life, not to hasten death or prolong life. The goal is to maintain for patients and families the level of comfort and calm that they wish and to offer education and guidance concerning their options at various stages of disease. (2) Delivery of care to patients and family is provided by an IDT that includes nurses, physicians, social workers, pastoral care givers, and volunteers. Often, additional members contribute through the arts, physical therapy, dietary consultations, and alternative therapies. (3) The patient and family group is considered the primary focus of care, not just the patient and not just the disease. After a patient's death, hospice provides bereavement services.

DIAGNOSES, ADMISSION GUIDELINES, AND ESTIMATING PROGNOSIS

The life-threatening illness most identified with hospice is cancer. In 1995, however, the National Hospice Organization census reported that malignant disease accounted for only 60% of hospice patients. From its beginnings, hospice services have been available to patients with other terminal illnesses, and criteria for admission to hospice with these diagnoses were formulated and, in 1996, accepted by Medicare. Most hospice patients are covered by Medicare under the Hospice Benefit.

Prognosis is generally taken in medicine to indicate whether a given disease is life-threatening and, if so, how long the patient can expect to live. Establishing a prognosis for an individual cancer patient is much more difficult than doing so for a population of such patients.

Three studies that included large numbers of patients with cancer at all stages found that functional or performance status was the most accurate predictor of survival. Decline in activities of daily living, including bathing, continence, dressing, and transfer, were very strongly associated with decreased survival. The Karnofsky performance status is another useful measure of prognosis, and it clearly differentiates the survival time of patients with terminal cancer. The median length of survival for three groups with Karnofsky scores of 10 to 20, 30 to 40, and 50 or higher were 17, 50, and 86 days, respectively. This predictive score was strengthened by five common findings: anorexia, weight loss within 2 weeks, dry mouth, shortness of breath, and dysphagia. Deteriorating mental status and cognitive ability are also predictors of shortened survival in cancer patients.

A model of survival at 2 and 6 months for seriously ill hospitalized patients has been developed as part of the SUPPORT study. This model uses primarily demographic, diagnostic, and physiologic variables as opposed to the symptom-based models. However, addition of a physician's prognosis improved the model's performance.

All authors agree that accurate prognosis for cancer patients is both important and difficult for physicians, patients, and families. Physician prognoses are often too optimistic (but not always). Overoptimistic prognoses can inappropriately commit the patient to futile interventions, thereby increasing the anguish of patient and family, and also increase the expenditure of valuable time and resources. In addition, unacceptably short survival times and resulting late referrals to hospice programs deprive patients and families of available support and of time to settle affairs and achieve closure. More research is needed to improve the accuracy of predicting life expectancy. The ultimate decision to seek admission to hospice must rest on the patient's, family's, and physician's acceptance of the futility of further curative treatments.

FUTILITY AND THE DECISION TO SEEK PALLIATIVE CARE

In the progression of most serious illnesses, therapeutic response eventually diminishes or disappears; risks begin to outweigh benefits as further therapy becomes futile.

Jecker and Schneiderman identify four common sources for the current debate over futility and health care: (1) Increasing costs raise societal concerns about equitable delivery and possible rationing of health care. (2) Expensive technical innovations make it possible to extend life in ways that only recently seemed impossible. (3) The aging of the population raises concerns about future costs during years of longer life in this increasingly numerous group. (4) The concept of patient autonomy is being challenged as society confronts the new concerns just mentioned. Physicians must be better prepared to educate patients and families about the options of palliative care as a desirable option in progressive terminal illness.

Acknowledgment of futility is a moment when optimal care of the patient shifts from a focus of cure and care to a palliative one of care only. Jonsen has formulated the following situations in which futility should be considered: (1) futility in process, in which a long and difficult course continues without any improvement; (2) futility in prognosis, when patients start treatment that has rarely or never proved useful in similar cases; (3) futility in result, when treatment is technically successful but the resulting quality of life is undesirable. Each of these decision points is frequently encountered by oncologists.

Recognizing these junctures and communicating them to patients and families requires physician sensitivity to the philosophy and practice of palliative care. The patient's concerns, fears, and goals can be elicited by using open-ended questions and probing the patient's response. Some patients sincerely question the advisability of pursuing or initiating new active therapy, thereby providing an opportunity for discussing other options. During such discussions, the physician can state that cure or control of disease is no longer possible. The choice of “no therapy” can hold the same stature as the alternative. Each physician must use his or her experience to influence the proper choice, always supporting the patient in the final decision and never implying disappointment, anger, or abandonment. Where patient and family insist on or demand futile treatments, it is incumbent upon the physician to begin discussion of palliative care as an acceptable option. Furthermore, the possibility for hope and the new goal of maintaining quality of life through palliative care are emphasized. Patients and families should understand that their role in developing symptom management may be greater than their role in directing curative therapies. This shift in goals and participation is a significant part of the process for patients and families in dealing with the end of life.

Many patients have fears and beliefs that make it difficult for them to accept palliative rather than curative care. Patients may fear that accepting death means that cure or control of disease is no longer possible. The choice of “no therapy” can hold the same stature as the alternative. Each physician must use his or her experience to influence the proper choice, always supporting the patient in the final decision and never implying disappointment, anger, or abandonment. Where patient and family insist on or demand futile treatments, it is incumbent upon the physician to begin discussion of palliative care as an acceptable option. Furthermore, the possibility for hope and the new goal of maintaining quality of life through palliative care are emphasized. Patients and families should understand that their role in developing symptom management may be greater than their role in directing curative therapies. This shift in goals and participation is a significant part of the process for patients and families in dealing with the end of life.

From the physician's perspective, providing palliative care rather than therapy with curative intent implies a change in his or her role with respect to patient and family. Within hospice, the physician is only one member of the IDT. The physician receives support from that team and, in turn, can help empower patients to see their medical care and symptom management as part of a more comprehensive approach to terminal illness.

The following description describes in greater detail the most common symptoms encountered at the end of life and the options available to physicians, patients, and families.
SYMPTOM MANAGEMENT

SYMPTOM PREVALENCE IN HOSPICE PATIENTS

Table 56.7-2 lists symptom prevalence as percent of patients affected in the surveyed populations; other comparable studies exist. 122 125 The results allow a few clear-cut conclusions: (1) Weakness, fatigue, pain, dyspnea, nausea, and vomiting remain important symptoms throughout much of the course of the disease. As cancer progresses, some decrease in pain may be due to adequate palliation. Others have noted increasing prevalence of dyspnea at the very end of life. 24 (2) Weight loss, anorexia, and insomnia become irrelevant in the last stages of disease, despite earlier importance. (3) Troublesome oral and respiratory secretions ("cheesy" symptoms), drowsiness, and myoclonus become prominent in the last days of life.

Several important points about symptom prevalence are not evident from Table 56.7-2: (1) Most cancer patients have multiple symptoms. 24 28 29 30 31 32 33 (2) The most common symptoms are often the most severe. 23 122 (3) The constellation of symptoms shows some variation with the site of primary disease. 31 41 42 43 For example, dyspnea is especially common in lung cancer, nausea and vomiting in carcinoma of pulmonary, gastrointestinal, and gynecologic origins, dysphagia in carcinoma of head and neck and of esophagus, and pain in bony metastases of any origin and in primary lung, gynecologic, and prostate cancers. 28 29 31 44 (4) Some symptoms either worsen or recur, and new ones appear as cancer progresses. In one study of the last 48 hours of life, 22% of patients had worsening of previously controlled pain, and 30% had new pain. 28 (5) Older patients tend, as a group, to have less pain than younger patients. 28

In the following sections, palliation of many of these symptoms is discussed; others are treated more fully in Chapter 55.1, Chapter 56.1, Chapter 56.2, and Chapter 56.5. Readers should consult the review by Ingham and Portenoy for extended discussion of symptom assessment tools.

FAILURE TO THRIVE

The effects of cancer disrupt normal anatomy and physiology, locally in the vicinity of the tumor or its metastases and globally in sites far removed from the tumor. The latter global effects may also be called constitutional or paraneoplastic. The signs and symptoms of failure to thrive are a prime example of constitutional change and occur in many (and probably most) cancers. 33 The phrase failure to thrive incorporates many terms, including anorexia, asthenia, cachexia, fatigue, lethargy, and weakness, which overlap in etiology and manifestations. Weakness implies generalized physical debility and lethargy refers to the inability to maintain normal physical and mental effort. In this discussion, fatigue is comprised of weakness and lethargy. Failure to thrive is defined as a symptom complex of anorexia and fatigue.

The intensity of the components of failure to thrive is not necessarily related to tumor size, tissue origin, cell type, or degree of differentiation. 32 Evidence now implicates tumor-associated cytokines and their interaction with normal components of the immune system creating these signs and symptoms. 33

Anorexia occurs in most patients with cancer at some time. 33 34 35 The goal of its treatment in hospice care is patient satisfaction and, in some cases, nonfluid weight gain.

Pharmacologic therapy can promote nutrition by increasing appetite, controlling nausea and vomiting, improving gastric reflux, and sometimes by relieving obstruction. Clear-cut improvement in anorexia has been documented with progestational drugs, especially megestrol acetate. At 800 mg/d, patients showed improved appetite, nonfluid weight gain, and reduction in nausea and vomiting. 33 34 35 Doses of more than 800 mg/d are not more effective. In a trial of chemotherapy with and without megestrol in patients with extensive small cell lung cancer, however, neither quality of life nor survival time was improved with megestrol. Corticosteroids may also be helpful in stimulating appetite and improving mood. Corticosteroids are less expensive than progestational agents but also have more significant side effects. 36 Other agents are being studied as therapy for anorexia and wasting. For surveys of these medications, the reader should consult available reviews. 37 38

Nonpharmacologic maneuvers may be helpful in treating anorexia and promoting nutrition. These maneuvers include mouth care, maintenance of regular bowel movements, and stress management in food preparation. Meals should consist of small portions served at the proper temperature, usually course by course, and seasoned to the patient's taste. Family and friends eating with the patient creates a shared experience that may be beneficial to all. 39 Mouth care involves simple measures such as gentle cleansing of the tongue, teeth, and gums; moistening with artificial saliva or ice chips; and promoting salivation with tart foods such as lemon ice. On occasion, oral comfort entails more intensive therapy to treat mucositis due to antitumor therapy or oral thrush. 34

In late stages of cancer, most patients neither wish nor profit from interventions to treat anorexia pharmacologically. Similarly, forced feedings or nutritional supplements urged on the patient by well-meaning clinicians and family often offer more risk (e.g., aspiration, anxiety) than benefit. Enteral and parenteral nutrition have not been shown to be helpful in improving the quality of life or prolonging survival of cancer patients at the end of life. 34 35

Fatigue is a major symptom in the failure to thrive of progressive illness. 33 34 35 36 The components of weakness and lethargy are multifactorial and appear to be driven by direct effects of tumor products creating deleterious changes in skeletal muscle and the central nervous system. 37 Many common elements of cancer and its treatment may contribute to fatigue: fluid and electrolyte imbalance, infection, anemia, paraneoplastic disorders, side effects of chemotherapy, radiation, other medications, and psychological reactions to disease and therapy.

In evaluation of fatigue, one monitors the patient for potentially correctable causes, such as anemia, dehydration, hypotension, hypokalemia, hypercalcemia, hypoglycemia, and renal and hepatic function. Medications that contribute to fatigue, including the opioids, sedatives, antidepressants, and muscle relaxants, can be adjusted by choosing agents for better side effect profiles. Rotation of opioids can maintain analgesia while decreasing side effects. Other medications can be discontinued if not important to comfort.

Nonpharmacologic approaches to improving fatigue include budgeting energy, delegating some daily tasks to others, and rescheduling activities to allow time for rest. Reassessment of goals in everyday life is necessary to form realistic expectations of physical abilities and energy capacity. Controlled programs of exercise and the use of physical and occupational therapy can improve a patient's tolerance of everyday activities. 37

Medications used to alleviate fatigue include psychostimulants and steroids. Psychostimulants such as methylphenidate 38 and pemoline 38 are used in palliative care to counter the sedative effects of opioid analgesia and as antidepressants. 39 40 Steroid therapy has shown some improvement in asthenia, although the beneficial effect seems to diminish 2 to 3 weeks after initial use. As was noted with anorexia, total parenteral nutrition does not reverse fatigue. 41

Finally, although the emphasis in palliative medicine is symptom control rather than curative therapy, palliative antineoplastic therapy is the most global means of
controlling the cancer and its underlying pathophysiology and improving failure to thrive.

PAIN

Pain pervades the physical being, social relationships, and spiritual dimensions of those who live with it. The presence or recurrence of pain is perceived as a sign of persistent disease and creates fear and anxiety. However, its treatment by physicians is often inadequate (see Chapter 56.1 for an extensive discussion of pain and its treatment). Twelve important considerations in pain management relative to the terminally ill patient are emphasized in this chapter:

1. Assess pain carefully and reassess frequently. Believe the patient and treat pain promptly. Successful analgesia is possible in 85% to 95% of cancer patients using basic pain management techniques. 2
2. The World Health Organization ladder is used to start treatment at the level most appropriate to the degree of pain, with escalation as necessary. 3
3. Morphine is the standard of opioid therapy for severe pain.
4. The oral route for opioids is preferred whenever possible.
5. Alternative preparations and routes of administration are available, including rectal suppositories, transdermal patches, and both subcutaneous and intravenous parenteral preparations. A percutaneous button for multiple injections provides a single subcutaneous route lasting 3 to 4 days before change of site is needed. Compact portable pumps can deliver medication by both intravenous and subcutaneous infusion.
6. Around-the-clock analgesia controls pain best, with breakthrough doses available as needed.
7. A good command of equianalgesic doses and oral-parenteral ratios of the available opioids is essential. Methadone is gaining more acceptance for chronic pain therapy. 4 Note that the equianalgesic ratio, published as 1:1, may be much smaller, implying that methadone is more potent than anticipated. 5 When switching to methadone, approximately 10% to 30% of the equivalent daily morphine dose should be used. 6
8. Rotation of opioids can be helpful in controlling side effects. 7 The cross-tolerance of opioids is incomplete, and using one-half to two-thirds of the equianalgesic dose of an alternate opioid can result in the same level of pain control with fewer side effects.
9. Avoid chronic use of inappropriate opioids. Accumulation of the active metabolite of meperidine, normeperidine, can produce central nervous system hyperexcitability with myoclonus and generalized seizures. The mixed agonist-antagonist analgesics have a ceiling dose for pain control and can block the pure agonists at the mu opioid receptor sites.
10. Use adjuvant medications in combination with opioids, particularly for neuropathic pain and pain due to bone metastases.
11. Always begin medications for bowel care when opioid therapy starts.
12. Understand tolerance, dependence, and addiction. Psychological dependence or addiction is extremely rare in the patient with cancer and chronic pain. This consideration should never be a barrier to good pain control in cancer patients, including those with a history of illicit drug use.

DYSPNEA

Dyspnea is the uncomfortable sensation of labored breathing. Shortness of breath can be a terrifying experience, and it frequently increases at the end of life. Pain, anxiety, and fear complicate its clinical presentation. For patients with terminal illness but months to live, proper evaluation of dyspnea may lead to at least temporary control of its underlying cause or causes. For those with days or weeks of life remaining and who are unable or unwilling to undergo further testing, one should proceed directly to symptom control.

Dyspnea can be multifactorial in many cancer patients. Investigation of dyspnea is often limited by patient tolerance. Full pulmonary function tests are not usually necessary. However, measuring the forced expiratory volume with and without bronchodilators, standard chest x-rays, ultrasound, and ventilation/perfusion scans are not invasive and can detect abnormalities that respond to tolerable remedies.

Therapy for dyspnea requires addressing both malignant and nonmalignant causes in cancer patients. Treatment of chronic lung disease, pulmonary infection, cardiac failure, and arrhythmias can improve the patient's comfort. Venous thrombosis and pulmonary embolism are common in malignant disease and, barring major contraindications, can be managed with oral or subcutaneous anticoagulants. Thoracentesis and paracentesis can be bedside procedures in a hospice inpatient setting. However, thoracentesis can result in pneumothorax, and the risks must be discussed, particularly when tube thoracostomy is not immediately at hand. For the dyspnea of obstructing pulmonary lesions with atelectasis, a short course of palliative chest radiation may be appropriate. Aspiration of a pericardial effusion can bring dramatic relief of dyspnea, but proceeding to a pericardial window requires careful consideration of benefits to the patient. Maximal supportive care may be more appropriate. Similarly, laser therapy of obstructing pulmonary lesions and endobronchial stents are available for patients who can tolerate the procedures. High-dose corticosteroids can temporarily improve the dyspnea of metastatic pulmonary lesions, especially that of the lymphangitic type. Steroids also are effective in treating superior vena cava syndrome and, to a lesser extent, radiation pneumonitis.

Respiratory sedatives must be considered for those patients very near the end of life who are in respiratory distress and cannot tolerate the treatments just mentioned. The benefit of these medications, including alcohol, barbiturates, benzodiazepines, phenothiazines, and opioids, comes from suppression of respiratory awareness. Parenteral opioids have become an established treatment of dyspnea in cancer patients, without causing significant deterioration in respiratory function. Morphine sulfate, 2.5 to 5.0 mg, subcutaneously as a single dose can be effective in the opioid naive patient or in patients receiving only intermittent analgesia. It may be necessary to repeat two or three doses at 20- to 30-minute intervals for satisfactory relief. For those patients already receiving opioids for pain on a regular basis, a larger dose is needed, one that is 1.5 to 2.5 times the patient's q4h dose. Morphine for dyspnea is usually prescribed on an as-needed basis, but for chronic dyspnea, administration is needed every 4 hours.

Nebulized morphine has been proposed as an alternative route of administration for therapy of dyspnea. Its use has been reported in both cancer patients and those with nonmalignant chronic lung disease. Although several authors report relief with nebulized opioids, the studies are uncontrolled case reports and retrospective chart reviews. Morphine and hydromorphone were the most commonly used medications. A subset of patients responded to this treatment, but additional randomized and controlled studies are needed.

Morphine is prepared for inhalation by addition of 5 mg of the standard parenteral product to 3 mL of normal saline as a starting dose. Doses as high as 50 mg have been used without undue side effects. In both normal volunteers and patients at surgery, systemic bioavailability of morphine after inhalation is only 5% to 35% of the comparable parenteral dose. Patients familiar with nebulizer therapy may prefer this route. Nebulizer therapy is easily used at home and is inexpensive. However, a word of caution is necessary. Rarely, inhaled morphine can induce bronchospasm, possibly related to the preservatives present. The first dose by inhalation should be administered in a controlled situation. In some patients, severe unremitting cough can contribute to breathlessness, and relief can be obtained with nebulized anesthetics. Nebulized lidocaine can be an effective cough suppressant.

Audible congestion in the last hours of life, the death rattle, is very disturbing to caregivers and family, if not the patient. Scopolamine can reduce secretions and control noisy respiration. A scopolamine patch may be sufficient, but a subcutaneous dose of 0.4 to 0.8 mg of scopolamine every 2 hours as needed is more potent and more rapid in onset. Scopolamine is sedating and may not be appropriate in some situations.

NAUSEA AND VOMITING

Increasingly, interest in nausea and vomiting has been directed toward terminally ill cancer patients not receiving chemotherapy. Prevalence can be as high as 40% to 46% in the last 6 weeks of life and, in the final days, may be so refractory that patients require sedation. The physiology of nausea and vomiting and appropriate therapies are reviewed in Chapter 56.1, especially as related to chemotherapy.

Workup of this problem in a terminally ill patient begins with a history and physical examination. Diagnostic studies must be consistent with the patient's condition and goals of palliative care. Invasive diagnostic studies may not be appropriate when no primary therapy exists.

Four anatomic centers initiate stimuli that produce nausea and vomiting: the central nervous system, the vestibular apparatus, the chemoreceptor trigger zone, and the viscera.

Recurrent primary or metastatic brain tumors often cause emesis. Dexamethasone up to 30 mg/d may relieve symptoms associated with increased intracranial pressure due to either primary or metastatic tumors. Fear, anxiety, and pain can cause nausea and vomiting, and can be controlled by benzodiazepines and...
Vestibular causes may respond to anticholinergics (scopolamine), antihistamines (medazine), and phenothiazines with H₁ antagonism (promethazine).

Relief of nausea and vomiting due to stimulation of the chemoreceptor trigger zone requires adjustment or replacement of medications. Chronic medications previously tolerated may become toxic because of altered drug metabolism or excretion as cancer progresses. Evaluation of metabolic abnormalities, such as hypercalcemia and uremia, may reveal correctable causes of nausea and vomiting.

The most problematic and refractory causes of emesis in advanced cancer patients result from gastrointestinal or visceral disease. If gastric irritation is suspected, as from nonsteroidal antiinflammatory drugs, cytoreductive and acid-blocking agents can be effective without the need for antiemetics. New medications time-related to onset of nausea and vomiting can be stopped or replaced.

Overfeeding can lead to vomiting; and small feeding satsify anxious oncopatients. At the end of life, tube feedings are associated with large gastric residues, gastric distension, vomiting, and increased risk of aspiration. Prokinetics, such as metoclopramide, may be helpful, but it is often appropriate to reduce or discontinue effective. Fecal overflow care controls nausea and vomiting associated with constipation. Laxatives must accompany routine opioid use. Urinary catheterization with relief of retention can end nausea, agitation, and restlessness.

The pain and nausea of hepatic metastases presumably caused by stretching the liver capsule are relieved by nonsteroidal antiinflammatory drugs and corticosteroids with gastroprotection. Paracentesis for tense ascites controls one cause of the “squashed stomach syndrome,” with restricted gastric volume, early satiety, and nausea.

Gastrointestinal obstruction, commonly due to ovarian, colonic, pancreatic, and gastric carcinomas, results in nausea and vomiting. Metastases from extramedullary cancers, such as lung and breast carcinoma and melanoma, can also obstruct. Gastric outlet obstruction from benign or malignant causes produces large-volymne vomiting. A percutaneous endoscopic gastrostomy (PEG) tube allows gastric drainage and relieves vomiting, while a jejunostomy tube provides feeding and medication.

Obstruction of both small and large bowel is a frequent terminal event in cancer patients. Obstruction may be partial or complete at single or multiple sites and may be due to benign causes (adhesions, radiation bowel damage, hernia) or malignant causes (new or recurrent tumor, abdominocarcinomatosis). Tumor infiltration of mesentery or bowel wall and, occasionally, of celiac plexus, may cause mechanical obstruction of the lumen or paralytic ileus. Common symptoms include intestinal colic, abdominal pain, and vomiting.

Surgical treatment of bowel obstruction remains controversial. Review of therapies for gastrointestinal obstruction compared exploratory laparotomy with bowel bypass and more conservative therapy with gastrostomy drainage. The authors concluded that intestinal obstruction due to chemotherapy-resistant tumors and peritoneal carcinomatosis associated with ascites or palpable masses should not be treated surgically, and neither should patients with intestinal paralysis secondary to tumor involvement of the mesentery. PEG tube placement was a simple procedure for drainage, and it improved quality of life without other surgical intervention. Consideration for surgical palliation of malignant obstruction requires careful individual patient evaluation.

The goal of medical management of bowel obstruction is relief of abdominal pain and vomiting in patients in whom surgical intervention is contraindicated. In partial obstruction, clear liquid diet, corticosteroids (dexamethasone, 12 to 24 mg/d) to reduce peritumoral edema, and bisacodyl suppositories to decompres the colon can improve intestinal passage. The steroid dose can be tapered and the diet advanced if bowel function resumes. In complete obstruction, drainage by PEG tube is the most important intervention to relieve nausea and vomiting, but antinemics (haloperidol or prochlorperazine) may be needed. Intestinal colic is controlled with scopolamine (0.15 to 0.30 mg subcutaneously every 6 to 8 hours as needed), and abdominal pain is controlled with opioids. Ondansetron (0.1 to 0.2 mg every 8 to 12 hours subcutaneously) reduces intestinal epithelial electrolyte and water secretion. This reduces bowel distention, vomiting, and pain and may preclude the need for gastric drainage.

Research has revealed four major neurotransmitter receptor systems involved in emesis: muscarinic (M₁, one of the cholinergic subclasses), dopaminergic (D₂), histaminic (H₁), and serotoninergic (5-HT₃). No one broad spectrum antiemetic is effective in all pathways despite the fact that many antiemetics affect more than one neurotransmitter pathway as shown in Table 56.7.3. Furthermore, nausea and vomiting in a patient may have more than one cause. When the probable causes of nausea and vomiting are established, the most effective medication should be selected from the appropriate class of medications.

Among commonly used antiemetics, phenothiazines such as perchlorperazine and chlorpromazine have a broad range (i.e., affect several pathways) and offer several routes of administration: chlorpromazine, however, is sedating and may cause hypotension. Haloperidol is available in concentrated solution (5 mg/mL) so that effective doses can be given subcutaneously in small injected volumes. Metoclopramide promotes gastric emptying. In severe nausea and vomiting, 5-HT₃ antagonists such as ondansetron, granisetron, and dolasetron can bring relief. One protocol for ondansetron is given in Table 56.7.3. In addition to control of intracranial pressure, adjuvant corticosteroids (dexamethasone) empirically enhance many antiemetics.

### FLUIDS AND NUTRITION

Provision of fluids and nutrition to terminally ill patients may be a contentious issue between families and hospice caregivers. Families often feel that fluids and nutrition prevent suffering by reducing dehydration and starvation. The issue often intensifies as patients begin to lose the ability to take sustenance and medications orally. Even a balanced discussion of not starting artificial fluid and nutritional support may cast the caregivers in the eyes of the family as threats to the patient’s comfort. At the same time, hospice caregivers differ personally and professionally concerning provision of nonoral fluids and about the degree of suffering resulting from thirst.

Estimation of the prevalence of thirst and dry mouth among cancer patients in palliative care ranges from 28% to 83%. Clinical concerns favoring provision of fluids include protection of patients from bed sores, constipation, nausea, delirium, myoclonus, and accumulation of drug metabolites with significant risk to patient comfort. Commonly used palliative medications (e.g., opioids, tricyclic antidepressants, phenothiazines, some antiemetics) all promote dry mouth. In some cases, intravenous fluids are delivered because the benefits to the family outweigh any risks.

On the other hand, intravenous hydration and nutrition may prolong life so that patients die from other less comfortable causes. They may cause prolonged suffering from other symptoms, including increased respiratory and gastrointestinal secretions, phlebitis at the intravenous site, ascites and edema, and need for a urinary tract catheter.

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**TABLE 56.7-3. Medications for Nausea and Vomiting with Associated Neurotransmitter Receptors**

<table>
<thead>
<tr>
<th>Medication (Brand)</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scopolamine (66)</td>
<td>0.4 mg SC Q12H, intramuscular (IM) or IV (2 mg)</td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>10-20 mg orally (PO), IM, IV (Q8H)</td>
</tr>
<tr>
<td>Prochlorperazine</td>
<td>5-10 mg IM, 25-50 mg orally (PO)</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>25-50 mg IM, 50-100 mg orally (PO)</td>
</tr>
<tr>
<td>Hydroxyzine (Vistaril)</td>
<td>25-50 mg PO, IM, IV</td>
</tr>
<tr>
<td>Metoclopramide (Reglan)</td>
<td>10-20 mg PO, IM, IV</td>
</tr>
<tr>
<td>Ondansetron (Zofran)</td>
<td>16-32 mg PO, IM, IV, subcutaneous (SC)</td>
</tr>
<tr>
<td>Dolasetron (Dasefect)</td>
<td>2-6 mg PO, IM, IV</td>
</tr>
<tr>
<td>Ibuprofen (Motrin)</td>
<td>150-200 mg PO, IM, IV</td>
</tr>
</tbody>
</table>

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catheter with its accompanying risks and discomfort. Some of these objections may be avoided by using subcutaneous delivery of fluids by hypodermoclysis. The symptom of thirst is not identical to dry mouth or other signs of dehydration, often defined clinically as serum sodium, osmolality, and azotemia above normal values. Thirst is best assessed by patient report. Substituting a workup of dehydration by physical and laboratory examinations may be misleading.

It is difficult to draw firm conclusions about the relations among thirst, dry mouth, dehydration, and suffering from the few clinical studies published. As a group, these studies support but do not prove the following statements:

1. Thirst, dry mouth, and fluid retention are not closely associated with demonstrable dehydration. Intravenous fluids do not uniformly alleviate dehydration or thirst nor improve awareness.
2. Asiduous mouth care and small amounts of ice chips or fluid may or may not relieve dry mouth or thirst.
3. Dehydration is associated with decreased awareness and may not be improved by intravenous fluids. In contrast, in a large study of a palliative care center, decreased prevalence of delirium was associated with increasing use of hydration and opioid rotation.
4. Thirst was not significantly related to length of survival in one study, although taken together, the studies cited show increasing prevalences of thirst and dehydration as patients approach death. Of note, these studies do not define subgroups of patients whose symptoms improve with hydration.

In hospice care, no single approach to provision of fluid by nonoral routes is used. Most caregivers would agree that the patient's choice is paramount. At the same time, institutional preferences for providing or withholding nonoral fluids exist and have been discussed. The scientific basis for such patterns is still not clear and needs more study.

The issues surrounding hydration in terminally ill patients are simpler than those concerning fluids. As cancer progresses, patients become increasingly anorexic rather than hungrier. Fewer than one-third of patients admitted to the hospice unit complained of hunger, and that occurred only during the first quarter of their stay. The issue of hunger is rarely mentioned among symptoms in patients in the last 24 to 48 hours of life. Furthermore, little or no evidence shows that enteral feeding by either nasogastric or by gastrostomy and jejunostomy tubes prevents malnutrition, infections, or pressure ulcers or that it improves functional status or survival compared to patients without feeding tubes. Conservative measures may be helpful to the patient and family without subjecting the patient to what appears to be a futile intervention in most cases, especially in the terminal phases of illness. Such measures involve frequent, careful feeding of small bites or boluses (generally less than a teaspoon) placed carefully into the mouth, encouragement to chew and to swallow, use of a patient's favorite foods, use of flavorful food and fluids, diets ad lib enriched with cream and fats, and the company of family and friends when desired.

**PSYCHIATRIC SYMPTOMS**

The major psychiatric complications in terminally ill cancer patients are anxiety, depression, and delirium. Uncontrolled physical symptoms, especially pain, increase their prevalence and intensity.

**Anxiety**

In many cancer patients, anxiety is a pervasive feeling of dread for themselves and others in their lives. Beginning in some patients before diagnosis, anxiety produces easy distraction, poor attention and concentration, and physical signs of autonomic activation. At times, anxiety may escalate into panic. Control is important for patient comfort and for adequate calm so that the patient can understand and cooperate with caregivers during workup and treatment of physical illness and psychosocial issues.

Diagnosis is based primarily in observing and talking to the patient and family; the goal is to elicit any previous history of anxiety disorders and treatment, as well as current history and symptoms. We ask the patient to describe the major sources of anxiety so that we can respond to them. Anxiety commonly concerns both self and others. The physical examination may reveal anxious facies; tics; and signs of autonomic hyperactivity, such as palpitations, tachycardia, dyspnea, sweating, nausea and vomiting, diarrhea, and paresthesias.

Some patients calm adequately in response to information and to empathic support from members of the IDT and from family and friends. Others require therapies and medications designed to control anxiety. Nonpharmacologic therapies include relaxation techniques such as meditation, biofeedback, and guided imagery, as well as "talk therapy." Such therapy should be tried, but success may depend on addition of medication, usually a benzodiazepine. A wide variety of benzodiazepines is available with differences in duration of action, metabolites, timing of onset, and routes.

In urgent situations, short-acting benzodiazepines, such as alprazolam and lorazepam, are used; the latter can be given intramuscularly or by slow intravenous push as well as by mouth. Shorter acting benzodiazepines provide easier titration of the medication. Longer acting benzodiazepines, such as diazepam and clonazepam, are used for routine control of anxiety and may be given two or three times a day.

Selective use of benzodiazepines depends on the clinical situation. Anxiety due to ongoing pain should be addressed first with analgesics. Anticipated pain can be treated with both analgesia and a benzodiazepine; lorazepam in this situation not only acts as an anxiolytic and adjuvant analgesic but also provides anterograde amnesia. Similarly, lorazepam given before chemotherapy works to relieve anxiety as well as nausea and vomiting.

Anxiety is a concomitant of dyspnea. Relief of dyspnea with oxygen and, in some cases, morphine may relieve anxiety. If not, trial of an antihistamine such as hydroxyzine may be effective and prevent the use of benzodiazepines, which can interact with opioids to depress respiration. Opioids and benzodiazepines used together for rapid relief of dyspnea are appropriate at the very end of life when more concern is focused on providing dying patients with calm and comfort during this irreversible process and less on drug interactions.

Benzodiazepines protect patients during withdrawal from habit-forming substances (e.g., barbiturates, alcohol, opioids, and other benzodiazepines). After 2 to 4 weeks of routine use, benzodiazepines should be tapered to prevent physiologic withdrawal.

On occasion, the clinical situation suggests that other medications be used to treat anxiety or supplement the benzodiazepines already used. Butyrophenones such as haloperidol or a lower potency phenothiazine such as thioridazine may be appropriate, especially in anxious patients with psychotic features of hallucinations and delusions. More sedating drugs, such as thioridazine or chlorpromazine, are helpful in agitated or insomniac patients. Methotrimeprazine is a phenothiazine that combines relief of both pain and anxiety. Like chlorpromazine, however, it is associated with sedation, hypotension and orthostasis, and the anticholinergic side effects. Anxiety escalating into panic attacks can be treated with tricyclics such as imipramine, the benzodiazepine clonazepam or a selective serotonin reuptake inhibitor such as paroxetine.

**Depression**

Diagnosis of depression in cancer patients relies heavily on psychological and cognitive signs and symptoms (e.g., feelings of guilt, worthlessness, futility, suicidal ideation) because many of its physical signs and symptoms (e.g., fatigue, anorexia, weight loss) can result from underlying cancer and its treatments. Prevalence of self-reported depression in cancer patients is near 25%; and increases with poor symptom control. Among hospitalized cancer patients referred for psychiatric consultations, almost 60% were seen for depression, suicidal ideation, or both.

Diagnosis and treatment of depression in early stages of cancer have been reviewed and are discussed in Chapter 56.5. In this chapter, we concentrate on depression in the last stages of disease, when patients and families cannot wait weeks for therapeutic response.

Psychostimulants such as dextroamphetamine, methylphenidate, and pemoline may improve depression in a few days, as well as counteract sedative side effects of opioids and promote appetite and concentration. In the presence of opioids, they also provide adjuvant analgesia. Initial dosing of methylphenidate is 2.5 mg at breakfast and lunch. The dose is increased every 3 to 4 days until relief of depression or unacceptable side effects (e.g. anxiety, autonomic hyperactivity, confusion) intervene; it is rarely necessary to go beyond 30 mg/d. Relief of depression is usually evident in a few days, as opposed to the few weeks with tricyclics and selective serotonin reuptake inhibitors. Pemoline is reported to be as effective as dextroamphetamine and methylphenidate and has fewer sympathomimetic side effects.
effects, although it should be used with caution in patients with liver dysfunction. 52

Patients with poor symptom control, especially pain and depression, are at high risk for suicidal ideation. Members of the IDT must be alert to protect them through symptom control, counseling, and pharmacotherapy. 32

Delirium

Clinically, confusion is most often divided into delirium and dementia, although other categories of cognitive disorders exist. Delirium refers to a fluctuating complex of mental states of “altered alertness and impaired cognition,” including some or all of the following presentations: variable attention, shifting awareness, disturbed sleep-wake cycles, disorientation, hallucinations, and difficulties of memory and speech. 22 In delirium, changes in mental status occur over hours to 1 or 2 weeks, which is much more rapidly than in dementia. Fluctuations of mental status and, in some cases, reversibility of delirium also distinguish it from dementia. Differentiation of dementia and delirium is especially difficult when they coexist, as they commonly do in older patients.

Prevalence of delirium increases as cancer progresses, estimated variously at 10% to 27% early in the course to 85% near death. 116,119 At the very end of life, it may be a major component of terminal restlessness or terminal agitation. The inability of patients to communicate with families and caregivers is frustrating. Stress created by a delirious patient can produce the “destructive triangle”: a distressed family creates pressure for relief on the nurse who then adds his or her own distress to the pressure transmitted to the prescribing physician who may treat by sedating the patient without an appropriate workup. At the very end of life, however, proceeding directly to sedation may be the most effective and appropriate help.

A wide range of etiologies exists for what is called by the single name delirium, and Table 56.7-4 lists some of these. In earlier stages of disease, when a desirable quality of life can potentially be restored, search for and treatment of causes related to both cancer and to comorbid conditions is appropriate. Causes may not be found, even in this multifactorial condition. In one study of confused terminally ill patients, only 44% had identifiable causes of confusion. 12

Delirium in Cancer Patients: Etiologies and Facilitators

Several tools exist to aid in predicting, diagnosing, and following the evolution of delirium. 11,12 The Mini-Mental State Examination measures cognitive function and has the advantage that it can be administered in a few minutes by caregivers without special training. Other instruments may be used to measure aspects of delirium other than cognitive failure and to check the validity of the Mini-Mental State Examination if in doubt. 11

Treatment of delirium, usually begun during workup, involves several steps: stabilization of the environment, modification of medications, and correction of contributory conditions when appropriate. 11

At all stages of disease, a stable environment minimizes delirium (e.g., the presence of trusted family and friends at the bedside, use of consistent and trusted caregivers, a well-lit environment with date and time readily available). Efforts to engage patients in conversation help to orient and to distract them from distressing thoughts and hallucinations. Personal observation is usually better than physical restraints in maintaining patients’ safety.

All patients should have medications reviewed to eliminate unneeded medications and substitute others less harmful whenever possible, including rotation of opioids to take advantage of partial cross-tolerance. Hydration and reduction of opioids may produce or contribute to clearing of mental status. 11

Pharmacotherapy for delirium varies depending on the stage of illness. Haloperidol has the advantage for some patients of being less sedating than other phenothiazines. Because haloperidol administered parenterally has a faster onset and is approximately twice as potent as the same dose orally, it is used intravenously or subcutaneously in urgent cases. For agitated delirium, the initial dose is 2 to 5 mg, preferably by the intravenous route, repeated every 15 to 30 minutes with a maximal dose of 5 mg every 15 minutes. For calmer patients, starting doses are 0.5 to 1.0 mg orally or parenterally, then titrated up every 45 to 60 minutes as necessary. 11 Ultimately, most patients receive 0.5 to 3.0 mg three times a day by mouth or parenterally. Side effects of haloperidol and other phenothiazines include extrapyramidal effects, including akathisia and, rarely, neuroleptic malignant syndrome.

At times, confused patients may be aided by a sedating benzodiazepine used with haloperidol (e.g., lorazepam, which has no active metabolites), initially started at 0.5 to 1.0 mg every 1 to 2 hours by mouth, intravenously, or intramuscularly. Effective doses of these two drugs are then adjusted so that haloperidol is given every 8 hours and lorazepam every 6 hours. Alternatively, the sedating phenothiazine chlorpromazine is usually successful in calming an agitated patient at doses of 12.5 to 50.0 mg given by mouth, intravenously, or intramuscularly every 4 to 12 hours. 22 As death nears, the benefit of imposing calm outweighs the risk of hypotension associated with chlorpromazine. In dying patients with poorly controlled agitation, a very short-acting benzodiazepine with rapid onset, midazolam, is used intravenously or subcutaneously for sedation; it does not correct disordered thought. Initially, midazolam is started at 0.4 mg/hr and is titrated up to control agitation, usually in the range of 20 to 60 mg/d, although higher doses up to 200 mg/d have been used. 114,115

ACTIVELY DYING PATIENTS: CALM, COMFORT, AND REFRACTORY SYMPTOMS AT THE END OF LIFE

Several groups have confirmed significant improvement in symptom control, especially pain, during hospice care. 22,29,111 Good control of overall symptom distress increased from 64% of patients on admission to a palliative care unit to 84% on the day of death. 112 and Saunders notes that only 2% did not die peacefully in her survey. 11 In contrast, the National Hospice Study showed that only 19% of patients were pain free at the time of last pain measurement before death, whereas 18% had persistent pain. 113

Management of refractory symptoms was sharply focused in 1990 by a prospective study of 120 Italian home care hospice patients with cancer, 52% of whom had such severe symptoms that only sedation provided comfort. 22 Subsequent reviews reported a range of 18% to 48% of hospice patients with refractory symptoms. 22,118 and 119 The most common symptoms requiring sedation were dyspnea, pain, delirium, and nausea. Time from starting sedation to death was, on average, 2 to 4 days. 22,118,119

Refractory symptoms, as thoughtfully discussed by Cheney and Portenoy, are those for which no adequate relief can be found despite rational and thorough trials of conventional approaches. In addition, other options cannot be effected in an acceptable length of time or may cause further suffering in trying them. These authors discuss efforts to control terminal pain as a guide to the workup of other symptoms before their classification as “refractory.” The emphasis on interdisciplinary teamwork is further stressed in a brief discussion of intolerable psychological or existential suffering.
In the studies cited, the common medications used to produce sedation were midazolam (more than any other benzodiazepines); neuroleptics, such as haloperidol and chlorpromazine; opioids; and barbiturates. Choice of sedating medications depends in part on the symptom to be controlled—for example, opioids for pain, and benzodiazepines for dyspnea, and neuroleptics for agitation. In some cases, higher doses entailed unacceptable side effects (e.g., myoclonus with neuroleptics); in this particular case, role of the "double dose" effect provides comfort to some caregivers. Additional medication may be helpful. At the beginning of sedation, medications with shorter half-lives provide physicians with better control, which is especially important when varying degrees of sedation may be sought. Among benzodiazepines, midazolam offers not only a short half-life but also a variety of routes. Special attention has been given to primary use of chlorpromazine and of barbiturates as agents of sedation for refractory symptoms.

Among the most difficult of all tasks for caregivers is withdrawal of life support and sedation for refractory symptoms to provide patients with calm and comfort as they die. Both professionally and personally, caregivers often feel frustrated and threatened by not being able to provide adequate comfort; this frustration can lead to a sense of division among members of the caregiving team. Some clinicians may have qualities that symptom control may hashen the patient's death rather than preserving the quality of life. The principle of the "double dose" effect provides comfort to some caregivers. The double effect refers to the fact that medication given for the purpose of symptom relief carries foreseeable risk and may unintentionally hasten a patient's death. This principle recognizes the ethical dilemma of promoting symptom relief and is meant to protect caregivers so long as they have sought comfort for their patients and not their deaths. These new concepts will, however, and in a simple statement of benign intent may not encompass all components of decision. Clinicians unable to accept the distinction between intended benefit and an unavoidable risk of death for the treatment patient may need to transfer the patient's care to another colleague.

CONCLUSION

Although still relatively recent in American medical history, hospice is becoming accepted practice in caring for the terminally ill. Insurers, providers, and patients and their families are increasingly aware that hospice is available to them and that it is often the best choice for care at the end of life. Nevertheless, hospice and palliative care practice standards remain outside the mainstream of medicine and are only now being included in medical education curricula at all levels of training from medical school to oncology fellowships. Practitioners, researchers, and funders are beginning to establish a clinical knowledge base, which can be used to guide the practice of palliative medicine that will grow with experience and systematic research. However, the practice of hospice care will face many challenges as well. Hospice stays have been shortening in many programs, suggesting that patients may be referred to hospice later than is desirable. Research is needed to understand better the sources of this shift, including possible changes in institutional barriers and the views of families and friends of the need for a hospice stay. Understanding of the underuse of hospice can inform a variety of approaches, including policy changes, health education interventions, and professional training resources. The desired outcome is continuing growth of knowledge and training in palliative care and its expanded use for patients with terminal illness.

CHAPTER REFERENCES

CHAPTER 57
Rehabilitation of the Cancer Patient

LYNN GERBER
JEANNE HICKS
JAY SHAH

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Functional Assessment
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Impairments and Their Impact
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Tumor-Associated Myopathy
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INTRODUCTION

The American Cancer Society predicts 1.2 million new cases of cancer diagnosed in 1999 and 8 million cancer survivors requiring care for cancer-related problems. These patients are likely to be older, will survive for years with their cancers, and will present considerable challenge to health professionals.

The incidence of cancer climbs appreciably with each decade of life, and the population is aging. The 5-year survival has improved over the last 20 years, such that more than 50% of those with cancer of the prostate, colon, bladder, breast, uterus, thyroid, and some lymphomas will survive 5 years. Patients with cancer, in part because of the likelihood that they are older and have preexisting medical conditions, are likely to present significant challenges and complex management decisions. They are complex because, often, cancer has many phases and may recur and remit throughout multiple life stages. The illness may not be stable, and the functional impact may vary with disease stage and may change with remote effects of treatments. Table 57-1 outlines one scheme for conceptualizing this view of cancer management needs.

<table>
<thead>
<tr>
<th>Phase of Disease</th>
<th>Interventions</th>
</tr>
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<tbody>
<tr>
<td>Pretreatment and Treatment</td>
<td>Functional Assessment, Pain Management, Psychosocial Support</td>
</tr>
<tr>
<td>Post–Definitive Treatment</td>
<td>Rehabilitation, Education, Pain Management</td>
</tr>
<tr>
<td>Intercurrent</td>
<td>Education, Rehabilitation, Pain Management</td>
</tr>
<tr>
<td>Recurrence</td>
<td>Rehabilitation, Education, Pain Management</td>
</tr>
</tbody>
</table>

TABLE 57-1. Rehabilitation Support throughout Phases of Cancer

The pretreatment and treatment phases should include a functional assessment to help to identify what the patient is able and wishes to do and to predict what is likely to influence function subsequently. A systematic evaluation of the neuromusculoskeletal system is essential for targeting areas likely to need intervention for maintaining or restoring function. Often, instruction in the use of gait aids can best be given before treatment, when pain and mobility loss have not occurred. Prosthetic and orthotic devices can be planned and provided intraoperatively when needed.

The post–definitive treatment phase is an opportunity for initiating preventive measures. Early mobilization, the use of wraps, and limb massage may help to mitigate disuse and deconditioning or control lymphedema and limb swelling. This phase usually includes preparing the patient and family for discharge and educating them about what the course is likely to be and what they (collectively) should be doing to keep the functional level high.

The intercurrent period, when the definitive treatment has been complete, may be psychologically difficult and require guidance to assist patients and family to enter or reenter an active and healthy life program and resume usual activities, when possible. Patients may need to plan for adjusting to late neurologic sequelae (plexopathies, neuropathies) or musculoskeletal sequelae (fibrosis, atrophy) of disease or treatment. Chronic pain, weakness, fatigue, and lymphedema may require ongoing and intensive therapy.

Recurrence may require that the cycle of assessment and treatment begin anew. This process may be fairly psychologically demanding and anxiety-provoking. The goals of rehabilitation management are to provide education about problem solving for issues relating to functional loss.

Rehabilitation professionals also have significant contributions to make at the end of life. During this phase, rehabilitation professionals can assist in answering...
questions pertaining to nonpharmacologic treatments for pain control and strategies for enhancing quality activities and independence and can help families, friends, and patients address issues at the end of life.

Cancer is common, chronic, and complex. Decision making about primary cancer treatment often factors elements reflective of these features. In fact, patients (our consumers) are not only requesting participation in decision making, they are asking for information about the impact of the tumor and its treatments on function and their quality of life. Patients, especially cancer patients, fear disability and have identified a host of concerns that include fatigue, independence, and pursuit of valued activity, in addition to mortality, that influence their ultimate treatment choices. In many concerns and needs of patients throughout the phases of cancer treatment can be ameliorated by rehabilitation professionals. Table 57-2 describes the functional areas affected by various symptoms and in need of rehabilitation.

### CANCER REHABILITATION TEAM

Rehabilitation specialists most frequently involved in treatment of the cancer patient include physiatrists; occupational, physical, and recreation therapists; speech-language pathologists; audiologists; and vocational counselors. Other health care professionals join the team as needed for particular problems (e.g., orthotists-prosthetists, psychologists, dietitians).

Physiatrists are trained in the specialty practice of physical medicine and rehabilitation. This training enables them to assess functional ability, relative strength and stamina, the basics of human mobility (biomechanics), the design and appropriate use of adaptive equipment, and orthotics and prostheses. Physiatrists often combine information about disease and its treatment with the impact it is likely to have on function. It is usually physiatrists that coordinate rehabilitation services and prepare a comprehensive plan for treatment and follow-up.

Occupational therapy is an integral part of the rehabilitation of the cancer patient. Therapists evaluate the impact of disease or treatment on function, roles and daily routines, and the coping strategies needed to compensate for changes in a person’s ability to participate as fully as possible in activity. Occupational therapists (OTs) determine which strengths and support networks are available to a person and identify interventions that are critical to potentiate quality of life for those who are terminally ill. Adaptive device training and safety training for activities of daily living (ADL); fabrication of splints or prosthetic training to maximize upper extremity function; counseling for the development of coping strategies; fracture risk education and assistance with mobility; and seating and environmental adaptations are examples of interventions that an OT can provide. Preparation for discharge requires input from an OT, with concentration on environmental safety (e.g., home, bathroom) and functional independence (Table 57-3).

### TABLE 57-2. Patient Functional Areas Affected by Cancer Symptoms in Various Phases of Disease

<table>
<thead>
<tr>
<th>Physical therapists (PTs) provide evaluation and treatment of human motion. Treatments include strategies and exercises to improve mobility, strength, and stamina. Therapists often help to relieve painful musculoskeletal symptoms using nonpharmacologic modalities and postural treatment. If therapy is instituted early, it can prevent muscle atrophy and joint contractures and maintain or promote fitness. Typically, PTs assess range of motion (ROM), muscle strength, exercise tolerance, gait, shoulder and trunk strength, and balance. PTs usually apply orthotics and prostheses for the lower extremities, apply modalities of heat and cold, and help to manage peripheral edema using compression pumps and stockings. Standardized evaluations are listed in Table 57-4.</th>
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<tbody>
<tr>
<td><strong>TABLE 57-3. Occupational Therapy: Evaluation and Treatment</strong></td>
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One of the most significant problems facing cancer patients is the impact of relative or absolute immobility. Bed rest in cancer patients is associated with numerous metabolic and physiologic changes that may impair the patient's medical and functional recovery. In patients who are already osteoporotic or who have metastatic involvement of the skeletal system, this may predispose to pathologic fractures and further disability. Muscle atrophy can be fairly rapid, often leading to an inability to walk in as short a time as a week. Decreased activity may result in contractures and changes in muscle and joint physiology. Lack of mobility can also lead to the development of deep venous thrombosis and pulmonary embolus. Changes in muscle physiology and fiber type have been documented as well. This is particularly true of patients with gastroenterologic tumors in which weight loss, anorexia, and inflammatory cytokine production negatively impact on function and quality of life. As muscle mass becomes reduced, the amount of soft tissue covering bony prominences can become marginal, predisposing to the development of pressure (decubitus) ulcers. In this state, pressure over peripheral nerves, especially as it crosses bony prominences, may lead to a neuropaxia. All these factors can significantly reduce mobility and independence.

Exercise, long used to build lean mass, is often ineffective in this population. In the setting of cachexia, the effects of exercise on nitrogen balance and other metabolic abnormalities are fairly modest. Rigor of exercise is significantly curtailed, in part limited by symptoms of pain, fatigue, depression, and aesthenia. As a rule, each week of immobility requires as much as a month of rehabilitation to regain functional mobility. Complications such as pathologic fractures and pressure ulcers can further delay recovery. Although it is sometimes impossible to fully mobilize a patient receiving chemotherapy or major surgery, some degree of mobilization under a PT's supervision may significantly reduce morbidity. For the patient who is mildly restricted by disease or treatment, active ambulation at least once or twice daily is strongly encouraged. If this is not possible, an exercise program in bed may be started, using resistance against gravity or against an elastic band. A tilt table may be used to maintain sympathetic tone, reduce orthostatic hypotension, or restore cardiovascular conditioning in the patient who is unable to stand. This also helps to minimize heel cord contractures, increase muscular tone, and facilitate venous compression and helps to maintain cardiovascular volume. In patients with severe dependent edema, compressive garments or manual therapy, such as massage and lymph drainage, may help to maintain the vascular volume.
and to reduce the degree of the edema while facilitating ambulation. Passive or active assistive stretching may be needed to maintain joints in functional alignment.

SKIN BREAKDOWN

Prevention of skin breakdown is critical for the bed-bound patient. Above all else, the patient must not be allowed to remain in a single position for more than 2 hours. If patients are unable to position themselves in bed, repositioning should be done with pillows or cushions, taking care not to encourage the development of contractures by, for example, persistently flexing the neck, hips, or knees. Air-cushioned beds can help to reduce the incidence of pressure injuries.

Shear forces and direct pressure are important in the development of decubitus ulcers. Care should be taken, therefore, to avoid dragging patients across sheets or examination tables.

If skin becomes dry, aqueous moisturizing creams should be applied. Healing is promoted in a moist wound environment. Greasy agents can predispose to maceration and breakdown. Irradiated skin is of particular concern, due to the loss of normal resilience and healing capacity. Hygiene is important with irradiated skin, and all open cuts and abrasions should receive scrutiny, because they can easily become infected.

When complications arise, they should be treated promptly. Areas of skin redness that do not blanch should be considered early pressure ulcers (stage 1) and treated by removing pressure over the affected area. Most tissue damage in pressure ulcers occurs in the deep layers of the dermis and underlying tissues, such that the visible portion of the ulcer may represent only a fraction of the total extent. In many instances, hydrotherapy (whirlpool) can aid in the process of debridement and cleansing.

Packing the wound with an antiseptic solution should be done only when proven infection is present. In the case of noninfected small lesions, absorptive hydrocolloid occlusive dressings can be effective in promoting healing, provided that they are used in accordance with the manufacturer's recommendations. The use of occlusive dressings with larger wounds is controversial. Management should include mechanical and enzymatic débridement when necrotic tissue is present. Although we have seen many cases of complete resolution with the use of absorptive granules and occlusive dressings in deeper wounds, the potential exists for developing a superinfection. Occlusive dressings cannot be used as a substitute for adequate nursing care.

CONTRACTURES

In cases of prolonged disuse or fixed joint positions, collagen fibers within muscles, tendons, and ligaments shorten, leading to contractures. Shoulder, heel cord, hamstring, and hip flexor contractures are most common.

ROM exercises should be practiced actively by the debilitated patient or passively by nursing or by the family at least two to three times each day, moving all major joints through their full ROM in all directions. In the case of the shoulder, this includes external and internal rotation, full abduction, and flexion. If flexion and abduction need to be limited, (e.g., in the patient after mastectomy or axillary lymph node dissection), internal and external rotation should be performed to stretch the joint capsule. Splinting may be used to maintain functional hand and foot position.

The role of upper extremity bracing during the acute or chronic stages of disease or treatment should not be overlooked. Because of the complexities of movement patterns and compensatory adjustments, patients can continue to manipulate objects despite progressive changes that, if left unattended, may render them nonfunctional. Splints are designed to maintain soft tissue length, place joints in functional positions, and align hands and wrists to prepare for grasp and release activities. Thumbs can be positioned to oppose fingers for pinch, fingers can be pulled into extension with dynamic forces to compensate for weakness, wrists can be supported to allow for better mechanical advantage of forefinger finger tendon function, and elbows or shoulders can be positioned by slings or splints to aid in the prevention of joint subluxation and ligamentous laxity. Rehabilitation goals are to prevent contractures, when possible. Uses for splinting devices are summarized in Table 57-7.

Table 57-7. Upper Extremity Orthoses

When neuropathy, immobility, weakness, pain, or the disease process itself has an impact on hand and wrist manipulation, appropriately designed splints need to be applied immediately, adjusted over time in accordance with the condition of the individual, and monitored for effectiveness. They also need to be used in conjunction with exercises and education regarding wearing schedules and precautions. When used appropriately and in a timely fashion, splints can make a difference in the functional outcome of patients and help to preserve alignment.

TUMOR-ASSOCIATED MYOPATHY

Tumor-associated myopathy may result in immobility and ADL deficits. The myopathy may be a result of direct tumor invasion of muscle and other soft tissues, paraneoplastic syndrome, carcinomatous myopathy, steroid myopathy, or carcinomatous neuromyopathy.

PARANEoplastIC SYNDROMe

Nonmetastatic paraneoplastic syndromes of malignancy have been recognized with polymyositis and dermatomyositis. Malignancy occurs primarily in association with
dermatomyositis rather than with polymyositis. The incidence is thought to be higher in men older than 50 years. A study by Lakhanpal et al. mentions a 25% incidence of malignancy in a polymyositis and dermatomyositis group and a 17% incidence in the control group. Breast cancers (19%) and lung cancers (16%) are most frequently associated with polymyositis and dermatomyositis.

Patients with paraneoplastic syndrome have decreased endurance, muscle weakness, pain, decreased joint motion, and problems with ambulation, self-care, sexual performance, and work-related activity. Treatment to increase joint motion with stretching exercise, to increase muscle strength with isometric exercise, to improve mobility with gait aids and bracing, and to improve ADL with assistive devices are all appropriate. The patient should be instructed in energy conservation, joint protection, and sexual and vocational counseling.

CARCINOMATOUS MYOPATHY

Carcinomatous myopathy may be seen with metastatic malignant disease. Histologically, there is widespread muscle necrosis and minimal or no inflammatory response. Clinically, there is proximal muscle weakness in this type of myopathy. Because of the necrosis of muscle, it is thought that these patients would probably not respond well to an exercise program, but function should be maintained if possible. They should be given appropriate pain-relieving medications and assistive and mobility devices to help with ADL and safe ambulation. The environment should be altered to help to ensure safety and easy access.

CARCINOMATOUS NEUROPATHY AND MYOPATHY

Simultaneous carcinomatous neuropathy and myopathy occur with metastatic disease and affect peripheral nerve and muscle due to either toxic or immunopathologic effects of the tumor. Diminished reflexes and diminished sensation ensue. The rehabilitative treatment is similar to that recommended in the management of carcinomatous myopathy. However, distal weakness occurs in addition to the proximal weakness, and appropriate bracing to improve ankle dorsiflexion may be needed. If weakness is severe, an electric scooter may be needed. Several assistive devices to help with hand function are useful.

STEROID MYOPATHY

Steroid-induced muscle weakness is really a selective atrophy of type II fibers in proximal muscles. It tends not to affect neck flexor muscles. It may be superimposed on the weakness of carcinomatous myopathy or polymyositis- and dermatomyositis-associated myopathy and exacerbate it. It is caused by catabolic and anabolic effects of steroid on muscle. Amino acids leak into the circulation, and there is decreased incorporation of protein into muscle. The condition may be diminished by providing exercise to enhance protein metabolism by muscle. Isometric exercise can be used to accomplish this goal. It may take up to 1 year after cessation of steroids for muscles weakened by steroid use to return to normal.

BONE REPLACEMENT BY TUMOR

Bone can be invaded by tumor via direct extension, as is frequently seen in sarcoma; via embolization through the right side of the heart, the most frequent cause of distant metastasis; or via direct venous spread through Batson's plexus involving vertebral bodies and pelvis, the most frequent cause for metastatic bone disease in prostate cancer. Some tumors, such as leukemias, lymphomas, or myelomas, invade bone marrow.

Bony metastatic disease is most frequently associated with breast, lung, prostate, colon, or kidney tumors. It is important to note that the survival for patients with these tumors and bony metastases is years. Although any tumor can metastasize to bone, the most likely to spread are prostate, breast, lung, kidney, and thyroid. The hematologic malignancies do frequently as well. Nearly 20% of tumors with distant spread will involve bone. Bony involvement is the third most frequent site for metastasis, with vertebral bodies, pelvis, femur, and ribs affected in order of frequency. Often, multiple sites are involved, of which 20% are in the upper extremities.

Pain is the most frequent symptom associated with bony metastasis. This is characteristically dull, aching, and nocturnal. The spine is the most frequently involved area for metastatic spread, and the lumbar region is the most common site. When there is vertebral involvement, 50% of patients will have radicular symptoms. Cord compression, on the other hand, most frequently arises from thoracic region involvement. Pain on weight bearing may be a sign of bony involvement or even a pathologic fracture. Bone scan is the simplest means of screening for bony tumor. Plain films offer definition of the local extent of the tumor, although computed tomography (CT) may be needed for better quantification of involvement.

PREVENTION AND MANAGEMENT OF PATHOLOGIC FRACTURES

Pathologic fractures can limit mobility in a marginally functioning patient and, in some cases, lead to significant morbidity and mortality. Hip fractures are particularly debilitating and often difficult to stabilize, and they may lead to a significant hemorraghe. Prevention of pathologic fracture is important. Fracture should be considered imminent when the size of a lytic lesion exceeds 60% of the total bone width (usually >2.5 cm in lower and >3.0 cm in upper extremities), if cortical involvement exceeds 50%, or if the axial extent of cortical destruction exceeds 13 mm in the femoral neck and 30 mm elsewhere. These calculations are difficult to measure accurately, in part because local osteopenia is common and margins are often irregular and difficult to distinguish.

Pain with weight bearing suggests a need to reduce load on or immobilize the affected structure. A cane used in the hand opposite the affected lower extremity can theoretically remove approximately 50% of body weight from that extremity. Such attachments as a quadraped base (quad-cane) or a forearm support (forearm or Lofstrand crutch) may help to stabilize the cane, but they cannot overcome the simple physics of gravitation loading. Canes or a single crutch can be used for the patient who has pain with weight bearing, but they should not be used for the patient with a fracture or one that is imminent.

Bilateral support is essential for the patient in whom no weight bearing is required. For the more debilitated patient, a simple walker suffices. For the more active patient, axillary or forearm crutches may be used. Toe touch of the affected leg can usually be allowed but, in the patient who has difficulty coordinating the use of the crutches or walker, total avoidance of weight bearing may be needed to avoid sudden weight bearing if the assistive device is not properly placed. Patients need to be evaluated for metastatic disease in the upper extremities. It is fairly possible to develop a pathologic fracture of an involved humerus if it is used as a weight bearing structure. The patient should be cautioned against torquing the affected extremity, because this can often lead to fracture, even without weight bearing.

After an affected extremity has been unweighted, options for stabilization can be considered. Radiation often can be used to treat lesions of the long bones. Irradiation does not directly repair damaged bone, and irradiated bone heals much more slowly than normal bone. For small lesions, irradiation, along with the use of a cane, is all that may be required. For larger lesions, surgical stabilization should be considered if possible. Intramedullary rods or methylmethacrylate can be used to increase the strength of the involved bone or, if used prophylactically, to stabilize a painful lesion and prevent fractures. This gives the patient a more functional limb and allows increased mobility.

 Destruction of the femoral head or acetabulum may be treated with hip joint arthroplasty, rendering ambulation a possibility while providing excellent palliation of pain.

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Destruction of the femoral head or acetabulum may be treated with hip joint arthroplasty, rendering ambulation a possibility while providing excellent palliation of pain. Fractures of the ischium may be painful during sitting and should be treated with cushions to reduce weight bearing over the fracture. Fractures of a single portion of the pelvic ring are generally not a problem. Multiple fractures, however, can interfere with ambulation and should be addressed appropriately. Fractures of the iliac wing may be painful during active hip flexion and abduction, due to the attachments of the iliacus and gluteal abductors, respectively. Assistive devices used to avoid activation of these muscles during ambulation can provide significant relief of pain.

When lower extremity and upper extremity are involved, use of gait aids may be contraindicated either because of pain or impending fracture. In this situation, a wheelchair may be needed until internal fixation can be performed. When upper extremity involvement is associated with pain but there is no immediate threat to bony integrity, a thermoplastic splint for forearm or a humeral cuff for lesions of the humerus may provide stability and symptom relief.

Ribs are also a common site of bony involvement and fracture. Generally, only a rib belt will be required. Pathologic fractures of non–weight-bearing bones can be managed with splinting or sling immobilization while radiation is delivered. ROM or isometric exercises may be appropriate to maintain function. If a dominant upper extremity is involved, assistive devices and training in one-handed strategies by an OT can significantly improve function. Devices such as reachers and dressing aids can help the patient to avoid torquing the spine or hips if the risk of fracture is high.

In the patient who presents with neurologic deficits, the physician must always rule out spinal cord compression by tumor. Other causes of paraparesis in the cancer
patient include peripheral neuropathy, lumbosacral plexitis, radiation myelitis, and pseudotumor, often from radiation fibrosis. Radiation-related paraparesis may not occur for some time after the completion of all treatment. We have seen patients with radiation myelitis presenting as long as 7 years after having been declared free of disease. Hyperreflexia may be masked by peripheral neuropathy or plexopathy related to chemotherapy or irradiation, and patients with extensive metastatic involvement of the vertebral column may even have little or no pain.

The prevention of serious spinal cord injury should be the primary goal of the cancer rehabilitation team in treating the patient with known vertebral destruction by primary or metastatic disease. Although radiation treatment may be used to control tumor growth and to relieve spinal cord compression, this does not address the issue of spinal stability.

Although no good models of vertebral collapse from tumor exist, it has been assumed that spinal stability in the cancer patient can be addressed in much the same way that it is in the patient with a traumatic injury of the spine. The most widely accepted method of stability evaluation involves the concept of three columns. This method considers the spine to be made up of three supporting columns—the anterior, middle, and posterior structures of the vertebrae roughly divided into equal thirds. Any two of these supporting columns must be intact for the spine to be stable. For example, complete destruction of a vertebral body puts the spinal cord at risk for compression, because the posterior structures (facet joints) can easily sublux. A simple compression fracture, however, is usually stable because the posterior and middle columns are relatively intact. Of particular concern are lesions at the atlantoaxial and thoracolumbar junctions, due to the significant bending and torquing moments generated at these interfaces.

Whenever possible, an unstable lesion of the bony spine should be stabilized surgically, because virtually no brace can be completely effective in preventing subluxation. Irradiated bone heals slowly and often incompletely, and continued malignant destruction may sometimes occur. It is desirable from the rehabilitation standpoint to mobilize the patient as quickly as possible to prevent the complications associated with immobility. Even if there is extensive vertebral destruction, surgical stabilization can usually be accomplished by means of rods, strut grafts, and cement. Occasionally, extensive multilevel involvement may render it impossible to find adequate healthy bone to which stabilizing hardware can be attached, or the patient’s health may preclude any surgical option. In such cases, bracing may provide the only means of protecting the spinal canal.

If it becomes necessary to use a more “practical” cervical stabilization, orthosis selection should be based on the level of potential instability and the directions of motion that might lead to instability. The Philadelphia collar, consisting of a foam collar with rigid supports, provides moderately successful stabilization of higher segments in flexion and extension but inadequate stabilization at lower levels and inadequate stabilization for side bending and rotation, and it is of limited usefulness as a spinal stabilization brace.

Two alternatives that provide excellent stabilization of lower segments in flexion and extension are the two-poster and sternal occipital mandibular immobilization (SOMI) braces (Fig. 57-1). The SOMI is particularly useful in managing debilitated patients, due to its open design and the ease with which it can be applied, because all components are attached from the front. It can be used with a light-weight chest piece, as supplied, or it can be bolted onto a lower spinal orthosis, making it useful in cases of multilevel instability (Fig. 57-2). An alternative cervical thoracic orthosis is the Yale brace, which essentially consists of a Philadelphia collar attached to a thoracic extension. With any of these orthoses, the patient must be informed that the brace is a compromise solution and that care is indicated, particularly with motions not well supported by the particular brace.

Stabilization of the thoracolumbar regions is generally achieved using two basic types of bracing. Metal braces, such as the Jewett or the Taylor-Knight (Fig. 57-3) orthoses, can be fit to the patient rapidly, providing optimum limitation of flexion and extension. The custom-molded plastic thoracolumbosacral orthosis, or body jacket, additionally provides limitation in rotation as well. These braces are frequently poorly tolerated in the debilitated patient with atrophic skin. Elastic back braces and corsets, often used in the management of mechanical low back pain, do not provide adequate spinal stabilization, although rigid corsets may be worthy of consideration in the patient who absolutely cannot tolerate anything else.
High thoracic lesions and cases of extensive vertebral involvement may require the use of a combination orthosis. A cervical extension or SOMI brace can, for example, be attached to a body jacket (Fig. 57-4), providing restricted mobility of the entire spine. These braces should be worn whenever the patient is upright or travels in a motor vehicle. When the patient lies in bed without the brace, the head of the bed should not be elevated more than 30°. Patients should be cautioned against twisting or torquing their backs, because this may potentiate the injury. Cervical orthoses should be worn even when the patient is recumbent and should be removed only in a supervised setting.

FIGURE 57-4. Body jacket for thoracic support and triplanar movement control.

The prescription of exercise and participation in vocational-avocation activity should be written by knowledgeable professionals. The goals for treatment should be limited to what the patient can do safely, and should promote independence and quality function at minimal risk. Exercise to promote fitness with minimal bony impact, such as aquatic, strengthening by using isometric rather than resistive exercise; and activity patterns that minimize single-limb weight bearing for lower extremities are recommended strategies. Education to help patients and caregivers to maximize safety is also important.

SPINAL CORD INJURY SYNDROMES AND REHABILITATION OF IMPAIRMENT

Spinal cord disorders in cancer patients may result from malignant invasion; bony compression or trauma; syring or hematoma formation; radiation myelitis; or vascular events. Radiation myelitis is directly related to radiation dose and often does not develop until years after the completion of therapy. Spinal cord dysfunction has been associated with high-dose intrathecal chemotherapy.

The degree of functional impairment in a spinal cord disorder is related to the level of the lesion and to its degree of completeness. The level of a lesion is, by American convention, the last fully functional spinal root level. For example, a C-5 (cervical root 5) quadriplegic has intact function of the biceps brachii (innervated primarily by C-5 and C-6), with intact sensation over the shoulders and lateral aspects of the arms. A C-5 quadriplegic is able to bring the hand to the mouth but will require assistance for most self-care. A level of C-4 is required for unassisted breathing. C-6 quadriplegics will have intact wrist extension, allowing some light grasp through the tenodesis effect. C-7 quadriplegics are able to extend the elbows, making it possible for them to lift themselves, performing their own weight shifts. C-8 and T-1 are required for intact hand function.

Damage of the central portion of the spinal cord may occur, with the outer portions being spared. This may occur with intramedullary tumors, with syring formation, or in certain vascular events. The central cord syndrome is characterized by loss of upper extremity function, with relative sparing of function in the legs. If only one side of the spinal cord is involved, the Brown-Sequard syndrome results, in which motor function is affected on the ipsilateral side while most sensory function is affected on the contralateral side.

Because of the complexities involved with spinal cord dysfunction, rehabilitation should be provided by those familiar with management of spinal cord injury. Assisted mobility using manual or motorized wheelchairs or crutches or canes with braces will usually be required. Adaptive equipment and strategies for self-care may be needed in the cancer patient with spinal cord involvement.

Bowel and bladder dysfunction in this patient population is virtually universal, requiring particular attention. Even in the patient with apparent normal voiding, silent bladder and sphincter spasticity may lead to infection, bladder reflux, and significant morbidity. We have seen cases of hydronephrosis with almost complete destruction of the kidneys in asymptomatic persons. Foley catheters may be used for short-term management if there are other medical indications. Otherwise, intermittent catheterization done frequently enough to keep the bladder volume at less than 500 mL is the method of choice during the acute phase. A urologist should be consulted after the patient has stabilized. Regular use of laxatives as part of a bowel-training program is frequently required.

Autonomic dysreflexia or hyperreflexia is a true emergency in the spinal cord–impaired patient. When the spinal cord level is T-6 or above, uncontrolled vasoconstriction and severe hypertension may result. Paradoxically, the heart rate is often slowed, due to the intact vagus nerve. The first objective should be to lower the blood pressure as quickly as possible. Sitting the patient upright will help to reduce intracerebral pressure. A fast-acting agent, such as sublingual nifedipine, may be used initially, followed by a longer-acting agent, such as nitroprusside, if needed. After the blood pressure has been stabilized, the causally a nosous stimulants should be isolated and corrected. The most common cause is an overdistended bladder, and distended bowel and skin trauma are other possible explanations.

NEUROPATHIES AND PLEXOPATHIES

Peripheral nerve involvement is a common diagnostic dilemma in the cancer patient. Dysfunction of peripheral nerves usually results from the use of cisplatin or vincristine and irradiation. Peripheral neuropathies and plexopathies can also be the result of direct tumor invasion or a paraneoplastic syndrome.

CHEMOTHERAPY-INDUCED NEUROPATHIES

Generally chemotherapy-related neuropathies tend to be distal and symmetric. Occasionally, initial symptoms are unilateral, mimicking a mononeuropathy or invasive lesion. Vincristine and cisplatin are documented causes of autonomic neuropathies. In some instances, this has been severe enough to mimic spinal cord involvement. Cytarabine has caused brachial plexus neuropathy, Suramin, largely an experimental drug, has caused a profound polynuropathy, mimicking Guillain-Barré syndrome. Agents that are lipid-soluble or that have metabolites with a prolonged half-life may lead to a progressive neuropathy, even after discontinuance of the drug.

Vincristine seems to induce distal axonal degeneration similar to that of other toxic neuropathies. Because of this, the duration of the neuropathy tends to be prolonged because of the time needed for nerve fiber regeneration. Many patients receiving this agent develop sensory complaints of numbness and paresthesias. Some patients develop severe neuropathic pain. Often, the degree of motor neuropathy is significant, sometimes resulting in a virtual quadriplegia. Although it may take months after cessation of chemotherapy to recover function, recovery is usually complete. Neurotoxicity is one of the most common reasons for limiting the dosage of vincristine chemotherapy.
Neuropathies due to cisplatin generally tend to be less frequent and often milder. We have treated several patients who have developed a severe permanent neuropathy from the use of cisplatin. There does not seem to be any common factor that can be used to predict the development of lasting neuropathy. Rarely is an adjustment in cisplatin dosage indicated.

BRACHIALPLEXOPATHIES

Radiation-induced brachial plexopathy is an uncommon problem in the conservative management of breast cancer if supraclavicular and axillary lymph nodes are irradiated. It may be seen as a late effect of mantle irradiation for Hodgkin's disease. Onset of symptoms is usually delayed. In one study, symptoms began more than 1 year after therapy, and the overall prognosis for recovery was poor.

Differentiation of radiation from neoplastic plexitis is essential. Severe pain has been documented in 80% of patients with infiltrating tumor, but only 19% of patients with radiation injury described this finding. Horner's syndrome is more common in cases of tumor involvement, and lymphedema is a much more common concomitant finding in radiation injury. The distribution of involvement of the brachial plexus is an important diagnostic criterion, with 72% of patients with invasive tumor having involvement of the lower trunk and 78% of patients with radiation injury having involvement of the upper trunk.

Electrodiagnostically, myokymic discharges are virtually diagnostic of radiation plexitis, occurring in 63% of patients. Other abnormalities are common in both types of injury, with nerve conduction studies being of limited usefulness. Tumor detection by magnetic resonance imaging (MRI) provides definitive evidence of neoplastic involvement. Even without visible tumor during surgery, neoplastic disease has sometimes been found microscopically, and it may not be possible to rule out neoplastic plexopathy for many months after the onset of symptoms.

LUMBOSACRALPLEXOPATHY AND RADICULOPATHY

Involvement of the lumbosacral plexus is common in pelvic tumors due to direct invasion. In a study of 11 patients with lumbosacral plexopathy, 6 had metastatic involvement, 2 had radiation-induced plexopathy, 1 had a primary tumor, and 2 had neuritis due to intraarterial chemotherapy. Direct imaging of tumor with CT or MRI may be difficult after irradiation or surgery. We have seen a preponderance of delayed painful plexopathy in patients receiving intraoperative radiation. It is important to attempt to differentiate plexus lesions from those of the spinal cord, due to the difference in treatment, rehabilitation management, and prognosis.

Neuropathic pain is commonly seen with peripheral neuropathies. Loss of sensation may render the patient susceptible to skin injury. The patient with insensate skin should be cautioned about the avoidance of potential injuries in the hands and sharp objects and about the need for daily skin inspection to avoid the development of infection. Loss of proprioceptive feedback, particularly in the patient with impaired vision, may interfere with simple fine-motor tasks and with ambulation. A cane can provide proprioceptive feedback to the upper extremities in the patient with impaired proprioception in the lower extremities. Motor impairment is treated similarly to other neurologic disorders, with bracing and adaptive devices as needed.

In addition to the use of narcotic agents, which has become the mainstay of palliative treatment in the cancer patient, the physical modalities of pain control may significantly help to alleviate suffering. More aggressive approaches, including nerve blocks and rhizotomies, have been used with limited success. Sympathetic nerve blocks and sympathocollypetic effects may be effective in patients with the reflex sympathetic dystrophy syndrome. Trigger point injections are also sometimes helpful in musculoskeletal pain disorders.

The use of physical modalities can be a particularly effective adjunct in the management of pain in the cancer patient. Heat modalities, including superficial heat, shortwave diathermy, and ultrasonography, may provide relief in musculoskeletal pain syndromes, but ultrasonography may help to spread lymphatic disease. Other heat modalities increase circulation to the affected area, questionably increasing the potential for metastatic spread. Therapeutic cold can also sometimes help to reduce pain.

Electrical stimulation has met with increasing criticism in the literature, but we have found electrical stimulation to be effective in reducing narcotics usage in a variety of cancer patients with a variety of pain syndromes. It seems to be particularly effective in the management of phantom limb pain and in treating radiculopathy and incisional pain. If effective, the patient can be provided with a pocket-sized transcutaneous electrical nerve stimulation (TENS) unit, which can be used as needed. Electrodes should be placed at the site of maximum pain or, in the case of referred pain, at the site of the lesion. A conventional high-frequency setting is usually most effective. Many TENS units are available at modest cost. Progressive muscle relaxation has also been reported to be useful.

LYMPHEDEMA AND DEEP VENOUS THROMBOSIS

The swollen extremity is often a diagnostic dilemma in the patient with a history of cancer. Because of the possibility of malignant compression or invasion of lymphatics or venous drainage, and because of the possibility of deep venous thrombosis, a swollen extremity should always be fully evaluated in the cancer patient or cancer survivor. Idiopathic lymphedema, rather than edema secondarily caused by infection or tumor, should be a diagnosis of exclusion. Tumor can usually be excluded by imaging studies, such as CT, MRI, or bone scan or, in extreme instances, by lymphangiogram.

Deep venous thrombosis can usually be ruled out using impedance plethysmography or ultrasonography. If certainty is required, a venogram can be performed. Suspected pulmonary embolism can be evaluated with a ventilation-perfusion scan or, more definitively, by pulmonary angiography. The greatest risk of embolization is from proximal thromboses.

Lymphedema in the cancer patient is frequent, with lymph node involvement or after lymph node dissection. Late edema is usually related to radiotherapy and the gradual development of fibrous tissue and change in the protein content of the fluid. Edema in a nonirradiated extremity should always be thoroughly evaluated, and remediable causes, such as infection or cardiovascular causes, should be treated.

The simplest means of minimizing edema is to keep the affected extremity elevated as much as possible. Legs should be placed on an elevated foot support, preferably keeping the feet above the level of the heart. Arms should be rested on a high table surface. A sling may be of short-term benefit. Isometric exercises, by increasing muscle tone, may help to minimize edema.

The management of lymphedema varies from treatment center to treatment center and from country to country. Rehabilitative therapies have typically included education about limb position to minimize gravity, use of massage, exercise to enhance lymph flow and maintain mobility, and the use of pneumatic compression devices and compression garments to control swelling. Even with the best understanding in the anatomy, physiology, and pathophysiology of the lymphatic system, a combination of techniques has evolved to manage lymphedema better.

Manual lymph drainage (MLD) is a specialized massage technique based on the concept of emptying the central regions first, to give the lymph from the periphery somewhere to go. The lymph is moved proximally and, across lymphatic watersheds, into the nearest normally drained lymphomes. The proximal region of the limb is always cleaned first, then the massage is extended distally; effleurage that starts at the distal end and attempts to push the lymph into the unemptied, proximal regions is ineffective.

After MLD, some treatment centers will continue lymph drainage with the use of a sequential pneumatic compression device. Other centers will follow MLD immediately with compression bandaging, using the low-elastic Comprilan (Beiersdorf, Germany) applied over padding (Artiflex Soft, Beiersdorf, Germany) and an undergarze (Tricofix, Beiersdorf, Germany). The compression bandages have been applied to the extremity, special exercises are performed to supplement the effects of the MLD.

The frequency and duration of the foregoing techniques vary from treatment center to treatment center. However, the greatest reduction in lymphedema usually occurs within the first week of treatment (when the treatment is provided by a highly trained and skilled PT). Just before discharge from the treatment program, the extremity is fitted with a compression garment to maintain the reduction in lymphedema. An example of a wrapped upper extremity is presented in Figure 57-5. The National Lymphedema Network located in San Francisco has a list of manual lymphatic drainage therapists and treatment centers throughout the United States.
Bowel obstruction or ureteral or urethral compromise is usually the result of malignant invasion or spinal cord or nerve root compression. Constipation and urinary hesitancy are frequently related to the use of medication, particularly narcotics and drugs with anticholinergic properties. Input from the rehabilitation team is most often needed if there is neurologic dysfunction or in ostomy care.

MANAGEMENT OF BOWEL DYSFUNCTION

Disorders of fecal elimination are frequently the most significant complaint of the cancer patient. Constipation is extremely common and is best treated using dietary modifications and medication. Often, a high-fiber diet with copious fluid intake will be all that is required to ensure regularity. If fiber supplements are used, the patient should be cautioned about the absolute need for fluid intake, because bulk in the absence of fluid can lead to impaction. If necessary, stool softeners (e.g., docusate sodium, 50 to 200 mg/d) can be added to reduce straining. A stimulant medication (e.g., metoclopramide hydrochloride, 10 mg 30 minutes before meals and at bedtime) can be used for delayed gastric emptying.

When spontaneous defecation does not occur, a stimulant agent may be required. A mild preparation with a well-controlled transit time, such as an over-the-counter senna preparation, is preferred. A standard dose of senna (e.g., Senokot, two tablets) at bedtime usually results in controlled defecation in the morning. Stronger agents, such as bisacodyl (5 to 15 mg) or magnesium hydroxide (milk of magnesia, 30 mL) may be used in more recalcitrant cases, although it should be kept in mind that magnesium is mildly nephrotoxic. Such cathartics as magnesium citrate should be used as a last resort and only if there is no suspicion of obstruction or impaction.

In the patient with neurogenic bowel dysfunction, stimulation from below may be required. Digital stimulation or, if needed, use of a glycerin or bisacodyl (10 mg) suppository should usually be sufficient to initiate evacuation. Rarely, an enema may be required. By instituting a regular bowel-training program in which full evacuation is achieved on a daily or every-other-day basis through the use of medications and rectal stimulation, it is usually possible to achieve continence.

Diarrhea in the cancer patient is usually the result of chemotherapy. Standard antidiarrheal preparations, narcotics, and anticholinergics may be used. If diarrhea occurs in the face of antibiotics, pseudomembranous colitis resulting from infection with Clostridium difficile should always be ruled out. Other bacterial or parasitic diarrhea should be treated with appropriate antibiotics, as determined by stool culture or smear. Narcotic antidiarrheal agents should be avoided in this case due to the potential for toxic megacolon development. Viral diarrhea should generally be allowed to run its course.

MANAGEMENT OF THE NEUROGENIC BLADDER

Proper evaluation and management of bladder dysfunction in cancer patients with neurologic abnormalities is essential to prevent significant morbidity. Although bladder dysfunction is often arbitrarily divided into disorders of incontinence or reduced bladder capacity and disorders of retention, this model is overly simplistic. Patients with spinal cord or brain stem involvement should always undergo formal evaluation of bladder function.

There may be various combinations of a spastic or flaccid bladder and a spastic or flaccid urinary sphincter. The combination of a spastic bladder and sphincter is the most dangerous, because this can lead to reflux, causing hydronephrosis or upper tract infection or to autonomic hyperreflexia. Such medications as oxybutynin chloride, 5 mg two to four times daily, can be used to reduce bladder spasticity, but mechanical means of drainage may be needed. Urinary tract infections are frequent in the patient with neurogenic bladder, and proper evaluation and treatment are mandatory.

In the acute phase of management, an indwelling catheter is usually sufficient if there are appropriate medical indications. Catheters should be removed as soon as the patient is stable, so as to minimize the risk of infection. In the patient who appears to be voiding normally, evaluation for possible retention should still be done. Postvoiding residual urine volumes as determined by catheterization or by ultrasonography should be less than 50 mL. If the patient does exhibit retention, intermittent catheterization should be instituted, taking care to catheterize frequently enough to keep bladder volumes at less than 500 mL. In the incontinent patient without retention, condom (Texas) catheters may be used for men. Collection devices for females are often less than satisfactory.

MANAGEMENT OF THE OSTOMY PATIENT

Cancer patients may have ostomies for a variety of reasons. Ureteral stents are often used in patients with ureteral obstruction, occasionally in combination with a temporary ostomy for kidney drainage. Patients with bladder carcinoma may have a ureteral diversion to an ileal loop, which is drained through an ostomy. Patients with bowel carcinoma or other types of bowel obstruction may need a temporary or permanent ostomy for fecal elimination. This may be required at any level of the small bowel or colon. Ileostomies, involving diversion of the terminal small bowel, are sometimes problematic because of the volume of fluid present in the fecal contents before entry into the colon. An ileal pouch is sometimes created surgically as a reservoir for urine or ileal fluid as a means of providing continence.

In cases of neck tumors or if there is impaired swallowing, a gastrostomy may be required for supplemental nutrition. This can often be placed by percutaneous endoscopic gastrostomy, eliminating the need for major surgery. Tracheostomies are often used in cases of head or neck tumors or if there is a need for prolonged access to the airway, as in the patient with severe cognitive impairment and uncontrolled tracheal secretions.

Ostomy training should be a regular part of the cancer patient's rehabilitation process. Proper cleaning technique avoids the likelihood of infection. Proper attention to skin care should avoid maceration and breakdown. Occasionally, a bowel-training program can be instituted for colostomy patients, regularizing emptying and sometimes eliminating the need for an ostomy bag. A variety of ostomy collection systems are available, including one-piece collection bags, applied directly to the skin using an adhesive, and two-piece collection bags involving an occlusive seal that is applied to the skin and a separate detachable bag. Collection bags may be closed and disposed of with each use or may be open, allowing for drainage and reuse. One- and two-piece barriers may be used to help patients to maintain continence. Support groups for ostomy patients are available in most areas, and a variety of patient information materials are available.

PSYCHOSOCIAL ASPECTS OF CANCER REHABILITATION

Accommodating to change in daily performance, to loss of function, and to modifications in lifestyle that accompany the diagnosis and treatment of cancer has relevance for all individuals. However, life management goals vary widely and may be influenced by each individual's values, stage in life and phase of disease, life experiences, and temperament. The challenge facing oncologists is identifying and addressing unique psychosocial reactions presented by the patient during all stages of oncologic management, including the terminal phase.

Table 57-8 summarizes some common emotional reactions to oncologic illness as they may be manifested during different stages of treatment. Also included are

FIGURE 57-5. Wraps to reduce limb edema.
**INITIAL PHASE.** Rehabilitation interventions begin preoperatively with instruction about crutch usage. The type of interventions and the rate at which rehabilitation progresses depend on a number of factors. Although general statements can be made about how a patient progresses, each resection is somewhat different, and the

### REHABILITATION AND MANAGEMENT OF SPECIFIC TUMORS

#### SARCOMA OF THE EXTREMITIES

Ablative extremity surgery (amputation), formerly the treatment of choice for local control of sarcomas, has been replaced by limb-sparing surgery in the majority of cases. Since clinical trials indicate no benefit from amputation in overall survival rate in selected cases and function and desirability favor limb preservation in many, limb-sparing surgery has become more prevalent.

Clinical trials have shown reduction of local tumor recurrences in soft tissue sarcomas (STS) with preoperative and postoperative radiotherapy treatments and brachytherapy and of distal metastatic disease in osteosarcoma (OS) with the use of preoperative and postoperative adjuvant chemotherapeutic regimens. Limb perfusion has reduced tumor size even when advanced, to permit limb-sparing surgery. For those in whom there was still no option for limb-sparing surgery, a reduction in tumor size is often associated with palliation of pain and better cosmesis.

Tumor size, pathologic type, and adequacy of excision remain the main predictors of local control. Tumor location, involvement of neurologic tissue, and size often are the better predictors of function.

In recent years, the chance for better functional outcome in limb-spared patients has resulted from (1) refined surgical interventions (abandonment of origin-to-insertion whole-muscle group excision in favor of partial group excisions); (2) use of endoprostheses and bone allografts, muscle transfers, and sophisticated soft tissue reconstructive procedures; (3) refined radiotherapy procedures (abandonment of full-dose radiotherapy to the entire port in favor of advanced simulation techniques), which permit a core-down high dose to the direct tumor site and lower doses to the rest of the port, with corrections also made to reduce dose and scatter to joints; and (4) the development of specific rehabilitation programs to follow up the limb-spared patient throughout the trajectory of the disease process.

In some patients, amputations are still needed. These tend to occur for large tumors involving other critical structures in which resection would result in poor functional outcome or poor local control. Often, these are high-level amputations. Amputation also occurs more often for hand and foot tumors where there is little leeway to obtain an adequate excision without severely compromising function. However, more sophisticated reconstructive procedures have recently been reported to salvage the hand and thumb. Children younger than 13 years with OS are too young for limb-sparing procedures using endoprostheses. Other procedures may be used in some cases.

Functional deficits, impairments, and symptoms from limb-sparing surgery result from (1) the local procedure itself (depending on the extent of the resection and resection of adjacent structures, such as nerves and vessels); (2) adjuvant therapy (chemotherapy, radiotherapy, and limb perfusion); (3) the effects of local recurrences and distal metastases; and (4) premorbid patient characteristics.

Specific impairments and symptoms include pain, edema, fatigue, reduced strength and joint motion, stress, and depression. Functional deficits occur in the areas of mobility; ADLs; vocational, social, and sexual adjustment; and recreation and leisure.

Rehabilitation plays a major role in assessing the person’s potential for limb sparing, predicting their functional outcome after the procedure, maximizing their function by treating their impairments and symptoms, and educating them in the proper care of their spared or amputated limb to prevent complications and encourage preservation and coping strategies related to impairment and handicap. Rehabilitation interventions should occur over the trajectory of the patient’s life span as new problems emerge in different disease phases.

#### Role of Rehabilitation

Resection may involve partial muscle group removal, muscle transfer, and bone replacement by endoprostheses or allograft (and less often, vessel and nerve removal). The surgeon predicts which structures will need to be removed for an adequate tumor excision. Based on the extent of the planned surgery, the physiatrist anticipates the level of function of the limb after surgery. Both surgeon and physiatrist discuss and concur on this prediction. A judgment is then made whether this would be acceptable function for the patient. A comparison of functional outcome resulting from amputation and limb sparing should be made before treatment selection. These discussions should be shared with affected patients before a treatment choice is selected, should be the best from such patients’ perspective, and should be supportive of their needs.

For adequate function, the limb may need some permanent postoperative bracing or splinting. These are usually needed if there has been sacrifice of a key nerve or muscle. The patient should be informed preoperatively that these adjunctive devices may be necessary for independent functioning. Special age, wear, and fracture risk considerations take place if an endoprostheses is used. In OS, usually a longer endoprostheses must be placed, rendering the spared limb longer for patients aged 15 to 17 years. This compensates for growth arrest in the operative limb. A major growth plate may need to be stapled on the normal side in OS if the limb grows disproportionately and exceeds the affected side by more than 2 cm. A heel lift of up to 1 inch may be used if the endoprosthetic side is shorter than on the normal leg. Endoprosthetic loosening may occur, depending on the amount of wear and tear from activities, but endoprostheses can last up to 10 years. For long-term survivors, endoprosthetic replacement will be needed. There is generally a limit of two to three replacement reconstructions. Reconstructions are also necessary for prosthetic dislocation, bone fracture, and loosening. Removal of the prosthesis is often necessary for serious bony infection. Infections with some organisms (Staphylococcus epidermidis) have been successfully treated with 3 months of appropriate intravenous antibiotics. Therefore, some patients who initially underwent limb-sparing procedures will need amputations later in their life. They need to be aware of the possibility of these problems preoperatively when choosing a limb-sparing surgery.

If the patient needs an amputation, the physiatrist should evaluate the patient preoperatively and recommend the most functional level. A very short above-knee amputation (AKA) can be fitted with a prosthesis and is much more functional and energy-efficient than a hip disarticulation. In some cases, a hip disarticulation can be converted to a short AKA by use of a custom-made short femoral endoprosthesis. A short below-elbow and below-knee amputation can be fitted appropriately with a prosthesis and is much more functional than its counterpart (above-elbow and AKA).

### Treatment during Phases of Disease

**INITIAL PHASE.** Rehabilitation interventions begin preoperatively with instruction about crutch usage. The type of interventions and the rate at which rehabilitation progresses depend on a number of factors. Although general statements can be made about how a patient progresses, each resection is somewhat different, and the
treatment plan and progression of treatment are individualized to each patient. Progression and intensity of rehabilitation are slower for bony reconstructive procedures.28

POSTSURGICAL PHASE. Postoperatively, the patient is reevaluated for level of pain, fatigue, stress, motivation, muscle strength, and joint motion. In general for STS patients, early treatment begins with correct positioning in bed to facilitate lymph drainage; a posterior splint or sling may be needed. Passive ROM by a PT or OT therapist is performed for joints distal to the resection and, in other joints, active motion is performed by the patient. On day 2, the patient is allowed to transfer out of bed with assistance and sit in a chair with proper limb positioning. For lower limb procedures, non–weight-bearing gait with crutches or a walker and posterior knee splint are initiated; if the upper extremity is the operative site, an appropriate sling or splint is used. The patient engages in active ROM of joints distal to the surgery. As the limb returns to normal and the drain is removed, activity progresses with both partial and full weight bearing. The shoulder, elbow, and the joint near the surgical procedure receives active assistive ROM with the PT or OT therapist. Arc of motion is increased as the wound heals. Assessment of wound healing is made before ROM progression. When the staples are removed at around 14 days, the patient should be fully weight bearing and can come off crutches in a week.

Special procedures, such as the Tinkoff-Lindberg procedure for shoulder STS, require extensive soft tissue reconstruction and an endoprosthesis. The rehabilitation course is slower and similar to that of resections for proximal humeral OS tumors. The functional outcome is also the same.

Early rehabilitation for bony reconstruction is usually performed for OS but has a longer postoperative rehabilitation course, and the progression of treatment is highly dependent on the type and extent of the excision. Any complications that occur postoperatively alter the progression of rehabilitation. Two of the complications that occur are skin breakdown at the initial closure site and soft tissue or joint infection. The former often requires reoperation for closure or skin grafting (or both), and the latter requires intravenous antibiotic therapy and sometimes endoprosthesis removal. During these complications, rehabilitation is often put on hold and restarted when appropriate.

If no complications occur, patients with humeral excisions can be given passive hand ROM on day 2 and actively use their hand 2 weeks postoperatively. Passive ROM is performed on the elbow for 3 weeks postoperatively. Patients usually lack approximately 40 degrees of extension. Use of moist heat over the elbow followed by gentle stretching can be started at approximately 4 weeks after the reconstructive procedure involving the shoulder if the wound is sufficiently healed and can withstand the tension of biceps lengthening. The therapist performs progressive passive ROM of the shoulder beginning with 20 degrees flexion-extension, then adding abduction and internal-external rotation. Close contact with the surgeon is maintained in increasing the degree of ROM. Usually, passive ROM in abduction and internal-external ROM is attained approximately 60 degrees. Active ROM is not expected to be functional.

Patients with distal femoral endoprosthetic replacements generally wear a knee immobilizer for 3 weeks. The therapist performs passive ROM of distal joints. The therapist is allowed to perform limited-arc passive knee ROM of the involved joint between 2 to 3 weeks, carefully observing the wound closure for any signs of potential breakdown from increased tension with weight bearing and then the sutures are removed, active assistive ROM is performed, and the ROM arc is gradually increased.

The patient should be able to perform some isometric exercise in the immobilizer on day 3 and begin active ROM at 1 month. Quadriiceps strengthening to improve knee biomechanics is very important. Exercise intensity is advanced with addition of some isometric light weight at 6 weeks. From a mobility point of view, patients walk with crutches and are non–weight bearing from day 4 to 10. Gradual weight bearing starts then to toe touching and progressing to weight bearing with metatarsal pads, while monitoring pain and looking for development of any knee effusion. Usually, weight-bearing status is decreased if the latter occurs. By 2 to 3 months, when the quadriiceps is sufficiently strengthened to support the knee and affected patients have no complications, they ambulate with a cane. Independent ambulation without a cane occurs anywhere from 3 to 4 months postoperatively.

Patients with proximal tibial resections have a slower course. One main reason for this is that the surgical procedure requires quadriiceps reconstruction with a gastrocnemius flap and reattachment of the quadriiceps mechanism to the metal endoprosthesis. Healing of the reconstruction takes longer. The limb is elevated for 10 days. Quadriiceps isometrics are started on day 2. ROM and weight bearing are introduced at a slower pace. The patient wears a bivalved cast for a month. Knee ROM and arc of motion when the cast is removed.

Active motion exercise starts when the patient is able to extend the knee. Often, the patient wears a long leg brace for an additional 2 months, which allows 30 degrees of flexion. Full weight bearing with a cane is not expected before 4 to 5 months. The quadriiceps mechanism is initially weaker than with the distal femoral procedure, due to the quadriiceps reconstruction. More intensive quadriiceps strengthening is needed to help to reduce knee extension lag, allow for active knee extension, and ensure safe gait. Final functional outcomes are pain-free, independent ambulation without a cane and ADL around 6 to 8 months.

Early rehabilitation for amputees begins with fitting the residual limb with an immediate postoperative prosthesis in the operating room. This is achieved for above-elbow amputation, below-elbow amputation, AKAs, and below-knee amputation levels. The purpose is to shape the residual limb and to reduce pain and edema.

High-level amputees, or hemipelvectomy, may have considerable phantom pain because of surgical severance of large nerve trunks. Often, reduction of edema by elastic compression on manual drainage, use of TENS, and pharmacologic interventions help with pain reduction.

In most centers where limb-sparing surgeries are performed, the patient's function is evaluated at intervals to document clinical progress and to follow function in drug trials. Patients are followed up long term for 10 to 15 years and are evaluated at 6-month intervals the first 3 to 5 years and yearly thereafter. If they are disease-free at 10 to 15 years, they are usually discharged.

Functional assessments include objective measures of strength (manual muscle test), ROM (goniometer), edema, and pain and fatigue by visual analog scales. A functional questionnaire may be used for determining level of participation in ADL and use of assistive devices and to identify psychosocial and vocational problems. A cancer-specific questionnaire is the Cancer Rehabilitation Evaluation Systems. A combined physical evaluation and patient questionnaire for assessing function of OS and atypical fibrous lesions was developed, the Tumor Extremity Salvage Score, was developed and validated for both STS and OS patients.51 Patients with STS and OS may also be assessed from a biomechanical standpoint in motion analysis laboratories looking at velocity, stride length, and substitutive gait patterns.

Patients with STS who undergo wide local excision generally have satisfactory to excellent functional outcomes because one of the criteria for surgery is predicted satisfactory outcome. The specific outcome depends on the extent of the excision and adjacent structures and postoperative complications.28,34

Patients are generally independent either with or without assistive devices and braces. Some patients may need a change in vocational status. OS limb-spared patients generally have good to excellent function, as judged by the Enneking Assessment and Gait Analysis.52 Some, however, fall into the poor to fair categories. Gait analysis reveals that such patients may have slower cadence and uneven stride lengths. They often use submissive muscle strategies. These vary widely. For instance, in the presence of a weak quadriiceps, such patients strike their toe first on stance rather than heel strike. This creates an extension moment at the knee to help to stabilize it and, therefore, to improve gait safety. Limb-spared procedures require a reconstruction if there is dislocation, fracture at the bone cement interface, severe, untreated unresponsive to intravenous antibiotics, or worn-out components. Studies of these reconstructions are limited to case reports but indicate good to excellent function.52

Amputations are still necessary if limb salvage cannot be performed or if a former limb-sparing procedure cannot be done. Amputation levels for sarcoma (OS and STS) are performed at all levels, depending on tumor site and size. Skip lesions often occur in OS; thus, the amount of bone involved by the primary tumor in these lesions requires a higher amputation level for cure. In comparison to amputations for diabetes and vascular disease, which are usually midlevel below-knee amputations and AKAs, those for sarcomas tend to be high-level procedures (hemipelvectomy, hip disarticulation, high AKAs, short below-elbow amputations, and forequarters). Prosthetic fitting in these cases is more difficult. Achieved functional level and compliance with use of some prosthesis, as hemipelvectomy, is low, and energy requirements for use are higher. Forequarter prostheses are rarely functional and often not used.

In general, amputees are usually independent in mobility and ADL with or without crutches. Vocational status often needs to be changed. Phantom pain may interfere with function and needs to be treated.

The function of limb-spared patients versus amputees has been addressed. Some amputees may be more functional than limb-spared patients and vice versa. Since some prosthetic limbs are durable, participation in contact sports, running, high-impact dances, tennis, and golf are no problem. However, amputees with cosmetic limbs, humeral OS or lower limb sparing, should have more restriction in sport activities. Limited sport may be needed to preserve endoprostheses. However, an upper extremity Tinkoff-Lindberg procedure for humeral OS is much more functional than a forequarter amputation.
Pain. Management of pain postoperatively is essential. Pharmacologic management with narcotics is essential in the first postoperative week. Rehabilitation treatments begin with proper limb positioning to reduce edema and avoid contracture. Immobilization of operative sites using splints and use of TENS are common adjuncts. Acupuncture may also be useful to reduce pain.

Lymphedema. Edema can cause pain and interfere with function. Significant lymphedema commonly occurs with STS resections involving the adductor and hamstring, anterior compartment muscle groups, and breast sarcoma. This is controlled by proper positioning and the use of a compression garment. With these four excisions, edema is often chronic and needs to be treated long-term with combined modalities of massage, wrapping, and pumping. It can usually be well controlled or reduced. A new technique of nonelastic wrapping has proven very effective in management.

Mobility. OS and STS limb-spared patients have short- and long-term mobility problems. In the immediate postoperative phase, crutches and walkers are often needed. Often, patients will not need these devices at 6 months. Orthoses are needed after some soft tissue resections to replace lost function. The most common brace used is for knee control after excision of the quadriceps; for ankle control after gastrocnemius with peroneal nerve removal; and for wrist extension after radial nerve or forearm extensor removal. For knee control, an AFO with 5-degree plantar flexion is often used. This creates an extension movement to stabilize the knee. The peroneal nerve brace is a plastic AFO to correct equinovarus of the foot. A cock-up splint is used to maintain wrist extension or a dynamic outrigger brace is used to restore finger extension if the long extensors have been resected.

Below-knee and above-knee and above-elbow and below-elbow amputees are fitted with an immediate postoperative cast, after the suture line is closed, and a temporary pylon and foot are added at day 10 postoperatively for the below-knee and above-knee amputees. A permanent limb is ordered when the residual limb is well shaped and the patient does not have fluid and weight shifts from chemotherapy. If no chemotherapy is involved, a permanent prosthesis is made 6 weeks postoperatively. For chemotherapy patients, this may be delayed by 3 months.

Two main types of prostheses are used: endoskeletal and exoskeletal. Endoskeletal prostheses have an internal metal support system and an external molded, soft skin-color cover. They are more cosmetic and lighter in weight than exoskeletal. However, they will tear when subjected to contact sports or even walking in the woods. They are cosmetically more acceptable to many. Exoskeletal prostheses have a hard durable shell and can be used for sports activities and are heavier. New components using graphite for joint components have lessened the weight of prosthesis. The choice of the particular types of components, such as knees and ankles, and strength of cables for an upper extremity prosthetic depend on the activities in which the patient is engaged. Young amputees (common in the case of OS) prefer hydraulic knees that facilitate such activities as dancing and ankles that are flexible, which facilitate push-off in the gait cycle and render gait more propulsive. These are useful for sports activities.

Better form-fitting, more naturally aligned prosthetic sockets are routinely used. More sporty socket suspensions and prostheses are available, including swim legs and adaptations for skiing. Myoelectric upper extremity prostheses with switches are sometimes used but are very expensive. They are more cosmetic, but the hand component can lift only light objects.

Cosmesis. Cosmesis is very important to cancer patients. Wide local excision of STS often causes soft tissue deficits. Some of these can be ameliorated by soft, contoured fillers. Some examples of these are a buttckk prosthesis for buttockectomies, a gastrocnemius prosthesis, a shoulder prosthesis for forequarter amputations and after the Tinkoff-Lindberg procedure, and a foot prosthesis after partial-ray resection. Breast prostheses made of various materials (gels, fluff, etc.) are used for mastectomy sites secondary to sarcoma.

Fatigue. Fatigue results from inactivity, the disease itself, depression, and chemotherapy (Adriamycin). Exercise to increase strength and joint motion is an important component in facilitating and maintaining regain of function in limb-spared patients. Often, low-intensity, low-impact aerobic programs are prescribed. Frequently, particular muscles are targeted for exercise (e.g., quadriceps in distal femoral and proximal tibial limb-sparing procedures for OS and partial quadriceps removal for STS). General strengthening and ROM exercises are performed for uninvolved muscles. Isometrics and isotonic strengthening with weights to 2 pounds using a short lever arm are permitted in patients with endoprostheses. Isokinetic machine exercise is not permitted.

Maintaining at least critical joint motion for function is important. It is not necessary that the joint motion be completely normal for adequate function.

Vocational Activity. STS can occur in all age groups, but the median age tends to be midlife and later. This places people in that part of their lives when they are working and supporting families. As a result, some may need to change their vocation, though many remain in their jobs with reasonable accommodation. Some studies have shown individuals with STS often enter into retirement.

OS occurs in children and young adults. Often, they are faced with career choices influenced by their level of physical as well as cognitive abilities. Career counseling is advised.

Recreational Activities. Recreational and social activities are important to cancer patients. Patients with wide local excision often can continue their premorbid recreational and social activities. With resections requiring bracing, some activities are not possible. Patients with STS and radiated bone and OS with endoprostheses must avoid contact sports and activities that cause torqueing. In addition, impact activities (running, some dances) are not appropriate for limb-spared OS patients. These more aggressive activities can result in bony fracture, bone-prosthetic interface fracture, endoprosthetic dislocation, and early breakdown of prosthetic components.

Education of the patient about which activities are appropriate is important in preventing complications. Adaptive methods of participating in some sports are appropriate. For instance, modification of stance, position, and swing may reduce torque and allow some lower limb–spared patients to play golf. Doubles tennis played at less aggressive levels may also be appropriate. A young teen going to the prom can dance but needs to avoid torqueing and high-impact dances.

LONG-TERM CARE PHASE. Limb-spared patients have had decreased morbidity, owing to appropriate adjunctive chemotherapeutic and radiotherapy regimens and defined and innovative surgical techniques. Limb-spared patients should be followed up from a rehabilitation standpoint to ensure that they are not developing any long-term radiotherapy problems (motion loss, radiolucency, and cord syndromes) that would decrease function. Any new development of pain should signal local recurrence or fracture at the endoprosthetic junction. Amputees generally need new prostheses every 4 to 5 years, depending on level of use.

Special problem areas that arise in this treatment phase include adjustment to disability and vocational change and recreational, social, and schooling issues. The important goal is to maintain function.

METASTATIC DISEASE AND LOCAL RECURRENCE PHASE. When metastases occur with OS, they are most common to the lung or other bones. Often, it is a single metastasis or a few, possibly amenable to local resections. With STS, lung metastases occur. Patients may have multiple surgical procedures over time, usually a median sternectomy or thoracotomy with pleura and chest wall resections. A newer procedure allows for removal of lung metastases without major chest surgery. Chemotherapy is reintroduced after the local chest resection. These surgical treatment interventions often are associated with postoperative chest pain. The patients may become deconditioned and experience fatigue, anxiety, and weight loss during these treatment periods and may require rehabilitation interventions much as they did in the initial phase. Vocational and educational endeavors are disrupted. Rehabilitation strategies to relieve postoperative pain (TENS) and reduce fatigue (assistive devices, energy conservation techniques) and anxiety (stress management, relaxation techniques, and imagery) are helpful. Referral to a dietitian is made to support good nutrition.

When metastases return and are inoperable, experimental chemotherapy regimens are used. Often, these have low success rates and high toxicities. Likewise, local recurrence may happen, particularly with STS. These also require additional therapies. At this stage, emotional support, comfort, and education about problem solving to promote and preserve independence can be provided by the rehabilitation team.

MELANOMA

In advanced or recurrent melanoma, oncologists have reported the efficacy of isolated limb perfusion with various chemotherapeutic agents (e.g., melphalan) and
biologic response modifiers (e.g., tumor necrosis factor and interferon) where mild to moderate limb toxicity has been reported. Complications resulting from these procedures include transient peripheral neuropathy, edema, skin breakdown, and vascular compromise with tissue necrosis. As a result of these complications, rehabilitation of these patients is often protracted and requires careful daily monitoring of the skin for areas of pressure combined with an active program of exercises and progressive ambulation. Management of edema, using compression garments and inelastic wraps, may be achieved for symptom relief and control. Amputation rarely must be performed to treat complications of limb perfusion. Prosthetic fitting and training may be undertaken.

**LUNG CANCER**

Lung cancer patients may benefit from rehabilitation interventions addressing pain control, cardiopulmonary conditioning, and work and home modifications. Rehabilitation of the patient with lung cancer is generally divided into a preoperative or pretreatment phase and a postoperative phase. The pretreatment phase consists of a medical review of the chart to ascertain the stage and type of the tumor and whether metastases are present. The physician should review the planned medical treatment. In addition to assessment of current medical status in regard to cardiopulmonary function, tests should be performed for hemoglobin, hematocrit, and electrolyte levels. The current vocational status and family support allows. Tension should be assessed. Structured comprehensive cancer rehabilitation services have not been widely available, especially to patients with brain tumors. Nevertheless, there is good evidence that cancer patients can benefit significantly from rehabilitation intervention and that recurrent or metastatic tumors and ongoing aggressive tumor therapy should not preclude admission to a rehabilitation unit.

Philip et al. demonstrated that after definitive treatment of primary brain tumors in children, rehabilitation significantly improves outcome in self-care activities, transfers into and out of bed, and locomotion by a wheelchair or walking. Furthermore, preliminary evidence supports the efficacy of post–acute brain injury rehabilitation services for patients with primary malignant tumors, resulting in sustained increases in productivity. Specific program interventions for these successful services include evaluation of cognitive, behavioral, affective, and social functioning; identification of impairments and their impact on patients’ daily functioning; individualized therapies to improve functioning; and return to desired vocational status.

Rehabilitation intervention most commonly begins after removal of the brain tumor. When affected patients are medically stable, a referral to rehabilitation should be initiated so that they can be helped to sit up, get out of bed, and start an active restoration program that is tailored to their general condition. Recovery may be fairly rapid, initially due to control of edema. Herniation or hemiparesis is a common sign of brain cancer and is often most profound just after the brain surgery. Some return of motor strength is common and may continue for several weeks or months. While muscles that are still paralyzed 4 to 8 weeks postoperatively generally remain so, functional improvement can still occur through routine daily activity as well as therapeutic exercise and use of appropriate assistive devices (orthoses or gait aids). Encouragement in the use of the affected limb is recommended, rather than learning to substitute for the affected side using one-sided activity. Data suggest that recovery of motor and language function can proceed over significant periods with proper encouragement and stimulation.

If patients are kept in bed, they should be placed on a special mattress designed to prevent pressure sores. To prevent capsular contractures of the shoulder, patients should lie with the affected arm abducted, externally rotated, and slightly elevated. The lower extremity should be positioned to minimize hip-knee flexion. Passive joint ROM exercises should be applied to the paralyzed extremities and active exercises to the unaffected parts twice a day.

Most patients are able to ambulate with assistive devices and training. Good sitting balance and standing balance are prerequisites for functional transfers and ambulation. Therapists use feedback mechanisms to correct patients’ tendency to lean toward the affected side. For example, “handing” is a therapeutic technique designed to establish normal alignment, reduce or eliminate abnormal tone and movement, reeducate muscles in normal patterns in the trunk and limbs, and produce an active movement pattern in hemiplegic patients. “Inhibition” techniques are manual techniques and hand placements used to decrease or eliminate spasticity.

Dynamic sitting balance is achieved through trunk exercises, use of mirrors, and verbal feedback regarding position. Potential ambulatory ability should be assessed by standing patients in the parallel bars. Patients should be taught bed-to-chair transfer activities as soon as sitting balance and weight shifting allow. Patients whose hip flexors and extensors remain weak will not ambulate independently because no satisfactory hip bracing is available. Weak knee extensors can be stabilized with a temporary knee-ankle-foot orthosis, which locks the knee in extension during weight bearing. Weak ankle dorsiflexors are often the last muscles to recover and can be stabilized with a plastic ankle-foot orthosis (AFO) to prevent toe dragging during the swing phase of gait. Elevation activities, such as climbing and descending stairs, ramps, or curbs, are started when a good gait pattern on level ground has been achieved. Patients with severe neurologic deficits may require a wheelchair, either for mobility at all times or only when ambulation endurance or safety is impaired.

The major goal in the rehabilitation of the patient with brain cancer is independence in ADL, which may be obtained through training, prescription of proper assistive devices (e.g., adaptive eating utensils, bathroom equipment, positioning and transferring equipment, and gait aids) and modification of the patient’s home and work environment (Fig. 57-6).

**FIGURE 57-6.** Adaptive eating utensils for patients with upper extremity spasticity or weakness.
Spasticity is a frequent impediment to mobility and performance of ADL. Factors that may aggravate spasticity, such as skin lesions, infections, and anxiety, need to be identified and treated. Thorough stretching of all joints should be performed daily. Medications, such as dantrolene, baclofen (starting at 5 mg three times daily and titrating to a therapeutic dose of 200 to 400 mg daily), clonidine (titrated until therapeutic dose is reached), and gabapentin (titrated until therapeutic dose is reached), are sometimes used to reduce spasticity. These medications are used sparingly because of their potential for producing somnolence. Selected nerve root blocks with dilute solutions of phenol or concentrated alcohol are usually effective in reducing spasticity. Botulinum toxin injections are also useful, and proper dosage and administration site are essential for a favorable response. Surgical procedures for reducing spasticity in this population are rarely indicated.

Joint contractures may be caused by muscle imbalance, spasticity, poor nursing care, prolonged immobility, improper bed positioning, or an inadequate exercise program. Whatever the cause, the contractures may adversely affect the rehabilitation prognosis. For example, development of a frozen shoulder may render independent dressing impossible. Therefore, prevention of contractures by proper positioning and posture and joint ROM exercises is imperative, since treatment of contracture is relatively ineffective.

Cancer of the brain may cause pain in different parts of the body. Pain in the hemiplegic shoulder is common and may benefit from shoulder support by an arm sling or a lap board, administration of analgesics, application of heat or cold modalities, and gentle ROM and strengthening exercises. Complex regional pain syndrome of the shoulder (previously known as shoulder-hand syndrome) may also occur and requires similar treatment, but more effective relief may be obtained by prescribing oral steroids. Dysesthetic thalamic pain is notably refractory to treatment, though various centrally acting agents may be helpful.

Varying degrees of sensory involvement are commonly seen in patients with brain cancer, either in the distribution of the cranial nerves or on one or both sides of the body. They may interfere with balance and mobility, since patients who cannot feel motion are unable to control it. Training with adaptive gait aids may help such patients to ambulate functionally again.

Vision deficits, such as double vision, homonymous hemianopsia, and anosognosia, may greatly interfere with function, especially in patients with a right brain lesion. Fortunately, specialized programs of cognitive remediation have been found to be effective with these patients. Such programs include basic scanning training, somatosensory awareness and size estimation training, and complex visual perceptual training.

Aphasia, a disorder of both the expression and reception of propositional language secondary to cortical or subcortical disease, may be seen in patients with cancer in the left dominant hemisphere of the brain. Listening, speaking, reading, and writing are usually affected to varying degrees; thus, several types of aphasia are recognized. Expressive or nonfluent aphasia is caused by lesions in the Broca area of the brain. Reduced language production, vocabulary, and grammar are characteristic of this condition. Patients are usually aware of these difficulties and are even able to write, though not fluently. Receptive or fluent aphasia is caused by lesions in the Wernicke area of the brain and results in difficulty in understanding language, both the patient's and that of others. Patients may be able to speak continuously at normal speed and with normal melody without giving any relevant information and be unaware of the errors. Speech therapy is indicated, whenever available, not only for psychological support but to stimulate patients to use their maximal speech ability and to adjust to new circumstances. It is also helpful to instruct affected families in proper communication with involved patients by such means as using proper sentences at a normal voice volume and using gestures and facial expressions while increasing respect, optimism, patience, and encouragement.

Dysarthria is a motor disturbance of speech characterized by weakness, slowness, or incoordination of the muscles that produce speech. Therefore, there is complete understanding of written or spoken language. The main problem is articulation, though speed, rhythm, sound, and intonation may also be impaired. Speech therapy emphasizes teaching the patient to use the remaining speech muscles more effectively or to bypass the effects of disturbed function.

Aprosia is a communication disorder caused by lesions of the nondominant right hemisphere. It results in the inability to express and comprehend variations in pitch, rhythm, and stress, which give emotional meaning to speech. Affected patients may speak in a relatively flat voice and are often unable to recognize the emotional tones of speech, including the meaning of nonlanguage speech sounds, such as grunts or sighs. Therefore, the clinician and family should communicate with the patient strictly by words, because specific therapy does not exist. Fortunately, considerable improvement usually occurs over time.

Dysphagia, or impaired swallowing, is most commonly seen in lesions involving the brain stem. With severe involvement, the patient may be totally unable to swallow or, in milder cases, there may be difficulty only with the swallowing of liquids. Whatever the degree of severity, the patient is at risk for aspiration with resulting pneumonia, so suspicion of the condition with timely intervention is key to treatment. Serial radiographic swallowing studies are indicated for proper monitoring of the condition until it resolves or other and safer means of nutrition are provided. Speech therapy may institute a swallowing training program in which patients attempt to swallow food of different consistency using different techniques and positions. If indicated, a nasogastric tube can be used for several weeks while waiting for spontaneous recovery. A more persistent dysphagia may warrant a gastrostomy tube for prolonged feeding.

Neurobehavioral problems often have an undereappreciated but large impact on the quality of life of patients with tumors and their families. Implementation of services directed toward these problems is only now receiving attention. The use of traditional cognitive and vocational rehabilitation for patients with brain tumors is complicated by the fact that existing programs are not entirely appropriate. The patterns and types of cognitive deficits experienced by these patients are different from those seen in AMI, stroke by stroke or TBI patients. Anderson et al. found that patients with brain tumors have milder cognitive deficits and greater variability in the nature and extent of their deficits, compared with people who have strokes that affect the same neuroanatomic site. Furthermore, the natural history of the disease process is different from that of cerebrovascular disease or TBI. The latter two are usually characterized by an acute onset and gradual recovery, while the onset of disease in brain tumors is relatively insidious. Although some recovery of function may be seen after surgery or other therapy, most patients experience a gradual deterioration of function as the tumor progresses.

The most common type of neurobehaviorally oriented program is the day treatment program, which emphasizes cognitive and vocational rehabilitation. Although these programs are frequently affiliated with an inpatient rehabilitation program, many are located in the community to provide better access to resources. The first step in cognitive and vocational rehabilitation is to identify realistic goals for the patient. Formal neuropsychological and vocational testing to identify preserved skills have been found to be useful. The major goal is to train patients to compensate for their neurobehavioral deficits at home and on the job. Memory, problem-solving skills, and social behavior are typical areas targeted for retraining. For example, patients with memory deficits may compensate by using tools, such as written reminders and alarm watches. Patients with behavioral problems should be taught to inhibit socially inappropriate remarks or to reduce frustration intolerance. Furthermore, patients and family members should be counseled about the need to select jobs that are less demanding although not as financially rewarding or prestigious.

In addition to providing rehabilitation to appropriate patients with brain cancer, patients' families should be offered education and emotional support. Families of such patients are often burdened by the patients' cognitive and behavioral changes in addition to the typical psychological problems of coping with cancer in a family member. Support groups for patients with brain cancer and their families may be of great benefit.

HEMATOPOIETIC TUMORS

Leukemias

Leukemia is the uncontrolled proliferation and incomplete maturation of leukocyte and lymphocyte precursors appearing in bone marrow and peripheral blood. Leukemia may occur in acute or chronic form. The acute leukemias include acute myelogenous leukemia (AML) and acute lymphoblastic leukemia (ALL). They are more common in childhood. Both leukemias are associated with anemia, fatigue, fever, bleeding gums, gastrointestinal tract or urinary tract symptoms, easy bruising, and pallor. Headache, mental changes, and cranial nerve palsy are common in ALL with CNS involvement. Joint pain is often seen with ALL but rarely in AML. The presence or absence of these symptoms is related to remission or response to treatment. Complete remissions are often seen. Treatment of AML consists of cytarabine, daunorubicin, and amrsconure. The mainstay treatment in ALL consists of vincristine and prednisone.

Chronic myelogenous leukemia is not usually seen before 20 years of age, and chronic lymphocytic leukemia is generally seen after 50 years of age. Both present with abdominal discomfort, organ enlargement, malaise, and fatigue. Anemia, low platelet count, bruising, and cutaneous bleeding are seen with chronic myelogenous leukemia.

The rehabilitation team must address the effects of the leukemia itself and the side effects of medications and irradiation. A leukemia that does not respond completely to treatment has a course of remissions and exacerbations that seriously affects the ability to attend school or continue working. Long periods of rest may...
be needed during treatment or during times of low platelets. Generalized deconditioning and decreased muscle strength occur. Steroids contribute to decreased strength when they cause a myopathy. They may be associated with osteoporosis, compression fractures, and painful aseptic necrosis of bone. CNS leukemia is associated with altered cognition, cranial nerve abnormalities, and other neurologic deficits. Vincristine causes peripheral neuropathy. Hair loss occurs with some chemotherapy agents. Bone marrow transplantation requires a 6-week hospital stay, usually with confinement in a bone marrow hospital unit because of the necessary immunosuppression (e.g., leukocyte count <1000/mm³).

Management of muscle weakness, decreased endurance, focal neurologic deficits, joint pain, cosmesis, and psychosocial and vocational problems are a challenge to rehabilitation specialists dealing with this group of patients. The type and intensity of exercises allowable depends mainly on the platelet count and hemoglobin level. Exercise may be nonprescriptive when the platelet count is less than 50,000/mm³. Nonprescriptive exercise is performed with counts below 20,000/mm³. Aerobic or endurance exercise is limited when hemoglobin measures less than 8 to 10 g/dL. Whenever exercise and activity are possible, they should be encouraged. Patients undergoing bone marrow transplantation are always placed on an exercise program to increase strength and endurance. Recent studies demonstrate the safety and efficacy of aerobic conditioning during bone marrow transplantation and during treatment with chemotherapy. Exercise should be performed either 2 hours before or 2 hours after radiation is delivered, to avoid a radiation-enhancing effect that occurs during increased blood flow resulting from exercise. Those who are on high-dose steroid therapy and are particularly susceptible to steroid myopathy, osteoporosis, and aseptic necrosis. Their exercise program includes weight-bearing activities, upper extremity ROM, an isometric program, and back extension exercises. An aerobic program is introduced when platelet and hemoglobin levels permit. Exercise also seems to be effective for reducing symptoms of nausea and fatigue and for improving psychological well-being.

Bracing and splinting are needed for neurologic deficits. A wig should be provided at initiation of treatment in anticipation of hair loss due to chemotherapy. Assessment of ADL and issuance of safety equipment and assistive devices may be needed. Energy conservation education is important. Assisting patients and their families in coping with acute and chronic problems is essential.

**Lymphomas**

Lymphomas constitute a group of malignant tumors that arise principally from lymph node cellular structures, other reticuloendothelial organs, and bone marrow. These tumors are classified as Hodgkin’s disease and non-Hodgkin’s lymphomas (NHLs). The type of cells and their growth pattern help to differentiate the types of lymphomas. Knowledge of the stage of the disease is important because medical and rehabilitation treatment regimens are oriented to the stage-specific problems and prognosis.

Treatment consists of combination chemotherapy and radiotherapy. Many multidrug regimens exist. Choice of an appropriate drug regimen depends on the stage of the disease. Most of the regimens include prednisone, and side effects of osteoporosis, compression fracture, myopathy, and aseptic necrosis may be seen in 10%. Other drugs with potential side effects that need to be addressed by rehabilitation include doxorubicin, which produces decreased cardiac ejection fraction, and vincristine, which causes peripheral neuropathy. Combination regimens may result in hair loss, aspirmia, and early menopause. Prolonged bed rest results in muscle weakness and decreased endurance. Treatment with radiotherapy can result in skin tightness, restricted joint motion, and aspirmia.

The disease itself can be asymptomatic (subtype A) or symptomatic (subtype B). Systemic symptoms of fever, night sweats, weight loss, and decreased endurance are present with stage I through IVB disease. Aggressive high-grade lymphomas, such as Burkitt’s, have a high propensity for metastasis to the CNS (e.g., meningeal carcinomatosis), causing symptoms of headache, diplopia, cranial nerve palsy, and weakness. Spinal cord compression can occur if lymphoma involves the epidural space. CNS and spinal cord involvement can occur with NHL and Hodgkin’s disease.

Other problems that arise with lymphomas include increased susceptibility to infection, pleural and pericardial effusion, and superior vena cava syndrome due to compression of the superior vena cava by enlarged lymph nodes.

Chemotherapy and irradiation regimens for NHL are chosen according to the grade and type of tumor. Vincristine, prednisone, and cyclophosphamide are commonly used in these regimens. (Side effects are similar to those described in Chapter 45.5 on Hodgkin’s disease.)

As for patients with any type of cancer, it is important to know the type and stage of lymphoma, the treatment indicated, and side effects and the general prognosis when planning a rehabilitation regimen. In general, patients have to cope with disease-related problems and the effects of complex chemotherapeutic and radiotherapy regimens. Some patients may have an early complete cure and be left with no residual problems. Others may have had more advanced or more malignant disease with incomplete remissions or recurrences and disease- and treatment-related morbidity. In this latter group, vocational and school status should be assessed. All members of the rehabilitation team are involved in the management of these patients.

Neurologic involvement may require bracing, mobility aids, assistive devices, and speech and language evaluation. Unweighting lower extremity joints involved with aseptic necrosis is appropriate. Muscle weakness and deconditioning should be addressed with appropriate strengthening and endurance exercises. The same precautions about platelet and hemoglobin levels hold true for lymphomas and leukemias. Patient attention should be paid to unweighting bony lower extremity lesions if there is more than 50% cortical involvement. Appropriate spinal bracing for vertebral involvement should be addressed. Usable lesions should be evaluated surgically. If the patient has advanced disease and surgery cannot be done, choice of a body jacket for thoracic and lumbar lesions and a four-point walker brace for cervical lesions may need to be used to help prevent spinal cord compression. When treating patients in rehabilitation, any early signs of spinal cord compression, such as new weakness, sensory deficits, or reflex changes, should be reported to the primary physician, because radiotherapy may be effective in reducing the size of spinal metastasis and relieving spinal compression. Likewise, any signs of superior vena cava syndrome, such as increased dyspnea, facial edema, and dilated chest wall veins, should be reported, because radiation may palliate these symptoms.

**CONCLUSION**

The cancer population presents a significant challenge to health care professionals because management is complex and is unique to individual patients and their phase in life and stage of disease. A model for planning treatment for the entire life expectancy of these patients, which is likely to be measured in years, is that of a chronic illness. This chronic illness may also have acute phases. Treatment goals should always support those of the patients and promote, restore, or preserve functional activity that has value to patients in their unique social, vocational, and physical environment.

**CHAPTER REFERENCES**

INTRODUCTION

The current health care environment has influenced the delivery of cancer care, with shifts in patient acuity levels, volume, and management of patients across care settings. In response to the dynamic health care changes and therapeutic advances in oncology over the past decade, a growing trend is evident to use advanced practice nurses (APNs) and midlevel practitioners (i.e., physician assistants [PAs]) in the effort to provide high-quality, cost-effective oncology care. This chapter describes the preparation and role implementation of the PA, defines the oncology APN, identifies the professional issues that influence regulations of practice, delineates the role components of the oncology APN, and identifies the benefits of a collaboration between physicians, APNs, and PAs in oncology practice.

PHYSICIAN ASSISTANTS

The first PA education program began at Duke in 1965. It was designed to train a general assistant, who could develop areas of expertise over time under the direct supervision of a physician, initially in the areas of primary care and general surgery. The American Academy of Physician Assistant estimates that there are 34,192 PAs practicing, predominantly in primary care (53%), family practice (40%), general surgery (19%), and emergency medicine (10). Currently, less than 6% of the PA population practices in one of the subspecialties of internal medicine, and only 1% work in adult or pediatric oncology. PA practice includes history and physical examinations, diagnosis and management, prescription of controlled and noncontrolled medications in those states allowed by law, screening procedures, ordering and interpreting laboratory and diagnostic tests, referrals and consultations, and counseling patients. Approximately one-half of the PAs in practice report performing invasive procedures, including bone marrows, lumbar punctures, and suturing and repair of lacerations.

EDUCATION AND CERTIFICATION

There are 116 PA training programs in the United States, with 42% offering a master's degree. Among the PAs in practice, 64% hold bachelor degrees and 22% hold master's degrees. Programs are divided into a didactic phase and a clinical phase. Postresidency programs at selected teaching hospitals offer advanced training in a specialty area.

Certification of PAs occurs at both national and state levels. National certification requires a certificate of completion from an accredited PA educational program and passing the Physician Assistant National Certification Examination, which is administered by the National Commission of National Certification of PAs. To maintain certification, PAs must fulfill annual continuing medical education requirements and must recertify every 6 years by written examination. Similar to initial certification, recertification focuses on primary care knowledge.

At the state level, 49 states plus the District of Columbia have licensing boards, which control prescriptive authority, reimbursement, and scope of practice. All states require physician collaboration in practice and for prescribing drugs. Most states have legislation that mandates Medicaid and Medicare coverage for PAs, but few have statutes requiring reimbursement from private insurers.

FUTURE DIRECTIONS FOR PHYSICIAN ASSISTANTS

In 1998, the Department of Health and Human Services asked the American Association of Physician Assistant Programs to develop a 3-year strategic plan stimulated by the current environment of the medical profession and the proliferation of training programs for nonphysician clinicians. Highlights of the plan include that education should continue to focus on primary care and allow for specialty developments over the course of one's career through continuing education requirements; competency should be promoted through continuing education programs and recertification examinations; PAs should continue to function in a delegated role under physician supervision, work with other health care disciplines to focus on underserved populations, enhance and empower patient populations through education, and attempt to provide cost-effective high-quality care.

ADVANCED PRACTICE IN ONCOLOGY NURSING

The oncology APN is defined as “a registered nurse, prepared with a minimum of a master’s degree in nursing, who has acquired advanced, in depth knowledge and preceptored clinical experiences in oncology that enable her or him to exhibit a high degree of independent and collaborative judgment and clinical skill in providing nursing care to patients with cancer and their families.” In 2000, the Oncology Nursing Society includes nearly 5000 members who are prepared at the master’s degree level or higher (World Wide Web site: http://www.ons.org). The acquired knowledge and clinical practice experience at the graduate level prepares the APN for expansion within areas of practice that overlap traditional medical practice and for integration of theory and research into practice. Improved patient outcomes, cost-effective care, and improved quality of life for patients and family are well-documented advanced practice nursing outcomes. Nursing, the core of advanced practice, is defined as assisting the individual in activities that contribute to health, recovery, or death and the diagnosis and treatment of human responses to health and illness. Collaborative practice between APNs and physicians results in better quality health care by combining the unique, documented contributions of the nursing discipline with the expert medical treatment of the illness.

EDUCATIONAL PREPARATION OF ONCOLOGY ADVANCED PRACTICE NURSES

Understanding the educational preparation of APNs is critical to decision making for employment and role implementation. The current recommendation for a master’s degree with a specialty in advanced practice oncology (Table 58-1), is designed for both the clinical nurse specialist (CNS) and nurse practitioner (NP), allowing for flexibility in emphasis of content for specific role preparation. Precepted clinical experiences in programs range from 600 to 800 hours. These recommendations are consistent with national recommendations for advanced nursing practice education and should prepare nurses to practice across settings of care.
Regulating Practice: Certification, Licensure, and Prescriptive Privileges

Regulation of advanced practice nursing is the responsibility of state legislators and boards of nursing. There are four levels of regulation and it is important to know the individual state regulations as they affect implementation of the role and prescriptive authority. The least restrictive is designation and recognition of the credentials of an APN, which in oncology is the CNS and the NP. The second level of regulation is registration with the state board of nursing, and certification is the third level of regulation. Certification for advanced practice nursing is a process, usually a written examination, that a nongovernment organization uses to establish that a licensed registered nurse has mastered a certain body of knowledge and skills. Certification is a voluntary professional activity but becomes mandatory for advanced practice licensure in most states. The American Nurses Association has provided leadership for certification and established a credentialing center in 1993, which offers advanced practice nursing certification (Table 58-2). Specialty organizations also offer certification. The Oncology Nursing Certification Corporation has objectively established criteria for delineating the role of advanced practice nursing in oncology. Eligibility for the Advanced Oncology Certified Nurse certification is open to those not only with advanced clinical preparation but anyone with a master’s degree or higher degree in administration, education, or research. Specialty certification is highly valued and recommended, but because Advanced Oncology Certified Nurse certification is not recognized by all states for licensure, many oncology APNs hold dual certification, one for licensure and one for specialty recognition (see Table 58-2).

TABLE 58-2. Certification for Advanced Practice Nurses Who Practice in Adult Oncology

Licensure is the fourth regulatory level that defines the scope of practice and qualifications, designed to protect public health, safety, and welfare and is associated with a high level of accountability. Advanced Practice Registered Nurse (APRN) licensure is granted by a governmental agency at the state level, and Pearson provides an annual review of the variations by each state on legal authority, reimbursement, prescriptive authority, scope of practice, and titling.

Reimbursement is provided by for-profit corporations and insurers, government [Medicare, Medicaid, Civilian Health and Medical Program of the Uniformed Services (CHAMPUS)], nonprofit, and self-insured corporations. Federal and state legislation dictate the level of reimbursement and the 1997 Balanced Budget Act provides direct reimbursement for NPs and CNSs across a variety of settings. NPs and CNSs are required to submit their own provider number in addition to the group practice number where applicable. Payments made to NPs and CNSs are “80% of the lesser of either the actual charge or 85% of the physician fee schedule amount.” The Health Care Financing Administration rules require a master’s degree, state authority granted to practice as an NP or CNS, and certification by a nationally recognized certifying body (World Wide Web site http://www.nurse.org/acnp/medicare/hcfa9804.shtml). The educational requirement does not include a grandfather clause for NPs who were not prepared at the master’s level and, thus, their services are not reimbursable under the current rules.

Prescriptive authority is part of state regulation and ranges from the APN as an independent prescriber to an interdependent relationship with a physician to the most restrictive, which only allows an APN to prescribe drugs from a list that has been preapproved by the state. Prescriptive authority includes controlled substances, as allowed by the individual state law (Table 58-3). For those states that include prescriptive authority for controlled substances, the APN can apply to the Drug Enforcement Agency and obtain individual Drug Enforcement Agency authorization.

TABLE 58-3. Nurse Practitioner Prescriptive Authority by State

Credentialing is a general term that refers to validation of the educational preparation, licensure, credentials, certification, and advanced scope of nursing practice. Credentialing is the term often used by institutions for the process of evaluating and granting clinical practice privileges.

Role Implementation of Advanced Practice Nurses

The APN implements the role as a direct caregiver, educator, consultant, administrator, and researcher. A role-delineation study confirmed that these role components were relevant to both the CNS and NP APNs in oncology, with less than 10% of the items differentiating the roles. This study supports the standards of practice for advanced practice nursing in oncology, supports identified competencies for role implementation, and further validates the similar and overlapping role.
functions of the CNS and NP in clinical practice, 34,35,36,37

Direct Care Provider

In provision of direct care to the patient, the roles of the CNS and NP are more blended than distinct, reflecting the similarity in advanced physical and psychosocial assessment and management. The distinction between these APNs lies in the emphasis and time spent on specific role functions. The NP direct care role is defined by comprehensive health assessment, diagnosis, health promotion, prescriptive authority, and management of acute and chronic problems. Oncology NPs also perform procedures, write orders, prescribe chemotherapy, admit patients to the hospital, and write inpatient progress notes. Some CNSs have adopted a practice model, in which the individual patient is the primary focus. In that model, the practice of the CNS and NP have little, if any, distinction. However, many CNSs continue a practice model, which was designed to promote improvement of nursing care by all nurses to a population of patients. Thus, the direct hands-on care role for the oncology CNS refers to direct patient care but also to the supportive role for nursing staff related to direct assessment, clinical decision making, introducing new skills into practice, and interventions. The reality of fewer professional registered nurses in hospitals, increased numbers of unlicensed personnel, continued specialization, and high patient acuity across settings of care have “recreated the scenario that first produced the need for specialized nurses earlier in the century.” In oncology, there is a real and persistent need to provide direction and consultation for direct patient care to less well-prepared nursing and nonnursing staff in order to deliver high-quality, safe, and competent nursing care.

Practice Setting

The changing nature of oncology practice creates continuous opportunities for diversity in role implementation across practice settings. The practice setting of the oncology APN is diverse, ranging from screening, detection, and genetic counseling programs to care of patients in the hospital, ambulatory clinics, private office practices, radiation therapy centers, home care, and hospice. In the hospital, implementation of the role of the acute care NP with critically ill cancer patients is increasingly evident, and a subacute NP role has been described for routine admissions of patients on a medical oncology service. Consistent with changes in the health care environment, there has been a recent shift of the oncology APN role to nontraditional settings, specifically home care, palliative care, ambulatory clinics and comprehensive cancer centers, and radiation therapy. Many APNs in clinics and private office settings have hospital privileges and provide care across settings.

Educator

The APN's educator role addresses the learning needs of the patient and family, other nurses, disciplinary colleagues, and the community. Teaching the patient and family is a primary role of the NP and the CNS across all settings and may include identification and use of appropriate culturally sensitive educational materials, development of practice standards for patient teaching, and evaluation of the effectiveness of educational interventions. Another major responsibility of the oncology APN is to improve patient care through staff education. In the current health care climate of high acuity and shortened stays in acute care settings and high volume and complex care required for patients in ambulatory settings, informal on-site education for nurses by the APN for diagnostic, therapeutic, and ethical reasoning in clinical judgment provides a critical method to improve nursing care and patient outcomes. Oncology APNs have made important contributions to nursing education, including the development of clinical knowledge through the publication of texts in specialty journals such as Cancer Nursing, Oncology Nursing Forum, Clinical Journal of Oncology Nursing, Cancer Practice, Seminars in Oncology Nursing, and oncology nursing texts. Many of these texts serve as excellent on-site resources for clinical staff.

Consultant

Providing expert advice to nursing and professional colleagues on individual patient cases and on complex problems of a specific patient population is a well-established function of the oncology APN. Consultation can be informal (verbal) or formal (written) and can be initiated with APNs from within or outside of the colleagues. A consultant role has an acutely focused role with an emphasis on a specific role function, skill, or knowledge. For example, consultative services in pain management, palliative care, and symptom management are available to patients under the care of the NP. The consultant role functions as a change agent, the primary purpose of which is to effect change to maintain or improve the quality of care delivered. The oncology APN by virtue of specialty knowledge and change agent skills is uniquely qualified to assess the process of care delivery; evaluate the clinical, psychosocial, financial, and patient satisfaction outcomes across the continuum of cancer care; determine what needs to be changed to achieve desired outcomes; and effectively implement change. Creative change agency is needed to challenge the status quo, introduce new skills or technology, integrate research findings into practice, and adapt care delivery within and across settings to improve continuity.

Clinical Leader

The clinical leader role should not be confused with institutional leadership activities of management. The APN leadership is directed at the practice environment, patient outcomes, and improving nursing care. The APN functions as a change agent, the primary purpose of which is to effect change to maintain or improve the quality of care delivered. The oncology APN by virtue of specialty knowledge and change agent skills is uniquely qualified to assess the process of care delivery; evaluate the clinical, psychosocial, financial, and patient satisfaction outcomes across the continuum of cancer care; determine what needs to be changed to achieve desired outcomes; and effectively implement change. Creative change agency is needed to challenge the status quo, introduce new skills or technology, integrate research findings into practice, and adapt care delivery within and across settings to improve continuity.

Researcher

Use of research in practice is dependent on the available body of research, dissemination of findings, and integration of the research findings by nurses in their clinical practice. Oncology nurses prepared at the doctoral level have made significant research contributions to the care of patients and families, with progression from earlier descriptive studies to intervention research. Symptom management is a major nursing focus. In 1994, a metaanalysis was performed on 28 studies that addressed nausea and vomiting, pain, anxiety, alopecia, infection, chemotherapy side effects, shivering, radiodermatitis, anorexia, and mucositis. Overall, interventions were successful in relieving symptoms and significant effectiveness was obtained for interventions used in the management of nausea and vomiting, pain, anxiety, alopecia, infection, and side effects of chemotherapy. In that same year, a State of the Knowledge Conference on the symptom of fatigue summarized existing data. That conference summary provided direction for future research, which has resulted in multiple publications from studies on measurement, prevalence, severity, perceived distress, and intervention effectiveness for the symptom of fatigue in cancer patients. These examples provide a small glimpse of the extent and scope of oncology nursing research that directly relates to practice.

RESEARCHER NURSING. Oncology is accountable to use research findings to support practice and maintain an evidence-based practice. As an example, Bockbinder and colleagues conducted a research utilization program in the Memorial Sloan-Kettering Cancer Center that was designed to improve quality patient care through integration of the Agency for Health Care Policy and Research Cancer Pain Management Clinical Practice Guideline into practice. APNs provided leadership for this project, which resulted in an organized clinical pain management program, pain management education programs, revision of assessment forms to include pain assessment and relief as the fifth vital sign, standards of care for professional and patient education and patient satisfaction, a systematic method to continually improve pain, and improved treatment outcomes. Collaboration of doctorally prepared clinical nurses and researchers with oncology APNs in clinical settings offers an opportunity to create environments that bridge the gap between practice and research, stimulate critical thinking among staff nurses, foster the value of research and application to practice, enhance practice-relevant nursing research, and ultimately, achieve the goal to improve patient care outcomes.

NURSES' CONTRIBUTION TO THERAPEUTIC CLINICAL TRIAL RESEARCH. The growth in numbers of APNs over the next 10 years presents an opportunity to develop a unique role in clinical research. Oncology nurses have traditionally played a major role in cancer clinical research by assuming the responsibility of safe study drug administration but also providing a full range of responsibilities related to research, including input into study design, feasibility assessments, and budgetary analysis; recruitment and education of patients; maintenance of regulatory documents; collection of data; and study summary and analysis. The role and number of APNs currently working in clinical trial research is unknown. However, the depth of specialty knowledge, research preparation, and advanced clinical nursing skills of the oncology APN offer unique qualifications to meet the challenges of a research coordinator for clinical trials. Additionally, the APN's autonomy as a direct care provider in toxicity assessment and in the management of complex cancer patients offers a model of care that combines resources to provide comprehensive care and maintain a high level of rigor in the research process. Few medical oncologists report any clinical research training, and many nurses involved in clinical trials do not have master’s degrees. Thus, nursing has identified the need for advanced level knowledge and skill in this area and has implemented programs for master's degrees and postmaster's certificates in clinical trials management at Duke University, University of California in San Francisco, and Columbia University. The content includes...
COLLABORATIVE PRACTICE

Collaborative practice among physicians and APNs or PAs is an appropriate model for oncology. The current health care environment and the increasing complexity of oncology have highlighted the need for professional interdependence and collaboration in order to provide safe care. A multidisciplinary approach has been an essential component of oncology care for a more comprehensive plan of care and to meet overall patient outcomes. The PA and APN offer significant contributions to the delivery of high-quality comprehensive oncology care, although educational preparation and disciplinary practice focus differentiates their unique contributions. All APNs are prepared at the master’s level and most within the specialty of oncology. Nursing is a distinct health profession and nurses practice under a professional nursing license. Primary care is the focus of the PA’s educational preparation and PAs practice within the medical model in a delegated role under the supervision of a physician. APNs may be supervised either by a physician or by a hospital’s collaborative practice agreement with an individual state law. Collaborative practice between a physician and an APN represents a relationship in which both disciplines share knowledge and have diverse but complementary expertise and skills. This type of interdisciplinary practice enhances communication and understanding, provides mutual support and results in an efficient approach to the delivery of comprehensive quality care, improved patient outcomes, and increased patient satisfaction.

The current health care environment presents significant challenges to the delivery of high-quality patient-centered oncology care. Innovative collaborative models of care among providers can create environments that support the oncology health care team to achieve high-quality clinical outcomes, efficient use of resources, empowerment of the patient and family, and successful clinical research and maintain a state-of-the-art evidence-based practice.

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CHAPTER REFERENCES

Chapter begins with an overview of clinical medical ethics and the doctor–patient relationship (DPR) and then examines ethical issues, primarily in medical oncology, relating to both clinical care and clinical research. With regard to cancer clinical care, an effort has been made to cover those topics of greatest importance to the cancer physician: informed consent and decision making; prognosis determination and communication; and ethical issues in the care of patient with life-threatening and life-ending disease, including such traditional areas as informed consent, medical confidentiality, and physician-assisted suicide (PAS). In examining cancer clinical research, the chapter focuses on specific ethical principles that ought to guide such research; the issues surrounding the concept and practice of informed consent for clinical trials; and the ethical issues and dilemmas associated with phase I, II, and III trials in oncology. Wherever possible, available empirical research is used in an attempt to address, and even resolve, the ethical issues and dilemmas that arise in cancer care and research settings.

ETHICAL ISSUES IN CANCER CLINICAL CARE

DOCTOR–PATIENT RELATIONSHIP AND CLINICAL MEDICAL ETHICS

To practice medicine competently and to provide high-quality care for cancer patients and others, physicians require both scientific and technical proficiency as well as a working knowledge of medical ethics. This specialized knowledge and proficiency is used to assist patients, sometimes by curing or managing their illness and disease and sometimes by helping them overcome the fear, pain, and suffering that are often associated with illness. Competent physicians need not only practical and technical skills, but also the ability to manage such issues as informed consent, decision making, as well as end-of-life and palliative care. A working knowledge of practical ethics is not a substitute for the traditional standards of character and virtue expected of the good physician: competency, integrity, honesty, compassion, and respect for patients and colleagues. Since 1985, medical ethics has emerged as a new and useful component of medical practice and has assisted physicians and patients to reach ethically acceptable decisions. Clinical ethics focuses on how patients and physicians work within existing administrative, economic, and political structures to reach mutual agreement on clinical decisions that affect the patient.

The DPR is at the center of clinical medical ethics. Most day-to-day ethical problems that arise in patient care present in the context of the DPR and most are resolved within this relationship. In the United States, the DPR has undergone two major changes in the past generation. Initially, in the 1970s and 1980s, the relationship began evolving from a paternalistic one, in which physicians made choices for patients based on physicians’ values, to a more equal relationship of shared decision making, in which physicians advised patients, but patients ultimately made their own health care choices. Patient preferences are the ethical and legal nucleus of the DPR. In addition, respect for patients and their preferences is a clinical obligation because patients who reach a shared health care decision have greater trust and loyalty in the DPR, cooperate more fully to implement the shared decision, express greater satisfaction with their health care, and most important, have been shown to have better clinical outcomes in several chronic diseases.

The second major change in the DPR has occurred more recently and relates to cost containment and managed care. To curtail health costs, private and government payers for health care have attempted to limit the freedom of decision making of both patients and physicians. Such actions have given rise to new and recurring ethical concerns within the DPR, as well as to potential repercussions (e.g., the so-called patient bill of rights). Changes in the relationship between patients and physicians to a more equal relationship of shared decision making demand attention to ethical issues such as honest disclosure, effective communication, and informed consent.

Sound ethical analysis in clinical settings rests on a foundation of trust between the patient and physician, in other words, within the DPR. Crucial components in the analysis of any ethical issue include an understanding by both parties of the medical and scientific facts; the preferences, values, and goals of both patient and the physician; and the external constraints such as cost, limited resources, and legal duties that shape or restrict choices. For instance, in the cancer setting, physicians have the excellent opportunity to cement trust and reduce the chances of conflict arising with respect to end-of-life care decisions by communicating clearly with patients about prognosis and treatment goals.

For a variety of reasons, ethical issues arise in oncology practice more frequently than in the past. Scientific advances and new technologies have raised unprecedented ethical problems: When should efforts to prolong life with ventilators or dialysis machines be stopped? To what populations of patients should potentially life-saving or life-prolonging (but highly toxic) therapies such as stem cell transplantation be applied? Changes in molecular medicine and genetics are generating new and life-saving ethical problems, such as the need for genetic counseling and confidentiality: Who should have access to an individual’s results of BRCA1 testing, and how should such information be used? Managed care has given rise to new ethical issues such as limitations on decision-making freedom for patients and physicians, and potential financial conflicts of interest associated with limiting the use of health resources.

Despite scientific developments of the past century, and despite the financial changes alluded to, the role of the medical profession in human societies has changed surprisingly little since the time of Hippocrates. In general, the DPR has also changed little and the encounter of healer and patient has remained the principal means by which medicine achieves its goals. Several reasons explain the extraordinary continuity over time of the DPR: (1) Medicine serves a universal and unchanging human need by responding to a patient’s sense of illness or disease; (2) medicine has an unchanging central goal, which is to help patients; and (3) most medical help is delivered in the direct encounter of patient and physician (i.e., in the DPR). It is hardly surprising, therefore, that the DPR is the context in which the important ethical issues such as informed consent, decision making, prognosis communication, and the care of those with life-threatening and life-ending cancer diagnoses (e.g., advanced care planning, end-of-life care, and PAS) must be examined.

INFORMED CONSENT AND SHARED DECISION MAKING

The process by which physicians and patients make decisions together is often summarized in the phrase informed consent. This doctrine, which reflects respect for patients, is at the heart of the DPR and is based on the ethical principle of respect for individual autonomy, dignity, and self-determination. Informed consent has three key components: disclosure, competency, and voluntariness.

Disclosure means that physicians tell patients about the medical diagnosis, prognosis, and risks and benefits associated with possible treatment options. Patients are entitled to enough information to permit them to ask reasonable questions about the diagnosis and the options that are available. Competency means that patients are
Prognosis Determination and Communication

Considering the life-threatening severity of their illness, it is not unreasonable to assume that prognostic information would play a pivotal role in shaping the overall manner decision-making process of cancer patients and lead to the most appropriate treatment decisions. In fact, from an ethical perspective, a discussion of prognosis should be an integral and necessary part of the communication and decision-making processes for cancer patients. This is the case, in part, because prognostic information has been shown to be significantly associated with cancer patients’ treatment choices. Nevertheless, several studies have suggested that advanced cancer patients have an inadequate understanding of their prognoses, whereas patients generally overestimate the probability of their long-term survival. As well, many terminally ill cancer patients believe that the purpose of their treatment, even in the palliative care setting, is to cure them. Despite this available empirical data, it should be recognized that this issue (i.e., awareness of prognosis) remains a difficult one to study because patient anxiety, fear, and the need to maintain hope in the face of a grave prognosis may affect advanced cancer patients’ understanding of their prognoses. In addition, this research may be limited because, from a methodological standpoint, these same emotions may affect their measured responses to queries about their awareness of when they believe they are going to die. Thus, these measured responses may not necessarily be an accurate reflection of cancer patients’ true awareness of prognosis. Moreover, no studies have examined the effect of physician anxiety and physician desire to help patients maintain hope on actual communication of prognoses to cancer patients.

Physician Disclosure of Prognosis

Early research, some of which dates from the 1940s and 1950s, examining physician communication with cancer patients, clearly documented a great reluctance to disclose a cancer diagnosis and virtually no willingness to discuss prognosis. Of those physicians surveyed in even the earliest of studies (most of whom did not disclose a cancer diagnosis), the majority said they would not disclose the diagnosis if there was no other way to get the patient to comply with a needed diagnostic or therapeutic intervention. Thus, it was not that cancer physicians did not wish to tell a diagnosis, but rather that they did not want to give a terminal prognosis. Interestingly, improvements in nonsurgical methods of evaluation (predominantly including radiologic, i.e., computed tomographic scans, and lesser invasive biopsy techniques) for confirming a cancer diagnosis have undoubtedly only resulted in the increasing need to better inform patients in order to obtain compliance for more complicated interventions. In addition, during the interval between these studies of the 1940s and 1950s and the later 1970s, when full disclosure of a terminal prognosis became the norm, the perceived threat of a cancer diagnosis as a fatal disease has lessened. This is a result of multiple factors, including community and public health education efforts toward early cancer detection, and the U.S. government’s declaration of the “War on Cancer,” and the ever increasing range of treatment options now available (including many with high rates of success).

Considering, and even in spite of, these events, it is still not difficult to imagine that physicians would remain reluctant to want to give a terminal prognosis. In fact, with regard to current practices toward disclosure of prognosis to cancer patients, the limited available empirical data document that physicians withhold information. Physicians would appear to be reluctant to disclose grim prognostic information for the same ethical and psychological reasons they traditionally withheld a diagnosis. Physicians may fear that the revelation of a grim prognosis would psychologically damage patients’ hope to survive. Physicians also feel discomfort when placing odds on survival, recurrence, and cure. Thus, while the behavior of physicians has changed regarding disclosure of diagnosis, only limited information is available regardless whether they have changed in regard to practices of disclosure of prognosis.

While, from an ethical perspective, physicians have obligations to disclose a terminal prognosis, a question remains as to how such prognostic information ought to be provided. Some cancer patients may better understand their prognosis when it is discussed through the use of numeric descriptors, whereas others understand their prognoses when it is conveyed in qualitative descriptors. Patients may also discern important information about their illness for information about their illness with patients generally overestimating the probability of their long-term survival. Yet, how, and even whether, physicians’ communication may contribute to patient misunderstanding remains unknown.

How oncologists make decisions about presenting prognostic information is undoubtedly a complex process, potentially influenced by multiple factors, including the patient’s clinical condition and sociodemographics. As well, the physician’s own sociocultural background may influence the depth and style of presenting prognostic information. In addition, the relationships between a particular oncologist and patient, the perceived patient desire for control over medical decisions, and a patient’s information-seeking preferences may influence a physician’s information-giving practices. An oncologist may provide more information about a patient’s prognosis when a patient requests it, or may present little information based on their understanding of a patient’s psychological state.

Ethical Issues in the Care of Patients with Life-Threatening and Life-Ending Disease

Oncologists deal almost exclusively with patients with serious and life-threatening diseases, many of whom are terminally ill. It is therefore essential that oncologists have a working knowledge regarding the ethical issues related to palliative care, advanced care planning, the specific dilemmas present in end-of-life cancer care, and PAAS.

Palliative Care

Oncologists must become experts in providing excellent palliative care, including both pain management and the relief of other symptoms such as nausea, dyspnea, and anxiety. Although palliative care has often come to be specifically emphasized in the setting of end-of-life care, oncologists must be equipped to provide excellent...
Advance Care Planning

ADVANCE CARE PLANNING FOR AWAKE PATIENTS WITH DECISION-MAKING CAPACITY. When oncologists and patients reach joint decisions about a plan for diagnosis and treatment, they are engaged in advance care planning. A fundamental ethical principle that underlies advance care planning is informed consent. Adult patients who have decision-making capacity, sometimes referred to by the legal term competence, have a right to make their own health care choices after being provided with appropriate information about the risks and benefits of reasonable alternative approaches. The principle of informed consent applies even to treatments that may be necessary to save a patient’s life. Competent adult patients have the ethical and legal right to decline, or ask to have discontinued, treatments that may be life-saving, including intensive care unit care, life support measures such as dialysis and mechanical ventilation, and chemotherapy. Before accepting a patient’s statement or decision, physicians must assess the following: (1) Has the patient been provided with adequate information to make life and death choices? (2) Does the patient understand the risks and benefits of the physician’s recommendation and the alternatives? (3) Does the patient understand that the refusal of the proposed treatment will result in death? (4) Why is the patient making the choice against treatment? (5) Does the patient have adequate decision-making capacity to make a life and death choice?

None of these questions is easy to answer, but physicians nevertheless have a responsibility to make a good faith effort before acceding to a patient’s wish to refuse life-sustaining treatment. Sometimes consultations with colleagues, including psychologists, may be necessary to resolve the question of decision-making capacity. In the end, however, the central principles of autonomy and patient rights mean that a competent patient may refuse life-sustaining treatment even if the physician believes such a refusal is a bad choice or is not consistent with the patient’s prior wishes or is morally wrong.

ADVANCE CARE PLANNING FOR PATIENTS WHO LACK DECISION-MAKING CAPACITY. Decision making for unconscious patients, or for patients who are conscious but lack decision-making capacity, follows the same informed consent model as applies to competent adults. Essentially, incompetent patients are accorded the right to have their previous wishes made known and acted on by their physicians. Advance care planning is a process in which patients, their families, and their physicians plan in advance for treatment decisions, including decisions about life-sustaining treatment, that may have to be made when the patient is no longer capable of participating in the decision. During the past 30 years, the traditional approach used for advance care planning in the United States has involved formal, written advance directives that indicate who should serve as the patient’s proxy or who should choose a proxy. If no proxy is named, a patient would want the person or the group of persons designated by the patient to have the final decision. In our view, advance directives have not been a successful strategy for achieving patients’ wishes and goals. There are many reasons to explain the failure of advance directives, but simply put, most people have not completed written advance directives and when they have, they are often overruled by a patient’s family, ignored by physicians, or simply misunderstood.

To achieve more successful advance care planning, written formal advance directives should not be exclusively relied on to make such extremely important decisions, but rather oncologists should commit themselves to the process of advance care planning. The process, rather than the simple event of signing a written advance directive, may involve a series of conversations over time between the oncologist and the patient (and often the patient’s family) in which the patient’s goals and preferences are discussed and clarified. Such conversations should always be specific to the individual patient and to the actual clinical circumstances that are likely to be present at some near or distant future time when the patient may have lost decision-making capacity.

These conversations should determine two things: (1) Who would the patient want to serve as a proxy decision maker if the patient were unable to make decisions? (2) Based on the most likely future scenario for a particular patient, what choices would the patient want the surrogate to make (e.g., for aggressive or curative care, palliative care, or focusing more exclusively on end-of-life care). These conversations should be documented in the physician’s notes and such conversations likely should occur on more than one occasion as the patient’s clinical and life circumstances change. These are not new or easy conversations to have, and many physicians feel ill prepared to discuss these matters with their patients. This is an educational and behavioral failure. Physicians must learn how to conduct these important conversations. Good patient care requires that we advise and counsel our patients on what is possible and what is reasonable. The advance care planning process is an opportunity to do that.

Ethical Dilemmas in End-of-Life Cancer Care

As previously discussed, in the setting of cancer care in which prognosis is known to result in eventual death (i.e., advanced cancer) how and when such prognoses should be communicated remain matters of concern and controversy. In addition, several equally important concerns arise in the specific setting of advanced cancer regarding how and when palliative care may be implemented, as opposed to care that includes further attempts with experimental agents. For advanced cancer patients who, by definition, have a life-ending diagnosis for which an anticancer standard of care has failed (or is unidentified), it remains unclear what factors influence their decision making. Clinical form may influence providers’ decisions. Patients who die of cancer after having been told that they have a terminal illness, and their families and still be able to facilitate the maintenance of hope; patients’ and families’ hesitancy or unwillingness to accept such prognoses; physicians’ reluctance or inability to effectively communicate terminal prognoses to cancer patients exist for this hesitancy and unwillingness including perceived dilemmas related to physicians’ desire to effectively communicate terminal prognoses to cancer patients and their families and still be able to facilitate the maintenance of hope; patients’ and families’ hesitancy or unwillingness to accept such prognoses; physicians’ reluctance or inability to effectively communicate terminal prognoses to cancer patients and their families and still be able to facilitate the maintenance of hope; patients’ and families’ hesitancy or unwillingness to accept such prognoses; physicians’ reluctance or inability to effectively communicate terminal prognoses to cancer patients and their families and still be able to facilitate the maintenance of hope; 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One potential slippery slope concern is empirically evaluate the practice of euthanasia reported that there were approximately 2300 cases of euthanasia per year (1.8% of all deaths) and 400 cases of PAS be encouraged or pressured by their families to choose PAS. In a benign variation of this approach, patients without direct coercion from their family may feel that the evaluation of the patient, even in cases in which the diagnosis of depression is suspected.

Psychiatric consultation. Despite the prevalence of potentially treatable mood disorders, data from the Netherlands suggest that only 3% of requests for PAS resulted in a diagnosis of cancer as association between suicide and depression in cancer patients.

Depression rather than physical pain is often associated with patient requests for PAS. Among cancer patients, the risk that PAS may harm the DPR by undermining trust between patients and physicians. The “slippery slope” risk that PAS may be performed in some patients who have not voluntarily requested it.

ARGUMENTS FOR AND AGAINST PHYSICIAN-ASSISTED SUICIDE. The strongest arguments favoring PAS are claims based on autonomy and beneficence. The autonomy argument maintains that individuals have moral authority over their lives and should be permitted to control all aspects of life based on their own assessment of benefits and burdens, including the timing and means of their deaths. The final distinction is the most subtle one (i.e., between PAS and aggressive pain management as occurs when a morphine drip is hung). Essentially, if the morphine drip is being used to palliate the patient's symptoms of pain, nausea, anxiety, and so forth, its use does not represent PAS, whereas if the morphine drip is being used deliberately to hasten the patient's death or kill the patient, it probably represents euthanasia rather than PAS.

Additional arguments against PAS are based on the following three risks of adverse consequences for individuals and for society:

- The risk that those requesting PAS are clinically depressed.
- The “slippery slope” risk that PAS may be performed in the following three patients who have not voluntarily requested it.
- The risk that PAS may harm the DPR by undermining trust between patients and physicians.

PHYSICIAN-ASSISTED SUICIDE AND DEPRESSION. Depression rather than physical pain is often associated with patient requests for PAS. Among cancer patients, depression is fairly common, probably two to four times more frequent than in the general population. Studies have found that 25% of cancer patients meet criteria for major or minor depression; whereas another series reported that 25% of patients on palliative care services are depressed. For these reasons, it is not surprising that suicide rates among cancer patients are substantially higher than those among the general public. Most important, as in other populations, there is a high association between suicide and depression in cancer patients. Among terminally ill patients with cancer, the disease often produces somatic symptoms of depression (insomnia, anorexia, fatigue) and makes it difficult to reach a diagnosis of depression. Furthermore, many physicians view depression following a diagnosis of cancer as appropriate, rather than as a symptom that needs treatment. Yet, depression among terminally ill patients can be treated with medications or with counseling. Despite the prevalence of potentially treatable mood disorders, data from the Netherlands suggest that only 3% of requests for PAS resulted in a psychiatric consultation.

These data suggest that many depressed oncology patients who express an interest in PAS may have a reversible condition, depression, that often is not diagnosed and frequently is not treated. In addition, current safeguards in the Oregon PAS laws are inadequate and contain no mandatory requirement for a formal psychiatric evaluation of the patient, even in cases in which the diagnosis of depression is suspected.

PHYSICIAN-ASSISTED SUICIDE AND THE SLIPPERY SLOPE. One potential slippery slope concern is encouraged PAS, in which chronically ill or terminally ill patients may be encouraged or pressured by their families to choose PAS. In a benign variation of this approach, patients without direct coercion from their family may feel that the availability of the PAS option requires them to do the noble thing to prevent becoming a burden to their families.

Data on PAS and the slippery slope have come primarily from the experiences in the Netherlands. One of the most important findings to emerge from the empirical studies of Dutch practices regarding PAS and euthanasia concern the practice of voluntary euthanasia. A report commissioned by the Dutch government to empirically evaluate the practice of euthanasia reported that there were approximately 2300 cases of euthanasia per year (1.8% of all deaths) and 400 cases of PAS.
per year (0.3% of all deaths) in the Netherlands. In addition, there were 1000 cases (0.6% of all deaths) in which patients received euthanasia either without explicitly requesting it or while deemed incompetent to make such a request. In 56% of these cases, the patient was no longer competent when euthanasia was performed. Overall, 27% of Dutch physicians who were interviewed indicated that they had performed euthanasia at least once without an explicit voluntary request for euthanasia by the patient.

These data suggest that in the Netherlands a slippery slope has developed in which euthanasia has been extended from competent adults who voluntarily request it to incompetent patients (both adults and children) who have never made such a request. More recently, a group of Dutch physicians reported on the high complication rate (23%) associated with efforts to perform PAS in 114 cases. In 21 of the 114 cases (18%), the physician decided to administer a lethal medication, which thus transferred the situation from PAS to actual direct to patients without the physician's explicit voluntary request for PAS was legalized generally. 8

Two studies of physicians in the state of Washington have been published to help characterize the current status of PAS in this country. In a 1994 study by Cohen and colleagues, 64% of physicians (95% response rate) thought that euthanasia should be legal in some situations, nearly one-half agreed with the statement that euthanasia is never ethically justified. Hematologists and oncologists were most likely to oppose PAS. Two years later, more research from Washington reporting on actual requests for PAS and physician responses was published. The major finding of this 828 physician survey study was that 12% had received one or more explicit requests for PAS and 4% for euthanasia in the past year. The requests were generally from patients with cancer, neurologic disorders, and acquired immunodeficiency syndrome. Patients requests were more than twice as likely to request PAS than euthanasia, a ratio that compares with the analgesic requests in this study reported providing PAS in 24% of cases in which it had been requested and intended to provide PAS more often to patients with physical symptoms. The authors express concern that physicians did not consult their colleagues in many cases, raising questions about the appropriate regulatory framework to ensure quality in the evaluations of patient requests for physician-assisted death.

Further information regarding attitudes and practices regarding PAS in the United States is available from an empiric, vignette-based study, by Emmanuel et al. The investigators examined the experiences of the public, cancer patients, and oncologists. In the setting of unrelenting pain, approximately two-thirds of cancer patients and the public found both euthanasia and PAS acceptable. They found it less acceptable in the setting of existential suffering, or in the setting in which there was the potential for a patient to be a “burden on the family” (vignette wording). Among patients actually experiencing pain, they were more likely to find euthanasia and PAS unacceptable. Among oncologists, more than one-half stated they had had a request for either euthanasia or PAS, and one in seven said they had performed either practice at least once. In a related set of data, nearly one-half of these oncologists could imagine a situation in which they would want PAS or euthanasia for themselves. Two-thirds of these oncologists were more likely to want PAS than euthanasia for their own patients. These oncologists were more likely to support PAS than euthanasia for their patients, as compared with oncologists who could imagine a situation in which they would want PAS or euthanasia for themselves (86% vs. 42%, respectively). Many oncologists (42%) who would find PAS or euthanasia unacceptable for themselves still found these practices ethical for their patients.

These data can be viewed as concerning as they suggest that there is significant, although not majority support, for the use of PAS and euthanasia in at least some cancer care cases, and that as many as 15% of oncologists have carried out such practices at least once in their professional careers. Interestingly, in subsequent research, Emmanuel found that some oncologists suffered adverse consequences (emotional or psychological) from having performed PAS or euthanasia. Further research is undoubtedly needed to better understand oncologists’ attitudes to PAS and their perception of pain and suffering and their perceived obligations in helping cancer patient to end their lives.

Another data source that is being closely scrutinized for evidence of the slippery slope derives from the experience of the state of Oregon, which legalized PAS on October 27, 1997. DB during the first year of PAS activity, 23 persons requested lethal medications and 15 died after taking the medication. Reports of the second-year experience indicate that 33 persons requested lethal medications and 26 died after taking the medication. In both years, the median age of the patients was 69 to 71; the most common underlying diagnosis was cancer; and the most common reasons for PAS were not physical pain but rather “loss of autonomy due to illness, loss of control of bodily functions,” and a wish to determine and control the manner of one’s death. Based on the first two reports from Oregon, the use of PAS occurs in a select group of patients who generally involved patients who were well-informed, educated, and already in hospice programs. It is too soon to know whether vulnerable populations will also be recruited to participate in Oregon’s PAS initiative.

THREAT TO PROFESSIONAL INTEGRITY AND TRUST BETWEEN PATIENT AND PHYSICIAN. Cancer patients often have a heightened sense of their own mortality and a need to trust a physician in a relationship that is based on honest communication but nurtures hope. The conflation of the concept of healing with procedures designed to bring about the patient’s death creates a serious threat to the integrity of the medical profession. PAS and euthanasia distort the fundamental norms of medicine in at least three ways: (1) by diverting attention from the substantive issues of providing good care for dying patients; (2) by subverting the social role of the physician as healer; and (3) by often undermining the trust that patients place in their physicians. Many patients benefit from knowing that PAS is not an option that their physician would contemplate, and this reassurance strengthens the trust that cancer patients place in their doctors. Similarly, physicians efforts to prolong life and aggressively relieve pain and suffering are bolstered by the fundamental prohibition against actively ending the lives of their patients with PAS and euthanasia.

Based on our analysis of the scanty but worrying data on these practices (especially those available from the Netherlands), along with our view that PAS and euthanasia will ultimately weaken, not strengthen, the relationship of oncologists and patients and will attenuate the fundamental prohibition against killing in the medical context, we recommend that at this time oncologists resist appeals to participate in PAS and euthanasia.

ETHICAL ISSUES IN CANCER CLINICAL TRIALS

This section of the chapter examines the ethical issues associated with the clinical research of cancer. Following a brief overview of certain principles that guide the ethical conduct of clinical research, the chapter discusses the history and development of ethical guidelines and requirements regarding human experimentation. Further discussion and background regarding to the concept and process of informed consent as it specifically relates to cancer patients and clinical research, including the use of consent forms for research, is also provided. The ethical aspects of clinical trials in oncology, including phase I, II, and III studies, are examined. Wherever possible, empiric information is incorporated into these discussions from research on the informed consent and clinical trial process in cancer.

ETHICAL PRINCIPLES GUIDING CLINICAL RESEARCH

The main objective of clinical research in oncology is to improve medical care for future cancer patients. From both a societal and ethical perspective, this is viewed as a laudable and important goal. As such, no meaningful criticisms can truly be offered against the need and desire to better care for those with cancer. However, when one examines the methods by which this goal is pursued, problematic issues can be found. As is discussed, it is the process of using current patients as research subjects to achieve this goal in which true ethical dilemmas are created.

Whether in the context of clinical practice or clinical research, several specific principles guide the management of patients by physicians. The first such principle worthy of mention in this context is, “One ought not to use others as means to an end.” In the process of clinical research this general ethical principle is, in many ways, allowed to be violated. However, to allow violation of this principle, it is expected that no patient can participate as a research subject unless there is the potential for benefit. No doubt, in considering what is an acceptable degree of potential benefit, this safeguard is in place for a great proportion of clinical research. (Here, benefit is implied as it is traditionally measured in oncology, i.e., as a specific antitumor response or improvement in a patient–subject’s symptoms.) However, as is discussed in the section regarding phase I trials (see Ethical Issues in Phase I Trials, later in this chapter), ethical dilemmas that challenge this safeguard are created in the early drug development process in which the potential for such benefit may be exceedingly small for involved cancer patients.

A second related ethical principle that must guide behavior in the research setting is, “One should not allow harm to come to others.” Certainly, oversimplification or generalization of this principle would lead to the prohibition of specific patterns of behavior in the clinical (nonresearch) setting of cancer care, where the harm from toxicities is deemed acceptable because of the known benefits to be achieved. Thus, as with the first principle mentioned, the specific issue of harm cannot truly be weighed without consideration of the relative benefit that may be achieved for cancer patients. However, when cancer patients participate as research subjects in early drug development trials, the treatment regimens for patients as a result of the specific methodologies and research objectives employed in these trials. In addition to the recognition that benefit is not likely, there is even an expectation that harm will come. In fact, it may even be a goal of the study to produce harm. The safeguard that must be in place to allow violation of this principle is that the potential for harm to participating subjects must be weighed against the potential for a patient to be a “burden on the family” (vignette wording). Among patients actually experiencing pain, they were more likely to find euthanasia and PAS unacceptable. Among oncologists, more than one-half stated they had had a request for either euthanasia or PAS, and one in seven said they had performed either practice at least once. In a related set of data, nearly one-half of these oncologists could imagine a situation in which they would want PAS or euthanasia for themselves. Two-thirds of these oncologists were more likely to want PAS than euthanasia for their own patients. These oncologists were more likely to support PAS than euthanasia for their patients, as compared with oncologists who could imagine a situation in which they would want PAS or euthanasia for themselves (86% vs. 42%, respectively). Many oncologists (42%) who would find PAS or euthanasia unacceptable for themselves still found these practices ethical for their patients.

Further research is undoubtedly needed to better understand oncologists’ attitudes to PAS and their perception of pain and suffering and their perceived obligations in helping cancer patient to end their lives.

Another data source that is being closely scrutinized for evidence of the slippery slope derives from the experience of the state of Oregon, which legalized PAS on October 27, 1997. During the first year of PAS activity, 23 persons requested lethal medications and 15 died after taking the medication. Reports of the second-year experience indicate that 33 persons requested lethal medications and 26 died after taking the medication. In both years, the median age of the patients was 69 to 71; the most common underlying diagnosis was cancer; and the most common reasons for PAS were not physical pain but rather “loss of autonomy due to illness, loss of control of bodily functions,” and a wish to determine and control the manner of one’s death. Based on the first two reports from Oregon, the use of PAS occurs in a select group of patients who generally involved patients who were well-informed, educated, and already in hospice programs. It is too soon to know whether vulnerable populations will also be recruited to participate in Oregon’s PAS initiative.

Further discussion and background pertaining to the concept and process of informed consent as it specifically relates to cancer patients and clinical research, including the use of consent forms for research, is also provided. The ethical aspects of clinical trials in oncology, including phase I, II, and III studies, are examined. Wherever possible, empiric information is incorporated into these discussions from research on the informed consent and clinical trial process in cancer.
A third ethical principle that guides behavior in this context is, “One ought never to deceive others.” Within clinical research, several safeguards are in place that are designed to prevent the deception of patients who become the subjects of research. The informed consent process itself, and other federal and institutional regulations, provide mechanisms in which oversight of both specific research protocols and the described methods of information provision are present to prevent any intentional or unintentional deception of patients. More importantly, the conscientious communication efforts of participating physician–investigators are also relied on to prevent any deceptive practice. However, in the setting of early trials of investigational agents, in which research subjects are most often those with advanced disease, many have wondered about the potential vulnerability of these subjects and the potential for them to be unintentionally deceived. Indeed, the very fact that the agents under study in early drug trials have shown promise in preclinical models creates a variety of stated or unstated inducements that may play on some advanced cancer patients potentially overwhelming desire for therapeutic benefit and lead to a process akin to deception, albeit unintentional.

In a final principle worthy of mention, medical ethics itself teaches us that, “The interests of an individual physician’s patient should be placed above the interests of others.” One can easily argue that placing a cancer patient on a clinical trial involving a new investigational agent does not at all compromise their interest in receiving state-of-the-art care. However, one must keep in mind that the overall goal of clinical research (improving care for future patients) remains intact whenever a patient enters a clinical trial. Thus, at the very least, other interests beyond the individual care of a patient are present when that patient enters a clinical trial. As is discussed, these potentially competing interests can lead to dilemmas. Further insight into these issues and dilemmas can be gained by specifically examining the early phases of cancer clinical research and the attendant informed consent process.

INFORMED CONSENT FOR CLINICAL RESEARCH

The concept of informed consent, which acknowledges the rights of patients to voluntarily participate in health care, applies both to clinical practice and clinical research. Generally, informed consent in clinical research is related to, but recognized as being more stringent than, informed consent outside the context of clinical trials. This heightened consent standard exists for at least two reasons. First, from an ethical perspective, a patient considering clinical trial participation is always viewed as potentially vulnerable. As a result of this potential vulnerability, he or she may have great difficulty in appreciating the differences between the therapeutic and research aspects of a given alternative of care or treatment. Without this distinction, patients cannot make uncoerced and autonomous health care decisions. Thus, the informed consent process, and the ethics of clinical research, require that such a clear distinction be made. Second, the physician–investigator is seen as having an intrinsic conflict of interest in the role both as a physician for an individual patient and as a scientific investigator attempting to develop improved methods of medical care and treatment. As previously mentioned, within the sole context of a therapeutic relationship, the physician places his or her patients’ interests above all else. However, within the context of clinical research, investigators have additional interests that may not be relative to their patients’ interests. Thus, an ethical issue exists about the ability of clinical researchers, many of whom are involved in both providing the research information to patients regarding participation in research in such a way that allows patients to recognize the distinction between research and therapy.

A definition of informed consent for clinical research that encompasses all relevant aspects of the process remains somewhat elusive, with varying definitions having been described. Generally, it is viewed as a process of communication between a patient–subject and a clinician–investigator regarding an investigational or experimental treatment. Within this communication process, several elements must be disclosed. These include the disclosure of the type of research to be performed, the risks and benefits of the treatment or research, the unrevealed nature of the research, the alternatives other than participation in the clinical trial, and finally, disclosure of the subject’s freedom to withdraw or not to participate in the research without any detrimental effect on the patient’s continued access to adequate health care. This type of understanding on the part of the patient is necessary for this process, but other elements also exist. Further, the methods used to regulate the informed consent process. More recent empiric research on informed consent, a great proportion of which were conducted in the cancer setting, may be helpful in attempting to objectively identify the current problems and deficiencies associated with written consent documents and their oversight. As reviewed elsewhere, several studies reported since 1980 have increasingly demonstrated that although regulations are being followed, informed consent documents have become increasingly unreadable, lengthy, and uninformative. Indeed, they may actually be interfering with what might otherwise be an ethically appropriate informed consent process for patients, including not only those with cancer, but many other patients considering therapeutic clinical trial participation.

Shaping the Regulatory Process for Consent

Beginning in the 1960s, several events occurred that significantly changed the practice and process of informed consent in therapeutic research. One of the most important events, and clearly of greatest significance with regard to cancer and other related therapeutic research, was the publication of Henry Beecher’s paper in the New England Journal of Medicine in 1966. This paper, written by a clinical epidemiologist at Harvard University, assembled 22 recent research reports that he pulled from the peer-reviewed medical literature that contained, in his view, clear violations of both patients’ human rights and the recognized ethical principles of informed consent. In this report, the investigators described excising one of the melanoma lesions from the patient and transplanting it onto the patient’s mother. Subsequently, serum was withdrawn from the mother and given to the patient in hopes of producing an immune-mediated tumor response. The patient went on to die relatively quickly of widespread metastatic disease. Even more horrific, the mother subsequently died of metastatic melanoma approximately 1 year later. Another of Beecher’s examples, although described without identifiers, clearly included the much publicized case of the Jewish Council on Bioethics. Researchers in this published study, in an attempt to gain information relevant to organ transplantation, injected malignant cells from cancer patients into elderly and debilitated noncancer patients at the hospital.

Beecher’s cancer research examples, and the other reports described, put a great deal of the medical research process into the public spotlight. The subsequent concerns regarding the medical community’s public retaliations and the forced involutions that resulted in increased scrutiny of government-sponsored clinical research. Clinical researchers themselves undoubtedly became more sensitive to the issues regarding the use of patients, including those with cancer, as research subjects. Other events, including the disclosure to the public regarding the United States Public Health Service Syphilis Studies (also known as the Tuskegee Syphilis Study) as well as the thalidomide experience and subsequent passage of the 1962 amendments to the Food, Drug, and Cosmetic Act also had a great effect on the regulatory requirements for informed consent in clinical research. All of these events eventually led to the creation of the National Commission for the protection of human subjects in biomedical and behavioral research. The resulting recommendations of the National Commission led to the now required and pervasive practice of formalized institutional review of clinical research protocols.

Undoubtedly, the use of consent forms for clinical trials of new anticancer agents is one such setting in which these issues take on great significance, especially if we are to continue to recognize the value of patient–subject autonomy and the moral importance of the consent process as a mechanism of protection for potentially vulnerable patients attempting to make difficult decisions regarding their medical care. Separate from the content of the consent forms themselves, concerns also exist about the overall effect of the forms on different aspects of the consent process, including its outcome and the decision-making process of patients before the eventual decision to actually participate in a therapeutic clinical trial.
patient–subject understanding. Other significant research contributions within the cancer setting to the informed consent literature can be found elsewhere. \[123, 129\]

In considering this available empiric data, one is certainly left to wonder about the utility and value of the current consent process for therapeutic clinical trials. Particular concerns develop when one recognizes that great emphasis continues to be placed on consent forms and their content. Such concerns become even more challenging in areas where consent forms detail investigational therapies with relatively extreme toxicities, and in which the therapeutic goals of the alternatives to clinical trial participation may be quite different from the inherent or perceived goals of investigational therapy.

**ETHICAL ISSUES IN PHASE I TRIALS**

It is in the specific setting of cancer trials involving new agents (i.e., phase I trials) in which the general concerns about informed consent in therapeutic clinical trials become especially troubling and challenging. \[123, 131, 135\] This is because phase I trials typically involve patients with advanced, eventually life-ending disease in a research endeavor where the chance of meaningful objective therapeutic benefit has traditionally been described as being quite low, less than 5%. \[123, 129, 130\] As a result of the dose-escalation methods in these trials, \[78, 130\] a more specific dilemma is the relative ratio of toxicity and benefit for patients who participate. Further complicating this is the fact that such patients are usually already informed and freely consent to participate in such studies. The complexities of the consent process for advanced cancer patients in phase I trials relate both to what degree such patients should be viewed as vulnerable, and to what extent a participating physician’s own expectations and interests play a role in guiding patients to decide to participate. This unique form of therapeutic clinical research creates an intense environment of medical decision making in which arguably, many patients may not benefit from the traditional informed consent process.

If patients were to participate in phase I trials solely for altruistic reasons, in other words, to help forward cancer research and potentially help future cancer patients, phase I trials would probably carry less ethical conflict. As well, this would imply that the traditional informed consent process might more readily achieve the desired ideal outcome of understanding all elements of consent, including an understanding of the nature of phase I research and the alternatives to trial participation, as these less vulnerable patients would not necessarily seek benefit for themselves. However, the objective information available regarding the informed consent process for patients participating as research subjects in phase I trials tells us that altruism is not the primary motivating factor for patients participating in such clinical research. As reviewed in this section, the empiric studies examining the phase I consent process highlight the true ethical dilemmas associated with this early stage of clinical research.

In the first such study, Rodenhuis et al. evaluated the quality of informed consent among patients with advanced cancer who were offerred participation in a phase I trial. \[132\] The majority of patients who gave their consent was motivated either by hope for improvement of their condition, pressure exerted by relatives and friends, or simply because they felt they had “no choice.” Some patients did mention the desire to contribute to the progress of medicine. The investigators concluded that encouragement by relatives or friends appears to be a powerful force in motivating some patients to participate in phase I trials. In a similar but much smaller series of European advanced cancer patients, Witten and Sessa found corroborating results with regard to patient motivations for participation in such trials. \[139\]

Investigators at the University of Chicago conducted an in-depth survey study of 27 cancer patients who had given informed consent to participate in phase I trials at their institution. \[133\] Concurrently, the oncologists identified by the surveyed patients as responsible for their care and consent were surveyed as well. Eighty-five percent of patients who participated in a phase I trial for reasons of possible therapeutic benefit, 11% because of the advice of their doctor or physican, and 4% because of family pressure. Ninety-three percent said they understood all (33%) or most (60%) of the information provided to them about the trial in which they had decided to participate. Only 33% were able to state the purpose of the trial in which they were participating, with patients able to state the purpose of phase I trials as dose-escalation or dose-finding studies being more educated (P = .01). The surveyed oncologists had wide ranging beliefs regarding expectations of possible benefits and toxicities for their patients participating in a phase I trial. The authors concluded that patients who participate in phase I trials are almost exclusively motivated by the hope of therapeutic benefit. Altruistic feelings, while perhaps present, appear to have a limited role in motivating patients to participate in these trials. In subsequent studies conducted by these investigators in a much larger series of subjects have found similar findings. In fact, in larger series of subjects, quantifiable survey data show that less than 15% of patients actually understand the research purposes of phase I trials and are unable to recall whether their consent was based on their understanding of the research purposes of phase I trials and the alternatives to trial participation.

Tomonichel and colleagues conducted an analysis of the communication process involved in informed consent for cancer patients agreeing to participate in phase I trials. \[141\] The authors concluded that the informed consent procedure was satisfactory from a quantitative point of view. Interestingly, they found that the most important items of information were acceptably communicated to patients. However, they also stated that greater attention should be paid to the indirect messages and implied critics of patients to improve their participation in decision making. They also conclude that physicians should become more skillful in providing adequate information and to improve their methods of communication.

Yoder and colleagues conducted a prospective study involving entry and exit interviews of 37 advanced cancer patients participating in phase I trials. \[142\] The investigators found that patients expected slightly increased support from family members and received more support than expected. Perhaps not surprisingly, patients, oncologists, and nurses responded to patients communicating therapeutic goals were not met. Their expectations were also met with an improvement of symptoms such as fatigue, nausea, and vomiting, and weight loss. They noted that one strong theme that emerged from the data was hope and optimism. They conclude that an issue that needs further exploration is the extent to which patients accurately understand information in the consent form and in the consent process itself. Their findings also support the importance of communication between the patient and family and all members of the health care team, and a stress the importance of oncology nurses who may be able to mediate the flow of information between physicians and patients.

Research results providing a cross-cultural perspective are available as well. Japanese investigators, conducting a similar study, attempted to characterize the reasons for entry, expectations, and expectations of patients who had given informed consent to participate in phase I trials at the National Cancer Center in Japan. \[143\] Before receiving any investigational agents, 32 of 33 subjects were approached and completed a multiple choice questionnaire addressing these issues. When questioned regarding their expectations, more than one-half of the subjects indicated that there might be personal benefit to themselves. As well, slightly more than one-third of the subjects (35%) believed that it was possible that their cancer could be cured, and 12 subjects fully expected to be cured as a result of participation in a phase I trial. The investigators found that older adults had slightly higher expectations of cure from participation in a phase I trial (although this did not reach statistical significance). With closed ended questioning, most patients appeared to comprehend the major features of a phase I trial, namely its investigational nature, the unknown effects of the investigational agents, and the unclear benefit to themselves. As well, nearly 60% of the patients anticipated they might suffer severe or life-threatening side effects from participation. As many as 43% of subjects were able to accurately indicate (again, in closed ended questioning) the research purpose of a phase I trial as a dose-determination study.

One disturbing finding from these studies is the potential discrepancies among what has been disclosed to patients, what they think they understand, and what they mentally understand. For example, the University of Chicago study found that 90% of patients stated they understood all or most of the information provided to them about the phase I trial in which they had agreed to participate. \[133\] However, only approximately one-third of the patients could state the purpose of a phase I trial, and an even smaller proportion of patients could state the research purpose of phase I trials in a much larger study. \[127\] This discrepancy likely results from several factors, including inadequate informed consent. It may also lie in the methodologic difficulties of determining what a patient actually understands in relation to the information they have been given.

The information gained from this research strongly supports the argument that the current process of obtaining informed consent for phase I trials may be inadequate to appropriately ensure that such advanced cancer patients understand both the nature of the research in which they are participating and the alternatives to trial participation. In addition, despite the recognition that such patients do not know how much they benefit from the trial and the patient’s specific desire for information. This supports the view that advanced cancer patient’s ability to give what is otherwise perceived to be adequate informed consent. It is possible that several poorly understood and seldom studied factors play a vital role in shaping the informed consent process for potentially vulnerable advanced cancer patients considering participation in phase I trials. These likely include factors such as death and dying, death and dying, and less apparent factors as may exist in other health care decision-making environments for advanced cancer patients, for example, a patient’s awareness of the certainty of his or her death and the patient’s cultural and ethnic background. In addition, advanced cancer patients’ religious or spiritual beliefs, their degree of hope and emotional well-being, and their attitudes toward medical decision making may likely influence the shape of the consent process in this setting. Further research will be necessary to better understand and delineate these issues and their importance on the informed consent process in this difficult and highly charged setting.
Some of the ethical issues related to phase II trials of new agents are similar to issues in phase I trials with regard to the participation of human subjects with otherwise incurable illnesses in biomedical research and the potential vulnerability of these patients in seeking therapy.\textsuperscript{147, 148} Although still troubling, issues in phase II trials can be viewed as potentially less complex for several reasons. In the phase II setting, there is less of the unknown for both oncologist-investigator and patient, as all agents studied in phase II trials have completed toxicity finding and dose-determination (phase I) studies. Thus, there may be greater attitudes of certainty with regard to expected toxicities. There may also be greater hope or expectations of benefit, in part because these agents are being administered at or near the maximum tolerated dose. Therefore, one unique issue in the phase II trial is the higher likelihood of toxicity development for all subjects in a trial, as they are being administered agents at relatively higher doses, as compared with patients in a prior phase I study investigating the same agents. The intentions and motivations of a participating oncologist, in the role of physician–healer or physician–investigator, are central issues in both phase I and II trials. Again, however, expectations or hope of benefit for their patients may be greater in the phase II setting. This may translate into greater therapeutic intent and subsequently be communicated to patients, resulting in greater expectations or hopes on their part as well.

Although these issues may be less complex and more easily examined in the phase II setting involving new agents, they are still troubling as there is an overall low probability of benefit with regard to tumor responses in these trials.\textsuperscript{145} In fact, this concern may actually increase even as a phase II study is accruing patient–subjects. This is related to the accepted statistical requirements present to exclude a treatment in phase II trials; there is a greater concern of a low level of efficacy for a new agent.\textsuperscript{145} Traditional stopping rules for many phase II trials would allow as many as 14 consecutive nonresponders to accrue to a trial before concluding that the agent lacks disease-specific efficacy. Yet, physician–investigators’ attitudes and beliefs may change significantly with regard to an agent under study as response data accumulate that suggest a lack of efficacy, but the trial remains open in order to reach the statistically required accrual.

How should evolving data be handled during a phase II trial that suggests a lack of efficacy, but is not sufficiently substantiated from a statistical standpoint? In a study of even a small number of patients, if an agent is given to initial patient–subjects without apparent benefits or tumor responses, but not enough patients have been involved to satisfy statistical requirements, what information should be provided to prospective patient–subjects? For example, in a simple phase I single-agent study seeking to accrue 14 to 20 patients, if six evaluable patient–subjects have been administered the agent and are known to have not received any apparent benefits, what should the informed consent process consist of for prospective patient–subjects with regard to risks and benefits?

We know oncologists’ attitudes, perceptions, and biases toward clinical trial chemotherapy may substantially affect clinical trial accrual.\textsuperscript{149, 150} These factors are likely to be important for phase II trial accrual. How oncologists, either as investigators or practitioners, interpret clinical trial data from ongoing trials could have a significant effect on their views toward continued accrual. How oncologists assimilate this information and communicate it to prospective cancer patient–subjects likely changes over the course of a trial. Yet, the consent forms for such trials are almost always static, potentially leading to subjects receiving conflicting information. As we relate to the accepted statistical requirements present to exclude a treatment in phase II trials; there is a greater concern of a low level of efficacy for a new agent.\textsuperscript{145} Traditional stopping rules for many phase II trials would allow as many as 14 consecutive nonresponders to accrue to a trial before concluding that the agent lacks disease-specific efficacy. Yet, physician–investigators’ attitudes and beliefs may change significantly with regard to an agent under study as response data accumulate that suggest a lack of efficacy, but the trial remains open in order to reach the statistically required accrual.

This may be well justified in order to establish confidence regarding lack of efficacy of a new agent in a specific disease, but the potential dilemma remains and is no less true. Some oncologists have expressed this concern in situations where equipoise should be allowed to help make decisions about patient–subjects. These discussions should be uniformly communicated to prospective patient–subjects. However, traditionally, after the initiation of a phase II trial, subsequent patients are accrued with little formal response or toxicity information available to prospective subjects about prior evaluable patients in the trial. Interestingly, if such information could be fully and appropriately withheld from involved clinician–investigators, some of the described dilemmas in phase II trials might resolve themselves. As well, if one could guarantee an unprecedented quick rate of accrual of all the subjects necessary to meet the statistical requirements to a phase II trial, these dilemmas could potentially be less challenging. Practically speaking, these actions are not likely to be routinely achievable. Research on these issues in the phase II setting is needed.

**ETHICAL ISSUES IN PHASE III TRIALS**

Although ethical issues are present throughout all phases of clinical research, and early trials of new agents certainly present troubling dilemmas, it is randomized phase III trials that have undergone the most intense scrutiny. Indeed, much of this scrutiny has centered on the randomized trial process specifically in cancer clinical research.\textsuperscript{151, 152} The consent process regarding the informed consent process itself should be conducted, remain issues of controversy. An even more basic and primary ethical concern is the application of the phase III trial design itself, with much debate and controversy focused on when, rather than if, it is ethically appropriate to perform randomized comparative trials. Indeed, no ethical arguments have been made against the actual intended goals of phase III trials. Rather, it is phase III methodology, in which patient–subjects are randomly assigned to receive either an investigational therapy or a standard of care, that has caused concerns for some.\textsuperscript{147, 153, 154, 155, 156} Such concerns deal with a perceived dilemma for the treating physician of a specific patient, and whether the physician’s therapeutic responsibilities to that individual patient outweigh any responsibilities to clinical research and the needs to improve medical care for future patients. Some have described this as a potential conflict that arises between the physician as investigator and the physician as an individual patient.\textsuperscript{150} Supporters of this view have argued that the responsibilities of the physician as healer carry far greater moral weight than those of the physician as investigator to the extent that it becomes unethical to allow a random process to be the determining factor in whether a patient receives a treatment. Complicating this further is the fact that in the phase III setting the lines separating research from therapy are sometimes less clear.\textsuperscript{153}

Much of the debate regarding ethical issues in phase III trials has centered around the issue of equipoise. As originally defined by Fried,\textsuperscript{149, 150} equipoise is viewed as a state of genuine uncertainty on the part of a clinical investigator or treating physician regarding the comparative merits of different treatments for a patient’s specific disease process, such as cancer. Some have argued that equipoise must exist for an individual investigator or physician in regard to an individual patient, in order that he or she can ethically act (or encourage) that patient to participate in an appropriately designed phase III trial. Others have argued that a broader definition of equipoise be accepted to justify randomized phase III trials; specifically, that clinical equipoise need not exist for an individual physician or investigator, but need only exist within a specified medical community.\textsuperscript{157, 158} In the cancer setting, clinicians, researchers, and ethicists have debated this issue of equipoise (whether it should be applied as an individual versus a community standard), and whether randomized studies are ethical at all.\textsuperscript{157} The empirical research available from the cancer setting strongly suggests that the issue of equipoise remains quite unresolved for investigators, clinicians, and even patients.\textsuperscript{152, 153, 154} The available evidence also suggests that many oncologists view the informed consent process requirements within randomized clinical trials as too cumbersome or potentially threatening to the patient, DNR, or both to the extent that they are a significant obstacle to patient accrual to phase III trials.\textsuperscript{154}

Keeping this view of equipoise in mind, and returning to the process of informed consent in phase III trials, Freedman has quite rationally argued that an individual physician or investigator is not the sole arbiter of appropriate or acceptable medical practice.\textsuperscript{159} Rather, the medical community as a whole determines equipoise and, as long as equipoise truly exists, an individual physician can remain ethically and morally justified in consenting patients to participate in a phase III trial, even if the physician himself is not in equipoise. With regard to the cited advantages of equipoise, Royall has extended this argument, noting that in situations involving an autonomous patient, the decision to participate in a randomized study does not rest with the physician but with the patient.\textsuperscript{156} This is certainly the case as long as an adequate (perhaps ideal) process of informed consent can be carried out, including full disclosure of alternatives to randomized trial participation. Royall argues that what is needed is not to be justified by the presence of equipoise, but more by the presence of uncertainty (or equipoise) regarding the preferred option for that particular patient.\textsuperscript{156} If there is equipoise or uncertainty, physicians without preferences. Rather, it is patients who are informed of the uncertainty (i.e., the existence of perceived equipoise and are autonomously willing to consent to randomized trial participation). Thus, within the context of phase III trials, the informed consent process becomes one of utmost importance. In the cancer setting this may be especially true because of the life-threatening nature of these diseases and the relative toxicities of potential therapies contained within arms of many randomized trials.

Some efforts have been undertaken to examine different methods of obtaining consent for randomized trials and the effect of these methods on the quality of consent.\textsuperscript{152, 153, 154, 155} Many of these investigations have examined alternatives to the conventional methods of informed consent for phase III trials (i.e., in which subjects are asked to consent to the trial and then random assignment (if not on a blinded trial). The alternatives to this ‘sleeping subjects’ consent model include the use of nonblinding, direct randomization and in some cases, consent prerandomization, where subjects are first randomized to one arm of the trial and then asked to consent to participation.

As reviewed by Altman and colleagues,\textsuperscript{152} and originally proposed by Zelen,\textsuperscript{154} these alternatives include single- and double-randomized consent designs. In the single-randomized consent design, eligible subjects are first randomized to one of the treatment arms, given their treatment in a trial before consent and without their knowledge. Subjects randomized to standard treatment are simply evaluated with routine follow-up and nothing is said to them about the trial or their participation (i.e., no formal consent is obtained from them). Subjects randomized to the experimental arm in such designs are consented to receive the investigational therapy. If these subjects refuse participation, they would then receive standard treatment and be followed similarly to those originally randomized to standard treatment. In the double-randomized consent design, all subjects are first randomized without their knowledge, then asked if they would consent to participate, receiving either the
standard treatment or the experimental treatment to which they had already been randomized. Those refusing trial participation would then be offered treatment with the standard treatment or the experimental treatment to which they had already been randomized. The investigators conclude that preconsent randomization methods are highly inefficient with regard to improving accrual, as subjects knowingly randomized to receive the opposite arm to which they had been randomized by the participating physician–investigator approaching them for inclusion in the trial. Interestingly, even considering such criticisms, nearly a dozen cancer clinical trials have employed these or similar consent designs. As reviewed elsewhere, 4 in many of these trials were in the cooperative group setting. Most of these trials had been originally initiated with conventional consent designs, but were then modified to include randomized consent designs in order to improve on patient accrual. Several of these trials increased their accrual rates substantially, some by a factor of three to six times the initial accrual rates. 5,6 Despite these improvements in accrual, these consent designs remain controversial. Gallo and colleagues examined consent designs, conventional consent designs for a hypothetical randomized trial among more than 25,000 healthy subjects. They have not been recommended for such use. CONCLUSIONS If cancer physicians and investigators are to provide high-quality cancer care and conduct research according to the highest possible standards, they must be sufficiently sensitive to the ethical issues discussed. Certainly, continued study and debate regarding these complex issues is unquestionably needed if the dilemmas present in cancer care and research are to be addressed and, it is to be hoped, resolved. Considering their long-standing awareness, cancer physicians and investigators remain well qualifie...


INTRODUCTION

As the twentieth century slipped into history, there could be little doubt that we live in an age in which information technology will continue to catalyze dramatic changes in society that affect our daily lives, especially in the field of health care. The Internet has revolutionized telecommunications, enabling electronic devices with different operating systems and data formats to communicate with each other seamlessly and making the "Net" and the "Web" ubiquitous terms in our lives. Computing power continues to increase steadily as more powerful chips become available, and powerful hand-held computers with wireless access to the Internet are now available. Direct Internet connections, once only available in academic centers, are now readily available in the home, workplace, and in public settings, such as public libraries and shopping malls. Internet access is available through dial-up, cable, and wireless Internet service providers at a reasonable cost.

Effective communication is central to efficient, high-quality health care. Information empowers individuals, enabling them to make informed decisions. Changes in the accessibility of medical information and the way the public can acquire it are altering the field of health care and the relationship between health care professionals and patients. A federally funded science panel on interactive health communication has concluded that few other interventions have greater potential to improve health outcomes, decrease costs, and enhance consumer satisfaction than communication.1 Data from CyberDialogue, a group that has followed Internet trends since 1993, reported that, in 1999, more than 69.3 million adult Americans (35% of the adult population) were actively online; more than 26.3 million (38%) searched the Internet to obtain health and medical information.1 In 2000, more than 33.5 million adults are expected to use the Internet to search for health information.2 Use of the Internet as a channel for communicating health information has increased from 5% in 1995 to 28% in 2000, according to a report issued by the Kaiser Family Foundation.3 Information on the Internet can be of mixed quality. Inaccurate information is not the only cause for concern. Some health-oriented sites hawk health care products or refer users to e-commerce partners and then take a cut of the sales.

It can be difficult for a novice to determine whether the information is current, accurate, and complete unless the information provider clearly articulates the standards that they can tailor information on the site to meet specific needs and preferences. Applications are being designed for a variety of dissemination vehicles, including standalone systems, locally networked computers, and Internet access via personal computers, mobile wireless digital devices, kiosks, and Web television.

The accessibility of accurate, credible information is essential for anyone making decisions about cancer care. Cancer patients, their families, and many of those who perceive themselves at risk of developing cancer face the arduous task of gathering and interpreting information they find or are given to make well-informed decisions about their care options. Cancer patients learn about their diagnosis and management options from many sources and, in today's health care environment, are more likely to ask their health care providers sophisticated and pointed questions. When faced with the task of gathering cancer information either for oneself or for a family member, the Internet provides an instantaneous, inexpensive, and voluminous source of information. Valuable information resources are available on Web sites, e-mail services, news and usenet groups, and online discussion groups that can help people learn about cancer, whether the focus of the search is on treatment, prevention, screening, or support. An increasing number of cancer-oriented Web sites offer significant opportunities for individuals to profile themselves so that they can tailor information on the site to meet specific needs and preferences.

However, as Internet access and Web site development tools have become basic software for computer systems, anyone with a computer, an Internet connection, and the appropriate software can create a Web site, a fact with staggering implications for the amount and quality of medical information available to consumers. A search on the term "cancer" via any of the popular Web search engines retrieves more than 2,000 Web sites offering cancer information from one of the more than 20,000 health-related Web sites.4 For patients and the lay public, the plethora of health information on the Internet often represents a mixed blessing. At present, the Internet is still an unregulated, uncensored medium. Information that is anecdotal, unreviewed, and undated can be found on many Web sites, e-mail services, and news and usenet groups. In an article on the accuracy of medical information on the Web, an oncologist searching the Web for information on Ewing's sarcoma found that 50% of the online material was irrelevant and 6% contained major errors. Inaccuracy of information is not the only cause for concern. Some health-oriented sites hawk health care products or refer users to e-commerce partners and then take a cut of the sales.5 Some post information in an attempt to advance unproven approaches to disease management that are not medically or scientifically sound.

It can be difficult for a novice to determine whether the information is current, accurate, and complete unless the information provider clearly articulates the standards of quality that are being used for the inclusion of materials on the site and the criteria for linking to other Web sites. Users must prepare to take responsibility for making decisions about the value and applicability of the information, just as those using more traditional information sources do.

The National Cancer Institute (NCI) has always had a formal review process for the inclusion of content in its databases and information services.6 It has established a formal process for ensuring that its Web site only provides hypertext links to Web sites that are accurate, useful, and current, and it provides information on how to evaluate electronic information (Table 60-1).7 Other medical information providers have begun to recognize the need to take responsibility for ensuring that patients are not exposed to bogus and potentially harmful cancer information by using criteria for selecting information they disseminate.8,9,10,11,12,13,14 To help users determine what Web sites are credible, the Health on the Net Foundation has established criteria for evaluating Web sites (Table 60-2).15 The principles embodied in these criteria have been widely adopted by credible health-related Web sites.

<table>
<thead>
<tr>
<th>Table 60-2</th>
<th>Criteria for Evaluating Web Sites</th>
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<tbody>
<tr>
<td>Principle 1</td>
<td>Accuracy and Relevance</td>
</tr>
<tr>
<td>Principle 2</td>
<td>Must be a valid source of information</td>
</tr>
<tr>
<td>Principle 3</td>
<td>Must be peer-reviewed</td>
</tr>
<tr>
<td>Principle 4</td>
<td>Must be updated regularly</td>
</tr>
<tr>
<td>Principle 5</td>
<td>Must be accessible 24/7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 60-1</th>
<th>Criteria for Evaluating Electronic Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Criterion 1</td>
<td>Accuracy</td>
</tr>
<tr>
<td>Criterion 2</td>
<td>Relevance</td>
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<tr>
<td>Criterion 3</td>
<td>Must be peer-reviewed</td>
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<td>Criterion 4</td>
<td>Must be updated regularly</td>
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<tr>
<td>Criterion 5</td>
<td>Must be accessible 24/7</td>
</tr>
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</table>
TABLE 60-1. Cancer-Oriented Web Sites

TABLE 60-2. Health on the Net Criteria for Site Evaluation

As profiling of users becomes a more common feature of interactive health communication, understanding a site's position on the confidentiality of personal information is becoming increasingly important. Users should determine what personally identifiable information is collected from them by the Web site; how the information will be used, with whom the information may be shared; what choices they have regarding the collection, use, and distribution of the information; the kind of security procedures that are in place to protect the loss, misuse, or alteration of information; and how they can correct any inaccuracies in the information. TRUSTe is an independent, nonprofit initiative whose mission is to build trust and confidence in the Internet by promoting these principles of disclosure and informed consent. Many health-related sites explicitly state their privacy policy or display the TRUSTe mark.

NATIONAL CANCER INSTITUTE'S INFORMATION SERVICES

For more than two decades, the staff of NCI's International Cancer Information Center (ICIC) have striven to meet the challenge of assisting health professionals and the public to effectively use current medical knowledge by providing current, high-quality information through a variety of media. The primary information resources are Physician Data Query (PDQ), a comprehensive database of current, peer-reviewed syntheses of state-of-the-art information on cancer care (http://cancernet.nci.nih.gov/pdq.html), and CANCERLIT, a comprehensive source of bibliographic citations on published cancer research (http://cancernet.nci.nih.gov/cancerlit.html). These databases are distributed through a variety of media, including CancerFax, one of the first fully automated fax-back services; CancerMail, an automated e-mail service; and CancerNet (http://cancernet.nci.nih.gov), an Internet Web site that provides point and click access to NCI's information resources and has become a primary mechanism for disseminating PDQ and CANCERLIT information. These information resources undergo well-established peer-review processes that draw on a broad base of cancer experts to ensure that content is current and accurate. These systems are updated on a monthly basis, which ensures that users are provided with more current information than can be provided by most hard-copy publications.

PHYSICIAN DATA QUERY

PDQ, the NCI's comprehensive cancer information database, first became available to health professionals in 1984. It is unique in the fact that its content is developed based on systematic reviews of the medical literature and expert opinion. Five editorial boards synthesize information from the literature into concise, clear summaries that are updated on a regular basis.

PDQ consists of three main types of information: (1) literature-based, full-text summaries that reflect current, state-of-the-art information on the treatment of adult and pediatric malignancies, the prevention and screening of cancer, the supportive care for cancer and its complications, and cancer genetics; (2) summaries of clinical trials currently accruing patients and those that are closed or completed; and (3) directories of physicians who provide cancer care and listings of health professionals who provide services related to cancer genetic risk assessment, counseling, and testing.

Cancer Information Summaries

TREATMENT OPTIONS. PDQ contains treatment information on all major types of cancer in children and adults, including autoimmune deficiency syndrome–related cancers (http://cancernet.nci.nih.gov/treatment.html). For each cancer, a detailed summary, designed to meet the information needs of health professionals, is provided that contains an overview, information on staging, and information on treatment options by important disease-specific parameters (e.g., stage, histology, anatomic location). Key citations to the literature are referenced to enable users to see the research data on which the texts of the PDQ summaries are based. Users can retrieve abstracts of these citations for review. Levels of evidence are provided for each summary (Table 60-3). A limited number of brief summaries on more rare cancers are also available. In addition, PDQ provides treatment summaries that contain similar information written in nontechnical language for patients and their families. All of the summaries are available in English and Spanish.

TABLE 60-3. Levels of Evidence for Therapeutic Benefit from Treatment Interventions

COPING WITH CANCER. PDQ contains summaries on issues that relate to coping with the management of side effects of cancer treatment, complications caused by
SCENING AND PREVENTION. The screening information in PDQ includes summaries on screening for breast, cervical, colorectal, endometrial, gastric, liver, lung, neuroblastoma, oral, ovarian, prostate, skin, and testicular cancers. Each summary contains the available data concerning screening for that particular disease site, the levels of evidence for that summary, and the significance and evidence of benefit for the summary statement. They include references to the current literature that support the information in the summary. In addition, PDQ contains a version of the summary on screening for breast cancer written for non–health professionals.

### Table 60-4. Levels of Evidence for Physician Data Query/CancerNet Screening Summaries

<table>
<thead>
<tr>
<th>Screening Category</th>
<th>Level of Evidence</th>
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<tbody>
<tr>
<td>Colorectal cancer</td>
<td>Level I evidence</td>
</tr>
<tr>
<td>Cervical cancer</td>
<td>Level II evidence</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>Level III evidence</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>Level IV evidence</td>
</tr>
</tbody>
</table>

### Table 60-5. Levels of Evidence for Physician Data Query/CancerNet Prevention Summaries

CANCER GENETICS. An editorial board was established in 1998 to address issues that relate to the impact of research in cancer genetics on cancer prevention, screening, and treatment strategies. An overview of cancer genetics and the genetics of breast and ovarian cancer are currently available. Summaries on the genetics of colorectal and prostate cancer, the elements of cancer risk assessment and counseling, and the multiple endocrine neoplasia type 2 syndrome are in preparation.

COMPLEMENTARY AND ALTERNATIVE APPROACHES. In collaboration with the National Institutes of Health's National Center for Complementary and Alternative Medicine, ICIC staff are preparing evidence-based summaries on nontraditional approaches to cancer prevention, treatment, and symptom control. An advisory board composed of oncologists and representatives of the complementary and alternative medicine community review the summaries to ensure that they are accurate, informative, up to date, and well balanced. Summaries on cartilage and hyaluronic sulfate are currently available, and summaries on Laetrile, antineoplastons, essiac, MTH-88 (Newcastle disease virus), 714-X, green and black tea, coenzyme Q10, mistletoe, IP-6 (inositol hexaphosphate), Cancell, and Coriolus versicolor are in preparation.

Peer Review: The Process

The information in PDQ is reviewed by five core editorial boards, each handling one of the following topics: adult treatment, pediatric treatment, supportive care, screening and prevention, and cancer genetics. These core boards are comprised of more than 80 cancer specialists who meet regularly to review the current literature and to update PDQ summaries based on scientific data. Most (67%) are not government employees. Each core board is supplemented by an external advisory board that reviews summaries annually. More than 100 additional health professionals with expertise in cancer screening, prevention, treatment, genetics, coping, and complementary and alternative care serve on these advisory boards.

A process has been developed to assist board members to efficiently identify literature with important new data. Each month, more than 80 biomedical journals are screened by professionals who identify citations of potential relevance. The boards may also review papers submitted for consideration by investigators, including important, but unpublished, manuscripts that have been accepted for publication.

After the articles are screened, those considered the most relevant and significant are sent to appropriate board members for review. If the board members believe the data warrant a change in a state-of-the-art summary, the manuscript is put on the agenda of an upcoming board meeting. At the meeting, members discuss the positive and negative points of the research and make decisions about whether to modify summaries based on the data. Changes may involve the addition of a new management option, the deletion of one that is no longer supported by data, the integration of new data that lend additional support to existing options, or an interpretation of controversial data. Literature citations are provided for each option so that users can make their own assessment of the current literature. Users can link to these citations as well.

Use of Formal Evidence-Based Criteria in Physician Data Query/CancerNet

Editorial board members understand the volume of medical knowledge and the increased emphasis on physician accountability and cost-effective practice. In an attempt to assist health professionals to apply data from the medical literature in daily practice, all of the editorial boards have moved from a consensus development approach to summary development to an evidence-based approach to evaluating the literature and summarizing it. The practice of developing evidence-based summaries of the existing literature enables the editorial boards to draw attention to significant gaps in medical evidence that are important to consider in making patient management decisions. Pointing out these gaps is not only important for health professionals and patients in decision-making decisions; it also helps to define areas that are most in need of additional research.

Evidence-based criteria have been used exclusively by the screening and prevention board to develop and refine screening and prevention summaries since the board's inception. This approach has proven to be useful in the consideration of scientific data on cancer screening and prevention and has proven to be well suited to the presentation of controversial information. Evidence-based methodology allows editorial board members to summarize the information currently available on a particular topic and to indicate the strength of that evidence. Annotations on the strength of the evidence for a particular approach afford the user a good
In therapeutic studies, a variety of end points may be measured and reported. These end points include total mortality (or survival from the initiation of therapy), cause-specific mortality, quality of life, or indirect surrogates of these three outcomes, such as disease-free survival, progression-free survival, or tumor response rate. End points may also be determined within study designs of varying strength, ranging from the gold standard (the randomized, double-blinded, controlled clinical trial) to case series experiences from nonconsecutive patients. The adult treatment editorial board uses a formal ranking system of levels of evidence to help the reader judge the strength of evidence linked to the reported results of a therapeutic strategy. For any given therapy, results can be ranked on each of the following two scales: (1) strength of the study design and (2) strength of the end points. Because studies or clinical experiences are ranked both by strength of design and importance of end points, a given study has a two-tiered ranking (e.g., I(ii)/A for a double-blinded randomized study showing a favorable outcome in overall survival, and III(iii)/D(ii) for a phase II trial of selected patients with response rate as the outcome). Thus, the two rankings give an idea of the overall strength of evidence (see Table 60-3).

In addition, all recommendations try to take into account other issues that cannot be so easily quantified, such as toxicity, width of confidence intervals of observations, trial size, quality assurance in the trial, and cost. Depending on their perspectives, different expert panels, professional organizations, and individual physicians may use different cut points of overall strength of evidence in formulating therapeutic guidelines or in taking action. Nevertheless, this ranking system does provide an ordinal categorization of strength of evidence as a starting point for discussions of study results, and the formal descriptions of the levels of evidence provide a uniform framework for the data. The editorial boards are currently integrating information on the levels of evidence into the summaries as they review and update summaries.

PDQ's state-of-the-art summaries are dynamic and can be updated as frequently as each month. On average in 1999, 15% of the summaries were revised each month. Approximately 90% of the changes were revisions of the summaries, and approximately 30% of the summaries underwent substantial revisions. All licensees are required to ensure that the information a user prints from PDQ is dated so that it is clear to the user when the information was retrieved from the database.

**Physician Directory**

The PDQ physician directory contains names, addresses, and telephone numbers for more than 25,000 physicians who devote a major portion of their practice to the treatment of cancer patients. Also included is information on medical specialties, oncologic subspecialty board certification, and organizational affiliations for each of these physicians. Physicians listed in the membership directories of major oncologic societies or organizations and clinical investigators who have protocols in PDQ or are members of NCI-sponsored clinical trials groups are also listed in this directory.

**Organization Directory**

The PDQ organization directory contains information on more than 3000 health care institutions that provide care for cancer patients, including NCI-designated comprehensive and clinical cancer centers, community clinical oncology programs, clinical trial groups, and members of the Association of Community Cancer Centers. Information on organizations is retrievable by any combination of name, city, state, county, or zip code. These directories are not yet available through CancerNet.

**Cancer Genetics Services Directory**

Cancer Genetics Services (http://cancernet.nci.nih.gov/generarch.shtml) is a directory of approximately 300 health professionals of various disciplines, such as genetic counseling, oncology, nursing, psychology, social work, and clinical genetics, who provide services related to cancer genetics, including cancer risk assessment, genetic counseling, and genetic susceptibility testing. Each individual listed must be licensed, certified, or eligible for board certification in their profession; have specific training in cancer genetics; and be affiliated with an interdisciplinary team with substantial expertise in cancer genetics. They must also be members of one of the professional organizations listed on the application for inclusion in the directory (http://cancernet.nci.nih.gov/genetics(gc_application.html) and be willing to accept referrals.

**Clinical Trials**

PDQ and CancerNet contain more than 1700 summaries of clinical trials that are open or approved for patient accrual (http://cancernet.nci.nih.gov/trialsrch.shtml). Treatment, screening, prevention, and supportive care protocols supported by the NCI are listed in PDQ. Each can be retrieved by diagnosis, stage, treatment modality, phase of investigation, location, and drug name, or any combination of these and other parameters. Approximately 45% of the active trials in PDQ are not directly sponsored by NCI and are submitted voluntarily by the study chairperson; 10% are submitted by the pharmaceutical industry. Criteria for including voluntary submissions include whether the study design is reasonable, whether the trial is based on rational scientific information, whether the trial is likely to yield some useful information, or if it is unduly risky to patients, and whether the entry criteria and statistical section are clear and complete. Trial summaries can be submitted to CancerNet online (http://cancernet.nci.nih.gov/protosub/protocol.html). CancerNet's trial summaries can also be found on ClinicalTrials.gov (http://www.clinicaltrials.gov), a Web site developed by the National Library of Medicine to provide patients, family members, and members of the public information about clinical research studies currently under way for anyone with a life-threatening disease. Collaboration with U.S. Food and Drug Administration and other National Institutes of Health staff to encourage submissions from the pharmaceutical industry is ongoing.

A member of the clinical trials review editorial board reviews protocols voluntarily submitted by investigators who are not directly supported by the NCI before their inclusion. Phase II and III trials that have been submitted to the Food and Drug Administration under the investigational new drug application regulations do not require further editorial review. Foreign clinical trials are included after the review process of the sponsoring organization is approved by the PDQ editorial board. If the clinical trials editorial board finds a reason not to include a trial in PDQ and CancerNet, a letter containing the board's concern(s) is sent to the investigator, who is invited to respond by either modifying the protocol document according to the reviewers' comments or by clarifying the information in the protocol document. Once a response is received from the investigator, the protocol is re-reviewed by the clinical trials review board. More than 90% of the trials submitted for review are included.

An archival file of more than 10,800 closed protocols provides a rich source of data on previously completed clinical research, some of which is not published and is not available elsewhere. Whenever possible, ICIC staff link the protocol summaries to published reports on trial outcomes.

Since 1996, PDQ and CancerNet also have contained consumer-oriented summaries of active clinical trials. On CancerNet, the technical terms in each summary are hyperlinked to a glossary. The technical and consumer-oriented trial summaries are also linked to one another.

Since April 1998, NCI staff has provided additional contextual information on clinical trials on its cancerTrials Web site (http://cancertrials.nci.nih.gov). The site was established to raise awareness about clinical trials and to address some of the perceived barriers to participation. The information contained on cancerTrials falls into the following categories: a framework for understanding what clinical trials are and deciding about participation; information about clinical research grouped by type of cancer; information on how to find trials, which features a hyperlink to the CancerNet clinical trials search form (http://cancernet.nci.nih.gov/trialsrch.shtml); news and features highlighting topics under clinical investigation and trial results; and resources for researchers, such as a library of downloadable resources for clinical investigators that includes templates, guidelines, and policy documents. Information on specific cancers features hypertext links to the cancer information summaries in PDQ on CancerNet, as well as news about clinical trials.

**CANCERLIT**

CANCERLIT is a bibliographic archival database containing more than 1.5 million citations and abstracts of published research in cancer biology, etiology, screening, prevention, and treatment published from 1963 to the present from more than 4000 different sources. It is updated monthly and provides a comprehensive, up-to-date resource of cancer literature. Preformatted search "digests" for more than 90 clinical topics are also available (http://cancernet.nci.nih.gov/canlit/canlit.htm). The complete database can be searched on CancerNet (http://cancernet.nci.nih.gov/cancerlit.shtml).
program that allows for use of the databases by a variety of commercial and nonprofit distributors. Through a trademark license, these distributors deliver PDQ and CANCERLIT data to worldwide audiences through a variety of media. The mechanisms fall into two general categories: online time-sharing systems with dial-up or Internet access; and “local” implementations in which the database resides on a computer, CD-ROM, kiosk, or local area network. CANCERLIT is also available online through a variety of commercial database vendors as an online or CD-ROM product. The program began in 1982 with one agreement, has grown to 72 agreements (39 for PDQ, 15 for CANCERLIT, and 18 for CancerMail), and continues to grow. All new requests to license are reviewed and evaluated on the following criteria:

- Does the organization share NCI’s goal of disseminating and sharing cancer information?
- What is the impact of the organization’s efforts?
- Would licensing the information to the organization enable ICIC to reach a larger or new audience?
- Is the organization willing and able to update the information monthly and provide ICIC with user feedback and statistics?

Licensing efforts include partnerships with vendors that produce Web sites and public kiosks with credible health information, as well as those that are developing health information “portal” sites.

**Toll-Free Search Services**

One of the problems faced by those responsible for disseminating cancer care information is how to make it easily accessible to people without direct personal access to the technology. The Cancer Information Service (CIS) is an NCI-supported nationwide network of 14 regional offices located at 34 sites in the United States, Puerto Rico, and the U.S. Virgin Islands. Through its toll-free telephone service (1-800-4-CANCER) and Web site (http://cis.nci.nih.gov), certified information specialists trained by the NCI use a variety of printed and computer resources to provide accurate, up-to-date information on cancer. In 1999, the CIS responded to more than 890,000 calls from patients, family members, health professionals, and the general public. More than 300,000 inquiries came over the Internet, and 17% of callers reported that they obtained the toll-free number from the Internet. CIS staff conduct customized searches of PDQ and make more than 100,000 referrals to clinical trials from PDQ each year. Staff also interpret research findings; explain diagnostic and treatment information; inform callers about emerging areas of science, such as hereditary risk; clarify media stories about scientific discoveries; and provide smoking cessation counseling.

The CIS makes available nearly 600 publications and materials on a range of topics, including treatment information and research studies, specific types of cancer, community services, screening tests and examinations, adopting healthier behavior, coping with cancer, and cancer risk. The CIS offers printed and audio-visual materials that are easy to read and culturally appropriate; materials are also available in Spanish. A Web-based publication-ordering service is available (http://publications.nci.nih.gov).

Each year, the CIS Partnership Program assists 4500 organizations that serve minority and medically underserved populations within their communities. CIS staff provide partners with access to the latest, most accurate cancer information; assist with coalition building and networking; offer program planning, implementation, and evaluation assistance; provide media assistance; identify resource experts; and assist with training. Efforts involve breast and cervical cancer, tobacco education, science awareness, and overcoming barriers to clinical trial participation.

The CIS serves as a health communications laboratory through an NCI-funded research consortium. CIS staff are involved in studies that test and identify the most effective ways to communicate health information to help people adopt healthier behaviors. These studies have evaluated types of information messages provided, the manner in which they are delivered, how often messages should be communicated to affect health behaviors, and the value of tailoring messages to an individual’s particular perspective.

The CIS intends to apply the strengths of the telephone service to the Internet and plans to provide real-time interactions over the Web to position the CIS as the world’s premier cancer information navigator. Under development is instant messaging, Web-based tailoring, Webcasting, an interactive voice response system for the publication ordering, and an interface with mobile wireless digital devices.

**Physician Data Query/CANCERNET Service Center**

The PDQ/CANCERNET Service Center provides customized searches from the NCI’s PDQ database to health professionals, who can request and receive information through a toll-free telephone service, e-mail, or facsimile. The goal of the service center is to make the information from PDQ available to health professionals who do not have the time or resources to access electronic systems directly. The service center can be reached by calling toll-free 1-800-345-3300 (in the United States), Monday through Friday, 9 a.m. to 6 p.m. Eastern time. Alternatively, requests can be faxed to 1-800-380-1575 or sent via e-mail to pdqsearch@icdc.niederhoffer.org. More information on the search center can be found on the Web site.

**PHYSICIAN DATA QUERY/CANCERNET REDESIGN**

In mid-1990, ICIC staff recognized that the infrastructure supporting PDQ, CancerNet, CancerFax, and CancerMail was old and obsolete. The legacy system had become increasingly difficult to adapt for cutting-edge information technology. It could only produce simple text (ASCII data) and could not support commonplace features such as spell-checking, that make information more user-friendly, and that make information searching, that make information easier to find on the Internet. Production processes were also hampered by a paper-based workflow/document management system used to identify, track, process, and update more than 800 peer-reviewed information summaries from more than 80 core editorial board members, many of whom receive materials for review every month.

In 1998, ICIC staff embarked on an initiative to restructure the infrastructure to take full advantage of advances in computing technology. A 2-day formal needs assessment was performed in February 1998 to identify functional requirements for the new system. This meeting provided an opportunity for more than 190 patients, advocates, clinical investigators, practicing oncologists, oncology nurses, librarians, health educators, social workers, and other health professionals, as well as experts in medical and consumer informatics and representatives from the pharmaceutical and insurance industries, to advise NCI on what should be included in the new system. Participants in the meeting provided specific input on the range of content, ease of navigation, user interface issues, use of current and emerging technologies, and barriers to access. Operational, marketing, and evaluation issues were also discussed. The recommendations were used to develop the specifications for a more robust and flexible system that could accommodate real-time updates and multimedia data and provide advanced concept search capabilities. Participants also directed NCI to develop evaluation strategies to ensure that user feedback is obtained on an ongoing basis and that enhancements are integrated and reevaluated in an iterative fashion.

Fundamental to the redesign initiative was the development of a flexible and scalable infrastructure to support a dynamic, broad-based, and modular information system. To meet this need, ICIC computer specialists developed a universal database (UBD) server that is both a repository and a powerful retrieval engine. It also contains pointers to data located in other databases and Web sites. The power of the UDB enables ICIC staff to develop a flexible and scalable new user interface to CancerNet. The UDB allows users to search across different data types with a single query and obtain information on a specific topic from resources in Web sites and databases produced and maintained by other divisions, institutes, and organizations. The UDB links and organizes on the fly related documents for users to review, integrates and reevaluates in an iterative fashion.

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Additional research and development is under way and includes instant messaging; the development of a CancerFax system that does not require handsets on facsimile machines; CancerVoice, an automatic text-to-speech conversion and speech recognition system that will permit the physically challenged and those without access to computers, fax machines, or the Internet to access CancerNet information via the telephone; audio supplements that will enable CancerNet users to simultaneously see and hear information, a feature that will be beneficial for the elderly and vision-impaired; a Web-based protocol application that will permit online clinical trial protocol submission, review, and updates; content enhancements that will provide information in additional levels of technical detail; intelligent software tools that will enable ICIC staff to customize output in response to user requests, download information to hand-held wireless communication devices, and dynamically link terms requiring explanation to the glossary; search wizards to help users find information; and improved indexing that will enhance search functionality. The UDB will enable ICIC staff to meet each section of more than 480 PDQ information summaries as “independent” documents with unique device identifiers, indexes, and links, so that it can compile responses on the fly that are precisely tailored to a user’s requests. This feature will also enable ICIC staff to provide advocacy organizations serving highly focused audiences with information on specific cancers and import trial summaries from trusted partners.
distribution, eliminating the need to duplicate their efforts.

Another core principle is that this new information infrastructure will be tightly integrated into the NCIC clinical trials system, an apparatus that is undergoing change. Staff are working in other NCIC offices to develop a comprehensive cancer informatics infrastructure that will support secure access to systems for electronic submission, review, manipulation, and updating of clinical trials data. The development of such resources will facilitate the rapid and efficient communication of information across systems and among the various components of the National Cancer Program.

The NCIC designated health communication as one of the extraordinary opportunities for investment in the bypass budget for 2001. ICIC staff are active participants in the development of a comprehensive strategy for funding research in cancer communications and developing strategies for improving access and use of cancer information regardless of race, ethnicity, health status, education, income, age, gender, or geographic area.

Site Design
In a study of 15 large Web sites, users asked away in frustration, complaining that they could not find the information they sought 58% of the time. Despite attractive graphic identities and volumes of valuable content, these sites did not provide intuitive information access because the information architecture did not assist users in finding information quickly and easily. Often, the site architecture is confusing because the developers did not obtain user input on the organization of information, hierarchy and layout of menus; ease of navigation; usability of search forms, site indexes, and instructions for users; and the overall graphic design of the system.

To ensure that the new CancerNet Web site would not fall prey to such problems, ICIC staff made use of emerging research on Web site usability engineering. The principles of usability engineering provide guidance on overall Web site design, navigation, and functionality. Usability engineering assists Web designers in achieving their objectives by requiring them to identify and focus on the goal of the Web site, the needs of the target audience, and the technical constraints that a typical user faces with regard to hardware, software, access, and experience before developing the Web site. It is a cost-effective technique that eliminates the need to build a site until key components of its functionality are evident from user input.

An integral part of the redesign was the prospective gathering of data on the information needs of the full spectrum of current and potential users. An online questionnaire provided input from more than 600 individuals: 37% were accessing the site for the first time, 23% were looking for information on a specific cancer, and 11% were seeking clinical trial information. After this stage, personal interviews were conducted with current and potential users to further define their information needs. Based on this feedback, the first prototype was constructed and then subjected to iterative evaluations with current and potential users to see if their needs were being served by the prototype. Test participants representing the various target audiences were recruited to search for information in response to a series of specific questions. While attempting to find the information required to answer the questions, test participants were asked to “think out loud” so that their thought processes could be captured and recorded on videotape to identify flaws in terminology, layout of information, hierarchy, menu structure, and navigational elements. The process proved to be an effective method of validating the information architecture and drove the redesign process. For example, usability tests conclusively documented that there was no single preferred way to search for information. Therefore, the new site was designed to permit users to find information in multiple ways, with each path linking to the same page, so that a primary document exists in only one place on the Web site.

In November 1999, ICIC staff launched the first version of the redesigned CancerNet Web site. One of the things that ICIC staff were most proud of was the fact that the new site was built with user input at every stage of development. Major enhancements include a new user interface that makes site navigation easy; cancer-specific ready access to the site about that cancer (http://cancernet.nci.nih.gov/cancerbytype.html), powerful new search capabilities (http://cancernet.nci.nih.gov/searchoptions.html); a network of hyperlinks between PDQ summaries, clinical trials, and CâNCER LiT citations; a guide for first time visitors with hyperlinks to the information described (http://cancernet.nci.nih.gov/firsttime.html); a site map; a dictionary of more than 1200 medical terms; a greatly expanded list of hyperlinks to other cancer-related Web sites; and a publication locator that allows users to view and download NCI publications or order them by e-mail. Updates on new enhancements, content, search tools, and other changes are featured in a What's New area (http://cancernet.nci.nih.gov/newsatnew.html). This area also will be used to highlight feedback from users, enable them to automatically receive updates on enhancements to CancerNet, and sign up for the CancerNet listserv. Feedback from this area and iterative usability testing will continue to drive development and implementation activities.

Multiple approaches for increasing awareness about the new site are being used to heighten the visibility of CancerNet as a primary source for high-quality cancer information, including a robust system of metalogs, an e-mail notification service for users, and reciprocal linking agreements with other Web sites. Licensing efforts include partnerships with vendors who produce kiosks and those developing health information "portal" sites. ICIC staff will also continue to work with public libraries to increase awareness and use. CancerNet information is featured in MEDLINE plus, the National Library of Medicine's health and medical information service for the public (http://www.nlm.nih.gov/medlineplus).

The "reinvention" of PDQ represents more than the mere updating of PDQ's content or the elaboration of new technologies. At a fundamental level, the redesign involves a complete rethinking of how technology products such as PDQ should be designed and maintained over time through a process of continuous refinement.22 23 The phases of product conceptualization, development, testing, and dissemination are no longer thought of as being consecutive, rather, all of these phases overlap by design. Consumer input throughout product conceptualization helped to focus the developers. Continuous feedback from consumers during early stages of development helped to inform a more substantive and comprehensive redesign that sometimes in dramatic departures from the site as originally conceived. Continued usability tests will provide additional input and result in further refinements and enhancements that are driven by continuous consumer review of blueprints and prototypes before new versions and major refinements are implemented and marketed.

CONCLUSION

The Internet will continue to revolutionize the way the world obtains and disseminates information, and rapidly advancing technology promises to continue to revolutionize the way that medicine is practiced. It is clear that computing and communication technologies have a major role to play in decision support in medicine. The Internet will continue to revolutionize the way the world obtains and disseminates information, and rapidly advancing technology promises to continue to revolutionize the way that medicine is practiced. It is clear that computing and communication technologies have a major role to play in decision support in medicine. Medical students have access to huge collections of information and can participate in training sessions anywhere in the world. Collaborating physicians can share patient charts, laboratory results, and x-rays and other images without considering distance or time delays. However, legal considerations, such as malpractice liability, license, accreditation, and reimbursement for teleconsultation, remain to be addressed. With encryption authentication, some sites are already offering

CHAPTER REFERENCES


DEFINITIONS

Alternative medicine is a somewhat contentious but generally accepted term that refers to a diverse assortment of philosophies, theories, and diagnostic, preventive, and therapeutic practices not generally viewed as arising from or belonging to the modern Western biomedical paradigm. Many of these interventions are used around the world by indigenous peoples of non-Western cultures as their primary form of health care. However, in most developed countries, these practices generally are used along with conventional Western medicine. Consequently, the terms complementary medicine and integrative medicine are used often to acknowledge the blending of these world views and therapeutic approaches. The term complementary medicine can be used also to refer to conventional modalities used in unconventional ways or to achieve unconventional end points (e.g., psychosocial support groups to prolong cancer patient survival).

In April 1995, the National Institutes of Health Office of Alternative Medicine established a Panel on Definition and Description, charging it "to establish a definition of the field of complementary and alternative medicine (CAM) for purposes of identification and research; and to identify factors critical to thorough and unbiased description of CAM systems and practices that would be applicable to both quantitative and qualitative research." The panel defined CAM as follows:

Complementary and alternative medicine (CAM) is a broad domain of healing resources that encompasses all health systems, modalities, and practices and their accompanying theories and beliefs, other than those intrinsic to the politically dominant health system of a particular society or culture in a given historical period. CAM includes all such practices and ideas self-defined by their users as preventing or treating illness or promoting health and well-being. Boundaries within CAM and between the CAM domain and the domain of the dominant system are not always sharp or fixed.

Other authors prefer to define complementary therapy separately, believing that it encompasses practices that can be integrated with conventional medicine, whereas so-called alternative medicines often are promoted as independent therapeutic approaches not amenable to combination with conventional therapy. Many other terms have been used to define this subject: unconventional, unproven, unorthodox, unsound, nontraditional, holistic, and non-Western. Table 61-1 presents a partial list of CAM modalities used for the prevention or treatment of cancer, of cancer symptoms, or of conventional treatment side effects.

TABLE 61-1. Commonly Used Complementary and Alternative Medicine Modalities in Cancer

PHENOMENOLOGY OF COMPLEMENTARY AND ALTERNATIVE MEDICINE IN CANCER

CAM usage by cancer patients is very prevalent all over the world (Table 61-2). Recent surveys have reported CAM use by cancer populations in Austria, Australia, Finland, Germany, Italy, the Netherlands, Norway, and Taiwan, the United Kingdom, the United States, and Canada.
A systematic review of surveys of various cancer populations has given some validation to the general gestalt that the prevalence of CAM usage is increasing. However, accurate assessment of trends in CAM usage by cancer patients is rendered difficult by the lack of consistency in the definition of CAM, by survey methodology, and by population demographics.

One study specifically attempted to gauge the change in prevalence of CAM use by cancer patients. Abu-Reaih et al. reviewed data from a subgroup of responders to the 1992 National Health Interview Survey to determine the growth in use of self-help therapies (e.g., relaxation exercises, imagery, humor, laughter, meditation, prayer, affirmations, self-hypnosis, and music, aroma, and color therapy) and psychosocial therapies (i.e., counseling and support groups). The authors compared the percentage of CAM users among individuals with diagnosed cancer prior to and after 1986 and found a 53% increase in use of those modalities (8.3% prior to 1986 vs. 13.6% after 1986).

The growth of general CAM usage in the United States has been investigated more thoroughly. Eisenberg et al. reported results of a follow-up to their 1990 survey of the American public for CAM use. The 1997 survey found that 42% of the interviewed participants had used at least one CAM modality in the last 12 months. Of the CAM users, 46% had at least one visit to an alternative medicine practitioner. These figures were significantly greater than the 34% overall CAM usage and the 36% of those visiting an alternative medicine practitioner reported in the 1990 survey. These surveys, and others from various countries, also found that CAM use was more prevalent among younger patients and those with higher education and higher income.

The largest survey of CAM use by U.S. cancer patients was reported by the American Cancer Society in 1992. Telephone interviews of approximately 36,000 households across the nation led to the identification of a group of 3272 living individuals who had had a cancer other than a nonmelanomatous skin cancer. Approximately two-thirds of these patients were interviewed, and information about the other one-third was obtained from family members. The authors found that 9% of cancer patients used CAM and that subpopulations of patients with certain tumor types had rates as high as 21% (e.g., brain cancer).

Ernst and Cassileth performed a comprehensive review of surveys of cancer patients’ use of CAM. Surveys of cancer patients in various settings have yielded rates ranging from 9% to 91%. Selected surveys are summarized in Table 61-2. The differences between the prevalence figures observed likely are due to differences in the demographics of the populations, the definition of CAM, and the survey methodology.

Some recurring themes are seen across surveys. Most cancer patients who use CAM use more that one modality, often simultaneously. Greater use has been noted among patients with advanced disease or a poor prognosis (or both). Many studies have found that most users of CAM therapies for cancer judged them to be effective and were satisfied with their outcomes. Both similarities and some important differences are seen in the types of CAM modalities used by the general public, by individuals with a known noncancer illness, and by cancer patients. The most commonly used U.S. CAM modalities identified among patients with a variety of noncancer illnesses are chiropractic, relaxation, massage, herbal medicines, spiritual healing, and imagery. Among U.S. and Canadian cancer patients, the modalities identified most frequently in the 1990s have been mind-body approaches (meditation, relaxation, hypnotherapy, visualization, and other imagery techniques); specialized diets and dietary supplements; herbal preparations; megavitamin therapy; and spirituality, prayer, and spiritual healing.

Two surveys reported the use of CAM approaches by pediatric cancer patients. Fernandez et al. surveyed patients attending the only tertiary-care pediatric oncology center in Canada and found that 41% of the patients in the study used a CAM modality, with herbal teas, plant extracts, relaxation therapy, imagery, and therapeutic vitamins being the most common. In a smaller study in the Netherlands, 31% of the patients were using alternative treatments, with a greater rate of usage among the subgroup of relapsed patients (46%).

REASONS FOR CANCER PATIENT USE OF COMPLEMENTARY AND ALTERNATIVE MEDICINE MODALITIES

Many patients use CAM approaches to “boost” the immune system, but many also choose them with hopes of slowing the progression of tumors or ultimately obtaining a cure. Even in a study of patients referred to a pain and symptom management clinic, most CAM users had used the modalities for a potential anticancer effect.

Some observers have suggested that disease recurrence or progression is the primary trigger for patients to seek CAM therapies. However, for many patients, the initial diagnosis of cancer raises enough concerns to investigate alternative or complementary modalities. For some patients, experimentation with CAM modalities may be due to fear of the uncertainty of response to conventional therapy; for others, this choice may be simply an attempt to participate in the healing process.

Burstein et al. reported that new use of CAM among a group of women with recently diagnosed early-stage breast cancer correlated with significantly more depression, less sexual satisfaction, greater fear of recurrence, and somatic symptoms. The problems of low sexual satisfaction and fear remained at the 12-month observation point, but the other areas improved and were not significantly different from those of nonusers. The authors suggested that initiation of CAM use should alert clinicians to inquire about anxiety, depression, or physical symptoms.

COMPLEMENTARY AND ALTERNATIVE MEDICINE THERAPIES

CAM therapies for cancer are legion, and many have multiple variations. In this section, some of the more prevalent therapies are described briefly, primarily from the standpoint of the published evidence. Other therapies are listed in Table 61-1 with references for those not discussed here. For most of these approaches, definitive clinical trials to assess their potential efficacy have not been performed. For many others, their use continues despite results of randomized controlled clinical trials indicating no efficacy.

ANTINEOPLASTONS

In the 1960s and 1970s, Dr. Stanislav Burzynski reported the identification of small peptide molecules in the blood and urine of normal humans, which he called antineoplastons. Burzynski postulated that these compounds were components of a natural anticancer defense system or “cherno-surveillance system” and named them for the original designation of the urine fractions from which they were extracted. Antineoplaston A10 is a 1:4 ratio of phenylacetylglutamine and phenylacetylglutaminamide, and AS2-1 is a 1:4 ratio of phenylacetylglutamine and phenylacetic acid.

Burzynski reported his clinical experience with antineoplastons in cancer patients. However, as pointed out in a comprehensive review of the subject, the use of unconventional definitions of response and the confounding factors of concurrent conventional therapies hamper the interpretation of the results of these studies. One study by a Japanese group evaluated the toxicity, and preliminarily evaluated the response rates, of patients with various tumors to AS2-1 and A10. Some of these patients received concurrent chemotherapy. The authors reported responses in 3 of 46 measurable tumors but gave insufficient information about the patients to assess the role of antineoplastons in these responses.

In 1991, the National Cancer Institute (NCI) reviewed a series of seven case reports of patients with brain tumors treated with antineoplastons. The reviewers found that presumptive evidence of antitumor activity was demonstrated, and phase II trials were initiated. A trial of patients with recurrent high-grade glioma was designed and initiated with significant input from Burzynski. Nine patients were treated with AS2-1 and A10 in the study before accrual was halted, owing to an inability to reach agreement with the supplier of the antineoplastons on protocol modifications designed to increase accrual. None of the six assessable patients manifested a radiographic remission, and all had progressive disease within less than 10 weeks of starting treatment. A recent study of continuous infusion of phenylacetate alone in patients with recurrent malignant gliomas has revealed low-level activity (3 partial responses of 40 patients).

METABOLIC THERAPIES
**Gerson Therapy**

A therapy for cancer and other illnesses was developed empirically by Max B. Gerson, a German-born physician, and was administered in his sanitarium during the 1930s, 1940s, and 1950s until his death in 1959. Gerson sought to "balance" potassium and sodium, as their "imbalance" was thought to support tumor growth. His therapy consisted of a low sodium, high potassium, lactovegetarian diet that emphasized fresh vegetables and fruit juices and vitamin supplements. Frequent enemas, including coffee enemas, and injections of a liver extract also were part of the regimen. Raw veal liver juice was discontinued in 1987, owing to contamination with Campylobacter fetus.

In 1977, the Gerson Institute was founded and based in Bonita, CA. The Institute oversees a clinic in Tijuana, Mexico [Centro Hospitalario Internacional del Pacifico, SA (CHIPS)] where the Gerson therapy is offered along with other adjunctive measures.

A retrospective study of 235 melanoma patients treated from 1975 to 1990 at the CHIPS clinic has been published. This report evaluated the 5-year survival rates of the 153 patients for which adequate staging information was available and compared them to historical controls. The authors reported 100% survival for stage I and stage II disease and a 71% survival for stage III disease, comparing favorably with the historical control. Other researchers have claimed that the Gerson regimen is useful to palliate pain and diminish the side effects of conventional irradiation and chemotherapy.

**Macrobiotic Diet**

Apparently, the macrobiotic philosophy was developed by George Ohsawa (1893 to 1966) (also known as Yukikazu Sakurazawa), who first introduced his concepts to the United States in 1959. Subsequently, macrobiotic theories and practices were developed and promoted by Michio Kushi who, in 1978, founded the Kushi Institute. This establishment offers courses in physical and psychological health and in ecology, spiritual development, and world peace.

Originally, Ohsawa described 10 stages of diet designated 3 to +7. The +7 diet consisted of 100% cereals and was prescribed for short periods to patients with various illnesses, including cancer. Reports of clinically significant vitamin and mineral deficiency states were reported with some versions of this diet. However, the standard macrobiotic diet currently recommended by Kushi is a better-balanced, high–complex carbohydrate, low-fat vegetarian diet that may include small amounts of seafood. Individuals consuming a macrobiotic diet have been found to have urinary levels of diphenolic phytoestrogens much higher than those of control groups of lacto-ovo vegetarians or omnivores.

Two unreported retrospective studies of survival of patients with prostate and prostate cancer and a series of case reports were reviewed by the Unconventional Cancer Therapies Panel of the Office of Technology Assessment. Despite this, no consensus of compelling evidence for activity was obtained.

**Kelley-Gonzalez Regimen**

In the 1950s and 1960s, Dr. William D. Kelley, a dentist from the Midwest, developed a theory of health and illness that classified people as metabolic types, with physiologies in which the activity either of the parasympathetic or of the sympathetic nervous system was dominant or the two were balanced. He then prescribed diets ranging from purely vegetarian (for sympathetic types) to predominantly meat-containing (for parasympathetic types) to compensate for years of "wrong" diets that had resulted in illness. Kelley also believed that pancreatic proteolytic enzymes were secreted into the blood stream and acted as the body’s first line of defense against malignancy.

The Kelley program for cancer treatment consists of six basic components: (1) the appropriate diet, (2) vitamin and mineral supplementation, (3) concentrates of raw beef organs and glands in pill form, (4) digestive enzymes including pepsin, hydrochloric acid, bile, and various pancreatic enzymes, (5) frequent doses of proteolytic pancreatic enzymes between meals, and (6) a “detoxification” regimen that included frequent coffee enemas.

Currently, variations of the Kelley regimen still are practiced by a few individuals in the United States. Dr. Nicholas Gonzalez has used this approach for several years and recently reported the results of a small prospective study in advanced pancreatic cancer patients. Over the period of the study, 36 patients with pancreatic cancer were seen. Eleven of these patients were considered assessable, and the other 25 were deemed unassessable because they either did not start the regimen or stopped taking the therapy in less than 8 weeks (n = 13) or had one of six other exclusion criteria (n = 12). The patients had stage I to stage IV pancreatic cancer. All patients’ tumors either were unresected or resected incompletely. The median survival was 17.0 months in the treatment group, compared to a literature control showing a 4- to 6-month median survival. A trial of this regimen versus gemcitabine in patients with advanced pancreatic cancer is under way at Columbia University.

**BIOLOGICALLY BASED THERAPIES**

**Cartilage (Shark and Bovine)**

Cartilage products of various sources long have been suspected of having anticancer activities and have been the subject of much lay literature. Frequently, shark cartilage is used by U.S. and Canadian cancer patients. Estimates for 1992 maintained that more than 50,000 Americans used shark cartilage products.

Some shark cartilage extracts and various isolated molecular species have in vitro antiangiogenesis and matrix metalloprotease inhibitor activity. Evidence of oral bioavailability of the active components on a water-soluble shark cartilage extract has been demonstrated in a rat model.

Reports of positive results from a Cuban trial of shark cartilage were aired on the television news magazine “60 Minutes” in 1994 but have not been followed by a published scientific article. Miller et al. reported a phase I and II trial of a powdered shark cartilage product in which 60 patients with advanced, previously treated cancers were treated with 1 g/kg/d orally. The dose was increased to 1.3 g/kg if no response was seen after 6 weeks. No patient experienced a complete or partial remission, but 10 of 50 assessable patients had stable disease for at least 12 weeks. Another single-arm trial has been reported, but the results were confounded by the presence of concurrent conventional therapy. Phase III trials of two oral shark cartilage products in advanced cancer patients are planned by the M.D. Anderson Community Clinical Oncology Program and the North Central Cancer Treatment Group.

Bovine cartilage has been administered either subcutaneously only or both orally and subcutaneously. Puccio et al. reported 3 partial remissions in 22 metastatic renal carcinoma patients. Another study by Romano et al. obtained one complete remission in nine patients with various types of tumors. The complete remission is reported to have been the resolution of lung metastases and a flank mass in a patient with metastatic renal cell carcinoma. This response had been continuous for 9 months when the trial was reported. The largest experience of human cancers treated with bovine cartilage was reported by Prudden. He reported a 90% response rate (61% complete response) in 31 cases of a variety of malignancies.

**Herbal Mixtures**

**ESSIAC.** The Essiac herbal mixture has been used widely in Canada since the 1920s. The original recipe for this mixture is said to have been developed by an Ojibwa healer and was given to Rene Caisse (Essiac is Caisse spelled backward), a nurse working in Ontario, Canada, by a woman who believed herself to have been cured of breast cancer through its use.

The original recipe contained four main herbs: burdock root (Arctium lappa) (also used in the Hoxsey treatment, discussed next in this chapter); Indian or turkey rhubarb (Rheum palmatum); sheep or sheephead sorrel (Rumex acetosella); and the inner bark of slippery elm (Ulmus fulva or Ulmus rubra). Later, watercress (Nasturtium officinale), blessed thistle (Cnicus benedictus L.), red clover (Trifolium pratense), and kelp were added. This mixture is manufactured by Essiac Products (New Brunswick, Canada) and is available directly from the manufacturer or, for Canadian patients, through the Emergency Drug Release Program of Health Canada.

The individual herbal components of Essiac have been tested, and reports show varying activities despite the fact that certain purified chemical moieties from each of the herbs have reproducible antitumor activities. To date, no published clinical trials have evaluated Essiac in cancer patients, but this product continues to be one
of the CAM anticancer therapies used most commonly by American and Canadian cancer patients. 

**HOXSEY TREATMENT.** The Hoxsey therapy is composed of a variety of herbal preparations made famous by Harry Hoxsey beginning in the 1920s. After attaining a wide-ranging popularity in the United States, a series of violations of U.S. Food and Drug Administration regulations resulted in the closing of the U.S. clinics and the export of the treatment to a CHIPSA clinic in Tijuana, Mexico (see Gerson Therapy, earlier in this chapter).

The internal Hoxsey treatment is composed of licorice (Glycyrrhiza glabra), red clover (Trifolium pratense), burdock (Arctium lappa), stillingia root (Stillingia sylvatica), berberis root (Berberis vulgaris), poke root (Phytolacca americana), cascara (Rhamnus purshiana), aromatic USP 14 (artificial flavor), prickly ash bark (Zanthoxyrum americanum), and buddhism bark (Rhamnus frangula). The clinical treatment includes other dietary and hygiene manipulations. As with Essiac, some of the purified components of individual herbs within the mixture have reproducible anticancer activities, but the whole form of the herbs have yielded variable results. Neither clinical trials nor in vitro or animal model testing of the entire mixture has been reported. Series of case reports were submitted to the NCI in 1945 and 1950 but were judged to contain no evidence of anticancer activity.

**MISTLETOE.** Mistletoe (Viscum album L.) is used extensively in Europe and is one of the CAM modalities used most frequently in Germany. A semiparasitic member of the Loranthaceae family, mistletoe draws water and minerals from host trees but produces carbohydrates by its own photosynthesis. Loranthaceae species were proposed in 1916 to be useful in cancer by Rudolf Steiner, an Austrian who founded a system of health promotion called anthroposophy, attempting to link science and spirituality.

The active moieties in mistletoe are thought to be lectins (glycoproteins) and viscositoxins (proteins). The lectin component has been demonstrated to have immunostimulant activity in vitro. It induces macrophage production of tumor necrosis factor and increases interleukin-1 and interleukin-6 production. The viscositoxins have been shown to have direct cytotoxic activity against certain cancer cell lines.

The currently available mistletoe products are Iscador, Helioxor, Abnoba Viscum, Isorel, and Eurixor. They are whole or purified extracts, fermented or nonfermented. Iscador also has added metals (silver, copper, and mercury).

A large body of clinical literature (case reports, retrospective analysis, and a variety of clinical trials) deals with the commercially available mistletoe products. A few randomized, controlled cancer clinical trials of mistletoe have been reported from Europe. In the largest study, 677 women who had received radical or simple mastectomy for breast cancer were randomly assigned to Hoxier (parenterally) with or without radiation therapy; to chemotherapy with cyclophosphamide, methotrexate, and fluorouracil with or without radiation therapy; or to no treatment. A statistically significant survival advantage was identified for the Hoxier arm as compared to no treatment, but no significant difference was found between the Hoxier arm and the chemotherapy arm. Although side effects reportedly were not documented systematically, the primary adverse reactions associated with Hoxier were said to be primarily inflammatory reactions at the injection site and occasional fevers.

In a study of patients with metastatic colorectal cancer, patients were randomly assigned to Hoxier and fluorouracil and folinic acid (n = 20) versus fluorouracil and folinic acid (n = 20). Ten complete remissions were reported in the Hoxier group, and six were reported in the control group. Median survival time was 14 months for controls and 26 months for the Hoxier arm (P = .06). The difference in side effects between the two arms was small. Further randomized, multicenter clinical trials are under way.

Other studies have investigated the immunomodulatory activity of mistletoe. A study of adjuvant therapy in glioma randomly assigned 35 patients either to receive subcutaneous injections of a standardized extract of mistletoe lectins for 3 months or to receive no therapy. Increased lymphocyte numbers and activity were noted in the mistletoe lectin arm as was an improved quality of life determined by a standardized questionnaire.

**SPES AND PC-SPES.** SPES and PC-SPES are herbal mixtures developed by Dr. Sophie Chen, a researcher at New York Medical College, and distributed by BotanicLab in Brea, CA. Reportedly, more than 2000 patients have used SPES-PC for the treatment of prostate cancer.


Hsieh et al. demonstrated the induction of apoptosis and down-regulation of bcl-6 in mutu i cells treated with ethanolic extracts of PC-SPES. Tumors induced in rats inoculated with a metastasizing prostate cancer cell line underwent apoptosis when the rats were fed rodent chow containing PC-SPES at levels of 0.05% and 0.045%. Neither obvious toxicity nor a significant difference in food intake was noted after 8 weeks. Dose-dependent inhibitory effects of dietary PC-SPES were observed on both effects of tumour incidence and rate of tumor growth.

A phase II study of PC-SPES has been performed at University of California, Los Angeles. The results of the treatment of 34 patients (20 hormone-naive, 14 androgen-independent) were reported. Prostatic-specific antigen (PSA) declined by more than 50% in nine of 12 hormone-naive patients and in 9 of 12 androgen-independent patients. Testosterone levels fell to anorchid levels by 1 month in 7 of 21 (33%). The toxicities noted were suggestive of estrogenic activity. Tender gynecomastia was seen in 71% of patients, and one patient had a thromboembolic event. Sixty percent of patients with previously normal testosterone levels lost libido and potency when present pretreatment.

Sixteen patients with advanced prostate cancer taking PC-SPES as a dietary supplement (2.7 g daily) were followed in another study. At 3 months, 10 of 16 patients showed a decrease in PSA levels in excess of 50%. In a report of prostate cancer patients treated with PC-SPES, decreased serum testosterone levels were noted in six of six men, and drops in the PSA level were noted in eight of eight patients.

**HYDRAZINE (OR HYDRAZINIUM) SULFATE**

Hydrazine is a chemical with a variety of uses and is an important intermediate in the synthesis of some pharmaceutical drugs, such as isoniazid, hydralazine, and procainamide. Gold reported that the growth of Walker 256 tumor in mice was inhibited by hydrazine sulfate. Another study found that Morris hepatoma growth in rats was inhibited when the animals were fed hydrazinium sulfate, 15 mg/kg orally twice daily for 5 days. However, this response was associated with reduction of body weight, anorexia, and decreased nitrogen metabolism and retention. An identical group that was fed parenterally sustained body weight but suffered stimulated tumor growth and symptoms of liver toxicity.

Hydrazine sulfate is also an inhibitor of phosphoenolpyruvate carboxykinase, a key enzyme in mammalian gluconeogenesis. This metabolic pathway has been recognized to play a role in cancer cachexia. Gold postulated that hydrazine sulfate interrupts host energy wasting by inhibiting the conversion of lactic acid to glucose in the liver. This process is also thought to decrease the glucose available to the tumor and therefore can lead to a slowing of tumor growth.

A report of a large patient experience (740 patients) from Russia calculated that 47% of the patients had symptomatic improvement. They also reported some patients with objective responses (4% of lung cancer patients) or stable disease (22% of lung cancer patients).

Gold studied 84 patients with various cancers and reported that 70% had symptomatic improvement (increased appetite, weight gain, decreased pain) and 17% had prolonged tumor stabilization or some degree of tumor regression. Three small single-arm trials by other investigators failed to substantiate these findings.

There have been four randomized, controlled clinical trials of hydrazine sulfate in cancer patients that have yielded mixed results. The first study by Chelboski et al. had the most promising findings but did not show a significant difference in survival between the two arms until a subgroup analysis was done.

The NCI sponsored three follow-up clinical trials. Two trials studied lung cancer patients simultaneously treated with platinum-based chemotherapy regimens with hydrazine sulfate or placebo, and a third study looked at hydrazine sulfate alone versus placebo alone in patients with advanced colorectal cancer. None of these follow-up studies showed a statistically significant improvement in survival in the hydrazine sulfate arm, and the Cancer and Leukemia Group B study showed...
a lesser quality of life in the hydrazine sulfate arm. All together, these three follow-up studies contained more than 600 patients.

There is still a significant quality of life in the hydrazine sulfate arm. All together, these three follow-up studies contained more than 600 patients.

LAETRILE
Laetrile is a mixture of amygdalin, a plant glycoside, and other compounds found in the pits of some fruits, raw nuts, and other plants. 

Although frequently called vitamin B17, in the lay literature, amygdalin is not recognized as a vitamin by the Committee on Nomenclature of the American Institute of Nutrition. Laetrile has been given orally and intravenously, with different pharmacokinetics and toxicity profiles.

The NCI supported a trial at the Mayo Clinic using amygdalin and a “metabolic therapy” containing vitamins A, C, E, and B complex and pancreatic enzymes. One hundred and seventy-nine patients with advanced cancer who had either failed attempts at prior standard therapy or for which no standard therapy with a curative potential was available were treated. Of the 175 assessable patients, only one met the criteria for a partial remission. There were no other responders, and all patients had progression by 7 months. The median survival from the start of therapy was 4.8 months.

Despite the fact that no new clinical trials have been reported, use of laetrile continues. No further research appears to be under way.

SUPPORTIVE CARE (COMPLEMENTARY MEDICINE)

ACUPUNCTURE
Dundee et al. found that acupuncture needling with 5 minutes of electrical stimulation at the P6 point (volar surface of the wrist) was effective in preventing chemotherapy-induced nausea and vomiting. Ten patients were studied in a randomized, crossover portion of the study in which patients received either P6 electroacupuncture or stimulation at a “dummy” point. The antiemetic effect lasted approximately 8 hours. After a systematic review of the literature, the NIH Consensus Development Panel on Acupuncture found sufficient evidence existed for efficacy in managing chemotherapy-induced nausea.

Preliminary evidence suggests that acupuncture may also be effective in the treatment of vasomotor symptoms (i.e., hot flushes) in men receiving gonadotropin analogues for prostate cancer therapy. A pilot study used electroacupuncture to a fixed set of acupuncture points for 30 minutes, twice a week for 2 weeks followed by once a week for 10 weeks. The mean number of flushes per day for the six men who continued therapy for more than 2 weeks decreased from 7.9 during the week before therapy to 2.5 after 10 weeks.

PAIN MANAGEMENT
A variety of CAM modalities have been used to aid in pain management. Reiki, an “energy healing system” based on Tibetan scriptures but developed in Japan, has been tested in at least one pilot study with reportedly positive effects.

Use of relaxation, imagery, and cognitive-behavioral training for the management of oral mucositis pain has been studied in a randomized, controlled trial. Ninety-four patients at the Fred Hutchinson Cancer Research Center undergoing their first bone marrow transplant completed the study. Oral mucositis pain levels were evaluated in four groups of patients. The two groups receiving relaxation and imagery reported significantly lower pain levels as assessed by a visual analogue scale.

A randomized controlled trial of 96 women with newly diagnosed large or locally advanced breast cancer compared standard care versus standard plus relaxation training and imagery. A significantly improved quality of life was seen in the group receiving relaxation and imaging. Other studies have used questionnaires designed to assess general patient comfort. One such randomized study by Kolcaba and Fox demonstrated an improved level of comfort among the patients undergoing a guided imagery intervention.

SELF-HELP AND SUPPORT GROUPS AND HYPNOSIS
There appears to have been an increase in the number of cancer patients attending support groups. Although patients are likely attending these groups mostly for psychosocial support, there is some evidence that these interventions may also be related to an increased survival for some groups.

Spiegel et al. were the first to report evidence for a beneficial effect on survival of a support group intervention in a group of cancer patients. Eighty-six patients with metastatic breast cancer were randomly assigned to intervention (n = 50) or control group (n = 36). The intervention consisted of 1 year of weekly 90-minute support groups led by a therapist who had breast cancer in remission. The groups were structured to encourage discussion of how to cope with cancer and for patients to express their feelings about the illness and its effect on their lives. Also, a self-hypnosis strategy was taught for pain control. The mean survival in control group was 18.9 months versus 36.6 months in the treatment group. Interestingly, a survival advantage was not seen until approximately 8 months after the completion of the group intervention (i.e., at 20 months from entry on study).

Spiegel and Spiro have written a manual explaining the details of their psychosocial intervention. Follow-up studies by Goodwin et al. in Toronto, Canada, and Spiegel et al. at the University of Rochester are under way.

Another study of a support group intervention with cognitive behavioral therapy in patients with metastatic breast cancer found no survival advantage for the treated group over a randomized control group. Also a retrospective cohort study of a group of breast cancer patients with localized, regional, or distant disease found no advantage for the combination intervention of patient and family support groups with directed relaxation, imagery, and meditation.

Fawzy et al. reported the survival of surgically resected stage I melanoma patients randomly assigned to either six weekly 1.5-hour sessions of group support and education or usual care. A significantly improved survival of the two groups, 6 years after the surgical excision of the melanoma, showed 10 of 34 dead in the control group and 3 of 34 in the treatment group. The difference was statistically significant.

COMPLEMENTARY AND ALTERNATIVE MEDICINE CANCER RESEARCH

Many medical and surgical oncologists as well as other health care practitioners and clinical and basic science researchers have recognized the need for good quality research into CAM modalities. However, concerns have been raised about the use of different standards of evidence.

Research programs are being established to focus on alternative medicine in cancer. The Osher Center for Integrative Medicine at the University of California at San Francisco has active protocols for patients with breast cancer and prostate cancer. Memorial Sloan-Kettering Cancer Center (MSKCC) has recently added an Integrative Medicine Service, and the University of Texas-Houston has had a center supported by the National Center for Complementary and Alternative Medicine. The National Center for Complementary and Alternative Medicine (NCCAM) and the NCI plan to support other centers for basic and clinical research in CAM and cancer.

NATIONAL CANCER INSTITUTE OFFICE OF CANCER COMPLEMENTARY AND ALTERNATIVE MEDICINE AND THE BEST CASE SERIES PROGRAM

In 1998, the NCI established the Office of Cancer Complementary and Alternative Medicine to focus and extend the efforts of the Institute in the arena of CAM. This office seeks to promote and support research in the various disciplines and modalities associated with the field of CAM as they relate to the diagnosis, prevention, and treatment of cancer.

Since 1991, the NCI has had a process for the evaluation of data from alternative medicine practitioners of groups of patients with cancer treated with alternative medical approaches. This process, the Best Case Series Program, provides an independent review of the medical records and primary source materials (medical
imaging and pathology) and an overall assessment of the evidence for a therapeutic effect.

In 1998, the NCCAM of the National Institutes of Health in collaboration with the NCI established a Cancer Advisory Panel for Complementary and Alternative Medicine that reviews evidence about CAM modalities and advises the director of the NCCAM about promising CAM approaches that warrant further research. The NCI works closely with this new body, and Best Case Series are now presented to this panel for their review and assessment.

EXAMPLES OF COMPLEMENTARY AND ALTERNATIVE MEDICINE TOPICS REQUIRING MORE RESEARCH

Controversy exists about the consequences of women with or at high risk for breast cancer using soy products or other plants containing phytoestrogens. Herbs such as dong quai (Angelica sinensis), black cohosh and ginseng as well as foods such as soy contain phytoestrogens. These estrogens bind both physiologic forms of the estrogen receptor, and some induce signs and symptoms of exogenous estrogen administration. Some of these herbs are used by cancer patients to alleviate menopausal symptoms. Further research is needed to assess the risk-benefit ratio of these various products. Similarly, with the recent growth of interest and use of the androgen dihydroepiandrosterone, which is available as a dietary supplement, research is needed about its potential effect on men with or at high risk for prostate cancer.

Another controversy rages over the potential risks and benefits of the use of antioxidants during chemotherapy or radiation therapy. With preclinical evidence on both sides of the issue, definitive clinical trials are needed. The toxicity profiles of herbs and the mechanisms of herb-drug interactions are other areas in which further research would be immediately rewarding.

PRACTICAL ISSUES IN THE INTERFACE OF ONCOLOGY AND COMPLEMENTARY AND ALTERNATIVE MEDICINE

PHYSICIAN-PATIENT COMMUNICATION

Cases have been reported of patients with potentially very curable tumors who delayed or interrupted conventional treatment to pursue unsuccessful alternative approaches and subsequently died of advanced cancer. Therefore, the physician's relationship with his or her patient and communication with patients about CAM are of primary importance. Eisenberg has described an approach for the physician to take in inquiring about and exploring a patient's use of CAM.

INTERACTIONS OF ALTERNATIVE MEDICINES WITH CONVENTIONAL MEDICINES

Oncologists often are not aware of their patients' use of CAM. One study found that 29% of cancer patients reported taking an herbal supplement while they were receiving chemotherapy. The potential for interactions of alternative medicines and conventional medicines is real. One group has reported that a mixture of nutraceutical remedies used by a 7-year-old child reduced the bioavailability of oral mercaptopurine used as maintenance therapy for acute lymphoblastic leukemia. Examples of other interactions are listed in Table 61-3. There are several herbs that theoretically could interact with anticoagulants or might be contraindicated in patients with thrombocytopenia. Some of these are listed in Table 61-4.

TABLE 61-3. Reported Toxicities or Drug Interactions of Herbs Used by Cancer Patients

<table>
<thead>
<tr>
<th>Herbs</th>
<th>Reported Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ginkgo biloba</td>
<td>Hypotensive actions, headache, nausea, abdominal pain, and signs of cholinergic stimulation</td>
</tr>
<tr>
<td>St. John's wort</td>
<td>Serotonin receptor antagonism, increased bleeding time, and depression</td>
</tr>
<tr>
<td>Ginseng</td>
<td>Increased bleeding time, decreased platelet aggregation</td>
</tr>
<tr>
<td>Echinacea</td>
<td>Increased bleeding time, increased platelet aggregation</td>
</tr>
</tbody>
</table>

TABLE 61-4. Potential and Documented Dietary Supplement–Drug Interactions

<table>
<thead>
<tr>
<th>Dietary Supplement</th>
<th>Drug Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin A</td>
<td>Increased risk of liver cancer</td>
</tr>
<tr>
<td>Black pepper</td>
<td>Increased risk of adverse effects of warfarin and other anticoagulants</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>Increased risk of bleeding</td>
</tr>
</tbody>
</table>

SOURCES OF INFORMATION FOR PATIENTS, PHYSICIANS, AND RESEARCHERS

A Canadian study of cancer patients attending an outpatient pain and symptom clinic found that the top two sources of information for CAM modalities that were used were health store staff and self-help literature followed by family members, friends, and herbalists. Even in a setting with more cultural acceptance of specific CAM therapies (i.e., Taiwan), the majority of the patients make their decisions about the use of alternative approaches based on information obtained by word of mouth or through advertisement rather than through consulting with a licensed practitioner in alternative medicine or a conventional health care practitioner.

The Office of Technology Assessment Report of the Unconventional Cancer Treatments Panel is a valuable source of background information about many CAM modalities still in use. This report may be downloaded from the Office of Technology Assessment Web site at http://www.ota.nap.edu/pdf/1990idx.html.

The American Cancer Society has summaries of various CAM modalities on its Web site at http://www.cancer.org. The NCCAM has a Web site at http://nccam.nih.gov that has links to useful information about CAM research.

The Office of Cancer Complementary and Alternative Research of the NCI has a Web site (http://www.cancer.gov/cam) with information about CAM cancer research. The Task Force on Alternative Therapeutics of the Canadian Breast Cancer Research Initiative has produced several useful reviews of CAM modalities.
INTRODUCTION

Gene therapy can be defined as the introduction of new genetic material into cells for therapeutic intent. This encompasses a broad array of experimental cancer therapies, including immunization with cytokine or tumor antigen genes as well as the introduction of toxic genes directly into tumors (Table 62.1-1). Since the first gene transfer trial in 1989, a large number of cancer gene therapy clinical trials have been initiated (Table 62.1-2). Results of the first clinical trials have been published, and they highlight not only the potential promise of gene therapy but also the current limitations and areas where further efforts are needed. For example, because cancer is the result of mutation or loss of genetic material within cells, perhaps the most obvious approach to cancer gene therapy is the introduction of genes to correct these aberrations. Restoration of the normal p53 gene in human tumor cells deficient of this gene because of gene loss or mutation causes decreased tumorigenicity in nude mice. However, current clinical efforts to apply this concept have been limited by the absence of technology that would allow efficient in vivo gene transfer into tumors. As vector technology improves, these approaches may become more feasible.

### TABLE 62.1-1. Cancer Gene Therapy Approaches

<table>
<thead>
<tr>
<th>Type of Therapy</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor Suppression Genes</td>
<td>Genes that inhibit tumor growth by killing tumor cells</td>
</tr>
<tr>
<td>Antigen and Ribozymes</td>
<td>Enzymes that cleave RNA to inhibit tumor cell growth</td>
</tr>
<tr>
<td>Suicide Genes</td>
<td>Genes that cause programmed cell death in tumor cells</td>
</tr>
<tr>
<td>Noncytokine Genes</td>
<td>Genes that cause tumor cell death by a mechanism other than the production of a cytokine</td>
</tr>
<tr>
<td>Genes that inhibit Proangiogenic Cytokines</td>
<td>Genes that inhibit the production of angiogenic cytokines</td>
</tr>
<tr>
<td>Genes with Antiangiogenic Properties</td>
<td>Genes that inhibit the production of angiogenic cytokines</td>
</tr>
</tbody>
</table>

### TABLE 62.1-2. Cancer Gene Therapy Clinical Trials Approved by the National Institutes of Health Recombinant Advisory Committee

Many gene therapy protocols have used ex vivo gene transfer. This technique involves the removal of cells from an individual followed by gene transfer and growth in the laboratory before reinfusion into the patient.

Two requirements exist for successful genetic manipulation of a eukaryotic cell. First, a method must exist to provide successful gene insertion into the correct cell type with adequate efficiency for a particular therapeutic purpose. Some therapeutic approaches may require permanent gene transfer, whereas for others, transient activity may suffice. Second, the inserted gene must be adequately expressed by that cell. A high level of expression is required for some purposes, whereas a low level of gene expression is sufficient for others. Constitutive or regulated expression may be necessary, depending on the specific application.

### METHODS OF GENE TRANSFER

Numerous techniques are available for gene transfer into mammalian cells (Table 62.1-3). The choice of a particular gene transfer technique depends on the biologic requirements of the specific therapeutic strategy. For example, to protect hematopoietic stem cells from the toxic effects of systemic chemotherapy, often given for several cycles, the multidrug resistance (MDR) gene must be stably integrated into stem cells, using gene transfer techniques that include retroviral vectors. However,
to immunize patients against tumors, it is possible that only transient expression of antigen genes by viral vectors such as adenovirus will be sufficient.

TABLE 62.1-3. A Comparison of Gene Transfer Methods

Many techniques of gene transfer make use of viruses to introduce genetic material, because viruses in most cases can deliver genes to cells with higher efficiencies compared to nonviral methods.

RETROVIRAL VECTORS

Retroviruses are RNA viruses that are capable of stably integrating DNA within the host cell genome. The replication cycle of a retrovirus begins with viral attachment to a cell by a specific receptor (Fig. 62.1-1). The virus enters the cell, and the viral RNA is reverse transcribed to DNA by the virally encoded reverse transcriptase. The viral DNA is then transported to the nucleus, where it integrates into the host cell genome. The integrated viral DNA, termed the provirus, is transcribed, and then both spliced and unspliced transcripts are translated to form the viral proteins. Some of the unspliced transcripts are packaged, via a packaging signal sequence (y), into viral capsids. The mature viruses then bud from the host cell membrane.

FIGURE 62.1-1. Retrovirus replication cycle. The retrovirus uses envelope glycoproteins to bind to specific receptors on the cell surface. Viral RNA then enters the cell and is reverse transcribed to DNA. The viral DNA is transported to the nucleus, where it integrates in the host chromosome and directs transcription of the provirus using the viral long terminal repeat. Viral transcripts are translated by the infected cell to form viral structural proteins. Some of the unspliced viral transcripts are packaged into the newly formed viral particles and are released by budding. (From ref. 243, with permission.)

Retroviral vectors for gene transfer have been constructed by substituting the gene of interest in place of the viral protein coding regions, thus making these vectors replication incompetent (Fig. 62.1-2). These vectors are packaged into retroviral particles using helper, or packaging, cell lines that contain the structural viral protein genes in trans (i.e., from another site in the packaging cell genome). Because the retroviral vector contains the y sequences, it is packaged into the mature virus and is capable of infecting target cells, but it is incapable of replication because of the absence of the retroviral protein coding regions. The viral structural genes, provided in trans, are not packaged because of the absence of the y sequences (Fig. 62.1-3).

FIGURE 62.1-2. Schematic diagram of the LNL6 retroviral vector. The protein-coding regions of the virus have been removed and replaced with the gene for neomycin resistance (NeoR). The viral packaging site (y) has been left intact. The vector is a derivative of the Moloney murine leukemia virus. LTR, long terminal repeats.

FIGURE 62.1-3. Production of retroviral vectors with packaging cells. The gene of interest is cloned into a retroviral vector (see Fig. 62.1-2), and then transfected into a helper cell line, which provides the retroviral structural genes in trans. The retroviral structural genes cannot be packaged because of the absence of a packaging sequence (y), whereas the retroviral vector can be packaged, thereby producing a replication-incompetent retrovirus. LTR, long terminal repeats. (From ref. 246, with permission.)
Retroviral vectors are one of the most common methods of gene transfer in currently approved gene therapy protocols. Their advantages include the ability to stably integrate into the host genome and the absence of viral protein expression. Current disadvantages of retroviral vectors include their inability to infect nondividing cells, resulting in low levels of gene transfer efficiency, although new methods have been described to concentrate retroviral supernatants using ultracentrifugation. 1

Retroviral packaging can use a variety of envelope genes from other viruses. Because the envelope protein is the primary determinant of the host range of the retrovirus, the particular envelope, or pseudotype, used can have a profound impact on transduction efficiencies. 1 Table 62.1-4 lists a number of envelope genes along with their relative host ranges. The development of packaging cell lines that use alternative envelope genes has resulted in significant advances in the ability to transduce primary lymphocytes. Retroviral vectors produced from the PG13 packaging cell line, 5 which uses the gibbon ape leukemia virus envelope (GALV), are capable of transducing B cells 1 and T cells 1 with significantly higher efficiencies compared with those derived from amphotropic packaging cell lines. In one study, transduction of primary T cells was 4- to 18-fold higher with PG13-packaged vectors compared with amphotropic PA317-packaged vectors. 4 This was found to correlate with an 8- to 19-fold higher expression of the GALV receptor (Pit-1) compared with the amphotropic receptor (Pit-2) in primary T cells, although other factors besides receptor expression have been found to play a role in transduction efficiency. 6 By combining the use of PG13-packaged vectors with a 1-hour centrifugation at 10000 g, Bunnen et al. 7 were able to obtain transduction efficiencies of primary T cells in the 40% range.

### Table 62.1-4. Envelopes Used for Retroviral Vectors

<table>
<thead>
<tr>
<th>Envelope Source</th>
<th>Host Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Envelope(Env)</td>
<td>Host(mice)</td>
</tr>
<tr>
<td>Murine amphotropic</td>
<td>Human, mouse, rat, etc.</td>
</tr>
<tr>
<td>Gibbon ape leukemia virus (GALV)</td>
<td>Human, mouse, rat, etc.</td>
</tr>
<tr>
<td>Tonsil tumor virus (Epstein-Barr virus)</td>
<td>Human, mouse, rat, etc.</td>
</tr>
</tbody>
</table>

In addition, future retroviral vectors may contain improved promoters for higher and regulatable levels of gene expression.

### LENTIVIRAL VECTORS

Stable gene transfer using vectors based on murine retroviruses is only possible in dividing cells. Human immunodeficiency virus (HIV) can infect and integrate into the genome of nonproliferating cells because of proteins that mediate the active transport of the lentiviral preintegration complex through the nucleopore. These proteins—integrate, matrix, and vpr—interact with the nuclear import machinery to transport the HIV preintegration complex from the cytoplasm to the nucleus.

Naldini et al. 12 designed lentiviral vectors based on HIV that are capable of stably infecting nondividing cells. A packaging construct was used to express HIV proteins in trans. To avoid production of wild-type HIV, the construct is defective for the production of viral envelope and the accessory protein Vpu, and has deletions in the 5' signal sequence. To make defective lentiviral vectors, packaging cells are transiently transfected with the packaging construct, along with a separate plasmid encoding a heterologous envelope protein, such as VSV-G protein. A third plasmid, the transfer vector, encodes the gene of interest, along with the packaging signal and other cis-acting sequences of HIV required for packaging, reverse transcription, and integration. 13 Lentiviral vectors are currently being refined to enhance safety, transduction efficiency, and convenience. 14 HIV-based lentiviral vectors have been shown to be efficient vehicles of gene transfer into postmitotic cells, including brain, liver, muscle, CD34+ hematopoietic cells, and retina. 15,16,17,18,19 Current efforts are focused on the use of lentiviral vectors in the transduction of hematopoietic stem cells in an attempt to enhance long-term engraftment of gene-modified cells. 20,21

### ADENOVIRAL VECTORS

The adenoviral genome is divided into four early gene regions, E1 to E4, which are expressed before viral DNA replication, and late genes, which primarily encode viral structural proteins. On infection, the E1 gene products are expressed first and are responsible for transcriptionally activating other genes that begin a cascade of events ultimately leading to viral replication. Removing the E1 region therefore results in an adenoviral particle that is replication deficient. These replication-deficient adenoviruses can be used for gene transfer by cloning the gene of interest into the deleted E1 region. 22 The recombinant adenovirus, however, must be produced using cell lines that provide the E1 products in trans, such as in 293 cells, which constitutively express Ad5 E1 genes.

Adenoviral gene transfer can be performed in many cells, both dividing and nondividing, with high efficiency, and it can result in high levels of gene expression. In addition, adenoviral vectors can be produced at high titers and are capable of infecting some tissues directly in vivo, such as pulmonary epithelial cells. 23 However, because adenoviral DNA exists episomally, with little or no incorporation into the host cell genome, expression of the transgene is transient, and it is lost as the infected cell divides. For some therapeutic strategies, this high-level transient expression may be adequate, whereas other treatment approaches may require more prolonged gene expression.

One potential problem with in vivo administration of current adenoviral vectors is their ability to trigger a host immune response. Both neutrophilic and lymphocytic inflammatory infiltrates can be seen histologically at sites of injection of adenoviral vectors. 24 In addition, antibody responses to adenoviral vectors have been demonstrated in a variety of animal models, and gene expression with repeated dosing is inversely proportional to the antibody response in some systems. 25 Nude mice expressing adenoviral vectors in the liver exhibit transgene expression for 60 days, compared with 21 days in normal mice, implying that the absence of T cells can lead to longer gene expression. Cytotoxic T lymphocyte (CTL) responses compared with adenoviral proteins also have been reported. 26 It has been postulated that late gene products, such as adenoviral hexon and fiber proteins, may be the cause of the T-cell response.

The effect of neutralizing antibodies on current clinical efforts with recombinant adenovirus is not clear. In a clinical trial with recombinant adenoviruses containing tumor antigen genes, high levels of neutralizing antibody were found in the pretreatment sera of patients, which may have impaired the ability of these viruses to immunize patients. 27 In another study, however, intratumoral administration of an adenoviral vector expressing b-galactosidase resulted in b-galactosidase-specific T helper, CTL, and antibody responses in three of four patients. 28 New generations of adenoviral vectors are attempting to limit the antiviral immune response by eliminating much of the adenoviral genome. Besides reducing immunogenicity, this also allows an increased gene carrying capacity by the adenoviral vector. Packaging of these “gutless” adenoviral vectors requires helper virus or the expression of additional adenoviral genes by the helper cell lines. In addition, adenoviral vectors are being developed that may allow targeted, regulatable gene expression.

Burgh and colleagues 29 have reported the construction of a recombinant adenovirus containing a tissue-specific, regulatable target gene. The recombinant adenoviral vector lacked all viral coding sequences to avoid immunogenicity, and it contained a transgene that could be induced in vivo with the antiprogestin mifepristone. Tissue specificity was conferred by coupling the regulator cassette to the liver-specific transthyretin promoter region. 30 Inducible expression of the transgene was
demonstrated in vivo, but the tissue specificity was not confirmed.

In an effort to confer targeting ability to adenoviral vectors, surface modification of the Ad fiber coat protein or use of adenoviral/antibody complexes has been attempted. Much work in vector development remains to be done for adenoviral vectors to be fully utilized in effective gene therapy strategies.

**ADENOASSOCIATED VIRUS VECTORS**

Adenoassociated virus (AAV), a member of the parvovirus family, can only replicate in the presence of a helper virus, such as adenovirus. The virus is nonenveloped and consists of a single-stranded linear DNA of 4.7 kilobases, which contains two major open reading frames. The left-hand open reading frame encodes the Rep protein, which is responsible for AAV replication. The right-hand open reading frame encodes the Cap protein, which form the structural proteins of the viral capsid. In the absence of a helper virus, such as adenovirus, AAV cannot replicate; instead, it integrates into the host genome through the AAV-inverted terminal repeats present on each end of the AAV genome. The ability to integrate makes AAV an attractive vehicle for gene transfer.

To provide room for a transgene, the majority of the AAV genome between the inverted terminal repeats can be removed and replaced with a gene of interest driven by an appropriate promoter. Once packaged, the replication-incompetent AAV vector has been shown to be capable of infecting and integrating into a target cell genome. However, producing recombinant AAV is cumbersome. The remainder of the AAV genome must be provided in trans, and a wild-type helper virus, such as adenovirus, must be present. The final recombinant AAV vector must be purified from the helper virus by heat or density centrifugation. Production of large quantities of high-titer AAV vector free of helper virus and wild-type AAV has been one of the obstacles to using AAV for clinical purposes. However, new packaging systems to produce helper virus-free recombinant AAV vectors may decrease this problem.

New hybrid vector techniques are under development that may combine the advantages of two systems. For example, adenovirus-AAV hybrid vectors may allow efficient, stable gene transfer.

**POX VECTORS**

The poxviruses are a family of DNA viruses characterized by a large enveloped virion containing enzymes for mRNA synthesis, a genome composed of a single, linear, double-stranded DNA molecule of 130 to 300 kilobases, and the ability to replicate within the cytoplasm of the infected cell. The poxvirus genome encodes 150 to 200 genes, which can be divided into early and late genes. Early genes are expressed before viral DNA replication, and late genes are expressed after DNA replication.

Several properties of poxviruses make them attractive vectors for the introduction of foreign genes. Because of the large size of the poxvirus genome, large amounts of foreign DNA can be incorporated without adversely affecting virulence. Several silent or nonessential regions of the genome have been identified for the insertion of foreign DNA by homologous recombination. Plasmids that provide viral promoters and regions to facilitate homologous recombination into nonessential sites, such as the viral thymidine kinase (TK) region, have been constructed to produce recombinant vaccinia vectors. Multiple genes each can be inserted at a different site in the virus. Screening methods have been designed to isolate and expand recombinant clones containing the genes of interest.

A primary advantage of recombinant poxviruses is the large amount of gene expression that is possible because of the use of vaccinia transcription factors. Because gene expression is entirely cytoplasmic and does not rely on host-cell transcriptional machinery, it is not dependent on potential regulatory mechanisms of the host cell, and hence, large quantities of gene expression have been observed in a wide variety of cell types.

Disadvantages of poxviruses are the transient nature of gene expression and the cell lysis that results after infection. Some attenuated vaccinia strains have been developed that result in delayed lysis of infected human target cells. Avipox viruses, such as fowlpox or canarypox, or swinepox viruses can infect human cells, but they do not result in cell lysis. Another problem with recombinant poxviruses is that up to 200 viral gene products are expressed, many of which may be immunogenic or may adversely interact with the target cell or the gene product of interest.

**NONVIRAL METHODS OF GENE TRANSFER**

Cationic lipids, complexed to DNA, have been developed that are capable of mediating high gene transfer efficiencies in vitro for some cell types. Cationic lipids, such as DOTMA (1,2-dioleoyl-sn-glycero-3-trimethyl ammonium bromide), the prototype cationic lipid, along with a neutral lipid, such as DOPE (dioleoylphosphatidyl ethanolamine), can be complexed with DNA and added to cultured cells. New formulations of lipids are currently under development that may allow improved in vivo gene transfer as well as in vivo administration. Cationic lipid formulations have already been used to deliver genes to the lung in vivo, as well as intratumorally. Most recently, DNA-gelatin nanospheres have been used to allow the slow release of DNA in vivo. In a murine model, intramuscular injection of nanospheres containing the b-galactosidase marker gene led to higher expression levels than injection with naked DNA or DNA/lipid complexes.

Physical methods of gene transfer include the “gene gun,” which propels gold beads coated with DNA into cells. Although this method results in low transfection efficiencies, gene transfer to epithelial cells can be performed in vivo, giving it a potential role in immunization strategies.

The direct in vivo injection of DNA alone into selected tissues, such as muscle, and thyroid, can result in gene transfer. This approach, termed naked DNA, has been used primarily for studies attempting to immunize against the products of the encoded genes.

Nonviral methods of gene delivery are more convenient and have obvious safety advantages over viral methods. However, the majority of current nonviral gene transfer methods result in transient gene expression, and the efficiency of gene transfer is lower compared with most viral methods.

**GENE MARKING STUDIES**

The first gene transfer study in humans in 1989 was designed to assess the safety and feasibility of gene transfer in humans, using a marker gene, neomycin phosphotransferase (Neo). The first gene transfer study in humans was performed in 1989 in the Surgery Branch of the National Cancer Institute. Tumor infiltrating lymphocytes (TILs) were introduced into cells, the fate of these cells could be followed in vivo. Adoptively transferred T cells could be followed for their survival in vivo, and patients receiving autologous bone marrow transplantations transduced with marker genes could be followed to see whether subsequent recurrences were in part due to viable tumor cells that were present in the transferred bone marrow.

**T-CELL MARKING STUDIES**

The first gene transfer study in humans was performed in 1989 in the Surgery Branch of the National Cancer Institute. Tumor infiltrating lymphocytes (TILs) were introduced into cells, the fate of these cells could be followed in vivo. Patients were treated, and no safety or toxicity problems were associated with the gene transfer. Using PCR analysis, TILs were found in tumor biopsies up to 64 days and in peripheral blood up to 189 days after infusion. Since this initial study, more than 300 human gene transfer and therapy studies have been approved by the RAC, and research in this field throughout the world has expanded tremendously.
T-cell marking studies have been performed using melanoma TILs, renal TILs, bone marrow stem cells, and anti-HIV CTLs. Using gene-marked Epstein-Barr virus (EBV)-specific CTLs in immunocompromised patients, Heslop et al. found that EBV precursors could proliferate in response to in vivo or ex vivo viral challenge for as long as 18 months (Fig. 62.1-5). Researchers at the University of Washington in Seattle have used Neo-marked, HIV-1, Gag-specific CD8+ CTL clones to treat HIV-infected individuals. Using PCR amplification for the neo gene followed by in situ hybridization with fluorescein-labeled neo-specific oligonucleotides, the percentage of circulating transduced cells could be quantitated by flow cytometry. One day after cell infusion, 2.0% to 3.5% of CD8+ cells circulating in the periphery were neo-positive. The frequency of neo-modified CTL was found to correlate inversely with the percentage of HIV-infected cells in the peripheral blood after cell infusion. In addition, neo-positive CTLs were found to accumulate in lymph node biopsies obtained 4 days after cell infusion (2.2% to 7.9%), compared with the concurrent percentages of neo-positive CTLs circulating in the periphery (0.5% to 0.7%). Interestingly, neo-positive CTL aggregates were found in the parafollicular regions of the lymph node near cells that were productively infected with HIV. This finding illustrates the utility of cell marking to determine not only the overall traffic and survival of infused cells, but also their microanatomic localization.

HEMATOPOIETIC STEM CELL MARKING STUDIES
The ability to label stem cells with unique, integrated DNA sequences has enabled investigators to track stem cells and their differentiated progeny, allowing such studies as, for example, the comparison of bone marrow stem cells with peripheral blood stem cells for their ability to reconstitute the host. In addition, because microscopic tumor deposits present within the marrow also are marked by retroviral vectors, attempts have been made to assess the source of disease recurrence after autologous bone marrow transplantation therapy in patients with acute myeloid leukemia and neuroblastoma. In one study, bone marrow was harvested during complete remission and retrovirally transduced with the Neo<sup>+</sup> gene before reinfusion. Three of 12 acute myeloid leukemia patients have relapsed, and in two of these patients, tumor cells from the relapse contained the Neo<sup>+</sup> gene. Of nine neuroblastoma patients studied, three have relapsed, and in all three cases, the Neo<sup>+</sup> gene was found in the recurrent tumor cells. Analysis of neomycin resistance (Neo<sub>R</sub>)-marked, EBV-specific T cells. (From ref. 51, with permission.)

In a similar study using Neo<sup>+</sup> transduced autologous CD34 cells in chronic myelogenous leukemia (CML) patients, two relapsing patients were studied, and both had leukemic cells that were positive for the Neo<sup>+</sup> gene. Thus, it is clear that remission marrow can contribute to disease relapse. Using similar techniques, a variety of bone marrow purging regimens can be evaluated within the same patient to assess their success in eliminating tumor cells from the marrow. This evaluation allows recurrent tumor cells to be analyzed genetically to determine if they had previously been exposed to a particular purging regimen.

Finally, gene transfer itself is being investigated as a purging technique, using antisense oligodeoxynucleotides against activated oncogenes as a means to eliminate tumor cells within the autologous marrow. Using this approach, inhibition of episomal replication of the virus and suppression of viral infections can be achieved by disrupting the expression of a viral gene, such as the LTR, which is necessary for viral replication. This technique can be used to purify autologous marrow of patients with acute myeloid leukemia and to eliminate tumor cells from the marrow. Thus, it is clear that remission marrow can contribute to disease relapse. Using similar techniques, a variety of bone marrow purging regimens can be evaluated within the same patient to assess their success in eliminating tumor cells from the marrow. This evaluation allows recurrent tumor cells to be analyzed genetically to determine if they had previously been exposed to a particular purging regimen.

GENETIC MODIFICATION OF THE IMMUNE RESPONSE
Several approaches have been proposed for cancer gene therapy (see Table 62.1-1). One strategy that has been pursued is an attempt to enhance the immune response against cancer using gene transfer techniques.

ACTIVE IMMUNIZATION
Much has been learned concerning the nature of the T-cell response to human cancers. Tumor antigens recognized by T cells have been cloned from melanoma cells. These antigens have been shown to be nonmutated melanocyte differentiation antigens, nonmutated proteins expressed only in selected tissues such as testes, or mutated intracellular proteins. Despite the expression of known antigens on tumor cells, however, these tumors grow in their hosts, seemingly unopposed by any antitumor immune response. This lack of an adequate immune response could be due to a number of reasons, including deficient tumor antigen processing and presentation, lack of immune costimulation, production of inhibitory factors by the tumor cell, and insufficient helper activity from CD4 cells. In an attempt to bypass these potential deficiencies and stimulate a stronger antitumor response in the host, tumor cells have been genetically modified with a variety of cytokine genes and costimulatory molecules, and these modified tumor cells have been used as antitumor vaccines.
Modification of Tumor Cells with Genes That Enhance Tumor Immunogenicity

CYTOKINE GENES. In contrast to the systemic administration of cytokines, which results in low concentrations in vivo, the introduction of genes encoding cytokines into tumor cells can result in the production of very high levels of cytokines in the tumor microenvironment. This approach is designed to more accurately mimic the paracrine nature by which cytokines normally interact to regulate immune responses. Tumors have been transduced with a variety of genes in an attempt to enhance immunogenicity.

Interleukin-2. In several murine models, tumors expressing the gene for interleukin-2 (IL-2) regress after an initial period of growth, leading to long-lasting protection from subsequent rechallenge. In some cases, the immune response was shown to be dependent on CD8, but not CD4. This suggests that the IL-2 released by the tumor could be bypassing the need for help from CD4 cells. In many studies, however, it was not clear whether systemic immunity was enhanced to levels greater than that which could be achieved using irradiated, nonmodified tumor cells.

In another study, intraperitoneal, irradiated, IL-2–transduced murine bladder cancer cells were capable of treating 7-day parental tumors established by orthotopic implantation of tumor cells into the bladder wall. Irradiated nontransfected cells showed no antitumor response in these experiments.

Forty-five patients with renal cell cancer, melanoma, and sarcoma were treated with intratumoral injections of a DNA plasmid encoding human IL-2 complexed to the cationic lipids DMRIE/DOPE in a phase III study. Partial responses in un.injected tumors were observed in 2 of 14 patients with renal cell cancer and 1 of 16 patients with melanoma. On immunohistochemical evaluation of pre- and posttreatment biopsy specimens of injected tumors, an increase in IL-2 expression and CD8+ infiltration was observed in some patients.

In another study, 23 patients with metastatic breast cancer and melanoma were treated with intratumoral injections of a recombinant adenosine expressing IL-2. No clinical responses were seen, but IL-2 protein was detected by enzyme-linked immunosorbent assay in tumor at 48 hours but not at 7 days after injection. This finding demonstrated that some transgene expression could be detected, despite the presence of preexisting neutralizing antibodies against adenosine. Other trials have used autologous tumor or fibroblasts expressing IL-2 in melanoma and colorectal cancer patients, but no clinical responses have been reported.

Granulocyte-Macrophage Colony-Stimulating Factor. Granulocyte-macrophage colony-stimulating factor (GM-CSF) is a cytokine with the unique ability to stimulate the differentiation of hematopoietic progenitor cells into dendritic cells, a potent antigen-presenting cell. This property may allow increased presentation of tumor antigens on dendritic cells after immunization with tumors that express GM-CSF. In a comparative study, mice were immunized with irradiated B16 melanoma cells that were transduced with either IL-2, IL-4, IL-5, IL-6, GM-CSF, interferon-g (IFN-g), tumor necrosis factor-a (TNF-a), intracellular adhesion molecule 1, or CD2. Only mice immunized with GM-CSF–transduced tumor cells were significantly protected against a subsequent tumor challenge. IL-4– and IL-6–transduced tumor cells were minimally protective, but none of the other groups displayed a significant systemic antitumor response. GM-CSF–transduced B16 melanoma cells were also capable of significantly impacting on 3-day subcutaneous implants of a small inoculum of nontransduced B16 cells. Immunization with GM-CSF–transduced tumor generated long-lasting systemic antitumor immunity that was dependent on both CD4+ and CD8+ T cells. Further studies have demonstrated that GM-CSF transduced tumor vaccines activate bone marrow–derived antigen-presenting cells to process and present tumor antigens to both CD4+ and CD8+ T cells. Activated, tumor-specific CD4+ T cells were in turn shown to express both Th1 and Th2 cytokines that recruited other effector cells to the tumor, including eosinophils and macrophages. In addition, antitumor activity of GM-CSF–transduced vaccines was found to depend on the production of IFN-g, IL-4, and IL-5.

Three clinical studies have been reported that used GM-CSF–transduced tumors in renal cell cancer, melanoma, and prostate cancer. In a phase I, randomized, double-blind dose-escalation study, patients with metastatic renal cell cancer were immunized with intradermal and subcutaneous injections of either nontransduced or GM-CSF–transduced autologous, irradiated renal cancer cells. Biopsy sites from patients receiving GM-CSF–transduced vaccines demonstrated infiltrates of macrophages, dendritic cells, eosinophils, neutrophils, and T cells consistent with preclinical studies. Delayed-type hypersensitivity responses using nontransduced autologous tumor cells revealed eosinophil infiltrates in only those patients who previously received GM-CSF–transduced vaccines. One partial response was seen out of nine patients treated with GM-CSF–transduced vaccines.

In a phase I trial for patients with metastatic melanoma, 21 patients were immunized intradermally and subcutaneously with autologous melanoma cells transduced to express GM-CSF. Again, immunization sites were found to be infiltrated with T lymphocytes, dendritic cells, macrophages, and eosinophils in all 21 patients. Although only 1 of 21 patients had an objective partial response, 11 of 16 patients evaluated had T lymphocyte and plasma cell infiltrates in tumor biopsies after immunization. In a phase I trial evaluating GM-CSF–transduced prostate cancer vaccination, delayed-type hypersensitivity reactions against nontransduced autologous tumor cells were positive in two of eight patients before vaccination and seven of eight patients after vaccination. However, no clinical responses were reported.

Interferon-g. The introduction of the IFN-g gene into tumor cells can lead to the up-regulation of major histocompatibility complex (MHC) class I and class II gene products. Although this effect can lead to decreased tumorigenicity, it is unclear whether systemic immunity is enhanced. In some tumor systems with low class I expression or antigen processing defects, however, IFN-g–transduced tumor allowed the isolation of CD8+ lymphocytes capable of treating established pulmonary products.

Modified MCA207 cells in the left flank on day 0, followed by treatment on day 3 with saline, MCA207-Neo, or GM-CSF–transduced. Thirty-three percent of mice were free of tumor by day 21 when treated with MCA207-IL-12 tumor, compared to no animals free of tumor that were treated with saline or MCA207-Neo tumor. However, it is not clear whether these effects were due to the paracrine secretion of IL-12 or to a systemic effect of secreted IL-12.

Although the transduction of tumor cells with a variety of cytokine genes can result in decreased tumorigenicity in murine models, few studies have demonstrated that...
this transduction leads to an enhanced immune response against the parental, nontransduced tumor compared to immunization with irradiated, nontransduced tumor cells. In one study, Hock et al. demonstrated that tumor cells modified with different cytokine genes (IL-2, IL-4, IL-7, TNF, or IFN-γ) were only slightly superior to irradiated parental cells as immunogens. Moreover, parental cells admixed with the classical adjuvant Cryptosporidium parvum were found to be superior to the cytokine-modified tumors in their ability to immunize mice against the tumor. 117

NONCYTOKINE GENES

B7-1 (CD80). The activation of T lymphocytes requires that they come in contact with a specific antigen and a costimulatory signal. One potential reason that some cancers develop and evade the immune system is that T lymphocytes are not adequately costimulated to become activated. The adhesion molecules B7-1 (CD80) and B7-2 (CD86) can interact with the CD28 receptor on T cells to provide costimulation. 124 Several groups have demonstrated that tumor cells transfected with B7-1 locally regress and lead to protection against subsequent tumor challenge with the parental tumor. 118,119 In one study, 122 regression of B7-transduced tumors was dependent on the intrinsic immunogenicity of the parental tumor.

Further studies are needed to assess the potency of B7 in the ability to stimulate an antitumor response. HLA-B7. Several clinical trials based on murine models have been performed using intratumoral injection with plasmid DNA encoding HLA-B7 in HLA-B7–negative patients in the hopes of generating a stronger immune response against unmodified tumor cells. Intratumoral injection of HLA-B7 plasmid DNA in a cationic lipid vector resulted in RNA or protein expression at the injection site in some patients, 125 but no tumor regression was seen in noninjected sites.

Immunization with Genes Encoding Tumor Antigens

RECOMBINANT VACCINES. Whole tumor cells have been used as immunogens because the specific antigens recognized by T cells have been largely unknown. However, the cloning of several melanoma antigens recognized by T cells 47,77,78,79,80,81 has opened new possibilities for active immunization strategies for cancer. Studies in murine models have demonstrated that antigens expressed at high levels in recombinant adenoviral, fowlpox, and vaccinia vector systems can induce a significant antitumor immune response against tumors bearing the same antigen. 126,127,128,129 Recombinant viral vaccines can result in the in vivo production of high quantities of heterologous proteins. However, expression of native viral proteins by these vectors can also result in a host immune response against the vector itself, thereby diminishing the effectiveness of repeated immunizations.

Immunization studies with “naked DNA” given intramuscularly, or DNA administered on gold beads using the “gene gun” technique, have resulted in significant antitumor effects. Because these methods do not use viral vectors, no irrelevant viral proteins are expressed, thus allowing repeated immunizations.

Current efforts are focused on enhancing immune responses through adjuvant exogenous cytokine administration or introduction of genes encoding cytokines or costimulatory molecules into the recombinant vectors.

DENDRITIC CELLS. Another strategy to actively immunize a patient against cancer is to use potent antigen-presenting cells, such as dendritic cells. These cells are capable of stimulating immune responses from quiescent lymphocytes. Dendritic cells pulsed with tumor peptide or protein antigens have been shown to have significant antitumor effects in murine models 130 and were reported to be effective in one study of patients with lymphomas. Nestle and colleagues, 131 treated 16 metastatic melanoma patients with intranodal injections of dendritic cells pulsed with tumor lysates or peptides derived from known tumor antigens. Eleven of 16 patients demonstrated a positive delayed-type hypersensitivity reaction to peptide-pulsed dendritic cells, and clinical responses were observed in five patients. 132

Although antitumor responses can be obtained in murine models by administering dendritic cells pulsed with peptide antigens or whole proteins, this approach limits immune responses to specific, defined MHC-binding epitopes within a given antigen or requires the production of recombinant proteins. For many tumor antigens, however, multiple epitopes have been described that bind to a variety of MHC molecules. One strategy that may enable the presentation of multiple, even undefined, epitopes within a given tumor antigen is the introduction of an antigen gene into the dendritic cell. This strategy may allow multiple epitopes to be presented in the context of both class I and class II molecules as well as the constitutive expression of these antigens in transduced dendritic cells. Several strategies have been proposed to genetically modify dendritic cells with tumor antigens. One is to transduce bone marrow cells and differentiate the cells in vitro into dendritic cells, using GM-CSF, 133,134,135 Another is the transient transfection of dendritic cells using cationic lipids, 136 gene gun, adenovirus, 137,138 or recombinant influenza virus. 139

GENETIC MODIFICATION OF IMMUNE EFFECTOR CELLS

Several lines of evidence indicate that adoptively transferred T cells can be therapeutically effective. TILs have been shown to mediate significant responses in patients with melanoma, even in those who have not been successful with previous therapy with IL-2. 140 Adoptively transferred cytomegalovirus-specific T cells have been shown to prevent cytomegalovirus infections in patients after allogeneic bone marrow transplantation. 141 Infusion of donor T cells has been effective in treating the EBV-driven lymphoproliferative disease that sometimes complicates allogeneic bone marrow transplantation. 142 Patients with CML recurrence after allogeneic bone marrow transplantation can experience remission after transfer of donor T cells. 143 Several strategies for the genetic modification of transferred T cells attempt to increase their effectiveness.

Enhancing Survival of Immune Cells

For T cells to be functional against a tumor, they must survive in vivo, recognize the target, and then execute an adequate antitumor effector mechanism, either by direct cell lysis or release of cytokines that may attract and stimulate other immune cells. There are several ways to potentially enhance these steps. T cells grow in response to stimulation by various cytokines, such as IL-2. On adoptive transfer of TILs in murine models, the administration of systemic IL-2 potentiates the antitumor effect, presumably by maintaining growth and viability of the administered TILs. 144 By inserting the gene for IL-2, TILs may become able to stimulate themselves in an autocrine fashion, as demonstrated by Yamada et al. 145 and Karasuyama et al., 146 in CTL line and murine HT-2 T cells, respectively. Treisman et al. 147 demonstrated that a T-cell clone transduced with the IL-2 gene could grow in an IL-2–independent fashion while maintaining antigen specificity. 148 However, further work must be done to obtain sufficient IL-2 secretion in primary lymphocytes for this approach to be clinically useful. In addition, insertion of the gene encoding the IL-2 receptor, which is normally up-regulated by lymphocytes after antigen stimulation, may also be required to obtain a proliferative response to IL-2.

Increasing Tumor Recognition by Using Novel Receptor Genes

CHIMERIC ANTIBODY/T-CELL RECEPTOR GENES. Although adoptive immunotherapeutic strategies have been developed for some cancers, tumor-reactive T cells are difficult to isolate and expand from most types of cancer. A variety of monoclonal antibodies have been developed that bind to specific cancers. Although cancer therapy with antibodies has been largely disappointing, partially because of the lack of an adequate effector mechanism to destroy tumor cells on binding. By combining the antigen-recognition domains from antibodies with the intracellular, signaling chains of T cells, chimeric receptors can be generated that activate T cells based on antibody-like recognition (Fig. 62-1-7). This approach, which uses the antigen-binding capabilities of antibodies with the potent antitumor activity of T cells, would allow the production of specific T cells against any antigen for which a monoclonal antibody exists. This strategy could widely generalize the use of adoptive immunotherapy for cancer and infectious diseases.
The successful combination of antibody-variable regions with T-cell signaling chains has been established for several model antigens, such as phosphorlycholine, digoxin, and trinitrophenyl. These initial approaches, however, required the use of two genes, because the antibody-variable region is encoded by a combination of light and heavy chains. This two-gene strategy, however, is impractical for use in clinical trials using primary T cells, because transduction efficiencies are relatively low for even one gene. Therefore, chimeric receptors encoded on a single gene were designed by making use of single-chain antibody variable (scFv) regions in which the light- and heavy-chain variable regions are connected by a flexible linker. These scFv fragments were joined to T-cell receptor (TCR) z or Fc receptor chains, both of which are closely related and have been demonstrated to be capable of mediating TCR signal transduction.

Using this single-gene approach, receptors have been constructed using the mAb MOv18, which binds to a folate-binding protein overexpressed on most ovarian adenocarcinomas. T cells retrovirally transduced with these receptor genes demonstrate specific cytokine secretion and cytolyis when cultured with human ovarian cancer cells. In addition, intravenously administered murine T cells transduced with this receptor could specifically treat experimental lung metastases from tumors that express the ovarian cancer antigen. Intraperitoneal administration of these T cells could also successfully treat human ovarian cancer cells growing intraperitoneal in nude mice. These studies demonstrate that T cells can be manipulated genetically to recognize and destroy tumor cells based on antibody-type specificity.

Besides triggering direct T-cell activation with g and z chains, antibody-variable regions can be coupled to other signaling chains, such as the intracellular portion of CD28, an important T-cell costimulatory receptor. This approach has been found to enhance T-cell survival and proliferation in vitro.

Most recently, the transduction of hematopoietic stem cells with chimeric receptor genes has been under investigation, because this may not only provide a stable supply of redirected T cells, but also granulocytes, macrophages, and natural killer cells, all of which may have significant antitumor activity on expression of chimeric receptor genes. Mice that received MOv-g-transduced bone marrow cells exhibited significant antigen-specific antitumor activity in vivo.

These strategies have the potential of widely generalizing the use of adoptive immunotherapy. scFv-g and -z receptors have been constructed against breast cancer using an anti-HER2 mAb. Colon cancer using an anti-GA733 mAb and HIV using an anti-gp41 mAb. This strategy could be applied to a wide range of cancer histologies or infectious diseases for which appropriate mAb exist.

**NATIVE T-CELL RECEPTOR GENES.** T-cell specificity can also be altered by the introduction of genes encoding native TCRs. The TCR consists of an a and b chain heterodimer that confers the ability to specifically recognize peptide/MHC complexes on antigen-presenting cells and target cells. TCRs derived from melanoma-specific CTLs have been identified, cloned, and characterized. Clay et al. transduced primary lymphocytes with a TCR gene specific for the MART-1 melanoma tumor rejection antigen. Because the TCR consists of two individual chains, a retroviral vector was constructed that uses internal ribosomal entry sites (IREs sequences) that allow the translation of multiple genes from a single transcript. Primary T cells transduced with this construct were capable of specifically recognizing tumor cells expressing the MART-1 melanoma tumor antigen in the context of HLA-A2. As more TCRs recognizing specific tumor antigens are characterized and cloned, this strategy may generalize the use of adoptive immunotherapy, circumventing the need to isolate T cells with specific reactivities from each individual patient.

**Transduction of T Cells and Donor Lymphocytes with Suicide Genes**

Adoptively transferred T cells have been safely administered to many patients for more than 10 years. In specific situations, however, the adoptively transferred cells may be toxic to the host, such as in the treatment of immunocompromised HIV patients. In the setting of allogeneic bone marrow transplantation for hematologic malignancies, donor lymphocyte infusions can be highly effective against tumor as well as EBV-induced lymphoma but may also incite graft-versus-host disease. In an attempt to increase the therapeutic index of adoptively transferred cells in these situations, “suicide” genes can be introduced into lymphocytes to specifically delete the transduced cells should they become toxic to patients in vivo. The gene for herpes TK (hTK) has been used for this purpose, because it specifically sensitizes cells to the antiviral agent ganciclovir.

In one study using hTK-transduced donor lymphocytes, three of eight patients receiving donor lymphocytes after allogeneic bone marrow transplantation for hematologic malignancies developed acute or chronic graft-versus-host disease. In these patients, ganciclovir administration significantly diminished the number of circulating hTK-transduced cells within 24 hours, resulting in complete or partial remissions of the disease (Table 62.1-5).

**TABLE 62.1-5.** Effect of Ganciclovir Treatment on Elimination of Herpes Thymidine Kinase–Modified Donor Lymphocytes and on Graft-Versus-Host Disease (GVHD)

In another study, anti-HIV CTLs were transduced with a fusion gene encoding hTK and the selectable marker hygromycin before administration in HIV-infected patients. Because HIV patients are immunocompromised, the CTLs could be irradiated with ganciclovir should the transduced cells become toxic. However, initial results of the trial revealed that the patients were developing cellular immune responses against the hTK-hyogromycin fusion protein, thus demonstrating that foreign genes, including selectable markers, can themselves become targets of the host immune response.

**Increasing Antitumor Efficacy of Immune Cells**

TNF has potent antitumor activity against large tumor burdens in some murine models. However, humans can only tolerate 2% of the systemic TNF dose (by weight) required in mice, due to dose-limiting hypotension. High doses of TNF, administered locally via direct tumor injection or isolated limb perfusion, can result in dramatic tumor regressions in some cancer patients. At the National Cancer Institute's Surgery Branch, regressions of liver metastases have been seen in patients treated with TNF administered as a component of an isolated hepatic perfusion. Therefore, tumor regressions seem possible in patients when adequate local concentrations of TNF can be achieved. Because TILs have been demonstrated to accumulate at sites of tumor, the transduction of TILs with the TNF gene may allow high concentrations of TNF to be delivered locally in the absence of systemic toxicity.

Twelve patients have been treated with TNF-transduced TILs in a phase I trial using escalating doses of TILs and IL-2. No safety problems or toxicity have been detected. Replacement of the TNF transmembrane region with the signal peptide from interferon-g, thus bypassing the transmembrane form, resulted in a fivefold increase in TNF production. Despite this improvement, however, primary lymphocytes transduced with the TNF gene probably do not produce high enough
levels of TNF constitutively to be clinically effective. To optimize this treatment strategy, current efforts are directed toward identifying promoter/enhancer regions that direct higher levels of gene expression in primary lymphocytes.

MODIFICATION OF TUMORS WITH GENES THAT HAVE DIRECT ANTITUMOR EFFECTS

The gene therapies that have been discussed thus far have all focused on the stimulation of the immune system to react against tumor cells. Another approach to cancer gene therapy is to introduce genes into tumor cells that have direct antiproliferative or toxic effects on that cell. This approach, however, requires techniques to directly administer genes into tumor cells in vivo with high efficiencies, which is not technically possible at this time. However, as vector development continues, the direct administration of genes into patients may play a more important role. Some preliminary studies have been initiated that use direct in vivo administration of genes into tumor cells.

TUMOR SUPPRESSOR GENES

Cancer can result from the abnormal expression of genes that control the cell cycle. Some genes, termed tumor suppressor genes, regulate cell growth, and their absence by mutation or deletion results in the malignant phenotype. One approach to treat tumors with deleted or mutated tumor suppressor genes is to replace these genes by in vivo gene transfer. Currently, gene transfer techniques do not exist that are capable of efficiently delivering these genes systemically to all tumor cells in the body, and significant technical improvements are required if this approach is to become practical.

Because of this limitation in systemic delivery, several groups have attempted local gene delivery of tumor suppressor genes. Swisher and colleagues treated 28 patients with non–small–cell lung cancer with intratumoral administration of an adenovirus vector containing wild-type p53 complementary DNA. Reverse-transcriptase PCR analysis of posttreatment biopsies were positive for the presence of vector-specific p53 mRNA in 12 of 26 patients. Partial response of the injected lesion was observed in 2 of 25 evaluable patients (8%). Because local therapy is of limited utility in the face of metastatic disease, these studies highlight the need for improved vectors that would allow efficient, systemic gene delivery.

ANTISENSE AND RIBOZYMES

Oncogenes are genes that cause uncontrolled cell growth when mutated or overexpressed, and neutralization of these genes can reverse the malignant phenotype. One approach to inactivate genes uses antisense oligodeoxynucleotides, which are short sequences that are complementary to target RNA transcripts and can inhibit translation of the RNA into protein.

Oligonucleotides have been shown to enter cells by at least two pathways (i.e., endocytosis and pinocytosis), and significant activity of antisense constructs has been observed in vitro using tissue culture cell lines. In vitro growth suppression has been demonstrated using antisense oligonucleotides against BCL-2 in leukemia cells, BCR-ABL in CML cells, MYC in lymphoma cell lines, and MYB in adenocarcinoma and leukemia cell lines.

Several studies have been performed in mice demonstrating in vivo efficacy of antisense oligonucleotides against tumors. Antisense inhibition of c-myc mRNA increased survival of scid mice bearing human K562 leukemia cells. In another study, antisense against the p65 subunit of nuclear factor kB inhibited the growth of the murine fibrosarcoma K-BALB and the murine melanoma B16.

Webb and colleagues treated nine patients with non-Hodgkin's lymphoma with daily subcutaneous BCL-2 antisense oligonucleotide for 2 weeks. BCL-2 overexpression can promote tumorigenesis by causing resistance to programmed cell death (apoptosis). A complete response was observed in one of nine patients, with resolution of left axillary lymphadenopathy.

A current limitation to this approach is the inability to successfully deliver antisense constructs to tumor cells in vivo with adequate efficiency. In addition, antisense studies must be interpreted carefully, because of the possibility of nonspecific effects. For example, because charged oligonucleotides are polyanions, they can bind nonspecifically to growth factors, such as basic fibroblast growth factor (bFGF).

Another potential method to target activated oncogenes is through the use of ribozymes. These are RNA enzymes that catalyze endoribonucleolytic cleavage of RNA. Several investigators have reported cleavage of the bcr-abl transcript, which is involved in the pathogenesis of chronic myelogenous leukemia, by specific hammerhead ribozymes. Anti-fos and anti-ras ribozymes also have been reported. At the present time, however, no adequate ex vivo or in vivo systems can deliver ribozymes to target cells.

SUICIDE GENES

Because retrovectors integrate preferentially into dividing cells, replicating tumor cells might be targeted with relative specificity compared to normal tissues. To test this hypothesis, Culver et al. implanted cell lines producing recombinant retrovirus containing the hTK gene into brain tumors in rats, then administered systemic ganciclovir therapy. Ganciclovir is a nucleotide analogue that is converted into a cytotoxic molecule by hTK, but it is a poor substrate for mammalian TK.

Because local therapy is of limited utility in the face of metastatic disease, these studies highlight the need for improved vectors that would allow efficient, systemic gene delivery.

For these approaches, however, the fundamental problem of inadequate gene delivery still remains.

Reference

1. Culver et al. 1996

2. Ram and colleagues treated 15 patients with brain tumors, including malignant glioma (n = 12), metastatic melanoma (n = 2), and metastatic breast cancer (n = 1), with intratumoral implantation of up to 1 X 107 producer cells making retroviral vectors encoding HSV-TK, followed by systemic ganciclovir therapy for 14 days. In situ hybridization revealed that vector producer cells survived up to 7 days in vivo but were associated with only a low level of gene transfer to tumors. Five of the smaller tumors (1.4 ± 0.5 mL) showed evidence of antitumor activity, but larger tumors did not respond.

Several groups have reported the local administration of recombinant adenovirus containing HSV-TK, but it is not clear whether these approaches have any advantages over other methods of local therapy. In addition, the tumor specificity of this approach is a potential problem, because, in contrast to retroviral vectors, no evidence indicates that adenovirus infects dividing tumor cells preferentially over nondividing normal tissue.

In an attempt to enhance the tissue specificity of suicide gene therapy, Pandha and colleagues treated 12 breast cancer patients with intratumoral injections of a plasmid construct encoding the E. coli cytosine deaminase suicide gene driven by the human erbB-2 promoter, followed by systemic produg administration. Significant levels of expression of the suicide gene were specifically restricted to erbB-2–positive tumor cells.

A major limitation in the current application of in vivo gene therapy approaches for cancer, such as suicide gene strategies, is the absence of an adequate delivery system that could transfer the suicide gene to all cancer cells within a patient's body. Despite a potential “bystander effect,” which may mediate the destruction of tumor cells surrounding those expressing the suicide gene, current gene transfer technology is too inefficient to allow the application of this strategy for the treatment of disseminated metastatic cancer. A second limitation to the use of suicide genes is that of specificity. For any cancer therapy to be effective, the toxicity for the tumor cells must be greater than for normal tissues. Retroviral vectors may theoretically be more selective for tumor cells than normal tissues, because retroviruses only infect proliferating cells. However, retroviruses are suboptimal for in vivo administration because of their low efficiency of transduction. Adenoviral vectors, on the other hand, show no selectivity towards tumor cells.

Enhanced tumor specificity might be accomplished by using tumor-specific promoter/enhancer regions to direct transcription of the suicide genes. For example, the a-fetoprotein promoter is primarily active in hepatoma cells, whereas the tyrosinase promoter is specifically active in melanocytes and melanoma cells. This approach also has been suggested to target tumor vasculature, using promoters that are relatively specific for endothelial cells, such as the E-selectin, vascular cell adhesion molecule, and CD31 promoters. The use of tumor- or tumor-vasculature–specific promoters might decrease destruction of normal cells, because they would not express the suicide gene product. For these approaches, however, the fundamental problem of inadequate gene delivery still remains.
SELECTIVE REPLICATION OF VIRUS IN TUMORS

In vivo gene delivery to tumors using replication-defective viral systems are presently inadequate to obtain sufficient transduction efficiency. The design of a virus that could specifically replicate in and destroy tumor cells would be of obvious value. Some efforts have used E1B-defective adenoviruses capable of specifically replicating and destroying tumor cells without affecting normal p53 tumor suppressor function. The p53 protein is a transcription factor that acts as a potent tumor suppressor by its ability to induce cell-cycle arrest and apoptosis. Functional p53 is present in normal cells but is absent in more than 50% of the common solid tumors. Normally, on viral infection, p53 triggers early apoptosis of the cell, thereby limiting viral replication and spread. However, many viruses have evolved proteins, such as the adenoviral E1B 55-kD protein, that inhibit normal p53 function, thereby allowing maximal viral replication. E1B-defective adenoviruses, therefore, cannot fully replicate in normal tissues expressing p53, but they can replicate in tumor cells that lack functional p53.

Blaschoff et al. found that an E1B-deleted adenovirus (ONYX-015) could lyse p53-deficient human tumor cells but not cells with functional p53. Intratumoral injection of ONYX-015 caused regression of human cervical carcinomas grown in nude mice. Heise and colleagues reported augmentation of anticancer effects of ONYX-015 by chemotherapy, as well as the efficacy of intravenously administered ONYX-015 in nude mice with subcutaneous human tumor xenografts. Clinical trials are ongoing to test this approach in patients with head and neck cancer.

Studies have questioned whether the tumor specificity of ONYX-015 is strictly related to p53 expression by the tumor cells. Rothmann et al. found that replication of ONYX-015 was independent of p53 status in tumor cells, and Hall and colleagues reported that productive adenovirus infection was dependent on the p53 pathway. Therefore, much needs to be determined regarding the host range and mechanism of action of ONYX-015. In addition, the next generation of tumor-specific “smart viruses” must address enhanced specificity and systemic delivery of the virus, as well as methods to prevent humoral and cellular host immune responses against the virus.

INTRODUCTION OF GENES INTO HEMATOPOIETIC STEM CELLS TO DECREASE TOXICITY FROM CHEMOTHERAPY

Expression of the MDR gene decreases the toxicity from certain chemotherapy drugs, such as Taxol, Adriamycin, vincristine, and actinomycin D, by encoding for a transmembrane molecule that actively pumps these cytotoxic agents out of the cell. Expression of the MDR gene in tumor cells is commonly associated with tumor resistance to these cytotoxic agents. Sorrentino et al. transplanted MDR-transduced bone marrow cells into mice and substantially enriched for these cells after treatment with Taxol. Several clinical trials are now under way that attempt to genetically modify bone marrow cells with the MDR gene, then reinforce them into the patient in an attempt to decrease hematopoietic toxicity from subsequent chemotherapy. However, clinical trials with patients receiving transduced bone marrow have shown that only a small percentage of circulating hematopoietic cells are gene modified. This limitation has been confirmed by several groups attempting to decrease chemotherapy toxicity with MDR-transduced hematopoietic progenitor cells. Cowan et al. found low levels of short-term engraftment of MDR-transduced cells in three of four patients treated, and Hershoffer and colleagues had similar results in two of five patients. Hanania et al. found that the method of transduction was important. They compared a 3-day transduction method on a stromal monolayer to a 4- to 6-hour transduction procedure in a culture bag. Three to 4 weeks after transplantation, none of ten patients receiving cells transduced with the supernatant method had MDR-positive cells, whereas five of eight patients receiving cells transduced with the stromal method had MDR-positive cells. However, the percentages of positive cells was not quantified and was presumably low because of the requirement for sensitive PCR methods for detection.

Therefore, the success of this strategy may depend on whether the level of gene transfer is sufficient to allow the administration of higher doses of chemotherapy. If this approach is to have a significant impact in cancer therapy, an effective chemotherapeutic regimen must exist that can eradicate tumor before the development of significant nonhematopoietic toxicities, such as liver failure.

ANTIANGIOGENIC GENE THERAPY

The discovery by Folkman in the 1970s that tumors produce substances that stimulate the growth of their vasculature has led to intensive investigation into methods to inhibit tumor neovessel formation. Production of proangiogenic cytokines, including vascular endothelial growth factor (VEGF) and FGF, result in angiogenesis, which is required for tumor growth. One gene therapy strategy, therefore, has focused on the inhibition of the production or function of proangiogenic cytokines. A second strategy involves the delivery of genes that encode inhibitors of angiogenesis. A number of endogenous proteins have been described that are capable of inhibiting angiogenesis, and their expression in vivo may result in antitumor activity through interference with tumor blood supply.

GENES THAT INHIBIT PROANGIOGENIC CYTOKINES

VEGF is a proangiogenic cytokine that can bind to two high-affinity receptors (VEGFR-1/FLT-1 and VEGFR-2/KDR) expressed on vascular endothelial cells. An endogenous, alternatively spliced soluble form of FLT-1 (sFLT-1) has been identified that is capable of inhibiting the effects of VEGF on vascular endothelial cells in vivo. Expression of recombinant sFLT-1 resulted in tumor inhibition in mice with preexisting lung or liver metastases. In another preclinical model using GS-9L gliosarcoma cells in rats, intracerebral or subcutaneous intratumoral injection of retrovirus-producing cells encoding a dominant-negative VEGFR-2 resulted in tumor inhibition that was associated with decreased vessel density within tumors.

Antisense approaches also are being tested as a means to inhibit VEGF. Use of a recombinant adenovirus-encoding antisense VEGF for intratumoral injection of subcutaneous human gliomas in nude mice resulted in the inhibition of tumor growth. The von Hippel-Lindau (VHL) gene has been shown to down-regulate VEGF production by human renal cancer cells. Therefore, gene therapy by introducing the VHL gene into tumors is a potential strategy to down-regulate VEGF expression in vivo. As with other approaches that depend on in vivo gene delivery into tumor cells, this approach is limited by the requirement for an efficient system that allows gene transfer to a majority of cancer cells in vivo.

Urokinase-type plasminogen activator (u-PA) is a FGF that can result in endothelial cell proliferation. Soluble N-terminal fragments of u-PA have been used to competitively inhibit the binding of endogenous u-PA with its receptor. Systemic administration of recombinant adenovirus encoding a competitor fragment of u-PA has been shown to inhibit liver metastases in an experimental model of human colon cancer in nude mice.

Tie2 is an endothelium-specific receptor tyrosine kinase that plays an important role in angiogenesis of embryonic vasculature through the interaction with its ligand, angiopoietin 1. Systemic administration of a recombinant adenovirus expressing a soluble Tie2 receptor (sTie2) capable of blocking Tie2 activation resulted in growth inhibition of subcutaneous murine mammary adenocarcinoma (4T1) and melanoma (B16F10.9). Cells in addition, the sTie2 recombinant adenovirus inhibited the development and neovascularization of pulmonary metastases.

GENES WITH ANTIANGIOGENIC PROPERTIES

A number of endogenous inhibitors of angiogenesis have been described. They include antiangiogenic proteolytic fragments, ILs, IFNs, thrombospondins, and tissue inhibitors of metalloproteinases (TIMPs). Angiostatin is a 38-kD internal fragment of plasminogen, and endostatin is a 20-kD fragment derived from the C-terminal noncollagenous domain of the basement membrane constituent collagen XVIII. Administration of angiotatin and endostatin can lead to tumor dormancy and regression in murine models. However, these proteins have been difficult to produce in large quantities for clinical use because of instability. Because it may be necessary to administer antiangiogenic agents chronically to maintain long-term tumor suppression, other strategies besides administration of recombinant protein may be required for these approaches to be effective. Gene therapy using genes encoding these proteolytic fragments may be an attractive alternative to exogenous dosing.

Systemic administration of recombinant adenovirus expressing angiostatin resulted in dose-dependent inhibition of the establishment and growth of C6 rat gliomas in nude mice. Using intravenous delivery of complexes of cationic liposomes and plasmid DNA-encoding angiostatin, Liu et al. demonstrated reduced B16F10 melanoma metastases in a 7-day tumor model. Feldman et al. demonstrated inhibition of subcutaneous MC38 murine colon adenocarcinomas using intravenous administration of recombinant adenovirus...
endostatin and another adenovirus. In this model, circulating levels of endostatin were as high as 2038 ng/mL in nude mice after injection of adenovirus. 241

Preclinical gene therapy approaches have been investigated using genes encoding a number of other antiangiogenic agents, including IL-4, IL-10, IL-12, IFN-b, thrombospondin-1, TIMP-1, TIMP-2, and platelet factor-4. In addition, the combination of ionizing radiation and intratumoral administration of a recombinant adeno virus expressing TNF-α resulted in tumor suppression in a murine xenograft model mediated by the destruction of tumor microvasculature. 242

CHAPTER REFERENCES


SECTION 62.2
Molecular Therapy

INTRODUCTION

The modern age of chemotherapy has its origins in ancient civilizations thousands of years ago, when therapists went to the forests to dig up roots, to peel the bark from trees, and to pick the leaves and flowers from plants as the first step in drug development. Through the time-consuming process of trial and error, extracts of the plant materials were identified that conferred a beneficial effect on the natural history of life-threatening diseases, such as cancer. It was not until the middle of the twentieth century that sufficient quantities of the purified active ingredients of these plant extracts were available for clinical trials.

The structure of these plant alkaloids, which were complex polycyclic hydrocarbon molecules, barely soluble in aqueous solvents and associated with very significant toxicities for the central nervous system, the kidney, and the hematopoietic and the gastrointestinal tissues, posed challenges for the therapist. Despite these limitations, plant compounds, such as the epiphelloslokins, the periwinkle alkaloids, the taxanes, and the camptothecins, have formed the basis of the most successful cancer treatment regimens of the first 30 years of chemotherapy.

Tremendous ingenuity has been displayed by pharmacologists and cancer treatment specialists, who have designed methods for limiting and circumventing the very significant toxicities of these compounds. Chemists working with synthetic organic compounds have continuously attempted to improve on the original natural products, which have spawned synthetic derivative compounds of the original natural products, such as vinorelbine tartrate, taxol, and irinotecan, which are now displaying exciting patterns of activity in refractory epithelial neoplasms.

The next phase of the development of chemotherapy was the cloning of the genes for naturally occurring biologically active molecules, such as interferon, interleukin-2, and the growth factors. During the last decade of the twentieth century, the enormous power of structural biology and computational chemistry was used to design totally synthetic compounds, which have no relationship to natural products but have displayed exciting activity in disease states: the protease inhibitors for human immunodeficiency virus, the kinase inhibitors for chronic myelocytic leukemia (CML), and the low-molecular-weight chemical inhibitors for virally associated cancers.

Now, at the dawn of the twenty-first century, the power of protein structure analysis, computational chemistry, combinatorial chemistry, and the engineering of biopolymers are being combined to produce an entirely new generation of antineoplastic drugs that are already reaching the clinic.

STRATEGIES OF NEW DRUG DESIGN

TYPES OF TARGETS

The drugs discussed here are those that will be designed to modify the assembly of subunits in a multimeric protein or to alter the assembly of complexes of multiple proteins into a receptor or a multiprotein array that is promoting the formation of a transcription initiation complex or a replication initiation complex. Thus, the ideal types of protein domains as targets for inhibition by low-molecular-weight chemicals must be considered before proceeding to the design of an inhibitor.

ATTRIBUTES OF AN IDEAL TARGET PROTEIN FOR MOLECULAR THERAPY

The attributes of an ideal target protein are outlined in Table 62.2-1. The ideal target for molecular therapy is a protein the sequence of which is unique to the tumor cell and is one that confers a selective growth advantage to the tumor cells. In addition, it is important that the target sequence be present in the tumor cells of all patients with that type of cancer and that 100% of the tumor cells in every patient have the target sequence.

The ideal target is present in 100% of the cells of a tumor population, because the presence of this protein target confers on the cell in which it resides a selective advantage over cells that do not contain this change. This type of target has dual advantages: The inhibition of the function of this target protein will suppress the transformed phenotype and, at the very least, will halt the progression of the disease state. It may also induce cell death of the neoplastic cell.

Another attribute that is important for an ideal target is that it presents some feature unique to the regulatory environment of the tumor cell that is not shared by the normal noncancerous cell. This type of tumor-specific target enhances the probability that an inhibitor will be specifically toxic for the tumor cell and will not adversely affect the normal cells. Examples of targets that are totally unique for the tumor cell include viral oncoproteins (proteins that may not have a correlate in normal mammalian cells), a chimeric gene that produces proteins with protein junctional domains that are not present in normal cells, a mutant primary structure of a widely expressed protein, posttranslational modification of a protein that is unique to the tumor cell, and a protein that is either expressed inappropriately in a particular type of tissue or appears in an intracellular location that is unique to the tumor cell. Table 62.2-2 presents a list of examples of such target oncoproteins that exhibit one or
In terms of the types of domains in the target protein that are more or less optimal for computational analysis and for interaction with low-molecular-weight chemical inhibitors of protein action, there is a general consensus in the field that protein-protein contact regions are very poor regions for modulation by chemical inhibitors. The interactions that represent the contact points for proteins often are hydrophobic areas that are binding to one another through van Der Waals forces. Such forces are at any given point extremely weak in terms of affinity. Thus, the interposition of a chemical that blocks interaction at a single point in this broad surface has very little effect on the overall assembly of a protein.

In contrast, receptors or pockets in which the catalytic site of an enzyme is located, or the crevice of a DNA binding domain, or a homodimerization domain that consists of interlocking invaginations, or stacking of flat aromatic amino acid side chains (e.g., tryptophans), which can bind to one another through sharing of electron orbitals, provide the structure within which a low-molecular-weight inhibitor can interact to disrupt a complex. Chemical inhibitors can act at multiple points with the local peptide domains to establish a very stable, high-affinity interaction that can have an impact on the entire protein.

Although receptors or enzyme pockets have a more stable conformation, all these regions of the protein are very mobile and are in continuous motion at the atomic level. Thus, interactions with low-molecular-weight chemical inhibitors may stabilize one of more of the conformations available to a protein domain. Low-molecular-weight chemicals that are designed to be inhibitors can stabilize a nonfunctional or inactive state of the protein. One example is the inactive state of a growth factor or an integrin receptor. Another example is the inactive state of the RAS proteins. A third example is a drug that can stabilize a conformal state of the protein, which limits access of a substrate, inhibits assembly of a multisubunit protein, or reduces the probability of assembly of a transcription initiation complex. Obviously, the more detailed the structural information, the more successful any design effort that is based on structure.

The alternative approach in developing drugs that stabilize one conformal state versus another is to select low-molecular-weight chemicals from a library of thousands of structural variants, each of which differs from the others by single atoms (i.e., two vs. one carbon atom in a side chain, etc.). Thus, the conformation of a chemical that best promotes the stabilization of an inactive conformal state of an enzyme or a receptor can be identified without any information about the structural details of the active and inactive states, merely by generating structural diversity, isolating relevant structures in a binding assay, and then assaying for loss of function of the protein molecules in the presence of that chemical. The same principle applies to the use of phage display libraries of random amino acid peptides. This requires the extra step of using computational and synthetic chemistry to create a chemical mimic of the peptide that produces the desired change in the protein. These two approaches can be combined by biasing the composition of the libraries on the basis of the structural information that exists about the target protein or the domain of the protein that is the contact point for the inhibitor.

Another issue is whether a domain that is in constant motion is a poor or good target as compared to a domain in which the order of the protein is so great as to reduce or restrict the excursions of the atoms and chemical functionalities. Accordingly, programs are available for simulating the possible trajectories of each atom in a biopolymer so that the dimensions of each state at very short expanses of time (nanoseconds) can be used to identify a useful target for engagement by a chemical inhibitor.

Thus, the true power of the use of structural data for drug design is revealed. Not only is there a possibility of identifying chemicals that could be selective for a particular primary amino acid sequence, but the possibility exists of identifying the chemical that is specific for the 1 in 1000 possible conformal states that can be engaged by a particular chemical structure for the purposes of stabilization or destabilization. The library approach exploits this vast expanse of possible targets by interrogating a large number of structural variants which can promote the conformal state of the target that is useful therapeutically.

**APPROACHES TO DRUG DESIGN**

**STRUCTURE ANALYSIS OF TARGET**

The recent example of the use of x-ray crystal structure of the human immunodeficiency virus protease for the development of successful drug treatment for the acquired immunodeficiency syndrome (AIDS) has led many researchers to apply this approach to the study of oncoproteins for drug development. The recent success in developing inhibitors of substrate-binding sites and cofactor-binding (adenosine triphosphate–binding) sites in the CML oncoprotein p210bcrabl led to the introduction into the clinic of a selective inhibitor of the p210bcrabl kinase in CML. This new low-molecular-weight chemical inhibitor of CML was developed through the application of a structural model for the analysis of the cofactor-binding site of the p210bcrabl kinase oncoprotein of CML.

**MIMICS OF INHIBITORS OR SUBSTRATES**

The application of analysis of substrates and mimics of ligands led to the RGD mimic inhibitors of integrin receptors that contribute to the ability of tumor cells to metastasize. Mimics of guanosine triphosphate (GTP) are also being used to develop inhibitors of the membrane RAS signal transduction proteins.

The development of chemical inhibitors of oncoproteins may start from computational analysis of the protein domain binding the cofactor or substrate, or it can start with the screening of combinatorial libraries of chemical mimics of a substrate or naturally occurring inhibitors of an oncoprotein. Alternatively, phage display libraries of random peptides can be used to collect all the peptide sequences that bind to an oncoprotein target. Analysis of the peptide motifs that are associated with high-affinity binding to the target can then lead to the design of mimics of the peptide inhibitors of the oncoprotein.

**Substrate Mimics for Tyrosine Kinase Inhibitors for Use in Chronic Myelocytic Leukemia**

CML is an ideal disease for the development of molecular therapy, since there is a single genetic change that is absolutely essential for the development of the leukemia, which is present in 100% of the patients and is present in 100% of the cells of each patient.  

The first hint that inhibition of an oncoprotein would suppress the phenotype of a neoplastic disease came from the antisense oligonucleotide field. Because CML is a disease of genetic instability and one in which the acquisition of sequential somatic mutations leads to evolution of the clinical phenotype of the disease, it was predicted that antisense oligonucleotides would have activity only in the very earliest stages of the disease process when the genetic complexity of the mutational change within the leukemic cells was lowest. Surprisingly, the anti-p210bcrabl antisense oligonucleotides were active in blast crisis cells both at the very end of the disease process and at the very earliest stages of the disease process. These findings now make sense in light of our understanding of the many actions of the p210bcrabl oncoprotein. Two of these pathways are activated within the CML cell. The first is the Pl3 kinase/Alt kinase/BAD pathway that results in the release of BCL-2 in the leukemic cells, prolonging survival in the absence of growth factors and extracellular matrix apoptosis rescue ligands and conferring chemotherapy resistance on these cells. The second results in increases in BCL-2 levels inside the CML cells through the GRB-2/RAS/RAF/BAD pathway. These two
pathways are important, even at the blast crisis stage, in conferring resistance to chemotherapy on these cells.

The next stage in the evolution of molecular therapy for CML was the discovery that peptide ligands, which are parts of naturally occurring negative regulatory proteins for the abl kinase, could be used to suppress the transformed phenotype of CML cells. This work led to the demonstration that expression vectors that carry inhibitory peptide transcription units directed to the ATP-binding sites of the tyrosine-specific protein kinases could also suppress the transformed phenotype of CML cells.

It was a natural extension of these findings to proceed to an examination of chemical inhibitors of either the substrate-binding site or the cofactor-binding (ATP) site of the tyrosine-specific protein kinase oncoproteins in CML. A picture of the catalytic pocket of this oncoprotein is presented in Figure 62.2-1. The tryphostins were the class of compounds found that inhibit tyrosine-specific protein kinases by binding to the substrate-binding site of p210bcrabl. These compounds were shown to decrease the in vitro proliferation of CML cells and to sensitize CML cells to the effects of chemotherapy. Interestingly, the tryphostins showed synergy when combined with cytokine therapy of chronic myelogenous leukemia cells.

![Image](Figure 62.2-1. Adenosine triphosphate (ATP) kinase pocket of the p210bcrabl oncoprotein, in which the abl tyrosine-specific protein kinase catalytic site is depicted. This kinase pocket contains a substrate-binding site (SBS), a catalytic site (CS), and a cofactor-binding site (ATP BS). The ATP cofactor is shown donating its gamma high-energy phosphate to the substrate.]

The next stage of development of chemical inhibitors was to engineer competitive inhibitors for the cofactor-binding (ATP) site of the tyrosine-specific protein kinase–binding site of p210bcrabl. This class of inhibitors is structurally distinct from the tryphostins. These compounds have been refined by Druker et al., who have introduced STI 571, a low-molecular-weight inhibitor of ATP binding, into the therapy of CML.

Druker et al. have already shown that these compounds in vitro are remarkably selective for the abl kinase and are able to reduce the circulating level of the white blood cell count in chronic-phase CML. Although the evaluation of these compounds is still at its early stage, cytogenetic remissions have already been achieved in some chronic-phase patients. In addition, the level of circulating leukemic cells is reduced even in myeloid blast crisis patients. These compounds exhibit inhibitory activity for the abl kinase at micromolar concentrations and are remarkably specific for the abl kinase, showing cross-inhibitory activity only for the platelet-derived growth factor kinase. These compounds are already producing great interest on the part of therapists as a vindication of the use of structural analysis of biopolymers and computational chemistry. The duration of these remissions and the extent to which all chronic-phase patients will exhibit such remissions are the subject of current clinical trials.

Building on this advance, other workers are attempting produce low-molecular-weight inhibitors that are more selective and more effective than the compounds of Druker. At Yale, Austin has proposed (D. J. Austin, personal communication, 1998) that a chemical mimic of ATP can be constructed by attaching adenosine to a bicyclic scaffold molecule, which is a mimic of the triphosphate of ATP (Fig. 62.2-2).

![Image](Figure 62.2-2. Adenosine-scaffold mimic in the adenosine triphosphate kinase pocket of the p210bcrabl oncoprotein. The interaction of the side chains of the adenosine scaffold with the local peptide domains of the kinase pocket is depicted. ATP BS, cofactor-binding site; CS, catalytic site; SBS, substrate-binding site.]

The bicyclic scaffold molecule contains five ligands that can interact with local protein domains in the abl kinase pocket. As shown in Figure 62.2-2, these chemical functionalities can engage multiple local protein domains in the kinase pocket and can be projected into a spherical three-dimensional space through the use of the bicyclic scaffold. In the example presented in Figure 62.2-2, adenosine, the natural ligand for ATP to the cofactor kinase–binding site of abl, is attached to the scaffold, leaving four other positions where chemical functionalities can be attached.

Automated, convergent, synthetic, combinatorial chemical synthesis can be used to generate low-complexity libraries of compound, all of which have the scaffold and the adenosine but in which the structure of the other chemical functionalities can be varied automatically to generate diversity. Recombinant clones of the kinase pocket are used for screening the libraries for the high-affinity binders, which may identify molecules that display therapeutic activity that is greater than existing compounds.

RAS Oncoproteins (Farnesyltransferase Inhibitors and G Pocket Inhibitors)

The RAS family of membrane-bound G proteins usually is activated in response to growth factor stimulation and trigger activation of at least two types of pathways within the cell: the MAP kinase pathway that ends in the nucleus at the level of transcription factor activation and the RAF/BAD pathway that results in the release of BCL-2 within the cell. In cancer, the acquisition of point mutations in RAS leads to continuous activation of these proteins, contributes to the dual phenotypes of chemotherapy resistance, and increases proliferation. This combination has the resultant effect of increasing the genetic instability of populations of cancer cells. These point mutations often are acquired as secondary mutations in a broad spectrum of epithelial neoplastic cells. In fact, very few neoplastic diseases exist in which RAS mutations do not occur. CML is an example of a disease in which the acquisition of RAS-activating point mutations is very rare, in part, perhaps, owing to the fact that the p210bcrabl kinase of CML results in activation of the RAS proteins.

The connections made by RAS, which are essential for it to be linked to its interacting pathways that link growth factor stimulation with gene expression of survival, depends on its localization to the plasma membrane. This localization depends on the action of a number of enzymes, which mediate posttranslational modifications of the RAS protein. Inhibitors of one of these posttranslational enzymes—protein farnesyltransferase—showed activity in animal models with respect to the suppression of human tumor xenografts. Interestingly, although the spectrum of clinical activity of the farnesylation inhibitors has been somewhat of a disappointment,
the interesting surprise is that these agents appear to display activity even in tumor populations in which farnesylation of RAS is not playing a role in the natural history of the disease. Despite the initially disappointing spectrum of activity in trials of the farnesylation inhibitors, the inhibition of RAS activity is still an important goal. Every time a transdominant negative inhibitor of RAS activation has been tested in animal models or cell lines, a dramatic effect on the phenotype of the cancer cells has been observed in a spectrum of malignancies, including CML, melanoma, and gastrointestinal cancer. Thus, many groups have been attempting to analyze the structure of RAS so as to design low-molecular inhibitors of RAS.

At the center of these new molecular approaches to the development of inhibitory agents for RAS is the GTP/GDP exchange role of RAS. As outlined previously, RAS acts as a molecular switch for cell growth. In its off state, p21RAS is bound to guanosine diphosphate (GDP), whereas on activation, GDP is exchanged for GTP (Fig. 62.2.3).

When GTP occupies the guanine nucleotide pocket of RAS, cell growth is promoted. In fact, many of the point mutations acquired in tumor cells by RAS prevent the hydrolysis of GTP. This maintains the activated state of RAS and prevents a return to its off state. The Karplus group at Harvard has designed molecules that would recognize the dimensions and charge of the guanine nucleotide pocket of RAS in its activated state. Such molecules would bind to activated RAS, not to RAS proteins in their nonactivated state. This group is undertaking a computational analysis of the molecular switch regions of RAS (residues 30–38 and residues 60–75).

Karplus and his coworkers studied the bicyclic scaffold shown in Figure 62.2.2, now attached to a guanosine molecule (Fig. 62.2.4) and found that the guanosine scaffold was energetically a good mimic of the GTP and engaged the same amino acid side chains in the RAS guanine nucleotide–binding pocket as does GTP. These computational models have suggested that the designing of chemical mimics of GTP such that they will bind more tightly and selectively to the inner protein domains lining the GTP pocket of RAS is feasible. The guanosine scaffold shown in Figure 62.2.5 may engage multiple domains in the RAS-binding pocket and, therefore, produce inhibitors that are selective and, therefore, nontoxic as well (M. Karplus, personal communication, 1996).

Metastasis Inhibitors

The integrin receptors constitute a complex class of surface cytoadhesion molecules that mediate apoptosis rescue signals from extracellular matrix proteins and stromal cells or supporting cell ligands into the cell, with connections to cytoskeletal structures and transcriptional regulation pathways within the cell. The integrin receptors can exhibit changes in the number of receptors on the membrane and changes in the composition of the available subunits that contribute to the heterodimeric arrays of integrin receptors, and they can undergo changes in conformation, sometimes associated with posttranslational modification, which define differing states of functionality. Integrin receptors can also be activated to functionally active conformal states from signals arising from within the cell. Thus, the integrin receptors, which are apoptosis rescue signal transduction elements, can be activated from “inside out” and from “outside in.”

Several researchers have reported that the transfection of integrin expression vectors carrying specific integrin subunits, such as the b3 integrin, can direct cells to metastasize to specific organs. Indeed, the aVb3 integrin receptor is commonly encountered in cancer cells that are metastatic and rapidly proliferating, whereas the aVb2 integrin receptor is often found in differentiating cells.

Extensive testing of the ligands and antibodies that can engage various integrin receptors have shown that the inhibitors of integrin receptors can be effective in
suppressing particular patterns of metastatic spread in preclinical animal models. Some groups have used phage display libraries in which thousands of phage clones, each with a different peptide, are injected into the tail vein of a mouse. This is followed by analysis of the endothelial cells from the vessels of different tissues. These studies have shown that peptide sequences exist that are characteristic of the vessels of different tissues. This knowledge has led to the speculation that chemical mimics of trafficking molecules on the endothelial surface of different tissues could be used to prevent metastases to a particular target organ. An example would be the treatment of individuals with stage III colon cancer with chemical mimics of peptides, which would bind to the cytoadhesion molecules characteristic of vasculatures of hepatic tissues.

Several groups have now reported the isolation of chemical mimics of the RGD peptide, which binds to the integrin receptor. The use of phage display peptide libraries led to the collection of peptide motifs, including RGD, that bind to integrin receptors. Now, combinatorial chemical libraries are being used to refine the structure of low-molecular-weight chemical inhibitors of integrin receptors that appear to reduce the metastatic potential of a cell. These types of drugs should be highly exciting therapeutically when they are brought into the clinic.

LOW-MOLECULAR-WEIGHT INHIBITORS FOR THE ANGIOGENESIS RECEPTOR

One of the most exciting paradigm shifts has been the attempt to target drug development to normal tissues. Angiogenesis is a process that takes place during tumor growth. Now, inhibitors of this process are being tested in the therapy of solid tumor malignancies. This approach was stimulated by the correlation between the density of the neovascularature in histopathologic specimens and the aggressiveness of the natural history of the disease in a given patient. Also stimulating interest in this area was the demonstration in animal models that a number of naturally occurring modulators of angiogenesis also displayed activity in modulating the rate of tumor growth in animal models. This has led to the isolation of a large number of agents (synthetic chemicals as well as naturally occurring biologically active proteins) that are known to affect angiogenesis in the treatment of solid tumors and hematopoietic neoplasms. There is immense interest in the current clinical trials of these natural products and naturally occurring proteins to determine whether they are selective for tumor neovascularature or whether they affect the formation of vasculature in normal tissues as well.

Computational and combinatorial biology is being used to test whether it is possible to develop synthetic inhibitors of angiogenesis that are specific for tumor cell neovascularature. The first step was to test whether computational analysis of the normal angiogenesis receptor could be used to design and synthesize low-molecular-weight chemical inhibitors of the angiogenesis receptor; this has been accomplished (C. Crews, personal communication, 1999). Two approaches are being used now to develop chemical therapy that is antiangiogenic. The first is to engineer low-molecular-weight inhibitors of the angiogenesis receptor. At Yale, Hu et al. have taken a second approach: chimeric immunoconjugate molecules that are composed of an amino-terminal targeting domain that binds specifically to tumor endothelial cells, and a carboxyl-terminal end that carries the Fc fragment of IgG. The latter molecule is known to bind to natural killer cells. Hu et al. have reported that the release of such chimeric immunoconjugate molecules into the systemic circulation of human tumor xenografts in nude mice results in regression of established tumor nodules. This reaction has been shown to depend on the binding of natural killer cells to the Fc fragment of the immunoconjugate molecules.

CHEMICAL INHIBITORS FOR ONCOPROTEINS OF DNA TUMOR VIRUSES

The oncoprotein products of DNA tumor viruses provide almost ideal targets for the development of low-molecular-weight chemical inhibitors for cancer treatment or prevention. As in many of the other targets we have discussed, the continued expression of these proteins is essential to the maintenance of the neoplastic phenotype. Moreover, since they are viral proteins, those proteins are unique targets that are not essential to the survival or proliferation of normal cells. Thus, drugs developed against these proteins may be highly selective for the tumor tissue and not toxic to the uninfected normal tissue.

The diseases associated with the DNA tumor viruses, human papilloma virus (HPV), and Epstein-Barr virus (EBV) are significant world health problems. HPV-associated malignancies represent the second leading cause of cancer death in the world among women. In addition, it is estimated that 40% of all AIDS patients alive today will eventually develop an EBV-associated non-Hodgkin's lymphoma. Again, the use of antisense oligonucleotides first showed convincingly that the continued expression of the protein products of the episomal DNA of these viruses was essential for the continued replication of tumor cell lines and growth of these cells in human tumor xenografts in severe combined immunodeficiency mice. HPV E6/E7 antisense oligonucleotide transcription units were shown to suppress the growth of cervical cancer cell lines in severe combined immunodeficiency mice. Antisense oligonucleotides to the EBNA I and LMP2 proteins of the EBV were shown to induce replication arrest of EBV-associated tumor cell lines and induction of apoptosis of these cells. Additionally, the use of the antisense oligonucleotides to these unique targets produces sensitization of these cells to chemotherapy.

Most surprising is that cervical cancer cell lines harboring HPV-transforming proteins E6 and E7 still retained dependency on these oncoproteins for the continued proliferation and survival of these cells in vitro as well as in animal models. Thus, drug development is being targeted to these two proteins and their associated proteins, with the aims of stopping progression of disease as well as sensitizing the cervical cancer cells to the effects of chemotherapy.

The E2 protein of HPV is also an interesting target for prevention of cervical cancer. Very commonly, the chronic infection of HPV in the cervical mucus, which is associated with dysplasia and chromosomal translocations, persists for years before the development of invasive cancer. In the United States, such dysplastic states of the cervical mucosa can be identified by repetitive Papanicolaou smear, and appropriate surgical action can be taken if the dysplasia is severe or persists. In contrast, in most areas of the world, the infrastructure necessary to screen women for HPV-associated dysplasia does not exist. Thus, the development of chemicals that would inhibit the replication of viral protein complexes necessary for the assembly of the replication initiation complex could be useful for the development of preventive therapy for cervical cancer.

Two of the viral proteins—E1, a helicase, and E2, a chaperone protein—are important for assembly of a functional replication initiation complex in HPV-infected cells. Once infected, the terminal epithelial cells of the cervical mucosa contain approximately 50 copies of HPV DNA per cell. These copies of HPV are retained at a stable copy number because the replication of the HPV DNA episome is coupled to the replication of the host cells. This is probably owing to the need for host DNA polymerase for the replication of the HPV DNA.

E2 must form a homodimer before binding to the E2-binding sites in the HPV origin of replication. E2 also connects with E1, which also binds to HPV DNA. The use of monoclonal antibodies has already shown that blocking of growth factor receptors can act to suppress the proliferation of tumor cells, enhance their chemotherapeutic sensitivity, and extend the duration of the progression-free interval in cancer patients. The Her2/neu receptor antibody Herceptin and the epidermal growth factor receptor inhibitor Iressa are two examples. Again, the use of antisense oligonucleotides first showed convincingly that the continued expression of the protein products of the episomal DNA of these viruses was essential for the continued replication of tumor cell lines and growth of these cells in human tumor xenografts in severe combined immunodeficiency mice. HPV E6/E7 antisense oligonucleotide transcription units were shown to suppress the growth of cervical cancer cell lines in severe combined immunodeficiency mice. Antisense oligonucleotides to the EBNA I and LMP2 proteins of the EBV were shown to induce replication arrest of EBV-associated tumor cell lines and induction of apoptosis of these cells. Additionally, the use of the antisense oligonucleotides to these unique targets produces sensitization of these cells to chemotherapy.

SUMMARY AND FUTURE DIRECTIONS

In the twenty-first century, drug development will no longer depend on going to the forests to dig up roots, to pick flowers and leaves, or to strip the bark from the trees to discover new drugs for cancer treatment. It is now possible for a laboratory scientist to recapitulate in a few months what once required millions of years of evolution to produce. The ability to analyze protein structure, to decipher the dynamic array of conformal states of oncoproteins (both activating and inactive), and to evolution to produce. The ability to analyze protein structure, to decipher the dynamic array of conformal states of oncoproteins (both activating and inactive), and to
The availability of computational chemistry and the ability to generate diversity in chemical structure have enabled scientists to reach beyond the limits of available data about structure and activity relationships and to probe deeply in the unknown repository of untapped chemical structures for molecules that may exhibit favorable binding and specificity properties. It is apparent that the explosion of information about genetic changes in tumor cells will provide the necessary clues with which the chemist can direct structural diversification and screening to isolate newer and more effective compounds. Recent successes in the development of drugs for AIDS and CML on the basis of protein structure is a dramatic validation of this new approach to drug design. It is possible that this paradigm will be reiterated many times in the development of an entirely new generation of cancer treatment drugs based on inhibitors of receptors, transcription factors, adaptor molecules, viral and somatic cell oncoproteins, and apoptosis arrest proteins. The dividends for cancer patients and society may be substantial in terms of reducing the cost of therapy and enhancing their efficacies.

CHAPTER REFERENCES


TABLE 62.2-3. Genetic Changes in Solid Tumor and Hematopoietic Neoplasms That Are Suitable Targets for Drug Development
INTRODUCTION

The high rate of morbidity and mortality attributable to cancer has stimulated concerted efforts to prevent malignancies from developing. The recognition that environmental factors may account for the majority of cancers has encouraged researchers to identify the exogenous factors that trigger the carcinogenic process and to define their role in tumorigenesis. Infectious agents make up one important class of environmental factors implicated in tumor development. Although the oncogenic potential of some infectious agents, such as hepatitis B virus (HBV), was recognized more than two decades ago, many of the infectious agents now believed to be oncogenic were discovered after 1975 (Table 63.1-1). These latter include the oncogenic papillomaviruses, hepatitis C virus, herpesvirus type 8, and Helicobacter pylori. It seems likely that further research will result in additional forms of cancer being attributed to infectious agents. The expanded list will arise via the demonstration that infectious agents already recognized as oncogenic may be causally involved with additional forms of cancer, by attributing these additional cancers to other infectious agents not yet recognized as oncogenic, or both.

Identification of an infectious agent in the etiology of a malignant process implies that timely interference with the infection could prevent the tumor from arising. The development of effective vaccines against infectious carcinogenic agents represents a potentially powerful approach and is the main focus of this chapter. The prototype for this approach is the HBV vaccine, which can protect immunized individuals against both acute disease and the malignant consequences attributable to this virus.

This chapter briefly considers how infectious oncogenic agents lead to cancer, discusses general issues related to developing vaccines against these agents, and presents individual sections devoted to the three agents that account for the most cancers worldwide. Vaccines against other infectious oncogenic agents are also in various stages of development.

INFECTIOUS AGENTS AND CANCER

Reducing exposure to an identified carcinogen represents the principal approach to reducing the carcinogenic effects of many environmental carcinogens. For carcinogens such as cigarette smoke, entrenched human behavior and conflicting economic interests may present considerable obstacles to reducing or eliminating exposure. By contrast, a vaccine against an infectious carcinogen does not require modification of the behavior that leads to exposure because the vaccine attenuates the oncogenic activity of the infectious agent by reducing or preventing infection of target tissue. Furthermore, the induction of herd immunity via the widespread use of an effective vaccine, offers the possibility of reducing the risk of nonimmunized individuals to exposure to the infectious agent. Vaccination also offers the long-term possibility of eliminating the agent from the environment.

Before considering vaccination itself, it is worthwhile reviewing some features of oncogenic infectious agents, as their characteristics may have implications for vaccine development, testing, and implementation. Viruses, bacteria, and parasites have all been implicated in the pathogenesis of human cancer (see Table 63.1-1). Investigators at the International Agency for Research on Cancer estimated that in 1990 approximately 15% of cancers worldwide could be attributed to infectious agents (Table 63.1-2). In the United States and other developed countries, a smaller proportion of cancers (approximately 9%) are associated with these agents, while they account for a higher proportion (approximately 20%) in developing countries.

Several factors probably account for these differences. Some of the infectious agents, such as parasites with oncogenic potential, are extremely uncommon in the United States, or the rate of infection may vary greatly, as with HBV. For others, such as human papillomaviruses (HPV), infection in the United States is common, but Pap smear screening for premalignant lesions in the cervix leads to effective treatment before carcinomas develop. In still other instances, strain differences or the interaction between the infectious agent and environmental, host factors, or both might help determine the rate of carcinogenic progression.
The identified oncogenic infectious agents share at least four characteristics: the ability to establish chronic infection, the actual establishment of chronic infection in those individuals destined to develop malignancy attributable to the infection, an interval of many years between the initial infection and the development of malignancy, and a benign (i.e., nonmalignant) outcome for most infected individuals. These characteristics imply that cancer attributable to infectious agents develops only after prolonged infection and that a malignant outcome arises only after the development of infection-dependent changes in the host.

Consistent with current concepts of the multistep nature of carcinogenesis, the changes in the host probably involve genetic alterations in potential target cells, impairment of the immune system, or both. Since not all infectious agents that establish a chronic infection are carcinogenic, chronic infection with agents not implicated in carcinogenesis must be much less efficient in inducing the types of changes that lead to cancer than are those agents that are implicated in carcinogenesis.

Infection seems to induce tumors by three main mechanisms, either singly or in combination, depending on the agent. In some instances, such as with the papillomaviruses, the agent infects the potential target cell population and induces a series of changes from within those cells that lead to cancer. Some of the changes include alterations in the agent, so that only a subset of its genetic information is expressed. The viral genes that continue to be expressed contribute directly to the tumorigenic phenotype by, for example, inactivating the activity of tumor suppressor genes. Other genes from the virus are presumably silenced to lower the likelihood of the tumor cells being recognized and destroyed by the immune system.

In a second scenario, as occurs with H. pylori, the infectious agent is present in the target tissue and induces cancer by local effects, usually chronic inflammation, but the agent remains outside the tumor cells. By the time the tumor is capable of distant metastasis, if not sooner, its growth becomes independent of the infectious agent.

The third mechanism, which is more indirect, results in increased tumor risk secondary to suppression of the host immune system. This process has been identified in tumors that arise as a consequence of infection with the human immunodeficiency virus (HIV), which predisposes infected individuals to a variety of tumors. As the immunosuppression associated with HIV renders patients much more susceptible to chronic infection with other agents, including some with oncogenic potential, many of the tumors result from the combined effects of coinfection with HIV and these other agents.

**PROPHYLACTIC VERSUS THERAPEUTIC VACCINATION**

Vaccination against an infectious oncogenic agent can be contemplated in three possible clinical settings: as a prophylactic vaccine to prevent infection or acute disease, as a therapeutic vaccine to treat an established infection before a malignancy has been induced, and as a therapeutic vaccine to treat the infection after the malignant tumor has developed, provided the growth, viability, or both growth and viability of the tumor still depend on the presence of the infectious agent. The use of vaccines in the treatment of cancer, which is the subject of intense investigation, is covered later in this chapter. This section examines the potential utility, complexity, and challenges for vaccines whose goals are to prevent established infection or to eradicate established infection before tumor development.

Ideally, a vaccine should be effective in both prevention and treatment. However, it has proven easier to develop prophylactic vaccines against infectious agents than therapeutic ones. Of the more than 20 approved vaccines in the United States, all are approved for prevention, rather than treatment, of established infection.

The cellular and humoral arms of the immune system generally function together to interfere either with the initial phases of infection or the eradication of established infection. Antibodies capable of neutralizing the infecting agent appear to be the prime effectors in preventing infection, while CD8+ T cells appear to serve more critical roles in the resolution of established infection. The success of prophylactic vaccines in inducing long-term protection against infection probably lies primarily in their ability to induce neutralizing antibodies, although other immune components probably also contribute to their overall effectiveness.

For infections that induce serious acute disease, such as polio, the main theoretical goal of vaccination is the prevention or modification of the acute disease. Since it is easier to reduce the incidence of acute disease by inducing widespread immunity with a prophylactic vaccine than by treating established infection, a prophylactic vaccine approach has an important theoretical advantage in this setting over a therapeutic one.

However, for cancer-causing microbes that induce benign primary infection, such as papillomaviruses, the long interval between infection and cancer, combined with the apparently necessary role played by the infectious agent during much of this period, provides a relatively long opportunity to identify and treat the infected population. Situations in which premalignant lesions attributable to the microbe are frequently identified, as in the case of Pap smear screening for cervical cancer, present an opportunity to intervene with a therapeutic vaccine.

The comparative ease with which prophylactic vaccines can be developed, relative to the continuing challenge posed by therapeutic vaccine development, makes prophylactic vaccination an important approach for cancer vaccines. Another advantage of prophylactic vaccines is that they do not depend on effective progress in identifying individuals with premalignant disease. Furthermore, worldwide public health vaccine efforts are designed primarily for the administration of prophylactic vaccines, and this vaccine approach has been extremely successful and highly cost-effective in combating many infectious diseases. In addition, the primary disease induced by many oncogenic infectious agents can provide sufficient rationale for development of a prophylactic vaccine, in addition to the long-term prevention of cancer.

Numerous theoretical and practical concerns arise when considering development of a prophylactic vaccine against cancer. Safety is especially important for a vaccine whose primary goal is to prevent cancer, as many individuals will never be infected by the agent, the majority of infected individuals will never develop malignancy, and malignancy only develops many years after infection. In addition, it requires many years to determine whether a candidate prophylactic vaccine can prevent cancer. The minimum theoretical duration of efficacy trials whose end point was prevention of malignancy was the length of the latent period between infection and malignancy. Thus, while vaccination against HBV was found more than 20 years ago to prevent primary infection, data showing this vaccination can actually reduce the frequency of hepatocellular carcinoma are only beginning to accumulate.

Although cancer prevention might appear to be a necessary end point for establishing vaccine efficacy, there can be serious ethical obstacles to using this clinical end point. For those clinical situations in which the standard of care involves the treatment of premalignant lesions to prevent the development of malignancy, as with cervical abnormalities related to Pap smear screening, it may be unethical to delay treatment until cancer develops. In addition, once a vaccine has been shown to be effective in preventing infection, it might be considered unethical to withhold the vaccine from the control group, despite the possible ambiguities such vaccination might create for efforts to determine directly whether the vaccine could reduce cancer frequency.

The most critical information for vaccine development lies in determining which antigens can induce protective immunity. For HBV, many aspects of its immunology and its role in carcinogenesis remain incompletely understood, but identification of a protective viral antigen was able to lead to development of an effective vaccine.

Many of the infectious agents with recognized oncogenic activity (see Table 63.1) induce nonmalignant diseases that carry significant morbidity and economic cost long before they cause cancer, although oncogenic HPV infection may be a notable exception. It may be more practical to use a nonmalignant end point in efforts to demonstrate efficacy, with the effect on cancer being determined, directly or indirectly, by follow-up studies. This was the approach taken with the hepatitis B vaccine, which has been approved for use in the United States because of its ability to prevent acute hepatitis. However, the presumption that the vaccine would prevent many liver cancers attributable to hepatitis B infection was also considered in recommending widespread use of the vaccine.

Some issues surrounding a therapeutic vaccine differ from those of a prophylactic one. As the individual is already infected, it is usually much easier to carry out therapeutic clinical trials that determine efficacy, compared with prophylactic trials. A therapeutic vaccine trial can limit its enrollment to infected individuals at a particular stage of disease, and the response to vaccine can be evaluated, usually within a short period, by suppression of infection and of the disease.

Another major theoretical advantage of an effective therapeutic vaccine is that it can have an effect on the incidence of malignant disease much sooner than a prophylactic vaccine. For cervical cancer, where the interval between HPV infection and cancer typically takes more than 20 years, it would take at least this length of time before a prophylactic vaccine, even if it were completely effective and were given to all at-risk individuals, would have any effect in the incidence of malignancy. By contrast, an effective therapeutic vaccine could reduce the incidence of cervical cancer after a much shorter interval. These considerations underscore the potential utility of determining whether successes with therapeutic vaccines in experimental animal systems, such as H. pylori and papillomaviruses, can be
HEPATITIS B VIRUS

The identification of HBV in the 1960s led to epidemiologic studies that have clarified its worldwide role in hepatocellular cancer. Although infection with this DNA virus can cause acute hepatitis, its most serious global consequences are chronic hepatitis, cirrhosis, and hepatocellular carcinoma, all of which are associated with chronic HBV infection. It is estimated that there are more than 1 million chronic HBV carriers in the United States and more than 300 million carriers throughout the world. The virus is believed to account for approximately 1 million deaths per year worldwide, approximately one-half of them secondary to hepatocellular carcinoma.

In highly endemic areas, the lifetime risk of exposure may exceed 50%, and most HBV infections occur perinatally or in early childhood. In areas of low endemicity, HBV transmission occurs mainly in adults, often via sexual exposure or parenteral exposure from infected shared needles used with illicit drugs. The risk of medical exposure to infected blood products has been greatly reduced by systematic screening of these materials for HBV.

The HBV carrier state, which is a measure of persistent infection, is a critical determinant of the long-term risk for hepatocellular carcinoma. HBV carrier rates vary dramatically in different populations, being less than 0.5% in the United States and many other countries with high standards of living, to rates of 10% to 20% in parts of Africa, Asia, and the South Pacific. The relative incidence of cancer attributable to HBV follows a similar geographic distribution, with many studies consistently showing chronic HBV infection is an important risk factor for hepatocellular carcinoma.

The frequency with which persistent HBV infection is established varies inversely with the age of exposure. The highest risk is by far occurs during the perinatal period and the first year of life. More than 70% of neonates born to infected mothers become chronic carriers, compared with around 8% of those exposed at 3 years of age and an even lower proportion in immunocompetent adults.

Conversely, HBV is much more likely to induce acute hepatitis in older age groups, while acute infection is usually asymptomatic when exposure occurs in the perinatal period. This difference occurs because the acute hepatic disease results from the immune response to infection, as HBV does not directly induce hepatocellular damage. Thus, the relative immunoincompetence of infants probably accounts for their lack of symptoms and for the high frequency with which the virus establishes persistent infection in this age group.

The precise role of the virus in the development of hepatocellular carcinoma has not been fully determined. Persistent infection appears to lead to cancer mainly as the result of chronic inflammation and repeated cellular regeneration, and some evidence implicates the viral X gene, which encodes a transcription factor, in this process.

Most cases of liver cancer associated with HBV infection arise after chronic hepatitis has lead to cirrhosis. Hepatocellular carcinoma may develop in as little as 5 to 10 years of infection, but it does not usually occur until an individual has been infected for at least 20 to 30 years. Ongoing infection continues to be a risk factor for carcinoma, with an estimated cumulative risk of 15% for an individual who has had persistent infection for 50 years.

The rate of hepatocellular carcinoma attributable to HBV is at least three times higher in male than in female subjects, even when a similar proportion of male and female subjects are exposed to HBV. The difference is explained in part by the higher frequency with which the HBV carrier state is established in male subjects (close to 2:1) and the greater likelihood of female subjects to eliminate the carrier state.

The HBV vaccine is the prototype prophylactic vaccine against an oncogenic infectious agent. A key to HBV vaccine development was the recognition that the neutralizing antibodies were directed against the hepatitis B surface antigen (HBsAg), and that there is only one HBV serotype. The HBsAg is expressed in relatively pure form as circulating enveloped virus-like particles (VLPs) in the blood of infected HBV carriers. The HBsAg particles do not carry the viral genome and are not infectious. It was possible to purify the particles, inactivate possibly contaminating infectious virus with formalin (which should also have inactivated other viruses), and to test the particles as a subunit vaccine in human clinical trials that were initiated in 1975.

The HBsAg vaccine was found to be well tolerated, to induce an immune response in almost all vaccinees, and to reduce the infection rate in adults by at least 95% and in neonates by at least 85%. The protection rates in neonates may be further increased by giving hepatitis B immune globulin in addition to the vaccine. The vaccine was licensed in the United States in 1981.

An analogous HBsAg particle vaccine has been produced in yeast by recombinant DNA technology, and it was licensed in the United States in 1986. The recombinant vaccine has replaced the blood-derived vaccine, although the immunogenic properties of the latter product are somewhat superior to the recombinant material. Efficacy trials have shown that the recombinant vaccine confers a similar rate of protection against HBV as the blood-derived vaccine.

Efficacy trials have shown that the recombinant vaccine confers a similar rate of protection against HBV as the blood-derived vaccine. In addition, the recombinant vaccine is less expensive to manufacture and does not have the theoretical concern of contaminating infectious material, although extensive analysis of the blood-derived vaccine recipients failed to document excess exposure to infectious agents.

The initial series of immunizations, with either vaccine preparation, confers protection against infection for at least several years. In instances in which breakthrough infection has occurred several years after immunization, it has not been associated with development of a chronic carrier state. Routine revaccination is not recommended at this time by vaccine advisory groups in the United States. Further studies, in progress, should determine whether this policy should remain in place or be modified.

The long interval between HBV infection and the development of hepatocellular carcinoma means that only limited data thus far indicate directly that vaccination can actually decrease the incidence of cancer attributable to HBV. Data from an HBV vaccination program in Taiwan, an area with high HBV endemicity where universal vaccination was instituted in 1984, do show such a reduction in children. From 1990 through 1994, the incidence of cancer in children aged 6 to 14 was one-half the rate before implementing vaccination, and that for children aged 6 to 9 was only one-fourth the rate of the earlier period.

These results indicate that HBV vaccination can achieve the long-term goal of cancer reduction. However, such a reduction will occur only if the populations most at risk are given the vaccine in a timely manner. Even in such a setting, reduction in cancer among adults, in whom the incidence is greatest, would not be expected to be seen until these children achieve adulthood.

HUMAN PAPILLOMAVIRUS

Papillomaviruses are epitheliotropic agents that induce benign papillomas of the skin and mucous membranes. A subset of HPV types, which are almost always transmitted sexually, are the main cause of human cervical cancer. Infection with these HPV types is a strong risk factor for cervical cancer, and HPV DNA from one or more of these types is found in virtually all cervical tumors.

The virus encodes oncoproteins that appear to be required both for the induction and the maintenance of the cancer. HPV infection has also been linked to the majority of anal cancers, in which the molecular pathogenesis seems to be similar to that of the cervix, as well as to other anogenital malignancies and to tumors of the upper aerodigestive tract. The precise relationship between HPV infection and the development of some of these cancers is not as firmly established as that with cervical cancer.

As with HBV, cancer attributable to HPV develops only after many years of persistent HPV infection and is an infrequent outcome of infection. Cervical HPV infection is remarkably common, with sensitive polymerase chain reaction assays indicating prevalence rates of 20% to 40% among young sexually active women. Most infections are self-limited, and clinical outcomes are associated with resistance to reinfection. The antigenic divergence between HPV types is such that protection appears to be largely type specific.

The HPV's associated with cervical and anal cancer are usually designated high-risk types, as contrasted with the low-risk types, which also participate in anogenital infection but are almost never found in cervical or anal cancers. Although there are several high-risk HPV types, HPV-16 is the most common type, being present in more than one-half of cervical cancers worldwide. The viral E6 and E7 genes are preferentially retained and expressed in the tumors, where they inactivate the p53 and Rb tumor suppressor proteins, respectively.
In principle, cervical cancer is already a largely preventable disease. In countries in which Pap smear screening reaches most women, the incidence of cervical cancer has decreased markedly. For example, in the United States, for example, the rate of cervical cancer has decreased several-fold since the 1950s, from more than 50 in 100,000 to less than 10 in 100,000. This decrease in cancer rates is even more impressive because it has occurred during a period in which increased sexual promiscuity has been associated with an increased frequency of genital HPV infection.

However, the cost of Pap smear screening and follow-up is high (estimated to be more than $5 billion annually in the United States), and Pap smear screening is not routinely available in many less well-developed countries. This situation has made cervical cancer the leading cancer among women in many developing countries, and it remains the third most common female cancer worldwide. Such a vaccine would have the long-term benefits of a purely prophylactic vaccine while reducing the incidence of gastric cancer after a much shorter interval.

Establishing the etiologic link between HPV infection and cervical cancer (and other tumors) has focused interest on developing an HPV vaccine. The main goal would be to protect against cervical cancer, which accounts for approximately 75% of the cancers worldwide attributable to HPV infection (see Table 63.1-1). Since cervical cancer is especially prevalent in developing countries, such a vaccine would potentially have its greatest public health effect in these populations. However, in some high-income countries, an effective HPV vaccine might further reduce the current incidence of cervical cancer by reaching populations that currently do not receive adequate Pap screening. In addition, by decreasing the frequency of genital HPV infection, a vaccine could decrease the anxiety and morbidity associated with cervical dysplasia and its treatment and reduce the social stigma associated with genital HPV infection. If widely used, a vaccine might reduce the frequency and overall cost of cervical cancer screening. The overall effectiveness of a vaccine, even for prevention of cervical cancer, would be greater if it were given to male subjects as well as to female subjects.

As papillomaviruses contain oncoproteins, and a prophylactic vaccine would be directed toward healthy young individuals, efforts to develop a prophylactic vaccine have emphasized a subunit approach, analogous to that used for HBV. Indeed, constitutive high-level expression of the L1 major structural viral protein, even in nonmammalian cells, will lead to its efficient self-assembly into VLPs that resemble authentic viral capsids structurally and antigenically. Preparative amounts of VLPs can be synthesized in insect cells or yeast. Such VLPs are suitable immunogens that, as is true of authentic virions, possess the immunodominant conformational epitopes capable of raising high titer neutralizing antibodies.

Since papillomaviruses are species specific, animal papillomavirus models have been used preclinically to evaluate VLPs as a candidate subunit prophylactic vaccine. Excellent results (90% to 100% protection, even without adjuvant, against high-dose virus challenge) have been obtained with systemic immunization in three models, one cutaneous and two oral mucosal. The neutralizing antibodies appear to be largely responsible for the protection, which can last at least 1 year. Excellent protection has also been reported in the cutaneous animal model when a vaccinia vector was used to express L1 or when the L1 gene was injected as naked DNA. However, administration of protein seems more likely to be readily accepted by regulatory authorities in developed countries.

Alternative approaches are also being considered. These include mucosal immunization via purified VLPs or via nonpathogenic enteric bacteria or the use of nonstructural viral proteins either alone or as incorporated into VLPs. Nonstructural viral proteins have been shown to prevent and, in some cases treat, animal papillomavirus infection, in addition to working in tumorigenic models with cells that express a papillomavirus protein. The utility of a vaccine that might treat established infection, especially if it were also effective prophylactically, makes it highly worthwhile to pursue the development of therapeutic HPV vaccines.

HPV-11 and HPV-16 L1 VLPs have been tested in early safety and immunogenicity trials of intramuscular injection of healthy human volunteers. The vaccines were well tolerated and induced serum antibody titers, with or without adjuvant, comparable with the protective levels induced in animals. Large-scale efficacy trials will be needed to determine if this approach, which is not specifically directed toward the mucosal immune system, will confer protection against cervical HPV infection.

As noted in the Prophylactic versus Therapeutic Vaccination section, it would take many years to establish unequivocally if a vaccine actually had an effect on cervical cancer, since cervical HPV infection usually precedes the development of malignancy by more than 20 years. In addition, ethical considerations would argue against allowing cervical lesions arising in women in a vaccine study population to progress to malignancy. However, since infection with high-risk HPV is highly associated with the development of Peyer's patch lymphomas, which in turn place women at increased risk of progression, it is likely that surrogate intermediate end points of infection will be used to determine vaccine efficacy in prospective trials.

If prophylactic vaccination with VLPs proves efficacious, the type specificity of neutralizing antibodies makes it likely that protection will also be type specific. Since multiple HPV types are found in cervical cancer, the type-specific nature of the immune protection implies that a polyvalent vaccine would be required to inhibit the majority of cervical cancers. For example, a vaccine that contained VLPs against HPV-16, 18, 31, and 45, might theoretically prevent close to 80% of cervical cancers.

**Helicobacter pylori**

*H pylori*, which was discovered in 1982, induces chronic gastric infection of almost one-half the world population. Infection with *H pylori* is associated with a variable proportion of several disorders, including duodenal ulcer, gastric ulcer, carcinoma of the gastric antrum and fundus, which is the second most common cancer worldwide, and gastric mucosa-associated lymphoid tissue lymphomas. *H pylori* is usually acquired in childhood. It disproportionately affects people of lower socioeconomic status, and the majority of adults from developing countries are infected. The bacterium is found less frequently among individuals in developed countries such as the United States, and the low rate of infection in children from developed countries suggests the proportion in adults will continue to fall.

Most *H pylori* infections are asymptomatic and have a benign outcome. When infection does lead to stomach cancer, it usually takes decades. In this process, bacterially induced chronic gastritis is believed to progress to atrophic gastritis and metaplasia, and then to cancer. The bacterium appears to be required only until atrophic gastritis develops, at which stage it frequently can no longer be cultured from the stomach. Experimental *H pylori* infection of Mongolian gerbils can induce these sequential pathologic changes, including gastric adenocarcinoma. Gastric mucosa-associated lymphoid tissue lymphoma is much less common than gastric carcinoma and has a distinct pathogenesis. This B-cell lymphoma arises from *H pylori*-dependent chronic inflammation of the Peyer's patches in the gastric mucosa. Localized mucosa-associated lymphoid tissue tumors often remain dependent on continued stimulation by bacterial antigens, and eradication of the bacteria with antibiotic treatment may frequently be associated with lymphoma regression at this stage. The growth of more invasive tumors, which may become widely disseminated, is usually autonomous, and these tumors typically do not respond to antibacterial therapy.

Several bacterial virulence factors account for the ability of *H pylori* to colonize and persist in the gastric mucosa. Although different isolates of *H pylori* are closely related antigenically, type I isolates, which are associated with carcinoma, contain a cassette of genes that are designated a pathogenicity-associated island called *cag*.

In principle, *H pylori* infection can be eradicated by combined treatment with several antimicrobial agents plus proton pump inhibitors. However, the high cost and the emergence of antibiotic resistance make this approach poorly suited for bacterial eradication from whole populations. These limitations have fostered efforts to develop *H pylori* vaccines. Encouraging preclinical studies have been obtained with a variety of animal models. Mucosal immunization with bacterial lysates, purified bacterial antigens, or with attenuated salmonellae encoding *H pylori* antigen can all prevent experimental *H pylori* infection. Some of these vaccines have also been used successfully to eradicate established infection in the animal models. It remains to be determined which of these approaches will prove efficacious in human vaccine trials. The most desirable outcome would be a cost-effective vaccine that could eradicate established infection while also protecting against new infections. Such a vaccine would have the long-term benefits of a purely prophylactic vaccine while reducing the incidence of gastric cancer after a much shorter interval.

### CHAPTER REFERENCES

SECTION 63.2
Therapeutic Cancer Vaccines

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INTRODUCTION

The term vaccine originally referred to use of live cowpox virus inoculated in the skin as prophylaxis against smallpox, and hence is derived from the Latin vacca, which means cow. This meaning was extended to include the use of live, attenuated, or killed microbes or derivatives of microbes given by virtually any route to prevent the development of an infectious disease. The most recent incarnations of this term include the use of any antigen or fragment of an antigen, or any collection of antigens used alone, or together with an adjuvant, to modulate an immune response.

Vaccines are traditionally thought of as preventing infectious diseases, but they may have new uses in the treatment of malignancies. In the case of cancer, it is now clear that the immune system can recognize and destroy even large quantities of established tumor. Evidence for this immune-mediated destruction comes primarily from clinical trials using interleukin-2 (IL-2), which is now approved by the U.S. Food and Drug Administration for treatment for melanoma and renal cell carcinoma. Although data are limited, experimental therapeutic vaccines have also been demonstrated to cause regression of cancer in a small percentage of patients.

The goal of designing vaccines to prevent cancer may be appealing, but a variety of practical and theoretical problems arise in creating a prophylactic vaccine. Predicting which patients will develop cancer remains difficult, although assessment of risk becomes more accurate with the expansion in knowledge of genetic and environmental factors that contribute to carcinogenesis. There are also theoretical reasons why prophylactic vaccination against defined antigens may not be feasible. For example, the difficulty in predicting which of myriad mutations may occur in any one of a large number of genes makes vaccination against mutated tumor antigens unlikely to be successful. Similarly, vaccination against self-antigens may be subject to chronic immunologic tolerization, or may produce untoward side effects resulting from the destruction of normal tissues that express the same antigen.

The only truly preventive cancer vaccines that are under serious consideration are vaccines designed to prevent infectious diseases linked to the development of cancer. For example, vaccines that prevent human papillomavirus or hepatitis B virus infections should also prevent cervical cancer and liver cancer, respectively. However, most cancers affecting individuals in developed countries have not been associated with viruses. Thus, prophylactic vaccines for cancer are likely to be the exception rather than the rule. Most research in the field of cancer vaccines is devoted to vaccines designed to activate the immune system to destroy established cancer cells.

The notion that cancer cells could be recognized by the immune system has been the subject of scientific investigation for over 100 years. The nineteenth-century physician William Coley attempted to treat tumor-bearing patients by injecting fluid cultures of living Streptococcus erysipelas and reported an apparent decrease in tumor burden in some of his patients. Since then, results from experiments first done by Gross, then by Prehn and Main, and finally expanded on by Klein and colleagues, indicated that mice could be immunized against subsequent challenge with methylcholanthrene-induced sarcomas.

Advances in molecular biology and immunology have since led to the identification of prospective tumor antigens and improved methods of immunization. Clinical studies of human immunotherapies and vaccination using purified or synthetic defined proteins have demonstrated that the immune system can recognize and destroy even large quantities of established tumor.

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Advances in molecular biology and immunology have since led to the identification of prospective tumor antigens and improved methods of immunization. Clinical studies of human immunotherapies and vaccination using purified or synthetic defined proteins have demonstrated that the immune system can recognize and destroy even large quantities of established tumor.
The principle that T cells were critically important in the immune response against cancer was derived originally in mice with methylcholanthrene-induced tumors. In both animal tumors and some human malignancies, T cells that accumulate within the mass of a tumor have been shown to specifically recognize autologous tumor cells in vitro, and to proliferate and specifically secrete cytokines, such as IL-2, interferon-γ (IFN-g), granulocyte-macrophage colony-stimulating factor (GM-CSF), and tumor necrosis factor-α (TNF-α), in response to stimulation with autologous tumor cells. The adoptive transfer of these antitumor T cells can treat substantial tumor burdens in both humans and mice. Furthermore, the antitumor activity observed with systemic administration of the T-cell growth factor IL-2 in animal models, and perhaps also in patients, appears to be mediated in large part by tumor antigen-specific T lymphocytes.

Several mouse studies have suggested that tumor rejection is largely dependent on CD8+, cytolytic T cells, with little if any role for CD4+ T cells. In addition, adoptive transfer of pure populations of CD8+ T lymphocytes was shown to mediate tumor regression in mice. Thus, many efforts to develop therapeutic anticancer vaccines have focused on CD8+ T lymphocytes, and the molecular targets of these cells have been identified in human and mouse systems.

Compared with the comprehensive studies using CD8+ T cells in tumor models, relatively little is known about how CD4+ T cells influence antitumor immunity. Early work demonstrated that disseminated murine leukemia could be eradicated by a combination of cyclophosphamide and adoptive transfer of CD4+ T cells.

We now understand some aspects of how CD4+ T lymphocytes help initiate and maintain the antitumor immune response. CD4+ T cells regulate antigen-specific immune responses by regulating the functions of other components of the immune system, including B lymphocytes and CD8+ T lymphocytes. In the B16 murine melanoma system, CD4+ T cells appear crucial for the induction of both antitumor and autoimmunity that is mediated by B lymphocytes, as well as eosinophils and macrophages.

Activated CD4+ T cells express CD40 ligand (CD40L), which can engage the CD40 receptor on antigen-presenting cells (APCs) such as dendritic cells (DCs). These DCs can secrete proinflammatory cytokines such as IL-12, which in turn trigger the activation of CD8+ T cells and their production of IFN-g and IL-2, resulting in the attraction of a host of other immune cells to the site.

One potentially important experimental thrust in the use of adoptively transferred T cells may be the intentional addition of helper CD4+ T cells to adoptively transferred CD8+ T cells. Walter and colleagues found that the cytotoxic activity of adoptively transferred cytomegalovirus-specific CD8+ T-cell clones declined in patients deficient in cytomegalovirus-specific helper CD4+ T cells.

Perhaps the most dramatic examples of the power of CD4+ T cells in the immune response to self proteins can be found in murine models of autoimmune diseases such as experimental allergic encephalomyelitis, systemic lupus erythematosus, and diabetes. In these models, disease can often be transferred to naive mice with purified, self-reactive CD4+ splenocytes or specific CD4+ T lymphocyte clones. These studies suggest that the full activation of autoreactive CD4+ T cells may be a key element missing from many current clinical cancer vaccine trials. Attempts to identify the molecular targets of antitumor CD4+ T cells have already been successful. Thus, current work focuses on efforts to harness the potential capabilities of tumor-specific CD4+ T cells.

TUMOR-ASSOCIATED ANTIGENS

Now that many tumor antigens have been identified (Table 63.2-2), how does one go about choosing an antigen appropriate for use in the design of a cancer vaccine? Some workers have picked target antigens because they are frequently mutated in tumors, as in the case of p53 or ras. At the site of joining of a translocation such as bcr-abl, or are aberrantly glycosylated and thus the subject of recognition by antibodies as is the case for MUC-1.

Identifying Tumor Antigens Recognized by T Lymphocytes

Because of the difficulty in predicting what peptides from a given potential antigen will be present on the cell surface, one of the most successful approaches to identifying tumor-associated antigens suitable for the development of cancer vaccines starts with the antitumor immune response. In many cases, the antitumor T cells were derived from cultures of tumor-infiltrating lymphocytes. Our own group [the Surgery Branch of the National Cancer Institute (NCI)] has focused on the T-cell reactivities that were associated with objective regressions of metastatic melanoma lesions after their adoptive transfer. cDNA libraries of expressed melanoma genes were screened by transfecting these genes, along with the gene for the restricting MHC molecule, into an antigen-negative cell line that was then admixed with T lymphocytes that have antitumor activity. If the T cells recognize the transfected cell line, they lyse it and release cytokines such as GM-CSF, TNF-α, and IFN-g, any of which can be measured. This process of cloning genes encoding tumor antigens is under constant improvement and has become considerably faster and more streamlined.

Targeting Self-Antigens

The identification of self-antigens as potential targets in the immunotherapy of cancer has been an important factor driving interest in cancer vaccine development. Many of the tumor antigens that have been identified, in the case of melanoma, are tissue differentiation antigens in melanocytes and include gp100 and tyrosinase, and tyrosinase-related protein-1 (gp75) and tyrosinase-related protein-2. Interestingly, these antigens are involved in the synthesis of melanin that gives both melanocytes and deposits of melanoma tumor their dark pigment. CEA expressed in gastrointestinal and some other malignancies, and prostate-specific antigen (PSA), are other examples of differentiation antigens that have relatively restricted expression in normal tissues and could be targeted by cancer vaccines.

A second group of self-antigens are recognized by a diversity of tumor histologies but are not expressed by normal tissues other than testis. Cloned in large part by Dr. Thierry Boon and his colleagues, these antigens are encoded by genes with family names like MAGE, BAGE, GAGE, RAGE, LAGE, and CAMEL.
The fact that differentiation antigens are nonmutated in most tumors has two important implications. First, expression of these antigens would be expected in subsets of patients with a defined tumor histology, thus an off-the-shelf vaccine strategy targeting these antigens is possible (a strategy that targets a mutated antigen may have to be individualized for every mutation). Second, the nonmutated nature of these antigens suggests that immunotherapies that target these antigens could elicit autoreactivity. One consequence of this autoreactivity may be vitiligo, the patchy and permanent loss of pigment from the skin and hair thought to result from the autoimmune destruction of pigment cells. Vitiligo has been correlated with objective shrinkage of metastatic melanoma in patients receiving high-dose IL-2, a cytokine known to activate and expand T lymphocytes. This correlation is among the strongest evidence that the antitumor effects of IL-2 are mediated by antigen-specific immune responses and supports the notion that targeting immune responses to recognize self-antigens expressed by tumor can lead to tumor regression.

Are Mutated Tumor Antigens Better Targets for Immune Recognition?

Besides shared antigens, human tumors also express mutated antigens that can be processed and presented for recognition by T cells. Neoantigens produced as a result of mutation often are found to originate in ubiquitously expressed proteins. Examples include epitopes from b-catenin, CDK4, MUM1, FLICE (caspase 8), HLA-A2, and a mutant gene from a bladder carcinoma that is recorded in databases under the name KIAA0205, whose function is unknown. Interestingly, some of these antigens are also oncogenic, including the mutations described for b-catenin and CDK4.

Mutated antigens may not lend themselves easily to off-the-shelf vaccines consisting of purely recombinant and synthetic components, because each neoantigen for each patient must be checked for sequence and that sequence must be verified to be present on the surface of a tumor cell. Some workers have asserted that mutated tumor antigens are superior targets for vaccine design because vaccine antigens will not be tolerated to these antigens. However, work has shown that even the most immunogenic foreign antigen, such as the hemagglutinin antigen from the influenza A virus, can be tolerized when expressed peripherally (i.e., outside the thymus) either in normal cells or tumor cells. Thus, mutated or otherwise foreign antigens may also induce peripheral tolerance when expressed by tumor cells.

ROLE OF DENDRITIC CELLS IN VACCINE FUNCTION

It is likely that DCs are a key mediator of vaccine function. DCs activate T-cell responses by capturing, processing, and presenting antigens in the context of MHC molecules to T lymphocytes. In addition, DCs express the costimulatory molecules B7-1 (CD80) and B7-2 (CD86), which provide a second signal on interaction with their receptors on the surface of T cells known as CD28 and CTLA-4. Engagement of CD28 is associated with proliferation and differentiation whereas CTLA-4 may trigger functional unresponsiveness. Blocking CTLA-4 engagement has been shown to enhance immune responses to tumor cells. Activating T cells by DC is thus facilitated by presenting antigen/MHC complexes in the context of a variety of other activating signals.

DCs can undergo maturation or super activation through the activity of GM-CSF and TNF-a and other macrophage-derived cytokines, greatly enhancing their ability to activate naive T cells. In addition, CD40 and its ligand have been shown to be important in B-cell activation, in the production of type 1 cytokines by T-helper cells, and in the generation of cytotoxic T-cell memory responses. We and others have found that the addition of CD40L, a trimer to DNA vaccination can significantly increase antitumor efficacy. Another molecule called FLT3 ligand can induce the apparent growth and differentiation of functional DC and has been reported to have antitumor effects and its effect on the function of recombinant and synthetic anticancer vaccines is the subject of a great deal of investigation in experimental mouse models.

ROLE OF ANTIBODIES IN IMMUNE-MEDIATED ANTITUMOR RESPONSES

Much of the experimental data generated with cancer vaccines in animal models suggests that immune-mediated antitumor activity is attributable to T cells. Nevertheless, adoptive transfer of antibodies directed against surface tumor antigens can cause regression of cancer in animal models, and vaccine-induced antibody responses have been demonstrated to reject a tumor challenge and to cause regression of small-volume established cancer. Antibodies mediate antitumor effects by complement-dependent lysis or by antibody-dependent cellular cytotoxicity. In addition, antibodies directed against growth factor receptors or other cell surface molecules have demonstrated antitumor activity in animal models and in human clinical trials, by mechanisms that appear to involve blocking or stimulating a cell signaling component of the target (Herceptin targets the human epidermal growth factor receptor, HER2/Neu). Nevertheless, antibodies that function in the HER2/Neu protooncogene, which is overexpressed in 25% to 30% of breast cancers, and causes objective tumor responses in approximately 15% of breast cancer patients with metastatic disease. It also significantly enhances the therapeutic effect of paclitaxel in these patients. Although the mechanism of action is thought to involve the inhibition of stimulatory signals provided by multiple neuregulins and epidermal growth factor–like molecules, there is some evidence that the therapeutic effect may also have an immunologic component through direct killing of antibody-coated tumor cells by natural killer cells.

Antibody responses are generally directed toward surface components of tumor cells. Similar to T-cell responses, several factors may influence the antitumor activity of an antibody response, including the density of the target on the cell surface, the type of target, the type of antibody response, the affinity of the antibody for its antigen, the strength of the response (the presence of the antibody in the serum and its effect on the function of recombinant and synthetic anticancer vaccines is the subject of a great deal of investigation in experimental mouse models).

MONITORING OF CANCER VACCINE TRIALS

A major challenge for cancer vaccine trials is determination of efficacy, as measured by immune response and patient benefit. Techniques for measuring antibody response have become relatively well established, although it is important to verify that the antibody responses actually recognize tumor cells bearing the antigen, and that affinity, titer, and biologic activity are sufficiently high to expect antitumor activity. In vivo, T-cell responses can be measured through a biologic assay, for example, a skin test of delayed-type hypersensitivity (DTH), by assessment of number and function of antigen-specific T cells in peripheral blood, and by assessment of histologic changes and antigen-specific T-cell number and function within the tumor. DTH is commonly used to measure responses to autologous and allogeneic cell vaccines. Application of appropriate controls for DTH testing is often difficult, and it is often not possible to be certain that a positive reaction truly indicates response to a relevant tumor antigen and not, for example, serum or other components of the tumoral growth medium.

Detection of antigen-specific cells in blood or tumor can be accomplished by a physical characteristic (presence of a particular T-cell receptor) or function (production of cytokine in response to the binding of a peptide-MHC complex with the T-cell receptor). The peptide to which the immune response is directed is known, peptide-MHC complexes can be joined to form a tetramer, which can be used to detect T cells bearing the appropriate T-cell receptor in a flow cytometer. By this technique, the number of peptide-specific T cells in a bulk population can be enumerated, and after sorting, the functional capacity of the T cells can be characterized. The tetramer technique is promising but is still limited by the sensitivity of the flow cytometer.

Perhaps the most sensitive techniques for assessing a T-cell response to immunization are based on detecting a particular function of a T cell when exposed to its antigen, such as the hemagglutinin antigen from the influenza A virus, can be tolerized when expressed peripherally (i.e., outside the thymus) either in normal cells or tumor cells. Thus, mutated or otherwise foreign antigens may also induce peripheral tolerance when expressed by tumor cells.
ELISPOT technique also has sensitivity limitations, but may become a useful tool in monitoring of some cancer vaccine trials.  

The Surgery Branch of the NCI has explored the use of quantitative reverse transcriptase polymerase chain reaction techniques to detect evidence of immunization to a peptide vaccine directly from peripheral blood and from tumor. The technique involves measurement of mRNA message for a particular cytokine normalized to a standard curve. Measurements can be made on fine-needle aspirates of tumor. Since the mechanisms of vaccine antitumor response likely involves infiltration of tumor by T cells, and activity is dependent on cytokine production by the infiltrating T cells, a sensitive measure of vaccine biologic activity is an increase in mRNA for a particular cytokine in the tumor site.  

ANTICANCER VACCINE APPROACHES DERIVED FROM AUTOLOGOUS AND ALLOGENEIC TUMOR CELLS

Many cancer vaccines in current development use autologous or allogeneic tumor cells as the source of antigen for immunizing patients. Autologous tumor cell vaccines must be prepared individually for each patient, but offer the potential to immunize against antigens generated by patient- and tumor-specific gene mutations. Allogeneic tumor cell vaccines provide a more reliable and uniform source of antigen for preparation of vaccines, but target only antigens that are shared between the cell lines in the vaccine and the patient’s tumor.

Final preparations of autologous or allogeneic tumor cell vaccines contain either whole cells, lysates, or extracts from the cells. Some attempts have been made to immunize with live autologous cancer cells, but, to avoid the concern that live cells might implant or metastasize, whole tumor cells are irradiated or otherwise killed before reimplantation. To ensure adequate presentation of antigens to the immune system, adjuvants such as bacille Calmette-Guérin (BCG), Corynebacterium parvum, DETOX, and alum must be added to the cells or cell extracts. Attempts to increase immunogenicity have also included the infection of allogeneic tumor cells with vaccinia virus, vesicular stomatitis virus, as well as other viruses to create oncolysates that contain both viral and tumor antigens. The strong foreign viral antigens serve as an immunologic adjuvant that enhances immune responses to the tumor antigens.

A significant body of work in experimental animals has shown that transfection of genes into tumor cells is capable of increasing their immunogenicity. Based on these results, patients have been treated with tumor cells genetically modified ex vivo or in vivo to express several different classes of genes, including cytokines, T-cell costimulatory molecules, or foreign genes encoding allogeneic or xenogeneic MHC class I molecules. The substantial work with gene-modified tumor cells is described in greater detail in Chapter 62.1.

More recent efforts to improve the immunogenicity of autologous and allogeneic cancer cell vaccines have involved the direct transfer to, or expression of, potential antigens in host APC. Methods under investigation in animal models, and either ongoing or planned for clinical trials, include expressing whole tumor cell RNA in host APC, pulsing APC with peptides extracted by acid elution from the surface of tumor cells, and creating DC–tumor cell fusions.

An alternative to the use of whole tumor cells in vaccines has been to enrich the relevant and immune-activating components of tumor cells while excluding the irrelevant and immune-suppressing substances that may be present. Partially purified fractions of allogeneic tumor cell lines, in this instance shed tumor antigens into the culture media, have been shown to yield preparations that are capable of stimulating immune responses in experimental murine models. This method of preparing a tumor vaccine has been extended into the clinic, in combination with adjuvants such as alum or DETOX. Srivastava and colleagues have shown that heat shock proteins carry antigenic peptide determinants of cellular proteins, including tumor antigens, to the MHC molecules in the endoplasmic reticulum. When isolated from tumor cells and administered as a vaccine, the heat shock proteins can apparently gain access to both the class I and class II antigen-processing pathways of certain APCs, including macrophages, and can induce both tumor-antigen specific helper and cytotoxic T-lymphocyte responses.

The heat shock protein preparations have generated protective and therapeutic antitumor activity in animal models, and on this basis, have entered clinical trials.

CLINICAL EXPERIENCE

Some of the vaccines that have progressed to randomized trials are listed in Table 63.2-3. Most of the clinical experience has been in patients with melanoma. A large number of clinical trials have been conducted including vaccinia-induced lysates of allogeneic melanoma cell lines; Melacine, lysates from two allogeneic melanoma cell lines (administered with DETOX); CancerVax, a combination of three allogeneic melanoma cell lines (with BCG as adjuvant); and autologous melanoma cells chemically modified with dinitrophenyl (DNP). For several of the vaccines, including Melacine, CancerVax, and the DNP-modified autologous melanoma cells, low rates of objective responses were observed in patients with metastatic disease, although usually not in patients with large tumor burdens or visceral involvement. A striking observation in trials of the DNP-modified autologous melanoma cells was the induction of inflammation and lymphocytic infiltrates in distant metastatic lesions. For all the vaccines, single-arm studies suggested that the vaccine improved disease-free survival of stage III patients (in general, patients following resection of their primary or regional nodes, or both, and at high risk for recurrence), and for some of the vaccines improved survival was also suggested for patients with metastatic disease. Comparisons were made with historical controls, or within the study, immune responders were compared with patients who had poor or no immunologic response to the vaccine.

Table 63.2-3. Moderate and Large Randomized Trials of Cancer Vaccines

<table>
<thead>
<tr>
<th>Vaccine Type</th>
<th>Outcome of Vaccine</th>
<th>Clinical Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>CancerVax</td>
<td>Improved survival</td>
<td>Two randomized trials involving stage II/III patients</td>
</tr>
<tr>
<td>Melacine</td>
<td>Improved survival</td>
<td>One randomized trial involving stage II patients</td>
</tr>
<tr>
<td>Vaccine admixed with DETOX</td>
<td>Improved survival</td>
<td>One randomized trial involving stage III patients</td>
</tr>
<tr>
<td>Vaccine admixed with BCG</td>
<td>Improved survival</td>
<td>One randomized trial involving stage III patients</td>
</tr>
</tbody>
</table>

Based on these data, several of the vaccines were tested or are currently in phase III randomized trials (see Table 63.2-3). The vaccinia melanoma oncolysate showed no benefit for patients with stage III disease in one trial, although another larger study of a vaccinia melanoma oncolysate is pending analysis. Melacine, a vaccine composed of lysates from two allogeneic melanoma cell lines admixed with DETOX, did not improve survival of patients with metastatic melanoma compared with chemotherapy. Two randomized trials of an autologous colon cancer vaccine admixed with BCG adjuvant involving stage II/III patients have been published. One of the studies indicated an improvement in disease-free survival for stage II patients only. The difference in outcome between the two trials was attributed to differences in tumor type, stage, and survival.

Several of the vaccines, including Melacine, CancerVax, and the DNP-modified autologous melanoma cells, showed no benefit for patients with stage III disease in one trial, although another larger study of a vaccinia melanoma oncolysate is pending analysis. Melacine, a vaccine composed of lysates from two allogeneic melanoma cell lines admixed with DETOX, did not improve survival of patients with metastatic melanoma compared with chemotherapy. Two randomized trials of an autologous colon cancer vaccine admixed with BCG adjuvant involving stage II/III patients have been published.

The clinical experience obtained with tumor cells modified with genes encoding cytokines or other immune-stimulatory molecules is covered in Chapter 62.1. Whether gene modification of tumor cells enhances their immunogenicity and therapeutic outcome in comparison with a simple admixture of tumor cells with nonspecific
Table 63.2-4 demonstrates that trials of recombinant viral vaccines have employed different routes of administration including scarification (multiple punctures of the vaccine solution into the skin), intradermal, subcutaneous, and intramuscular injection. Some patients also received the nonreplicating fowlpox–gp100 vaccine intravenously (S. A. Rosenberg et al., personal communication, 2000). A large range of doses has been explored in the phase I trials. Immunizations were repeated monthly in most trials for a maximum of three to four doses. Using immune responses to the viral vector antigens as a guide, no route of administration has proven to be superior, and no relationship between dose and protective efficacy has been established, although higher doses are predicted to be more effective for the nonreplicating vectors. Exploration of schedule issues (e.g., a longer interval between doses) has been difficult in the selected patient populations with progressing metastatic disease. For the vaccinia vaccines, a take (formation of an inflammatory response and a bleb at the injection site) has occurred in most patients receiving the vaccine by scarification or intradermal injection despite preexisting immunity to vaccinia. However, second and third doses of vaccinia are usually not associated with a significant local reaction, suggesting that the vaccinia is cleared too quickly to allow boosting of immune responses to the encoded tumor antigen.

In order to improve the effects of these vectors, current studies are combining different viral vectors that are non–cross-reactive in patients, or viral vectors combined with the corresponding peptide epitopes of the antigen gene, administered sequentially. These heterologous boost strategies were superior to repeated immunizations with single vectors in animal models. Examples of ongoing trials include sequential immunizations with vaccinia-CEA and ALVAC-CEA in patients with CEA-expressing malignancies, and vaccinia-tyrosinase sequenced with fowlpox-tyrosinase in metastatic melanoma patients. Investigators are also combining genes for T-cell costimulatory signals with the antigen gene within a single viral vector, or combining viral vectors that respectively express the antigen gene and genes for cytokines or one or more T-cell costimulatory signals. Clinical trials of vaccinia containing genes for both CEA and B7-1 (CD80) have been initiated, but
Various peptides of longer length, usually greater than 10 to 12 amino acids, have also been studied in clinical trials. Longer peptides are most often intended to elicit responses to various MHC class I binding peptides in patients, but these immune responses do not necessarily recognize tumor, and therefore would not be expected to naturally process and present on HLA-A201 molecules sufficiently by most tumor cells to allow T-cell activation. Therefore, it is possible to generate potent T-cell responses.

A small experience with an HLA-A201 restricted peptide from the her2 protein illustrates an important principle in selection of peptides for clinical trials. The her2 restricted peptides from the E7 human papillomavirus-16 have been administered in adjuvant or attached to a lipidated peptide designed to elicit broad nonspecific T-cell helper responses.

The clinical experience with other peptides selected to induce only CD8+ lymphocyte responses remains limited. Results of studies involving peptide-pulsed DCs are not yet available. Occasional mixed and true objective antitumor responses have been observed in a small minority of patients receiving melanoma peptide vaccines. However, no correlation has been made between detection of immune response and clinical outcome in these trials. In a study of an HLA-A1 restricted peptide from the cancer testis antigen MAGE-3, administered without an adjuvant to 39 patients with metastatic melanoma, three complete responses and four other patients with objective regression were reported, despite the inability to detect immune responses to the peptide.

A substantial experience has been developed in studies of a synthetic peptide immunogen corresponding to an epitope from the gp100 melanoma antigen. The epitope, consisting of amino acids 209 to 217 and restricted by HLA-A*0201, was identified by determining reactivities of tumor-infiltrating lymphocytes from patients with metastatic melanoma. When the second amino acid from the amino terminus was modified from a threonine to a methionine to create a peptide called g209-2M, an epitope, consisting of amino acids 209 to 217 and restricted by HLA-A*0201, was identified by determining reactivities of tumor-infiltrating lymphocytes from patients with metastatic melanoma. The clinical results of selected trials conducted with peptide vaccines. Peptides have been derived from various antigens, including melanoma antigens MART-1, gp100, tyrosinase, and tyrosinase-related protein-1; cancer testis antigen MAGE-3; PSA and prostate-specific membrane antigen; CEA; the mucin MUC-1; the hormone human chorionic gonadotropin-a; the oncogene HER-2/ner; mutated ras and p53; and human papillomavirus E6 and E7 proteins. Several conclusions can be drawn from the series of studies conducted with MHC class I (HLA-A201 in most trials) restricted peptides derived from the melanoma antigens. In those trials, doses of 1 mg administered in an emulsion with a type of incomplete Freund's adjuvant were adequate to induce immune responses, and within the range of doses studied (100 µg to 10 mg), the immune response did not appear to be dose related. While scheduling was not examined in detail, the studies revealed that the immune response was observed in vivo, 91% of patients vaccinated with this peptide were successfully immunized on the basis of immunologic assays in peripheral blood, a substantial improvement over the immunization results reported, despite the inability to detect immune responses to the peptide.

Like viral vaccines, the activity of DNA vaccines appears to be mediated through DCs and other professional antigen-presenting cells. While the HER-2/ner peptide could be administered without an adjuvant to 39 patients with metastatic melanoma, and tyrosinase peptides in HLA-A201 stage IV melanoma patients who have had resection of all metastatic disease, compared with placebo, is ongoing, and is designed to test whether immunization against these antigens will have greater effect in patients with minimal tumor burdens.

The clinical experience with other peptides selected to induce only CD8+ lymphocyte responses remains limited. Results of studies involving peptide-pulsed DCs are discussed in the section on DC tumor vaccines [see Vaccination Using Most Antigen-Presenting Cells (Dendritic Cell Vaccines), later in this chapter]. HLA-A201 restricted peptides from the E7 human papillomavirus-16 have been administered in adjuvant or attached to a lipidated peptide designed to elicit broad nonspecific T-cell helper responses. Human papillomavirus-16 E7 peptide-specific T-cell responses were observed in several patients without evidence of antitumor activity. A small experience with an HLA-A201 restricted peptide from the her2 protein illustrates an important principle in selection of peptides for clinical trials. The her2 peptide was shown to bind to HLA-A201 in vitro, and CTL raised to the peptide and some tumor-infiltrating lymphocyte preparations could kill peptide-pulsed target cells. On this basis, a clinical trial was initiated administering the peptide in Montanide ISA 51 similar to the melanoma trials. While the HER-2/ner peptide could be demonstrated to induce peptide-specific T-cell responses in patients, the CTL did not recognize HER-2/ner+ HLA-A201+ tumors, suggesting that the peptide is not naturally processed and presented on HLA-A201 molecules sufficiently by most tumor cells to allow T-cell activation. Therefore, it is possible to generate potent T-cell responses to various MHC class I binding peptides in patients, but these immune responses do not necessarily recognize tumor, and therefore would not be expected to have antitumor effects.

Various peptides of longer length, usually greater than 10 to 12 amino acids, have also been studied in clinical trials. Longer peptides are most often intended to induce CD8+ T-helper cell responses, although long peptides are capable of inducing CD8+ lymphocyte responses if they are trimmed or processed in vivo to a peptide of correct length that can bind to the patient's class I MHC molecules. Disis et al. demonstrated that immunization with peptides 15 to 18 amino acids in length...
and selected from the HER-2/neu protein could induce T-cell proliferative responses to the her2 protein in six of eight patients with HER-2/neu+ tumors.\textsuperscript{188} Demonstration of responses to the protein, rather than just the peptide itself, suggests that the immune responses are relevant and could recognize antigen presented by tumor cells or picked up by host APC. The investigators also reported evidence of epitope spreading, manifest as the induction of proliferative responses to her2 peptide epitopes not in the vaccine. Clinical antitumor responses could not be assessed as most patients had minimal or no disease at the start of vaccination. Immunization with a 105 aa peptide composed of five tandem repeats derived from MUC-1 did not produce antitumor activity among 83 patients with advanced adenocarcinomas, although T-cell infiltrates were observed in the peptide delayed-type hypersensitivity skin test sites of 44 of 55 patients.\textsuperscript{189} Immunization of 25 metastatic adenocarcinoma patients with a MUC-1 mannan fusion protein produced high antibody titers in 13, but T-cell responses were limited.\textsuperscript{190} Low-level antibody and T-cell proliferative responses, as well as regression of liver lesions in two patients, were reported among 21 patients immunized against a carboxy-terminal peptide of human choriionic gonadotropin-b, conjugated to diphtheria toxoid.\textsuperscript{191} The results have been extended to a randomized controlled trial in advanced colon cancer.

Cytokines have been administered together with peptide vaccines to enhance presentation, for example, by recruiting and activating host APC, or to affect the development of T-cell responses by directly interacting with the T cells. When the T-cell growth and differentiation cytokine IL-2 was added to the g209-2M melanoma peptide treatment regimen, 13 of 31 patients (42\%) had objective clinical responses and four additional patients had mixed or minor responses (Table 63.2-5). These results are significantly different from results obtained in clinical trials using high-dose IL-2 alone, in which objective response rates are in the range of 15\%, and a randomization of IL-2 plus peptide with IL-2 alone is due to start in 2000. Of note, high-dose IL-2 diminished the CTL response to peptide as measured in peripheral blood. Coadministration of IL-12 or GM-CSF with the g209-2M peptide in adjuvant also diminished CTL reactivity to the peptide, and among the 14 patients treated with peptide and IL-12 and 13 treated with peptide and GM-CSF, there were no objective antitumor responses.\textsuperscript{192} GM-CSF has been an effective adjuvant in studies of the her2 peptides, which were not admixed with a nonspecific adjuvant. The cytokine IL-13, which increases the number of circulating and tissue APC, has generated substantial interest and is being administered before peptide vaccination in a number of clinical studies, although results are not yet available.

Future directions in the development of synthetic peptide vaccines may include the use of modified peptides embedded into microspheres or coated onto microbeads, a maneuver that can target antigen for uptake and MHC class I restricted presentation by professional APC.\textsuperscript{195} Other novel strategies developed in experimental animal systems use toxin-linked peptides\textsuperscript{196} and peptides linked to endoplasmic reticulum insertion signal sequences covalently attached to the amino terminus of a peptide immunogen.\textsuperscript{197}

**VACCINATION USING PURIFIED OR SYNTHETIC DEFINED PROTEINS**

In relative terms, only a few vaccines are in development that are composed of synthetic or purified proteins. Proteins provide the opportunity for immunization against multiple epitopes, and also have the potential for inducing both CD4+ and CD8+ T-cell responses. However, for some self-antigens, immunization with proteins may be limited by tolerance to its dominant epitopes. Animal models have shown that immunization with xenogeneic proteins may be superior to the syngeneic self-protein, due to amino acid differences that induce helper CD4+ T-cell responses, and the chance occurrence that the xenogeneic protein will contain a peptide epitope just different enough from the native epitope to be highly immunogenic, but still induce T-cell responses to the native epitope.\textsuperscript{198} An alternative to immunization with a purified or recombinant protein is to insert the gene into a viral vector, which theoretically enters the cytoplasmic compartment of an APC to produce large amounts of the protein for processing and antigen presentation.

Clinical experience with vaccines containing defined proteins is limited, with the exception of idiotypic lymphoma vaccines (see Vaccination Using Idiotypes or Anti-idiotypes, later in this chapter). Results of trials of liposome-encapsulated PSA protein vaccines have been presented in abstract form.

**VACCINATION USING HOST ANTIGEN-PRESENTING CELLS (DENDRITIC CELL VACCINES)**

In order to improve the immunogenicity of antigens, investigators have increasingly adopted the approach of placing the antigen directly into host APCs, which when fully differentiated present surface molecules and produce cytokines that result in optimal activation of T cells. Interpretation of the many clinical trials is confounded by the many different approaches to generating APC in vivo and in vitro; by the different types and functions of APC; by difficulty in fully defining the characteristics of APC that result in optimal antigen presentation; by the many different approaches to place antigen into or onto APC; and by the variety in dose, route of administration, and use of concurrent cytokines in the clinical studies. Few if any studies have compared APC-based vaccines with other immunization approaches, for example, peptide pulsed on APC to peptide in adjuvant. A representative sample of tumor vaccines employing host APC is presented in Table 63.2-6. APC used to deliver antigens derived from autologous tumor cells, for example, tumor cell-DC fusions, is discussed earlier (see Anticancer Vaccine Approaches Derived from Autologous and Allogeneic Tumor Cells, earlier in this chapter).

### Table 63.2-6. Clinical Trials Using Vaccines Based on Antigen-Presenting Cells

The majority of clinical studies have used APC by ex vivo culture of nonadherent peripheral blood mononuclear cells (PBMC) in the presence of the cytokines IL-4 and GM-CSF (monocyte-derived APC). After several days of culture, the APC are incubated with the antigen, and then administered to the patient. In some cases an additional signal to mature APC is provided before the final harvest for injection, for example, addition of TNF or monocyte-conditioned media. Some clinical studies use as the APC preparation all PBMC obtained from apheresis with minimal ex vivo manipulation, or apply centrifugation and elutriation techniques to isolate circulating APC from blood, which are then directly cultured in vitro with antigen only. The optimal route of administration for APC has not been determined, but clinical protocols have employed intravenous, intradermal, subcutaneous, and intralymphatic routes, as well as direct injection into lymph nodes.

Preliminary data from immunization with monocyte-derived APC pulsed with melanoma peptides suggest that the approach is less effective than administering peptide in adjuvant for generating CTL responses in peripheral blood (F. M. Marincola, personal communication, 2000). Nevertheless, some antitumor responses have been observed in the clinical trials. Nestle et al. reported two complete and three partial responses among 16 melanoma patients treated with melanoma peptides or tumor lysates pulsed onto monocyte-derived APC and injected directly into lymph nodes. Immunorepons were assessed by delayed-type hypersensitivity reactions to APC alone versus APC plus antigen, and 15 of the 16 patients appeared to have increased delayed-type hypersensitivity responses to the antigen-pulsed APC.

Declines in the PSA levels of prostate cancer patients have been observed following administration of APC-based vaccines. Approximately 25\% of 70 patients, including 33 with hormone-refractory disease, were reported to achieve complete or partial responses when treated with monocyte-derived APC pulsed with two HLA-A2 restricted peptides from prostate-specific membrane antigen.\textsuperscript{199}

**VACCINATION USING IDIOTYPES OR ANTI-IDIOTYPES**

The antigen-binding region of an antibody (the idiotype), which is formed from recombination of genes within the B cells, can theoretically be processed by the B cells to peptides that bind self-MHC molecules and are presented on the surface of the cell, thus forming a unique antigen that can be recognized by T cells. Antigen-binding regions of antibodies can also be recognized by other antibodies; therefore, it is possible to raise antibodies to the idiotype present on the surface of malignant B cells. The specific antibody idiotype to be used in a vaccine must be prepared individually from each patient using hybridoma or recombinant DNA
techniques, processes that can take several weeks to months to generate a clinical product. Nevertheless, a substantial clinical experience is now available with these unique lymphoma idiotype vaccines.\textsuperscript{208} Optimal induction of immune responses requires conjugation of the idiotype protein to KLH and administration with a strong nonspecific adjuvant. The Stanford group demonstrated induction of antibody responses to the idiotype in 20 of 41 immunized patients with follicular lymphoma.\textsuperscript{209} Fifteen of the immune responders were among the 20 patients who were in complete remission at the beginning of vaccine treatment. There was a marked increase in progression-free survival and overall survival in immune responders versus nonresponders. Two of 21 patients had regression of residual disease with the vaccine treatment. A similar vaccine was studied at the NCI in follicular lymphoma patients in their first complete remission.\textsuperscript{210} T-cell responses, including proliferation to the idiotype and cytolytic toxicity toward autologous tumor, were reported in 19 of the 20 patients, and antibody responses to the idiotype in 15 of 20. Eight of 11 patients with detectable bcl-2 translocations in peripheral blood following chemotherapy developed molecular complete remissions with vaccination. Furthermore, 18 of 20 patients were relapse-free from 28+ to 53+ months from initiation of initial chemotherapy. Although the results of the two series are promising, the data must be interpreted with caution since the beneficial clinical effects are occurring primarily in complete remission patients whose natural history of disease is already quite favorable. A phase III randomized trial of the lymphoma idiotype vaccine is expected to begin in 2000.

The antibodies directed to the antigen-binding regions of other antibodies carry within their own antigen-binding region a physical resemblance to the original antigen. For example, if CEA is the intended tumor antigen, an antibody is first raised to CEA. That antibody (termed Ab1) is itself used as an immunogen in mice to raise a second group of antibodies (Ab2), some of which recognize the CEA-binding site of the Ab1. The antigen-binding site of Ab2 physically resembles CEA, and when used to immunize animals or patients, can generate antibodies (Ab3) that recognize CEA. The Ab2 is capable of generating more potent immune responses to the original antigen than the antigen itself in some circumstances, since the antigenic epitope is being presented outside of immune-tolerizing influences.

Clinical results of representative antidiotypic vaccine are presented in Table 63.2-7. A polyclonal goat antiidiotype mimicking the 17-1A antigen was the subject of a small randomized trial in advanced colon cancer, and despite inducing antibodies to 17-1A in 12 of the 21 patients in the treatment arm, no survival benefit was observed compared with the control (immunization with nonspecific goat polyclonal antibody).\textsuperscript{211,212} An antiidiotype mimicking CEA was reported to induce high titer anti-CEA antibodies in all 32 immunized patients.\textsuperscript{211} Furthermore, because the antiidiotype contained sequences that were similar to the protein sequence of CEA, some patients developed CD4+ T-cell proliferative responses to CEA. No antitumor responses were observed, but 18 of 23 patients with no evidence of disease, including eight of nine with completely resected metastatic disease, were progression free at the time of the publication. Combination with 5-fluorouracil–containing regimens did not appear to reduce the immunogenicity of the antiidiotype, and a phase III trial in the adjuvant setting is planned.

VACCINES USING CARBOHYDRATE AND GANGLIOSIDE CELL SURFACE ANTIGENS

Certain tumors, particularly melanoma and small cell lung cancer, are known to express gangliosides that can be recognized by antibodies. Induction of antibody responses against the ganglioside antigen can have therapeutic value in animal models, particularly in micrometastatic settings. A vaccine composed of purified GM2 conjugated with BCG was administered subcutaneously in a randomized controlled trial in patients with stage llb/lll melanoma. Patients received low-dose cyclophosphamide before immunization. The GM2/BCG vaccine was shown to induce low to moderate titers of IgM anti-GM2 antibodies in the majority of patients, and produced a trend toward improved disease-free survival.\textsuperscript{220,221} When patients with preexisting anti-GM2 responses, which are associated with a better prognosis, were excluded from the analysis of both arms, the differences between arms became statistically significant. Pilot studies of GM2 conjugated to the protein KLH and admixed with QS-21 produced higher titers of IgM antibodies to GM2 compared with the GM2/BCG vaccine, and also high titers of IgG antibodies to GM2, although none of the patients developed antibodies to GM2. Among the patients who develop IgM anti-GM2 antibodies, only approximately 40% to 50% have antibody responses that are cytotoxic for GM2-expressing melanoma cells. A phase III trial of the GM2-KLH/QS-21 vaccine compared with high-dose IFN for patients with stage llb/lll melanoma completed accrual in 1999 and is awaiting analysis.

A vaccine containing both GM2 and GD2 gangliosides has been developed and appears to induce IgM and IgG antibody responses to both gangliosides.\textsuperscript{222} Another ganglioside, Fucosyl-GM1, which is expressed on small cell lung cancer, has been conjugated to KLH and administered with QS-21 to ten patients with small cell lung cancer in partial or complete remission following chemotherapy.\textsuperscript{223} The vaccine induced cytotoxic antibody responses in the majority of patients.

STn is a carbohydrate antigen from the MUC-1 glycoprotein, expressed on various adenocarcinomas including breast, ovarian, and colon cancer.\textsuperscript{224} The carbohydrate epitopes are revealed due to abnormal glycosylation patterns in tumors. A synthetic STn was conjugated to KLH and administered with the DETOX adjuvant in several trials involving patients with metastatic breast, ovarian, and colon cancer. High-titer IgG responses to natural mucin STn epitopes were demonstrated, and a correlation was found between development of IgM (colon cancer) or IgG (breast cancer) titers above the median.\textsuperscript{225,226,227} Of note, there was no correlation in these same studies between survival and anti-KLH antibody responses. The STn-KLH/QS-21 vaccine is the subject of a large randomized phase III trial in metastatic breast cancer patients who are stable or have a partial or complete response after initial chemotherapy.

ENHANCING VACCINE-INDUCED IMMUNE RESPONSES

OPTIMIZING DOSE, BOOSTING, AND ROUTE OF THE IMMUNIZATION

There are a bewildering number of choices that the immunotherapist must make when designing an anticancer vaccine, including choice of antigen, immunogen, and adjuvant. In addition, it becomes important to consider the appropriate dose, route of administration, and the length of intervals between boosting. The answers to these questions require an understanding of the immunology of vaccination in vivo. In vitro work with human cells is of limited benefit, while work in human subjects must necessarily be limited in its scope. Thus, in practice, questions regarding dose, route, and boosting are generally addressed in mouse models.

Based on the idea that more antigen is better, most viral and DNA vaccines are geared toward maximum expression and use the strongest available promoters. In our preclinical trials using immunogens based on vaccinia viruses, as well as DNA given by blasts with the gene gun, efficacy improves as the dose of immunogen

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<th>TABLE 63.2-7. Clinical Trials Using Vaccines Based on Idiotypes and Antiidiotypes</th>
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<td><strong>Antidiotypic Vaccines</strong></td>
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It has long been known that boosting an immune response can increase its intensity. When primary and booster immunization using a single vector (i.e., homologous boosting) is compared with a regimen that uses two different vectors (i.e., heterologous boosting), the heterologous boosting generally resulted in significantly more potent antigen-specific cytolytic T-lymphocyte responses. This is likely due to absence of a neutralizing antivector immune response during the booster immunization.

The route of immunization can determine its efficacy; for example, administration of a synthetic peptide by the intraperitoneal route can lead to tolerization, whereas administration of the same peptide immunogen subcutaneously leads to activation. For poxviral vectors, the intravenous route of immunization is optimal in mice. For any given immunogen, we surmise that the optimal route of immunization is likely to be dictated by the route that leads to the presence of the antigen on the maximal number of activated DCs, perhaps with the least amount of antigen presentation by normal, potentially tolerizing cells.

**CYTOKINES, CHEMOKINES, AND COSTIMULATORY MOLECULES AS MOLEcularly DEFINED ADJUVANTS**

From the vaccinologist's point of view, cytokines, chemokines, and costimulatory molecules can be used as molecularly defined adjuvants, significantly improving vaccine-induced immune responses. They can be administered systemically as protein or through insertion of their genes into recombinant vaccines. Studies using vaccinia virus-based immunogens have revealed that IL-2 and IL-12 are extremely potent in their ability to increase the efficacy of cancer vaccines. In addition, the costimulatory molecules B7-1, B7-2, and CD40L have a beneficial effect on vaccination.

Importantly, not all of the findings in murine models were confirmed in human clinical trials. When patients with metastatic melanoma were immunized with a modified immunodominant peptide derived from gp100, no increase in efficacy as measured by objective clinical response was observed using GM-CSF or IL-12. Only IL-2 was found to have a beneficial effect as an adjuvant for peptide immunization.

Bacterial DNA sequences called immunostimulatory sequences have been reported to be potent adjuvants. Nonmethylated, palindromic DNA sequences containing CpG-oligodeoxynucleotides can activate an innate immune response by activating monocytes, natural killer cells, DCs, and B cells in an antigen-independent manner. Thus, the use of large amounts of plasmids for immunization may not only overcome the low transfection efficiency in vivo, but may also serve as an adjuvant, driving a Th1 response.

**FUTURE CHALLENGES: TUMOR ESCAPE FROM IMMUNE RECOGNITION**

Every cancer that kills a person is a cancer that has not been destroyed by the immune system, and many mechanisms have been hypothesized for this apparent lack of immunogenicity (Table 63.2-2).

**TABLE 63.2-8. Potential Impediments to Immunization against Tumor Antigens and Development of Effective Antitumor Immune Responses**

**LACK OF INFLAMMATION**

One mechanism that may explain why patients with cancer usually do not reject their tumors involves the lack of inflammation at the tumor site. There are important differences between the site of a tumor deposit and a site of infection. Tumors produce few, if any, immunologic danger signals to stimulate the immune response. In contrast, at a site of infection, the innate immune response is triggered because of tissue destruction. Inflammatory cells, such as monocytes, macrophages, and DCs, are activated as a result of this tissue destruction, and by components of the infectious agents themselves, such as lipopolysaccharide, nonmethylated CpG sequences, and double-stranded RNA, each of which are components of invading microbes that are not shared by either normal host cells or growing cancer cells. In the absence of these danger signals, the immune system may not become fully activated.

**INDUCTION OF TOLERANCE BY TUMOR CELLS**

Despite cancer cells' expression of clearly immunogenic molecular targets, the host usually does not mount an effective immune response to these antigens. One reason could be the lack of expression of costimulatory molecules necessary for efficient T-cell activation by tumor cells. In the absence of costimulation, T cells tend to become anergic, a process thought to protect against autoimmune disease. The costimulatory molecules CD80 (B7-1) and CD86 (B7-2) are expressed on professional APC and on a variety of other tissues after exposure to inflammatory cytokines. Transfection of tumor cells with both B7 isomers has been used successfully to trigger their immune-mediated rejection of experimental mouse tumors, which have some inherent immunogenicity. However, this strategy is insufficient for nonimmunogenic tumors, a category into which most, if not all, human tumors would likely fall.

A number of groups have conducted experiments in which highly immunogenic foreign antigens, such as the hemagglutinin protein from influenza, the b-galactosidase enzyme from Escherichia coli, and the ovalbumin protein from chicken are expressed in tumor cells. The results are fairly uniform: Tumors tend to grow progressively, retaining their lethality despite the expression of a foreign and highly immunogenic protein by the tumor cell.

Alternative immune mechanisms designated tolerance and ignorance have been used to explain why the immune system fails to recognize tumors expressing even these normally highly immunogenic antigens. Tolerance generally refers to the lack of a destructive immune reaction to a given antigen. In the tumor context, we might distinguish an active state of tolerance, in which the immune system undergoes a functional and phenotypic change after encounter with antigen, from ignorance, a passive process in which immune cells do not have any contact with the antigen that alters their phenotype or function. Both mechanisms likely play a role in the immune system's unresponsiveness to tumor cells.

**PRODUCTION OF IMMUNOSUPPRESSIVE FACTORS**

Tumor cells may ectopically employ normal immunosuppressive mechanisms, such as the production of transforming growth factor-b, normally produced by certain immune and other somatic cells, but potentially antiproliferative for CTL, natural killer, and lymphokine-activated killer cells. Another example, IL-10, produced by activated T cells, B cells, monocytes, and keratinocytes may be produced by certain solid tumors and may interfere with macrophage-mediated antigen presentation.
It has been reported that expression of Fas ligand (Fasl/CD95SL) by melanoma cells was responsible for their escape from immune recognition. Because Fasl was reportedly expressed in areas of immune privilege such as the eye and testis, it was reasoned that expression of Fasl by melanoma cells indicated that the tumor bed was also an “immune privileged” site. In our own study, however, we found no Fasl, expressed by a panel of 26 human melanoma lines we tested. Thus, our data do not support a role for Fasl expression in the escape of melanoma cells from immune destruction.

**TUMOR AS A MOVING TARGET**

Tumor cells can be a moving target when it comes to immune recognition. The field of chemotherapy has produced a number of well-known examples of tumor escape from treatment including the induction of the expression of the multidrug resistance (MDR) gene. As combinatorial and synthetic vaccines become more effective, the selective pressure on the loss of particular target antigens may indeed be increased. Indeed, there is some evidence that tumor cells may preferentially lose the gp100 tumor antigen as a result of treatment with the gp100 209 to 217 (2M) peptide plus IL-2.

Tumors have unstable genomes that lead them to be heterogenous for the expression of tumor-associated antigens. Further, their unstable genomes may enable them to escape immune recognition because they lose or mutate key elements of the antigen processing machinery such as the TAP transporter associated with antigen processing) transporters, β2-microglobulin, or the MHC class I chain molecules. Other mechanisms underlying the poor immunogenicity of tumors includes the down-regulation of two IFN-γ-inducible proteasomal components called LMP2 and LMP7 in certain human tumors. The proteasome is a large multienzymatic complex involved in the degradation of many of the peptides that later find their way into the MHC class I pathway.

**CONCLUSION**

The field of cancer vaccines has been greatly advanced by a wave of technological innovation as well as a deeper understanding of the immunological response to both cancer cells and potential vaccines. Vaccines using whole tumor cells have been optimized by transfection or addition of costimulatory molecules, cytokines, and chemokines. In addition, target antigens that can mediate tumor cell recognition by immune cells have been cloned and are currently used in a variety of vaccine approaches. The antigens that are most practical for application in vaccines are the self-antigens shared among cancer patients. Encoded in combinatorial vaccines and bacterial, viral, fungal, or cell-free vaccines, these antigens can induce immune responses that can destroy established tumors in animal models and in some instances even in cancer patients. The great genomic plasticity and poor inherent immunogenicity of tumor cells make them difficult targets for complete eradication by the immune system. Yet our growing understanding of the important roles of CD4+ and CD8+ T cells and APC, as well as the importance of dosing and the frequency and route of vaccine administration, will further improve on these initial attempts at therapeutic cancer vaccines.

**CHAPTER REFERENCES**


Allison J, Stephens LA, Kay TW, et al. The threshold for autoimmune T cell killing is influenced by B7-1.


Allison J, Stephens LA, Kay TW, et al. The threshold for autoimmune T cell killing is influenced by B7-1.


INTRODUCTION

With the introduction of the x-ray at the turn of the twentieth century heralding the advent of modern medical imaging, the surgeon's eye has been supplemented with indirect imaging data that better defines local disease. Conventional x-ray techniques have been supplemented, or even supplanted, by radiographic contrast agents, nuclear imaging techniques, ultrasound (US), computed tomography (CT), and magnetic resonance (MR) imaging. There is no reason to believe that even more powerful imaging techniques will not follow. These increasingly sophisticated imaging techniques have steadily improved the identification of local disease, and this development, in combination with concomitant improvements in surgical techniques, has resulted in dramatic improvements in surgical outcomes. Newer imaging techniques now allow disease that cannot easily be visualized with the naked eye to be "seen." Furthermore, the diseased tissue can be better visualized in relationship to adjacent normal tissue, allowing for more precise anatomic treatment. In contemporary practice, fewer and fewer diseases are treated on the basis of direct observation alone. Such is the heritage of twentieth-century medicine.

Until relatively recently, however, the surgeon was still personally responsible for transferring the imaging data to the patient. That is, the surgeon usually reviewed the various imaging studies before surgery and then mentally, but indirectly, incorporated this information into the actual surgical procedure. The future of image-guided surgery (IGS) rests with the development of techniques that allow the operator to more directly incorporate the images into delivery of the therapy. The goal is to enable more precise and less invasive access to a tumor and to monitor its resection, ablation, or other form of local therapy.

MEDICAL IMAGING TECHNIQUES

Any type of image (medical or otherwise) has two intrinsic properties: spatial and signal. 1 The former defines the location and geometric features of a structure or lesion. The latter, generally reflected by gray tone or color, is important for lesion detection and the definition of tissue type. Spatial features of an image include the number of dimensions represented and the resolution. Most medical images are either two-dimensional (2D) projections, such as with a chest film, or three-dimensional (3D), such as with thin section CT or MR. Obviously, 3D images provide more data for guiding a therapeutic device (including a scalpel) into a 3D object (a patient). High spatial resolution, although generally desirable, is often impractical, being associated with longer examination times or poorer image quality. There is also no reason to have higher resolution images than is necessary to detect a lesion or guide therapy. In general, "high-resolution" medical images have 0.5 to 1.0 mm 2 resolution. The biophysical interactions of the imaging technique and the tissues of the body determine the "signal" properties of medical images. Different imaging techniques report different features of tissues. The following are general characteristics of current medical imaging techniques. 2

X-RAY IMAGES

The measurements of x-ray emitted by a point source and transmitted through the human body depends on the integral of the electron density along rays projected through the body, which is a function of the mean atomic number of the tissue. These measurements of "radiodensity" have traditionally been made on films or by image intensifiers, both of which are devices that create analog images that can then be digitized. Digital images are required for most IGS applications. More recently, x-ray–sensitive solid state detector systems in linear or planar arrays are being used to directly generate digital x-ray images. 3 The spatial resolution of most 2D x-ray images is less than 0.5 mm. Conventional x-ray images are used primarily to image bony structures, but also to image the distribution and temporal evolution of contrast agents such as iodine in soft tissues (e.g., blood vessels). Soft tissue contrast is very poor on conventional x-ray studies.

Rotation of the x-ray source and detector around the longitudinal axis of a patient produces projections that can be used for tomographic reconstruction of slices, with typical series of parallel 1- to 10-mm thick sections of 512 ¥ 512 pixels, each 0.25 to 1.0 mm 2 in size. Because this reconstruction process provides a correct approximation of tissue densities and not integrals of tissue densities as in x-ray projections, CT images accurately differentiate bony and soft tissues. Since the advent of CT in the 1970s, the technology has rapidly evolved. Now a common technique, the spiral CT uses a continuous rotation of the x-ray source and a 2D-detector array synchronized with a linear continuous motion of the patient. 1 This technique provides individual slices in approximately 1 second. On the horizon is the use of planar detectors for real 3D volumetric acquisitions instead of reconstruction of 3D images from 2D sections. These x-ray volume images will become increasingly important for IGS.

MAGNETIC RESONANCE IMAGING

MR imaging (MRI) provides information about molecular properties of tissues. 4 A body first is set into an intense constant magnetic field (ranging from 0.1 T to a few Tesla). MRI studies the way tissues behave when they are submitted to a weak, transient perturbation of this strong magnetic field. Radiofrequency (RF) pulses induce spinning motions of nuclei that come back to an equilibrium. Using a select sequence of perturbations, information is provided about the concentration (often called density) of atoms (mainly hydrogen in H2O) and about their physicochemical environment. Several components of the received signals, which relate to intrinsic MR parameters (proton density, relaxation times T1 and T2) are used to create images. Although each of these MR tissue parameters reflects a unique aspect of the biophysical milieu of tissue water, they remain poorly understood from a biologic perspective. However, they have been empirically shown to provide great contrast between different types of normal and abnormal tissues, including benign and malignant neoplasms. MRI is a true 3D-imaging technique, because the application of magnetic field gradients can define any point of the volume studied. Whereas most standard devices provide series of parallel sections in sagittal, coronal, or axial planes, it is possible to obtain homogeneous 3D volumes of 256 ¥ 256 ¥ 256 voxels having a spatial resolution of 1 mm 3. A valuable modification of MRI is MR angiography, which produces clear images of blood vessels noninvasively. 5

MR spectroscopy allows for metabolic studies of complex biologic systems: Spectra in the frequency domain correspond to the composition of molecules of a region. 6 Clinical applications of MR spectroscopy are increasing, with protons being the main nuclei that are observed. Chemical shift imaging techniques (multivoxel spectroscopy) have been developed, but more work still is necessary before these will be ready for routine clinical use. Miniaturization of RF coils for
ULTRASOUND

US is a relatively inexpensive, portable, real-time imaging system with a typical spatial resolution of 1 mm. These features make US a major imaging tool for IGS. After the emission of an US wave from a piezoelectric element, the sound signal reflected by the discontinuities of acoustic impedances of tissues is analyzed. Time of flight measurements of the reflected echoes gives spatial information of acoustical interfaces. Acoustic impedances of tissues are primarily related to physical features rather than to their biologic properties. Selection of US frequency depends on a trade-off of resolution versus attenuation. High-resolution, 12-MHz US images of the thyroid gland have 0.5 mm[3] resolution, but the depth of view is only a few centimeters. Mechanically or electronically moving the direction of US allows one to obtain a 2D or 3D image. Images may be corrupted by a rather strong texture noise and by distortions due to such things as bone and air.

The analysis of blood velocities is achievable through the use of Doppler US probes, some of which have been miniaturized and mounted at the tip of a needle. Newer US imaging modalities include color and power Doppler sonography, which produce 2D or 3D color images of blood velocities superimposed on a standard grayscale US image.13

NUCLEAR MEDICINE

In contrast to the imaging techniques already described, which are primarily dependent on physical, morphologic properties of tissue, nuclear imaging is usually directly dependent on biochemical or physiologic properties. In nuclear medicine imaging, or scintigraphy, a source of photons (gamma) or positrons (beta) is attached to a specific radiopharmaceutical and injected into the body. External detectors observe the emission of such radioactive elements. A typical image is a planar projection of the density of radioactive elements, which is related to the metabolism of the radiopharmaceutical in the studied region.12 Rotation of the gamma camera around the patient provides a set of projections that is fed onto tomographic algorithms similar to those used for x-ray CT. The result is a 3D volume of datamatoscintigraphy, or single photon emission CT (SPECT).13 A more complex strategy studies the emission of positrons (negative electrons). Each emitted positron collides with an electron of the environment and gives rise to two high-energy photons that go in opposite directions. A ring of detectors set around the patient detects these two photons at very near instants. Thus, the associated events lie on a straight line between these two corresponding detectors. The intersection of such lines gives rise to a 3D region of emission from which a 3D image can be reconstructed. Such is the technique of positron emission tomography (PET).14 Both SPECT and PET have relatively poor spatial resolution when compared with CT or MRI (typically a set of 64 × 128 × 102 voxels, each 2 to 10 mm3, is obtained), but these methods provide functional information that is not available with other techniques.

IMAGE GUIDANCE

These various modalities provide images of anatomic or pathologic structures that can form the basis for surgical planning and subsequent image guidance of a procedure. In traditional surgery that depends heavily on physician inferences and qualitative decisions based on human perception of these images (and other data), IGS depends on quantitative decisions (e.g., direction and depth of a needle) based on digital image data processed by computers that are directly linked to surgical devices. The engineering requirements of such a system are extraordinarily demanding; system fidelity and reliability must be superb. Even with the most sophisticated system, however, the physician operator remains the critical unit.

Generally, five important elements make up IGS: (1) high-quality digital images, (2) advanced computer image processing that includes tissue classification or segmentation algorithms and 2D and 3D visualization tools, (3) a computer modeling system for simulation, (4) a registration system that links the medical images with the real patient, and (5) digital interfaces to therapeutic devices.15

DATA ACQUISITION

In most cases, image information is provided by preoperative or intraoperative studies. Medical a priori knowledge (e.g., an anatomic atlas) as well as video images or different types of signals (e.g., Doppler, electrophysiology) can also be used.

IMAGE PROCESSING

The "raw" image data must be processed to allow the surgeon to intuitively perceive the pertinent image information and relate it to the planned surgical procedure. Often, this process requires that images be reformatted into 3D or pseudo-3D images and that key structures or tissues be identified, either implicitly or explicitly. The former step requires state of the art computer visualization tools, whereas the latter step requires accurate tissue classification or segmentation algorithms. Although current segmentation techniques can quickly and accurately classify spatially well-defined and high-contrast tissues, such as bone on x-ray CT, much more work is necessary for the accurate segmentation of subtle soft tissue differences, such as those related to infiltrating neoplasms.

REGISTRATION

The problem of matching all of the image data available for a patient into a unique coordinate system is commonly referred to as registration. Registration is a crucial technology in IGS for three reasons. First, the coregistration of medical data allows the surgeon to plan an operation using all of the available information. Second, registration of preoperative and postoperative data is crucial for individual patient follow-up and statistical analysis of results. Third, registration of preoperative and intraoperative data provides the crucial step required to create the "virtual patient," which permits the visualization of the patient's anatomy to a high degree of accuracy, the verification of surgical plans, and the real-time monitoring of treatment. Ideally, all patient data should be correlated with the physical space of the real surgery and made available to the surgeon. A variety of registration techniques have been developed, some of which use external markers or fiducials placed on the patient, whereas other methods use intrinsic anatomic structures to register images and physical spaces.16 This latter capability is important because it is more direct, logistically easier, and potentially more robust. Although accurate rigid registration is usually the former step requires state of the art computer visualization tools, whereas the latter step requires accurate tissue classification or segmentation algorithms. Although current segmentation techniques can quickly and accurately classify spatially well-defined and high-contrast tissues, such as bone on x-ray CT, much more work is necessary for the accurate segmentation of subtle soft tissue differences, such as those related to infiltrating neoplasms.

SURGICAL PLANNING

A 3D model of the patient and pathology is created into which all the relevant image data has been incorporated. The operator (surgeon or physician) can then manipulate the model in a virtual reality mode. This permits the surgeon to define the surgical strategy, which can then be simulated and modified.

PERFORMING THE SURGERY

Different types of guiding systems can be used to execute the surgical plan. Passive systems enable the surgeon to compare the actual intervention with the planned one. This is the case with systems such as the ISG Wand (ISG Technologies, Mississauga, Ontario, Canada),17 in which previously obtained images have been registered to the patient using a computer system with a digital articulated arm. Surgical instruments are then attached to the articulated arm and manipulated by the surgeon who can observe the tool in real patient space as well as on the workstation in image, or virtual, space. Semiactive systems enable the physical guiding of the instrument that is still controlled by the operator, which is the case, for example, with the stereotactic neurosurgical system described by Lavallee and Troccaz.18 Finally, active systems execute part of the intervention. Kellygg developed a system in which a laser is used for brain microsurgery. The laser is directed toward a tumor that has been localized by MRI. The laser is digitally manipulated until a synthesized image built from MRI data can be superimposed on an intraoperative video image.
position control by the surgeon and, on instruction, would perform the defined task, prompted by the surgeon at each stage. The system would be required to react to given situations in real time by comparison of actual behavior with sophisticated reference models, few of which exist.

**SPECIFIC APPLICATIONS OF IMAGE-GUIDED SURGERY**

A variety of imaging techniques have become an integral part of the surgeon's approach to managing tumors, both benign and malignant. Many can be used for both preoperative and intraoperative localization. Several surgical specialties have incorporated IGS into their approach to patient management.

**NEUROSURGERY**

IGS has its origins in the development of techniques for stereotactic brain biopsy. These early studies used CT to localize lesions in the brain through coordinates provided by a device fixed to the patient's skull. In one study, RF ablation was applied to a deep brain lesion with symptomatic relief for the patient. This may represent one of the earliest applications of IGS.

The techniques and equipment used for image-guided neurosurgery have evolved substantially since the late 1970s. Improvements in biopsy techniques paved the way for therapeutic interventions using a variety of ablative procedures, culminating in dedicated operating suites with real-time imaging from CT and MRI. The success of these techniques is predicated on their ability to allow surgeons to perform their procedures more safely and efficiently. The approach to lesions that are located deep in the brain presents challenges that help to illustrate where image guidance may prove its utility.

Microsurgery of deep brain lesions is often complicated by the close proximity of major vessels, eloquent brain, and the need to work in a confined space where standard microscopic visualization may be limited. By combining images from CT, MRI, and digital angiography, a 3D rendering of the surgical field has been successfully applied to guide microsurgical resections of deep-seated cerebral lesions. The information obtained allows the surgeon to visualize the relationship between the lesion and cerebral vessels as well as brain structures of high functional significance. 3D rendering allows the surgeon to overlay the position of surgical instruments and to predict and simulate the trajectory of the approach.

Similar guidance systems have been used to allow for the ablation of brain tumors using heat generated by RF devices. In this setting, the accurate position of the RF ablation probe is critical to minimizing the potential for collateral thermal injury of adjacent structures. In a study of 12 patients (14 lesions treated) with primary or metastatic brain tumors, an MR-guided stereotactic RF procedure was evaluated. Using MRI, the stereotactic coordinates of the tumor and the angle of the RF probe were calculated. Once the probe was properly positioned, the tissue was heated to the target temperature, and full ablation of the tumor was confirmed by real-time MRI. All procedures were performed in awake patients, and patients were followed for up to 10 months. MRI was successful in demonstrating well-defined lesions in all cases, documenting accurate placement of the RF probe. Characteristic changes in the appearance of the lesions during treatment on T2-weighted images allowed for confirmation of focal energy delivery during the procedure.

In addition to providing for accurate localization and real-time anatomic feedback, newer computer-guided imaging systems also have been designed to give functional information during the surgical procedure. Using real-time MR images in conjunction with superimposed functional data from somatosensory evoked potentials derived from dipole tracings, investigators have been able to localize the central sulcus in 12 patients with intracranial disorders. In six of the patients, 3D computer graphics were reconstructed from MRIs, which allowed for the visualization of lesions deep in the brain. The 3D functional images were then superimposed on the anatomic images. This technique allowed the surgeons to see the 3D relationship between the lesion and the functional sensorimotor cortex. This type of data can potentially allow for greater preservation of normal brain function during surgery.

A significant advance for intraoperative IGS has been the open-bore MR unit (Fig. 64-1). This is an open MR device, which allows for optimal vertical access of the surgeon and assistant to the patient. Using such a system, surgeons at the Brigham and Women's Hospital in Boston published their experience with 110 cases, which included 47 biopsies, six catheter placements, four cyst drainage procedures, 47 craniotomies for resection, three spinal cases, and three laser tumor ablations. This intraoperative MR surgery unit was especially useful in guiding biopsies and resections near cysts, ventricles, and critical vascular structures. Standard approaches using prior image data with framed and frameless techniques would be inadequate to show anatomic changes during the procedure. The acquisition of real-time images of the biopsy needle within the lesion were found to be very useful. The information obtained from this system allowed for more complete resection of infiltrative tumors. Image fusion of SPECT and neurofunctional data into the imaging space enabled the surgeons to better visualize tumor invasion or neural function with real-time imaging during resection.

**FIGURE 64-1.** Open magnetic resonance imaging for image-guided surgery as implemented at the Brigham and Women's Hospital, Boston.

The true test of whether image-guided techniques are of benefit in neurosurgery is whether an impact on outcome is the result. Studies focusing on outcome analysis are beginning to emerge. Early data indicate that the addition of image-guided techniques can reduce operative time, patient morbidity, and the need for repeat procedures. Further prospective studies of cost analysis are necessary to definitively demonstrate these benefits.

**HEAD AND NECK SURGERY**

Because of anatomic similarities, IGS techniques developed for neurosurgery have found several applications in the management of patients with both benign and malignant tumors of the head and neck. For patients with skull base tumors, an intraoperative guidance system has been used to provide nearly instantaneous CT and MRI images with computer reconstruction to the surgeons. The ISG viewing wand can correlate any point within the operative field to its corresponding locus on the reformatted images. The use of this wand in 14 patients with skull base, cerebellar pontine angle, or temporal bone lesions has allowed for minimally invasive incisions, intraoperative navigation, and identification of important anatomic structures. This precision allowed for a greater margin of safety and a more precise assessment of the extent of lesion resection.

Endoscopic techniques have revolutionized the approach to nasal and sinus surgery. A computer-assisted surgery system has been applied to help in intraoperative localization during endoscopic surgery of the paranasal sinus region. This system allows for the continuous orientation of the scope by using a 3D reconstruction of the preoperative CT scan with superimposed positioning of the endoscope. By using a dual display on the endoscopic monitor, the surgeon can see the video-endoscopic picture and the information from the localizer simultaneously. This allows for positional adjustments of the scope without the need for the surgeon to look away from his or her operative field. This system also has been used for complex skull base and head and neck resections.

3D intraoperative navigational systems have been used to assist in craniofacial procedures ranging from corrections of craniofacial asymmetry to tumor resections. A study of 17 patients undergoing craniofacial procedures demonstrated the utility of the ISG navigation system in precisely orienting the surgeon to his exact location throughout the procedure. The system was particularly useful in determining ocular globe position, and in delineating tumor margins.
No additional operative time or adverse events were attributed to the use of the system.

The development of virtual endoscopy is another useful application of real-time imaging. A virtual otoscope has been designed that provides a precise view of the structures of the inner ear. The precision of the images derived from this device may replace the more invasive endoscopes in current use.

**SURGICAL ONCOLOGY**

The application of IGS to the management of malignancies of soft tissues in the abdominal cavity has required imagination as well as modifications of the approaches used in neurosurgery. Unlike the brain, which is fixed in its position, the abdominal contents, such as small bowel, are more fluid and present certain difficulties in making use of imaging techniques for “target” acquisition. The liver, however, represents a relatively fixed anatomic structure for which image-guided therapies have been used.

A variety of ablation techniques have been applied to the treatment of liver tumors in situations in which surgical resection may not be appropriate. These techniques, such as RF ablation, cryotherapy, and interstitial laser thermoablation are discussed in greater detail elsewhere in this text. These techniques share in common the need to not only localize the target lesion, but also to monitor the effects of the therapy during the time it is being applied.

Several imaging modalities, including US, CT, and MRI, have been used to accurately position the ablation probes into the lesion and to monitor the effects of the therapy. Using an Nd:YAG (neodymium:yttrium-aluminum garnet) laser system and real-time MRI, a group of 12 patients had a total of 27 lesions in the liver treated under local or general anesthesia. An MR colorization sequence was used to monitor changes in the tissue temperature during therapy. The patients tolerated the procedure well, with 8 of the 12 being discharged home on the day after the procedure. Thermal zones of ablation up to 5 cm were achieved with two patients with 3-cm lesions, achieving complete ablation with a single procedure. Seven of the patients required multiple procedures to successfully ablate their lesions. Similar procedures also have been performed laparoscopically.

Using intraoperative US and a laparoscopic approach, RF ablation has been applied to the treatment of liver metastases from neuroendocrine tumors. In six patients (13 lesions treated) no intraoperative complications were reported. US was used successfully to position the thermal ablation probe and to monitor the treatment effect in the operating room to determine when an adequate zone of necrosis was achieved. US is able to detect the “outgassing,” which occurs as the tissue is heated and gas is released into the surrounding parenchyma.

A trial at the National Cancer Institute is currently under way to evaluate US, CT, and MRI to determine the best modality for positioning the probes and monitoring the effects of RF ablation in the liver. Figure 64-2 demonstrates a real-time CT image of a lesion in the liver before and after RF ablation. Patients are imaged with dynamic enhanced MRI preoperatively and in follow-up as a means of following response.

![Figure 64-2](image)

**FIGURE 64-2.** A tumor (arrow) located in the right lobe of the liver in a patient with metastatic adrenal cancer as seen on computed tomographic (CT) scan. Panel A shows the lesion before radiofrequency (RF) ablation on a noncontrast scan. Panel B shows a three-dimensional rendering of the lesion, illustrating the path of the needle. This image was obtained while the patient was on the table, as a means of directing the therapy. Panel C demonstrates the lesion post–RF ablation on an arterial phase postcontrast CT scan. Note that the lesion appears larger than at preablation. This is because of the 1-cm zone of necrosis achieved around the lesion.

Nuclear imaging has been applied to the preoperative and intraoperative detection of malignancy in the abdominal cavity. This approach has been most extensively evaluated with respect to colon and rectal cancer. Two strategies have been pursued, one using anti-carcinoembryonic antigen (CEA) antibody immunoscintigraphy and the other using PET and the radiopharmaceutical [18F]fluorodeoxyglucose (FDG).

Radioimmunoguided surgery (RIGS) has relied on the ability of radio labeled monoclonal antibodies or antibody fragments to bind specifically to markers expressed on tumor tissue. The specificity and sensitivity of these antibodies is based to a large degree on the tumor marker itself and how restricted its expression is to neoplastic tissue. CEA has been extensively studied as a target for this approach.

Radioimmunoguided surgery using an intraoperative probe to detect radioactivity has been evaluated as an adjunct to second-look laparotomy in the evaluation of colorectal cancer patients with rising serum CEA levels. Sixteen asymptomatic patients with a history of colorectal cancer surgery and a rising serum CEA level underwent second-look surgery using the RIGS approach. Patients received the anti–tumor-associated glycoprotein iodine 125–labeled monoclonal antibody (MoAb) B72.3 preoperatively. RIGS exploration was combined with a standard exploratory laparotomy. Recurrent disease was observed in 14 of the 16 patients as the result of this combined exploration. Standard exploration alone demonstrated recurrent disease in 9 of 16 patients (56.2%). In five patients (31.2%), RIGS detected disease that would otherwise have been overlooked. The additional RIGS-detected tumor sites were resectable for cure. In this study, RIGS improved the results of colorectal cancer, CEA-guided, second-look procedures in asymptomatic patients by recruiting one-third of patients to curative resections.

Preoperative SPECT imaging studies can be obtained using a gamma camera in addition to the use of the intraoperative probe. This combined approach was used in a study evaluating in vivo post-targeting of tumor by means of anti-CEA monoclonal antibodies and the avidin-biotin three-step system. Six patients with primary or recurrent rectal cancer were preoperatively injected with 1 mg of F223C5 (anti-CEA) and/or B72.3 anti–tumor-associated glycoprotein (TAG-72) biotinylated monoclonal antibody. At 24 hours after injection, 1 mg of avidin was administered and, after a further 24 hours, biotin-labeled indium 111 was also injected. Eight tumor sites were localized in the six patients. Four of the eight lesions were identified preoperatively by the gamma camera; and six intraoperatively using a nuclear probe. An advantage of this method was the ability to perform preoperative scintigraphy and intraoperative radioimmunodetection with a single radioactive compound injection of biotin labeled with 111In within a few days before surgery.

Radioimaging using antibody-directed immunoscintigraphy relies on the ability of the antibody to bind efficiently to the target tissue and to be imaged above background. It also requires multiple antibodies to be derived against a number of tumor markers, depending on the histology of the target lesion. Many of these limitations could be overcome by using a more universal reagent that would be taken up by tumor tissue selectively, regardless of the tumor histology and independent of the need for antibody-antigen interactions. The radiopharmaceutical FDG has many of these properties.

Several studies have shown that malignant lesions demonstrate elevated glycolysis when compared to normal tissues. By using the radiolabeled glucose analog FDG, investigators have documented increased uptake of FDG in cancer tissue. PET scanning with FDG has been used to image a variety of malignant neoplasms, including breast cancer, head and neck tumors, lung cancer, lymphoma, melanoma, ovarian tumors, bone cancers, and colorectal carcinomas.

The mechanism whereby FDG is selectively accumulated in neoplastic tissue is based primarily on increased uptake of FDG and conversion to FDG-6-phosphate. The inability of cells to further metabolize FDG-6-phosphate causes the molecule to be trapped in the cells, facilitating accurate imaging. Figure 64-3 shows a representative PET image using FDG. The intensity in this image is proportional to the amount of FDG that has entered the cells, begun the first steps of the metabolic conversion of sugar to energy, and then been trapped. The reasons why so many tumors avidly accumulate glucose are only partly understood. The energy...
The standard approach of bilateral neck exploration for the patient with primary hyperparathyroidism has been questioned. In a retrospective study, a group of 68 patients with superior parathyroid adenoma was found at operation.

FIGURE 64-4. A: Technetium Tc 99m sestamibi scan demonstrating a parathyroid adenoma on the left in a patient with primary hyperparathyroidism. B: A large left inferior parathyroid adenoma was found at operation.

Currently, a study is under way at the National Cancer Institute evaluating the use of FDG-PET scanning and anti-CEA antibody immunoscintigraphy in the preoperative and intraoperative detection of recurrent colon and rectal cancers. Patients are recruited based on a rising serum CEA value in the absence of imageable disease, or with a single site of otherwise resectable disease. Patients are explored, and in some cases, a probe designed to detect FDG is used intraoperatively. This study is ongoing and is designed to evaluate the sensitivity, specificity, and predictive value of these scans as well as second-look laparotomy for the detection of recurrent tumor.

FIGURE 64-3. Positron emission tomographic image obtained using $^{18}F$fluorodeoxyglucose in a patient with rising serum carcinoembryonic antigen in the setting of metastatic colon cancer. The lesion is seen in the right lobe of the liver in all three views.

IGS has made possible a more minimally invasive approach to the diagnosis and management of breast lesions. The use of mammography and breast US has resulted in successful localization of lesions. Percutaneous core sampling of lesions guided by specialized, computerized, stereotactic radiographic equipment is less painful and can be done under local anesthesia. Tissue cores obtained are adequate to make the diagnosis in most cases.

Using an open MRI scanner, excisional biopsies of breast lesions have been successfully performed. Intraoperative real-time scanning assisted in determining adequacy of resection margin and in positioning and minimizing the size of the incision. In a study of women undergoing excision of benign lesions, the MR demonstrated that all lesions were adequately excised with pathologic confirmation of clean margins.

During an exploratory laparotomy, the surgeon is limited in the examination of the hollow viscera by the inability to adequately assess the mucosal surfaces. Although intraoperative endoscopy can be performed, this procedure is often difficult logistically and complicates the exploration because of the need to insufflate gas into the bowel. Furthermore, the small bowel is virtually inaccessible. Virtual endoscopy may help to overcome these limitations.

Virtual colonoscopy, for example, is a method of colon examination in which computer-aided 3D visualization of spiral CT simulates fiberoptic colonoscopy. In one study, a colon phantom containing spheres of various sizes was used to determine the influence of CT acquisition parameters on lesion detectability and sizing. Results demonstrated that detection of beads of 4 mm or more was 100%. Detection decreased to 78% to 94% for 2.5 mm beads. The authors concluded that CT scanning at 5 mm collimation and up to pitch 2 is adequate for detection of high-contrast lesions as small as 4 mm in their model. As the imaging algorithms are improved, virtual colonoscopy may be used as a screening modality both preoperatively and intraoperatively in a CT-equipped operating suite.

Virtual endoscopic techniques also have been applied to the examination of the biliary and pancreatic ducts. MR cholangiography is a noninvasive technique that allows one to image the biliary system without the need for a contrast agent. Depending on the MR sequence chosen and the image processing, the ductal anatomy can be highlighted as a light or dark image. Because this is an MRI-based approach, there is no radiation exposure. Images can be rendered in three dimensions to give an accurate representation of the ductal anatomy. Studies have demonstrated that the image quality compares favorably to endoscopic retrograde cholangiopancreatography of pancreatic (duct).

A similar approach has been used to image the pancreatic duct in patients with mucin-producing pancreatic tumors. In a group of 13 patients with a total of 18 lesions, a computer-based virtual endoscopy system was used to render 3D reconstructions of the pancreatic ductal anatomy. The virtual pancreatoscopy was successful in demonstrating the surfaces of the bile and pancreatic duct and could distinguish cystic from solid tumors. The surfaces of the malignant mucin-producing tumors were shown to be more irregular than those of the benign lesions. The data were useful for surgical planning with regard to extent of resection.

ENDOCRINE SURGERY

Nuclear imaging, making use of radioisotopes that target specific tissue types, has made significant contributions to IGS, allowing for more minimally invasive procedures. The application of technetium Tc 99m sestamibi scanning to the preoperative and intraoperative localization of parathyroid adenomas has improved detection and allowed for less morbid surgical procedures. For the majority of patients, routine preoperative imaging may not be necessary. In experienced hands, 95% of patients with primary hyperparathyroidism (HPT) are cured after a careful bilateral neck exploration.

Imaging becomes critical for those patients who have persistent or recurrent HPT. In this patient population, reexploration is complicated by scarring, which not only makes it difficult to identify the parathyroid glands, but also increases the risk of injury to the recurrent laryngeal nerves. Furthermore, in patients who are not cured at the first operation, it is possible that the abnormal parathyroid gland is located in an ectopic site, such as the pharynx or mediastinum.

Compared to other noninvasive imaging studies, such as CT, US, and MRI, the sestamibi scan has been shown to be superior, with a positive predictive value as high as 95%. Sestamibi scans can localize the parathyroid adenoma to the correct side of the neck and to the position within the neck relative to other structures ( Fig. 64-4). The accuracy of sestamibi has led to the introduction of a minimally invasive approach to parathyroid surgery.
patients were reviewed with respect to localisation studies and the need for bilateral neck exploration. Forty-four patients were treated with localization study–aided imaging. Twenty-two patients were treated with image-guided parathyroid exploration without localization. Patients with both the localization study and the image-guided exploration were done in a single sitting. The authors suggest that, at best, the success rate of unilateral exploration using cooperative parathyroid hormone measurements can be expected to be 85%. Although these strategies are a good example of how image guidance can change surgical management, the ultimate utility of this approach compared with standard bilateral neck exploration with a historical success rate of 95% must invariably define more definitive studies.

CONCLUSIONS

The ultimate goal of any medical therapy is obvious: precisely define the site and nature of disease and deliver the most effective therapy to the diseased tissue while doing no harm to normal tissue. Two main therapeutic approaches have been followed: systemic (generally medicinal) and surgical. The fundamental basis of surgery is simplicity: if an operation is not necessary, then the "surgical" element of the "medical therapy" is a redundant term. Some type of "imaging" of the disease must guide surgery and other forms of traditional therapy. Traditionally, the imaging has been performed by the surgeon's naked eye, supplemented by other, cruder sensory facilities, such as palpation. As advanced imaging techniques and technology become available, the surgeon will be able to expand the repertoire of available information and deliver medical care in a more precise fashion.

CHAPTER REFERENCES

INTRODUCTION

There is a growing interest in developing techniques that produce extremely conformal x-ray dose distributions. Several means of reducing treatment volumes are under active development and clinical testing. These new techniques include three-dimensional treatment planning, stereotactic patient positioning, and conformal delivery technology, such as intensity-modulated radiation therapy. The results of these efforts support the concept that higher doses of radiation can be delivered with equal or reduced normal tissue complications. The ability to deliver higher doses of radiation using proton radiation therapy should lead to improved local control and survival rates.

PHYSICAL ASPECTS OF PROTONS

Protons have comparable biologic effects in tissue relative to high-energy x-rays used in conventional radiation therapy. Evidence of this comes from the fact that the relative biologic effectiveness (RBE) of protons is approximately 1.1. The RBE of a proton beam is the ratio of the dose required to produce a specified effect using a reference radiation, usually cobalt 60 photons, to the proton dose required to produce the same effect. Most recent studies have reported RBE values for clinical protons in the range of 1.0 to 1.25.

Therefore, the advantage of proton radiation therapy is because of the superiority of the physical dose distributions compared with those for conventional therapy beams, rather than a biologic advantage.

A proton loses its energy in tissue through coulombic interactions with electrons, although a small fraction of energy is transferred through nuclear collisions. The energy loss per unit path length is relatively small and constant until near the end of the proton range, where the residual energy is lost over a short distance, resulting in a steep rise in the absorbed dose (energy absorbed per unit mass). This portion of the particle track, where energy is rapidly lost over a short distance, is known as the Bragg peak (see the curve labeled “Unmodulated Proton Beam” in Fig. 65-1). In physical terms, the magnitude of the transfer of energy to tissue per unit path length traversed by the protons is inversely proportional to the square of the proton velocity. The initial low-dose region in the depth-dose curve, before the Bragg peak, is referred to as the plateau of the dose distribution and is 30% to 40% of the maximum dose.

The Bragg peak is too narrow to treat any but the smallest of targets. For irradiation of larger targets, the beam energy is modulated to widen the Bragg peak, which is accomplished by superimposing several beams of closely spaced energies (ranges) to create a region of uniform dose over the depth of the target; these extended regions of uniform dose are called spread-out Bragg peaks. This is illustrated in Figure 65-1. For comparison, Figure 65-1 also shows the depth-dose curve for a 10-MV x-ray beam, an energy commonly used to treat deep-seated tumors. Note that the x-ray beam dose rises to a maximum value at relatively shallow depths, then falls off exponentially as depth increases. This fundamental difference in energy loss in tissue leads to superior dose distributions with protons.

The physical superiority of proton dose distributions is illustrated for the treatment of a paranasal sinus cancer (Fig. 65-2) and a large Ewing’s sarcoma of the pelvis (Fig. 65-3). In this comparison, intensity-modulated x-ray therapy and intensity-modulated proton therapy are used. Both x-ray and proton treatment plans of the paranasal sinus make use of multiple beam portals and identical constraints. The two treatment plans are designed to provide equal doses of 76 Gy to the target volume. The differences in the two plans are shown in the lower panels of Figure 65-2. This illustration reveals that x-rays deliver an additional 5 to 15 Gy throughout the brain. In the region of the right eye, which is magnified, the x-ray plan delivers up to 40 Gy more than the proton plan. The constraint on the right eye retina was 50 Gy. Had this been reduced, the x-ray dose would have been lower in this region, but at the expense of increased dose elsewhere or greater dose inhomogeneity in the target. This comparison illustrates that protons can be made to stop sharply beyond a target volume, sparing a critical structure distal to the target.
large tumors, respectively. Independent risk factors for enucleation were involvement of the ciliary body, tumor height more than 8 mm, and distance between the
survival. The probability of eye retention at 5 years was estimated to be 90% for the entire group and 97%, 93%, and 78% for patients with small, intermediate, and

As of October 1998, a total of 2586 patients have been treated for uveal melanoma at MGH with protons in collaboration with the Massachusetts Eye and Ear

UVEAL MELANOMA

observed.


differentiated tumors, respectively. This study randomized patients to two different proton boost dose levels, with patients receiving a total dose of either 79.2 Gy or

Grade 1 and 2 rectal bleeding was higher in the proton arm (32% vs. 12%), as was urethral stricture (19% vs. 8%). In conclusion, dose escalation to 75.6 CGE by

Based on the results of this trial, the Proton Radiation Oncology Group (PROG) 95-09 was initiated. Participants in the trial were MGH and Loma Linda University

CLINICAL RESULTS

In 1946, Robert Wilson proposed that proton beams would provide superior dose distributions and should be considered for clinical radiation treatment. Initial efforts

Investigators at MGH completed a phase III trial comparing 67.2 Gy of photons versus 75.6 Cobolt Grey Equivalent (CGE) using a conformal perineal proton boost. 2

From 1982 through 1992, 202 patients with T3–T4 prostate cancer received 50.4 Gy by four-field photons. Patients then received either 25.2 CGE with conformal

PROSTATE CARCINOMA

The second example is a Ewing's sarcoma of the ilium in an 18-year-old man as shown in the transverse computed tomography images in Figure 65-3. The x-ray plan
delivers greater dose to the anterior small bowel and midline structures, such as the bladder, prostate, and large bowel. This plan also dispels the commonly held
misconception that protons only offer significant advantages over x-rays for small treatment volumes. The effects of excess dose outside of the target volume are not
well understood, although late effects of radiation do not occur in unirradiated tissues. Such excess radiation may also be important in the acute tolerance to treatment
as well as the tolerance to combined treatment with chemotherapy and radiation. These two examples illustrate the superiority of protons in treating both small and
large targets.

FIGURE 65-2. Paranasal sinus tumor treated with intensity-modulated proton therapy (upper left) and intensity-modulated x-ray therapy (upper right). The difference
in the two plans is shown in the lower right panel and magnified in the lower left panel. Note the additional 5 to 15 Gy that the brain receives and the increased dose
to the right eye. The plans were developed by one of the authors (A. L.) at the Paul Scherrer Institute in Villigen, Switzerland.

FIGURE 65-3. Ewing's sarcoma of the right pelvis treated with intensity-modulated proton therapy (upper left) and intensity-modulated x-ray therapy (upper right). The
lower panel shows the difference in the two plans. Note the additional 8 to 28 Gy that the small bowel, midline structures, and contralateral sacrum receive. The plans
were developed by one of the authors (A. L.) at the Paul Scherrer Institute in Villigen, Switzerland.

PROTON BEAM RADIATION TREATMENT: HISTORICAL NOTE

In 1946, Robert Wilson proposed that proton beams would provide superior dose distributions and should be considered for clinical radiation treatment. Initial efforts
were directed at intracranial targets and used single-dose protocols. The first treatments using proton or helium ion beams were at the University of California at Berkeley (1955), University of Uppsala, Sweden (1957), Massachusetts General Hospital (MGH; 1961), Physics Research Institute, Dubna, Russia (1964), and the Institute for Experimental and Theoretical Physics, Moscow (1969). As of 1999, approximately 24,500 patients have received part or all of their radiation treatment by proton beams (for a historical review, see ref. 4). Today 19 proton treatment centers are established worldwide. Only one prospective randomized trial reporting on the efficacy of proton beam radiation therapy versus photon therapy has been published. 3

The proton treatment program at MGH began in 1961. It was led by the neurosurgical group of W. Sweet and R. Kjellberg using the 160-MeV cyclotron in the
department of physics at Harvard University. Their targets were principally pituitary adenomas, arteriovenous malformations, and other benign intracranial neoplasms
and were treated by single-dose protocol. In January 1974, the MGH department of radiation oncology began a program of fractionated proton treatment. This clinical
research program represents an active collaboration between the Harvard Cyclotron Laboratory (HCL), the Massachusetts Eye and Ear Infirmary, the Harvard Medical
School, and MGH.

CLINICAL RESULTS

PROSTATE CARCINOMA

Investigators at MGH completed a phase III trial comparing 67.2 Gy of photons versus 75.6 Cobolt Grey Equivalent (CGE) using a conformal perineal proton boost. 2

From 1982 through 1992, 202 patients with T3–T4 prostate cancer received 50.4 Gy by four-field photons. Patients then received either 25.2 CGE with conformal
protons or a 16.8 Gy proton boost. No differences were found in overall survival, total recurrence-free survival, or local recurrence-free survival in the two groups. The
local recurrence-free survival rate at 7 years for patients with poorly differentiated (Gleason 9 and 10) tumors was 85% on the proton arm and 37% on the photon arm.
Grade 1 and 2 rectal bleeding was higher in the proton arm (32% vs. 12%), as was urethral stricture (19% vs. 8%). In conclusion, dose escalation to 75.6 CGE by
conformal proton boost led to increased late radiation sequelae, but not to increased total survival in any subgroup. However, there was an improved local
recurrence-free survival in patients with poorly differentiated tumors.

Based on the results of this trial, the Proton Radiation Oncology Group (PROG) 95-09 was initiated. Participants in the trial were MGH and Loma Linda University
(LLU) Medical Center. PROG 95-09 is a randomized phase III trial using conformal photons with proton boost in early-stage prostate cancer. The study was proposed
because long-term follow-up of T1–T2 irradiated patients demonstrated biochemical disease-free survival rates of 90%, 35%, and 20% for well, moderate, and poorly
differentiated tumors, respectively. This study randomized patients to two different proton boost dose levels, with patients receiving a total dose of either 79.2 Gy or
70.2 Gy. Patients deemed to be a low risk for local failure (prostate-specific antigen less than 4 ng/ml) and patients with high risk for distant disease (prostate-specific
antigen greater than 15 ng/ml and/or positive lymph nodes) are not likely to benefit from this dose escalation and thus were excluded. This randomized trial was

designed to detect a 20% increase in freedom from local failure and biochemical relapse at 5 years. With 390 patients entered, this trial is now closed and is awaiting
analysis.

The results of the LLU experience in early-stage prostate cancer have been published. 3 Three hundred and nineteen men with T1–T2b tumors were treated with 74 to
75 CGE protons, or combined protons and x-rays. The overall 5-year biochemical disease-free survival rate was 88%. No severe treatment-related morbidity was
observed.

UVEAL MELANOMA

As of October 1998, a total of 2586 patients have been treated for uveal melanoma at MGH with protons in collaboration with the Massachusetts Eye and Ear

Infirmary. Patients were treated with 70 CGE in five fractions over 7 to 9 days. The 5-year actuarial local control rate is 96% for all sites within the globe, with an 80%
survival. The probability of eye retention at 5 years was estimated to be 90% for the entire group and 97%, 93%, and 78% for patients with small, intermediate, and
large tumors, respectively. Independent risk factors for enucleation were involvement of the ciliary body, tumor height more than 8 mm, and distance between the
posterior tumor edge and the fovea. These results compare favorably with local control rates of 89% reported with protons in Nice, France. 

Because some patients have experienced deteriorating vision after doses of 70 CGE, a randomized trial compared 50 and 70 CGE for small- and intermediate-size lesions located within 6 mm of the optic disc or macula. This dose-reduction study was completed in June 1994 with accrual of 188 patients. Interim analysis based on patients followed through September 1997 (median follow-up 60 months) suggested no reduction in either local control or survival rate. No marked improvement in visual outcome or complications has been observed. However, visual field analysis does show a smaller mean defect in the patients randomized to 50 CGE.

A study has been completed comparing iodine 125 plaques to helium ions by the group at University of California, San Francisco (UCSF) and Lawrence Berkeley Laboratories (LBL). Patients with melanomas less than 10 mm in height and less than 15 mm in diameter were randomized by the UCSF/LBL group to receive either 70 CGE in five treatments with helium ions, or 70 Gy to the tumor apex with iodine plaque brachytherapy. Local control was 100% in those patients treated with helium ions compared with 87% in those patients treated with 125I plaques.

**SARCOMAS OF THE SKULL BASE AND CERVICAL SPINE**

Treatment of patients with a sarcoma of the skull base is challenging because of the large number of critical structures penetrating the skull base and the proximity of these tumors to the brain stem and optic pathways. These factors have limited the success of conventional photon radiation therapy and surgery. The results of the MGH series has been analyzed. One hundred and sixty-nine patients with chordoma and 165 patients with chondrosarcoma were treated with protons between 1975 and 1998. The 5-year actuarial local control rates for skull-base chondrosarcomas was 88% and was 73% for chordoma patients. For cervical spine patients, local control rates were 54% and 48% for chondrosarcoma and chordoma patients, respectively. The LLU proton experience for skull-base tumors showed 5-year actuarial local control rates of 75% for chondrosarcoma and 59% for chordoma. The MGH results compare favorably with the experience (median dose 50 Gy) from Princess Margaret Hospital in Toronto of 55%.

**OPTIC PATHWAY GLIOMA**

Seven patients with optic pathway glioma were treated at LLU between 1992 and 1997. Tumor volumes ranged from 3.9 cm³ to 127 cm³. At a median follow-up of 37 months, all patients were locally controlled. A reduction in tumor volume was seen in three patients, and tumor volumes remained stable in four patients. Visual acuity remained stable in patients who presented with useful vision. Proton radiation therapy was shown to reduce the dose to the contralateral optic nerve by 47%, compared with three-dimensional photon techniques.

**ASTROCYTOMA**

Between 1993 and 1998, 48 patients were treated for nonresectable grade II and III intracranial tumors at the Center for Proton Therapy in D’Orsay, France. Mean tumor doses ranged from 63 to 67 Gy at 1.8 Gy per fraction. With a median follow-up of 18 months, local control was 97% (33 of 34 cases) and 43% (6 of 14 cases) for nonparenchymal and parenchymal lesions, respectively.

Twenty-three patients with the diagnosis of glioblastoma multiforme were treated to 90 CGE with twice-daily protons. Median survival time was 20 months from the date of surgery and 18.6 months from the start of radiation treatment. Actuarial survival at 2 and 3 years was 34% and 18%, respectively. Sixteen of the 23 patients were judged to have had tumor progression. Of these, 15 had progression in tissues that received 60 to 70 CGE (or less). In only one patient was there evidence of failure within the 90-CGE volume. All patients developed new areas of gadolinium enhancement during the follow-up period. Pathologic material was examined in 15 patients. Radiation necrosis was only demonstrated in seven patients. The survival rate for this group of 23 patients is comparable to that of the best brachytherapy or radiotherapy series. However, a trend toward larger and less accessible tumors was seen in this patient population. This regimen has achieved an apparent high frequency of tumor eradication in the 90-CGE volume, although toxicity has been significant.

**BENIGN MENINGIOMA**

Between 1981 and 1996, 46 patients with incompletely resected or recurrent benign meningioma were treated at the HCL with a combined proton-photon technique. The median dose to the tumor volume was 59.0 CGE. Overall survival at 5 and 10 years was 93% and 77%, respectively, and recurrence-free survival at 5 and 10 years was 100% and 88%. Three patients developed local tumor recurrence at 61, 95, and 125 months, although no patient died from recurrent disease. Complications have included focal brain stem necrosis in two patients and grade 3 memory loss in another patient. In four patients who developed ophtalmologic toxicity, the maximum dose to the optic structures was 58.4, 59.2, 59.3, and 63.0 CGE. Unilateral saccular leakage was observed in 11 patients.

Nineteen patients with inextirpable skull-base meningiomas were treated at the Svedberg Laboratory in Uppsala, Sweden, with 24 Gy in four fractions. With a minimum follow-up time of 36 months, no patients have experienced disease progression.

**PARanasal Sinus CARcinoma**

Between 1991 and 1996, 32 patients with carcinomas of the paranasal sinuses were treated on an accelerated-dose proton-photon protocol. The stage distribution was T3 in two cases and T4 in 30 cases, and all were N0 and M0. Four patients had had a gross total resection, whereas the others had had only a biopsy (7) or subtotal resection (19). The median observation period was 2.7 years. Actuarial disease-specific survival at 3 years was 62%. Ten deathsthree with intercurrent endocrinopathy in 11 patients.

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**HEPATOCellular CARcinoma**

Investigators at Tsukuba University, Japan, have reported impressive long-term control and survival results in patients with primary hepatocellular carcinoma treated with proton radiation therapy. The dose per fraction was 4 Gy and the mean total dose was 72 Gy. The 7-year local control and survival results in this series of 122 patients were reported as 94% and 27%. Proton therapy did not cause clinically symptomatic changes in liver function.

**LUNG CARcinoma**

Between 1994 and 1998, 37 patients with medically inoperable stage I–IIa lung cancer were treated at LLU with conformal photons and protons. Between 1991 and 1996, 32 patients with carcinomas of the paranasal sinuses were treated on an accelerated-dose proton-photon protocol. The stage distribution was T3 in two cases and T4 in 30 cases, and all were N0 and M0. Four patients had had a gross total resection, whereas the others had had only a biopsy (7) or subtotal resection (19). The median observation period was 2.7 years. Actuarial disease-specific survival at 3 years was 62%. Ten deathsthree with intercurrent endocrinopathy in 11 patients.

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**LUNG CARcinoma**

Between 1994 and 1998, 37 patients with medically inoperable stage I–IIa lung cancer were treated at LLU with conformal photons and protons. Patients received either photons and protons or photons alone to 73.8 CGE over 5 weeks. Patients with poor lung function received 51 CGE in ten fractions over 2 weeks to the gross tumor volume. With a median follow-up time of 14 months, disease-free survival at 2 years was 63% for all patients and 86% for stage I patients.

**PROTON RADIOSURGERY**

Between 1961 and 1993, 2987 patients were treated with single-fraction proton therapy (proton radiosurgery). This effort was led by the late Dr. Raymond Kjellberg, a neurosurgeon at MGH. The majority of patients were treated for inoperable arteriovenous malformations and pituitary adenomas. Beginning in 1991, a second proton radiosurgery technique was developed using a patient positioning system capable of stereotactic alignment for radiosurgery (STAR). This system was developed because of the inherent restrictions of the fixed horizontal beam at the HCL. The STAR unit was based on target coordinates obtained directly from computed tomography, magnetic resonance imaging, or angiography. Early results with arteriovenous malformations, acoustic neuromas, and brain metastases are comparable with those produced by other stereotactic techniques (Gamma Knife, linear accelerator, Elektra Corporation, Stockholm, Sweden).

**DESIGN OF CLINICAL TRIALS USING PROTON BEAMS**

The fixed horizontal, 160-MeV HCL proton beam, with an effective treatment depth of 15.9 cm, constrained the number of sites that could effectively be treated. For
this reason, past efforts have focused on intracranial targets, skull-base tumors, head and neck tumors, eye tumors, and prostatic carcinoma. The Northeast Proton Therapy Center (NPTC) at MGH will have a more energetic beam (220 MeV) capable of treating to depths of 32 cm, a gantry-based delivery system, and state-of-the-art patient positioning. These improvements will increase the numbers of patients that can be treated and will facilitate treatment at a number of new sites, including lung, rectum, and liver. In addition, a major effort will be placed on developing protocols for the treatment of pediatric malignancies.

Several examples of the potential advantages of the NPTC proton beam have been documented. Medulloblastoma is a pediatric malignancy that occurs in the posterior fossa and can spread through the cerebrospinal fluid to seed in the cranial cavity and the spinal axis, requiring radiation treatment to the cranial contents as well as the spinal axis. As a result, these patients frequently experience hearing, neurologic, neuropsychological, endocrine, musculoskeletal, cardiac, and fertility deficits because of the combined chemotherapy and radiation treatment. Figure 65-4 illustrates the dramatic reduction in the volume of normal tissue irradiated in the thorax (heart, lung, and esophagus) seen with protons. In addition, similar reductions would be seen in the abdomen (stomach, small bowel, pancreas, and liver) and pelvis (ovaries, bladder, and bowel). Also, not illustrated here, the dose to the middle ear can be reduced by 50% using photon techniques. Another example for which proton therapy can reduce treatment-related morbidity is the treatment of rectal carcinoma. Current treatment of patients with stage II and III rectal carcinoma includes surgical resection, pelvic radiation, and infusional 5-fluorouracil. Significant treatment-related morbidity results from this regimen because of the irradiation of large volumes of normal bowel and bladder with conventional photon radiation techniques. Proton beam treatment allows for irradiation of the target lymph nodes with minimal dose to the small bowel and the bladder (Fig. 65-5).

The reduction in normal tissue irradiation with protons has significant implications for combined radiation and chemotherapy protocols. Even when modest doses of radiation are prescribed, as in the case of rectal carcinoma, proton radiation should improve tolerance to the combined regimen. This should result in fewer dose-limiting toxicities and improved treatment intensity and treatment compliance, which may allow for higher chemotherapy doses and, ultimately, lead to higher cancer control rates.

CONCLUSIONS AND FUTURE DIRECTIONS

The history of radiation oncology has demonstrated that major improvements in local control have occurred because of improvements in dose distributions. Proton radiation therapy represents one of the most precise and sophisticated treatment delivery systems in radiation oncology. Proton therapy will also make use of some of the same improvements that have developed in conformal x-ray therapy (intensity modulation, rotational delivery, multileaf collimation, stereotactic localization) to further improve the dose distribution of protons. Such improvements will allow for continued escalation in tumor doses while minimizing dose to normal, nontarget tissues. With the installation of a high-energy (220 MeV) hospital-based proton therapy facility at the NPTC at MGH and the existing facility at LLU Medical Center, the technology exists for continuing clinical research in proton radiation therapy. Efforts for the first decade of the twenty-first century will include: (1) comparing intensity-modulated x-ray therapy and intensity-modulated proton therapy, (2) assessing the gains in treatment intensity in combined modality therapy with protons, and (3) assessing the impact of proton therapy on improving cure rates in pediatric cancer and reducing late effects.
BCC-1. Nodular basal cell carcinoma on nasal tip. Note pearly, translucent appearance with telangiectasias.


BCC-3. Nodular basal cell carcinoma of the left glabella with central depression. Note classic rolled borders and pearly appearance. There is also a large violaceous nodule in the left medial canthus. This long-standing lesion is an eccrine acrospiroma.

BCC-4. Large nodular basal cell carcinoma of the forehead with classic rolled border.

BCC-5A. Nodular basal cell carcinoma of the forehead at the site of a previous automobile injury. The patient states that she had multiple fragments of glass removed over a long period of time. Basal cell carcinoma and squamous cell carcinoma are known to develop at the site of chronic scar.
BCC-5B. Microscopical example of nodular basal cell carcinoma demonstrating peripheral palisading of basal cells, retraction of tumor masses from dermis, and hyperchromatic cells.

BCC-5C. Defect following Mohs micrographic excision, demonstrating extension of cancer to the periosteum. The patient subsequently underwent skin flap repair.

BCC-6. Superficial basal cell cancer on the left upper lip of a 27-year-old woman. The patient, an aspiring actress, did not want treatment with surgery or radiation therapy. A course of intralesional interferon was successful at eliminating the cancer. It should be noted that this approach should only be used in superficial, easy to monitor basal cell cancer and has a recurrence rate of 20%.

BCC-7. Superficial basal cell cancer on an extremity. This lesion had been treated for many years as eczema and psoriasis. Topical corticosteroids provided no benefit. Any persistent rash that does not respond to topical treatment or is not otherwise diagnosed should be promptly biopsied.

BCC-8. Superficial basal cell carcinoma on trunk.

BCC-10. Large pigmented basal cell carcinoma. The differential diagnosis includes melanoma.

BCC-11. Ulcerating basal cell carcinoma of the angle of the jaw.

BCC-12. Extensive basal cell carcinoma of the medial eyebrow and nasal root. Proximity to the supraorbital nerve raises the possibility of perineural extension of cancer in this long-standing carcinoma.

BCC-13A. Large nodular basal cell carcinoma in the medial canthus. Deep extension of the cancer in this area can involve the lacrimal duct.
BCC-13B. Defect following Mohs micrographic surgery indicates complete elimination of cancer. The lacrimal duct was not involved.

BCC-14. Extensive basal cell carcinoma of the right medial canthus, nasal sidewall, and distal nose. Basal cell cancer is typically a slow-growing tumor, but neglect can result in extensive destruction sometimes requiring removal of the orbital contents.

BCC-15. Cystic basal cell carcinoma of the glabella. This tumor was misdiagnosed as a cyst until a biopsy confirmed that it was a basal cell carcinoma, cystic type.

BCC-16. Morpheaform basal cell carcinoma of the chin. Note light coloration and smooth texture. Although it appears to be well demarcated, the infiltrative histologic nature of this cancer can be expected to result in a larger defect upon complete extirpation.

BCC-17. Long-standing morpheaform basal cell carcinoma of the left cheek. Note smooth, white appearance, slightly elevated from the surrounding tissue. Crust in the center is an indication of tumor necrosis. Patients who have this type of cancer diagnosed histologically must be prepared for the large extent of the defect.

BCC-18. Morpheaform basal cell carcinoma, a form of aggressive growth basal cell cancer, is noted on the right cheek of a 30-year-old woman. It had been long-standing and was noted to grow very slowly. Especially in young patients, the true extent of the cancer must be discussed in advance and proper preparation must be made so that optimal reconstruction results in the best aesthetic outcome. This cancer, located in the embryonic fusion plain, must be removed with Mohs micrographic surgery to minimize the chance of recurrence. Recurrent basal cell cancer, especially in this region, is at high risk for extension deep in the facial planes.
**BCC-19.** Poorly defined morpheaform basal cell carcinoma of the right upper eyebrow in a 55-year-old woman. The patient had this lesion for some time before noting that it had changed. The extent of the cancer is larger than it appears clinically. It is best treated with the Mohs micrographic surgery method.

**BCC-20.** Morpheaform basal cell carcinoma of the right upper eyebrow. The patient believed that she had a scar at the site for many years but could not identify an episode of related trauma. This is the classic appearance of a morpheaform basal cell cancer, the true extent of which is significantly greater than appears clinically.

**BCC-21.** Large basal cell cancer of the left upper outer arm. The cancer had been present for approximately three years before the patient sought treatment.

**BCC-22.** Extensive basal cell carcinoma of the left face. Although this is an extreme example, it highlights the potentially aggressive nature of basal cell carcinoma. Despite the very low risk of metastasis, the cancer can be extremely locally destructive and, if present near vital organs, lethal.

**BCC-23.** Young patient with a nevus sebaceous on the left cheek. This is a benign tumor of sebaceous glands but is associated with basal cell carcinoma. Current recommendations are that a nevus sebaceous be removed in young adulthood to minimize the risk of basal cell cancer.
BCC-24A. Multiple small papules in the periorbital region. Patients may present concerned that these represent cancer. In fact, they are syringomas, or benign tumors of the sweat glands. No treatment is necessary.

BCC-24B. This patient was referred because of concern that the red patch on the cheek, of long-standing duration, represented basal cell cancer. This is the classic appearance of rosacea, an adult form of acne. The condition responds promptly to topical therapy.

BCC-25. Severe solar damage of left face. This is the classic setting for the development of nonmelanoma skin cancer. Note fair skin, mottled pigmentation, and telangiectasias.

BCC-26. Close-up of patient in Figure BCC-25. This patient has skin type I. When exposed to ultraviolet radiation from the sun, he always burns and never tans. The absence of the tanning response probably increases the risk for epidermal mutations from solar radiation. Actinic keratoses, hypopigmentation from previous cryotherapy, and telangiectasias are noted.

BCC-27. This patient has had lifelong problems with basal cell carcinoma. Some patients who received radiation therapy for acne later developed multiple basal cell cancers. Despite multiple surgeries, topical chemotherapy, and cryotherapy, the patient continues to develop new basal cell carcinomas.
BCC-28A. This patient worked for many years in his youth as a lifeguard. Evidence of basal cell cancer and solar damage, as well as scar related to previous surgery, are noted.

BCC-28B. The same patient 10 years later with progressive basal cell cancer and areas of scar associated with basal cell cancer recurrence. Although we refer to these lesions as recurrences, histologic evaluation of the patient's facial skin indicates widespread basaloid budding in the epidermis, consistent with a field defect.

BCC-29. Elderly patient with multiple basal cell cancers. This patient has a history of arsenic exposure, which is associated with the development of basal cell carcinomas.

BCC-30. Nodular basal cell carcinoma on the nasal sidewall of a 40-year-old woman. Although most likely to be basal cell carcinoma, all such lesions must be biopsied. Melanoma and other forms of nonmelanoma skin cancer are in the differential diagnosis, although they are less likely.

BCC-31. Ulcerated nodular basal cell carcinoma of the nose.
BCC-32. Nodular basal cell carcinoma of the left upper lip and alar groove. Basal cell cancer is thought to double in size over approximately 1 year. The size of this lesion suggests it has been present for many years. It is at risk for deep infiltration into the nasolabial groove.

BCC-33. Basal cell carcinoma of the tip of the nose. Because of the ill-defined margins of this cancer and its technically challenging location, Mohs micrographic surgery is indicated.

BCC-34. Basal cell carcinoma of the right nose. Patients must be advised of the likely size of the cancer, which is often larger than appears clinically. The final wound and reconstruction may be unsettling to the patient if he or she has not been properly prepared.

BCC-35. Small basal cell carcinoma of the left upper lip.

BCC-36. Basal cell carcinoma of the nose. Note the extensive nodularity under the surface of the skin. This cancer is likely to be at least 50% larger than it appears on the surface.
BCC-37. Nodular basal cell carcinoma of the left ala. This lesion is easily treated by Mohs micrographic surgery. Because of its presence in the alar groove, healing by second intention is often an acceptable alternative to plastic reconstruction.

BCC-38A. Recurrent basal cell carcinoma on the left nose of an individual who works outdoors. Although very little scar tissue is noted on clinical exam, the cancer proved to be approximately twice the clinical size because of the extension of cancer cells within and under scar tissue.

BCC-38B. The defect following Mohs micrographic surgery.

BCC-38C. Immediately after Mohs micrographic surgery, the defect was repaired in a linear fashion, which will result in a fine-line scar. Patients must be advised that the complete healing process takes approximately twelve months. Maturation and fading of the scar continues during this whole period.

BCC-39. Ulcerating nodular basal cell carcinoma of the left alar rim. Because of its proximity to the alar rim as well as to the embryonic fusion plain, Mohs micrographic excision is indicated. A shallow defect in this area can be allowed to heal by second intention with excellent results. Alternatively, plastic reconstruction may be required to preserve normal anatomic and functional relationships.
BCC-40. Linear erosions on the right alar rim of a patient with a history of squamous cell cancer of the cheek. The patient also has a history of prurigo. The area was biopsied and failed to reveal any cancer. The patient admits to scratching. If topical treatment with corticosteroids fails to resolve the problem, a deeper biopsy may be indicated.

BCC-41. Nodular basal cell carcinoma on the left ala, similar to Figure BCC-39.

BCC-42. Extensive basal cell carcinoma of the left nose. Mohs micrographic treatment surgery is the treatment of choice. The reconstruction technique depends on the final defect.

BCC-43. Large eroding basal cell carcinoma of the nasal bridge. This patient, of northern European ancestry, had worked outdoors his whole life. Several other basal cell carcinomas are noted on the cheek and lip.

BCC-44A. Large basal cell carcinoma of the left ala. Note elevation and retraction of the alar rim. This is an indication of extensive deep infiltration by basal cell carcinoma.
BCC-44B. Defect following Mohs micrographic surgery. The patient was referred for complex flap reconstruction.

BCC-45A. Large nodular basal cell carcinoma of the left upper lip and left nostril.

BCC-45B. Defect following Mohs micrographic surgery. It is essential to minimize the recurrence of cancer in this location, as recurrent tumor is likely to invade deeply. The patient was referred for plastic reconstruction. Recurrence of cancer under complex flaps may be concealed, so careful examination including bimanual palpation of the region is necessary.

BCC-46A. Extensive basal cell carcinoma of the left upper lip. Excision with conventional margins may not have adequately removed the cancer. Mohs micrographic surgery was performed.

BCC-46B. Following Mohs micrographic excision with preservation of the orbicularis oris.
BCC-46C. After reconstruction using an Abbe flap. (Figure BCC-46C courtesy of Dr. Stephan Ariyan).

BCC-47. Nodular basal cell carcinoma of the right upper lip.

BCC-48A. Morpheaform basal cell carcinoma of the left cheek with indistinct margins. Excision by the Mohs micrographic surgery technique resulted in a 5-cm defect. The wound was repaired under local anesthesia at the time of Mohs surgery.

BCC-48B. Three months following reconstruction with cheek advancement flap.

BCC-49A. Long-standing basal cell carcinoma of the left cheek. Note areas of nodularity, hypopigmentation, and crusting resulting from bleeding from the surface of the cancer.
BCC-49B. Extensive defect following Mohs micrographic excision demonstrates histologic extent of cancer. Incomplete excision of cancer is an important cause of recurrence. Proper preparation of the patient for the extent of this defect was essential. Repair was performed without complication.

BCC-50. Ill-defined extensive basal cell carcinoma of the left temporal region.

BCC-51A. Neglected basal cell carcinoma of the right temporal region and ear. Cancer in this area, especially when long-standing, has the potential for deep invasion.

BCC-51B. Defect following Mohs micrographic surgery reveals temporalis muscle.

BCC-51C. Despite the very high cure rates associated with Mohs micrographic surgery, risk of recurrence is proportional to the size of the cancer. Because of concern about concealing any recurrence, the wound was allowed to heal by second intention. The wound is pictured here at approximately 4 weeks status post excision.

BCC-51D. Completely healed wound at 3 months. The patient did not wish to have reconstructive surgery done on the helix of the ear.
BCC-52. Basal cell cancer within the triangular fossa of the ear. Basal cell cancer on the antihelix is not uncommon, and the recommended treatment is Mohs micrographic excision.

BCC-53. Ill-defined nodular basal cell carcinoma of the forehead.

BCC-54. Large basal cell carcinoma of the right lower eyelid. Retraction of surrounding tissue indicates deeply infiltrative nature of the cancer. The patient was treated with Mohs micrographic surgery and referred for reconstruction to minimize the risk of ectropion.

BCC-55. Very large ulcerated basal cell carcinoma of the glabella.

BCC-56. Basal cell carcinoma of right lower eyelid in an African-American. Although basal cell carcinoma is most common in light-skinned people, it can occur in more darkly pigmented individuals.
BCC-57. Ulcerated basal cell carcinoma on the root of the nose. The majority of facial basal cell carcinomas occur on the nose.

BCC-58. Extensive basal cell carcinoma of the left nose extending into the medial canthus and along the lower eyelid. Treatment of this cancer requires an interdisciplinary approach. Following Mohs micrographic surgery, the patient was referred for plastic reconstruction. Because of the large size of the lesion, the patient must be monitored for recurrence.

BCC-59A. Extensive basal cell carcinoma in a young man. The location in the medial canthus, the long-standing nature of the cancer, and its size create a high risk that if the lesion recurs it will extend into the orbit. The patient was treated with Mohs micrographic surgery.

BCC-59B. Defect following Mohs micrographic surgery demonstrating the canthal ligament.

BCC-60. Basal cell cancer of the nasal root extending into the medial canthus.
BCC-61. Large nodular basal cell cancer of the lower eyelid. Mohs micrographic excision was performed followed by plastic reconstruction. Based on its size, this lesion had been present for many years.

BCC-62. Extensive basal cell carcinoma with retraction of the medial canthus. This clinical appearance suggests that the cancer likely extends deeply and may be at risk for involving the infraorbital nerve.

BCC-63. Recurrent nodular basal cell carcinoma of the post-auricular sulcus. Basal cell cancer in this region can extend widely along the cartilage and posterior scalp before it is diagnosed. Mohs micrographic excision is indicated.

BCC-64. Nodular basal cell carcinoma within an area of previous excision consistent with recurrent cancer.

BCC-65. Extensive basal cell carcinoma of the ear and temple. Because of the extensive nature of this cancer, radiation therapy was used with a good result. The therapeutic plan was to use Mohs micrographic surgery if the cancer recurred.
**BCC-66.** Multiple nodular and papular lesions on the scalp in an individual with severe solar damage. Although the clinical diagnosis of the large lesion on the right is basal cell cancer, the red nodular lesions are concerning and require biopsy as well to obtain a definitive diagnosis.

**BCC-67.** Large superficial basal cell carcinoma on the right breast. This was successfully treated with radiation therapy, although Mohs micrographic surgery and reconstruction would have been an equally acceptable alternative.

**BCC-68.** Large nodular basal cell carcinoma on the chest. The differential diagnosis includes squamous cell carcinoma.

**BCC-69.** Basal cell carcinoma on the shin of a 60-year-old woman. Basal cell carcinoma on the lower extremity is more common in women than in men. This highlights the likely association between solar exposure, secondary to clothing styles, and basal cell cancer.

**BCC-70.** Additional basal cell cancer on the lower extremity in the same patient as in Figure BCC-69.
Multiple basal cell carcinomas of the lower extremity with evidence of venous stasis changes. Treatment of cancer in this area is extremely difficult because of the dependent location and the resultant slow healing in older patients. Treatment by Mohs micrographic excision with healing by second intention provides excellent results. While skin grafting creates secondary wounds in the patient that require additional healing, new biologic dressings and allograft permit excellent healing while minimizing limitations on activity.

Large nodular basal cell carcinoma on the upper extremity.

Nodular basal cell carcinoma on the upper extremity, side view, indicating the exophytic nature. The differential diagnosis includes squamous cell cancer and melanoma.

Superficial basal cell carcinoma on the shoulder of a 45-year-old male. This lesion can be treated easily with electrodesiccation and curettage.

Basal cell carcinoma on the instep of an elderly woman.
BCC-76A. Basal cell carcinoma with ill-defined clinical margins on the nasal tip of a 50-year-old man. The lesion had been treated for several years as rosacea. Biopsy confirmed the presence of rosacea but also revealed a few foci of superficial basal cell carcinoma.

BCC-76B. Defect following Mohs micrographic surgery.

BCC-77. Basal cell carcinoma on the philtrum complicated by an outbreak of herpes labialis. Surgery was deferred until the lesion resolved. Prophylactic antiviral medication was used. This case highlights the occasional misdiagnosis of basal cell carcinoma for herpes labialis. The chronic, recurring nature of both, in certain circumstances, may be responsible for the confusion. Basal cell cancer is not associated with a prodrome.

BCC-78A. Basal cell carcinoma of the right medial canthus. This red, scaling lesion had been treated for many years as a form of eczema. Biopsy was eventually performed when the patient was seen by his dermatologist, and it revealed basal cell cancer.

BCC-78B. Defect following Mohs micrographic surgery.
BCC-78C. Two weeks after placement of a full-thickness skin graft.

BCC-78D. After complete healing of skin graft.

BCC-78E. Recurrent basal cell carcinoma at upper edge of graft 10 years after original surgery.

BCC-79. Multiple basal cell carcinomas in a severely sun-damaged patient. Compare this clinical presentation with that in Figure BCC-25, Figure BCC-26, Figure BCC-27, Figure BCC-28, and Figure BCC-29. Surgery and radiation therapy are generally the only treatments currently available. Photodynamic therapy, incorporating the use of topical aminolevulinic acid, which avoids systemic adverse effects, holds promise for treatment of large numbers of lesions. The long-term benefit of this approach remains to be determined.

BCC-80. Multiple basal cell carcinomas in a patient who received radiation therapy for acne 50 years earlier. Any new therapeutic modality that is practiced on the skin today may yield unanticipated complications decades later. In most cases, it is difficult to anticipate what those effects might be, and the need for effective current management typically outweighs unknown delayed risks.